Association of Renin-Angiotensin-Aldosterone Inhibitors with COVID-19 Infection and Disease Severity among Individuals with Hypertension

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ABSTRACT **Background:** The association between use of renin-angiotensin-aldosterone (RAAS) inhibitors and both SARS-CoV-2 infection and the development of severe COVID-19 has been presented in the recent medical literature with inconsistent results.

Objectives: To assess the association between RAAS inhibitor use and two outcomes: infection with SARS-CoV-2 (Model 1) and severe COVID-19 among those infected (Model 2).

Methods: We accessed used electronic health records of individuals from Israel who were receiving anti-hypertensive medications for this retrospective study. For Model 1 we used a case-control design. For Model 2 we used a cohort design. In both models, inverse probability weighting adjusted for identified confounders as part of doubly robust outcome regression.

Results: We tested 38,554 individuals for SARS-CoV-2 who had hypertension and were being treated with medication; 691 had a positive test result. Among those with a positive test, 119 developed severe illness. There was no association between RAAS inhibitor use and a positive test. Use of RAAS inhibitors was associated with a decreased risk for severe COVID-19 (adjusted odds ratio [OR] 0.47, 95% confidence interval [95%CI] 0.29–0.77) compared with users of non-RAAS anti-hypertensive medication. The association remained significant when use of angiotensin-converting-enzyme inhibitors (adjusted OR 0.46, 95%CI 0.27–0.77) and angiotensin II receptor blockers (adjusted OR 0.39, 95%CI 0.16–0.95) were analyzed separately.

Conclusions: Among individuals with hypertension using RAAS inhibitors, we found a lower risk of severe disease compared to those using non-RAAS anti-hypertensive medications. This finding suggests that RAAS inhibitors may have a protective effect on COVID-19 severity among individuals with medically treated hypertension.

IMAJ 2022; 24: 310–316

KEY WORDS: angiotensin-converting-enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), coronavirus disease 2019 (COVID-19), renin-angiotensin-aldosterone (RAAS) inhibitors, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been defined as a pandemic by the World Health Organization [1]. As of 24 April 2022, more than 500 million people worldwide has been diagnosed with SARS-CoV-2 and over 6 million deaths have been reported globally [2].

SARS-CoV-2 gains entry to the cell by binding to angiotensin converting enzyme 2 (ACE-2). Renin-angiotensin-aldosterone system (RAAS) inhibiting agents have been shown to increase expression of the ACE-2 receptors in several organs, including the heart and brain [3]. Consequently, there is a debate regarding the role that RAAS inhibitors play in the risk of COVID-19 infection and severity.

Since ACE-2 serves as a functional receptor for cell entry by SARS-CoV-2, its increased expression could result in increased susceptibility for infection [3]. RAAS inhibitor agents have been hypothesized to affect disease severity as well. Lung damage caused by COVID-19 may be, at least partially, mediated by the presence of Angiotensin II. One small study of 12 patients with COVID-19 showed a positive correlation between plasma levels of Angiotensin II, SARS-CoV-2 viral load, and the severity of lung injury [4]. The two main classes of RAAS inhibitors, angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), functionally inhibit Angiotensin II's effect, either by diminishing its amount or by blocking its receptor. Thus, treatment with either ACEIs or ARBs could mitigate COVID-19 associated lung damage [3,5-8].

Recent observational studies on the association between chronic treatment with RAAS inhibitors and the severity of COVID-19 have yielded conflicting results. A multi-site study of hospitalized patients in China, found treatment with RAAS inhibitors was associated with lower mortality [9]. A study in Spain found that treatment with RAAS inhibitors was associated with a decreased risk of COVID-19 requiring hospital admission, but only among individuals with diabetes [10]. Conversely, a study by Mehta et al. [11] found an association between RAAS use and a higher risk of hospitalization or admission to

the intensive care unit (ICU), though the authors were cautious about interpreting their findings, as they noted that they were likely affected by residual confounding [11,12]. Additional studies found no association between treatment with RAAS inhibitors and illness severity among COVID-19 patients [13-15]. None of these studies, however, limited the main analysis to hypertensive individuals receiving anti-hypertensive medication.

Three recent meta-analyses estimating the association between RAAS inhibitors use and COVID-19 have also yielded conflicting results. One study found no association between RAAS inhibitors use and COVID-19 mortality [16]. Two other studies found an association between RAAS inhibitors use a lower odds of critical disease or mortality, but found different effects for the two sub-classes of medications, with one finding an association for ACE-I, but not ARBs [17], and the other finding an association for ARBs, but not ACE-I [18]. For the two meta-analyses that reported heterogeneity data, a substantial heterogeneity of the effect estimates was present (I^2=65% P = 0.004 [18]; and I^2=63.1% P = 0.0001) [17], and all three indicate that many studies included in the pooled analysis did not adjust, or only partial adjusted, for identified confounders.

There is little evidence regarding the association between chronic treatment with RAAS inhibitors and infection with SARS-CoV-2. Previous studies found no adjusted association between treatment with RAAS inhibitors and COVID-19 infection [11,15,16,19].

In this study, using data from Israel's largest healthcare organization, we assessed the association between treatment with RAAS inhibitors and the risk for contracting SARS-CoV-2 as well as the risk for illness severity among those infected. We compared RAAS inhibitor users to users of other classes of anti-hypertensive drugs.

PATIENTS AND METHODS

DATA SOURCES

Data on patients were taken from Clalit Health Services (CHS), Israel's largest integrated payer-provider healthcare organization, with over 4.5 million members. CHS has a comprehensive data warehouse, which combines community and hospital medical data, medication prescription and purchasing records, medical care utilization and medical history details, and information on current medical conditions, as well as socio-demographic and administrative information.

For this study, the CHS data warehouse was merged with data from the Israeli Ministry of Health's (MOH) central registry, which includes data on all SARS-CoV-2 tests conducted in the country. The MOH registry also includes a categorical severity score (mild/moderate/severe), which is assigned to all COVID-19 patients. The MOH classifies COVID-19 as severe if any of the following is present: respiratory rate > 30 breaths/minute; $PaO_2/FiO_2 < 300$; or $SpO_2 \leq 93\%$ in room air.

STUDY DESIGN

This study consisted of two models with two different study designs. Model 1 used a test-negative design, a variant of the case-control study, comparing individuals who tested positive for SARS-CoV-2 (cases) with individuals who tested negative for SARS-CoV-2 (controls) during the study period (1 February 2020 to 10 June 2020). Model 2 used a retrospective rolling cohort design that included individuals who tested positive for SARS-CoV-2 during the study period up to 10 May 2020 (so that everyone in the cohort had at least one month of follow-up). In both models, for individuals who tested positive for SARS-CoV-2 at any point, the date of the first positive test was considered as the index date. For individuals who only tested negative, the index date was the date in which they first tested negative. COVID-19 disease severity outcomes were recorded from the index date until 10 June 2020. All background clinical variables, including history of hypertension, were extracted from 1 January 2015 onward. The last recorded value was taken for socio-demographic variables, body mass index (BMI), and smoking status.

STUDY POPULATION

Model 1's study population consisted of CHS members who had a diagnosis of hypertension, were using anti-hypertensive medication, were not pregnant, and had undergone a SARS-CoV-2 test in either an inpatient or outpatient setting. Individuals who met the inclusion criteria for Model 1 and had at least one positive test for SARS-CoV-2 were included in Model 2.

VARIABLES

For Model 1, individuals were defined as cases if they had at least one positive test result and as controls if they had one or more negative test results. For Model 2, disease severity was a dichotomous outcome, defined as severe if an individual was either assigned an MOH severe status at any point in the disease or had an in-hospital COVID-19-related death. The outcome was defined as not severe if neither were documented. Exposure to an anti-hypertensive medication was defined as any dispensation within the 4 months preceding the index date. Individuals using any type of RAAS inhibitor, either as monotherapy or part of a combination therapy, were included as RAAS inhibitor users, whereas individuals in the non-users group were not using any RAAS inhibitors.

A set of confounders was adjusted for in each model, defined by a clinical domain expert. A directed acyclic graph (DAG) was drawn for each model. Model 1 was adjusted for age, sex, BMI, smoking (current), socioeconomic status (SES), diabetes, and chronic kidney disease. Model 2 was adjusted for age, sex, BMI, smoking (current), SES, type 2 diabetes, chronic kidney disease, cardiovascular disease, and obstructive respiratory disease. Chronic diseases were identified from diagnoses starting in 2002 (when the CHS data warehouse became comprehensive) from primary care doctors, specialists, and hospitals. The DAGs for both models and a list of International Classification of Diseases,

Ninth Revision codes used for diagnoses are available in the supplemental Table 1, Figure 1, and Figure 2, which are available in the online version only. The same set of confounders was adjusted for in both in the main analysis and sensitivity analyses.

ETHICS

CHS institutional review board approved utilizing the electronic health records for the conduct and publication of COVID-19 research.

ANALYSIS

The frequency of the outcome measures was calculated. A positive versus negative test for SARS-CoV-2 and severe COVID-19 illness among study participants was stratified by treatment groups (RAAS inhibitor users versus non-users). The distribution of socio-demographic and clinical variables was presented across these groups.

To estimate the causal effect of the exposure with the outcome, a doubly robust estimator was used that combined covariate adjustment within an outcome model with inverse probability weighting to adjust for confounders [20]. For the purpose of inverse probability weighting, a propensity score model was developed. Logistic regression was used both for the propensity and outcome models.

For the main analyses for Models 1 and 2, RAAS inhibitor users were defined as those who purchased any type of RAAS

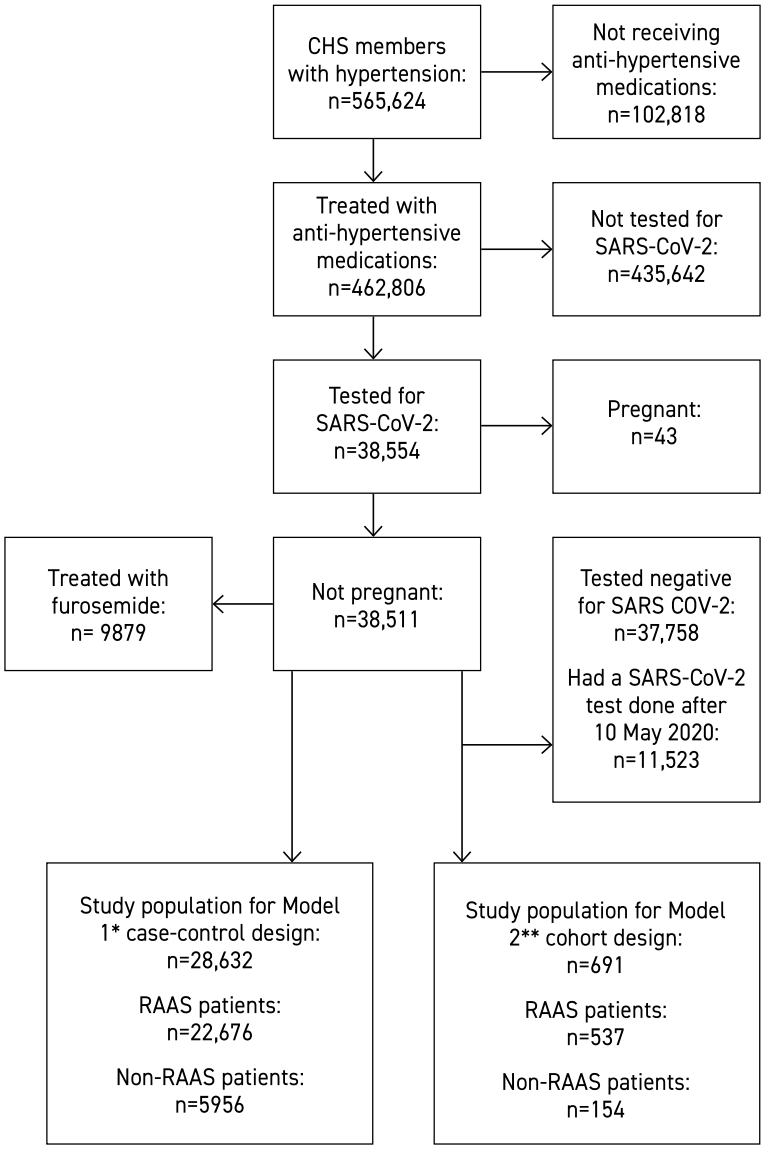
Table1. Characteristics of the study population for main analyses

	Model 1 study population* Patients tested for SARS-CoV-2		Model 2 study population** Patients who tested positive for SARS-CoV-2	
Characteristic	**Non-RAAS**	**RAAS**	**Non-RAAS**	**RAAS**
Individuals: n	5,956	22,676	154	537
Age, years, median (IQR)	76.0 (65.0–86.0)	71.0 (61.0–82.0)	79.0 (68.0–87.0)	69.0 (61.0–79.0)
Sex, n (%): female	3566 (59.9%)	12,754 (56.2%)	81 (52.6%)	257 (47.9%)
BMI Median (IQR) Missing	 27.3 (24.1–30.8) 217 (3.6 %)	 28.4 (25.3–32.0) 395 (1.7 %)	 29.1 (24.5–32.2) 4 (2.6)	 29.3 (26.2–33.2) 3 (0.6)
Smoking, n (%): Current Missing	 672 (11.5%) 118 (1.98 %)	 2972 (13.3%) 289 (1.27 %)	 12 (8.1%) 5 (3.25%)	 24 (4.5%) 3 (0.6 %)
Population sector, n (%)*** General Jewish Ultra-Orthodox Jewish Arab	 5189 (87.1%) 262 (4.4%) 505 (8.5%)	 18,870 (83.2%) 925 (4.1%) 2,881 (12.7%)	 115 (74.7%) 30 (19.5%) 9 (5.8%)	 362 (67.4%) 115 (21.4%) 60 (11.2%)
Socioeconomic status, n (%)*** Low Medium High Missing	 1579 (27.2%) 2991 (51.5%) 1237 (21.3%) 149 (2.5 %)	 7351 (32.8%) 10,407 (46.5%) 4633 (20.7%) 285 (1.26%)	 46 (30.5%) 83 (55.0%) 22 (14.6%) 3 (1.95 %)	 218 (40.7%) 221 (41.3%) 96 (17.9%) 2 (0.4 %)
Immigrant since 2000, n (%)	225 (3.8%)	958 (4.2%)	5 (3.2%)	13 (2.4%)
Number of children, median (IQR)	1.0 (0.0-3.0)	2.0 (0.0–3.0)	1.0 (0.0–3.0)	2.0 (0.0–3.0)
Diabetes, n (%)	1,901 (31.9%)	8,404 (37.1%)	54 (35.1%)	214 (39.9%)
Chronic kidney disease, n (%)	832 (14.0%)	1,476 (6.5%)	37 (24.0%)	54 (10.1%)
Cardiac arrhythmia, n (%)	1,539 (25.8%)	4,184 (18.5%)	56 (36.4%)	123 (22.9%)
Heart failure, n (%)	558 (9.4%)	1,450 (6.4%)	41 (26.6%)	79 (14.7%)
Hypertension duration, months, median (IQR)	46.0 (27.0–58.0)	47.0 (27.0–58.0)	44.5 (28.0–56.0)	47.0 (28.0–58.0)
Test positive for COVID-19, n (%)	114 (1.9%)	488 (2.2%)	154 (100.0%)	537 (100.0%)
Severe illness, n (%)	27 (0.5%)	52 (0.2%)	47 (30.5%)	72 (13.4%)

*Model 1: A case-control design assessed the association between treatment with RAAS inhibitors and the likelihood of a positive test for SARS-CoV-2
**Model 2: A cohort design assessed the association between treatment and severe illness among those who tested positive. Model 2 study population includes fusoremide users
***Population sector and socio-economic status data were based on the aggregate classification of the patient's primary care clinic [24]
BMI = body mass index, COVID-19 = coronavirus disease 2019, IQR = interquartile range, RAAS = renin-angiotensin-aldosterone, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Figure 1. Study population flowchart

CHS = Clalit Health Services, COVID-19 = coronavirus disease 2019, RAAS = renin-angiotensin-aldosterone, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2



*For Model 1, individuals were defined as cases if they had at least one positive SARS COV-2 test result and as control if they had only negative test results

**For Model 2, disease severity was a dichotomous outcome, defined as severe if an individual was either assigned a severe status by the Israeli Ministry of Health at any point or had an in-hospital COVID-19-related death

inhibitor, whereas non-RAAS inhibitor users did not purchase any RAAS inhibitor. To estimate the sensitivity of the main analysis results with the definitions of the treatment groups, the main analysis was repeated with two other treatment definitions. In the first, clean RAAS definition variation, the study population was limited to individuals who either received only RAAS inhibitors (users), only other types of anti-hypertensive medications (non-users), or excluded individuals who received medications of both types. This sensitivity analysis was applied to both Model 1 and Model 2. The second variation applied only to Model 2, no furosemide, and excluded furosemide users. Last, subgroup analyses were conducted for both models that compared individuals using ACEIs with individuals using only non-RAAS medications, and similarly, compared individuals using ARBs with individuals using only non-RAAS medications. Missing data were minimal and relevant for BMI, smoking, and SES. In all models, complete-case analyses were conducted. Complete data on all variables were available for 95.6% of cases of the main Model 1 population, 97.3% of the cases in the main Model 2 population, and 97% or more of the cases in the sensitivity and sub-group analyses.

Odds ratios (ORs) were estimated and 95% confidence intervals (95%CI) were reported. All presented estimates are adjusted, unless otherwise stated. Analyses were conducted with the use of the statistical software package R, version 3.6.1.

RESULTS

PATIENT CHARACTERISTICS

As of 10 June 2020, a total of 38,554 CHS members who were tested for SARS-CoV-2 presented with hypertension and used anti-hypertensive medications [Figure 1]. Of those, 43 were excluded due to pregnancy. The remaining 38,511 individuals were included in the tested case and control groups of Model 1. Clinical characteristics were then examined across anti-hypertensive medication classes. The population taking furosemide was the oldest and had more co-morbidities compared to the other classes. After consultation with a clinical expert, it was decided to exclude this class from the study population in Model 1, which is also consistent with the findings of Reynolds and colleagues [13]. Of this study population, 9879 furosemide users were excluded, leaving 28,632 individuals in the case-control study population (Model 1), 79.2% taking RAAS inhibitors (n=22,676) and 20.8% taking non-RAAS medications (n=5956).

Among the population with hypertension who used anti-hypertensive medications and were tested for SARS-CoV-2 as of 10 May 2020, 691 (2.43%) had a positive test result (cohort population of Model 2). Those taking furosemide were included in Model 2, as their observed characteristics were similar to the other classes in the test positive study population. Of the Model 2 cohort population, 119 (17.2%) developed a severe COVID-19 illness.

The distribution of socio-demographic and clinical characteristics of study participants across treatment groups is presented in Table 1. Overall, in the Model 1 population, RAAS inhib-

itor users were younger than non-users (median age 71 and 76 years, respectively) and had a lower prevalence of chronic kidney disease (6.5% vs. 14%) and heart failure (6.4% vs. 9.4%). Similar differences were reflected in the Model 2 population.

MULTIVARIABLE MODEL

Applying inverse probability weights successfully balanced the two treatment groups with respect to each of the identified confounders, achieving standardized mean differences that were less than 0.1. Tables 2 and 3 present the effect estimates for all models. In Model 1, there was no association between treatment with RAAS inhibitors and testing positive for SARS-CoV-2, either in the main Model 1 (OR 1.1, 95%CI 0.88–1.36) or in the clean-RAAS sensitivity analysis (OR 1.07, 95%CI 0.85–1.34). In the main analysis of Model 2, treatment with RAAS inhibitors was significantly associated with a lower odds of severe

Table 2. Case-control analysis of the association between the use of RAAS inhibitors vs. other blood pressure lowering drugs and the odds ratio of testing positive vs. negative for SARS-CoV-2 (Model 1)

	Unadjusted OR (95% CI)	*P* value (Unadjusted)	Adjusted* OR (95% CI)	*P* value (Adjusted)
Main model**	1.13 (0.91–1.38)	0.25	1.1 (0.88–1.36)	0.38
Clean-RAAS sensitivity analysis***	1.09 (0.87–1.35)	0.46	1.07 (0.85–1.34)	0.47

*Adjusted for age, sex, body mass index, smoking (current), socio-economic status, type 2 diabetes, and chronic kidney disease

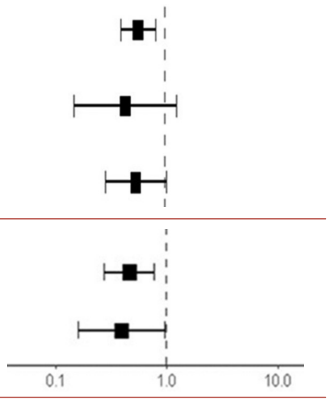
**For the main Model, RAAS inhibitor users were defined as those who purchased any type of RAAS inhibitor, whereas non-RAAS inhibitor users (non-users) did not purchase any RAAS inhibitor

***The clean-RAAS sensitivity analysis was limited to individuals who either received only RAAS inhibitors (users) or only other types of anti-hypertensive medications (non-users)

OR = odds ratio, RAAS = renin-angiotensin-aldosterone, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Table 3. Cohort design of the adjusted association between use of renin-angiotensin-aldosterone inhibitors vs. other blood pressure lowering drugs and severe illness among those who tested positive for SARS-CoV-2 (model 2)

	Severe COVID-19 among positive patients treated with non-RAAS medication	Severe COVID-19 among positive patients treated with RAAS medication	Adjusted OR (95%CI)Δ
Main model⁎	47/154 (30.5%)	72/537 (13.4%)	0.47** (0.29–0.77)
Clean-RAAS sensitivity analysis⁎⁎	52/209 (24.9%)	13/152 (8.5%)	0.33 (0.08–1.35)
No furosemide sensitivity analysis⁎⁎⁎	25/102 (24.5%)	52/449 (11.6 %)	0.44 (0.19–1.03)
ACEI⊕	52/209 (24.9%)	39/281 (13.9%)	0.46** (0.27–0.77)
ARB⊕⊕	52/209 24.9%)	23/153 (15%)	0.39* (0.16–0. 95)



ΔAdjusted for age, sex, body mass index, smoking (current), socio-economic status, type 2 diabetes, chronic kidney disease, cardiovascular disease, and obstructiverespiratory disease. Doubly robust outcome regression was used for all models

⁎ For the main model, RAAS inhibitor users were defined as those who purchased any type of RAAS inhibitor, whereas non-RAAS inhibitor users (non-users) did not purchase any RAAS inhibitor

⁎⁎ The Clean RAAS sensitivity analysis was limited to individuals who either received only RAAS inhibitors (users) or only other types of anti-hypertensive medications (non-users).

⁎⁎⁎ The furosemide sensitivity analysis excluded individuals who purchased furosemide in the 4 months prior to the index date.

⊕Sub-group analyses compared individuals using ACEIs with individuals using non-RAAS medications

⊕⊕Sub-group analyses compared individuals using ARBs with individuals using non-RAAS medications

*$P > 0.05$

**$P \leq 0.05$

95%CI = confidence interval, ACEI = angiotensin-converting-enzyme inhibitors, ARB = angiotensin II receptor blockers, COVID-19 = coronavirus disease 2019, OR = odds ratio, RAAS = renin-angiotensin-aldosterone, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

illness compared to non-RAAS inhibitors (OR 0.47l 95%CI 0.29–0.77). In both the clean-RAAS and the no furosemide sensitivity analyses there were lower odds of severe illness among users of RAAS inhibitors, but the results were not statistically significant (OR 0.33, 95%CI 0.08–1.35 and OR 0.44, 95%CI 0.19–1.03, respectively). Unadjusted analyses for Model 2 are presented in Supplemental Figure 2 in the online version only.

When analyzed separately, both ACEI and ARB use were significantly associated with lower odds for severe illness (OR 0.46, 95%CI 0.27–0.77 and OR 0.39 95%CI 0.16–0.95, respectively).

DISCUSSION

In this retrospective observational study of a large cohort of individuals with hypertension who were tested for SARS-CoV-2, there was no association between treatment with RAAS inhibitors and testing positive for SARS-CoV-2. Treatment with RAAS inhibitors, however, was associated with a significantly lower risk for severe COVID-19 illness among those infected, and this association was statistically significant after adjusting for confounders.

There was no association between chronic treatment with RAAS inhibitors and testing positive for SARS-CoV-2 in the clean-RAAS sensitivity analysis, which was limited to individuals taking only RAAS or only non-RAAS medications. Several previous studies also found no association between RAAS inhibitor use and COVID-19 infection [11,15,16,19].

We found a significant protective association between treatment with RAAS inhibitors and severe COVID-19 illness. This association persisted but did not remain significant in the sensitivity analyses with smaller sample sizes. The subgroup analyses, which separately analyzed ACEI and ARB use, suggested that both classes were significantly associated with a lower risk of severe illness compared with non-RAAS medication use, further supporting the findings of our main analysis. Three previous meta-analyses on the topic have yielded conflicting results, with one finding no association between RAAS inhibitors use and COVID-19 mortality, one finding an association for ACE-I but not for ARBs, and the other, conversely, finding an association for ARBs but not for ACE-I [16-18]. In our study, it was not possible to answer the question as to whether there was an association between individual RAAS inhibitor agents and the outcomes due to the small sample sizes. These associations warrant additional studies with larger numbers of COVID-19 patients.

Our study had several limitations. First, inherent to every observational study is the possibility of residual confounding, that is, the absence of observed or unobserved confounders that were not controlled for in the model. Second, our findings are limited to individuals with hypertension who receive anti-hypertensive medications. It is thus unknown if the findings are generalizable to other patient populations, including individuals who use RAAS inhibitors for indications other than hypertension. Third, as our study population was limited to individuals who had a SARS-CoV-2 test performed, if RAAS users were different from RAAS non-users in ways that impacted their probability of being tested, this could have created a selection bias in the study population and also could influence the generalizability of results to other settings. Fourth, similar to other work in the field, as highlighted in the research by Cohen et al. [21], our study defined the exposure and confounders in a non-time dependent fashion, thus not taking into consideration time-varying confounding. Last, the date of the patient severity status was inconsistently documented and often documented with a delay, and thus using a survival analysis approach taking right-censoring into account was not possible. However, the U.S. Centers for Disease Control and Prevention [22] reported the median time it takes from symptom onset until the development of acute respiratory distress syndrome when infected with COVID-19 is 8–12 days (based on multiple studies from Wuhan, China). Hence, we believe that this study's minimum follow-up time of one month is long enough to capture most individuals who ended up developing severe illness.

Our analysis had many strengths. First, the application of a doubly robust outcome regression, which included inverse probability weighting, allowed us to estimate the causal effect and reduce the bias of unweighted estimators. Second, the study population was limited to individuals with a history of hypertension who received an anti-hypertensive medication. If hypertension is associated with the pathophysiologic course of COVID-19 as has been suggested by prior studies [23], then having comparison groups who both have medically-treated hypertension could potentially diminish unmeasured confounding associated with hypertension in itself. Third, the results looking at severe disease as an outcome were reproduced in sub-group analyses in which ACEIs and ARBs were studied separately. Fourth, several previous studies assessing the association between RAAS inhibitors and severe COVID-19 illness were limited to hospitalized patients [9,10,14] or individuals who sought medical care during their illness [15]. These patients could have introduced biases if individuals with certain medical backgrounds or who presented with more co-morbidity were more likely to seek health care. CHS's comprehensive database allowed us to include all eligible CHS members who tested positive in both the inpatient and outpatient setting. Last, the Model 1 analysis was strengthened by our test-negative design, where individuals who tested positive were compared with individuals who tested negative. Since only a small proportion of individuals in a population undergo testing, and the indications for testing vary over time [21], this design diminishes the risk for confounding by health-seeking behavior and misclassification bias.

CONCLUSIONS

We found no association between chronic treatment with RAAS inhibitors and the likelihood of a positive test for SARS-CoV-2. We identified an association between chronic treatment with RAAS inhibitors and a lower likelihood for the development of severe disease among hypertensive patients who tested positive

for SARS-CoV-2. Multiple clinical studies have been designed to study treatments with different RAAS inhibitors (ACEIs and ARBs) among COVID-19 patients. These clinical trials, and additional observational studies, will shed more light on the studied association.

ACKNOWLEDGEMENTS

The authors thank Sydney Krispin MPH, Clalit Research Institute, for her editorial support

AVAILABILITY OF DATA AND MATERIALS

Access to the data used for this study can be made available on request, subject to an internal review by the corresponding author to ensure that participant privacy is protected, and subject to completion of a data sharing agreement, approval from the institutional review board of Clalit Health Services, and institutional guidelines and in accordance with the current data sharing guidelines of Clalit Health Services and Israeli law. Pending the aforementioned approvals, data sharing will be made in a secure setting, on a per-case-specific manner, as defined by the chief information security officer of Clalit Health Services. Please submit such requests to the corresponding author.

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When I approach a child, he inspires in me two sentiments;
tenderness for what he is, and respect for what he may become.
Louis Pasteur (1822–1895), French biologist, microbiologist, and chemist
renowned for his discoveries of the principles of vaccination, microbial fermentation and pasteurization