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Hypertension, medications, and risk of severe COVID-19: A Massachusetts community-based observational study

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Abstract

It remains uncertain whether the hypertension (HT) medications angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) mitigate or exacerbate SARS-CoV-2 infection. We evaluated the association of ACEi and ARB with severe coronavirus disease 19 (COVID-19) as defined by hospitalization or mortality among individuals diagnosed with COVID-19. We investigated whether these associations were modified by age, the simultaneous use of the diuretic thiazide, and the health conditions associated with medication use. In an observational study utilizing data from a Massachusetts group medical practice, we identified 1449 patients with a COVID-19 diagnosis. In our study, pre-infection comorbidities including HT, cardiovascular disease, and diabetes were associated with increased risk of severe COVID-19. Risk was further elevated in patients under age 65 with these comorbidities or cancer. Twenty percent of those with severe COVID-19 compared to 9% with less severe COVID-19 used ACEi, 8% and 4%, respectively, used ARB. In propensity score-matched analyses, use of neither ACEi (OR = 1.30, 95% CI 0.93 to 1.81) nor ARB (OR = 0.94, 95% CI 0.57 to 1.55) was associated with increased risk of severe COVID-19. Thiazide use did not modify this relationship. Beta blockers, calcium channel blockers, and anticoagulant medications were not associated with COVID-19 severity. In conclusion, cardiovascular-related comorbidities were associated with severe COVID-19 outcomes, especially among patients under age 65. We found no substantial increased risk of severe COVID-19 among patients taking antihypertensive medications. Our findings support recommendations against discontinuing use of renin–angiotensin system (RAS) inhibitors to prevent severe COVID-19.

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the novel coronavirus (SARS-CoV-2) is a major global health threat. Mortality and severe outcomes from SARS-CoV-2 have been associated with cardiovascular disease, diabetes, and hypertension (HT).[1,2] These disorders share underlying pathophysiology related to the renin–angiotensin system (RAS). Activity of the angiotensin-converting enzyme 2 (ACE2) is dysregulated in cardiovascular disease and also serves as the receptor for SARS-CoV-2 to gain entry and replicate in target cells.[3] The commonly used treatments for cardiovascular disorders, including HT, of angiotensin-converting enzyme inhibitors (ACEi), and angiotensin receptor

blockers (ARB), have been reported to increase ACE2 abundance in animal models.[4,5] While ACEi and ARB act on different targets of the renin–angiotensin–aldosterone system,[6] it has been postulated that these RAS inhibiting medications may enhance SARS-CoV-2 viral entry and ability to infect cells thus increasing SARS-CoV-2 severity.[7,8] Conversely, mechanistic evidence from related coronaviruses suggests that SARS-CoV-2 infection may downregulate ACE2, leading to toxic over accumulation of angiotensin II inducing inflammation, acute respiratory distress syndrome, and fulminant myocarditis. RAS inhibition by ACEi or ARB could in this case be protective, potentially mitigating these effects.[9,10]

With conflicting mechanistic evidence concerning risk of SARS-CoV-2 from some of the most widely used drugs for cardiovascular disease, HT and diabetes, an urgent request for epidemiologic evidence was issued to attempt to determine the role of RAS inhibitors in relation to SARS-CoV-2 severity.[1] To date, several studies of hospitalized (HT) COVID-19 patients suggest no association with severe infections or mortality.[11–15]

In this community-based case–control study of central Massachusetts COVID-19 patients, we investigated whether RAS inhibitors exposure increased the risk of severe sequelae defined as hospitalization or death. Additionally, we investigated the novel hypothesis that the diuretic thiazide, often prescribed for HT in conjunction with RAS inhibitors, may modify the risk of severe SARS-CoV-2. This hypothesis evolved from the observation that thiazide has been suggested to decrease ACE2 expression in animals[16] and some country level usage data appeared to correlate with COVID-19 death rates.[17–19]

During our study period, evidence emerged suggesting the virus attacks blood vessels with reports of high prevalence of thrombotic events in COVID-19 patients[20] so we additionally investigated whether pre-infection anticoagulant medication modified the risk of severe COVID-19.

Finally, because advanced age itself is a major risk factor, we investigated the risks deriving from comorbidities in those 65 or younger.

2 | METHODS

2.1 | Study population

We used de-identified administrative claims and electronic health record (EHR) data from a large comprehensive health care system serving central Massachusetts. We identified 1449 hospitalized and non-hospitalized patients, 18–100 years old, with clinically or RT-PCR laboratory test confirmed COVID-19 from March 1, to May 15, 2020.

2.2 | Study design and data

For each identified patient with a COVID-19 diagnosis, we extracted medical history data from the EHR for the previous 12 months including encounter diagnosis codes, medication order data, laboratory tests and results, problem lists, and demographics (eg, gender, age, smoking status, body mass index (BMI)). COVID-19 diagnosis was based either on PCR test or on symptoms, following CDC guidelines.[21] We conducted a subset of manual chart reviews to develop our extraction algorithm, to conduct data cleaning, and to validate proper categorization. We used encounter and diagnostic codes to characterize patients as having a history of hypertension, diabetes, chronic respiratory disease, congestive heart failure, immunosuppressed conditions (HIV or history of solid organ transplant), chronic kidney disease, chronic liver disease, and cancer. We defined previous treatment with an antihypertensive medication as use of the medication within the previous 12 months, provided that there was no evidence that the medication was discontinued in the month of the COVID-19 diagnosis. We report here on five classes of HT medications: ACEi, ARB, beta blockers, calcium channel blockers, and thiazide diuretics. Because the ACEi and ARB act on the same system and are the HT medications of primary interest, we analyzed these together, as well as separately.

Demographic characteristics including age, gender, race, ethnicity, smoking status, and body mass index (BMI) were extracted from the EHR. Patients were divided into two groups based on COVID-19 severity and compared using a case–control approach. “Cases” were all individuals with severe COVID-19, defined by hospitalization or death, while “controls” included all non-hospitalized COVID-19-positive individuals. Data on severity were obtained from the medical record at the moment of enrollment into the study. This study was approved by the Institutional Review Board of the University of Massachusetts Lowell.

2.3 | Statistical analysis

Differences in demographics and pre-existing conditions between severe and not severe COVID-19 patients were compared using the chi-square or Wilcoxon tests, as appropriate. Logistic regression models were then fit to evaluate COVID-19 severity and use of hypertension medications, conditional on potential confounders: age, gender, smoking, BMI, race, ethnicity, history of diabetes, chronic respiratory disease, kidney disease, arterial disease, congestive heart failure, and systolic and diastolic blood pressure (BP).

Because of the very strong effect of older age on COVID-19 severity, we restricted the data to ages ≤65 and used logistic regression to estimate the associations between COVID-19 severity and the same set of pre-existing comorbidities.

After initial multiple logistic regression models to evaluate the contributions of ACEi, ARB and other medications revealed a number of strong risk factors, and descriptive analyses showed complex correlations among these variables, we turned to propensity score matching to provide tighter control over multiple confounders and potential selection bias.[22] The first step in using propensity scores was to construct a logistic regression model to predict the

TABLE 1 Demographics, baseline characteristics

All COVID-19 patients	Total COVID-19 patients (*N* = 1449)	Severe[a] COVID-19 275 (19%)	Not severe[b] COVID-19 1174 (81%)	Test of difference[c]
Males	529 (37%)	114 (41%)	415 (35%)	.06
Age (mean, SD)	54.7 (22.5)	72.0 (19)	50.6 (21)	<.001
BMI (mean, SD)	30.0 (7.1)	29.9 (7.8)	30.1 (6.9)	.35
Race				
White	762 (53%)	169 (61%)	593 (51%)	.01
Black	156 (11%)	21(8%)	135 (12%)	
Unknown	455 (31%)	75 (27%)	380 (32%)	
Other	76 (5%)	10 (4%)	66 (6%)	
Ethnicity				
Hispanic	133 (9%)	9 (3%)	124(11%)	<.001
Not Hispanic	682 (47%)	146(53%)	536(46%)	
Unknown	634 (44%)	120(44%)	514(44%)	
Ever smoker Y/N	331 (23%)	88(32%)	243(21%)	<.001
Systolic pressure (mean, SD)	124 (16)	128 (20)	123 (15)	<.001
Diastolic pressure (mean, SD)	75 (10)	73 (10)	76 (9)	<.001
Resident of long term care Y/N	290 (20%)	107(39%)	183(15%)	<.001

Abbreviation: SD, standard deviation.

[a]Severe: COVID-19-positive patients admitted to the hospital/died at the time of the data cut.

[b]Not Severe: COVID-19-positive patients not admitted to hospital/deceased at the time of the data cut.

[c]*p*-value testing H0: no difference between severe and not severe COVID-19 patients. Chi-square test and Wilcoxon as appropriate.

probability of an individual being exposed to each of the medications of interest, within the population.

The candidates for predictors were 11 factors found in initial univariate logistic regression models to be associated with medication use, as well as their two-way interactions: age, gender, BMI, race, ethnicity, systolic BP, diabetes, chronic respiratory disease, chronic kidney failure, arterial disease, and congestive heart failure. The saturated models failed to converge so terms were dropped one at a time beginning with two-way interaction terms among variables until convergence was achieved. BMI was imputed for those patients for whom it was missing (16%), using the overall population median BMI of 28.9 (IQR = 8.6). We defined the propensity score by using the predicted values from the logistic regression, which represent the probability that someone is exposed to the medication of interest. We performed 1:3 matching between medication recipients and non-recipients based on nearest neighbor propensity scores.[22]

Each exposed subject was matched (using Greedy Matching) to up to three unexposed subjects without replacement having the closest available propensity scores. Matched sets never differed by more than 0.25 of the standard deviation of the propensity scores as recommended by Rosenbaum and Rubin.[23] Rarely, three unexposed subjects did not meet this criterion in which case only two or one was selected. Conditional logistic regression was then used to calculate the hazard ratio (equivalent to the conditional OR in these case–control data) for risk of severe COVID-19 from the dichotomous exposure variable within propensity score-matched sets. We repeated this procedure with all of the different HT medications. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc).

3 | RESULTS

As of May 2020, we identified 1449 patients, 85% of whom were lab positive for COVID-19 and 15% were clinically diagnosed in the central Massachusetts group medical practice (Table 1). Two hundred and seventy-five (19%) were categorized as severe; 186 (13%)

were hospitalized and did not die, while 89 (6%) died. The ratio of female to male participants was nearly 2:1 (63% versus 37%). More severe cases were older (72 years) than the less severe (51 years). Consistent with Massachusetts data, more women were diagnosed with COVID-19 than males.[24] Mean systolic and diastolic blood pressures were within normal range for both severe and non-severe patients.

Diabetes, chronic respiratory disease, arterial disease, congestive heart failure, chronic kidney disease, and cancer were associated with more severe COVID-19. (Table 2) In COVID-19 patients under 65 years of age, HT, diabetes, congestive heart failure, and cancer were even more strongly associated with increased risk of severe COVID-19 than in the population of all ages (Table 2). Chronic respiratory disease was not associated with increased risk in the younger patients. We statistically confirmed each comorbidity using interaction terms. Terms that were significant in those under 65 also had significant interaction terms: OR's for interaction terms <65 with hypertension (OR = 2.4, 95% CI 1.3–4.5), diabetes (OR = 3.6, 95% CI 1.9–7.0), CHF (OR = 4.7, 95% CI 1.2–18.6) and cancer (OR = 3.4, 95% CI 1.3–8.9).

In the propensity score models, we calculated the absolute standard mean differences of the continuous demographic variables including age and BMI. These differences were small, none larger than 0.140. Additionally, we compared the demographic characteristics for ARB or ACEi users before and after propensity score matching (Table S1). Together, this suggests propensity score matching resulted in groups that were demographically similar.

Among COVID-19 patients, 20% of those with severe COVID-19 and 9% with less severe COVID-19 used ACEi and 8% and 4%, respectively, used ARB (data not shown). We evaluated whether these angiotensin-converting enzyme inhibitors were associated with COVID-19 severity (Table 3). In propensity score-matched analyses, use of neither ACEi (OR = 1.30, 95% CI 0.93 to 1.81) nor ARB (OR = 0.94, 95% CI 0.57 to 1.55) was associated with increased risk of severe COVID-19. The additional use of thiazide did not modify the relationship between ACEi and ARB or ACEi alone. We could not evaluate ARB alone because of limited sample size. Independent analyses of thiazide, beta blockers, calcium blockers, and anticoagulant medications showed no associations with disease severity.

Two hundred and eighteen patients (15%) were clinically diagnosed and had no PCR test. We conducted sensitivity analyses excluding these patients, and the results for each propensity score model in Table 3 were substantively the same (data not shown). For example, for one of our primary hypotheses, the effect of ACE medications, the odds ratio changed from 1.24 to 1.28 and remained statistically insignificant (p = .2).

TABLE 2 Analyses of comorbidities and COVID-19 severity

	All participants			Under 65 years	
		OR (95% CI)	Adj OR (95% CI)		Adj OR (95% CI)
		Severe COVID-19	Severe COVID-19		Severe COVID-19
Comorbidities	(*N*, %)	Total (*N* = 1449)	Total (*N* = 1449)	(*N*, %)	Total (*N* = 1003)
Hypertension	(525, 36%)	3.66 (2.79, 4.81)	1.33 (0.95, 1.84)	(202, 20%)	1.72 (1.03, 2.87)
Diabetes mellitus	(250, 17%)	2.67 (1.97, 3.62)	1.47 (1.06, 2.04)	(108, 11%)	2.48 (1.43, 4.31)
Chronic respiratory disease	(317, 22%)	1.59 (1.18, 2.13)	1.42 (1.03, 1.97)	(196, 20%)	1.03 (0.60, 1.77)
Arterial disease	(114, 8%)	5.12 (3.45, 7.60)	1.70 (1.10, 2.63)	(16, 2%)	2.34 (0.71, 7.69)
Congestive heart failure	(104, 7%)	5.03 (3.34, 7.58)	1.72 (1.09, 2.70)	(10, 1%)	5.86 (1.55, 22.2)
Immunosuppressed	(37, 3%)	1.84 (0.90, 3.77)	0.97 (0.44, 2.04)	(14, 1%)	1.82 (0.48, 6.92)
Chronic kidney disease	(208, 14%)	5.22 (3.81, 7.15)	1.80 (1.24, 2.61)	(22, 2%)	2.56 (0.90, 7.29)
Cancer	(108, 7%)	3.76 (2.50, 5.64)	1.72 (1.11, 2.67)	(30, 3%)	3.05 (1.30, 7.17)
Chronic liver disease	(19, 1%)	1.99 (0.75, 5.29)	2.14 (0.76, 6.07)	(14, 1%)	0.54 (0.07, 4.30)

Abbreviations: Adj OR, adjusted odds ratio controlled for age and gender; OR, odds ratio.

TABLE 3 Propensity score-matched analyses[a]: hypertension medications and COVID-19 severity

Hypertension medication	Severe COVID-19 Odds ratio (95% CI)
ACEi or ARB	1.03 (0.76, 1.41)
ACEi	1.22 (0.86, 1.72)
ARB	1.00 (0.61, 1.65)
Thiazide diuretics without ACEi or ARB	1.00 (0.47, 2.14)
Any thiazide diuretic	1.16 (0.75, 1.78)
ACEi without thiazide	0.94 (0.62, 1.42)[b]
Calcium channel blockers	1.02 (0.70, 1.48)
Beta blockers	1.32 (0.94, 1.84)[b]
Anticoagulation medication	1.44 (0.96, 2.16)[b]

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers.

[a]Each medication exposure was matched (using Greedy Matching) to up to three unexposed subjects having the closest available propensity scores, without replacement.

[b]Propensity score model was simplified by omitting gender to allow convergence.

4 | DISCUSSION

In this analysis of data on COVID-19 patients from a large group medical practice, we investigated the relationship between pre-infection treatment with hypertension medications and severe COVID-19, among all individuals diagnosed with COVID-19 in a community-based population in central Massachusetts. Our primary focus was on RAS inhibitors as they may induce elevated expression of ACE2, the cellular receptor of SAR-CoV-2, raising concern that these medications might increase the risk of severe sequelae of COVID-19.

Our findings are consistent with other recent studies which have found no deleterious effect of these or any of five hypertension medication classes with regard to COVID-19 severity.[12–14,25,26] Further, we investigated the potential for effect modification by additional use of the diuretic thiazide on the RAS inhibitors and found no such relationship. Collectively, these findings do not support a change to the current use of these medications in relation to COVID-19. While this is consistent with the guidance of the professional societies' recommendations,[27] our results are based only on reported use of hypertension medications prior to COVID-19 diagnosis. We did not have data to investigate the effect on severity of continued or discontinued use of these medications after COVID-19 diagnosis.

New research detailing the biologic mechanism by which the SARS-CoV-2 virus enters human cells may explain the findings.[28] It has been suggested that cell entry of coronaviruses depends not only on binding of the viral spike (S) proteins to cellular ACE2 receptors but also the serine protease TMPRSS2 for S protein priming.[29] Even if ACEi/ARB do upregulate ACE2 receptors, which they may[30] or may not,[31] the absence of upregulation of TMPRSS2 may inhibit enhanced viral entry into cells.[28]

Our study is limited by the fact that it was observational and thus may have been subject to bias and confounding. We conducted a propensity score-matched analysis to reduce as far as possible biases when estimating treatment effects.[32] We categorized patients' use of medications based on an EHR prescription order within the prior year.

Our findings, we believe, are the first to suggest pre-infection, HT, congestive heart failure, cancer, and diabetes mellitus are more likely to increase risk of severe outcomes in COVID-19 patients who are under 65 years old. The younger population has not been well studied because the elderly have so dominated the COVID-19-related hospitalizations and deaths. This potentially enables identification of higher risk younger patients so they can be monitored more closely and possibly given prophylaxis should that become available in the future.[33,34] Strengths of this study include that the large majority (85%) of patients were confirmed by RT-PCR, and we were able to conduct chart reviews to check the accuracy of case definitions and the categorization of prescription data.

We were able to assess five different classes of hypertension medications including independent analyses of ARB and ACEi, as well as thiazide, calcium channel blockers, and beta blockers. ACEi, ARB, and beta blockers act on different points in the RAS system so their effects could have potentially differed. Calcium channel blockers do not increase expression of ACE2, and thiazide may decrease expression[16] so they were also good comparators.[35] Our findings that these drugs do not increase or decrease severity risk are consistent with other newly published studies which also address the research gaps of evaluation of non-hospitalized COVID-19 patients.[12,13,26,36]

Our findings do not support the discontinuation of ACEi or ARB in the management of hypertension, as a preventive measure to reduce risk of severe COVID-19 disease. Other studies should also investigate whether or not hypertension medications were continued during hospitalization. Findings should be confirmed using other populations and study designs including randomized controlled trials. More investigation of pre-infection risk factors such vitamin D3 level,[37] anticoagulant medication use,[38] diabetes control,[39] blood type,[40] MMR, and flu vaccine status,[41] in both the general and younger populations, is warranted.

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CONFLICT OF INTEREST

AB, RG, SRS, RR, LG, DS, AM, P.A, and DK have no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.B., R.G., S.R.S., D.K., R.R., and L.G. contributed to the design of the research. A.B., R.G., S.R.S., D.K., A.M., D.S., and P.A. were involved in data collection and implementation of the research. A.B., R.G., S.R.S., D.K., R.R., and L.G. contributed to the analysis and writing of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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