COVID-19 outcomes among hospitalized men with or without exposure to alpha-1-adrenergic receptor blocking agents

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Abstract (294 words)

Importance: Alpha-1-adrenergic receptor antagonists (α_1-blockers) can abrogate pro-inflammatory cytokines and may improve outcomes among patients with respiratory infections. Repurposing readily available drugs such as α_1-blockers could augment the medical response to the COVID-19 pandemic.

Objective: To evaluate the association between α_1-blocker exposure and COVID-19 mortality

Design: Real-world evidence study

Setting: Patient level data with 32,355 records tested for SARS-CoV-2 at the Mount Sinai Health System including 8,442 laboratory-confirmed cases extracted from five member hospitals in the New York City metropolitan area.

Participants: 2,627 men aged 45 or older admitted with COVID-19 between February 24 and May 31, 2020

Exposures: α_1-blocker use as an outpatient or while admitted for COVID-19

Main Outcomes and Measures: In-hospital mortality

Results: Men exposed to α_1-blockers (N=436) were older (median age 73 vs. 64 years, P<0.001) and more likely to have comorbidities than unexposed men (N=2,191). Overall, 758 (28.9%) patients died in hospital, 1,589 (60.5%) were discharged, and 280 (10.7%) were still hospitalized as of May 31, 2020. Outpatient exposure to α_1-blockers was not associated with COVID-19 hospital outcomes, though there was a trend towards significance (OR 0.749, 95% CI 0.527-1.064; P=0.106). Conversely, inpatient use of α_1-blockers was independently associated with improved in-hospital mortality in both multivariable logistic (OR 0.633, 95% CI 0.434-0.921; P=0.017) and Cox regression analyses (HR 0.721, 95% CI 0.572-0.908; P=0.006) adjusting for patient demographics, comorbidities, and baseline vitals and labs. Age-stratified analyses suggested greater benefit from inpatient α_1-blocker use among younger age groups: Age 45-65 OR 0.384, 95% CI 0.164-0.896 (P=0.027); Age 55-75 OR 0.511, 95% CI 0.297-0.880 (P=0.015); Age 65-89 OR 0.810, 95% CI 0.509-1.289 (P=0.374).

Conclusions and Relevance: Inpatient α_1-blocker use was independently associated with improved COVID-19 mortality among hospitalized men. Clinical trials to assess the therapeutic value of α_1-blockers in COVID-19 are warranted.

Introduction

Severe coronavirus disease 2019 (COVID-19) has been linked to dysregulated immune responses, including an overexuberant inflammatory response marked by high levels of proinflammatory cytokines such as interleukin-6 (IL-6).[1,2] Immunosuppressive drugs such as glucocorticoids have become a standard component of treatment for severe COVID-19,[3] and several trials of anti-cytokine or anti-inflammatory agents are underway or have reported promising results.[4–10] Despite these advances, there remains a pressing need for safe, effective, and widely available therapeutic options.

Adrenergic signaling has been linked to hyperinflammation in models of bacterial sepsis and cytokine release syndrome. In pre-clinical experiments, a positive feedback loop of adrenergic signaling was identified wherein macrophages responded to catecholamines by producing more catecholamines and inflammatory cytokines; this adrenergic loop could be interrupted by blockade of α_1-adrenergic receptors with prazosin.[11] In a retrospective clinical study of patients with acute respiratory distress and pneumonia, exposure to α_1-adrenergic receptor antagonists (α_1-blockers) was associated with a significant reduction in risk of mechanical ventilation or death.[12] Similarly, a recent retrospective analysis of 25,130 patients with COVID-19 across the United States Veterans Health Administration hospital system showed that outpatient exposure to any α_1-blocker was associated with decreased in-hospital mortality compared to matched controls not on any α_1-blocker at the time of hospital admission.[13]

These observations have led to the hypothesis that α_1-blockers in routine clinical use (e.g. prazosin, doxazosin, tamsulosin, etc.) may be repurposed for COVID-19 treatment.[14] We therefore conducted this real-world evidence study based on electronic medical record (EMR) data to determine whether exposure to α_1-blockers is independently associated with mortality among patients hospitalized with COVID-19.

Methods

Data sources

This retrospective study utilized de-identified electronic medical record (EMR; Epic systems, Verona, WI) data from 5 member hospitals within the Mount Sinai Health System (MSHS) in the New York City metropolitan area. De-identified EMR data were obtained via the Mount Sinai Data Warehouse (https://labs.icahn.mssm.edu/msdw/). We identified 8,442 MSHS patients with PCR confirmed diagnosis of COVID-19 from February 24 through May 31, 2020 during the peak of pandemic in NYC. COVID-19 was diagnosed by real-time reverse transcriptase polymerase chain reaction (RT-PCR)-based clinical tests from nasopharyngeal swab specimens.

We retrieved patient demographics, social history, medication history, and disease comorbidities from the EMR including age, gender, race/ethnicity, smoking status, asthma, chronic obstructive pulmonary disease (COPD), hypertension, obstructive sleep apnea, obesity, diabetes, chronic kidney disease, human immunodeficient virus (HIV) infection, cancer, coronary artery disease, atrial fibrillation, heart failure, chronic viral hepatitis, alcoholic nonalcoholic liver disease, and acute kidney injury (AKI). Patients aged $\geq$ 89 years were assigned an age of 89 to prevent re-identification. Medications by prescription or hospital administration captured in EMR from January 1, 2019 till May 31, 2020 were included in the medication history. We identified disease comorbidities through their corresponding ICD-10-CM codes before hospital admission and during hospitalization.

We also extracted data from each hospital encounter, including vital sign and laboratory data at the time of presentation, and medications administered during hospitalization. Vital sign and laboratory data extracted included: white blood cell count (WBC), serum creatinine, anion gap, potassium, alanine aminotransferase (ALT), body mass index (BMI), temperature, oxygen saturation, heart rate, respiratory rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

We defined three possible outcomes for each hospitalization: in-hospital death (deceased), discharged to home or other locations not associated with acute medical care (recovered), and continued hospitalization (right censored). The duration of hospitalization was calculated from the beginning of the hospital encounter till death or discharge.

This study was approved by the Mount Sinai institutional review board (IRB): IRB-17-01245.

Study design

This was a retrospective EMR-based study designed to test the independent association of α_1-blocker exposure with in-hospital death among COVID-19 patients. We first identified 6,218 inpatients positive for COVID-19 in one of 5 hospital systems within the MSHS as of May 31, 2020 (Figure 1). The majority (93%) of α_1-blocker users in this cohort were men aged 45 or older. We therefore limited the analysis cohort to men aged 45 or older (N=2,627).

We defined α_1-blocker exposure as an active prescription from January 1, 2020 for an α_1-blocker (tamsulosin, alfuzosin, silodosin, terazosin, doxazosin, and prazosin) up to and including hospitalization for COVID-19 (N=436). We further defined a subset of patients (N=343) with documented α_1-blocker administration during their hospitalization, which we defined as "α_1-blocker inpatient use".

Potential confounders in the analysis included demographic characteristics, comorbidities, baseline labs and vitals, and exposure to medications used to treat hypertension, hyperlipidemia, and inflammation. Detailed medication names included in these categories are shown in supplement Table S1.

Statistical analysis

Patient characteristics were summarized as median and interquartile range (IQR) for continuous variables or mean and standard deviation (SD). We displayed categorical variables as number and percentage (%). We performed a statistical test of hypothesis for differences using the Kruskal-Wallis test or two sample t-test for continuous variables, and the χ^2 test for categorical variables.

We employed multivariate logistic regression models with potential confounders to estimate the odds ratio and corresponding 95% confidence interval for COVID-19 in-hospital mortality (deceased=1) versus recovery (recovered=0) associated with α_1-blocker use. We considered the following potential confounders: age, hospital stay duration, race, smoking status, BMI, temperature, O2 saturation, heart rate, respiratory rate, hypertension, asthma, COPD, obstructive sleep apnea, obesity, diabetes mellitus, chronic kidney disease, HIV, cancer, coronary artery disease, atrial fibrillation, heart failure, chronic viral hepatitis, liver disease, AKI, ICU stay, WBC, creatinine, anion gap, potassium, and ALT. We applied the Wald-based power and sample size formulas for logistic regression to calculate the power given the observed sample size.[15] We used two-tailed test to estimate the probability of event under the null hypothesis which was the in-hospital mortality rate and we used the binomial distribution for α_1-blocker with the prescription rate as the probability.

To account for right-censored patients (N=280), we used multivariate Cox proportional hazard models to evaluate the association between α_1-blockers and survival (in-hospital mortality). We estimated the hazard ratio of α_1-blockers on COVID-19 patient in-hospital survival, adjusting for the same confounders mentioned above.

We utilized propensity score weighting to adjust the potential confounders between those exposed or unexposed to α_1-blockers. We utilized the R package 'twang' and calculated the propensity scores based on average treatment effect on the treated (ATT) and Kolmogorov-Smirnov evaluation criterion. We then employed the 'survey' R package by fitting logistic regression models with propensity scores as the weights to assess the α_1-blocker treatment effect on COVID-19 patients.

Statistical significance was defined as a two-sided P-value < 0.05, unless otherwise noted.

Sensitivity analysis

To evaluate the robustness of the associations between α_1-blockers and COVID-19 in-hospital mortality, we performed sensitivity analysis to assess the impact from potential unmeasured or uncontrolled confounding. We calculated E-values for odds and hazard ratios as point estimates, in addition to E-values for their upper confidence limits.[16] The point estimates represent the strength of unmeasured or uncontrolled confounding required to explain away the observed associations. The upper limits signify the strength of unmeasured or uncontrolled confounding needed to move the confidence interval to include the null, i.e. OR=1 or HR=1. If the effect of unmeasured or uncontrolled confounding is weaker than the calculated E-value, the association of α_1-blockers with COVID-19 in-hospital mortality could not be fully biased by a weaker confounder.

Results

Patient characteristics and outcomes

We identified 6,218 inpatients positive for COVID-19 admitted to one of 5 hospitals within the MSHS as of May 31, 2020. Among these 6,218 patients, 464 patients (7.5%) had been prescribed α_1-blockers between January 1, 2020 up to and including their hospitalization, with at least 2 months prior to admission; most of these patients were men aged 45 or older (N=436, 93%). Therefore, we limited the analysis cohort to men aged 45 years or older (N=2,627). This cohort was divided into an α_1-blocker-exposed group (N=436) and an unexposed group (N=2,191). All patients in the α_1-blocker group had been prescribed α_1-blockers at some point from January 1, 2020 up to and including their COVID-19 hospitalization ("α_1-blocker exposure"); a subset of these patients (N=343) had documented α_1-blocker administration during their hospitalization ("inpatient α_1-blocker use").

The α_1-blocker exposed group was older (median age 73 vs. 64 years, P<0.001) and more likely to have comorbidities than the unexposed group. Chronic diseases such as COPD, hypertension, diabetes mellitus, chronic kidney disease, cancer, and cardiovascular disease were significantly enriched in the α_1-blocker group. Additional patient demographics for the two groups are shown in Table 1 and Figure S1.

Overall, 758 (28.9%) patients died, 1,589 (60.5%) were discharged, and 280 (10.7%) were still hospitalized as of May 31, 2020. Unadjusted in-hospital mortality was 32.3% in the exposed group and 28.2% in the unexposed group.

α_1-blocker exposure and COVID-19 in-hospital mortality

We evaluated the association of α_1-blockers on COVID-19 patients with known outcomes (death: N=758; discharge: N=1,589) using multivariate logistic-regression models. In the overall population, α_1-blocker exposure was not significantly associated with in-hospital mortality (OR 0.749; 95% CI, 0.527-1.064;

P=0.106) with the power β = 0.62 based on the sample size of 2347. There was a trend towards a protective association for α_1-blocker exposure in the subset of patients who were hospitalized for at least 24 hours, though this was not significant (N=2,276; OR 0.722; 95% CI, 0.505-1.034; P=0.075) (Table 2). This might be due to limited sample size (β = 0.71 in the Wald-based power analysis).

To account for right-censored patients (N=280), we used Cox proportional hazard models to evaluate the association of α_1-blocker exposure and COVID-19 in-hospital survival. There was a trend towards a protective effect of α_1-blocker exposure in the overall cohort (HR 0.808; 95% CI, 0.652-1.002; P=0.052) and among those hospitalized for at least 24 hours (HR 0.823; 95% CI, 0.660-1.027; P=0.085), though these associations were not significant (Table 3).

Inpatient α_1-blocker use and COVID-19 in-hospital mortality

We further assessed the impact of α_1-blockers on mortality for patients with documented administration of α_1-blockers while admitted to the hospital (N=343) compared to unexposed patients. We observed that inpatient α_1-blocker use significantly reduced the risk of in-hospital mortality overall (OR 0.633; 95% CI 0.434-0.921; P=0.017) and among those hospitalized for at least 24 hours (OR 0.607; 95% CI, 0.415-0.890; P=0.01) (Table 2).

The survival analysis also showed improved in-hospital survival for those with inpatient α_1-blocker use overall (HR 0.721; 95% CI, 0.572-0.908; P=0.006), and among patients hospitalized for at least 24 hours (HR 0.751; 95% CI, 0.593-0.950; P=0.017) (Table 3).

Sensitivity analysis

We assessed the impact of potential unmeasured or uncontrolled confounding on the observed associations between inpatient α_1-blockers use and COVID-19 in-hospital mortality using the E-value metric (Table S2).[16] Based on this analysis, an unmeasured confounder would have to have an odds ratio of at least 1.25 (in the logistic regression analysis) or a hazard ratio of at least 1.34 (in the survival analysis) to cause the 95% confidence interval for the treatment effect of inpatient α_1-blockers use to include the null.

Age-stratified associations of α_1-blockers and COVID-19 in-hospital mortality

We assessed the interaction between age and inpatient α_1-blocker use for overall cohort and patients with hospital stay > 1 day, respectively, and we did not find any significance between the interaction and in-hospital mortality. Therefore, to identify differences in the treatment effect of α_1-blockers on different age groups, we segmented the population into three age groups (45-65; 55-75; 65-89) and analyzed each

group separately using logistic regression, adjusting for the same covariates as the unstratified analysis. The age groups were overlapped by 10 years to preserve sample size. Inpatient α_1-blocker use was associated with a significantly lower risk of in-hospital mortality in the 45-65 (OR 0.384; 95% CI 0.164-0.896; P=0.027) and 55-75 age groups (OR 0.511; 95% CI 0.297-0.880; P=0.015), but not the 65-89 age group (OR 0.810; 95% CI 0.509-1.289; P=0.374) (Table 4).

Propensity score analysis

We further assessed the effect of α_1-blockers on in-hospital mortality using propensity-weighted logistic regression. These yielded similar results as the multivariable regression and age-stratified analyses. Inpatient α_1-blocker use was associated with reduced in-hospital mortality (OR 0.630; 95% CI 0.424-0.935; P=0.022) whereas α_1-blocker exposure was not (OR 0.740; 95% CI 0.512-1.070; P=0.110) (Table S3). In age-stratified analyses, patients in younger age groups had greater benefit from α_1-blocker exposure and inpatient α_1-blocker use than patients in the oldest age group (Table 4).

Discussion

Using a racially and ethnically diverse cohort from New York City comprising 2,627 men aged 45 or older hospitalized COVID-19 patients seen between February 24 and March 31, 2020, we found that inpatient use of α_1-blockers was significantly associated with reduced in-hospital mortality, whereas outpatient exposures were not associated with benefit, although there was a trend towards significance. In age stratification analysis, we found that α_1-blocker use was more beneficial to younger age groups.

Drug repurposing is the process of finding new indications for drugs already in clinical use. The appeal of rapidly validating and deploying an existing drug against a deadly global pandemic is clear, especially if the drug is widely available and affordable. Dexamethasone, now a standard in COVID-19 treatment, is an example of a commonly used drug repurposed for a new indication.[3] However, the saga of hydroxychloroquine, which was touted as a cure early in the pandemic but has since proven ineffective, is a cautionary tale.[17] The allure of rapid drug repurposing must be balanced against rigorous scientific method.

α_1-blockers, commonly used to treat benign prostatic hyperplasia and hypertension, have become a target for drug repurposing due to pre-clinical data linking α_1-adrenergic signaling to pro-inflammatory cytokines which may contribute to dysregulated immunity and adverse outcomes in COVID-19.[1,2,11] These pre-clinical findings have been bolstered by recent retrospective clinical analyses linking α_1-blockers with improved outcomes in hospitalized patients with both COVID-19 and non-COVID-19 respiratory infections.[12,13] In a large COVID-19 cohort drawn from the US Veterans Health

Administration hospital system, outpatient α_1-blocker exposure was associated with a relative risk reduction of 18% for in-hospital mortality compared to matched controls.[13] Interestingly, the non-selective α_1-blocker doxazosin, which inhibits all three α_1-adrenergic receptor subtypes (α_{1A}, α_{1B}, α_{1D}), was associated with a greater relative risk reduction (74%) than the uroselective (α_{1A}, α_{1D}) α_1-blocker tamsulosin (18%).

In the present study, we found that in-hospital use of α_1-blockers was consistently and independently associated with reduced in-hospital mortality using both multivariable regression and propensity score-based methods. In age-stratified analyses, we observed that this protective effect was more pronounced in relatively younger age groups. In contrast to the studies by Koenecke et al. and Rose et al., which defined α_1-blocker exposure based on outpatient prescriptions only, we were able to use inpatient medication administration records to identify patients treated with α_1-blockers during their COVID-19 hospitalization. These results lend additional support the hypothesis that α_1-blockers may have a beneficial effect in COVID-19.

Our results also include tests of association between other common medication classes and COVID-19 outcomes, including beta blockers, angiotensin-converting enzyme (ACEi) inhibitors, angiotensin II receptor blockers (ARBs), and glucocorticoids. Results pertaining to these other medications should be taken in the context of a selected cohort designed to study α_1-blocker use and COVID-19 outcomes. Exposures to these other classes were not ascertained with the same granularity as they were for the primary exposure. That said, it is interesting to note that α_1-blocker and beta blocker exposure were associated with opposite COVID-19 outcomes in our cohort. There is evidence to suggest that β-adrenergic signaling can promote an anti-inflammatory M2 phenotype in macrophages, in contrast to the pro-inflammatory effect of α_1-adrenergic signaling.[11,18] Additional efforts to dissect the interactions between adrenergic signaling and the COVID-19 immune response are warranted. A prior diagnosis of asthma was associated with reduced in-hospital mortality in this analysis. While this observation deserves further scrutiny, it is conceivable that early exposure to inhaled glucocorticoids or β-adrenergic agonists may have contributed to this signal.

Limitations

Our study has several limitations. The cohort did not include women since most α_1-blockers were prescribed to men, most likely for benign prostatic hyperplasia. Male sex is a recognized risk factor for adverse COVID-19 outcomes, possibly due to sex-specific differences in immunity.[19] Thus, these results may not extrapolate to women. We did not account for different types of α_1-blockers, which differentially target the three α_1-adrenergic receptor subtypes. Importantly, a causal relationship cannot be definitively

established between α_1-blockers and improved COVID-19 outcomes in this retrospective study. Several confounders, such as older age and comorbidities were more common in the α_1-blocker group. However, these adverse risk factors would be expected to bias the study result towards the null rather than inflate a protective association. Furthermore, our findings are consistent with prior data, and were robust to different methods of adjustment for confounding and sensitivity analysis. The ongoing randomized clinical trial of prazosin against placebo among hospitalized COVID-19 patients (NCT04365257) will include women and provide more definitive data on the therapeutic value of α_1-blockers. Finally, our study is based on a single center EMR and medication via outpatient use cannot be tracked for adherence. Therefore, analyzing in-hospital medication administration is more robust. Furthermore, EMR in MSHS is the one of the largest and most comprehensive EMR systems, representing racial/ethnic diversity in New York City, and EMR implementation is from various data sources, so our findings are supported by large patient cohort and were robust from applying multiple methods of adjustment for confounding.

Conclusions

In conclusion, this retrospective study found a protective association between α_1-blockers use and COVID-19 outcomes in a cohort of hospitalized men. These results augment the rationale for studying and repurposing α_1-blockers as a COVID-19 therapeutic. We await the results of the ongoing randomized clinical trial.

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FIGURES

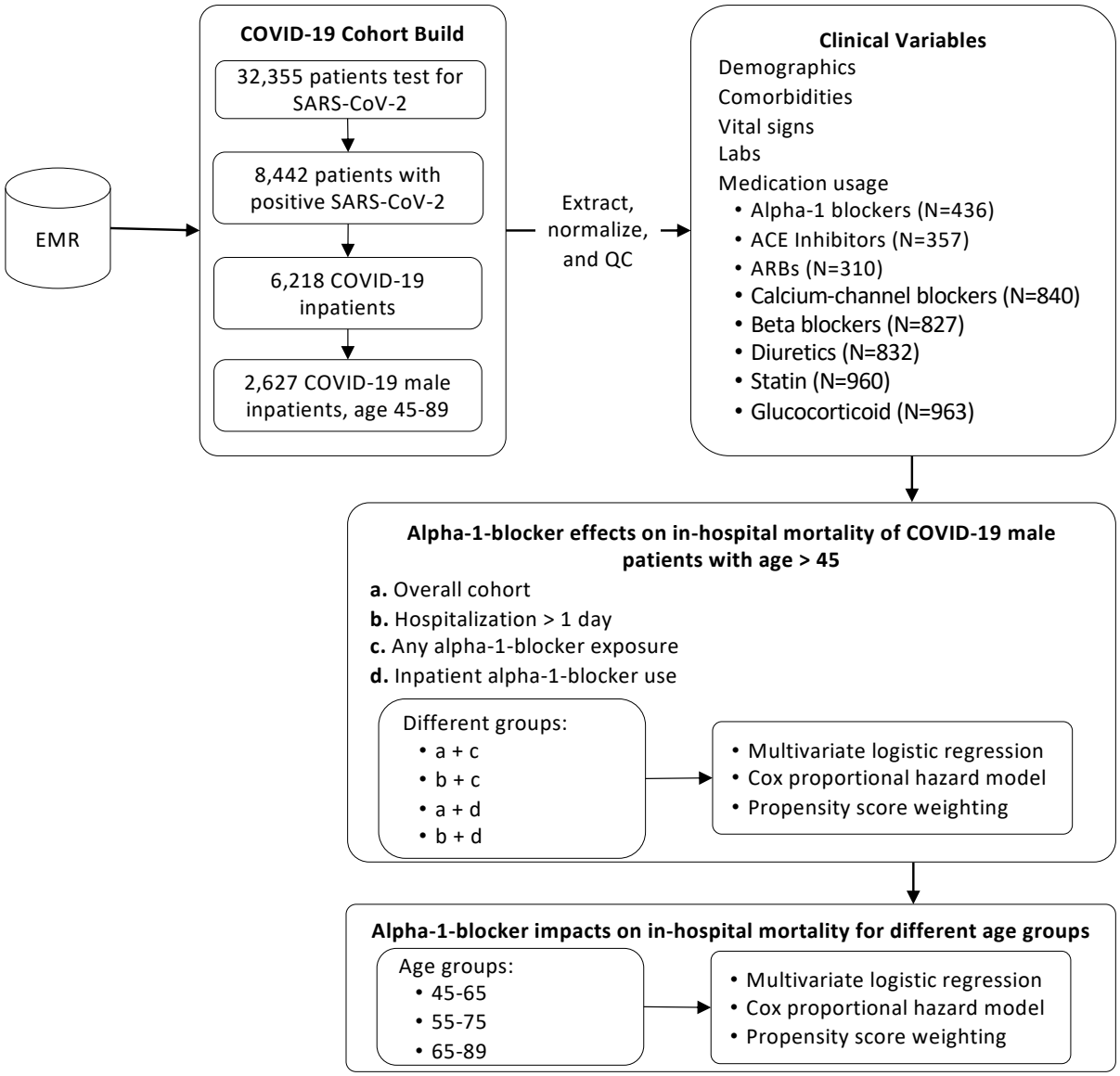

Figure 1. Schematic flowchart of data extraction and analysis plan

TABLES

Table 1. Baseline characteristics and hospitalization outcomes, by alpha-1-blocker exposure

	Non-Alpha-Blockers	Alpha-Blockers	P-Value
n	2191	436	
Patient Characteristics			
Age, median [Q1,Q3]	64 [56,74]	73 [66,81]	<0.001
Race, n (%)			0.004
African-American	514 (23.5)	86 (19.7)	
Asian	114 (5.2)	19 (4.4)	
Hispanic	624 (28.5)	130 (29.8)	
Other	336 (15.3)	49 (11.2)	
Unknown	69 (3.1)	10 (2.3)	
White	534 (24.4)	142 (32.6)	
BMI (kg/m^2), median [Q1,Q3]	27.0 [23.8,30.9]	26.0 [23.2,30.0]	0.003
Smoking status, n (%)			<0.001
Never	1023 (46.7)	202 (46.3)	
Not asked	525 (24.0)	66 (15.1)	
Quit	527 (24.1)	148 (33.9)	
Yes	116 (5.3)	20 (4.6)	
Temperature (F), median [Q1,Q3]	98.6 [97.9,99.8]	98.5 [98.0,99.5]	0.365
Max. temperature (F), median [Q1,Q3]	100.4 [99.1,102.1]	100.8 [99.6,102.4]	<0.001
O2 saturation (%), median [Q1,Q3]	96.0 [92.0,98.0]	95.0 [92.0,97.0]	0.168
Min. O2 saturation (%), median [Q1,Q3]	90.0 [82.0,94.0]	88.0 [78.0,91.0]	<0.001
Heart rate (BPM), median [Q1,Q3]	94.0 [82.0,108.0]	91.0 [77.0,104.0]	0.001
Respiratory rate >25, n (%)	317 (14.5)	64 (14.7)	0.968
High BP (SBP>140 or DBP>90), n (%)	817 (37.3)	163 (37.4)	0.987
Drugs			
ACE inhibitors, n (%)	267 (12.2)	90 (20.6)	<0.001
ARBs, n (%)	222 (10.1)	88 (20.2)	<0.001
Diuretics, n (%)	629 (28.7)	203 (46.6)	<0.001
Beta blockers, n (%)	623 (28.4)	204 (46.8)	<0.001
Calcium-channel blockers, n (%)	627 (28.6)	213 (48.9)	<0.001
Statin, n (%)	711 (32.5)	249 (57.1)	<0.001
Glucocorticoid, n (%)	745 (34.0)	218 (50.0)	<0.001
Comorbidities			
Asthma, n (%)	52 (2.4)	17 (3.9)	0.098
COPD, n (%)	76 (3.5)	30 (6.9)	0.002
Hypertension, n (%)	625 (28.5)	186 (42.7)	<0.001
Obstructive Sleep Apnea, n (%)	36 (1.6)	14 (3.2)	0.046
Obesity, n (%)	127 (5.8)	29 (6.7)	0.563
Diabetes Mellitus, n (%)	405 (18.5)	130 (29.8)	<0.001
Chronic Kidney Disease, n (%)	216 (9.9)	75 (17.2)	<0.001
HIV, n (%)	48 (2.2)	9 (2.1)	0.989
Cancer, n (%)	165 (7.5)	66 (15.1)	<0.001
Coronary Artery Disease, n (%)	255 (11.6)	90 (20.6)	<0.001
Atrial Fibrillation, n (%)	119 (5.4)	59 (13.5)	<0.001
Heart Failure, n (%)	131 (6.0)	51 (11.7)	<0.001

Chronic Viral Hepatitis, n (%)	27 (1.2)	7 (1.6)	0.691
Liver Disease, n (%)	47 (2.1)	13 (3.0)	0.372
Acute Kidney Injury, n (%)	150 (6.8)	47 (10.8)	0.006
Labs			
WBC (K/uL), median [Q1,Q3]	7.9 [5.7,10.9]	7.7 [5.4,11.4]	0.531
Creatinine > 1.2, n (%)	903 (41.2)	231 (53.0)	<0.001
Anion Gap (mEq/L), median [Q1,Q3]	12.3 [10.7,15.0]	12.4 [10.2,15.0]	0.413
Potassium (mmol/L), median [Q1,Q3]	4.4 [4.0,4.8]	4.3 [3.9,4.8]	0.622
ALT (U/L), median [Q1,Q3]	34.0 [21.0,57.0]	29.0 [18.0,50.0]	<0.001
Hospital Conditions			
ICU, n (%)	431 (19.7)	112 (25.7)	0.006
Days after infection, median [Q1,Q3]	4.7 [1.1,9.5]	7.0 [3.6,11.5]	<0.001
Hospital status, n (%)			<0.001
Censored	214 (9.8)	66 (15.1)	
Deceased	617 (28.2)	141 (32.3)	
Discharged	1360 (62.1)	229 (52.5)	

Abbreviations: BMI, body mass index; BPM, beats per minute; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficient virus; WBC, white blood cell count; ALT, alanine aminotransferase

Table 2. Multivariable logistic regression results for COVID-19 in-hospital mortality, by cohort (overall vs. hospitalization >1 day) and alpha-1-blocker exposure (any vs. inpatient use)

	Overall cohort, any exposure (N=2347)		**Overall cohort, inpatient use (N=2276)**		**Hospital stay > 1 day, any exposure (N=1789)**		**Hospital stay > 1 day, inpatient use (N=1744)**	
	Adjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Drugs								
Alpha-1 blockers	0.749 (0.527-1.064)	0.106	0.633 (0.434-0.921)	0.017	0.722 (0.505-1.034)	0.075	0.607 (0.415-0.890)	0.010
ACE inhibitors	1.331 (0.880-2.014)	0.175	1.237 (0.808-1.893)	0.327	1.317 (0.861-2.016)	0.205	1.220 (0.787-1.891)	0.373
ARBs	1.005 (0.660-1.528)	0.983	1.030 (0.667-1.592)	0.893	0.872 (0.562-1.353)	0.541	0.900 (0.572-1.419)	0.652
Diuretics	1.595 (1.147-2.217)	0.006	1.571 (1.123-2.199)	0.008	1.520 (1.084-2.132)	0.015	1.464 (1.037-2.067)	0.030
Beta blockers	1.448 (1.067-1.966)	0.017	1.534 (1.123-2.094)	0.007	1.505 (1.103-2.054)	0.010	1.578 (1.148-2.168)	0.005
Calcium-channel blockers	0.736 (0.535-1.012)	0.059	0.698 (0.503-0.968)	0.031	0.758 (0.547-1.050)	0.095	0.710 (0.508-0.991)	0.044
Statin	0.866 (0.624-1.200)	0.386	0.903 (0.647-1.261)	0.550	0.925 (0.661-1.293)	0.646	0.967 (0.686-1.361)	0.844
Glucocorticoid	1.368 (0.981-1.904)	0.064	1.422 (1.014-1.994)	0.041	1.467 (1.044-2.061)	0.027	1.495 (1.058-2.115)	0.023
Patient Characteristics								
Age	1.079 (1.063-1.095)	<0.001	1.081 (1.064-1.099)	<0.001	1.084 (1.067-1.102)	<0.001	1.085 (1.068-1.103)	<0.001
Race: African American	0.701 (0.463-1.063)	0.095	0.722 (0.473-1.102)	0.131	0.826 (0.539-1.266)	0.381	0.838 (0.542-1.293)	0.424
Race: Asian	0.637 (0.311-1.307)	0.219	0.554 (0.260-1.179)	0.126	0.708 (0.342-1.468)	0.354	0.600 (0.279-1.294)	0.193
Race: Hispanic	0.776 (0.525-1.147)	0.202	0.786 (0.526-1.174)	0.238	0.872 (0.582-1.306)	0.507	0.872 (0.577-1.319)	0.516
Race: Other	0.650 (0.405-1.043)	0.074	0.673 (0.417-1.087)	0.105	0.763 (0.470-1.237)	0.273	0.780 (0.479-1.273)	0.321
Race: Unknown	0.725 (0.293-1.795)	0.488	0.737 (0.296-1.839)	0.513	0.818 (0.329-2.030)	0.664	0.825 (0.330-2.065)	0.682
Smoking Status: Not Asked	1.001 (0.678-1.477)	0.996	0.982 (0.662-1.456)	0.930	0.932 (0.626-1.388)	0.731	0.941 (0.629-1.406)	0.765
Smoking Status: Quit	1.351 (0.949-1.923)	0.095	1.302 (0.906-1.872)	0.154	1.306 (0.909-1.876)	0.148	1.309 (0.902-1.896)	0.156
Smoking Status: Yes	1.274 (0.637-2.545)	0.494	1.353 (0.676-2.710)	0.393	1.232 (0.604-2.514)	0.566	1.335 (0.652-2.732)	0.430
BMI	1.011 (0.989-1.035)	0.326	1.013 (0.991-1.037)	0.251	1.013 (0.990-1.038)	0.271	1.014 (0.991-1.039)	0.233
Temperature	0.991 (0.930-1.057)	0.779	0.993 (0.931-1.061)	0.842	0.991 (0.928-1.059)	0.781	0.992 (0.928-1.061)	0.820
Max. Temperature	1.221 (1.122-1.331)	<0.001	1.212 (1.112-1.322)	<0.001	1.262 (1.154-1.380)	<0.001	1.247 (1.139-1.366)	<0.001
O2 Saturation	1.013 (0.991-1.037)	0.243	1.014 (0.992-1.037)	0.220	1.006 (0.983-1.029)	0.617	1.008 (0.984-1.031)	0.513
Min. O2 Saturation	0.932 (0.919-0.946)	<0.001	0.932 (0.919-0.946)	<0.001	0.934 (0.920-0.947)	<0.001	0.933 (0.919-0.946)	<0.001
Heart Rate	0.996 (0.989-1.004)	0.353	0.995 (0.987-1.003)	0.201	0.995 (0.987-1.003)	0.219	0.994 (0.986-1.002)	0.164
Respiratory Rate > 25	1.699 (1.151-2.504)	0.007	1.649 (1.107-2.452)	0.014	1.511 (1.010-2.261)	0.045	1.476 (0.977-2.228)	0.064
High BP (SBP>140 or DBP>90)	1.161 (0.863-1.560)	0.324	1.169 (0.863-1.584)	0.312	1.219 (0.900-1.650)	0.200	1.234 (0.905-1.682)	0.184
Comorbidities								
Asthma	0.259 (0.088-0.765)	0.015	0.299 (0.099-0.900)	0.032	0.280 (0.095-0.823)	0.021	0.323 (0.109-0.962)	0.042

COPD	1.505 (0.771-2.939)	0.231	1.342 (0.672-2.678)	0.405	1.498 (0.752-2.980)	0.250	1.296 (0.633-2.651)	0.479
Hypertension	0.825 (0.570-1.196)	0.311	0.851 (0.580-1.249)	0.409	0.817 (0.558-1.196)	0.299	0.837 (0.564-1.241)	0.376
Obstructive Sleep Apnea	3.025 (1.175-7.791)	0.022	3.019 (1.163-7.838)	0.023	3.074 (1.164-8.125)	0.023	3.152 (1.179-8.415)	0.022
Obesity	1.048 (0.568-1.935)	0.880	1.064 (0.567-1.998)	0.847	0.919 (0.485-1.742)	0.797	0.924 (0.479-1.784)	0.815
Diabetes Mellitus	1.043 (0.710-1.533)	0.829	0.986 (0.664-1.465)	0.946	1.099 (0.737-1.639)	0.643	1.025 (0.679-1.547)	0.907
Chronic Kidney Disease	1.188 (0.737-1.914)	0.479	1.264 (0.774-2.063)	0.349	1.322 (0.810-2.158)	0.264	1.412 (0.854-2.333)	0.179
HIV	1.846 (0.688-4.948)	0.224	1.696 (0.600-4.792)	0.319	1.702 (0.604-4.802)	0.314	1.480 (0.494-4.433)	0.484
Cancer	0.959 (0.601-1.530)	0.861	0.862 (0.530-1.398)	0.546	0.882 (0.546-1.426)	0.609	0.831 (0.506-1.365)	0.464
Coronary Artery Disease	0.807 (0.514-1.265)	0.350	0.783 (0.492-1.249)	0.305	0.880 (0.550-1.406)	0.593	0.899 (0.555-1.455)	0.663
Atrial Fibrillation	0.779 (0.457-1.330)	0.360	0.740 (0.428-1.279)	0.281	0.768 (0.444-1.328)	0.345	0.726 (0.414-1.275)	0.266
Heart Failure	1.004 (0.576-1.749)	0.989	1.041 (0.587-1.846)	0.891	0.838 (0.466-1.507)	0.554	0.836 (0.454-1.540)	0.566
Chronic Viral Hepatitis	0.546 (0.146-2.040)	0.368	0.596 (0.158-2.255)	0.446	0.580 (0.155-2.179)	0.420	0.630 (0.166-2.394)	0.497
Liver Disease	1.448 (0.593-3.536)	0.417	1.486 (0.607-3.636)	0.386	1.573 (0.639-3.873)	0.325	1.613 (0.654-3.983)	0.299
Acute Kidney Injury	1.157 (0.689-1.944)	0.581	1.009 (0.582-1.747)	0.975	1.204 (0.708-2.048)	0.493	1.107 (0.635-1.933)	0.718
Labs								
WBC	1.028 (1.000-1.058)	0.052	1.029 (1.001-1.060)	0.043	1.019 (0.988-1.052)	0.234	1.020 (0.988-1.053)	0.212
Creatinine > 1.2	1.660 (1.184-2.330)	0.003	1.598 (1.130-2.261)	0.008	1.462 (1.035-2.067)	0.031	1.438 (1.009-2.048)	0.045
Anion Gap	1.074 (1.035-1.114)	<0.001	1.075 (1.036-1.116)	<0.001	1.063 (1.024-1.103)	0.001	1.063 (1.023-1.104)	0.001
Potassium	1.223 (1.016-1.471)	0.033	1.191 (0.985-1.441)	0.072	1.219 (1.010-1.473)	0.039	1.184 (0.975-1.438)	0.088
ALT	1.001 (0.999-1.003)	0.309	1.001 (0.999-1.004)	0.271	1.001 (0.999-1.003)	0.349	1.001 (0.999-1.003)	0.364
Hospital Conditions								
ICU	3.547 (2.433-5.165)	<0.001	3.740 (2.550-5.479)	<0.001	3.219 (2.197-4.711)	<0.001	3.425 (2.323-5.048)	<0.001
Duration (days)	0.956 (0.933-0.979)	<0.001	0.958 (0.934-0.981)	<0.001	0.959 (0.936-0.983)	0.001	0.962 (0.939-0.986)	0.002

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficient virus; WBC, white blood cell count; ALT, alanine aminotransferase

Table 3. Multivariable Cox regression results for COVID-19 in-hospital mortality, by cohort (overall vs. hospitalization >1 day) and alpha-1-blocker exposure (any vs. inpatient use)

	Overall cohort, any exposure (N=2627)		**Overall cohort, inpatient use (N=2534)**		**Hospital stay > 1 day, any exposure (N=2037)**		**Hospital stay > 1 day, inpatient use (N=1973)**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Drugs								
Alpha-1 blockers	0.808 (0.652-1.002)	0.052	0.721 (0.572-0.908)	0.006	0.823 (0.660-1.027)	0.085	0.751 (0.593-0.950)	0.017
ACE inhibitors	1.166 (0.910-1.494)	0.224	1.149 (0.887-1.487)	0.292	1.151 (0.892-1.486)	0.280	1.121 (0.859-1.462)	0.402
ARBs	1.330 (1.035-1.709)	0.026	1.319 (1.018-1.710)	0.036	1.152 (0.880-1.509)	0.302	1.145 (0.867-1.512)	0.341
Diuretics	0.895 (0.729-1.098)	0.286	0.863 (0.700-1.065)	0.169	0.859 (0.694-1.064)	0.164	0.825 (0.663-1.026)	0.084
Beta blockers	1.073 (0.895-1.287)	0.446	1.090 (0.905-1.313)	0.363	1.100 (0.912-1.327)	0.317	1.120 (0.925-1.356)	0.247
Calcium-channel blockers	0.637 (0.530-0.766)	<0.001	0.613 (0.508-0.740)	<0.001	0.649 (0.537-0.785)	<0.001	0.629 (0.518-0.764)	<0.001
Statin	0.970 (0.800-1.175)	0.753	0.951 (0.778-1.162)	0.621	1.007 (0.825-1.228)	0.949	0.999 (0.812-1.228)	0.990
Glucocorticoid	0.767 (0.627-0.938)	0.010	0.789 (0.642-0.971)	0.025	0.801 (0.649-0.988)	0.038	0.820 (0.661-1.016)	0.070
Patient Characteristics								
Age	1.035 (1.025-1.044)	<0.001	1.033 (1.024-1.043)	<0.001	1.037 (1.027-1.047)	<0.001	1.035 (1.025-1.045)	<0.001
Race: African American	0.813 (0.633-1.043)	0.104	0.824 (0.639-1.064)	0.137	0.906 (0.699-1.175)	0.457	0.909 (0.698-1.184)	0.480
Race: Asian	0.829 (0.536-1.284)	0.401	0.773 (0.488-1.224)	0.272	0.841 (0.533-1.326)	0.456	0.760 (0.470-1.230)	0.264
Race: Hispanic	0.881 (0.698-1.112)	0.286	0.866 (0.682-1.099)	0.237	0.928 (0.727-1.184)	0.548	0.919 (0.716-1.178)	0.504
Race: Other	0.972 (0.738-1.279)	0.839	0.972 (0.737-1.284)	0.843	1.043 (0.784-1.389)	0.773	1.035 (0.775-1.382)	0.816
Race: Unknown	0.961 (0.578-1.599)	0.879	0.982 (0.589-1.636)	0.944	1.043 (0.625-1.741)	0.871	1.060 (0.634-1.772)	0.824
Smoking Status: Not Asked	1.089 (0.865-1.371)	0.467	1.084 (0.858-1.369)	0.499	1.065 (0.840-1.351)	0.603	1.085 (0.853-1.379)	0.507
Smoking Status: Quit	1.262 (1.022-1.558)	0.030	1.277 (1.027-1.587)	0.028	1.251 (1.006-1.558)	0.044	1.293 (1.033-1.620)	0.025
Smoking Status: Yes	1.090 (0.714-1.664)	0.690	1.104 (0.719-1.695)	0.652	1.065 (0.689-1.645)	0.778	1.094 (0.704-1.702)	0.689
BMI	1.008 (0.996-1.020)	0.168	1.008 (0.996-1.021)	0.172	1.009 (0.997-1.022)	0.134	1.009 (0.997-1.021)	0.153
Temperature	1.021 (0.972-1.072)	0.406	1.013 (0.966-1.062)	0.595	1.012 (0.964-1.062)	0.621	1.006 (0.960-1.055)	0.789
Max. Temperature	1.016 (0.963-1.071)	0.562	1.013 (0.959-1.069)	0.646	1.061 (1.007-1.117)	0.025	1.058 (1.004-1.115)	0.035
O2 Saturation	0.990 (0.979-1.000)	0.057	0.991 (0.980-1.002)	0.112	0.988 (0.977-0.999)	0.036	0.989 (0.978-1.001)	0.069
Min. O2 Saturation	0.991 (0.988-0.995)	<0.001	0.991 (0.988-0.995)	<0.001	0.993 (0.989-0.997)	0.001	0.993 (0.989-0.997)	<0.001
Heart Rate	1.000 (0.995-1.004)	0.939	0.999 (0.994-1.003)	0.605	1.000 (0.995-1.005)	0.920	0.999 (0.994-1.004)	0.779
Respiratory Rate > 25	1.155 (0.939-1.420)	0.173	1.136 (0.918-1.405)	0.241	1.109 (0.893-1.378)	0.349	1.101 (0.882-1.374)	0.395
High BP (SBP>140 or DBP>90)	1.070 (0.898-1.275)	0.451	1.095 (0.915-1.310)	0.323	1.135 (0.946-1.361)	0.172	1.156 (0.960-1.392)	0.125
Comorbidities								
Asthma	0.501 (0.234-1.072)	0.075	0.534 (0.249-1.147)	0.108	0.536 (0.250-1.149)	0.109	0.582 (0.271-1.250)	0.165

COPD	1.254 (0.871-1.805)	0.224	1.121 (0.758-1.657)	0.568	1.280 (0.876-1.872)	0.202	1.130 (0.752-1.699)	0.557
Hypertension	0.877 (0.696-1.103)	0.261	0.881 (0.695-1.118)	0.298	0.857 (0.676-1.088)	0.205	0.850 (0.665-1.086)	0.193
Obstructive Sleep Apnea	1.257 (0.721-2.193)	0.420	1.405 (0.794-2.486)	0.242	1.138 (0.631-2.054)	0.667	1.267 (0.690-2.329)	0.445
Obesity	0.954 (0.667-1.363)	0.795	0.998 (0.695-1.434)	0.992	0.954 (0.658-1.382)	0.802	0.999 (0.685-1.456)	0.996
Diabetes Mellitus	0.986 (0.785-1.239)	0.904	0.981 (0.776-1.240)	0.873	0.970 (0.765-1.229)	0.798	0.954 (0.748-1.216)	0.703
Chronic Kidney Disease	0.920 (0.694-1.220)	0.564	0.958 (0.718-1.278)	0.769	1.050 (0.784-1.405)	0.743	1.090 (0.809-1.468)	0.572
HIV	0.943 (0.515-1.728)	0.850	0.878 (0.467-1.653)	0.688	0.901 (0.478-1.698)	0.748	0.848 (0.437-1.644)	0.625
Cancer	1.255 (0.947-1.663)	0.114	1.213 (0.903-1.627)	0.199	1.237 (0.922-1.660)	0.156	1.200 (0.884-1.630)	0.243
Coronary Artery Disease	1.190 (0.917-1.544)	0.192	1.231 (0.940-1.613)	0.131	1.236 (0.941-1.625)	0.128	1.298 (0.978-1.721)	0.071
Atrial Fibrillation	1.306 (0.944-1.807)	0.107	1.353 (0.966-1.893)	0.078	1.278 (0.905-1.806)	0.163	1.295 (0.904-1.854)	0.158
Heart Failure	1.499 (1.092-2.058)	0.012	1.538 (1.108-2.135)	0.010	1.314 (0.932-1.852)	0.119	1.299 (0.908-1.859)	0.153
Chronic Viral Hepatitis	1.193 (0.482-2.954)	0.703	1.336 (0.537-3.321)	0.534	1.326 (0.533-3.300)	0.544	1.501 (0.600-3.755)	0.386
Liver Disease	1.191 (0.708-2.004)	0.509	1.184 (0.698-2.009)	0.531	1.276 (0.750-2.170)	0.369	1.268 (0.739-2.173)	0.389
Acute Kidney Injury	0.878 (0.656-1.175)	0.381	0.823 (0.603-1.123)	0.219	0.935 (0.690-1.266)	0.664	0.887 (0.643-1.223)	0.464
Labs								
WBC	1.012 (0.995-1.028)	0.162	1.018 (1.000-1.036)	0.047	1.005 (0.987-1.023)	0.605	1.010 (0.991-1.029)	0.315
Creatinine > 1.2	1.353 (1.108-1.654)	0.003	1.337 (1.089-1.641)	0.006	1.281 (1.042-1.575)	0.019	1.288 (1.043-1.591)	0.019
Anion Gap	1.042 (1.022-1.062)	<0.001	1.040 (1.019-1.061)	<0.001	1.032 (1.010-1.054)	0.004	1.028 (1.005-1.051)	0.015
Potassium	1.125 (1.019-1.241)	0.019	1.103 (0.996-1.221)	0.060	1.103 (0.994-1.225)	0.064	1.081 (0.971-1.204)	0.154
ALT	1.000 (0.999-1.001)	0.727	1.000 (0.999-1.001)	0.757	1.000 (0.999-1.001)	0.688	1.000 (0.999-1.001)	0.758
Hospital Conditions								
ICU	1.350 (1.094-1.667)	0.005	1.425 (1.149-1.768)	0.001	1.382 (1.109-1.723)	0.004	1.437 (1.148-1.800)	0.002

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficient virus; WBC, white blood cell count; ALT, alanine aminotransferase

Table 4. Age-stratified multivariable logistic regression and propensity-weighted logistic regression analyses for COVID-19 in-hospital mortality, by cohort (overall vs. hospitalization >1 day) and alpha-1-blocker exposure (any vs. inpatient use)

	Age 45-65 (N=1159)		**Age 55-75(N=1312)**		**Age 65-89 (N=1176)**	
	Adjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Multivariate logistic regression						
Overall cohort, any exposure	0.511 (0.232-1.126)	0.096	0.603 (0.362-1.003)	0.051	0.908 (0.588-1.402)	0.663
Overall cohort, inpatient use	0.384 (0.164-0.896)	0.027	0.511 (0.297-0.880)	0.015	0.810 (0.509-1.289)	0.374
Hospital stay > 1 day, any exposure	0.530 (0.240-1.174)	0.117	0.590 (0.352-0.987)	0.045	0.880 (0.563-1.374)	0.574
Hospital stay > 1 day, inpatient use	0.397 (0.170-0.927)	0.033	0.507 (0.294-0.874)	0.015	0.789 (0.492-1.265)	0.325
Inverse propensity-weighted logistic regression						
Overall cohort, any exposure	0.298 (0.132-0.672)	0.004	0.552 (0.337-0.903)	0.018	0.876 (0.557-1.379)	0.568
Overall cohort, inpatient use	0.268 (0.109-0.658)	0.004	0.424 (0.247-0.725)	0.002	0.801 (0.487-1.317)	0.382
Hospital stay > 1 day, any exposure	0.314 (0.141-0.698)	0.005	0.535 (0.321-0.89)	0.016	0.800 (0.500-1.280)	0.353
Hospital stay > 1 day, inpatient use	0.262 (0.112-0.61)	0.002	0.451 (0.268-0.759)	0.003	0.752 (0.455-1.242)	0.265

SUPPLEMENTARY MATERIALS

Figure S1. Age distributions of α_1-blockers exposed and unexposed groups

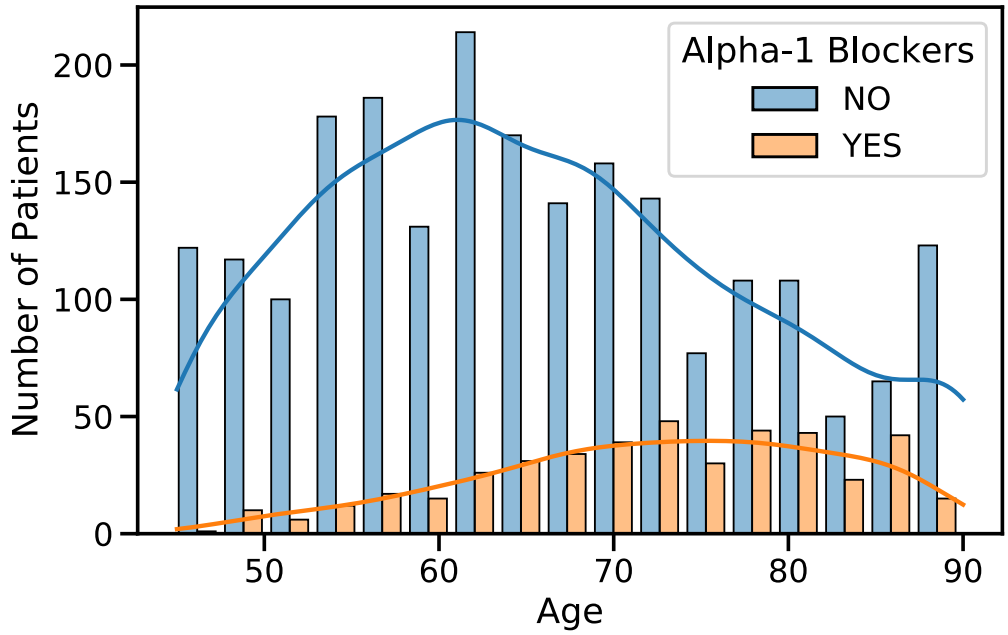

Table S1a. Medication categories and individual medications

Medication Category	Medication Names
Alpha-1 Blockers	Tamsulosin, Alfuzosin, Silodosin, Terazosin, Doxazosin, Prazosin
ACE inhibitors	Benazepril hydrochloride, Captopril, Enalapril maleate, Fosinopril sodium, Lisinopril, Moexipril, Perindopril, Quinapril hydrochloride, Ramipril, Trandolapril
ARBs	Azilsartan, Candesartan, Eprosartan mesylate, Irbesartan, losartan potassium, Olmesartan, Telmisartan, Valsartan
Diuretics	Chlorthalidone, Chlorothiazide, Hydrochlorothiazide, Indapamide, Metolazone, Amiloride hydrochloride, Spironolactone, Triamterene, Eplerenone, Furosemide, Bumetanide, Torsemide, Ethacrynic acid
Beta Blockers	Acebutolol, Atenolol, Betaxolol, Bisoprolol fumarate, Carteolol hydrochloride, Metoprolol, Nadolol, Nebivolol, Penbutolol sulfate, Pindolol, Propranolol hydrochloride, Solotol hydrochloride, Timolol maleate
Calcium-channel Blockers	Amlodipine, Bepridil, Diltiazem hydrochloride, Felodipine, Isradipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil hydrochloride
Statin	Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin
Glucocorticoid	Methylprednisolone, Prednisone, Hydrocortisone, Dexamethasone, Fludrocortisone, Triamcinolone, Prednisolone, Betamethasone

Table S1b. Number of patients exposed to glucocorticoid medications

Drug Name	Number of Patients
Methylprednisolone	621
Prednisone	269
Hydrocortisone	242
Dexamethasone	189
Fludrocortisone	41
Triamcinolone	29
Prednisolone	23
Betamethasone	10

Table S2. Sensitivity analysis using E-values to assess the threshold effect size of unmeasured confounders required to nullify the significant associations between inpatient alpha-1-blocker use and COVID-19 in-hospital mortality

	Point estimate for OR (Upper limit of CI)	Point estimate for HR (Upper limit of CI)
Overall cohort, inpatient use	1.83 (1.25)	1.82 (1.34)
Hospital stay > 1 day, inpatient use	1.89 (1.31)	1.74 (1.23)

Table S3. Inverse propensity-weighted logistic regression for COVID-19 in-hospital mortality, by cohort (overall vs. hospitalization >1 day) and alpha-1-blocker exposure (any vs. inpatient use)

	Adjusted OR (95% CI)	p-value
Overall cohort, any exposure	0.740 (0.512-1.070)	0.110
Overall cohort, inpatient use	0.630 (0.424-0.935)	0.022
Hospital stay > 1 day, any exposure	0.760 (0.520-1.110)	0.157
Hospital stay > 1 day, inpatient use	0.622 (0.419-0.924)	0.019