COVID

MDPI

Article

The Associations of Antihypertensive Medications, Steroids, Beta Blockers, Statins and Comorbidities with COVID-19 Outcomes in Patients with and without Chronic Kidney Disease: A Retrospective Study

Paul Kim [1,†], Vidhya Nadarajan [1,†], Maham Ahmed [1], Katerina Furman [1], Zoya Gurm [1], Priyanka Kale [1], Zaina Khoury [1], Sara Koussa [1], Dana LaBuda [1], Margo Mekjian [1], Pooja Polamarasetti [1], Leticia Simo [1], Charlotte Thill [1], Sophie Wittenberg [1], Sorabh Dhar [1,2] and Dragana Komnenov [1,*]

[1] Department of Internal Medicine, Nephrology, Wayne State University, Detroit, MI 48201, USA
[2] John D. Dingell VA Medical Center, Detroit, MI 48201, USA
* Correspondence: dkomneno@med.wayne.edu; Tel.: +1-313-576-4503
† These authors contributed equally to this work.

Abstract: (1) Background: Data on COVID-19 outcomes and disease course as a function of different medications used to treat cardiovascular disease and chronic kidney disease (CKD), as well as the presence of different comorbidities in primarily Black cohorts, are lacking. (2) Methods: We conducted a retrospective medical chart review on 327 patients (62.6% Black race) who were admitted to the Detroit Medical Center, Detroit, MI. Group differences (CKD vs. non-CKD) were compared using the Pearson χ^2 test. We conducted univariate and multivariate regression analyses for factors contributing to death during hospitalization due to COVID-19 (primary outcome) and ICU admission (secondary outcome), adjusting for age, sex, different medications, and comorbidities. A sub-analysis was also completed for CKD patients. (3) Results: In the fully adjusted model, a protective effect of ACEi alone, but not in combination with ARB or CCB, for ICU admission was found (OR = 0.400, 95% CI [0.183–0.874]). Heart failure was significantly associated with the primary outcome (OR = 4.088, 95% CI [1.1661–14.387]), as was COPD (OR = 3.747, 95% CI [1.591–8.828]). (4) Conclusions: Therapeutic strategies for cardiovascular disease and CKD in the milieu of different comorbidities may need to be tailored more prudently for individuals with COVID-19, especially Black individuals.

Keywords: antihypertensive drugs; chronic kidney disease (CKD); COVID-19 mortality; COVID-19 disease severity

Citation: Kim, P.; Nadarajan, V.; Ahmed, M.; Furman, K.; Gurm, Z.; Kale, P.; Khoury, Z.; Koussa, S.; LaBuda, D.; Mekjian, M.; et al. The Associations of Antihypertensive Medications, Steroids, Beta Blockers, Statins and Comorbidities with COVID-19 Outcomes in Patients with and without Chronic Kidney Disease: A Retrospective Study. *COVID* **2023**, *3*, 682–692. https://doi.org/10.3390/covid3050050

Academic Editor: Daniela Ponce

Received: 22 March 2023
Revised: 11 April 2023
Accepted: 21 April 2023
Published: 25 April 2023

1. Introduction

Since the start of the COVID-19 pandemic caused by the SARS-CoV-2 virus in 2020, there have been over 760 million cases and 6.8 million deaths reported as of March 2023 [1]. SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) receptor for cellular entry, and the ACE2 enzyme is involved in increasing blood pressure via activation of the renin-angiotensin-aldosterone system (RAAS) pathway. The derangements in the RAAS pathway have also been implicated in chronic kidney disease (CKD) and hypertension disease pathogenesis. One recent meta-analysis demonstrated that the prevalence of CKD in patients with COVID-19 was as high as 9.7% [2]. Several studies have shown that patients with CKD and COVID-19 have increased morbidity and mortality and an increased risk for hospitalization, ICU admission, and mechanical ventilation [2–4]. COVID-19 patients with CKD have also been shown to have a higher rate of cardiovascular death at 30 days compared to patients without CKD [5]. In fact, a decline in the glomerular filtration rate has been associated with an increased risk of all-cause mortality [5]. However, data regarding the impact of medications typically used in the management of CKD, cardiovascular disease,

and hypertension on COVID-19 disease severity and mortality are lacking in cohorts of races other than white. Additionally, whether and how these interactions are further complicated by the presence of comorbidities other than CKD is still largely unexplored. The present study was designed to fill these voids and was aimed at identifying independent predictors of COVID-19 mortality and severity of the disease, as well as high-risk patient groups that would necessitate targeted intervention strategies.

Most of the studies investigating the impact of chronic use of antihypertensive medications on COVID-19 outcomes reported either neutral or protective effects. In the initial stages of the pandemic, there was a concern for a potential increase in susceptibility to SARS-CoV-2 infection and/or severity of the disease in patients on ACE inhibitors (ACEi) because these medications have been shown to upregulate ACE2 receptor expression [6]. However, this, in turn, has been disputed, with studies indicating that such is not the case in the lung [7]. A retrospective study from France found that the antihypertensive medications ACEi and angiotensin receptor blockers (ARB), whose mechanism of action involves the RAAS pathway, demonstrated decreased morbidity and mortality compared to calcium channel blockers (CCB) in hypertensive patients with COVID-19 and without CKD [8]. However, a randomized clinical trial investigating the outcomes of COVID-19 patients with hypertension and without CKD who took losartan (an ARB) versus amlodipine (CCB) showed no difference between the two in morbidity and mortality [9]. Two additional studies found that the use of ACEi and ARB in hypertensive patients with COVID-19 did not alter the survival or severity of the disease compared to normotensive patients [10,11]. One study investigating the use of CCBs in COVID-19 patients found that CCB use in hypertensive patients with COVID-19 reduced mortality rates [12]. Subsequent studies designed to answer this question more equivocally indeed reported no association of ACEi/ARB with more severe outcomes in COVID-19 patients [11,13–21]. However, most of these studies involved White or Asian individuals. One study investigated the association between ACEi/ARB and COVID-19 outcomes in Black patients without CKD and found no significant associations [22]. Studies investigating these effects in the milieu of CKD are scarce. In fact, only one study has been published to date, and it reported no significant associations between RAAS blockers and mortality in a CKD cohort of exclusively White patients [23]. The present investigation was designed to explore associations between medications typically used to manage cardiovascular and renal disease and COVID-19 outcomes in both Black and White patients with and without CKD.

2. Materials and Methods

2.1. Patient Population

We completed a retrospective analysis of patients admitted for COVID-19 to the Detroit Medical Center, Detroit, MI, USA, between July and October of 2020. The inclusion criteria consisted of age > 18 years and a positive SARS-CoV-2 PCR test obtained via nasopharyngeal or oropharyngeal swab. We excluded pregnant patients. The analysis was completed on 327 patients. CKD status was discerned from the medical record review. Thirty-six patients had end-stage renal disease, and almost half of CKD patients had stage 3 CKD (N = 61). Forty-two patients received hemodialysis at some point. The study protocol was approved by the Institutional Review Board at Wayne State University (IRB # 21-05-3579) and the Detroit Medical Center (study # 19717).

2.2. Study Measures and Outcomes

Data from electronic medical records were obtained at the time of patient admission for SARS-CoV-2 infection. The collected data included demographics (age, sex, race/ethnicity), vitals on admission (blood pressure, pulse and temperature), long-standing medications used by the patients obtained from their medication history (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, mineralocorticoid receptor antagonists, vasodilators (all types other than ACEi, ARB, and CCB), diuretics, steroids, beta blockers and statins), comorbidities (hypertension, diabetes, lupus, car-

diomyopathies, heart failure, vasculopathies, other cardiovascular disease, pulmonary fibrosis, chronic obstructive pulmonary disease, other pulmonary disease) and clinical course of the disease during hospitalization (ventilation, ICU admission, anticoagulants, anti-inflammatories, remdesivir administration, palliative care consult, acute stroke, sepsis, dialysis at any point during hospitalization). Study data were collected and managed using REDCap electronic data capture tools hosted at Wayne State University School of Medicine [24,25]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

The primary outcome was defined as all-cause mortality during hospitalization for SARS-CoV-2 infection, and the secondary outcome was defined as necessitation for ICU admission due to SARS-CoV-2 infection.

2.3. Statistical Analysis

For statistical analysis, we used Statistical Package for the Social Sciences (SPSS) version 28.01.0. A total of 327 patients were included in the analysis. For baseline characteristics, the patients were divided into two groups: (1) those without chronic kidney disease and (2) those with chronic kidney disease. We used numbers and percentages for the patient's characteristics description, and comparisons were made with a Pearson χ^2 test. Continuous variables (blood pressure (BP) and respiratory rate (RR)) were converted to categorical variables (systolic BP < 140 mmHg and $\geq$140 mmHg, diastolic BP < 90 mmHg and $\geq$90 mmHg and RR < 16 BPM and $\geq$16 BPM). Statistical significance was identified with p-values of <0.05. We completed univariate and multivariate binary logistic regression analyses for medication classes contributing to the primary and secondary outcomes (all-cause in-hospital mortality and ICU admission, respectively). We used corresponding odds ratios for patients who were on particular medication(s) vs. those who were not. Multivariate regression (fully adjusted model) was used to adjust for age, sex, race, comorbidities, medications, and remdesivir use.

3. Results

A total of 327 patients were included in the final analysis. One hundred and thirty (39.8%) patients were in the chronic kidney disease (CKD) group, and one hundred and ninety-seven patients (60.2%) were in the non-CKD group. Baseline characteristics are presented in Table 1. The two groups were significantly different for sex (p = 0.041) and race, with most of the cohort being Black (74.6% with CKD and 54.8% without CKD, p = 0.002). Age distribution was also different between the groups, with more patients younger than 65 being in the non-CKD group (34.3%) compared to the CKD group (16.7%, p = 0.003). Patients in the CKD group were more likely to be on CCBs (39.2% vs. 28.1% in non-CKD, p = 0.036), sympatholytic (9.2% vs. 1.0% in non-CKD, p < 0.001), beta blockers (54.6% vs. 28.6% in non-CKD, p < 0.001), and statins (61.5% vs. 40.7% in non-CKD, p < 0.001). Patients in the CKD group were more likely to have pre-existing diabetes (61.5% in CKD vs. 45.7% in non-CKD, p = 0.005) and heart failure (33.1% in CKD vs. 11.6% in non-CKD, p < 0.001).

No statistical significance was observed for pre-existing hypertension, lupus, cardiomyopathies, vasculopathies, other cardiovascular disease, pulmonary fibrosis, or COPD. Likewise, no statistical significance was observed between the groups for having elevated systolic (p = 0.272) or diastolic (p = 0.638) blood pressure vs. not (as per the most current American Heart Association guidelines [26]). Similarly, there was no difference in having an elevated respiratory rate vs. not (p = 0.173) on admission.

Table 1. Patient characteristics and comorbidities; comparison of patients with and without CKD.

	All Patients (% Total)	CKD (% All CKD)	No CKD (% All Non-CKD)	*p*-Value
Age				
<50	44 (13.4)	8 (6.1)	36 (18.2)	
50–65	122 (37.7)	47 (36.2)	75 (38.1)	0.003
≥65	161 (48.9)	75 (57.7)	86 (43.7)	
Sex				
Male	176 (53.8)	79 (60.8)	97 (49.2)	0.041
Female	151 (46.2)	51 (39.2)	100 (50.8)	
Race				
White	28 (8.5)	4 (3.1)	24 (12.1)	
Black	206 (62.6)	97 (74.6)	109 (54.8)	
Hispanic	4 (1.2)	1 (0.8)	3 (1.5)	0.002
Other	33 (10.0)	13 (10.0)	20 (10.1)	
Unknown	58 (17.6)	15 (11.5)	43 (21.6)	
Medications				
ACEi *, n (% total)	81 (24.6)	27 (20.8)	54 (27.1)	0.190
ARB *, n (% total)	46 (14)	21 (16.2)	25 (12.6)	0.359
CCB *	107 (32.5)	51 (39.2)	56 (28.1)	0.036
MR *	11 (3.3)	6 (4.6)	5 (2.5)	0.300
Sympatholytic	14 (4.3)	12 (9.2)	2 (1.0)	<0.001
Diuretic	96 (29.2)	41 (31.5)	55 (27.6)	0.447
Steroid	27 (8.2)	13 (10.0)	14 (7.0)	0.338
Beta blocker	128 (38.9)	71 (54.6)	57 (28.6)	<0.001
Statin	161 (48.9)	80 (61.5)	81 (40.7)	<0.001
Comorbidities				
Hypertension	317 (96.4)	123 (94.6)	194 (97.5)	0.174
Diabetes	171 (52.0)	80 (61.5)	91 (45.7)	0.005
Lupus	4 (1.2)	2 (1.5)	2 (1.0)	0.666
Cardiomyopathies	19 (5.8)	4 (3.1)	15 (7.5)	0.090
Heart failure	66 (20.1)	43 (33.1)	23 (11.6)	<0.001
Vasculopathies	61 (18.5)	28 (21.5)	33 (16.6)	0.258
Other cardiovascular disease	136 (41.3)	57 (43.8)	79 (39.7)	0.455
Pulmonary fibrosis	2 (0.6)	1 (0.8)	1 (0.5)	0.761
COPD	66 (20.1)	33 (25.4)	33 (16.6)	0.051
*SBP * on admission*				
<140 mmHg	185 (58.2)	68 (54.4)	117 (60.6)	0.272
≥140 mmHg	133 (41.8)	57 (45.6)	76 (39.4)	
*DBP * on admission*				
<90 mmHg	235 (74.4)	94 (75.8)	141 (73.4)	0.638
≥90 mmHg	81 (25.6)	30 (24.2)	51 (26.6)	
*RR * on admission*				
<16	14 (4.5)	3 (2.5)	11 (5.8)	0.173
≥16	298 (95.5)	118 (97.5)	180 (94.2)	

* ACEi = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; MR = mineralocorticoid receptor antagonist; SBP = systolic blood pressure; DBP = diastolic blood pressure; RR = respiratory rate.

The data on hospital course in CKD and non-CKD COVID-19 patients are presented in Table 2. Patients with CKD were more likely to be admitted to the ICU (48.7% vs. 29.3%, $p < 0.001$), to have necessitated ventilation (29.9% vs. 18.6%, $p = 0.021$), palliative care consult (8.0% vs. 2.6%, $p = 0.029$), dialysis during hospitalization (36.6% vs. 3.6%, $p < 0.001$) and to have developed sepsis (27.8% vs. 14.4%, $p = 0.004$). No statistical significance was observed for having received vasopressor, anticoagulant, anti-inflammatory, or COVID-19 (remdesivir) therapy, or for acute stroke or all-cause mortality in the hospital.

Table 2. Patient outcomes and clinical course during hospitalization; comparison of patients with and without CKD.

	All Patients (% Total)	CKD (% All CKD)	No CKD (% All Non-CKD)	*p*-Value
ICU *	113 (36.7)	57 (48.7)	56 (29.3)	<0.001
Ventilation	71 (22.8)	35 (29.9)	36 (18.6)	0.021
Vasopressors	42 (14.0)	17 (15.0)	25 (13.4)	0.685
Anticoagulants	236 (76.1)	88 (75.2)	148 (76.7)	0.768
Anti-inflammatory	161 (52.8)	58 (51.3)	103 (53.6)	0.695
Remdesevir	54 (17.7)	20 (18.0)	34 (17.5)	0.914
Palliative care consult	14 (4.6)	9 (8.0)	5 (2.6)	0.029
Acute stroke	10 (3.3)	2 (1.8)	8 (4.2)	0.278
Sepsis	60 (19.4)	32 (27.8)	28 (14.4)	0.004
Dialysis at any point	49 (15.9)	42 (36.8)	7 (3.6)	<0.001
Death in the hospital	38 (12.1)	18 (15.1)	20 (10.3)	0.199

* ICU = intensive care unit.

Unadjusted and adjusted odds ratios for the entire cohort (n = 327) are shown in Table 3 for the primary and secondary outcomes, death in the hospital and ICU admission, respectively, based on the exposure to medications typically used to treat hypertension, other CVDs, and CKD. Regarding the primary outcome, the use of ACEi, ARBs, combination of ACEi/ARB with CCB, diuretics, vasodilators, steroids, beta blockers, or statins was not significantly associated with all-cause in-hospital mortality in neither unadjusted nor adjusted models. The risk of death was increased two-fold with the use of CCB alone (OR = 2.064, 95% CI [1.048–4.063], p = 0.036) only in the unadjusted analysis. After adjusting for confounders (age, sex, race, other chronic medications, comorbidities, and COVID-19 therapeutics (remdesivir)) this association was no longer present (OR = 1.756, 95% CI [0.384–8.019], p = 0.468). On univariate analyses for comorbidities, heart failure was significantly associated with an increased risk of all-cause in-hospital mortality (OR = 3.478, 95% CI [1.706–7.091], p < 0.001). Likewise, COPD was significantly associated with an increased risk of all-cause mortality (OR = 3.864, 95% CI [1.904–7.840], p < 0.001). These associations were maintained in the fully adjusted model (OR = 4.088, 95% CI [1.1661–14.387], p = 0.028 for heart failure, and OR = 3.747, 95% CI [1.591–8.828], p = 0.003 for COPD).

Regarding the secondary outcome, no significant risk was observed for the use of ACEi, ARB, ACEi/ARB, ACEi/ARB and CCB, CCB alone, MR, diuretic, sympatholytic, or steroids in the unadjusted model. However, increased risk of ICU admission was significantly associated in the unadjusted model with the use of vasodilators (OR = 2.485, 95% CI [1.276–4.840], p = 0.007), beta blockers (OR = 1.623, 95% CI [1.013–2.600], p = 0.044) and statins (OR = 2.275, 95% CI [1.417–3.654], p < 0.001). After adjusting for age, sex, race, chronic medications, comorbidities, and COVID-19 therapeutics, significant associations with the use of vasodilators and beta blockers were no longer observed, and only the use of statins remained statistically significant (OR = 3.559, 95% CI [1.763–7.184], p < 0.001). Additionally, in the fully adjusted model, a protective effect of ACEi alone, but not in combination with ARB or CCB, for ICU admission was revealed (OR = 0.400, 95% CI [0.183–0.874], p = 0.022). In terms of comorbidities, admission to the ICU was significantly associated in unadjusted analyses with having CKD (OR = 2.290, 95% CI [1.420–3.694], p < 0.001), diabetes (OR = 1.675, 95% CI [1.047–2.680], p = 0.032), heart failure (OR = 1.953, 95% CI [1.096–3.479], p = 0.023), and COPD (OR = 2.880, 95% CI [1.632–5.110], p < 0.001). After adjustment for demographics, medications, and COVID-19 therapeutics, the associations with CKD, diabetes, and heart failure were no longer significant. The risk of ICU admission remained significantly associated with COPD (OR = 3.074, 95% CI [1.429–6.614], p = 0.004) in the fully adjusted model.

Table 3. Primary and secondary outcomes in all patients with regards to medication exposure and comorbidities.

	Unadjusted			Adjusted		
	OR	**(95% CI)**	***p*-Value**	**OR**	**(95% CI)**	***p*-Value**
All-cause in-hospital mortality						
ACEi * vs. no	1.179	0.557–2.492	0.667	0.721	0.144–3.618	0.691
ARB * vs. no	0.478	0.141–1.624	0.237	0.700	0.118–4.160	0.695
ACEi/ARB vs. no	0.858	0.427–1.723	0.667	0.815	0.350–1.900	0.636
CCB * vs. no	**2.064**	**1.048–4.063**	**0.036**	1.756	0.384–8.019	0.468
ACEi/ARB and CCB vs. none	1.680	0.817–3.454	0.158	0.854	0.132–5.503	0.868
diuretic vs. no	1.587	0.791–3.183	0.194	1.212	0.468–3.137	0.692
vasodilator vs. no	0.921	0.339–2.502	0.872	0.284	0.059–1.375	0.118
steroids vs. no	2.606	0.966–7.031	0.059	2.060	0.449–9.447	0.352
beta blockers vs. no	1.741	0.888–3.414	0.107	2.104	0.759–5.832	0.153
statin vs. no	1.371	0.698–2.695	0.359	1.414	0.518–3.860	0.499
CKD *	1.559	0.788–3.085	0.202	1.509	0.655–3.478	0.334
Hypertension	0.989	0.118–8.260	0.992	0.815	0.062–10.694	0.876
Diabetes	1.069	0.546–2.095	0.845	0.936	0.422–2.076	0.871
Heart Failure	**3.478**	**1.706–7.091**	**<0.001**	**4.088**	**1.161–14.387**	**0.028**
COPD *	**3.864**	**1.904–7.840**	**<0.001**	**3.747**	**1.591–8.828**	**0.003**
	Unadjusted			**Adjusted**		
	OR	**(95% CI)**	***p*-Value**	**OR**	**(95% CI)**	***p*-Value**
ICU admission						
ACEi vs. no	0.771	0.450–1.322	0.345	**0.400**	**0.183–0.874**	**0.022**
ARB vs. no	1.300	0.684–2.472	0.424	1.594	0.680–3.738	0.284
ACEi/ARB vs. no	0.904	0.563–1.450	0.674	0.736	0.408–1.327	0.308
CCB vs. no	1.414	0.871–2.296	0.161	1.062	0.556–2.028	0.856
ACEi/ARB and CCB vs. none	1.107	0.690–1.776	0.674	0.526	0.142–1.939	0.334
diuretic vs. no	1.486	0.903–2.448	0.119	1.514	0.762–3.008	0.236
vasodilator vs. no	**2.485**	**1.276–4.840**	**0.007**	1.352	0.492–3.714	0.559
steroids vs. no	1.466	0.612–3.511	0.390	1.167	0.348–3.911	0.803
beta blockers vs. no	**1.623**	**1.013–2.600**	**0.044**	1.315	0.653–2.651	0.443
statin vs. no	**2.275**	**1.417–3.654**	**<0.001**	**3.559**	**1.763–7.184**	**<0.001**
CKD	**2.290**	**1.420–3.694**	**<0.001**	1.414	0.706–2.831	0.328
Hypertension	0.341	0.080–1.453	0.146	0.361	0.051–2.559	0.308
Diabetes	1.675	1.047–2.680	0.032	1.141	0.612–2.127	0.678
Heart Failure	1.953	1.096–3.479	0.023	1.193	0.499–2.852	0.691
COPD	**2.880**	**1.623–5.110**	**<0.001**	**3.074**	**1.429–6.614**	**0.004**

* ACEi = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; statistically significant results are bolded for emphasis.

Table 4 contains unadjusted and adjusted odds ratios for factors associated with primary and secondary outcomes in patients with CKD (n = 130). In this sub-analysis regarding the primary outcome in the multivariate model, the use of vasodilators was found to be protective (OR = 0.046, 95% CI = [0.004–0.481], p = 0.010). Significant associations were found for heart failure and COPD in the univariate analysis (OR = 3.259, 95% CI [1.167–9.099], p = 0.024, and OR = 6.364, 95% CI = [2.191–18.490], $p < 0.001$, respectively). In the fully adjusted model, only COPD remained significant (OR = 12.115, 95% CI = [2.129–68.949], p = 0.005). Regarding the secondary outcome, statin use in CKD patients was found to pose a significant risk in both unadjusted and adjusted analyses (OR = 2.873, 95% CI, p = 0.009, and OR = 5.767, 95% CI = [1.621–20.516], p = 0.007, respectively). Diabetes was significantly associated with the secondary outcome (OR = 2.513, 95% CI = [1.142–5.531], p = 0.022), albeit only in the univariate model. CKD stage was not significantly associated with neither

the primary (OR = 0.453, 95% CI = [0.198–1.038], $p = 0.061$) nor the secondary outcomes (OR = 1.067, 95% CI = [0.728–1.563], $p = 0.740$).

Table 4. Primary and secondary outcomes in CKD patients with regards to medication exposure and comorbidities.

	Unadjusted			Adjusted		
	OR	**(95% CI)**	***p*-Value**	**OR**	**(95% CI)**	***p*-Value**
All-cause in-hospital mortality						
ACEi vs. no	1.558	0.498–4.878	0.447	1.226	0.192–56.994	0.830
ARB vs. no	0.271	0.034–2.172	0.219	0.144	0.005–3.970	0.252
ACEi/ARB vs. no	0.865	0.300–2.497	0.788	0.376	0.057–2.470	0.308
CCB vs. no	1.171	0.426–3.217	0.760	1.084	0.191–6.143	0.928
ACEi/ARB and CCB vs. none	1.851	0.613–5.586	0.275	2.850	0.394–20.634	0.300
diuretic vs. no	1.437	0.509–4.056	0.494	2.472	0.405–15.106	0.327
vasodilator vs. no	0.452	0.122–1.673	0.234	**0.046**	**0.004–0.481**	**0.010**
steroids vs. no	2.325	0.554–9.760	0.249	7.929	0.304–206.2	0.213
beta blockers vs. no	1.263	0.453–3.522	0.656	2.387	0.359–15.868	0.368
statin vs. no	1.705	0.564–5.152	0.344	2.130	0.309–14.664	0.443
Hypertension	0.885	0.097–8.056	0.914	0.475	0.020–11.377	0.646
Diabetes	0.723	0.262–1.992	0.530	**0.136**	**0.022–0.850**	**0.033**
Heart Failure	**3.259**	**1.167–9.099**	**0.024**	4.473	0.557–35.910	0.159
COPD	**6.364**	**2.191–18.490**	**<0.001**	**12.115**	**2.129–68.949**	**0.005**
	Unadjusted			**Adjusted**		
	OR (95% CI)		***p*-Value**	**OR**	**(95% CI)**	***p*-Value**
ICU admission						
ACEi * vs. no	0.717	0.298–1.729	0.459	0.510	0.151–1.729	0.280
ARB * vs. no	1.064	0.406–2.786	0.900	1.563	0.418–5.842	0.507
ACEi/ARB vs. no	0.757	0.358–1.599	0.465	1.174	0.362–3.809	0.789
CCB * vs. no	0.822	0.393–1.720	0.603	0.588	0.197–1.756	0.341
ACEi/ARB and CCB vs. none	0.739	0.348–1.571	0.432	0.391	0.095–1.609	0.193
diuretic vs. no	1.361	0.630–2.943	0.433	1.464	0.472–4.541	0.509
vasodilator vs. no	1.516	0.669–3.438	0.319	1.417	0.457–4.393	0.545
steroids vs. no	1.346	0.343–5.286	0.670	0.938	0.153–5.768	0.945
beta blockers vs. no	0.852	0.410–1.770	0.667	0.856	0.300–2.438	0.770
statin vs. no	**2.873**	**1.307–6.315**	**0.009**	**5.767**	**1.621–20.516**	**0.007**
Hypertension	0.457	0.080–2.597	0.377	0.157	0.016–1.534	0.111
Diabetes	**2.513**	**1.142–5.531**	**0.022**	2.219	0.786–6.262	0.132
Heart Failure	0.917	0.418–2.013	0.829	0.533	0.181–1.565	0.252
COPD *	1.846	0.794–4.293	0.154	2.568	0.831–7.935	0.101

* ACEi = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; statistically significant results are bolded for emphasis.

4. Discussion

This retrospective study conducted at our tertiary care hospital in mostly Black patients hospitalized with SARS-CoV-2 infection showed that a less severe COVID-19 course, as indicated by a lower risk of ICU admission, was observed for patients who were on ACEi, irrespective of their CKD status, and after adjustment for patient demographics and covariates. The use of CCBs alone in unadjusted analyses was associated with an increased risk of all-cause mortality. However, this significance was lost once the model was adjusted for patient demographics, other medications, comorbidities, and COVID-19 therapeutics. CKD patients were more likely to have been admitted to the ICU and have required ventilation, dialysis, and palliative care consult. However, after adjusting for patient demographics, medications used to treat CVD and CKD, and remdesivir use, the association of CKD with a more severe COVID-19 clinical course lost significance.

It is becoming increasingly apparent that the suggestion of poorer COVID-19 outcomes in patients on RAAS blockers early in the pandemic has not been substantiated to date. In fact, a prospective, parallel-group, randomized, controlled, open-label trial found no negative associations between RAAS blocker usage and the clinical course of COVID-19 and suggested a potential for a faster and better recovery from SARS-CoV-2 infection with RAAS blocker usage [27]. In addition to this potential beneficial effect of RAAS inhibitors on recovery, a prospective cohort study of 8.28 million people found protective effects on infection rates in individuals on ACEi/ARB [16]. The same study also found that ARBs were less protective in Black individuals compared to White. Indeed, we found that in our mostly Black cohort, ACEi but not ARB, was significantly associated with a milder course of the disease, as indicated by a lower need for ICU admission. Multiple studies worldwide have been conducted showing that ACEi/ARB use was neither associated with an increased risk of infection [17,18,28] nor with more severe clinical outcomes [18,28,29]. Other studies point to the potential reduction in risk of death in patients who were on ACEi/ARB prior to SARS-CoV-2 infection [19] as well as in those who received in-hospital ACEi/ARB [20,21]. All of the previously published studies, however, were not designed to evaluate the potential difference in the CKD patient population that was also on ACEi/ARB and CCBs. Moreover, a recently published systematic review and meta-analysis underlined that most of the studies on RAAS inhibitors in COVID-19 outcomes had a critical risk of bias, and in fact, only two of them [8,30] met the criteria of the absence of critical bias that was relevant to this meta-analysis [31]. Moreover, in both of these studies, only patients with uncomplicated hypertension were considered, eliminating pre-existing conditions, such as cardiovascular diseases and CKD [8,30]. Our study, albeit observational, addresses this void in the literature and adds to the body of data on COVID-19 outcomes in a predominantly Black cohort with comorbid CKD and CVD who were on different classes of medications used to treat these diseases.

In our unadjusted analyses, we identified CCB as being associated with an increased risk of all-cause mortality. However, after adjusting for confounders, including race, this significance was no longer present. Additionally, ACEi/ARB in combination with CCB was not found to be associated with either all-cause mortality or the severity of the COVID-19 clinical course. One recently published study in a population similar to ours (albeit without CKD) reported that ACEi/ARB and CCB therapy in combination, but not CCB alone, was associated with improvement in ICU admissions [32]. Previous studies investigating CCB associations with similar outcomes have found mild benefits [20,21,33,34]; however, these were all associated with limitations such as a small sample size (i.e., less than 25) or a lack of adjustment for race as a confounder. A recently concluded multicenter, international clinical trial, the Recovery-SIRIO (NCT04351763) study, found that neither amiodarone nor verapamil significantly accelerated short-term clinical improvement [35], which is in agreement with our data.

Studies completed in Europe in Spanish [36] and Italian [37] cohorts, as well as in the United States in Hispanic-only cohorts [38], showed a reduction in mortality with previous use of statins in COVID-19 patients. However, in the study on American veterans made up of predominantly White individuals, the use of statins alone was not associated with reduced mortality [39]. Rather, the combination use of metformin with statins as well as ACEi with statins was associated with a decreased 30-day mortality risk. Likewise, the INSPIRATION/INSPIRATION-S multicenter, randomized controlled trial found no association between atorvastatin and all-cause mortality [40]. In all of these studies, the Black race was underrepresented. On the other hand, in the present investigation, we found that statin use was associated with an increased risk of ICU admission in our mostly Black cohort. Another study conducted in Tehran found that, on univariate analysis, the use of statins was significantly associated with mortality rate, ICU admission, and length of hospitalization [41]. A study previously conducted at our hospital (Detroit Medical Center) found that statins were associated with reduced mortality in their COVID-19 cohort, consisting of mostly Black individuals, while they found no difference in ICU admission [42].

Their study, however, used multivariate logistic regression models that did not adjust for other medications that we did consider as confounders (CVD and CKD medications), and they only considered statins. Additionally, their cohort was bigger (n = 1014 vs. n = 327 in ours) and contained 11.2% CKD patients, whereas ours was comprised of 40% CKD patients. These may all be important factors driving the differences in observed outcomes. Nevertheless, given that our study is observational in nature, the possibility of unknown confounders cannot be excluded, attributable to the observed association of statins with a higher risk of ICU admission.

Limitations to our study include the observational nature and the sample size. Additionally, we also recognize that between July and October of 2020, which is the time span of our admitted patients, the predominant SARS-CoV-2 variants were B.1.1.7 (alpha), B.1.351 (beta), and P.1 (gamma) [43]. Since then, other variants of concern have emerged with significant substitutions/deletions in the spike protein [43]. It is unclear whether these differences contribute to COVID-19 outcomes as a function of the variables we included in our current analysis. Therefore, the applicability of our data to all other and current variants may be limited. Nevertheless, our data contribute significantly to the body of literature regarding the risks associated with the medications for CVD and CKD and co-morbidities in Black individuals and may inform more targeted treatment for those with COVID-19.

5. Conclusions

In this retrospective observational analysis of 327 patients, the majority of whom were of Black race, we found significant associations between ACEi use and reduced COVID-19 disease severity as assessed by ICU admission. Additionally, we also found significant associations between statin use and increased ICU admissions in the entire cohort as well as in the subpopulation of CKD patients. We did not find in our fully adjusted model that patients with CKD had poorer outcomes compared with patients without CKD. Comorbidities found to be significantly associated with all-cause in-hospital mortality were heart failure and COPD, whereas the latter was found to be additionally associated with ICU admissions. Our study underlines that individuals who present with COVID-19 and who also have CKD and CVD, particularly those of Black race, may necessitate a more prudent crafting of therapeutic regimens to treat these and other comorbid conditions.

Author Contributions: Conceptualization, D.K.; methodology, D.K.; formal analysis, D.K.; data curation, P.K. (Paul Kim), V.N., M.A., K.F., Z.G., P.K. (Priyanka Kale), Z.K., S.K., D.L., M.M., P.P., L.S., C.T., S.W., S.D. and D.K.; writing—original draft preparation, D.K.; writing—review and editing, P.K. (Paul Kim), V.N., M.A., K.F., Z.G., P.K. (Priyanka Kale), Z.K., S.K., D.L., M.M., P.P., L.S., C.T., S.W., S.D. and D.K; supervision, D.K.; funding acquisition, D.K. All authors have read and agreed to the published version of the manuscript.

Funding: The APC was funded by the National Institutes of Health, National Heart, Lung and Blood Institute, HL-163844.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Wayne State University (IRB # 21-05-3579 approved on 22 June 2021) and the Detroit Medical Center (Study # 19717).

Informed Consent Statement: Patient consent/HIPPA authorization was waived due to the nature of the study being a retrospective medical record review. All patient identifiers were removed.

Data Availability Statement: Details regarding where data supporting reported results can be made available upon request to the corresponding author (D.K.).

Acknowledgments: We acknowledge Samah Suleiman for assisting in the preparation of the IRB form.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. WHO. WHO Coronavirus Disease (COVID-19) Dashboard. 2020. Available online: https://covid19.who.int/ (accessed on 20 March 2023).
2. Singh, J.; Malik, P.; Patel, N.; Pothuru, S.; Israni, A.; Chakinala, R.C.; Hussain, M.R.; Chidharla, A.; Patel, H.; Patel, S.K.; et al. Kidney disease and COVID-19 disease severity—Systematic review and meta-analysis. *Clin. Exp. Med.* **2021**, *22*, 125–135. [CrossRef] [PubMed]
3. Pecly, I.M.D.; Azevedo, R.B.; Muxfeldt, E.S.; Botelho, B.G.; Albuquerque, G.G.; Diniz, P.H.P.; Silva, R.; Rodrigues, C.I.S. COVID-19 and chronic kidney disease: A comprehensive review. *Braz. J. Nephrol.* **2021**, *43*, 383–399. [CrossRef] [PubMed]
4. Jdiaa, S.S.; Mansour, R.; El Alayli, A.; Gautam, A.; Thomas, P.; Mustafa, R.A. COVID–19 and chronic kidney disease: An updated overview of reviews. *J. Nephrol.* **2022**, *35*, 69–85. [CrossRef] [PubMed]
5. Lambourg, E.J.; Gallacher, P.J.; Hunter, R.W.; Siddiqui, M.; Miller-Hodges, E.; Chalmers, J.D.; Pugh, D.; Dhaun, N.; Bell, S. Cardiovascular outcomes in patients with chronic kidney disease and COVID-19: A multi-regional data-linkage study. *Eur. Respir. J.* **2022**, *60*, 2103168. [CrossRef] [PubMed]
6. Fang, L.; Karakiulakis, G.; Roth, M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infec-tion? *Lancet Respir. Med.* **2020**, *8*, e21. [CrossRef]
7. Wysocki, J.; Lores, E.; Ye, M.; Soler, M.J.; Batlle, D. Kidney and Lung ACE2 Expression after an ACE Inhibitor or an Ang II Receptor Blocker: Implications for COVID-19. *J. Am. Soc. Nephrol.* **2020**, *31*, 1941–1943. [CrossRef]
8. Semenzato, L.; Botton, J.; Drouin, J.; Baricault, B.; Vabre, C.; Cuenot, F.; Penso, L.; Herlemont, P.; Sbidian, E.; Weill, A.; et al. Antihypertensive Drugs and COVID-19 Risk: A Cohort Study of 2 Million Hypertensive Patients. *Hypertension* **2021**, *77*, 833–842. [CrossRef]
9. Nouri-Vaskeh, M.; Kalami, N.; Zand, R.; Soroureddin, Z.; Varshochi, M.; Ansarin, K.; Rezaee, H.; Taghizadieh, A.; Sadeghi, A.; Ahangari Maleki, M.; et al. Comparison of losartan and amlodipine effects on the outcomes of patient with COVID-19 and primary hyper-tension: A randomised clinical trial. *Int. J. Clin. Pract.* **2021**, *75*, e14124. [CrossRef]
10. Nakhaie, S.; Yazdani, R.; Shakibi, M.; Torabian, S.; Pezeshki, S.; Bazrafshani, M.S.; Azimi, M.; Salajegheh, F. The effects of antihypertensive medications on severity and outcomes of hypertensive patients with COVID-19. *J. Hum. Hypertens.* **2022**, 1–8. [CrossRef]
11. Cohen, J.B.; Hanff, T.C.; William, P.; Sweitzer, N.; Rosado-Santander, N.R.; Medina, C.; Rodriguez-Mori, J.E.; Renna, N.; Chang, T.I.; Corrales-Medina, V.; et al. Continuation versus discontinuation of renin-angiotensin system inhibitors in patients admitted to hospital with COVID-19: A prospective, randomised, open-label trial. *Lancet Respir. Med.* **2021**, *9*, 275–284. [CrossRef]
12. Alsagaff, M.Y.; Mulia, E.P.B.; Maghfirah, I.; Luke, K.; Nugraha, D.; Rachmi, D.A.; Septianda, I.; A'Yun, M.Q. Association of calcium channel blocker use with clinical outcome of COVID-19: A meta-analysis. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2021**, *15*, 102210. [CrossRef] [PubMed]
13. Fosbøl, E.L.; Butt, J.H.; Østergaard, L.; Andersson, C.; Selmer, C.; Kragholm, K.; Schou, M.; Phelps, M.D.; Gislason, G.H.; Gerds, T.A.; et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With COVID-19 Diagnosis and Mortality. *JAMA* **2020**, *324*, 168–177. [CrossRef] [PubMed]
14. Mancia, G.; Rea, F.; Ludergnani, M.; Apolone, G.; Corrao, G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N. Engl. J. Med.* **2020**, *382*, 2431–2440. [CrossRef]
15. Liu, X.; Long, C.; Xiong, Q.; Chen, C.; Ma, J.; Su, Y.; Hong, K. Association of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with risk of COVID-19, in-flammation level, severity, and death in patients with COVID-19: A rapid systematic review and meta-analysis. *Clin. Cardiol.* **2020**, *126*, 1671–1681.
16. Hippisley-Cox, J.; Young, D.; Coupland, C.; Channon, K.M.; San Tan, P.; Harrison, D.A.; Rowan, K.; Aveyard, P.; Pavord, I.D.; Watkinson, P.J. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: Cohort study includ-ing 8.3 million people. *Heart* **2020**, *106*, 1503–1511. [CrossRef] [PubMed]
17. An, J.; Wei, R.; Zhou, H.; Luong, T.Q.; Gould, M.K.; Mefford, M.T.; Harrison, T.N.; Creekmur, B.; Lee, M.; Sim, J.J.; et al. Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers Use and COVID-19 Infection Among 824,650 Patients With Hypertension From a US Integrat ed Healthcare System. *J. Am. Heart Assoc.* **2021**, *10*, e017773. [CrossRef] [PubMed]
18. Morales, D.R.; Conover, M.M.; Chan You, S.; Pratt, N.; Kostka, K.; Duarte-Salles, T.; Fernández-Bertolín, S.; Aragón, M.; DuVall, S.L.; Lynch, K.; et al. Renin-angiotensin system blockers and susceptibility to COVID-19: An international, open science, cohort analy-sis. *Lancet Digit. Health* **2021**, *3*, e98–e114. [CrossRef]
19. Bean, D.M.; Kraljevic, Z.; Searle, T.; Bendayan, R.; O'Gallagher, K.; Pickles, A.; Folarin, A.; Roguski, L.; Noor, K.; Shek, A.; et al. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are not associated with severe COVID-19 infection in a multi-site UK acute hospital trust. *Eur. J. Heart Fail.* **2020**, *22*, 967–974. [CrossRef]
20. Zhang, P.; Zhu, L.; Cai, J.; Lei, F.; Qin, J.-J.; Xie, J.; Liu, Y.-M.; Zhao, Y.-C.; Huang, X.; Lin, L.; et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized with COVID-19. *Circ. Res.* **2020**, *126*, 1671–1681. [CrossRef]
21. Yan, F.; Huang, F.; Xu, J.; Yang, P.; Qin, Y.; Lv, J.; Zhang, S.; Ye, L.; Gong, M.; Liu, Z.; et al. Antihypertensive drugs are associated with reduced fatal outcomes and improved clinical characteristics in elderly COVID-19 patients. *Cell Discov.* **2020**, *6*, 77. [CrossRef]
22. Shah, P.; Owens, J.; Franklin, J.; Jani, Y.; Kumar, A.; Doshi, R. Baseline use of angiotensin-converting enzyme inhibitor/AT1 blocker and outcomes in hospitalized coronavirus disease 2019 African-American patients. *J. Hypertens.* **2020**, *38*, 2537–2541. [CrossRef] [PubMed]

23. Filev, R.; Rostaing, L.M.; Lyubomirova, M.M.; Bogov, B.M.; Kalinov, K.; Svinarov, D.M. Renin-angiotensin-aldosterone system blockers in Bulgarian COVID-19 patients with or without chronic kidney disease. *Medicine* **2022**, *101*, e31988. [CrossRef] [PubMed]
24. Harris, P.A.; Taylor, R.; Thielke, R.; Payne, J.; Gonzalez, N.; Conde, J.G. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* **2009**, *42*, 377–381. [CrossRef] [PubMed]
25. Harris, P.A.; Taylor, R.; Minor, B.L.; Elliott, V.; Fernandez, M.; O'Neal, L.; McLeod, L.; Delacqua, G.; Delacqua, F.; Kirby, J.; et al. The REDCap consortium: Building an international community of software platform partners. *J. Biomed. Inform.* **2019**, *95*, 103208. [CrossRef]
26. Unger, T.; Borghi, C.; Charchar, F.; Khan, N.A.; Poulter, N.R.; Prabhakaran, D.; Ramirez, A.; Schlaich, M.; Stergiou, G.S.; Tomaszewski, M.; et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J. Hypertens.* **2020**, *38*, 982–1004. [CrossRef] [PubMed]
27. Bauer, A.; Schreinlechner, M.; Sappler, N.; Dolejsi, T.; Tilg, H.; Aulinger, B.A.; Weiss, G.; Bellmann-Weiler, R.; Adolf, C.; Wolf, D.; et al. Discontinuation versus continuation of renin-angiotensin-system inhibitors in COVID-19 (ACEI-COVID): A prospec-tive, parallel group, randomised, controlled, open-label trial. *Lancet Respir. Med.* **2021**, *9*, 863–872. [CrossRef] [PubMed]
28. Christiansen, C.F.; Pottegård, A.; Heide-Jørgensen, U.; Bodilsen, J.; Søgaard, O.S.; Maeng, M.; Vistisen, S.T.; Schmidt, M.; Lund, L.C.; Reilev, M.; et al. SARS-CoV-2 infection and adverse outcomes in users of ACE inhibitors and angiotensin-receptor blockers: A nationwide case-control and cohort analysis. *Thorax* **2021**, *76*, 370–379. [CrossRef]
29. Lopes, R.D.; Macedo, A.V.; Silva, P.G.; Moll-Bernardes, R.J.; Dos Santos, T.M.; Mazza, L.; Feldman, A.; Arruda, G.D.; de Albuquerque, D.C.; Camiletti, A.S.; et al. Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted with COVID-19: A Randomized Clinical Trial. *JAMA* **2021**, *325*, 254–264. [CrossRef]
30. Loader, J.; Lampa, E.; Gustafsson, S.; Cars, T.; Sundström, J. Renin-Angiotensin Aldosterone System Inhibitors in Primary Prevention and COVID-19. *J. Am. Heart Assoc.* **2021**, *10*, e021154. [CrossRef]
31. Loader, J.; Taylor, F.C.; Erik Lampa, E.; Sundström, J. Renin-Angiotensin Aldosterone System Inhibitors and COVID-19: A Systematic Review and Meta-Analysis Reveal-ing Critical Bias Across a Body of Observational Research. *J. Am. Heart Assoc.* **2022**, *11*, e025289. [CrossRef]
32. Choksi, T.T.; Zhang, H.; Chen, T.; Malhotra, N. Outcomes of Hospitalized COVID-19 Patients Receiving Renin Angiotensin System Blockers and Calcium Channel Blockers. *Am. J. Nephrol.* **2021**, *52*, 250–260. [CrossRef] [PubMed]
33. Neuraz, A.; Lerner, I.; Digan, W.; Paris, N.; Tsopra, R.; Rogier, A.; Baudoin, D.; Cohen, K.B.; Burgun, A.; Garcelon, N.; et al. Natural Language Processing for Rapid Response to Emergent Diseases: Case Study of Calcium Channel Blockers and Hypertension in the COVID-19 Pandemic. *J. Med. Internet Res.* **2020**, *22*, e20773. [CrossRef] [PubMed]
34. Solaimanzadeh, I. Nifedipine and Amlodipine Are Associated With Improved Mortality and Decreased Risk for Intubation and Me-chanical Ventilation in Elderly Patients Hospitalized for COVID-19. *Cureus J. Med. Sci.* **2020**, *12*, e8069.
35. Navarese, E.P.; Podhajski, P.; Andreotti, F.; La Torre, G.; Gajda, R.; Radziwanowski, A.; Nowicka, M.; Bukowski, P.; Gajda, J.; Omyła, M.; et al. Ion channel inhibition with amiodarone or verapamil in symptomatic hospitalized nonintensive-care COVID-19 patients: The ReCOVery-SIRIO randomized trial. *Cardiol. J.* **2022**, *29*, 739–750. [CrossRef] [PubMed]
36. Barge-Caballero, E.; Marcos-Rodríguez, P.J.; Domenech-García, N.; Bou-Arévalo, G.; Cid-Fernández, J.; Iglesias-Reinoso, R.; López-Vázquez, P.; Muñiz, J.; Vázquez-Rodríguez, J.M.; Crespo-Leiro, M.G. Survival impact of previous statin therapy in patients hospitalized with COVID-19. *Med. Clin Engl. Ed.* **2023**, *160*, 1–9. [CrossRef]
37. Antonazzo, I.C.; Fornari, C.; Rozza, D.; Conti, S.; Di Pasquale, R.; Cortesi, P.A.; Kaleci, S.; Ferrara, P.; Zucchi, A.; Maifredi, G.; et al. Statins Use in Patients with Cardiovascular Diseases and COVID-19 Outcomes: An Italian Population-Based Cohort Study. *J. Clin. Med.* **2022**, *11*, 7492. [CrossRef]
38. Khalafi, S.; Evans, J.; Lumbreras, T.; Tiula, K.; Helmsdoerfer, K.; Dwivedi, A.K.; Dihowm, F. Effects of Statins on Outcomes in Hispanic Patients with COVID-19. *J. Investig. Med.* **2022**, *70*, 1697–1703. [CrossRef]
39. Hunt, C.M.; Efird, J.T.; Redding, I.V.T.S.; Thompson, A.D., Jr.; Press, A.M.; Williams, C.D.; Hostler, C.J.; Suzuki, A. Medications Associated with Lower Mortality in a SARS-CoV-2 Positive Cohort of 26,508 Veterans. *J. Gen. Intern. Med.* **2022**, *37*, 4144–4152. [CrossRef]
40. Investigators, I.-S. Atorvastatin versus placebo in patients with covid-19 in intensive care: Randomized controlled trial. *BMJ* **2022**, *376*, e068407.
41. Nateghi, S.; Gomari, M.M.; Hosamirudsari, H.; Behnoush, B.; Razmjoofard, A.; Azimi, G.; Ordookhani, S.; Jafarpour, A.; Faraji, N. A historical cohort study to investigation of statins safety in COVID-19 hospitalized patients. *Therapies* **2021**, *77*, 453–460. [CrossRef]
42. Lohia, P.; Kapur, S.; Benjaram, S.; Mir, T. Association between antecedent statin use and severe disease outcomes in COVID-19: A retrospective study with pro-pensity score matching. *J. Clin. Lipidol.* **2021**, *15*, 451–459. [CrossRef] [PubMed]
43. CDC. SARS-CoV2 Variant Classification. Available online: https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html (accessed on 13 January 2023).