FEATURED ARTICLE

Clinical outcomes of COVID-19 infection among patients with Alzheimer's disease or mild cognitive impairment

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Abstract

Introduction: Alzheimer's disease (AD) and COVID-19 share common risk factors including hypertension. Angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are frequently prescribed antihypertension medications.

Methods: This study analyzed 436,823 veterans tested for SARS-CoV-2 infection. We conducted both classical and propensity score weighted logistic models to compare COVID-19 outcomes between patients with AD or mild cognitive impairment (MCI) to those without cognitive impairment, and examined effect of ACEI/ARB prescription.

Results: There was a statistically significant association between AD and increased odds of infection and mortality. MCI was not found to be a risk factor for infection. Subjects with MCI exhibited poor clinical outcomes. Prescribing ARBs but not ACEIs was significantly associated with a lower risk of COVID-19 occurrence among AD and MCI patients.

Discussion: Exploring beneficial effects of existing medications to reduce the impact of COVID-19 on patients with AD or MCI is highly significant.

KEYWORDS
Alzheimer's disease, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, COVID-19, mild cognitive impairment, severe acute respiratory syndrome coronavirus 2

Highlights

- There is significant association between Alzheimer's disease (AD) and increased risk of COVID-19 infection and odds of mortality.
- Subjects with mild cognitive impairment (MCI) defined by claims data exhibit poor clinical outcomes, but MCI was not found to be a risk factor for severe acute respiratory syndrome coronavirus 2 infection.
- Prescribing angiotensin II receptor blockers was significantly associated with a lower risk of COVID-19 occurrence among AD/MCI patients.

1 | BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the original COVID-19 pandemic, causes a wide spectrum of symptoms with central nervous system (CNS) complications involving confusion and delirium.[1] A few cases have revealed direct SARS-CoV-2 viral infection in the brain;[2] SARS-CoV-2 has been postulated as a virus with high neuroinvasive potential and may penetrate the blood brain barrier (BBB).[3] In addition, growing evidence suggests a bidirectional relationship between CNS pathology and COVID-19.[4] Previous reports indicate that COVID-19 patients had >50% probability to have memory issues at 7 months after infection.[5,6]

Comparing 26 COVID-19–positive Alzheimer's disease (AD) patients to 58 COVID-19–negative AD patients in the UK Biobank database reveals that pre-existing diagnosis of AD predicts higher risk of COVID-19 and mortality among elderly individuals.[7] Thus, it is critical to explore any association between COVID-19 and AD as well as mild cognitive impairment (MCI).

AD is a degenerative disease characterized by neuritic plaques and neurofibrillary tangles in the brain, accompanied by chronic brain inflammation and a compromised BBB,[8] which potentially predisposes AD patients to SARS-CoV-2 infection and severe CNS complications. The fact that COVID-19 and AD have a series of common risk factors like age, hypertension, diabetes, cardiovascular disease,[9,10] and the presence of the apolipoprotein E (*APOE*) ε4 allele,[11,12] predisposes patients with AD to more likely infection by the SARS-CoV-2 virus.[11,13] Recent studies showed an increase of SARS-CoV-2 infection in *APOE* ε4-expressing neurons and astrocytes in vitro.[11,13] For severity, it has been postulated that the increased viral load and cytokine storm observed in COVID-19 patients elevate the levels of proinflammatory cytokines/chemokines in the brain and increase mortality.[14] Currently there is no report on occurrence of COVID-19 among patients with MCI.

SARS-CoV-2 invades host cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in various human organs. The expression of ACE2 was found in neurons and non-neuron cells (mainly astrocytes and oligodendrocytes) of the human brain.[15] Analysis of *post mortem* tissue showed that ACE2 expression is upregulated in the brain of AD patients compared to those from cognitively normal controls.[16] It is not clear whether patients with AD are more susceptible to COVID-19 infection due to an increase in ACE2 expression.

Electronic health records (EHR) of 61.9 million subjects were analyzed to examine the associations between COVID-19 and different types of dementia.[17] Patients with dementia were at increased risk for COVID-19 infection, where AD demonstrated a strong association with an unadjusted odds ratio (OR) of 1.86.[17] In this study, we investigated the association of AD with the risk of COVID-19 infection with covariate adjustments for comorbidities and other sociodemographic factors. Previously, we and others reported the beneficial effects of long-term use of antihypertension medications on the time to occurrence of a diagnosis of AD, including angiotensin II receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) in a number of epidemiological studies.[18–23] We further explore in this paper the associations of ARB and ACEI that are prescribed on the occurrence of COVID-19 among patients with AD or MCI.

2 | METHODS

2.1 | Study population

This retrospective case-control study included 436,823 adult patients (≥ 50 years old and < 90 years old) tested for SARS-CoV-2 nucleic acid real-time polymerase chain reaction (RT-PCR) test between February 28, 2020, and Nov 19, 2020 in the Department of Veterans Affairs (VA)

RESEARCH IN CONTEXT

1. Systematic Review: The authors extracted and analyzed 436,823 adult patients (≥ 50 and < 90 years of age) tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection between February 28, 2020, and November 19, 2020 in the Department of Veterans Affairs (VA) national health-care system. Similar studies describing the association between Alzheimer's disease (AD) and COVID-19 in different cohorts are discussed and cited.

2. Interpretation: Our results do not justify any potential changes in clinical practice. The association between AD and COVID-19 is consistent with the observation of high prevalence of symptoms with central nervous system (CNS) complications among COVID-19 patients, implicating neuropathological changes linked to viral infection.

3. Future Directions: The article proposes new directions for additional studies related to COVID-19 and AD: first, investigating molecular pathways involved in SARS-CoV-2-infection–triggered CNS responses and related cognitive impairment; second, exploring beneficial effects of existing medications to reduce the impact of COVID-19 on patients with AD or mild cognitive impairment (MCI); third, understanding the risk factors associated with AD and MCI to reduce occurrence and severe clinical outcomes of COVID-19.

national health-care system, including 5128 patients (1.2%) who were diagnosed with AD, and 431,695 non-AD subjects (Table 1).

The COVID-19 testing was administrated by VA and non-VA clinics and recorded in VA clinical notes. A total of 40,993 subjects (9.4%) showed positive COVID-19 test outcomes.

The analyses of the possible association of MCI and COVID-19 outcomes focused on a subgroup of the entire study population described above, which excluded the patients with AD. In these analyses, we compared the COVID-19 outcomes between patients with MCI but no AD diagnosis to those without cognitive impairment. Among 431,695 patients without AD diagnosis, there were 405,365 non-MCI subjects and 26,330 (7.7%) patients who had been diagnosed with MCI.

We obtained the data through the COVID-19 Shared Data Resource at the VA Informatics and Computing Infrastructure (VINCI) Resource Center. We extracted the patients who have been diagnosed with AD before their COVID-19 test according to their International Classification of Disease (ICD)[24] ICD-9 or ICD-10 codes between April 1, 2008, and November 25, 2020. We used ICD-9 code 331.0 and ICD-10 code G30.x to identify patients with possible AD, and ICD-9 code 331.83 and ICD-10 code G31.84 for MCI for at least one inpatient visit or two outpatient visits.[20] This study was approved by the Bedford VA Healthcare System Institutional Review Board, and all data were fully anonymized before access.

TABLE 1 Demographics and comorbidities of patients tested for COVID-19 negative or positive infection

		Total (N = 436,823)	AD (N = 5128)	Non-AD (N = 431,695)	MCI (N = 26,330)	Non-MCI (N = 405,365)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age at index date		67.93 (8.91)	77.25 (7.38)	67.82 (8.87)	71.15 (8.69)	67.61 (8.83)
CCI		2.73 (2.53)	3.97 (2.52)	2.71 (2.53)	3.64 (2.76)	2.65 (2.5)
		N (%)	N (%)	N (%)	N (%)	N (%)
Sex	Female	33,059 (7.6%)	158 (3.1%)	32,901 (7.6%)	1612 (6.1%)	31,289 (7.7%)
	Male	403,764 (92.4%)	4970 (96.9%)	398,794 (92.4%)	24,718 (93.9%)	374,076 (92.3%)
Race	White	301,282 (69.0%)	3794 (74.0%)	297,488 (68.9%)	19,015 (72.2%)	278,473 (68.7%)
	American Indian or Alaska Native	3,182 (0.7%)	36 (0.7%)	3,146 (0.7%)	193 (0.7%)	2,953 (0.7%)
	Asian	2,976 (0.7%)	19 (0.4%)	2,957 (0.7%)	148 (0.6%)	2,809 (0.7%)
	Black	103,541 (23.7%)	992 (19.3%)	102,549 (23.8%)	5542 (21.0%)	97,007 (23.9%)
	Native Hawaiian or Other Pacific Islander	3387 (0.8%)	40 (0.8%)	3347 (0.8%)	176 (0.7%)	3171 (0.8%)
	Unknown	22,455 (5.1%)	247 (4.8%)	22,208 (5.1%)	1256 (4.8%)	20,952 (5.2%)
Ethnicity	Not Hispanic or Latino	399,294 (91.4%)	4507 (87.9%)	394,787 (91.5%)	24,043 (91.3%)	370,744 (91.5%)
	Hispanic or Latino	28,813 (6.6%)	533 (10.4%)	28,280 (6.6%)	1829 (6.9%)	26,451 (6.5%)
	Unknown	8716 (2.0%)	88 (1.7%)	8,628 (2.0%)	458 (1.7%)	8170 (2.0%)
Nursing home stay	Yes	14,462 (3.3%)	1126 (22.0%)	13,336 (3.1%)	2174 (8.3%)	11,162 (2.8%)
	No	422,361 (96.7%)	4002 (78.0%)	418,359 (96.9%)	24,156 (91.7%)	394,203 (97.2%)
Diabetes	Yes	190,667 (43.6%)	2455 (47.9%)	188,212 (43.6%)	13,240 (50.3%)	174,972 (43.2%)
	No	246,156 (56.4%)	2673 (52.1%)	243,483 (56.4%)	13,090 (49.7%)	230,393 (56.8%)
Pulmonary disease	Yes	192,014 (44.0%)	2205 (43.0%)	189,809 (44.0%)	13,131 (49.9%)	176,678 (43.6%)
	No	244,809 (56.0%)	2923 (57.0%)	241,886 (56.0%)	13,199 (50.1%)	228,687 (56.4%)
Hypertension	Yes	332,750 (76.2%)	4107 (80.1%)	328,643 (76.1%)	21,315 (81.0%)	307,328 (75.8%)
	No	104,073 (23.8%)	1021 (19.9%)	103,052 (23.9%)	5015 (19.0%)	98,037 (24.2%)
Heart failure	Yes	67,798 (15.5%)	1083 (21.1%)	66,715 (15.5%)	5783 (22.0%)	60,932 (15.0%)
	No	369,025 (84.5%)	4045 (78.9%)	364,980 (84.5%)	20,547 (78.0%)	344,433 (85.0%)
Kidney disease	Yes	121,425 (27.8%)	1814 (35.4%)	119,611 (27.7%)	9285 (35.3%)	110,326 (27.2%)
	No	315,398 (72.2%)	3314 (64.6%)	312,084 (72.3%)	17,045 (64.7%)	295,039 (72.8%)
CAHD 2yrs	Yes	128,749 (29.5%)	1947 (38.0%)	126,802 (29.4%)	9947 (37.8%)	116,855 (28.8%)
	No	308,074 (70.5%)	3181 (62%)	304,893 (70.6%)	163,83 (62.2%)	288,510 (71.2%)
Chronic liver disease	Yes	19,927 (4.6%)	187 (3.6%)	19,740 (4.6%)	1422 (5.4%)	18,318 (4.5%)
	No	416,896 (95.4%)	4941 (96.4%)	411,955 (95.4%)	24,908 (94.6%)	387,047 (95.5%)
Hyperlipidemia	Yes	310,268 (71.0%)	3761 (73.3%)	306,507 (71.0%)	19,735 (75.0%)	286,772 (70.7%)
	No	126,555 (29%)	1367 (26.7%)	125,188 (29%)	6,595 (25%)	118,593 (29.3%)
HIV	Yes	5370 (1.2%)	19 (0.4%)	5351 (1.2%)	330 (1.3%)	5,021 (1.2%)
	No	431,453 (98.8%)	5109 (99.6%)	426,344 (98.8%)	26,000 (98.7%)	400,344 (98.8%)
Cancer	Yes	145,636 (33.3%)	1520 (29.6%)	144,116 (33.4%)	9394 (35.7%)	134,722 (33.2%)
	No	291,187 (66.7%)	3608 (70.4%)	287,579 (66.6%)	16,936 (64.3%)	270,643 (66.8%)
Smoke	Never smoker	137,060 (31.4%)	1662 (32.4%)	135,398 (31.4%)	8019 (30.5%)	127,379 (31.4%)
	Current smoker	86,261 (19.7%)	542 (10.6%)	85,719 (19.9%)	4377 (16.6%)	81,342 (20.1%)
	Former smoker	200,419 (45.9%)	2463 (48.0%)	197,956 (45.9%)	12,940 (49.1%)	185,016 (45.6%)
	Unknown	13,083 (3.0%)	461 (9.0%)	12,622 (2.9%)	994 (3.8%)	116,28 (2.9%)

(Continues)

TABLE 1 (Continued)

		N (%)	N (%)	N (%)	N (%)	N (%)
Stroke	Yes	38,692 (8.9%)	1022 (19.9%)	37,670 (8.7%)	5108 (19.4%)	32,562 (8.0%)
	No	398,131 (91.1%)	4106 (80.1%)	394,025 (91.3%)	21,222 (80.6%)	372,803 (92.0%)
Alcohol dependency	Yes	54,314 (12.4%)	482 (9.4%)	53,832 (12.5%)	3822 (14.5%)	50,010 (12.3%)
	No	382,509 (87.6%)	4646 (90.6%)	377,863 (87.5%)	22,508 (85.5%)	355,355 (87.7%)
Drug dependency	Yes	30,290 (6.9%)	183 (3.6%)	30,107 (7.0%)	2236 (8.5%)	27,871 (6.9%)
	No	406,533 (93.1%)	4945 (96.4%)	401,588 (93.0%)	24,094 (91.5%)	377,494 (93.1%)
BMI	Normal	106,726 (24.4%)	2313 (45.1%)	104,413 (24.2%)	7757 (29.5%)	96,656 (23.8%)
	Overweight	109,233 (25.0%)	1387 (27.0%)	107,846 (25.0%)	6766 (25.7%)	101,080 (24.9%)
	Obese	110,755 (25.4%)	895 (17.5%)	109,860 (25.4%)	6333 (24.1%)	103,527 (25.5%)
	Extremely obese	110,109 (25.2%)	533 (10.4%)	109,576 (25.4%)	5474 (20.8%)	104,102 (25.7%)

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; CAHD, coronary atherosclerotic heart disease; CCI, Charlson Comorbidity Index; HIV, human immunodeficiency virus; MCI, mild cognitive impairment; SD, standard deviation.

2.2 | Medications

We used the first COVID-19 test date as the index date. This date was approximated by the date of the hospital admission that is closest (within 15 days) to the first test date if the patients' first test date was not available. The medication prescribed before the index date was extracted from the database. The patients who used ACEI but did not use ARB were labeled as the ACEI only group. Similarly, those who were prescribed ARB but not ACEI were defined as the ARB only group. The patients who did not receive any ACEI or ARB prescriptions before the index date were considered the comparator group. This group included patients who used other antihypertension medications such as beta blockers, and patients who were not prescribed any antihypertension medications. We do not have access to blood pressure levels of our subjects. All patients who were recorded as prescribed both ACEI and ARB concomitantly were excluded, reducing the total 5128 AD patients (Table 1) to 5010 AD patients (Table 2).

2.3 | Outcomes

The primary dependent variable for this study was COVID-19 infection, which was defined by a positive nucleic acid RT-PCR test recorded in the database. An index date was created if a patient received a COVID-19 nucleic acid RT-PCR test.

The second dependent variable of the study was a nominal response composed of four categories: (1) alive and not hospitalized; (2) alive, hospitalized but not admitted to the intensive care unit (ICU) and not requiring mechanical ventilation; (3) alive and admitted to ICU or requiring mechanical ventilation; (4) mortality. Hospitalization, use of ICU or ventilator, and mortality were evaluated within 60 days of the index date. All four categories are mutually exclusive. If a patient had been admitted to the ICU, then died within 60 days of the index date, this patient was categorized as a mortality event.

2.4 | Covariate adjustments

Sociodemographic characteristics and clinical characteristics of the patient were listed including the Charlson Comorbidity Index (CCI; Table 1). Body mass index (BMI) distribution within our cohort (Figure S1 in supporting information) was divided into four categories: normal, overweight, obese, and extremely obese (Table 1). The relevant comorbidities and risk factors were defined based on ICD-10 codes from the 2-year period preceding the index date. The BMI and the CCI were measured or created at the index date. The status of nursing home stay was collected to limit the influence of a known confounder, that is, patients with AD are less likely to continue practicing good personal hygiene and common prevention routines, such as wearing a facial mask, washing hands regularly, and maintaining social distancing protocols.

2.5 | Statistical analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. Continuous variables were described in terms of means and standard deviations (SDs), and categorical variables were summarized as counts and percentages.

Due to the potential imbalance between AD versus non-AD groups and MCI versus non-MCI group on baseline covariates, we used propensity score weighting (PSW). This technique is commonly used in non-experimental studies to account for selection assignment differences between exposure and comparison groups.[25] The propensity score weights were estimated using demographic characteristics of the patients and their status of nursing home stay. We used the gradient boosting method (GBM) to compute a propensity score (PS) for each patient.

Multivariate logistic regressions with and without PSW were used to analyze the association between AD/MCI and COVID-19 infection, and the association of the ACEI/ARB prescriptions with

TABLE 2 Characteristics of ACEI/ARB use in AD patients tested for COVID-19 infection

		Total (N = 5010) (excluding ACEI+ARB)	No ACEINo ARB (N = 2564)	ACEI only (N = 1761)	ARB only (N = 685)
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
CCI		3.92 (2.5)	3.4 (2.32)	4.38 (2.54)	4.71 (2.59)
Age at index date		77.26 (7.4)	77.42 (7.61)	76.94 (7.28)	77.49 (6.83)
BMI	Normal	22.12 (2.42)	21.97 (2.43)	22.23 (2.42)	22.56 (2.31)
	Overweight	27.13 (1.08)	27.12 (1.05)	27.15 (1.12)	27.13 (1.06)
	Obese	31.06 (1.23)	30.97 (1.18)	31.13 (1.29)	31.14(1.24)
	Extremely obese	37.44 (4.5)	37.23 (5.16)	37.66 (4.18)	37.37 (3.83)
		N (%)	N (%)	N (%)	N (%)
Sex	Female	156 (3.1%)	79 (3.1%)	49 (2.8%)	28 (4.1%)
	Male	4854 (96.9%)	2485 (96.9%)	1712 (97.2%)	657 (95.9%)
Race	White	3710 (74.1%)	1922 (75%)	1300 (73.8%)	488 (71.2%)
	American Indian or Alaska Native	34 (0.7%)	17 (0.7%)	13 (0.7%)	4 (0.6%)
	Asian	19 (0.4%)	11 (0.4%)	5 (0.3%)	3 (0.4%)
	Black or African American	968 (19.3%)	474 (18.5%)	345 (19.6%)	149 (21.8%)
	Native Hawaiian or Other Pacific Islander	40 (0.8%)	17 (0.7%)	14 (0.8%)	9 (1.3%)
	Unknown	239 (4.8%)	123 (4.8%)	84 (4.8%)	32 (4.7%)
Ethnicity	Not Hispanic or Latino	4411 (88%)	2277 (88.8%)	1533 (87.1%)	601 (87.7%)
	Hispanic or Latino	513 (10.2%)	237 (9.2%)	201 (11.4%)	75 (10.9%)
	Unknown	86 (1.7%)	50 (2%)	27 (1.5%)	9 (1.3%)
Nursing home stay	Yes	1096 (21.9%)	576 (22.5%)	397 (22.5%)	123 (18.0%)
	No	3914 (78.1%)	1988 (77.5%)	1364 (77.5%)	562 (82.0%)
Diabetes	Yes	2374 (47.4%)	894 (34.9%)	1047 (59.5%)	433 (63.2%)
	No	2636 (52.6%)	1670 (65.1%)	714 (40.5%)	252 (36.8%)
Hypertension	Yes	3993 (79.7%)	1693 (66.0%)	1640 (93.1%)	660 (96.4%)
	No	1017 (20.3%)	871 (34%)	121 (6.9%)	25 (3.6%)
Pulmonary disease	Yes	2139 (42.7%)	1051 (41%)	763 (43.3%)	325 (47.4%)
	No	2871 (57.3%)	1513 (59%)	998 (56.7%)	360 (52.6%)
Heart failure	Yes	1750 (34.9%)	707 (27.6%)	763 (43.3%)	280 (40.9%)
	No	3260 (65.1%)	1857 (72.4%)	998 (56.7%)	405 (59.1%)
Kidney disease	Yes	1873 (37.4%)	788 (30.7%)	761 (43.2%)	324 (47.3%)
	No	3137 (62.6%)	1776 (69.3%)	1000 (56.8%)	361 (52.7%)
CAHD	Yes	181 (3.6%)	82 (3.2%)	75 (4.3%)	24 (3.5%)
	No	4829 (96.4%)	2482 (96.8%)	1686 (95.7%)	661 (96.5%)
Chronic liver disease		3665 (73.2%)	1706 (66.5%)	1410 (80.1%)	549 (80.1%)
	No	1345 (26.8%)	858 (33.5%)	351 (19.9%)	136 (19.9%)
Hyperlipidemia	Yes	1018 (20.3%)	362 (14.1%)	454 (25.8%)	202 (29.5%)
	No	3992 (79.7%)	2202 (85.9%)	1307 (74.2%)	483 (70.5%)
Cancer	Yes	1472 (29.4%)	745 (29.1%)	510 (29.0%)	217 (31.7%)
	No	3538 (70.6%)	1819 (70.9%)	1251 (71.0%)	468 (68.3%)

(Continues)

TABLE 2 (Continued)

		N (%)	N (%)	N (%)	N (%)
Smoke	Never smoker	1622 (32.4%)	863 (33.7%)	526 (29.9%)	233 (34%)
	Current smoker	529 (10.6%)	255 (9.9%)	214 (12.2%)	60 (8.8%)
	Former smoker	2405 (48.0%)	1188 (46.3%)	866 (49.2%)	351 (51.2%)
	Unknown	454 (9.1%)	258 (10.1%)	155 (8.8%)	41 (6%)
Stroke	Yes	981 (19.6%)	406 (15.8%)	417 (23.7%)	158 (23.1%)
	No	4029 (80.4%)	2158 (84.2%)	1344 (76.3%)	527 (76.9%)
Alcohol dependency	Yes	474 (9.5%)	248 (9.7%)	175 (9.9%)	51 (7.4%)
	No	4536 (90.5%)	2316 (90.3%)	1586 (90.1%)	634 (92.6%)
Drug dependency	Yes	180 (3.6%)	88 (3.4%)	68 (3.9%)	24 (3.5%)
	No	4830 (96.4%)	2476 (96.6%)	1693 (96.1%)	661 (96.5%)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AD, Alzheimer's disease; ARB, angiotensin II receptor blocker; BMI, body mass index; CAHD, coronary atherosclerotic heart disease; CCI, Charlson Comorbidity Index; CLC, ; MCI, mild cognitive impairment; SD, standard deviation.

COVID-19 infection. Multivariate nominal logistic regressions with and without PSW were used to investigate the association between AD/MCI and COVID-19 severity (hospitalization, use of ICU or ventilator, and mortality), and the association of ACEI/ARB prescriptions with COVID-19 severity among those patients diagnosed with COVID-19.

All analyses were adjusted for demographic and clinical characteristics, and the ORs were estimated with 95% confidence intervals (CI), for maximum likelihood method iterations (ML). A *P*-value of less than .05 is considered significant.

In addition, we applied bootstrap method as the sensitivity analysis to estimate the CI of the regression coefficients and examine the robustness of our major results. We re-estimated the 95% bootstrapped CI of ORs from a simulation with 1000 samples. The bootstrapping procedure confirmed the stability of the results because it is asymptotically more accurate than the standard CIs obtained from sample variance and assumptions of normality. To further confirm the significant association of AD with those diagnosed with COVID-19, we performed a sensitivity analysis among the subcohort of patients not living in a nursing home.

3 | RESULTS

3.1 | Demographics, clinical characteristics of the patients, and their status of nursing home stay

A total of 436,823 adult patients (≥ 50 years old and < 90 years old) were tested for COVID-19 during the study period, of whom 40,993 (9.38%) were positive. The majority (92.4%) of the study population were male, and our study population had a higher proportion of men than in the general population (Table 1). Racial breakdown was 69.0% White, 0.7% American Indian or Alaska Native, 0.7% Asian, 23.7% Black, 0.8% Native Hawaiian or other Pacific Islander, and 5.1% unreported race (Table 1). Higher proportions of male (AD: 96.9% vs. non-AD: 92.4%), White (AD: 74.0% vs. non-AD: 68.9%), and Hispanic or

Latino (AD: 10.4% vs. non-AD: 6.6%) are reported here among the AD patient group (Table 1).

The average age at the index of the study population was 67.93 ± 8.91 years. The average age at the index date was higher among the AD patients (77.25 ± 7.38 years) than the non-AD patients (67.82 ± 8.87 years), and higher among the MCI patients (71.15 ± 8.69 years) than the non-MCI patients (67.61 ± 8.83 years; Table 1).

More than half (76.2%) of the entire study population was hypertensive; nearly half (44.0%) had pulmonary disease; and other comorbidities were diabetes (43.6%), heart failure (15.5%), kidney disease (27.8%%), coronary atherosclerosis or other heart diseases (29.5%), and other diseases (Table 1). AD patients had worse health conditions with a higher average CCI of 3.97, compared to that of 2.71 among non-AD patients (Table 1). Likewise, the mean CCI among MCI patients (3.64) was higher than the mean CCI among non-MCI patients (2.65; Table 1). Higher rates of diabetes, hypertension, heart failure, and kidney diseases were observed among the AD and MCI patient groups (Table 1). Twenty-two percent of AD patients were in a nursing home and 3.1% of non-AD patients were in a nursing home. Among all non-AD patients, 8.3% of MCI patients were in a nursing home and 2.8% of non-MCI patients were in a nursing home (Table 1).

3.2 | Profiles of clinical outcomes among COVID-19–positive AD and MCI patients prescribed ARB or ACEI

Among the 5010 AD patients, 176 patients had an ACEI prescription only and 685 patients had an ARB prescription only (Table 2). Among the 685 patients who were prescribed ARB, long-term care facility patients made up 18.0%, and among the 1761 patients who were prescribed ACEI, 22.5% patients were in long-term care.

We examined the distribution of our study population based on their COVID-19 positive/negative test results and their clinical severity levels (Table 3). We specifically analyzed the profiles of COVID-19–positive AD (Table 4) and MCI patients (Table 4) prescribed ARB or

TABLE 3 Distribution of clinical outcomes of COVID-19 patients with or without AD/MCI

	AD (N = 639)	Non- AD (N = 28,779)	MCI (N = 1749)	Non-MCI (N = 27,171)
Not hospitalized	284 (44.4%)	19,742 (68.6%)	952 (54.4%)	18,912 (69.6%)
Hospitalized	119 (18.6%)	3832 (13.3%)	320 (18.3%)	3522 (13.0%)
Used ICU or ventilator	49 (7.7%)	2184 (7.6%)	180 (10.3%)	2012 (7.4%)
Mortality	187 (29.3%)	3021 (10.5%)	297 (17.0%)	2725 (10.0%)

Abbreviations: AD, Alzheimer's disease; ICU, intensive care unit; MCI, mild cognitive impairment.

TABLE 4 Distribution of clinical outcomes among COVID-19 positive AD and MCI patients prescribed ARB or ACEI

	AD			MCI		
	No ACEI/ARB	ACEI only	ARB only	No ACEI/ARB	ACEI only	ARB only
Not hospitalized	154 (45.6%)	89 (40.3%)	31 (46.3%)	441 (55.5%)	353 (55.1%)	135 (51.7%)
Hospitalized	63 (18.6%)	45 (20.4%)	10 (14.9%)	146 (18.4%)	115 (17.9%)	44 (16.9%)
Used ICU or ventilator	22 (6.5%)	22 (10.0%)	4 (6.0%)	71 (8.9%)	74 (11.5%)	28 (10.7%)
Mortality	99 (29.3%)	65 (29.4%)	22 (32.8%)	136 (17.1%)	99 (15.4%)	54 (20.7%)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AD, Alzheimer's disease; ARB, angiotensin II receptor blocker; ICU, intensive care unit; MCI, mild cognitive impairment.

TABLE 5 Association of AD with COVID-19 infection and clinical outcomes

		Logistic regression			Propensity score weighted logistic regression		
		OR	95% CI	P-value	OR	95% CI	P-value
COVID-19 infection (reference: negative)		1.688	(1.558, 1.828)	< 0.001	1.565	(1.383, 1.769)	< 0.001
COVID-19 clinical outcomes (reference: non-hospitalized)	Hospitalization	1.428	(1.139, 1.791)	.002	1.407	(0.998, 1.984)	.051
	ICU or ventilator	1.051	(0.767, 1.441)	.757	1.117	(0.704, 1.772)	.637
	Mortality	1.695	(1.383, 2.078)	<.001	1.653	(1.219, 2.242)	.001

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

ACEI in each severity level. Overall, non-AD COVID-19 patients exhibited less severe clinical outcomes. Lower proportions of AD patients were not hospitalized (AD: 44.4% vs. non-AD: 68.6%), and higher proportions of AD patients died after COVID-19 infection (AD: 29.3% vs. non-AD: 10.5%), compared to patients without AD (Table 3). Similarly, lower proportion of MCI patients were not hospitalized (MCI: 54.4% vs. non-MCI: 69.6%; Table 3).

3.3 | Association of AD with an increased risk of COVID-19 infection and death after COVID-19 diagnosis

Patients with AD were associated with higher odds than patients without AD of being diagnosed with COVID-19 (OR = 1.688, 95% CI [1.558, 1.828] and OR = 1.565, 95% CI [1.383, 1.769] with PSW; Table 5,

Figure 1). Compared to patients without AD, patients with AD had a significantly increased risk of death (OR = 1.695, 95% CI [1.383, 2.078] and OR = 1.653, 95% CI [1.219, 2.242] with PSW; Table 5, Figure 1). An increased odds of hospitalization associated with AD patients was observed in multivariable logistic regression analyses (OR = 1.428, 95% CI [1.139, 1.791], P = .002) and attenuated with PSW balance (OR = 1.407, 95% CI [0.998, 1.984], P = 0.051; Table 5, Figure 1). We did not observe a statistically significant association between AD and the use of ICU or mechanical ventilation (Table 5, Figure 1).

Sensitivity analyses using bootstrapping for the CI of the ORs (Table S1A in supporting information) were comparable to our main findings (Table 5, Figure 1), supporting the robustness of the associations reported in our analyses. Because AD patients living in nursing homes could be a risk factor for COVID-19 infection, we extracted AD patients living outside of nursing homes and observed a similar, statistically
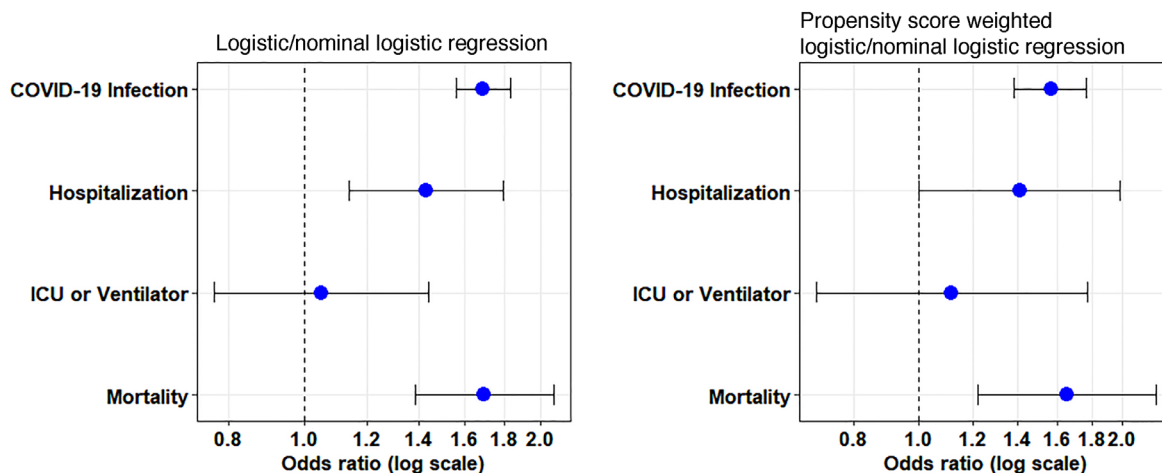
FIGURE 1 Odds ratios of association of Alzheimer's disease (AD) with COVID-19 infection and clinical outcomes. Odds with and without propensity score weighting of COVID-19 infection, hospitalization, use of intensive care unit (ICU) or mechanical ventilation, and mortality were illustrated in patients with AD compared to patients without AD, after adjusting for age at index date, race, sex, ethnicity, diabetes, pulmonary disease, kidney disease, coronary atherosclerotic heart disease, chronic liver disease, hyperlipidemia, cancer, smoking status, stroke, heart failure, alcohol dependency, drug dependency, body mass index, Charlson Comorbidity Index, and status of nursing home stay

TABLE 6 Association of AD with COVID-19 infection among patients outside of nursing homes

Reference: negative	OR	95% CI	P-value
Logistic regression	1.797	(1.643, 1.965)	<.001
Propensity score weighted logistic regression	1.655	(1.431, 1.914)	<.001

Abbreviations: AD, Alzheimer's disease; CI, confidence interval; OR, odds ratio.

significant positive association (OR = 1.797, 95% CI [1.643, 1.965] and OR = 1.655, 95% CI [1.431, 1.914] with PSW; Table 6).

3.4 | Association of MCI with an increased risk of COVID-19 hospitalization, use of ICU or mechanical ventilators, and death after COVID-19 diagnosis

When we examined the patients with MCI, we did not observe a significant association of MCI with COVID-19 infection using multivariate logistic regression with or without PSW (OR = 0.974, 95% CI [0.932, 1.019], P = .252) or PSW model (OR = 0.953, 95% CI [0.895, 1.014], P = .125; Table 7, Figure 2). The comparison between MCI patients versus non-MCI patients revealed that patients with MCI associated with higher ORs of hospitalization (OR = 1.309, 95% CI [1.140, 1.503] and OR = 1.370, 95% CI [1.113, 1.686] with PSW), use of ICU or mechanical ventilators (OR = 1.290, 95% CI [1.085, 1.534] and OR = 1.315, 95% CI [1.013, 1.706] with PSW), and mortality (OR = 1.211, 95% CI [1.045, 1.404] and OR = 1.265, 95% CI [1.022, 1.565] with PSW; Table 7, Figure 2).

Sensitivity analyses using bootstrapping for the confidence intervals for logistic regression were comparable to our findings (Table S1A), supporting the robustness of the associations reported in our analyses.

3.5 | Association between ACEI/ARB prescriptions and COVID-19 occurrence/severity among AD patients

Patients prescribed ARBs had a lower risk of a positive COVID-19 test outcome (OR = 0.657, 95% CI [0.501, 0.861], P-value = .002), compared to patients not prescribed ACEI or ARB. These results were confirmed with the logistic model with PSW (OR = 0.644, 95% CI [0.567, .731], P-value < .001; Table 8, Figure 3). However, prescription of ACEIs had no significant association with a positive COVID-19 test result. We further examined the association of medications prescribed on the clinical outcomes. Among AD patients who tested positive for COVID-19, neither ACEIs nor ARBs had a significant association with any of the severity levels (Table 8, Figure 3) in both the logistic and the PSW logistic models.

## 3.6 | Association between ACEI/ARB prescription and COVID-19 occurrence/severity among MCI patients

MCI patients prescribed ARBs have a lower risk of a positive COVID-19 test (OR = 0.874, 95% CI [0.765, 0.999], P-value = .048) compared to the reference group (no ACEI and no ARB; Table 9, Figure 4). This result was confirmed with the PSW logistic model: the OR for ARB was 0.886 with 95% CI (0.827, 0.949) and P-value = .001 (Table 9, Figure 4).

TABLE 7   Association of MCI with COVID-19 infection and clinical outcomes

		Logistic regression			Propensity score weighted logistic regression		
		OR	95% CI	P-value	OR	95% CI	P-value
COVID-19 infection (reference: negative)		0.974	(0.932, 1.019)	0.252	0.953	(0.895, 1.014)	0.125
COVID-19 clinical outcomes (reference: non-hospitalized)	Hospitalization	1.309	(1.140, 1.503)	<.001	1.370	(1.113, 1.686)	.003
	ICU or ventilator	1.290	(1.085, 1.534)	.004	1.315	(1.013, 1.706)	.040
	Mortality	1.211	(1.045, 1.404)	.011	1.265	(1.022, 1.565)	.031

Abbreviations: CI, confidence interval; ICU, intensive care unit; MCI, mild cognitive impairment; OR, odds ratio.
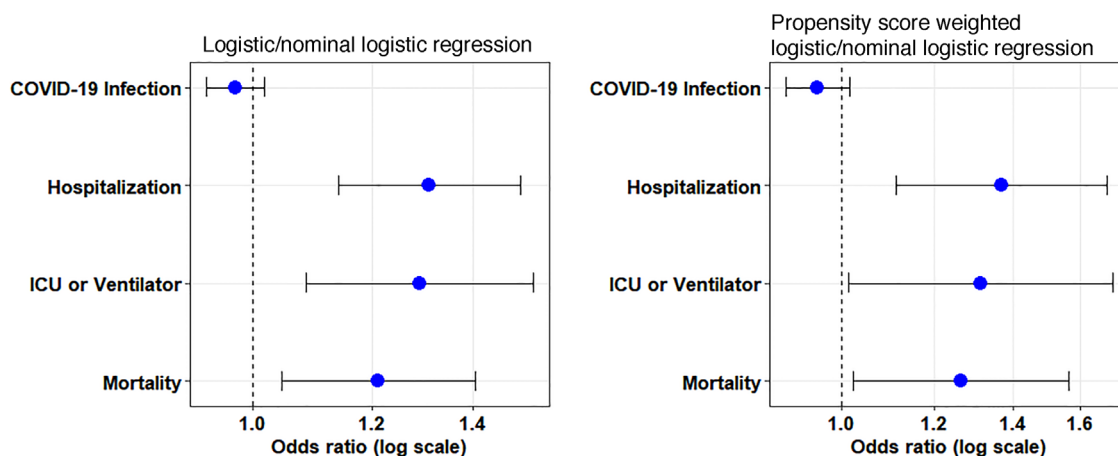
FIGURE 2   Odds ratios of association of mild cognitive impairment (MCI) with COVID-19 infection and clinical outcomes. Odds with and without propensity score weighting of COVID-19 infection, hospitalization, use of intensive care unit (ICU) or mechanical ventilation, and mortality were illustrated in patients with MCI compared to patients without MCI

TABLE 8   Association of ACEI/ARB use with COVID-19 infection and clinical outcomes among AD patients

|			Logistic regression			Propensity score weighted logistic regression		
		ACEI/ARB	OR	95% CI	P-value	OR	95% CI	P-value
COVID-19 infection (reference: negative)		ACEI	0.930	(0.775, 1.116)	0.434	.901	(0.801, 1.013)	0.081
		ARB	0.657	(0.501, 0.861)	0.002	.644	(0.567, 0.731)	<0.001
COVID-19 severity (reference: non-hospitalized)	Hospitalization	ACEI	1.285	(0.760, 2.173)	.148	1.204	(0.635, 2.284)	.192
	ICU or ventilator	ACEI	2.039	(0.936, 4.439)	.046	1.461	(0.601, 3.552)	.113
	Mortality	ACEI	1.361	(0.847, 2.188)	.377	1.295	(0.724, 2.315)	.556
	Hospitalization	ARB	0.723	(0.311, 1.683)	.271	0.730	(0.357, 1.490)	.170
	ICU or ventilator	ARB	0.786	(0.224, 2.762)	.323	0.646	(0.233, 1.796)	.153
	Mortality	ARB	1.203	(0.613, 2.362)	.924	1.273	(0.695, 2.331)	.647

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AD, Alzheimer's disease; ARB, angiotensin II receptor blocker; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

However, compared to the ARB association with COVID-19 positivity among AD patients, the effect size of ARB among MCI patients is smaller based on small effect size threshold.[26]

For ACEI, there was no significant association with the outcome in both logistic model and the PSW logistic model. Among all the MCI patients with a positive COVID-19 test result, both ACEI and ARB had no significant association with any severity level (Table 9) in both models.

For AD patients, the bootstrap estimation of OR of ARB is 0.657 with 95% CI (0.467, 0.819) and for MCI patients, the OR is 0.872 with
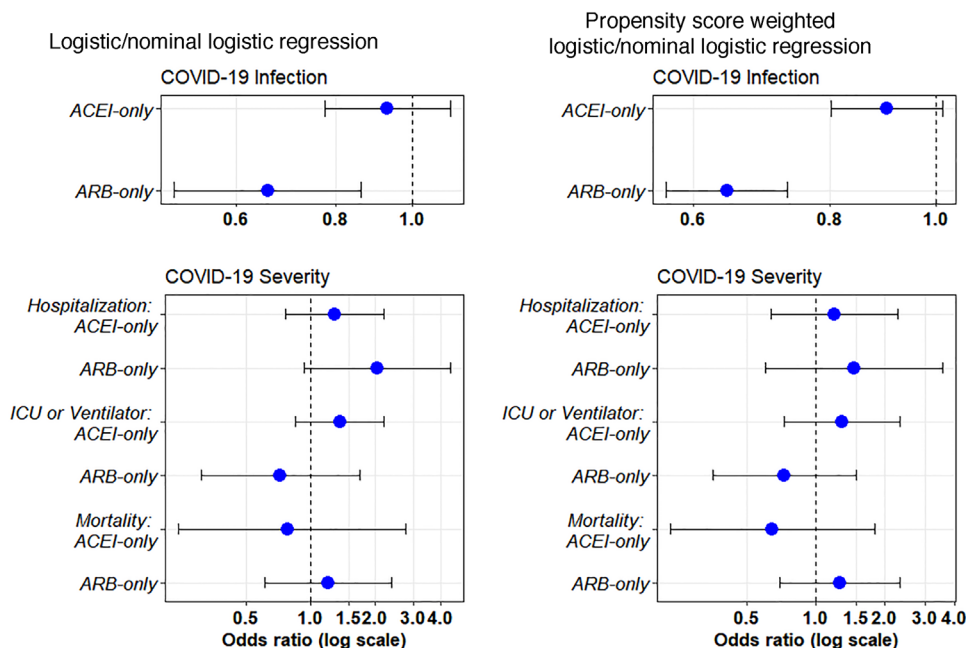
FIGURE 3 Odds ratios of COVID-19 infection and clinical outcomes in Alzheimer's disease (AD) patients with records of using angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). Veterans with records of having been prescribed ACEI only or ARB only were compared to those with no record of having been prescribed ACEI or ARB using a logistic regression model, with or without propensity score weighting. The use of ARBs is associated with reduced odds of a positive COVID-19 test. Among COVID-19–positive veterans with AD, no significant association was observed between ACEI/ARB use and hospitalization (excluding those admitted to the intensive care unit [ICU] or using ventilators), ICU admission/use of ventilators, or mortality

TABLE 9 Association of ACEI/ARB use with COVID-19 infection and clinical outcomes among MCI patients

|			Logistic regression			Propensity score weighted logistic regression		
		ACEI/ARB	OR	95% CI	P-value	OR	95% CI	P-value
COVID-19 infection (reference: negative)		ACEI	0.938	(0.845, 1.041)	0.231	.944	(0.883, 1.009)	0.090
		ARB	0.874	(0.765, 0.999)	0.048	.886	(0.827, 0.949)	0.001
COVID-19 severity (reference: non-hospitalized)	Hospitalization	ACEI	0.830	(0.607, 1.135)	.709	0.822	(0.588, 1.151)	.666
	ICU or ventilator	ACEI	1.189	(0.799, 1.770)	.411	1.227	(0.798, 1.886)	.458
	Mortality	ACEI	0.828	(0.594, 1.152)	.135	0.824	(0.579, 1.174)	.131
	Hospitalization	ARB	0.772	(0.505, 1.181)	.404	0.764	(0.533, 1.096)	.262
	ICU or ventilator	ARB	1.042	(0.615, 1.765)	.850	1.166	(0.742, 1.834)	.779
	Mortality	ARB	1.096	(0.724, 1.660)	.332	1.061	(0.742, 1.517)	.298

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; ICU, intensive care unit; MCI, mild cognitive impairment; OR, odds ratio.

95% CI (0.757, 0.985; Table S1B). These results confirmed our findings on the effect of ARB usage.

4 | DISCUSSION

To the best of our knowledge, this is one of the largest retrospective case-control studies evaluating the association of those diagnosed with AD/MCI and COVID-19 infection together with informa-

tion on medication treatment and clinical outcomes. The association between AD and COVID-19 in our study is consistent with another large cohort study on dementia that leveraged 61.9 million EHRs.[17] However, important differences in the study design should be noted. Our results suggest a 69% increased odds of a COVID-19 infection among AD patients and beneficial effect of ARB prescription. The relationship between AD and mortality among COVID-19–positive patients revealed by this study has significant clinical implications. Next, the hospitalization and mortality status were evaluated using
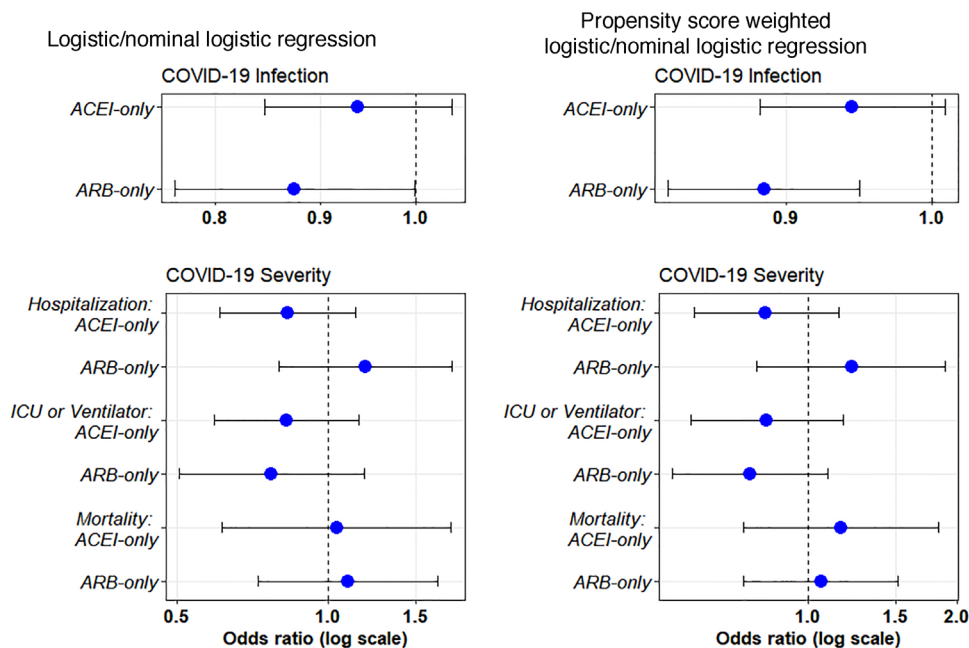
FIGURE 4   Odds ratios of COVID-19 infection and clinical outcomes in mild cognitive impairment (MCI) patients with records of using angiotensin converting enzyme inhibitors (ACEIs) only or angiotensin II receptor blockers (ARBs) only. Veterans with records of having been prescribed ACEI only or ARB only were compared to those with no record of having been prescribed ACEI or ARB using a logistic regression model, with or without propensity score weighting. The use of ARB is associated with reduced odds of a positive COVID-19 test. Among COVID-19–positive veterans with MCI, no significant association was observed between ACEI/ARB use and hospitalization, intensive care unit (ICU) admission/use of ventilators, or mortality

different time windows.[17] The published study investigated risks of 6-month hospitalization and mortality, while this study analyzed risks of 2-month (60-day) hospitalization and mortality. Furthermore, the previous published study compared the unadjusted percentage rate among patients with both dementia (or AD) and COVID-19, patients with COVID-19 but no dementia, and patients with dementia (or AD) with demographic disparities. Our study compared the adjusted ORs with and without PSW between AD versus non-AD subjects, controlling for some of the disparities through balancing the groups on both demographic and clinical characteristics.

A strength of this study was in the PSW reported results that were statistically significant with a balance between the exposure group and the comparison group (without exposure). We checked the status of living in nursing homes and found no difference between those AD patients living inside or outside of nursing homes (Table 5). It is not clear whether social and biological determinants play potential roles in enhancing the occurrence and severity of COVID-19 among AD and MCI patients.

Previously, we found that the use of ACEIs significantly decreased the odds of a positive COVID-19 test among veterans with hypertension,[27] which is different from the cohort presented in this study. In this study, we found that ARBs but not ACEI were associated with a lower occurrence of COVID-19, and there is no significant association between the ARB or ACEI use and the severity of COVID-19 among AD and MCI patients. The difference between two study populations, patients with hypertension versus AD/MCI, contributes to the new finding of beneficial effect of ARBs.

Mechanistically, our findings are consistent with the speculation that the increased BBB permeability renders patients with AD vulnerable to viral infections.[28–30] Prior studies have shown that BBB impairment is a stable characteristic of AD patients[31–34] and suggested that many infectious agents in the CNS, including viruses, bacteria, and fungi, were associated with AD patients.[30,35–40]

Our study has several limitations. First, there were substantial differences in terms of demographics, clinical characteristics, and the status of nursing home stay between AD/MCI versus non-AD/MCI patients, even though we attempted to limit the biases by balancing and adjusting these differences using multivariable regression with PSW. Second, the participants in our study took the COVID-19 test voluntarily. We did not account for the various social and behavioral reasons associated with the decision for COVID-19 testing. Several unmeasured variable factors, such as behavioral attitudes, sociodemographic disparities, and cultural attitudes may have contributed to this decision. Third, due to the overall nature of the population of veterans who had served in the US military, our study population had a higher proportion of males than the general population, and results are limited to males, predominantly White (Table 1).

The impact of the SARS-CoV-2 infection on AD and MCI patients is multifaceted,[41] and the effects on clinical outcomes of COVID-19 are heterogeneous in general, except for a specific increase in mortality.[42] We understand that our results may be statistically significant but not clinically important to change current practices. The sample size of this study is very high and the significance of results should be interpreted with caution. The effect size of our primary finding is larger

than small effect size,[26] using the effect size as the approach is appropriate and conveys the clinical importance of our findings.[43,44] While we are still exploring molecular pathways involved in SARS-CoV-2-infection–triggered CNS responses and its related neuropsychiatric manifestation,[45] we need to identify a clear path forward to specifically reduce the impact of COVID-19 on AD and MCI patients.[46] Future studies are needed to understand the pathological changes that may explain increased occurrence of COVID-19 among AD and MCI patients.

CONFLICTS OF INTEREST

REFERENCES

1. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020;77(6):683-690.
2. Puelles VG, Lütgehetmann M, Lindenmeyer MT, et al. Multiorgan and renal tropism of SARS-CoV-2. *N Engl J Med*. 2020;383(6):590-592.
3. Ciaccio M, Lo Sasso B, Scazzone C, et al. COVID-19 and Alzheimer's Disease. *Brain Sci*. 2021;11(3):305.
4. Karuppan MKM, Devadoss D, Nair M, Chand HS, Lakshmana MK. SARS-CoV-2 Infection in the Central and Peripheral Nervous System-Associated Morbidities and Their Potential Mechanism. *Mol Neurobiol*. 2021;58(6):2465-2480.
5. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019. https://doi.org/10.1016/j.eclinm.2021.101019
6. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med*. 2021;27(4):626-631.
7. Yu Y, Travaglio M, Popovic R, Leal NS, Martins LM. Alzheimer's and Parkinson's Diseases Predict Different COVID-19 Outcomes: A UK Biobank Study. *Geriatrics (Basel)*. 2021;6(1):60. https://doi.org/10.3390/geriatrics6010010
8. Zenaro E, Piacentino G, Constantin G. The blood-brain barrier in Alzheimer's disease. *Neurobiol Dis*. 2017;107:41-56.
9. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ*. 2020;368:m1198. https://doi.org/10.1136/bmj.m1198
10. Sanyaolu A, Okorie C, Marinkovic A, et al. Comorbidity and its Impact on Patients with COVID-19. *SN Compr Clin Med* 2020;2(8):1069-1076.
11. Wang C, Zhang M, Garcia G, Jr., et al. ApoE-Isoform-Dependent SARS-CoV-2 Neurotropism and Cellular Response. *Cell Stem Cell*. 2021;28(2):331-342.e5.
12. Kuo C-L, Pilling LC, Atkins JL, et al. ApoE e4e4 genotype and mortality with COVID-19 in UK Biobank. *J Gerontol A Biol Sci Med Sci*. 2020;75(9):1801-1803.
13. Xiong N, Schiller MR, Li J, Chen X, Lin Z. Severe COVID-19 in Alzheimer's disease: APOE4's fault again? *Alzheimers Res Ther*. 2021;13(1):111.
14. De Santis G. SARS-CoV-2: A new virus but a familiar inflammation brain pattern. *Brain Behav Immun*. 2020;87:95-96. https://doi.org/10.1016/j.bbi.2020.04.066
15. Chen R, Wang K, Yu J, et al. The Spatial and cell-type distribution of SARS-CoV-2 receptor ACE2 in the human and mouse brains. *Front Neurol*. 2021;11:573095. https://doi.org/10.3389/fneur.2020.573095
16. Ding Q, Shults NV, Harris BT, Suzuki YJ. Angiotensin-converting enzyme 2 (ACE2) is upregulated in Alzheimer's disease brain. *bioRxiv*: the preprint server for biology. 2020:2020.10.08.331157. https://doi.org/10.1101/2020.10.08.331157
17. Wang Q, Davis PB, Gurney ME, Xu R. COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US. *Alzheimers Dement*. 2021;17(8):1297-1306.
18. Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *Bmj*. 2010;340:b5465. https://doi.org/10.1136/bmj.b5465
19. Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM. Associations of antihypertensive treatments with Alzheimer's disease, vascular dementia, and other dementias. *J Alzheimers Dis*. 2011;26(4):699-708.
20. Li M, Reisman J, Morris-Eppolito B, et al. Beneficial association of angiotensin-converting enzyme inhibitors and statins on the occurrence of possible Alzheimer's disease after traumatic brain injury. *Alzheimers Res Ther*. 2020;12(1):33.
21. Barthold D, Joyce G, Diaz Brinton R, Wharton W, Kehoe PG, Zissimopoulos J. Association of combination statin and antihypertensive therapy with reduced Alzheimer's disease and related dementia risk. *PLoS One*. 2020;15(3):e0229541.
22. Zhuang S, Wang HF, Wang X, Li J, Xing CM. The association of renin-angiotensin system blockade use with the risks of cognitive impairment of aging and Alzheimer's disease: A meta-analysis. *J Clin Neurosci*. 2016;33:32-38. https://doi.org/10.1016/j.jocn.2016.02.036
23. Oscanoa TJ, Amado J, Vidal X, Romero-Ortuno R. Angiotensin-Receptor Blockers (ARBs) and risk of Alzheimert's Disease: A meta-analysis. *Curr Clin Pharmacol*. 2021;16(1):73-78.
24. ICD-10. *International statistical classification of diseases and related health problems*. World Health Organization. 2004;tenth revision, 2nd ed.
25. Olmos A, Govindasamy P. A practical guide for using propensity score weighting in R. *PARE*. 2015;20(1):13.
26. Chen H, Cohen P, Chen S. How Big is a Big Odds Ratio? Interpreting the Magnitudes of Odds Ratios in Epidemiological Studies. *Commun Stat Simul Comput*. 2010;39(4):860-864.
27. Li M, Wang Y, Ndiwane N, et al. The association of COVID-19 occurrence and severity with the use of angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers in patients with hypertension. *PLoS One*. 2021;16(3):e0248652.
28. Kamer AR, Dasanayake AP, Craig RG, Glodzik-Sobanska L, Bry M, De Leon MJ. Alzheimer's disease and peripheral infections: the possible contribution from periodontal infections, model and hypothesis. *J Alzheimers Dis*. 2008;13(4):437-449.
29. Honjo K, van Reekum R, Verhoeff NP. Alzheimer's disease and infection: do infectious agents contribute to progression of Alzheimer's disease? *Alzheimers Dement (N Y)*. 2009;5(4):348-360.
30. Sochocka M, Zwolinska K, Leszek J. The infectious etiology of Alzheimer's disease. *Curr Neuropharmacol*. 2017;15(7):996-1009.

31. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85(2):296-302.

32. Bowman G, Kaye J, Moore M, Waichunas D, Carlson N, Quinn J. Blood–brain barrier impairment in Alzheimer disease: stability and functional significance. *Neurology*. 2007;68(21):1809-1814. https://doi.org/10.1212/01.wnl.0000262031.18018.1a

33. Bowman GL, Quinn JF. Alzheimer's disease and the blood–brain barrier: past, present and future. *Aging Health*. 2008;4(1):47-55.

34. Magaki S, Tang Z, Tung S, et al. The effects of cerebral amyloid angiopathy on integrity of the blood-brain barrier. *Neurobiol Aging*. 2018;70:70-77.

35. Mawanda F, Wallace R. Can infections cause Alzheimer's disease? *Epidemiol Rev*. 2013;35(1):161-180.

36. Licastro F, Carbone I, Raschi E, Porcellini E. The 21st century epidemic: infections as inductors of neuro-degeneration associated with Alzheimer's Disease. *Epidemiol Rev*. 2014;11(1):1-9.

37. Kristen H, Santana S, Sastre I, Recuero M, Bullido MJ, Aldudo J. Herpes simplex virus type 2 infection induces AD-like neurodegeneration markers in human neuroblastoma cells. *Neurobiol Aging*. 2015;36(10):2737-2747.

38. Hemling N, Röyttä M, Rinne J, et al. Herpesviruses in brains in Alzheimer's and Parkinson's diseases. *Ann Neurol*. 2003;54(2):267-271.

39. Bibi F, Yasir M, Sohrab SS, et al. Link between chronic bacterial inflammation and Alzheimer disease. *CNS Neurol Disord Drug Targets*. 2014;13(7):1140-1147.

40. Pisa D, Alonso R, Rábano A, Rodal I, Carrasco L. Different brain regions are infected with fungi in Alzheimer's disease. *Sci Rep*. 2015;5(1):1-13.

41. Numbers K, Brodaty H. The effects of the COVID-19 pandemic on people with dementia. *Nat Rev Neurol*. 2021;17(2):69-70.

42. Liu N, Sun J, Wang X, Zhao M, Huang Q, Li H. The Impact of Dementia on the Clinical Outcome of COVID-19: A Systematic Review and Meta-Analysis. *J Alzheimers Dis*. 2020;78(4):1775-1782.

43. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. *Med Care*. 1989;27(3 Suppl):S178-S189.

44. Johnston BC, Alonso-Coello P, Friedrich JO, et al. Do clinicians understand the size of treatment effects? A randomized survey across 8 countries. *CMAJ*. 2016;188(1):25-32.

45. Yamamoto V, Bolanos JF, Fiallos J, et al. COVID-19: Review of a 21st Century Pandemic from Etiology to Neuro-psychiatric Implications. *J Alzheimers Dis*. 2020;77(2):459-504.

46. Brown EE, Kumar S, Rajji TK, Pollock BG, Mulsant BH. Anticipating and Mitigating the Impact of the COVID-19 Pandemic on Alzheimer's Disease and Related Dementias. *Am J Geriatr Psychiatry*. 2020;28(7):712-721.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.