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FEATURED ARTICLE

COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US

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Abstract

Introduction: At present, there is limited data on the risks, disparity, and outcomes for COVID-19 in patients with dementia in the United States.

Methods: This is a retrospective case-control analysis of patient electronic health records (EHRs) of 61.9 million adult and senior patients (age ≥ 18 years) in the United States up to August 21, 2020.

Results: Patients with dementia were at increased risk for COVID-19 compared to patients without dementia (adjusted odds ratio [AOR]: 2.00 [95% confidence interval (CI), 1.94–2.06], $P < .001$), with the strongest effect for vascular dementia (AOR: 3.17 [95% CI, 2.97–3.37], $P < .001$), followed by presenile dementia (AOR: 2.62 [95% CI, 2.28–3.00], $P < .001$), Alzheimer's disease (AOR: 1.86 [95% CI, 1.77–1.96], $P < .001$), senile dementia (AOR: 1.99 [95% CI, 1.86–2.13], $P < .001$) and post-traumatic dementia (AOR: 1.67 [95% CI, 1.51–1.86] $P < .001$). Blacks with dementia had higher risk of COVID-19 than Whites (AOR: 2.86 [95% CI, 2.67–3.06], $P < .001$). The 6-month mortality and hospitalization risks in patients with dementia and COVID-19 were 20.99% and 59.26%, respectively.

Discussion: These findings highlight the need to protect patients with dementia as part of the strategy to control the COVID-19 pandemic.

KEYWORDS
Alzheimer's disease, COVID-19, dementia, patient electronic health records

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) and rapidly escalated into a global pandemic.[1] Severe illness of COVID-19 predominantly occurs in older people and in individuals with underlying medical comorbidities.[2] Dementia including Alzheimer disease (AD) is a common cause of morbidity and mortality in the aging population.[3] In addition, the majority of people with dementia were living with one or two additional chronic health conditions.[4–6] Currently, there is little if any quantitative analysis of the risks and outcomes for COVID-19 in individuals with AD or dementia in the United States.

An estimated 5.8 million Americans age 65 and older and 50 million people worldwide are living with AD and other dementias.[7] Strong risk factors for cognitive decline and dementia include cardiovascular diseases, diabetes, obesity, and hypertension.[4–6] Many of these common comorbidities in patients with dementia are also demonstrated risk factors for COVID-19 and are associated with worse clinical outcomes.[2,8–10] In patients with dementia including vascular dementia and AD, the blood-brain barrier (BBB) is damaged, which allows certain bacteria and viruses to access the brain more easily[11–13] and make patients more susceptible to bacterial, viral, and fungal infection.[14–15] In addition, the memory impairment associated with dementia may interfere with the patient's ability to comply with preventive measures for COVID-19 such as social distancing, mask wearing, and frequent hand sanitizing. Therefore, we tested the hypothesis that patients with dementia have increased risk for contracting COVID-19 over and above what is predicted from their comorbid conditions.

SARS-CoV2 has also been shown to affect the brain directly with reports of encephalitis, thrombotic events, and brain invasion.[16] Indeed an early sign of disease is the loss of the sense of taste and smell. Moreover, the brain is affected by organ failure elsewhere (e.g., heart or lung), and hypoxemia is a hallmark of severe infection, and can itself lead to cerebral edema and brain malfunction.[16] Because of these frequent brain complications and autopsy findings, we hypothesized that preexisting dementia, especially with involvement of the blood vessels in the brain (vascular dementia) predisposes patients to greater risk of morbidity and mortality from COVID-19. Therefore, we tested the hypothesis that patients with dementia, once infected, are at greater risk for adverse outcomes.

Substantial inequalities of age, race, and sex were observed for COVID-19 outcomes. COVID-19 affects Blacks at a disproportionately high rate.[17] The risk of dying from COVID-19 increases significantly with age and is twice as high in men as in women.[18–20] Similarly, dementia burden in the United States varies substantially by age, race, and sex.[21–23] However, it remains unknown how race and other demographic factors such as age and sex affect the risk of COVID-19 in patients with dementia. The large database available to us permitted us also to test the impact of sex, race, and age on the association of dementia with COVID-19 in the United States.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using PubMed sources. Although risk factors for dementia overlap with those for COVID-19, there is little research on how patients with dementia are susceptible to COVID-19 and its adverse outcomes. It remains unknown how race and other demographic factors such as age and sex differentially affect the risk of COVID-19 infection among patients with dementia. The relevant citations are appropriately cited.
2. **Interpretation**: Our findings show that patients with dementia are at significantly increased risk for COVID-19 and outcomes, which is further exacerbated among Blacks, highlighting the need to protect patients with dementia as part of the strategy to control the pandemic.
3. **Future directions**: Findings from this electronic health records–based study on a nationwide population are associational not causal. These associational findings need to be replicated in and compared to other patient databases and registries.

2 | METHODS

2.1 | Database description

We performed a retrospective case-control study using de-identified population-level electronic health record (EHR) data collected by the IBM Watson Health Explorys from 360 hospitals and 317,000 providers across 50 states, representing 20% of the US population.[24] The EHR data are de-identified according to the Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act standards as described in an early study using this database.[25] After the de-identification process, a manual curation process normalizes the data through mapping key elements to widely accepted biomedical terminologies and ontologies.[26] Specifically, disease terms are coded using the Systematized Nomenclature of Medicine–Clinical Terms (SNOMED-CT), a global standard for health terms that provides the core general terminology for EHRs.[27] More than 100 published studies showed that with this large-scale and standardized EHR database and the cloud-based Explorys Cohort Discovery informatics tools, large case-control studies can be undertaken efficiently.[28] In our recent study using the Explorys EHR database and informatics tools, we showed that patients with substance use disorders, mental disorders, and cancers were at increased risk for COVID-19.[29–31]

2.2 | Study population

At the time of this study (August 21, 2020), the study population consisted of 61,916,260 adult and senior patients (age 18 years and above) including 1,064,960 who had dementia, 15,770 with COVID-19, and 810 with both dementia and COVID-19. The status of COVID-19 was based on the concept "Coronavirus infection (disorder)" (Concept Code 186747009) and we further limited the diagnosis time frame to within the past year to capture the timing of new cases arising during the COVID-19 pandemic. The outcome measures were COVID-19 diagnosis, death, and hospitalization. The SNOMED-CT concepts "Hospital admission (procedure)" (ID 32485007) was used to obtain hospital admission status from patient EHRs. Explorys regularly imports from the Social Security Death Index for the "deceased" status. We examined the risk association between COVID-19 and dementia, including five specific types of dementia that had sufficient number of COVID-19 cases.

The status of dementia was based on the diagnosis of "Dementia (disorder)" on SNOMED-CT (Concept Code 52448006), AD on the diagnosis of "Alzheimer's disease (disorder)" (code 26929004), vascular dementia on the diagnosis of "Vascular dementia (disorder)" (code 429998004), senile dementia on the diagnosis of "Senile dementia (disorder)" (code 15662003), presenile dementia on the diagnosis of "Presenile dementia (disorder)" (code 12348006), and post-traumatic dementia on the diagnosis of "Post-traumatic dementia (disorder)" on (code 230282000). Other subtypes of dementia such as Lewy body dementia, fronto-temporal dementia, and mixed dementia were not examined due to their insufficient sample sizes for COVID-19 cases.

The following analyses were performed. (1) We examined how dementia was associated with the risk of COVID-19, adjusted for age, sex, race, comorbidities, transplantation procedures, and nursing home stay. The exposure groups were patients diagnosed with dementia, the

unexposed groups were patients without dementia, and the outcome measure was diagnosis of COVID-19. Separate analysis was done for each of five dementia types. (2) We examined in the patients with dementia how demographic factors differentially affected COVID-19 risk. The case groups were patients with dementia and one of the following demographic factors: female, senior (> 65 years of age), Black. The comparison groups were patients with dementia and one of the following corresponding demographic factors: male, adult (age 18–65 years), White. The outcome measure was diagnosis of COVID-19. Known COVID-19 risk factors were adjusted. For example, we examined whether Blacks with dementia were more likely to get COVID-19 compared to Whites with dementia, adjusting for age, sex, and known COVID-19 risk factors or if older patients with dementia (age >65 years old) were more like to get COVID-19 compared to younger patients with dementia (age 18–65 years old), adjusting for race, sex, and known COVID-19 risk factors. Separate analysis was done for dementia in general, and for AD and vascular dementia in specific, as there were sufficient sample sizes for patients with these dementia types (and COVID-19 cases) stratified by age, sex, and race. (3) The 6-month (February–August 2020) mortality risk and hospitalization risk in patients with COVID-19 and dementia were compared to those for COVID-19 patients without dementia and with patients with dementia without COVID-19.

2.3 | Statistical analysis

The EHR data are de-identified population-level (not patient-level) data, therefore we used odds ratios instead of performing regression analyses. For a given input set of patient characteristics (e.g., age, sex, race, diagnosis, finding, medications), the Explorys Explore Cohort Discovery tool built a patient cohort by querying the underlying EHR databases for patients matching the inputs. Patients with missing values for the input queries were not included in the returned cohort. The adjusted OR (AOR), 95% confidence interval (CI), and P-values were calculated using the Cochran-Mantel-Haenszel (CMH) method[32] by controlling for age groups (adults age 18–65 years, senior age >65 years); sex (female/male); race (White/Black); common comorbidities considered risk factors for COVID-19, including asthma, cardiovascular diseases, cancer, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, substance use disorders (including alcohol use disorders, tobacco use disorder, opioid use disorder, cannabis use disorder, cocaine use disorder); transplant procedures (bone marrow, solid organ); and nursing home stay.[2,29] Among demonstrated COVID-19 risk factors, asthma, cardiovascular diseases, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, substance use disorders also predispose patients to increased risk for dementia.[33–40] There is an intriguing relationship between cancers and dementia.[41] About two thirds of all US nursing home residents have some type of cognitive impairment such as dementia.[42] Other demographic groups were not included due to insufficient sample sizes for COVID-19 cases. Two-sided, 2-sample test for equality of proportions with continuity correction were used to compare outcomes. Multiple comparisons were corrected by Bonferroni correction. Statistical tests were conducted with significance set at *P*-value < .05 (two-sided). All analyses were done using R, version 3.6.3.

3 | RESULTS

3.1 | Patient characteristics

The baseline characteristics of the study population (as of August 21, 2020) are presented in Table 1. Among 61,916,260 adult (age 18–65 years) and senior patients (age > 65 years), 1,064,960 had dementia (1.72% of the study population) including 351,590 with AD (0.57%), 126,450 with post-traumatic dementia (0.20%), 31,960 with presenile dementia (0.05%), 172,630 with senile dementia (0.28%), and 117,860 with vascular dementia (0.19%).

Among 15,770 adult and senior patients diagnosed with COVID-19, 810 patients had dementia (5.14% of the COVID-19 population) including 260 patients with AD (1.65% of the COVID-19 population), 70 with post-traumatic dementia (0.44%), 40 with presenile dementia (0.25%), 140 with senile dementia (0.89%), and 170 with vascular dementia (1.08%).

3.2 | Odds of COVID-19 in patients with dementia

We examined associations of dementia and its subtypes with COVID-19, after adjusting for age, sex, race, and COVID-19 risk factors,[2,29] including cardiovascular diseases, obesity, type 2 diabetes, asthma, chronic kidney diseases, chronic obstructive pulmonary disease, cancer, substance use disorders, transplant (bone marrow, solid organ), and nursing home stay. Patients with dementia were at significantly increased risk for COVID-19 (AOR: 2.00 [95% CI, 1.94–2.06], $P < .001$), with the strongest effect for vascular dementia (AOR: 3.17 [95% CI, 2.97–3.37], $P < .001$), followed by presenile dementia (AOR: 2.62 [95% CI, 2.28–3.00], $P < .001$), AD (AOR: 1.86 [95% CI, 1.77–1.96], $P < .001$), senile dementia (AOR: 1.99 [95% CI, 1.86–2.13], $P < .001$), and post-traumatic dementia (AOR: 1.67 [95% CI, 1.51–1.86] $P < .001$; Figure 1).

To examine how COVID-19 risk factors, alone and together, affected the odds of COVID-19 in patients with dementia, we calculated the odds of COVID-19 in patients with dementia adjusted for age, sex, and race, but not for COVID-19 risk factors (Figure 2). These medical conditions and procedures indeed contributed to the increased risk for COVID-19 in dementia patients as evidenced by the reductions of AORs after adjusting for these comorbidities (Figure 2 vs. Figure 1). For example, after adjustment for known COVID-19 risk factors, the majority of which are also risk factors for dementia, the odds of COVID-19 decreased from 3.17 to 2.00 for patients with dementia, from 2.98 to 1.86 for patients with AD, and from 5.26 to 3.17 for patients with vascular dementia. However, after adjusting for known COVID-19 risk factors, patients with dementia still had higher risk for COVID-19 compared to patients without dementia (Figure 1).

TABLE 1 Patient characteristics. Number of cases and percentage (%) are shown. The categories of race did not sum up to 100% for the following reasons: (1) only shows major subcategories of race; (2) not everyone in the EHR database has the race information, (3) a patient can report more than one race

Patient	Study population	Dementia	AD	COVID-19	COVID-19 + Dementia	COVID-19 + AD
Total	61,916,260	1,064,960	351,590	15,770	810	260
Sex						
Female	33,724,140 (54%)	635,200 (60%)	221,870 (63%)	9,360 (59%)	490 (60%)	170 (65%)
Male	27,818,100 (45%)	427,510 (40%)	128,880 (37%)	6,380 (40%)	310 (38%)	90 (35%)
Unknown	374,550 (< 1%)	2,250 (< 1%)	840 (< 1%)	30 (< 1%)	10 (< 1%)	0 (0%)
Age						
Adult (18 to 65)	44,002,620 (71%)	169,740 (16%)	13,590 (4%)	11,800 (75%)	130 (16%)	10 (4%)
Senior (> 65)	17,954,440 (29%)	895,810 (84%)	338,130 (96%)	3,980 (25%)	680 (84%)	240 (92%)
Race						
White	35,148,340 (57%)	817,070 (77%)	273,600 (78%)	7,940 (50%)	520 (64%)	170 (65%)
Black	6,408,230 (10%)	129,280 (12%)	40,080 (11%)	6,450 (41%)	260 (32%)	80 (31%)
Asian	1,009,910 (2%)	16,120 (2%)	4,510 (1%)	150 (1%)	0 (0%)	0 (0%)
Hispanic/Latino	860,230 (1%)	6,930 (1%)	2,020 (1%)	10 (< 1%)	0 (0%)	0 (0%)
Unknown	7,969,270 (13%)	144,910 (14%)	52,130 (15%)	850 (5%)	80 (10%)	20 (8%)

Abbreviations: AD, Alzheimer's disease; EHR, electronic health records.

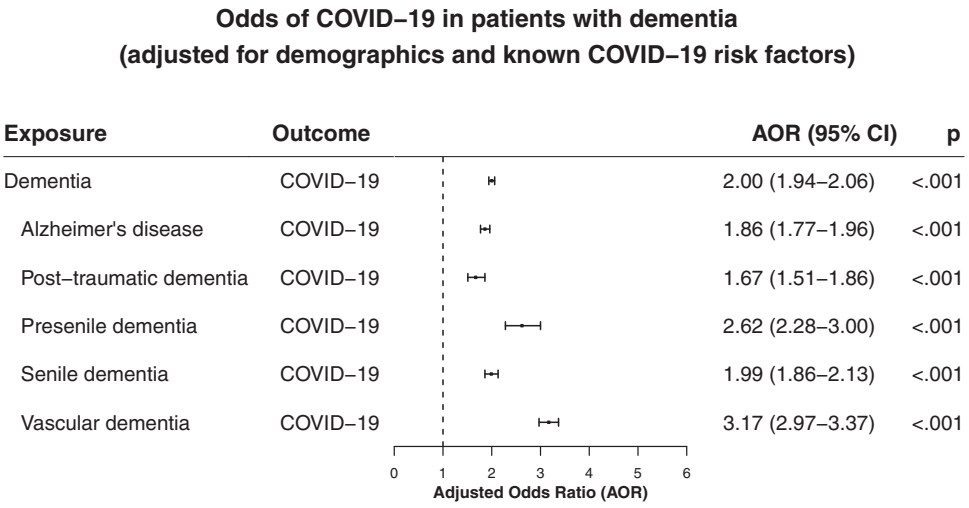

FIGURE 1 Odds of COVID-19 in patients with dementia compared to patients without dementia, after adjusting for age, sex, race, and COVID-19 risk factors including asthma, cardiovascular diseases, cancer, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, substance use disorders, transplant procedures (bone marrow, solid organ), and nursing home stay status. AOR, adjusted odds ratio; CI, confidence interval

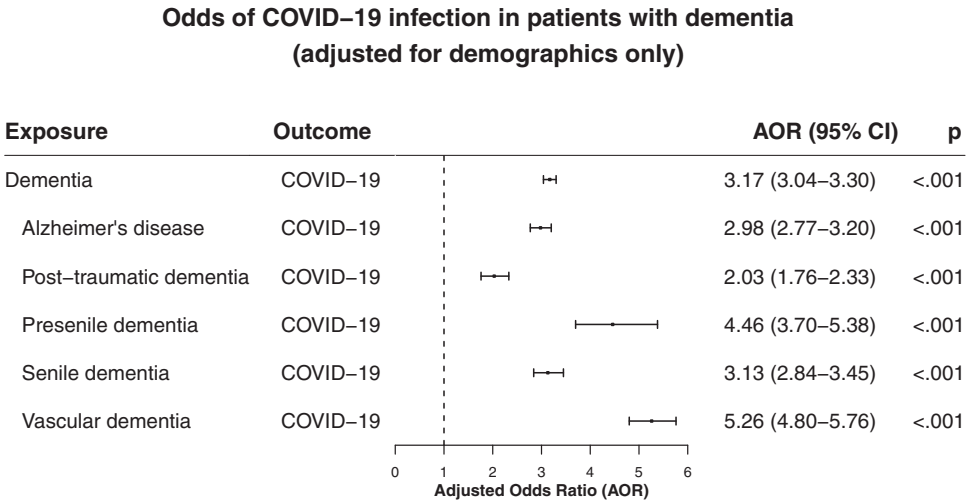

FIGURE 2 Odds of COVID-19 in patients with dementia compared to patients without dementia, after adjusting for demographics (age, sex, race). AOR, adjusted odds ratio; CI, confidence interval

3.3 | Demographic disparity of COVID-19 risk among patients with dementia

We examined how demographic factors (age, sex, race) affected COVID-19 risk among patients with dementia after adjusting for potential COVID-19 risk factors. Blacks with dementia were more likely to be infected by COVID-19 than Whites with dementia after adjusting for age, sex, and COVID-19 risk factors (AOR: 2.86 [95% CI, 2.67–3.06], $P < .001$), with similar racial disparity for AD and for vascular dementia. Data for presenile dementia, senile dementia, and post-traumatic dementia were not shown because sample sizes were limited for patients with both these types of dementia and COVID-19 when stratified by age, race, and sex. Interestingly, similar racial disparity was observed for patients with dementia without adjusting for COVID-19 risk factors (FigureS1 in supporting information, suggesting that factors other than known COVID-19 risk factors may have contributed to the significantly increased risk for COVID-19 in Blacks with dementia compared to Whites with dementia. Sex in general had no additional effects on risk of COVID-19 in patients with dementia. Age had no additional effects in patients with dementia in general and with AD in specific. Senior patients (age >65 years) with vascular dementia were less likely to be infected by SARS-CoV2 than adults (age 18–65 years) with vascular dementia (Figure 3).

3.4 | Hospitalization and mortality risk in adult and senior patients with dementia and COVID-19

The overall hospitalization risk over a 6-month period (from the start of the pandemic in February up to August 21, 2020) for 15,770 adult and senior patients with COVID-19 (age > 18 years) was 25.17%. Among 810 patients with COVID-19 and dementia, 480 were hospitalized (59.26%), higher for Blacks (73.08%) than Whites (53.85%; $P < .01$). Among 260 patients with COVID-19 and AD, 160 were hospitalized (61.54%), higher for Blacks (75.00%) than Whites (58.82%; $P = .02$). Among 14,960 adult and senior patients with COVID-19 but without dementia, 3480 were hospitalized (23.26%) in the 6-month period, higher for Blacks (31.99%) than Whites (18.57%; $P < .001$). The 6-month hospitalization risk for adult and senior patients with dementia but without COVID-19 was 12.40%, higher for Blacks (16.92%) than Whites (12.24%; $P < .001$). The 6-month hospitalization risk for adult and senior patients with AD but without COVID-19 was 13.80%, higher for Blacks (19.90%) than Whites (13.37%; $P < .001$; Figure 4). Overall the 6-month hospitalization risk for patients with dementia and COVID-19 (59.26%) was higher than for patients with COVID-19 but no dementia (23.26%; $P < .001$) and that for patients with dementia but no COVID-19 (12.40%; $P < .001$). COVID-19 and dementia had a synergistic effect on 6-month hospitalization risk because the risk was greater than the sum of their individual effects.

The 6-month mortality risk for 15,770 adult and senior (age > 18 years) patients with COVID-19 was 5.64%. Among 810 patients with COVID-19 and dementia, 170 died (20.99%), similar for Blacks (23.08%) and Whites (19.23%). Among 260 patients with COVID-19 and AD, 50 died (19.23%), similar for Blacks (25.00%) and Whites (17.65%). Among 14,960 adult and senior patients with COVID-19 but no dementia, 720 died (4.81%), higher for Blacks (6.46%) than Whites (3.77%; $P < .001$). The 6-month mortality risk for adult and senior patients with dementia but no COVID-19 was 7.64%, higher for Blacks (9.61%) than Whites (7.68%; $P < .001$). The mortality risk for adult and senior patients with AD but no COVID-19 was 9.71%, higher for Blacks (11.82%) than Whites (9.82%; $P < .001$; Figure 4). Overall the 6-month mortality risk for patients with dementia and COVID-19 (20.99%) was higher than for patients with COVID-19 but no dementia (4.81%; $P < .001$) and that for patients with dementia but no COVID-19 (7.64%; $P < .001$). COVID-19 and dementia had a synergistic effect on 6-month mortality risk as the risk was greater than the sum of their individual effects.

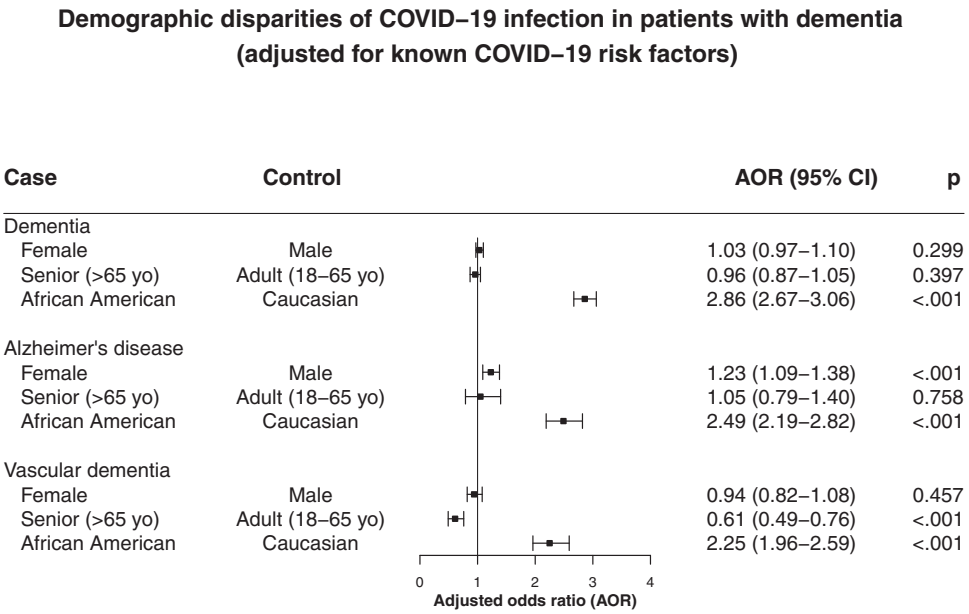

FIGURE 3 Effects of demographics on odds of COVID-19 among patients with dementia, after adjusting for age, sex, race, and COVID-19 risk factors including asthma, cardiovascular diseases, cancer, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive pulmonary disease, substance use disorders, transplant procedures (bone marrow, solid organ), and nursing home stay status. AOR, adjusted odds ratio; CI, confidence interval

4 | DISCUSSION

Based on analyses of a nationwide patient EHR database in the United States we show that patients with dementia had significantly increased risk for COVID-19 compared to patients without dementia. Among patients with dementia, Blacks were twice as likely to be infected by COVID-19 than Whites. Patients with dementia and COVID-19 had significantly worse outcomes (6-month hospitalization risk and mortality risk) than patients with dementia but no COVID-19 and patients with COVID-19 but no dementia, with synergistic effects of COVID-19 and dementia on patient outcomes observed. This study highlights the need to protect patients with dementia, especially those who are Black, as part of the strategy to control the pandemic.

In our study, patients with dementia were at significantly increased risk for COVID-19 compared to patients without dementia after adjusting for demographics and COVID-19 risk factors, many of which are also risk factors for dementia (AOR: 2.00). Comparing the odds of COVID-19 in patients with dementia before and after adjusting COVID-19 risk factors (AOR: 3.17 vs. 2.00), it is clear that these factors, many of which are also risk factors for dementia (e.g., cardiovascular diseases, type 2 diabetes, obesity, asthma, chronic kidney disease) indeed contributed to the high risk for COVID-19 in patients with dementia. Although a higher proportion of patients with dementia may reside in nursing homes and chronic care facilities, and close encounters predispose to transmission of the virus, the impact of dementia on the risk for SARS-CoV2 infection persists after controlling for nursing home care. Yet, even after adjusting for these risk factors, patients with dementia still had high risk for COVID-19 compared to patients without dementia. Reasons for this observed high risk for viral infection are the following: first, certain residual and unmeasured confounding factors (e.g., socioeconomic determinants, behavioral factors, lifestyle) may have contributed to the increased risk for COVID-19 in patients with dementia. For example, patients with dementia may be particularly prone to SARS-CoV2 infection because their impaired memory limits their ability to comply with recommendations for social distancing, mask wearing, or hand washing; second, dementia as a disease entity may have direct effects on patients' increased susceptibility to SARS-CoV2 infection because of a damaged BBB.[11–13] Prior studies suggested that increased BBB permeability in patients with dementia including vascular dementia and AD predisposes patients to bacterial and viral infections including herpes infection, pneumonia, syphilis, Lyme disease, and gum disease.[43–46] However, due to the limited number of patients with dementia and COVID-19 in our database and due to limited information for socioeconomic determinants, behavioral factors, and lifestyle factors available in the EHR database, we were unable to assess which and how these factors (e.g., dementia itself, socioeconomic determinants, behavioral factors, lifestyle), alone and together, contributed to the increased COVID-19 in patients with dementia.

There were substantial differences in dementia subtypes available in the database with respect to risk of COVID-19, with the greatest risk associated with vascular dementia. We were unable to examine some rarer types of dementia including Lewy body dementia, frontotemporal dementia, and mixed dementia due to their insufficient sample sizes for COVID-19 cases. In vascular dementia, cognitive impairment is attributable to cerebrovascular pathologies and alteration in cerebral blood vessels[47–48] with damage to the BBB.[13] Because the virus can attack the brain or its blood vessels directly, and receptors

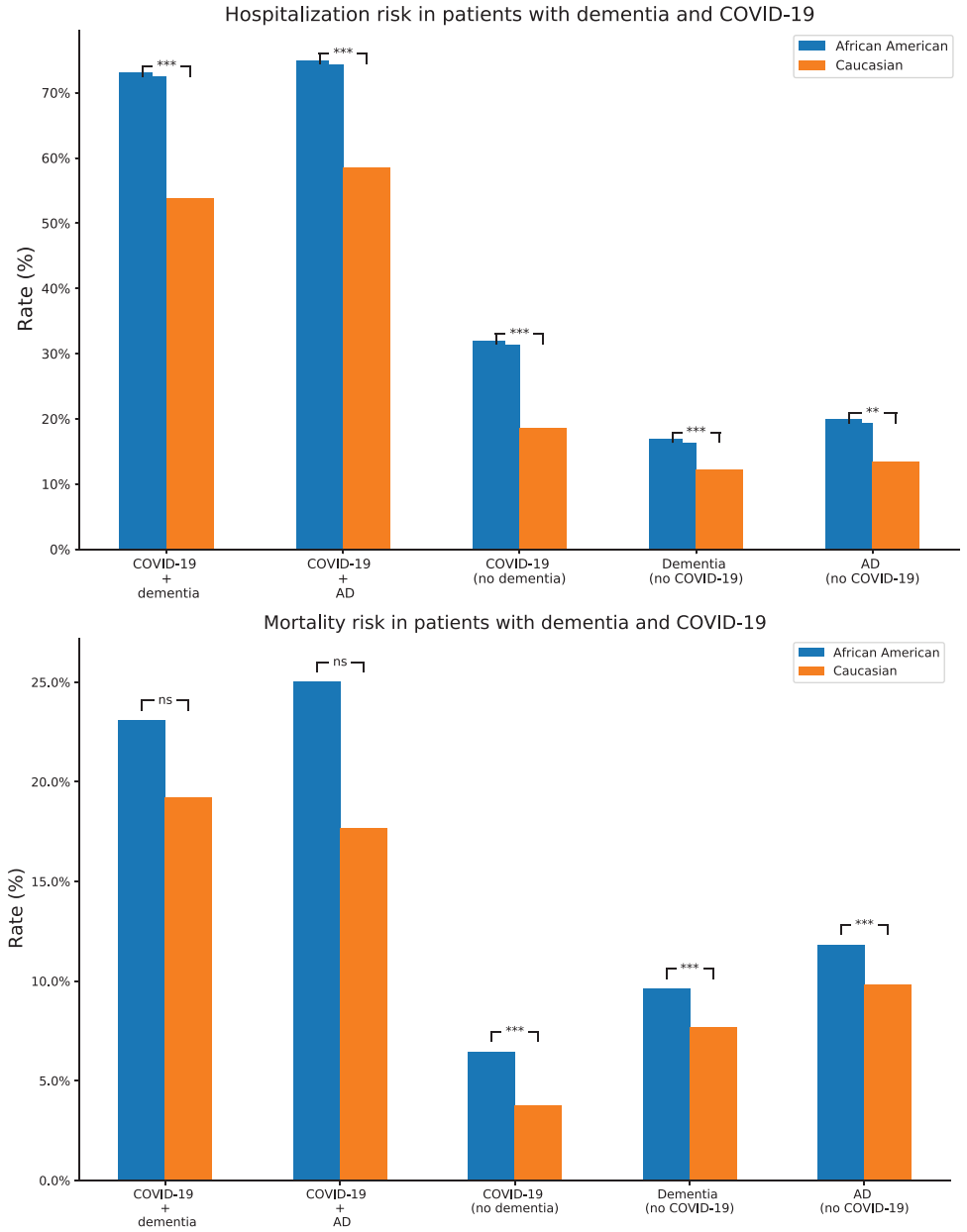

FIGURE 4 Six-month hospitalization and mortality risks among three adult (age > 18) population: patients with both dementia (or Alzheimer's disease [AD]) and COVID-19, patients with COVID-19 but no dementia, and patients with dementia (or AD) but no COVID-19. ***: $P < .001$; **: $P < .01$; ns, not significant

for the virus are found in the vicinity of brain vasculature,[16] we speculate that underlying brain pathology, especially impaired cerebral blood flow, or damaged endothelium, is a risk for SARS-CoV 2 entry. Consistently, our analyses showed that the odds of SARS-CoV 2 infection for patients with vascular dementia remained more than three times increased over patients without vascular dementia even after adjusting for cardiovascular diseases, type 2 diabetes, obesity, chronic kidney diseases, chronic obstructive lung disease, and other known risk factors. These results suggest that while comorbidities and other COVID-19 risk factors increased the risk for COVID-19 in patients with vascular dementia, the brain vascular pathology itself could also be involved in SARS-CoV 2 infection or subsequent damage in the brain.

An important finding of our study is that Blacks with dementia are more likely to be infected by SARS-CoV 2 compared to Whites with dementia (AOR = 2.86), with similar racial disparity observed for the five specific types of dementia we tested. This is consistent with prior data showing that COVID-19 affects Blacks at a disproportionately high rate.[17] Our study showed similar racial disparity for COVID-19 risk before and after controlling for COVID-19 risk factors, suggesting that factors other than strictly medical conditions, including access to health care, socioeconomic status, and social adversity, may have contributed to this profound racial disparity. However, due to limited socioeconomic information on patients in the EHR database, we were unable to assess how these factors differentially affected the risk for

COVID-19 in Blacks with dementia. The risk of death in patients with COVID-19 increases significantly with age and the mortality risk in men is twice that in women.[18–20] This is consistent with the fact that age is the major risk factor for death from COVID[49] and that the mortality risk in men is in general higher than women because of the influences of healthy behaviors, cardiorespiratory fitness, and other factors.[50–51] However, it is less obvious how advanced age and sex affected the susceptibility to COVID-19 in patients with dementia. Our study showed that advanced age had no additional effect on the risk of getting COVID-19 among patients with dementia after adjusting for medical conditions, sex, and nursing home stay. We speculate that older people, including older patients with dementia, although they have weakened body systems and function compared to younger people, may be more likely to stay at home, less likely to go to work and socialize, which creates exposure to virus. Although prior studies showed substantial sex disparities in dementia risk and COVID-19 mortality, our study showed no sex disparities in COVID-19 risk in patients with dementia.

Our study showed that 5.64% of adult COVID-19 patients died over a 6-month period, consistent with the percentage of death (5.9%) attributed to COVID-19 for the period of February to August reported by the Centers for Disease Control and Prevention.[1] This mortality risk was actually less than that recorded in our study population for patients with dementia who were not infected with SARS-CoV 2. However, patients with both dementia and COVID-19 had significantly worse outcomes than either patients with COVID-19 but no dementia or patients with dementia but no COVID-19 (Figure 4). We observed these synergistic effects between COVID-19 and dementia on both mortality risk and hospitalization risk. Mechanisms underlying this remarkable synergy warrant further investigation. We speculate that preexisting damage to the brain, especially vascular damage, may permit greater virus entry into the brain and promote the brain pathology of COVID-19, both inflammatory and thrombotic, which is then exacerbated by hypoxia and failure of other organs such as the heart or lungs. Blacks with dementia had higher hospitalization risk than Whites, which is consistent with recent reports of disproportionately high COVID-19 hospitalizations in this population in general.[17] However, in our analysis of a small sample size, Blacks with dementia were not significantly more likely to die from COVID-19 than White patients. A limitation in our outcome analysis was our inability to control for medical comorbidities and other factors that might have contributed to the mortality and hospitalization risks due to the limited sample size of patients with COVID-19 and dementia in our study, and the multiplicity of medical conditions and social/environmental factors that are likely to have contributed to the synergistic effect in mortality and hospitalizations we observed in patients with dementia and COVID-19.

There is evidence for a bidirectional relationship between viral infections and dementia: people with dementia have an increased risk for infection while a poor immune response to infection places individuals at increased risk for dementia.[52] In this study, we hypothesized that patients with dementia were more vulnerable to SARS-CoV 2 infection because known COVID-19 risk factors (e.g., cardiovascular diseases, obesity, type 2 diabetes) overlap with those for dementia, the damaged BBB in patients with dementia predisposes them to bacterial and viral infections, and the memory impairment associated with dementia may interfere with the patient's ability to comply with preventive measures for COVID-19. We showed that patients with dementia were at increased risk for COVID-19 compared to patients without dementia. It remains to be determined whether a SARS-CoV 2 infection will accelerate cognitive decline in patients with dementia or lead to long-term cognitive impairments and trigger dementia in infected people. Neurological manifestations of COVID-19 range from headache, loss of smell, confusion, strokes, brain hemorrhage to memory loss.[16] Increasing evidence shows that SARS-CoV 2 can infect neurons and affect brain function through chronic hypoxia, metabolic dysfunction, systemic inflammation, and immune dysregulation.[16,53–55] Prior studies have suggested that infections by Chlamydia pneumoniae, herpes virus, or spirochetes could then potentially trigger, or worsen, neurodegeneration.[56] Based on these considerations, we anticipate significant long-term neurological effects of SARS-CoV 2 infection in triggering or worsening dementia in survivors of COVID-19 and expect higher prevalence of dementia in patients with COVID-19 compared to the non-infected population in the future.

Our study is based on retrospective analysis of patient EHR data. Patient EHR data have been widely used for observational studies,[57–60] although they have inherent limitations when used for research purposes, including underdiagnosis, overdiagnosis, or misdiagnosis, and limited information on socioeconomic and lifestyle determinants, among others. The number of COVID-19 cases in the database is substantially lower, proportionately to sample size, than reported cases in the United States. Because COVID-19 is regularly tested at drive-ups and pop-up testing locations, many of the reported cases may have not be captured by diagnosis codes in EHRs. Another limitation is that the patients in this study were individuals who have encounters with health-care systems and are not necessarily representative of the general population in the United States. Despite these limitations, this large nationwide database allows us to identify early trends in risks, disparities, and outcomes of COVID-19 in dementia patients engaged with health-care systems on a nationwide basis.

Findings from this EHR-based study on a nationwide population basis are associational not causal. These associational findings need to be replicated in and compared to other EHR databases and patient registries, and preferably validated in contemporaneous prospective data collection studies in which specific biologic hypotheses can be tested. Our study can serve as a baseline study of initial COVID-19 risk, racial disparity, and outcomes observations in patients with dementia across the United States.

AUTHOR CONTRIBUTIONS

QuanQiu Wang and Rong Xu conceived the study, designed the study, conducted the analysis, and authored the manuscript. Pamela B. Davis and Mark E. Gurney critically contributed to data interpretation, results, discussion, and manuscript preparation. All authors approved the manuscript. QuanQiu Wang and Rong Xu had access to the original data.

CONFLICTS OF INTEREST

QuanQiu Wang, Pamela B. Davis, Mark E. Gurney and Rong Xu have no financial interests to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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