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MAJOR ARTICLE

New-Onset Dementia Among Survivors of Pneumonia Associated With Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Adnan I. Qureshi,[1] William I. Baskett,[2] Wei Huang,[1] S. Hasan Naqvi,[3] and Chi-Ren Shyu[2,3,4]

[1]Zeenat Qureshi Stroke Institutes and Department of Neurology, University of Missouri, Columbia, Missouri, USA, [2]Institute for Data Science and Informatics, University of Missouri, Columbia, Missouri, USA, [3]Department of Medicine, University of Missouri, Columbia, Missouri, USA, and [4]Department of Electrical Engineering and Computer Science, University of Missouri, Columbia, Missouri, USA

Background. Case series without control groups suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may result in cognitive deficits and dementia in the postinfectious period.

Methods. Adult pneumonia patients with SARS-CoV-2 infection (index hospitalization) and age-, gender-, and race/ethnicity-matched contemporary control pneumonia patients without SARS-CoV-2 infection were identified from 110 healthcare facilities in United States. The risk of new diagnosis of dementia following >30 days after the index hospitalization event without any previous history of dementia was identified using logistic regression analysis to adjust for potential confounders.

Results. Among 10 403 patients with pneumonia associated with SARS-CoV-2 infection, 312 patients (3% [95% confidence interval {CI}, 2.7%–3.4%]) developed new-onset dementia over a median period of 182 days (quartile 1 = 113 days, quartile 3 = 277 days). After adjustment for age, gender, race/ethnicity, hypertension, diabetes mellitus, hyperlipidemia, nicotine dependence/tobacco use, alcohol use/abuse, atrial fibrillation, previous stroke, and congestive heart failure, the risk of new-onset dementia was significantly higher with pneumonia associated with SARS-CoV-2 infection compared with pneumonia unrelated to SARS-CoV-2 infection (odds ratio [OR], 1.3 [95% CI, 1.1–1.5]). The association remained significant after further adjustment for occurrence of stroke, septic shock, and intubation/mechanical ventilation during index hospitalization (OR, 1.3 [95% CI, 1.1–1.5]).

Conclusions. Approximately 3% of patients with pneumonia associated with SARS-CoV-2 infection developed new-onset dementia, which was significantly higher than the rate seen with other pneumonias.

Keywords. severe acute respiratory syndrome coronavirus 2; coronavirus disease; dementia; pneumonia; cognitive impairment.

Understanding the long-term burden of disability among survivors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is a current priority [1, 2]. There are several reports of mild to severe cognitive impairment including decline in memory, concentration, executive functioning, and visuospatial functioning after recovery from SARS-CoV-2 infection [3–6]. It remains unclear whether the frequency and severity of cognitive deficits in SARS-CoV-2 infection are distinct from the known cognitive impairment that occurs following other respiratory diseases [7, 8]. Further research is required to increase our understanding of cognitive impairment, particularly severe impairment among the 200 million SARS-CoV-2 infection survivors worldwide [9]. The prevalence and risk of dementia in survivors of SARS-CoV-2 infection have multiple implications for screening, postrecovery care and resources, caregiver burden, and financial and productivity loss. The impact on public health may be much larger than the acute manifestations of SARS-CoV-2 infection due to lifelong burden of dementia. We performed the study using a large cohort representative of the United States (US) to analyze the occurrence of dementia and associated risk factors and outcomes after SARS-CoV-2 infection.

METHODS

Patients

We analyzed the Cerner Real-World Data extracted from the electronic medical records of healthcare facilities that have a data use agreement with Cerner Corporation [10, 11]. The Cerner Real-World Data are available through Cerner Corporation. The Cerner Real-World Data, quarter 3 2021 through July 2021, was collected from 110 contributing Cerner Real-World Data health systems that had records from approximately 1.4 billion

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Correspondence: Adnan I. Qureshi, MD, Zeenat Qureshi Stroke Institutes and Department of Neurology, University of Missouri, One Hospital Drive CE507, Columbia, MO 65212, USA (qureshai@gmail.com).

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medical encounters. The analysis used electronic medical records from encounters prior to 31 July 2021. The dataset, as part of de-identification procedure, does not provide an identifier for the medical institution of a patient's data or its precise location. The healthcare networks were classified as regional hospital (n = 27), community healthcare (n = 23), integrated delivery networks (n = 21), community hospitals (n = 12), academic hospitals (n = 10), critical access hospitals (n = 7), and others (n = 10). The distribution of hospitals according to first digit of zip code of location is as follows: 6 (n = 28), 9 (n = 13), 5 (n = 12), 7 (n = 11), 2 (n = 9), 3 (n = 9), 8 (n = 8), 4, (n = 8), 0 (n = 7), and 1 (n = 5). Participating hospitals are somewhat disproportionately located in the Midwest and Pacific West areas.

Selection of Patients

We selected patients who qualified for inclusion based on the following criteria:

1. Patients diagnosed with pneumonia during a hospitalization lasting >24 hours designed as index hospitalization. Pneumonia was defined based on *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) primary diagnosis codes J12–J18. The hospital admission with pneumonia diagnosis was used as the index encounter. All events were recorded relative to this hospitalization;
2. Patients had at least 4 encounters within 2 years prior to their index encounter; AND
3. Patients had at least 2 encounters >30 days after the index encounter.

Motivations for Selection Criteria

Only patients with pneumonia were included in this analysis to ensure that observed effects were due to SARS-CoV-2 infection and not generic respiratory illness. The requirement of ≥4 encounters in the preceding 2 years was intended to ensure that patients did not have undiagnosed dementia prior to their index encounter. The requirement for ≥2 subsequent encounters following the index encounter was intended to increase the yield of identifying patients who developed dementia.

Identification of Patients With SARS-CoV-2 Infection

Patients with a positive laboratory test for SARS-CoV-2 were identified based on Logical Observation Identifiers Names and Codes (LOINC) 41458-1, 94309-2, 94500-6, 94533-7, 94534-5, and 94646-7. These codes denote detection of SARS-CoV-2 RNA in respiratory (nasopharyngeal swabs, bronchoalveolar lavage, sputum) and other specimens or detection of SARS-CoV-2 N gene or RdRp gene in respiratory secretions, all by nucleic acid amplification with probe detection. The Food and Drug Administration has only approved assays for detection of SARS-CoV-2 N gene or RdRp gene in respiratory secretions in the US.

Identification of Controls

We attempted to reduce confounders resulting from differences in the population of patients with SARS-CoV-2 infection and control patients by selecting a control group with an identical demographic distribution to the SARS-CoV-2–infected patients. We identified control patients from a sample of patients admitted to the hospital without SARS-CoV-2 infection with lack of infection confirmed by 1 of the previously listed tests. Each SARS-CoV-2–infected patient was matched with a pneumonia patient using age, gender, race/ethnicity, and index encounter admission date. This resulted in 2 cohorts with nearly identical distributions of demographics and hospitalization dates.

Identification of New-Onset Dementia

We used the *ICD-10-CM* primary diagnosis codes F01.5, F02.8, F03.9, G30, G31, and G32 to identify patients diagnosed with new-onset dementia. Our analysis included only patients with significant recent medical history to ensure completeness of the records of potential comorbidities. We excluded all patients with previous medical encounter diagnosis of dementia in any encounters prior to index encounter.

Data Ascertained

Factors known or suspected to affect the risk of new-onset dementia as identified in previous studies [12, 13] were extracted for each patient at any encounter. The following *ICD-10-CM* codes were used to identify patients with hypertension (I10, O10.0, O10.9, I16, and I67.4), diabetes mellitus (E08, E09, E10, E11, and E13), hyperlipidemia (E78), nicotine dependence/tobacco use (F17), alcohol use or abuse (F10), atrial fibrillation (I48), stroke (ischemic stroke, I63, I65 and I66; intracerebral hemorrhage, I61 and I62.9; or subarachnoid hemorrhage, I60), myocardial infarction (I21), congestive heart failure (I09.81, I11.0, and I50), and septic shock (R65.21). We used occurrence of intubation/mechanical ventilation and septic shock at the medical encounter for pneumonia as surrogate markers for severity of pneumonia, consistent with previous studies [14]. Intubation and mechanical ventilation were identified by *ICD-10* Procedure Coding System codes 0BH17EZ and Z99.11 or *Current Procedural Terminology* codes 31500, 94656, and 94657 (for intubation) or 94002 to 94005 (for mechanical ventilation). We also identified occurrence of stroke during index encounter by identifying ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage as mentioned above to adjust for any disproportionate occurrence of stroke (a risk factor for dementia) [15] among SARS-CoV-2–infected patients. To increase the sensitivity of detecting any preexisting cognitive deficits prior to occurrence of pneumonia, we identified other concurrent diagnoses that may

be associated with cognitive deficits such as multiple sclerosis (G35), previous mental disorders due to drug use (F10–F19), encephalopathy (G93.4). delirium (F05), other mental disorders due to known physiological condition (F06), personality and behavioral disorders due to known physiological condition (F07) [16], and depression (F20.4, F31.3–F31.5, F32–F33, F34.1, F41.2, and F43.2) [17].

Outcomes were assessed by evaluating discharge status from hospitalizations >30 days after the index encounter. These were categorized into routine, nonroutine, and death. Patients with routine discharges were considered to have none or mild disability while patients discharged to nonroutine locations such as skilled nursing facilities or nursing homes were considered to have moderate to severe disability, as previously described and validated [18].

Statistical Analysis

We calculated the proportion of patients who had new-onset dementia with 95% confidence interval (CI) without continuity correction. We performed a case-control analysis by comparing cardiovascular risk factors, septic shock, intubation/mechanical ventilation, and discharge status for pneumonia patients in strata based on presence or absence of SARS-CoV-2 infection. We performed logistic regression analysis including all cases and controls to identify the independent effect of SARS-CoV-2 infection and included age, gender, race/ethnicity, hypertension, diabetes mellitus, hyperlipidemia, nicotine dependence/tobacco use, alcohol use/abuse, atrial fibrillation, previous stroke, and congestive heart failure in the multivariate model. We repeated the analysis after adding occurrence of stroke, septic shock, and intubation/mechanical ventilation during index encounter in the model, which provide a measure of severity of pneumonia [14].

All the hypothesis tests were 2-sided, with $P < .05$ considered statistically significant, and all the analyses were done using R software (version 3.6.1).

RESULTS

Overall Rates of New-Onset Incident Dementia

Among 10 403 patients with pneumonia associated with SARS-CoV-2 infection, 312 patients (3% [95% CI, 2.7%–3.4%]) developed new-onset dementia. The median time interval between pneumonia associated with SARS-CoV-2 infection and new-onset dementia was 182 days (quartile 1 = 113 days, quartile 3 = 277 days). Among 10 403 patients with pneumonia unrelated to SARS-CoV-2 infection, 263 (2.5% [95% CI, 2.2%–2.9%]) developed new-onset dementia. The rates of new-onset dementia according to age group in pneumonia patients and presence or absence of SARS-CoV-2 infection are presented in Figure 1 and suggest that the most prominent difference in occurrence of new-onset dementia occurred in patients aged >70 years.

Comparison of Risk Factors in Patients With Pneumonia

There was a significantly higher rate of hyperlipidemia, diabetes mellitus, and hypertension among pneumonia patients with SARS-CoV-2 infection compared with those without SARS-CoV-2 infection (Table 1). The proportions of patients with nicotine dependence/tobacco use, alcohol use or abuse, atrial fibrillation, previous stroke, congestive heart failure, mental disorders due to drug use, depression, and encephalopathy were significantly lower among patients with SARS-CoV-2

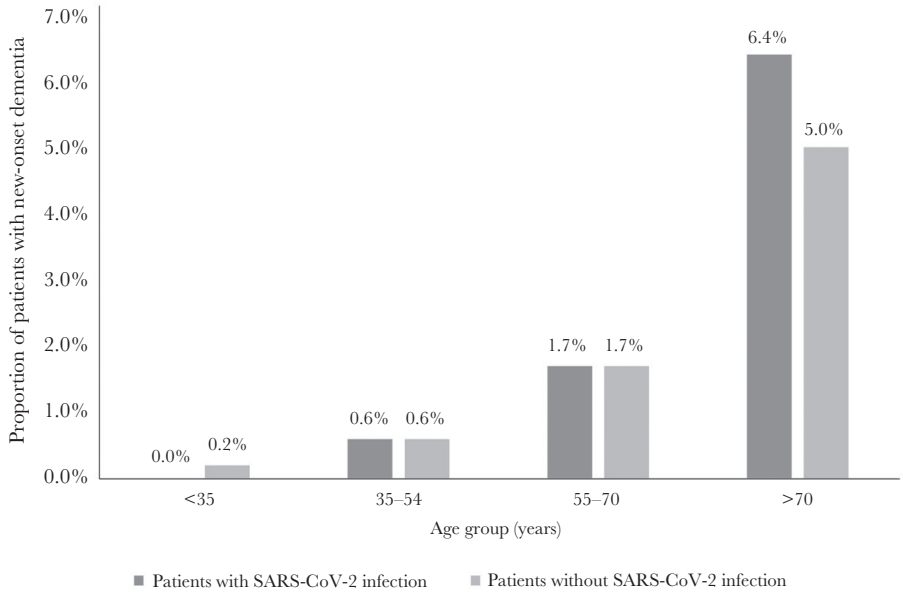

Figure 1. New-onset dementia according to age groups in pneumonia patients. Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Demographic and Clinical Characteristics of Pneumonia According to Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Variable	Patients With SARS-CoV-2 Infection	Patients Without SARS-CoV-2 Infection	*P* Value
Total	10403	10403	
Demographics			
Age (in years)			.9913
<35	552 (5.3)	552 (5.3)	
35–54	2162 (20.8)	2162 (20.8)	
55–70	4131 (39.7)	4151 (39.9)	
>70	3558 (34.2)	3538 (34)	
Gender			1
Men	5050 (48.5)	5050 (48.5)	
Women	5351 (51.4)	5351 (51.4)	
Race/ethnicity			1
White	6810 (65.5)	6810 (65.5)	
Black	1172 (11.3)	1172 (11.3)	
Hispanic	529 (5.1)	529 (5.1)	
Asian	52 (0.5)	52 (0.5)	
Other	1840 (17.7)	1840 (17.7)	
Cardiovascular risk factors/diseases			
Hypertension	8286 (79.7)	7885 (75.8)	<.0001
Diabetes mellitus	5701 (54.8)	4701 (45.2)	<.0001
Hyperlipidemia	6803 (65.4)	5940 (57.1)	<.0001
Nicotine dependence/tobacco use	2014 (19.4)	3638 (35)	<.0001
Alcohol use or abuse	664 (6.4)	1203 (11.6)	<.0001
Atrial fibrillation	2237 (21.5)	2802 (26.9)	<.0001
Previous stroke	940 (9)	1134 (10.9)	<.0001
Previous myocardial infarction	1218 (11.7)	1246 (12)	.548
Congestive heart failure	3018 (29)	4178 (40.2)	<.0001
Mental disorders due to drug use	1983 (19.1)	3242 (31.2)	<.0001
Depression	2151 (20.7)	2544 (24.5)	<.0001
Encephalopathy	699 (6.7)	1000 (9.6)	<.0001
Multiple sclerosis	66 (0.6)	61 (0.6)	.656
Delirium	68 (0.7)	58 (0.6)	.372
Other mental disorders due to known physiological condition	57 (0.5)	60 (0.6)	.781
Personality and behavioral disorders due to known physiological condition	40 (0.4)	39 (0.4)	.91
Events during index hospitalization			
Septic shock	279 (2.7)	444 (4.3)	<.0001
Intubation/mechanical ventilation	624 (6)	627 (6)	.9303
Stroke	238 (2.3)	406 (3.9)	<.0001
Nonroutine discharge (excluding death)	7672 (73.7)	7548 (72.6)	.052

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

infection compared with those without SARS-CoV-2 infection. The proportion of patients who had septic shock (4.3% vs 2.7%, $P < .001$) or stroke (3.9% vs 2.3%, $P < .001$) during index hospitalization was significantly higher among pneumonia patients without SARS-CoV-2 infection. There were no differences in the proportion of patients with delirium between the 2 groups.

Risk of New-Onset Dementia in Multivariate Analysis

There was a significantly higher rate of new-onset dementia among patients with SARS-CoV-2 infection compared with those without SARS-CoV-2 infection (3% vs 2.5%, $P = .04$). After adjustment for age, gender, race/ethnicity, hypertension, diabetes mellitus, hyperlipidemia, nicotine dependence/tobacco use, alcohol use or abuse, atrial fibrillation, previous stroke, congestive heart failure, mental disorders due to drug use, depression, encephalopathy, multiple sclerosis, delirium, other mental disorders due to known physiological condition and personality and behavioral disorders due to known physiological condition, the risk of new-onset dementia was significantly higher in patients with pneumonia associated with SARS-CoV-2 infection compared in patients with pneumonia unrelated to SARS-CoV-2 infection (odds ratio [OR], 1.3 [95% CI, 1.1–1.5], $P = .003$) (Table 2). After adjusting for septic shock, intubation/mechanical ventilation, and occurrence of stroke during index encounter in addition to the abovementioned confounders, the risk of new-onset

Table 2. Predictors of New-Onset Dementia Among Patients With Pneumonia in Multivariate Analysis

	Model 1[a]	Model 2[b]
Predictors	OR (95% CI)	OR (95% CI)
Primary study predictor		
SARS-CoV-2 infection	1.3 (1.1–1.5)	1.3 (1.1–1.5)
Demographics		
Age (in years)		
<35	1 (1–1)	1 (1–1)
35–54	5.4 (.7–40.1)	5.4 (.7–39.6)
55–70	13.9 (1.9–100.2)	13.1 (1.8–94.1)
>70	54.0 (7.5–387.9)	49.0 (6.8–352.1)
Men	1.1 (.9–1.3)	1.1 (.9–1.3)
Race/ethnicity		
White	1 (1–1)	1 (1–1)
Asian	1.9 (.8–4.9)	2.1 (.8–5.3)
Black	1.3 (.99–1.8)	1.3 (.97–1.7)
Hispanic	2.0 (1.5–2.8)	1.8 (1.4–2.5)
Other	1.3 (1–1.6)	1.3 (.99–1.6)
Cardiovascular risk factors/diseases		
Hypertension	1.3 (.99–1.8)	1.3 (.98–1.8)
Diabetes mellitus	1.1 (.9–1.3)	1.1 (.9–1.3)
Hyperlipidemia	1.0 (.8–1.3)	1.0 (.8–1.3)
Nicotine dependence/tobacco use	1.2 (.9–1.6)	1.2 (.9–1.6)
Alcohol use or abuse	1.8 (1.3–2.4)	1.8 (1.3–2.4)
Atrial fibrillation	1.1 (.9–1.3)	1.1 (.9–1.3)
Previous stroke	1.2 (.9–1.5)	1.1 (.8–1.3)
Congestive heart failure	1.2 (.96–1.4)	1.1 (.9–1.4)
Mental disorders due to drug use	0.9 (.7–1.3)	0.95 (.7–1.3)
Depression	1.3 (1.1–1.6)	1.3 (1.1–1.6)
Encephalopathy	2.2 (1.7–2.8)	2.2 (1.7–2.8)
Multiple sclerosis	0.3 (.05–2.5)	0.3 (.04–2.3)
Delirium	3.3 (1.8–5.8)	3.1 (1.8–5.6)
Other mental disorders due to known physiological condition	0.7 (.2–2.2)	0.7 (.2–2.3)
Personality and behavioral disorders due to known physiological condition	1.1 (.3–3.8)	1.2 (.4–4.0)
Events during index hospitalization		
Septic shock	…	0.97 (.6–1.5)
Intubation mechanical ventilation	…	1.1 (.8–1.6)
Stroke	…	1.8 (1.3–2.6)

Abbreviations: CI, confidence interval; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Model 1 includes age, gender, race/ethnicity, hypertension, diabetes mellitus, hyperlipidemia, nicotine dependence/tobacco use, alcohol use or abuse, atrial fibrillation, previous stroke, congestive heart failure, mental disorders due to drug use, depression, encephalopathy, multiple sclerosis, delirium, other mental disorders due to known physiological condition, and personality and behavioral disorders due to known physiological condition.

[b]Model 2 includes age, gender, race/ethnicity, hypertension, diabetes mellitus, hyperlipidemia, nicotine dependence/tobacco use, alcohol use or abuse, atrial fibrillation, previous stroke, congestive heart failure, mental disorders due to drug use, depression, encephalopathy, multiple sclerosis, delirium, other mental disorders due to known physiological condition, personality and behavioral disorders due to known physiological condition, septic shock, intubation/mechanical ventilation, and stroke.

dementia was significantly higher with pneumonia associated with SARS-CoV-2 infection (OR, 1.3 [95% CI, 1.1–1.5], $P = .004$).

Other variables associated with new-onset dementia (Table 2) included age 55–70 years (OR, 13.1), age >70 years (OR, 49.0), Hispanic ethnicity (OR, 1.8), alcohol use or abuse (OR, 1.8), previous depression (OR, 1.3), previous encephalopathy (OR, 2.2), previous delirium (OR, 3.1), or stroke during index hospitalization (OR, 1.8).

DISCUSSION

New-Onset Dementia in SARS-CoV-2 Infection Survivors

We found an increased rate of new-onset dementia among survivors of pneumonia associated with SARS-CoV-2 infection compared with those without SARS-CoV-2 infection. Our study only included new-onset dementia associated with hospital admission with a short follow-up period. Therefore, minor cognitive deficits and dementia diagnosis over longer period are not ascertained. There are several reports of cognitive impairment ranging from mild to severe after recovery from SARS-CoV-2 infection [19, 20]. Previous studies have demonstrated a very high rate of delirium with a combination of acute attention, awareness, and cognition disturbances in patients with severe SARS-CoV-2 infection [20]. Recent studies have suggested that the severe cognitive deficits continue to be seen after recovery from initial SARS-CoV-2 infection [3, 5]. Among survivors of SARS-CoV-2 infection who require inpatient rehabilitation due to impairments in mobility and/or activities of daily living, 80% demonstrate cognitive deficits of various severities. The dementia seen in survivors of SARS-CoV-2 infection mainly affects executive, memory, attentional, and visuospatial functions, with relatively preserved orientation and language [5].

Identification of Independent Association Between SARS-CoV-2 Infection and New-Onset Dementia

We used patients admitted with pneumonia not associated with SARS-CoV-2 infection as controls. Cognitive dysfunction and dementia can occur following any pneumonia [21] and using a case-control design helped identify the association between SARS-CoV-2 infection and new-onset dementia, which was greater than seen with other pneumonias in our study. We adjusted for cardiovascular risk factors and cardiovascular diseases in our analysis. There may be a high rate of cardiovascular risk factors and diseases among patients with SARS-CoV-2 infection [22–24]. Since cardiovascular risk factors and diseases may increase the risk of dementia [12, 13], any unadjusted imbalance may confound the relationship between SARS-CoV-2 infection and dementia. We found that proportions of patients with hypertension and diabetes mellitus were higher among SARS-CoV-2–infected patients compared with controls. Surprisingly, proportions of patients with other cardiovascular risk factors and cardiovascular diseases such as cigarette smoking, alcohol use, previous stroke, atrial fibrillation, and congestive heart failure were higher among controls. The risk of new stroke during index hospitalization was not

higher among pneumonia patients with SARS-CoV-2 infection, consistent with recent studies [25]. Adjustments for such imbalances were subsequently made in the multivariate analysis. The risk of new-onset dementia following pneumonia increases with greater severity of illness [7, 8]. Respiratory failure or shock during hospitalization was associated with a high rate of dementia and cognitive impairment within 3–12 months after discharge [7, 8]. Since the risk of new-onset dementia is also related to severity of pneumonia, we adjusted for severity of pneumonia using 2 surrogate markers of severity of pneumonia, septic shock, and intubation/mechanical ventilation [14].

Our findings are similar to those of Taquet et al [16], who used the TriNetX Analytics Network data to identify the risk of dementia in 3 propensity score–matched cohorts of patients, including those with SARS-CoV-2 infection, those with influenza, and those with other respiratory infections. The hazard ratio (HR) for dementia was higher among patients with SARS-CoV-2 infection compared with those admitted with influenza (HR, 2.3 [95% CI, 1.8–3.1]) and those with other respiratory tract infections (HR, 1.7 [95% CI, 1.5–2.0]). However, Taquet et al [16] included occurrence of dementia as an outcome at any time between 1 and 180 days after the index event. Our study included occurrence of dementia after 30 days of index event to focus on occurrence of dementia in the convalescent phase and to avoid the confounding effect of events in the acute phase.

Mechanism of Dementia in Patients With SARS-CoV-2 Infection

Acute hypoxic injury in the cerebrum and cerebellum and loss of neurons in the cerebral cortex, hippocampus, and cerebellar Purkinje cell layer, with foci of perivascular lymphocytes and focal leptomeningeal inflammation, are seen in patients with SARS-CoV-2 infection [26]. Subcortical micro- and macrohemorrhages, cortico-subcortical edematous changes evocative of posterior reversible encephalopathy syndrome, and nonspecific deep white matter changes have also been observed [27]. Plasma biomarkers of central nervous system injury, neurofilament light chain protein (neurofilament light chain protein, a marker of intra-axonal neuronal injury), and glial fibrillary acidic protein (glial fibrillary acidic protein, a marker of astrocytic activation/injury) are increased in patients with severe SARS-CoV-2 infection compared with controls [28]. The pattern suggests a sequence of early astrocytic response and more delayed axonal injury. The current evidence does not support SARS-CoV-2 directly entering the brain to infect and damage neural tissue, but occurrence of prominent neuroinflammatory changes support a role for inflammation [29]. Inflammatory cytokines were elevated up to 8 months after SARS-CoV-2 infection [30]. Three mechanisms have been proposed in mediation of neural injury as a consequence of inflammation. First, inflammatory events in the thoracic abdominal cavity result in increased activity of vagal-nerve sensory afferents, vagal efferent outflow, and acetylcholine secretion, which may modify these inflammatory events [31]. Vagus nerve activity inhibits proinflammatory cytokine release through the cholinergic anti-inflammatory pathway [32]. Second, systemic cytokines and inflammatory mediators enter the brain via defects in blood–brain barrier in the circumventricular organs to initiate inflammatory pathways by microglia activation. Third, the cytokines and other inflammatory mediators [33] interact directly with the brain endothelium, communicating directly across the blood–brain barrier and to perivascular macrophages, possibly through the induction of lipid mediators, in particular prostaglandin E_2 [34]. Prostaglandin E_2 is an inflammatory mediator with small size and lipophilic properties that can diffuse into the brain parenchyma.

Implications

The findings suggest a role for screening for cognitive deficits among survivors of SARS-CoV-2 infection. Several screening tests are available for use in survivors of SARS-CoV-2 infection including Saint Louis University Mental Status Examination, the Montreal Cognitive Assessment, and the Mini–Mental State Examination [35]. If there is evidence of impairment during screening that remains persistent and the patient continues to report cognitive symptoms, a referral for comprehensive neuropsychologic assessment may be necessary. A neuropsychologist can assess the validity and nature of the cognitive symptoms, along with severity of impairment and whether psychologic factors may be contributing to the presentation. Additionally, a neuropsychologist can provide treatment recommendations and facilitate return to work. Cognitive screening tools to assess individuals for cognitive symptoms after coronavirus disease 2019 (COVID-19) have limitations; there are none to date designed specifically for use in a SARS-CoV-2–infected patient population. Thus, cognitive screening tests developed for other patient populations may be implemented at this point.

Occurrence of new-onset dementia may increase the burden of disability among survivors of SARS-CoV-2 infection [1, 2]. The US President has suggested that long-term symptoms of SARS-CoV-2 infection could be considered a disability under federal civil rights laws of the Americans With Disabilities Act [36]. National Institutes of Health research emphasizes that "long COVID" can be debilitating and some people will require assistance with personal care months after the initial infection, with 80% reporting difficulty in ability to work and 36% reporting negative financial consequences. Social Security has released an emergency message giving its employees some guidance on how to handle applications that allege "post-COVID conditions." Social Security may have to establish new-onset dementia as a "medically determinable impairment" to determine whether survivors of SARS-CoV-2 infection are unable to work for 12 months and thus eligible for benefits [37].

Like previous studies [38, 39], the risk of new-onset dementia was seen in older patients with pneumonia in our study. We

did observe 1 patient (approximately 0.2% risk) with new-onset dementia among young pneumonia patients without SARS-CoV-2 infection. Taquet et al [16] had reported a 2% risk of new-onset dementia among relatively young patients (mean age of 46 years) with influenza. Our results and those of Taquet et al [16] could be suggestive of the vulnerability of young individuals to occurrence of dementia following exposure to infection and metabolic abnormalities [40], although small numbers preclude any definitive conclusions. Further studies may have to identify if any age criteria are required for screening for cognitive deficits among pneumonia survivors with or without SARS-CoV-2 infection.

Limitations

We used *ICD-10* codes to identify new-onset dementia as used in previous studies [41]. The diagnosis of dementia requires the presence of multiple cognitive deficits in addition to memory impairment [42, 43], with impairment of social or occupational function representing a decrease in the patient's normal ability. In addition to cognitive tests, adjustment for age and education level and additional neuroimaging and laboratory tests may be required [44, 45]. In administrative datasets, the diagnosis of dementia may be based on various local institutional criteria with variations in both diagnostic criteria and coding practices between institutions. The *ICD-10* codes have a sensitivity of 92.7% and specificity of 98.9% for dementia reported previously [46]. In 1 study [47], a diagnosis of dementia was made for 198 patients and there was 100% agreement ($\kappa = 1.0$) between *ICD-10* and the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* based diagnoses. Specificity was consistently high (>84%) in a review of 8 studies [48]. Studies that used inpatient and outpatient claims databases such as ours revealed higher sensitivity than those that used inpatient claims only, outpatient claims only, or death certificates. Our longitudinal design increased the chance of identifying dementia by using multiple encounters with greater chance of recording dementia codes. The documentation of dementia diagnosis in medical encounters is usually based on more rigorous criteria than other medical diagnoses due to the associated social stigma [49] and additional review during assessment for Social Security's Disability Insurance Benefits [50]. We did not find any statistically significant differences in proportion with patients with other preexisting diagnoses that can be associated with cognitive deficits between patients with and without SARS-CoV-2 infection. Therefore, the differential risk in occurrence of new-onset dementia was not accounted by differences in occurrence of other related conditions.

However, patients with dementia are at increased risk for SARS-CoV-2 infection compared to patients without dementia, particularly those with vascular dementia [51]. The elevated risk of SARS-CoV-2 infection in dementia patients is attributable to cognitive symptoms causing difficulty in following safeguarding procedures and to living arrangements in long-term care homes facilitating viral spread [51]. The Cerner Real-World data include many different types of medical encounters such as emergency department visits, inpatient encounters, and outpatient encounters. We acknowledge that the effect of variability in hospitalization criteria over time and between institutions on our analysis is not known. Certain lifestyle risk factors for dementia such as educational attainment, socioeconomic status, and physical activity [12, 13] could not be ascertained using the Cerner Real-World data and therefore could not be adjusted for in the multivariate analysis. Our ability to quantify the severity of the pneumonia observed in our cohort of hospitalized patients was limited due to the nature of our data. Additional variables including physical examination, laboratory, and radiographic findings, which were not available, can provide more accurate grading of the severity of the pneumonia [14].

CONCLUSIONS

Approximately 3% of patients with a hospitalization containing pneumonia associated with SARS-CoV-2 infection developed new-onset dementia in the postinfectious period, which was significantly higher than the rate seen with other pneumonias. Future studies should investigate the underlying pathophysiological processes associated with SARS-CoV-2 infection to identify optimal strategies to prevent long-term disabling sequelae like new-onset dementia.

Notes

Patient consent. This study did not include factors necessitating patient consent.

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