



The Impact of the COVID-19 Pandemic on Alzheimer's Disease and Other Dementias

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Introduction: Numerous countries went into lockdown to contain the COVID-19 outbreak, which has impeded follow-up of chronic diseases, such as cognitive impairment (CI). Cognitive and neuropsychiatric changes during the COVID-19 pandemic are neglected in China, which is the world's whistleblower. To investigate the cognitive and neuropsychologic changes in CI, as well as the proportions of rapid cognitive decline (RCD) before and during the COVID-19 pandemic to provide clinical evidence for CI intervention during a public health emergency.

Methods: We performed a descriptive and retrospective study based on medical records from the memory clinic of Tianjin Dementia Institute collected through face-to-face evaluations. Information of 205 patients with CI, including patients with mild cognitive impairment and dementia, of whom 131 with Alzheimer's disease (AD) were analyzed and compared to a control group before the COVID-19 pandemic.

Results: Among the 205 CI patients, the scores on the Chinese Mini Mental State Examination (C-MMSE), the Montreal Cognitive Assessment (MoCA), activities of daily living (ADLs), and the global Neuropsychiatric Inventory (NPI) were significantly different at the baseline and follow-up evaluations ($p < 0.05$) after 14.07 (± 2.87) months. The same findings were recorded among AD patients, and they exhibited more sleep disturbances at the follow-up than at baseline (32.8 vs. 20.6%, $p = 0.035$). When compared to the control group, slightly worse performance of cognitive, -1.00 ($-4.00, 1.00$) from the C-MMSE, -1.00 ($-2.00, 0.00$) on the MoCA, 1.00 ($0.00, 9.00$) on ADLs and neuropsychological 0.00 ($-1.00, 3.50$) on the global NPI profile, at the follow-up were presented, particularly for delusion, agitation, irritability, and appetite disturbances ($p < 0.05$). Twenty-five (19.1%) AD patients and 48 (36.6%) controls suffered RCD during the COVID-19 pandemic. Moreover, AD patients during the COVID-19 pandemic were 0.408 times (95% confidence interval: 0.232–0.716) less likely to suffer RCD than the control.

Conclusion: Confinement might ease the cognitive and neuropsychiatric deterioration of AD patients compared to those not in crisis and help prevent RCD in AD patients.

Keywords: Alzheimer's disease, COVID-19, cognitive, dementia, neuropsychiatric symptom

INTRODUCTION

In December 2019, the coronavirus disease 2019 (COVID-19) outbreak caused by the novel coronavirus SARS-CoV-2, which primarily affects the lower respiratory tract, occurred, and aggressively spread around the world (1). To fight the pandemic and limit the spread, many governments, including the Chinese government were obliged to impose a variety of “lockdown” measures in January 2020. By December 2020, COVID-19 has caused a 1-year pandemic affecting the lives and livelihoods of the entire human population.

According to some studies, COVID-19 is more severe in older adults (2, 3) and most of whom have comorbidities (4–6). Patients with dementia need long-term treatment and specialized care, and their cognitive and neuropsychological status differ from that of the general population. COVID-19 patients with dementia, particularly in the severe stage, suffer higher mortality than those without (62.2 vs. 26.2%) (7). The double hit of dementia and the COVID-19 pandemic has raised great concern for patients living with dementia. The present report on the prevalence of cognitive impairment (CI) in China shows that the overall prevalence of dementia is 6.0% and that of mild cognitive impairment (MCI) is 15.5%. These proportions represent 15 million patients with dementia and nearly 38 million patients with MCI in China (8). CI has emerged as a pandemic in the aging society.

The apolipoprotein E (ApoE) $\epsilon 4$ genotype is associated with dementia, and the $\epsilon 4\epsilon 4$ (homozygous) genotype is associated with a 14-fold increase in the risk of Alzheimer’s disease (AD) (9) compared to the common $\epsilon 3\epsilon 3$ genotype. Abnormal amyloid- β ($A\beta$) and tau aggregation are the major features of AD pathology. Furthermore, AD patients with ApoE $\epsilon 4$ undergo an accelerated memory decline. A recent study also showed that the ApoE $\epsilon 4\epsilon 4$ allele increases the risk of severe COVID-19 infection, independent of pre-existing dementia, cardiovascular disease, and type-2 diabetes by affecting lipoprotein function (and subsequent cardio-metabolic diseases moderating macrophage pro-/anti-inflammatory phenotypes) (10).

Dementia patients primarily live with their spouses or children, or in nursing homes. The lockdown attempted to limit the spread of COVID-19; thus, patients with dementia and their caregivers stayed at home together. Moreover, patients with dementia may not understand changes in their life and it may be difficult for them to adapt to lockdown because of their disturbed routines. The ability to explain COVID-19 and the lockdown to a patient with dementia depends on disease severity and the patient’s need to acclimatize themselves to a new routine. These changes may affect the quality of care, as well as the progress of dementia. The follow-up of chronic diseases, including dementia, has been delayed or relegated in many cases due to the pandemic.

We carried out the first longitudinal study on the consequences of the COVID-19 pandemic on dementia. We followed up patients with dementia who visited the memory clinic of Tianjin Dementia Institute from 1 January to 12 December 2019 and evaluated their cognitive and neuropsychological profiles face-to-face during the COVID-19 pandemic to investigate cognitive and neuropsychologic changes, as well as the proportion of rapid cognitive decline (RCD) during

the COVID-19 pandemic. These findings provide clinical evidence for CI interventions during a public health emergency.

MATERIALS AND METHODS

Participants

A total of 436 subjects were seen by a CI specialty clinical service at the memory clinic of Tianjin Dementia Institute, Tianjin Huanhu Hospital from 1 January to 12 December 2019. Among them, 332 patients were given a definitive diagnosis. A two-specialist panel was used to confirm the diagnoses. If there was disagreement, the subject was excluded ($n = 104$). The panel was diagnosed based on the corresponding diagnostic criteria; the MCI diagnostic criteria were based on the International Working Group’s description (11). Dementia was diagnosed according to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition (12). AD was based on the National Institute on Aging-Alzheimer’s Association criteria by McKhann et al. in 2011 (13). Blood tests, the ApoE genotypes, neuroimaging (including CT scans and MRI), and positron emission computed tomography were performed, if necessary, to make the diagnosis (14). Twelve patients were diagnosed with mixed or secondary dementia, 61 patients were lost to follow-up and 54 patients had stopped antedementia drug therapy for more than 1 week and were excluded. Finally, 205 participants with CI, of whom 131 had AD, 14 had MCI, and 60 had other dementias, including vascular dementia (15), frontotemporal lobe dementia (16), dementia with Lewy bodies (17), and Parkinson’s disease with dementia (18), had at least the first follow-up and continuous antedementia drug therapy records between 1 April and 30 November 2020 (during the COVID-19 pandemic) and were enrolled in this study.

To explore the correlation between the COVID-19 pandemic and RCD, we strictly selected 131 age-, gender-, educational-, course-, and severity-matched AD patients as a control group, who visited the same memory clinic from 1 January 2017 to 31 December 2018 as a control group before the COVID-19 pandemic, and experienced an average of 13.63 (SD = 0.81, $p = 0.178$) months of follow-up. All controls were treated with antedementia drugs, and no differences in the drugs were observed among participants during the COVID-19 pandemic. The same information was collected from the controls.

This study was designed and conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Assessment

Neuropsychological Measurements

We reviewed 205 face-to-face evaluation records during the COVID-19 pandemic, with an average of 14.07 months follow-up. Demography, medical history, and a neuropsychological evaluation that included the Chinese Mini-Mental State Examination (C-MMSE) (19), the Montreal Cognitive Assessment (MoCA) (20), activities of daily living (ADL) (21), the Neuropsychiatric Inventory (NPI) (22), and the etiological data at baseline and follow-up were reviewed. The Clinical Dementia Rating Scale (CDR) (23) was used to assess the

severity of CI as 0.5, 1.0 (mild), 2.0 (moderate), or 3.0 (severe). RCD due to AD was defined as a loss of ≥ 3 C-MMSE points at the 12-month follow-up assessment (24).

ApoE Genotyping

Genomic DNA was extracted from whole peripheral blood, and the ApoE gene was amplified by polymerase chain reaction (PCR) (25). The PCR primers were: 5'-TCCAAGGAG-GTGCAGCG GCGCA-3' (upstream) and 5'-ACAGAATTCGCCCGGCCT GGTACTACTGCCA-3' (downstream). Each amplification reaction contained 200 ng of genomic DNA, 25 pmol of the primers, 2.5 μ l of 10% dimethyl sulfoxide, and 0.5 units of Taq DNA polymerase in a final volume of 25 μ l. The thermal reactor was programmed as follows: initial denaturation at 94°C for 5 min, 40 cycles at 94°C for 1 min, annealing at 65°C for 1 min, extension at 72°C for 1 min, and final extension at 72°C for 10 min. The amplification product (20 μ l) was digested with 5 units of Cfo1 for at least 3 h at 37°C. The samples were resolved by 12% native polyacrylamide gel electrophoresis for 2 h at 200 V. The gels for patient genotyping were stained with 0.5 μ g/ml ethidium bromide, and DNA sizes were determined by imaging under ultraviolet light. We determined all genotypes without knowledge of the patient/control status.

PET Imaging

^{11}C -Pittsburgh compound-B (PIB) PET and ^{18}F -AV45 PET scans can be used to evaluate A β deposition (26). Patients were diagnosed with A β deposits (positive) based on both visual interpretations of elevated binding in the neocortex and semi-quantitative PIB-positive assessments (SUVR > 1.40 for; SUVR > 1.11 for AV45-positive).

Statistical Analysis

Quantitative variables (age, courses, scores on the C-MMSE, MoCA, ADL, global NPI, CDR, and the follow-up and COVID-19 pandemic intervals) are presented as mean \pm standard deviation (SD) when the data were normally distributed and the median (Q_{25,75}) for non-normally distributed data. Categorical data (education, marriage status, and RCD) are presented as frequency counts and percentages. Student's *t*-tests were used for the normally distributed AD data of the COVID-19 pandemic confinement and control groups, and the Mann-Whitney *U*-test was used for non-normally distributed data.

We compared baseline and follow-up data during the COVID-19 pandemic in all patients. The chi-square test was used to assess differences between the baseline and follow-up on the global NPI. The Wilcoxon signed-rank test was used to compare the scores on the C-MMSE, MoCA, NPI, and ADL at baseline and follow-up. A logistic regression analysis was performed to explore the correlation between the COVID-19 pandemic and RCD.

All data were descriptively analyzed using SPSS version 25.0 software (SPSS 25.0; IBM, Armonk, NY, USA). A *p*-value < 0.05 was considered significant.

RESULTS

Changes in Cognitive and Neuropsychological Symptoms

A total of 205 patients (103 females; mean age = 70.62 years) were included in this study, and their baseline characteristics are shown in **Table 1**. The majority (131, 63.9%) of the participants were diagnosed with AD, with a mean course of 52.67 (SD = 30.87) months and the highest proportion of A β deposition (95.1%). The mean duration of confinement of the 131 AD patients was 8.89 months (SD = 1.91). As shown in **Table 2**, no significant differences in the CDR scores or the proportions of neuropsychiatric symptoms were found between the initial and final evaluations. The scores on the C-MMSE, MoCA, ADLs, and global NPI were significantly different between the baseline and follow-up evaluations (*p* < 0.05) after almost 14 months. The same findings were observed in AD patients, but AD patients had more sleep disturbances at follow-up (*p* = 0.035).

The worsened proportions of cognitive and neuropsychological symptoms during the follow-up are shown in **Figure 1**. AD patients during the COVID-19 pandemic presented slightly worse cognitive (AD during COVID-19 pandemic vs. control: 53.44 vs. 61.83% in C-MMSE; 51.15 vs. 56.49% in MoCA; 51.59 vs. 66.64%) and neuropsychiatric (36.64% vs. 42.75% in NPI) profiles at the follow-up examination, compared with the control group, but no significant differences were observed except in ADLs (*p* = 0.049). Overall, those who experienced the COVID-19 pandemic had a lower proportion of neuropsychiatric symptoms, particularly delusion, agitation, irritability, and appetite disturbances (*p* < 0.05).

Figure 2 shows the cognitive and neuropsychiatric changes at baseline and the follow-up between the COVID-19 pandemic and control groups. The median scores on the C-MMSE changed -1.00 (-4.00, 1.00), those on the MoCA changed -1.00 (-2.00, 0.00), ADLs changed 1.00 (0.00, 9.00), and the NPI changed 0.00 (-1.00, 3.50) during the COVID-19 pandemic, but no significant differences in the scores were observed between the two groups. The point proportions of neuropsychiatric symptoms at baseline and follow-up are shown in **Figure 2E**. The proportions for most symptoms changed similarly in the groups, and hallucinations, euphoria, disinhibition, irritability, and aberrant motor behavior increased from baseline to the final follow-up. Delusions, agitation, sleep disturbances, and appetite disturbances in the patients with AD during the COVID-19 pandemic were opposite in trend compared with the control group. Notably, 20.6% of AD patients during the COVID-19 pandemic developed sleep disturbances at baseline and 32.8% had sleep disturbances at the final examination, which was more frequent than the controls (22.9% at baseline, 19.8% at final examination, *p* < 0.05).

Association Between RCD and the COVID-19 Pandemic

A total of 73 patients had RCD at the follow-up [25 (19.1%) in the AD group during the COVID-19 pandemic and 48 (36.6%) in the control group]. The proportions of RCD among patients with AD of different severities, ApoE genotypes, and

TABLE 1 | Baseline characteristics of the 205 patients with CI.

	Overall (n = 205)	AD (n = 131)	ODs (n = 60)	MCI (n = 14)
Gender (n, %)				
Male	102 (49.8)	61 (46.6)	35 (58.3)	6 (42.9)
Female	103 (50.2)	70 (53.4)	25 (41.7)	8 (57.1)
Age, mean (SD)	70.62 ± 7.96	70.81 ± 7.54	71.15 ± 7.75	66.64 ± 11.60
Years of education (n, %)				
0	12 (5.9)	8 (6.1)	4 (6.7)	0 (0.0)
1–6	32 (15.7)	20 (15.4)	11 (18.3)	1 (7.1)
7–9	55 (26.8)	42 (32.3)	12 (20.0)	1 (7.1)
10–12	61 (29.8)	30 (23.1)	24 (40.0)	7 (50.0)
13 +	44 (21.5)	30 (23.1)	9 (15.0)	5 (35.8)
Marriage (n, %)				
Married	162 (79.0)	104 (79.4)	47 (78.3)	11 (78.6)
Single	2 (1.0)	1 (0.8)	1 (1.7)	0 (0.0)
Divorced	4 (2.0)	2 (1.5)	1 (1.7)	1 (7.1)
Widow	37 (18.0)	24 (18.3)	11 (18.3)	2 (14.3)
Remarried	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Living states (n, %)				
With spouse	156 (76.1)	103 (78.6)	44 (73.3)	9 (64.3)
With children	28 (13.7)	15 (11.5)	11 (18.3)	2 (14.3)
Alone	14 (6.8)	8 (6.1)	4 (6.7)	2 (14.3)
Others ^a	7 (3.4)	5 (3.8)	1 (1.7)	1 (7.1)
Courses of disease, mean (SD)	48.61 ± 31.18	52.67 ± 30.87	43.70 ± 31.00	31.71 ± 27.99
Smoking, yes (n, %)	55 (26.8)	34 (26.0)	19 (31.7)	2 (14.3)
Alcohol consumption, yes (n, %)	36 (17.6)	23 (17.6)	11 (18.3)	2 (14.3)
DM, yes (n, %)	31 (15.1)	19 (14.5)	10 (16.7)	2 (14.3)
Hypertension, yes (n, %)	72 (35.1)	46 (35.1)	23 (38.3)	3 (21.4)
Heart disease, yes (n, %)	12 (5.9)	8 (6.1)	2 (3.3)	2 (14.3)
Stroke, yes (n, %)	21 (10.2)	14 (10.7)	6 (10.0)	1 (7.1)
Aβ deposition (n, %)				
Positive	43 (78.2)	39 (95.1)	1 (11.1)	3 (60.0)
Negative	12 (21.8)	2 (4.9)	8 (88.9)	2 (40.0)
ApoE ε4 genotypes (n, %)				
ApoE ε4 (+)	13 (23.6)	11 (26.8)	1 (11.1)	1 (20.0)
ApoE ε4 (–)	42 (76.4)	30 (73.2)	8 (88.9)	4 (80.0)

^aOthers means living with other relatives, friends, or in nursing home. CI, cognitive impairment; AD, Alzheimer's disease; ODs, other dementias; MCI, mild cognitive impairment; SD, standard deviation; DM, diabetes mellitus; Aβ, Amyloid β; ApoE, Apolipoprotein E.

Aβ deposition are presented in **Table 3**. AD patients in the control group developed RCD more frequently than those during the COVID-19 pandemic, particularly patients with mild (40.4 vs. 18.4%, $p = 0.017$) and severe (35.1 vs. 10.3%, $p = 0.009$) AD. AD patients with the ApoE ε4 allele, and Aβ deposition during the COVID-19 pandemic had a lower proportion of RCD than those in the control group. In this study, AD patients during the COVID-19 pandemic were less likely to have RCD with a risk of 0.408 (95% confidence interval: 0.232–0.716) compared with the control. Mild and severe AD patients were 0.332 and 0.211 times less likely to have RCD, respectively.

DISCUSSION

This is the first study on the cognitive and neuropsychiatric symptoms in patients with CI, particularly those with AD, during the COVID-19 pandemic. Among the 205 patients with CI, 131 had AD, and the average scores on the MMSE, MoCA, ADLs, and NPI decreased during the pandemic. More patients with AD during the COVID-19 pandemic had poor ADLs and neuropsychiatric symptoms (delusion, agitation, irritability, and appetite disturbances) compared with the control, but no significant differences were observed in the scores. Also, patients with AD during

TABLE 2 | Changes in neuropsychiatric performance during COVID-19 pandemic confinement.

	Overall			AD		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
Follow-up Interval, mean (SD)	14.07 ± 2.87			13.95 ± 2.61		
Confinement Interval, mean (SD)	9.01 ± 1.82			8.89 ± 1.91		
CDR, (n, %)	1.81 ± 0.89	1.83 ± 0.91	0.038	1.92 ± 0.82	1.91 ± 0.83	ns
0.5	20 (9.8)	27 (13.2)	ns	-	7 (5.3)	ns
1	67 (32.7)	55 (26.8)	ns	49 (37.4)	38 (29.0)	ns
2	60 (29.3)	63 (30.7)	ns	43 (32.8)	49 (37.4)	ns
3	58 (28.3)	60 (29.3)	ns	39 (29.8)	37 (28.2)	ns
C-MMSE, mean (SD)	16.50 ± 8.16	14.96 ± 9.02	<0.001	15.64 ± 7.32	14.24 ± 8.15	<0.001
MOCA, mean (SD)	12.60 ± 7.54	11.47 ± 8.18	<0.001	11.76 ± 6.84	10.65 ± 7.41	<0.001
ADL, mean (SD)	30.97 ± 13.60	36.67 ± 18.61	<0.001	31.06 ± 13.31	37.40 ± 18.12	<0.001
NPI, (n, %)	8.15 ± 10.35	10.40 ± 12.70	0.001	7.27 ± 9.61	9.63 ± 12.37	0.028
Delusions	36 (17.6)	34 (16.6)	ns	20 (15.3)	17 (13.0)	ns
Hallucinations	39 (19.0)	47 (22.9)	ns	21 (16.0)	29 (22.1)	ns
Agitation	53 (25.9)	46 (22.4)	ns	30 (22.9)	25 (19.1)	ns
Depression	56 (27.3)	63 (30.7)	ns	37 (28.2)	36 (27.5)	ns
Anxiety	53 (25.9)	53 (25.9)	ns	32 (24.4)	30 (22.9)	ns
Euphoria	6 (2.9)	10 (4.9)	ns	3 (2.3)	7 (5.3)	ns
Apathy	73 (35.6)	72 (35.1)	ns	48 (36.6)	40 (30.5)	ns
Disinhibition	20 (9.8)	23 (11.2)	ns	9 (6.9)	12 (9.2)	ns
Irritability	70 (34.1)	73 (35.6)	ns	38 (29.0)	42 (32.1)	ns
Aberrant motor behavior	41 (20.0)	48 (23.4)	ns	25 (19.1)	33 (25.2)	ns
Sleep disturbances	57 (27.8)	76 (37.1)	ns	27 (20.6)	43 (32.8)	0.035
Appetite disturbances	39 (19.0)	37 (18.0)	ns	28 (21.4)	25 (19.1)	ns

CI, cognitive impairment; AD, Alzheimer's disease; SD, standard deviation; CDR, Clinical Dementia Rate; C-MMSE, Chinese Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment; ADL, the activities of daily living; NPI, the Neuropsychiatric Inventory.

the COVID-19 pandemic were less likely to have RCD, particularly those with mild and severe AD, compared with the control.

As demonstrated by our study, half of the patients with AD in both groups presented significant cognitive decline over time. Interestingly, COVID-19 confinement resulted in fewer poor cognition cases than controls, even though we did not find differences in the MMSE and MoCA scores between the two groups. Thus, the cognitive differences between the two groups appeared to be intrinsic and not to have been influenced by confinement. Although no significant cognitive changes were observed in Barguilla's study of AD caregivers (27), 60% of CI caregivers perceived worsening cognition during COVID-19 confinement. This may have resulted from more intense observations provided by the caregivers and was affected by caregiver anxiety. The investigation of CI caregiver factors (including cohabitation, care burden, and mental health) has not been completed and more examinations of CI patients are expected. Similarly, although most of China's economic work was carried out by November 2020, COVID-19 must be controlled and prevented.

When comparing the two groups with neuropsychiatric symptoms at follow-up, the point proportion at baseline and the follow-up was not significantly different regardless of the

group, except for sleep disturbances in the AD group during the pandemic. This is roughly the same as the follow-up results for 60 CI patients in Spain (27) and suggests that the neuropsychiatric profile worsened globally ($p < 0.000$), as well as appetite ($p = 0.004$). However, not all of the results have been consistent, and some studies that followed up patients with AD during confinement have reported an increase in the occurrence of psychiatric symptoms (28), particularly depression and anxiety (29). In a population-based survey among Chinese workers, epidemic-related factors were significantly associated with 4–5 times higher risk of anxiety and depression symptoms than before the break (30, 31). However, the neuropsychiatric symptoms changed more in the control group. The majority of the controls showed increases in neuropsychiatric symptoms, particularly delusions, insomnia, irritability, and appetite disturbances; thus, suggesting that COVID-19 has slowed down the onset of mental symptoms. These results are encouraging. We suspect it has something to do with the time spent in care during the COVID-19 pandemic or time spent with relatives. Relatives left home less frequently and some children chose to work at home during the pandemic confinement, which increased the time spent caring for AD patients and to some extent alleviated their loneliness and anxiety. A previous study before the COVID-19 pandemic

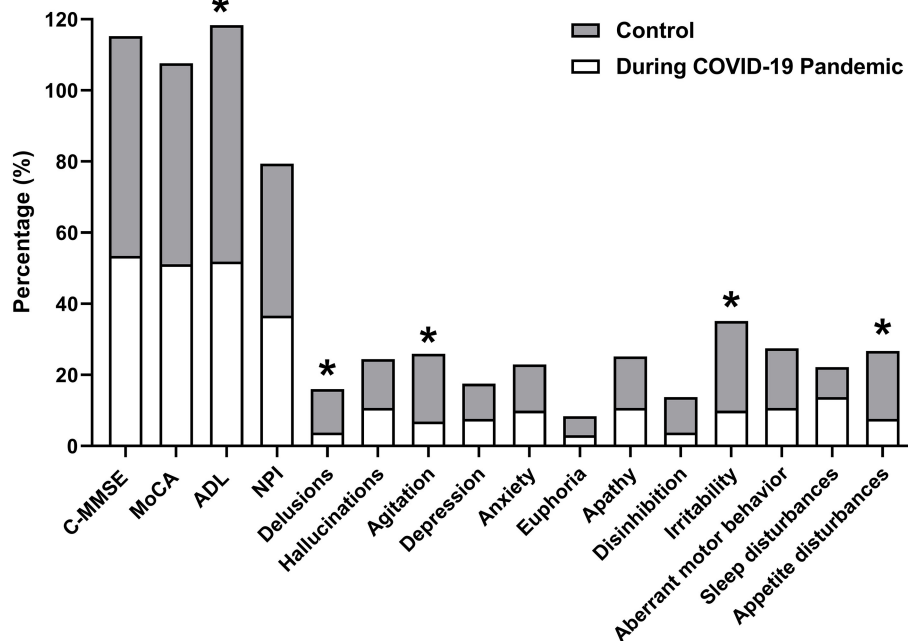


FIGURE 1 | Worsened proportions of cognitive and neuropsychological symptoms during follow-up. The proportions of patients with decreases on the C-MMSE and MoCA scores, and increases on ADL and the NPI (including all items) scores are analyzed and described. C-MMSE, Chinese Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment; ADL, activities of daily living; NPI, the Neuropsychiatric Inventory. * $p < 0.05$.

revealed that closer caregiver-care recipient relationships are associated with a 5-point lower NPI score, as well as an increase of 1-point fewer per year (32). Patients with dementia, who are living long-term with a spouse, have significantly lower NPI median total scores than those who live with children or in a nursing home (5.00 with spouse vs. 9.00 with children, 19.50 at nursing home, respectively). These same patients performed well on the MMSE and Alzheimer's Disease Assessment Scale-Cognitive Subscale (33).

However, some neurologists (34–36) have suggested that social distancing measures and diminished physical contact with family and the outside world (e.g., attending neighborhood meetings), as well as social and physical decline, may have increased loneliness and impacted mental health among patients with AD, which is not conducive to improving their cognitive capacity. Therefore, the impact of various lifestyle changes on dementia patients has differed during the COVID-19 pandemic, particularly for patients with different types or severities of dementia. The advantages and disadvantages of lifestyle changes need personal analyses.

Confinement due to the COVID-19 pandemic reduced the risk of RCD in AD patients compared with the control. Previous studies have shown that women (37), lower education (38), psychiatric symptoms (39), the ApoE $\epsilon 4$ allele (40), and positive A β deposition (24) are risk factors for RCD. Mild to moderate AD patients, with the ApoE $\epsilon 4$ allele and A β deposition are more likely to present with RCD, which was not completely consistent with our results. Previous studies have reported that the prevalence of RCD varies from 9.5 to 54% (24, 41). In our

study, patients with mild and severe AD had only about half the risk of RCD during confinement compared with the control (36.6%), with a proportion of 19.1%. We used the definition of 3 points within 12 months between the two groups, and the percentage (36.6%) of RCD in the controls was very similar to that (40.9%; 95% confidence interval, 36.7–45.1) observed in Tchalla's cohort (37), but slightly lower than that of other reports [e.g., 46% in O'Hara et al. (42); 47.9% in Masse et al. (43); and 51.2% in Buccione et al. (44)]. However, the incidence of 19.1% is much lower than that observed in the REAL-FR cohort study (54%) where RCD was defined as loss of 3 points within 6 months (41) and lower than the incidence of RCD in the ELSA cohort (25%), which used loss of 4 points within 6 months. A longitudinal population-based study (CHAP) (45) reported that participants with the APOE $\epsilon 4$ allele are at higher risk of incident AD, and have a greater proportion of RCD than those without the APOE $\epsilon 4$ allele. A β deposition has also been demonstrated to be associated with a greater decline in memory in a prospective study (46). The small sample size may have prevented us from detecting the accelerated effect of the ApoE $\epsilon 4$ allele and A β deposition on RCD. We suppose that the COVID-19 pandemic played a protective effect on the incidence of RCD. While confinement has dramatically changed most people's daily lives, it may have indirectly changed the RCD risk factors due to AD.

We assume that long-term care during the COVID-19 confinement provided more opportunity for caregivers to detect a change in the condition of the dementia patients and take timely measures to reduce other complications. Secondly, because

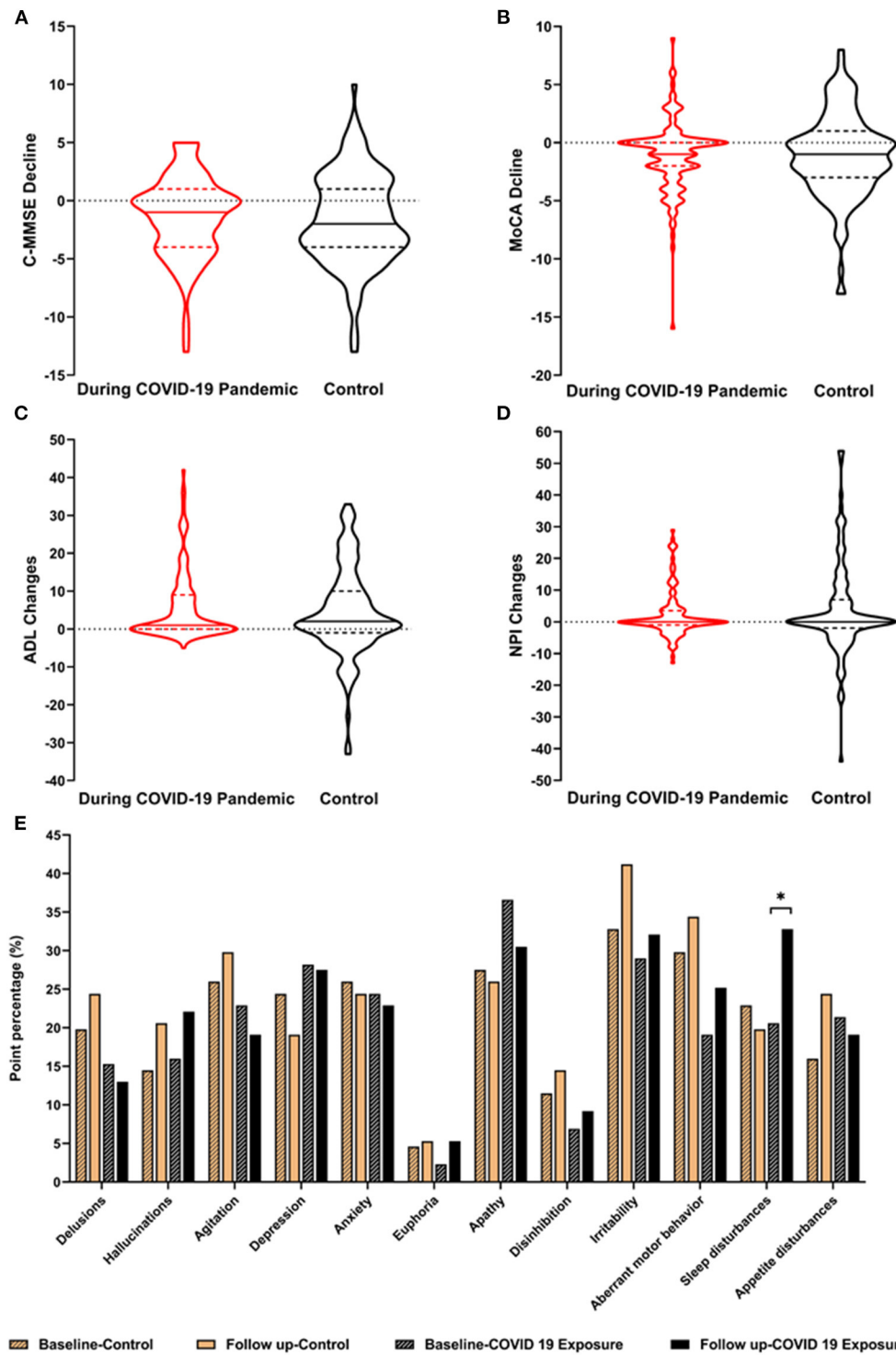


FIGURE 2 | Cognitive and neuropsychiatric changes between the AD groups. The changes in the cognitive and neuropsychiatric scores before and after the COVID-19 pandemic are described in **A–E**. The point percentages of the 12 NPI items are described to show the comparison before (control group) and after COVID-19 (COVID-19 exposure group) at baseline and at the 1-year follow up. AD, Alzheimer’s disease; C-MMSE, Chinese Mini-Mental State Examination; MoCA, the Montreal Cognitive Assessment; ADL, activities of daily living; NPI, the Neuropsychiatric Inventory. * $p < 0.05$.

TABLE 3 | Proportions of RCD in AD patients at the follow-up.

	With COVID-19 pandemic		Control		OR, 95%CI
	Num.	RCD proportion (n, %)	Num.	RCD proportion (n, %)	
Overall	131	25 (19.1)	131	48 (36.6)*	0.408 (0.232–0.716)*
Initial CDR					
1	49	9 (18.4)	47	19 (40.4)*	0.332 (0.131–0.839)*
2	43	12 (27.9)	47	16 (34.0)	ns
3	39	4 (10.3)	37	13 (35.1)*	0.211 (0.061–0.726)*
ApoE genotypes					
ApoE ϵ 4 (+)	11	3 (27.3)	19	8 (42.1)	ns
ApoE ϵ 4 (-)	30	7 (23.3)	33	12 (36.4)	ns
Aβ deposition					
Positive	39	9 (23.1)	49	20 (40.8)	ns
Negative	2	1 (50.0)	3	0 (0.0)	ns
ApoE genotypes + Aβ deposition					
ApoE ϵ 4 (+), A β (+)	10	2 (20.0)	19	8 (42.1)	ns
ApoE ϵ 4 (+), A β (-)	1	1 (100.0)	0	0 (0.0)	ns
ApoE ϵ 4 (-), A β (+)	29	7 (24.1)	30	12 (40.0)	ns
ApoE ϵ 4 (-), A β (-)	1	1 (100.0)	3	0 (0.0)	ns

In this study, only 55 patients, including 41 AD patients, in "during COVID-19 pandemic" group, and 52 patients with AD in control group had ApoE genotyping and A β deposition records. RCD, rapid cognitive decline; AD, Alzheimer's disease; Num., number of samples; OR, odds ratio; CI, confidence interval; CDR, Clinical Dementia Rate; ApoE, Apolipoprotein E; A β , Amyloid β . * $p < 0.05$.

RCD is associated with psychiatric symptoms (37), cognitive decline and psychiatric symptoms often co-exist in dementia patients, and the overall deterioration of psychiatric symptoms during confinement was lower in AD patients than that in the control group. Therefore, this may be the main reason why RCD was lower in the COVID-19 pandemic group than in the control group. Thus, long-term companionship, as non-pharmaceutical management, played an important role in the treatment of AD during the pandemic. However, individualized coping strategies should be developed for different dementia patients in the future.

The strength of our study includes the assessment of neuropsychological performance using face-to-face interviews of patients with CI, as cognitive and neuropsychiatric changes can be depicted more clearly in this way. Our method was more scientific by setting a strict control group. The long-term neuropsychological impact of the COVID-19 pandemic on dementia patients will provide new evidence for treating AD during future similar crises. The limitations of our study include the relatively small cohort and the lack of relevant reasons for the cognitive changes, such as suffering from other morbidities, exercise, social work, and other circumstances during confinement. The study on caregivers of dementia was not completed, so it could not be used to explain the neuropsychological changes.

CONCLUSION

In conclusion, our study has offered helpful insight into the effects of confinement on neuropsychological function in

patients with AD during the COVID-19 pandemic. Our study demonstrates that the cognitive and psychiatric symptoms of CI patients, mainly those with AD, tended to deteriorate, and the confinement eased RCD in AD patients, particularly in those with mild and severe AD. This study provides a reference for similar crises and a basis for the formulation of personalized dementia care.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Committee for Medical Research Ethics at Tianjin Huanhu Hospital and the Tianjin Health Bureau. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YJ designed the study. JG, SL, and HW wrote the report. YD and ZC did the statistical analyses. MF, JX, and XW

contributed to the interpretation and discussion of results and reviewed the manuscript. The collaborating authors contributed to the collection of clinical data. All the authors and the collaborating authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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