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Research Article

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Cognitive function among COVID-19 survivors in subacute phase during epidemic of Omicron variant in China

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Abstract: Following the relaxation of pandemic control measures in China, the impact of coronavirus disease 2019 (COVID-19) on cognitive function in the Chinese population has not been investigated. Therefore, this study aimed to assess cognitive function and identify its risk factors in the subacute phase (<3 months) of COVID-19 patients during the epidemic wave of the Omicron variant. In this nationwide smartphone-based online assessment from January 15 to 29, 2023, the Integrated Cognitive Assessment (ICA) and the Number Ordering Test (NOT) were used to assess cognitive function. Among the 9,663 participants, 8,905 (92.2%) were COVID-19 survivors. These patients performed poorly in most neuropsychological results ($p<0.05$), but only the ICA accuracies were lower, controlling for socio-demographics ($p<0.05$, partial $\eta 2 \leqslant 0.001$). After the initial recovery, 5,832 (65.5%) COVID-19 survivors reported inflexible thinking, 5,419 (60.9%) noted slowed information processing speed, and 4,344 (48.8%) reported insomnia. Being a female, older age, low education level, living in Northwest China, and insomnia were significantly associated with poor performance in the key neuropsychological results (range, absolute value of β 0.023-0.430, $p<0.05$). In the subacute phase of COVID-19, subjective cognitive complaints were highly prevalent, whereas objective cognitive differences were subtle. Despite the mild overall impact, vulnerable subgroups—such as females, older adults, low education level and patients with insomnia—showed greater susceptibility to these cognitive changes.

Key words: Cognitive function; COVID-19; Risk factors; Omicron variant; Subacute phase

1 Introduction

After the Chinese government relaxed coronavirus disease 2019 (COVID-19) prevention and control measures on December 7, 2022, the number of COVID-19 cases increased rapidly and reached its peak between December 19 and 21, 2022. It is estimated that, as of February 7, 2023, 82.4% of the Chinese population had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Fu et al., 2023). Before and after the Chinese government relaxed prevention and control measures, all the locally infected COVID-19 variants reported across China were Omicron (Prevention, 2023). This unique epidemiological context provides a crucial opportunity to investigate the specific cognitive effects of the Omicron variant.

Evidence points to COVID-19 being a systemic disease that affects multiple organ systems beyond the

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respiratory tract. Neurological symptoms, including loss of taste and smell, fatigue, and cognitive impairment, may appear immediately after infection or following initial recovery from acute COVID-19 (Soriano et al., 2022). These clinical observations have prompted researchers to explore the underlying pathophysiological mechanisms in depth. The potential mechanisms of COVID-19-related cognitive impairment include systemic inflammation affecting the nervous system, autoimmune responses, direct SARS-CoV-2 infection of the central nervous system, herpesvirus reactivation, neurovascular dysfunction, and hypoxia-induced neural damage (Monje & Iwasaki, 2022). Recent research has also implicated mitochondrial dysfunction as a potential mechanism contributing to persistent cognitive symptoms, particularly chronic fatigue and cognitive disturbances observed in long COVID (Molnar et al., 2024).

Based on these mechanistic studies, extensive epidemiological research has established the prevalence of the cognitive impact of COVID-19. For instance, a meta-analysis showed that 19.5% – 34.0% of COVID-19 patients had self-reported or observer-reported cognitive complaints 4–15 weeks after discharge or recovery, while neuropsychological tests found that about 15.0%–40.0% of COVID-19 patients exhibited objective cognitive impairment 10 – 105 days after discharge (Vanderlind et al., 2021). Another meta-analysis found that 61.5%–80% of acute COVID-19 patients and 54%–65% of COVID-19 survivors had cognitive impairment in studies using the Montreal Cognitive Assessment (MoCA) (Crivelli et al., 2022). Memory, attention and executive function are the most commonly affected cognitive domains, while processing speed, working memory, delayed control, inhibition control, learning, semantic verbal fluency, and visuospatial ability can also be affected (Crivelli et al, 2022; Vanderlind et al, 2021). A recent comprehensive meta-analysis of 54 studies confirmed these findings, demonstrating small but significant deficits across multiple cognitive domains, with the largest effects observed in cognitive screeners, processing speed, and attention tasks (Knapp et al., 2024).

Despite the above results, the relationship between objective cognitive performance and patients' subjective complaints remains controversial. While some studies reported a significant association between subjective cognitive complaints and objective cognitive impairment caused by COVID-19 (Cavaco et al., 2023; Delgado-Alonso et al., 2022; Miskowiak et al., 2023), others found no such link (Ariza et al., 2022; Duindam et al., 2022; Gouraud et al., 2021). Recent evidence from 2024 suggests that subjective distractibility is more strongly predicted by anxiety and fatigue symptoms than by objective attention performance, with a hierarchical regression model explaining 58.8% of variance in subjective complaints (Zamarian et al., 2024). Thus, the relationship between them remains to be further clarified.

Once the complexity of cognitive impact was confirmed, identifying the risk factors became a key need for clinical management. Previous studies have specified some risk factors for COVID-19-related cognitive impairment, such as being a female, older age, ethnic minority, low education level, comorbidities, and severe disease (Frontera & Simon, 2022; Kubota et al., 2023; Liu et al., 2021; Miskowiak et al, 2023; Ollila et al., 2022; Pillay et al., 2022; Schou et al., 2021; Tavares-Júnior et al., 2022; Valdes et al., 2022). Other studies have shown that higher body mass index (BMI), a short time since infection, long duration of symptoms, loss of smell or taste, and sleep disturbances are also associated with neuropsychiatric sequelae of COVID-19, including cognitive impairment (Ariza et al, 2022; Miskowiak et al, 2023; Peter et al., 2022; Schou et al, 2021). More recent longitudinal studies have confirmed that cognitive deficits can persist for years after infection, with Taquet et al. (2024) demonstrating that psychiatric and cognitive symptoms can worsen or emerge over the first 2 – 3 years post-hospitalization, driven by both progression of existing symptoms and new symptom onset. Furthermore, Liu et al. (2024) tracked cognitive trajectories in older survivors up to 2.5 years post-infection and found that the overall incidence of cognitive impairment was 19.1%, with decline primarily manifesting in individuals with severe COVID-19 during the initial year, after which the rate of decline decelerated. However, the results were inconsistent (Frontera & Simon, 2022; Ollila et al, 2022). Given that cognitive impairment seriously affects the social function and quality of life of COVID-19 survivors (Miskowiak et al, 2023), and that recent evidence shows strong associations between cognitive deficits and occupational change in 26.9% of survivors (Taquet et al, 2024) and a reduced likelihood of full-time employment (Jaywant et al., 2024), the early identification of COVID-19-related cognitive impairment and its risk factors is necessary for implementing effective interventions.

Recognizing the importance of cognitive assessment, methodological issues have become a key constraint on research quality. Previous studies on post-COVID-19 cognitive function mostly employed

paper-and-pencil neuropsychological assessments (Ariza et al, 2022; Hosp et al., 2021; Nersesjan et al., 2022). However, these are not sensitive enough to identify mild cognitive impairment (Diana et al., 2023; Hampshire et al., 2022), and this traditional form of assessment requires more human and material resources. In contrast, online computerized tests can sensitively detect minor cognitive impairment (Diana et al, 2023; Hampshire et al, 2022). Moreover, they are more convenient to implement and can obtain data from a large number of participants in a short time. Hampshire et al. (2024) implemented a large-scale online cognitive assessment of 112,964 participants in England, demonstrating the feasibility and validity of such approaches for detecting COVID-19-related cognitive deficits in community samples. Previous studies using online or computerized assessments consistently found impairments in cognitive functions such as attention, executive function, and processing speed in COVID-19 patients or survivors. However, few such studies exist, and their sample sizes are not large enough (Ariza et al, 2022; Delgado-Alonso et al, 2022; Hampshire et al, 2022).

Furthermore, evidence on post-COVID-19 cognitive function in the Chinese population is limited, with only little research conducted to date (Liu et al., 2022; Liu et al, 2021), and even fewer have utilized computerized tests (He et al., 2023; Zhou et al., 2020) with small sample sizes. Notably, while previous online assessments have frequently relied on computers or tablets, despite the ubiquity of smartphones, smartphone-based assessments remain scarce. A longitudinal study conducted by Liu et al. in Wuhan, China, assessed cognitive function through telephone interviews and found cognitive impairment in COVID-19 patients correlated with disease severity. However, this study only focused on discharged patients over 60 years of age (Liu et al, 2022; Liu et al, 2021). Zhou et al. and He et al. used iPad-based and gamified online neuropsychological tests, respectively, and found cognitive impairment in COVID-19 survivors, while the sample sizes were small (n = 58 and n = 145) (He et al, 2023; Zhou et al, 2020). The technological gap regarding smartphones became particularly prominent after the adjustment of China's prevention and control measures, and the impact of COVID-19 on cognitive function in the Chinese population remains unknown.

Considering COVID-19 variants, most of the previous studies on post-COVID-19 cognitive function focused on wild-type SARS-CoV-2 — the alpha and delta variants — while few studies focused on the currently dominant Omicron variant (Taquet et al., 2022). Hampshire et al (2024) further confirmed the existence of variant-specific differences in cognitive outcomes: participants infected with the original virus or B.1.1.7 variant showed larger cognitive deficits (e.g., -0.17 SD for B.1.1.7 vs B.1.1.529/Omicron) compared to those infected with later variants including Omicron, suggesting that the Omicron variant may be associated with milder cognitive sequelae than earlier strains. A large-scale retrospective cohort study compared the effects of different variants, including Omicron, on cognitive function. They found that in the United States, the risk of cognitive deficits increased just after the emergence of the delta variant compared to just before, while the risk of cognitive deficits for the alpha and Omicron variants between these periods was similar (Taquet et al, 2022). The possible impacts of infection with Omicron variant on cognitive function are also worthy of attention (Kubota et al, 2023).

To address the above research gaps in China's unique epidemiological context after the relaxation of prevention and control measures, we conducted a large-scale nationwide smartphone-based survey to assess cognitive function among Chinese individuals in the subacute phase (< 3 months) of COVID-19 during the Omicron variant epidemic. Our aims were to identify the impact of COVID-19 (particularly the Omicron variant) on cognitive function in this population, determine the associated risk factors to be able to inform early prevention and intervention strategies and minimize adverse effects.

2 Methods

2.1 Design and participants

This study was a large-scale nationwide online assessment of cognitive function in people across China, conducted from January 15 to 29, 2023 using the snowball sampling method. The researchers sent the assessment link through WeChat groups and official accounts and encouraged people who received the message to spread the assessment link further to their WeChat groups or moments. The inclusion criteria were: 1) over 18 years old; 2) living in the Chinese mainland; 3) COVID-19 infection status was ascertained

by self-reporting: never infected with SARS-CoV-2, or only once and the time since infection (positive SARS-CoV-2 nucleic acid or antigen test) was less than 90 days, and had recovered (main symptoms such as fever, pain, and upper respiratory symptoms disappeared, or SARS-CoV-2 nucleic acid or antigen test turned negative; or asymptomatic infection and SARS-CoV-2 nucleic acid or antigen test showed negative); 4) normal or corrected-to-normal vision; and 5) no severe upper extremity joint disease or movement disorder that might prevent the participant from completing the test independently. The exclusion criteria were: 1) dementia; 2) current mental disorders or taking drugs for treating mental disorders, which might interfere with the assessment results; and 3) severe physical illnesses that might interfere with the assessment results.

2.2 Procedures

Participants completed a questionnaire followed by neuropsychological tests in a quiet environment. The voluntary assessment, lasting about five minutes, required focused attention. Each individual participated once, with their given informed consent and the option to withdraw at any time.

2.2.1 Clinical measures

The socio-demographic characteristics of the participants were collected by means of a questionnaire designed by the researchers, which included gender, date of birth, height, weight (BMI was calculated as weight divided by height squared [kg/m2]), ethnicity (later merged into Han ethnicity or ethnic minorities), education level, and city of residence (later merged into seven geographical regions of China) (Li et al., 2020). COVID-19-related factors were also collected. First, participants were asked if they had ever been infected with SARS-CoV-2. Then, they were further asked for the date of infection and recovery, whether there were underlying diseases; during the acute phase, whether they had certain conditions, including asymptomatic infection, upper respiratory tract infection, loss of smell or taste, and severe pneumonia; after the initial recovery, whether there were cognitive complaints including inflexible thinking and slowed information processing speed, and whether they experienced insomnia.

2.2.2 Procedures

In this study, participants' cognitive function was evaluated by two online neuropsychological tests based on smartphones: the Integrated Cognitive Assessment (ICA) and the Number Ordering Test (NOT).

ICA is a rapid visual categorization task that evaluates cognitive functions such as information processing speed and semantic processing (Kalafatis et al., 2021; Khaligh-Razavi et al., 2019). In this test, 100 grayscale natural images (50 animal and 50 non-animal) with different levels of difficulty were presented in the center of the screen. Each image was presented for 100 ms, followed by a 20-ms inter-stimulus interval and a 250-ms dynamic noisy mask. Subsequently, participants were asked to categorize the images by sliding to the right (animal) or left (non-animal) on the screen as quickly as possible. In addition, before the main task, 10 trial images (five animal, five non-animal) were shown to familiarize participants with the task. Participants who performed above chance (> 50%) on the 10 images continued to the main task. There was no time limit for this test. We calculated the average reaction time (RT) of non-outliers (between the lower quartile [Q1] minus 1.5 times the interquartile range [IQR] and the upper quartile [Q3] plus 1.5 times the IQR) in all images, animal images and non-animal images of correct categorization, the upper and lower quartiles of RT of all images, as well as the accuracy of all images, animal images, and non-animal images. Among them, the average RT and accuracy of all images are the key indicators of ICA, which reflect information processing speed and semantic processing, respectively. The ICA has a high sensitivity for detecting mild cognitive impairment, and the cognitive function it measures is highly correlated with global cognitive function (Kalafatis et al, 2021; Khaligh-Razavi et al, 2019).

NOT evaluates cognitive functions such as visual search, working memory, information processing speed, motor speed, and mental flexibility. This test is an adaption and combination of the Digit Ordering Test (DOT) and the Trail Making Test-A (TMT-A) (Bowie & Harvey, 2006; Werheid et al., 2002) to facilitate online assessment through smartphones. It presents several non-repeating numbers simultaneously at different locations on the screen and requires participants to click on the numbers in ascending order. The number of numbers presented each time increases gradually from three to seven. The test comprises 12 items and each item includes 3 – 15 trials. The numbers presented are all integers with an ascending absolute value range of 20, 50, 70, or 100. Moreover, negative numbers are included in the second half of the item in which

four numbers are presented, and the number of negative numbers increases gradually from one to five. If the participant clicks incorrectly, the trial will immediately move on to the next one. The detailed requirements of the test are shown in Online Resource Table S1. The test is limited to one minute. We recorded the number of completed and correctly completed trials, the average completion time, and the number of clicked and correctly clicked numbers. We also calculated the accuracy of completed trials and clicked numbers and obtained the total score of NOT by multiplying the number of correctly clicked numbers by the accuracy of completed trials. As a key indicator of NOT, the NOT total score comprehensively measures visual-motor skills, working memory, information processing speed, and mental flexibility, and indirectly reflects executive function (Bowie & Harvey, 2006; Werheid et al, 2002).

2.3 Statistical analysis

We cleaned the data by excluding participants who answered carelessly, missed questionnaire answers, or showed extreme neuropsychological test results. Specifically, we removed RT outliers exceeding three SDs from the mean, excluded ICA cases with accuracy $\leqslant$ 50%, and DOT cases with accuracy or total score below three SDs of the normative mean.

Categorical sample characteristics were presented as counts (percentages), while continuous variables were described as mean $\pm$ SD for normal or near-normal distributions (skewness $\leqslant$ 2, kurtosis $\leqslant$ 7), or as median (IQR) for non-normal distributions (Kim, 2013). In univariate analysis, chi-square tests were used to compare group proportions, t-tests or ANOVA to assess normally distributed continuous variables, and rank sum tests to address non-normal distributions. Post hoc analyses followed multi-group ANOVA, and ANCOVA controlled for demographics when comparing neuropsychological test results between COVID-19 survivors and uninfected individuals. Pearson's correlation was employed to analyze normally distributed variables, while Spearman's correlation was used to assess non-normally distributed or ordinal-continuous variable relationships, with coefficients indicating weak (<0.30), moderate (0.30-0.49), or strong (>0.49) correlations (Delgado-Alonso et al, 2022). In multivariate analysis, the three key indicators of the neuropsychological tests (the average RT and accuracy of all images in ICA, and the NOT total score) were used as dependent variables. To balance theoretical rigor with the exploratory identification of novel risk factors during the Omicron wave, we employed a hybrid modeling strategy. Core socio-demographic confounders with established links to cognitive function (i.e., age, gender, and region) were forced into the model using the enter method. The remaining socio-demographic and COVID-19-related factors, for which strong a priori theoretical precedence is lacking, were evaluated using the stepwise method (entry $p < 0.05$, removal $p > 0.10$) to identify salient predictors while minimizing overfitting. The large sample size ($n = 8,905$) reduces the risk of model instability typically associated with stepwise selection. For unordered categorical variables (such as regions) in the independent variables, the group with the largest number of participants was coded as a dummy variable.

All statistical analyses were performed using IBM SPSS 26.0, and a p-value < 0.05 was considered statistically significant.

3 Results

3.1 Sample characteristics

A total of 10,618 respondents completed the online assessment. Data cleaning proceeded in sequential stages: 236 participants were excluded for being under 18 years old, 160 for residing outside the Chinese mainland or having inconsistent date information (e.g., illogical infection or recovery dates), and 51 for not having recovered from COVID-19 at the time of the survey. From the remaining 10,171 participants, a further 508 were excluded based on neuropsychological test quality criteria (ICA reaction time outliers exceeding 3 SDs from the mean, ICA accuracy $\leqslant$ 50%, or NOT accuracy/total score below 3 SDs of the normative mean) or incomplete questionnaire responses. The final analytic sample comprised 9,663 participants (effective rate 91.0%). They came from all 31 provinces, autonomous regions and municipalities of the Chinese mainland. Among them, 6,902 (71.4%) were female, and the average age was 35.28 $\pm$ 10.01 years (range, 18 – 91 years); 8905 (92.2%) were COVID-19 survivors and 758 (7.8%) were uninfected.

There were significant differences in gender, age and education level between COVID-19 survivors and uninfected participants ($p < 0.05$). The detailed socio-demographic characteristics and their comparisons between COVID-19 survivors and uninfected participants are listed in Table 1.

3.2 Cognitive performance of COVID-19 survivors and uninfected participants

There were significant differences in the results of neuropsychological tests between COVID-19 survivors and uninfected participants. Specifically, in the ICA, the RTs of COVID-19 survivors were longer (RT [ms]: 963.43 ± 133.60 vs. 949.37 ± 129.31, $p = 0.005$; RT-animal [ms]: 954.28 ± 131.14 vs. 939.69 ± 128.20, $p = 0.003$; RT-non-animal [ms]: 973.62 ± 142.40 vs. 959.82 ± 135.72, $p = 0.008$), and accuracies were lower (accuracy [%]: 90.54 ± 6.18 vs. 91.64 ± 5.32, $p < 0.001$; accuracy-animal [%]: 88.95 ± 8.94 vs. 90.30 ± 8.17, $p < 0.001$; accuracy-non-animal [%]: 94.00 [90.00, 96.00] vs. 94.00 [90.00, 96.00], $p = 0.033$), compared with those of uninfected participants. In NOT, the total score (52.77 ± 12.01 vs. 53.70 ± 12.10, $p = 0.040$) and trial accuracy (%, 87.74 ± 9.86 vs. 88.49 ± 9.96, $p = 0.044$) of COVID-19 survivors were lower than those of uninfected participants, and there was no significant difference in the other results (all $p > 0.05$). However, the ANCOVA results showed that after controlling for the socio-demographic characteristics such as gender, age, BMI, ethnicity, education level, and region, only the accuracies of ICA were lower in COVID-19 survivors than in uninfected participants ($p < 0.05$, partial $\eta 2 \leqslant 0.001$), while no significant differences were found in the RTs of ICA and the results of NOT (all $p > 0.05$) (Table 2). To explore whether demographic associations with cognitive performance were specific to COVID-19 survivors, we conducted exploratory subgroup analyses among the 758 uninfected participants. Gender differences were not significant for any of the three key cognitive indicators (all $p > 0.05$). Ethnic minorities scored lower than Han participants on the NOT total score ($p = 0.033$), but not on ICA measures (all $p > 0.05$). Regional differences were significant for ICA accuracy ($F = 3.655$, $p = 0.001$) and NOT total score ($F = 3.316$, $p = 0.003$), with participants from Northwest China scoring the lowest on both measures.

3.3 Characteristics of COVID-19 survivors

Among the 8,905 COVID-19 survivors, 6,419 (72.1%) were female, 8,253 (92.7%) were of Han ethnicity, and 1,056 (11.9%) had underlying diseases. The average time since infection was 29.82 ± 8.76 days (range, 3 – 89 days); 8,397 (94.3%) were infected after December 7, 2022. The average duration of infection was 11.74 ± 8.75 days (range, 1 – 49 days). There were 395 (4.4%) survivors with asymptomatic infection, 8,109 (91.1%) with symptoms of fever, fatigue and upper respiratory tract infection, 3,485 (39.1%) with loss of smell or taste, and 105 (1.2%) with severe pneumonia. After the initial recovery from the acute phase, 5,832 (65.5%) participants reported inflexible thinking, 5,419 (60.9%) reported slowed information processing speed, and 4,344 (48.8%) had insomnia (Table 3).

3.4 Factors related to cognitive performance in COVID-19 survivors

We further analyzed the association of socio-demographic characteristics and COVID-19-related factors with the neuropsychological test results among COVID-19 survivors. In the univariate analysis, for the categorical variables in socio-demographics and COVID-19-related factors, the results of the t-test, ANOVA, or rank sum test showed that being a female, living in certain areas (i.e., Northwest, Northeast, and Central China), having underlying diseases, severe pneumonia, and insomnia after recovery were related to poor performance in most of the results of ICA and NOT ($p < 0.05$). Meanwhile, inflexible thinking and slowed information processing speed after recovery were related to poor performance in accuracies of ICA and most results of NOT ($p < 0.05$). Belonging to an ethnic minority and loss of smell or taste were related to poor performance in most results of NOT ($p < 0.01$) (Table 3, Table 4, Online Resource Table S2 and Table S3).

For continuous or ordinal variables in socio-demographics and COVID-19-related factors, the results of Pearson's or Spearman's correlation analysis revealed a moderate positive correlation between age and RTs

in ICA and NOT (range, r 0.354 – 0.444, $p < 0.001$), and a weak to moderate negative correlation with the accuracy in ICA and most other results in NOT (range, r -0.374 – -0.261, $p < 0.001$; except for the trial accuracy and number accuracy). BMI and duration of infection showed similar correlations as above, but both were weak (range, absolute value of r 0.024 – 0.102, $p < 0.05$). The education level showed diametrically opposite correlations as presented above, all of which were weak (range, absolute value of r 0.045 – 0.230, $p < 0.001$). The time since infection had no significant correlation with most results in ICA ($p > 0.05$) and a weak negative correlation with most results in NOT (except RT, which was positively correlated; range, absolute value of r 0.024 – 0.053, $p < 0.05$) (Table 5).

In the multivariate analysis, the results of linear regression analysis indicated that being a female, older age, low education level, living in Northwest China (compared with living in South China), and having insomnia after recovery were significantly associated with poor performance on the three key neuropsychological indicators (i.e., longer RT and lower accuracy in ICA and a lower NOT total score) (range, absolute value of β 0.023 – 0.430, $p < 0.05$); meanwhile, living in East China was significantly associated with better performance on these indicators (range, absolute value of β 0.028 – 0.053, $p < 0.05$), and living in North China was significantly associated with shorter RT in ICA ($\beta = -0.050$, $p < 0.001$). Having underlying diseases was significantly associated with longer RT and lower accuracy in ICA (range, absolute value of β 0.020 – 0.026, $p < 0.05$). Belonging to an ethnic minority and longer duration of infection were significantly associated with lower accuracy in ICA and a lower NOT total score (range, β -0.033 – -0.020, $p < 0.05$). Higher BMI and slowed subjective information processing speed after recovery were significantly associated with lower accuracy in ICA (range, β -0.054 – -0.026, $p < 0.05$), and subjective inflexible thinking after recovery was significantly associated with a lower NOT total score ($\beta = -0.032$, $p = 0.002$) (Table 6).

4 Discussion

Our study assessed the cognitive performance of COVID-19 survivors during the Omicron variant epidemic following the relaxation of prevention measures in China. A key finding is that over 60% of these patients reported cognitive complaints in the subacute phase (<3 months), while objective cognitive differences were primarily observed in semantic processing. Being a female, older age, low education level, living in some areas (such as Northwest China), and insomnia after the initial recovery had significant adverse effects on objective cognitive function, including information processing speed, semantic

processing, visual-motor ability, working memory, mental flexibility, and executive function. Belonging to an ethnic minority, higher BMI, underlying diseases, longer duration of infection, slowed subjective information processing speed, and inflexible thinking after recovery also had negative impacts on certain objective cognitive domains.

In our study, COVID-19 survivors exhibited subtle cognitive differences compared to an uninfected cohort, primarily in semantic processing, despite the baseline demographic differences between groups. Multiple mechanisms may contribute to such post-viral neurological changes, including neuroinflammatory responses, direct nervous system infection, and vascular damage (Monje & Iwasaki, 2022). Recent neuroimaging studies provide compelling evidence for these pathways. Wood et al. (2025) demonstrated that cognitive deficits at one year post-hospitalization were associated with elevated brain injury markers (including neurofilament light chain and glial fibrillary acidic protein) and reduced anterior cingulate cortex volume, supporting the hypothesis that moderate to severe COVID-19 may cause immune-mediated brain injury. Similarly, Serrano Del Pueblo et al. (2024) found that patients with neurological long COVID had thinner cortex in the left posterior superior temporal gyrus and widespread white matter abnormalities, with altered connectivity correlating with impairments in episodic memory, overall cognitive function, attention, and verbal fluency. Furthermore, Vakani et al. (2025) demonstrated that a higher persistent COVID-19 symptom load was associated with smaller putamen volume, which fully mediated the relationship between symptom load and poor executive function. In fact, neuroimaging studies have found many abnormalities in brain structure and function in COVID-19 patients (Douaud et al., 2022; Hosp et al, 2021). These abnormalities may be associated with post-COVID-19 cognitive impairment.

Our findings suggest a relatively mild objective cognitive impact of the Omicron variant. After controlling for socio-demographic characteristics, the only significant difference between COVID-19 survivors and uninfected individuals was in semantic processing (i.e., categorizing images as animal or non-animal). This indicates that COVID-19-related objective cognitive differences may be relatively limited during the Omicron wave, which aligns with the findings of a large community study by Hampshire et al (2024). Therein, it was demonstrated that individuals infected with the Omicron variant (B.1.1.529) showed smaller cognitive deficits compared to those infected with earlier variants, with an effect size difference of -0.17 SD between B.1.1.7 and B.1.1.529 variants. A previous study found no significant difference in the risk of cognitive impairment after the emergence of the Omicron variant (Taquet et al, 2022). This is likely attributable to both the lower neurotropism of that variant and the predominantly mild disease presentation in our sample, where 91.1% of survivors reported only mild to moderate symptoms and only 1.2% experienced severe pneumonia. This is consistent with evidence that milder disease severity is associated with smaller cognitive effects (Liu et al., 2021; Ollila et al., 2022). However, it is important to note that even these relatively smaller deficits can have meaningful functional impacts, as demonstrated by Jaywant et al (2024). They found that cognitive symptoms in post-COVID-19 condition were associated with lower odds of full-time employment (adjusted OR=0.92, 95% CI 0.88-0.97) and greater functional impairment, even in individuals who were not severely ill during acute infection. Moreover, given that over 80% of the Chinese population was infected during this wave (Fu et al., 2023), even a negligible effect at the individual level could translate into a substantial aggregate burden at the population level, underscoring the public health significance of monitoring cognitive outcomes following widespread infection.

Our study further validated traditional demographic risk factors for poorer cognitive performance. Consistent with previous research (Demmer et al., 2025; Liu et al, 2021; Miskowiak et al, 2023; Valdes et al, 2022), we found that cognitive function in COVID-19 survivors was negatively correlated with age. Females also exhibited slightly worse cognitive function than males in the COVID-19 survivor group, whereas no significant gender differences were observed in the uninfected group (all $p > 0.05$), suggesting that this effect may be related to infection-specific mechanisms such as a greater vulnerability to autoimmune-mediated nervous system injury (Frontera & Simon, 2022), rather than pre-existing gender differences in cognitive ability. Notably, Wang et al. (2025) found no difference in cognitive function between pandemic and pre-pandemic assessments in a large cohort of middle-aged women (n=5,191), suggesting that female-specific risk may vary by population characteristics, age group, or infection context. Furthermore, cognitive function was positively correlated with education level, suggesting that the cognitive reserve may play a protective role against cognitive decline (Ariza et al, 2022; Liu et al, 2021; Valdes et al, 2022).

Notably, we also found significant regional disparities: cognitive function in COVID-19 survivors was related to the region of residence. In particular, the cognitive function of participants in Northwest China was lower than that in the southeast coastal areas of China. To determine whether these demographic associations were specific to COVID-19 survivors, we conducted exploratory subgroup analyses among uninfected participants. Regional and ethnic differences showed similar patterns in both groups, with participants from Northwest China and ethnic minorities scoring lower on key cognitive measures regardless of infection status. These findings suggest that regional and ethnic disparities in cognitive function largely reflect pre-existing population-level differences related to socioeconomic and educational factors, rather than COVID-19-specific effects (Frontera & Simon, 2022).

Beyond these core demographic factors, several other risk factors also showed weaker but important effects. Ethnic minorities performed poorly in some cognitive domains, similar to previous studies reporting low cognitive function in ethnic minorities (Chen et al., 2022; Valdes et al, 2022). This phenomenon may also be related to socioeconomic status, such as nutrition, income and education level, as well as physical health (Chen et al, 2022; Valdes et al, 2022). However, the low standardized regression coefficient of ethnicity to the results of neuropsychological tests (range, β -0.033 – -0.020) indicates that the actual effect was very slight. In addition, participants with a higher BMI performed poorly in semantic processing, which may be due to the fact that these people are susceptible to metabolic syndrome, which is often accompanied by subclinical inflammation (Peter et al, 2022), and the disease severity may be higher during the acute phase of COVID-19. Nonetheless, the low correlation coefficient (r = -0.084) and standardized regression coefficient (β = -0.026) between the BMI and the accuracy in ICA also revealed that the actual effect of this parameter is limited. Additionally, poorer cognitive performance was more pronounced in COVID-19 survivors with underlying diseases, consistent with previous studies (Liu et al, 2021). This may be because those with underlying diseases experience relatively severe illness during the acute phase, which may aggravate cognitive decline.

From the perspective of disease course, infection severity and duration showed complex association patterns; the duration of infection was negatively correlated with cognitive function. Previous research has shown that the duration of infection can reflect disease severity to some extent: the more severe the disease is, the more severe the cognitive impairment (Liu et al, 2021; Ollila et al, 2022; Tavares-Júnior et al, 2022). This may be due to severe illness leading to more severe neural inflammation and injury (Monje & Iwasaki, 2022). Different from the duration of infection, the time since infection was not related to any cognitive domains according to multivariate analysis. This null finding is likely attributable to the fact that the vast majority of participants (94.3%) were infected during the same epidemic wave within a narrow time window, resulting in a highly concentrated distribution of time since infection, limiting the ability to detect variation across distinct recovery phases. Consistently, correlation analyses showed no meaningful association between time since infection and cognitive performance. Previous studies have indicated that post-COVID-19 cognitive function may gradually improve over time (Cecchetti et al., 2022; Nersesjan et al, 2022). However, recent longitudinal evidence provides a more nuanced picture of the recovery trajectories. Liu et al (2024) found in a 2.5-year follow-up study that cognitive decline primarily manifested during the initial year after severe COVID-19 infection, after which the rate of decline decelerated, with an overall incidence of cognitive impairment of 19.1% at 2.5 years. Conversely, Taquet et al (2024) reported that psychiatric and cognitive symptoms appeared to increase over the first 2 – 3 years post-hospitalization, driven by both the worsening of existing symptoms and emergence of new symptoms, particularly in individuals who already had symptoms at 6 months. Hampshire et al (2024) reported that participants with unresolved persistent symptoms showed larger deficits compared to those with resolved symptoms, suggesting that symptom resolution rather than time per se may be a more important predictor of cognitive recovery. However, this study mainly focused on the cognitive function during the subacute phase (< 3 months) of COVID-19, so the trajectory of cognitive function over a long time remains to be further explored.

In this study, loss of smell or taste in the acute phase was associated with poor cognitive function, including visual-motor ability, working memory, mental flexibility, and executive function after the initial recovery according to univariate analysis but not multivariate analysis. Previous studies have found that loss

of taste and smell may indicate cognitive impairment (Braga-Paz et al., 2022; Cecchetti et al, 2022; Delgado-Alonso et al, 2022), which may be related to direct viral invasion of the central nervous system or the disruption of brain homeostasis through the activation of signaling pathways (Braga-Paz et al, 2022). Meanwhile, multivariate analysis might obscure negative results due to stronger influences. Although univariate analysis linked severe pneumonia in the acute phase with poorer post-recovery cognitive performance, multivariate analysis showed no significant correlation. Severe pneumonia could impair cognition through systemic inflammation and hypoxia-induced neuroinflammation and nervous system damage (Monje & Iwasaki, 2022), but the negative results in the multivariate analysis may also be masked due to other stronger influencing factors. Kaushik et al. (2024) found that in-hospital delirium during COVID-19 hospitalization was associated with increased functional disability and cognitive impairment over 6 months after discharge, suggesting that acute neuropsychiatric complications may be more important predictors of long-term outcomes than pneumonia severity per se.

A marked discrepancy was found between subjective complaints and objective performance observed in our study, where over 60% of COVID-19 survivors reported inflexible thinking or slowed processing speed, yet the adjusted between-group differences in objective measures were minimal. This discordance suggests that subjective cognitive complaints following COVID-19 may be substantially driven by factors other than measurable cognitive decline. The results showed that subjective inflexible thinking was associated with poor objective visual-motor skills, working memory, mental flexibility, and executive function, but only slow subjective processing speed correlated with semantic processing deficits, rather than reaction time. The partial and inconsistent nature of these associations is consistent with the broader literature. Some studies have found correlations between cognitive complaints and objective cognitive performance (Cavaco et al, 2023; Delgado-Alonso et al, 2022; Miskowiak et al, 2023), while others have not (Ariza et al, 2022; Duindam et al, 2022; Gouraud et al, 2021), with the latter attributing subjective complaints primarily to psychological and somatic factors. In particular, anxiety and depressive symptoms, persistent fatigue, and sleep disturbances have each been shown to independently amplify perceived cognitive difficulties in the absence of proportionate objective deficits. Zamarian et al (2024) demonstrated that subjective distractibility was significantly predicted by current anxiety and fatigue symptoms rather than objective attention performance, with their hierarchical regression model explaining 58.8% of variance. Similarly, for a large community sample, Hampshire et al (2024) reported that subjective cognitive symptoms (brain fog) only weakly correlated with objective deficits. Although our study did not directly assess anxiety, depression or fatigue, it is notable that 48.8% of COVID-19 survivors in our sample reported insomnia after initial recovery, a symptom closely linked to emotional distress and fatigue, and that insomnia was the strongest and most consistent predictor of poor objective cognitive performance across all domains. This raises the possibility that much of the subjective cognitive burden reported by survivors may reflect the combined influence of sleep disruption, psychological distress and post-infectious fatigue rather than direct neurocognitive damage from the virus. These findings collectively suggest that subjective and objective cognitive measures capture partially distinct constructs: subjective complaints appear to be more strongly driven by affective and somatic symptoms, while objective performance is more closely tied to demographic and clinical factors. Clinically, this dissociation underscores the need for a comprehensive assessment that includes not only cognitive testing but also systematic evaluation of mood, anxiety, fatigue, and sleep quality in COVID-19 survivors presenting with cognitive concerns.

In this study, among all identified risk factors, insomnia showed the strongest and most consistent association, highlighting its importance as a key modifiable factor. Among COVID-19 survivors, those with insomnia showed poorer cognitive performance than those without. This was reflected in all cognitive domains assessed in this study, and the association was more significant than other COVID-19-related factors, even including subjective cognitive complaints. Previous research also showed a relationship between sleep quality and cognitive function in COVID-19 patients (Delgado-Alonso et al, 2022). Studies have confirmed that sleep loss can impair cognitive functions such as attention and working memory by changing brain activity and connectivity. Sleep disturbance may also contribute to cognitive impairment by increasing amyloid-β accumulation, disrupting neurogenesis, and promoting neuroinflammation (Yaffe et al., 2014). The robustness of the insomnia-cognition relationship in our study aligns with emerging evidence on the role of sleep in post-COVID-19 recovery and suggests that sleep disturbances may be both a symptom

and a modifiable risk factor for persistent cognitive dysfunction. Recent systematic reviews of rehabilitation interventions have identified promising approaches for managing post-COVID-19 symptoms. Zeraatkar et al. (2024) found moderate certainty evidence that cognitive behavioral therapy (CBT) reduces fatigue and improves concentration, and that combined physical and mental health rehabilitation programs improve overall health, depressive symptoms, and quality of life. Similarly, Pollini et al. (2024) found uncertain but suggestive evidence that pulmonary rehabilitation improves exercise capacity and respiratory function in mild COVID-19 and post-COVID-19 condition patients, with several interventions showing promise for reducing anxiety and depression. Given that our study identified insomnia as the strongest modifiable risk factor for poorer cognitive performance, interventions targeting sleep quality—such as CBT for insomnia—may represent a critical component of comprehensive rehabilitation programs for COVID-19 survivors in the subacute phase.

Our findings contribute to the growing body of literature on COVID-19-related cognitive outcomes by providing novel insights specific to the Omicron variant period in a large Chinese population. First, the relatively modest cognitive differences observed in our study (effect sizes $\leqslant 0.001$) are consistent with the findings of Hampshire et al (2024) that Omicron-infected individuals showed smaller cognitive effects than those infected with earlier variants, supporting the hypothesis that Omicron may have reduced neurocognitive impact. Second, the striking discrepancy between the high prevalence of subjective complaints (65.5% reporting inflexible thinking; 60.9% reporting slowed processing speed) and the negligible objective between-group differences after covariate adjustment reinforces recent evidence that subjective and objective cognitive measures reflect partially independent constructs (Zamarian et al, 2024). Moreover, it highlights the likely contribution of affective symptoms, fatigue, and sleep disturbance to perceived cognitive difficulties following COVID-19. Third, the strong association between insomnia and cognitive function across all assessed domains suggests that sleep disturbance may be a critical mediator of cognitive outcomes, potentially representing a modifiable target for intervention. Finally, our choice of smartphone-based assessment demonstrates the feasibility of large-scale, population-level cognitive screening in the immediate aftermath of widespread infection, providing a scalable model for monitoring cognitive health in future public health emergencies.

Based on these findings, we propose clinically practical management recommendations. This study highlights the short-term effects of COVID-19 on some cognitive domains during the epidemic of Omicron variant. Although the adjusted between-group effect sizes were small, the sheer scale of infection during this wave means that even minor cognitive effects, when multiplied across hundreds of millions of individuals, may carry meaningful public health implications. This study therefore highlights the importance of attending to cognitive recovery following COVID-19, particularly among high-risk subgroups, especially for older adults, women, and people with low education and living in certain areas (such as Northwest China) (Pillay et al, 2022). During the acute phase of COVID-19, infection should be controlled as soon as possible to avoid potential adverse effects on cognitive function caused by prolonged infection. For those with insomnia after the initial recovery, cognitive behavioral therapy or sedative hypnotics are necessary for the treatment of insomnia in order to reduce its possible impact on cognitive function. Recent evidence supports the effectiveness of such interventions. Zeraatkar et al (2024) provided moderate-certainty evidence that CBT improves concentration (mean difference -5.2, 95% CI -7.97 to -2.43 on the Checklist for Individual Strength concentration subscale); combined physical and mental health rehabilitation programs improve depressive symptoms and quality of life in the post-COVID-19 condition.

The current study has several strengths. This is the first large-scale nationwide survey of cognitive function among Chinese people in the subacute phase (< 3 months) of COVID-19 during the epidemic of Omicron variant. Computerized neuropsychological tests were used, which have better sensitivity and accuracy in detecting mild cognitive impairment when compared with traditional paper-and-pencil tests such as MoCA (Diana et al, 2023; Hampshire et al, 2022). What is more, these smartphone-based online tests are more convenient to implement, and they are not limited by time and space and can obtain a large number of participants' data in a short time (Khaligh-Razavi et al, 2019). Hampshire et al (2024) demonstrated the validity of large-scale online cognitive assessment in 112,964 participants, providing additional support for the methodology employed in our study.

However, this study also has some limitations. First, the snowball sampling strategy via WeChat likely over-represented younger, more educated, and urban populations, limiting the generalizability of our findings to older adults, individuals with lower education levels, and rural populations who may be more vulnerable to post-COVID-19 cognitive effects. Second, this study was cross-sectional, so causal relationships between cognitive performance and related factors cannot be drawn. Third, this study used smartphone-based ICA and NOT to evaluate cognitive function. The lack of established population norms for these tests limits the generalizability of results. However, the 758 uninfected participants served as age- and education-matched internal controls, partially mitigating this limitation. Furthermore, device characteristics such as screen size and touch latency were not recorded, which may have introduced uncontrolled variability in the reaction time measurements. Fourth, the uninfected control group was small. Although ANCOVA was applied to adjust for these covariates, residual confounding from unmeasured factors could not be excluded, hence the between-group comparisons should be considered suggestive rather than confirmatory.

In summary, this study provides the first large-scale assessment of cognitive effects in surviving COVID-19 patients infected with the Omicron variant in China using smartphone-based testing. Our findings demonstrated relatively modest objective differences, consistent with emerging evidence of variant-specific differences in neurocognitive impact. Critically, we identified insomnia as the strongest modifiable risk factor for cognitive dysfunction. To promote recovery and minimize long-term cognitive sequelae, evidence-based interventions should be implemented, including cognitive behavioral therapy and combined physical-mental health rehabilitation programs (Pollini et al, 2024; Zeraatkar et al, 2024).

Data availability statement

Data are available from the corresponding author upon reasonable request.

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Author contributions

Xue LUO contributed to conceptualization, methodology, formal analysis, and wrote and edited the manuscript. Shufei ZENG contributed to conceptualization. Shuai LIU contributed to conceptualization, data curation, and wrote and edited the manuscript. Yuanhui LI contributed to formal analysis. Leqin FANG contributed to data curation and formal analysis. Dai LI contributed to data curation. Qianqian XIN, Shixu DU, and Yan XU contributed to investigation and validation. Bin ZHANG contributed to conceptualization, writing and editing of the manuscript, supervision, project administration, and funding acquisition. All authors contributed to and have approved the final manuscript and, therefore, had full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Xue LUO, Shufei ZENG, Shuai LIU, Yuanhui LI, Leqin FANG, Dai LI, Qianqian XIN, Shixu DU, Yan XU, Bin ZHANG declare that they have no conflicts of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom identifying information is included in this article.

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

Table 1 Comparisons of socio-demographic characteristics between COVID-19 survivors and uninfected participants

	Total sample	Uninfected	COVID-19	t/χ^2	p-value[a]

	n = 9,663	**participants n = 758**	**survivors n = 8,905**		
Gender (female)	6902 (71.4)	483 (63.7)	6419 (72.1)	23.937	**<0.001**[a]
Age (years)	35.28 ± 10.01	34.17 ± 10.32	35.38 ± 9.97	-3.186	**0.001**[b]
BMI	22.68 ± 3.53	22.52 ± 3.46	22.69 ± 3.54	-1.309	0.191[b]
Ethnicity (Han)	8953 (92.7)	700 (92.3)	8253 (92.7)	0.112	0.738[a]
Education level				17.311	**0.004**[a]
Junior high or below	231 (2.4)	26 (3.4)	205 (2.3)		
Secondary	528 (5.5)	39 (5.1)	489 (5.5)		
Junior college	1355 (14.0)	99 (13.1)	1256 (14.1)		
Undergraduate	5065 (52.4)	388 (51.2)	4677 (52.5)		
Master's	1943 (20.1)	142 (18.7)	1801 (20.2)		
Doctoral	541 (5.6)	64 (8.4)	477 (5.4)		
Regions				9.497	0.147[a]
North China	1817 (18.8)	129 (17.0)	1688 (19.0)		
Northeast China	435 (4.5)	26 (3.4)	409 (4.6)		
East China	1883 (19.5)	162 (21.4)	1721 (19.3)		
Central China	791 (8.2)	49 (6.5)	742 (8.3)		
South China	2692 (27.9)	220 (29.0)	2472 (27.8)		
Southwest China	1163 (12.0)	95 (12.5)	1068 (12.0)		
Northwest China	882 (9.1)	77 (10.2)	805 (9.0)		

P-values in bold indicate statistical significance. [a]χ^2test. [b]Student's t-test.

COVID-19: coronavirus disease 2019; BMI: body mass index.

Table 2 Comparisons of the results of neuropsychological tests between COVID-19 survivors and uninfected participants

	Total sample n = 9,663	**Uninfected participants n = 758**	**COVID-19 survivors n = 8,905**	***t/Z***	***p*-value**	**Adjusted *F***	***p*-value**[c]	**Partial η^2**
Integrated Cognitive Assessment								
RT (ms)	962.33 ± 133.31	949.37 ± 129.31	963.43 ± 133.60	-2.789	**0.005**[a]	1.870	0.172	<0.001
RT-animal (ms)	953.13 ± 130.97	939.69 ± 128.20	954.28 ± 131.14	-2.945	**0.003**[a]	2.424	0.120	<0.001

RT-non-animal (ms)	972.54 ± 141.93	959.82 ± 135.72	973.62 ± 142.40	-2.677	**0.008**[a]	1.338	0.247	<0.001
RT-Q1 (ms)	875.08 ± 116.71	866.33 ± 114.75	875.83 ± 116.86	-2.151	**0.031**[a]	0.442	0.506	<0.001
RT-Q3 (ms)	1099.76 ± 183.91	1079.58 ± 175.37	1101.48 ± 184.52	-3.149	**0.002**[a]	3.231	0.072	<0.001
Accuracy (%)	90.63 ± 6.13	91.64 ± 5.32	90.54 ± 6.18	5.361	**<0.001**[a]	11.857	**<0.001**	0.001
Accuracy-animal (%)	89.05 ± 8.89	90.30 ± 8.17	88.95 ± 8.94	4.031	**<0.001**[a]	8.281	**0.004**	0.001
Accuracy-non-animal (%)	94.00 (90.00, 96.00)	94.00 (90.00, 96.00)	94.00 (90.00, 96.00)	-2.134	**0.033**[b]			
Number Ordering Test								
Total score	52.84 ± 12.02	53.70 ± 12.10	52.77 ± 12.01	2.051	**0.040**[a]	0.923	0.337	<0.001
RT (ms)	3230.38 (2952.07, 3567.85)	3217.19 (2937.87, 3573.15)	3231.25 (2953.87, 3567.75)	-0.697	0.486[b]			
Completed trials	16.86 ± 2.41	16.91 ± 2.51	16.86 ± 2.40	0.567	0.571[a]	0.751	0.386	<0.001
Correct trials	14.74 ± 2.30	14.89 ± 2.33	14.73 ± 2.30	1.794	0.073[a]	0.251	0.616	<0.001
Trial accuracy (%)	87.80 ± 9.87	88.49 ± 9.96	87.74 ± 9.86	2.016	**0.044**[a]	3.618	0.057	<0.001
Correct numbers	59.84 ± 10.42	60.39 ± 10.56	59.80 ± 10.40	1.506	0.132[a]	0.005	0.943	<0.001
Number accuracy (%)	96.48 ± 3.16	96.67 ± 3.16	96.46 ± 3.16	1.741	0.082[a]	2.389	0.122	<0.001

P-values in bold indicate statistical significance. [a]Student's t-test. [b]Mann-Whitney U test. [c]Analysis of covariance (ANCOVA) adjusted for socio-demographics.

COVID-19: coronavirus disease 2019; RT: reaction time; Q1: lower quartile; Q3: upper quartile.

Table 3 The key results of neuropsychological tests in COVID-19 survivors with different socio-demographic characteristics

	COVID-19 survivors n = 8,905	**RT-ICA (ms)**		**Accuracy-ICA (%)**		**NOT total score**	
	n (%)	**Mean ± SD**	**p-value[a]**	**Mean ± SD**	**p-value[a]**	**Mean ± SD**	**p-value[a]**
Socio-demographics							
Gender			**0.007**		**<0.001**		**<0.001**
Male	2486 (27.9)	957.28 ± 135.12		91.23 ± 6.10		53.67 ± 12.01	
Female	6419 (72.1)	965.81 ± 132.94		90.28 ± 6.19		52.42 ± 11.99	
Ethnicity			0.717		0.180		**<0.001**
Han	8253 (92.7)	963.29 ± 133.86		90.57 ± 6.12		52.90 ± 11.96	
Minority	652 (7.3)	965.26 ± 130.35		90.20 ± 6.87		51.08 ± 12.47	
Regions			**<0.001**		**<0.001**		**<0.001**
North China	1688 (19.0)	964.13 ± 133.80		90.23 ± 6.43[b]		52.48 ± 12.13[b]	
Northeast China	409 (4.6)	983.25 ± 145.87[b]		89.91 ± 6.29[b]		51.57 ± 11.95[b]	
East China	1721 (19.3)	952.54 ± 132.12		90.96 ± 5.86		54.32 ± 12.06	
Central China	742 (8.3)	980.20 ± 134.79[b]		90.06 ± 6.21[b]		51.70 ± 11.04[b]	
South China	2472 (27.8)	952.99 ± 128.16		91.22 ± 5.75		53.90 ± 11.84	

Southwest China	1068 (12.0)	967.40 ± 135.05		90.63 ± 6.33	51.74 ± 12.58[b]	
Northwest China	805 (9.0)	986.53 ± 137.58[b]		88.90 ± 6.90[b]	49.53 ± 11.35[b]	

P-values in bold indicate statistical significance. [a]Student's t-test. [b]Values with significant differences from the South China group in Student-Newman-Keuls post hoc multiple comparisons.

COVID-19: coronavirus disease 2019; RT: reaction time; ICA: Integrated Cognitive Assessment; NOT: Number Ordering Test; SD: standard deviation.

Table 4 The key results of neuropsychological tests in COVID-19 survivors with different socio-demographic characteristics and COVID-19-related factors

	COVID-19 survivors n = 8,905	**RT-ICA (ms)**		**Accuracy-ICA (%)**		**NOT total score**	
	n (%)	**Mean ± SD**	**p-value[a]**	**Mean ± SD**	**p-value[a]**	**Mean ± SD**	**p-value[a]**
COVID-19-related factors							
Underlying diseases			**<0.001**		**<0.001**		**<0.001**
Yes	1056 (11.9)	1008.81 ± 143.23		88.52 ± 7.23		49.88 ± 12.17	
No	7849 (88.1)	957.33 ± 131.07		90.82 ± 5.98		53.16 ± 11.94	
Loss of smell or taste			0.145		0.067		**<0.001**
Yes	3485 (39.1)	966.01 ± 134.38		90.39 ± 6.13		52.13 ± 11.88	
No	5420 (60.9)	961.78 ± 133.08		90.64 ± 6.21		53.18 ± 12.08	
Severe pneumonia			**0.002**		**<0.001**		**<0.001**
Yes	105 (1.2)	1002.77 ± 131.92		87.97 ± 7.50		48.59 ± 12.95	
No	8800 (98.8)	962.96 ±		90.57 ± 6.16		52.82 ±	

		133.56			11.99
Inflexible thinking after recovery			0.538	**<0.001**	**<0.001**
Yes	5832 (65.5)	964.07 ± 132.27		90.30 ± 6.31	52.44 ± 11.93
No	3073 (34.5)	962.23 ± 136.09		91.01 ± 5.90	53.40 ± 12.15
Slowed processing speed after recovery			0.168	**<0.001**	**0.001**
Yes	5419 (60.9)	965.00 ± 133.39		90.23 ± 6.37	52.43 ± 11.92
No	3486 (39.1)	961.00 ± 133.91		91.04 ± 5.85	53.29 ± 12.13
Insomnia after recovery			**<0.001**	**<0.001**	**<0.001**
Yes	4344 (48.8)	971.14 ± 136.15		89.98 ± 6.46	51.90 ± 11.98
No	4561 (51.2)	956.10 ± 130.72		91.08 ± 5.85	53.59 ± 11.98

P-values in bold indicate statistical significance. [a]Student's t-test. COVID-19: coronavirus disease 2019; RT: reaction time; ICA: Integrated Cognitive Assessment; NOT: Number Ordering Test; SD: standard deviation

Table 5 Correlations of some socio-demographic characteristics and COVID-19-related factors (continuous or ordinal variables) with neuropsychological test results

	Socio-demographics			**COVID-19-related factors**	
	Age (years)	**BMI**	**Education level[a]**	**Time since infection**	**Infection duration**
Integrated Cognitive Assessment					
RT	0.439***	0.078***	-0.113***	0.018	0.070***

RT-animal	0.426***	0.074***	-0.103***	0.017	0.068***
RT-non-animal	0.433***	0.078***	-0.118***	0.019	0.070***
RT-Q1	0.444***	0.078***	-0.093***	0.016	0.060***
RT-Q3	0.404***	0.070***	-0.128***	0.015	0.074***
Accuracy	-0.374***	-0.084***	0.125***	-0.016	-0.087***
Accuracy-animal	-0.304***	-0.061***	0.090***	-0.005	-0.076***
Accuracy-non-animal[a]	-0.261***	-0.084***	0.105***	-0.028**	-0.048***
Number Ordering Test					
Total score	-0.264***	-0.064***	0.196***	-0.048***	-0.067***
RT[a]	0.354***	0.102***	-0.207***	0.042***	0.056***
Completed trials	-0.371***	-0.100***	0.200***	-0.042***	-0.061***
Correct trials	-0.325***	-0.083***	0.219***	-0.052***	-0.071***
Trial accuracy	0.023*	0.013	0.045***	-0.019	-0.024*
Correct numbers	-0.363***	-0.093***	0.230***	-0.053***	-0.075***
Number accuracy	-0.004	0.004	0.049***	-0.024*	-0.027*

[a]Spearman correlation; others unmarked are Pearson correlation. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

COVID-19: coronavirus disease 2019; BMI: body mass index; RT: reaction time; Q1: lower quartile; Q3: upper quartile.

Table 6 Linear regression analysis of socio-demographic characteristics and COVID-19-related factors on the results of neuropsychological tests

	RT-ICA				**Accuracy-ICA**				**NOT total score**			
	B	***SE***	***β***	***p*-value[a]**	***B***	***SE***	***β***	***p*-value[a]**	***B***	***SE***	***β***	***p*-value[a]**
Socio-demographics												
Gender	8.330	2.835	0.028	**0.003**	-0.906	0.143	-0.066	**<0.001**	-0.946	0.272	-0.035	**0.001**
Age	5.763	0.133	0.430	**<0.001**	-0.218	0.006	-0.351	**<0.001**	-0.289	0.012	-0.240	**<0.001**
BMI					-0.045	0.019	-0.026	**0.014**				
Ethnicity					-0.468	0.235	-0.020	**0.044**	-10.533	0.471	-0.033	**0.001**
Education level	-9.760	1.291	-0.072	**<0.001**	0.568	0.061	0.091	**<0.001**	20.023	0.123	0.167	**<0.001**
Regions[b]												
North China	-17.027	3.812	-0.050	**<0.001**	0.193	0.182	0.012	0.289	0.157	0.363	0.005	0.664
Northeast China	-7.914	6.409	-0.012	0.217	0.360	0.305	0.012	0.238	0.073	0.610	0.001	0.905

East China	-17.932	3.759	-0.053	**<0.001**	0.433	0.178	0.028	**0.015**	10.420	0.357	0.047	**<0.001**
Central China	2.673	5.013	0.006	0.594	-0.128	0.238	-0.006	0.590	-0.754	0.477	-0.017	0.114
Southwest China	-6.048	4.386	-0.015	0.168	0.361	0.210	0.019	0.085	-0.545	0.421	-0.015	0.195
Northwest China	14.147	4.869	0.030	**0.004**	-1.304	0.234	-0.061	**<0.001**	-20.462	0.468	-0.059	**<0.001**
COVID-19-related factors												
Underlying diseases	8.419	4.019	0.020	**0.036**	-0.503	0.191	-0.026	**0.008**				
Infection duration					-0.020	0.007	-0.029	**0.004**	-0.039	0.014	-0.028	**0.006**
Inflexible thinking after recovery									-0.809	0.262	-0.032	**0.002**
Slowed processing speed after recovery					-0.691	0.127	-0.054	**<0.001**				
Insomnia after recovery	6.222	2.553	0.023	**0.015**	-0.476	0.124	-0.039	**<0.001**	-0.829	0.248	-0.035	**0.001**

P-values in bold indicate statistical significance. [a]Linear regression with age, gender, and regions forced into the model (enter method) based on established theoretical relevance, and other socio-demographic and COVID-19-related variables selected using the stepwise method (entry $p < 0.05$, removal $p > 0.10$). Only the variables entered into one of the three regression equations above are included in the table. [b]Among the seven regions, South China, with the largest number of participants, was used as the reference group.

COVID-19: coronavirus disease 2019; RT: reaction time; ICA: Integrated Cognitive Assessment; NOT: Number Ordering Test; B: unstandardized coefficients; SE: standard error; β: standardized coefficients; BMI: body mass index

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Supplementary information:
Table S1-S3; Materials and methods