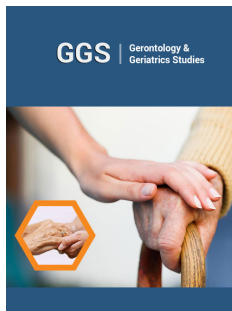


Assessment of Cognitive Status in Geriatric Individuals with a History of COVID-19 Exposure

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Abstract

Background: Post COVID-19 infection effects on cognitive impairment are a significant concern, particularly given the varying reports of impairment across specific cognitive domains in different populations. With India ranking high in confirmed cases and COVID-19-related fatalities and considering the scarcity of studies on cognitive health impacts, it becomes imperative to comprehend the Indian perspective. The current study aims to address this need by examining the effect of COVID-19 infection on cognition in an Indian aging cohort.

Methods: Data for this study was derived from the ongoing TATA Longitudinal Study of Aging in urban Bengaluru, India. The dataset includes cognitive and clinical information for 72 participants both before (from January 2018 to December 2019) and after the COVID-19 outbreak (from January 2020 to December 2021). These individuals self-reported a history of COVID-19 infection. Cognitive performance was assessed using Addenbrook's Cognitive Examination- ACE-III and Hindi Mental State Examination (HMSE) scores among these 72 individuals before and after COVID-19 infection.

Results: Unadjusted ACE memory scores significantly declined ($p=0.02$) while the language skills improved in post-COVID-19 infection. Other cognitive measures showed no significant differences between pre- and post-COVID-19 infection, whereas the linear mixed-effects model suggested no notable impact of COVID-19 on cognitive decline.

Conclusion: This study lays the groundwork for further exploration of protective elements lifestyle impacts and the intricate relationship between COVID-19 and cognitive health in elderly population.

Keywords: COVID-19; Cognition; India; Elderly

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Introduction

The impact of COVID-19, originating from the severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2), has been a focal point in epidemiological studies, particularly in low and middle-income countries. India ranks second globally in confirmed cases and third in COVID-19-related deaths [1]. Gender, ethnicity, geographic elements and comorbidities like diabetes, hypertension, obesity and dyslipidemia are identified as potential influencers of disease severity [2]. These concerns are especially heightened among the elderly population due to their increased vulnerability arising from compromised immune systems and prevalent comorbidities [3]. Controlling the outbreak in India's densely populated regions presents a remarkable challenge. The elderly, comprising approximately 53% of COVID-19-related fatalities, emerged as the most at-risk demographic during the pandemic [4]. Although the central government enforced a nationwide lockdown during the initial wave, inadequate responses during subsequent waves led to a sharp surge in cases and fatalities. The aftermath of COVID-19 has significantly impacted affected individuals, manifesting in cardiovascular

issues, heightened anxiety, depression and even observed instances of mild cognitive impairment [5].

Numerous researchers globally anticipate increased rates of cognitive impairment in the consequences of the COVID-19 pandemic, particularly among the geriatric population. Studies in the UK's population aged 50 years and above revealed an accelerated memory decline during both the initial and subsequent waves of the pandemic [6]. Among a cohort of 1539 infected individuals in China aged 60 and older, 37% exhibited cognitive decline during infection, with over 59% reporting long-term cognitive impairment observed during a 6-month post-pandemic follow-up [7]. Additionally, a study conducted on a smaller Indian cohort of 30 individuals with a history of COVID-19 infection displayed impaired cognition and psychological well-being compared to 30 healthy controls [8]. Investigating the impact of COVID-19 on the elderly within the Indian population holds significant scientific importance. Considering the COVID-19 situation in India and the subsequent health-related complications post-infection, this study aims to investigate the potential associations between COVID-19 infection and cognitive impairment in the Indian population.

Materials and Methods

Study participants

Study subjects belong to the urban TATA Longitudinal Study of Aging (TLISA) cohort study [9]. Subjects are predominantly city-dwelling, educated and belong to the working middle/high-income socioeconomic status. The study sample includes cognitively healthy, 45 years and above-aged individuals who were enrolled in the study. The study has been cleared by the Institutional Ethics Committee (IEC) of the Centre for Brain Research, Indian Institute of Science, Bengaluru, Karnataka, India. Written, informed consent was obtained from all participants before recruitment into the study.

Study design

The study involved 72 participants with a history of COVID-19 infection for whom both pre-and post-pandemic cognitive and clinical data were obtained. Pre-pandemic data encompassed information gathered before December 2019, with data from 2018 being utilized for individuals who missed the 2019 visit. Conversely, post-pandemic data was collected from January 2022 onwards and for those who missed the 2022 visit, information from the 2023 visit was considered. The analysis in this study is based on the data obtained from these 72 participants.

Clinical and cognitive assessments

All the participants have undergone both clinical and neuropsychiatric assessments. Hindi Mental State Examination (HMSE) and Addenbrooke's cognitive examination III (ACE III) were performed for everyone to evaluate their cognitive ability. Depression was assessed by using the 7-item version of the Geriatric Depression Scale (GDS-7). Sociodemographic details such as age, gender and education level (number of years) were collected, and systolic and diastolic blood pressure were measured.

Biochemical analysis

Overnight fasting blood samples were collected from all participants. Detailed panel of biochemical investigations that included glucose, triglycerides and HDL. Glucose estimation was done using the hexokinase method, whereas the enzymatic method was used for the lipid parameters.

Statistical analysis

All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) software, version 28. The normality of the continuous variables was established using the Shapiro-Wilk test. Participants' age at the baseline was used as a continuous variable for which mean (or median) and standard deviation (or interquartile range, IQR) were reported based on normality check. Gender, diabetes, hypertension, GDS were used as categorical and data were expressed as frequency and percentages. The association between two categorical variables was checked using the Chi-square test and independent t-test/Mann-Whitney U test for the continuous variables. The McNemar test was used for related categorical variables. The linear mixed-effects model was used to investigate the effect of covariates on cognition. Since participants in the study entered at different ages, to account for between-person differences, we used age at baseline as a random effect in the model and the time difference between the study participants' pre-and post-COVID periods was treated as a fixed effect. Statistical significance was checked at a 5% level of significance.

Results

Basic characteristics of the study participants

The mean age of 72 infected individuals was 66.83 years, with a standard deviation of 8.95 years and an education level of 17 years (IQR=3). The gender distribution was 52.8% male and 47.2% female. Hypertension was significantly higher (pre vs post; 37% vs 47%, $p=0.028$), during post-COVID periods than pre; while there were no significant change in the proportions of depression (pre vs post; 10% vs 5%, $p=0.081$), diabetes (pre vs post; 18% vs 20%, $p=0.250$), body mass index (pre vs post; median (IQR), 27(6) vs 26.9 (4.9), $p=0.349$) and dyslipidemia (pre vs post; 60% vs 61%, $p=0.209$) between the individuals' pre- and post-COVID periods.

Comparative analysis of cognitive profile

The comparison of cognitive scores before and after COVID-19 infection revealed specific changes: ACE memory displayed a significant decrease in the post-COVID condition compared to the pre-COVID state ($p=0.02$). Conversely, language skills exhibited improvement in the post-COVID-19 condition. However, the remaining cognitive measures, including ACE-total, attention, fluency and visuospatial abilities, did not exhibit any significant differences between pre- and post-COVID periods (Table 1). A linear mixed-effects model was employed, utilizing cognitive scores to compare individuals' post-COVID status with their pre-COVID-19 condition. Age at baseline was considered as a random factor, while the time difference (post minus pre-COVID periods) was treated

as a fixed factor in the model. The lack of statistically significant differences in HMSE or ACE scores between the pre-and post-COVID-19 periods indicated that the rate of cognitive deterioration

in this cohort, as shown in (Table 2), was not influenced by either the COVID-19 infection nor age at baseline. Furthermore, the time difference may not be sufficient to detect the cognitive deterioration.

Table 1: Cognitive profile comparison between pre- and post-COVID-19 infection of the study participants.

HMSE: Hindi Mental State Examination, ACE III: Addenbrooke's Cognitive Examination.

IQR: Inter Quartile Range. Data are presented as IQR of the median of the scores.

Affected Individuals with Pre and Post Data	Median (IQR)		
	Pre Covid-19	Post Covid-19	p-value
HMSE	31 (1)	31 (1)	0.087
ACE Total	96 (4)	96 (6)	0.839
ACE Attention	18 (1)	18 (1)	0.169
ACE Memory	26 (1)	25 (2)	0.020
ACE Fluency	13 (2)	13 (2)	0.583
ACE Language	25 (2)	26 (1)	0.039
ACE Visuospatial	15 (2)	16 (1)	0.363

Table 2: Results of linear mixed-effects model controlling for the random effect of age at baseline and the fixed-effect of time difference on cognitive profile.

HMSE: Hindi Mental State Examination, ACE III: Addenbrooke's Cognitive Examination, Data are presented as Beta coefficient with Standard Error (SE) of the scores.

Variables	Beta Coefficient (SE)	p-value
HMSE	0.348 (0.712)	0.625
ACE_TOTAL	0.540 (4.82)	0.911
ACE Attention	(-0.447) (1.031)	0.666
ACE Memory	(-2.056) (1.856)	0.27
ACE Fluency	0.330 (1.464)	0.822
ACE Language	1.379 (1.362)	0.313
ACE Visuospatial	1.334 (1.273)	0.297

Discussion

In this study, we analyzed the impact of COVID-19 infection on cognitive decline using the Hindi Mental State Examination (HMSE) and Addenbrooke's Cognitive Examination III (ACE-III) scores. In the unadjusted model, we saw a slight decline in ACE memory scores when comparing pre-COVID-19 and post-COVID-19 data while ACE language scores improved in post-Covid-19 status. After adjusting for age there was no significant difference in the cognitive profile between the pre-and post-COVID-19 data.

Several studies have investigated the cognitive effects following post-COVID-19 infection, spanning from short durations of a few weeks to several months, yielding varied results. A meta-analysis assessing the prevalence of cognitive deficits highlighted more than a 50% decline in cognitive function among individuals from various European cohorts post-COVID-19 infection [10]. In contrast, a study with a two-year follow-up reported cognitive deficits persisting in those with ongoing symptoms and severity of the infection, while individuals who fully recovered did not exhibit such deficits [11]. During the acute phase of infection, a potential higher cognitive decline was observed, as evidenced by improved cognitive scores after one month compared to at the time of hospital admission

scores [12]. Our study, based on data collected in early 2022 after the pandemic's peak, faces limitations due to the lack of sufficient post-COVID-19 infection follow-up data. This limitation challenges the establishment of a definitive link between COVID-19 infection and its impact on individuals' cognitive performance. However, comparing the pre-and post-cognitive profile subgroup of the individuals indicated no such impact of COVID-19 or age factors on cognitive impairment in our cohort. May be further investigation requires us to understand that any other protective factors have a vital role in this process. The current study adds information to the existing evidence that fully recovered participants may not show any cognitive deficits. Also, there may be several other factors to be considered including lifestyle, comorbidities and confounding factors to understand if they had any protective factors during the COVID-19 crisis.

Strengths and limitations

Comparative analysis of cognitive profiles pre-and post-COVID-19 infection, with appropriate age adjustments is the strength of the current study. A notable limitation pertains to the insufficient granularity of information about the COVID-19 infection status. The lack of detailed data, including precise dates of infection,

duration of symptomatic manifestation and the severity grading of the infection, introduces a potential confounding factor. This dearth of specific information hinders the establishment of a robust causal relationship between cognitive alterations and COVID-19 infection.

Conclusion

A comparison of cognitive profiles before and after infection among 72 participants showed no cognitive decline. The varied clinical presentation of COVID-19 may not consistently affect cognitive abilities among individuals due to its diverse symptomatology, leading to varying prevalence of cognitive impairment. Individual variations in baseline health, genetics and medical conditions, education, socioeconomic status, physical exercise could influence the severity and susceptibility to cognitive consequences following COVID-19. The wide spectrum of COVID-19 severity, spanning from asymptomatic to severe cases, might result in diverse neurological manifestations, with more pronounced cognitive effects in severe cases compared to milder instances. Further follow-up and investigation into infection severity, symptom duration and post-infection phases could significantly advance our understanding of the relationship between COVID-19 and cognitive impairment, potentially shedding light on post-viral cognitive effects.

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