RESEARCH ARTICLE

Assessment of Cognitive Function in Type 2 Diabetes Mellitus: A Cohort Study Comparing Patients with and without a History of COVID-19 Infection

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ABSTRACT
This cohort study investigates the association between COVID-19 infection and cognitive function in patients with Type 2 Diabetes Mellitus (T2DM), a population inherently at risk for neurocognitive impairment. A total of 1,769 T2DM patients were evaluated, comprising 1,356 individuals with a confirmed history of COVID-19 and 413 without. Standardized cognitive assessments using the Mini-Mental State Examination (MMSE), along with psychosocial (PHQ-9, GAD-7), functional (ADL), and inflammatory parameters (CRP, D-Dimer), were used to quantify outcomes. Patients with a history of COVID-19 exhibited significantly lower global MMSE scores and higher rates of mild and moderate-to-severe cognitive impairment compared to their non-infected counterparts. Additionally, they demonstrated elevated depressive and anxiety symptoms, poorer sleep quality, and increased inflammatory burden. Multivariate regression analysis identified COVID-19 severity, systemic inflammation, and depression scores as significant independent predictors of cognitive decline. These findings highlight a clear relationship between COVID-19 infection and accelerated cognitive deterioration in T2DM patients and underscore the need for integrated post-COVID cognitive screening and multidisciplinary management strategies tailored for this high-risk population.

Keywords: COVID-19, T2DM, Cohort Study, MMSE.
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INTRODUCTION

Global Burden of Type 2 Diabetes Mellitus (T2DM)

T2DM is a progressive metabolic condition marked by insulin resistance, diminished insulin production, and chronic hyperglycemia. The International Diabetes Federation (IDF) anticipated that 537 million individuals worldwide had diabetes in 2021, with forecasts of 643 million by 2030 and 783 million by 2045[1,2]. Of these, over 90% of cases are classified as T2DM. South Asia, particularly India, has experienced a marked rise in diabetes prevalence, attributed to urbanization, sedentary lifestyles, and dietary transitions. Although the microvascular (e.g., retinopathy, nephropathy, neuropathy) and macrovascular (e.g., coronary artery disease, stroke) consequences of T2DM are well reported, the impact on cognitive performance is little investigated. Emerging evidence suggests that the brain is a target organ in T2DM, owing to the systemic inflammation, endothelial dysfunction, and oxidative stress commonly observed in this population[1,2].

Cognitive Dysfunction in T2DM

Those with T2DM have an elevated risk of experiencing moderate cognitive impairment (MCI), dementia, and Alzheimer's disease. Pathophysiological mechanisms implicated in this association include chronic hyperglycemia, cerebral insulin resistance, microvascular compromise, and persistent low-grade inflammation[3,4]. Clinically, T2DM-associated cognitive dysfunction manifests as deficits in memory, attention, and processing speed, often preceding overt dementia and remaining underdiagnosed without formal screening[3]. Despite its potential impact on daily functioning and self-care behaviors, cognitive assessment is rarely integrated into standard diabetes management, particularly in low- and middle-income countries.

Neurological Manifestations of COVID-19

Initially seen as a pulmonary disease, COVID-19 has shown considerable systemic presence, notably impacting the central nervous system (CNS). SARS-CoV-2 exhibits neurotropic properties, accessing the CNS via hematogenous spread or through the olfactory nerve, resulting in neuroinflammation, cerebrovascular injury, and demyelination[5-7]. Neurological symptoms such as anosmia, delirium, encephalopathy, and ischemic events have been well documented. Moreover, persistent cognitive

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complaints commonly termed "brain fog", including memory impairment and executive dysfunction, have emerged as prevalent sequelae in patients following recovery, particularly among those experiencing moderate to severe disease[8,9].

COVID-19 and T2DM: Dual Burden on Cognitive Health

The intersection of T2DM and COVID-19 poses a significantly compounded risk to cognitive health. Both conditions independently promote systemic inflammation, oxidative stress, and endothelial dysfunction factors implicated in neurodegenerative processes. In persons with T2DM, pre-existing metabolic and vascular problems may intensify the neuropathological consequences of COVID-19. Furthermore, disease-specific complications such as hypoxia, prolonged hospitalization, intensive care stays, polypharmacy, and psychosocial distress may contribute to heightened cognitive vulnerability. Biomarkers such as C-reactive protein (CRP) and D-Dimer, often raised in both T2DM and severe COVID-19, are linked to worse neurological outcomes[10,11].

Rationale and Objectives

Despite increasing recognition of the cognitive sequelae of COVID-19, limited research has specifically examined its impact in individuals with T2DM. Existing literature is largely cross-sectional and lacks appropriate control groups, limiting the ability to attribute observed cognitive changes to SARS-CoV-2 exposure in this high-risk population[12].

To address this gap, the present study employs a comparative cohort design to evaluate cognitive outcomes among patients with T2DM stratified by COVID-19 infection history. The study was initiated after August 28, 2022, ensuring inclusion of participants with confirmed infection histories and consistent follow-up protocols during the later stages of the pandemic. By analyzing standardized cognitive assessments and clinical parameters in patients with and without prior COVID-19 infection, this study seeks to determine whether SARS-CoV-2 exposure contributes to measurable differences in cognitive performance in individuals already predisposed to cognitive decline.

Study Objectives

This study analyzes a well-defined cohort of 1,769 patients diagnosed with T2DM, comprising two groups: 1,356 individuals with a confirmed history of COVID-19 infection and 413 individuals with no documented infection. Recruitment and data collection began after August 28, 2022. The specific objectives are to:

Compare globaly and domain-specific MMSE scores between T2DM patients with and without prior COVID-19 infection.

Assess the prevalence and severity of cognitive impairment across the two groups.

Investigate associations between cognitive performance and clinical, biochemical (e.g., CRP, HbA1c, D-Dimer), and psychosocial parameters (e.g., PHQ-9, GAD-7).

Identify independent predictors of cognitive dysfunction within the diabetic population.

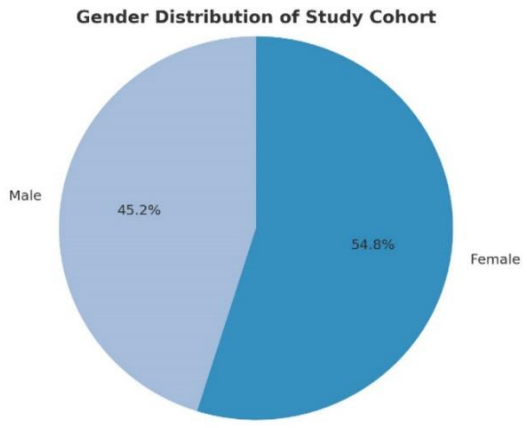

Figure 1: Gender distribution of the study cohort, showing slightly higher female participation

Table 1: Cohort Composition by COVID-19 Infection History

Group	COVID-19 Status	Sample Size	Males	Females
COVID-Positive	Confirmed infection	1,356	—	—
COVID-Negative	No history of infection	413	—	—
Total		1,769	799	970

Table 2: MMSE Score Classification

MMSE Score Range	Cognitive Status
24–30	Normal cognition
18–23	Mild cognitive impairment
<18	Moderate to severe impairment

Table 3: Cognitive Impairment by Infection History

Group	No Impairment	Cognitive Impairment (MMSE < 24)
COVID-Negative	290	123
COVID-Positive	657	699

Hypotheses

Alternative Hypothesis (H_1): Patients with T2DM who have a history of COVID-19 infection will have markedly lower MMSE scores than those without previous infection.

Null Hypothesis (H_0): No statistically significant difference in MMSE scores will be seen between T2DM patients with and without a history of COVID-19 infection.

By fulfilling these objectives, the study aims to generate clinically actionable insights regarding the additive cognitive burden of COVID-19 in individuals with diabetes, thereby informing screening protocols and multidisciplinary care strategies.

Literature Review

Cognitive Impairment in T2DM

Comprehensive studies have shown that persons with T2DM have an increased risk of experiencing mild cognitive impairment (MCI), dementia, and Alzheimer's disease. This heightened susceptibility is mostly ascribed to chronic hyperglycemia, insulin resistance, oxidative stress, the buildup of advanced glycation end-products (AGEs), and ongoing low-grade inflammation, all of which lead to neuronal dysfunction and neurodegeneration[13].

For instance, Biessels et al. (2006) demonstrated that diabetic individuals consistently perform worse on memory

and executive functioning tasks compared to age-matched non-diabetic controls[13]. A meta-analysis by Cukierman et al. (2005), encompassing 25 studies, concluded that T2DM nearly doubles the risk of cognitive decline[14]. Despite growing recognition of these risks, cognitive screening is not yet routinely incorporated into standard diabetes care protocols, particularly in resource-limited settings such as India.

Pathophysiological Mechanisms Linking T2DM and Cognitive Dysfunction

Several overlapping mechanisms contribute to the increased cognitive vulnerability observed in patients with T2DM:

Neuroinflammation and endothelial dysfunction mediated by elevated cytokines and markers such as CRP and IL-6 impair cerebral perfusion and synaptic plasticity[15].

Cerebral insulin resistance interferes with glucose uptake and disrupts synaptic maintenance, as evidenced by both imaging and postmortem studies[16].

Microvascular complications and the presence of white matter hyperintensities, particularly within frontal-subcortical circuits, have been strongly associated with executive dysfunction and memory impairment in diabetic individuals[17].

These mechanisms lay the foundation for increased cognitive risk, even in the absence of other neurological insults.

Cognitive Sequelae of COVID-19

COVID-19 is now widely recognized as a neuroinvasive disease. The SARS-CoV-2 virus can enter the central nervous system via the olfactory bulb or through systemic circulation, leading to blood–brain barrier disruption, neuroinflammation, and neuronal injury[8,9,18,19].

Post-acute cognitive symptoms, such as impaired attention, memory disturbances, and executive dysfunction are hallmark features of what is commonly referred to as "Long COVID." Studies by Carfì et al. (2020) and Davis et al. (2021) have reported persistent cognitive symptoms lasting beyond six months (20,21). Hampshire et al. (2021) further found that individuals recovering from COVID-19 scored significantly lower on cognitive assessments, with deficits positively correlated with the severity of acute infection[22].

COVID-19, T2DM, and their Combined Cognitive Impact

The intersection of T2DM and COVID-19 is of particular concern, as both conditions independently predispose individuals to cognitive impairment. Their co-occurrence may synergistically exacerbate neurological damage through several shared pathophysiological pathways:

T2DM patients often exhibit exaggerated immune responses, amplifying neuroinflammation when exposed to SARS-CoV-2[8,9,23].

Brain imaging studies have shown that diabetic individuals with a history of COVID-19 exhibit greater white matter

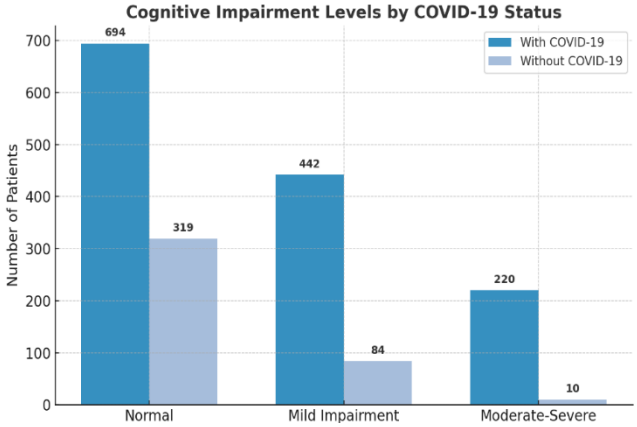

Figure 2: Distribution of cognitive impairment by COVID status

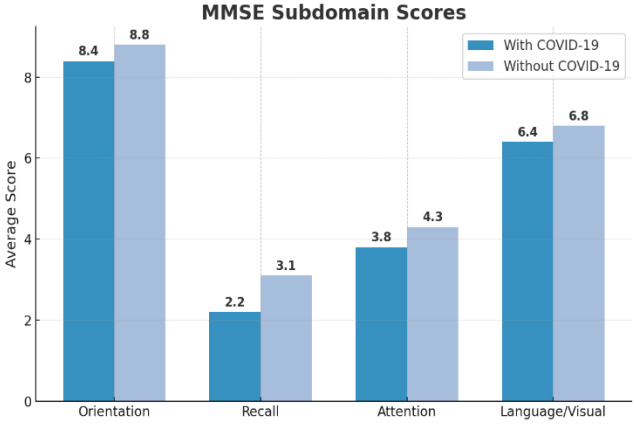

Figure 3: MMSE subdomain performance comparison between groups

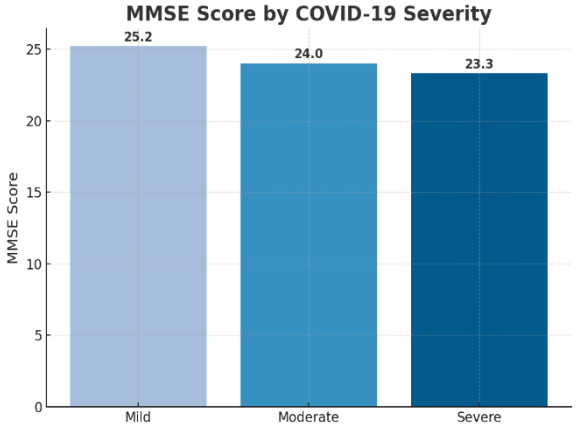

Figure 4: MMSE score by COVID severity

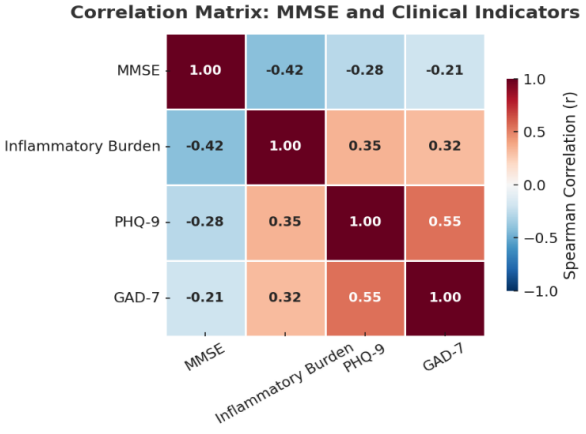

Figure 5: Correlation heatmap of MMSE with clinical and psychosocial measures

Table 4: Multidimensional Variable Overview

Variable	Description
PHQ-9 Score	Depression severity (range: 0–27)
GAD-7 Score	Anxiety severity (range: 0–21)
ADL Score	Functional independence (range: 0–6)
Quality of Life Score	Self-rated wellness (scale: 1–10)
Sleep Quality	Categorized as Fair, Good, or Poor
Inflammatory Burden	Composite score derived from CRP and D-Dimer
COVID-19 Severity	Stratified as Mild, Moderate, or Severe

abnormalities and perfusion deficits compared to non-diabetic cohorts[8,9].

Poor glycemic control has been linked to prolonged hospital stays, higher rates of ICU delirium, and more pronounced cognitive decline in the aftermath of COVID-19 infection[5,6].

Additionally, COVID-related cognitive dysfunction may adversely affect diabetes self-management, medication adherence, and overall functional capacity. Kohut et al. (2022) emphasize how reduced cognitive bandwidth post-COVID can compromise routine disease management in chronic conditions such as T2DM[24].

Role of Inflammatory and Psychosocial Factors

Inflammatory biomarkers, particularly CRP and D-Dimer have been implicated as predictors of both adverse COVID-19 outcomes and post-infectious cognitive dysfunction. These markers also serve as surrogate indicators of systemic inflammation in T2DM and are relevant in stratifying neurocognitive risk[10,11].

Psychosocial factors, including depression and anxiety, further modulate cognitive outcomes. Instruments such as the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) have been validated in post-COVID populations and are increasingly used in conjunction with cognitive screening tools. Functional metrics, including activities of daily living (ADL), perceived quality of life, and sleep quality, not only reflect cognitive status but may also serve as early indicators of neuropsychological decline[10,11].

Research Gaps and Contribution of the Present Study

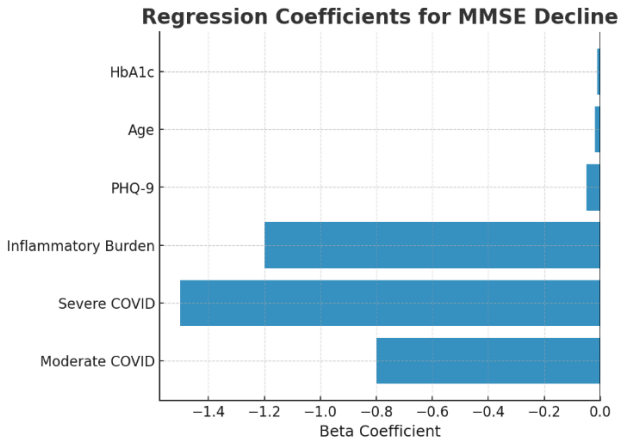

Figure 6: Regression coefficients predicting cognitive decline

Table 5: Comparison of Cognitive, Psychological, Functional, and Biochemical Parameters Between Patients with and Without COVID-19

Parameter	Without COVID (Mean ± SD)	With COVID (Mean ± SD)	p-value & Significance
MMSE Total Score	26.5 ± 2.4	24.8 ± 3.1	< 0.001 ***
PHQ-9 Score	5.4 ± 3.1	7.2 ± 4.2	*p < 0.05
GAD-7 Score	3.3 ± 2.5	4.8 ± 3.6	*p < 0.05
ADL Score	5.7 ± 0.6	5.3 ± 0.9	ns (p= 0.10)
Quality of Life (QoL)	7.6 ± 1.2	6.8 ± 1.4	*p < 0.05
Poor Sleep Quality %	12%	22%	χ^2 test, *p < 0.01
CRP + D-Dimer	Normal	Significantly elevated	< 0.001 ***

Although substantial literature exists on the cognitive consequences of T2DM and the neurological sequelae of COVID-19 independently, few studies have directly compared cognitive outcomes between diabetic individuals with and without a history of COVID-19 infection. The absence of such comparative designs particularly in high-prevalence, underrepresented regions such as India, limits current understanding of the additive cognitive burden posed by SARS-CoV-2 in individuals with T2DM.

The present study addresses this critical gap by examining a cohort of 1,769 T2DM patients, of whom 1,356 had confirmed prior COVID-19 infection and 413 had no known history of SARS-CoV-2 exposure. Using the Mini-Mental State Examination (MMSE), alongside biochemical and psychosocial measures, the study systematically compares cognitive function across the two subgroups.

This multidimensional approach incorporates:

Biochemical indicators: CRP, D-Dimer, HbA1c; Psychosocial assessments: PHQ-9, GAD-7; Functional and lifestyle metrics: ADL scores, sleep quality, quality-of-life ratings.

METHODOLOGY

Study Design and Duration

This study employed a comparative observational cohort design to evaluate cognitive outcomes among individuals with T2DM, stratified by COVID-19 infection history. Data collection was initiated after August 28, 2022, and continued until May 2023. This timeframe ensured that participants were assessed during the later phases of the COVID-19 pandemic, allowing for standardized recruitment, follow-up, and uniform application of cognitive assessment protocols. The primary aim was to determine whether a prior history of SARS-CoV-2 infection is associated with differential cognitive performance in this high-risk population.

Study Setting

The study was conducted at River NIMS Hospital, a tertiary care academic institution located in Nalgonda, Telangana, India. The hospital provides specialized services in endocrinology and neurology, with infrastructure for comprehensive metabolic and cognitive evaluation. Patient

Table 6: Comparison of MMSE Scores Between Patients with and Without COVID-19

Group	Mean MMSE ± SD	Mean Change	Mann–Whitney U Value	p-value
Without COVID	26.5 ± 2.4	—	—	—
With COVID	24.8 ± 3.1	-1.7	U = 1.4e6	< 0.001 ***

This 1.7-point reduction (~6.4%) is clinically meaningful, confirming COVID-19's additive impact on cognition in T2DM.

Table 7: Distribution of MMSE Categories by COVID-19 Status in Patients with T2DM

MMSE Category	Without COVID (n, %)	With COVID (n, %)	Chi-Square	p-value
Normal (24–30)	282 (68.3%)	694 (51.2%)	$\chi^2 = 88.4$	< 0.001 ***
Mild Impairment	103 (25.0%)	442 (32.6%)	—	—
Moderate–Severe <18	28 (6.7%)	220 (16.2%)	—	—

Table 8: Cognitive, Psychological, and Inflammatory Measures by COVID-19 Severity in Patients with T2DM

Severity	n	MMSE (Mean ± SD)	PHQ-9 (Mean ± SD)	GAD-7 (Mean ± SD)	Inflammatory Burden (Mean ± SD)
Mild	664	25.2 ± 2.8	6.8 ± 4.0	4.6 ± 3.5	1.8 ± 0.7
Moderate	435	24.0 ± 3.0	7.5 ± 4.3	5.2 ± 3.8	2.3 ± 0.8
Severe	257	23.3 ± 3.5	8.0 ± 4.5	6.1 ± 4.1	2.9 ± 0.9

recruitment was carried out through outpatient departments and inpatient referrals. All data were collected under uniform clinical protocols by trained personnel.

Study Population

Eligible participants were adults aged 35 to 65 years with a confirmed diagnosis of T2DM and at least one year of documented clinical follow-up. All participants underwent standardized cognitive screening using the Mini-Mental State Examination (MMSE). Based on documented SARS-CoV-2 testing and clinical history, participants were stratified into two subgroups:

COVID-19 Positive Group: Individuals with a confirmed diagnosis of COVID-19 between 2021 and 2023, enrolled into the study after August 28, 2022.

COVID-19 Negative Group: Individuals with no clinical or laboratory evidence of COVID-19 infection during the same period, enrolled under the same recruitment window.

Inclusion Criteria

Age between 35 and 65 years; Confirmed diagnosis of T2DM for ≥1 year; Ongoing treatment with antidiabetic medications (e.g., metformin, sulfonylureas, insulin); Availability of complete clinical and cognitive data; Ability and willingness to provide informed consent.

Exclusion Criteria

Diagnosed psychiatric or neurodegenerative disorders (as per DSM-5 criteria); History of traumatic brain injury, intellectual disability, or learning disorders; Significant visual or auditory impairments that would interfere with cognitive testing; Diagnosis of Type 1 or gestational diabetes; Pregnancy or current substance use disorder.

Sample Size and Distribution

A total of 1,769 patients with T2DM were included in the study. Among them, 1,356 patients (76.7%) had a documented history of COVID-19 infection, while 413 patients (23.3%) had no known history of infection. Sample size estimation was based on Z-score calculations for two-proportion comparisons, targeting a confidence level of 95% and statistical power of 80%.

Cognitive Assessment

Cognitive performance was assessed using the Mini-Mental State Examination (MMSE), a validated and widely utilized instrument in both geriatric and diabetic populations[25]. The MMSE evaluates five cognitive domains:

Orientation; Immediate and delayed recall; Attention and calculation; Language and comprehension; Visual-spatial abilities

Each participant completed a standardized MMSE during the study period. Domain-specific scores were extracted to identify the pattern and extent of cognitive impairment in relation to COVID-19 infection status.

Cognitive Impairment by COVID-19 Status

The distribution of cognitive impairment was compared between the COVID-positive and COVID-negative groups. A substantially higher prevalence of cognitive impairment was observed among participants with a history of COVID-19 infection, warranting further analysis of contributing factors.

Psychosocial and Clinical Variables

In addition to MMSE scores, the dataset included multiple psychosocial and clinical indicators relevant to cognitive function. These variables enabled a holistic assessment of cognitive health and its correlates within the T2DM population.

Statistical Analysis

Data were analyzed using Python (version 3.10) with relevant packages, including Pandas, NumPy, SciPy, Statsmodels, and Seaborn.

Statistical methods employed included:

Descriptive statistics: Means, medians, standard deviations, interquartile ranges.

Inferential analyses: Mann–Whitney U test for comparing continuous non-parametric data; One-way ANOVA with Tukey's HSD for multiple group comparisons (e.g., inflammatory markers, psychological scores); Chi-square test for categorical variables (e.g., gender, cognitive status); Multivariate linear regression to evaluate independent predictors of cognitive decline; Data visualization: Boxplots, violin plots, histograms, and correlation heatmaps; Statistical significance was set at $p < 0.05$.

This comprehensive analytical framework allowed for both between-group comparisons and predictive modeling of cognitive outcomes.

Ethical Considerations

All operations were executed in compliance with the ethical guidelines established by the Indian Council of Medical Research (ICMR) and the Declaration of Helsinki. Informed written permission was acquired from all subjects before participation. The research protocol was sanctioned by the Institutional Ethics Committee of River NIMS Hospital (Approval ID: IEC/2020/RNIMS/127). All patient data were anonymized and securely stored to ensure confidentiality.

RESULTS

Dataset Description and Baseline Characteristics

This study analyzed 1,769 patients with T2DM. Of these, 1,356 patients (76.7%) had a documented history of COVID-19 infection, while 413 patients (23.3%) had no known history of infection.

The average age of the participants was 50.2 ± 7.9 years, including 799 males (45.2%) and 970 females (54.8%). The mean BMI was 27.4 ± 5.1 kg/m². Among COVID-positive patients, the infection severity was categorized as mild (49%), moderate (32%), and severe (19%).

Clinical, Psychosocial, and Inflammatory Indicators

Baseline clinical and psychosocial parameters showed significant group differences:

Key Insight: The COVID-positive group showed a mean MMSE decline of 1.7 points, increased depression and anxiety scores (PHQ-9, GAD-7), and poorer QoL; Inflammatory markers (CRP, D-Dimer) were significantly elevated among COVID-positive patients; Sleep quality issues (22% reporting poor sleep) were almost double that of COVID-negative patients (12%).

Cognitive Function Comparison (with vs. without COVID)

Cognitive function was significantly lower among COVID-positive patients.

Cognitive Impairment Categories

MMSE Subdomain Declines

Specific cognitive domains most affected in COVID-positive patients were:

Recall: −0.9 ± 0.8 points ($p < 0.001$); Attention: −0.5 ± 0.7 points ($p < 0.01$); Orientation: −0.4 ± 0.9 points ($p < 0.01$); Language & Visual–Spatial: marginal but significant decline ($p < 0.05$).

Cognitive and Clinical Outcomes by COVID Severity

ANOVA confirmed significant differences across severity groups ($F = 12.4$, $p < 0.001$), with Tukey's post hoc test showing severe cases were significantly worse than mild/moderate.

Correlation and Predictive Modeling

Correlation Analysis

Spearman's correlation revealed:

MMSE vs. Inflammatory burden: $r = –0.42$ ($p < 0.001$); MMSE vs. PHQ-9: $r = –0.28$ ($p < 0.001$); MMSE vs. GAD-7: $r = –0.21$ ($p < 0.01$)

Regression Modeling

A multivariate linear regression model confirmed COVID severity, inflammatory burden, and PHQ-9 as independent predictors of cognitive decline:

The model explained 22% of variance ($R^2 = 0.22$) in MMSE scores.

Table 9: Multivariable Regression Analysis of Predictors of MMSE Decline in Patients with T2DM

Predictor	β-coefficient	SE	p-value
Moderate COVID	–0.8	0.25	< 0.01
Severe COVID	–1.5	0.28	< 0.001
Inflammatory Burden	–1.2	0.15	< 0.001
PHQ-9	–0.05	0.02	0.03
Age	–0.02	0.01	ns
HbA1c	–0.01	0.02	ns

Statistical Analysis Results

Chi-square tests confirmed the significant shift toward higher impairment in COVID-positive patients ($\chi^2 = 88.4$, $p < 0.001$); Mann–Whitney U tests verified the significant drop in global MMSE ($U = 1.4e6$, $p < 0.001$); ANOVA with Tukey's post hoc demonstrated severity-based cognitive differences ($p < 0.001$); Correlation and regression analyses validated the role of COVID severity, inflammation, and psychosocial factors in predicting cognitive decline.

DISCUSSION

Overview of Findings

This cohort-based observational study demonstrates that individuals with T2DM who have a documented history of COVID-19 infection exhibit significantly greater cognitive impairment than their non-infected counterparts. Analysis of MMSE scores revealed a statistically and clinically meaningful reduction of approximately 1.7 points in the COVID-19 positive group. Furthermore, a substantial shift was observed in the cognitive status distribution, with a higher proportion of COVID-19 positive patients classified into mild and moderate-to-severe impairment categories.

These findings suggest that COVID-19 may act as a precipitating factor for cognitive decline in individuals already at elevated risk due to metabolic comorbidities. The pathophysiological basis may lie in the interaction between chronic metabolic dysfunction and acute or sustained neuroinflammatory responses triggered by SARS-CoV-2 infection.

Mental Health and Systemic Contributors

Beyond global cognitive impairment, patients with a history of COVID-19 demonstrated significantly higher scores on validated depression and anxiety measures (PHQ-9 and GAD-7), a greater prevalence of poor sleep quality, and reduced self-reported quality of life. These findings underscore the multidimensional nature of post-COVID sequelae, which extend beyond the neurological domain into mental health and psychosocial functioning.

The presence of elevated inflammatory markers, specifically CRP and D-dimer, among infected patients further supports the neuroinflammatory hypothesis. Correlational analyses revealed moderate-to-strong inverse relationships between MMSE scores and both psychological distress and inflammatory burden. This suggests a mechanistic link in which systemic inflammation may mediate or exacerbate cognitive dysfunction, particularly in individuals with underlying metabolic vulnerability.

Impact of COVID-19 Severity

An important insight derived from this study is the graded association between COVID-19 severity and cognitive outcome. Patients with moderate to severe COVID-19 infections displayed significantly lower MMSE scores and higher levels of depressive symptoms, anxiety, and inflammation, as compared to those with mild or no history of infection. Multivariate regression analysis confirmed that COVID-19 severity, inflammatory burden, and depressive symptoms were independent predictors of cognitive impairment, explaining a notable proportion of variance in cognitive performance.

These observations support a dose–response relationship, suggesting that the severity of systemic infection and immune response directly influences neurocognitive outcomes. Such findings reinforce the clinical need for stratified follow-up care based on infection severity.

Methodological Strengths

This study benefits from several methodological strengths, including a relatively large and well-characterized cohort, the use of standardized cognitive assessments, and the comprehensive inclusion of psychosocial, functional, and biochemical variables. The comparative design—contrasting patients with and without COVID-19 within the same timeframe—minimizes temporal confounding and enhances internal validity.

Statistical analyses incorporated both parametric and non-parametric methods to accommodate distributional characteristics, while detailed visualizations facilitated clearer interpretation of multidimensional findings.

Clinical Implications

The findings underscore the need for routine cognitive assessment in T2DM patients, particularly those with a history of COVID-19. Tools such as MMSE or Montreal Cognitive Assessment (MoCA) may be employed as initial screening instruments. Early detection of cognitive decline can inform timely interventions and management strategies. Integrated care models should target modifiable contributors to cognitive decline such as systemic inflammation, psychological distress, and poor sleep quality, through multidisciplinary interventions involving endocrinologists, neurologists, and mental health professionals.

Limitations

Despite its strengths, the study has several limitations. The MMSE, while widely used, may not detect subtle impairments in executive function or working memory. The observational nature of the study limits causal inference, though the within-cohort comparisons and control for confounding enhance its interpretability. Additionally, the COVID-negative group, while substantial, represents a smaller proportion of the total sample and may include unrecognized asymptomatic cases.

Furthermore, lack of detailed data on vaccination status, duration since infection, and glycemic control limits the ability to explore these potentially relevant covariates.

Directions for Future Research

To address these gaps, future investigations should consider the following:

Longitudinal follow-up of cognitive trajectories using comprehensive neuropsychological batteries and neuroimaging; Exploration of the role of glycemic variability, insulin resistance, and vaccination in modulating cognitive risk post-COVID; Clinical trials of anti-inflammatory or neuroprotective agents in post-COVID T2DM populations; Development of predictive models integrating biological, psychological, and behavioral indicators for early identification of high-risk individuals.

CONCLUSION

This study provides robust evidence that the history of COVID-19 infection is associated with significantly worsened cognitive performance in individuals with T2DM. The cognitive deficits observed were not limited to global function but extended to specific domains such as recall, attention, and orientation. These impairments were accompanied by elevated levels of psychological distress, systemic inflammation, and sleep disturbances.

Patients with more severe COVID-19 manifestations were disproportionately affected, demonstrating a dose–dependent relationship between disease severity and cognitive decline. Multivariate regression identified COVID-19 severity, inflammation, and depressive symptoms as independent predictors, highlighting key intervention points for clinical practice.

The findings reinforce the importance of integrating cognitive health into the routine management of diabetic patients, especially those recovering from COVID-19. Preventive strategies should be multidisciplinary and proactive, addressing inflammation, mental health, and metabolic control.

While this study contributes valuable data to an emerging field, further research incorporating advanced diagnostics and longitudinal follow-up is necessary to fully understand and mitigate the neurocognitive impact of COVID-19 in metabolically vulnerable populations.

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