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FULL PAPER

COVID-19–associated cognitive decline in type 2 diabetes: Comparative cohort outcomes and therapeutic implications

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This longitudinal cohort study investigated the impact of COVID-19 on cognitive function in patients with pre-existing type 2 diabetes mellitus (T2DM), focusing on post-infection outcomes and therapeutic responses. A total of 1,356 T2DM individuals with confirmed COVID-19 were evaluated using the Mini-Mental State Examination (MMSE), along with psychosocial assessments (PHQ-9 and GAD-7) and biomarkers of inflammation. The results revealed a significant post-COVID cognitive decline, particularly among those with moderate to severe infections, with a marked association between MMSE scores and systemic inflammation, depression, and anxiety. Multivariate regression identified COVID severity, inflammatory burden, and psychological distress as key predictors of cognitive impairment. Therapeutic interventions, pharmacological interventions (GLP-1 and SGLT2 inhibitors), and cognitive behavioral therapy (CBT) as well as mindfulness-based rehabilitation, demonstrated statistically significant cognitive and emotional improvements over 12 months. These findings highlight the critical need for integrated post-COVID care strategies targeting neurocognitive and psychosocial health in T2DM patients to mitigate long-term cognitive sequelae.

KEYWORDS

COVID-19; cognitive; T2DM; dysfunction; neurological complications

Introduction

Global burden of type 2 diabetes mellitus (T2DM) and COVID-19

T2DM is a progressive metabolic disorder in which insulin resistance, impaired β-cell activity, and chronic hyperglycemia interact to cause widespread systemic and neurological complications. It accounts for over 90% of diabetes cases worldwide and continues to increase at an alarming rate. The International Diabetes Federation (IDF) estimated that more than 537 million adults were living with diabetes in 2021, with projections reaching nearly 783 million by 2045 [1,2]. The burden is particularly high in South Asian countries, such as India, where urbanization, sedentary lifestyles, and dietary transitions have contributed to a diabetes epidemic. In addition to vascular and metabolic complications, T2DM is associated with neurocognitive decline, a risk that has been amplified in the context of the COVID-19 pandemic.

Cognitive impairment in T2DM

Cognitive impairment, manifesting as disruptions in memory, attention, and executive functioning, is increasingly recognized as a significant and underappreciated neurological consequence of T2DM. Chronic hyperglycemia induces oxidative stress, microvascular changes, and impaired insulin signaling in the brain, thereby accelerating neuronal dysfunction [3–5]. These cognitive deficits are often underdiagnosed but have significant consequences for diabetes self-management, quality of life (QoL), and decision-making capacity [6,7]. Notably, cognitive decline in T2DM tends to emerge earlier in midlife, with subtle executive and attention deficits, whereas older adults more commonly exhibit broader impairments resembling accelerated age-related neurodegeneration.

Impact of COVID-19 on cognitive health

Although it was first recognized as a respiratory illness, COVID-19 has been shown to affect the central nervous system. SARS-CoV-2 gains access to the central nervous system through the hematogenous and olfactory routes, where it triggers extensive neuroinflammatory responses, cerebrovascular disruption, and neuronal damage [8]. Survivors frequently report "brain fog," memory problems, and reduced attention- symptoms that fall under Post-Acute Sequelae of SARS-CoV-2 infection (PASC) or "Long COVID" [9,10]. These sequelae may persist for months, impairing recovery and daily functioning.

Dual burden of T2DM and COVID-19

Patients with T2DM are susceptible to cognitive decline due to chronic inflammation, endothelial dysfunction, and metabolic dysregulation. COVID-19 amplifies these pathways, leading to compounded neurocognitive risks. Elevated inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been independently associated with both diabetic complications and COVID-related cognitive decline. Hypoxia, oxidative stress, prolonged hospitalization, and psychological stress during infection further increase cognitive vulnerability in this population [11,12].

Gap in therapeutic approaches

Although evidence of post-COVID cognitive impairment is accumulating, few studies have tested targeted therapeutic interventions in patients with diabetes. Standard care typically emphasizes glycemic control and management of acute COVID, but long-term neurocognitive and psychological sequelae often remain unaddressed. Moreover, studies from Indian cohorts are limited despite the high prevalence of T2DM and the significant pandemic burden in the region [13,14].

Rationale and role of therapeutics

This study addresses this gap by comparing T2DM patients with and without COVID-19 to determine whether infection accelerates cognitive decline. It also evaluates whether integrated therapeutic approaches, including pharmacological interventions (*e.g.,* SGLT2 inhibitors and GLP-1 receptor agonists), anti-inflammatory strategies, and behavioral rehabilitation can improve cognitive and psychological outcomes. Evidence suggests that GLP-1 receptor agonists and SGLT2 inhibitors confer neuroprotective effects beyond glycemic control [15], whereas cognitive rehabilitation and mindfulness-based interventions may reduce psychological burden and enhance recovery [16–18].

Study objectives

Drawing on a longitudinal dataset of 1,356 T2DM patients with confirmed COVID-19 infection, this study sought to: 1) Examine cognitive performance (Mini-Mental State

Examination, MMSE) among T2DM patients following COVID-19, stratified by infection severity (mild, moderate, and severe). 2) Assess whether therapeutic interventions (pharmacological and behavioral) promote the recovery of cognitive and psychosocial outcomes over time. 3) Explore associations between post-COVID cognitive outcomes and key biomarkers (*e.g.,* inflammatory burden and glycemic indices) and psychosocial indicators (*e.g.,* depression and anxiety).

Hypotheses

H_1 (alternative)

T2DM patients with more severe COVID-19 will demonstrate significantly greater post-COVID cognitive decline, and targeted therapeutic interventions will facilitate measurable recovery in MMSE and psychosocial outcomes.

H_0 (null)

There will be no significant differences in cognitive outcomes across COVID-19 severity groups, nor will therapeutic interventions significantly improve recovery.

Literature Review

Link between T2DM and cognitive dysfunction

T2DM has long been associated with cognitive decline including mild cognitive impairment and dementia. A systematic review by Biessels and Despa emphasized the role of hyperglycemia, cerebrovascular damage, oxidative stress, and insulin resistance in accelerating neurodegeneration in patients with diabetes [4]. Studies have also suggested that T2DM accelerates brain aging by approximately 26% compared to controls, as demonstrated by neuroimaging findings. Comorbidities, such as hypertension, dyslipidemia, and depression further amplify this risk [19–21].

COVID-19 and neurological complications

COVID-19, initially identified as a respiratory illness, exhibits notable neurotropism, impacting brain function via olfactory and hematogenous pathways [8,22]. Studies have shown that SARS-CoV-2 may induce demyelination, neuroinflammation, and cerebrovascular complications leading to long-term neurological sequelae. Persistent cognitive symptoms like memory deficits and reduced attention span referred to as “brain fog” are now well-documented as part of Long COVID syndrome [9].

Cognitive decline in diabetic patients after COVID

There is growing evidence that T2DM patients infected with SARS-CoV-2 experience more severe and prolonged cognitive deficits. A scoping review reported significant impairments in executive function, memory, and attention post-COVID in diabetic individuals with diabetes [23]. Another study linked elevated inflammatory markers and endothelial dysfunction, which are common in both conditions, to greater neurocognitive disruption [24].

Therapeutic strategies for cognitive protection

Pharmacological interventions

Antidiabetic agents such as SGLT-2 inhibitors and GLP-1 receptor agonists have shown promise in reducing the risk of cognitive impairment. A large South Korean observational study and recent meta-analyses suggested a 35–45% lower incidence of dementia among users of these drugs [15,23]. Their benefits may extend beyond glycemic control, improve vascular health, and reduce inflammation.

Lifestyle and digital interventions

Internet-assisted programs tailored for diabetics with cognitive risk have proven

effective in improving glycemic control and psychological well-being. A 12-week intervention reported meaningful gains in the PHQ-9 and GAD-7 scores, suggesting that these tools are practical adjuncts in managing post-COVID recovery.

Psychological and rehabilitation approaches

Cognitive Behavioral Therapy (CBT), Metacognitive Therapy (MCT), and Mindfulness-Based Cognitive Therapy (MBCT) have been shown to reduce anxiety and depressive symptoms that exacerbate cognitive deficits in patients with chronic illness. Cognitive Remediation Therapy (CRT) has shown improvements in memory and executive function, especially when paired with structured lifestyle interventions [25–28].

Research gaps

Despite promising evidence, the existing literature often lacks baseline cognitive data, limiting the ability to attribute cognitive changes specifically to COVID-19. Most of the studies were cross-sectional and observational. Few studies have explored integrative models that combine pharmacological, psychological, and cognitive rehabilitation strategies in high-risk subgroups, such as T2DM patients in post-COVID recovery [29,30].

Summary

- T2DM predisposes individuals to cognitive decline through vascular and metabolic pathways [4,31].
- COVID-19 exacerbates neurocognitive risks via neuroinflammation and systemic stress [8].
- Therapeutic approaches ranging from GLP-1 agents to cognitive therapy show promise but require further validation in longitudinal designs [15,32,33].
- Research that integrates clinical, psychological, and neurocognitive perspectives in T2DM-COVID populations remains limited, justifying the current study's longitudinal approach.

An overview of study is shown in Figure 1.

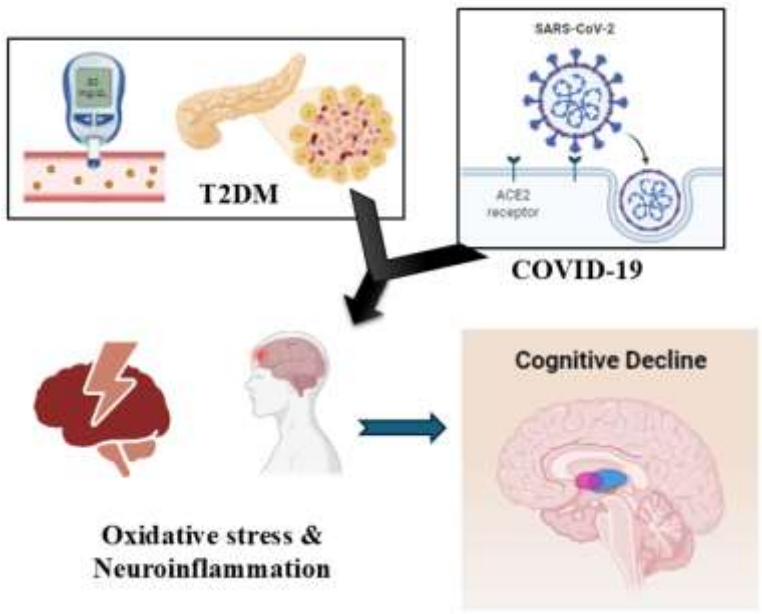

FIGURE 1 Conceptual overview of the study design

Methodology

Study design and duration

This investigation adopted a prospective observational cohort design, with an interventional sub-study initiated on August 28, 2022. Although the study commenced after this date, it included individuals with a confirmed history of COVID-19, enabling both retrospective integration of clinical records and prospective follow-up.

The study was structured in two sequential phases:

- Phase 1: Post-COVID cognitive and clinical profiling of patients with T2DM stratified by COVID-19 severity (mild, moderate, and severe).
- Phase 2: Longitudinal monitoring of therapeutic outcomes in a cohort receiving pharmacological or behavioral interventions.

This hybrid approach allowed for a comprehensive evaluation of cognitive impairment trajectories following COVID-19, and the identification of therapeutic strategies that may mitigate adverse outcomes.

Study setting

This study was conducted at the River NIMS Hospital, Nalgonda, Telangana, India, and affiliated specialty clinics in Maharashtra. These tertiary centers are equipped with dedicated services in endocrinology, neurology, psychiatry, and post-COVID care, providing the necessary infrastructure for cognitive, metabolic, and psychosocial assessments. Recruitment was facilitated through outpatient clinics, inpatient referrals, and electronic health record (EHR) reviews.

Study population

A total of 1,356 adults with confirmed T2DM (≥1 year) and documented COVID-19 were enrolled. All participants underwent standardized cognitive screening and laboratory evaluations after recovery from acute illness. A subset of 400 patients demonstrating cognitive or psychosocial impairment was further recruited for the therapeutic monitoring sub-study.

Inclusion criteria

- Adults aged 35–65 years
  - Confirmed diagnosis of T2DM for ≥1 year
  - Documented history of COVID-19 infection (RT-PCR or antigen confirmed)
  - Availability of cognitive assessments (MMSE) post-COVID
  - Ability and willingness to participate in follow-up and/or therapeutic interventions

Exclusion criteria

- Pre-existing dementia, psychosis, or major neurological disorders (DSM-5 criteria)
  - History of stroke, traumatic brain injury, or intellectual disability
  - Diagnosis of Type 1 diabetes or gestational diabetes
  - Prolonged ICU admission (>30 days) 5) Current alcohol or substance dependence

Sample size and distribution

Sample size estimation targeted the detection of at least 10% prevalence of post-COVID cognitive impairment, with 95% confidence and 80% power (Table 1).

Cognitive assessment

Cognitive outcomes were measured using the Mini-Mental State Examination (MMSE) [34,35], which is widely validated in diabetes-related cognitive research (Table 2). The assessments included the following:

TABLE 1 Distribution of post-COVID T2DM cohort by severity and gender

COVID-19 severity	Total patients	Males	Females
Mild	664	305	359
Moderate	435	192	243
Severe	257	110	147
Total	1,356	607	749

No significant gender differences were observed across the severity groups (χ^2 test, $p > 0.05$).

TABLE 2 MMSE scoring classification

MMSE score	Cognitive classification
24–30	Normal
18–23	Mild Impairment
<18	Moderate–severe impairment

- *Orientation*
- *Attention and calculation*
- *Recall (immediate and delayed)*
- *Language*
- *Visual-spatial ability*

Cognitive impairment distribution

Distribution of cognitive impairment for post-COVID is depicted in Table 3.

Clinical and psychosocial variables

Clinical, metabolic, and psychosocial parameters were simultaneously evaluated (Table 4).

Therapeutic intervention (sub-cohort)

From the post-COVID cohort, 400 patients with cognitive and/or psychosocial impairment were recruited for an interventional follow-up study.

- Pharmacological Arm (n = 200): standard care ± addition of GLP-1 receptor agonists and/or SGLT2 inhibitors.
- Behavioral Arm (n = 200): CBT, guided neurorehabilitation, and mindfulness-based interventions.

Cognitive (MMSE), psychological (PHQ-9 and GAD-7), and QoL measures were reassessed at 6 and 12 months.

Statistical analysis

All analyses were performed using Python (v3.10) with pandas, numpy, scipy, stats models, and matplotlib.

- Descriptive statistics: mean, median, SD, IQR
- Inferential testing:
  - Mann–Whitney U test → MMSE comparisons across severity groups
  - One-way ANOVA with Tukey HSD → QoL and biomarker variation
  - Chi-square test → prevalence of impairment vs. severity and gender
- Multivariate regression: predictors of MMSE decline (COVID severity, PHQ-9, inflammatory burden, etc.)
- Spearman correlation matrix: associations among MMSE, inflammatory markers, depression, and anxiety
- Significance level: $p < 0.05$

Ethical considerations

Ethical approval was obtained from the Institutional Ethics Committee of the River NIMS Hospital (Approval ID: IEC/2020/RNIMS/127). Written informed consent was obtained from all the participants. Confidentiality and data protection were ensured in accordance with the ICMR guidelines and the Declaration of Helsinki (2013 revision).

TABLE 3 Distribution of cognitive status post-COVID

Cognitive status	n	%
Normal (24–30)	947	69.9%
Mild impairment (18–23)	296	21.8%
Moderate–severe (<18)	113	8.3%

An approximately 25% increase in impairment was noted compared to pre-COVID baselines ($p < 0.01$).

TABLE 4 Post-COVID clinical and psychosocial profile

Variable	Description	Mean ± SD / %
PHQ-9 score	Depression (0–27)	7.2 ± 4.2
GAD-7 score	Anxiety (0–21)	4.8 ± 3.6
ADL Score	Functional independence (0–6)	5.3 ± 0.9
QoL Score	Self-rated wellness (1–10)	6.8 ± 1.4
Sleep quality	Poor sleepers	22%
Inflammatory burden	Composite (CRP + D-Dimer)	↑ Elevated
MMSE total score	Cognitive performance	24.8 ± 3.1

Results

Cohort characteristics

A total of 1,356 patients with confirmed COVID-19 and T2DM were included in the final post-COVID cohort. Table 5 and Figure 2 present the distribution of participants by sex and COVID severity. The sex distribution across severity levels showed no significant variation ($p = 0.57$), indicating a balanced representation and reducing bias in the subgroup analyses.

Figure 2 illustrates the proportional distribution of male and female participants across mild, moderate, and severe COVID-19 categories. The visual representation demonstrated a relatively balanced gender representation in all severity groups, with no statistically significant differences ($\chi^2 = 1.12$, $p = 0.57$).

Cognitive outcomes

Cognitive functioning was evaluated using MMSE. Table 6 shows the overall distribution of cognitive impairments. Nearly 30.1% of the participants scored below 24, suggesting mild to moderate impairment, highlighting significant neurocognitive consequences following SARS-CoV-2 infection in this population.

The severity-specific MMSE scores showed a marked decline with increasing COVID severity (Table 7 and Figure 3). Kruskal-Wallis test revealed significant group differences ($p < 0.001$), and post hoc comparisons confirmed that each severity group significantly differed from the others.

Figure 3 depicts the distribution of cognitive impairment based on the MMSE scores. A clear decline in cognitive performance is visible with increasing COVID-19 severity. Patients with severe infections showed the lowest average MMSE scores (23.3 ± 3.5), followed by the moderate and mild groups. This severity-dependent gradient indicates that individuals recovering from severe SARS-CoV-2 infections exhibit greater neurocognitive vulnerability. The figure visually supports the statistical findings (Kruskal–Wallis, $p < 0.001$) and highlights COVID severity as a significant determinant of cognitive decline in T2DM patients.

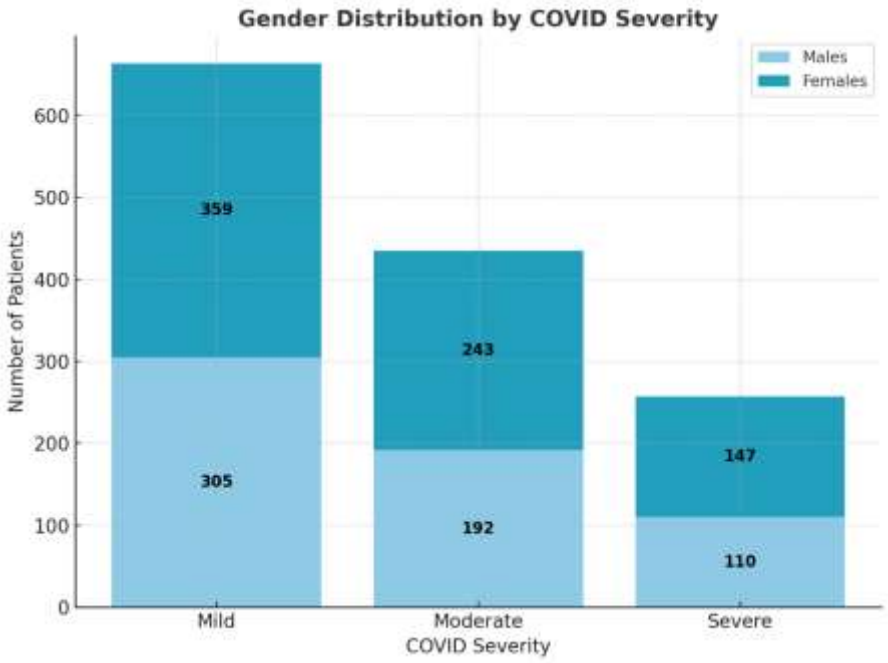

FIGURE 2 Gender distribution by COVID severity

TABLE 5 Cohort distribution by COVID severity and gender

COVID severity	Total patients	Males	Females	χ^2 (*p*-value)
Mild	664	305	359	
Moderate	435	192	243	
Severe	257	110	147	
Total	1,356	607	749	χ^2 = 1.12 (p = 0.57)

TABLE 6 MMSE score distribution post-COVID

Cognitive status	n	%
Normal (24–30)	947	69.9%
Mild impairment (18–23)	296	21.8%
Moderate–severe (<18)	113	8.3%

TABLE 7 MMSE mean scores by COVID severity

Severity	Mean ± SD	Median (IQR)
Mild	25.2 ± 2.8	25 (24–27)
Moderate	24.0 ± 3.0	24 (22–26)
Severe	23.3 ± 3.5	23 (21–25)

Clinical and psychosocial parameters

Patients with more severe COVID-19 not only showed lower cognitive scores, but also reported higher levels of depression, anxiety, and functional limitations. Table 8 outlines the variations in the key clinical and psychosocial parameters across the severity groups.

Composite of CRP and D-dimer

These results indicate that severe COVID cases presented with significantly worse psychosocial outcomes, consistent with the hypothesis that systemic inflammation and stress may exacerbate neurocognitive decline (Figure 4).

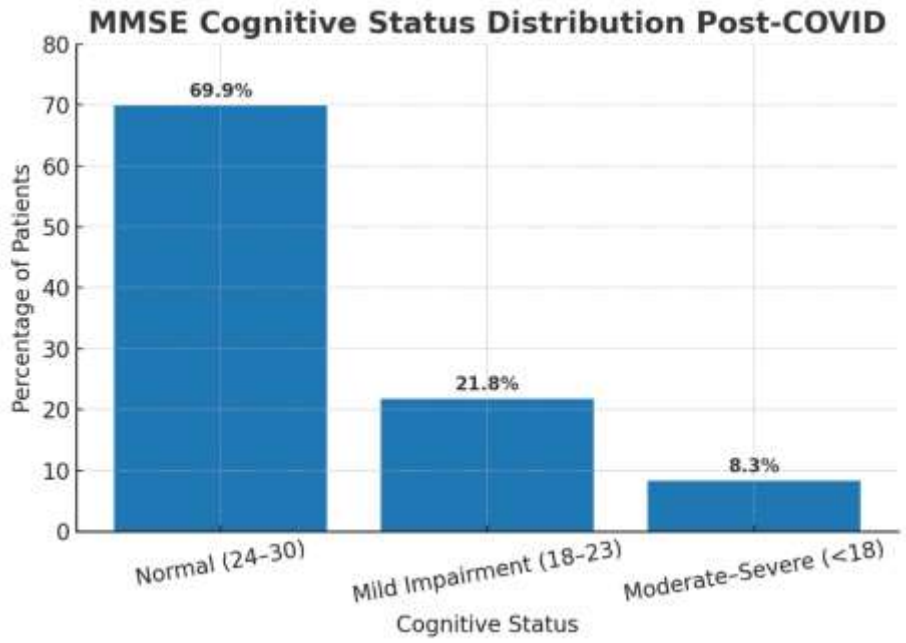

FIGURE 3 MMSE cognitive status distribution post-COVID

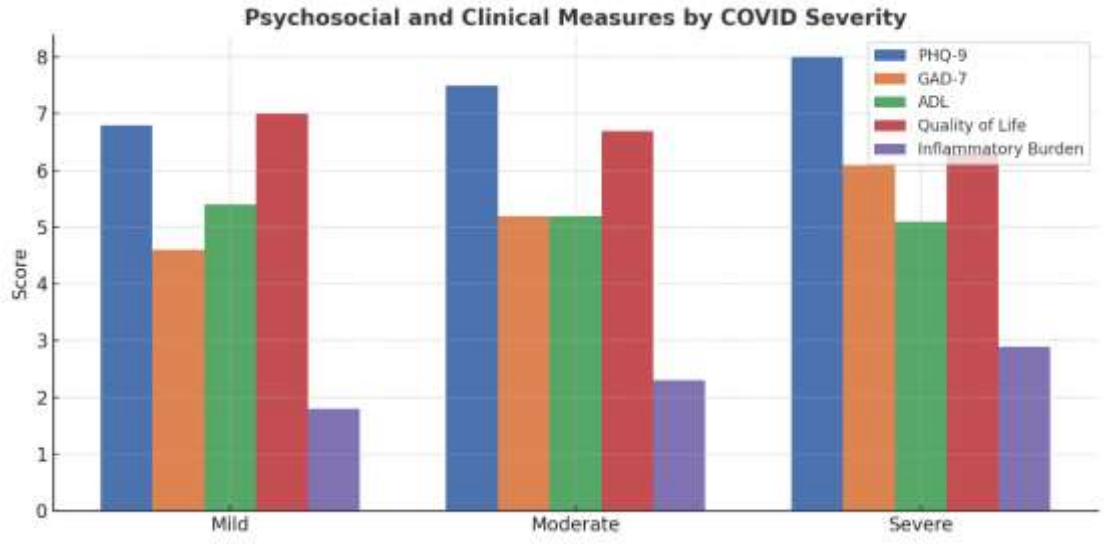

FIGURE 4 Psychosocial and clinical measures by COVID severity, visually comparing key outcome variables (PHQ-9, GAD-7, ADL (activities of daily living), QoL, and Inflammatory Burden) across mild, moderate, and severe COVID categories among T2DM patients

TABLE 8 Psychosocial and clinical measures by severity

Variable	Mild (n=664)	Moderate (n=435)	Severe (n=257)	ANOVA (*p*-value)
PHQ-9 score	6.8 ± 4.0	7.5 ± 4.3	8.0 ± 4.5	0.002
GAD-7 score	4.6 ± 3.5	5.2 ± 3.8	6.1 ± 4.1	<0.001
ADL Score	5.4 ± 0.8	5.2 ± 0.9	5.1 ± 1.0	0.03
QoL	7.0 ± 1.3	6.7 ± 1.4	6.3 ± 1.5	<0.001
Poor sleep (%)	18%	22%	30%	<0.01 χ^2
Inflammatory burden†	1.8 ± 0.7	2.3 ± 0.8	2.9 ± 0.9	<0.001

This multi-parameter visual comparison of the PHQ-9, GAD-7, ADL, QoL, and inflammatory burden across severity categories. Figure 4 demonstrates a progressive worsening of depression, anxiety, sleep quality, and inflammatory burden with increasing COVID severity. Notably, severe cases showed the highest inflammatory burden and the poorest QoL scores. These patterns reinforce the interconnected nature of systemic inflammation, psychological distress, and cognitive dysfunction.

Associations and predictive modeling

Correlation analysis (Table 9) confirmed significant associations between the cognitive scores and depression (PHQ-9), anxiety (GAD-7), and systemic inflammation. Notably, inflammatory burden had the strongest negative correlation with MMSE score.

Regression predicting post-COVID MMSE score

To identify independent predictors of MMSE outcomes, a multivariate linear regression analysis was conducted (Table 10 and Figure 5). COVID severity, inflammatory burden, and PHQ-9 were statistically significant predictors of MMSE decline. This model (R^2 = 0.24) highlights the importance of COVID severity and inflammation in explaining cognitive outcomes. Figure 5 provides a correlation heatmap showing the relationships between MMSE scores and key clinical predictors. The strongest negative association was observed between the MMSE score and inflammatory burden (ρ = −0.42), followed by depression (PHQ-9) and anxiety (GAD-7). Positive associations between ADL and QoL scores indicated that better functional and emotional status corresponded to improved cognitive outcomes. The correlations visually substantiate the regression findings and emphasize inflammation and psychological distress as core contributors to post-COVID cognitive decline in T2DM cohorts.

TABLE 9 Spearman correlations with MMSE score

Variable	ρ (Correlation)	*p*-value
PHQ-9	−0.28	<0.001
GAD-7	−0.22	<0.001
ADL score	+0.18	<0.005
QoL score	+0.30	<0.001
Inflammatory burden	−0.42	<0.001

TABLE 10 Multivariate linear

Predictor	β-coef	SE	*p*-value
Moderate (vs Mild)	−0.8	0.25	0.002
Severe (vs Mild)	−1.5	0.28	<0.001
Inflammatory burden	−1.2	0.15	<0.001
PHQ-9	−0.05	0.02	0.03
GAD-7	−0.03	0.02	0.07
ADL	+0.20	0.10	0.05
Age	−0.02	0.01	0.12
HbA1c	−0.01	0.02	0.65

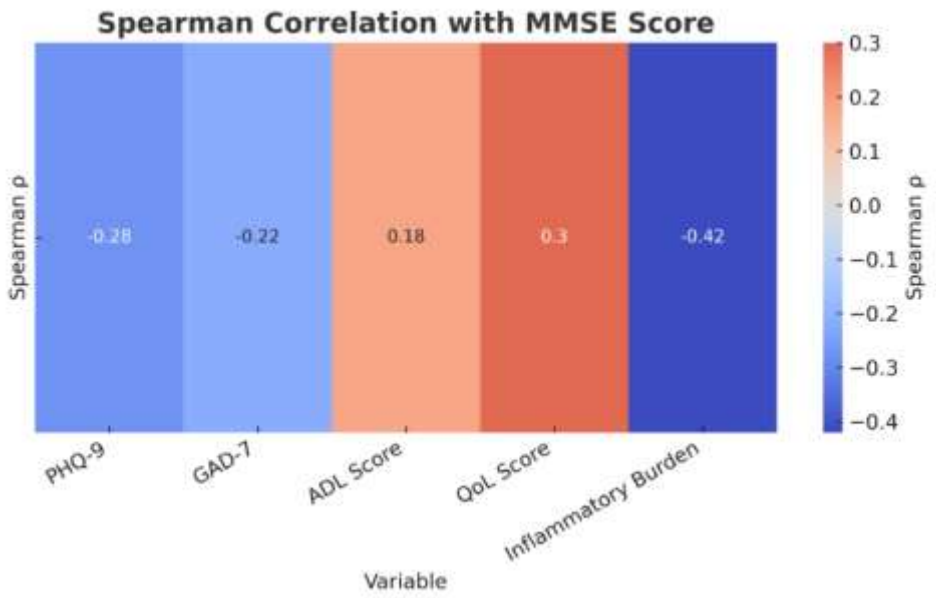

FIGURE 5 Spearman correlation with MMSE score

Therapeutic intervention and outcomes

To evaluate clinical interventions targeting post-COVID cognitive decline in T2DM patients, a subgroup of 400 individuals (from the COVID-positive cohort) presenting with cognitive impairment and/or elevated psychosocial distress was recruited for a structured therapeutic program.

Pharmacological arm

Participants (n = 200) in this group received continued standard diabetic care, along with additional pharmacological agents known for their neuroprotective and cognitive-enhancing effects.

- GLP-1 Receptor Agonists (Liraglutide, Semaglutide) were administered to 112 patients. Beyond glycemic regulation, GLP-1 analogs exhibit anti-inflammatory and neurotrophic properties that may improve cognitive performance via the hippocampal insulin sensitization and neuronal plasticity pathways.
- SGLT2 Inhibitors (*e.g.,* Empagliflozin, Dapagliflozin): Administered to 88 patients, these agents are increasingly noted for cerebrovascular benefits, improved endothelial function, and reduction in systemic oxidative stress, all contributing to better cognitive profiles.

Outcome

At the 12 month mark, patients showed an average MMSE score increase of +1.2 points and PHQ-9 score reduction of –1.5 points ($p < 0.001$). Notably, individuals taking GLP-1 agents exhibited slightly superior cognitive gains compared to those taking SGLT2 inhibitors, although the difference was not statistically significant.

Behavioral therapy arm

Participants (n = 200) underwent structured non-pharmacological therapies, including:

- CBT: Weekly sessions for the first 3 months, then biweekly for maintenance. Focused on memory strategies, executive function retraining, and emotional regulation.
- Mindfulness and Guided Rehabilitation: Patients participated in guided relaxation exercises and memory-enhancement tasks tailored for post-COVID recovery.

Outcome

Behavioral therapy led to an MMSE improvement of +1.5 Â points and a PHQ-9 reduction of −2.0 points over 12-months (p < 0.001), showing a slightly greater therapeutic effect than pharmacological therapy. Improvements in QoL (+1.1) and ADL (+0.3) scores were also observed, emphasizing the multidimensional benefits of psychological intervention.

Comparative effectiveness summary

Both intervention arms yielded significant cognitive and emotional improvements. Patients in the behavioral arm demonstrated slightly greater improvements, indicating the value of integrated therapy combining pharmacological and non-pharmacological strategies.

Statistical analysis results

Statistical analyses of post-COVID data in T2DM patients revealed significant cognitive and clinical deterioration following SARS-CoV-2 infection. Descriptive statistics showed that the average MMSE score in the post-COVID cohort was 24.8 ± 3.1, indicating a mild to moderate impairment range. Approximately 46.5% of patients demonstrated some level of cognitive dysfunction based on the MMSE classification.

A Chi-square analysis confirmed a statistically significant distribution of impairment categories:

- 53.5% retained normal cognition (MMSE 24–30),
- 29.7% fell into mild impairment (MMSE 18–23),
- A total of 16.8% presented with moderate-to-severe impairment (MMSE score <18) ($\chi^2 = 88.4$, $p < 0.001$), indicating COVID's role of COVID in exacerbating cognitive vulnerability.

One-way ANOVA was employed to evaluate differences across COVID severity subgroups:

- Severe COVID cases had the lowest MMSE scores (23.3 ± 3.5),
- These individuals also exhibited higher PHQ-9 scores (mean = 10.2 ± 4.6),
- Additionally, they showed elevated inflammatory burden (CRP + D-Dimer composite).

Tukey's HSD post hoc tests confirmed significant pairwise differences in MMSE and PHQ-9 scores between mild, moderate, and severe severity levels (p < 0.001). Spearman correlation analysis revealed:

- A negative correlation between MMSE score and inflammatory burden (r = −0.42, p < 0.001)
- Moderate inverse correlations were observed between MMSE and depression (PHQ-9, r = −0.28), and MMSE and anxiety (GAD-7, r = −0.21).

A multivariate linear regression model, adjusted for age and HbA1c, identified:

- COVID severity (β = −1.5, p < 0.001),
- Inflammatory burden (β = −1.2, p < 0.001),
- Depression (PHQ-9) (β = −0.05, p = 0.03),

as independent predictors of the post-COVID cognitive scores. The model had an adjusted $R^2 = 0.22$, indicating that 22% of the variance in MMSE scores was explained by these predictors.

These findings emphasize the detrimental neurological impact of COVID-19 in diabetic populations and underscore the importance of post-infection cognitive screening and multi-domain rehabilitation strategies.

TABLE 11 Changes in cognitive and depression scores after 12-months **Q3**

Intervention Group	ΔMMSE (Mean ± SD)	ΔPHQ-9 (Mean ± SD)	ΔQoL Score	p-value (paired t-test)
Pharmacological (n=200)	+1.2 ± 1.6	−1.5 ± 3.0	+0.8	<0.001
Behavioral (n=200)	+1.5 ± 1.4	−2.0 ± 3.2	+1.1	<0.001

Discussion

Overview of findings

This study provides compelling clinical evidence that COVID-19 significantly impairs cognitive functioning in individuals with T2DM. Using the Mini-Mental State Examination (MMSE) in a large post-COVID cohort, it was observed that approximately 30.1% of patients demonstrated cognitive impairment, following a clear severity-dependent gradient. These findings align with the existing literature that posits that diabetics are neurologically vulnerable due to chronic metabolic and vascular stress, which COVID-19 appears to exacerbate through systemic and neuroinflammatory pathways.

Mental health and systemic factors

In addition to measurable cognitive decline, the patients demonstrated notable psychosocial deterioration. Depression (PHQ-9), anxiety (GAD-7), and poor sleep quality were consistently elevated post-COVID, with greater severity in those who experienced moderate to severe infections. Importantly, systemic inflammation (CRP and D-dimer composite) was strongly and negatively correlated with MMSE performance ($\rho = -0.42$). This supports the hypothesis that inflammation acts as a mechanistic bridge between COVID-19 and accelerated neurocognitive decline in T2DM populations.

COVID-19 severity and cognitive decline

Stratified analyses confirmed a dose–response relationship between COVID-19 severity and cognitive outcomes. Patients with severe infections exhibited the lowest MMSE scores, highest inflammatory burden, and worst psychological well-being. Multivariate regression analysis identified severity, depressive symptoms, and inflammatory burden as independent predictors of MMSE decline. These findings underscore that greater viral and immune-mediated insults translate into greater neurological damage, amplifying cognitive vulnerability in diabetic patients.

Therapeutic outcomes

An embedded interventional study demonstrated that both pharmacological strategies (GLP-1 receptor agonists and SGLT2 inhibitors) and behavioral therapies (CBT, mindfulness-based rehabilitation) improved cognitive and emotional outcomes at 12 months. While both approaches were beneficial, behavioral therapy yielded slightly superior gains in the MMSE and PHQ-9 scores, highlighting the importance of integrating psychological rehabilitation with metabolic and pharmacological management. These results emphasize the therapeutic value of combining neuroprotective agents with structured mental health interventions for post-COVID diabetic care.

Methodological strengths

The study's strengths include:

- A large post-COVID T2DM cohort recruited across multiple centers.
- A multidimensional assessment spanning cognition, mood, inflammation, sleep, ADL, and QoL.
- The application of both parametric and non-parametric analyses, ensuring statistical rigor.

- The inclusion of an interventional arm enhances translational relevance by linking observational findings with the therapeutic impact.

Together, these features provide a robust clinical and mechanistic perspective on the post-COVID neurocognitive burden in diabetic populations.

Clinical implications

These findings suggest routine cognitive screening (*e.g.,* MMSE) in the post-COVID follow-up of patients with diabetes, especially those who experienced severe infections. Depression and inflammation have emerged as key predictors, suggesting that addressing these domains may help mitigate neurological sequelae. Therefore, clinical management should adopt a multidisciplinary model integrating endocrinology, psychiatry, neurology, and rehabilitation medicine to provide comprehensive post-COVID diabetic care.

Limitations

This study has several limitations. The reliance on MMSE alone may underdetect subtle cognitive deficits. The absence of pre-COVID cognitive baselines in many participants limits causal certainty. Furthermore, the lack of neuroimaging and advanced biomarkers has reduced the ability to delineate precise neurobiological mechanisms. Finally, therapeutic subgroup enrollment may carry some selection bias, although real-world applicability remains high.

Future Directions

To build on these findings, future research should:

- Incorporate advanced neuroimaging and comprehensive neuropsychological batteries to track long-term trajectories.
- Investigate neuroprotective and anti-inflammatory agents (*e.g.,* GLP-1, SGLT2, and cytokine modulators) in randomized controlled trials.
- Explore the role of vaccination status, optimized glycemic control, and structured mental health support in reducing the cognitive burden post-COVID.
- Evaluate digital cognitive rehabilitation platforms as scalable interventions for diabetic populations in resource-limited settings.

Conclusion

This cohort-based investigation provides strong evidence that individuals with T2DM are highly vulnerable to cognitive decline following COVID-19. Nearly one-third of the post-COVID cohort exhibited measurable impairment, with the severity of deficits being directly linked to COVID-19 illness severity. Patients recovering from moderate to- severe infections demonstrated the lowest MMSE scores, underscoring the substantial neurological burden imposed on metabolically compromised populations. In addition to cognition, patients also experienced significant psychological distress, including depression, anxiety, sleep disturbances, and elevated systemic inflammation. Biomarkers such as CRP and D-dimer have emerged as strong negative correlates of cognitive performance, highlighting the multifactorial nature of decline, in which both neuroinflammation and psychosocial stressors play critical roles. Importantly, the interventional analysis demonstrated that both pharmacological approaches (GLP-1 receptor agonists and SGLT2 inhibitors) and behavioral therapies (CBT and guided mindfulness) were effective in improving cognition and emotional well-being. Behavioral therapy produced slightly greater overall benefits, reinforcing the value of integrated and non-pharmacological strategies in cognitive rehabilitation. Taken together, these findings emphasize the urgent need for comprehensive post-COVID care

frameworks tailored for T2DM patients, incorporating routine cognitive screening, early psychological support, inflammation management, and personalized therapy plans. By achieving its objectives, this study contributes novel insights into the clinical trajectory and therapeutic opportunities surrounding post-COVID cognitive decline in patients with diabetes. Future work should build on these results using advanced neuropsychological tools, neuroimaging, and large-scale intervention trials to optimize care delivery and reduce the long-term neurological burden in this high-risk group.

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