Middle East Current Psychiatry

RESEARCH

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Cognitive impairment, depressive and anxiety disorders among post-COVID-19 survivors: a follow-up study

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Abstract

Background Psychiatric signs may be induced by the cytokine storm that is implicated in the immune response to coronavirus through neuro-inflammation. Survivors disclosed symptoms of obsessive–compulsive disorder, melancholy, anxiety, panic disorder, and post-traumatic stress disorder. For the first year following the SARS disease, they generally suffer from suicide and psychosis.

Aim To evaluate the presence of cognitive impairment, anxiety disorders, and depression in adult survivors of COVID-19, 1 month and 3 months post-recovery.

Method It is an observational longitudinal study. Forty-four COVID-19 survivor patients, with no past psychiatric history were evaluated at 3 months and 1 month after recovery. The Montreal Cognitive Impairment Basic (MoCA-B) was employed to evaluate cognitive impairment. However, anxiety and depressive disorders were identified via structured clinical interview for DSM IV, axis I (SCID-I) and their severity was examined by the Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) consecutively.

Results Regarding cognitive impairment, MoCA-B results showed a mean score of 25.95 ± 1.98 in the 1st interview and 27.7 ± 1.05 in the 2nd interview, with a marked change, *P*-value = 0.001. SCID-I showed that 43.2% of our sample was diagnosed with both anxiety and depression at 1 month post-recovery, with the improvement of some cases at 3 months to affect only 18.2%, showing a statistically significant difference, *P*-value = 0.036. The percentage of patients who suffered from sleep difficulties was 59.1% at 1st interview and 27.3% at 2nd interview. While 61.4% of patients suffered from fatigue and low concentration at 1st interview and went down to 31.8% at 2nd interview, showing a statistically significant difference, *P*-value < 0.001. The severity of depression and anxiety in those diagnosed also declined from the 1st interview to the 2nd, BDI mean score in 1st interview was 12.30 ± 10.46, and in the 2nd interview was 7.09 ± 9.24 with marked variation *P*-value < 0.001, while BAI means score at the 1st interview was 18.18 ± 16.85 and at the 2nd interview was 11.32 ± 16.12 with statistically significant difference *P* = 0.001.

Conclusion Impairment of cognitive functions; especially delayed recall; was one of the important COVID-19 psychiatric sequelae, In addition to anxiety and depressive signs in the form of depressed/anxious mood, fatigue, decreased concentration, and sleep disturbances. The severity of symptoms declined over the 3 months period of the study.

Keywords COVID-19, Depression, Anxiety, Cognitive Impairment, MoCA Scale

Introduction

A new coronavirus, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), was discovered in Wuhan, China at the end of 2019 [1]. The virus afflicted nearly 180,000,000 individuals and resulted in the

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deaths of approximately 4,000,000 individuals globally (2.2% death rate). The expression "post-acute sequelae of COVID-19" (PASC) has acquired broad acceptance. Subjects reported experiencing remaining signs and experiencing challenges in regaining their pre-COVID performance scores [2]. The World Health Organization (WHO) defined PASC officially in October 2021 [3]. As the global community prepares to transition beyond the COVID-19 pandemic and the incidence of fresh infections reaches a plateau, there are apprehensions regarding the potential healthcare impact of PASC [4]. COVID-19 survivors are anticipated to experience long-term sequelae, with a 30% incidence of the condition predicted by multiple investigations [5, 6]. COVID-19 survivors will suffer from gastrointestinal, respiratory, cardiovascular, and musculoskeletal symptoms [7, 8]. In addition to this, the elevated incidence of neuropsychiatric signs between COVID-19 survivors is increasingly supported by studies [9, 10].

Fears of morbidity and mortality, as well as ambiguity regarding tomorrow, are substantial psychological burdens that have the potential to exacerbate public mental health [11]. Consequently, a number of organizations have advocated for the creation and execution of mental health testing in pandemics [12, 13]. Research on previous pulmonary viral outbreaks indicates that a variety of mental health issues may manifest during acute viral illness or after an extended amount of time following infection. Numerous neuropsychiatric conditions, including encephalitis, Guillain–Barre syndrome (GBS), encephalopathy, and other demyelinating and neuromuscular processes, have been identified during the Middle East respiratory syndrome coronavirus (MERS-CoV outbreak in 2012) and other coronavirus infections (SARS-CoV-1 epidemic in 2003 and the 2009 influenza (H1N1) pandemic [14–17].

Post-traumatic stress disorder (PTSD), Obsessive–compulsive disorder (OCD), melancholy, and panic disorder were reported by survivors [18–20]. Also, seropositive patients for coronaviruses usually experience psychosis and suicide for 1 year following SARS infection [21]. The recent information explores that cases with COVID-19 may induce insomnia, depression, delirium, and anxiety [22]. In the initial phase of COVID-19, Limcaoco et al. [23] conducted research that collected data from 41 nations. The results indicated that anxiety levels were elevated. Kowal et al. [24] analyzed information from 26 nations and found that younger individuals, who had a smaller amount of education, were single, had more children, and resided in a country that had been significantly impacted by COVID-19 experienced greater amounts of stress.

Social isolation and the traumatic memories of the illness and its effects throughout the COVID-19 pandemic are critical psychological triggers that may result in a psychopathological consequences [11, 25]. It is more challenging to visit outpatient clinics for evaluation and obtain prescription psychotropic substances during outbreaks due to national quarantine regulations. This may additionally contribute to the return or deterioration of their pre-existing indications and conditions [26].

Mentally ill individuals might be more vulnerable to the COVID-19 epidemic, which may result in a frequency of recurrence that is higher and the exacerbated signs of pre-existing psychiatric disorders [27]. The COVID-19 pandemic resulted in a rise in unemployment rates, which restricted access for people with psychiatric disorders to food, permanent lodging, and medication, as well as their ability to maintain a consistent income [28]. In addition, restricted physical activity and reduced sunlight exposure [29].

Various studies have demonstrated that a substantial proportion of individuals who recover from pneumonia do not completely restore their prior cognitive and affective capabilities during the most recent outbreaks of corona respiratory viruses [MERS-COV and SARS-COV-1]. The prevalence of OCD was 15.6%, depression was 36.4%, PTSD was 40%, and anxiety disorders were equally prevalent, according to research on the neuropsychiatric impacts of SARS-COV-1 conducted 30–50 months after the infection [30]. In addition to this, In a meta-analysis of SARS-COV-1 individuals, neurological impairments were observed up to 18 months after hospital release[31], such as modest cognitive decline [32].

Cognitive decline is one of the dangers of white matter damage in COVID-19, and the integrity of subcortical white matter is essential for the preservation of mental abilities [33]. This was evident by radiological findings of the white matter and disruption of functional integrity in cerebral regions like the hippocampus, in recovered COVID-19 cases, at 3 months follow-up, which was associated with memory loss [34]. SARS-COV-2 neuroinvasion via olfactory nerve fibers or vasculature leading to post-infective injury of the central nervous system (CNS) [35], explains the MRI of COVID-19 patients' brains which showed white matter changes including foci of hemorrhage in two cases and evidence of posterior reversible encephalopathy syndrome in another [36].

The immune response to coronaviruses may induce mental health symptoms through neuroinflammation, which is characterized by a "cytokine storm." [37, 38]. The neuro-immune theory suggests a possible pathophysiological link between impaired central and peripheral immune function, as evidenced by the discovery of

neurobiological alterations in MDD [39]. Monocytes exert their inflammatory effects by emitting proinflammatory cytokines as a consequence of the activated NF-κB signaling pathway. These cytokines affect neurons, astrocytes, and microglia. In addition, these stress-inducing stimuli induce neurogenesis impairment, neuronal dendrite retraction [40], particularly in the hippocampus [41], and the absence of dendritic spines in the prefrontal cortex. These physiological alterations can result in signs that are congruent with numerous signs of depression, including anhedonia, anhedonia, fatigue, and social withdrawal [42].

In numerous studies, the severity of the disease was proposed as a contributing indicator [43–45]. According to de Graaf [46], patients who were recuperating from severe COVID-19 presented with the greatest amounts of depression and/or anxiety. Depressive symptoms were found to be correlated with hospitalization time by Gennaro et al. [47]. De Graaf et al. [46] demonstrated that depression was associated with a worse post-COVID functional status, while Alemanno et al. [48] reported an association between the degree of the initial illness and depressive signs and depression.

To assess and examine the short-term impacts of COVID-19, we decided to examine cognitive actions, depression, and anxiety disorders in Egyptian cases with no past history of psychiatric illnesses; suffering from mild to moderate COVID-19 (according to the WHO severity criteria) who followed up at post-COVID-19 clinic (no history of hospitalization); 1 month and 3 months post-recovery.

Method and subjects

The investigation was a follow-up observational study with a convenient sample of forty-four COVID-19 survivors, diagnosed using the Center for Disease Control and Prevention (CDC) diagnostic and recovery criteria (positive RT-PCR test outcomes for pharyngeal and nose swabs, thus suggesting an established case of SARS-CoV-2 virus disease). They were recruited consecutively from Kasr Al Aini Post-COVID-19 follow-up clinic. The Inclusion criteria were as follows: both genders, age range 18 to 54 years, of clinically average intelligence, can read and write (at least primary school education). Regarding the exclusion criteria, patients with a pre-COVID psychiatric history, cognitive disorders, substance use disorders, or history of significant head trauma were excluded. The Kasr Al-aini Department of Psychiatric Scientific and Ethical Committee accepted the research proposal. The ethical committee of Cairo University accepted the work on 16 March 2022, registration number: (MS-40–2022). A written informed consent was acquired from patients after discussing with them the aim of the study.

Screening was done using a specially designed semi-structured interview derived from the Kasr Al-Ainy sheet to cover the following parameters: Socio-demographic information: Including sex, age, marital state, occupation, education, residence, smoking, and history of presenting conditions: Including onset, duration of the disease, number of episodes, presence of psychotic features and suicidality and finally family history of depressive, anxiety or sleep conditions.

Structured Clinical Interview for DSM IV, Axis I disorders (SCID-I) clinical version [49], the Arabic version [50] verified the diagnosis of depression and anxiety-related illnesses. Designed for mental health practitioners, this is a clinical assessment. It evaluates 33 of the prevalent mental illnesses included in the American Psychiatric Association's fourth edition of the diagnostic and statistical handbook [51]. It generates a useful and user-friendly tool so that the benefits of structured interviews can be utilized in therapeutic environments. It is constituted of seven clinical categories: substance abuse, mood, psychotic, anxiety, eating, somatoform, and adjustment conditions.

The Beck Depression Inventory (BDI) [52] includes 21 inquiries regarding how the individual has been behaving in the past week, therefore evaluating the severity of depression. The following were the conventional cut-off scores: Minimal depression is indicated by 0–9; mild depression by 10–18; severe depression by 30–63; moderate depression by 19–29. An Arabic version of the revised edition of the BDI in its complete form was used [53].

Utilizing the Beck Anxiety Inventory (BAI) [54], which comprises 21 self-report variables evaluating signs of anxiety separate from depression, the degree of anxiety was evaluated. For every item, subjects must answer on a 4-point Likert-type scale spanning 0 to 3. There are twenty-one items in the BAI, with answers evaluated on a 0 (not at all) to 3 (severely). A higher total rating points to higher-level signs of anxiety. The cutoffs are 8–15: mild, 26–63: severe, 16–25: moderate, and 0–7: minimal. For the Egyptian diagnosis of anxiety, the modified Arabic version of BAI [55] was shown to be a consistent and efficient scale.

One often-used diagnostic tool for dementia is the Montreal Cognitive Assessment Basic (MoCA-B). It has been implemented in many contexts after being verified in the framework of mild cognitive decline. Comprising thirty points, this test requires 10 min from the subject. MoCA-B ratings run from 0 to 30. Considered normal is a score of 26 or above. MoCA-B showed reliability in distinguishing between normal and ill participants and strong internal consistency (Cronbach's alpha = 0.915). An Arabic adaptation of MoCA-B was used [56, 57].

Symptoms like insomnia, fatigue, and decreased concentration were obtained from the semi-structured interview sheet.

Patients did not receive any psychiatric treatment or medication during the study period. Forty-four patients finished assessments at 1 month and 3 months post-recovery and therefore were involved in this work.

Statistical analysis

Following data collection, they were scored, labeled, and recorded with the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). For quantitative data, data was compiled utilizing mean, median, standard deviation, maximum, and minimum; for categorical data, relative frequency (%) and frequency (count). Non-parametric Kruskal–Wallis and Mann–Whitney tests allowed comparisons across quantitative variables. The non-parametric Wilcoxon signed-rank test was applied for the comparison of serial measurements within each subject [58]. The chi-square ($\chi 2$) test was utilized to compare categorical data. When the expected frequency is less than five, exact tests were used instead. Marginal homogeneity tests and non-parametric McNemar tests were applied to compare serial measurements within every subject [59]. Using the Spearman correlation coefficient [60], correlations across quantitative factors were computed. *P*-values below 0.05 were regarded as marked significant.

Results

The number of cases recruited at the beginning of the study was 75, but those who came again at 3 months were 44, and those who were involved in the research. The age range for cases was 18 to 54 years; the mean age ± SD was 33.39 ± 9.20 years. The percentage of male patients shared in the study was 32%, while female patients were 68%. Table 1 shows the participants' socio-demographic features.

Regarding the participant's medical history, only 11% of our patients were smokers and 9% of patients were asthmatic, 11% suffered from hypertension, 2% were diabetic, and 2% had renal problems (renal calculi). All the patients were in a fully controlled state of their medical co-morbidities during the study. During COVID illness, patients received some prescribed medications, 100% of patients received antipyretics, but 80% of patients were prescribed antibiotics, 16% of patients received corticosteroids, and only 9% of patients were prescribed anticoagulant therapy.

The mean score of MoCA-B in the 1st interview was 25.95 ± 1.98, which is slightly below the normal cut-off value, while in the 2nd interview, it was 27.7 ± 1.05 showing a marked variation (*P*-value < 0.001). In the 1st interview, the mean score of delayed recall was 3.4 (out of 5) and it improved in the 2nd interview to 4.4.

Table 1 Sociodemographic features of the studied group

		Number	Percentage
Age (years)	18–34	32	73%
	35–55	12	27%
Gender	Male	14	32%
	Female	30	68%
Education level	University education	32	73%
	Secondary education	11	25%
	Below secondary education	1	2%
Marital status	Single	17	38.6%
	Married	24	54.5%
	Widow	2	4.5%
	Divorced	1	2.3%

Regarding the diagnosis of depression and anxiety disorders; at the 1st interview; depression without anxiety affected 4.5% of the sample while both combined depression and anxiety cases constituted 43.2% of the sample. At the 2nd interview, combined depression and anxiety affected only 18.2% with no cases of depression alone, showing a statistically significant difference between diagnoses at 1st and 2nd interviews *(P*-value = 0.036). Regarding anxiety disorders without depression, 13.6% of patients were sufferers; while in the 2nd interview, they became 11.4% with marked variation (*P*-value = 0.036), (Table 2 and Fig. 1).

Regarding the severity of depression using the BDI; at the 1st interview, 52.3% of patients suffered from minimal depression while 4.5% of patients suffered from severe depression. In the 2nd interview, 84.1% of patients suffered from minimal depression, while 4.5% of patients suffered from severe depression. While the BAI showed at the 1st visit; 40.9% of patients suffered from minimal anxiety, 31.8% of patients suffered from severe anxiety, while at the 2nd visit; 65.9% of patients suffered from minimal anxiety, and 18.2% of patients suffered from severe anxiety (*P*-value < 0.001), (Figs. 2 and 3 and Tables 3 and 4).

The percentage of patients suffering from insomnia was 59.1% at 1st interview and became 27.3% at 2nd interview. Besides the percentage of patients suffering from fatigue and decreased concentration at 1st interview was 61.4% and went down to 31.8% at 2nd interview, showing a statistically significant difference (*P* < 0.001) (Figs. 4, 5, and 6).

There was no marked relation between gender and cognitive function scores, according to MoCA-B, nor the severity of depression and anxiety according to Beck's

Table 2 The comparison between 1st interview and 2nd interview regarding depressive disorders and anxiety disorders in COVID patients using SCID I scale

		1st visit		2nd visit		*P*-value
		Count	%	Count	%	
SCID	Anxiety disorder	6	13.6%	5	11.4%	0.036
	Depression	2	4.5%	0	0.0%	
	Depression and anxiety	19	43.2%	8	18.2%	
	No	17	38.6%	31	70.5%	

P < 0.05 is significant

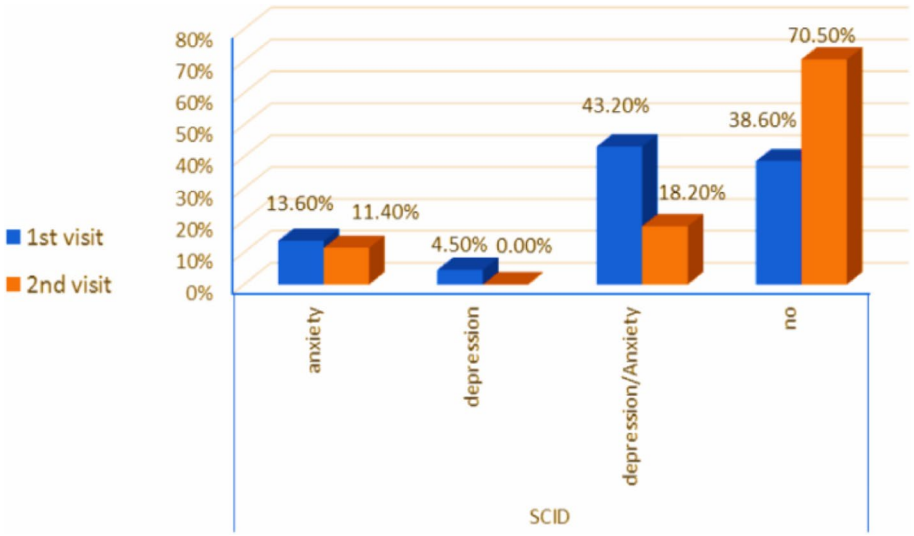

Fig. 1 Percentages of patients with depression and anxiety disorders at both 1st and 2nd interviews

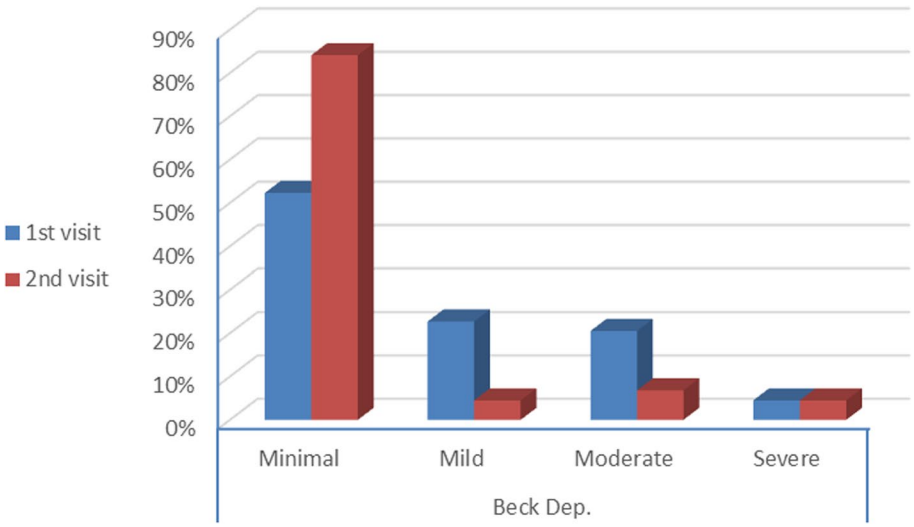

Fig. 2 Severity of depression at 1st and 2nd interviews

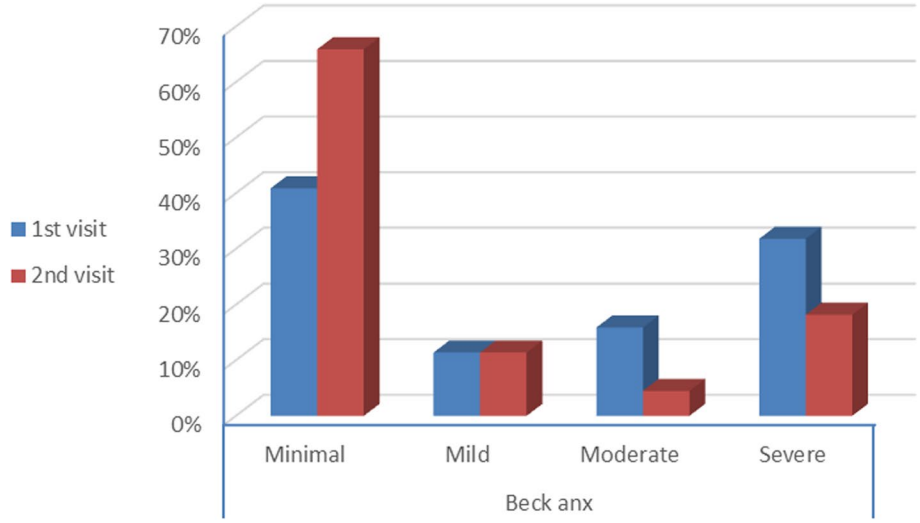

Fig. 3 Severity of anxiety at 1st and 2nd interviews

Table 3 Comparison between grades of depression and anxiety at 1st and 2nd interviews, using Beck depression and anxiety scales

		1st visit		2nd visit		*P*-value
		Count	%	Count	%	
BDI	Minimal	23	52.3%	37	84.1%	0.001
	Mild	10	22.7%	2	4.5%	
	Moderate	9	20.5%	3	6.8%	
	Severe	2	4.5%	2	4.5%	
BAI	Minimal	18	40.9%	29	65.9%	0.001
	Mild	5	11.4%	5	11.4%	
	Moderate	7	15.9%	2	4.5%	
	Severe	14	31.8%	8	18.2%	

P < 0.05 is significant

Table 4 Comparison between 1st interview and 2nd interview regarding mean values of Beck depression and anxiety inventories

	1st visit					2nd visit					*P*-value
	Mean	SD	Median	Mini.	Maxi.	Mean	SD	Median	Mini.	Maxi.	
BDI	12.30	10.46	9.00	0.00	44.00	7.09	9.24	4.00	0.00	42.00	< 0.001
BAI	18.18	16.85	14.00	0.00	55.00	11.32	16.12	4.00	0.00	54.00	< 0.001

P < 0.05 is significant

depression and anxiety inventories, neither in the 1st nor in the 2nd interview. There was also no relation, neither between gender and SCID results, nor between gender and insomnia, fatigue, and low concentration in both interviews (Tables 5, 6, and 7).

There was no marked association between age and MoCA-B mean score at 1st and 2nd interviews. In addition to this, there was no marked association between age and severity of depression and anxiety either at the 1st interview or in the 2nd interview. There was additionally no marked relation between age and sleep difficulties, low concentration, and fatigue in COVID patients at 1st interview and 2nd interview (Tables 8 and 9).

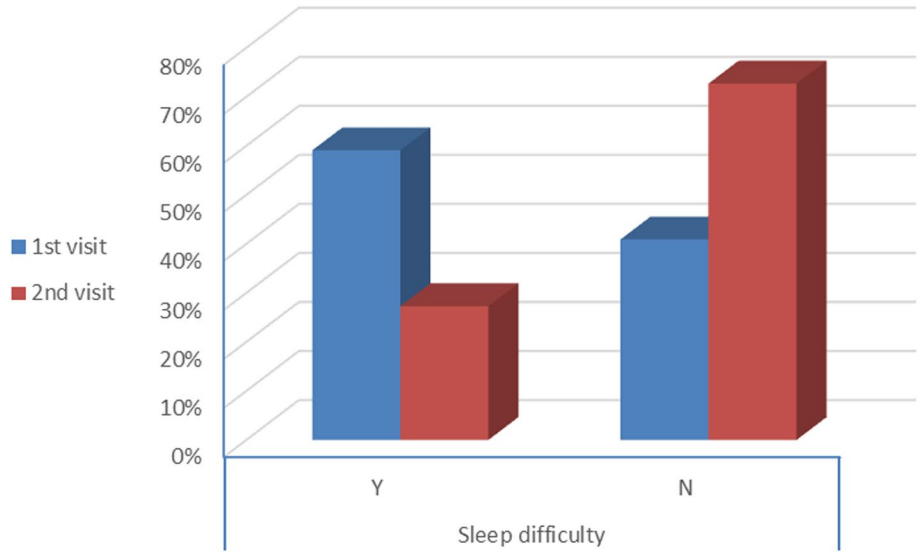

Fig. 4 Percentage of patients with sleep difficulty in 1st and 2nd interviews

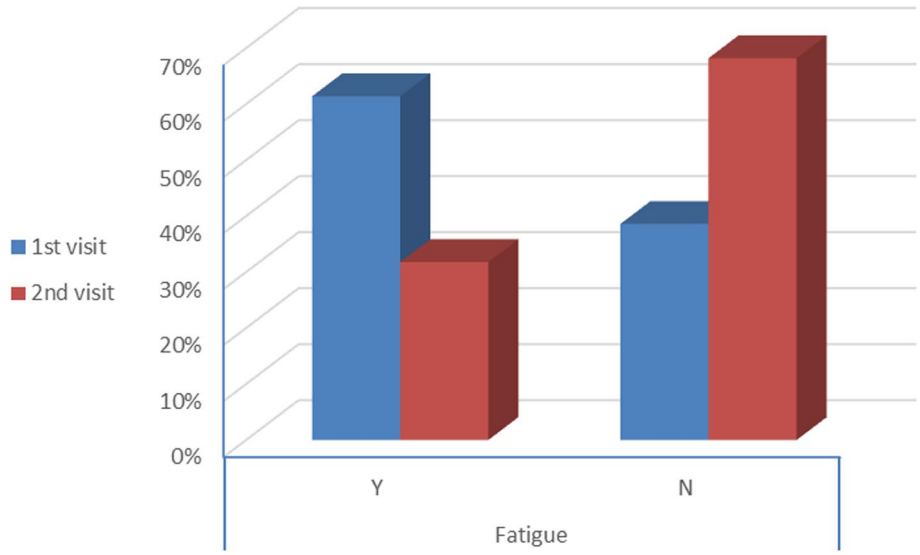

Fig. 5 Percentage of patients with fatigue at 1st and 2nd interview

Discussion

This study assessed cognitive impairment, anxiety, and depressive conditions in a sample of 44 adult cases who recovered from mild to moderate COVID-19 and were following up at the Covid out-patient clinic at Kasr Alaini, with no past history of psychiatric disorders, at 1 month and 3 months post-recovery.

By applying MoCA-B at the 1st interview, the mean score was 25.95 ± 1.98 and in the 2nd interview, the mean score improved to 27.7 ± 1.05 with a marked difference of $P < 0.001$. Most of the patients had specific difficulty in the delayed recall domain, which also improved from the mean value of 3.4 (out of 5) in the first interview to 4.4 (out of 5) in the second interview.

Well-known measures in clinical practice for basic cognition assessment, the Mini-mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) have been applied in research of post-COVID psychological effects. On the MoCA, a cut-off value of 26 was set as the threshold separating mild cognitive impairment (MCI) from healthy controls. MoCA is easy to use, with higher sensitivity and specificity than MMSE,

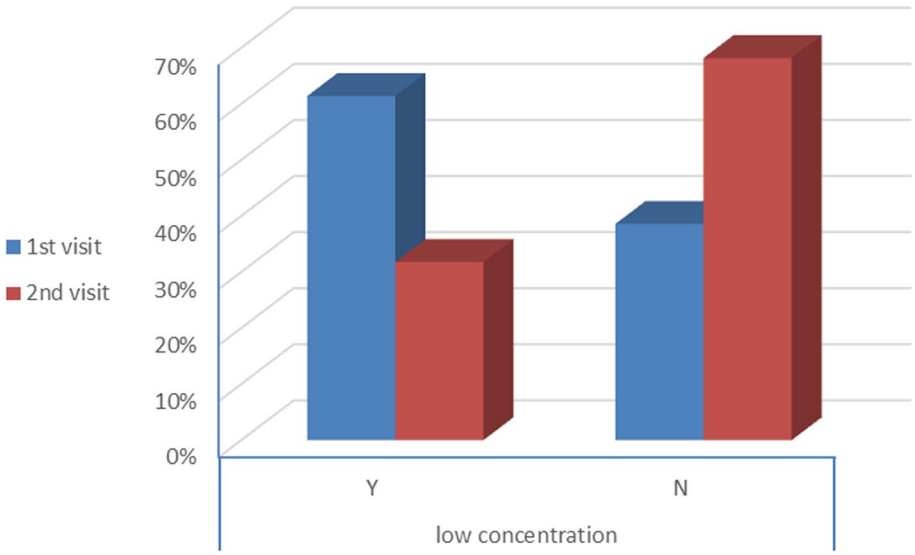

Fig. 6 Percentage of cases with low concentration at 1st and 2nd interviews

Table 5 The relation between gender and cognitive impairment, severity of depression, and anxiety disorders in COVIDcasesat 1st interview and 2nd interview

	Gender										
	Male					**Female**					***P*-value**
	Mean	**SD**	**Median**	**Mini.**	**Maxi.**	**Mean**	**SD**	**Median**	**Mini.**	**Maxi.**	
MoCA (1st)	26.29	1.86	26.00	24.00	30.00	25.80	2.04	26.00	18.00	28.00	0.797
BDI (1st)	13.00	9.11	15.50	0.00	26.00	11.97	11.16	7.50	0.00	44.00	0.561
BAI (1st)	14.71	14.15	10.50	0.00	42.00	19.80	17.97	18.00	0.00	55.00	0.512
MOCA (2nd)	28.00	1.04	28.00	26.00	29.00	27.57	1.04	28.00	26.00	29.00	0.175
BDI (2nd)	5.29	7.84	4.00	0.00	30.00	7.93	9.83	4.00	0.00	42.00	0.353
BAI (2nd)	5.86	11.69	2.50	0.00	45.00	13.87	17.40	5.50	0.00	54.00	0.194

P-value < 0.05 is significant

the assessment takes 10 to 15 min, and its Arabic version is valid and reliable, therefore it is widely used in research in Kasr Alaini Hospital, and was a good choice for our study. Mild cognitive impairment is defined as less than 24 on MoCA, therefore the results of this study are in the normal range, may be because of a small sample size or because the cases had mild signs and symptoms of COVID with no history of hospitalization.

The choice of cases to be of young adults was to avoid any possible cognitive impairment due to aging or cognitive disorders of the elderly such as Alzheimer's. In addition to this, mild to moderate cases were preferred for this research to eliminate possible confounding factors related to severe illnesses, such as prolonged illness, hospitalization, isolation, or the fear of dying.

The biological etiology underlying these cognitive deficits remains unclear. Evidence from post-mortem studies suggests there is minimal presence of the virus in the brain in COVID-19 patients [61]; therefore, the effect of the virus may be indirect via a range of possible mechanisms, including microvascular changes and immunological reactions. Subcortical white matter integrity is crucial for cognitive function [62]**.** White matter damage in COVID-19 was seen by neuroradiological evidence. White matter injury and disruption of functional integrity in cerebral regions like the hippocampus, at 3-month follow-up in recovered COVID-19 cases, was associated with memory loss.

Our study results regarding the "delayed recall" domain are in line with the study of Daroische [63]; a review of studies on objective cognitive decline among COVID-19 survivors, using Ovid MEDLINE based on a PECO scheme; in which all studies detected cognitive decline in 15% to 80% of the cases. Three studies reported memory

Table 6 The relation between gender and SCID, the severity of depression and anxiety, insomnia, fatigue, and low concentration in 1st interview

		Gender				
		Male		Female		*P*-value
		Count	%	Count	%	
SCID (1st)	Anxiety disorder	1	7.1%	5	16.7%	0.799
	Major depression	1	7.1%	1	3.3%	
	Depression/anxiety	7	50.0%	12	40.0%	
	No	5	35.7%	12	40.0%	
BDI (1st)	Minimal	6	42.9%	17	56.7%	0.547
	Mild	4	28.6%	6	20.0%	
	Moderate	4	28.6%	5	16.7%	
	Severe	0	0.0%	2	6.7%	
BAI (1st)	Minimal	6	42.9%	12	40.0%	0.508
	Mild	3	21.4%	2	6.7%	
	Moderate	2	14.3%	5	16.7%	
	Severe	3	21.4%	11	36.7%	
Insomnia (1st)	Y	8	57.1%	18	60.0%	0.858
	N	6	42.9%	12	40.0%	
Fatigue (1st)	Y	8	57.1%	19	63.3%	0.694
	N	6	42.9%	11	36.7%	
Low concentration (1st)	Y	8	57.1%	19	63.3%	0.694
	N	6	42.9%	11	36.7%	

Table 7 The relation between gender and SCID, severity of depression and anxiety, insomnia, fatigue, and low concentration in 2nd interview

		Gender				
		Male		Female		*P*-value
		Count	%	Count	%	
SCID (2nd)	Anxiety disorder	0	0.0%	5	16.7%	0.109
	Major depression	0	0.0%	0	0.0%	
	Depression/anxiety	1	7.1%	7	23.3%	
	No	13	92.9%	18	60.0%	
BDI (2nd)	Minimal	13	92.9%	24	80.0%	0.560
	Mild	0	0.0%	2	6.7%	
	Moderate	0	0.0%	3	10.0%	
	Severe	1	7.1%	1	3.3%	
BAI (2nd)	Minimal	12	85.7%	17	56.7%	0.360
	Mild	1	7.1%	4	13.3%	
	Moderate	0	0.0%	2	6.7%	
	Severe	1	7.1%	7	23.3%	
insomnia (2nd)	Y	3	21.4%	9	30.0%	0.722
	N	11	78.6%	21	70.0%	
Fatigue (2nd)	Y	3	21.4%	11	36.7%	0.489
	N	11	78.6%	19	63.3%	
low concentration (2nd)	Y	4	28.6%	10	33.3%	1
	N	10	71.4%	20	66.7%	

Table 8 The correlation between age and MOCA, severity of depression and anxiety at 1st interview and 2nd interview

		Age
MOCA (1st)	*r* coefficient	−0.054-
	P-value	0.726
	N	44
BDI (1st)	*r* coefficient	0.171
	P-value	0.266
	N	44
BAI (1st)	*r* coefficient	0.110
	P-value	0.478
	N	44
MOCA (2nd)	*r* coefficient	−0.187-
	P-value	0.224
	N	44
BDI (2nd)	*r* Coefficient	0.058
	P-value	0.707
	N	44
BAI (2nd)	*r* coefficient	0.180
	P-value	0.242
	N	44

difficulties, specifically short-term memory deficits in two of them. Regarding other cognitive domains, our study results are not in line with other studies which detected some language impairment, and impairment in executive and attention actions, with different findings based on different tests.

Having a notable drop in all cognitive domains except orientation, our study findings contradict Abdelghani et al. [64] who stated that COVID-19 survivors were more likely to suffer cognitive impairment than the control participants (51.8% vs. 7%, *P*-value). Impaired cognitive areas included visuo-executive abilities, attention, name, abstraction, language, and delayed recollection. After adjusting for connected anxiety and depressive symptoms, COVID-19 survivors exhibited significantly higher odds of CI compared to control subjects. This was evident in the domains of visuo-executive skills ($P<0.001$, OR 0.3, 95% CI 0.2–0.5), delayed recall ($P<0.001$, OR 0.5, 95% CI 0.4–0.6), language ($P<0.001$, OR 0.2, 95% CI 0.1–0.5), attention ($P=0.002$, OR 0.4, 95% CI 0.3–0.7), and total MOCA scores ($P<0.001$, OR 0.1, 95% CI 0.04–0.2).

The variation of the results regarding cognitive domains affected might be explained by the variation of the cognitive tests used and that most of these studies focused on severe COVID-19 patients who were hospitalized.

Using SCID-I at the 1st interview, cases diagnosed with both depression and anxiety constituted 43.2% of the sample and by follow-up at the 2nd interview, they turned out to be 18.2% only, with a marked difference $P=0.036$. A large number of cases (70.5%) had no depressive or anxiety disorders by 3 months, although no psychiatric medications or therapies were provided during the study period.

Regarding the severity of depression using the BDI; at the 1st interview, 52.3% of patients suffered from minimal depression while 4.5% of patients suffered from severe depression. In the 2nd interview, 84.1% of patients suffered from minimal depression, while 4.5% of patients suffered from severe depression. While the BAI showed at the 1st visit; 40.9% of patients suffered from minimal

Table 9 The relation between age and sleep difficulties, low concentration, and fatigue in COVID patients at 1st interview and 2nd interview

		Age					
		Mean	**Standard deviation**	**Median**	**Mini.**	**Maxi.**	***P*-value**
Sleep difficulty (1st interview)	Yes	33.15	9.54	32.00	18.00	54.00	0.981
	No	33.72	8.93	30.00	25.00	52.00	
Fatigue (1st interview)	Yes	33.56	9.59	32.00	18.00	54.00	0.744
	No	33.12	8.82	30.00	25.00	52.00	
Low concentration (1st interview)	Yes	33.56	9.59	32.00	18.00	54.00	0.744
	No	33.12	8.82	30.00	25.00	52.00	
Sleep difficulty (2nd interview)	Yes	30.92	7.12	32.00	18.00	42.00	0.594
	No	34.31	9.80	30.50	19.00	54.00	
Fatigue (2nd interview)	Yes	30.57	6.86	31.50	18.00	42.00	0.398
	No	34.70	9.93	30.50	19.00	54.00	
Low concentration (2nd interview)	Yes	32.64	8.82	32.00	18.00	53.00	0.890
	No	33.73	9.49	30.00	19.00	54.00	

N is number, $P<0.05$ is significant

anxiety, 31.8% of patients suffered from severe anxiety, while at the 2nd visit; 65.9% of patients suffered from minimal anxiety, and 18.2% of patients suffered from severe anxiety (P-value < 0.001).

The findings of this investigation align with those of research that examined for psychological signs in 402 adults who survived COVID-19 (mean age 58) at a 1-month follow-up following hospitalization at IRCCS San Raffaele Hospital in Milan. A counseling session and a series of questionnaires for self-reporting were employed to assess depression, PTSD, insomnia, anxiety, and obsessive–compulsive symptoms. A notable percentage of cases experienced psychological distress, with 28% exhibiting PTSD, 31% showing signs of depression, 42% affected by anxiety, 20% presenting OCD symptoms, and 40% suffering from insomnia. A total of 56% exhibited scores within the pathological range across at least one clinical dimension. Females experienced higher degrees of depression and anxiety, despite having substantially lower baseline inflammation indicators. Individuals with a prior psychiatric diagnosis exhibited elevated scores on the majority of psychopathological assessments, while baseline amounts of inflammation remained comparable [65].

Evidence supports the neuroimmune hypothesis, stating that there is a pathophysiological connection between defective central and peripheral immune function, with some neurobiological changes observed in MDD [39]; for example, Monocytes act by releasing proinflammatory cytokines as a result of the activated NF-κB signaling pathway, affect neurons, microglia, and astrocytes. These stress-inducing stimuli cause neuronal dendrite retraction, neurogenesis impairment; especially in the hippocampus, and a loss of dendritic spines in the prefrontal cortex (PFC) [40]. These physiological changes can lead to behavioral pathologies that coincide with many depressive symptoms, such as fatigue, anhedonia, social withdrawal, and headaches [42]. This hypothesis might also explain the improvement noticed in the severity of depression and anxiety; from 1 to 3 months post-recovery; with the resolution of inflammation over time.

In our study, there was no marked relation between gender and depression and anxiety according to Beck's depression and anxiety inventories, neither in the 1st nor in the 2nd interview. This is consistent with random-effects meta-analysis and the systematic review conducted by Deng et al. [65]. The study evaluated the incidence of anxiety, depression, and sleep disturbances in post-COVID-19 cases. The researchers looked at PubMed, EMBASE, MEDLINE, and Web of Science and determined that the overall incidence of anxiety was 47%, sleeping disturbances were 34%, and depression was 45%. They did not observe any significant shift in the incidence rates among distinct genders.

Although there was no marked connection between gender and anxiety, the diagnosis of anxiety disorders alone was higher in females (16.7%) vs (7.1%) in males in the 1st interview and (16.7%) in females vs (0%) in males in the 2nd interview, even the severity of anxiety was higher in females and also did not improve much at 3 months (severe anxiety was 36.7% in females vs 21.4% in males at the 1st interview, 23.3% in females vs 7.1% in males in the 2nd interview).

This is consistent with the multicenter monitoring investigation carried out by Maher et al. [66], in which cases were selected sequentially from three quarantine hospitals in Egypt. Data were gained via Google Forms like BDI, the Taylor Manifest Anxiety Scale (TMAS), and the Arabic versions of the General Health Questionnaire (GHQ-12). PTSD, depression, and anxiety signs were evaluated 6 months later. Females had the highest incidence of anxiety-induced insomnia, sleep disturbances, melancholy, and distress-induced anxiety. After 6 months, BDI scores improved dramatically in males but not females. The seriousness of anxiety was still greater among females, despite the fact that TMAS did not exhibit any significant alterations. In comparison to males, females were more likely to experience post-traumatic stress disorder (PTSD) (26 (37.1%) versus 4 (9.5%), respectively, P-value = 0.02). A greater degree of anxiety was observed in female participants with varying degrees of COVID-19 severity than in male participants.

González-Sanguino et al. [67] showed that female gender is a significant predictor of anxiety and PTSS, as the prevalence of anxiety, stress, and depression is generally higher among women. Haro et al.[68] stated that females are more vulnerable to stress, anxiety, and depression than males due to interactions between biological factors, social factors, gender stereotypes and roles, social stigma, and inequality.

Regarding specific clinical symptoms, at the 1st interview, 59.1% of patients suffered from insomnia while 61.4% of patients suffered from fatigue and low concentration. In the 2nd interview, patients showed improvement as 27.3% only suffered from insomnia while 31.8% suffered from fatigue and low concentration with a statistically significant difference of $P < 0.001$.

The results of our investigation involving insomnia are consistent with those of Hoang etal. 2024 [69], who reported that over 75% of the subjects experienced insomnia, a figure that is significantly higher than the 10–20% of the general population that has been earlier documented. This percentage is additionally significantly greater than the general incidence of insomnia among

hospitalized COVID-19 survivors, as reported in prior systematic reviews (12–47%) [70–72].

This can be attributed to the criteria for choice, which included subjects who recuperated from COVID-19 within 6 months. As a result, insomnia was anticipated to be more common among people who were recently healed from an illness, particularly a novel viral epidemic, as survivors are at an increased risk of chronic health issues, chronic pain, and psychiatric conditions, which can result in increased insomnia [73].

Research suggests that most people with acute insomnia recover within a year's time [74]. Patients with insomnia exhibit heightened sympathetic and β-adrenergic activation [75, 76], which increase the levels of pro-inflammatory cytokines [77]. Studies have also shown that insomnia is associated with elevated plasma- and serum-based markers of inflammation, such as interleukin-6 (IL-6), C-reactive protein (CRP), interleukin-1 beta (IL-1β), and tumor necrosis factor-alpha (TNF-α) [78–80].

In our sample, the improvement in insomnia, fatigue, and low concentration at 3 months might be associated with the improvement of depression and anxiety. These signs are in themselves indicative of depression and anxiety; consequently, it is probable that there is an intersection of these features.

Our study results regarding depression and anxiety are in line with Gramaglia C et al.[81] follow-up study, which included 196 participants who recovered from COVID-19. A skilled psychiatrist, who was instructed in the execution of the Mini-International Neuropsychiatric Interview (MINI), conducted a clinical interview with patients to evaluate the existence of tension, anxiety, and depressive signs. Beck Anxiety Inventory, Resilience Scale for Adults, Beck Depression Inventory-II, COVID-19 Peritraumatic Distress Index (CPDI), and Impact of Event Scale, additionally served as self-administered questionnaires. At the clinical interview, depressive ($P<0.0003$) and anxiety ($P<0.0001$) signs exhibited significant reductions from the 4- to 12-month monitoring. Our study results regarding the relationship between gender and depression or anxiety are similar to theirs. Based on a logistic regression model, the continued presence of anxiety symptoms at 12 months was correlated with anxiety ($P<0.0001$), arterial hypertension ($P=0.01$), female gender ($P=0.006$), obesity (0.04), and depressive ($P=0.02$) complaints at the 4-month monitoring. Female gender ($P=0.02$) and signs of depression at the 4-month monitoring ($P=0.01$) were correlated with depressive signs following 12 months, as determined by a logistic regression study.

In summary, the results of multiple investigations on the psychiatric sequelae of COVID-19 are challenging to assess due to the high degree of heterogeneity in the selection of the sample, the use of diagnostic instruments, and the subsequent monitoring strategy.

Limitations

The relatively small sample; fulfilling the tight inclusion and exclusion criteria; might have led to missing some differences between groups. Another point to be considered is that the study was done during the third wave of COVID-19 with much milder cases and a lesser rate of seeking medical care in outpatient clinics. Finally, as this was a follow-up study, the dropout risk was higher; therefore, we chose MoCA-B rather than more extensive cognitive tests that would have probably detected other affected cognitive domains, to encourage patients to come again for assessment.

Conclusions

This study showed that COVID-19 illness is related to neuropsychiatric issues in the first few months post-recovery and would need psychiatric care for a better physical and psychological outcome. Impairment of cognitive functions is important sequelae of COVID-19; especially the delayed recall domain. Also, SCID-I showed that 43.2% of our sample (with no previous psychiatric history) was diagnosed with both anxiety and depression at 1-month post-recovery, with the improvement of most cases at 3 months to affect 18.2%, showing that COVID-19 cases are prone to suffer from anxiety and depression disorders and would need proper psychiatric care. In addition to this, a significant number of COVID-19 patients suffered from sleep disturbance (59.1%), fatigue, and inability to properly concentrate (61.4%) during the post-recovery period and would definitely need psychological support for a better quality of life. The severity of symptoms declined over the 3 months period of the study.

Abbreviations

BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
MCI	Mild Cognitive Impairment
CNS	Central Nervous System
GBS	Guillain-Barre syndrome
GHQ-12	General Health Questionnaire
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MINI	Mini-International Neuropsychiatric Interview
MMSE	Mini-mental State Examination
MoCA-B	Montreal Cognitive Assessment-Basic
OCD	Obsessive-compulsive disorder
PASC	Post-acute sequelae of COVID-19
PTSD	Post-traumatic stress disorder
RT-PCR	Positive real-time reverse-transcriptase polymerase chain reaction
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SCID-I	Structured Clinical Interview for DSM-IV, axis I
TMAS	Taylor Manifest Anxiety Scale

Acknowledgements
Not applicable.

Authors' contributions
All authors agreed with the content of the work and gave explicit consent to submit and they obtained consent from the responsible institute where the work has been carried out, before the work is submitted. All authors made substantial contribution to the conception and design of the work. A.A carried out the clinical part while S.E and A.L revised it critically. S.E drafted the version to be published, wrote the main text while A.A prepared all figures and tables. The manuscript has been read and approved by all of the authors, and each author believes that the manuscript represents honest work.

Funding
This research did not receive any specific grant from funding agencies in the. public, commercial, or not-for-profit sectors.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All procedures involving human subjects/patients were approved by the research ethics committee, Faculty of Medicine, Cairo University, number MS-40-2022, Date: 16 March 2022.
All participants provided their written informed consent to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 13 October 2024 Accepted: 13 January 2025
Published online: 22 January 2025

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