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RESEARCH

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Cognitive assessment of a sample of Egyptian patients with amyotrophic lateral sclerosis

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Abstract

Background Cognitive and behavioral changes in ALS are featured as an integral part of the disease. A noticeable proportion of ALS patients present with a full-blown picture of frontotemporal dementia, which is considered the most common form of cognitive impairment in ALS.

Results A total of 30 ALS cases and 30 sex, age and education matched healthy controls were enrolled; their sociodemographic data were statistically insignificant as regards (age, sex, education). Regarding cognitive and behavioral assessment using the ECAS-EG, both ECAS mean total score and subdomains mean scores were significantly lower in ALS patients compared to controls (p-value < 0.001), with statistically significant relation between ALS clinical staging and ECAS total scores (p-value < 0.001). Furthermore, it was found that mean scores of nearly all ECAS domains are lower in early-onset group with longer duration of illness than late onset with short duration of illness but with a non-statistically significant difference.

Conclusion ALS causes significant cognitive impairment, with relation between functional status and clinical staging of the disease with the severity of cognitive and behavioral dysfunctions and although early-onset cases had lower score on ECAS compared to those with late onset, but it was non-significant.

Keywords Cognitive, ALS-FTD, Early onset, Late onset, ECAS

Background

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder, which was first described as a pure motor neuron disease but is now recognized as a multisystem neurodegenerative, characterized by heterogeneity in phenotype, pathological substrate and genetic predisposition with its core feature being degeneration of both upper motor neuron and lower motor neurons [1].

It was found that 30–50% of ALS patients may suffer from cognitive and behavioral decline along the course of their illness, the most reported cognitive functions to be affected are executive functions with deficit in letter fluency, otherwise, the most reported behavioral change is apathy, especially initiation apathy, also reported irritability, inflexibility, restlessness, and disinhibition [2].

On the other hand, some recent studies demonstrated that there may be a relation between cognitive changes and disease progression, which assessed by ALS Functional Rating Scale (ALSFRS-R) and staging of disease according to involvement of upper limbs, lower limbs, respiratory and nutritional aspects [3].

Moreover, a new term known as ALS with cognitive impairment (ALSci) has been announced referring to the subpopulation that has distinct cognitive impairment which does not meet the criteria for frontotemporal

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dementia, in addition to another term known as ALS with behavioral impairment (ALSbi) referring to the subpopulation that predominantly exhibit behavioral changes which does not fulfill criteria for frontotemporal dementia. Therefore, determining the cognitive and behavioral status of ALS patients is important, especially that severe forms have a worse prognosis than the previously described terms [4].

Many studies showed the significance of early identification of cognitive and behavioral impairment in ALS patient as they are associated with worse quality of life with an increase in the care giver burden and a decrease in the survival rates [5].

In this study, we aimed to compare cognitive functions between ALS patients and healthy controls, as well as comparing cognitive functions between early onset with longer duration of illness and late onset with short duration of illness ALS patients.

Methods

Ethical committee: After receiving an ethical approval from Ain Shams University Ethical committee (FWA 000017585), this case control study was performed at the Neuromuscular Unit at Neurology Department, Ain shams University hospitals from September 2020 till April 2021

Patient's requirements: 30 patients were enrolled, with 30 healthy controls by convenient sampling, matched as regards age, sex and education, after a formal written consent and were subjected to a full neurological assessment including history and examination.

Sample size was calculated by PASS 11.0, a sample size of 30 ALS patients achieves 81% power to detect difference of − 0.47 between the null and the alternative hypothesis correlation using a two sided hypothesis test with a significance level of 0.01.

Inclusion and exclusion criteria: The cases enrolled were those with clinical presentation fulfilling criteria of ALS (Revised El Escorial diagnostic criteria for Amyotrophic lateral sclerosis) [6], by clinical history and examination, with age ranging from 10 to 60 years, both gender and could read and write, and excluded patients with either motor neuron disease mimics, or diagnosed with dementia or other disorders causing cognitive dysfunction (by Stanford Binet Intelligence scale for adults) [7], illiterate patients and those with psychiatric disorders (patients with cutoff point > 7 in general health questionnaire) [8] and patients on medications that may affect cognitive functions.

Assessment tools: Cases were assessed for clinical staging by King's clinical staging scale for anatomical staging of ALS [9] and severity by Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) Arabic validated version, a 10-item inventory designed for use in therapeutic trials for amyotrophic lateral sclerosis (ALS). Each item is evaluated on a scale from 0 to 4 by either the patient or caregiver, with a total possible score of 40 points. The ALSFRS measures patients' self-sufficiency in the areas of feeding, grooming, mobility, and communication [10], then cases and controls cognitive functions were assessed by the Edinburg cognitive and behavioral ALS screen (ECAS-EG) Egyptian version, the optimal ALS cutoff value was determined to be ≤ 104, yielding a sensitivity of 79% and a specificity of 64.4%. According to the ECAS, 39 patients scored below 104, indicating cognitive impairment. For ALS-specific scores, the best cutoff value was ≤ 72, with a sensitivity of 72.6% and a specificity of 68.9% [11].

Statistical analysis: The collected data were analyzed using Statistical package for Social Science (SPSS) version 20.

As regards descriptive statistics, mean, standard deviation (± SD) and range for parametric numerical data were used, while median and interquartile range (IQR) were used for non-parametric numerical data. Moreover, frequency and percentage were used for non-numerical data.

As for analytical statistics, Student's T test was used to assess the statistical significance of the difference between two study group means, repeated measure ANOVA test was used to assess the statistical significance of the difference between repeated measurements of the same variable, Chi-square test was used to examine the relationship between two qualitative variables, Pearson correlation test was used to examine the linear dependence between two quantitative variables, with p-value < 0.05 was considered significant.

Results

In this study, 30 ALS patients were enrolled, after exclusion of patients with IQ less than 90 and GHQ more than 7, all of which met the Revised El Escorial diagnostic criteria for amyotrophic lateral sclerosis [6] and were compared to 30 healthy matched controls.

As regards the sociodemographic data and clinical history of ALS patients (age of onset and duration of illness), both ALS and control groups were matched showing no statistical difference (Table 1).

Regarding the clinical staging (according to King's staging system) and their functional status mean score (according to ALS-FRS R) (Table 2).

On performing ECAS, 13 ALS patients (43.33%) showed low score on performing both language and verbal fluency subdomains, on ECAS executive functions subdomains, 6 ALS patients (20%) showed impaired

Table 1 Sociodemographic data of both ALS and control groups and clinical history of ALS patients

		Group		T-test	
		ALS	Control	*t*	*p*-value
Age	Range	17–60	18–60	− 0.318	0.752
	Mean ± SD	40.000 ± 13.091	41.033 ± 12.059		

Chi-square		*N*	%	*N*	%	X^2	*p*-value
Age group	< 45 years	15	50.00	18	60.00	0.606	0.436
	> 45 years	15	50.00	12	40.00		
Sex	Female	5	16.67	5	16.67	0.000	1.000
	Male	25	83.33	25	83.33		
Address	Urban	24	80.00	26	86.67	0.480	0.488
	Rural	6	20.00	4	13.33		
Education	Non-University	19	63.33	20	66.67	0.073	0.787
	University	11	36.67	10	33.33		
Habits	No	19	63.33	17	56.67	4.302	0.116
	Smoker	8	26.67	13	43.33		
	Ex-smoker	3	10.00	0	0.00		
Age of onset			Range			16–58	
			Mean ± SD			36.800 ± 12.840	
Duration			Range			0.5–8	
			Mean ± SD			2.243 ± 1.629	

SD standard deviation, *ALS* amyotrophic lateral sclerosis

Table 2 Clinical staging and functional status of ALS patients

ALS-FRS R		Range	12–48
		Mean ± SD	33.833 ± 8.887
		N	%
Stage of disease	Stage 1	3	10.00
	Stage 2	13	43.33
	Stage 3	12	40.00
	Stage 4	2	6.67

ALS-FRS R ALS Functional Rating Scale-Revised, *SD* standard deviation

performance, so on ALS specific scale 33% of patients showed significant impairment (Table 3).

As regards ECAS-nonspecific score, 1 ALS patient (3.33%) showed lower score for visuospatial and 3 ALS patients (10%) showed lower score on memory subdomain (Table 3).

As regards ECAS total score, 7 ALS patients showed impaired score, which means that 23.33% of the ALS patients in the study showing cognitive impairment (Table 3).

Regarding psychiatric morbidities screened using general health questionnaire (GHQ) (Arabic version), the mean score was significantly higher in ALS patients than the control group but still less than 7 (cutoff point of GHQ) with a p-value < 0.001, which means that ALS

Table 3 Using ECAS for cognitive and behavioral assessment of ALS patients

	Normal		Abnormal	
	N	%	*N*	%
ECAS language	17	56.67	13	43.33
ECAS fluency	17	56.67	13	43.33
ECAS executive	24	80.00	6	20.00
ALS-specific	20	66.67	10	33.33
ECAS memory	27	90.00	3	10.00
ECAS visuospatial	29	96.67	1	3.33
ALS-non-specific	28	93.33	2	6.67
ECAS	23	76.67	7	23.33

ECAS Edinburgh Cognitive and Behavioral ALS screen, *ALS* amyotrophic lateral sclerosis

patients has a greater possibility of psychological distress (Table 4).

Regarding cognitive and behavioral assessment using the Edinburg cognitive and behavioral ALS screen (ECAS) (Arabic version), both ECAS mean total score and subdomains mean scores were significantly lower in ALS patients compared to controls, except language naming, memory, delayed recognition and visuospatial total and subdomains mean scores, that showed non-significant difference between both groups (Table 5).

There was a significant relation between the clinical stages of ALS, ECAS total score and ECAS subdomains (Supplementary material Table 1).

These results showed that performance in ECAS is significantly impaired with advanced clinical staging of illness, as clinical stage 4 showed the most affected performance (Supplementary material Table 1).

There were significant positive correlations between ALS-FRS R and almost all ECAS subdomains except ECAS language comprehension, ECAS fluency letter seen, ECAS memory delayed recognition and ECAS visuospatial subdomains, which mean that high functional status is associated with significantly better performance in ECAS (Supplementary material Table 2).

There was a significant negative correlation between ECAS memory immediate recall and GHQ mean score with a p-value = 0.052, which means that patients with a high mean score on GHQ with high probability of psychological distress are more impairment on ECAS memory subdomain (Supplementary material Table 3).

Also, there was a significant positive correlation between ECAS behavioral subdomain and GHQ mean score with a p-value = 0.001, which means that higher mean score on GHQ with high probability of psychological distress associated with more behavioral changes (Supplementary material Table 3).

ECAS memory delayed recognition mean score was significantly lower in patients with illness onset < 45 years than those > 45 years with a p-value = 0.046, also it was found that mean scores of nearly all other ECAS domains are lower in early-onset group with longer duration than late onset with short duration with a non-statistically significant difference except language spelling, executive reverse digit span, memory immediate recall, memory delayed recall and visuospatial dot counting, which means that patient with early-onset ALS have more cognitive impairment than late-onset ALS patients (Table 6).

There was a non-significant difference between both group regarding ALS-FRS R and GHQ mean scores (Table 6).

Table 4 Comparison of general health questionnaire mean score in both ALS and control groups

GHQ score	Group		T-test	
	ALS	Control	*t*	*p*-value
Range	2–6	1–4	4.230	< 0.001*
Mean ± SD	3.633 ± 1.217	2.500 ± 0.820		

P-value > 0.05: significant, *SD* standard deviation, *GHQ* General Health Questionnaire, *ALS* amyotrophic lateral sclerosis

Discussion

In this study, cognitive and behavioral impairment were investigated in 30 ALS patients compared to 30 healthy controls, aiming to increase our understanding and awareness of these non-motoric features of ALS which affect the quality of life and magnifies the patient's disabilities and aiming to add cognitive and behavioral changes into ALS diagnostic criteria and to be included in future staging systems.

In this study, it was found that cognitive functions in form of language, verbal fluency, executive functions, and memory are affected in ALS patients in comparison to healthy controls, using ECAS with p value < 0.001 of ECAS total score (ALS specific and nonspecific). These findings were similar to a study involving 84 ALS patients and 84 matched controls in China [12], also these findings agree to a study in the Netherlands of 428 ALS patients with lower scores for language, executive functions, verbal fluency and memory on performing ECAS [13], as well as another study in UK involving 139 ALS patients, of which 55% of them had lower scores than the cutoff points in executive functions and memory [14].

Furthermore this study showed that on performing ECAS, 43.3% of the patients showed language deficit, 43.3% had impaired verbal fluency, 20% had executive dysfunction, 3.33% of ALS patients showed impaired visuospatial functions and 10% of ALS patients showed defective memory, these findings were in accordance with findings in a study in Ireland [15].

Also ALS patients in this study showed behavioral changes in form of apathy (46.6%) and emotional lability (26.7%), these findings were matching with a cross-sectional population-based study of 317 ALS patients and 66 healthy controls [16], also these findings were in accordance with a study in USA [17].

Moreover, this study showed that patients with ALS had a greater possibility of psychological distress more than healthy controls, using General Health Questionnaire (GHQ), but still less than 7 (cutoff point of GHQ) with p value < 0.001, those findings were matching to study conducted by Larsson, which involved 36 ALS patients, most of them scored above the cutoff score in the hospital anxiety and depression scale with p value = 0.002 [18].

Table 5 Comparison between ECAS mean total score and subdomains mean scores in both ALS and control groups

ECAS		Group		T-test	
		ALS	Control	*t*	*p*-value
Language naming	Range	5–8	6–8	− 1.588	0.118
	Mean ± SD	7.667 ± 0.844	7.933 ± 0.365		
Language comprehension	Range	5–8	7–8	− 3.043	0.004*
	Mean ± SD	7.500 ± 0.820	7.967 ± 0.183		
Language spelling	Range	4–12	12–12	− 3.330	0.002*
	Mean ± SD	10.767 ± 2.029	12.000 ± 0.000		
Language total score	Range	15–28	25–28	− 3.553	0.001*
	Mean ± SD	25.933 ± 2.982	27.900 ± 0.548		
Fluency letter seen	Range	2–12	8–12	− 7.163	< 0.001*
	Mean ± SD	7.667 ± 2.916	11.667 ± 0.922		
Fluency letter kaf	Range	2–12	8–12	− 7.419	< 0.001*
	Mean ± SD	7.733 ± 2.753	11.667 ± 0.922		
Fluency total score	Range	4–24	16–24	− 7.415	< 0.001*
	Mean ± SD	15.400 ± 5.562	23.333 ± 1.845		
Executive reverse digit span	Range	4–12	6–11	− 3.335	0.001*
	Mean ± SD	7.867 ± 1.795	9.267 ± 1.437		
Executive alternation	Range	2–12	12–12	− 4.934	< 0.001*
	Mean ± SD	9.533 ± 2.738	12.000 ± 0.000		
Executive sentence completion	Range	2–12	12–12	− 3.248	0.002*
	Mean ± SD	10.500 ± 2.529	12.000 ± 0.000		
Executive social cognition	Range	8–12	12–12	− 1.980	0.052*
	Mean ± SD	11.667 ± 0.922	12.000 ± 0.000		
Executive total score	Range	22–48	42–47	− 4.679	< 0.001*
	Mean ± SD	39.567 ± 6.516	45.267 ± 1.437		
ALS-specific	Range	41–98	88–99	− 6.364	< 0.001*
	Mean ± SD	80.900 ± 13.166	96.500 ± 2.636		
Memory immediate recall	Range	4–10	8–10	− 1.994	0.051*
	Mean ± SD	8.700 ± 1.685	9.367 ± 0.718		
Memory delayed recall	Range	2–10	8–10	− 2.829	0.006*
	Mean ± SD	8.000 ± 2.244	9.233 ± 0.817		
Memory delayed recognition	Range	0–4	3–4	− 1.748	0.086
	Mean ± SD	3.667 ± 0.922	3.967 ± 0.183		
Memory total score	Range	6–24	20–24	− 2.605	0.012*
	Mean ± SD	20.367 ± 4.406	22.567 ± 1.406		
Visuospatial dot counting	Range	4–4	4–4	–	–
	Mean ± SD	4.000 ± 0.000	4.000 ± 0.000		
Visuospatial cube counting	Range	2–4	4–4	− 1.361	0.179
	Mean ± SD	3.900 ± 0.403	4.000 ± 0.000		
Visuospatial num location	Range	3–4	4–4	− 1.795	0.078
	Mean ± SD	3.900 ± 0.305	4.000 ± 0.000		
Visuospatial total score	Range	9–12	12–12	− 1.795	0.078
	Mean ± SD	11.800 ± 0.610	12.000 ± 0.000		
ALS-non-specific	Range	15–36	32–36	− 2.593	0.012*
	Mean ± SD	32.167 ± 4.871	34.567 ± 1.406		
ECAS total score	Range	56–134	120–135	− 5.629	< 0.001*
	Mean ± SD	113.067 ± 17.166	131.067 ± 3.473		
Behavioral	Range	0–3	–	–	–
	Mean ± SD	1.167 ± 0.950	–		

P-value > 0.05: significant, *SD* standard deviation, *ALS* amyotrophic lateral sclerosis, *ECAS* Edinburgh Cognitive and Behavioral ALS Screen

Table 6 Comparison of ALS-FRS R, GHQ and ECAS mean scores between early and late-onset ALS

	Age group		T-test	
	< 45 years	> 45 years		
	Mean ± SD	Mean ± SD	*t*	*p*-value
ALS-FRS R	35.133 ± 7.791	32.533 ± 9.963	0.796	0.433
GHQ score	3.733 ± 1.100	3.533 ± 1.356	0.444	0.661
Language naming	7.600 ± 0.910	7.733 ± 0.799	− 0.426	0.673
Language comprehension	7.267 ± 0.961	7.733 ± 0.594	− 1.600	0.121
Language spelling	10.800 ± 2.242	10.733 ± 1.870	0.088	0.930
Language total score	25.667 ± 3.374	26.200 ± 2.624	− 0.483	0.633
Fluency letter seen	7.467 ± 2.560	7.867 ± 3.314	− 0.370	0.714
Fluency letter k	7.467 ± 2.532	8.000 ± 3.024	− 0.524	0.605
Fluency total score	14.933 ± 4.935	15.867 ± 6.266	− 0.453	0.654
Executive reverse digit span	8.067 ± 1.534	7.667 ± 2.059	0.603	0.551
Executive alternation	9.267 ± 3.011	9.800 ± 2.513	− 0.527	0.603
Executive sentence completion	10.333 ± 2.968	10.667 ± 2.093	− 0.355	0.725
Executive social cognition	11.600 ± 1.121	11.733 ± 0.704	− 0.390	0.699
Executive total score	39.267 ± 7.025	39.867 ± 6.198	− 0.248	0.806
ALS-specific	79.867 ± 13.169	81.933 ± 13.541	− 0.424	0.675
Memory immediate recall	8.733 ± 1.870	8.667 ± 1.543	0.107	0.916
Memory delayed recall	8.000 ± 2.478	8.000 ± 2.070	0.000	1.000
Memory delayed recognition	3.333 ± 1.234	4.000 ± 0.000	− 2.092	0.046*
ECAS memory total score	20.067 ± 5.284	20.667 ± 3.478	− 0.367	0.716
Visuospatial dot counting	4.000 ± 0.000	4.000 ± 0.000	–	–
Visuospatial cube counting	3.800 ± 0.561	4.000 ± 0.000	− 1.382	0.178
Visuospatial num location	3.800 ± 0.414	4.000 ± 0.000	− 1.871	0.072
Visuospatial total score	11.600 ± 0.828	12.000 ± 0.000	− 1.871	0.072
ALS-non-specific	31.667 ± 6.043	32.667 ± 3.478	− 0.555	0.583
ECAS total score	111.533 ± 18.400	114.600 ± 16.335	− 0.483	0.633
ECAS behavioral	1.467 ± 0.915	0.867 ± 0.915	1.795	0.083

p-value > 0.05: significant, *SD* standard deviation, *GHQ* General Health Questionnaire, *ALS* amyotrophic lateral sclerosis, *ECAS* Edinburgh Cognitive and Behavioral ALS Screen, *ALS-FRS-R* ALS Functional Rating Scale-Revised

In this study, there was a significant positive correlation between disease severity and cognitive and behavioral deterioration in ALS patients, as those with deteriorated functional state had more cognitive and behavioral impairment in ECAS total score and most of its subdomains with p value 0.004 for ECAS total score, these findings were similar to a study in Italy by Bersano et al. [19].

Also, there was a significant relation between clinical staging of ALS and cognitive and behavioral dysfunction in almost all ECAS subdomains, as progression of illness (clinical stage 4) was associated with increased cognitive deficit, these findings were matching to a study in England in which ECAS scores were significantly higher in ALS patients with advanced clinical disease staging [3].

Similar results were in another study in Italy, which investigated the association between decline of cognitive functions in ALS patients and clinical staging of the disease [20].

At last, it was found that ALS patients with illness onset < 45 years had lower mean scores of nearly all ECAS subdomains except for memory and visuospatial subdomains, this was against a study performed in Japan that assessed cognitive functions using ACE (Addenbrooke's Cognitive Examination Revised Scores) which showed that ALS patients with older age had lower score on almost all the cognitive subdomains except visuospatial subdomain [20], also was against another study in Japan that assessed cognitive functions using the Montreal Cognitive Scale (MoCA) and Frontal Assessment Battery (FAB) [4], this difference could be due to the difference in the scales used in assessment as well as the difference in the sample size between both studies), but it agreed to a study that assessed the decline of social cognition, executive functions and verbal memory in patient with early disease onset and longer duration [21] so further work is needed to understand if the cognitive and behavioral

symptoms are related to aging process or a core symptom of the illness and it can happen in early-onset ALS.

Limitations of our study

However, the study had few limitations as it did not include patients with severe bulbar symptoms combined with motor disability. It was done in a single center, needs to be done in multiple centers for more generalized results.

Also there was no initial assessment for cognitive function of the study's patients.

Conclusion

This study showed that 23.3% of ALS patients had non-motoric symptoms in form of cognitive and behavioral impairment affecting their quality of life and increasing the burden on their caregiver and stressing on the possibility of adding cognitive and behavioral changes to diagnostic criteria for ALS in the future.

Also, this study showed there is a significant relation between functional status, clinical staging of the disease and severity of cognitive and behavioral dysfunctions, with a greater possibility of psychological distress.

Meanwhile, this study showed that early-onset ALS patients had lower score on cognitive and behavioral scales compared to those with late onset.

Abbreviations

ALS	Amyotrophic lateral sclerosis
ALS-FTD	Amyotrophic lateral sclerosis-frontotemporal dementia
ALS-FRS-R	Amyotrophic Lateral Sclerosis-Functional Rating Scale-Revised
ALSci	Amyotrophic lateral sclerosis cognitive impairment
ALSbi	Amyotrophic lateral sclerosis behavioral impairment
GHQ	General Health Questionnaire
IQ	Intelligence quotient
ECAS-EG	Edinburgh Cognitive and Behavioral ALS Screen-Egyptian version
PC	Personal computer
SPSS	Statistical Package for Social Science
SD	Standard deviation
IQR	Interquartile range
ANOVA	Analysis of variance
FH	Family history
HTN	Hypertension
DM	Diabetes mellitus
PH	Past medical history
UL	Upper limb
LL	Lower limb
ACE	Addenbrooke's Cognitive Examination
MoCA	The Montreal Cognitive Assessment
FAB	Frontal Assessment Battery

Supplementary Information

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Additional file 1.

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Author contributions

All authors have agreed to conditions noted on the Authorship Agreement Form and have read and approved the final manuscript version submitted. NT: sample collection, drafting the manuscript and analysis of data. HE: contribution in writing and reviewing the manuscript. MA: design and conceptualization of the study, reviewing the manuscript. TR: conception of the work, design, and conceptualization of the study, reviewing the manuscript.

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Availability of data and materials

The corresponding author takes full responsibility for the data, has full access to all of the data; and has the right to publish any and all data separate and apart.

Declarations

Ethics approval and consent to participate

All procedures performed in the study were per the ethical standards of the faculty of medicine, Ain Shams University research and ethical committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. We obtained approval from the Faculty of Medicine, Ain Shams University Research Ethics Committee (FMASU REC) under Federal Wide Association No. (FWA 000017585) in 21/9/ 2020.

Consent to participate

Written informed consent was obtained from participants for participation.

Consent for publication

Not applicable.

Competing interests

No conflict of interest to be declared.

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