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Adult attention-deficit hyperactivity disorder among patients with substance use disorders

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is a childhood neurodevelopmental disorder that persists into adulthood. ADHD is a well-known risk factor for substance use disorder (SUD). However, the actual contribution of comorbidity is largely unknown. The current study investigated the prevalence of ADHD in a sample of abstinent patients compared to healthy controls.

Compared to 51 healthy controls, 51 patients seeking medical treatment for SUD were abstinent from any substance for at least 1 month, interviewed by the use of the ICD-10 symptom checklist, the Social Classification Scale, the Addiction Severity Index, Conners adult ADHD Rating Scales Self-Report (CAARS-S:L), and the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL).

Results: Using CAARS-S:L, the ADHD index showed that 9 subjects (17.6%) were diagnosed with adult ADHD. Using K-SADS-PL, 8 of the participants (15.7%) were found to have an adult ADHD diagnosis. Lower scores of the ADHD index are related to increased patients' age, while increased scores of the ADHD index are related to more alcohol-related problems of the patients. The strongest predicting factors of increased ADHD index were drug problems and legal status.

Conclusions: The current study provides evidence of an increased diagnosis of adult ADHD in patients with substance use disorder, regardless of the type of substance abuse.

Keywords: Adult, ADHD, Substance use, Hyperactivity, Addiction

Background

Attention deficit/hyperactivity disorder (ADHD) is an impairing condition affecting 3–7% of children and 3–5% of adults [1]. It was found to be a major risk factor for the development of substance use disorders (SUDs) and is associated with greater addiction severity as well as worse substance use outcomes compared with substance users without ADHD [1–3]. ADHD is a difficult diagnosis and is particularly complicated when associated with SUD. There is no objective test for this diagnosis, which is usually made according to the diagnostic criteria, through clinical interviews and self-reports [4].

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Although ADHD diagnosis in adults is based on child-specific symptoms, it has been suggested that more specific criteria should be developed for adults. For example, hyperactivity symptoms in adults may rather be expressed through restlessness, constant activity, and trend to orient themselves toward very active jobs, leading to tension with environment. Furthermore, impulsivity in adulthood may have more serious consequences than during childhood, such as ending relationships, quitting jobs, overreacting to frustrations, or committing more driving violations. Most inattention symptoms include procrastination, difficulty making decisions, poor time management, and difficulties in organizing activities [4, 5].

Considering the high rate of ADHD comorbidity among SUD patients, it is crucial to promote and integrate an active and systematic diagnostic approach to this

disorder in specialized addiction treatment settings [4]. It is worth mentioning that untreated ADHD leads to significant consequences and may impair a patient's ability to benefit from SUD treatment [2]. A meta-analysis that included 14 studies of the prevalence of adult ADHD in the SUD population with a sample size of 2635 arrived at a prevalence rate of 21% among adults [6]. Moreover, a multicenter study across ten countries in Europe with a total of 3558 patients with SUD reported a prevalence ranging from 5.4 to 31.3% [7]. Therefore, the issue of studying the prevalence of adult ADHD in the SUD population in Egypt was of substantial importance.

We assumed that SUD is associated with increased rates of ADHD. Consequently, the current study investigated the prevalence of ADHD in a sample of abstinent patients compared to healthy controls. The relationship between ADHD symptoms and addiction severity was assessed as well.

Methods

Participants

This study is a cross-sectional descriptive study. The participants were recruited from the outpatient clinic and the inpatient department of the Institute of Psychiatry at Ain Shams University. Sample selection was carried out over 18 months. Fifty-one patients seeking medical treatment for SUD were selected by systematic random selection. They were male patients with an age range of 18–35 years old. The patients were eligible for the study if they were abstinent from any substance for at least 1 month prior to the interview, which was confirmed by urine toxicological screening. Ineligibility includes the presence of any medical or neuropsychiatric comorbidity and illiteracy. They were compared to 51 healthy controls recruited from hospital workers and their relatives. The controls were eligible for the study if they have no history of substance abuse or psychiatric morbidity which was confirmed by the ICD 10 symptom checklist [8]. Healthy controls were excluded from the study if they were illiterate or have associated medical conditions to avoid any confounding factor that might affect attention or behavior. The ethical committee of the Faculty of Medicine, Ain Shams University, approved the study, and written consent was obtained from all participants.

Measures

1) A detailed history taking was performed using the neuropsychiatry sheet of Ain-Shams University hospitals. Abstinence from substances was further verified by urine toxicological screening.
2) The ICD-10 symptom checklist to confirm the diagnosis of SUD and exclude psychiatric comorbidities [8].
3) The Social Classification Scale: it includes 7 domains: education and culture, occupation, family, family possessions, economic, home sanitation, and health care with a total score of 84. Higher scores indicate better socioeconomic status [9].
4) The Addiction Severity Index [10]: it is an assessment instrument that gathers information about 7 domains in the patients' lives which include medical, employment, support, drug and alcohol use, legal, family history, family/social relationships, and psychiatric problem.
5) The Kiddie schedule for affective disorders and schizophrenia present and Lifetime Version (K-SADS-PL) to determine the presence of a past diagnosis of ADHD in childhood [11].
6) Conners Adult ADHD rating scale self-report (CAARS-S:L), long version [12]: It is a self-report version composed of 66 questions. An Arabic version was used after forward and backward translation and validation. It gives ideas about 8 domains: inattention/memory problems, hyperactivity/restlessness, impulsivity/emotional lability, problems with self-concept, DSM IV inattentive symptoms, DSM IV hyperactive-impulsive symptoms, total DSM IV symptoms, and ADHD index. The results are categorized according to T score into 9 groups: very much above average (A), much above average (B), above average (C), slightly above average (D), average (E), slightly below average (D), average (E), below average (F), much below average (H), and very much below average (I).

Operational definition

The Conners adult scale categorizes the patients into 9 distinct categories according to their T score. To facilitate statistical analysis and due to the relatively small number of the sample, the authors merged some groups, which have the same clinical significance together. The final classes were class 1 with the highest affinity for diagnosis of adult ADHD (T score > 66) corresponding to very much above average and above average categories, class 2 with subclinical symptoms (T score: 56–65) corresponding to above average and slightly above average categories, and class 3 with average or below average ADHD symptoms (T score < 55) corresponding to remaining classes.

Statistical analysis

IBM SPSS statistics package (V. 22.0, IBM Corp., USA, 2013) was used for data analysis. Data were expressed as

median and percentiles for quantitative non-parametric measures and as numbers and percentages for categorized data. The following tests were done: Comparison between two independent groups for non-parametric data using the Mann–Whitney test, comparison between more than 2 patient groups for non-parametric data using the Kruskal–Wallis test and chi-square test to study the association between every 2 variables, or comparison between 2 independent groups as regards the categorized data and logistic multiple regression analysis was used to search for a panel (independent parameters) that can predict the target parameter (dependent variable). The level of significance was $p < 0.05$.

Results

Patients' characteristics

The mean age of the patient was 27.47 ± 5.27. 54.9% of patients were from high social class and 60.78% were college graduates or college students. They were compared to 51 healthy volunteers recruited with a mean age of 29.1 + 3.712 (years), and 50.98% of them were from high social class. Consequently, patients and controls were matched in age and social class ($p = 0.07$ and $p = 0.9$, respectively) (Table 1). DSM IV inattentive symptoms, hyperactive-impulsive symptoms, total symptoms, and ADHD index scores were highly and significantly higher among patients with SUD compared to controls ($p < 0.001$) (Table 1).

Using CAARS-S:L showed that patients with a potential diagnosis of DSM IV inattentive symptoms were 23 (45.1%), potential diagnosis of DSM IV hyperactive-impulsive symptoms were 14 (27.4%), potential diagnosis of mixed symptoms of ADHD were 24 (47.06%), and finally with significant ADHD index were 9 (17.65%). Further clarification of past diagnosis of ADHD was done using K-SADS-PL, which showed that 8 (15.69%) (5 patients had inattentive (9.80%), 2 patients had hyperactive-impulsive type (3.92%), and a patient had combined type (1.96%)) of the participants were found to have ADHD diagnosis since their childhood. There was no statistically significant relationship between the type of substance abused and the CAARS results and KSAD results (Table 2).

Comparing ADHD total CAARS classes

There were significant differences between ADHD classes regarding patients' age ($p = 0.048$) and alcohol-related problems ($p = 0.026$). Post hoc analysis showed that patients with the lower scores of CAARS-ADHD-DSM IV total symptoms index (class III) were significantly older ($p = 0.017$) and had lower alcohol problems ($p = 0.008$) compared to class I scores (Table 3). Furthermore, CAARS-ADHD index was significantly related to drug-related problems of ASI ($P = 0.018$), and post hoc analysis confirmed that patients with the least CAARS-ADHD-total symptoms have the least drug-related problems according to ASI (Table 4).

On multivariate regression analysis, the most powerful factors from ASI items that predicted increased CAARs-ADHD index were drug problems ($P = 0.026$) followed by legal status ($P = 0.06$).

Discussion

The current study used strict criteria for abstinence, which required at least 30 days of abstinence, to avoid confounding symptoms of intoxication or withdrawal.

Table 1 Demographic characteristics and ADHD scores in patients and controls

Sociodemographic data	SUD patients ($n = 51$)	Controls ($n = 51$)	Statistical value	*P* value
Age (years) (mean + SD)	27.47 ± 5.27	29.1 ± 3.712	$T = 1.8$	$P = 0.07$
Social class				
High	28 (54.9%)	26 (50.98%)	Chi = 0.4	$P = 0.9$
Middle	11 (21.56%)	13 (25.4%)		
Low	4 (7.84%)	5 (9.8%)		
Very low	8 (15.58)	7 (13.72%)		
ADHD domain according to CAARS-S:L (mean + SD)				
DSM-IV Inattentive Symptoms	77.61 ± 8.09	48.9 ± 7.76	$T = 18.2$	$P < 0.001$
DSM-IV Hyperactive-Impulsive symptoms	72.43 ± 7.02	46.3 + 6.81	$T = 19.08$	$P < 0.001$
DSM-IV ADHD Symptoms, total	76.54 ± 7.54	46.7 ± 7.05	$T = 20.6$	$P < 0.001$
ADHD Index	70.56 ± 3.68	46.5 ± 5.58	$T = 32.1$	$P < 0.001$

CAARS Conner's adult rating scale, *ADHD* Attention-deficit hyperactivity disorder, *N* Number, *SD* Standard deviation

Table 2 Type of substance abused in correlation to CAARS

CAARS results		Type of substance abused				Chi-square test	
		Hash (12)	Heroin	Multiple substance	Tramadol	χ^2	*P*-value
DSM-IV Inattentive Symptoms	Class 1	1 (4.3%)	5 (21.7%)	7 (30.43%)	10 (43.5%)	8.579	0.198
	Class 2	1 (12.5%)	3 (37.5%)	4 (50.0%)	0 (0.0%)		
	Class 3	1 (5.0%)	9 (45.0%)	3 (15.0%)	7 (35.0%)		
DSM-IV-Hyperactive-Impulsive Symptoms	Class 1	0 (0.0%)	3 (20.0%)	6 (40.0%)	6 (40.0%)	4.404	0.622
	Class 2	1(11.1%)	4 (44.4%)	2 (22.22%)	2 (22.2%)		
	Class 3	2 (7.4%)	10 (37.0%)	6 (22.22%)	9 (33.3%)		
DSM-IV ADHD Symptoms Total	Class 1	0 (0%)	5 (20.83%)	9 (37.5%)	10 (41.67%)	10.905	0.091
	Class 2	2 (20.0%)	5 (50.0%)	2 (20.0%)	1 (10.0%)		
	Class 3	1 (5.88%)	7 (41.18%)	3 (17.65%)	6 (35.29%)		
ADHD Index	Class 1	0 (0.0%	1 (11.11%)	5 (55.56%)	3 (33.33%)	5.646	0.464
	Class 2	1 (6.25%)	6 (37.5%)	3 (18.75%)	6 (23.08%)		
	Class 3	2 (7.69%)	10 (38.46%)	6 (23.08%)	8 (30.77%)		

Class 1 the highest affinity for diagnosis as adult ADHD (*T*-score > 66), *Class 2* subclinical values of ADHD (*T*-score 56 to 65), *Class 3* no ADHD (*T*-score < 55), *CAARS* The Conners Adult ADHD Rating Scale

Table 3 Comparison of ASI between CAARS-ADHD-DSM-IV total symptoms index classes

Items of ASI	CAARS-ADHD-DSM-IV total symptoms Class 1		CAARS-ADHD-DSM-IV total symptoms Class 2		CAARS-ADHD-DSM-IV total symptoms Class 3		Kruskal–Wallis test	
	N = 24		*N* = 10		*N* = 17			
	Mean	SD	Mean	SD	Mean	SD	H	P
Age of onset	16.583	4.7996	16	3.8586	18	3.2016	2.504	0.286
Age	26	5.4133	26.7	4.8774	30	4.5689	6.083	0.048*
Med-Status	2.542	1.9332	2.5	1.9579	2.118	2.3152	0.947	0.623
Empl-Supp-Status	4.708	1.6545	4.6	2.1705	4.765	1.9852	0.047	0.977
Delirium Tremens	0	0	0	0	0	0	0	1
Overdose	2.75	4.3961	0.5	0.8498	3.471	5.2929	4.974	0.083
Ttt-sud	2.75	3.1519	5.4	6.4153	3.882	3.5511	1.545	0.462
Drug detox	1.167	2.4436	1.2	3.1198	1.882	3.039	1.017	0.601
Alcohol problems	2.292	0.7506	2.1	0.8756	1.706	0.686	7.261	0.026*
Drug problems	7.917	0.9286	7.5	1.1785	7.471	1.4194	1.219	0.544
Legal status	2.25	3.1519	1.3	1.9465	1.294	2.1727	0.499	0.779
Fam-Soc-Relation	5.625	1.6101	5.9	1.3703	5.059	1.8865	1.352	0.509
Post hoc tests								
Parameters	Class I vs Class II		Class I vs Class III		Class II vs class III			
Age	0.726		0.017		0.089			
Alcohol problems	0.66		0.008		0.103			

CAARS Conners adult rating scale, *ASI* Addiction Severity Index, *Class 1* highest affinity for the diagnosis of adult ADHD (*T* score > 66), *Class 2* with subclinical symptoms (*T* score: 56–65), *Class 3* with average or below average ADHD symptoms (*T* score < 55)

*p value <0.005

On the other hand, other studies required 4 days of abstinence prior to the interview [13]. Since the diagnosis of adult ADHD depends on the presence of significant clinical symptoms in childhood, the researchers used KSAD-PL to investigate this part of patients' lives and to ensure that the current symptoms of ADHD are not secondary to intake of drugs. It is noteworthy to note that none of the potential cases of ADHD received medication to treat ADHD during their childhood period. The current study showed that the number of potential ADHD cases

Table 4 Comparison of ASI values in CAARS-ADHD index classes

Items of ASI	CAARS-ADHD index Class 1 (*N* = 9)		CAARS-ADHD index Class 2 (*N* = 16)		CAARS-ADHD index Class 3 (*N* = 26)		Kruskal–Wallis test	
	Mean	SD	Mean	SD	Mean	SD	H	P
Age of onset	14.667	3.5355	18.25	4.8374	16.923	3.6543	4.159	0.125
Age	25.556	5.5478	29	5.6804	27.192	4.8416	3.063	0.216
Med-Status	3.222	1.5635	1.813	2.0073	2.462	2.1583	3.7	0.157
Empl-Supp-Status	4.556	1.6667	5.375	1.8212	4.346	1.8535	3.187	0.203
Delirium tremens	0	0	0	0	0	0	0	1
Overdose	1.444	1.1304	2.938	6.7376	2.692	3.172	3.703	0.157
Ttt-sud	2.556	1.6667	3.875	4.6458	3.885	4.4392	0.251	0.882
Drug detox	0.889	1.6915	1.563	2.8277	1.5	3.0496	0.472	0.79
Alcohol problems	2.333	0.5	2.25	0.8563	1.846	0.7845	4.295	0.117
Drug problems	8.111	0.7817	8.188	0.9811	7.231	1.2102	7.95	0.018*
Legal status	3	3.2787	2.313	2.7741	0.962	2.1257	5.058	0.08
Fam-Soc-Relation	5.778	1.9221	5.938	1.6112	5.115	1.5831	2.825	0.244
Post hoc tests								
Parameters	Class I vs Class II		Class I vs Class III		Class II vs class III			
Drug problems	0.842		0.050		0.040			

CAARS Conners adult rating scale, *ASI* Addiction Severity Index, *Class 1* highest affinity for the diagnosis of adult ADHD (*T* score > 66), *Class 2* with subclinical symptoms (*T* score: 56–65), *Class 3* with average or below average ADHD symptoms (*T* score < 55)

*p value <0.005

according to CAAR-S:L nearly doubled that of the controls, consistent with previous studies [14, 15].

Potential adult ADHD among the present sample of patients seeking treatment from SUD was 17.65% according to the CAARS-S:L ADHD index and past history of childhood ADHD was 15.69% according to K-SAD-S PL DSM-IV. The current result is nearly similar to the results of the meta-analysis by *Van* Emmerik-van Oortmerssen et al., which revealed an overall rate of 22% [6]. In this meta-analysis, studies focused on treatment-seeking patients showed ADHD prevalence of 23.3%, while community-based studies reported ADHD prevalence of 44.3% and 15.5%, among adolescent and adult populations, respectively [16]. Interestingly, no significant association was observed between clinical variables such as male gender, age, or the study setting and ADHD prevalence [6, 16].

The comorbidity with ADHD is influenced as well by the type of instruments used, for instance, a study using the Diagnostic Interview for Children and Adolescents (DICA) or the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) for the diagnosis of ADHD showed significantly higher comorbidity rates than studies using the Diagnostic Interview Schedule for Children (DISC), Diagnostic Interview Schedule for DSM-IV (DIS), or other assessment instruments [6].

As much as a diagnostic instrument used affected the prevalence of co-morbidity, the type of substance abuse played a significant role. Lower prevalence of ADHD was associated with cocaine than other substances. The prevalence among methadone maintenance patients was 24.9% [3]. On the other hand, benzodiazepines addicts had a higher rate of probable ADHD reaching 31.7% of screened subjects and more associated with polysubstance abuse [17].

ADHD was over-represented among SUD populations. General population surveys indicate an average prevalence of 3–4% of adult ADHD [18–20], with a pooled estimated prevalence of 2.5% [21], whereas among treatment-seeking adult SUD patients, the prevalence of adult ADHD is substantially higher, ranging from 10 to 46% [6, 22, 23]. Possible explanations for this variability include differences in diagnostic criteria, primary drug of abuse, country-specific factors (treatment offer, service structure), treatment setting (e.g., inpatient versus outpatient treatment), clinical biases, and demographic factors.

In the current study, using CAARS as a diagnostic tool in SUD patients is consistent with a previous study by Dakwar et al. [24]. In that study, every instrument tested demonstrated adequate sensitivity, specificity, and positive and negative predictive values, with the CAARS outperforming the rest overall, particularly when ADHD NOS (not otherwise specified) was labeled as not ADHD

and exhibiting the greatest degree of agreement with the CAADID (Conners' adult ADHD Diagnostic Interview for DSM-IV). Of the 3 instruments, (Wender Utah Rating Scale (WURS), CAARS, and the Adult ADHD Self-Report Scale-Version 1.1 (ASRS-V1.1)), CAARS adheres to *DSM-IV* criteria in the most comprehensive manner, thus explaining its superior agreement with the CAADID as the gold standard of the study. The ASRS-V1.1, also predicated on the DSM-IV, is much shorter at only 6 items, while the WURS draws on the Utah conceptualization of ADHD [24].

Previous studies that used K-SAD-S in diagnosing adult ADHD in SUD patients showed wide variations (8–44.3%), which could be explained by multiple factors especially the short period of abstinence before the interview that could lead to overestimation. Unfortunately, all studies using K-SAD-S were performed for adolescents rather than adult populations [6].

In the current study, patients coming from a high social class were predominant (54.9%). Also, the university graduates or students (60.78%) were highly represented. Other studies reported higher social classes in patients with SUDs with adult ADHD compared to those having SUDs only [25]. Egyptian reports suggest more prevalence of SUDs among urban areas and less educated populations [26]. However in the sample of this study, illiterate patients were excluded, while the overrepresented university students may seek treatment for substance use more commonly due to high awareness.

The previous studies differed in their ways to explain the relationship between the type of substance abuse and ADHD. Some clinicians have suggested that individuals with ADHD may preferentially use cocaine to "self-medicate" their underlying psychiatric disorders [27]. Others attribute this association to increased impulsivity or feelings of social incompetence.

However, the higher rates of current marijuana use among cocaine abusers with adult ADHD suggest that other drugs, and not simply cocaine, are used by adults with ADHD. These findings are consistent with Biederman et al. who found that marijuana dependence, and not cocaine dependence, was the most common substance use disorder among adults seeking treatment for their ADHD symptoms [28]. Marijuana may continue to help individuals with ADHD to "feel calm" despite its ability to produce other negative social and occupational consequences [29]. Other researchers have found ADHD rates to be elevated in alcoholics as well as opiate abusers. A previous study reported that the alcohol use disorder outpatient adult ADHD prevalence rates ranged from 4 to 14% and the drug use disorder outpatient adult ADHD prevalence rates ranged from 10 to 33% [7].

Levin and colleagues suggested it may be that individuals with adult ADHD do not initially choose a specific class of substances, e.g., stimulants, but rather adult ADHD may be a significant contributing factor to substance abuse in general [13]. However, the potential additive contribution of comorbid ADHD to drug-specific dependence in SUD populations is largely unknown. Drug dependence complexity and chronicity are increased in SUD patients with ADHD, particularly for alcohol, amphetamine, and opiates rather than heroin, methadone, and benzodiazepines [30].

The present study is consistent with multiple studies showing that individuals with ADHD diagnosis have an earlier onset of substance abuse than those without ADHD diagnosis, a greater likelihood of having continuous problems if they develop substance dependence, a reduced likelihood of going into remission, and a tendency to take longer to reach remission [31]. The literature investigating the association between ADHD subtypes and SUDs is mixed. Some studies do not report a significant relationship [32], while others have suggested that hyperactive/impulsive symptoms are more associated with the risk for SUDs than inattentive symptoms [33]. Furthermore, a study in adults with ADHD reported that the combined subtype had a higher incidence of lifetime SUDs than the inattentive subtype, suggesting the greater contribution of hyperactive/impulsive symptoms [34]. Other studies—in contrast—reported that inattention has been associated with early illicit drug use, frequency and recency of alcohol and marijuana use, heavier cigarette use [35], tobacco and marijuana use, and nicotine dependence [36].

Using a meta-regression analysis of ASI values revealed that the most important factors affecting the ADHD index as a dependent variable were drug problems and legal status, while the most important factor that affected ADHD diagnosis by K-SAD-S as a dependent variable was the drug problems. Putting into consideration the wide range of problems included in the term "drug problems", the result of regression analysis is considered consistent with other previously mentioned studies.

Conclusions

The present study points to the magnitude of the problem of associated co-morbidity between substance abuse and ADHD. It is advisable to use screening tools for ADHD among patients with substance of abuse, to select patients who are in need to use stimulant medication. The addition of stimulant medications for ADHD and substance abuse patients has shown to have a positive effect in reducing the number of drugs used by the patients, decreasing the relapse rate over long-term treatment, with more frequent voluntary treatments, and

being socially and vocationally rehabilitated [37]. Nevertheless, a significant reduction in associated criminality has been observed by those patients receiving stimulant medications [38].

Abbreviations
ADHD: Attention-deficit/hyperactivity disorder; CAARS-S:L: Conners Adult ADHD rating scale self-report; DISC: Diagnostic Interview Schedule for Children; DSM: Diagnostic and Statistical Manual of Mental Disorders; ICD: International Classification of Diseases; K-SADS-PL: The Kiddie schedule for affective disorders and schizophrenia present and Lifetime Version; SUD: Substance use disorders; WURS: Wender Utah Rating Scale.

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Authors' contributions
HE: interpretation of data, drafting and revision of the manuscript. AN: data collection, statistical analysis, analysis and interpretation of data, drafting and revision of the manuscript. SE, HE, GR, MR: analysis and interpretation of data design and concept of the study, critical revision of the manuscript. All authors reviewed and approved the final version of this manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The ethical committee of the Faculty of Medicine, Ain Shams University, has allowed doing this study. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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