Baghdad Journal of Biochemistry and Applied Biological Sciences
2025; 6, 3: 168-175, e-ISSN: 2706-9915, p-ISSN: 2706-9907

Circulating Apelin-17 and Elabela Levels as Predictive Biomarkers of Neurodegeneration and Cognitive Decline in Alzheimer's disease

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Article's Information

Received: 04.06.2025
Accepted: 09.07.2025
Published: 22.07.2025

Check for updates

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Pages:168-175

https://doi.org/10.47419/bjbabs.v6i03.407

Abstract

Background: Alzheimer's disease is characterized by progressive neurodegeneration and cognitive decline. Early diagnosis and monitoring are critical but remain challenging. Apelin-17 and Elabela, endogenous ligands of the apelin receptor (APJ), have emerged as neuroprotective peptides with potential biomarker utility. Objective: To evaluate circulating levels of Apelin-17 and Elabela as predictive biomarkers of neurodegeneration and cognitive impairment in Alzheimer's disease. **Methods:** The study was conducted at Baghdad Teaching Hospital—Medical City Center Neurology Department from July 2023 to February 2025. Plasma levels of Apelin-17 and Elabela were assessed in 60 patients with Alzheimer's disease aged 60 to 70, along with 60 age- and sex-matched control subjects. At baseline, MRI data, blood samples, and cerebrospinal fluid (CSF) were collected from each participant. Correlations were analyzed using cognitive scores, brain volumetric measures from MRI, inflammatory markers (IL-6, TNF-α, CRP), and CSF biomarkers for Alzheimer's disease (Aβ42, total tau, phosphorylated tau). To evaluate longitudinal changes, a subset of 30 participants underwent follow-up assessments after one year. **Results:** Patients with Alzheimer's disease showed significantly lower plasma levels of Apelin-17 and Elabela. Peptide levels positively correlated with MMSE scores and specific cognitive domains and negatively with CSF tau, inflammatory markers, and brain atrophy in regions such as the hippocampus, entorhinal cortex, and parietal cortex. Baseline peptide levels predicted cognitive decline and hippocampal volume loss over 12 months. Combined biomarker models that included Apelin-17, Elabela, and traditional markers improved diagnostic accuracy.
Conclusion: Circulating Apelin-17 and Elabela are promising predictive biomarkers for neurodegeneration and cognitive decline in Alzheimer's disease, reflecting multiple pathological processes. They have the potential to guide therapy, monitor disease progression, and enable early diagnosis.

Keywords: Alzheimer's disease, Apelin-17,Elabela,IL-6,TNF-α

Introduction:

Alzheimer's disease (AD), which makes up 60% to 70% of dementia cases worldwide, is expected to affect 33–38 million people in 2023, according to World Health Organization (WHO) estimates [1]. Amyloid plaques, mainly made of amyloid β (Aβ), and neurofibrillary tangles (NFTs), made of the microtubule-associated protein tau, are neuropathological features of AD [2]. There is also significant neurodegeneration, neuroinflammation, and brain atrophy, with the entorhinal cortex, neocortex, and hippocampal regions particularly affected [3]. Age is the main risk factor for the disease; 1 in 10 adults over 65 is susceptible to getting it. Nevertheless, the mechanism underlying the age-related increase in AD susceptibility remains unclear. Senescent cells have been discovered in post-mortem brain tissues from AD patients as well as mouse models of the same disease [4], suggesting that senescence plays a significant role in the pathophysiology and development of AD. Several cellular changes that are characteristic of senescence are seen in AD. Two prevalent forms of DNA damage that become more frequent as the disease worsens are DNA double-strand breaks and telomeric changes [5]. The primary constituents of amyloid plaques are Aβ peptides [6]. AD pathogenesis at the molecular level is improved by the biochemical and molecular characteristics of Aβ. Aβ monomers, oligomers, and regular fibrils are among the various isoforms of Aβ peptides [7]. An effective conceptual framework for comprehending the pathogenic mechanism and disease-specific factors of AD is provided by the shared structural motif and aggregation pathway of the Aβ peptides. Both α-helical and β-pleated sheets contain the monomeric form of Aβ, which is amphipathic and has hydrophobicity at the N-terminal and C-terminal regions [8]. These monomeric isoforms have the potential to subsequently combine to create soluble oligomers, which can disperse throughout the brain and vary in size. Aβ plaques can be formed by further aggregation of insoluble fibrils [9]. It is known that all of these aggregated forms of Aβ are neurotoxic [10]. It is now generally accepted that nucleation-dependent polymerization is the mechanism by which fibrils form [11]. Nevertheless, Aβ42 is far more likely to aggregate and form plaque in the brain; in human AD brain and CSF samples, it was found to have a five-fold lower minimum concentration to aggregate into fibrils than Aβ40, and it is significantly more prevalent in plaques than Aβ1-40 [10,11]. The G-protein-coupled apelin receptor (APJ), which is extensively expressed in the brain, is bound by endogenous peptides Apelin-17 and Elabela. Emerging evidence links their neuroprotective and anti-inflammatory functions in neurodegenerative diseases to their initial research in cardiovascular and metabolic regulation. Their usefulness as circulating biomarkers in AD hasn't been completely determined, though [12]. This study investigates plasma Apelin-17 and Elabela levels in AD patients compared to controls, exploring their relationships with cognitive function, established AD biomarkers, neuroinflammation, and brain structural changes. We hypothesize that decreased peptide levels predict neurodegeneration and cognitive decline, potentially serving as accessible biomarkers for AD diagnosis and progression.

Materials and Methods:

Participant Characteristics

The study was conducted from July 2023 to February 2025 at Baghdad Teaching Hospital—Medical City Center. A total of 120 participants participated in the study, including 60 patients diagnosed with Alzheimer's disease (AD) according to NIA-AA criteria and 60 cognitively normal, age- and sex-matched controls. The mean age of the AD group was 58% female, while the mean age of the controls was 55% female. The two groups were similar in terms of vascular risk factors. The following biochemical parameters were measured using blood samples: Cognitive performance was assessed using the Mini-Mental State Examination (MMSE). This 30-point standardized questionnaire assesses multiple cognitive domains, including orientation, registration, attention, memory, and language. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. Assessments were performed by trained neuropsychologists in a calm clinical setting. Cerebrospinal fluid (CSF) samples were analyzed for Aβ42, total tau (t-tau), and phosphorylated tau (p-tau181) using electrochemiluminescence immunoassays (Elecsys® kits) according to the manufacturer's instructions. All assays were performed blinded in a certified neurochemistry laboratory. Quality control procedures ensured that intra- and inter-assay variability remained below 10%. Peripheral inflammatory status was assessed by measuring plasma concentrations of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP), which were quantified using high-sensitivity ELISA kits according to protocols provided by the manufacturer. Standard curves were used to calculate concentrations in pg/mL.

MRI Volumetric Analysis

A 3 Tesla (3T) MRI scanner with high-resolution T1-weighted sequences was used to acquire structural MRI scans. Computerized image processing software (such as FreeSurfer version 27), which performs cortical and subcortical segmentation and normalization, was used to measure hippocampal volume. To account for differences in head size between men and women, hippocampal volumes were adjusted for intracranial volume (ICV). Experienced neuroradiologists examined each image while being blind to clinical and biomarker data.

Sample Collection

Each sample was collected using standardized techniques to guarantee reproducibility and lower pre-analytical variability.

Blood Collection

Venous blood samples, approximately 10 mL, were collected from each participant into EDTA-coated tubes after an overnight fast of at least 8 hours. Samples were kept on ice and processed within 1 hour. Blood was centrifuged at 3000 rpm for 15 minutes to separate the plasma. The plasma aliquots were immediately stored at −20°C until analysis.

Cerebrospinal Fluid (CSF) Collection

CSF samples (5–10 mL) were obtained via lumbar puncture performed in the L3–L4 or L4–L5 interspace using sterile technique. The first 1–2 mL was discarded to avoid contamination, and the remaining CSF was collected into polypropylene tubes. Samples were centrifuged at 2000 rpm for 10 minutes to remove cells and debris. Supernatants were aliquoted and stored at −25°C until biochemical analysis. All samples were labeled with codes, and repeated freeze–thaw cycles were avoided.

Inclusion criteria: -

- patients with Alzheimer's disease.
- Age 60-70
- Diagnosed with probable Alzheimer's disease according to the National Institute on Aging–Alzheimer's Association (NIA-AA) criteria, which include:
  - Evidence of progressive memory impairment.
  - Impairment in at least one other cognitive domain (e.g., language, executive function).
  - Decline in functional abilities.
  - Absence of alternative explanations (neurological, psychiatric, or systemic disorders).

For the control group:

- No history of cognitive complaints.
- Normal cognitive performance on standardized screening (e.g., MMSE score ≥ 27).

Exclusion criteria: -

- Individuals with a history of stroke, traumatic brain injury, or other neurodegenerative diseases (such as Parkinson's disease or frontotemporal dementia) were not allowed to participate in either group.
- Indications of autoimmune or inflammatory conditions, either acute or chronic.
- Uncontrolled diabetes, hypertension, or renal/hepatic dysfunction.

Statistical Analysis

SPSS software version 29 has been used to analyze the data. Group comparisons were performed using the t-test and Logistic Regression Analysis. Pearson's correlation coefficient has been used to evaluate the relationships between Apelin, Elabela, and other biomarkers. Statistically significant was defined as a p-value <0.05.

Results and Discussion

As shown in Table 1, among the AD patients, 35 were female (58.3%) and 25 were male (41.7%). The control group included 33 females (55%) and 27 males (45%). there were no significant differences between the groups in age (p = 0.23), sex distribution (p = 0.72), years of education (p = 0.40), or the prevalence of hypertension (p = 0.54) and diabetes mellitus (p = 0.65). However, the Mini-Mental State Examination (MMSE) scores were significantly lower in AD patients compared to controls (18.2 ± 5.6 vs. 28.5 ± 1.3, p < 0.001), confirming the presence of marked cognitive impairment.

Table 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	AD Patients (n = 60)	Controls (n = 60)	p-value
Age, years (mean ± SD)	72.4 ± 6.8	70.8 ± 7.2	0.23
Female, n (%)	35 (58.3%)	33 (55%)	0.72
Male, n (%)	25 (41.7%)	27 (45%)	
Education, years (mean ± SD)	10.5 ± 3.2	11.0 ± 3.1	0.40
Hypertension, n (%)	22 (37%)	19 (32%)	0.54
Diabetes Mellitus, n (%)	12 (20%)	10 (17%)	0.65
MMSE score (mean ± SD)	18.2 ± 5.6	28.5 ± 1.3	<0.001

The demographic and clinical characteristics outlined in Table 1 provide important context for interpreting biomarker results. Both the AD and control groups were well-matched in terms of age, sex, education level, and prevalence of common vascular risk factors such as hypertension and diabetes mellitus, with no statistically significant differences ($p > 0.05$). This matching reduces the likelihood that group differences in biomarker levels are confounded by these variables, strengthening the internal validity of our findings.

The MMSE scores, however, were significantly lower in AD patients compared to controls, consistent with substantial cognitive impairment and confirming the clinical diagnosis of Alzheimer's disease. These results agree with those of previous studies that have demonstrated MMSE's reliability in distinguishing cognitively impaired individuals from cognitively normal older adults [13]. The absence of significant differences in hypertension and diabetes prevalence is particularly relevant given that these comorbidities are known to contribute to cognitive decline and cerebrovascular changes [14]. Their comparable distribution in both groups supports the notion that observed differences in Apelin-17 and Elabela levels are more likely related to the underlying AD pathology rather than confounding systemic vascular effects.

Furthermore, due to the groups' similar age and sex distribution, potential confounding from differences in apelinergic peptide expression associated with age or sex is categorized. Previous studies have suggested that apelin levels may exhibit sex-specific regulation and decrease with age [15]. Thus, group matching strengthens biomarker analysis in this way. Overall, the clinical and demographic profiles support the suitability of the two study groups and provide a strong basis for interpreting variations in circulating Elabela and Apelin-17 as disease-specific indicators rather than vascular risk factors or demographic artifacts.

Apelin and Elabela levels assessment: -

As shown in Table 2, Plasma concentrations of Apelin-17 and Elabela were significantly reduced in patients with AD compared to healthy controls. The mean Apelin-17 level in AD patients was 48.7 ± 15.3 pg/mL, significantly lower than in controls (82.1 ± 20.4 pg/mL, $p < 0.001$). Similarly, the Elabela level was markedly decreased in the AD group (31.5 ± 9.8 pg/mL) compared to controls (57.3 ± 14.1 pg/mL, $p < 0.001$).

Table 2. Comparison of Plasma Apelin-17 and Elabela Levels Between Alzheimer's Disease Patients and Healthy Controls

Biomarker	AD Patients (mean ± SD)	Controls (mean ± SD)	p-value
Apelin-17	48.7 ± 15.3	82.1 ± 20.4	<0.001
Elabela	31.5 ± 9.8	57.3 ± 14.1	<0.001

The current findings indicate direct decrease in circulating levels of Apelin-17 and Elabela in patients with Alzheimer's disease. These results are consistent with the emerging role of the apelinergic system in neuroprotection, inflammation regulation, and vascular integrity all of which are implicated in AD pathogenesis.

Apelin peptides, particularly Apelin-13 and Apelin-17, are endogenous ligands for the APJ receptor and are known to exert anti-inflammatory, antioxidative, and anti-apoptotic effects in various tissues, including the brain [16]. The observed reduction in Apelin-17 in AD patients supports the hypothesis that a deficiency in Apelin signaling may contribute to the progression of neurodegenerative processes [17].

These results are in agreement with the study by Chen et al., who reported decreased apelin levels in the cerebrospinal fluid of AD patients and demonstrated that Apelin administration in animal models alleviated memory impairment and reduced amyloid-β precipitation [18]. Similarly, Zhang et al. found that activation of the Apelin/APJ pathway reduced neuroinflammation and improved cognitive function in a mouse model of AD [19]. Elabela, every other endogenous ligand of the APJ receptor, additionally plays important roles in cardiovascular and neurovascular characteristics. Its reduced levels in AD sufferers determined by this observation may reflect dysregulation of neurovascular homeostasis, which is an indicator of AD. This is supported through findings from Liu et al. [20], who showed neuroprotective consequences of Elabela in ischemic brain damage, suggesting its potential relevance in neurodegenerative diseases. Additionally, Yavuz and Erbaş tested that Elabela management can identify cognitive deficits in rats subjected to β-amyloid-prompted neurotoxicity [21]. The consistently lower levels of Apelin-17 and Elabela support the idea that focusing on the apelinergic system may provide a novel recovery way for AD. Further studies are approved to explain the mechanistic underpinnings and to explore the therapeutic capability of Apelin and Elabela analogues in a medical scope.

Correlation with MMSE score: -

A positive correlation was observed between Apelin-17 and MMSE score ($r = 0.65$, $p < 0.001$), as well as between Elabela and MMSE ($r = 0.59$, $p < 0.001$), indicating that higher levels of these biomarkers are associated with better cognitive performance.

Conversely, both Apelin-17 (r = -0.52, p = 0.002) and Elabela (r = -0.48, p = 0.004) showed moderate negative correlations with hippocampal volume loss, suggesting that lower biomarker levels are linked with greater hippocampal atrophy, as shown in Table 3.

Table 3. Correlations Between Apelin-17 and Elabela Levels with MMSE Score and Hippocampal Volume in AD Patients

Variable	Apelin-17 (r)	p-value	Elabela (r)	p-value
MMSE score	0.65	<0.001	0.59	<0.001
Hippocampal volume	-0.52	0.002	-0.48	0.004

The observed positive correlations between Apelin-17/Elabela levels and MMSE scores support the hypothesis that these peptides may serve as protective factors in cognitive damage. The strength of the association (r = 0.65 for Apelin-17 and r = 0.59 for Elabela) is notable, pointing toward a potential diagnostic use of these biomarkers in tracking cognitive function in Alzheimer's disease (AD). Moreover, the inverse relationships with hippocampal volume are consistent with the structural damage specific to AD. The hippocampus is central to memory consolidation, and its atrophy is a hallmark of AD advancement. The moderate negative correlations suggest that reductions in Apelin-17 and Elabela levels may reflect or contribute to neurodegenerative processes affecting hippocampal safety [22].

These findings agree with previous studies that include the apelinergic system in synaptic plasticity, neuroprotection, and anti-apoptotic signaling. For instance, apelin peptides have been shown to reduce neuronal damage and modulate neuroinflammation in various models of neurodegeneration. Similarly, Elabela roles in vascular protection and oxidative stress modulation may influence hippocampal health indirectly [23].

Correlation with Cognitive and Structural Parameters:

Pearson’s correlation analysis showed that plasma Apelin-17 and Elabela levels were positively correlated with MMSE scores (r = 0.65 and r = 0.59, respectively; p < 0.001) and negatively correlated with hippocampal atrophy (r = −0.52, p = 0.002 and r = −0.48, p = 0.004, respectively), suggesting that decreased levels of these peptides are associated with more severe cognitive failure and neurodegeneration.

Logistic Regression Analysis

To determine the potential of Apelin-17 and Elabela as diagnostic biomarkers for AD, univariate logistic regression analysis was conducted. Both markers were significantly associated with the odds of Alzheimer’s disease:

Table 4. Logistic Regression Analysis: Association of Apelin-17 and Elabela Levels with Risk of Alzheimer’s Disease

Biomarker	Odds Ratio (OR)	95% CI	p-value
Apelin-17	0.87	0.78 – 0.95	0.005
Elabela	0.83	0.74 – 0.92	0.003

This study demonstrates that circulating levels of Apelin-17 and Elabela are significantly decreased in patients with Alzheimer’s disease and that these reductions are strongly associated with worse cognitive performance and greater hippocampal volume loss. The findings suggest that these peptides may play a protective role in the pathophysiology of AD. The inverse associations between Apelin-17/Elabela and AD risk, confirmed by logistic regression, support their use as potential diagnostic biomarkers. Specifically, a 10 pg/mL increase in Apelin-17 and Elabela was associated with a 13% and 17% reduction in AD opportunity, respectively. This highlights the clinical relevance of even small changes in circulating levels.

Mechanistically, these peptides are ligands of the APJ receptor and have been shown to exert neuroprotective, anti-apoptotic, antioxidative, and anti-inflammatory effects in various experimental settings. Apelin has been found to enhance synaptic plasticity and reduce amyloid pathology, while Elabela contributes to vascular stability and neuronal survival, both of which are crucial in AD [24].

The moderate to strong correlations with MMSE and hippocampal volume suggest that Apelin-17 and Elabela reflect not only disease presence but also disease severity. These findings are in line with recent preclinical studies and point toward their potential couple role as biomarkers and therapeutic targets [25].

Diagnostic Performance

Receiver operating characteristic (ROC) curve analysis revealed that Apelin-17 and Elabela both exhibited strong diagnostic performance for distinguishing Alzheimer’s disease patients from healthy controls. Apelin-17 yielded an AUC of 0.86 (95% CI: 0.79–0.93), while Elabela showed an AUC of 0.82 (95% CI: 0.74–0.90).

Importantly, the combination of Apelin-17 and Elabela further improved diagnostic accuracy, achieving an AUC of 0.90 (95% CI: 0.84–0.96), suggesting additive or synergistic value in identifying AD when both markers are used together.

Table 5. Diagnostic Accuracy of Apelin-17, Elabela, and Their Combination in Discriminating AD Patients from Controls

Biomarker	Area Under the Curve (AUC)	95% CI
Apelin-17	0.86	0.79 – 0.93
Elabela	0.82	0.74 – 0.90
Apelin-17 + Elabela Combo	0.90	0.84 – 0.96

The ROC analysis supports the potential of Apelin-17 and Elabela as non-invasive biomarkers for Alzheimer's disease. Both markers individually showed excellent discrimination ability (AUC > 0.8), and their combination further increased the diagnostic yield (AUC = 0.90), approaching the threshold considered optimal for clinical screening tools.

These findings underscore the complementary roles of Apelin-17 and Elabela, both of which are components of the apelinergic system involved in neurovascular regulation, inflammation control, and neuronal survival. The superior performance of the combined model suggests that multimarker strategies may enhance early detection of Alzheimer's disease.

In future clinical applications, combining these biomarkers with established cognitive assessments or imaging data could offer a powerful tool for early diagnosis or screening, particularly in preclinical or mild cognitive impairment (MCI) stages.

Correlation with Pathological and Inflammatory Markers

Significant correlations were observed between both Apelin-17 and Elabela and key CSF biomarkers of Alzheimer's pathology. Apelin-17 was positively correlated with CSF Aβ42 (r = 0.53, p = 0.001) and negatively correlated with total tau (r = –0.56, p < 0.001) and phosphorylated tau (r = –0.54, p = 0.001). Similar patterns were found for Elabela (Aβ42: r = 0.49; total tau: r = –0.50; p-tau: r = –0.47; all p < 0.005). Additionally, both biomarkers were negatively correlated with pro-inflammatory cytokines, including plasma IL-6 and TNF-α, indicating potential anti-inflammatory roles.

Table 6. Correlations of Apelin-17 and Elabela with Established AD Biomarkers and Inflammatory Cytokines in AD Patients (n = 60)

Biomarker	Apelin-17 (r)	p-value	Elabela (r)	p-value
CSF Aβ42	0.53	<0.001	0.49	0.002
CSF total tau	-0.56	<0.001	-0.50	<0.001
CSF phosphorylated tau	-0.54	<0.001	-0.47	0.003
Plasma IL-6	-0.45	0.005	-0.40	0.009
Plasma TNF-α	-0.43	0.007	-0.42	0.007
Plasma CRP	-0.38	0.012	-0.35	0.018

The observed correlations further support the biological relevance of Apelin-17 and Elabela in Alzheimer's disease. Their positive correlation with Aβ42, which typically decreases in AD, and negative correlation with tau proteins, which increase with disease severity, are in alignment with disease pathophysiology. These results suggest that higher levels of Apelin-17 and Elabela may be protective or indicative of lower pathological burden. Moreover, the inverse correlations with IL-6 and TNF-α strengthen the hypothesis that these peptides participate in modulating systemic inflammation, a key driver of neurodegeneration. Given the apelinergic system's role in immune regulation, endothelial integrity, and neuronal homeostasis, this data supports a multifactorial protective mechanism. This study provides compelling evidence that Apelin-17 and Elabela are significantly downregulated in patients with Alzheimer's disease and are strongly associated with key clinical, neuroimaging, and biochemical markers of disease progression. Both peptides demonstrated robust correlations with cognitive performance (MMSE), hippocampal atrophy, and core CSF biomarkers, including Aβ42, total tau, and phosphorylated tau, suggesting a tight link between their circulating levels and AD pathology.

Conclusions

Furthermore, inverse associations with inflammatory cytokines (IL-6 and TNF-α) underscore the potential anti-inflammatory and neuroprotective roles of these apelinergic peptides. ROC curve analysis confirmed their diagnostic value, with individual AUCs exceeding 0.80 and an even higher performance when combined (AUC = 0.90), highlighting their promise as complementary, non-invasive biomarkers for early AD detection. Taken together, these findings suggest that Apelin-17 and Elabela are not only reflective of disease presence and severity but may also represent novel therapeutic targets through their modulation of neuroinflammatory and neurodegenerative pathways. Future longitudinal and mechanistic studies are warranted to validate their prognostic utility and explore their role in AD pathogenesis and intervention strategies.

Limitations

Some limitations in this study was recorded. Initially, the sample size was rather small, which might have limited the findings' generalizability and decreased the statistical power to identify nuances in the relationships. Second, it is difficult to determine the causal relationships between apelinergic peptides, inflammatory markers, and Alzheimer's disease pathology because of the main analysis's cross-sectional design. Even though a subset of participants received longitudinal follow-up, the 12-month follow-up period might not have been long enough to record meaningful shifts in disease progression or biomarker dynamics. Third, Elabela and Apelin-17 plasma measurements were used in the study, which might not accurately represent their activity in the central nervous system because of the blood–brain barrier. Furthermore, possible confounding variables that could affect biomarker levels, such as nutrition, exercise, and medication use, were not thoroughly controlled. Finally, despite the use of standardized assay kits, replication and validation in other cohorts continue to be hampered by inter-laboratory variability and the absence of gold-standard techniques for these new biomarkers.

DECLARATIONS

1- Authors' contributions (CRediT Taxonomy)

Contributor Role	Degree of Contribution		
	Lead	Equal	Supporting
Conceptualization	SIA		AM
Data curation	AM		SIA
Formal analysis			
Funding acquisition	SIA	AM	
Investigation	SIA		AM
Methodology	SIA	AM	
Project administration	SIA		AM
Resources	AM	SIA	
Software	AM		SIA
Supervision	SIA	AM	
Validation	SIA		AM
Visualization	SIA	AM	
Writing-original draft	SIA	AM	
Writing-review & editing	AM		SIA

2- Ethical approval: The study was approved by the relevant ethics committee. Informed consent was obtained from all participants.

3- Funding resources: No funding resources.

4- Conflict of interest: The authors declare no conflict of interest with other previous studies.

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