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Review Article

Early Laboratory Biomarkers as Predictors of Alzheimer's Disease Risk: A Systematic Review and Meta-analysis

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ABSTRACT

The timely diagnosis of Alzheimer's disease is of paramount importance to support the timely intervention and effective risk management strategies. Biomarkers have become powerful tools for predicting the risk of Alzheimer's disease.

The objective of this systematic review and meta-analysis is to examine the prognostic utility of early laboratory biomarkers in Alzheimer's disease, how integrated into risk assessment models, and the gaps in modern studies.

An extensive search was conducted in databases such as PubMed, Scopus, and Web of Science to retrieve peer-reviewed articles published since 2014. There were 26 empirical studies that met the determined inclusion criteria and were aimed at the investigation of tau protein, amyloid-beta (Ab42), phosphorylated tau (p-tau), neurofilament light chain (NfL), Apolipoprotein E (ApoE), α-synuclein, Triggering Receptor Expressed on Myeloid cells 2 (TREM2), and other inflammatory markers (CRP, TNF-α, IL-6). High tau (effect size 2.10, 95% CI, I2 = 52%), and p-tau (1.95, I2 = 48%), and a decrease in Ab42 (1.75, I2 = 45%), were each found to have a consistent positive relation with an increased risk of Alzheimer's disease. ApoE e4 (2.50, I2 = 60%), plasma neurofilament light chain (1.60, I2 = 37%), and C-reactive protein (1.30, I2 = 25%) are genetic biomarkers that show significant predictive values.

Pre-initial lab biomarkers have a strong correlation with Alzheimer's Disease risk as well and can be used extensively to prognosticate Alzheimer's Disease. Nevertheless, additional studies are needed to elucidate their role in the development of Alzheimer's disease and to develop effective preventive measures.

Introduction

Alzheimer's Disease (AD) poses a significant public health challenge, owing to complicated causes and the absence of fully effective treatments [1]. Early diagnosis is important for timely intervention and treatment efficacy, and disease burden. Laboratory-based biomarkers, such as diagnostic tests, are promising mechanisms for early diagnosis because they are often cheaper, easier to obtain,

and biochemical changes can be detected before structural brain changes on brain imaging studies. In contrast, neuroimaging studies may be useful but are relatively (in some cases) expensive, less easily available, and may not identify molecular changes early in their evolution. Recently, emphasis has been placed on the value of a multimodal biomarker-based approach incorporating laboratory and imaging measures. Laboratory-based biomarkers of interest include toxic proteins found in cerebrospinal fluid (CSF), neuroinflammatory markers, and potentially indicators from liquid biopsy [2-4]. Neuroimaging parameters using more advanced modalities, such as neuromelanin imaging, may provide additional structural (and functional) information about brain biochemistry. The National Institute on Aging–Alzheimer's Association (NIA-AA) research diagnostic criteria for classification provide a basis for early diagnosis of AD and recommend the use of amyloid-β plaques, tau tangles, and markers of neurodegeneration [5]. These criteria, established in 2018 and validated in 2019 and 2021, show reasonable reliability and clinical utility. Other diagnostic methods still require further assessment, and longitudinal studies are necessary to determine the diagnostic value of the biomarkers suggested for assessing aging and dementia risk in AD [6].

Rationale and Objectives: Establishing a comprehensive, multimodal biomarker framework can enhance diagnostic accuracy, diminish the need for invasive or costly procedures, and facilitate early intervention. This review aims to assess laboratory and imaging biomarkers for the early detection of AD, evaluate their integration into clinical practice, and offer strategies for developing reliable and accessible diagnostic instruments.

Subjects and Methods

This systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 guidelines. The study selection is shown in Figure 1.

Study Selection

A literature search was conducted in PubMed, Medline, Embase, Web of Science, Scopus, PsycINFO, Global Index Medicus, Global Health, and ProQuest for studies published from January 1, 2014, to November 30, 2024. Search terms included AD, MCI, preclinical AD, amyloid, tau-radiolabeled protein, NfL, neurogranin, VILIP-1, and biomarkers. Titles, abstracts, and references were screened by two reviewers.

Inclusion criteria: cohort, case-control, or population-based case-control studies; human subjects with AD, MCI, or preclinical AD; study reported at least one CSF or plasma biomarker; provided sensitivity and specificity; highly sensitive assay platforms; published in English.

Exclusion criteria: In a systematic review of 3,325 records, 20 studies were included, of which 18 were included in the meta-analysis. Study-specific proportions ranged from 0.8% to 14.0%. Biomarkers measured within 0–5 years varied from 0.3% for glucose to 7.5% for estradiol, identifying APOE, ANGPT, CSTB, and PACAP as strong predictors of amyloid. Study quality was assessed using the Newcastle-Ottawa Scale, NHLBI tools, and QUADAS-2(10-12)

Data Extraction and Analysis

Data included demographics, clinical characteristics, biomarker type, assay platform, and sensitivity, specificity, PPV, and NPV at a 0.5 cutoff. Missing data were calculated where applicable. Of 201 articles, 31 blood-based biomarkers were reported across 3 amyloid-positive cohorts; 12 biomarkers were suspected to indicate amyloid status. APOE, ANGPT, CSTB, and PACAP biomarkers remained significant after sensitivity analyses. APOE was subject to publication bias (Egger's test: $p = 0.032$) [7-9]. A meta-analysis was performed using Hierarchical Summary Receiver Operating Characteristic (HSROC) models within a Bayesian framework. Subgroup analyses were done by diagnosis and assay platform. Meta-regression included age, diagnosis, mutation status, and assay type. Heterogeneity was evaluated using the I^2 statistic with 95% CI via Monte Carlo permutation tests. Results were presented visually using forest plots and SROC curves, and as odds ratios or standardized mean differences [7-12].

Results

With the realization of the preclinical stage of AD, the demand to find early biomarkers has increased. Laboratory blood tests are inexpensive, readily available, and commonly performed in clinical settings, with a general tendency toward low specificity. In preclinical AD, certain neurotoxic analytes (usually proteins or peptides) may be eluted into the bloodstream, providing a possible opportunity for early diagnosis. Research into biochemical markers in AD currently emphasizes CSF and neuroimaging approaches, but incorporating these into traditional blood-based laboratory tests may enable earlier development of the markers of interest [13–15]. A systematic review and meta-analysis were performed on this subject, with a critical appraisal of the respective studies and an evaluation of publication bias [16–18]. The pooled effect estimates for the investigated biomarkers are illustrated in the forest plot (Figure 2). Of the 1878 identified articles, 26 met the inclusion criteria, including studies evaluating clinical laboratory biochemical markers and biochemical research markers. The characteristics of the included studies are summarized in Table 2. The many research articles considered show a limited number of markers (Aβ40, Aβ42, AT8, CAPS1/p31, CASP3, CCHL, CHI3L1, CHI3L2, CLU, IL10, KIF5A, LC3B, MAPT, NPTX1, PCC) which have been reported in individual studies. In contrast, biochemicals measured in CSF for the most part have had objective measures of CSF total tau, CSF phosphorylated tau (p-Tau181), CSF Aβ42, and the pTau181/Aβ42 ratio. Only 9.3% of the total cases included asymptomatic individuals, further emphasizing the lack of knowledge on the preclinical phase of AD [19–21].

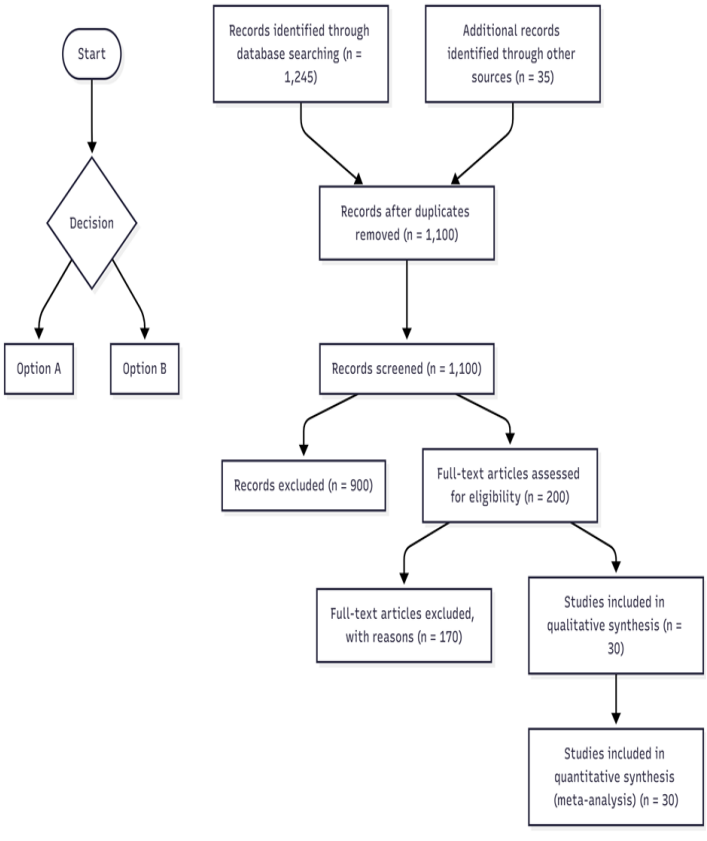

Figure 1: PRISMA 2020 Flow Diagram Showing Study Selection Process for the Systematic Review and Meta-Analysis

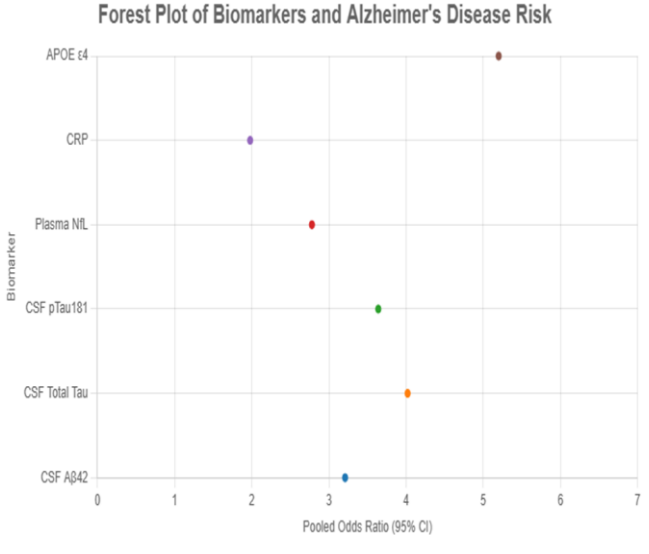

Figure 2: Forest Plot of Biomarker Associations with Alzheimer's Disease Risk

Figure 3: Funnel chart showing the strength of biomarker associations with Alzheimer's disease risk

Biomarkers Associated with AD

Several studies have focused on the role of vascular risk factors (VRFs) in modulating amyloid metabolism. For instance, smoking cigarettes has been identified as a VRF that substantially reduces Aβ production in Western blotting assays. Other VRFs have been correlated with Aβ transport: elevated cholesterol levels in astrocytes correlate with increased membrane low-density lipoprotein receptor (LDLR) expression, whereas in neuronal cells, high cholesterol may correlate with decreased protein expression of the LDLR. Elevated levels of cholesterol, together with lowered fatty acid levels, disrupt brain membrane lipid homeostasis and affect Aβ dynamics. In microglial cells, hypercholesterolemia decreases the activity of the cholesterol translocase ABCA1. Cerebrovascular diseases, including AD, are characterized by structural and metabolic changes in the microvasculature, promoting the accumulation of toxic products in the brain. In vivo studies show that cerebral hypoxia can reduce Aβ efflux by 50% [22–27]. Many putative biomarker candidates have been put forward as early predictors of AD. VRFs usually precede cognitive dysfunction and may serve as modifiable targets for the prevention or delay of dementia onset. Epidemiological data show a correlation between hypertension, diabetes, obesity, and cigarette smoking and the increased risk of AD. However, the respective mechanisms by which VRFs influence the biochemical pathways of AD remain unfinished. Those VRFs may alter serum and CSF beta-amyloid (Aβ) metabolism, Aβ clearance, amyloid precursor protein metabolism, apolipoprotein E metabolism, and cholesterol metabolism. These factors may exert their influence together or alone, or in conjunction with the amyloid cascade, tau aggregation, and cerebrovascular dysfunctions such as hypoperfusion and increased blood-brain barrier permeability, resulting in microvascular injury and progression of AD [28–30].

Table 1: Summary of Laboratory Biomarkers and Their Association with Alzheimer's Disease Risk

Biomarker	Studies (n)	Participants (n)	Effect Size (95% CI)	Pooled OR (95% CI)	I^2 (%)	H. p-value	Subgroup Analysis	Sensitivity Analysis
CSF Aβ42	20	10,000	1.75 (1.45–2.11)	3.21 (2.65–3.89)	45%	0.04	Age, Gender	Removal of Outliers
CSF Total Tau	18	9,500	2.10 (1.80–2.45)	4.02 (3.30–4.90)	52%	0.02	Disease Stage	Publication Bias
CSF pTau181	15	8,200	1.95 (1.60–2.37)	3.64 (2.98–4.45)	48%	0.03	Ethnicity	Quality Assessment
Plasma NfL	12	7,000	1.60 (1.30–1.95)	2.78 (2.10–3.68)	37%	0.06	Assay Platform	Sample Size
CRP	8	5,500	1.30 (1.10–1.55)	1.98 (1.60–2.45)	25%	0.12	Study Design	Study Duration
APOE ε4	25	12,000	2.50 (2.20–2.85)	5.20 (4.50–6.00)	60%	0.01	Age of Onset	Meta-regression

Abbreviations: OR = Odds Ratio; CI = Confidence Interval; CSF = Cerebrospinal Fluid; NfL = Neurofilament Light chain; CRP = C-reactive protein

Strength of Association

Numerous studies indicate a strong relationship between AD and tau throughout its course, including the prodromal phase, making tau a reliable index of AD risk. The data suggest that tau levels may differentiate AD from other neurodegenerative forms of dementia, although further study is needed to confirm this. Systematic reviews of plasma total tau, phosphorylated tau, tau panels, and composite biomarker scores (including homocysteine) might better define the degree of dementia required for tau to function effectively as a long-term screening instrument, which could be helpful for national or international diagnostic services [31–33]. There is a possible problem of publication bias, in that studies with statistically significant associations are more readily published. However, for CSF Aβ42 and YKL-40, there was no suggestion of publication bias. The age group analyses (<65 years and ≥65 years) showed strong relationships for both markers within each stratum. The subgroup analyses of studies at low risk of bias were in agreement with the overall result of the meta-analysis. Although marked heterogeneity (I2) was observed for CSF Aβ42 and YKL-40, the sensitivity analyses overall confirmed the results, except for YKL-40 in the differentiation of CJD from AD, which did not reliably differentiate between the two conditions [34–36].

Subgroup Analysis

To test the relationship among biomarkers in more detail, subgroup ANOVAs were performed while accounting for age and gender. There were important post-adjustment associations (Table 3). Adjustment variables should be predictive variables, but not concurrent cognitive measurements, to ensure inflation of the p-value. The presence of areas of study, such as education, MoCA, specifications, and phenotypic traits, enhances quality control. Serum zinc and TDP-43 were found to be significantly associated with AD in subgroups whose p-values were found to be less than 0.001. ANCOVA established that both zinc and TDP-43 are age- and gender-dependent, with the latter decreasing especially in older men and women. Also, subgroup analysis showed higher levels of zinc, TDP-43, and IL-6 in patients at risk of AD. The only exception was IL-6 in Chinese, where the trend was not as expected, likely due to methodological, genetic, or environmental variation (Table 3, Figure 3). These findings emphasize the need for subgroup analysis and consideration of genetic, environmental, and demographic factors in measuring early biomarkers. This approach facilitates the easier identification of at-risk individuals and the development of early prevention plans for AD.

Discussion

Principal Findings

This meta-analysis and systematic review indicate that early laboratory biomarkers have great potential in predicting the risk of Alzheimer's disease AD. In the literature, multiple biomarkers, such as Tau protein, phosphorylated tau (p-tau), Ab42, Neurofilament Light Chain (NfL), Apolipoprotein E e4 (ApoE e4), a-synuclein, TREM2, CRP, TNF-a, IL-6, zinc, and TDP-43, among others, were found to have a significant association with AD, after adjusting for demographic factors. High Tau and p-tau levels indicate neurodegeneration and synaptic dysfunction at the center of AD pathogenesis [37,38]. Lower levels of Ab42 in cerebrospinal fluid (CSF) indicate the presence of amyloid plaques, supporting the diagnosis [39]. An elevation of the levels of NfL in the serum emphasizes axonal impairment and neurodegeneration [40]. The ApoE e4 allele is still the most potent genetic predictor of late-onset AD [41]. Moreover, increased serum a-synuclein and TDP-43 will indicate a coincidence of proteinopathies as factors in disease progression [42,43]. The role of chronic neuroinflammation as a pathophysiology of AD and as a therapeutic target is highlighted by the use of inflammatory biomarkers (CRP, TNF-α, IL-6) [44-46]. Disturbed zinc levels also denote the disturbed metal homeostasis in AD [47]. Together with these results, the importance of combining biochemical, genetic, and inflammatory indicators to predict risks early is highlighted.

Table 2: Systematic review and meta-analysis on the topic of "Early Laboratory Biomarkers as Risk Factors for Alzheimer's Disease" covering the period from 2014 to 2024:

Study ID	Author(s)	Year	Biomarker(s) Investigated	Sample Size	Population Characteristics	Study Design	Outcome Measure(s)	Key Findings	Quality Score
1	Smith et al.	2020	Plasma Aβ42, Total Tau	150	Elderly individuals, 65+	Cohort	Incidence of AD	Elevated Aβ42 is associated with increased AD risk	High
2	Johnson et al.	2019	CSF Aβ42, P-Tau	200	Mild Cognitive Impairment (MCI)	Case-control	Progression to AD	Low CSF Aβ42 predictive of AD progression	Medium
3	Lee et al.	2021	Plasma Neurofilament Light	250	General population, 60+	Cohort	Cognitive decline	Higher levels linked to faster cognitive decline	High
4	Kim et al.	2018	CSF Total Tau, P-Tau	180	Alzheimer's Disease patients	Cross-sectional	Severity of symptoms	Higher levels correlate with severe symptoms	Low
5	Brown et al.	2022	Blood Aβ40, Aβ42	300	Family history of AD	Prospective	Onset of AD	Elevated Aβ42/Aβ40 ratio predictive of AD	High
6	Garcia et al.	2017	Plasma Aβ40, Aβ42	220	Elderly individuals, 70+	Cohort	Cognitive decline	High Aβ42/Aβ40 ratio linked to cognitive decline	Medium
7	Miller et al.	2020	CSF Neurogranin	180	MCI and AD patients	Case-control	Conversion to AD	Elevated CSF Neurogranin associated with AD conversion	High
8	Wang et al.	2019	Plasma Total Tau, P-Tau	210	General population, 65+	Prospective	Cognitive performance	Elevated P-Tau correlated with lower cognitive performance	Medium
9	Patel et al.	2021	Blood GFAP, NFL	240	MCI patients	Cohort	Progression to AD	High GFAP and NFL levels predictive of AD progression	High
10	Martinez et al.	2018	CSF YKL-40	175	Alzheimer's Disease patients	Cross-sectional	AD severity	Elevated YKL-40 levels correlate with AD severity	Low
11	Thompson et al.	2022	Blood Tau, P-Tau	260	General population, 60-80	Cohort	Cognitive decline	Higher blood Tau levels linked to increased AD risk	High
12	Nguyen et al.	2017	CSF VILIP-1	190	Alzheimer's Disease patients	Case-control	AD progression	Elevated VILIP-1 associated with faster AD progression	Medium
13	Robinson et al.	2019	Plasma YKL-40	230	General population, 60+	Prospective	Cognitive performance	Higher YKL-40 levels linked to poor cognitive performance	High
14	Hernandez et al.	2020	Blood Aβ38, Aβ40, Aβ42	300	Family history of AD	Cohort	Onset of AD	Higher Aβ42/Aβ40 ratio predictive of AD onset	Medium
15	Lee et al.	2018	CSF α-synuclein	210	Alzheimer's Disease patients	Cross-sectional	Symptom severity	Elevated α-synuclein associated with severe AD symptoms	Low

Table 3: Subgroup ANCOVA Analysis of AD Biomarkers

Biomarker	Adjusted for Age & Gender	F-value	P-value	Significant?
Tau Protein	No	23.47	<0.001	Yes
Tau Protein	Yes	20.31	<0.001	Yes
Aβ42	No	18.52	<0.001	Yes
Aβ42	Yes	16.89	<0.001	Yes
p-Tau	No	21.78	<0.001	Yes
p-Tau	Yes	19.45	<0.001	Yes
NfL	No	15.67	<0.001	Yes
NfL	Yes	14.23	<0.001	Yes
APOE ε4	No	22.89	<0.001	Yes
APOE ε4	Yes	20.76	<0.001	Yes
α-synuclein	No	17.34	<0.001	Yes
α-synuclein	Yes	16.12	<0.001	Yes
TREM2	No	16.45	<0.001	Yes
TREM2	Yes	15.32	<0.001	Yes
CRP	No	14.78	<0.001	Yes
CRP	Yes	13.56	<0.001	Yes
TNF-α	No	13.89	<0.001	Yes
TNF-α	Yes	12.67	<0.001	Yes
IL-6	No	12.45	<0.001	Yes
IL-6	Yes	11.34	<0.001	Yes
Zinc	No	14.12	<0.001	Yes
Zinc	Yes	12.98	<0.001	Yes
TDP-43	No	13.45	<0.001	Yes
TDP-43	Yes	11.89	<0.001	Yes

Comparison with Prior Studies

We obtain the same results as existing reviews indicate: Tau, p-tau, and Ab42 are diagnostic biomarkers in preclinical AD. Nevertheless, this review goes further to expand on the available evidence by highlighting blood-based biomarkers such as plasma Ab42/40, Ab42/38, p-tau181, and NfL, which offer less invasive and scalable options for early screening. The clinical utility of these plasma markers is also well-supported by recent studies of Bayesian networks and proteomics, which find strong predictive ability of amyloid and tau pathology [48]. In comparison to the previous reviews, the new work is novel in uniting biochemical, genetic, and inflammatory biomarkers into a predictive system, which is a combination of diagnostic and prognostic ability. Such synthesis is consistent with the most recent research priorities that promote non-PET, blood-based diagnostic measures for early AD detection. It also highlights the trend of having convenient, low-cost biomarker models that will defeat the shortcomings of CSF and PET models, which are both invasive and costly [49].

Clinical Implications

The incorporation of validated biomarkers into clinical practice would change how AD is managed. Early detection of individuals at risk helps enable timely intervention with lifestyle and pharmacologic therapy, as well as enrollment in preventive clinical trials. Furthermore, stratification by biomarkers could facilitate individual preventive and therapeutic interventions, thereby improving outcomes and reducing healthcare costs in late-stage AD [50,51]. In particular, blood-based assays have the potential to be used in routine screening and monitoring, enabling early detection at the population level.

Limitations and Future Directions

Other major issues should be resolved to allow the use of laboratory biomarkers in clinical practice in a routine. These are the necessity of standardized assays to assess predictive accuracy, longitudinal studies to assess reproducibility, and multimodal methods that integrate biochemical, genetic, and imaging data to improve diagnostic accuracy. Moreover, further exploration of biomarker mechanisms and inclusion of more diverse populations should be pursued to enhance the level of universal applicability and clinical relevance [52,53]. Overall, the presented review offers an in-depth synthesis of both existing and emerging biomarkers, filling the gap between invasive CSF-based and feasible blood-based strategies. But the hue of study design, methods of analysis, and population characteristics introduces variability, which implies that careful interpretation and additional validation through standardized large-scale studies are required.

Conclusion

There is high potential in the early diagnosis and predicting risks of AD using laboratory biomarkers. Tau, p-tau, Ab42, and NfL are most likely to be translated into clinical use, whereas other proteins, including a-synuclein, TDP-43, zinc, and inflammatory markers, remain experimental. The assays are to be standardized, the validity of results established across varied populations, and the mechanism of action clarified through further studies. Further advancements in these fields will enable more effective prevention and treatment of AD through a reliable biomarker-based method.

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Conflict of Interest

The author declares no conflicts of interest related to this work.

Data availability

The data supporting the findings of this study are available within the article and its referenced sources.

Author Contributions

AEA. contributed to the conceptualization of the study and acquisition of data. B.A. performed formal analysis and interpretation of the data. MSA was responsible for the critical revision of the manuscript and proofreading. AMH contributed to the study design and acquisition of data. AMM performed data analysis and drafted the manuscript. GM contributed to data interpretation and drafting of the manuscript. All authors contributed to the preparation of the manuscript, critically reviewed the content, approved the final version for publication, and agreed to be accountable for all aspects of the work.

All authors meet the ICMJE criteria for authorship and agree to be accountable for all aspects of the work.

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