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Detecting Periodontal Destruction with Saliva Biomarkers in Aging: Systematic Review

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ABSTRACT (The content cannot exceed first page)

Immuno-inflammatory responses to bacteria in dental biofilms can lead to periodontal destruction, which can be indicated by inflammatory markers in saliva. This review highlights salivary biomarkers for detecting periodontal damage as elderly.Two independent reviewers conducted a systematic literature search on PubMed for English publications from 1961 to 2024 using keywords like “aging,” “saliva,” “biomarkers,” and “periodontitis.” The search included only randomized controlled trials that examined salivary biomarkers in aging populations. Out of 160,647 publications, four high-quality studies were included—two from Europe (Switzerland and Slovakia), one from the United States, and one from South Korea. The identified salivary biomarkers included Interleukin-1β, Interleukin-6, matrix metalloproteinases (MMP-3, MMP-8, MMP-9), advanced glycation end products (AGEs), advanced oxidation protein products (AOPP), and total antioxidant capacity (TAC). Based on the published studies, saliva biomarkers are valuable indicators of periodontal disease during aging.

Keywords: Aging, Biomarkers, Periodontal Destruction, Saliva

ABSTRAK (The content cannot exceed first page)

Respons imun-inflamasi terhadap bakteri dalam biofilm gigi dapat menyebabkan kerusakan periodontal, yang ditunjukkan melalui biomarker inflamasi pada saliva. Tinjauan ini menunjukkan biomarker saliva dapat mendeteksi kerusakan periodontal pada lansia. Dua peninjau independen melakukan pencarian literatur sistematis di PubMed untuk publikasi berbahasa Inggris dari tahun 1961 hingga 2024 menggunakan kata kunci seperti "penuaan," "saliva," "biomarker," dan "periodontitis." Pencarian hanya mencakup uji coba terkontrol acak yang meneliti biomarker saliva pada populasi lansia. Dari 160.647 publikasi, empat studi berkualitas tinggi dimasukkan—dua dari Eropa (Swiss dan Slovakia), satu dari Amerika Serikat, dan satu dari Korea Selatan. Biomarker saliva yang diidentifikasi meliputi *Interleukin-1β, Interleukin-6, matriks metaloproteinase (MMP-3, MMP-8, MMP-9), advanced glycation end products (AGEs)*, *advanced oxidation protein products (AOPP),* dan *total antioxidant capacity (TAC).* Berdasarkan studi yang telah dipublikasikan, biomarker saliva merupakan indikator berharga untuk penyakit periodontal pada lansia.

Kata kunci: Penuaan, *Biomarker*, Destruksi Periodontal, Saliva

1. Introduction

The biological aging phenomenon is a major factor that causes the organs and networks of adults to function less effectively. In general, infections and chronic conditions such as periodontal disease are more common among adults. The prevalence of oral disorders, particularly periodontal diseases, has been increasing as the world's population ages, which can impact health and quality of life [1]. The aging level of each individual is different, although the exact chronology and biological age describe the functional status [2].

World Health Organization (WHO) describes the young middle-aged, young elderly, elderly, and longevity elderly as those under 44, between 45 to 59, 60 to 74, 75 to 89, and beyond 90 years, respectively. According to World Population Prospects, one in 11 individuals globally was 65 or older in 2019, and one in six will be over 65 by 2050 [3]. Over 90% have some form of periodontal disease, such as periodontitis, commonly experienced when significant tooth loss impairs chewing ability, appearance, and general quality of life [4]. The immune system deteriorates with age, and immunosensitized adults are more susceptible to harmful microorganisms, particularly species connected to periodontal disease. This increases the probability of the oral health problem manifesting in older individuals [5]. The aging process can push the colonization of the periodontal pathogens and damage the vitality of the mesenchymal stromal parent cell, which causes the periodontal environment to become micro-proinflammatory and worsens infiltrated inflammation [6].

Clinical parameters such as dental radiography, clinical attachment loss, and probing pocket depth are traditionally used to detect periodontal disease. Even though these fundamental methods work effectively, oral diagnosis has advanced considerably. Non-invasive biomarkers provide a rapid and effective diagnostic substitute, specifically in saliva. Pathogenic bacteria in the sulcus, a compromised host immune response, and adhesion network degradation are the hallmarks of periodontal disease, which is an inflammatory process. Three stages comprise the biochemical signals in the impacted tissues, namely alveolar bone loss, connective tissue deterioration, and inflammation. Patients with periodontitis have high levels of circulating molecules in these biological stages in the saliva and gingival crevicular fluid (GCF), thereby serving as helpful disease indicators. Salivary biomarkers have become attractive options for early detection, risk assessment, and monitoring of periodontal disease [7–9].

Numerous salivary indicators, including bacteria, host enzymes, cytokines, and bone metabolism, have been studied over the past few decades as potential targets for distinguishing patients with periodontitis from healthy individuals. However, many results still show differences [10], and the combination of biomarkers can be used more successfully to diagnose periodontal conditions because changes in biomarkers occur in the disease stages. *Porphyromonas gingivalis (Pg)*, metalloproteinase matrix (MMP)-8, and salivary interleukin (IL)-1β all show increased prevalence, and this condition is closely connected to periodontal disease [11,12]. According to Zhang et al.'s study, IL-1β, MMP-8, and *Pg* found in saliva are highly useful for identifying periodontal disease [10].

Saliva represents a healthy mouth and provides important systemic information about the physiological features of periodontal disease, particularly periodontitis. To aid in patient therapy, saliva can evolve into a trustworthy marker for evaluating and tracking the progression of periodontal disease [13].

2. Methods and Materials

2.1 Protocol, registration, conduct, and reporting

This systematic review was carried out following the Cochrane Handbook (Cochrane Handbook for Systematic Reviews of Interventions, 2020) as well as the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) to guarantee a higher level of methodological quality. As the authors have clarified, no conflicts of interest are related to this study.

2.2 Eligibility criteria

The process of this systematic review included only human studies investigating salivary biomarkers to detect periodontal destruction during aging. The parameters considered in the studies were MMP-1, MMP-3, MMP-8, MMP-9, IL-1β, IL-6, gingival recession, plaque index (PI), gingival index (GI), papillary bleeding

score index (PBI), clinical attachment level (CAL), bleeding on probing (BOP), serum calcium levels, and Oral Health Impact Profile (OHIP), while there were no limits based on gender.

2.3 Exclusion criteria

The analysis did not include abstracts, systematic reviews, case reports, case series, descriptive studies, or expert opinions. Exclusion criteria included carrying pregnancy, currently smoking cigarettes, using smokeless tobacco, suffering from diabetes, being immunocompromised, receiving periodontal therapy in the last six months, taking antibiotics or anti-inflammatory drugs, and being edentulous.

2.4 Population, Intervention, Comparison, Outcomes, Study (PICOS)

The PICOS framework formulated the study question, where the Population aspect included elderly participants aged 60 years and older, the Intervention used Saliva biomarkers, and Comparison was based on Non-periodontitis. Outcomes were in the form of Periodontal destruction, as identified by increased probing depth (PD), CAL, BOP, serum calcium levels, OHIP, PI, GI, PBI, MMP-1, MMP-3, MMP-8, MMP-9, IL-1β, and IL-6 levels, and gingival recession.

2.5 Search strategy

PubMed was the only electronic database thoroughly searched up until January 2025. There were no year limits, and the search was restricted to English, while the method included all terms related to aging, periodontitis, and saliva biomarkers.

2.6 Study selection

The final studies were selected in two stages, where two reviewers (PW and JM) separately filtered the abstracts and titles of all the references acquired in the first stage. Reviewers evaluated the full-text studies in the second round to validate the initial choice. Disagreements were resolved by conversation, and when required, a third party (OAH/SH/IE) was consulted.

2.7 Risk of bias in individual studies

Two reviewers used the Revised Cochrane risk-of-bias instrument for randomized trials (RoB 2.0) to assess the studies. The risk of bias was evaluated using a critical evaluation checklist tool for studies including randomized controlled trials. The components of this evaluation tool are true random sequence generation, allocation concealment, blinded outcome assessment, selective outcome assessment, and appropriate statistical analysis. Studies with uncertain sequence generation and allocation concealment were categorized as having the highest risk of bias.

Five categories comprise the Risk of Bias (RoB) assessment, leading to a general evaluation of the trials, and the results are as follows. The first domain was selection bias or bias from the randomized procedure. Two trials showed a minimal risk of bias, while the other two were deemed concerning because of ambiguous statements of randomized or processed allocation concealment. Second, because there was no information on whether variations from the intended intervention went beyond what would be expected in standard practice, all studies were rated to present some concerns (100%) regarding performance bias or departures from the intended intervention. Third, all studies were deemed to have a 100% low risk for attrition bias, which often originates from missing outcome data. Fourth, there was bias in the measurement outcome (detection bias). However, considering that the assessors were blinded, all the investigations were rated with a low risk of bias. Finally, because all pre-specified outcomes were reported across the studies, 100% of trials were rated as low risk due to bias in the selection of reported results (reporting bias).

3. Results

3.1 Study selection

The PRISMA flowchart shows that the search found 195 studies in a single database (Figure 1). After screening, duplicates were examined, and six studies were selected to be read in full following the review of the abstract and title. Four studies satisfied the inclusion requirements and answered the investigated topic

appropriately. The full-text evaluation excluded studies based on irrelevant design, comparison, intervention, or population.

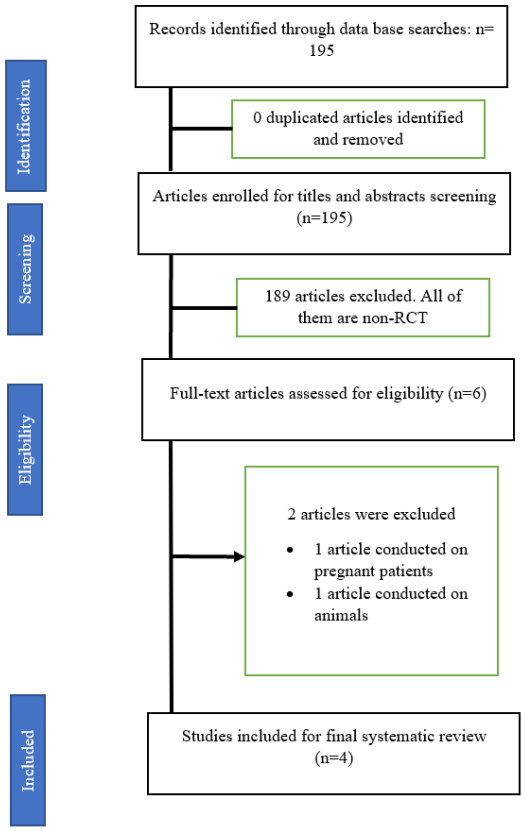

Figure 1. The flow diagram of the literature search is divided into the identification, screening, eligibility, and inclusion stages. Reasons for study exclusions are included in the eligibility stage.

3.2 Study characteristics

Table 1 shows the study characteristics, with the entire four using a randomized controlled trial design [14–17]. The studies were conducted in South Korea, Slovakia, Switzerland, and the United States. The total sample size was 210 individuals, while every study was released between 2010 and 2021.

Table 1. Study Characteristics

Table 1. Study Characteristic/ Study	Year of publication	Country	Study design	Sample size	a. Groups	Parameters	Results
Bashutski et al., [14]	2010	United States	RCT	40	b. Teriparatide (test) c. Placebo (control)	PD, CAL, BOP, alkaline phosphatase level, serum calcium levels, 25-hydroxyvitamin D	Clinical improvement was greater with a reduction in PD, CAL, and an increase in 25-hydroxyvitamin D; serum calcium levels

							remained stable.
Ramseier et al., [15]	2021	Switzerland	RCT	60	Electric toothbrush with irrigator (test) Manual toothbrush (control)	PI, GI; IL-1β, MMP-3, MMP-8 (whole saliva and GCF)	Clinical improvements were found by a reduction in PI and GI. Reduction in IL-1β.
Lee et al., [16]	2012	United States	RCT	30	IL-1 genotype positive IL-1 genotype negative	PI, GI, PBS, IL-6, MMP-1, IL-8	Increased PI, GI, PBS, and higher levels of IL-6, MMP-1, and IL-8 are substantial risk of inflammation;
Park et al., [17]	2021	South Korea	RCT	80	Mangosteen and propolis extract capsule (test) Placebo (control)	PD, CAL, BOP, GR, GI, PI, IL-1β, IL-6, MMP-8, MMP-9	A reduction in PD, CAL, BOP, GR, GI, PI, IL-1β, IL-6, MMP-8, and increased MMP-9 reduced the risk of periodontitis.

3.3. Risk of bias within studies

Table 2 presents the results from using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2.0) (RoB 2.0, 2019). The proportion of yes equal to or less than 49%, between 50% to 69%, and equal to or greater than 70% was classified as high, moderate, and low, respectively. All four studies showed a low risk of bias following these criteria (Table 2).

Table 2. Risk of Bias Assessment

Study	Bias Arising from the Randomization Process	Bias Due to Deviations from Intended Interventions	Bias Due to Missing Outcome Data	Bias in Measurement of Outcome	Bias in Selection of Reported Results	General Risk of Bias
Bashutski et al., [14]	Low	Some concerns	Low	Low	Low	Low
Ramseier et al., [15]	Low	Low	Low	Low	Low	Low
Lee et al., [16]	Low	Low	Low	Low	Low	Low
Park et al., [17]	Low	Low	Low	Low	Low	Low

3.4. Results of individual studies

Table 1 shows the studies that compared salivary biomarkers to identify periodontal damage. These investigations assessed the variations in MMP-1, MMP-3, MMP-8, MMP-9, IL-1β, IL-6, gingival recession, PI, GI, PBI, CAL, BOP, calcium levels, and gingival recession.

Every patient examined had a periodontitis diagnosis, but the investigations differed in terms of the disease severity and scope (to describe the type of periodontitis found in each study). The duration of the follow-up varied from two to twelve months, and after a year, only one study released data. Two studies presented outcomes after eight weeks, and one presented results after thirty-five days. The included study used a variety of plaque indicators, including gingival and plaque indices. There have been reports of plaque, inflammation, pocket depth, IL-6, and MMP-8 levels.

A comparative non-randomized clinical study that identified potential salivary biomarkers in the test and control groups showed significant variations in salivary biomarkers across all included trials compared to placebo or no adjuncts, where IL-1β levels were lower despite being statistically insignificant [15]. According to one study, people with high baseline levels of salivary IL-6 and MMP-1 have a higher probability than those with low levels of the biomarkers to experience an increased gingival inflammatory response [16]. IL-6 dramatically decreased in the test group between the baseline and eight-week periods [17]. Procollagen type 1 N-propeptide (P1NP), osteocalcin, and ICTP (pyridinoline cross-linked carboxy-terminal propeptide of type 1 procollagen) from GCF were among the bone turnover markers examined in relation to salivary biomarkers, also known as oral-fluid biomarkers. There were no appreciable variations in these biomarkers between the teriparatide and placebo groups. Although it was not statistically significant, there was a trend toward an increase in P1NP after six weeks, which suggested bone-forming activity. Bashutski et al. point out that systemic indicators of bone turnover changed over time, such as increased serum levels of bone-specific alkaline phosphatase, without appreciable variations in oral-fluid markers between the groups [14].

Over eight weeks, Ramseier et al. examined the clinical results and oral fluid indicators of the individuals. The amounts of matrix metalloproteinases MMP-3, MMP-8, and interleukin (IL)-1β in GCF and

whole saliva (WS) were measured to analyze salivary biomarkers. Compared to MMP-3 and IL-1β, MMP-8 levels were greater in WS and GCF. All through the eight weeks, no statistically significant differences were found between the test and control groups. After controlling for multiple comparisons, the numerical trend of IL-1β in the GCF toward lower levels in the test group at weeks four and eight was not statistically significant. Despite apparent clinical improvements in gingival health of the test group, none of the oral fluid indicators showed any significant between-group differences. The study concluded that while clinical improvements were observed, these were not accompanied by significant changes in the measured salivary biomarkers [15].

Lee et al. investigated the connection between periodontal inflammation and salivary biomarkers. The best indicators of the inflammatory response were the baseline levels of IL-6 and IL-8 in saliva. Individuals with significant gingival inflammation were classified as "high responders" by these two biomarkers, while those without inflammation were classified as "low responders." High baseline levels of MMP-1 and MMP-8 are connected to a more robust inflammatory response, making both significant biomarkers. With an area under the curve (AUC) of 0.89 and an odds ratio of 17.0, combining the levels of MMP-1 and IL-6 produced the best predictive value for identifying the individuals who would show a more pronounced inflammatory response. This implies that participants with high levels of both were 17 times more prone to be high responders. Several salivary biomarkers correlated with the onset and remission of periodontal inflammation were examined during the trial, including IL-1α, IL-1β, TIMP-1, and MMP-9. This study shows that some salivary biomarkers, particularly IL-6 and MMP-1, can forecast the degree of periodontal inflammation, potentially having diagnostic significance for identifying individuals susceptible to more severe inflammatory reactions [16].

Park et al. examined immunological markers to determine the clinical success of the treatments. Pro-inflammatory cytokines and other salivary biomarkers were reviewed to evaluate immunological responses and inflammation. This study emphasized the decrease in the biomarkers, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), suggesting that the medication enhanced oral health by regulating inflammatory processes. The results showed that salivary biomarkers could be used as non-invasive measures of periodontal disease treatment effectiveness. Salivary biomarkers were assessed to gauge patient inflammation levels, namely IL-1β and TNF-α. The two biomarkers are important markers of the immune response in the mouth. The inflammatory condition of periodontal tissue improved due to treatment that decreased the inflammatory cytokines, showing the use of salivary biomarkers for tracking the development of periodontal disease and response to treatment. Based on the collected data, TNF-α and IL-1β in the extract-treated group were significantly lower than the levels found in the placebo group. This study showed how the two indicators could be used to track and assess the performance of periodontal treatments [17].

4. Discussion

This systematic study reports that scientists have drawn more attention to using salivary biomarkers to identify periodontal disease in the elderly. The investigation reported inflammatory biomarkers and ratio variations in elderly patients with periodontitis. The results of this systematic review offer a comprehensive examination of the therapeutic and diagnostic applications of salivary biomarkers in identifying aging-related periodontal disease.

Every analyzed patient had a diagnosis of periodontitis, but the degree and severity of the condition differed, signifying a spectrum of mild to severe presentations. Some studies concentrated on more advanced instances, and others included cases of chronic periodontitis (CP). A more comprehensive understanding of how various degrees of periodontal inflammation react to treatment and the measurement of biomarkers is made possible by this variation in disease type. Studies that discovered a difference are considered less likely to be biased among the few comparing the same biomarkers. There appears to be no correlation between the danger of bias and the possibility that a study would uncover a meaningful difference. Significant differences were found in four investigations where the selection satisfied the higher criteria. In general, the entire results for all salivary biomarkers were comparable. The quantity of studies is significant when restricting the field of focus to diagnosis and using stringent inclusion and exclusion criteria. Randomized controlled trials comprising data of 210 participants from four studies conducted in South Korea, the US, and Europe between 1961 and 2024 were included in the review. Pro-inflammatory cytokines (IL-1β and IL-6), matrix metalloproteinases (MMP-1, MMP-3, MMP-8, and MMP-9), oxidative stress indicators, and calcium levels were the primary biomarkers investigated.

Individuals with periodontitis frequently have higher levels of salivary biomarkers, such as IL-1β, IL-6, and MMPs, which represent active inflammation and tissue degradation. According to a 1999 workshop, the elderly were most frequently seen to have the start of CP [18]. Clinical studies show that gingival inflammation, periodontitis severity, and periodontal disease advancement are correlated with increased levels of IL-1β and periodontal disease progression [19,20]. The presence of bacterial components connected to the osseous resorption process in periodontal diseases stimulates the production of IL-1β, which is a cytokine generated by macrophages, a major modulator of the inflammatory response, and the most investigated protein-based salivary biomarker [19–21].

IL-1β has the most differential expression and potential for therapeutic application in distinguishing between gingivitis and periodontitis [19]. The upregulation of this biomarker is important in patients with severe periodontitis and cognitive deterioration, which can occur in the elderly population [22]. Clinical evidence not only presents the connection between IL-1β and periodontitis but also shows that increased IL-1β causes a cascade of inflammatory responses and promotes bone resorption [23]. IL-1β strongly stimulates the deterioration of periodontal tissue, while the characteristics include promoting bone resorption and synthesizing tissue-degrading proteinases [24]. Cytokines that promote inflammation, such as IL-1β and IL-6, influence systemic diseases [25]. Correspondingly, cytokine-based strategies can potentially improve both periodontitis and systemic health [23]. Following secretion, the accumulating IL-1β contributes to the pathophysiology of periodontitis by inciting a sequence of inflammatory responses [26]. Leucocyte recruitment, neutrophil infiltration, and enhanced local blood flow are primarily attributed to IL-1β in the inflammatory site [27]. Furthermore, IL-1β is a strong stimulator of bone resorption, making it a featured cytokine in periodontitis.

Collagenolytic enzymes and MMPs, which aid in the breakdown of extracellular matrix and cause bone resorption and tissue damage, are expressed more when IL-1β is present [27]. Higher baseline levels of biomarkers such as MMP-1 and IL-6 in saliva predicted a greater inflammatory response in periodontal tissues, suggesting the potential for determining the disease severity. Numerous studies have examined IL-6 levels in other diseases and used these biomarkers as diagnostic criteria for disease grades [28]. IL-6 is significant because it contributes to forming certain cellular and humoral immune responses through terminal B-cell differentiation, immunoglobulin production, and T-cell activation, in addition to inducing active-phase responses. In the context of these facts, IL-6 is a modulator of inflammation from the acute to the chronic phase [29].

The changes were not often statistically significant, but some studies have shown clinical improvements with decreased biomarkers and periodontal inflammation levels in treatment groups. The study by Deng et al. shows that serum inflammatory markers (IL-6, MMP-8, and TNFα) and periodontal indicators (PI, sulcus bleeding (SBI), GI, pocket depth (PD), and clinical attachment loss (CAL)) can be used to evaluate periodontal improvements [30]. According to Sorsa et al., individuals with periodontal disease had significantly increased MMP-8 levels in the GCF, which were connected with periodontitis severity [31].

Based on the results of this comprehensive review, salivary biomarkers are promising methods for monitoring and diagnosing periodontal damage early in older populations. Measuring pocket depth and clinical attachment loss are two invasive traditional diagnostic methods for periodontitis that cannot show the condition until considerable tissue damage has occurred. Meanwhile, biomarkers such as matrix metalloproteinases (MMP-1, MMP-3, MMP-8, and MMP-9) and interleukins (IL-1β, IL-6) may be early indications of inflammation and connective tissue deterioration in periodontal disease. This review supports the diagnostic use of specific biomarkers by showing the correlation between increased levels of the biomarkers in saliva and inflammation of periodontal tissue and the advancement of the disease.

This review supplements other new data to clarify the potential of salivary biomarkers for identifying periodontal degradation with aging, and the results appear to be consistent with the current investigation. The definition of salivary biomarkers implicated in periodontitis was uniform across the included studies. The generalizability of the results was impacted by the selection procedures, which were frequently disclosed sufficiently, and blinding at any stage has been discussed.

The included studies showed that biomarker levels mainly dropped after treatment interventions, but the results were not often statistically significant. Variables, including limited sample sizes, brief follow-up periods, and variations in biomarker responses, tend to cause the discrepancy. Although biomarkers such as MMP-1 and IL-6 are predictive in identifying "high responders" to periodontal inflammation, individual differences in biomarker expression imply that a panel of markers may be more accurate in diagnosing the condition than a single usage. This review emphasizes the need for additional studies to standardize the use of biomarkers in clinical settings, particularly for elderly individuals who may have immunosenescence-related variations in immunological function. Salivary biomarker studies can lead to non-invasive, affordable methods for detecting high-risk patients and monitoring the course of periodontal disease and the effectiveness of treatment over time.

This review shows the potential of salivary biomarkers as noninvasive markers for detecting and tracking periodontal disease. Numerous studies reported clinical benefits, but the corresponding changes in biomarkers have occasionally been inconsistent. This suggests that more standardized methods of measuring and interpreting salivary biomarkers are required before the markers can be extensively used in clinical practice.

5. Conclusion

In conclusion, salivary biomarkers are valuable indicators of periodontal disease in aging, which provide a non-invasive method of detecting and monitoring periodontal destruction. These biomarkers hold the potential to predict disease progression and evaluate treatment effectiveness, although further studies with larger sample sizes are recommended to establish stronger clinical guidelines.

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7. Conflict of Interest:

The authors declare no conflicts of interest.

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Author's Contribution

W.P.; manuscript draft, Conceptualization, Methodology, Accuration data, MJ and HOA.; writing original draft preparation, Methodology and Editing, SHS and EI.; Supervision, Methodology, NMA; Editing. All authors have read and agreed to the published version of the manuscript.