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# Procalcitonin and C-reactive Protein as Alternative Salivary Biomarkers in Infection and Inflammatory Diseases Detection and Patient Care: A Scoping Review

Francesco Carlo Tartaglia[1], Shahnawaz Khijmatgar[2], Massimo Del Fabbro[3], Cinzia Maspero[2], Alberto Caprioglio[2], Francesco Amati[1,4], Davide Sozzi[5]

**Affiliations**

[1] Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Italy.

[2] UOC Maxillo-facial Surgery and Dentistry, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, 20100 Milan, Italy.

[3] Department of Biomedical, Surgical and Dental Sciences, University of Milan, School of Dentistry.

[4] IRCCS Humanitas Research Hospital, Respiratory Unit, Via Manzoni 56, 20089 Rozzano, Milan, Italy.

[5] MD, Operative Unit of Maxillo-Facial Surgery, Fondazione IRCCS San Gerardo dei Tintori, 20900 Monza, Italy;
Department of Medicine and Surgery, School of Medicine and Surgery, University of Milano Bicocca, 20900 Monza, Italy.

**Correspondence:**
Dr. Shahnawaz Khijmatgar
E-mail: khijmatgar@gmail.com



**Abstract**

**Background** In ambulatory and hospital settings, inflammatory diseases stand a significant challenge for both patients and clinicians. These conditions, often serving as precursors to sepsis, necessitate effective differentiation between bacterial and viral respiratory diagnoses. Procalcitonin (PCT) and C-Reactive Protein (CRP) have played crucial roles in this differentiation process, aiding in risk stratification and guiding decisions on antibiotic therapy initiation and duration. While blood has been a conventional medium for detecting these biomarkers, there is a lack of evidence regarding their detection in saliva. Hence, the scoping review aimed to assess the potential of procalcitonin (PCT) and C-reactive protein (CRP) in saliva as alternative biomarkers for identifying and monitoring infectious and inflammatory diseases.

**Materials and Methods** PRISMA guidelines for scoping reviews was followed. Electronic databases including PUBMED, Scopus, Web of Science, Cochrane database, and OVID Medline were systematically searched using specific terms combined with boolean operators. Studies evaluating both salivary and blood levels of PCT, CRP, or both and reporting on correlation in biomarkers level between the two body fluids were included. No limitations regarding study design, publication year and language were applied. Data extraction utilized a piloted template, and descriptive statistics was employed.

**Results** The studies included in the review involved a range of conditions from respiratory infections and systemic diseases to metabolic and cardiac conditions. Significant

correlations between salivary and serum PCT and CRP levels were reported across multiple studies. While most studies reported positive correlations, indicating saliva's potential to reflect systemic inflammatory states, the degree of correlation varied, and a few studies found no significant correlation, highlighting the need for further research.

**Conclusion** The review emphasized the promising role of salivary diagnostics to identify systemic inflammatory states, which could prove pivotal in detecting and managing various health conditions. The importance of standardizing saliva collection and biomarker detection methods to enhance non-invasive, patient-centered healthcare approaches is underscored.

**Keywords:** Procalcitonin, C-reactive Protein, Salivary biomarkers, Infection detection, Inflammatory diseases, Non-invasive diagnostics

# 1 Introduction

Saliva is increasingly promoted as an alternative bio-fluid to blood for point-of-care diagnostics[1]. The emergence of salivary diagnostics introduces a shift away from the conventional reliance on blood-based assessments. Procalcitonin (PCT) and C-reactive protein (CRP), key markers for bacterial infections and inflammation, have traditionally been measured in blood, yet recent advancements have piloted in a new direction where these crucial markers are detectable in saliva[2].

Inflammation and infection impact CRP and PCT levels in serum and saliva differently. CRP rises in both fluids during inflammation, but for example; salivary CRP is more tied to oral problems while serum CRP shows body-wide inflammation. PCT spikes in serum during severe bacterial infections and can also go up in saliva for oral infections separately from serum levels. Genetic differences affect how much of these markers show up, with IL-6 gene variations influencing CRP and possibly PCT too, though more research is needed.

Collecting serum through blood gives a full picture but is invasive, while saliva is easy and non-invasive but can be affected by diet, oral care, gingival crevicular fluid, oral microbiome and hydration. For diagnosis, serum CRP is a solid marker for overall inflammation, and checking both serum and salivary CRP can improve accuracy. Serum PCT is very specific for bacterial infections, and salivary PCT can help spot oral infections [3–7].

Interestingly, the scientific literature presents a complex dynamic of PCT and CRP levels in both saliva and blood. Serum CRP levels span an extensive spectrum, ranging from 0.14 mg/L[8] to a 106.1 mg/L[9], while saliva CRP levels vary from 0.05 μg/L[10] to approximately 3.1 ng/mL[9]. Similarly, serum PCT levels vary between 0.05 ng/mL[11] and 210.1 ng/mL[12], with salivary concentrations ranging from 0.03 ng/mL[13] to 68.6 ng/mL[12].

## Procalcitonin (PCT) and C-Reactive Protein (CRP) in Serum and Saliva

Normal serum concentrations of PCT are typically <0.05 ng/mL. In cases of systemic inflammation, particularly bacterial infection, PCT levels can rise rapidly. For example, in sepsis, PCT levels can range from 0.5 ng/mL to >10 ng/mL, with higher levels indicating more severe infection and potential organ dysfunction [14]. While PCT is primarily measured in serum, recent studies have explored its presence in saliva. Salivary PCT levels are generally lower than serum levels, but they can still provide valuable diagnostic information. The detection of PCT in saliva is challenging due to its lower concentration, but advances in analytical techniques have

improved its detection [3].

There are other reports as well. Normal serum CRP levels are typically <10 mg/L. In response to inflammation or infection, CRP levels can rise significantly, often exceeding 100 mg/L. Elevated CRP levels are associated with a variety of conditions, including cardiovascular disease, diabetes, and autoimmune disor- ders [15]. Salivary CRP levels are generally lower than serum levels, but they can still serve as a useful marker of systemic inflammation. The optimal collection volume for salivary CRP is 225 $\mu$L, with a sensitivity of 1.79 pg/mL and an assay range of 25 pg/mL to 1600 pg/mL [16].

To determine the presence of certain infections and conditions, specific cut-off levels for pro-calcitonin (PCT) and C-reactive protein (CRP) are used. For upper respiratory tract infections, a PCT level between 0.1 and 0.25 nanograms per milliliter (ng/mL) suggests limiting antibiotic treatment in intensive care settings [17]. When it comes to urinary tract infections, a PCT level of 0.25 ng/mL helps assess how much the kidneys are affected. In cases of ventilator-associated pneumonia, PCT levels between 0.1 and 0.25 ng/mL aim to reduce unnecessary antibiotic use without causing harm [18].

For CRP, a serum level above 10 milligrams per liter (mg/L) usually points to inflammation or infection. Elevated CRP levels above 3 mg/L are linked to a higher risk of cardiovascular events. These cut-off levels help healthcare providers make more accurate diagnoses and treatment decisions [19].

The diagnostic reliability of CRP and PCT in saliva and serum depends on the context of the infection and the specific clinical question being addressed. For systemic infections, serum PCT and CRP are reliable markers. However, for localized oral infections, salivary PCT and CRP can provide additional diagnostic value [5].

This article, through a scoping review of existing studies, not only explores the complex differences within these variations but also synthesizes findings to interpret the clinical significance of these correlations. Additionally, the review expands the scope of diagnostic possibilities and presents a non-invasive and convenient alternative for early disease detection.

Therefore, the primary objective of the review is to determine whether salivary CRP and PCT could be detected and quantified. Secondly, it focuses on exploring the possibility of using salivary diagnostics as a feasible alternative or complement to conventional blood tests by examining the strength of the correlations between salivary and blood-based PCT and CRP markers in patients with underlying inflammatory conditions. The review also highlights the challenges associated with methodological variability, such as differences in saliva collection techniques (e.g., stimulated versus unstimulated) and assay methodologies, which significantly impact biomarker correlation and reliability. Through a detailed analysis and insights into the effectiveness and potential uses of salivary diagnostics, the review provides an overview of the current knowledge. By adopting this approach, we establish a groundwork for future studies.

# 2 Materials and Methods

## 2.1 Search Strategy

The literature search was conducted by two independent researchers, F.C.T. and S.K., utilizing multiple databases including PubMed, Scopus, Web of Science, and Google Scholar. Scoping review guidelines, as outlined by Tricco et al. [20] were followed. The objective was to gather and analyze studies investigating the use of salivary diagnostics as either an alternative or a

supplementary method to traditional blood assays for the detection of Procalcitonin (PCT) and C-reactive protein (CRP).

## 2.2 Inclusion Criteria and Search Terms

The search was designed to encapsulate scientific literature relevant to our research question. A broad array of search terms was employed: “Saliva”, “Procalcitonin (PCT)”, “C-reactive Protein (CRP)”, “Inflammation”. The following search strings were applied across the databases to ensure a thorough investigation:

- **PubMed/Scopus/Web of Science:** (((saliva) OR (Saliva)) AND (((c-reactive protein) OR (CRP)) OR (procalcitonin))) AND (Inflammat*)
- **Google Scholar:** (TITLE-ABS-KEY ( saliva ) ) AND ( ( TITLE-ABS-KEY ( procalcitonin ) ) OR ( ( TITLE-ABS-KEY ( c-reactive AND protein ) ) OR ( TITLE-ABS-KEY ( crp ) ) ) ) AND ( TITLE-ABS-KEY ( inflammat* ) )

Additionally, the reference lists of the most pertinent studies and reviews identified were scrutinized for further eligible research articles.

## 2.3 Scoping Review Protocol

The review was pre-registered on the Open Science Framework (OSF)[21]. We included studies published up until February 29th, 2024, focusing exclusively on research conducted with human subjects and presented in the English language.

## 2.4 Exclusion Criteria

The exclusion criteria were rigorously followed, excluding studies that did not directly relate to the research topic, lacked adequate data or detailed methodology, were review articles, or were not available in full text.

## 2.5 Data Management

Relevant information from selected studies was gathered, consisting of publication details, study design, participant characteristics, sample size, and levels of PCT and CRP in saliva and blood, along with correlations, clinical implications, and limitations. The extracted data underwent a qualitative synthesis to identify trends, patterns, and correlations between salivary and blood levels of PCT and CRP. The results were summarized using tables and narrative descriptions. No risk of bias assessment was performed, and no meta-analysis of the included studies was attempted, due to the nature of the scoping review.

## 2.6 Quality Assessment of Studies

The studies were assessed for quality using criteria such as clear objectives, sampling methods, exposure and outcome measurements, confounder adjustments, blinding, follow- up adequacy, group comparability, and statistical analysis. The Newcastle-Ottawa Scale (NOS) was applied to scoping review as there were some non-randomised studies [22], while other studies were assessed based on the variables mentioned in the quality assessment of studies. Each study received an overall rating, such as ”High” or ”Moderate,” based on these factors. Low, moderate and high overall rating was given based on other domains included. The quality assessment of studies was done by F.T and S.K

# 3 Results

After screening of the initially retrieved articles, 23 studies investigated the correlation between salivary and blood PCT and/or CRP and are listed in Table 1.

| Author and Year | Type of Study | Number of Patients | Disease group | Method of detection | Timing of detection | p-value | Correlation Presence | Correlation Coefficient | CRP/PCT/Both | Quality of Study |
|---|---|---|---|---|---|---|---|---|---|---|
| Ogura et al.2023 | Cross-sectional case control | N/A | Aspiration pneumonia | LC-MS/MS | N/A | 0.0001 | YES | 0.16 | CRP | Moderate |
| Monib et al. 2023 | Case-control study | N/A | Acne vulgaris | ELISA kits (Sun Red Biological Technology, China) | N/A | <0.001 | YES | r=0.79 | CRP | Moderate |
| Hatami et al.2022 | Cross-sectional | N/A | Oral lichen planus (OLP) | ELISA kit (Fine test, Wuhan Fine Biotech, China) | 10 am-12:30 pm | N/A | YES, positive correlation in oral potentially malignant disorders | N/A | CRP | High |
| C¸elik et al.2022 | Comparative study | 87 | Pneumonia | ELISA kit | Post neurophysiological test | <0.001 | YES | PCT=0.737, CRP=0.703 | PCT | Moderate |
| Plank et al.2021 | Cross-sectional study | 136 | NO | ELISA | N/A | <0.001 | YES | 0.59 | CRP | High |
| Datla et al. 2021 | Cross-sectional study | Disease=30, Control=30 | Sepsis | CRP-Turbilatex method | N/A | 0.01 | YES | 0.63 | CRP | Moderate |
| Uppal et al.2021 | Prospective | Disease=35, Control=35 | Leukoplakia, OLP, OSMF | N/A | 7:00 AM | 0.04 | YES | r=0.370 | CRP | Moderate |
| Omran et al.2021 | Observational | N/A | Sepsis | ELISA kit (Modified) | N/A | N/A | NO | N/A | CRP | Moderate |
| Gofine et al. 2021 | Cross-sectional | 64 | Acute respiratory infection | ELISA kit (Kinesis) | N/A | <0.001 | YES | 0.670 | CRP | Low |
| Mohan et al.2021 | Cross-sectional study | Disease=26, Control=26 | Periodontitis | Latex agglutination test for CRP, ELISA for PCT | N/A | <0.001 | YES | r=0.78 (correlation with disease) | PCT | Moderate |
| Galhardo et al.2020 | Observational | N/A | Sepsis | ELISA kit | 5:30-7:30 am | <0.05 | NO | N/A | Both | Moderate |
| Wettero et al.2020 | Observational | 129 | Life conditions, Stress and Health Study (LSH) cohort | MILLIPLEX MAP Human e CRP Assay | Morning | 0.26 (morning), <0.05 (evening) | YES (evening) | 0.54 | CRP | Low |
| Tvarijonaviciute et al.2020 | Case-control study | Disease=100, Control=100 | Healthy | N/A | N/A | <0.001 | YES | Total=0.770, Boys=0.805, Girls=0.775 | CRP | Moderate |
| Tsai et al.2020 | Comparative study | 35 | Pneumonia | ELISA | N/A | <0.001 | YES | r=0.679 | CRP | Low |
| Foley et al.2012 | Laboratory-based analytical study | Healthy=55, Disease=31 | Hypertrophic Cardiomyopathy | BCA kit (Thermo Scientific) | N/A | "0h: p<0.001, 8h: p=0.0217, 16h: p=0.0899, 24h: p=0.0491, 48h: p=0.0108" | YES/NO | "0h: r=0.8, 8h: r=0.71, 16h: r=0.49, 24h: r=0.52, 48h: r=0.66" | CRP | High |
| Bhavsar et al.2015 | Cross-sectional study | 35 | COPD | Bio-plex Array reader | 9am-12pm | N/A | YES | Disease: r=0.86, Control: r=0.62 | CRP | Moderate |
| Iyengar et al.2014 | Cross-sectional study | 259 | Nil | ELISA (Salimetrics, UK) | 3 min after overnight fast | <0.001 | YES | 0.62 | CRP | Low |
| Byrne et al.2013 | Experimental study | N/A | DSM-IV depressive illness | Luminex IS100-based multiplex kits | 8 am-6 pm | <0.05 (non-parametric), <0.01 (parametric) | YES | Multiple values | CRP | Moderate |
| Labat et al.2013 | Observational | 28 MI, 28 Healthy | Subclinical cardiovascular disease | CRP ELISA (BioVendor) | N/A | P<0.0001 | YES | r=0.73 | CRP | Moderate |
| Dizgah 2012 | Cross-sectional study | 55 | Myocardial infarction | ELISA kit (Salimetrics, Assaypro) | N/A | Unstimulated: p=0.038, Stimulated: p=0.044 | YES | Multiple values | CRP | Low |
| Gustafsson et al.2011 | Observational | N/A | Nil | Aminoprocalcitonin ELISA assay | N/A | N/A | NO | N/A | CRP | Low |
| Punyadeera et al.2011 | Cross-sectional case control | N/A | Cardiac conditions | LC-MS/MS | N/A | N/A | YES | $r^2$=0.84, Slope=0.032, Intercept=0, p>0.1 | CRP | High |
| Dillon et al.2010 | Case-control study | N/A | Nil | ELISA kits (Sun Red Biological Technology) | N/A | N/A | NO | $R^2$=0.001 | CRP | Low |

Table 1: Summary of studies analyzing CRP and PCT correlations.

The studies, conducted globally from 2008 to 2023, appear in respected journals such as *Clinical Proteomics*, *Journal of Cosmetic Dermatology*, and *Frontiers in Immunology*. The research designs which are most prevalent are cross-sectional and case-control study designs which have been applied to explore diseases like aspiration pneumonia, acne vulgaris, and periodontitis. Furthermore, it can be noted that most utilized methods include ELISA kits and liquid chromatography, emphasizing non-invasive diagnostic approaches.

In 2023, Ogura et al.[23] reported a positive correlation in aspiration pneumonia patients ($r = 0.16$, $p = 0.0001$), suggesting that salivary CRP can reflect serum levels. Similarly, Hatami et al. in 2022[24] showed a positive correlation in oral lichen planus, a potentially malignant oral disorder, suggesting that saliva can reveal systemic inflammation. Monib et al. in 2022[25] found a robust correlation ($r = 0.79$, $p < 0.001$) in acne vulgaris, further underscoring saliva's diagnostic value. Ç elik et al. in 2022[12] identified a strong correlation for both PCT and CRP in pneumonia, which could significantly impact pediatric care where non-invasive methods are particularly beneficial. Uppal et al. in 2021[26] revealed a correlation in potentially malignant oral disorders such as leukoplakia, Oral Lichen Planus (OLP), and Oral Submucous Fibrosis (OSMF) ($r = 0.370$, $p = 0.04$).

Gofin et al. in 2021[13] demonstrated a correlation in acute respiratory infection ($r = 0.67$, $p < 0.001$), and Mohan et al.[11] reported a robust correlation in periodontitis ($r = 0.78$, $p < 0.001$) for PCT, whereas Plank et al. in 2021 [27] reported a correlation between salivary and ematic values of CRP in healthy adolescents. Similarly, Tsai et al. in 2020[28] found a strong correlation in pneumonia ($r = 0.68$, $p < 0.001$), and Labat et al. in 2013[29] reported a significant correlation in subclinical cardiovascular disease ($r = 0.73$, $p < 0.0001$).

These studies collectively support the potential of saliva as a diagnostic tool. However, some diseases, such as sepsis (Galhardo et al. 2020[30]) and hypertrophic cardiomyopathy (Foley et al. 2012[31]), show varied results in the correlation strength over time, indicating the complexity of biological responses captured by saliva. Dizgah in 2012[32] also showed a positive correlation in myocardial infarction, albeit with a lower coefficient for stimulated versus unstimulated saliva, suggesting that the collection method matters.

The presence of a correlation in conditions ranging from respiratory diseases, oral pathologies, metabolic syndromes, to cardiac conditions reinforces the hypothesis that salivary biomarkers can effectively mirror systemic states. However, the variability in correlation strength and the occasional lack of significant correlation, as seen in studies by Omran et al. (2021)[33] and others, necessitate further research to understand the limitations and optimize saliva-based diagnostics.

Table 2 presents the results of 35 studies that investigated the levels of CRP and/or PCT in serum and saliva and correlated them to the pathological condition of the patients. The studies utilize a range of research designs, including cross-sectional, case-control, meta-analysis, and observational studies, and they cover a variety of conditions such as aspiration pneumonia, oral lichen planus, obesity, and more. These studies aim to explore the potential of saliva as a diagnostic fluid, providing a non-invasive alternative to blood samples for monitoring disease markers.

| Author and Year | Year | Study Design | Disease Group | No. of Patients | Saliva Collection Timing | CRP (Serum) | CRP (Saliva) | PCT (Serum) | PCT (Saliva) |
|---|---|---|---|---|---|---|---|---|---|
| Ogura et al. | 2023 | Cross-sectional case control | Aspiration pneumonia | N/A | N/A | N/A | N/A | N/A | N/A |
| Hatami et al. | 2022 | Meta-analysis | Oral lichen planus (OLP) | 45 | N/A | 0.97 mg/L (95% CI: 0.56, 1.38) | 0.64 $\mu$g/L (95% CI: 0.37, 0.90) | N/A | N/A |
| Safabakhsh et al. | 2022 | Comparative study | Obesity | Obese=46, Control=46 | 8–10 am | N/A | Control = 2.84 (SD=1.03) ng/mL, Disease = 2.63 (SD=0.69) ng/mL | N/A | N/A |
| Monib et al. | 2022 | Case-control study | Acne vulgaris | N/A | N/A | Control: 0.46 ± 0.32 mg/L, Disease: 1.31 ± 0.85 mg/L | Control: 0.92 ± 0.16 mg/L, Disease: 2.59 ± 1.17 mg/L | N/A | N/A |
| C¸elik et al. | 2022 | Cross-sectional | Pneumonia | N/A | 10 am–12:30 pm | Admission: 10.3 (7.6–14.8) mg/L, Discharge: 7.9 (5.9–9.9), Healthy: 3.0 (1.9–4.3) | Admission: 1.9 (1.5–3.5) mg/L, Discharge: 1.4 (1.1–1.8), Healthy: 24.0 (16.4–33.4) | 210.1 (122.2–317.6) ng/mL | 68.6 (50.6–133.1) ng/mL |
| Plank et al. | 2021 | Comparative study | NO | 87 | Post neurophysiological test | 0.97 (SD=1.43) mg/L | 155.63 (SD=159.28) pg/mL | N/A | N/A |
| Datla et al. | 2021 | Cross-sectional study | Sepsis | 136 | N/A | All= 19, 57.7 mg/L, Group I= 44.6, 83 mg/L, Group II= 19.4, 43.8 mg/L, Group III= 6.2,9 mg/L, Control= 0.11–1.39 ng/mL | All= 0.4, 20.6 ng/mL, Group I=0.54, 2.95 ng/mL, Group II=0.33, 1.44 ng/mL, Group III=0.13,0.3 ng/mL, Control= 0.11–1.39 ng/mL | N/A | N/A |
| Uppal et al. | 2021 | Cross-sectional study | Leukoplakia, OLP, OSMF | Disease=30, Control=30 | N/A | Disease: 5.91 ± 3.11 mg/L, Group 1a= 7.31±3.34 mg/L, Group 1b=4.51±2.83 mg/L, Control= 2.18 ± 0.66 mg/L | Disease: 1.00 ± 0.45 mg/L, Group 1a= 1.21±0.44 mg/L, Group 1b=0.69±0.46 mg/L, Control= 0.48 ± 0.33 mg/L | N/A | N/A |
| Good et al. | 2021 | Observational | Bronchiectasis | 30 | N/A | N/A | N/A | 1.5 $ng{\cdot}mL^{-1}$ (95% CI: 1.0–2.1) | Healthy: 0.4 $ng{\cdot}mL^{-1}$ (95% CI: 0.2–0.9) |
| Dizgah et al. | 2012 | Observational | Myocardial infarction | 28 MI, 28 healthy | N/A | Day 2 MI: 7.03 ± 0.36 $\mu$g/mL, Control: 3.84 ± 0.60 $\mu$g/mL | Stimulated: Day 1 MI= 3.75 ± 0.92 ng/mL, Healthy= 0.26 ± 0.11 ng/mL, Unstimulated: Control= 0.68 ± 0.21 ng/mL | N/A | N/A |
| Punyadeera et al. | 2011 | Laboratory-based analytical study | Cardiac conditions | Healthy=55, Disease=31 | N/A | Disease: 1–406 mg/L, Median: 33 mg/L | Healthy: 50.6–872.4 pg/mL, Mean: 285 pg/mL, Disease: 11.9–11330 pg/mL, Median: 727 pg/mL | N/A | N/A |

Table 2: Studies correlating CRP and/or PCT levels in serum and saliva to a pathological condition.

## Serum CRP Levels

For CRP levels in serum, the minimum reported value for healthy individuals is 0.11-1.39 mg/L, as found in the study by Datla et al. (2021)[34] concerning sepsis. The lowest value for diseased individuals is 0.14 to 31.1 mg/L, with a median of 2.0 mg/L as documented by Dillon et al. (2010)[8], although the specific disease context in this entry is not provided. The maximum reported value on the other hand, for diseased individuals is documented as 406 mg/L by Punyadeera et al. (2011)[35] for cardiac conditions.

## Saliva CRP Levels

Regarding CRP levels in saliva, the lowest value for healthy individuals is 0.08 mg/L, which comes from the study by Byrne et al. (2013)[36] on DSM-IV depressive illness. The minimum salivary CRP value for diseased individuals is $0.48 \pm 0.33$ mg/L, found by Uppal et al. (2021)[26], which studied leukoplakia, oral lichen planus (OLP), and oral submucous fibrosis (OSMF). The highest reported value of salivary CRP for diseased individuals is $2.59 \pm 1.17$ mg/L, as found in the study by Monib et al. (2022)[25] concerning acne vulgaris. In a study by Safabakhsh et al. [37] salivary levels of CRP of control and case group was 2.84 and 2.63 ng/mL when comparing obese and normal-weighted patients.

### Serum PCT Levels

For PCT levels in serum, the minimum value found for healthy individuals was reported as $< 0.05$ to $0.4$ ng/mL by Good et al. (2020)[38], who studied patients with bronchiectasis, where the lower range indicates the healthy participants in the study. The lowest value for diseased individuals is 0.05 ng/mL from the study by Mohan et al. (2021)[11] regarding periodontitis. Considering the maximum values, the highest reported value for diseased individuals is $210.1$ ($122.2-317.6$) ng/mL, which has been documented by Çelik et al. (2022)[12] for pneumonia.

### Saliva PCT Levels

For PCT levels in saliva, the minimum value reported in healthy individuals is 0.03 ng/mL found in the study by Mohan et al. (2021)[11] for periodontally healthy patients. The lowest value recorded for diseased individuals is 0.20 ng/mL, noted in the research by Redman et al. (2019)[39] concerning medullary thyroid carcinoma and hyperreactive gingiva. The highest reported value for diseased individuals is $68.6$ ($50.6-133.1$) ng/mL, as found in the study by Çelik et al. (2022)[12] for pneumonia.

### Causation

Aspiration pneumonia is often caused by the inhalation of oropharyngeal or gastric contents into the lungs. Common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* [23]. These bacteria can in fact trigger a robust inflammatory response, leading to elevated C-reactive protein (CRP) and procalcitonin (PCT) levels. Elevated CRP and PCT levels in both serum and saliva indicate a systemic inflammatory response [23]. The presence of these biomarkers in saliva suggests that local oral infections can contribute to systemic inflammation.

Periodontitis is primarily caused by bacterial infections, with *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola* being key pathogens. These bacteria can induce local inflammation in the gums and surrounding tissues [11]. The local production of these biomarkers in saliva indicates that periodontal infections can contribute to systemic inflammation, highlighting the importance of oral health in overall health.

Hypertrophic Cardiomyopathy (HCM) is a genetic disorder characterized by the thickening of the heart muscle. While not directly caused by infections, it can be associated with systemic inflammation due to the chronic stress on the heart [40]. Elevated CRP levels in serum and saliva have been reported in patients with HCM, indicating a state of chronic inflammation [31]. PCT levels may also be elevated due to systemic stress and the potential for secondary infections.

## Discussion

Biomarkers like CRP and PCT levels in serum and saliva are routinely used in clinical practice to assess inflammation and infection. However, CRP levels are influenced by a wide range of systemic and local conditions, including acute infections, chronic inflammatory diseases, and even stress, leading to considerable variability[41, 42]. Similarly, PCT is used for inflammatory conditions, but the values obtained from various studies which have used different methodologies and assays for measurement are not standardized, contributing to the variability in the reported levels.

The presence of PCT in both serum and saliva can indicate the systemic and local (oral) inflammatory status, respectively[25]. Procalcitonin is a marker often used to assess the presence and severity of bacterial infections, and its levels can rise significantly in response to a systemic

bacterial infection. For instance, studies like Ç elik et al. (2022)[12] demonstrated robust correlations for PCT ($r = 0.737$), reflecting its clinical relevance. The variations in the levels of PCT in serum and saliva may be due to differences in the assay methods used, the timing of sample collection, and the health status of the subjects from whom the samples were collected. It is also worth noting that the values provided in some research articles come with a large standard deviation, indicating variability within the study population[11, 38, 43].

In terms of biomarker dynamics, CRP is a well-established marker of inflammation, rapidly increasing in response to acute inflammation and infections[39]. PCT, on the other hand, is more specific to bacterial infections and might not rise significantly in viral infections or inflammatory diseases that are not caused by bacteria[11, 43, 44]. The variability in CRP levels in both serum and saliva is considerable, suggesting that CRP can be influenced by a wide range of conditions and is a less specific marker compared to PCT. The concentration levels vary between these two biomarkers. The serum levels of CRP appear to be much higher than those of PCT in most cases, reflecting its broader response to inflammatory stimuli. Salivary levels of both CRP and PCT are generally lower than their serum counterparts, which is consistent with the understanding that systemic concentrations of these biomarkers are usually higher than those found locally in saliva[45, 46].

The articles found in the present scoping review suggest some degree of correlation between serum and saliva levels for both CRP and PCT, indicating that saliva might be a viable medium for non-invasive monitoring of systemic inflammation. However, the strength and clinical significance of this correlation vary widely. For CRP, saliva levels may reflect both local oral inflammatory conditions and systemic inflammation[40, 47], whereas PCT in saliva could be more directly linked to systemic bacterial infections due to its lower baseline levels and more specific response[48]. Nevertheless, the relationship between these biomarkers in saliva and serum is complex. CRP levels in saliva may be influenced by both systemic inflammation and localized oral conditions, such as periodontitis, which elevate salivary CRP disproportionately[49]. In contrast, PCT, with its lower baseline levels and bacterial specificity, exhibits stronger serum-saliva correlations in systemic conditions like sepsis[35]. The presence and levels of CRP in saliva and serum can be used for the diagnosis and monitoring of various diseases, but due to its non-specific nature, it should be used in conjunction with other clinical findings and biomarkers. PCT, with its specificity for bacterial infections, could potentially guide antibiotic therapy and might be an important marker in distinguishing bacterial from viral infections or non-infectious inflammation when assessed in serum[49]. Saliva testing for PCT could offer a less invasive method for monitoring, but its clinical utility requires further validation.

The variability in study outcomes, including a wide range of values for CRP and PCT, can be linked to the diversity in the studied population, assay techniques, and research design. For instance, demographic factors such as age and sex further influence biomarker levels; for example, Tvarijonaviciute et al. (2020)[50] observed higher median CRP correlations in boys ($r = 0.805$) compared to girls ($r = 0.775$), potentially reflecting physiological or hormonal differences. Comorbidities such as smoking and COPD also introduce variability. Bhavsar et al. (2015)[51] highlighted elevated CRP levels in smokers with COPD, underscoring the interplay between systemic conditions and salivary biomarker behavior.

Standardization of testing methods and timing of sample collection is crucial for the accurate interpretation of both CRP and PCT levels. The potential for non-invasive testing and detection of CRP and PCT in saliva opens the advantageous possibility for repeated measurements or monitoring, reducing patient discomfort and infection risk associated with blood draws. Therefore, while both CRP and PCT levels in serum and saliva show promise as biomarkers for inflammation and infection, their clinical interpretation requires careful consideration of the context, underlying conditions, and methodological differences across studies. Further research is needed to standardize saliva testing and to clarify the clinical implications of saliva-based measurements

for both CRP and PCT.

Various techniques were used for the detection of biomarkers in saliva. The most common method is the Enzyme-Linked Immunosorbent Assay (ELISA), which is used in various forms, including standard ELISA kits from different suppliers, modifications to the ELISA protocol, and sandwich ELISA designed specifically for saliva. Some studies utilized the Bio-Plex platform, which is compatible with the Luminex xMAP system for multiplex assays, allowing for the simultaneous measurement of multiple biomarkers.

Additionally, liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) is mentioned, which is a highly sensitive and specific method for biomarker detection. The CRP-Turbilatex method[26] and the Vidas BRAHMS PCT assay[52] are noted for the detection of C-reactive protein (CRP) and Procalcitonin (PCT), respectively. The Kryptor® method is also used for PCT measurement[46], while immunoassays on the Bio-plex Array[53] reader and MILLIPLEX MAP Human assays[29] are employed for cytokine profiling.

Some studies specify using enzyme immune assay kits developed for salivary measures by Salimetrics, which are likely tailored for the specific complexities of saliva as a sample matrix[8, 10, 29, 54]. The use of immunochemistry, typically more common in tissue analysis, was also reported for PCT. The detection methods reflect a balance between specificity, sensitivity, and the ability to multiplex, which is the simultaneous measurement of multiple biomarkers, increasing efficiency and providing a broader picture of the biological status.

Studies utilizing LC-MS, like Ogura et al. (2023)[23], demonstrated lower correlation coefficients for CRP compared to ELISA-based studies such as Monib et al. (2022)[25], emphasizing how assay sensitivity and specificity align with the detection of causal agents, such as bacterial or viral pathogens, thereby impacting reported outcomes. For PCT, Çelik et al. (2022)[12] highlighted a robust correlation using ELISA methods ($r = 0.737$), suggesting method-specific reliability. Timing of saliva collection also emerged as a critical factor; Wettero et al. (2020) reported diurnal variations in CRP levels, with stronger evening correlations ($r = 0.54$) compared to morning ($r = 0.26$)[41]. Additionally, saliva collection methods—stimulated versus unstimulated—significantly influenced biomarker levels. Dizgah et al. (2012) demonstrated stronger correlations for CRP with unstimulated saliva ($r = 0.289$) compared to stimulated saliva ($r = 0.249$), highlighting the dilution effect and the need for consistency in protocols[32].

The scoping review's results underline the need for rigorous methodologies and high-quality studies in evaluating biomarkers like CRP and PCT in saliva and serum. The studies included have employed a range of detection methods, enhancing the robustness of the findings and providing a broad perspective on biomarker behavior across different conditions and assay sensitivities.

To mitigate challenges in variability and enhance reliability for CRP and PCT measurements, standardized saliva collection and analysis protocols are crucial. Uniform guidelines should emphasize specific timing (e.g., morning samples for CRP to avoid diurnal effects) and consistent use of unstimulated saliva to minimize dilution variability across studies, also prioritizing techniques with validated sensitivity and specificity. For instance, Bio-Plex platforms demonstrated robust CRP correlations in Bhavsar et al. (2015)[51], while ELISA methods for PCT, as utilized by Çelik et al. (2022)[12], showed promising reliability. Implementing such standardization will address methodological inconsistencies and improve clinical utility.

There are several factors that influence these correlations and the limitations that impose on salivary diagnostics. Hormonal variations, particularly in women, can significantly impact biomarker levels. For instance, women often exhibit higher coefficients of variation (CV) for certain serum biomarkers due to menstrual cycle influences. However, studies have shown that these hormonal variations do not significantly affect salivary analytes, suggesting that saliva may be more stable in this regard. Another factor that affect is analysis.The precision of biomarker assays is crucial for accurate measurements. Studies have demonstrated that certain biomarkers, such as TNF-$\alpha$ A, sCD163, and sgp130, exhibit higher variability, which can affect the reliability

of salivary diagnostics. . To overcome this, analytical goals for biomarker tests should be set to maintain a coefficient of variation (CV) below 0.50 times the intraindividual biological variation (CVI) [4, 55, 56].

Other factors, including diet, oral hygiene, and hydration levels affect variation in diagnostics. These factors can introduce variability in salivary biomarkers. For example, hydration status can affect saliva viscosity, total protein concentrations, and osmolality, which in turn can influence biomarker levels [57–61].

Studies have shown that saliva generally exhibits weaker correlations with serum biomarkers compared to other biofluids like sebum. This is partly due to the lower concentrations of biomarkers in saliva compared to serum. For instance, metabolites like glycolithocholic acid 3-sulfate (GLCAS) and certain triglycerides were found to have significant correlations in serum but weaker correlations in saliva. The correlation between salivary and serum biomarkers can also be influenced by disease states. For example, COVID-19 positivity was found to alter the correlation maps between saliva and serum, resulting in weaker diagnostic power overall [56].

Saliva composition varies because it comes from different glands, each with unique makeup. This affects diagnostic results. Saliva also changes with taste, smell, and chewing, and blood contamination can skew findings. Collection methods like passive drool are simple but not ideal for everyone, while stimulated methods can alter analyte levels. Swabs are useful but can be tricky and lead to noncompliance. Many saliva analytes are temperature-sensitive, complicating storage, and repeated freezing and thawing can degrade biomolecules. Identifying biomarkers specific to certain health conditions is hard, as many are also found in blood [62].

Before collecting saliva, donors should be requested to avoid eating, drinking, using tobacco, or chewing gum for at least 30 minutes. For general use, the passive drool method works well for unstimulated saliva but consider swabs or stimulated methods for specific analytes or disease conditions or populations. Optimal times for specific biomarkers should be considered (e.g., cortisol: 7:30 AM to 9:00 AM; oral cancer metabolites: 2:00 PM to 8:00 PM). For DNA analysis, process samples right away without centrifuging or freezing. Store other samples at -70$^{o}$C to -80$^{o}$C after centrifugation and use stabilized kits if needed. Aliquot samples to avoid repeated freezing and thawing. Implement standardized protocols for biomarker analysis across labs to ensure consistency. Use internal and external quality control measures to validate tests. Provide clear instructions and practice sessions for participants and have trained professionals oversee collection in clinical studies [63–68].

Beyond ELISA and LC/MS, several alternative diagnostic methods can be utilized for detecting CRP and PCT. These include Meso Scale Discovery (MSD) with its electrochemiluminescence (ECL) detection and multiplexed immunoassay platform, which offers high sensitivity and the ability to measure multiple analytes simultaneously. Fluorescence-Linked Immunosorbent Assay (FLISA) provides high sensitivity and specificity with a direct sandwich technique for quantitative results. Lateral Flow Immunoassay (LFIA) is a rapid and simple method suitable for point-of-care testing, especially when enhanced with fluorescent labels. Photoluminescence-based immunochemical methods offer high sensitivity and reduced analysis time. Lastly, immunoassays based on chemiluminescence (CLIA) provide enhanced sensitivity and rapid detection capabilities[69, 70].

The use of established and novel assay methods further strengthens the findings by ensuring that the data reflects advancements in detection technology. However, the limitations are noteworthy; methodological inconsistencies remain a major barrier, as differences in saliva collection protocols (e.g., stimulated vs. unstimulated) and variability in assay methods significantly impact biomarker reliability[41, 71]. Additionally, the biological variability of salivary biomarkers, influenced by demographic factors such as age, sex, and comorbidities like smoking or chronic diseases, complicates their interpretation[30, 41, 44]. Age has been specifically identified as a significant confounder in studies of salivary biomarkers[30]. Another critical challenge is the

lack of large-scale validation studies to establish universal thresholds and diagnostic ranges for salivary biomarkers[26, 31, 35, 53, 72, 73]. Without these, the adoption of salivary diagnostics in clinical settings will remain limited.

## Conclusion

This scoping review provides a comprehensive summary of data across a spectrum of diseases, demonstrating the versatility of saliva as a diagnostic fluid. While the presence of a correlation has been documented, the causality and the exact nature of the relationship between salivary and serum levels remain to be fully elucidated. Methodological inconsistencies, variability due to biological factors, and a lack of large-scale validation studies remain major obstacles. Future research should focus on conducting longitudinal studies to explore the dynamic relationship between salivary and serum biomarkers across different diseases and demographics. Additionally, efforts to standardize assay techniques and establish reference ranges for salivary biomarkers are critical for widespread adoption in clinical practice.

## Conflict of Interest

None

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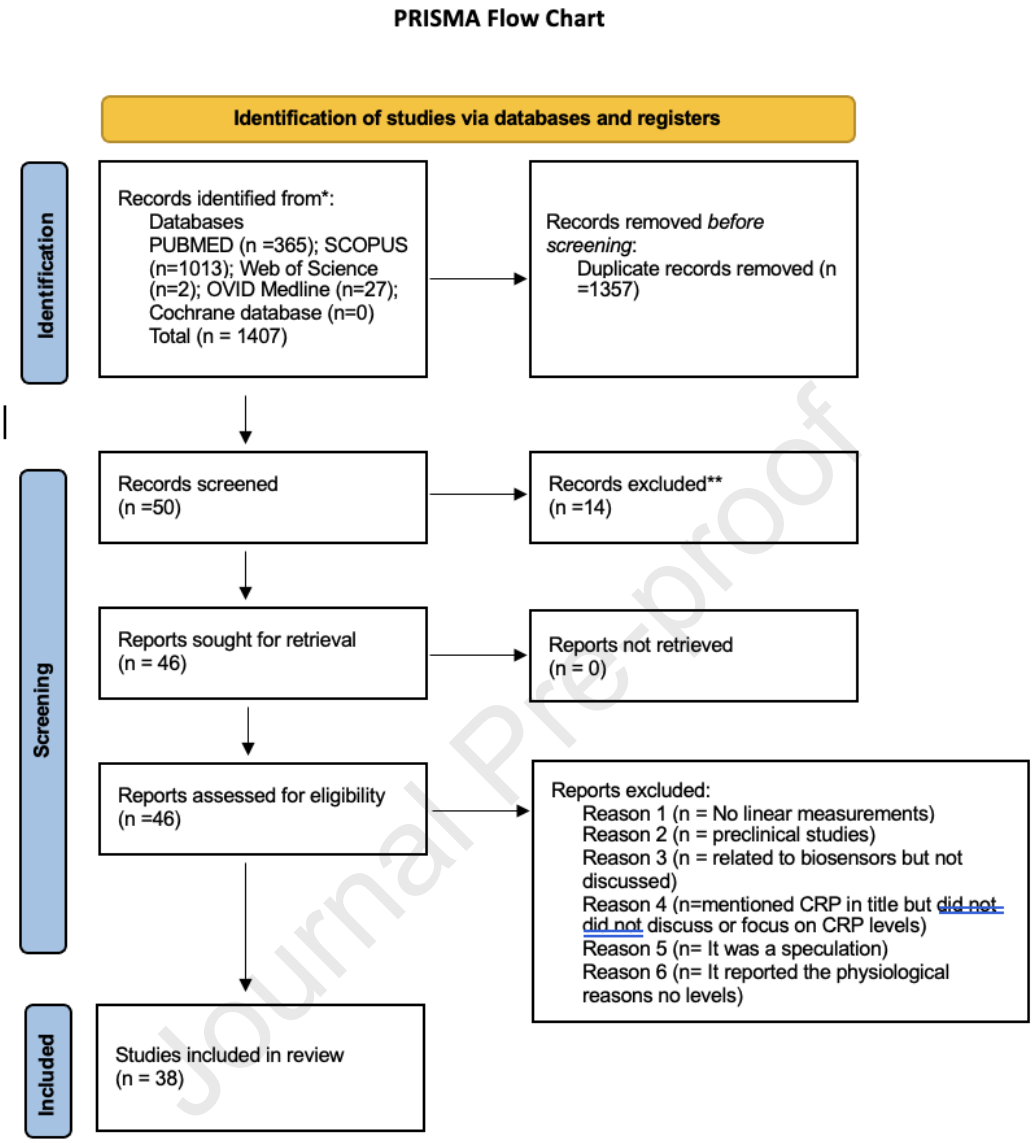


**Figure 1: PRISMA Flow chart on the stages of selection of articles**

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: