Research Article

Cytokine Profiling in Oral Chronic Graft-Versus-Host Disease: A Systematic Review of Salivary and Serum IL-6, IL-1α and IL-17

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Abstract

Background: Oral chronic graft-versus-host disease (cGVHD) is a frequent complication of allogeneic hematopoietic stem cell transplantation, characterized by mucosal inflammation and salivary gland dysfunction. Cytokines such as IL-6, IL-1α, and IL-17 have been proposed as potential biomarkers.

Objective: To evaluate the clinical significance of salivary and serum IL-6, IL-1α, and IL-17 in oral cGVHD.

Methods: A systematic review was conducted following PRISMA 2020 guidelines. Databases including PubMed, Scopus, Web of Science, and Google Scholar were searched. Original human studies assessing these cytokines in saliva or serum were included. Data were qualitatively synthesized and risk of bias was assessed using a domain-based methodological quality assessment.

Results: Out of 132 records, three studies met the inclusion criteria. Salivary IL-6 showed association with disease severity but inconsistent findings overall. Serum IL-17 was consistently elevated in cGVHD and significantly reduced following therapy, indicating its role in disease activity and treatment response. IL-1α showed no consistent clinical relevance. Salivary biomarkers demonstrated variability whereas serum cytokines, particularly IL-17 were more reliable.

Conclusion: Serum IL-17 appears to be the most promising biomarker for oral cGVHD. IL-6 shows moderate, context-dependent relevance while IL-1α has limited utility. Further large-scale studies are needed.

Keywords: Oral chronic graft-versus-host disease, cGVHD, IL-6, IL-1α, IL-17, cytokines; saliva, serum, biomarkers, inflammation

Introduction

Chronic graft-versus-host disease (cGVHD) is a major long-term complication following allogeneic hematopoietic stem cell transplantation (HSCT) and represents a significant cause of late morbidity and mortality among transplant recipients.[1,2] It is a multisystem disorder characterized by immune-mediated tissue injury that can affect the skin, liver, gastrointestinal tract, lungs and oral cavity. Among these oral involvement is one of the most frequent and clinically significant manifestations often presenting with mucosal erythema, ulceration, lichenoid changes and salivary gland dysfunction leading to xerostomia. These oral manifestations not only cause pain and functional impairment but also substantially compromise nutritional intake, speech and overall quality of life.[4-6]

The pathogenesis of oral cGVHD is complex and multifactorial, involving a dynamic interplay between donor-derived immune cells and host tissues. It is primarily driven by immune dysregulation, persistent antigenic stimulation, and chronic inflammatory responses that lead to epithelial damage and fibrosis.[7,8] T lymphocyte activation, particularly involving cytotoxic T cells and helper T-cell subsets, plays a central role in initiating and sustaining tissue injury. Additionally, damage to salivary gland structures contributes to reduced salivary flow and altered oral homeostasis further exacerbating disease severity.[9-11]

Cytokines are key mediators in the immunopathogenesis of cGVHD, acting as signaling molecules that regulate immune cell activation, differentiation and inflammatory cascades.[12,13] They contribute to both local tissue damage and systemic immune responses, making them attractive candidates as biomarkers for disease activity and progression. The identification of reliable cytokine biomarkers is of particular clinical importance, as it may enable early diagnosis, objective disease monitoring, and evaluation of therapeutic response, thereby improving patient management and outcomes.[14-16]

Among the various cytokines implicated, interleukin-6 (IL-6), interleukin-1 alpha (IL-1α), and interleukin-17 (IL-17) have gained increasing attention due to their established roles in inflammatory and autoimmune processes. IL-6 is a pleiotropic cytokine involved in acute and chronic inflammation, promoting immune cell activation and contributing to epithelial injury and tissue remodeling.[17,18] IL-1α is an early-response pro-inflammatory cytokine released by damaged epithelial cells, playing a critical role in initiating local inflammatory signaling

and amplifying tissue injury.[19,20] IL-17, predominantly produced by T-helper 17 (Th17) cells, has emerged as a key mediator in chronic inflammatory diseases, with evidence suggesting its involvement in fibrosis, mucosal damage, and sustained immune activation in cGVHD.[21,22]

The evaluation of cytokines in biological fluids has been explored as a potential diagnostic and prognostic tool.[23] Saliva, in particular, offers a non-invasive, easily accessible medium that reflects local inflammatory changes within the oral cavity, making it an attractive option for biomarker assessment. In contrast, serum cytokine levels provide insight into systemic immune activation and may better represent overall disease burden.[24-26] However, despite these advantages, the clinical applicability of salivary and serum cytokines in oral cGVHD remains uncertain. Variability in cytokine expression, methodological differences in detection techniques, and heterogeneity in study populations have contributed to inconsistent findings across studies.

Given these considerations, there is a need for a comprehensive and critical evaluation of the available evidence to clarify the role of these cytokines in oral cGVHD. Therefore, the present systematic review aims to assess the clinical significance of salivary and serum IL-6, IL-1α and IL-17 levels in patients with oral chronic graft-versus-host disease with particular emphasis on their potential as biomarkers for disease activity and therapeutic response.

Materials And Methods

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[27] ensuring a structured and transparent approach to the identification, selection, and synthesis of relevant studies.

Review Question

The review aimed to address the following research question:

What is the clinical significance of salivary and serum levels of IL-6, IL-1α and IL-17 in patients with oral chronic graft-versus-host disease?

Search Strategy

A comprehensive electronic literature search was performed across multiple databases including PubMed/MEDLINE, Scopus, Web of Science and Google Scholar. The search strategy incorporated combinations of Medical Subject Headings (MeSH) and free-text terms related to the condition and biomarkers of interest.

The following keywords were used:

“oral chronic graft-versus-host disease,” “cGVHD,” “cytokines,” “IL-6,” “IL-1 alpha,” “IL-17,” “saliva,” and “serum.”

Boolean operators (AND/OR) were applied to refine the search and ensure comprehensive retrieval of relevant studies. In addition, the reference lists of all included articles were manually screened to identify any further eligible studies.

Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria.

Inclusion criteria:

- Original peer-reviewed human clinical studies
- Studies involving patients diagnosed with oral chronic graft-versus-host disease
- Studies evaluating IL-6, IL-1α and/or IL-17
- Studies analyzing cytokine levels in saliva and/or serum

Exclusion criteria:

- Animal or in vitro studies
- Review articles, editorials or expert opinions
- Studies lacking relevant cytokine outcome data
- Studies not specifically focused on oral cGVHD

Study Selection

All retrieved records were initially screened based on titles and abstracts to exclude irrelevant studies. Full-text articles of potentially eligible studies were subsequently assessed against the predefined criteria. The selection process resulted in the inclusion of three studies in the final qualitative synthesis.

Data Extraction

Data extraction was performed using a standardized approach to ensure consistency. The following information was obtained from each included study:

- Author(s) and year of publication
- Study design
- Sample size and population characteristic

- Cytokines evaluated
- Type of biological sample (saliva and/or serum)
- Key findings and outcome measures

Data Synthesis

Due to heterogeneity in study design, sample characteristics and outcome measures, quantitative meta-analysis was not feasible. Therefore, the findings were synthesized qualitatively using a narrative approach focusing on the clinical relevance of cytokine levels in oral cGVHD.

Risk of Bias Assessment

The methodological quality of the included studies was assessed using a domain-based evaluation of potential bias, including confounding, selection bias, measurement of exposure, outcome assessment, missing data, and reporting bias.

Results

Study Selection

The systematic search identified a total of 132 records across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. After removal of 32 duplicate records, 100 unique records remained for title and abstract screening.

Following initial screening, 82 records were excluded due to irrelevance to the review topic, non-clinical study design, or absence of cytokine-related outcomes. The full texts of 18 articles were assessed for eligibility.

Of these, 15 studies were excluded for the following reasons:

- Review articles or expert opinions (n = 6)
- Animal or in vitro studies (n = 4)
- Studies not specific to oral cGVHD (n = 3)
- Studies lacking relevant cytokine data (n = 2)

Ultimately, 3 studies met all inclusion criteria and were included in the final qualitative synthesis.

The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Study Characteristics

The included studies comprised three original human clinical studies with varying methodological designs:

- One cross-sectional study evaluating salivary cytokines and clinical parameters[28]
- One prospective cohort study comparing cytokine levels between cGVHD patients and controls[29]
- One longitudinal study assessing cytokine changes following therapeutic intervention[30]

The key characteristics of the included studies are summarized in Table 1.

Cytokine Analysis

IL-6

The cross-sectional study by Fall-Dickson et al. demonstrated that salivary IL-6 levels were significantly associated with oral cGVHD severity, including mucosal erythema and ulceration and were also correlated with reduced health-related quality of life.

In contrast, the prospective cohort study by Pugliese et al. (2024)[29] reported no statistically significant differences in IL-6 levels between cGVHD patients and control groups, indicating variability in its diagnostic utility.

The longitudinal study by Ferella et al. (2026)[30] showed a non-significant reduction in salivary IL-6 levels following treatment, suggesting limited value as a biomarker for monitoring therapeutic response.

IL-17

Serum IL-17 emerged as the most consistent biomarker across the included studies. Pugliese et al. demonstrated that serum IL-17 levels were significantly elevated in patients with oral cGVHD compared to controls, indicating its role in disease pathogenesis.

Similarly, Ferella et al. (2026)[30] reported a significant reduction in serum IL-17 levels following topical corticosteroid therapy ($p = 0.006$), suggesting its potential as a marker of disease activity and treatment response.

IL-1α

IL-1α demonstrated no consistent association with disease severity or therapeutic outcomes. Both Pugliese et al. (2024)[29] and Ferella et al. (2026)[30] reported no statistically significant differences or changes in IL-1α levels, indicating limited clinical relevance.

Saliva vs Serum Findings

Salivary cytokine measurements demonstrated considerable variability and limited reproducibility, likely due to local factors such as salivary gland dysfunction and variations in secretion. In contrast, serum cytokine levels particularly IL-17 showed more consistent and clinically meaningful findings, suggesting greater reliability as biomarkers.

Risk of Bias

Risk-of-bias assessment indicated that all included studies had a moderate risk of bias primarily due to:

- Small sample sizes
- Single-center study designs
- Potential confounding variables
- Lack of standardized outcome measures

The detailed risk-of-bias assessment is presented in Table 2.

Discussion

This systematic review evaluated the clinical significance of IL-6, IL-1α, and IL-17 in oral chronic graft-versus-host disease (cGVHD) and demonstrated a progressive evolution in biomarker understanding. The included studies collectively suggested that serum IL-17 emerged as the most consistent and clinically relevant biomarker whereas IL-6 reflected localized inflammatory burden with variable reliability and IL-1α showed limited diagnostic and prognostic value.

The earliest included study by Fall-Dickson et al. (2010)[28] demonstrated a significant association between salivary IL-6 levels and oral disease severity, including erythema, ulceration, and symptom burden. This finding suggested that IL-6 functioned as a marker of local mucosal inflammation. However, this observation was not consistently supported in subsequent studies. Pugliese et al. (2024)[29] reported no significant difference in IL-6 levels between cGVHD patients and controls, and Ferella et al. (2026)[30] observed only a non-significant reduction in IL-6 following treatment. When these findings were correlated, IL-6 appeared to be context-dependent, influenced by disease phenotype rather than representing a stable biomarker of disease activity.

The heterogeneity of oral cGVHD provided a plausible explanation for these inconsistencies. Foundational work by Schubert et al. (1984)[31] established that oral cGVHD presented with diverse manifestations, including lichenoid lesions, ulceration, and mucosal atrophy. This was further supported by Noce et al. (2011)[32] and Fassil et al. (2012)[33], who demonstrated that oral cGVHD comprised multiple phenotypic patterns, including mucosal disease and salivary gland dysfunction. Additionally, Imanguli et al. (2008)[34] highlighted the involvement of salivary glands as a distinct pathological component, while Bassim et al. (2014, 2015)[35,36] confirmed that oral cGVHD represented a spectrum of disease rather than a single entity. These findings suggested that IL-6 may correlate strongly with mucosal inflammatory activity, but not with glandular or fibrotic disease components.

Further supporting studies reinforced this interpretation. Gomes et al. (2014)[37] demonstrated that mucosal lesions typically appeared earlier in the disease course, whereas salivary gland dysfunction developed later, indicating temporal variation in disease expression. Boer et al. (2015)[38] reported significant alterations in salivary composition following HSCT, suggesting that salivary biomarkers reflected multiple overlapping biological processes. These findings indicated that salivary IL-6 was influenced by both inflammatory and glandular factors, thereby limiting its specificity and reproducibility.

In contrast, IL-17 demonstrated consistent and clinically meaningful findings across the included studies. Pugliese et al. (2024)[29] reported significantly elevated serum IL-17 levels in oral cGVHD patients, while Ferella et al. (2026)[30] demonstrated a significant reduction in serum IL-17 following topical corticosteroid therapy ($p = 0.006$). These findings suggested that IL-17 was not only associated with disease presence but also responsive to treatment, indicating its potential as a dynamic biomarker of disease activity.

The role of IL-17 was further supported by extensive mechanistic and clinical evidence. Klimczak et al. (2019)[39] demonstrated increased IL-17 expression in oral mucosal lesions, confirming its involvement at the tissue level. Forcade et al. (2017)[40] demonstrated that an activated Th17-prone T-cell subset was associated with chronic graft-versus-host disease, highlighting the role of IL-17–mediated immune dysregulation. Furthermore, Pinto et al. (2022)[41] demonstrated upregulation of inflammatory gene expression consistent with Th17-mediated pathways. Collectively, these studies indicated that IL-17 played a central role in immune dysregulation and chronic inflammation in cGVHD.

Therapeutic studies further strengthened this association. Studies by Sari et al. (2007)[42], Park et al. (2013)[43] and Mawardi et al. (2010)[44] demonstrated significant clinical improvement with topical corticosteroid therapy. Similarly, Treister et al. (2016)[45] and Shazib et al. (2020)[46] reported favorable outcomes with topical immunosuppressive treatments. The findings of Ferella et al. (2026)[30], which showed a reduction in serum IL-17 following treatment, provided direct evidence linking cytokine modulation with clinical improvement. This suggested that IL-17 could serve as a treatment-responsive biomarker, bridging the gap between immunopathology and clinical outcomes.

IL-1α, in contrast, demonstrated limited clinical relevance. Although Fall-Dickson et al. (2010)[28] associated IL-1α with oral dryness, both Pugliese et al. (2024)[29] and Ferella et al. (2026)[30] found no significant association with disease severity or treatment response. This suggested that IL-1α primarily functioned as an early

epithelial injury marker and did not reflect sustained inflammatory activity, limiting its utility in chronic disease monitoring.

The comparison between salivary and serum biomarkers further clarified these findings. Salivary biomarkers demonstrated considerable variability due to factors such as glandular dysfunction, altered secretion, and microbial influences. Proteomic studies by Devic et al. (2014)[47] and Bassim et al. (2012)[48] demonstrated complex alterations in salivary protein profiles, while Costa-da-Silva et al. (2021)[49] identified loss of acinar cell-specific proteins in oral cGVHD. Additionally, microbiome studies by Rashidi et al. (2024)[50] demonstrated significant alterations in oral microbial composition, further influencing salivary biomarker variability. These findings suggested that saliva reflected a multifactorial biological environment, limiting the reliability of single cytokine measurements.

Conversely, serum biomarkers provided a more stable and reproducible measure of systemic immune activity. This was supported by consistent findings related to IL-17 across studies, suggesting that serum-based biomarkers were more reliable than salivary biomarkers in oral cGVHD.

Further supporting evidence from systemic biomarker studies reinforced this conclusion. Greinix et al. (2015)[51] demonstrated immune cell alterations associated with cGVHD, while Yu et al. (2016)[52] identified a biomarker panel predictive of disease activity. Du et al. (2018)[53] further identified novel cytokine biomarkers, suggesting that multimarker approaches may be superior to single cytokines.

Additional studies highlighted the multifactorial nature of oral cGVHD. Agha-Hosseini et al. (2007)[54] and Bardellini et al. (2019)[55] demonstrated that xerostomia and salivary dysfunction were independent disease components. Albert et al. (2007)[56] and Kaurinovic et al. (2022)[57] showed variability in response to immunosuppressive therapies, while Pengpis et al. (2023)[58] confirmed clinical heterogeneity using NIH criteria. Furthermore, Siripornkitti et al. (2024)[59] demonstrated variable therapeutic responses to corticosteroids, reinforcing the complexity of disease mechanisms.

Biomarker-focused studies by Rozmus and Schultz (2011)[60] and Wolff et al. (2018)[61] emphasized the need for standardized biomarker validation, while Sava et al. (2020)[62] highlighted variability in therapeutic outcomes across clinical trials. Histopathological studies by Santos et al. (2014)[63] further demonstrated the complexity of tissue-level changes in oral cGVHD.

Despite these insights, the evidence remained limited by small sample sizes, single-center designs, and methodological heterogeneity. Differences in assay techniques, sampling methods, and patient populations limited direct comparability across studies. However, the overall pattern across included and supporting studies suggested a clear hierarchy of biomarker relevance.

Overall, the findings indicated that:

- IL-17 demonstrated the strongest and most consistent evidence for disease activity and treatment response
- IL-6 showed moderate, context-dependent relevance, primarily reflecting local inflammation
- IL-1α demonstrated limited clinical utility

Importantly, this review highlighted a paradigm shift in biomarker understanding, with earlier studies emphasizing IL-6 and more recent evidence identifying IL-17 as a central mediator of disease activity. The findings of this review are limited by the small number of included studies and heterogeneity in study design, which restricts generalizability.

Future research should focus on multicenter longitudinal studies integrating cytokine panels with clinical scoring systems.

TABLES

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Population	Sample Type	Cytokines	Intervention	Follow-up	Key Findings
Fall-Dickson et al. (2010)[28]	USA	Cross-sectional	Oral cGVHD patients (n=42)	Saliva	IL-6, IL-1α	None	Not applicable	IL-6 correlated with severity, erythema, and ulceration; IL-1α was associated with oral dryness

Pugliese et al. (2024)[29]	Italy	Prospective cohort	cGVHD (n=10), oral lichen planus (n=10), healthy controls (n=10)	Saliva and serum	IL-6, IL-1α, IL-17	None	Cross-sectional	Serum IL-17 was significantly elevated in cGVHD; salivary cytokines did not differ significantly across groups; IL-6 and IL-1α were not significant
Ferella et al. (2026)[30]	Italy	Longitudinal	Oral cGVHD patients (n=10)	Saliva and serum	IL-6, IL-1α, IL-17	Topical clobetasol	Pre–post	Serum IL-17 decreased significantly after treatment; salivary IL-6 showed a non-significant trend; IL-1α remained unchanged; pain and OMRS improved significantly; no significant cytokine-symptom correlation was found

Table 2. Risk of Bias Assessment

Study	Confounding Bias	Selection Bias	Measurement of Exposure	Outcome Assessment	Missing Data	Reporting Bias	Overall Risk
Fall-Dickson et al. (2010)[28]	Moderate (clinical heterogeneity, symptom variability)	Moderate (single-center, limited sample)	Low (standardized salivary cytokine assays)	Low (validated clinical scoring and QoL tools)	Low	Low	Moderate
Pugliese et al. (2024)[29]	Moderate (group variability: cGVHD, OLP, controls)	Low (comparative group design)	Low (standardized ELISA methods)	Low (objective cytokine measurement)	Low	Low	Moderate
Ferella et al. (2026)[30]	Moderate (small sample size, no control group)	Moderate (single-center, limited cohort)	Low (validated serum and salivary assays)	Low (pre–post clinical and biochemical evaluation)	Low	Low	Moderate

FIGURES

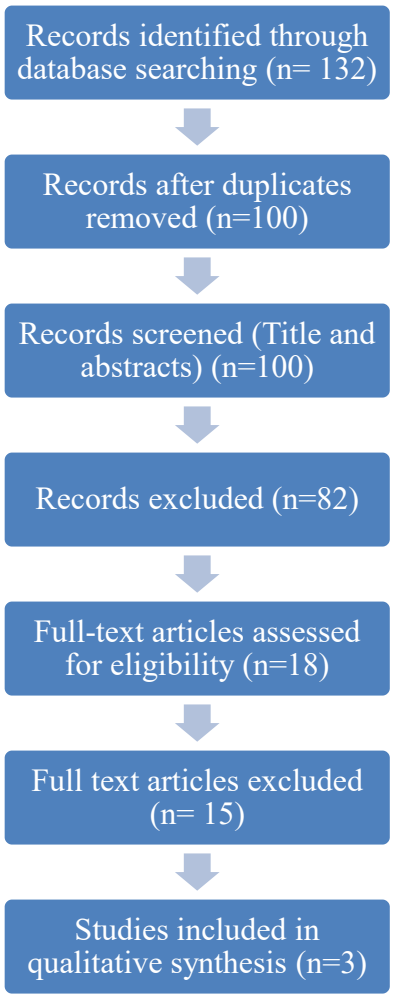

Figure 1: PRISMA Flowchart

Conclusion

This systematic review demonstrated that among the evaluated cytokines, serum IL-17 emerged as the most reliable and clinically relevant biomarker for oral chronic graft-versus-host disease, showing consistent association with disease activity and responsiveness to therapeutic intervention. In contrast, IL-6 exhibited moderate and context-dependent significance, primarily reflecting localized mucosal inflammation, while IL-1α showed limited and inconsistent clinical utility. The findings also highlighted that serum-based biomarkers were more reproducible and reliable than salivary cytokines, which were influenced by multiple confounding factors including salivary gland dysfunction and microbial variations. Overall, the evidence suggested a shift from traditional inflammatory markers toward immune pathway-driven biomarkers such as IL-17, emphasizing the need for future multicenter, longitudinal studies incorporating standardized methodologies and multimarker approaches to establish robust, clinically applicable biomarker models in oral cGVHD.

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