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IL-1β Expression and Change Following SRP in Gingival Crevicular Fluid in Patients with Periodontitis: A Systematic Review and Meta-Analysis

(Pengekspresan dan Perubahan IL-1β Mengikuti SRP dalam Cecair Krevikular Gingival pada Pesakit dengan Periodontitis: Suatu Kajian Sistematik dan Meta-Analisis)

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ABSTRACT

Periodontitis is a chronic inflammatory periodontal lesion, characterised by progressive destruction of connective tissue and continuous loss of marginal bone surrounding the teeth. Cytokines and chemokines play a role in the pathogenesis of chronic periodontitis (CP). Among these, IL-1β is considered one of the most important inflammatory factors and tissue-destructive cytokines. Despite numerous investigations identifying the role of IL-1β in gingival crevicular fluid (GCF) in bone resorption and connective tissue destruction, the efficacy of GCF IL-1β in assisting the diagnosis and predicting the progression of CP remains undetermined. The objective of this study was to ascertain whether IL-1β can be used as a diagnostic and progressive biomarker for CP. To this end, GCF IL-1β levels were compared between periodontally healthy controls and subjects diagnosed with CP, as well as between subjects before and after scaling and root planning (SRP) for CP. Additionally, the correlations between GCF IL-1β levels and various clinical parameters, including probing depth (PD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI), and gingival index (GI), were analysed within the CP group. A comprehensive search of the PubMed, Embase and Cochrane databases was conducted from their inception up to 1 April 2022. The electronic search terms employed were 'periodontitis OR periodontal diseases' AND 'Interleukin-1β OR IL-1β' AND 'gingival crevicular fluid'. The review includes cross-sectional, case series, single arm studies, prospective and retrospective cohort studies, as well as randomised controlled trials (RCTs) and non-RCTs. The studies that compared IL-1β levels (either the concentration or the total amount) between healthy controls and subjects with CP, or between subjects with CP before and after SRP, were included in the review. The meta-analysis was conducted using Review Manager 5.3. The analysis included data from 50 studies comprising 1,502 patients. The concentration, total amount of GCF IL-1β, and GCF volume in subjects with CP were found to be significantly higher than in healthy controls ($P < 0.01$). The concentrations of GCF IL-1β in CP group decreased significantly at 1 month ($P = 0.04$), 1.5 months and 3 months following SRP compared with the preoperative baseline ($P < 0.01$). The total amounts of GCF IL-1β in CP group decreased significantly at postoperative 1 month, 1.5 months, 3 months, and 6 months compared with the baseline, and the *P*-values are all less than 0.01 except $P = 0.02$ for 1.5 months. GCF volumes in CP group decreased significantly at 1 months, 3 months, and 6 months following SRP compared with the baseline ($P < 0.01$). The total amount of GCF IL-1β was found to be correlated positively and closely with BOP ($r = 0.894$, $P = 0.041$) in CP group. No significant correlations were identified between the total amount of IL-1β and other clinical parameters, nor between the concentration of IL-1β and any clinical parameter ($P > 0.05$). GCF IL-1β may serve as a diagnostic and progressive biomarker of chronic periodontitis (CP). The measurement of GCF IL-1β levels may prove beneficial in the diagnosis of initial periodontitis, the assessment of the therapeutic efficacy of SRP for CP, the determination of disease severity and activity, and the prediction of CP progression.

Keywords: Chronic periodontitis; gingival crevicular fluid; IL-1β; periodontal diseases; scaling & root planning

ABSTRAK

Periodontitis adalah lesi periodontal radang kronik, dicirikan oleh kemusnahan progresif tisu penghubung dan kehilangan berterusan tulang marginal di sekeliling gigi. Sitokin dan kemokin memainkan peranan dalam patogenesis periodontitis kronik (CP). Antaranya, IL-1β dianggap sebagai salah satu faktor keradangan yang paling penting dan sitokin yang merosakkan tisu. Walaupun banyak penyelidikan mengenal pasti peranan IL-1β dalam cecair krevikular gingival (GCF) dalam penyerapan tulang dan pemusnahan tisu penghubung, keberkesanan GCF IL-1β dalam membantu diagnosis dan

meramalkan perkembangan CP masih tidak dapat ditentukan. Objektif kajian ini adalah untuk memastikan sama ada IL-1β boleh digunakan sebagai biopenanda diagnostik dan progresif untuk CP. Untuk tujuan ini, tahap GCF IL-1β dibandingkan antara kawalan sihat periodontal dan subjek yang didiagnosis dengan CP, serta antara subjek sebelum dan selepas penskalaan dan perancangan akar (SRP) untuk CP. Selain itu, korelasi antara tahap GCF IL-1β dan pelbagai parameter klinikal, termasuk kedalaman probing (PD), tahap lampiran klinikal (CAL), pendarahan semasa probing (BOP), indeks plak (PI) dan indeks gingival (GI) dianalisis dalam kumpulan CP. Carian komprehensif bagi pangkalan data PubMed, Embase dan Cochrane telah dijalankan daripada penubuhannya sehingga 1 April 2022. Istilah carian elektronik yang digunakan ialah 'periodontitis ATAU penyakit periodontal' DAN 'Interleukin-1β ATAU IL-1β' DAN 'cecair krevikular gingiva'. Kajian itu termasuk keratan rentas, siri kes, kajian lengan tunggal, kajian kohort prospektif dan retrospektif, serta ujian terkawal rawak (RCT) dan bukan RCT. Kajian yang membandingkan tahap IL-1β (sama ada kepekatan atau jumlah keseluruhan) antara kawalan sihat dan subjek dengan CP atau antara subjek dengan CP sebelum dan selepas SRP telah dimasukkan dalam semakan. Meta-analisis telah dijalankan menggunakan Pengurus Kajian 5.3. Analisis termasuk data daripada 50 kajian yang terdiri daripada 1,502 pesakit. Kepekatan, jumlah amaun GCF IL-1β dan GCF dalam subjek dengan CP didapati jauh lebih tinggi daripada kawalan sihat (P <0.01). Kepekatan GCF IL-1β dalam kumpulan CP menurun dengan ketara pada 1 bulan (P = 0.04), 1.5 bulan dan 3 bulan selepas SRP berbanding dengan garis dasar praoperasi (P <0.01). Jumlah keseluruhan GCF IL-1β dalam kumpulan CP menurun dengan ketara pada 1 bulan, 1.5 bulan, 3 bulan dan 6 bulan selepas operasi berbanding dengan garis dasar dan nilai-P semuanya kurang daripada 0.01 kecuali P = 0.02 selama 1.5 bulan. Jumlah GCF dalam kumpulan CP menurun dengan ketara pada 1 bulan, 3 bulan dan 6 bulan selepas SRP berbanding dengan garis dasar (P <0.01). Jumlah keseluruhan GCF IL-1β didapati berkorelasi secara positif dan rapat dengan BOP (r=0.894, P=0.041) dalam kumpulan CP. Tiada korelasi yang ketara dikenal pasti antara jumlah IL-1β dan parameter klinikal lain, mahupun antara kepekatan IL-1β dan mana-mana parameter klinikal (P > 0.05). GCF IL-1β boleh berfungsi sebagai biopenanda diagnostik dan progresif periodontitis kronik (CP). Pengukuran tahap GCF IL-1β mungkin terbukti bermanfaat dalam diagnosis periodontitis awal, penilaian keberkesanan terapeutik SRP untuk CP, penentuan keterukan dan aktiviti penyakit serta ramalan perkembangan CP.

Kata kunci: Cecair krevikal gingiva; IL-1β; penskalaan & perancangan akar; penyakit periodontal; periodontitis kronik

INTRODUCTION

Periodontitis is a chronic inflammatory disease of the gums and surrounding bone that affects the teeth. It is characterised by progressive destruction of connective tissue and loss of bone around the teeth (Papapanou et al. 2018). The results of an epidemiological study demonstrated that the prevalence of chronic periodontitis (CP) was 59% in the adolescent population, 73% in the adult population, and 82% in the elderly population. Furthermore, CP has become one of the most common causes of tooth loss (Fatimah Maria et al. 2017). Despite the high prevalence, early diagnosis of CP remains challenging due to the lack of typical symptoms and signs at the early stage of periodontitis. The current diagnostic approach to CP relies on a combination of clinical measurements and radiographic parameters, including probing depth (PD), bleeding on probing (BOP), clinical attachment loss (CAL), plaque index (PI), gingival index (GI), and bone loss. Although the aforementioned diagnostic techniques were straightforward and non-invasive, the clinical indices were merely the consequence of disease progression and represented the current disease status. They did not reflect early lesions nor predict the progression of future lesions (Armitage 2004; Reddy 1997). It is therefore necessary to introduce a new indicator or approach to identify the initiation or predict the progression of CP. It would be advantageous if a new indicator could be developed that would identify active sites and predict the risk of disease progression in specific locations.

Gingival crevicular fluid (GCF) is an exudate derived from periodontal tissues and consists of a variety of host- and bacteria-derived products, as well as biomarkers. GCF has been widely used to evaluate the diagnosis, therapy, and prognosis of CP (Fatima et al. 2021). Pro-inflammatory cytokine IL-1β is one of the most extensively researched biomarkers in GCF. It has been demonstrated to play a role in periodontal tissue destruction and bone absorption, through the stimulation of osteoclast formation and prostaglandin E2 synthesis and release (Preshaw & Taylor 2011). Many studies had investigated GCF IL-1β level with conflicting results. Most studies reported both the concentration and the total amount of GCF IL-1β were significantly higher in CP group compared to healthy controls (Oh et al. 2015; Tsai, Ho & Chen 1995; Uraz et al. 2013) and decreased significantly following scaling and root planning (SRP), a most basic periodontal therapy (Buduneli et al. 2010; Goutoudi, Diza & Arvanitidou 2004; Oh et al. 2015; Sağlam et al. 2017; Tsai, Ho & Chen 1995). However, some studies showed IL-1β concentration did not differ between healthy control and CP group (Becerik et al. 2012; Goutoudi, Diza & Arvanitidou 2004; Tüter, Kurtiş & Serdar 2001; Wei et al. 2004; Yücel et al. 2008), and even decreased (Cetinkaya et al. 2013; Rawlinson et al. 2003). A better understanding of IL-1β level involved in CP could be helpful in identifying the initiation, activity state, progression of CP, and even in host-targeted preventive and therapeutic strategies.

Previous reviews had reported the cytokine profile in GCF and explored the roles of various cytokines in CP (Akram et al. 2016; Koidou et al. 2020; Stadler et al. 2016). So far, no study has systematically investigated GCF IL-1β, one of the most classical cytokines in CP. Considering GCF is easily accessible and can be collected frequently and non-invasively, if IL-1β can differentiate CP from healthy controls, can identify active sites from inactive sites, and can predict the disease's progression in certain sites, then, routine GCF IL-1β testing could become a personalized diagnostic, and progressive tool in clinical practice.

The present study was thus designed to focus on GCF IL-1β, with the objective of evaluating the validity of predicting disease initiation, severity, activity, and progression by comparing the difference in IL-1β levels between periodontally healthy subjects and subjects with CP, recording IL-1β level change following SRP for CP, and analysing the correlation of IL-1β levels with the clinical parameters including PD, CAL, BOP, PI, and GI in patients diagnosed with CP.

METHODS

FOCUSED QUESTIONS

(1) "Could GCF IL-1β level be used to distinguish healthy subjects from subjects diagnosed with CP?"
(2) "Could GCF IL-1β level be used to evaluate the treatment efficacy of SRP by comparing the difference of IL-1β level before and after SRP?"
(3) "Could GCF IL-1β level be used as a biomarker to judge the active sites and to predict the progression of CP?"

PROTOCOL REGISTRATION

The article was prepared according to Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic reviews and Meta-Analysis Statement guidelines (Higgins et al. 2019; Moher et al. 2009). The study protocol was registered on PROSPERO (http://www.crd.york.ac.uk/prospero) and the registration number is CRD42021289867.

LITERATURE SEARCH AND SELECTION CRITERIA

PubMed, Embase and the Cochrane Database were searched by two independent examiners (JW and QL) for articles published from the start of the database until April 1, 2022. Combinations of subject heading terms (MeSH and EMTREE) and free text terms utilized were '(periodontitis OR periodontal diseases) AND (Interleukin-1β OR IL-1β) AND gingival crevicular fluid' in the research. The language restriction was in English. Some articles in PubMed database from China were searched for full text in Chinese. Hand-searched potential articles were founded in the list of the references included in previous articles.

Inclusion criteria was as followed: 1) Clinical studies in which IL-1β level in GCF was compared between healthy controls and subjects with periodontal diseases or between before and after SRP for CP. 2) Cross-sectional studies, longitudinal studies, case series studies, single-arm studies, prospective/retrospective cohort studies, and randomized controlled trials (RCTs). 3) Studies providing valid data including the numerical values of mean and standard deviation (SD), or the data by which mean, and SD can be calculated according to relevant computational formula.

Exclusion criteria was as followed: 1) Animal studies, cellular models, *in vitro* studies, review papers, case reports, and letters to the editor; 2) Studies evaluating IL-1β level in gingival tissue, serum or saliva rather than GCF; 3) Subjects with a clear history of smoking or with systemic diseases including diabetes, hypertension, hyperlipidemia, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosus, or receiving local or systemic antibiotics, inhibitors of cyclooxygenase within the past 3 months, or receiving any periodontal treatment within the past 6 months; 4) Subjects with pregnancy, in menstrual period or menopause; and 5) Subjects with peri-implantitis, inflammation from tooth movement, aggressive periodontitis or only gingivitis.

DATA EXTRACTION AND OUTCOMES ASSESSED

Data were extracted on a self-designed sheet: first author, year of publication, country, study design, sample size (or number of patients), GCF collection tool and storage, GCF detection method, and the outcomes (IL-1β concentration, IL-1β total amount, GCF volume). Two investigators (JW and JLL) were responsible for data extraction and ensured the completeness and accuracy of the data. Any discrepancy was resolved by consensus with the third investigator (BC).

The corresponding author was contacted if data were not presented in the publication or needed clarification. The median was used as an estimate of the mean if it was not provided in the article. SD was calculated using the range (R) between the minimum and maximum value with the formula SD=R/4, using the interquartile range (IQR) with the formula SD=IQR/1.35, or using standard error (SE) with the formula $SD=SE*\sqrt{n}$ (n=sample size or number of patients) as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2019; Luo et al. 2018; Wan et al. 2014).

The present outcomes included GCF IL-1β levels (the concentration and the total amount) and GCF volume. This present study compared the differences of IL-1β levels between healthy controls and subjects with CP, recorded the changes of IL-1β levels at different timepoints following SRP and analyzed the correlation of IL-1β levels with the clinical parameters in CP group. Meta-analysis was performed based on the data of at least 4 studies.

RISK OF BIAS ASSESSMENT

Two investigators (JW and QL) were responsible for Risk of bias assessment. Any discrepancy was resolved by consensus with the third investigator (YCD). For cross-sectional studies, the risk of bias was assessed using AHRQ Evidence-based Practice Center (EPC) guidelines (Chang 2011; Viswanathan et al. 2008). An item would score 0 if answered NO or UNCLEAR, and 1 if answered YES. Article quality was assessed as low quality if the total score is 0~3, moderate quality if score is 4~7 and high quality if score is 8~11.

For RCTs, the risk of bias was assessed using the Cochrane Collaboration tool (Higgins et al. 2019). It was classified as 'high', 'low' or 'unclear' in the following seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. RCTs were considered high risk of bias if one or more domains were at high risk of bias, low risk of bias if all domains were at low risk of bias, and otherwise unclear risk of bias.

For cohort studies, the risk of bias was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS) (Norris et al. 2021; Stang 2010). According to the rules from NOS, studies were considered high risk of bias if four or more items were not described or answered, moderate risk of bias if two or three criteria were not described or answered, and low risk of bias otherwise.

For non-RCTs, case series, and single-arm clinical studies, the risk of bias was assessed using the MINORS (Slim et al. 2003). This instrument consists of 8 methodological items for case series, single-arm clinical studies and 12 items for non-RCT studies. Each primary study was assigned one score independently by two reviewers. Each item receives a maximum of 2 scores, so the ideal score is 16 or 24. The score more than 16 was considered as high quality.

STATISTICAL ANALYSIS

Data were expressed as mean ± SD. According to Cochrane guideline (Higgins et al. 2019), IL-1β concentration, total amount, and GCF volume were analyzed using the standardized mean difference (SMD) with 95% confidence intervals (95% CI) since the testing units varied or were not described in the included studies. Heterogeneity was estimated using the Q statistic and quantified using I^2 statistic. When I^2 >50%, the heterogeneity was considered significant (Higgins & Thompson 2002). A random-effects model was used regardless of heterogeneity. Publication bias was assessed by visually inspecting a funnel plot. The correlations between GCF IL-1β levels and the clinical parameters were analyzed using the Spearman rank correlation analysis. Review Manager 5.3 was used to conduct all statistical analyses and a two-sided P <0.05 was considered statistically significant.

RESULTS

STUDY SEARCH

A detailed flowchart of the literature search is shown in Figure 1. The search of the databases including PubMed, Embase, and the Cochrane identified 1094 potentially relevant articles. After duplicates removed 562 articles remained for title and abstract screening, one hundred and forty-three articles remained for full text reading after title and abstract screening. Finally, 50 full-text studies with 1502 patients fulfilling the eligibility criteria were included in the present meta-analysis after 93 articles were excluded for the following reasons: 1) 35 studies for smoking or systemic diseases; 2) 15 studies for aggressive or refractory periodontitis, only gingivitis, peri-implantitis, inflammation from tooth movement or *in vitro* teeth; 3) 30 studies for results in graphic format, absent of baseline, mean or SD or cannot be calculated using relative formulas; 4) 8 studies are lack of control group; 5) 5 studies are off-topic including IL-1β gene polymorphism and saliva IL-1β level.

CHARACTERISTICS OF STUDIES

The main characteristics of 50 studies included in the present meta-analysis are presented in Table 1, among which 20 studies were from Turkey, 10 studies from China, 5 studies from Japan, 3 studies from India, 2 studies from USA, 2 studies from Brazil, and 8 studies from other 8 countries. The most prevalent study design was cross-sectional studies (n=20), followed by RCTs (n=17) and cohort studies (n=10).

GCF sampling was mostly collected using filter paper strips except several studies used microcapillary pipettes (Bolyarova-Konova et al. 2020; Chaudhari et al. 2011; Faizuddin, Bharathi & Rohini 2003; Jacob, Nath & Patel 2014; Patel et al. 2018). The storage condition for GCF before detection is minus 80 or 70 degrees in most studies, minus 40 to 20 degrees in several articles, plus 4 degrees in only one article (Chaudhari et al. 2011), and another one article did not describe the storage temperature (Gamonal et al. 2000). All the studies used Elisa or Multiplex bead immunoassay techniques to detect IL-1β level except 2 studies used flow cytometry and radioimmunoassay, respectively (Cheng, Qi & Du 2010; Üstün et al. 2014).

In the clinical studies comparing the efficacy of SRP on healthy CP patients (control group) with CP patients with smoking or systemic diseases (test group), or those comparing the efficacy of SRP on CP patients (control group) with SRP combined with other therapies including laser therapy or antibiotics (test group), only the data of control group rather than test group were extracted. The present meta-analysis was performed based on at least 4 studies.

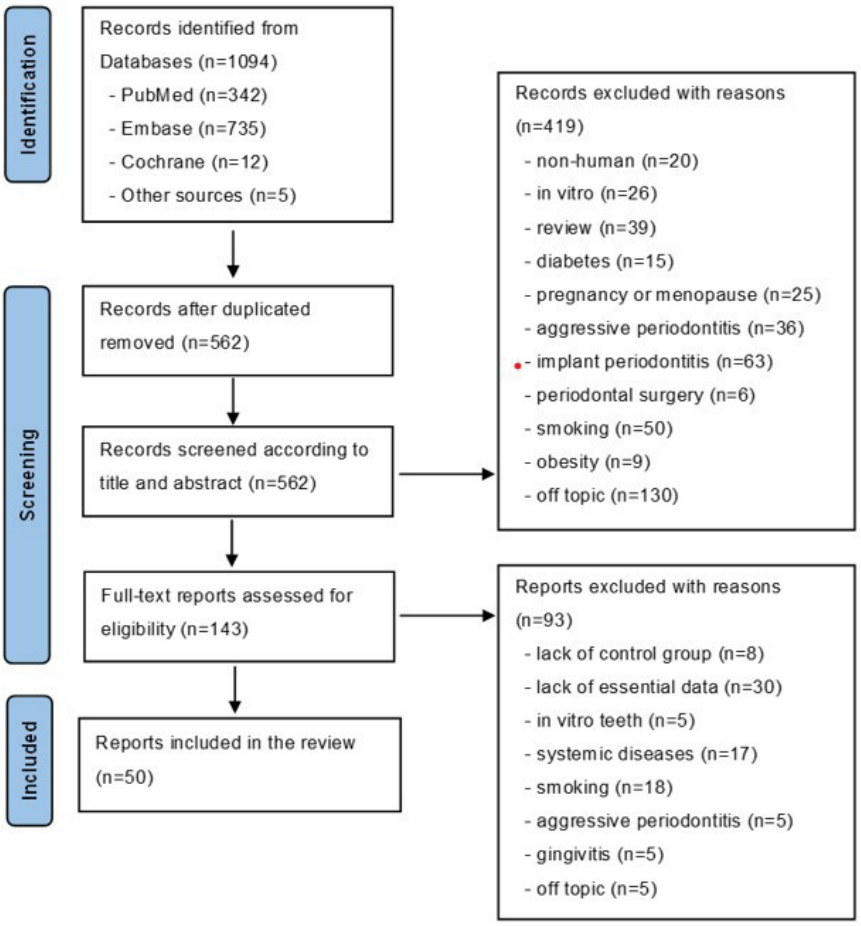

FIGURE 1. Flow chart of studies included in systematic review

TABLE 1. Characteristics of 50 studies included in the systematic review and meta-analysis

Author (year)	Country	Study design	Sample size (M/F)		Method	Collection tool and storage	Outcomes
			case	control			
Abduljabbar 2017	USA	RCT	28		Elisa	paper strips, -70 °C	IL-1b Con. GCF volume
Alexander 1996	UK	single arm study	13		Elisa	paper strips, -70 °C	IL-1b Con. GCF volume
Ambrosio 2017	Brazil	PCS	0/7		Elisa	paper strips, -80 °C	IL-1b Con. GCF volume
Buduneli 2010	Turkey	RCT	10/10		Elisa	paper strips, -40 °C	Unclear
Becerik 2012	Turkey	CSS	10/10	9/11	Elisa	paper strips, -40 °C	IL-1b Con. GCF volume
Bolyarova 2020	Bulgaria	CSS	24	19	Elisa	microcapillary pipettes, -80 °C	IL-1b Con.
Bulut 2001	Turkey	CSS	10/7	12/5	Elisa	paper strips, -70 °C	IL-1b Con. GCF volume

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Cheng 2010	China	non-RCT	11		Radioimm-unoassay	paper strips, -80 ℃	IL-1b Con.
Cetinkaya 2013	Turkey	CSS	10/6	8/8	Elisa	paper strips, -70 ℃	IL-1b Con. IL-1b amount
Chaudhari 2011	India	CSS	30	30	Elisa	microcapillary tubes, 4 ℃	IL-1b Con.
Cutler 1999	Turkey	CSS	1/6	2/4	Elisa	paper strips, -80 ℃	IL-1b Con.
Eltas 2012	Turkey	RCT	10/10		Elisa	paper strips, -80 ℃	IL-1b Con. GCF volume
Erbil 2020	Turkey	RCT	13/16		Elisa	paper strips, -80 ℃	IL-1b Con.
Escalona 2016	Venezuela	CSS	5/15	3/8	Elisa	paper points, -30 ℃	IL-1b Con.
Faizuddin 2003	India	CSS	20	20	Elisa	microcapillarypipettes, -70 ℃	IL-1b Con.
Fujita 2011	Tokyo	CSS	50	50	MBI	paper strips, -80 ℃	IL-1b Con. GCF volume
Gao 2018	China	CSS	37/31	35/32	Elisa	paper strips, -80 ℃	IL-1b Con.
Gamonal 2000	Spain	PCS	4/8		Elisa	paper strips, Unclear	IL-1b Con. IL-1b amount GCF volume
Gorgun 2021	Turkey	PCS	13/17		Elisa	paper strips,-80 ℃	IL-1b amount
Gundogar 2016	Turkey	RCT	9/16		MBI	paper strips,-80 ℃	IL-1b amount
Goutoudi 2004	Greece	RCT	15	15	Elisa	paper strips,-70 ℃	IL-1b Con. GCF volume
Hu 2017	China	RCT	6/5		Elisa	paper strips,-80 ℃	IL-1b Con.
Jacob 2014	India	CSS	11/4	10/5	Elisa	microcapillary pipettes, -70 ℃	IL-1b Con. GCF volume
Keles 2021	Turkey	CSS	25/25	13/12	Elisa	paper strips, -80 ℃	IL-1b amount GCF volume
Konopka 2012	Poland	PCS	14/16		Elisa	paper strips, -80 ℃	IL-1b amount
Liu 1999	China	RCT	8		Elisa	paper strips, -80 ℃	IL-1b Con.
Lu 2005	China	RCT	8/7		Elisa	paper strips, -80 ℃	IL-1b amount
Lui 2011	China	RCT	10/14		Elisa	paper strips, -70 ℃	IL-1b amount
Miyazaki 2003	Japan	RCT	18		Elisa	paper strips, -80 ℃	IL-1b amount GCF volume
Mogi 1999	Japan	CSS	19	70	Elisa	paper strips, -80 ℃	IL-1b Con.
Oh 2015	Japan	PCS	6/7		Elisa	paper strips, -80 ℃	IL-1b Con. IL-1b amount GCF volume
Patel 2018	Saudi Arabia	CSS	15		Elisa	microcapillary pipettes, -70 ℃	IL-1b Con.
Rabelo 2020	Brazil	PCS	15	15	MBI	paper strips, -80 ℃	IL-1b Con.
Shimada 2013	Japan	CSS	22	11	MBI	paper strips, -80 ℃	IL-1b amount GCF volume
Saglam 2014	Turkey	RCT	8/7		Elisa	paper strips, -80 ℃	IL-1b amount GCF volume

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Saglam 2017	Turkey	RCT	10/15	Elisa	paper strips, -80 °C	IL-1b Con. IL-1b amount
Sezen 2020	Turkey	RCT	27	Elisa	paper strips, -80 °C	IL-1b amount GCF volume
Tasdemir 2019	Turkey	RCT	18/18	Elisa	paper strips, -80 °C	IL-1b Con.
Teymouri 2016	Iran	non-RCT	12	Elisa	paper points, -70 °C	IL-1b Con.
Thunell 2010	USA	PCS	24	MBI	paper strips, -80 °C	IL-1b amount GCF volume
Toker 2012	Turkey	PCS	7/8	Elisa	paper strips, -80 °C	IL-1b amount
Tsai 1995	China	PCS	10/6	Elisa	paper strips, -70 °C	IL-1b Con. IL-1b amount GCF volume
Tuter 2001	Turkey	PCS	14/11	Elisa	paper strips, -70 °C	IL-1b Con. IL-1b amount GCF volume
Ustun 2014	Turkey	RCT	7/12	Flow cytometry	paper strips, -20 °C	IL-1b amount GCF volume
Ustun 2018	Turkey	RCT	12/8	Elisa	paper strips, -20 °C	IL-1b amount
Uraz 2013	Turkey	CSS	9/6 5/5	Elisa	paper strips, -20 °C	IL-1b Con. IL-1b amount GCF volume
Wei 2004	China	CSS	11/8 3/5	Elisa	paper strips, -20 °C	IL-1b Con. IL-1b amount GCF volume
Wu 2004	China	CSS	14/19 5/5	Elisa	paper strips, -80 °C	IL-1b Con.
Yucel 2008	Turkey	CSS	5/7 9/5	Elisa	paper strips, -80 °C	IL-1b Con. IL-1b amount GCF volume
Zhu 2015	China	CSS	13/14 12/16	MBI	paper strips, -20 °C	IL-1b Con.

Con., concentration; CSS, cross-sectional study; MBI, multiplexed bead immunoassay; PCS, prospective cohort study; RCT, randomized controlled trial; Temp., temperature

RISK-OF-BIAS ASSESSMENT

The risks of bias of 20 cross-sectional studies were assessed using AHRQ (Table 2). All studies defined the source of information, listed inclusion and exclusion criteria for exposed and non-exposed subjects, and indicated if evaluators of subjective components of study were masked to other aspects of the status of the participants. Nine articles were unclear in indicating time period used for identifying patients (Bolyarova-Konova et al. 2020; Bulut et al. 2001; Chaudhari et al. 2011; Escalona, Mastromatteo-Alberga & Correnti 2016; Faizuddin, Bharathi & Rohini 2003; Mogi et al. 1999; Uraz et al. 2013; Wei et al. 2004; Zhu et al. 2015). Two studies did not indicate whether or not subjects were consecutive if not population based (Faizuddin, Bharathi & Rohini 2003; Wu et al. 2004), and 14 studies were unclear (Bolyarova-Konova et al. 2020; Bulut et al. 2001; Cetinkaya et al. 2013; Chaudhari et al. 2011; Cutler et al. 1999; Escalona, Mastromatteo-Alberga & Correnti 2016; Jacob, Nath & Patel 2014; Keles Yucel et al. 2022; Mogi et al. 1999; Patel et al. 2018; Shimada et al. 2013; Uraz et al. 2013; Wei et al. 2004; Zhu et al. 2015). One study was all unclear in defining the source of information, in describing any assessments undertaken for quality assurance purpose, in explaining any patient exclusions from analysis, and in describing how confounding was assessed and/or controlled (Chaudhari et al. 2011).

Risk of bias for RCTs is summarized in Figure 2. All the 17 studies reported random sequence generation and selective reporting (Abduljabbar et al. 2017; Buduneli et al. 2010; Eltas & Orbak 2012; Erbil et al. 2020; Goutoudi, Diza & Arvanitidou 2004; Gündoğar et al. 2016; Hu et al. 2017; Liu et al. 1999; Lu & Chei 2005; Lui, Corbet & Jin

TABLE 2. Risk of bias for cross-sectional studies according to the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) guidelines

Study ID	Define the source of information (survey, record review)	List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Indicate time period used for identifying patients	Indicate whether or not subjects were consecutive if not population-based	Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	Explain any patient exclusions from analysis	Describe how confounding was assessed and/or controlled.	If applicable, explain how missing data were handled in the analysis	Summarize patient response rates and completeness of data collection
Becerik 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Bolyarov 2020	Y	Y	U	U	Y	Y	Y	Y	Y	Y
Bulut 2001	Y	Y	U	U	Y	Y	Y	Y	Y	Y
Cetinkaya 2013	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Chaudhari 2011	U	Y	U	U	Y	U	U	U	Y	Y
Cutler 1999	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Escalona 2016	Y	Y	U	U	l	Y	Y	Y	Y	Y
Faizuddin 2003	Y	Y	U	N	Y	Y	Y	Y	Y	Y
Fujita 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Gao 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Jacob 2014	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Keles 2021	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Mogi 1999	Y	Y	U	U	Y	Y	Y	Y	Y	Y
Patel 2018	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Shimada 2013	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Uraz 2013	Y	Y	U	U	Y	Y	Y	Y	Y	Y
Wei 2004	Y	Y	U	U	Y	Y	Y	Y	Y	Y
Wu 2004	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Yucel 2008	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Zhu 2015	Y	Y	U	Y	Y	Y	Y	Y	Y	Y

Y: Yes; N: No; U: Unclear

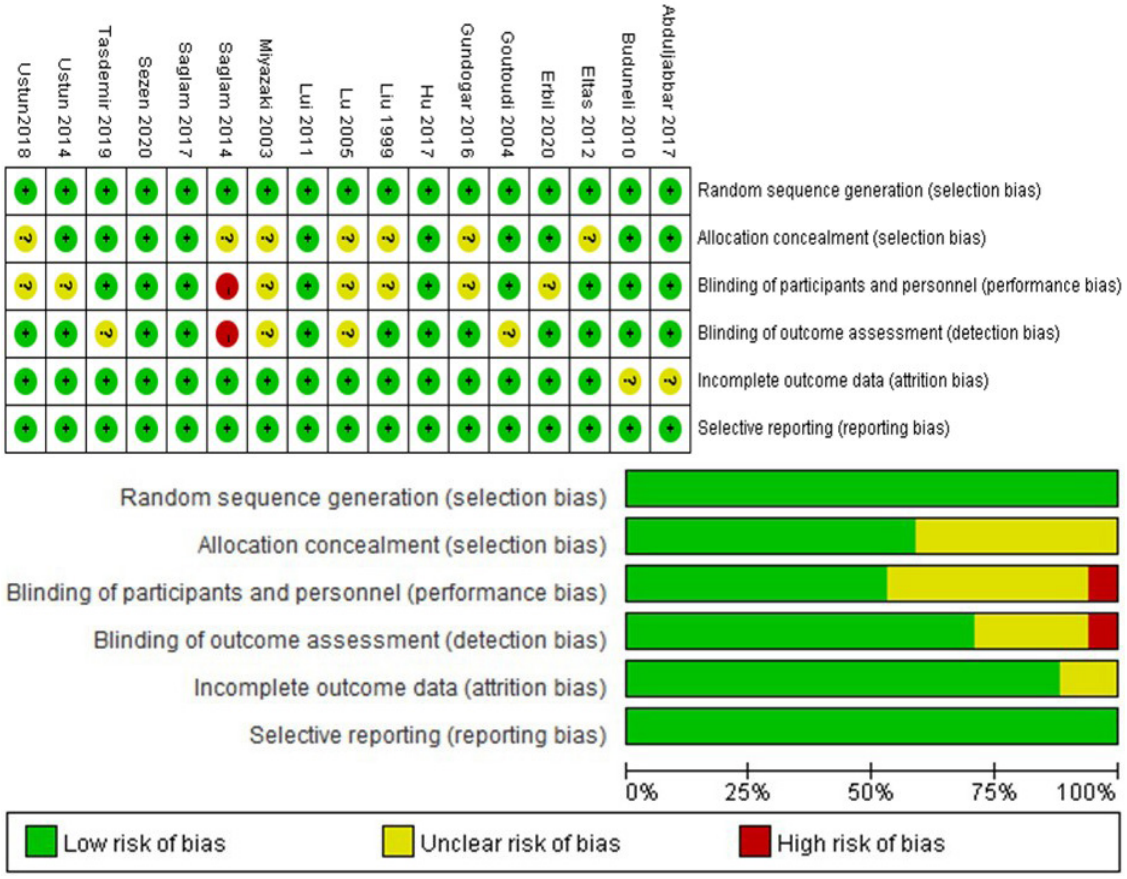

FIGURE 2. Risk of bias for randomized controlled trials according to the Cochrane Collaboration guideline

2011; Miyazaki et al. 2003; Saglam et al. 2014; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Tasdemir et al. 2019; Üstün et al. 2014; Ustun et al. 2018), 10 studies reported allocation concealment (Abduljabbar et al. 2017; Buduneli et al. 2010; Erbil et al. 2020; Goutoudi, Diza & Arvanitidou 2004; Hu et al. 2017; Lui, Corbet & Jin 2011; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Tasdemir et al. 2019; Üstün et al. 2014), and 9 studies reported blinding of participants and personnel (Abduljabbar et al. 2017; Buduneli et al. 2010; Eltas & Orbak 2012; Goutoudi, Diza & Arvanitidou 2004; Hu et al. 2017; Lui, Corbet & Jin 2011; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Tasdemir et al. 2019), and 12 studies reported blinding of outcome assessment (Abduljabbar et al. 2017; Buduneli et al. 2010; Eltas & Orbak 2012; Erbil et al. 2020; Gündoğar et al. 2016; Hu et al. 2017; Liu et al. 1999; Lui, Corbet & Jin 2011; Saglam et al. 2014; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Üstün et al. 2014; Ustun et al. 2018), 15 studies reported incomplete outcome data (Eltas & Orbak 2012; Erbil et al. 2020; Goutoudi, Diza & Arvanitidou 2004; Gündoğar et al. 2016; Hu et al. 2017; Liu et al. 1999; Lu & Chei 2005; Lui, Corbet & Jin 2011; Miyazaki et al. 2003; Saglam et al. 2014; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Tasdemir et al. 2019; Üstün et al. 2014; Ustun et al. 2018). Blinding of participants and personnel was not performed in 1 study (Saglam et al. 2014), nor was blinding of outcome assessment in the same study. Four studies were on high quality with low risk of bias in all items (Hu et al. 2017; Lui, Corbet & Jin 2011; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020).

Ten prospective cohort studies were assessed for risk of bias using NOS scale, and the results showed 9 articles were all at low risk (Ambrósio et al. 2017; Gamonal et al. 2000; Görgün, Toker & Poyraz 2021; Konopka, Pietrzak & Brzezińska-Błaszczyk 2012; Oh et al. 2015; Thunell et al. 2010; Toker et al. 2012; Tsai, Ho & Chen 1995; Tüter, Kurtiş & Serdar 2001) (Appendix 1).

The risks of bias of 2 non-RCTs and 1 single-arm clinical study were assessed using the MINORS and the result showed 2 non-RCT articles (Cheng, Qi & Du 2010; Teymouri, Farhad & Golestaneh 2016) were at high quality and 1 single-arm clinical study (Alexander et al. 1996) was at low quality based on MINORS (Appendix 2).

DIFFERENCES OF GCF IL-1β LEVELS AND GCF VOLUME IN HEALTHY SUBJECTS AND SUBJECTS WITH CP

Figure 3 shows the differences of GCF IL-1β levels and GCF volume in healthy subjects and subjects with CP in 30 studies (Ambrósio et al. 2017; Becerik et al. 2012; Bolyarova-Konova et al. 2020; Bulut et al. 2001; Cetinkaya et al. 2013; Chaudhari et al. 2011; Cutler et al. 1999; Escalona, Mastromatteo-Alberga & Correnti 2016; Faizuddin, Bharathi & Rohini 2003; Fujita et al. 2012; Gao & Hao 2018; Görgün, Toker & Poyraz 2021; Goutoudi, Diza & Arvanitidou 2004; Jacob, Nath & Patel 2014; Keles Yucel et al. 2022; Konopka, Pietrzak & Brzezińska-Błaszczyk 2012; Mogi et al. 1999; Oh et al. 2015; Patel et al. 2018; Rabelo et al. 2021; Shimada et al. 2013; Thunell et al. 2010; Toker et al. 2012; Tsai, Ho & Chen 1995; Tüter, Kurtiş & Serdar 2001; Uraz et al. 2013; Wei et al. 2004; Wu et al. 2004; Yücel et al. 2008; Zhu et al. 2015) among which 24 studies (Ambrósio et al. 2017; Becerik et al. 2012; Bolyarova-Konova et al. 2020; Bulut et al. 2001; Cetinkaya et al. 2013; Chaudhari et al. 2011; Cutler et al. 1999; Escalona, Mastromatteo-Alberga & Correnti 2016; Faizuddin, Bharathi & Rohini 2003; Gao & Hao 2018; Görgün, Toker & Poyraz 2021; Jacob, Nath & Patel 2014; Keles Yucel et al. 2022; Konopka, Pietrzak & Brzezińska-Błaszczyk 2012; Mogi et al. 1999; Rabelo et al. 2021; Toker et al. 2012; Tsai, Ho & Chen 1995; Tüter, Kurtiş & Serdar 2001; Uraz et al. 2013; Wei et al. 2004; Wu et al. 2004; Yücel et al. 2008; Zhu et al. 2015) compared the difference between periodontally healthy controls and patients with CP and 6 articles (Fujita et al. 2012; Goutoudi, Diza & Arvanitidou 2004; Oh et al. 2015; Patel et al. 2018; Shimada et al. 2013; Thunell et al. 2010) adopted split-mouth design and compared the differences between diseased sites and healthy sites in the same patients with CP.

The concentration of GCF IL-1β described in 23 studies (Ambrósio et al. 2017; Becerik et al. 2012; Bolyarova-Konova et al. 2020; Bulut et al. 2001; Cetinkaya et al. 2013; Chaudhari et al. 2011; Cutler et al. 1999; Escalona, Mastromatteo-Alberga & Correnti 2016; Faizuddin, Bharathi & Rohini 2003; Gao & Hao 2018; Goutoudi, Diza & Arvanitidou 2004; Jacob, Nath & Patel 2014; Mogi et al. 1999; Oh et al. 2015; Patel et al. 2018; Rabelo et al. 2021; Tsai, Ho & Chen 1995; Tüter, Kurtiş & Serdar 2001; Uraz et al. 2013; Wei et al. 2004; Wu et al. 2004; Yücel et al. 2008; Zhu et al. 2015) was increased significantly in 17 studies (Ambrósio et al. 2017; Bolyarova-Konova et al. 2020; Bulut et al. 2001; Chaudhari et al. 2011; Cutler et al. 1999; Escalona, Mastromatteo-Alberga & Correnti 2016; Faizuddin, Bharathi & Rohini 2003; Gao & Hao 2018; Jacob, Nath & Patel 2014; Mogi et al. 1999; Oh et al. 2015; Patel et al. 2018; Rabelo et al. 2021; Tsai, Ho & Chen 1995; Uraz et al. 2013; Wu et al. 2004; Zhu et al. 2015), not different in 5 studies (Becerik et al. 2012; Goutoudi, Diza & Arvanitidou 2004; Tüter, Kurtiş & Serdar 2001; Wei et al. 2004; Yücel et al. 2008), and decreased significantly in 1 study (Cetinkaya et al. 2013) as compared to healthy controls. The result of the meta-analysis founded L-1β concentration was significantly higher in subjects with CP compared to healthy controls (SMD: 1.34, 95% CI 0.78-1.90; $P < 0.00001$). The heterogeneity was high (I^2=93%, $P < 0.00001$) and Funnel plots indicated several articles at high risk of bias (data not shown). Subgroup analysis was performed based on the GCF resources and IL-1β detection approach, respectively. The results showed L-1β concentration was significantly higher not only in periodontitis patients compared to healthy controls, but also in diseased sites compared to healthy sites in periodontitis patients. In addition, the results did not change based on different IL-1β detection approach (Elisa or other approaches). Meanwhile, the sensitivity analysis did not yield significant change in the estimates.

The total amount of GCF IL-1β in all 15 studies (Cetinkaya et al. 2013; Fujita et al. 2012; Görgün, Toker & Poyraz 2021; Goutoudi, Diza & Arvanitidou 2004; Keles Yucel et al. 2022; Konopka, Pietrzak & Brzezińska-Błaszczyk 2012; Oh et al. 2015; Shimada et al. 2013; Thunell et al. 2010; Toker et al. 2012; Tsai, Ho & Chen 1995; Tüter, Kurtiş & Serdar 2001; Uraz et al. 2013; Wei et al. 2004; Yücel et al. 2008) was increased significantly in subjects with CP as compared to healthy controls (SMD: 1.76, 95% CI 1.25-2.27; $P < 0.00001$). The heterogeneity was high ($I^2 = 87\%$, $P < 0.00001$) and Funnel plots indicated 6 studies at high risk of bias (data not shown), but the sensitivity analysis and subgroup analysis based on GCF resources and IL-1β detection approach showed the heterogeneities were still over 80% and the estimates did not change significantly.

GCF volume in 14 studies (Ambrósio et al. 2017; Becerik et al. 2012; Bulut et al. 2001; Fujita et al. 2012; Jacob, Nath & Patel 2014; Keles Yucel et al. 2022; Oh et al. 2015; Shimada et al. 2013; Thunell et al. 2010; Tsai, Ho & Chen 1995; Tüter, Kurtiş & Serdar 2001; Uraz et al. 2013; Wei et al. 2004; Yücel et al. 2008) was much higher in subjects with CP compared to healthy controls (SMD: 2.62, 95% CI 1.75-3.48, $P<0.00001$) with a high degree of heterogeneity ($I^2 = 94\%$, $P < 0.00001$). However, sensitivity analysis and subgroup analysis showed the heterogeneities were still over 90% and did not yield significant change in the estimates.

CHANGES OF GCF IL-1β LEVELS AND GCF VOLUME FOLLOWING SRP IN SUBJECTS DIAGNOSED WITH CP

The present meta-analysis was performed from the data of at least 4 studies, so the recorded postoperative timepoints included 1 m, 1.5 m, 3 m, 6 m following SRP. Figure 4 presented the concentrations of GCF IL-1β in CP group decreased significantly at 1 m (P =0.04)(Alexander et al. 1996; Ambrósio et al. 2017; Buduneli et al. 2010; Liu et al. 1999; Lui, Corbet & Jin 2011; Sağlam et al. 2017; Tsai, Ho & Chen 1995), 1.5 m (P = 0.004) (Erbil et al. 2020; Goutoudi, Diza & Arvanitidou 2004; Hu et al. 2017; Liu

et al. 1999; Teymouri, Farhad & Golestaneh 2016; Tüter, Kurtiş & Serdar 2001), and 3 m ($P < 0.00001$) (Abduljabbar et al. 2017; Ambrósio et al. 2017; Eltas & Orbak, 2012; Erbil et al. 2020; Hu et al. 2017; Liu et al. 1999; Sağlam et al. 2017; Tasdemir et al. 2019) following SRP compared with the preoperative baseline, and the *p* values are all less than 0.01.

Meanwhile, the changes of the total amount of GCF IL-1β in CP group following SRP were reported and the results showed IL-1β total amounts decreased significantly at postoperative 1 m ($P = 0.0001$) (Alexander et al. 1996; Buduneli et al. 2010; Gündoğar et al. 2016; Konopka, Pietrzak & Brzezińska-Błaszczyk 2012; Miyazaki et al. 2003; Saglam et al. 2014; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Tsai, Ho & Chen 1995; Üstün et al. 2014; Ustun et al. 2018), 1.5 m ($P = 0.02$) (Görgün, Toker & Poyraz 2021; Goutoudi, Diza & Arvanitidou 2004; Toker et al. 2012; Tüter, Kurtiş & Serdar 2001), 3 m ($P < 0.00001$) (Miyazaki et al. 2003; Saglam et al. 2014; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Üstün et al. 2014; Ustun et al. 2018), and 6 m ($P = 0.002$) (Saglam et al. 2014; Sezen, Hatipoglu & Ustun 2020; Üstün et al. 2014; Ustun et al. 2018) compared with the baseline (Figure 5).

In addition, GCF volume in CP group decreased significantly at postoperative 1 m ($P < 0.00001$) (Ambrósio et al. 2017; Buduneli et al. 2010; Lui, Corbet & Jin 2011; Miyazaki et al. 2003; Saglam et al. 2014; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Tsai, Ho & Chen 1995; Üstün et al. 2014), 3 m ($P < 0.00001$) (Abduljabbar et al. 2017; Ambrósio et al. 2017; Eltas & Orbak, 2012; Miyazaki et al. 2003; Saglam et al. 2014; Sağlam et al. 2017; Sezen, Hatipoglu & Ustun 2020; Üstün et al. 2014), and 6 m ($P = 0.0006$) (Abduljabbar et al. 2017; Saglam et al. 2014; Sezen, Hatipoglu & Ustun 2020; Üstün et al. 2014) following SRP compared to baselines, and the *P* values are all less than 0.01 (Figure 6).

CORRELATION OF GCF IL-1β LEVEL WITH THE CLINICAL PARAMETERS IN SUBJECTS DIAGNOSED WITH CP

The correlations between GCF IL-1β levels and clinical parameters including PD, CAL, BOP, PI, GI were analyzed using the analysis of Spearman rank correlation in CP group of 30 studies which compared the differences of GCF IL-1β levels in healthy subjects and subjects with CP (Ambrósio et al. 2017; Becerik et al. 2012; Bolyarova-Konova et al. 2020; Bulut et al. 2001; Cetinkaya et al. 2013; Chaudhari et al. 2011; Cutler et al. 1999; Escalona, Mastromatteo-Alberga & Correnti 2016; Faizuddin, Bharathi & Rohini 2003; Fujita et al. 2012; Gao & Hao 2018; Görgün, Toker & Poyraz 2021; Goutoudi, Diza & Arvanitidou 2004; Jacob, Nath & Patel 2014; Keles Yucel et al. 2022; Konopka, Pietrzak & Brzezińska-Błaszczyk 2012; Mogi et al. 1999; Oh et al. 2015; Patel et al. 2018; Rabelo et al. 2021; Shimada et al. 2013; Thunell et al. 2010; Toker et al. 2012; Tsai, Ho & Chen 1995; Tüter, Kurtiş & Serdar 2001; Uraz et al. 2013; Wei et al. 2004; Wu et al. 2004; Yücel et al. 2008; Zhu et al. 2015). The results showed the total amount of GCF IL-1β was positively and significantly correlated to BOP ($r = 0.894$, $P = 0.041$) (Table 3). There were no correlations between the total amount of IL-1β and other clinical parameters including PD, CAL, PI, and GI, nor were between IL-1β concentration and all the clinical parameters.

DISCUSSION

The present study was focused on proinflammatory IL-1β in GCF and established the role of IL-1β as a predictor of diagnosis and progression of periodontal disease. Thus, the detection of GCF IL-1β level may be valuable in diagnosing initial periodontitis, differentiating active from inactive periodontal lesions, and predicting the risk of the progression of periodontal disease.

Zhang, Kashket and Lingstrom (2002) reported the total amount and the concentration of GCF IL-1β increased significantly during the early stage of plaque accumulation after 3 days without tooth brushing, and the changes of GCF IL-1β levels are prior to the changes of any clinical signs and imaging features of CP. Oh et al. (2015) founded the total amount, the concentration of IL-lβ in GCF and GCF volume were significantly higher at deep than shallow PD sites of periodontitis teeth. According to Bolyarova-Konova et al. (2020), IL-1β concentrations both in GCF and in saliva of healthy individuals were significantly lower than those in patients with gingivitis or periodontitis, however, there were no differences between gingivitis patients and periodontitis ones. In agreement with these studies, in the present study, the great majority of studies (17/23) described increased concentration of IL-1β, and all the studies (15/15) reported the increased total amount of IL-1β in CP group compared with the healthy controls. Thus, GCF IL-1β could differentiate periodontitis patients from healthy controls and differentiate diseased sites from healthy sites in periodontitis patients, which indicated IL-1β may be an early diagnostic biomarker of CP and can reflect the disease severity, the analysis of GCF IL-1β will be helpful for the early diagnosis of periodontal diseases.

It is well-known that SRP is a basic therapy for CP and can yield significant changes of IL-1β levels and improvements of clinical features (Habashneh et al. 2019). Goutoudi, Diza and Arvanitidou (2004) found the total amount of IL-1β still reduced significantly at 4 months and increased at 8 months following SRP. According to Engebretson et al. (2002), IL-1β level decreased significantly at the beginning and returned to the baseline at 6 months following SRP. The present meta-analysis founded SRP significantly decreased GCF IL-1β levels as well as the values of clinical parameters not only at early stage (1 m and 1.5 m) but also at mid-late stage (3 m and 6 m) following SRP, suggesting IL-1β was a sensitive indicator to evaluate the therapy efficacy of SRP. In

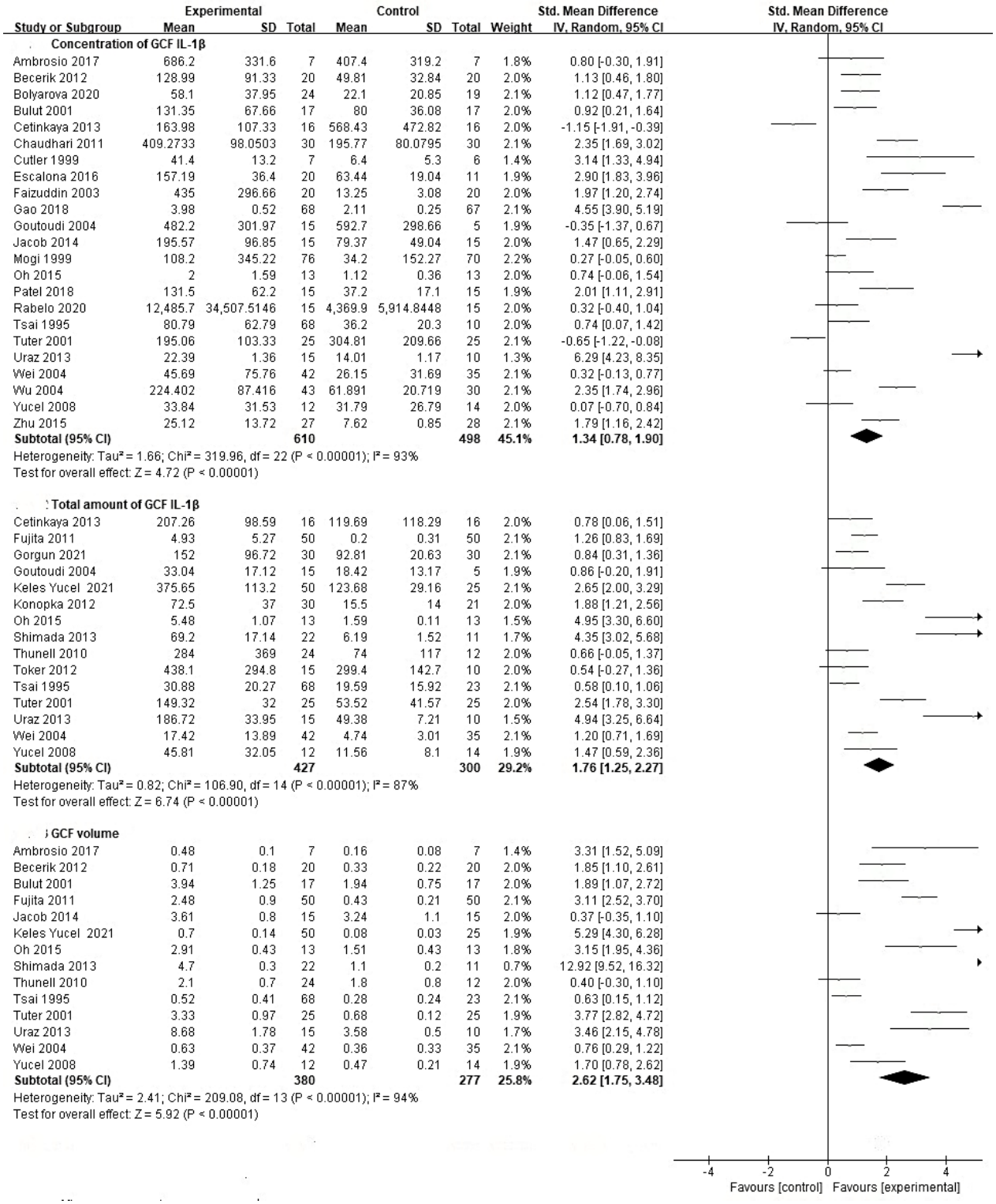

FIGURE 3. Differences of GCF IL-1β levels and GCF volume in healthy subjects and subjects with CP

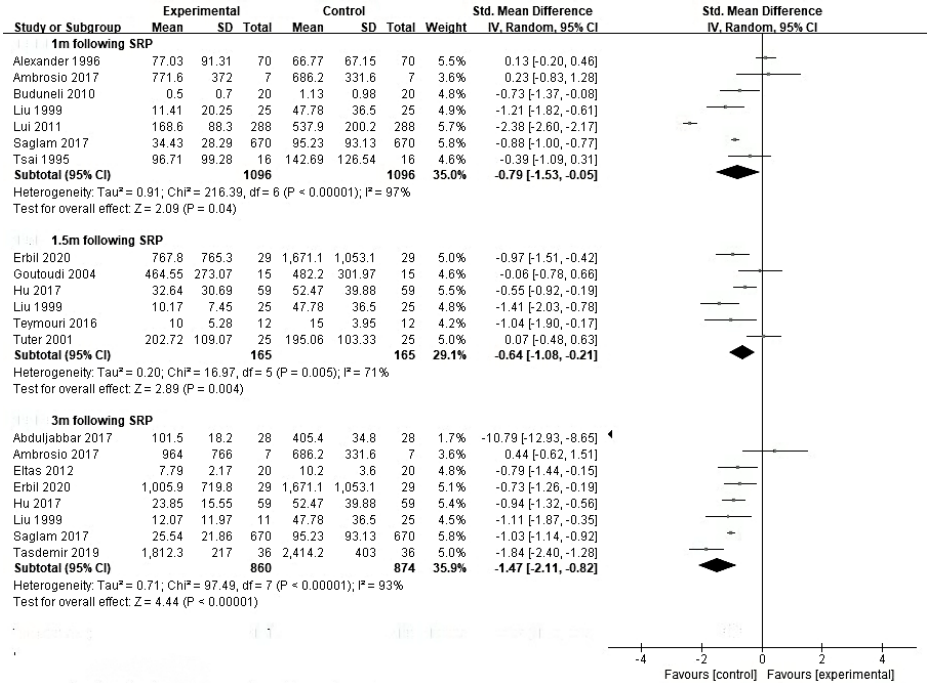

FIGURE 4. Changes of GCF IL-1β concentration at 1 m, 1.5 m, 3 m following SRP in CP group

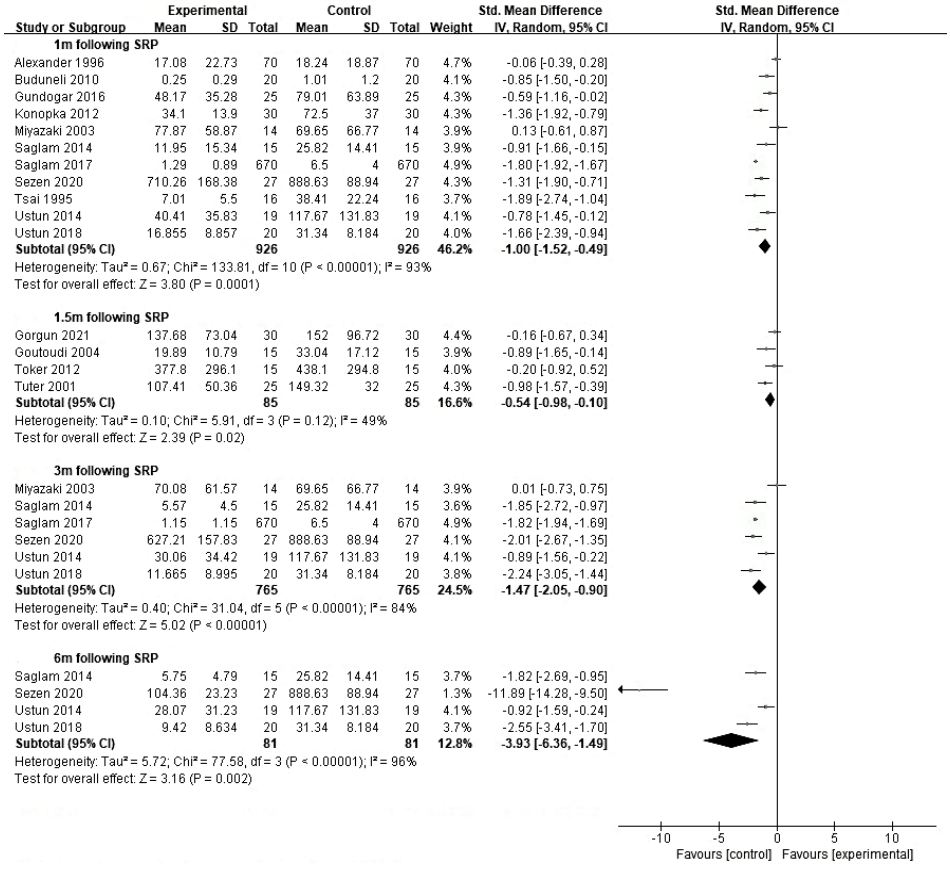

FIGURE 5. Changes of GCF IL-1β total amount at 1 m, 1.5 m, 3 m, 6 m following SRP in CP group

addition, the result also show the periodontal inflammation began to subside at postoperative 1 m and the therapy efficacy of SRP could persist for more than 6 m, so there is no need to receive next SRP at postoperative 6 m and the internal of SRP may be appropriately extended.

In the previous review from Stadler et al. (2016), no relationship of IL-1β level with the risk of disease progression was concluded due to the absence of strong evidence to support. In the present study, a remarkably positive correlation between the total amount of IL-1β and BOP was found in CP group, and subjects with higher total amount of IL-1β had higher BOP. In several studies, the researchers found the similar results that IL-1β level was positively correlated with BOP (Chaudhari et al. 2011; Fujita et al. 2012; Keles Yucel et al. 2022; Mogi et al. 1999). BOP is a locally acting cytokine and reflects the inflammatory state of periodontal tissues and activity of the periodontal disease (Chaudhari et al. 2011). Taken together, IL-1β is considered to differentiate active and inactive diseased sites and to predict the progression of periodontal disease other than evaluating the response to SRP.

Several studies reported the total amount of GCF IL-1β increased significantly in periodontitis subjects compared to healthy control whereas the concentration did not differ significantly (Becerik et al. 2012; Goutoudi, Diza & Arvanitidou 2004; Tüter, Kurtiş & Serdar 2001; Wei et al. 2004; Yücel et al. 2008). In addition, the total amount of IL-1β, not the concentration, was correlated positively with some clinical parameters including PI, GI, or PD (Goutoudi, Diza & Arvanitidou 2004; Hou, Liu & Rossomando 1995; Tsai, Ho & Chen 1995; Wei et al. 2004). The result of the present meta-analysis showed the total amount of IL-1β, not the concentration, was positively correlated with BOP. These findings suggested the total amount of IL-1β in GCF may be more important than its concentration in the diagnosis, the judgment of therapeutic effect of SRP, and the CP progression prediction.

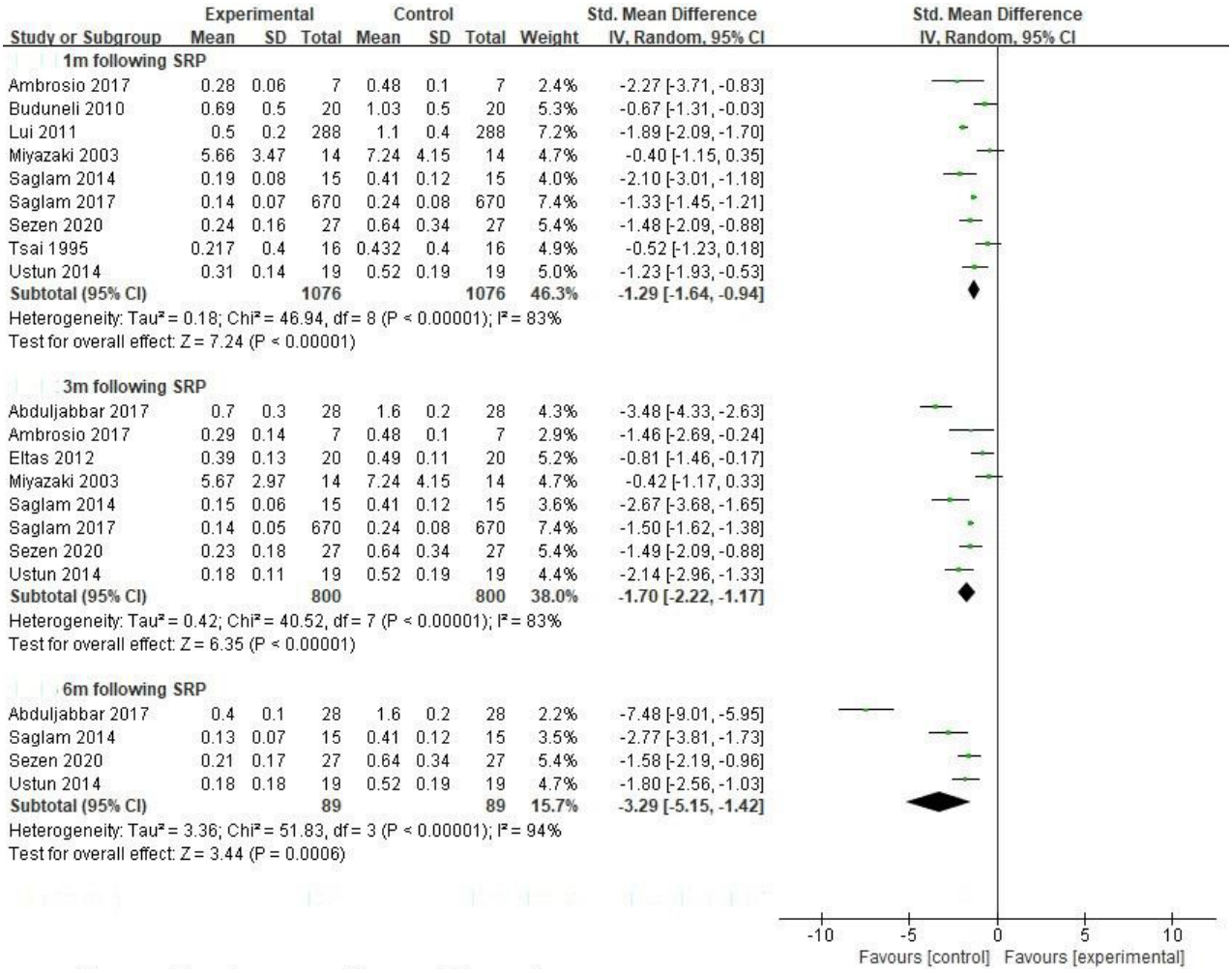

FIGURE 6. Changes of GCF volume at 1 m, 3 m, 6 m following SRP in CP group

TABLE 3. Pearson' correlation coefficients between clinical parameters and IL-1β in 30-s samples of gingival crevicular fluid

	PD	CAL	BOP	GI	PI
IL-1β[C]	-0.271	-0.325	-0.2	-0.285	-0.098
IL-1β[TA]	0.079	0.445	0.894*	-0.236	-0.661

IL-1β, interleukin-1β; [C], concentration; [TA], total amount; PD, parameters including probing depth; CAL, clinical attachment level; BOP,bleeding on probing; PI, plaque index; GI, gingival index
*Significant correlation ($p < 0.05$)

The smokers were not included in the present study because smokers with CP exhibited higher IL-1β levels and had a higher risk of periodontal destruction compared with nonsmokers (Haffajee & Socransky 2001; Patel et al. 2018). Goutoudi, Diza and Arvanitidou (2004) thought that smoking did not influence the basic value of GCF IL-1β level, but it could influence postoperative IL-1β level and clinical status, and reduced therapeutic effect of SRP. In addition, Javed, Al-Askar, Samaranayake and Al-Hezaimi (2013) suggested smoking had detrimental effects on periodontal health and jeopardized periodontal tissue healing after therapy. The aggressive periodontitis (AgP) was also excluded from the present study because AgP is an exceptional disease variant with unclear pathogenesis, mainly occurs in systematically healthy young subjects. Its characterization of rapid and severe periodontal tissue destruction is very different from general CP discussed in the present study (Albandar 2014).

The methods of detecting the levels of GCF biomarkers are critical. In the present study, the detection methods were Elisa or Multiplex bead immunoassay except two studies used radioimmunoassay and flowcytometry, respectively. In fact, Multiplex bead immunoassays and Elisa are both immunoassays, the difference lies in that Elisa only detects one protein while Multiplex method can detect multiple different proteins simultaneously (Cox 2021). A previous meta-analysis from Koidou et al. (2020) only included the studies in which the expressions of GCF biomarkers were detected using Multiplex bead immunoassays rather than Elisa or other techniques, which might lose several valuable studies in which IL-1β level was detected using Elisa. Anyhow, future studies may be simplified if many cytokines are assessed simultaneously using high-sensitivity Multiplex bead immunoassay.

There were some limitations in the review. Limited RCT articles were included. Some studies included in the review had a small sample size and a short follow-up. The presentation of data was not identical in units. For example, IL-1β concentration was recorded in μg/mL, pg/mL, pg/μL, and the total amount was recorded in pg, μg, ng, or other units. In addition, the parameters were not identical, and some studies only reported the concentration without the total amount of IL-1β or the volume of GCF.

Further research should concentrate on the development of appropriate experimental designs and the standardisation of GCF collection, storage, and detection, recording unit, measurement of clinical outcomes and follow-up interval, in order to ensure greater comparability. If these factors are all taken into account, the data from different studies will be more comparable, thus facilitating a more precise result in meta-analysis. Furthermore, research in the fields of GCF proteomics, metabolomics, genotypes, and gene polymorphism may prove to be a fruitful avenue for the site-specific diagnosis and progression of periodontitis (Kozak et al. 2020; Overmyer et al. 2021).

CONCLUSION

In conclusion, the current evidence indicates that proinflammatory cytokines IL-1β in GCF have utility as a biomarker for diagnosing the initiation of CP, reflecting disease severity, and evaluating the efficacy of SRP. Furthermore, they have value as a biomarker for determining disease activity and predicting CP progression.

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APPENDIX 1. Risk of bias for prospective cohort studies according to the Newcastle–Ottawa Quality Assessment Scale (NOS)

Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Ambrosio 2017	√	√	√	√	√	√	√	√
Gamonal 2000	√	√	√	√	√	√	√	√
Gorgun 2021	√	√	√	√	√	√	√	√
Konopka 2012	√	√	√	√	√	√	√	√
Oh 2015	√	√	√	√	√	√	√	√
Thunell 2010	√	√	√	√	√	√	√	√
Toker 2012	√	√	√	√	√	√	√	√
Tsai 1995	√	√	√	√	√	√	√	√
Tuter 2001	√	√	√	√	√	√	√	√

APPENDIX 2. Risk of bias for non-RCT and single-arm clinical studies according to the MINORS

Study ID	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contempor-ary groups	Baseline equivalence of groups	Adequate statistical analyses	Overall
Alexander 1996	2	1	2	2	0	2	2	0					11
Cheng 2010	2	2	2	2	2	2	2	0	2	2	2	2	22
Teymour 2016	2	1	2	2	2	2	1	0	2	2	2	2	20