

INPLASY PROTOCOL

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None declared.

Potential interaction between oral microbiotas and COVID-19: a meta-analysis and bioinformatics prediction

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Review question / Objective: What is the nature of the alternation of oral microbiome in COVID-19 patients?

Condition being studied: In order to find the potential role of oral microbiome in COVID-19 disease, a amount of studies have depicted oral microbial features in COVID-19 patients. However the outcomes are often inconsistent to some extent . Until now the oral microbial features of COVID-19 patients had not been analysed by a meta-analysis. Therefore, it is meaningful and necessary to conduct a summative and evidence-based meta-analysis of the current study results in this area.

Eligibility criteria: Inclusion criteria were studies (case-control studies, cross-sectional studies, cohort studies, and clinical trials) comparing the composition of the oral microbiome by using high-throughput analyses (e.g., 16S rDNA/rRNA sequencing) between laboratory-confirmed SARS-CoV-2 infection patients (CP) and healthy control (HC) (age \geq 18 years). Exclusion criteria were reviews, commentaries, short surveys, case reports, and letters. Further exclusion criteria were studies focusing on specific diseases.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 October 2022 and was last updated on 10 November 2022 (registration number INPLASY2022100113).

INTRODUCTION

Review question / Objective: What is the nature of the alternation of oral microbiome in COVID-19 patients?

Rationale: Coronavirus disease 2019 (COVID-19), caused by a respiratory virus known as SARS-COV-2, was identified as a global epidemic in late 2019. The immune dysregulation and bacterial co-infection are closely related to the high mortality rate of the COVID-19. However, the role of oral

bacteria in affecting immune dysregulation and bacterial co-infection in COVID-19 is pertinent, yet overlooked.

Condition being studied: In order to find the potential role of oral microbiome in COVID-19 disease, a amount of studies have depicted oral microbial features in COVID-19 patients. However the outcomes are often inconsistent to some extent . Until now the oral microbial features of COVID-19 patients had not been analysed by a meta-analysis. Therefore, it is meaningful and necessary to conduct a summative and evidence-based meta-analysis of the current study results in this area.

METHODS

Search strategy: Searching strategy and focused issue was developed with key words of 'COVID-19', 'SARS-CoV-2', 'Coronavirus Disease 19', 'Coronavirus Disease 19', 'oral microbes', 'oral microbiota' and 'oral bacteria', and expanded through the author's knowledge or reference to other literature. Subsequently, Boolean and truncation operations ('OR', 'AND') were employed to implement search strategies based on sensitivity and specificity, and were adapted for each database. e.g., Pubmed search strategy has been exhibited in Table 1 (we have uploaded the detailed search strategy used for EMBASE and cochrane as Table S1 and Table S2.).

Participant or population: Patients with COVID-19.

Intervention: None.

Comparator: Healthy people without COVID-19 in the same or historical cohort.

Study designs to be included: Inclusion: randomized controlled trials, cohort studies and case-controlled studies, case-series, and case reports of the oral microbiome in COVID-19 patients.

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Information sources: Three well known databases (PubMed, EMBASE, Cochrane Library) related to previous published studies in COVID-19 and oral microbiotas were screened. Furthermore, these databases will be searched for relevant articles, until October 2022. There are no language restrictions on filtering articles to ensure the integrity of included data.

Main outcome(s): Changes in the human mouth microbiome in COVID-19 patients.

Additional outcome(s): First author's name, year of publication, country where the study was executed, type of study, study population, mean age, gender, COVID-19 severity of the cases, comorbidity(ies), microbiota analysis technique, type of sample, whether use antibiotic and studied value of oral microbiota alterations in COVID-19.

Data management: A narrative synthesis was performed for all included studies screening by inclusion criteria while a meta-analysis was confined to results which were quantitatively presented in form of means and standard deviations, or in the form of enabling manual calculation (i.e. frequency tables) through Excel 2010 (Microsoft Corporation, Washington, USA) . For the study that the data in the outcomes are presented as the median, minimum and maximum values and the first and third quartiles, the method of McGrath et al. (2020) will be used to convert these data from the reported summary data into the mean or standard deviation for analysis. If none of the above methods can obtain the

raw data that can be analyzed, we will send an email to ask the author to provide the these data. The ImageJ 1.38e software (Wayne Rasband, National Institutes of Health, USA) was used to obtain raw data that were presented in graphs but not provided by the author.

Quality assessment / Risk of bias analysis:

Two independent investigators (LT and QY) used a Cochrane-based (Cochrane) Modified Bias in Trials of Non-randomized Interventions (ROBINS-I) tool to assess bias [34]. After that, discuss and negotiate with a third author, if needed, to resolve disagreements. The revision of the ROBINS-I tool includes the following six domains of biases: (1) confounding, (2) participants selection, (3) exposure assessment, (4) missing data, (5) outcome measures, (6) selective reporting of the results, together with signalling issues that can facilitate the judgement of potential risk of bias for each domain. The overall risk of bias was assessed as low, moderate or serious. If at least one domain is identified as serious risk and the other is not considered serious risk, the overall assessment of risk is considered serious. If all regions are considered to be at risk of low, the overall rating is low. If all areas are of low or moderate risk, the overall rating is moderate.

Strategy of data synthesis: All included studies were synthesized narratively according to the inclusion criteria, but meta-analyses were limited to present of quantifying results as means and standard differences, or enabling manual calculations using Excel 2010 (Washington, Microsoft, USA). For the study that the data in the outcomes are presented as the median, minimum and maximum values and the first and third quartiles, the method of McGrath et al. (2020) will be used to convert these data from the reported summary data into the mean or standard deviation for analysis. If none of the above methods can obtain the raw data that can be analyzed, we will send an email to ask the author to provide the these data. The ImageJ 1.38e software (Wayne Rasband, National Institutes of Health, USA) was

used to obtain raw data that were presented in graphs but not provided by the author. In order to further study the influence of age and whether to use antibiotics on oral microbiota alterations, a subgroup meta-analysis was performed for CP with respect to HC. Outcomes were shown in forest plots where the edges and middle of the rhombus respectively represented the 95% confidence interval (95% CI) and the standard mean difference (SMD) point estimate. The 95% CI and point estimate for each studies are respectively presented as a horizontal line and a central symbol. Chi-squared analyses and I² scores were displayed to analyze homogeneity. Random-effects models were used for the meta-analysis. All calculations were carried out through Review Manager 5.4.

Subgroup analysis: If the data is available, subgroup analyses will be performed according to the type of treatment, the age of the patients, and Whether to use antibiotics.

Sensitivity analysis: Sensitivity analysis was performed by omitting each study from the meta-analysis until heterogeneity decreased significantly. If there is no difference in the meta-analysis synthesis results before and after excluding the relevant literature, it proves that the original synthesis results are relatively stable.

Language restriction: None.

Country(ies) involved: China.

Other relevant information: None.

Keywords: Oral microbiota, COVID-19, Meta-analysis, Bioinformatics prediction, SARS-CoV-2.

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