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None declared.

The role of oral bacteria in COVID-19: A systematic review and meta-analysis

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Review question / Objective: **What is the nature of the alternation of oral microbiome in COVID-19 patients?**
Condition being studied: **Little is known about the alternation of the oral microbiome in the COVID-19 cases. SARS-CoV2 primarily infects the respiratory organs, and develops into systemic diseases. Given the emerging evidence that the oral microbiome, and its distribution and alternation in the mouth, plays a role in the pathogenesis or severity COVID-19, this review will analyze the current knowledge of the interaction between COVID-19 infection and the oral microbiome.**
Eligibility criteria: **Inclusion criteria were studies (retrospective and prospective cohort studies, case-control studies, cross-sectional studies, and clinical trials) comparing the composition of the oral microbiome between Participants with COVID-19 and healthy population that without COVID-19 (age ≥ 18 years) A further inclusion criterion was that the oral microbiome was measured by means of high-throughput analyses (e.g., 16S rDNA/rRNA sequencing, shotgun metagenomics) in saliva samples. Exclusion criteria were reviews, commentaries, short surveys, case reports, and letters. Further exclusion criteria were studies focusing on specific diseases, written in a language other than English, or published as abstract, editorial or comment were also excluded.**

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 28 October 2022 (registration number INPLASY2022100113).

INTRODUCTION

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

Rationale: **Oral microbiotas are communities of microorganisms living in symbiosis with humans. They play an important role in the host immune response to respiratory viral infection. However, evidence on the oral microbiome**

and coronavirus disease (COVID-19) relationship is insufficient.

Condition being studied: Little is known about the alternation of the oral microbiome in the COVID-19 cases. SARS-CoV2 primarily infects the respiratory organs, and develops into systemic diseases. Given the emerging evidence that the oral microbiome, and its distribution and alternation in the mouth, plays a role in the pathogenesis or severity COVID-19, this review will analyze the current knowledge of the interaction between COVID-19 infection and the oral microbiome.

METHODS

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.

Eligibility criteria: Inclusion criteria were studies (retrospective and prospective cohort studies, case-control studies, cross-sectional studies, and clinical trials) comparing the composition of the oral microbiome between Participants with COVID-19 and healthy population that without COVID-19 (age ≥ 18 years) A further inclusion criterion was that the oral microbiome was measured by means of high-throughput analyses (e.g., 16S rDNA/rRNA sequencing, shotgun metagenomics) in saliva samples. Exclusion criteria were reviews, commentaries, short surveys, case reports, and letters. Further exclusion criteria were studies focusing on specific diseases, written in a language other than English, or published as abstract, editorial or comment were also excluded.

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 researchers (LT and QY) appraised the risk of bias using an adapted version of the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool [31], a tool proposed by Cochrane that can be also applied to appraise the risk of bias in observational

studies. Discrepancies were resolved by discussion and consultation with a third author where necessary. The adapted version of ROBINS-I tool comprised six domains of bias due to: (1) confounding, (2) selection of participants, (3) exposure assessment, (4) missing data, (5) measurement of the outcome, and (6) selective reporting of the results, together with the signaling questions that facilitated the judgement of potential risk of bias for each domain as described in Supplement Table S2. The overall judgment of risk of bias was categorized as low, moderate or serious as previously described [31]. If at least one domain was judged to be of serious risk but not at critical risk in any other domain, then the overall judgment of the risk of bias was deemed as serious. If all domains were rated as being at low risk of bias, then the overall judgment was deemed as low. If all domains were rated at low or moderate risk of bias, then the overall judgement was deemed as moderate.

Strategy of data synthesis: Since all the measurement index included in the studies such as values of mean and standard deviation of shannon index have the different measurement units, Standard Mean Difference (SMD) were used to compare these variables. Outcomes were shown in forest plots where the edges and middle of the rhombus respectively represented the 95% confidence interval (95% CI) and the 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 perfomed 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, SARS-CoV-2, dysbiosis, systematic review.

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