Detection and consistency of mucosal fluid T lymphocyte phenotypes and their relationship with blood, age and gender

Shervin Dokht Sadeghi Nasab[1], Muruganantham Lillimary Eniya[2], Albert Judith[2], Frederick Clasen[1], Beulah Faith[2], Selvamuthu Poongulali[2], Jayaraman Bhagavad Gita[3], Chakrapani Ashok[3], Velmurugan Raghavi,[3] Subramanian Vedavalli[3], Chandra Lavanya[4], Kannan Ranganathan[4], Gunaseelan Rajan[3], Nagalingeswaran Kumarasamy[2], David Moyes[1], Mark Ide[1], Saeed Shoaie[1], Yuko Kurushima[1], Daljit Jagdev[1], Mina Pun[1], Newell Johnson[1,5], Priya Kannian[2], Stephen Challacombe[1]

[1] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK, [2] The Voluntary Health Services, Chennai, India, [3] Chennai Dental Research Foundation, Chennai, India , [4] Ragas Dental College and Hospital, Chennai, India [5] Griffith University Dental School, Queensland, Australia

Abstract

Innate and adaptive immune responses at mucosal surfaces play a role in protection against most infectious diseases. However, the relative importance either of mucosal versus systemic, or of cellular versus humoral immunity in protection against such infections remains unclear. We aimed to determine the relative percentages and reproducibility of detection of major T lymphocyte phenotypes in stimulated whole mouth fluid (SWMF); to compare matched mucosal and blood phenotypes; to evaluate the consistency of phenotypes in SWMF over time; and to determine any associations with age or gender. Peripheral blood and SWMF samples were collected from 194 participants and sequential concomitant samples were collected from 27 of those. Samples were also collected from a subset of 12 subjects living with HIV. CD3, CD4, CD8, Th1 and Th2 T lymphocyte phenotypes were determined by FACS. Mean values in SWMF were lower than in blood and there was significant correlation between the fluids, except for CD8. Individual values in SWMF samples taken at 0 and 4 weeks were strongly correlated ($p<0.001$). Mean values and distribution of CD3, CD4, CD8 or Th2 were similar in SWMF and blood in males and females, except for Th1 percentages in females in blood ($p<0.05$). Age and CD3 and CD4 percentages were negatively correlated in blood ($p<0.001$) but no obvious diminution in the mean numbers of any of the five T lymphocyte phenotypes in SWMF was detected. Distributions were similar in those living with HIV. This study demonstrated that consistent detection of T lymphocyte phenotypes in a mucosal fluid (SWMF) using FACS is possible and that participant values remain steady over at least four weeks. Except CD8, all other major T lymphocyte percentages correlated with those in blood, and do not appear to be affected by gender or age. It should now be possible to examine function of mucosal fluid T lymphocytes in relation to infectious diseases.

T cell phenotypes in mucosal secretions are different from those in blood and not related to age or gender.

Publication reference:

Nasab SDS, Eniya ML, Judith A, Clasen F, Faith B, Poongulali S, Gita JB, Ashok C, Raghavi V, Vedavalli S, Lavanya C, Ranganathan K, Rajan G, Kumarasamy N, Moyes D, Ide M, Shoaie S, Kurushima Y, Jagdev D, Pun M, Johnson N, Kannian P, Challacombe S. Detection and consistency of mucosal fluid T lymphocyte phenotypes and their relationship with blood, age and gender. J Immunol Methods. 2024;532:113731. doi: 10.1016/j.jim.2024.113731. PMID: 39059745.

Abstract for IADR New Orleans 2024 ID#3997925

Salivary anti-spike antibodies associate with a decline in SARS-CoV2 burden.

Muruganantham L Eniya[1], Albert Judith[1], Shervin Sadeghi Nasab[2], David Moyes[2], Beulah Faith[1], Selvamuthu Poongulali[1], Jayaraman Bhagavad Gita[3], Chakrapani Ashok[3], Nagalingeswaran Kumarasamy[1], Newell Johnson[4], **Stephen Challacombe[2]**, Priya Kannian[1]

[1] The Voluntary Health Services, Chennai, India. [2] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK, [3] Chennai Dental Research Foundation, Chennai, India [4] Griffith University Dental School, Queensland, Australia

Abstract

SARS-CoV2 gains access to the body across mucosal surfaces, largely those of the upper respiratory tract including the oral cavity. Both innate and adaptive immunity at mucosa are likely to influence this process. The aims of this study were to determine whether antibodies in secretions might influence the SARS-CoV2 burden and thus possibly the severity of infection. Blood and stimulated whole mouth fluid samples (SWMF) were collected at the time of recruitment (day 0), and at 14, 30 and 90 days later from 80 COVID patients identified by positive nasopharyngeal swabs of SARS-CoV2 RT-PCR (N=80). Anti-SARS-CoV2 spike antibodies were detected by electro-chemiluminescence assay (ECLIA) using a Cobas e411 automated analyser (Roche, Germany). 92% of the patients had anti-SARS-CoV2 spike antibodies in the serum, but only 39% had detectable antibodies in the SWMF samples. Anti-SARS-CoV2 spike antibody levels in the SWMF samples, and the associated antibody secretion rates correlated significantly with those in serum. The same relationship was maintained at all the four time points. No patient was positive for SWMF if negative in serum. Antibodies in both fluids increased by day 14 and decreased by day 90. SARS-CoV2 RNA copies become negative by day 14 in most subjects. At day 14, 5/18 SWMF samples continued to be RT-PCR positive. In samples from both day 0 (n=80) and at day 14 (n=18), RNA copy numbers in SWMF were inversely proportional to both the salivary and serum anti-SARS-CoV2 antibody levels. Higher levels of anti-SARS-CoV2 spike antibodies in saliva were significantly associated with a more rapid decline in SARS-CoV2 burden. Taken together our data suggests a potential functional role for the anti-SARS-CoV2 spike antibodies in SWMF in reducing the SARS-CoV2 burden.

Indo-UK Collaborative project BT/IN/Indo UK/02/PK/2021-22 and Medical Research Council UK MR/V040170/1

Concise one sentence summary:

Few studies in COVID have studied mucosal antibodies and this research shows an inverse relationship between salivary antibodies and the SARS-CoV2 burden

Oral presentation at the Regional Young Investigator's Meeting conducted by India Bioscience

Salivary flow cytometry: a reliable tool for immunophenotyping

Priya Kannian[1], Eniya Lillimary Muruganantham[1], Albert Judith[1], Shervin Dokht Sadeghi Nasab[2], Frederick Clasen[2], Beulah Faith[1], Selvamuthu Poongulali[1], Nagalingeswaran Kumarasamy[1], David Moyes[2], Newell Johnson[2,3], Stephen Challacombe[2]

[1] The Voluntary Health Services, Chennai, India,
[2] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK,
[3] Griffith University Dental School, Queensland, Australia

Abstract

Host immune responses at mucosal surfaces play a protective role against most infectious diseases. However, tools to determine cellular responses at the mucosal surfaces remain less explored. We aimed to determine the relative percentages, consistency of detection and reproducibility of detection of immunophenotypes in stimulated whole mouth fluid (SWMF). SWMF samples were collected from 100 healthy participants and sequential concomitant samples were collected from 8 of those. CD3, CD4, CD8, Th1, Th2, Th17, Th22, Tfh, Tregs, ILC, NK and NKT cells phenotypes were determined by FACS. All the immunophenotypes were detected consistently by FACS in experimental replicates (N=5; PBMC CV: 3-30%; SWMF CV: 9-41%). The detection rates in longitudinal samples were reproducible in both fluids but showed variations that were higher in SWMF (CV: 12-74%) than PBMC. Correlation analyses of these immunophenotypes in the PBMC and SWMF samples were done and results will be discussed in the meeting. Thus our study provides a robust FACS protocol for the detection of the major immunophenotypes in mucosal fluid like SWMF.

Poster presentation at the Immunocon 2024, the annual meeting of the Indian Immunology Society

Mucosal T cell phenotypes in mild COVID-19 among vaccinated and unvaccinated individuals

Muruganantham Lillimary Eniya[1], Albert Judith[1], Beulah Faith[1], Selvamuthu Poongulali[1], Shervin Dokht Sadeghi Nasab[2], Frederick Clasen[2], Jayaraman Bhagavad Gita[3], Velmurugan Raghavi,[3] Subramanian Vedavalli[3], Chandra Lavanya[4], Kannan Ranganathan[4], Gunaseelan Rajan[3], Nagalingeswaran Kumarasamy[1], David Moyes[2], Mark Ide[2], Saeed Shoaie[2], Yuko Kurushima[2], Daljit Jagmer[2], Mina Pun[2], Newell Johnson[2,5], Stephen Challacombe[2], Priya Kannian[1]

1 The Voluntary Health Services, Chennai, India
2 Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK
3 Chennai Dental Research Foundation, Chennai, India
4 Ragas Dental College and Hospital, Chennai, India
5 Griffith University Dental School, Queensland, Australia

SARS-CoV2 primarily infects the epithelial cells lining the aerodigestive mucosa. Delineation of the T cell phenotypes involved in mucosal host defense may provide insights into COVID-19 pathogenesis. We aimed to compare the T cell phenotypes in the oral mucosa and PBMCs of vaccinated healthcare workers who developed mild COVID-19 (VM; N=9) or recovered from COVID-19 (VR; N=12) with those of normal uninfected controls (NIC; N=5), unvaccinated individuals with mild COVID-19 (UVM; N=3) or recovered from COVID-19 (UVR; N=12). PBMCs and stimulated whole mouth fluid (SWMF) from 41 participants were stained with anti-human PerCP-CD3, PerCP-CD4, APC-R700-CD8, BV711-ICOS, BV786-CD25, BV605-PD-1, BV421-CCR4, BB515-CCR10, PE-Cy7-CXCR5 BV480-T-bet, BV421-GATA-3, BB515-ROR-γt, APC-Foxp3 antibodies and analysed by FACS. SARS-CoV2 RNA was quantified in SWMF by real time RT-PCR. Anti-SARS-CoV2 spike Ig antibodies in serum and SWMF were measured by ECLIA. UVM were antibody negative, while VM, VR and UVR had similar levels of antibodies in both serum and SWMF. SARS-CoV2 clearance was achieved 14 days earlier in VM compared to UVM. UVM and VM did not show any statistical differences between mean T cell percentages in PBMCs/SWMF except CD4 T cells in PBMCs ($p=0.03$). CD3, CD4, Th1, Tfh, Treg, ILC-1 and ILC-2 cells in SWMF showed no statistical differences among the groups. In SWMF, Th2 cells were higher among the vaccinees, while Th17 cells were highest in UVM. All the tissue-resident T cells – Th17, Tfh, ILC-1 and ILC-2 were significantly greater in SWMF than PBMCs. Thus the SARS-CoV2 exposed groups showed a differential expression of mucosal T cells suggesting a strong local immune response in COVID-19.

Email Id of Eniya Lilly Muruganantham: enianand98@gmail.com

SARS-CoV2 clearance was achieved 14 days earlier in vaccinated than unvaccinated. The SARS-CoV2 exposed groups showed a differential expression of mucosal T cells suggesting a strong local immune response in COVID-19.

Oral presentation at the Regional Young Investigator's Meeting conducted by India Bioscience July 2024

Temporal mucosal SARS-CoV2-specific antibodies in COVID patients before and after COVID vaccination

Eniya Lillimary Muruganantham[1], Albert Judith[1], Shervin Dokht Sadeghi Nasab[2], Frederick Clasen[2], Beulah Faith[1], Selvamuthu Poongulali[1], Nagalingeswaran Kumarasamy[1], David Moyes[2], Newell Johnson[2,3], Stephen Challacombe[2], Priya Kannian[1]
[1] The Voluntary Health Services, Chennai, India,
[2] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK,
[3] Griffith University Dental School, Queensland, Australia

Oral/nasal mucosae are the primary portals of entry for SARS-CoV2. Both innate and adaptive immunity at the mucosa are likely to influence this process. The aims of this study were to determine whether COVID vaccination impacted the elicitation of SARS-CoV2-specific IgG, IgA and/or secretory IgA (sIgA) antibodies in stimulated whole mouth fluid (SWMF) during subsequent exposures to COVID. SWMF samples were collected within 2-4 days of onset from 126 mild COVID patients (N=74 before vaccination; N=52 after vaccination) and longitudinal SWMF samples were collected at day 14 and day 90 from 12 of these vaccinated patients. COVID was confirmed by RT-PCR positive nasopharyngeal swabs. Anti-SARS-CoV2 spike IgG, IgA and sIgA antibodies were detected by ELISA. The mean IgG antibodies were 2.5-fold higher in patients who were vaccinated, while IgA (monomer) and SIgA (dimer) antibodies were 3-folds ($p<0.00001$) and 2.3 folds ($p=0.0001$) higher than in the unvaccinated group, respectively. Longitudinal measurements in the 12 vaccinated COVID patients showed a 4-fold increase in IgG antibodies at day 14, which declined 2.6-fold by day 90 ($p=0.0003$; Anova of repeated measures). However, IgA and SIgA antibodies showed only a marginal increase and decline at these time points. Thus our findings suggest that IgA and SIgA antibodies are only marginally boosted by prior antigen memory unlike IgG antibodies, while the former are elicited at markedly higher levels during the first natural infection. Longitudinal analyses showed higher sustained levels of IgA and SIgA antibodies compared to IgG antibodies in the SWMF. Taken together our data suggests a potential role for the anti-SARS-CoV2 spike mucosal antibodies (IgA and SIgA) in SWMF in COVID.

One sentence:

Immunisation against SARS-CoV2 prior to infection resulted in higher IgG, IgA and SIgA antibodies in secretions, and a longer lasting SIgA response

Poster presentation at the 2nd Global Immunology Summit

Innate lymphoid cells: key drivers of mucosal immunity in COVID-19

Muruganantham Lillimary Eniya[1], Albert Judith[1], Beulah Faith[1], Selvamuthu Poongulali[1], Shervin Dokht Sadeghi Nasab[2], Frederick Clasen[2], Jayaraman Bhagavad Gita[3], Velmurugan Raghavi,[3] Subramanian Vedavalli[3], Chandra Lavanya[4], Kannan Ranganathan[4], Gunaseelan Rajan[3], Nagalingeswaran Kumarasamy[1], David Moyes[2], Mark Ide[2], Saeed Shoaie[2], Yuko Kurushima[2], Daljit Jagmer[2], Mina Pun[2], Newell Johnson[2,5], Stephen Challacombe[2], Priya Kannian[1]

1 The Voluntary Health Services, Chennai, India
2 Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK
3 Chennai Dental Research Foundation, Chennai, India
4 Ragas Dental College and Hospital, Chennai, India
5 Griffith University Dental School, Queensland, Australia

Abstract

Innate lymphoid cells (ILC) may play an important role in innate mucosal immunity. SARS-CoV2 primarily infects the aerodigestive tract. We aimed to compare the frequency and tissue homing tendency of ILC in peripheral blood and stimulated whole mouth fluid (SWMF) in those with and without COVID-19. PBMC and SWMF were processed from 201 individuals: non-infected controls (NIC), asymptomatic COVID (AC); mild COVID (MC); moderate COVID (MOC); post COVID (PC); recovered from COVID (RC) by FACS using anti-human antibodies specific for natural killer (NK) cells, ILC1, ILC2 and ILC3. Frequencies of ILC1 (2.3% vs 0.5/1.0%), ILC2 (0.9% vs 0.1/0.2%) and ILC3 (0.1% vs 0.06/0.006%) were significantly higher in PBMCs of MC compared with NIC/RC. Frequencies of NK cells (15% vs 7.4%), ILC1 (5.9% vs 2.3%), ILC2 (8.1% vs 0.9%) and ILC3 (0.9% vs 0.1%) in MC were significantly higher in SWMF than PBMC, but were not significantly correlated. The frequencies of SWMF ILC1, ILC2 and ILC3 in MC declined over three months to levels similar to RC/NIC, but remained high in SWMF of PC. The tissue retention marker, CD69 and airway homing marker, Integrin α4β1 of ILC were significantly greater in SWMF of MC (ILC1-51%; ILC2-54%; ILC3-47%); but lower in PC (ILC1-48%; ILC2-29%; ILC3-14%). Thus ILC1, ILC2 and ILC3 are elevated during active COVID and declined to normal levels upon recovery; but persist in PC. Increased frequency of ILC in SWMF; not correlated with PBMC; high expression of tissue retention and airway homing markers indicate their role in oral mucosal immunity against COVID-19 for the first time.

Innate lymphoid cells (ILC) may play an important role in innate mucosal immunity. ILC1, ILC2 and ILC3 in SWMF were elevated during active COVID and declined to normal levels upon recovery; but persist in Long COVID indicating their role in oral mucosal immunity against COVID-19 for the first time.

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TITLE: Ethnicity, COVID Severity And Periodontal Status With SARS-CoV2 Infection

PREFERRED PRESENTATION TYPE: Poster

SCIENTIFIC GROUP/NETWORK CATEGORY: Periodontal Research-Diagnosis/Epidemiology

PRESENTER: Mark Ide

PRESENTER (INSTITUTION ONLY): King's College London

AUTHORS (FIRST NAME INITIAL LAST NAME): S. Nasab[2], F. Clasen[2], M. Eniya[4], A. Judith[4], D. Moyes[2], S. Shoaie[2], B. Faith[4], S. Poongulali[4], N. Kumarasamy[4], D. Jagdev[2], N. Johnson[5], P. Kannian[4], S. J. Challacombe[2], G. Ide[6], R. Wadera[3], M. Ide[1]

AUTHORS/INSTITUTIONS: M. Ide, King's College London, London, UNITED KINGDOM;
S. Nasab, F. Clasen, D. Moyes, S. Shoaie, D. Jagdev, S.J. Challacombe, King's College London Dental Institute, London, UNITED KINGDOM;
R. Wadera, University of Portsmouth, Plymouth, UNITED KINGDOM;
M. Eniya, A. Judith, B. Faith, S. Poongulali, N. Kumarasamy, P. Kannian, The Voluntary Health Services, Chennai, INDIA;
N. Johnson, Griffith University, Queensland, Queensland, AUSTRALIA;
G. Ide, Maidstone and Tunbridge Wells NHS Trust, Maidstone, UNITED KINGDOM;

ABSTRACT BODY:

Objectives: SARS-CoV2 accesses the body across mucosal surfaces, largely those of the upper respiratory tract including the oral cavity. In the UK, those of South Asian heritage (SA group) were considered more affected by COVID than those of white British heritage (WB group). This study aimed to investigate relationships between periodontal status, self reported COVID severity and other factors in 247 participants in a study of cellular and humoral innate immunity focused on these ethnic groups.

Methods: Participants completed a range of questionnaires related to factors such as age, ethnicity and diabetes status and underwent a periodontal assessment including full intraoral charting. Summary variables, including PISA scores, were generated.

Results: 30% of participants had a PSR score of <=2, 52% PSR=3 and 19% PSR=4. Periodontal status (sites probing over both 3mm and 5mm, and PISA score) was impacted by smoking (20 participants). Mean CSS was greater (p=0.0322) in those of SA heritage (46.55, SD 36.69) than those in the WB group (36.92, SD 37.23), and in women (44.34, SD 37.98 versus 32.42, SD 33.76, p=0.0346) but not in smokers or those with diabetes. There were weak negative correlations (rho = -0.12) approaching statistical significance between CSS and the number of sites probing >3mm and >5mm, but both these periodontal variables and smoking status were not related to ethnicity.

Conclusions: These results suggest that further investigation is needed to better understand interactions between periodontal status, ethnicity and SARS-CoV2 severity.

ONE SENTENCE SUMMARY: In this study population, periodontal health was impacted by smoking, and COVID severity by ethnicity, but there was minimal evidence of association between periodontal status and COVID severity score.

Abstract for IADR Barcelona 2025

Salivary lymphocyte phenotypes and cytokines in relation to SARS-CoV2 infection.

Shervin Sadeghi Nasab[1,] Frederick Clasen[1,] Muruganantham L Eniya[2], Albert Judith[2], David Moyes[1], Mark Ide[1], Saeed Shoaie[1,] Beulah Faith[2], Selvamuthu Poongulali[2], Nagalingeswaran Kumarasamy[2], Daljit Jagdev[1], Newell Johnson[3], Priya Kannian[1], **Stephen Challacombe[1]**,

[1] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, UK. [2] The Voluntary Health Services, Chennai, India, [3] Griffith University Dental School, Queensland, Australia,

Abstract

SARS-CoV2 gains access to the body across mucosal surfaces, largely those of the upper respiratory tract including the oral cavity. Innate immune factors at mucosae are likely to influence this process. In the UK, those of South Asian heritage (SA group) were significantly more affected by COVID than those of white British heritage (WB group). The aims of this study were to determine whether cellular and humoral innate immunity differed in the two populations. Levels of innate immune cytokines and of five major T lymphocyte phenotypes were assayed by ELISA/cytokine bead arrays and FACS respectively in stimulated whole mouth fluid (SWMF) and blood from over 194 subjects who had recovered from COVID or who remained infection free. Blood and SWMF were collected at the time of recruitment and sequentially up to 90 days later. Subjects of SA heritage had a significantly greater mean COVID severity score than those in the WB group. In general, CD4, Th1, and Th2 levels in blood were lower in SA than WB, while CD8 levels were higher. However, there were no significant differences in either group in the mean CD4, CD8 Th1 and Th2 lymphocyte levels in SWMF or blood in non-infected controls compared with those recovered from COVID. Mucosal cytokines showed a very different pattern in SWMF compared with blood. The SA group had lower mean levels than the WB group for CCL20, IL-1a in SWMF and for IL-8, MCP-1, IP-10 in blood. These results reveal differences between SA and WB groups in lymphocyte phenotype levels and in innate mucosal cytokine levels in both blood and saliva, that may influence susceptibility to mucosal SARS-CoV2 infections.

Indo-UK Collaborative project BT/IN/Indo UK/02/PK/2021-22 and Medical Research Council UK MR/V040170/1

Concise one sentence summary:

Mucosal innate immune factors may influence susceptibility to Sars-Cov2 infection and this study found that mean levels of salivary innate cytokines were significantly lower in those of South Asian heritage compared with those of white British heritage.

MIMSA Abstract 9
Poster presented at the 109th annual meeting of the American Academy of Periodontology 2023

Exploring the Role of Mucosal Immunity in COVID19 patients with Periodontitis - An Approach via Salivary Cytokines and Chemokines.

Bagavad Gita Jayaraman, Priya kannian, Gunaseelan Rajan, Raghavi V, Ranganathan Kannan, Kumarasamy N, Lavanya C, Vedavalli Subramanian, Stephen Challacombe, Newell Johnson, David Moyes, Mark Ide

Introduction

The role of mucosal immunity is more relevant in understanding the host response to the SARS CoV-2 virus as it gains entry into the body via the respiratory mucosa. Immune compromised individuals with co-morbidities such as diabetes mellitus, chronic obstructive pulmonary disease and cancer have been observed to have increased circulating systemic pro-inflammatory markers in response to the SARS-CoV2 virus increasing the risk of a cytokine storm. and disease severity. Mucosal immunity as reflected in the oral cavity plays a critical role in susceptibility/severity of COVID-19. It is known that in viral diseases T-cells and cytokines are altered in both systemic and mucosal immunity but have not been much explored in the mucosal response of the upper aero-digestive tract.

Periodontitis is associated with systemic diseases including respiratory illnesses like pneumonia and COPD. The anatomical continuity of the aerodigestive tract facilitates the translocation of potential respiratory pathogens from the oral cavity. Both diseases are characterized by an exaggerated immune response. A hyperinflammatory host response to a dysbiotic oral microbiome in periodontitis can result in a breakdown of the connective tissue around the teeth. Significantly higher levels of chemokines and cytokines have been detected in the saliva and gingival crevicular fluid of periodontitis patients.

In this study, we primarily aimed to understand if pre-existing periodontal disease increases susceptibility to SARS-CoV2 infection and affects mucosal immunity to COVID-19. We also aimed to estimate the levels of salivary cytokines and chemokine in COVID 19 patients and periodontitis and explore any possible association between salivary cytokines and chemokines in the UK South Asian /White British and the South Indian populations.

Methods

This cross-sectional analytical study included 232 subjects from VHS – IDMC (Infectious diseases medical centre) Chennai, India, who are participating in the *Role of oral microbiome & mucosal immunity in COVID-19 disease: diagnostic and prognostic utility in South Asian populations (MIMSA)* under UK-India partnership (UKRI-DBT COVID 19 Initiative). Subjects initially included the healthy, asymptomatic, mild, moderate and severe COVID-19 subjects. We also recruited patients with no apparent exposure to covid, post-covid and recovered groups.

Periodontal status was recorded by periodontal screening and recording index (PSR) in 180 subjects. A self-reported questionnaire for COVID-19 symptoms and previous history of periodontitis was given.

Patient-related characteristics: Covariates lincluding age, sex, smoking habits and other COVID 19-related comorbidities/risk factors such as diabetes, hypertension, pulmonary disease, chronic

kidney disease, cancer, coronary artery disease, obesity and any other co-morbidities were also recorded.
Stimulated whole mouth fluid (SWMF) and serum samples were collected from the subjects. Salivary Cytokines and chemokine MIG, MCP-1, TNF-a, Il-8, Il-6 and Il-1B of 55 Indian subjects and 39 white British and South Asians subjects living in the UK were estimated.

Results
The average age for males was 38.3±16.9 and for females 34.3±68.4 years (mean±SD). 68% of examined subjects were found to have gingivitis and 23% early periodontitis. 61% of the subjects belonged to the recovered COVID group and 23% to the mild covid group. Salivary IL-6 was significantly high in the mild COVID group ($p<0.05$). Post- COVID patients were found to have higher mean probing depth ($p<0.01$) than non-infected controls.

Conclusion
In the South Indian population, salivary IL-6 was significantly higher in mild COVID subjects than asymptomatic or control patients. Post- COVID patients were found to have higher mean probing depths. However there was no significant association between COVID-19 and periodontitis in these subjects. Early periodontitis patients had significantly high UCFP levels. IL-6 and TNF alpha showed high statistical significance in the advanced periodontitis group. There were no significant differences in salivary cytokine levels between the UK and South Indian subjects. Based on these findings we can conclude that mucosal immunity particularly IL-6 can play a pivotal role in COVID 19 subjects with periodontitis in the South Indian population.

There were no significant differences in mean salivary cytokine levels between the UK and South Indian subjects but Post- COVID patients were found to have higher mean probing depth ($p<0.01$) than non-infected controls.