Clinical Oral Investigations
https://doi.org/10.1007/s00784-021-04111-3

ORIGINAL ARTICLE

The clinical association between Periodontitis and COVID-19

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Received: 28 May 2021 / Accepted: 27 July 2021

Abstract

Objectives The study aimed to clinically assess the association between periodontitis and COVID-19-related outcomes.

Material and methods Data pertaining to patient demographics, medical history, blood parameters, periodontal clinical examination and aMMP-8 point-of-care diagnostics (both site-level and patient-level) was recorded for eighty-two COVID-19-positive patients. COVID-19-related outcomes such as COVID-19 pneumonia, death/survival, types of hospital admission and need of assisted ventilation were also assessed.

Results Males were predominantly afflicted with COVID-19, with advanced age exhibiting a greater association with the presence of periodontitis. Higher severity of periodontitis led to 7.45 odds of requiring assisted ventilation, 36.52 odds of hospital admission, 14.58 odds of being deceased and 4.42 odds of COVID-19-related pneumonia. The aMMP-8 mouthrinse kit was slightly more sensitive but less specific than aMMP-8 site-specific tests.

Conclusions Based on the findings of the present study, periodontitis seems to be related to poorer COVID-19-related outcomes. However, within the constraints of this work, a direct causality may not be established. Periodontitis, by means of skewing the systemic condition for a number of comorbidities, may eventually influence COVID-19 outcomes in an indirect manner.

Clinical relevance The study is the first to clinically, and by means of a validated point-of-care diagnostic methodology, assess the association between periodontal health and COVID-19-related outcomes. Assessment of the periodontal status of individuals can aid in the identification of risk groups during the pandemic along with reinforcing the need to maintain oral hygiene and seeking periodontal care.

Keywords SARS-CoV-2 · COVID-19 · Periodontitis · Oral health · Oral hygiene · Matrix metalloproteinases · Prevention · Comorbidities · Ventilation · Diagnostics · Periodontics · Periodontal · Dental

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Introduction

The COVID-19 pandemic has presented a conundrum like never before in terms of understanding its pathophysiology. With no cure in sight, it remains a significant aspect of research to identify and delineate factors which may alter the course of the disease in order to aid in its understanding and subsequent management. This would continue to assume importance even with the advent of anti-COVID-19 vaccinations.

Periodontal disease is considered a pandemic in its own right, with the reported case load far exceeding that of COVID-19. The disease process, though being non-fatal and chronic in nature, plays a crucial role not only in determining oral health but also as a significant contributor to the pathophysiology of a number of systemic conditions. There is sufficient evidence in literature to warrant an association between the presence of periodontal disease and the development and

Published online: 27 August 2021

course of respiratory illnesses [1]. These mechanistic links range from a direct aspiration of these pathogens into the lungs to more indirect mechanisms wherein virulence factors and enzymes released by periodontopathogens may modify mucosal surfaces to make them more amenable to colonisation, destroy bacterial salivary pellicle to inhibit their subsequent clearance or modify the respiratory epithelium via cytokines in order to promote infection [2].

Indeed several hypotheses have pointed towards the possibility of a link between periodontal disease and COVID-19 [3, 4]. Detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the gingival crevicular fluid (GCF) further gives credence to this theory and introduces the possibility of another point of entry [5].

SARS-CoV has been known to cause alterations in lung tissue due to numerous pathways, of which one involves mediation via matrix metalloproteinases (MMPs) [6]. MMPs cause extracellular matrix degradation along with mediating lung tissue remodelling; these factors eventually contribute to enhanced vascular permeability as well as damage to the endothelium. Acute respiratory distress syndrome (ARDS) management involves the utilisation of mechanical ventilation which can further lead to lung injury via ventilation-induced MMP-8 expression [6, 7]. Indeed, the eventual mortality of patients has been related to the expression of MMP-8, MMP-9, MMP-2 and TIMP-1, as is observed in early sepsis. MMPs have also been implicated in facilitating early virus entry into cells [8].

Over time, it has also become clear that proteinases, particularly collagenase-2, responsible for causing matrix degradation are chiefly obtained from polymorphonuclear leukocytes (PMNs) found in the diseased periodontium [9, 10]. Upon release from PMNs, the latent forms of these MMPs convert to their activated states by means of their interaction with reactive oxygen species or by proteolytic cleavage. Indeed, PMN-derived MMP-8 activity is elevated in the gingival tissue, GCF, and saliva of patients suffering from periodontitis [9].

The active MMP-8 point-of-care (aMMP-8 POC) test has been validated in various countries in both adolescent and adult populations as a means to define active and inactive sites of periodontal disease, assess prognosis and evaluate patients in the treatment and maintenance phases [11–14]. This particular point-of-care testing methodology possesses a sensitivity of 76–83% and specificity of 96% with results being returned within 5–7 minutes [15, 16].

A number of hypothetical models have been put forth to assess the possibility of a link between oral hygiene and/or periodontal disease and the COVID-19 disease process [3, 17, 18]. A few studies based on patient data have also been published, which generally point towards periodontal disease as a determinant of poorer COVID-19-related outcomes [19, 20]. These studies, however, suffer from the fatal flaw of simply utilising previously collected patient data or few self-reported oral health indicators and correlating it to their current COVID-19 disease process.

In the present study, the authors went several steps further and performed real-time clinical assessments of patients suffering from COVID-19 along with utilising a validated aMMP-8 point-of-care bedside diagnostic test kit in order to evaluate the presence of active periodontal disease.

It is the belief of the authors that this is the first such study to perform clinical and diagnostic assessments in COVID-19 patients in the manner described. The aim of this study was to assess the association of periodontal health on the complications of COVID-19.

Methods

The cross-sectional analytical study was carried out by the Unit of Periodontics, Oral Health Sciences Centre, in collaboration with the Department of Internal Medicine, Department of Anaesthesia & Department of Virology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. The study was performed according to the Declaration of Helsinki. Due approval was taken from the Postgraduate Institute of Medical Education and Research, Chandigarh Institutional Ethics Committee (INT/IEC/2021/SPL-636). The present study conforms to STROBE guidelines. Eighty-two patients reporting to the communicable diseases ward or admitted in the hospital between 15·January·2021 and 20·February·2021 were recruited into the study after their COVID-19 status was confirmed by nasopharyngeal swab (NPS) testing. A patient information sheet was given to all the patients, and written informed consent was obtained from all the subjects. Pregnant ladies, patients less than 18 years old and those unwilling or not in a position to give written informed consent were excluded from the study. The sample size was based on convenient sampling owing to the fact that the study setting was a dedicated COVID-19 centre and the close proximity required on part of the healthcare worker (HCW) with a potentially infectious patient to conduct intraoral examination and aMMP-8 analysis. However, as no sample size estimation was done a priori, a post hoc power analysis was performed to validate the same. Demographic data was recorded, and chairside tests run for evaluating the expression of aMMP-8 at the site with maximum periodontal breakdown as well as via a mouthrinse-based kit for general disease activity.

Training and calibration

For training and calibration of the examiners, a COVID-19-negative cohort of 10 subjects was enrolled from the Out Patient Department of the Oral Health Sciences Centre. It involved comprehensive periodontal clinical examination by

a single examiner (SG) and running of chairside tests for evaluating expression of aMMP-8 by another examiner (MS). Interexaminer reliability was found to be 0.91 using Cohen kappa for categorical variable and 0.93 using intraclass correlation coefficient for continuous variable.

Patient-related characteristics

Covariates

Covariates like 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 comorbidities were recorded.

Blood parameters relevant to the disease progression such as C-reactive protein (CRP), D-dimer, platelet count, ferritin, glycosylated haemoglobin (HbA1c), haemoglobin (Hb), vitamin D3, neutrophil/lymphocyte ratio (N/L), troponin, procalcitonin and N-terminal-pro-brain natriuretic peptide (NT-proBNP) were recorded. These parameters were noted from the patients' records, if available. Hence, the number of samples varied in each parameter.

Periodontal clinical examination

Periodontal clinical examination was conducted by a single calibrated examiner (SG) using a 10-mm round-tip manual Williams's periodontal probe. All permanent teeth, excluding the third molars, were examined at six sites per tooth (disto-buccal, mid-buccal, mesio-buccal, disto-palatal, mid-palatal, mesio-palatal). Gingival recession (GR), gingival marginal level (GML), periodontal probing depth (PPD), bleeding on probing (BOP) and number of teeth present/missing/carious were recorded. Clinical attachment loss (CAL) was calculated. Patients were categorised into periodontally healthy, gingivitis and stage I–IV periodontitis, as per the new classification of periodontitis as described by Chapple *et al.* (2018), Trombelli *et al.* (2018) and Tonetti *et al.* (2018), based on their clinical examination alone, as conducting intra-oral radiographs for COVID-19-positive patients was not feasible [21–23].

Sample collection and qualitative analysis for aMMP-8 PoC mouthrinse- and site-specific kits

These tests were conducted by a second periodontist (MS) a priori unaware of the clinical examination results. aMMP-8 chairside lateral flow mouthrinse immunoassay test (PerioSafe, Dentognostics GmbH, Solingen, Germany) and aMMP-8 chairside lateral flow site-specific immunoassay test (ImplantSafe, Dentognostics GmbH, Jena, Germany) were run step by step according to the manufacturer's instructions as described in literature [11–14]. The colour changes due to immunoreactions were read after exactly 5 min. In both cases, a single blue line indicated aMMP-8 levels less than 20 ng/ml (negative; no risk), whereas two blue lines were representative of aMMP-8 levels more than 20 ng/ml (positive; increased risk), indicating active periodontal disease.

Outcome variables

COVID-19-related complications such as presence of COVID-19 pneumonia, death due to COVID-19, type of hospital admission and need of assisted ventilation were also assessed. Patients requiring oxygen via high-flow nasal cannula (HFNC), non-invasive ventilation (NIV) or through intubation and ventilator were categorised as patients requiring assisted ventilation, whereas those able to maintain their status quo on room air were categorised as patients not requiring assisted ventilation. Admissions were categorised into those isolated at home and those admitted in the hospital either in the wards or in the ICU as per their disease severity and treatment requirements. An attempt was made to evaluate the presence of active periodontal disease using a validated aMMP-8 point-of-care bedside diagnostic test kit.

Statistical analysis

Descriptive and inferential statistical analyses have been carried out in the present study. The results were analysed by using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Results for continuous measurements were presented as mean ± SD (Min-Max) and those for categorical as frequency (Percentage). Normality of the data was assessed using Shapiro Wilk test/Kolmogorov-Smirnov test. Bivariate associations were examined using Fischer exact test/chi-square test. Kruskal-Wallis test was used to compare the variables at different levels of periodontal disease. Mann-Whitney *U* test/Kruskal-Wallis test was also used to compare within the group. Logistic regressions were applied to obtain odds ratio with 95% confidence interval wherever possible. Since no sample size calculation was undertaken a priori, a post hoc power analysis was calculated from clinical.com (http://clincalc.com/stats/Power.aspx) using primary endpoint as dichotomous. A maximum power of 98.9% was achieved between periodontal status of the patient and requirement of assisted ventilation.

Results

COVID-19-positive cohort characteristics

Table 1 presents the association of various parameters with stages of periodontitis. Forty-eight male patients and thirty-

Table 1 Association of patient-related data with stages of periodontitis

Parameters		Periodontally healthy (n = 27) (%)	Gingivitis (n = 21) (%)	Stage I periodontitis (n = 3) (%)	Stage II periodontitis (n = 2) (%)	Stage III periodontitis (n = 17) (%)	Stage IV periodontitis (n = 12) (%)	p value
Age (in years)	Mean ± SD	34.44 ± 11.06	37.71 ± 10.0	52.33 ± 16.25	44.00 ± 18.38	62.94 ± 12.76	61.58 ±9.07	0.001*
Sex	Male	18 (22)	11 (13.4)	3 (3.7)	1 (1.2)	10 (12.2)	5 (6.1)	0.486
	Female	9 (11)	10 (12.2)	0 (0.0)	1 (1.2)	7 (8.5)	7 (8.5)	
COVID-19 symptoms	Symptomatic	18 (22)	16 (19.5)	2 (2.4)	0 (0.0)	8 (9.8)	7 (8.5)	0.219
	Asymptomatic	9 (11)	5 (6.1)	1 (1.2)	2 (2.4)	9 (11)	5 (6.1)	
CT chest (ground-glass opacities)	Present	3 (3.7)	3 (3.7)	1 (1.2)	0 (0.0)	5 (6.1)	2 (2.4)	0.554
	Absent	24 (29.3)	18 (22)	2 (2.4)	2 (2.4)	12 (14.6)	10 (12.2)	
Comorbidities	Present	18 (22)	14 (17.1)	1 (1.2)	0 (0.0)	7 (8.5)	3 (3.7)	0.431
	Absent	9 (11)	7 (8.5)	2 (2.4)	2 (2.4)	10 (12.2)	9 (11)	
Type of comorbidity	Diabetes mellitus	3 (3.7)	0 (0.0)	2 (2.4)	0 (0.0)	5 (6.1)	4 (4.9)	0.006*
	Hypertension	6 (7.3)	4 (4.9)	2 (2.4)	0 (0.0)	8 (9.8)	5 (6.1)	0.163
	Chronic kidney disease	1 (1.2)	2 (2.4)	2 (2.4)	0 (0.0)	3 (3.7)	2 (2.4)	0.075
	Cardiovascular diseases	0(0.0)	1 (1.2)	1 (1.2)	1 (1.2)	2 (2.4)	5 (6.1)	0.001*
	Pulmonary disease	3 (3.7)	1 (1.2)	1 (1.2)	1 (1.2)	2 (2.4)	0 (0.0)	0.158
	Cancer	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.2)	4 (4.9)	1 (1.2)	0.023*
	Obesity	0 (0.0)	0 (0.0)	0 (0.0)	0	1 (1.2)	1 (1.2)	0.241
	Any other comorbidity	3 (3.7)	5 (6.1)	0 (0.0)	1 (1.2)	5 (6.1)	3 (3.7)	0.431
Hospital admission	Required	11 (13.4)	9 (11.0)	3 (3.7)	2 (2.4)	17 (20.7)	11 (13.4)	0.001*
	Not required	16 (19.5)	12 (14.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2	
Oxygen requirement	Required	3 (3.7)	5 (6.1)	2 (2.4)	0 (0.0)	14 (17.1)	6 (7.3)	0.001*
	Not required	24 (29.3)	16 (19.5)	1 (1.2)	2 (2.4)	3 (3.7)	6 (7.3)	
COVID-19 pneumonia	Present	3 (3.7)	4 (4.9)	1 (1.2)	0	9 (11.0)	5 (6.1)	0.025*
	Absent	24 (29.3)	17 (20.7)	2 (2.4)	2 (2.4)	8 (9.8)	7 (8.5)	
Survival	Deceased	0	1 (1.2)	0	0	6 (7.3)	1 (1.2)	0.009*
	Survived	27 (32.9)	20 (24.4)	3 (3.7)	2 (2.4)	11 (13.4)	11 (13.4)	
Bleeding on probing	Present	0	20 (26.3)	3 (3.9)	2 (2.6)	11 (14.5)	4 (5.3)	0.001*
	Absent	27 (35.5)	1 (1.3)	0	0	3 (3.9)	5 (6.6)	

*Statistically significant ($p < 0.05$)

four female patients were enrolled in the study. Age has been shown to be associated with periodontitis in literature. The present study results also exhibited an overall increase in age distribution with increasing stages of periodontitis in COVID-19 patients. Fifty-one patients had typical symptoms of COVID-19, whereas thirty-one were asymptomatic on presentation. Presence or severity of periodontal diseases was not found to be associated with gender or presence/absence of COVID-19 symptoms. Of the patients, 52.43% presented with one or more comorbidities. A statistically significant association was observed for diabetes mellitus, cardiovascular diseases and cancer. Predictors of COVID-19-related outcomes such as hospital admission, requirement of assisted ventilation, COVID-19 pneumonia and eventual survival were observed to increase with a concomitant rise in the stage of periodontitis. Particularly, patients with a higher stage of periodontitis underwent ICU admission as opposed to those with a healthy periodontium or gingival disease who were found to be under home isolation or ward admission.

Likewise, requirement of assisted ventilation was more amongst patients with stage III and IV periodontitis. Twenty-two patients presented with COVID-19 pneumonia and fourteen had ground-glass opacities on CT chest. Majority of the patients survived and 9.7% (n = 8) of the patients succumbed. These patients had a greater severity of periodontitis. One of the eight deceased patients had diabetes along with hypertension. Five of the deceased had other comorbidities like hypertension, CKD, history of CAD and acute necrotising pancreatitis. Bleeding on probing was commensurate with the stage of periodontal disease.

Blood parameters

Tables 2, 3 and 4 report the associations between the periodontal status and blood parameters recorded at the time of examination. Bleeding on probing was not associated with any recorded blood parameter. Gingival recession and number of teeth missing due to periodontal reasons were associated with D-dimer and troponin values. Probing depth was significantly associated with HbA1c, CRP, D-dimer and ferritin levels. Higher CAL was associated with elevated levels of CRP, D-dimer, pro-BNP, troponin and procalcitonin. Subjects with more severe forms of periodontitis had higher levels of D-dimer, pro-BNP and troponin.

Association of periodontal and blood parameters with COVID-19 complications

Table 5 presents the association between selected periodontal parameters and COVID-19 complications, in terms of requirement of assisted ventilation, hospital admission, presentation of COVID-19 pneumonia and survival.

Patients with bleeding on probing had 4.14 odds of requiring assisted ventilation, 3.18 odds for hospital admission and 3.63 odds of suffering from COVID-19 pneumonia. Probing depth, gingival recession and CAL were significantly associated with all the included complications of COVID-19. Increasing probing depth, CAL and presence of gingival recession in these patients put them at increased odds for these complications. Patients with gingival recession required assisted ventilation (OR = 8.22), had less chances of survival (OR = 14.07), and 6.50 odds of COVID-19 pneumonia. However, missing teeth was only associated with increased odds of hospital admission (OR = 12.52). Also, it was found that deceased patients had significantly higher mean probing depth, gingival recession and CAL compared to the survivors. Periodontal status was associated with all the included complications of COVID-19 in the present study. Higher severity of periodontitis led to 7.45 odds of requiring assisted ventilation, 36.52 odds of hospital admission, 14.58 odds of death and 4.42 odds of COVID-19 pneumonia.

Table 6 presents the association of COVID-19 complications and blood parameters recorded at the time of examination. Subjects requiring admission in hospital had significantly elevated levels of HbA1c, CRP, D-dimer, ferritin, N/L ratio, haemoglobin, pro-BNP, troponin and procalcitonin. Survival was found to be associated with elevated N/L ratio and platelet count, whereas subjects with higher levels of HbA1c, CRP, D-dimer, ferritin and procalcitonin required assisted ventilation.

aMMP-8 mouthrinse tests and aMMP-8 site specific tests

aMMP-8 mouthrinse kit was positive in 38.1% , and aMMP-8 site-specific kit was positive in 33.3% of patients with periodontal disease. However, the kits also tested positive for 21.1% (mouthrinse kit) and 13.9% (site specific kit) in periodontally healthy subjects (**Table 7**).

Discussion

The findings of the present study establish an association between periodontal disease and COVID-19-related outcomes.

The results are in concordance with a study conducted by Marouf *et al.* (2021) who found a significant association to exist between periodontal disease and COVID-19-related outcomes [20]. This study utilised patient records available to predict periodontal outcome measures as risk factors for COVID-19 prognosis. However, no clinical assessment of their periodontal status at the time of suffering from the COVID-19 infection was made and hence patients with previous bone loss, but no active disease at the time of the study, might have been grouped along with those experiencing active disease. In our study, we not only conducted a real-time clinical examination of all the patients involved but also ran the aMMP-8 PoC chairside kits to determine the current activity of periodontal disease in the cohort. The current study, hence, makes the important distinction of assessing active periodontal disease and its relation to COVID-19-related outcomes.

The failure to maintain adequate ventilation has been touted as a significant marker of worsening COVID-19-related outcomes. Indeed, hypoxemia has been observed to have been independently associated with in-hospital mortality [24]. In the present study, the authors found a significant association between bleeding on probing, increased periodontal probing depth, the presence of gingival recession, clinical attachment loss and oxygen requirement in COVID-19 patients. By this extension then, it would seem logical to conclude that poorer periodontal disease outcome measures might imply a worse COVID-19-related prognosis. Compromised periodontal outcome measures correlated significantly with the event of death in this patient population. Based on this finding it would thus be justified to state that patients with periodontal disease seemed to have a poorer chance of survival when compared to those without this ailment.

It is generally regarded that patients necessitating admission had taken or were expected to take a turn for the worse in terms of their prognosis. A significant rate of mortality has been demonstrated in patients hospitalised as a result of COVID-19 [25].

Compromised periodontal outcome measures correlated significantly with the event of hospital admissions; i.e.

Table 2 Periodontal findings and blood parameters (HbA1c , CRP, vitamin D3, D-dimer)

		HbA1c			CRP			Vitamin D3			D-dimer		
Parameters		***N***	**Mean ± SD**	***p* value**	***N***	**Mean ± SD**	***p* value**	***N***	**Mean ± SD**	***p* value**	***N***	**Mean ± SD**	***p* value**
Bleeding on probing	Present	17	7.635 ± 3.52	0.059	21	80.001 ± 102.87	0.262	16	32.15 ± 29.70	0.649	23	3853.00 ± 6032.62	0.050
	Absent	15	6.06±2.01		12	50.34 ± 73.32		15	26.47 ± 25.89		15	810.04 ± 1015.76	
Recession	Present	6	8.15 ± 3.5	0.20	9	119.20 ± 133.33	0.057	5	50.67 ± 35.16	0.113	11	6080.30 ± 7656.01	0.002*
	Absent	26	6.6 ± 2.8		24	50.47 ± 67.36		26	25.31 ± 24.68		27	1255.05 ± 2244.89	
Mean probing depth	0–2mm	21	6.1 ± 1.8	0.015 *	19	47.326 ± 69.92	0.041*	21	26.31 ± 24.79	0.823	21	733.25 ± 906.71	0.014*
	> 2–5mm	7	7.6 ± 4.5		6	46.490 ± 79.05		6	32.86 ± 29.62		8	6702.35 ± 9084.66	
	> 5mm	4	9.8 ± 3.2		8	138.258 ± 124.16		4	40.44 ± 42.55		9	3528.07 ± 9084.66	
Mean CAL	0–2mm	23	6.6 ± 3.0	0.188	21	44.174 ± 64.50	0.013*	23	25.54 ± 25.85	0.098	23	1069.51 ± 1894.92	0.035*
	3–4mm	7	7.2 ± 2.7		7	52.233 ± 65.15		6	26.33 ± 16.89		10	6180.67 ± 8255.01	
	> 5mm	2	9.1 ± 4.1		5	198.184 ± 132.75		2	83.10 ± 23.90		5	2872.86 ± 2474.22	
Periodontal status	Periodontally healthy	11	6.1 ± 2.3	0.161	10	31.745 ± 53.01	0.173	12	23.74 ± 26.03	0.056	12	776.31 ± 1139.01	0.042*
	Gingivitis	6	6.2 ± 1.5		7	42.146 ± 69.02		6	25.91 ± 24.09		6	541.28 ± 581.08	
	Stage I periodontitis	2	11.8 ± 8.4		2	125.750 ± 110.74		2	8.340 ± 3.76		2	4700.13 ± 5809.78	
	Stage II periodontitis	2	5.4 ± 1.0		1	8.00		1	32.00		1	2788.00	
	Stage III periodontitis	6	7.3 ± 2.3		8	96.484 ± 111.94		6	59.45 ± 30.43		9	2303.00 ± 4798.86	
	Stage IV periodontitis	5	7.4 ± 3.2		5	128.072 ± 133.31		4	16.44 ± 11.99		8	6911.38 ± 7942.74	
Number of teeth missing due to periodontal reasons	No missing teeth	18	6.8 ± 3.3	0.500	17	53.959 ± 68.08	0.789	17	19.90 ± 16.55	0.129	19	1153.42 ± 2076.65	0.005*
	1–4 teeth lost	7	7.04 ± 2.2		9	79.706 ± 112.71		8	48.88 ± 37.40		9	2218.18 ± 4834.87	
	> 4 teeth lost	7	6.8 ± 2.8		7	92.791 ± 124.42		6	30.34 ± 28.69		10	5889.10 ± 7343.67	
Number of carious teeth	No caries	28	6.8 ± 2.9	0.133	29	71.019 ± 94.55	0.482	27	30.15 ± 28.83	0.743	33	2208.03 ± 4683.42	0.132
	Caries in 1 tooth	2	9.9 ± 4.6		2	9.980 ± 8.31		2	27.59 ± 29.28		2	11619.50 ± 4797.71	
	Caries in 2 teeth	1	5.8		1	196.70		1	10.20		2	938.80 ± 1001.40	
	Caries> 2 teeth	1	4.7		1	8.0		1	32.00		1	2788.00	

*Statistically significant ($p < 0.05$); *CAL* clinical attachment loss; *HbA1c* glycated haemoglobin; *CRP*: C-reactive protein

Table 3 Periodontal findings and blood parameters (ferritin, N/L ratio, Hb, platelet count)

Parameters		Ferritin			N/L ratio			Hb			Platelet count		
		N	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value
Bleeding on probing	Present	22	921.50 ± 318.63	0.088	14	11.66 ± 16.43	0.453	28	10.874 ± 2.93	0.320	27	238.74 ± 96.98	0.465
	Absent	13	381.36 ± 915.22		8	9.15 ± 12.34		20	11.830 ± 3.15		18	219.50 ± 94.37	
Recession	Present	10	667.76 ± 649.51	0.884	7	22.42 ± 21.74	0.053	11	9.789 ± 2.40	0.075	11	228.00 ± 107.42	0.833
	Absent	25	742.13 ± 850.40		15	5.30 ± 5.16		37	11.714 ± 3.08		34	232.03 ± 92.83	
Mean probing depth	0–2mm	19	473.72 ± 554.62	0.014*	13	7.084 ± 9.88	0.204	30	11.830 ± 2.90	0.206	27	229.44 ± 96.66	0.873
	> 2–5mm	7	1434.71 ± 913.94		4	6.420 ± 3.07		9	10.178 ± 3.98		9	242.33 ± 102.70	
	> 5mm	9	687.44 ± 859.25		5	23.756 ± 24.04		9	10.509 ± 2.06		9	224.56 ± 94.22	
Mean CAL	0–2mm	21	563.84 ± 621.13	0.386	14	4.988 ± 5.204	0.092	33	11.739 ± 2.93	0.222	30	237.07 ± 97.46	0.701
	3–4mm	9	1125.60 ± 111.056		4	14.52 ± 10.298		10	10.558 ± 3.47		10	228.40 ± 92.30	
	> 5mm	5	651.92 ± 282.29		4	27.15 ± 27.934		5	9.620 ± 2.30		5	200.20 ± 102.33	
Periodontal status	Periodontally healthy	10	341.44 ± 256.53	0.162	7	5.49 ± 7.24	0.141	16	12.444 ± 3.21	0.195	14	211.93 ± 71.05	0.196
	Gingivitis	6	673.83 ± 890.75		5	3.77 ± 2.083		10	11.830 ± 2.50		9	249.33 ± 103.80	
	Stage I periodontitis	2	1627.00 ± 134.35		1	8.22		3	11.567 ± 2.82		3	314.67 ± 45.56	
	Stage II periodontitis	1	2000.0		1	3.35		1	6.400		1	166.00	
	Stage III periodontitis	9	890.50±908.03		5	13.41 ± 13.636		9	10.044 ± 3.54		9	187.67 ± 96.180	
	Stage IV periodontitis	7	643.55±911.65		3	33.54 ± 26.84		9	10.242 ± 1.99		9	265.22 ± 116.82	
Number of teeth missing due to periodontal reasons	No missing teeth	16	722.90	0.861	13	4.88 ± 5.52	0.060	23	11.913 ± 2.91	0.081	23	236.30 ± 86.92	0.793
	1–4 teeth lost	10	649.65		4	16.169 ± 13.95		14	11.514 ± 3.44		11	213.36 ± 87.81	
	> 4 teeth lost	9	796.43		5	21.664 ± 25.00		11	9.625 ± 2.25		11	237.73 ± 123.29	
Number of carious teeth	No caries	31	646.57±735.11	0.217	19	11.919 ± 15.66	0.773	39	11.484 ± 3.08	0.493	38	240.92 ± 98.04	0.249
	Caries in 1 tooth	2	377.05±76.43		0	0		5	11.000 ± 1.93		4	198.50 ± 63.75	
	Caries in 2 teeth	1	2433.0		2	3.377 ± 1.509		3	10.600 ± 3.79		2	141.00 ± 60.811	
	Caries > 2 teeth	1	2000.0		1	3.350		1	6.400		1	166.00	

*Statistically significant ($p < 0.05$); *CAL* clinical attachment loss; *N/L* neutrophil/lymphocyte; *Hb* haemoglobin

Table 4 Periodontal findings and blood parameters (Pro-BNP, troponin, procalcitonin)

Parameters		Pro-BNP			Troponin			Procalcitonin		
		N	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value
Bleeding on probing	Present	22	21636.27 ± 67137.3	0.299	23	141.55 ± 367.5	0.392	23	4.83± 14.5	0.221
	Absent	14	3033.75 ± 6271.8		14	171.78 ± 548.2		15	0.346 ± 0.5	
Recession	Present	9	16231.70 ± 26810.8	0.060	10	299.75 ± 528.2	0.010 *	10	3.5 ± 8.7	0.097
	Absent	27	13792.04 ± 59593.9		27	98.63 ± 396.2		28	2.89 ± 12.4	
Mean probing depth	0–2mm	21	16908.5 ± 67409.8	0.139	21	120.89 ± 448.4	0.212	22	3.23 ± 13.9	0.081
	> 2–5mm	6	12837.68 ± 5240.9		7	58.92 ± 96.1		8	1.29 ± 2.8	
	> 5mm	9	27079.81 ± 9026.6		9	301.04 ± 562.2		8	4.34 ± 9.6	
Mean CAL	0–2mm	23	14663.93 ± 64488.7	0.031*	23	109.69 ± 429.1	0.040*	24	2.95 ± 13.3	0.023 *
	3–4mm	8	5531.4 ± 11034.8		9	51.9 ± 84.7		9	1.23 ± 2.7	
	> 5mm	5	27389.76 ± 32816.5		5	534.07 ± 692.5		5	6.83 ± 11.9	
Periodontal status	Periodontally healthy	11	1411.23 ± 3805.8	0.038*	11	14.22 ± 31.5	0.039 *	12	0.31 ± 0.57	0.301
	Gingivitis	7	44658.0 ± 44262.4		7	19.12 ± 31.7		7	9.43 ± 24.8	
	Stage I periodontitis	2	176.5 ± 164.75		2	6.8 ± 5.3		2	0.46 ± 0.59	
	Stage II periodontitis	0	0		1	252.0		1	0.7	
	Stage III periodontitis	9	15643 ± 26943.4		9	420.11± 140.0		8	4.80 ± 9.7	
	Stage IV periodontitis	7	7028.69 ± 11741.1		7	833.62 ± 315.0		8	0.88 ± 1.5	
Number of teeth missing due to periodontal reasons	No missing teeth	18	18324.47 ± 72910.1	0.052	18	18.04 ± 30.9	0.018 *	19	3.72 ± 15.0	0.406
	1–4 teeth lost	10	13621.42 ± 26123.9		10	149.17 ± 400.9		9	4.24 ± 9.3	
	> 4 teeth lost	8	6551.98 ± 10953.5		9	743.40 ± 247.80		10	0.73 ± 1.3	
Number of carious teeth	No caries	32	6463.22 ± 16079.7	0.583	32	164.80 ± 468.7	0.558	33	1.52 ± 5.0	0.376
	Caries in 1 tooth	2	587.65 ± 499.7		2	21.56 ± 25.5		2	0.59 ± 0.009	
	Caries in 2 teeth	2	155236.0 ± 219193.2		2	45.9 ± 60.6		2	32.93 ± 46.3	
	Caries > 2 teeth	0	0		1	252.00		1	0.07	

*Statistically significant ($p < 0.05$); *CAL* clinical attachment loss

Table 5 Association between periodontal parameters with COVID-19 complications

Parameters		Assisted ventilation				Hospital admission			
		Not required	Required	*P* value	OR	Not required	Required	*P* value	OR
Bleeding on probing	Absent	29 (35.4)	7 (8.5)	0.004*	Ref	18 (22)	18 (22)	0.014*	Ref
	Present	23 (28)	23 (28)		4.14(1.51–11.34)*	11 (13.4)	35 (42.7)		3.18(1.24–8.15)*
Mean probing depth	0–2mm	44 (53.7)	11 (13.4)	0.001*	Ref	29 (35.4)	26 (31.7)	0.001*	Ref
	> 2–5mm	5 (6.1)	9 (11)		7.20 (2.00–25.82)*	0 (0.0)	14 (17.1)		-
	> 5mm	3 (3.7)	10 (12.2)		13.33(3.12–56.81)*	0 (0.0)	13 (15.9)		-
Recession	Absent	47 (57.3)	16 (19.5)	0.001*	Ref	29 (35.4)	34 (41.5)	0.001*	Ref
	Present	5 (6.1)	14 (17.1)		8.22(2.55–26.45)*	0 (0.0)	19 (23.2)		-
Periodontal status	Healthy, Gingivitis and Stage I periodontitis	41 (50)	10 (12.19)	0.001*	Ref	28 (34.14)	23 (28.04)	0.001*	Ref
	Stage II–IV periodontitis	11 (13.41)	20 (24.39)		7.45(2.71–20.45)*	1 (1.21)	30 (36.58)		36.52(4.62–288.64)*
Mean clinical attachment loss	0–2mm	45 (54.9)	13 (15.9)	0.001*	Ref	29 (35.4)	29 (35.4)	0.001*	Ref
	3–4mm	7 (8.5)	11 (13.4)		5.43 (1.75–16.85)*	0 (0.0)	18 (22)		-
	> 5mm	0 (0.0)	6 (7.3)		-	0 (0.0)	6 (7.3)		-
No. of teeth missing due to periodontal reasons	No missing teeth	24 (29.3)	12 (14.6)	0.658	Ref	17 (20.7)	19 (23.2)	0.022*	Ref
	1–4 teeth lost	20 (24.4)	11 (13.4)		1.10 (0.40–3.02)	11(13.4)	20 (24.4)		1.62(0.60–4.35)
	> 4 teeth lost	8 (9.8)	7 (8.5)		1.75(0.51–5.97)	1 (1.2)	14 (17.1)		12.52(1.48–105.58)*
Parameters		**Survival**				**COVID-19 pneumonia**			
		Survived	**Deceased**	***P* value**	**OR**	**Absent**	**Present**	***P* value**	**OR**
Bleeding on probing	Absent	34 (41.5)	2 (2.4)	0.456	Ref	31 (37.8)	5 (6.1)	0.019*	Ref
	Present	40 (48.8)	6 (7.3)		2.55(0.48–13.46)	29 (35.4)	17 (20.7)		3.63(1.18–11.12)*
Mean probing depth	0–2mm	52(63.4)	3 (3.7)	0.030*	Ref	46 (56.1)	9 (11)	0.001*	Ref
	> 2–5mm	13 (15.9)	1 (1.2)		1.33 (0.12–13.88)	10 (12.2)	4 (4.9)		2.04(0.52–7.98)
	> 5mm	9 (11)	4 (4.9)		7.70 (1.47–40.34)*	4 (4.9)	9 (11)		11.50(2.90–45.59)*
Recession	Absent	61 (74.4)	2 (2.4)	0.002*	Ref	52 (63.4)	11 (13.4)	0.001*	Ref
	Present	13 (15.9)	6 (7.3)		14.07(2.54–77.72)*	8 (9.8)	11 (13.4)		6.50 (2.12–19.90)*
Periodontal status	Healthy, Gingivitis and Stage I periodontitis	50 (60.97)	1 (1.21)	0.004*	Ref	43 (52.43)	8 (9.75)	0.005*	Ref
	Stage II–IV periodontitis	24 (29.26)	7 (8.53)		14.58(1.69–125.33)*	17 (20.73)	14 (17.07)		4.42(1.57–12.45)*
Mean clinical attachment loss	0–2mm	56 (68.3)	2 (2.4)	0.005*	Ref	48 (58.5)	10 (12.2)	0.001*	Ref
	3–4mm	14(17.1)	4 (4.9)		7.71(1.27–46.49)*	12 (14.6)	6 (7.3)		2.40(0.72–7.91)
	> 5mm	4(4.9)	2 (2.4)		13.50 (1.48–122.75)*	0 (0.0)	6 (7.3)		-
No. of teeth missing due to periodontal reasons	No missing teeth	34(41.5)	2 (2.4)	0.387	Ref	26 (31.7)	10 (12.2)	0.732	Ref
	1–4 teeth lost	26 (31.7)	5 (6.1)		3.26(0.58–18.21)	24 (29.3)	7 (8.5)		0.75(0.24–2.31)
	> 4 teeth lost	14 (7.1)	1 (1.2)		1.21(0.10–14.49)	10 (12.2)	5 (6.1)		1.30(0.35–4.75)

*Statistically significant ($p < 0.05$); *OR* odds ratio

Table 6 COVID-19 complications and blood parameters

Parameters		HbA1c			CRP			Vitamin D3			D-dimer		
		N	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value
Hospital admission	Not required	7	5.4 ± 0.56	0.047 *	7	3.034 ± 1.93	0.001*	8	24.8 ± 32.09	0.269	8	160.50 ± 65.40	0.001*
	Required	25	7.304 ± 3.2		26	87.03 ± 97.6		23	30.99 ± 26.4		30	3316.19 ± 5369.8	
Assisted ventilation	Not required	18	5.9 ± 1.9	0.005 *	16	31.756 ±57.00	0.002*	17	24.04 ± 27.40	0.077	17	3105.70 ± 6229.22	0.001*
	Required	14	8.1 ± 3.6		17	104.47 ± 107.5		14	35.92 ± 27.4		21	2284.41 ± 3687.5	
Survival	Survived	31	6.923 ± 3.02	0.54	32	64.37 ± 90.29	0.141	30	28.18 ± 27.21	0.219	36	2743.16 ± 5052.42	0.601
	Deceased	1	6.20		1	224.23		1	66.20		2	1007.92 ± 5.54	
Parameters		**Ferritin**			**Neutrophil/lymphocyte ratio**			**Haemoglobin**			**Platelet count**		
		N	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value
Hospital admission	Not required	7	175.77 ± 152.56	0.004*	3	1.24 ± 0.65	0.019*	9	14.34 ± 2.53	0.002*	9	249.22 ± 86.99	0.787
	Required	28	857.15 ± 826.7		19	12.25 ± 15.4		39	10.56 ± 2.6		36	2358.92 ± 10377.0	
Assisted ventilation	Not required	16	526.05 ± 750.03	0.040 *	8	5.18 ± 6.68	0.088	27	11.337 ± 3.15	0.925	24	246.67 ± 102.04	0.172
	Required	19	884.94 ± 804.0		14	13.93± 17.3		21	11.18 ± 2.9		21	570.44 ± 1682.0	
Survival	Survived	33	718.39 ± 809.91	0.522	20	8.72 ± 13.91	0.040*	46	11.354 ± 3.07	0.256	43	237.26 ± 97.50	0.036*
	Deceased	2	761.95 ± 445.54		2	30.99 ± 5.40		2	9.390 ±.1556		2	97.50 ± 12.02	
Parameters		**Pro-BNP**			**Troponin**			**Procalcitonin**					
		N	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value	*N*	Mean ± SD	*p* value			
Hospital admission	Not required	7	103.28 ± 162.9	0.001 *	7	4.01± 2.2	0.018*	8	0.42± 0.2	0.001*			
	Required	30	18424.91 ± 57725.7		9	278.65 ± 677.0		30	3.86 ± 12.8				
Assisted Ventilation	Not required	16	3621.25 ± 8940.7	0.220	16	158.49 ± 514.1	-	18	0.28 ± 0.53	0.019*			
	Required	21	23596.69 ± 68453.7		0	-		20	5.55 ± 3.4				
Survival	Survived	35	14977.47 ± 53810.56	0.107	16	158.49 ± 51.10	-	36	3.18 ± 11.75	0.170			
	Deceased	2	14629.50 ± 9540.99		0	-		2	0.89 ± 0.55				

*Statistically significant ($p < 0.05$); *ICU* intensive care unit; *HbA1c* glycated haemoglobin; *CRP* C-reactive protein; *HFNC* high-flow nasal cannula; *NIV* non-invasive ventilation

Table 7 aMMP-8 PoC/chairside test results

	Test result	Periodontally diseased n(%)	Periodontally healthy *n* (%)
aMMP-8 mouthrinse test	Positive	29 (38.1)	16 (21.1)
	Negative	20 (26.3)	11 (14.2)
aMMP-8 site-specific test	Positive	24 (33.3)	10 (13.9)
	Negative	21 (29.2)	17 (23.6)

patients suffering from COVID-19 with periodontal disease were more likely to be admitted to a hospital as compared to those who were not.

It is established that a number of comorbidities such as diabetes mellitus, obesity and those affecting the cardiovascular and respiratory systems do play a significant role in determining the prognosis of COVID-19 [26]. At the same time, it is also well established in literature that periodontal disease has definitive links to these chronic disease processes and is a bonafide part of their overall pathophysiological presentation [27, 28].

Periodontal infections incite events which involve both innate and adaptive host immunity. That periodontitis, despite being a largely chronic disease is a systemic inflammation, is confirmed by the presence of acute-phase reactants as part of the innate immune response. These acute-phase reactants, such as CRP, are pro-inflammatory in nature and develop complement activation along with stimulating tissue healing and neutralising invading pathogens. [29]

CRP levels have been touted as an early biomarker for triaging the severity of COVID-19 infections [30]. The present study found that poorer periodontal outcome measures correlated with increased CRP levels in patients suffering from COVID-19. This increase in CRP levels in relation to periodontal compromise is individually substantiated in literature predating the pandemic [29].

Similarly, elevated D-dimer, ferritin, neutrophil lymphocyte ratio and NT-proBNP have been reported to be prognostic markers associated with deteriorating prognosis in patients afflicted with COVID-19, wherein D-dimer is a cross-linked fibrin considered to be a sensitive marker for venous thromboembolism, ferritin is an indicator of systemic inflammation and NT-proBNP is a marker of reduced left ventricular systolic function [31–35].

Brain natriuretic peptide (BNP) is primarily released from the myocardium of the ventricles in response to stress exerted upon the myocardial walls. Produced as a pro-hormone, BNP, a thirty-two amino acid peptide, is cleaved into two peptides, one of which is the active form and the other, N-terminal-pro-BNP (NT-pro-BNP), which remains inactive biologically. A longer half-life renders NT-pro-BNP a more viable biomarker of inflammation [36].

Increased levels of serum ferritin, an acute phase reactant, have been detected in inflammation and have been demonstrated to correlate positively with CRP levels as well. The concentration of serum ferritin occurs as a result of tissue leakage of this intracellular protein shell. Serum ferritin differs slightly from its tissue form in that it contains minimal to no levels of iron. Inflammation may render clearance of serum ferritin ineffective or suboptimal which may account for its elevated levels. In the midst of an acute phase response, TNF-alpha and IL-1 beta upregulate the synthesis of ferritin H- and L-subunits which is reflected as an increase in serum ferritin levels [37].

Another cardiac biomarker, troponin, has been evidenced to be increased significantly in severe forms of COVID-19 [38]. Myocardial infarct size is significantly related to eventual patient outcomes and troponins (cTnI and cTnT) form the gold standard biomarkers for this evaluation. Of the two types, cTnI is considered to possess greater reliability for the purposes of determining survival and risk stratification [39].

Neutrophil lymphocyte ratio (NLR) has been evidenced as a marker for systemic inflammation. Epidemiological studies have revealed that NLR correlated with classical systemic inflammation risk factors such as obesity, smoking, diabetes mellitus, hypercholesterolemia, hypertension and metabolic syndrome. In such a manner then, it is safe to say that NLR may be indicative of the severity of inflammatory disease processes [40].

Serum levels of ferritin, NT-proBNP, neutrophil lymphocyte ratio and troponin have been found to be significantly associated with periodontal disease [36, 38, 39, 41, 42]. This association points towards a commonality between periodontal disease and COVID-19-related adverse outcomes. Our study found that there was a correlation between periodontal compromise and increased levels of these blood parameters in COVID-19 patients.

HbA1c is regarded as the gold standard in blood glucose estimation along with providing an average value over the past 3 months with high levels being associated with complications in diabetic patients. Inflammatory markers such as CRP and serum ferritin have been found to be positively correlated with levels of HbA1c [43]. It has generally been acknowledged that increased levels of HbA1c are associated with hypercoagulability, low oxygen saturation and inflammation in patients suffering from COVID-19. The overall mortality rate of diabetic COVID-19 patients is also reportedly high [43]. In our

study, we found high levels of HbA1c correlating with compromised periodontal outcome measures.

Procalcitonin levels remain within reference ranges in patients suffering from non-complicated forms of COVID-19 infection. However, these values increase in patients with super-added bacterial infection [44]. In our study, we found that periodontal disease correlated significantly with elevated procalcitonin levels. Indeed, there is evidence in literature to support the contribution of periodontal disease in the pathophysiology of respiratory illnesses [45].

It has recently also been hypothesised that the breakdown of the oral immune barrier, as may occur in periodontitis, may lead to the dissemination of the SARS-CoV-2 into systemic circulation via its oral reservoirs in saliva and GCF [5, 46]. Within the constraints of the sample size utilised in the present study, it would be plausible to argue that, while the results seem indicative of this, a direct causal relationship may not be established between the presence of periodontitis and poorer COVID-19-related outcomes.

It would hence be prudent to state that an indirect link may exist in the form of periodontal disease resulting in chronic systemic compromise which may further cascade into a so-called comorbidity affecting the eventual outcome of COVID-19 infection. Periodontal disease would then have both a direct and indirect impact upon COVID-19-related outcomes by virtue of its presence.

The aMMP-8 mouthrinse and site-specific kits were able to correctly identify periodontal disease in 38.1% and 33.3% of patients with periodontal disease, respectively. However, the kits also tested positive for 21.1% (mouthrinse kit) and 13.9% (site specific kit) in periodontally healthy subjects. A higher number of false positives were being recorded by the kits on account of the elevated aMMP-8 levels in the oral cavity due to the ensuing cytokine storm associated with COVID-19 wherein various inflammatory cytokines could have led to an upregulation in the expression and degranulation of aMMP-8.

A previous study utilised three self-reported oral health indicators to determine a relationship between the presence of periodontal disease and COVID-19 prognosis and found significant association of the indicators with mortality [19]. The authors, in the current study, found a similar relation in the included cohort.

Seeing as periodontal disease predominantly stems from bacterial interactions with the host, the maintenance of oral hygiene assumes greater importance in the face of this novel entity. However, it would serve the scientific community well to base recommendations on substantiated claims and avoid the temptation of joining certain dots where none may exist. In the same vein, maintenance of oral hygiene does continue to be of importance in the COVID-19 era, not only due to a direct correlation between periodontal compromise and the COVID-19 disease process but also due to the indirect systemic effects periodontal disease may have, to eventually determine COVID-19-related prognosis and in the identification of potentially at-risk patient populations.

Most research currently seems to have been concentrated on verifying whether the presence of periodontal disease affects COVID-19-related outcomes. It would, however, be interesting to see whether there exists the possibility of cross-talk between the SARS-CoV-2 and the oral microbiome either directly or in a phage-mediated manner [47, 48].

Limitations

The study had some limitations and results need to be extrapolated with caution. A causal relationship cannot be established due to the cross-sectional design of the study. Another limitation can be the small sample size. However, this is the first study in literature to conduct intra-oral examination among potentially infectious patients. Further studies are required to validate the result of the present work.

Conclusion

There is a direct association between periodontal disease and COVID-19-related outcomes. However, as periodontal disease is both reflective and deterministic of systemic health, it might also play an indirect role in worsening the status of comorbidities more directly associated with a poorer prognosis of COVID-19-related adverse outcomes.

Authors' contribution S.G. contributed to the conception, design, data acquisition, analysis and interpretation; drafted the manuscript; and critically revised the manuscript. R.M. contributed to the conception and design, acquisition, analysis and interpretation and critically revised the manuscript. M.S. contributed to the acquisition and critically revised the manuscript. S.K. contributed to the acquisition and critically revised the manuscript. V.S. contributed to the analysis and interpretation and drafted the manuscript. P.K. contributed to the analysis and interpretation and critically revised the manuscript. R.K.S. contributed to the acquisition and critically revised the manuscript. A.K. contributed to the analysis and interpretation and drafted the manuscript. Kr.G. contributed to the analysis and interpretation and critically revised the manuscript. Ka.G contributed to the analysis and interpretation and critically revised the manuscript. M.P.S. contributed to the analysis and interpretation and critically revised the manuscript. K.K. contributed to the analysis and interpretation and critically revised the manuscript. V.M. contributed to the analysis and interpretation and critically revised the manuscript. A.B. contributed to the analysis and interpretation and critically revised the manuscript. T.S. contributed to the analysis and interpretation and critically revised the manuscript. I.R. contributed to the analysis and interpretation and critically revised the manuscript. All authors gave final approval and agree both to be personally accountable for the authors' own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the authors were not personally involved are appropriately investigated, resolved and the resolution documented in the literature.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication The authors confirm that they have obtained consent from the study participants to publish the data.

Conflict of Interest T. Sorsa is the inventor of US-patents 5652223, 5736341, 5866432, 6143476, 2017/0023571A1 (granted 6.6.2019), WO2018/060553A1 (granted 31.5.2018), 10488415B2, and a Japanese patent 2016-554676.

The authors declare that they have no conflict of interest.

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