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Alveolar bone loss and tooth loss are associated with COVID-19 severity but are not independent risk factors. An explorative study

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ABSTRACT

Purpose: This study explores the association between alveolar bone loss, tooth loss and severity of COVID-19.
Materials and methods: In this retrospective cohort study, we included patients with confirmed COVID-19 who have had a dental panoramic radiograph within a maximum period of 5 years, providing information about alveolar bone loss and tooth loss. The severity of COVID-19 was determined based on the WHO clinical progression scale: (1) Mild/Ambulatory; (2) Moderate/Hospitalized; (3) Severe/Intensive care unit (ICU) or death.
Results: 1730 patients were identified with COVID-19 from until October 31, 2020 in the Isala Hospital. Of these patients, 389 ever visited the OMFS department. 133 patients have had an orthopantomograph within a maximum period of 5 years and were included for analysis. The results showed a significant association between alveolar bone loss and COVID-19 severity (p = 0.028). Patients with alveolar bone loss had 5.6 times higher odds to be admitted to ICU or died, compared to ambulatory patients (OR: 5.60; 95%CI: 1.21; 25.99; P = 0.028). More tooth loss was significantly associated with COVID-19 severity (p = 0.047). Per tooth lost, patients had 4.2% higher odds for severe than mild COVID-19 (OR: 1.04; 95%CI: 1.00; 1.09; P = 0.047) and 6.0% higher odds for severe than moderate COVID-19 (OR: 1.06; 95%CI: 1.01; 1.11; P = 0.017). When adjusting for confounders in multivariate analyses, the significant associations of COVID-19 with alveolar bone loss and tooth loss were no longer present.
Conclusion: In this retrospective explorative pilot study, alveolar bone loss and tooth loss are associated with the severity of COVID-19, however they are not independent risk factors. The current study could contribute to the design of further studies on the relationship between oral health and COVID-19.

1. Introduction

At the end of 2019, the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first detected in China. The later designated coronavirus disease 2019 (COVID-19) rapidly developed in a worldwide pandemic [1]. Indication of risk factors for severe disease, hospital admission and death became crucial. Age is one of the highest risk factors for morbidity and mortality due to infection with SARS-CoV-2 [2]. Additionally, cardiovascular disease, male sex, chronic kidney disease, and obesity are associated with hospital admission and

unfavorable outcomes [3–5].

Several epidemiological and pathological associations between poor oral health and systemic diseases have been reported. Periodontal disease and its ultimate sequela tooth loss, are associated with an increased risk of non-communicable diseases (NCDs), including cardiovascular diseases, cancer, diabetes, Alzheimer's disease and respiratory tract infection [6,7]. In addition, several studies have demonstrated that bacteria, microbial products and cytokines translocated from oral inflammatory conditions, cause exacerbations of inflammatory reactions in distant organs, for example increased vascular damage in

atherosclerosis and other cardiovascular processes [8]. However, causality has never been demonstrated and associations are probably the result of shared risk factors and comorbidities.

There are sufficient data demonstrating that coexisting conditions in patients with COVID-19 influence clinical outcomes. Potential risk factors could help clinicians to identify patients with poor prognosis at an early stage. It has been hypothesized that poor oral health is associated with the severity of the clinical progression of COVID-19 [9]. Marouf et al. recently found an association between periodontal disease and the severity of COVID-19 in hospitalized patients [10]. Tooth loss is the ultimate state of dental pathology and poor oral health. The current retrospective cohort study explored the association between periodontal disease and tooth loss, and the course and outcome of COVID-19.

2. Material and methods

2.1. Study oversight

This retrospective cohort study was approved by the Medical Ethics Committee, Isala Academy, Zwolle, the Netherlands (200710). Requirement for informed consent was waived. This study was done in accordance with the Declaration of Helsinki guidelines for human research, 1964, and amended in 2013 (64th World Medical Association General Assembly, Fortaleza, Brazil). Data were collected, interpreted and analyzed by the authors.

We included hospitalized patients and outpatients from the Isala Hospital (Zwolle, the Netherlands) with confirmed COVID-19 who visited the Department of Oral and Maxillofacial Surgery (OMFS) and who have had a dental panoramic radiograph (Orthopantomograph – OPG), obtained up to a maximum of 5 years until the end of the current study. The patient inclusion cutoff for the study was October 31, 2020. Confirmed COVID-19 was defined as a positive SARS-CoV-2 real-time reverse transcription polymerase chain reaction (rRT-PCR) on swab material, sputum or bronchoalveolar lavage samples.

The electronic health records provided information about age, sex, body mass index (BMI), diabetes mellitus, cardiovascular diseases, chronic kidney disease and smoking. When a medical condition such as diabetes mellitus or cardiovascular disease was not mentioned in a patient file, but the corresponding medication was documented (e.g. metformin and/or insulin, statins and antihypertensive drugs), the patient was scored positively for that disorder. For all patients, the BMI was calculated based on the height and weight noted in the health records (maximum retrieval period 365 days).

2.2. COVID-19

The course and outcome of COVID-19 was determined based on the WHO Clinical progression Scale: (1) Mild disease: Ambulatory; (2) Moderate disease: Hospitalized; (3) Severe disease: intensive care unit (ICU) admission or death [11].

2.3. Oral health

Each dental panoramic radiograph was scored by three investigators blinded for the COVID-19 severity. Periodontal disease was defined when alveolar bone loss (ABL) $\geq 1/3$ of the root length was detected at two or more non-adjacent teeth, according the recent Classification of Periodontal and Peri-implant Diseases [12]. Periodontal disease (PD) was scored as present of absent. Alveolar bone loss related to periodontal-endodontic lesions, cracked and fractured roots, caries, restorative factors and impacted third molars was not scored. The number of teeth present was measured by counting all teeth visible on the OPG, including third molars and radices relictae; dental implants, pontics of fixed partial dentures and prosthetic dentures were not counted as teeth. The number of missing teeth was calculated by subtracting the number of present teeth from the expected total of 32 teeth.

Patients were noted as dentate or edentulous.

2.4. Statistics

Descriptive statistics (mean $\pm$ standard deviations [SD] or numbers [%] of subjects) were used to present patient characteristics and dental findings. Group differences were tested by one-way analysis of variance (ANOVA) for quantitative variables or Chi-square analysis for categorical variables. P-value of 0.5 was set at the significance level. Univariate multinomial logistic regression analyses were used to assess the unadjusted associations between periodontal disease, the number of teeth lost and the outcome of COVID-19. Next, we screened important confounders between COVID-19 and the two independent variables, respectively, by performing separate multinomial logistic regression analyses. In each multinomial logistic regression analysis, only confounder was included with the independent variable. Next, the confounders with $P < 0.05$ were included in the subsequent fully adjusted multivariate models. Statistical analyses were performed using IBM SPSS Statistics 26 software (SPSS Inc., Chicago, IL, USA).

3. Results

1730 patients were identified with COVID-19 from March 1st until October 31, 2020 in the Isala Hospital. Of these patients, 389 ever visited the Department of Oral and Maxillofacial Surgery (OMFS). We retrieved 157 patients with confirmed COVID-19 who visited the OMFS department within a maximum period of 5 years. 133 patients have had a dental panoramic radiograph (Orthopantomograph – OPG) (Fig. 1). In 115 (86.5%) patients the OPG was assessed before COVID-19 and in 18 (13.5%) patients COVID-19 was before their visit to the OMFS department. The mean intermediate period between COVID-19 and the OPG was 695 days (SD 543).

Fig. 1 displays the age, sex and BMI of the total COVID-19 population and the included patients. There was no significant difference between the sex (p = 0.688). Compared to the total COVID-19 population, the 133 included patients were significant younger (p = 0.008) and the BMI was significant lower (p = 0.007). All patient characteristics of these
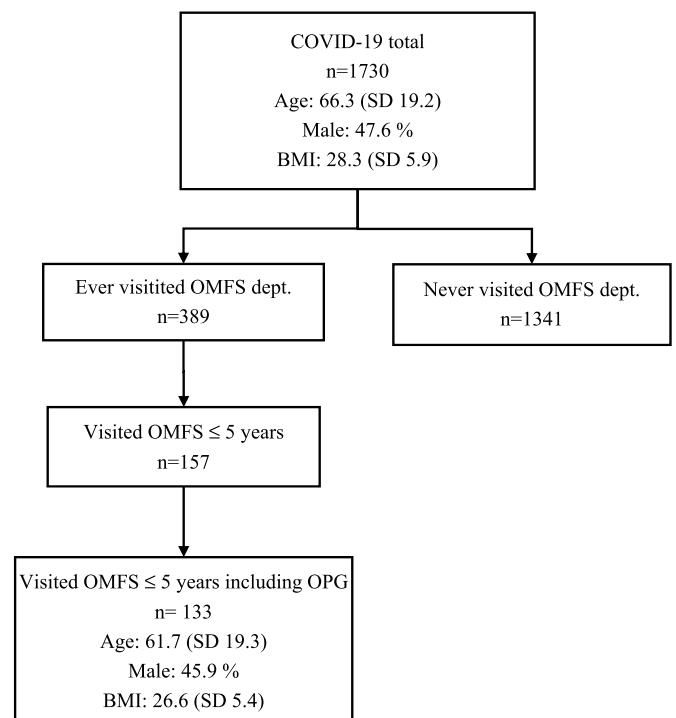

Fig. 1. Inclusion flowchart.

included 133 patients are presented in Table 1. The population of this study consisted of 46% (n = 61) male patients. The mean age was 61.7 years (SD 19.3). The BMI of 25 patients was unknown, for 108 patients the mean BMI was 26.6 kg/m^2 (SD 5.4). 15.8 percent (n = 21) of the patients were having diabetes mellitus (2 unknown), 48.9% (n = 65) of the patients suffered from cardiovascular disease, and 9.8% (n = 13) of the patients suffered from chronic kidney disease. The smoking status of 7 patients was unknown, while among 126 patients, 12 (9%) were current smokers.

In Table 2 we present dental pathology findings of the COVID 19 patients based on the OPG assessments. Within the group of dentate patients (n = 92), 14.1% was scored positive for periodontal disease based on the alveolar bone loss. The results showed a significant association between alveolar bone loss and the progression categories of COVID-19 (P = 0.028). Patients with alveolar bone loss had 5.6 times higher odds to be admitted to the ICU or die, compared to the ambulatory COVID-19 patients (OR: 5.60; 95%CI: 1.21; 25.99; P = 0.028).

The number of teeth was significantly associated with the severity of COVID-19 based on one-way ANOVA (p = 0.043). The patients with more missing teeth, were more likely to have a severe clinical outcome (ICU admission or death) than a mild or moderate outcome. With the number of teeth decreasing by one unit, the patients had 4.2% higher odds to have severe COVID-19 than mild clinical outcome (OR: 1.04; 95%CI: 1.00; 1.09; P = 0.047). Also, with the number of teeth decreasing by one unit, the patients had 6.0% higher odds for a severe clinical outcome than a moderate clinical outcome (OR: 1.06; 95%CI: 1.01; 1.11; P = 0.017). We observed 9 out of 16 (42.9%) edentulous patients in the group of patients with severe clinical outcome, compared to 34.1% and 13.3% in the mild and moderate categories, but there was no significant association between edentulousness and COVID-19.

To further explore whether the dental pathologies could be independent risk factors for the severity of COVID-19, we first screened for the confounders. Separate multinomial logistic regression analyses performed identified that age, male sex, diabetes mellitus, cardiovascular diseases, chronic kidney disease and smoking were the significant confounders between periodontal disease and the progression of COVID-19. In the multivariate analysis adjusting for these confounders, alveolar bone loss was not significantly associated with the severity of COVID-19 when the mild clinical outcome was compared with severe outcome (OR: 3.332; 95%CI: 0.394; 28.148; p = 0.269) and when the moderate clinical outcome was compared with the severe outcome (OR: 3.214; 95%CI: 0.354; 29.197; p = 0.300).

Another set of separate multinomial logistic regression analysis identified that age, male sex and cardiovascular diseases were the significant confounders between the number of teeth and the clinical outcome of COVID-19. When adjusting for age, male sex and cardiovascular disease in the multivariate model, tooth loss was not significantly associated with the clinical outcome of COVID-19 (P = 0.453 when mild clinical outcome was compared with severe outcome, and P = 0.263 when moderate clinical outcome was compared with severe outcome).

4. Discussion

This retrospective, cohort study was initiated to explore the association between parameters of poor oral health and the severity of COVID-19. We observed a statistically significant association between the COVID-19 severity with alveolar bone loss and the most obvious and definitive dental pathological event: tooth loss. However, when adjusted for the well-known risk factors of COVID-19, these dental parameters were not identified as independent risk factors for the course and outcome of COVID-19 in our study population.

We included rRT-PCR-confirmed COVID-19 patients who visited the Department of Oral and Maxillofacial Surgery (OMFS) and who have had a dental panoramic radiograph obtained up to a maximum of 5 years. This population was younger and showed a lower BMI than the total population of confirmed COVID-19 patients. This possible selection bias is corrected with the multivariate logistic regression analysis, where we included these confounders.

Tooth loss is the ultimate state of dental pathology. Beyond middle age, most tooth loss is the "end point" of periodontal disease. This prolonged state of chronic inflammation with increased levels of C-Reactive Protein (CRP) is a proven risk factor for non-communicable diseases (NCDs) which are also associated with unfavorable outcomes of COVID-19 [3,7]. However, most tooth loss before middle age is caused by dental caries. Dental caries is a disease with a multifactorial etiology; consumption of dietary carbohydrates is one of the most important etiological factors. Carbohydrate intake is also associated with increased risk for infection and mortality rates of COVID-19 across the world [13,14]. Besides, tooth loss might affect dietary intake and nutritional status among adults and thereby affecting the general condition and strength to fight COVID-19 [14,15]. Above all, tooth loss might cause harmful health benefits and has been considered to impact quality of life [16].

In the current study we used a dental panoramic radiograph (Orthopantomograph – OPG) to measure the alveolar bone loss due to periodontal disease and to count the number of present teeth. Regarding the alveolar bone loss, for reasons of a possible degree of uncertainty of minor alveolar bone loss to be observed on OPG, we identified subjects having severe periodontal disease with at least 2 non-adjacent teeth with bone loss ≥1/3 of the root length according to the current classification [12]. Since only radiographical and no clinical information was obtained to determine the periodontal disease, no assumptions could be made on the activity of the dental pathology. Periodontal disease can be in an active, in a chronic or in a remission state.

The number of teeth present, and correspondingly the tooth loss, is an easily accessible marker and can be determined by most; the general practitioner, the dentist or even the patient itself. We assumed that loss of teeth was a result of dental pathology with dental caries and periodontal disease as leading causes. This should be carefully interpreted since in some cases a tooth may have been lost due to non-pathological causes such as orthodontic treatment, dental trauma and agenesis. However, the incidence of those events is low.

The maximum time allowed between the OPG and the COVID-19

Table 1
Background characteristics of patients with COVID-19.

	Total COVID19 n = 133	Mild; Ambulatory n = 82	Moderate; Hospitalized n = 30	Severe; ICU/Death n = 21	p-value
Age (years)	61.7 ± 19.3	57.3 ± 21.0	63.5 ± 13.9	75.9 ± 10.6	0.000*
Male sex	61 (45.9)	29 (35.4)	16 (53.3)	16 (76.2)	0.001**
Body Mass Index	26.6 ± 5.4	26.3 ± 5.3	27.1 ± 3.4	27.9 ± 4.7	0.420*
Diabetes mellitus	21 (15.8)	9 (11.1)	5 (16.7)	7 (33.3)	0.013**
Cardiovascular disease	65 (48.9)	34 (41.5)	14 (46.7)	17 (81.0)	0.003**
Chronic kidney disease	13 (9.8)	6 (7.3)	2 (6.7)	5 (23.8)	0.055**
Smoking	12 (9.0)	6 (7.3)	4 (13.3)	2 (9.5)	0.013**

Values represent number of subjects (%) or mean ± standard deviation. Group differences were tested by * one-way analysis of variance (ANOVA) or ** Chi-square analysis (linear by linear). Statistically significant, P-value <0.05.

Table 2

Dental pathologies of patients with COVID-19.

	Total COVID19n = 133	Mild; Ambulatory n = 82	Moderate; Hospitalized n = 30	Severe; ICU/Death n = 21	p-value
Periodontal disease[a]	13 (14.1)	5 (9.3)	4 (15.4)	4 (57.1)	0.028**
Number of teeth	16.0 ± 12.2	16.4 ± 12.7	18.8 ± 10.4	10.3 ± 11.0	0.043*
Edentulous	41 (30.8)	28 (34.1)	4 (13.3)	9 (42.9)	0.961**

Values represent number of subjects (%) or mean ± standard deviation.

Group differences were tested by * one-way analysis of variance (ANOVA) or ** Chi-square analysis (linear-by-linear). Statistically significant, P-value <0.05.

[a] determined as alveolar bone loss ≥1/3 of the root length for dentate patients (N = 92).

diagnosis was five years. However, the average time between these two radiographic assessments was less than 2 years (695 days). We are aware that there is the possibility that the number of teeth, could have decreased in the course of the time between COVID-19 and the radiographic status. We assumed that the progression of the studied dental pathologies, is a rather slow processes and changes within this time-frame will not be large. For this study we deemed the maximum of 5 years acceptable. Nevertheless, more periodontal disease and less teeth present than currently scored at the actual time of COVID-19, most likely would have strengthened the current findings.

Another limitation of our study is the sample size. It would have been superior to have more dental records or OPGs of the confirmed COVID-19 patients. However, the current study was set up as a retrospective explorative study to assess whether the most clear dental events, tooth loss and alveolar bone loss, were associated with COVID-19 severity. Obviously due to the retrospective design, it was not possible to include more patients with available dental records or OPGs during this rapidly developing pandemic.

5. Conclusion

This study provides suggestive evidence that the severity of COVID-19 is associated with alveolar bone loss and the ultimate "hard" endpoint of dental pathology, i.e. tooth loss. However, when adjusted for the well-known risk factors of COVID-19, these dental parameters were not identified as independent risk factors for the course and outcome of COVID-19 in our study population. The current clinical investigation should be considered as an explorative pilot study that could contribute to the design of further studies on the relationship between poor oral health and the severity of COVID-19. Nevertheless, the current findings add to the wealth of research showing the relationship between oral health and general health, which is probably the result of shared risk factors and underlying conditions. Tooth loss is as an easily and quick accessible proxy for a severe COVID-19 course of disease, hospital admission and death, which is crucial during this worldwide pandemic. Dental professionals must be aware that patients with extensive tooth loss may have increased risk for more severe clinical progression and outcome of COVID-19.

Author contribution

H.C.M. Donders: Conception and design of study/review/case series; Acquisition of data: laboratory or clinical/literature search; Analysis and interpretation of data collected; Drafting of article and/or critical revision; Final approval and guarantor of manuscript. **J.M. van der Sleen:** Acquisition of data: laboratory or clinical/literature search; Drafting of article and/or critical revision. **Y.J. Kleinbergen:** Acquisition of data: laboratory or clinical/literature search; Drafting of article and/or critical revision. **N. Su:** Analysis and interpretation of data collected; Drafting of article and/or critical revision. **J. de Lange:** Conception and design of study/review/case series; Analysis and interpretation of data collected; Drafting of article and/or critical revision; Final approval and guarantor of manuscript. **B.G. Loos:** Conception and design of study/review/case series; Analysis and interpretation of data collected; Drafting of article and/or critical revision; Final approval and guarantor of manuscript.

Declaration of competing interest

None.

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