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Is there an association between stage of periodontitis and severity of chronic medical burden? A retrospective cohort study

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ABSTRACT

Aim The aim of this study was to evaluate the relationship between the severity of periodontitis, measured through stage of the disease, and the severity of chronic medical burden.

Materials and methods The present retrospective longitudinal cohort study was conducted in a private practice. Medical and periodontal records were assessed. Subject were classified as affected by periodontitis or without periodontitis. Comorbidities were evaluated in number through the chronic comorbidity count (CC) and in severity applying the Total Score (TS) of the Cumulative Illness Rating Scales. A multivariate linear regression model was built to evaluate predictors affecting the stage of periodontitis, adjusting for age, sex and smoke. A two-steps clustering algorithm was done to evaluate clusters of presentation of variables.

Results The multivariate analysis showed that there was 0.046 increase in stage for each year of age and 0.347 increase in stage for each point of total score, (stage=-1.225 + 0.046*(age) + 0.347*(total score)). The adapted R2 value was 0.546. Two-step cluster analysis revealed the presence of 2 main clusters.

Conclusions A positive association between stage of periodontitis and severity of comorbidities was detected: as the severity of periodontitis increased, the severity of systemic medical burden worsened. Age influenced this association.

KEYWORDS Periodontitis; Periodontal medicine; Systemic health.

INTRODUCTION

Periodontitis represents a complex disease that involves iterative interactions between the host's immune system, the disbiotic subgingival microbiota and the modifying environmental factors (1). Although bacteria are required for the onset of periodontal disease, the severity and the rate of progression could be influenced by other risk factors such as age, smoking, genetic factors and systemic conditions (2).

The World Workshop in Periodontics introduced the term 'periodontal medicine' in 1996, to describe the role played by periodontitis in exacerbating or initiating systemic diseases (3). Research activity in periodontal medicine has grown continuously and periodontal medicine constitutes an important part of clinical research (4). Inflammation seems to be the link between periodontitis and systemic conditions (5). Periodontitis in fact represents a source of low-grade chronic inflammation which contributes to the cumulative systemic inflammatory burden (6). Low-grade chronic inflammation has been recognized to be a key player in the pathogenesis of most chronic non-communicable disease (CNCD) (7); periodontitis is defined a CNCD, and it shares social determinants and risk factors with the major of these conditions (8). Solid scientific evidence established the association between periodontitis and systemic disorders such as cardiovascular disease (9), cerebrovascular disease (10), diabetes (11), respiratory disease (12), and adverse pregnancy outcomes (13). Recent research has focused on whether periodontitis contributes to the progression of other inflammatory-based diseases; fifty-seven systemic conditions have been hypothesized to be linked with periodontal diseases: chronic kidney disease, rheumatoid arthritis, erectile disfunction, cognitive impairment, obesity, metabolic syndrome and cancer are potentially associated with periodontitis (4).

Although the detailed mechanisms underlying the association between periodontitis and systemic diseases are still unclear (14), available literature suggests that patients with poor periodontal condition showed significantly more comorbidities than their counterparts

(15). It is plausible from a biological point of view, to investigate not only the number of comorbidities but also their severity, in relation to the severity of periodontitis. The aim of this study was to evaluate the association between the severity of periodontitis, and the severity of chronic medical burden of the patient.

MATERIALS AND METHODS

Study design

This paper followed STROBE guidelines (16) and it was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013. Due to the retrospective nature of this study, no ethical approval was needed.

This was a retrospective longitudinal cohort study and it was conducted in a private practice setting: Poliambulatorio Odontostomatologico Santa Apollonia (Lazzate, Monza and Brianza, Italy), from September 2019 to March 2020. Medical records and periodontal data (charting and radiology) registered by two calibrated operators (MF and PG), were assessed.According to the first diagnosis, the cohort was divided as follows: subjects with periodontitis (clinical attachment loss of periodontal origin) and subjects without periodontitis. According to 2017 World Workshop (17) subjects with CAL of periodontal origin were affected by periodontitis, defined as interdental CAL detectable at ≥2 non adjacent teeth, or buccal or oral CAL ≥3 mm with pocketing >3 mm detectable at ≥2 teeth and the observed CAL cannot be ascribed to non periodontal causes. When no CAL of periodontal origin was detected, the subject was considered not affected by periodontitis, for example in cases of vertical root fracture or tooth malposition (18). Periodontal data were registered by two calibrated operators (MF and PG)

Inclusion and exclusion criteria

The following inclusion criteria were considered.

- Adult subjects aged between 30 and 70 years.
- Diagnosis of periodontitis or absence of periodontitis, according to 2017 World Workshop.
- Complete medical records and periodontal charting.

The exclusion criteria concerned limits of age, incomplete medical or periodontal records, presence of fixed (implant-supported or implant-retained) or mobile full prosthetic rehabilitations of both arches (full edentulism).

Variables

For each included subject, the following variables were recorded in SPSS dataset.

Stage, grade and extension of periodontitis or absence of periodontitis (coded as 0), according to 2017 World Workshop. Periodontal records were used.

Comorbidity assessment through Chronic Comorbidity Count (CC): the total sum of chronic systemic conditions was registered. Chronic Condition Indicator (CCI Version 2020.1, beta version) was used to define chronic conditions. To determine the number of distinct chronic diseases per patient, avoiding double counting of chronic conditions for the same basic condition, we used the method proposed by Hwang et al. (2001) (19). Patients were affected by chronic disease if they had one or more conditions classified as chronic and these were in a separate category of the International Classification of Diseases for Mortality and Morbidity Statistics (ICD-11 MMS). Medical history of the patient was used to retrospectively calculate CC.

Comorbidity assessment through the Total Score (TS) of Cumulative Illness Rating Scales (CIRS); this is an instrument to measure the severity of chronic medical burden (severity and complexity of diseases): higher scores indicate higher severity of systemic conditions (maximum score = 56 points). Medical history again was used to calculate TS (20,21).

Statistical analysis

There were no similar studies investigating the relationship between stage of periodontitis and severity of medical burden. Continuous variables were presented as means ± standard deviations; dichotomic variables were presented as frequencies. Periodontal health group and periodontitis group were compared using statistical inference tests. Independent Sample T-test was used to compare means and Chi-Square test was used to study dichotomic variables. One-way ANOVA was used when comparing more means of >2 groups and One-way ANCOVA was used to adjust results for age, gender, and smoking. Characteristics of comorbidities in terms of TS and CC, were evaluated for the study population and then stratified for age (bands of ten years), gender, smoking habits, and stage of periodontitis (considering absence of periodontitis as stage 0).

A multivariate linear regression model was built to evaluate predictors affecting the stage of periodontitis. Stage of periodontitis was considered a continuous ratio variable, and it was selected as dependent variable. Absence of periodontitis was coded with 0. Firstly, we run a model for comorbidity count and total score, as independent continuous variables (ratio variables), using a backward approach. Then, in order to control for potential confounders, we run the regression adding gender, age and smoking habits, with a backward approach again. Gender and smoking habits were introduced as dichotomic variables.

Clustering is the process of nosography grouping into meaningful associations, so that the objects within a cluster have high similarity in comparison to one another, but are dissimilar to objects in other clusters (22). In order to evaluate the existence of clusters of presentation of variables, we carried out a 2-step clustering algorithm. The algorithm identifies groups of cases that exhibit similar response patterns following a two stages approach:

	Cohort	No Periodontitis	Periodontitis	p-value
N	234	62	172	-
Age (yrs)	53.37 (10.61)	45.2 (9.2)	56.3 (9.4)	0.0001
Sex	108 M	14.5% (M) 12% (F)	31.6% (M) 41.9% (F)	0.11
Smoking habits	76 smokers	5.1% (Y) 21.4% (N)	27.4% (Y) 46.2% (N)	0.01
Comorbidity Count*	0.90 (1.17)	0.36 (0.40)	1.09 (1.24)	0.0005
Total Score*	1.90 (2.22)	0.89 (0.63)	2.26 (2.29)	0.0005

TABLE 1 Characteristics of the cohort and comparison between no periodontitis group and periodontitis group. Data were summarized as frequency or mean and standard deviation as appropriate. Independent Sample T-test was used to compare means and Chi-Square test was used for dichotomic ones. One-way ANCOVA was used for comorbidity count and total score, and results were adjusted for age, sex and smoke (*). Statistical significance was set at 0.05.

(1) pre-clustering and (2) hierarchical clustering, the pre-clusters are merged into the final clusters via the agglomerative hierarchical method. In order to detect the number of final clusters automatically, the algorithm incorporates both the Bayesian information criterion and the change in the distance metric (log-likelihood ratio) (23). The procedure can automatically select the optimal number of clusters given the input variables, handling both continuous and categorical segmentation variables (24). Stage, gender and smoking habits were considered as categorical variables and comorbidity count, total score and age were considered as continuous ones. Quality of clusters were evaluated through Kaufman and Rousseeuw (25); ratings and using silhouette measure averages. IBM SPSS Statistics software was used to conduct all statistical analysis.

RESULTS

Cohort profiles and characteristics

In this study periodontal and medical records of 448 subjects were retrospectively evaluated: 214 were excluded (161: limits of age, <30 yrs or >70 yrs; 53: full implant-prosthetic rehabilitations); 234 subjects with a mean age of 53.37 ± 10.61 years, were included, 108 males (mean age 52.44 ± 10.92 years) and 126 females (mean age 54.16 ± 10.31 years). In this cohort 172 patients were affected by periodontitis and 62 were not affected by periodontitis. Characteristics of the whole sample and the comparison between the two groups are presented in table 1. Significant differences were found for CC (p=0.0005) and TS (p=0.0005), indicating that patients affected from periodontitis had a greater number of more severe comorbidities. When considering periodontitis group, 20.9% of subjects (N=36) had Stage 1, 23.3% (N=40) had Stage 2, 33.2% (N=57) had Stage 3, and 22.6% (N=39) had Stage 4; considering the grade: 13.3% (N=23) had a grade A, 54.3% (N=94) had a grade B, and 32.4% (N=56) a grade C; 52.3% of patients (N=90) showed generalized periodontitis and 47.7% (N=82) showed localized periodontitis, 39.2% patients (N=64) were smokers.

Stratification of results for age, gender, smoking habits and stage of periodontitis

	Comorbidity Count	Total Score
Age		
30-40	0.27 ± 0.57	0.63 ± 0.89
40-50	0.51 ± 0.94	1.05 ± 1.57
50-60	0.92 ± 1.18	2.04 ± 2.31
60-70	1.52 ± 1.27	3.08 ± 2.4
p.value	0.00001	0.00001
Sex		
Males	0.93 ± 1.22	1.86 (2.26)
Females	0.88 ± 1.13	1.93 (2.19)
p.value	0.77	0.817
Smoking habits		
Yes	0.84 (1.18)	2.5 (2.35)
No	0.93 (1.17)	1.61 (2.1)
p.value	0.60	0.0038
Stage		
0	0.16 (0.39)	0.51 (0.62)
1	0.32 (0.57)	0.84 (0.76)
2	0.64 (0.80)	1.29 (1.21)
3	1.39 (1.20)	2.91 (2.21)
4	2.20 (1.24)	4.31 (2.39)
	0.0005	0.0005

TABLE 2 Stratification of comorbidity count and total score for age (bands of 10 years), sex, smoking habits, stage of periodontitis (considering 0 as periodontal health). Data were summarized as mean and standard deviation. Indipendent Sample T-test was used to compare means and one-way ANOVA was used when comparing more means of >2 groups. For the stage, one-way ANCOVA was used to adjust results for age, sex and smoke.

The stratification of CC and TS, for age, gender, smoking habits and stage of periodontitis is presented in table 2. Stratification of results for gender, revealed no significant difference between males and females for both considered outcomes. Age stratification using bands of ten years, revealed statistically significant results for both outcomes with a positive trend: CC (P=0.00001) and TS (P=0.00001). The stratification for smoking

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	p-value
1	(Costant)	-1,148	0,355		-3,228	0,001
	Total Score	0,229	0,076	0,350	3,030	0,003
	Comorbidity Count	0,223	0,138	0,180	1,610	0,109
	Age	0,045	0,007	0,329	6,705	0,000
	Sex	-0,270	0,129	-0,093	-2,100	0,037
	Smoke	0,316	0,157	0,102	2,015	0,045
2	(Costant)	-1,136	0,357		-3,184	0,002
	Total Score	0,339	0,033	0,518	10,355	0,000
	Age	0,045	0,007	0,330	6,705	0,000
	Sex	-0,247	0,128	-0,085	-1,922	0,056
	Smoke	0,197	0,139	0,064	1,419	0,157
3	(Costant)	-1,063	0,354		-3,005	0,003
	Total Score	0,348	0,032	0,531	10,818	0,000
	Age	0,045	0,007	0,326	6,619	0,000
	Sex	-0,237	0,128	-0,081	-1,846	0,066
4	(Costant)	-1,225	0,344		-3,556	0,000
	Total Score	0,347	0,032	0,529	10,722	0,000
	Age	0,046	0,007	0,334	6,759	0,000

TABLE 3 Multivariate linear regression model adjusted for age, sex and smoking habits. Backward approach was used.

Model	R	R Square	Adjusted R square	Std. Error of the Estimate
1	,752°	0,565	0,555	0,970
2	,748b	0,560	0,552	0,974
3	,746c	0,556	0,550	0,976
4	,741d	0,550	0,546	0,981

TABLE 4 Summary of the model adjusted for age, sex and smoking habits.

	Cluster 1	Cluster 2	p-value
Age	49.51 ± 10.39	59.01 ± 8.15	0.0005
Sex			
M	30.3%	15.8%	0.068
F	29.1%	24.8%	
Smoke			
Y	16.7%	16.9%	0.0005
N	42.7%	23.7%	
Comorbidity count	0.33 ± 0.62	1.74 ± 1.29	0.0005
Total score	0.72 ± 0.98	3.62 ± 2.40	0.0005

TABLE 5 Main characteristics of clusters. Cluster 1 contained subjects without periodontitis or initial (stage 1) to moderate (stage 2) periodontitis, and cluster 2 contained patients suffering from advanced periodontitis (stage 3 and 4). One-way anova was used for age, comorbidity count and total score; Chi-square test was used for sex and smoke.

habits revealed significant difference for TS (p=0.0038) indicating that smokers had more severe comorbidities than non-smokers. Finally, considering the stage (0 for absence of periodontitis), a significant difference was found between stages of disease for both outcomes, CC (p=0.0005) and TS (P=0.0005); a positive trend was detected.

Multivariate linear regression analysis

Multivariate linear regression model was carried out to investigate the predictors of stage of periodontal disease. The multivariate analysis not adjusted for age, gender and smoking habits, presented total score as potential predictor of the stage (stage= 1.033 + 0.445*, total score). When considering the adjusted multivariate model, results were confirmed (Table 3). The analysis showed that there was 0.046 increase in stage for each year of age and 0.347 increase in stage for each point of total score, (stage= -1.225 + 0.046*, age + 0.347*, total score). The adapted R2 value was 0.546, so 55% of the variation of the stage could be explained by the model containing age and total score (Table 4). The scatterplot

of standardized predicted values versus standardized residuals, showed that the data met the assumptions of homogeneity of variance and linearity and the residuals were approximately normally distributed.

Cluster analysis

Two-step cluster analysis revealed the presence of 2 main clusters with different characteristics in terms of stage, age, smoking habits, gender, comorbidity count, total score. According to the method previously presented, quality of clusters was considered sufficient. Cluster 1 contained 140 subjects (59.8%) and Cluster 2 contained 94 subjects (40.2%). Interestingly, cluster 1 contained subjects without periodontitis or initial (stage 1) to moderate (stage 2) periodontitis, and cluster 2 contained patients suffering from advanced periodontitis (stage 3 and 4). Considering the medical burden of patients, cluster 1 showed lower comorbidity count (0.33 ± 0.62) and lower total score (0.72± 0.97) than cluster 2, respectively 1.74 ± 1.21 and 3.62 ± 2.4. Table 5 shows the main characteristics of clusters compared with inference tests.

DISCUSSION

More advanced periodontitis and more severe systemic medical burden were found in middle-aged and older patients.

Patients affected by periodontitis had a higher CC and more severe chronic comorbidities (TS) than patients without periodontitis.

Stage of periodontitis was positively associated with the severity of comorbidities, with age influencing this association.

Stage, CC, TS, age and smoking habits combined in two specific clusters. In the first one, patients were not affected by periodontitis or affected by initial to moderate periodontitis, they had a lower number and severity of comorbidities and there were fewer smokers; in the second one, subjects presented with severe periodontitis (stage III to IV), higher number and severity of chronic systemic diseases, with a higher percentage of smokers.

Firstly, we have to discuss about the number of comorbidities in periodontitis patients. Data on the prevalence of comorbidities in patients with periodontitis are still limited (28). Multimorbidity adds additional care demands to the already complex periodontal treatment. Subjects with worse periodontal status exhibited a greater number of comorbidities if compared to their counterparts (15). Our results confirmed these findings: patients affected by periodontitis had a higher number of chronic comorbidities than subjects without periodontitis.

Then, we have to assess the severity of the entire medical burden in patients affected by periodontitis. Currently, there is a lack of literature regarding this relationship. The severity of periodontitis may be a potential predictor of comorbidities and may reflect the host susceptibility to disease (29). For example, moderate-to-severe periodontitis was associated with a 22% raised risk for hypertension, while severe periodontitis was linked with 49% higher odds of hypertension (30). Higher tooth attachment loss was positively correlated with poor glycemic control (31,32). Patients affected by rheumatoid arthritis with more severe periodontitis suffered more active rheumatoid disease (33). These studies examined specific comorbidities from the perspective of a specific index disease not considering other co-occurring chronic conditions.

Periodontitis is a significant source of systemic inflammatory molecules (34) and it adds to the systemic inflammatory burden of affected individuals (35). It is conceivable that periodontal infections might be an additional risks factor for systemic diseases, in particular in susceptible people (36) and middle-aged or older patients (37). Prevalence of periodontitis increased in these age groups (38), as in the same way number and severity of chronic comorbidities increase (23), so most of patients affected by periodontitis are exposed to the burden of comorbidities. Our results showed that severity of periodontitis and severity of medical burden were influenced by age.

Assessing periodontal conditions with appropriate parameters is crucial to define correctly the severity of periodontitis (15). In the current study stage of the disease, according to 2017 World Workshop, was used to measure the severity of periodontitis. Medical burden assessment is a key element too, simply counting the number of comorbid conditions does not really capture whether a patient is complex (39). For this reason, we assessed severity of chronic medical burden using the TS of CIRS scale to reflect both the severity and complexity of systemic conditions (20,21).

As mentioned previously, we obtained two specific clusters of presentations for age, smoking habits, stage and severity of medical burden. Patients without periodontitis or incipient to moderate periodontitis, had a lower number and severity of comorbidities and there were fewer smokers. However, we must consider the exceptions to the rule, in fact there were individuals who experienced a level of disease severity disproportionate to that experienced by the majority of their peers (40).

Results must be considered with caution due to some limitations. Firstly, the study was conducted in a private practice and it was designed as retrospective. Private practice settings make the research challenging; some of the obvious obstacles to progress in this area are time, funding and standardization. However, standard operating procedures, calibrated operators and periodical debriefing meetings helped us to overcome this issue. The design of the study as retrospective did not allow to evaluate the directionality of the association

between periodontitis and systemic diseases.
Secondly, systemic conditions were assessed using patient's medical history and no systemic examination or diagnostic tests were done, thus the systemic conditions might be underestimated. In fact, patients often report their medical history incompletely. Diseases with clear diagnostic criteria tend to be reported more accurately than those that may be more complicated to diagnose or more difficult for the patient to understand (26,27).
In order to confirm the results obtained from the current study, it is necessary to design prospective studies, enrolling a greater number of subjects. The emerging evidence advocates for personalized medicine and oral care, owing to individual's unique genetic trait, environmental condition, personal profile, and host susceptibility (41). Ignoring concurrent diseases may lead to ineffective control of periodontitis.
In conclusion, our findings could have a very important role in general medicine; the existence of systemic diseases should be suspected and investigated in patients affected by periodontitis. It is essential that dentists know more about systemic diseases, and that medical doctors know about oral diseases and their associations with systemic disorders.

CONCLUSIONS

Currently, there is a lack of literature investigating the association between periodontitis and systemic medical burden. Positive association between stage of periodontitis and severity of chronic comorbidities was found: the more the stage of periodontitis is advanced, the more the systemic medical burden is severe. In other words, patients with severe systemic impairment may experience more advanced periodontitis.

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Conflict of interests
The authors have declared that no competing interests exist.

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