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Periodontal Disease As Risk Factor For Severity Of Covid-19 Infection: A Hospital Base Comparison Study

Dr. Muhammad Safdar Baig[1*], Prof. Dr. Rubeena Zakar[2] , Assist Prof. Dr. Muhammad Tariq Karim. M.S.P.H.[3], Dr. Muhammad Zeeshan Baig[4]

[1*]PhD Scholar (Public Health) HoD Dept. of Dentistry Quaid-e-Azam Medical College and Bahawal Victoria Hospital, Bahawalpur – Pakistan. Cell No.+923006821103 E-mail: safdarbeg@gmail.com
[2]PhD (Public Health) Director Institute of Social & Cultural Studies & Public Health Program, Dept. of Public Health, University of the Punjab, Quaid-e-Azam Campus,Lahore – Pakistan. Cell No. +923324337299 Email: rubeena499@gmail.com
[3]HPE, Head of Research and Evaluation Unit, College of Physicians & Surgeons, Karachi – Pakistan. Cell No. +923332353981Email: tkarim@cpsp.edu.pk
[4]B.D.S., Intern Dental Surgeon, Dow International Dental College & Hospital, Dow University of Health Sciences, Karachi – Pakistan. Cell No. +92304177784 E-mail: mzeeshanbaig07@gmail.com

***Corresponding Author:** Dr. Muhammad Safdar Baig
*PhD Scholar (Public Health) HoD Dept. of Dentistry Quaid-e-Azam Medical College and Bahawal Victoria Hospital, Bahawalpur – Pakistan. Cell No.+923006821103 E-mail: safdarbeg@gmail.com

Abstract
Introduction: Periodontal Disease is group of diseases characterized by gingivitis to destruction of supporting structure of teeth. A chronic inflammatory process usually initiated by local factors like dental plaque and calculus further associated with systemic factors and depicted by biomarkers like bradykinin and cytokines along with certain comorbidities, cardiovascular, diabetes, responsible for atherosclerosis as determined in severity of Covid-19 infection.
Objective: This study aims and objectives was to assess periodontal disease as risk factor for severity of corona disease as per WHO Oral Health Assessment criteria from survivor of corona infection from our national data.
Methodology: A hospital base comparison study to determine association of periodontal disease with severity of the Covid-19 infection among patients with rCT-PCR positive who suffered from survival of at corona infection dedicated hospital national data Pakistan. Periodontal disease assessment determined by WHO define criteria through Oral Health Assessment.
Results: The prevalence of mild periodontal disease was 42 (11.0%), moderate77 (20.1%) severe form 186 (48.6%) while advance periodontitis was 78 (20.4%). From the study final model revealed association of periodontal disease with severity of Covid-19 infection as adjusted Odd's Ratio 9.567, P-value 0.000 and its 95% CI, 1.982 – 46.186. Similarly, patients of diabetes mellitus aOR 36.739 was statistically significance < 0.017 with 95% CI 1.924 – 701.666, lactase dehydrate enzyme aOR analysis 0.100, P-value < 0.010 and 95% CI 0.017 – 0.575 and for C-reactive protein OR 0.028, P-Value < 0.006 and its 95% CI 0.002 – 0.362. The study results identifying the public health implication of periodontal disease with severity of corona infection through simple routine investigation of biomarkers.
Conclusion: Periodontal disease has an association with severity of the Covid-19 infection and the finding is further explained by the presence of certain inflammatory mediators as biomarkers like serum ferritin, cytokines as C-reactive protein in association history of chronic diseases like diabetes mellitus and cardiovascular. The study result also determine that severity of the Covid-19 is preventable through simple measures of oral hygiene maintenance for its better prognosis through control of the periodontal disease, simple measure of public health implication in our setting.

Keywords: Periodontal Disease, Risk Factor, Association, Severity, Covid-19 Infection

Introduction:

Oral literature search reveal that Periodontal Disease (PD) comprises of the group of the chronic inflammatory diseases due to local irritating factors like poor oral hygiene, plaque and dental calculus deposit which initiate the process of gingivitis with its progression towards chronic adult's periodontitis responsible for the destruction of supporting structure of the teeth [1]. It is an established fact that certain microorganisms predominantly the gram-negative anaerobic flora has been found to be associated for development and progression of periodontal disease also responsible for chronic inflammation of the epithelium of the cardiovascular systems as arteriosclerosis as well [2]. According to World Health Organization (WHO) severe form of the periodontal disease affects more than 10% of the world population associated with poor oral health and in relation to excessive use of tobacco along with systemic diseases like diabetes mellitus, elderly age, obesity, liver and kidney and cardiovascular diseases [3].
After the emergence of novel corona virus as the CoV-2 infection, trigger lungs parenchymal damage in the form of lungs alveoli fibrosis has also been associated for respiratory distress with low oxygen saturation which further lead to multiple organ failure. Although SARS MERS usually cause mild to moderate symptoms of acute pneumonia, while the corona infection

caused by the mutated form of CoV-2 was declared global pandemic by WHO on March 11, 2020 [4]. Studies from oral health literature search have identified the Periodontal Disease to be associated with certain systemic diseases like diabetes mellitus, hypertension, chronic liver and cardiovascular diseases, asthma [5]. Literature search emphasis the need to evaluate the possible link between Periodontal Disease and development of severity of the Covid-19 infection among admitted cases at our tertiary care corona dedicated hospital in Southern Punjab, Pakistan during its 1st wave March 2020 to 3rd wave till Nov 2021 [6].
As per WHO, Oral Health has been declared not only an integral part of an individual general health but also an important health indicator of general health as a whole [7]. From the results of several studies, the chronic inflammatory response mediator like cytokines and bradykinin have been established as microbial end products toxins [8], when released from periodontal disease cause inflammation of distant organs ultimately responsible for development of systemic diseases severity of the condition [9]. The results of studies support the evidence that poor oral health in the form of periodontal disease increases the burden of complications of systemic diseases [10] like diabetes mellitus [11], renal, liver diseases and is responsible for atherosclerosis in case of cardiovascular and pulmonary diseases for lungs fibrosis as well [12].

Study Rationale:
It is well known fact that older adults are prone to be suffering from systemic diseases like, cardiovascular, hepatic, pulmonary, diabetes mellitus, hypertension and renal and immune deficiencies [13]. All these conditions put them at increased risk of corona infection, being its natural reservoir and when dislodged to respiratory tract, it may cause corona infection. Therefore, there is need to pay due emphases to reduce the risk of periodontal disease with fatal consequences by reducing the Covid-19 severity of the disease morbidity through simple measures of biomarkers like bradykinin and cytokines as C-reactive protein along with D-dimers, serum ferritin along with neutropenia, absolute leukocyte, neutrophils, lymphocytes count [14]. From the oral health literature search, there is lack of reliable data in this regard and the studies conducted so for measured periodontal disease as their study subjects perceived opinion, as data collected through Email or Google doc as subjective in nature [15]. In our study we have assessed periodontal disease as per define WHO oral health assessment define criteria by administering WHO Oral Health Assessment Form by the calibrated principal investigator as objectively structured format [16].

Study Objectives:
1. The objective of this study was to assess Periodontal Disease among Covid-19 infection survival from corona dedicated three tertiary care hospitals from Bahawalpur division using WHO defined criteria.
2. To determine association of Periodontal Disease with severity of Covid-19 Corona Infection survivors cases to put forward the factors responsible as the inflammatory mediator.

Study Material and Methods:
This study has been conducted using Hospital Base Comparative study design, data from three tertiary care hospitals of Bahawalpur Division attached with the Quaid-e-Azam Medical College, from Southern Punjab – Pakistan. The study data consists hospital records of the admitted corona PCR positive cases from March 2020 to September, 2021 discharged alive
The written informed consent already obtained during the time of these corona patients admission and for oral health assessment WHO Oral Health Assessment Form 2013 for adults have been administered as per defined criteria for assessment of periodontal disease as diagnosed by the calibrated principal investigator along with his data collector team. All the patients were categorized in two groups as PCR positive, as the cases and PCR negative study subjects as our comparable controls.

Ethical Approval:
The study has been approved for its Ethical Review Board from the main data collection and corona dedicated institution, the Quiad-e-Azam Medical College and Bahawal Victoria Hospital, Bahawalpur via Letter No.2048/DME/QAMC dated 2nd February, 2023 and the advance board of studies, University of the Punjab, Lahore via its Letter DNo.640 dated 18th January, 2023 the study is part of work in progress from PhD Public Health Thesis from the platform of Public Health Doctoral Program, University of the Punjab, Lahore Pakistan. While an individual coronal patient informed consent has already been obtained during the time of admission of each study subject.

Sample Size:
The study sample size has been calculated using WHO Sample Size Estimation practical manual for health studies version 2.0 based upon the assumption, prevalence of periodontitis 15% among general population figure from WHO Oral Global Data Bank at alpha 0.05 statistical significance with power of the study 80% with an absolute precision of 5% with confidence level 95% number of study subjects in each group 141 further inflated 10% and enrolled total of 383 study subjects accordingly.

Statistical Analysis:
We have analyzed total of 383 study subjects data as descriptive, binary and multiple logistic regression analysis models. For the continuous variables by calculating their mean ± standard deviation while the categorical variables by their frequency and its corresponding percentages at alpha $\alpha = 0.05$ as statistical significance, calculating through Pearson Chi-square test χ^2 and binary regression and logistic regression to come up with final model to determine association as adjusted odd's ratio for various exposure variables which came to be statistically significant in the univariate analysis with the dependent variable severity of Covid-19 infection as predictor for severity of Covid-19 infection in association with periodontal disease.

Study Results:
We have analyzed our study data as descriptive, univariate and multivariate as final model to come up for association of periodontal disease with its severity of Covid-19 infection and study results have been tabulated as follows:

Table No. 1 Descriptive Study Results Showing Variables with Observed No and Their %age

Gender n= 383	
Male	191 (49.9%)
Female	192 (50.1%)
Age Groups Mean 56.56 ± 14.93	
Group1= 25-45 Years	85 (22.2%)
Group2= 46-70 Years	238 (62.1%)
Group3= Above 70 Years	60 (15.7%)
Comorbidities e Covid-19	
None	(23.2%)
Diabetes Mellitus	(26.6%)
CVS + HTN	(20.4%)
Pulmonary Infection	(14.1%)
Arthritis (Senile/Degenerative)	60 (15.7%)
Serum Sugar Levels	
≥ 200 mg/dL	(60.6%)
201 - 350 mg/dL	101
– 600 mg/dL	(26.4%)
	50
	(13.1%)
Serum D Dimers	
≤ 500 ng/mL	19
501 – 5000	(05.0%)
5001 – 10000	258
>10000	(67.4%)
	73
	(19.1%)
	33
	(08.6%)
Severity of Covid-19 Infection	
Moderate	30 (07.8%)
Severe	(38.4%)
Critical	206 (53.8%)
Serum Ferritin Levels	
≥250 ng/mL	82 (21.4%)
251 – 450	110 (28.7%)
451 – 695	191 (49.9%)
Absolute WBC Count	
Mild to moderate	180 (47.0%)
Severe to critical	203 (53.0%)
C-reactive Protein Level	
≥35mg/L	68 (17.8%)
36 – 55	73 (19.1%)
56 - 109	242 (63.2%)
NLR Ratio	
1 – 2 Normal micr/L	16 (04.2%)
3 – 7 Moderate	110 (28.7%)
≥8 – 11 Inflam + stress	179 (46.7%)
≥11 – 17 Severe inflame	78 (20.4%)
PLR Ratio	
1 – 2 Normal micr/L	20 (05.2%)
3 – 7 Moderate	97 (25.3%)
≥8 – 11 Inflam + stress	217 (56.7%)

≥11 – 17 Severe inflame	49	(12.8%)
MLR Ratio		
1 – 2 Normal micr/L	21	(05.5%)
3 – 7 Moderate	84	(21.9%)
≥8 – 11 Inflam + stress	151	(39.4%)
≥11 – 17 Severe inflame	127	(33.2%)
LDH Enzyme level		
Mild to moderate unit/L	51	(13.3%)
Severe inflammation	332	(86.7%)
Severity of Covid-19		
Mild to moderate	30	(07.8%)
Severe infection	147	(38.4%)
Critical condition	206	(53.8%)
Periodontal Disease		
Yes	340	(88.8%)
No	43	(11.2%)

Tabe No.2 Bivariate Results for Association of Periodontal Disease Severity of Covid-19 Infection

Study Variable Names	**Severity of Covid-19 Infection categories**			**Results**	**Statistical Significance**	
	Moderate	**Severe**	**Critical**	**Chi-Sqre**	**Sig P-Value**	
Periodontal Disease						
Yes	05 (16.7%)	129 (87.8%)	206 (100.0%)	182.7.6	0.000	
No	25 (83.3%)	18 (12.2%)	00 (00.0%)			
Age Groups in Years						
≥25 – 45	12 (40.0%)	34 (23.1%)	39 (18.9%)			
46 - 70	16 (53.3%)	89 (60.5%)	133 (64.6%)	6.902	0.141	
>70 Years	02 (06.7%)	24 (16.3%)	34 (16.5%)			
Gender						
Male	15 (50.0%)	76 (51.7%)	100 (48.5%)	0.432	0.843	
Female	15 (50.0%)	71 (48.3%)	106 (51.5%)			
Co-morbidities						
None	09 (30.0%)	39 (26.5%)	41 (19.9%)			
Diabetes	05 (16.7%)	42 (28.6%)	55 (26.7%)	25.291	0.001	
CVD+HTN	03 (10.0%)	16 (10.9%)	59 (28.6%)			
Pulmonary	06 (20.0%)	20 (13.6%)	28 (13.6%)			
Arthritis	07 (23.3%)	30 (20.4%)	23 (11.2%)			
Covid-19 Vaccination						
Unvaccinated	18 (60.0%)	116 (78.9%)	170 (82.5%)	8.146	0.017	
Vaccinated	12 (40.0%)	31 (21.1%)	36 (17.5%)			
D-Dimers Level						
<500 mg/L	12 (40.0%)	05 (03.4%)	04 (01.9%)			
501 – 5000	00 (0.00%)	09 (06.1%)	27 (13.1%)	96.937	0.000	
5001 – 10000	01 (06.7%)	17 (11.6%)	54 (26.2%)			
>10000	16 (53.3%)	116 (78.9%)	121 (58.7%)			
Serum Ferritin Level						
≥250 ng/mL	24 (80.0%)	58 (39.5%)	00 (00.0%)			
251 – 450	06 (20.0%)	86 (58.5%)	18 (08.7%)	342.56	0.000	
451 – 695	00 (0.00%)	03 (02.0%)	188 (91.3%)			
WBC Count ($x10^3mm^{-2}$						
Mild to moderate	30 (100.0%)	145 (98.6%)	05 (02.4%)	355.495	0.000	
Severe to critical	00 (00.0%)	02 (01.4%)	201 (97.6%)			
C-reactive Protein						
≤ 35mg/L	26 (86.7%)	40 (27.2%)	03 (01.9%)			
36 – 55	02 (10.0%)	56 (38.1%)	12 (05.8%)	226.139	0.000	
56 – 109	01 (03.0%)	51 (34.7%)	190 (92.2%)			

NLR Ratio micro/L						
1 – 2 Normal	08 (26.7%)	08 (05.4%)	0.00 (0.00%)			
3 – 7 Moderate	16 (53.3%)	92 (62.6%)	01 (01.0%)	250.997	0.000	
>7 – 11 Severe	06 (20.0%)	46	127 (61.7%)			
>11 – 17severe inflm	00 (0.00%)	(31.3%)	77 (37.4%)			
		01 (0.07%)				
PLR Ratio micro/L						
1 – 2 Normal	06 (20.0%)	14 (09.6%)	00 (0.00%)			
3 – 7 Moderate	18 (60.0%)	72 (49.0%)	07 (03.4%)	176.511	0.000	
>7 – 11 Severe	06 (20.0%)	60 (40.8%)	151 (73.3%)			
>11 – 17severe inflm	00 (0.00%)	01 (0.07%)	48 (23.3%)			
MLR Ratio micro/L						
1 – 2 Normal	08 (26.7%)	13 (08.8%)	00 (00.0%)			
3 – 7 Moderate	14 (46.7%)	68 (46.3%)	01 (01.0%)	214.344	0.000	
>7 – 11 Severe	08 (26.7%)	59 (40.1%)	84 (40.8%)			
>11 – 17severe inflm	00 (0.00%)	07 (04.8%)	120 (58.3%)			
LDH Enzyme level U/L						
Mild to moderate	21 (70.0%)	30 (20.4%)	00 (00.0%)	121.559	0.000	
Severe inflame	09 (30.0%)	117 (79.6%)	206 (100.0%)			
Serum Sugar Level						
≤ 200 mg/dL	21	101 (68.7%)	110 (53.4%)			
201 – 350	(70.0%)	34 (23.1%)	62 (30.1%)	11.113	0.021	
>350 mg/dL	05 (16.7%)	12 (08.2%)	34 (16.5%)			
	04 (13.3%)					

Table 3. Binary and Multinomial Logistic Regression Model Assessing Association of Periodontal Disease With Severity of Covid-19 Infections and its Factors Responsible

Variables	Un-adjusted Binary Model		P-Vale	Adjusted Multinomial Model		P-Value
	Odd's Ratio	95% CI	Significance	Odd's Ratio	95% CI	Significance
Serum Sugar						
≤ 200 mg/dL	1			1		
201 – 350	4.283	0.296 - 61.845	< 0.286	36.739	1.924 – 701.666	< 0.017
>350 mg/dL	1.462	0.091 – 23.422	< 0.788	18.789	0.865 – 408.232	< 0.062
C-reactive Protein						
≤ 35mg/L	1			1		
36 – 55	6.047	1.061 – 39.437	< 0.039	0.028	0.002 – 0.362	< 0.006
56 – 109	1.682	0.267 – 10.590	< 0.043	0.599	0.030 – 10.275	< 0.695
Periodontal Disease						
Yes	1			1		
No	0.046	0.001 – 1.465	< 0.081	9.567	1.982 – 46.186	< 0.005
LDH Enzyme						
Mild to moderate	1			1		
Severe inflame	20.556	2.337 – 180.769	< 0.006	0.100	0.017 – 0.575	< 0.010

Discussion:

It is evident from the results of our study the prevalence of periodontitis, advance form of periodontal disease has statistically significant association with severity of the Covid-19 infection [17]. Periodontitis itself is responsible for teeth supporting structure destruction, being multifactorial in nature, already proved to be in associated with many systemic comorbidities like cardiovascular diseases, diabetes mellitus, hepatic and renal insufficiencies [18]. The pathophysiology explained in this regard is the dysbiosis because of dental plaque [19], principal causative agent for development of periodontal disease acting as reservoir for transportation of respiratory tract pathogens associated with Covid-19 infection complications [20]. Results from the scientific studies and its systemic review carried out by Scannapieco et al revealed significant association between poor oral health and hospital acquired pneumonia [21].

The periodontal disease also linked with chronic obstructed pulmonary disease thought to be associated with aspiration of the pathogens to lungs, causing some alteration in lungs mucous membrane of the respiratory tract adhesion and invasion because of these pathogens colonization in the respiratory tract [22]. The results of our study are in consistent with the results of the

studies explaining this association of periodontal disease with severity of the Covid-19 infection further supported by the fact of periodontal pathogenic bacteria to induce certain pro-inflammatory cytokines into respiratory tract which have their role for Covid-19 severity of disease [23]. The oral cavity severs as reservoir for the SARS-CoV-2 virus identified from respiratory tract, dislodged from the periodontal pockets has already been proved by many researchers [24].
The significant observation revealed from our study is statistically strong association of serum CRP level among Covid-19 infection with history of lungs lesions as depicted through HRCT lesions as well [25]. The elevated serum reactive protein proved to be significant inflammatory parameter among survivor of corona infection patients, this finding is in consistent with results from studies almost all over the world and our neighbor-hood from Multan by Waqas Hanif et al [26]. Similarly, an increased level of LDH lactate dehydrogenase came out to be associated as significant factor, although couldn't retain its significance in multivariate model [27[. Study by Acharya et al from India in 2019 demonstrated reduction in level of NLR and PLR levels among patients of periodontal disease who maintained their periodontal health. Scientific literature search support absolute leukocytes count to be associated with prevalence of periodontal disease in relation to severity of Covid-19 infection [28].

Study Limitations:
One of the limitation of our study is the data of the healthcare patient management during acute phase of the Covid-19 infection, dedicated hospital records collected for NIH through NCOC for corona infection from three tertiary care hospitals of Bahawalpur Division Southern, Punjab - Pakistan.

Conclusion:
This study results revealed that along with known cardiovascular, pulmonary, hepatic and renal comorbidities, patients suffering from diabetes mellitus have been identified to be at increased risk to suffer from complications of the severity of the Covid-19 infection because of its strong association with periodontal disease. Hence, just by taking care of bleeding gums its further progression to advance periodontal disease condition, can be controlled through personal oral hygiene and professional dental care. The severity of the Covid-19 infection can be monitored through simple blood complete tests for the circulating biomarkers, like cytokines, bradykinins, serum ferritin and C-reactive protein identified as chronic inflammatory biomarkers to reduce the public health burden for such a lethal complication of the disease in our settings with scarce resources.

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Conflict of Interest: There has been no any potential conflict of interest declared among the authors.

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