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Associations of periodontitis and oral manifestations with CD4 counts in HIV-pregnant women in Thailand

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Abstract

Objectives—To investigate the associations of CD4 count with chronic periodontitis and HIV-related oral lesions in pregnant HIV-infected Thai women.

Study Design—292 HIV-infected pregnant women were interviewed for health information and examined for their periodontal condition and HIV-related oral lesions during weeks 16-34 of gestation. Logistic regression, t-tests and chi-squared tests were used to examine the associations of CD4 count with oral lesions and periodontal conditions.

Results—133 women (45.6%) had at least 1 tooth with a periodontal pocket over 4 mm. Thirty-eight (17.76%) subjects had oral candidiasis and 53 subjects (24.77%) had oral hairy leukoplakia (OHL). Low CD4 count was significantly associated with periodontitis at OR=2.06 with 95%CI [1.00-4.27], p-value 0.05. A significant association was found for low CD4 count with oral hairy leukoplakia with OR 3.57, 95%CI [1.34-9.46], p-value 0.01.

Conclusions—Chronic periodontitis and OHL were associated with CD4 count lower than 200 cells/mm^3 in HIV-infected women.

Key findings

(Clinical Relevance): There are associations of low CD4 count with periodontitis and oral hairy leukoplakia

Background

There have been few clinical studies that investigated whether CD4 count in Human immunodeficiency virus infection (HIV) could be associated with chronic periodontitis[1-3]. Many studies in the last ten years focused more on oral manifestions[4-6]. The current regular

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use of antiretroviral therapy (ARV) results in lower incidence of HIV-related oral manifestations[7]. However, recent studies show the highly active antiretroviral therapy (HAART) has an adverse effect on HIV patients[8, 9]. A study found that chronic periodontitis progression in HIV-infected patients and non-infected populations were similar[10]. Moreover, in a microbiology study, HIV-seronegative periodontitis patients showed significantly more periodontal destruction and inflammation than HIV-seropositive periodontitis patients, whereas HIV-infected patients with no chronic periodontitis presented a greater percentage of sites with bleeding than patients who were HIV-seronegative with no chronic periodontitis[11]. There was higher prevalence of levels of bacterial species in HIV-seronegative than that of HIV-seropositive patients[11]. However, a recent animal experimental study shows the presentation of T-cells (including CD4) attenuates the progression of periodontitis[12]. Moreover, a study done in HIV-infected subjects found more progression of periodontitis related to low CD4[13] whereas another study found CD4 has no association with periodontitis progression but high viral load was associated with increased tooth loss[10]. The criteria used to define periodontitis in previous studies varied greatly[14]. There have been many attempts to categorize and define periodontitis in a person[15, 16]. A Center for Disease Control workshop also tried to define the criteria of periodontitis for population-based studies[17]. In our study, we tried to approach this issue by using a variety of criteria to define periodontitis.

Pregnancy itself is known to be associated with changes in periodontal conditions[18]. Pregnancy has special effects due to the changing of hormones including estrogen, progesterone, gonardotropins and relaxin. Some studies found prevalences of 50%-98.25% of gingival bleeding[19], among pregnant women, some reported increased tooth mobility and one study reported that pregnancy accelerated periodontitis progression and resulted in more severe lesions in pregnant women[20]. There has not been a study of oral health solely in HIV-pregnant women.

In our pilot study on prevalence of oral manifestations and oral health status related to CD4 count in HIV positive pregnant women in the Preventive Mother-to-Child Transmission (PMTCT) program and Antenatal clinic (ANC) in Thailand, we found a marginally significant association of more periodontitis across the decreasing range of CD4 counts. This study aims to assess the associations of CD4 count with prevalence of periodontitis and also with the prevalence of other oral lesions among Thai HIV-infected pregnant women in multiple hospital settings.

Methods

This study was a cross-sectional study that had one data collection visit. It was done in multiple settings in 2 periods of time, during April 2005 – June 2006 and September 2008 – October 2010 under the PMTCT program, in the Antenatal Clinic and Obstetric and Gynecology departments. This study involved the use of baseline data collected as a part of a cohort study of HIV-infected women designed to evaluate risks of adverse birth outcomes (preterm birth and low-birth-weight) associated with periodontitis in Thai human immunodeficiency virus-positive pregnant women. The results of that study have been published [21]. Since they are based on the same sample, some of the descriptive data here overlap with that study, but the present study evaluates associations of CD4 counts with periodontitis and oral manifestations in the presence of pregnancy, not the risk of adverse birth outcomes with periodontitis.

Setting

The study was conducted in 10 hospitals in the Bangkok, Pathumthani and Chonburi provinces, in the central part of Thailand. Vajira Hospital, Bangkok Metropolitan General

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Hospital, Taksin Hospital, Charoenkrung Pracharak Hospital, were affiliated with the Medical Service Department of Bangkok Metropolitan Administration (BMA). King Chulalongkorn Memorial Hospital, and Police General Hospital in Bangkok), Thammasat University Hospital in Pathumthani, Queen Savang Vadhana Memorial Hospital, and Queen Sirikit Hospital in Chonburi were affiliated with the PMTCT program of the Thai Red Cross organization. Bamrasnaradura Institute of the Ministry of Health is the specialized hospital for infectious disease and HIV. Treatment guidelines for HIV-infected pregnant women in each setting are comparable. The estimated number of cases of HIV-pregnancy from these 10 hospitals is about 360 cases annually.

Subjects

We recruited HIV-seropositive pregnant women in these hospitals from the central part of Thailand during the 2 time periods. We included HIV-pregnant women who were in their 16^{th} to 34^{th} week of gestation, were at least 15 years of age, and had at least two teeth in each quadrant. They had to understand the study and sign the informed consent form.

Sample size calculation

From previous published studies, we anticipated the incidence of periodontitis in Thailand to be very high. Our pilot study indicated a prevalence of having periodontitis (using CDC's criteria of mild periodontitis) to be 0.47 in the low CD4 group (<200 cells/mm^3) and prevalence of periodontitis at 0.29 in the higher CD4 group (≥200 cells/mm^3). We then used a sample size calculation in STATA 10 program to determine the sample size needed to have power of 0.80 to detect such a difference in prevalence to be significant using a significance level of 0.05. Ten percent more were added to compensate for any anticipated incomplete data, which brought the total targeted number to 273. We finished this study with 292 subjects, which exceeded our goal.

IRB approval

Human Subjects approval for the study was obtained from IRBs at the University of Washington, Thammasat University, Bangkok Metropolitan Administration, the Ministry of Health of Thailand, and each of the hospitals.

Enrollment and Data Collection

After consent was obtained, a unique study code was assigned to each participant. Dr. Pattrapornnan interviewed the subjects and filled out the first questionnaire on the subject's behalf. The questionnaire consisted of questions including the demographic profile, medical and health history, as well as oral health information. Birth date, age, education level, marital status and income level, gestation stage at time of enrollment, CD4 counts, antiretroviral (ARV) medications used, ARV first time used, antibiotic medication used, genital infection, presence of hypertension and/or Diabetes Mellitus, smoking status, alcohol consumption status and stress level were collected. Oral health information such as the frequency of cleaning and type of cleaning were collected. Variables such as age, BMI, gestational age, CD4 counts, ARV used, hypertension, diabetes mellitus, and genital infection were confirmed by medical chart.

Dr. Pattrapornnan performed all oral examinations. An extra-oral examination was done first. Head and neck lymph nodes and salivary gland were examined. In the absence of a dental unit, the participants were asked to tilt their head back and the Mirrorlite®, a special mouth mirror that contains a light source in its handle, was used to examine them. Intra-oral examinations were conducted including the examination of the lips, cheeks, tongue, palate, and floor of the mouth. Tooth conditions (decay, missing, filling) and dental plaque were

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examined in a clockwise manner with upper-right third molar to lower-right third molar. Probing was done on 6 positions of the tooth: mesiobuccal, mid-buccal, distobuccal, mesiolingual, mid-lingual and distolingual. The measurements were recorded in millimeters (mm.) by an attending dental assistant, who was not aware of the scientific questions being addressed.

Variables and measurements

CD4 count was taken from the medical record, as recorded by the physician who was in charge of the HIV care. HIV subjects generally have a blood test to evaluate CD4 count every 6 months. However, some of the pregnant women didn't know that they were HIV-infected until they came in to the prenatal clinic. Once they were identified as HIV-positive, the blood test for CD4 count would be scheduled for a subsequent visit to determine if they should be on ARV. Therefore, at the visit of enrollment into our study, some of the subjects didn't have CD4 counts available. In that case, the investigator obtained the data from the nurse in the next visit. It was recorded as number of cells/mm^3. We then categorized the CD4 into 3 groups, Low: 0 to 199 cell/mm^3; Medium: 200 to 500 cell/mm^3; and High: more than 500 cell/mm^3 with the 'High' group as a reference group.

Clinical Attachment Loss (CAL) and periodontal pocket depth (PPD) were examined and recorded simultaneously for 6 positions measured on each individual tooth. Since there are many criteria proposed to define periodontitis in individual persons, we provided a variety of categories and subcategories of periodontitis in order to compare our results with other studies. We used the same criteria from the previous published study[21]. We focused on periodontal pocket depth and categorized periodontitis by the percentage of teeth that had periodontal pockets of at least 4 mm in 4 categories: none (0%), low (0.1-20%), medium (21-40%) and high (41% or above).

We also combined these and other measures into three general categories of periodontitis status in order to compare the study with others and Centers for Disease Control (CDC) criteria[17]. Therefore, we have 3 general categories (with subcategories): (at least) mild periodontitis, (at least) moderate periodontitis and severe periodontitis. The details of categories and definition of subcategories of periodontitis criteria are shown in Table 1[21-27].

In order to evaluate the calibration of clinical measurements of clinical attachment loss (CAL) and periodontal depth (PPD), repeat measurements of 15 women subjects were done in the same manner as in the study for a separate reliability study. Intraclass Correlation Coefficients in measuring gingivitis, CAL and PPD of 0.79, 0.70 and 0.84 were achieved. For the HIV-related oral manifestations, the presentation of oral lesions was recorded in a dichotomous manner (present or absent). The diagnosis is done clinically. Dr. Pattrapornnan, a trained oral medicine specialist, examined the lesions and the assistant recorded the data.

The overall distribution of CD4 categories, as well as prevalences of periodontitis measures and oral manifestations are given in Table 2.

Potential confounders were those variables that were suspected to be associated with CD4 count and periodontitis or oral manifestations. Their associations were evaluated using stratified analyses with chi-square tests, but are not shown because of space limitations. Potential confounders examined included age, mental status, education, income, body mass index, parity, gestation, alcohol consumption, stress, smoking, hypertension, diabetes, and ARV use. The verified confounders were those variables that demonstrated significant associations with CD4 and periodontitits or oral lesions, and included age, income, BMI, parity, ARV use, current smoking and living with a smoker. We then used logistic regression, with presence of periodontitis or oral manifestations as the dependent variable,

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and a forward selection stepwise procedure was used to identify an adequate subset of confounders for which to provide adjustment while avoiding problems introduced by colinearity of multiple covariates. We ended up with categorical age and ARV as the key confounders, for which we adjusted in the analyses.

STATA 10.0 version was used for the analyses. Logistic regression was used to determine the association of CD4 count with oral manifestations and periodontal status. Odds ratios were used to report the size of the associations.

Result

All 292 pregnant women approached were enrolled into the study (100% response rate), for the periodontitis analysis. However, for the oral lesions, we obtained data on 214 subjects, since there were time limitations for completing the oral examination in some settings.

As previously reported[21], subjects' mean age was 28 (27.55, sd 0.31) years and 61.99 % of subjects were in the age range of 25-34 years. Body Mass Index (BMI) (at time of enrollment) mean was 24.6 (sd 0.22) and 50.7% of them were in the normal weight range (18.5-24). We also calculated the BMI prior to the pregnancy and found that 49.3% of them were in the normal weight range. There were 132 subjects (45.21%) experiencing their first pregnancy. From 160 multi-parous pregnancies, 37 subjects had a history of giving birth to a preterm delivery and/or low birth weight baby. At the enrollment, 189 subjects (64.7%) were already on antiretroviral medication. We found 10 subjects with hypertension and 8 subjects with diabetes mellitus. From 292 subjects, 288 (98.6%) reported no current smoking, 17 of them reported history of smoking years prior to pregnancy. However, 46.58% of subjects lived with smokers with 127 subjects were exposed while their housemates were smoking. Also, 288 subjects reported no alcohol consumption during their pregnancy, but 122 subjects (41.78%) reported a history of alcohol use. And 161 subjects (55.14%) reported no stress.

With respect to CD4 count first being reported here, mean CD4 was 352.7 cells/mm^3 (sd 11.11), there were 63 subjects (21.58%) in the Low CD4 category; 161 subjects (55.14%) in 200-499 cells/mm^3 range; and 68 subjects (23.29%) had CD4 count at least 500 cells/mm^3. We didn't examine the oral lesion and periodontal status in the same visit as the CD4 test, and the dates of the CD4 tests were not always available since HIV-infected mothers sometimes presented with only ANC booklet but not hospital chart. Especially those who had many appointments in the same day, the hospital charts were with other departments and sometimes unable to access. However, we obtained 74 records of the mean time of CD4 measurement to the oral examination. It was found that the mean time was 56.2 days. The maximum date from CD4 count to the examination was 103 days and the minimum was 0 day (the date of examination).

Several different measures of periodontal conditions were used, and the terms defining them are given in Table 1. Most cases were in the low percentage and mild periodontitis categories respectively. For the Mild periodontitis category, we found PERIO4 (periodontal pockets of 4 mm or more on at least one tooth) was present for 133 (45.6%) subjects and Low periodontitis 78 (26.71%) subjects. The Moderate periodontitis category included P44SITE present in 85 (29.1%) subjects, PERIO5 in 22 (7.5%) subjects and Medium with 34 (11.6%) subjects. In Severe periodontitis, we found P54SITE present in 4(1.4%) subjects, PERIO6 present in 2(0.7%) subjects and High with 21(7.2%) subjects. Note that the mild and moderate categories are inclusive of those more severe, so that a more accurate description of mild might be “mild or more severe”.

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For oral manifestations first being reported in this manuscript, there were completed examinations available for 214 subjects, Candidiasis was found in 38 subjects (17.76%), oral hairy leukoplakia in 53 subjects (24.77%), and only 2 subjects (0.95%) presented with herpes infection. There were 14 subjects (6.67%) with aphthous ulcer and no kaposi's sarcoma was found. For HIV-related periodontal lesions, there were 9 subjects (4.90%) with necrotizing gingivitis and only one (0.48%) subject had necrotizing periodontitis.

The prevalence of CD4 count, periodontitis by various criteria and oral lesions were summarized in Table 2. As shown in Table 3, after adjusting for confounders and using CD4 >500 cells/mm^3 as reference group, we found significant associations of low CD4 count (less than 200 cells/mm^3) with PERIO4 at OR 2.06 with 95%CI [1.00-4.27], p-value 0.05. A marginally significant association was found for low CD4 count and low level of periodontitis at OR 2.28 with 95%CI [0.98-5.30], p-value 0.06. For the oral manifestations, we found a marginally significant association between low CD4 count and candidiasis at OR 3.15 with 95%CI [0.92-10.78], p-value 0.07. For oral hairy leukoplakia, we found a statistically significant association of the lesion and low CD4 count with OR 3.57, 95%CI [1.34-9.46], p-value 0.01. We didn't find any significant associations for CD4 range 200 – 499 cell/mm^3 with periodontitis or oral manifestations. The adjusted odds ratios of periodontitis defined various ways including CDC population-based case criteria with CD4 category, and the adjusted odds ratios of oral manifestations by CD4 category are shown in Table 3.

Discussion

We were 100% successful in enrolling subjects who were identified as eligible, and the sample size of 292 subjects is sufficient to detect an association of CD4 count with periodontitis at power 0.80. We found the prevalence of women who had at least one PPD greater than 4 mm. to be 45 percent. These numbers corresponded to the expected number we projected from the pilot data.

Even though the study was done in multi-institutions, the setting of those institutions was very similar since they were all from the government/public section and they shared the same protocol of HIV-treatment. Therefore, there was a minimal bias introduced by differential protocols or procedures. We had a good level of agreement in examiner reliability and measurement validity with intraclass correlation coefficients of 0.70 or higher. We had accurate data of CD4 count, BMI, gestation week, and medical history confirmed by medical record. There was minimal opportunity for bias in the process of recording data, since it was recorded by a research assistant, who was not aware of the associations of CD4 count with periodontitis/ oral manifestations.

Previous studies of periodontitis with systemic diseases (i.e. periodontitis and pregnancy outcomes, periodontitis and heart disease) have proposed many metrics for the definitions of periodontitis[14-16]. Our study used both quantitative and qualitative methods. The quantitative measure indicates periodontitis level by using the frequency of the teeth that were affected or whether a patient has at least one 4 mm. pocket, and converted it into a percentage. The benefit of our study is that we recorded and measured the depth on every tooth so we can apply our data using other criteria along with CDC's working group criteria, compare the results from other studies and also to investigate the association in many levels. Overall, we found only one association of CD4 count and peridontitis. The significant OR showed the association of low CD4 count (<200 cells/mm^3) with mild or more serious periodontitis (at least 1 tooth affected with periodontal pocket depth at least 4 mm.). This finding is similar to a previous study done in an HIV population[13]. They found the greater risk of periodontal progression in the low CD4 category. We found no association of CD4

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count and periodontitis in other levels/criteria, which corresponds to the majority of other previous studies[10, 11, 31].

For the analysis of oral manifestations, we found a strong significant association of low CD4 count with oral hairy leukoplakia. This finding confirmed the results of previous studies in similar ethnicity and socioeconomic populations[5, 32]. However, in this study, OHL is diagnosed clinically by bilateral, elevated, white patches of the lateral borders and dorsum of the tongue and cannot be wiped away. Histological diagnosis should be added in any future study. We found a marginally statistically significant association of oral candidiasis with low CD4 count.

In antiretroviral (ARV) therapy era, oral manifestations were not seen regularly. HIV-patients who are on any monitoring program would benefit and get healthier overall than those who were not in the program. This could be the reason that we didn't find many subjects with oral lesions or periodontitis. Our subjects were in an institution program, therefore, most of them automatically received the ARV medication when their CD4 was lower than 200 cells/mm^3. This could cause some bias. However, we adjusted for ARV use in our analysis, so we expect the bias to be minimal. Moreover, the most recent reports including a Thai study showed that HAART didn't affect the oral lesion presentation[8, 9].

This study has some limitations. Since the CD4 counts were done every 6 months, some of the subjects had CD4 tests done several months prior to the study's oral examination and this could lead to misclassification. However, periodontitis is a chronic infection and the periodontal pocket (from bone destruction) occurs gradually in most cases, so we expect this misclassification to be minimal. Although sample size is quite sufficient overall, sometimes there were small numbers of subjects left in some strata when we stratified the subjects into categories and sub-categories. In the second period (2010) of data collection, the hospitals' IRBs allowed periodontal status examination as well as the oral lesion examination. However, in some hospitals, the patients had many doctor appointments in the same day and had to go through many procedures, therefore, some of the patients were available for only 30 minutes of examination. We then chose to measure mainly periodontal status. We briefly looked at the oral mucosa in such cases, but we couldn't confirm the presence or absence of oral lesions in those cases. Therefore, we lacked some oral lesions data. Finally, given that we looked at many potential associations and only found two to be significant, they could be spurious associations although they are consistent with expectations. Though this study found significant associations of CD4 count with periodontitis and oral hairy leukoplakia, associations are not sufficient to prove a causal relationship.

To confirm the findings of significant associations of low CD4 with periodontitis and oral hairy leukoplakia, future studies would benefit from microbiological and salivary assays to confirm that the apparent periodontitis progression is accompanied by higher concentrations of bacterial infection or inflammatory markers. A larger sample size would be beneficial in future studies because of the need to stratify data into sub-categories. Any future study should also investigate the non-pregnant population in order to clearly explain the mechanism of the associations, as well as take into account the timing of CD4 tests and monitoring for ARV use.

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Table 1

Periodontitis criteria used in the analysis (using the same criteria as previous published study[21])

Periodontitis	Definition
Mild periodontitis	
• PERIO4	At least one tooth with CAL>2 mm., PPD≥4 mm.
• Low	0.1-20% of remaining teeth have PPD≥4 mm.
Moderate periodontitis	
• P44SITE	At least 4 teeth with CAL>2 mm., PPD≥4 mm.
• PERIO5	At least one tooth with CAL>2mm., PPD≥5 mm.
• Medium	21-40% of remaining teeth have PPD≥4 mm.
Severe periodontitis	
• P54SITE	At least 4 teeth with CAL>2 mm., PPD≥5 mm.
• PERIO6	At least one tooth with CAL>2mm., PPD≥6 mm.
• High	41% or more of remaining teeth have PPD≥4 mm.

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Table 2

Distribution of CD4 counts, periodontitis and HIV-related oral manifestations in HIV pregnant women in Thailand from data 2005-2006 and 2008-2010

Variables	Frequency	Percent
CD4 (N=292)		
<200 cells/mm^3	63	21.58
200-499 cells/mm^3	161	55.14
≥500 cells/mm^3	68	23.29
Periodontitis (N=292)		
PERIO4	133	45.55
Low periodontitis	78	32.91
P44SITE	85	29.11
PERIO5	22	7.53
Medium periodontitis	34	17.62
P54SITE	4	1.37
PERIO6	2	0.68
High periodontitis	21	11.67
Oral manifestations (N=214)		
Oral candidiasis	38	17.76
Oral hairy leukoplakia	53	24.77
Herpes infection	2	0.95
Aphthous	14	6.67
Gingival erythema	33	15.42
Necrotizing gingivitis	9	4.21
Necrotizing periodontitits	1	0.47

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Table 3

The odds ratios and 95% CI of periodontitis and HIV-related oral manifestations after adjusting for ARV, and BMI

Periodontitis & Oral lesions	CD4 count					
	≥500 cells/mm^3 (reference group)	P-value	200-499 cells/mm^3	P-value	<200 cells/mm^3	P-value
Mild periodontitis						
• PERIO4	1.00	-	1.44 [0.80-2.58]	0.22	*2.06 [1.00-4.27]*	*0.05**
• Low	1.00	-	1.38 [0.67-2.81]	0.38	2.28 [0.98-5.30]	0.06
Moderate periodontitis						
• P44SITE	1.00	-	1.16 [0.61-2.20]	0.65	1.45 [0.66-3.18]	0.36
• PERIO5	1.00	-	0.96 [0.32-2.88]	0.94	1.54 [0.42-5.68]	0.52
• Medium	1.00	-	1.27 [0.52-3.16]	0.60	1.20 [0.36-4.00]	0.77
Severe periodontitis						
• P54SITE	1.00	-	0.83 [0.07-9.34]	0.88	0.74 [0.04-13.73]	0.84
• PERIO6	1.00	-	N/A	N/A	1.37 [0.04-42.38]	0.86
• High	1.00	-	1.28 [0.83-2.00]	0.26	1.38 [0.83-2.32]	0.22
Oral candidiasis	1.00	-	2.41 [0.77-7.51]	0.13	3.15 [0.92-10.78]	0.07
Oral hairy leukoplakia	1.00	-	1.31 [0.53-3.22]	0.55	*3.57 [1.34-9.46]*	*0.01**
Herpes infection	1.00	-	N/A	N/A	N/A	N/A
Aphthous ulcer	1.00	-	0.68 [0.18-2.58]	0.57	1.17 [0.24-5.71]	0.85
Gingival erythrema	1.00	-	0.81 [0.63-1.05]	0.12	0.98 [0.76-1.26]	0.86
Necrotizing gingivitis	1.00	-	0.82 [0.59-1.14]	0.24	0.82 [0.56-1.19]	0.29
Necrotizing periodontitis	1.00	-	N/A	N/A	N/A	N/A

N/A = Not applicable,

* Significant with p-value <0.05