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Association of Poor Periodontal Health in Younger Schizophrenia Patients with a Worsening of Symptoms During Remission: a Prospective Cohort Study

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Abstract – Objectives- The aim of this prospective cohort study was to investigate whether the association of periodontal status with schizophrenia treatment outcomes differs by patient's age. Subjects and methods- The study was performed on the consecutive sample of 67 patients diagnosed with schizophrenia and discharged because achieving remission criteria. Papilla bleeding index (PBI) was measured at hospital discharge. Positive and negative syndrome scale (PANSS) total score, positive, negative and general symptoms subscales' scores were measured at hospital discharge, after three, and after six months. Results: - After the adjustment for potential confounders, baseline PBI was significantly unfavorably associated with PANSS total score, negative and general symptoms subscales scores in the patients younger than 45 three and six months after the hospital discharge, and with the positive symptoms sub-scale in patients younger than 34. At youngest 10% of patients, a unit difference in baseline PBI resulted in the 8.12 (95% CI 2.78-13.47; p=0.004) points higher total PANSS score three months later. Our study showed that the younger patients with worse periodontal status are at higher risk for poorer schizophrenia treatment outcomes and faster worsening of remission. This study demonstrates the necessity of more rigorous and more frequent control of younger schizophrenia patients with worse periodontal status after hospital discharge to achieve overall improvement of the patients' quality of life as well as the efficacy of psychiatric therapies aimed toward the primary mental disorder.

Key words: papilla bleeding, PANSS, schizophrenia, periodontal status

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Introduction

Many studies have shown the association between poor periodontal status and schizophrenia [1-5] which may be influenced by different factors. First generation antipsychotics as well as anticonvulsants used as mood stabilizers in the treatment of schizophrenia, may cause a hypo-salivation by blocking the parasympathetic stimulation of salivary glands and so increase the risk for oral illnesses [4, 6, 7]. Lithium may cause dry mouth, sialorrhoea, ulceration of the oral cavity and infections [8]. Almost all antidepressants may cause xerostomia, and significant number of them causes dysgeusia [7]. Tricyclic antidepressants and other drugs with anticholinergic or antiadrenergic effects may cause hypo-salivation and consequent candidiasis and other oral infections [8]. Majority of anxiolytics and hypnotics causes xerostomia as well [7]. In addition to medication used in schizophrenia treatment, prevalence of heavy smoking is higher in the population of patients diagnosed with schizophrenia [9] and smoking has a strong negative effect on periodontitis [10, 11]. In patients with higher negative symptoms the motivation and persistence in maintaining a proper oral hygiene may be impaired [4]. Poorer periodontal status and more advanced average stage of a newly diagnosed periodontal disease in schizophrenia patients may partially be a consequence of the lower dental healthcare utilization [12]. Patients diagnosed with schizophrenia may erroneously interpret the symptoms of periodontal disease, may have a lower pain sensitivity caused by antipsychotic drugs and may have a suppressed gingival bleeding due to the excessive smoking. All of these can make patients seek treatments from dental medicine professionals less often and less than necessary [13-15]. Moreover, tremor and other motor symptoms or antipsychotic drugs side-effects in addition to orally specific ones, may affect the patients' ability to maintain oral hygiene [16]. Schizophrenia patients die from the same causes as the general population [17-20], however their expected life-span is 15 to 20 years shorter and their quality of life severely impaired [21]. Poor periodontal status further deteriorates patients' quality of life. In addition, a growing body of literature indicates there are possible effects of the somatic illness on the efficacy of treatment of psychosis itself [22-24]. Kalakonda et al. proposed the hypothetical model of bidirectional association between periodontal disease and schizophrenia in which psychosis and its treatment determines the poor oral hygiene, xerostomia and lower utilization of dental healthcare, while periodontal disease causes elevation in interleukins and in that way indirectly modulates the dopaminergic metabolism [5]. Consequently, periodontal status may affect schizophrenia treatment outcomes. The objective of our study was to investigate whether the association of periodontal/gingival status with schizophrenia treatment outcomes is moderated by patients' age. This is an especially important issue due to potential higher/lower efficacy of schizophrenia treatment in certain age groups. Keeping in mind serious consequences schizophrenia has on the health system, caregivers and patients' families, as well as overall poor quality of life of schizophrenia patients [25], this research can hopefully add to the control of the effect physical comorbidities have on the outcomes of psychiatric therapies thus making them more efficient.

Subjects and methods

Study design

We performed this single-center, prospective cohort study during 2018 at Psychiatric

Hospital 'Sveti Ivan', Zagreb, Croatia. The study protocol was approved by Ethics Committees of Psychiatric Hospital 'Sveti Ivan' and School of Dental Medicine, University of Zagreb, Zagreb, Croatia. All participants verified their informed consent to the principal investigator who did the enrollment. The study complied with the World Medical Association Declaration of Helsinki [26]. Zero time for the assembly of the cohort was the date of the hospital discharge because of achievement of remission criteria. Remission criteria were defined according to The Remission in Schizophrenia Working Group [27]: sum of eight Positive and negative syndrome scale (PANSS) items [28] lower than 21 and no result on any particular item >4. Eight items were: P1. Delusions, P2. Conceptual disorganization, P3. Hallucinatory behavior, N1. Blunted affect, N4. Social withdrawal, N6. Lack of spontaneity, G5. Mannerisms/posturing, G9. Unusual thought content. The follow up measurement was performed at third and sixth month after the enrollment.

Study population

Targeted population was the patients of both genders, diagnosed with schizophrenia (ICD-10: F20), 30-65 years old, discharged from the psychiatric hospital because of achievement of remission criteria, who had 2-5 previous relapses of schizophrenia, and recommended maintenance therapy with the 2nd generation antipsychotics. Schizophrenia diagnosis was established according to the DSM 5 outlines [29] that two or more of the following symptoms must be present for at least one-month time period: delusions, hallucinations, disorganized speech (e.g. frequent derailment or incoherence), grossly disorganized or catatonic behavior, negative symptoms (such as diminished emotional expression), and at least one of the symptoms must be delusions, hallucinations or disorganized speech. Exclusion criteria was acute suicidality. We chose a consecutive sample of patients by the order of their hospital discharge.

Sample size

Data on the expected prevalence of periodontal disease in schizophrenic patients were obtained from the Morales-Chavez et al. study conducted in 2014 [2]. A sample size of 59 is required in order to determine, with statistical significance, the minimal, clinically relevant association of periodontitis with the weakening of remission defined as a partial coefficient of determination of R^2=0.35, after the adjustment for ten potential confounders. The targeted statistical power was set at 80% and the level of statistical significance at 0.05. With the expected maximum of 10% lost for follow-up, the initially required sample size was 66. The power analysis was calculated using PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Treatment outcomes

The primary outcome was the PANSS total score at three months follow up, adjusted for the baseline PANSS score at hospital discharge. Secondary outcomes were positive, negative and general symptoms PANSS subscales scores at third month follow up, adjusted for their baseline values, and all PANSS scores at sixth month follow up.

Papilla bleeding index (PBI) measurement

The independent variable for analysis in this research was PBI. Bleeding was provoked by the periodontal probe withdrawing from the base to the tip of the papilla with a slight

pressure, first in the distal and then in the mesial sulcus. After the whole quadrant was prostrate, after 20-30 seconds, the bleeding intensity was estimated: 0. no bleeding, 1. only one blood point occurred after the stimulation, 2. there was a thin line of blood or several bloody points at the gingival edge, 3. the interdental triangle is more or less filled with the blood soon after probing; 4. profuse bleeding immediately after probing. The PBI was expressed as the sum of the bleeding values divided by the number of the examined papilla.

Pre-planned covariates

Pre-planned possible confounders whose effects we controlled by multivariable analysis were: gender, education, having children, number of household members, working status, monthly income per household member in EUR, current smoking of tobacco, body mass index (kg/m^2), having a chronic physical comorbidity, number of previous psychiatric hospitalizations, treatment with antipsychotics mono or combination therapy, treatment with benzodiazepines, antidepressants, mood stabilizers.

Statistical analysis

The primary analysis was performed using a Johnson-Neyman technique as implemented in the Andrew Hayes 'Process' macro release 2.16.2 [30, 31]. We used Hayes Model

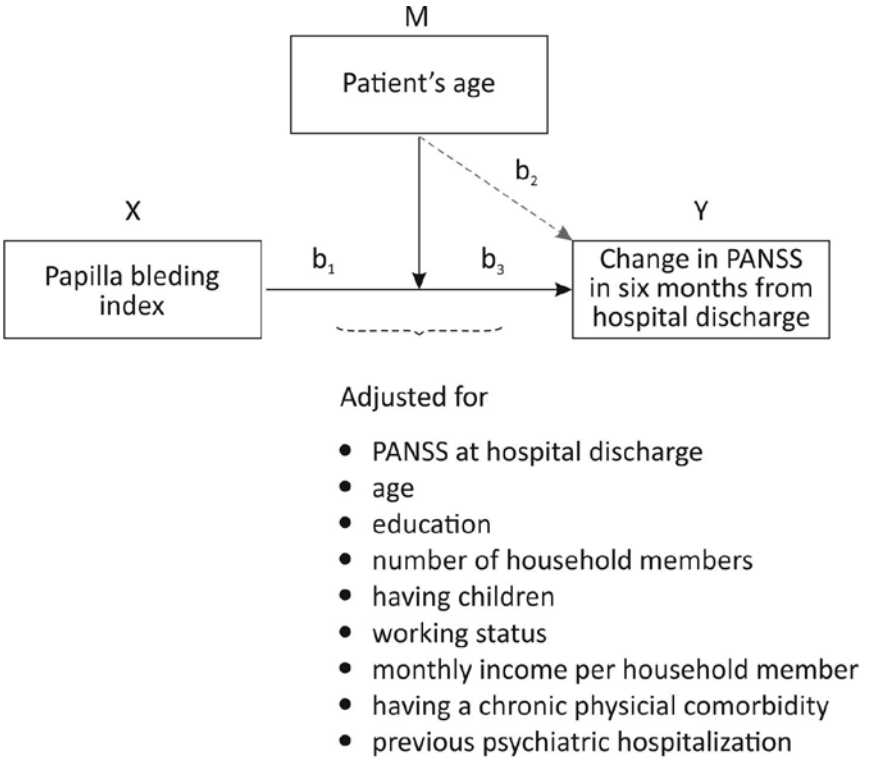

Figure 1. Analysis conceptual diagram; Andrew F. Hayes Model 1; conditional effect of X (PBI) on Y (change in PANSS) = $b_1 + b_3M$ (patients' age); estimates are based on setting covariates to their sample means

1 (Figure 1). Unstandardized linear regression coefficients were presented with their 95% confidence intervals (*CI*). All coefficients were adjusted for all preplanned confounders. Statistical significances of PBI and age interaction were not corrected for multiple testing because we interpreted only four analysis that were pre-planned and described in Statistical analysis plan. The significance of the difference in PANSS total score and particular subscales scores from the baseline to sixth month, was calculated by Wilcoxon Signed Ranks Test. Level of statistical significance was set at a two-tailed $p<0.05$ with CI set at 95% level. The analysis was carried out using the NCSS 12 Statistical Software (2018) (NCSS, LLC. Kaysville, Utah, USA).

Results

We enrolled 67 patients diagnosed with schizophrenia (Table 1), treated with the 2nd generation antipsychotics (Table 2), and discharged from the psychiatric hospital after achieving the first criteria for remission. The

Table 1. Participants sociodemographic, vital and life-style characteristics at hospital discharge (n=67)

	Baseline	
Gender		
man	37	(55.2)
woman	30	(44.8)
Age (years), median (*IQR*)	47	(40-53)
Education		
primary or secondary	52	(77.6)
university	15	(22.4)
Having children	19	(28.4)
Number of household members		
single	10	(14.9)
2	19	(28.4)
3	27	(40.3)
≥ 4	11	(16.4)
Working status		
employed	20	(29.9)
unemployed	24	(35.8)
retired	23	(34.3)
Monthly income per household member (EUR), median (*IQR*)	269	(169-337)
Smoking	35	(52.2)
Body mass index (kg/m^2), median (*IQR*)	27	(22-29)

Data are presented as number (percentage) of participants if not stated otherwise
Abbreviations: *IQR* = interquartile range

Table 2. Participants clinical characteristics at hospital discharge (*n*=67)

	Baseline	
Having a chronic physical comorbidity	21	(31.3)
Previous psychiatric hospitalizations,median (*IQR*)	5	(3-6)
Treatment with antipsychotics*		
monotherapy	48	(71.6)
combination	19	(28.4)
Particular antipsychotics†		
paliperidone	22	(32.8)
risperidone	15	(22.4)
aripiprazole	13	(19.4)
quetiapine	12	(17.9)
olanzapine	11	(16.4)
other antipsychotics‡	6	(9.0)
Benzodiazepines	29	(43.3)
Mood stabilizers	39	(58.2)
Antidepressants	14	(20.9)
Anticholinergics	2	(3.0)
Other, non-psychiatric pharmacotherapy		
proton pump inhibitors or H2 antagonists	7	(10.4)
other pharmacotherapy∫	9	(13.4)
Papilla bleeding index, median (*IQR*)	1.3	(1.00-2.21)
Papilla bleeding index (PBI)		
no bleeding	10	(14.9)
only one bleeding point	26	(38.8)
several isolated bleeding points or small blood area	20	(29.9)
interdental triangle filled with blood soon after probing	8	(11.9)
profuse bleeding when probing, blood spreads towards the marginal gingiva	3	(4.5)

Data are presented as number (percentage) of participants if not stated otherwise
Abbreviations: *IQR* = interquartile range
* All patients were treated with antipsychotics
† The sum exceeds 100% because of combination therapies
‡ Other antipsychotics: zuclopentixol, amisulpiride, ziprasidone, sulpiride
∫ Other pharmacotherapy included: beta blockers, diuretics, ACE inhibitors, statins, thyroid hormones, antidiabetics

cohort median age was 47 years (interquartile range 41 to 53); 30 (45%) of participants were women (Table 1). During the three and six months follow-up after the hospital discharge, total PANSS score as well as all three symptoms PANSS sub-scales' scores were significantly lowered, indicating the further improvement in treatment outcomes (Table 3). After the adjustment for all confounders the baseline PBI was significantly associated with the change of PANSS total score after three months, in patients younger than 45 years what was 48% out of all patients, and in the patients older than 61 what was 4% out of all patients. In the younger patient group, higher baseline PBI increased the risk for higher, less favorable PANSS score. In youngest 10% of patients, a unit difference in baseline PBI resulted in the 8.12 (95% CI 2.78-13.47; p=0.004) points higher total PANSS score three months later (Table 4). In the second youngest group (~ 40 years of age), a unit difference in baseline PBI resulted in 5.79 (95% CI 1.69-9.89; p=0.007) points higher total PANSS score at the 3rd month follow up. In the patients older than 61, the higher baseline PBI significantly lowered the risk for higher PANSS. After the adjustment for all 14 preplanned confounders, PBI was independently and significantly associated with the change in negative and general symptoms PANSS sub-scales' scores at third month follow up in the patients younger than 40, and in positive symptoms sub-scale in the patients younger than 34 (Table 4). At the sixth month follow up the results were comparable but less pronounced and PBI was not a significant predictor of the positive symptoms PANSS sub-scale score (data not shown). In all these cases the association was positive (unfavorable) (Figure 2). The association of baseline PBI and the general symptoms PANSS score was significant but reversed in the oldest age group (data not shown). In this

Table 3. Changes in PANSS score during three and six-months follow up after the hospital discharge (n=67)

	At hospital discharge		After three months		After six Months		Δ	(95% *CI*)	Δ%	*p*
PANSS total score	54	(47-64)	46	(40-53)	43	(39-53)	-11	(7-15)	-20%	<0.001
Subscales										
positive symptoms	14	(11-16)	10	(8-11)	9	(8-11)	-5	(4-6)	-36%	<0.001
negative symptoms	14	(12-17)	13	(11-14)	12	(10-14)	-2	(0.4-4)	-14%	0.015
general symptoms	26	(23-32)	23	(21-29)	23	(21-29)	-4	(2-6)	-15%	<0.001

Data are presented as median (interquartile range)
Abbreviations: PANSS = Positive and Negative Syndrome Scale; Δ = absolute difference in medians after six months and at hospital discharge; 95% *CI* = Bonett-Price 95% confidence intervals; Δ% = relative difference in medians calculated as (median after-six-months subtracted from the baseline value) and divided by the baseline value; *p* = two-tails statistical significance of the difference in medians calculated using Wilcoxon Signed Ranks test

Table 4. Adjusted* changes of PANSS score in three months after the hospital discharge at unit difference of baseline papilla bleeding index (PBI) in different patients' age percentiles (*n*=67)

	Change in PANSS at unit PBI change	(95% *CI*)	*p*
PANSS total score			
Age percentile (years)			
10th (34 years)	8.12	(2.78-13.47)	0.004
25th (39 years)	5.79	(1.69-9.89)	0.007
Median (47 years)	2.52	(-0.32-5.36)	0.081
75th (53 years)	-0.75	(-3.63-2.13)	0.601
90th (56 years)	-2.16	(-5.49-1.18)	0.200
Positive symptoms scale			
Age percentile (years)			
10th (34 years)	1.83	(0.06-3.60	0.043
25th (39 years)	1.32	(-0.04-2.67)	0.057
Median (47 years)	0.59	(-1.06-1.51)	0.205
75th (53 years)	-0.14	(-1.06-0.79)	0.768
90th (56 years)	-0.45	(-1.52-0.62)	0.405
Negative symptoms scale			
Age percentile (years)			
10th (34 years)	1.94	(0.50-3.38)	0.009
25th (39 years)	1.44	(0.34-2.54)	0.012
Median (47 years)	0.74	(-0.02-1.50)	0.056
75th (53 years)	0.04	(-0.73-0.80)	0.927
90th (56 years)	-0.27	(-1.16-0.63)	0.552
General symptoms scale			
Age percentile (years)			
10th (34 years)	4.12	(1.41-6.83)	0.004
25th (39 years)	2.87	(0.79-4.96)	0.008
Median (47 years)	1.13	(-0.32-2.57)	0.125
75th (53 years)	-0.62	(-2.09-0.85)	0.399
90th (56 years)	-1.37	(-3.08-0.33)	0.112

Data are presented as median (interquartile range). Abbreviations: PANSS = Positive and Negative Syndrome Scale; PBI = papilla bleeding index; 95% *CI* = 95% confidence intervals; *p* = two-tails statistical significance of the effect of PBI on PANSS score at particular patients' age percentile. * Coefficient were adjusted for baseline PANSS score (total, positive, negative, general respectively), gender, education, having children, number of household members, working status, monthly income per household member in EUR, current smoking of tobacco, body mass index (kg/m^2), having a chronic physical comorbidity, number of previous psychiatric hospitalizations, treatment with antipsychotics mono or combination therapy, treatment with benzodiazepines, antidepressants, mood stabilizers

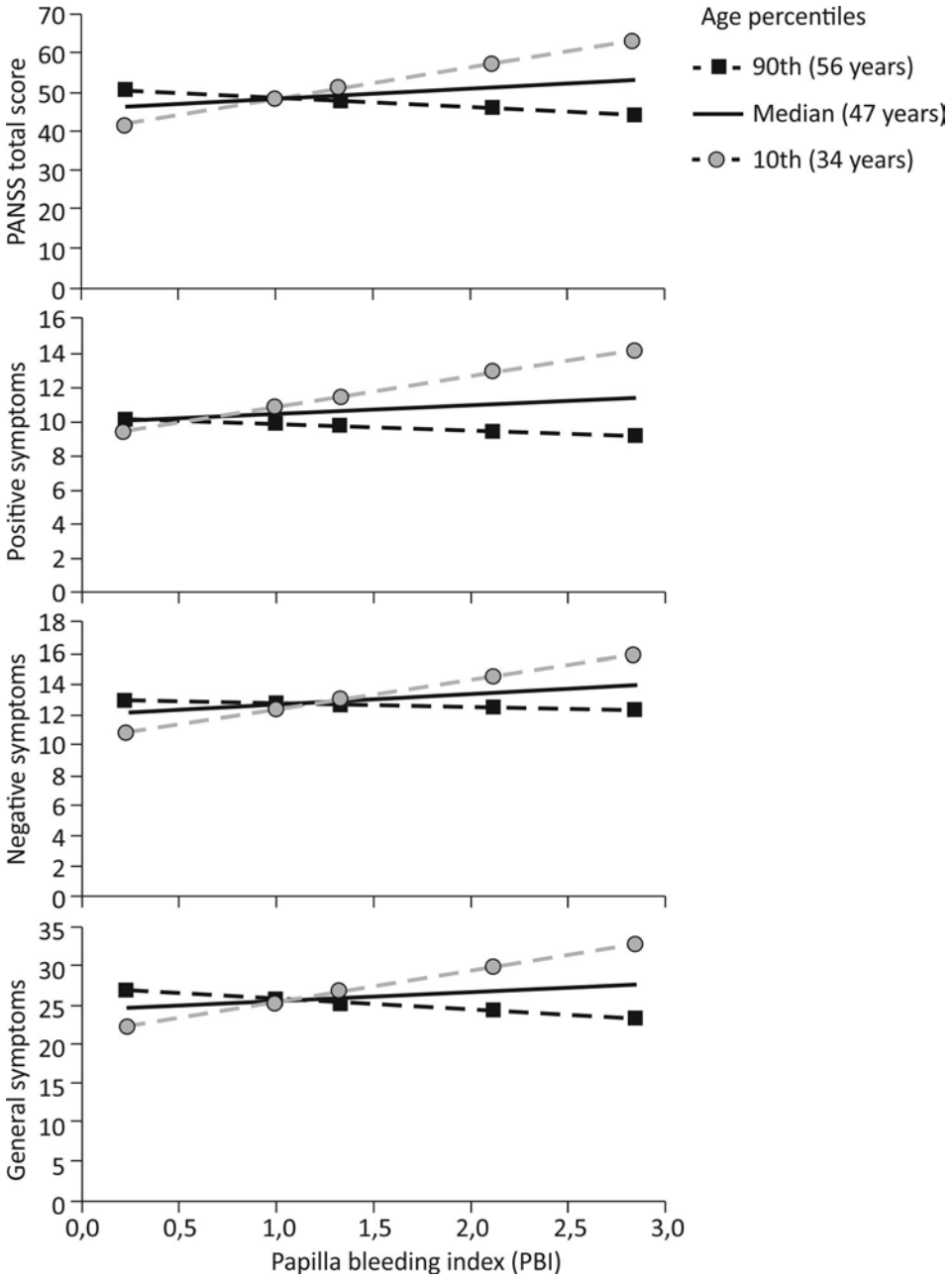

Figure 2. PANSS scores at three months after the hospital discharge by baseline papilla bleeding index (PBI) in different patients' age percentiles, adjusted for baseline PANSS score (total, positive, negative, general respectively), gender, education, having children, number of household members, working status, monthly income per household member in EUR, current smoking of tobacco, body mass index (kg/m^2), having a chronic physical comorbidity, number of previous psychiatric hospitalizations, treatment with antipsychotics mono or combination therapy, treatment with benzodiazepines, antidepressants, mood stabilizers (n=67)

age group, higher baseline PBI was associated with a more favorable outcome as measured by PANSS general symptoms scale.

Discussion

This prospective cohort study revealed that in schizophrenia patients, the association of PBI with the change in total PANSS score and in general symptoms subscale scores, was different in patients of different age indicating a correlation between periodontal/gingival health status and risk for poorer schizophrenia treatment outcomes during remission. More specifically, schizophrenia patients younger than 45 with worse periodontal status are at higher risk for poorer schizophrenia treatment outcomes and faster relapse (Table 4).

Objectively assessed oral health in patients diagnosed with schizophrenia is associated with patients age [32]. One explanation may be that the pathogenesis of schizophrenia is less associated with periodontal disease in older patients where, as it was described, periodontal status and inflammation exist partially independently of the psychosis. In younger patients, worse periodontal status may indicate worse underlying psychotic pathological processes that we are not able to assess by the baseline PANSS and so-defined achievement of criteria for remission.

In patients with higher negative symptoms the motivation and persistence in maintaining a proper oral hygiene may be impaired [4]. In addition, poorer periodontal status and more advanced average stage of a newly diagnosed periodontal disease in schizophrenia patients may partially be a consequence of the lower dental healthcare utilization [12]. Patients diagnosed with schizophrenia may erroneously interpret the symptoms of periodontal disease, may have a lower pain sensitivity caused by antipsychotic drugs and may have a suppressed gingival bleeding due to the excessive smoking [14, 15]. All of these can make patients seek treatments from dental medicine professionals less often and less than necessary. Moreover, tremor and other motor symptoms or antipsychotic drugs side-effects in addition to orally specific ones, may affect the patients' ability to maintain oral hygiene [16]. Regular dental exams are associated with better periodontal status and less oral health problems, which is not the case with regular visits to the general medicine practitioner [33]. Therefore there is a growing need to utilize routine, systematic oral health monitoring for psychiatric hospital inpatients [34].

There are some other limitations of our study. First, we performed this study in the single center in a highly urbanized country capital and in a specialized psychiatric hospital. Although we can only speculate about the extent and direction of the difference between this institution and a small, regional psychiatric ward in the less affluential regions with lower availability of periodontal healthcare, this possible limitation should be taken into account. Second, we used PBI as an assessment of periodontal/gingival status hoping that, if our hypothesis was correct, PBI relative simplicity and minimal invasiveness may encourage the introduction of periodontal exams in routine psychiatric practice. However, one has to keep in mind that more comprehensive indicators of periodontal status are available, e.g. periodontal inflamed surface area [35] or Bleeding on Brushing index [36], whereas PBI values mainly indicate the superficial inflammation of the gingiva. It is possible that internal validity of our study was slightly lower because of PBI limited usability as an indicator of periodontal status,

but on the other hand, the use of PBI gives our study high translational value. This result could potentially lead to implementation of a quick and non-expensive method for assessing periodontal status in schizophrenia patients and therefore indirectly lead to identification of patients that are at higher risk of disease relapse.

In conclusion, our study demonstrates the need for more rigorous and more frequent control of younger patients with worse periodontal status after hospital discharge not solely on the account of periodontal disease affect the patients' quality of life, but also for the improvement of efficacy of psychiatric therapies aimed toward the primary mental disorder.

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Conflict of Interest

The authors declare no conflict of interest.

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Povezica narušenog periodontalnog zdravlja u mlađih bolesnika sa shizofrenijom s pogoršanjem simptoma tijekom remisije: prospektivno kohortno istraživanje

Sažetak – Cilj ove prospektivne kohortne studije bio je istražiti postoji li razlika u povezanosti parodontnog statusa sa slabljenjem kvalitete remisije shizofrenije ovisno o dobi pacijenta. Ispitanici i metode:- Istraživanje je provedeno na susljednom uzorku od 67 pacijenata s dijagnosticiranom shizofrenijom koji su otpušteni iz bolnice radi ostvarenih kriterija remisije. Indeks krvareće papile (PBI, engl. *papilla bleeding index*) izmjeren je pri otpustu iz bolnice. Ispitanici su procijenjeni ljestvicom pozitivnih i negativnih simptoma (PANSS) pri otpustu iz bolnice, nakon tri i nakon šest mjeseci. Rezultati:- Nakon prilagodbe za potencijalne zbunjujuće varijable, indeks krvareće papile bio je značajno inverzno povezan s ukupnim PANSS rezultatom, te rezultatom subljestvica za negativne i generalne psihotične simptome kod pacijenata mlađih od 45 godina nakon tri i nakon šest mjeseci poslije otpusta iz bolnice, te s rezultatom subljestvice za pozitivne simptome kod pacijenata mlađih od 34 godine. Kod najmlađih 10% pacijenata, jedinična razlika u indeksu krvareće papile bila je za 8.12 (95% CI 2.78-13.47; p=0.004) viša za ukupni PANSS rezultat tri mjeseca nakon otpusta iz bolnice. Zaključci:- Naše je istraživanje pokazalo da mlađi pacijenti s lošijim parodontnim statusom imaju povećan rizik za lošiju kvalitetu remisije shizofrenije, odnosno brže pogoršanje simptoma tijekom remisije. Ovo istraživanje ukazuje na potrebu za pojačanom i češćom kontrolom mlađih pacijenata sa shizofrenijom koji imaju lošiji parodontni status nakon otpusta iz bolnice kako bi poboljšali kvalitetu života pacijenta kao i pridonijeli učinkovitijoj terapiji primarnog mentalnog poremećaja.

Ključne riječi: krvareća papila, PANSS, shizofrenija, parodontni status