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Original Scientific Paper



# MULTIDIMENSIONALITY AND MULTIDISCIPLINARITY OF CHRONIC NEUROPATHIC NONODONTOGENIC OROFACIAL PAIN

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SUMMARY – This study compared the self-assessed health-related quality of life (HRQoL) and degree of depression between patients with chronic neuropathic nonodontogenic orofacial pain (NOFP) and healthy controls using the Short Form Survey (SF-36) health status questionnaire and Beck Depression Inventory II (BDI-II). This controlled cross-sectional study included 100 patients and 119 healthy controls. The diagnostic protocol recorded the following: 1) pain intensity using a visual analog scale for the time of examination and during the one-month prior; 2) evidence for neuropathic pain using the Leeds questionnaire for neuropathic signs and symptoms (LANSS); 3) emotional status using the BDI-II; and 4) HRQoL using the SF-36 questionnaire. The mean LANSS score was 17.18 in the patient group and 0.0 in the control group. The mean BDI-II score was 18.31 in the patient group and 5.87 in the control group. The SF-36 scores were shown with Mann-Whitney U testing to have statistically significant differences between the patient and healthy control groups in all categories. Vitality was the only SF-36 category in which the patient group scored higher than the control group. In conclusion, NOFP significantly reduces the self-reported HRQoL. NOFP is also related to the development of depression, but does not affect its severity. There is a significant correlation between depression and low quality of life in patients with NOFP.

Key words: *Neuropathic pain; Orofacial pain; Nonodontogenic pain; Quality of life; Depression*

## Introduction

Pain is an unpleasant companion to most illnesses. While once considered a little more than a troublesome side effect, pain has recently been recognized as a significant health impact in and by itself. This acknowledgment has led to including pain as the fifth vital sign, and alleviation of pain as a basic human right[1]. Although acute pain can have a protective role by indicating injury or disease development, chronic neuropathic pain provides no real or potential benefits but only brings unnecessary suffering[2]. The treatment of orofacial pain (OFP) is often limited after it has developed into a chronic pain condition. The efficacy

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of treatment may be enhanced by early diagnosis and understanding of the mechanisms leading to pain development[3].

The exact prevalence of nonodontogenic orofacial pain (NOFP) is unknown, in part due to the unmet need for an effective classification system that can be applied in clinical settings. Epidemiological studies show that more than 22% of all Americans over the age of eighteen occasionally feel pain in the orofacial region[4], a prevalence similar to studies conducted in the UK[5,6], Germany[7] and regional pain centers in the United States[8,9]. The proportion of these results that can be attributed to neuropathic pain and NOFP remains unknown.

Depression is one of the most serious medical disorders affecting individual person. The World Health organization (WHO) had projected that depressive disorders would remain the leading cause of disability in the year 2020. According to the WHO, depression is going to be one of the largest challenges to public health[10,11]. The lifetime prevalence of depressive disorders has been estimated to range between 5% to 12% in men and 12% to 20% in women[12,13]. The presence of depression can worsen other medical illnesses, interfere with therapy, and increase negative impact on the quality of life in patients with higher pain intensity, longer duration of pain, reduced life control, use of passive coping life strategies, and intensive behavioral changes[14]. Depression and pain share biological pathways and neurotransmitters, often coexist, respond to similar treatments, and exacerbate one to another[15]. The severity of personal burden caused by disease cannot be completely described by using only numerical values of exact parameters. Methods of exact measurements of pain that would cover all aspects of this complex personal experience, which would be applicable in everyday practice have not been developed yet. The Health Related Quality of Life (HRQoL) is a term that goes beyond the impacts of direct manifestations of the disease, and takes into account various consequences that disease and treatment have on daily life and life satisfaction.

Orofacial region has great psychological significance given the importance of this region for speech, chewing, swallowing, and communication[16]. These connections may help explain why chronic NOFP is often associated with emotional, psychological and social disorders that impact HRQoL[17].

The aim of this study was to compare the self-assessed HRQoL and degree of depression between patients with NOFP and healthy controls using the Short Form Survey (SF-36) health status questionnaire and Beck Depression Inventory-II (BDI-II).

## Patients and Methods

### *Patient selection*

The research included 100 patients treated at the Department of Neurology and Outpatient Pain Clinic, Bjelovar General Hospital; Outpatient Pain Clinic, Sveti Duh University Hospital; and Department of Neurology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia, in a two-year period.

Subjects of both sexes, aged above 18 years, meeting inclusion criteria were recruited consecutively as they arrived to the Clinic. Study participants were selected amongst 136 patients with a clinical diagnosis of NOFP of various etiologies. Participants had to meet the criteria for a diagnosis of NOFP as defined by the International Headache Society (IHS) International Classification of Headache Disorders, Third Edition (ICHD-3)[18], and achieve at least 12 points on the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire[19,20]. All patients had a disease duration of at least six months as established by a neurologist during history taking and clinical examination. After discussing the aims and methods of the study, patients provided their signed informed consent to be included as study participants. The patients were not examined by a doctor of dental medicine, as pain of dental origin was not an aim of this study.

From the pool of potential subjects, 100 patients aged 18-75 years (72 women and 28 men) met the inclusion criteria for patient group in this study. The mean age of subjects in the patient group was 56.95±13.58 years. It was necessary to exclude 36 potential participants for a variety of reasons. In 14 patients, the LANSS questionnaire score was less than 12, which indicated that the neuropathic component was not likely the mechanism responsible for their pain. Long-term treatment with either antidepressants or antipsychotics excluded 7 patients from the study. Comorbid conditions involving functional deficits that could interfere with interpreting the directionality of pain and physical effects caused 6 patients to be excluded. Uncovering dental-related pain diagnoses led to exclusion of 4 patients. Failing to respond to one or more questions in the survey excluded 3 patients

and cognitive limitations excluded 1 patient. Hearing loss significant enough to prevent comprehension of oral questioning also caused 1 patient to be excluded from the study.

The control group comprised of 119 healthy age- and sex-matched subjects including 72 women and 47 men, mainly medical staff of the Bjelovar General Hospital and members of their families. The mean age of participants in the control group was 57.21±13.87 years. None of the control subjects had any psychiatric diagnoses or history of chronic pain in the orofacial region or another part of the body. Subjects regularly taking analgesic, antidepressant or antiepileptic drugs for any reason were excluded from the control group.

***Ethical considerations***

Patients and respondents were informed about the purpose of the research, the manner of its execution, and the fact that participation in the study was voluntary. Confidentiality and data protection was ensured with regard to all patient information. Respondents were required to indicate their consent by signing the informed consent form approved by the Ethics Committee of the participating institutions and the School of Dental Medicine, University of Zagreb. Respondents could withdraw from the study at any time and without explanation.

***Data collection***

The LANSS was used to evaluate the mechanisms contributing to NOFP in the patient group. A score of 12 or greater was required for inclusion in the patient group as it supports a diagnosis of neuropathic pain. The LANSS method consists of two parts, the first of which is verbal administration of the questionnaire in order to evaluate the qualitative characteristics of each patient's pain. The second portion of the LANSS is a brief clinical examination by a neurologist[21-25]. Not only does this step confirm the presence of sensory disorders and the capacity to evoke pain, it is also necessary to exclude the existence of functional deficits that could influence the patient perception of their quality of life. The questionnaire used in this study was two-way translated from English to Croatian by a licensed translator working with a neurologist.

The HRQoL was measured using a previously validated Croatian version of the SF-36 health survey[26]. This questionnaire measures the areas involved in the physical components of health such as physical functioning (PF), role limitation due to physical problems (RP), bodily pain (BP) and general health perceptions (GH). It also assesses the mental components of health including vitality (VT), social functioning (SF), role limitation due to emotional problems (RE), mental health (MH) and health changes referred to as health transitions (HT). Results are reported as a percentage of scale maximum (SM)[27-29].

The impact of pain on mental health was investigated by the Croatian version of the revised Beck Depression Inventory (BDI-II)[30]. Pain intensity was measured using a visual analog scale (VAS) with the range of responses from 0 ('no pain') to 10 ('worst pain ever').

***Statistical analysis***

All data are presented in tables. Smirnov-Kolmogorov test was used to analyze data normality and non-parametric statistical analysis was used in further analyses. Quantitative data were expressed as median and interquartile range, and nominal and categorical data as absolute frequencies and corresponding frequency. Differences between the groups in the parameters measured with continuous values were analyzed using Mann-Whitney U test. Differences between the groups in parameters measured as nominal and categorical values were analyzed using the $\chi^2$-test. Spearman's correlation coefficients were used to describe differences in certain clinical parameters. Ordinary least squares (OLS) regression was used to investigate the predictors of each SF-36 HRQoL domain. All p values less than 0.05 were considered significant. All statistical analysis was conducted using STATISTICA software version 10.0 (www.statsoft.com).

## Results

***Etiology of pain***

Unilateral pain in the trigeminal innervation area was the symptom in 88% of the patient group subjects. The second or third branch of the trigeminal nerve was involved in most cases and remained clinically stable for several months to several years. Paroxysmal pain was reported by 70% and persistent pain by 30% of patients. Postoperative or post-traumatic trigeminal neuralgia was the cause of OFP in 8% of the patient group. In this subgroup, surgical indication was facial trauma in six patients and tumor of the cerebellopontine angle in two patients. These patients reported on the periods of persistent and periods of

paroxysmal pain. The remaining 4% of test subjects suffered from persistent pain caused by post-herpetic neuralgia located in the innervation area of the ophthalmic branch. Basic demographic and clinical history data are shown in Table 1. The two groups were comparable considering age, marital status, education, employment status, smoking, and alcohol consumption. By definition, all of the test subjects and none of the control subjects experienced NOFP. As such, questions related to the presence and characteristics of NOFP could not be compared between the study groups.

***Quantitative characteristics of pain***

Subjects in the patient group experienced NOFP ranging in duration from 7 to 300 months, mean 46.52±42.69 months, median 36.0 months. In only

*Table 1. Sociodemographic and history data of OFP patients and healthy controls*

| Parameter | OFP | HC | p-value |
|---|---|---|---|
| Age (years; median) | 57.00 | 59.00 | 0.870* |
| Women, n (%) | 72 (72.00) | 72 (60.50) | 0.074** |
| Married, n (%) | 65 (65.00) | 96 (80.70) | 0.009** |
| Employed, n (%): | | | |
| Yes | 42 (42.00) | 57 (47.90) | 0.481** |
| No | 9 (9.00) | 5 (4.20) | |
| Retired | 47 (47.00) | 54 (45.40) | |
| Student | 2 (2.00) | 3 (2.50) | |
| Education, n (%): | | | |
| Elementary school | 16 (16.00) | 6 (5.00) | 0.034** |
| High school | 58 (58.00) | 86 (72.30) | |
| University | 26 (26.00) | 27 (22.70) | |
| Smoking, n (%) | 26 (26.00) | 42 (35.30) | 0.048** |
| Alcohol consumption, n (%) | 32 (32.00) | 57 (47.90) | 0.017** |

*Mann-Whitney U-test; **$\chi^2$-test; OFP = orofacial pain; HC = healthy controls

*Table 2. Pain indicators and medication in the group of OFP patients*

| Parameter | OFP |
|---|---|
| LANSS median (min-max) | 16.00 (12.00-24.00) |
| Pain duration (months; median, min-max) | 36.00 (7.00-300.00) |
| VAS 1 median (min-max) | 6.00 (0.00-10.00) |
| VAS 2 median (min-max) | 7.00 (1.00-10.00) |
| NSAID, n (%) | 61 (61.00) |
| Tramadol, n (%) | 34 (34.00) |
| Antiepileptics, n (%) | 20 (20.00) |
| Antidepressants, n (%) | 0 (0.00) |
| Antispasmodics, n (%) | 0 (0.00) |
| Strong opioids, n (%) | 0 (0.00) |

OFP = orofacial pain; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; VAS = visual analog scale; VAS 1 = mean VAS at the time of examination; VAS 2 = mean VAS in the previous month; NSAID = nonsteroidal anti-inflammatory drug

one patient, the disease lasted for about 25 years. In 99% of subjects, attacks of pain occurred 1-3 times *per* year. At least one of these attacks lasted for more than 30 days in 80% of test subjects. During the preceding month, 47% of subjects had experienced daily pain, 26% had experienced pain 2-6 times *per* week, and 25% had experienced several episodes of pain. Only 2% of respondents had not experienced pain in the preceding month. Present pain intensity, as recorded on the VAS, ranged from zero to 10, mean 5.78±2.47, median 6.0. VAS pain intensity in the preceding month ranged from 1 to 10, mean 7.04±1.95, median 7.0.

***Qualitative characteristics of pain***

The range of results obtained by the LANSS questionnaire was between 12 and 24 points, mean 17.18±3.82, median of 16.0.

***Medication***

Based on medical history, our study revealed that 61% of patients used nonsteroidal anti-inflammatory drugs (NSAIDs), while 34% used a weak opioid tramadol alone or in a fixed combination with paracetamol. Only 20% of the study participants were irregularly receiving an anticonvulsant. Medicines from the group of strong opioids, tricyclic antidepressants, corticosteroids and spasmolytics were not used by any respondent (Table 2). A minor number of patients reported using some other treatment such as acupuncture or biofeedback. Some respondents were not receiving any ongoing therapies.

***Mental health***

Results obtained by the BDI-II questionnaire in the control group ranged from 0 to 17, mean 5.87±6.19, median 2.0. In the patient group, the results ranged from 0 to 41, mean 18.31±9.92, median 18.5 (Table 3). According to the diagnostic criteria of the Croatian version of BDI-II, 71.43% of the control group showed no or minimum depression, whereas 28.57% had mild depression. In the patient group, 28.0% had minimal depression, 27.0% had mild depression, 27.0% had moderate depression, and 18.0% had severe depression.

***Health-related quality of life***

Each of the health areas assessed by the SF-36 questionnaire was shown by Mann-Whitney U test to differ statistically significantly between the patient and control groups (Table 3). The control group scored higher than the patient group in all areas of the SF-36 except for questions assessing vitality. The control group exceeded a total score of 60% of the scale maximum (SM) in 6 scale categories, while the patient group did not exceed 60% in any category. Table 3 shows the HRQoL parameters measured by the SF-36 scale. Figure 1 shows mean values of the HRQoL parameters in the group of OFP patients, healthy controls, and a randomized sample of 5,048 people from the general population of the Republic of Croatia[26].

***Correlations to health-related quality of life***

The interdependence between SF-36 categories and key parameters of other assessment instruments

*Table 3. SF-36 and BDI-II scores in OFP patients and healthy controls*

| SF-36 | OFP median (min-max) | HC median (min-max) | p-value |
|---|---|---|---|
| Physical functioning | 55.75 (5.00-100.00) | 89.71 (65.00-95.00) | <0.001 |
| Role physical | 31.00 (0.00-100.00) | 81.09 (0.00-100.00) | <0.001 |
| Bodily pain | 38.50 (10.00-90.00) | 75.71 (40.00-80.00) | <0.001 |
| General health | 40.69 (0.00-100.00) | 41.98 (30.00-72.00) | 0.001 |
| Vitality | 38.50 (0.00-90.00) | 31.64 (20.00-55.00) | <0.001 |
| Social functioning | 53.38 (0.00-100.00) | 75.74 (50.00-87.50) | <0.001 |
| Role emotional | 37.00 (0.00-100.00) | 63.03 (0.00-66.67) | <0.001 |
| Mental health | 52.84 (16.00-96.00) | 59.43 (40.00-64.00) | 0.002 |
| Health transition | 39.50 (0.00-100.00) | 61.13 (50.00-100.00) | <0.001 |
| BDI-II | 18.50 (0.00-41.00) | 2.00 (0.00-17.00) | <0.001 |

*Mann-Whitney U-test; OFP = orofacial pain; HC = healthy controls; SF-36 = Short Form Survey; BDI-II = Beck Depression Inventory-II

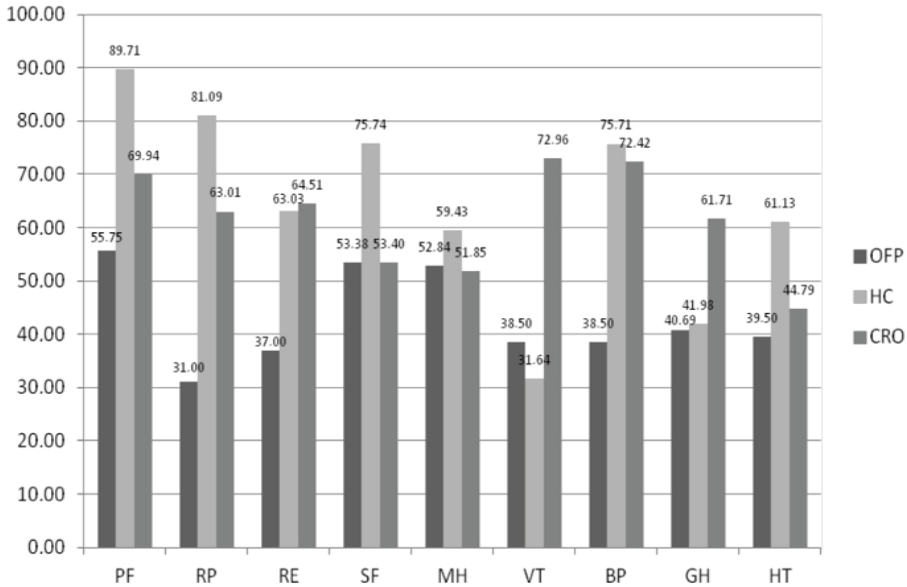


*Fig. 1. Mean values of the SF-36 scale dimensions in the groups of orofacial pain patients (OFP), healthy controls (HC) and randomized sample of the population of the Republic of Croatia (CRO)[27].*

PF = physical functioning); RP = role physical; RE = role emotional; SF = social functioning; MH = mental health; VT = vitality; BP = bodily pain; GH = general health; HT = health transition.

*Table 4. Correlation between the SF-36 domains and other parameters in OFP patients*

| | Spearman's correlation coefficient | Physical functioning | Role physical | Bodily pain | General health | Vitality | Social functio-ning | Role emotional | Mental health | Health transition | BDI-II |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BDI-II | Rho | -0.212 | -0.18 | -0.103 | -0.211 | -0.356 | -0.229 | -0.405 | -0.416 | -0.149 | |
| | p | 0.034 | 0.073 | 0.306 | 0.035 | <0.001 | 0.022 | <0.001 | <0.001 | 0.138 | |
| | n | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | |
| LANSS | Rho | -0.051 | 0.061 | -0.055 | -0.061 | 0.045 | 0.006 | 0.007 | -0.029 | 0.076 | 0.108 |
| | p | 0.612 | 0.548 | 0.589 | 0.549 | 0.658 | 0.952 | 0.945 | 0.772 | 0.45 | 0.286 |
| | n | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| VAS 1 | Rho | -0.271 | -0.077 | -0.32 | 0.01 | -0.279 | -0.144 | -0.363 | -0.277 | -0.161 | 0.302 |
| | p | 0.006 | 0.448 | 0.001 | 0.925 | 0.005 | 0.153 | <0,001 | 0.005 | 0.11 | 0.002 |
| | n | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| VAS 2 | Rho | -0.067 | -0.121 | -0.283 | -0.009 | -0.173 | -0.133 | -0.239 | -0.111 | -0.171 | 0.063 |
| | p | 0.507 | 0.232 | 0.004 | 0.93 | 0.084 | 0.185 | 0.016 | 0.272 | 0.088 | 0.535 |
| | n | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Duration of OFP (months) | Rho | -0.025 | -0.072 | -0.067 | -0.016 | 0.085 | 0.054 | -0.076 | 0.128 | -0.022 | -0.011 |
| | p | 0.802 | 0.478 | 0.507 | 0.874 | 0.402 | 0.595 | 0.45 | 0.205 | 0.826 | 0.915 |
| | n | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Age | Rho | -0.299 | -0.258 | -0.226 | -0.27 | -0.027 | -0.121 | -0.066 | 0.039 | 0.013 | -0.006 |
| | p | 0.002 | 0.01 | 0.024 | 0.006 | 0.788 | 0.229 | 0.513 | 0.698 | 0.901 | 0.949 |
| | n | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

VAS = visual analog scale; VAS 1 = mean VAS at the time of examination; VAS 2 = mean VAS in the previous month; OFP = orofacial pain; SF-36 = Short Form Survey; BDI-II = Beck Depression Inventory-II

*Table 5. Prediction of higher scores of each SF-36 HRQoL domain: multivariate linear regression models*

| | Physical functioning | | Role physical | | Role emotional | | Social functioning | | Mental health | | Vitality | | Bodily pain | | General health | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β* | p | β | p | β | p | β | p | β | p | β | p | β | p | β | p |
| Investigated group (compared to healthy controls) | -0.419 | 0.003 | -0.283 | 0.058 | 0.357 | 0.046 | -0.070 | 0.687 | 0.363 | 0.049 | 0.845 | <0.001 | -0.178 | 0.148 | 0.218 | 0.278 |
| Age (years) | -0.208 | 0.005 | -0.289 | <0.001 | -0.136 | 0.145 | -0.077 | 0.401 | 0.030 | 0.752 | 0.008 | 0.935 | -0.084 | 0.190 | -0.073 | 0.487 |
| Female gender | -0.053 | 0.318 | -0.029 | 0.600 | 0.039 | 0.558 | 0.016 | 0.808 | -0.043 | 0.534 | 0.046 | 0.523 | -0.025 | 0.591 | 0.121 | 0.108 |
| BMI (kg/m$^2$) | 0.029 | 0.609 | 0.030 | 0.621 | 0.046 | 0.522 | -0.084 | 0.231 | -0.150 | 0.043 | -0.050 | 0.520 | -0.069 | 0.162 | -0.135 | 0.096 |
| Smoking | 0.025 | 0.616 | 0.007 | 0.899 | 0.028 | 0.664 | 0.070 | 0.265 | 0.120 | 0.070 | -0.002 | 0.980 | 0.042 | 0.344 | -0.034 | 0.637 |
| Alcohol | 0.041 | 0.439 | 0.020 | 0.719 | -0.011 | 0.865 | 0.046 | 0.490 | -0.063 | 0.367 | 0.103 | 0.160 | 0.017 | 0.719 | 0.033 | 0.665 |
| Employment | 0.039 | 0.524 | -0.052 | 0.418 | 0.142 | 0.066 | 0.009 | 0.907 | 0.111 | 0.159 | 0.138 | 0.097 | -0.008 | 0.878 | 0.037 | 0.672 |
| Marriage | 0.030 | 0.566 | -0.040 | 0.474 | 0.097 | 0.149 | 0.085 | 0.199 | 0.184 | 0.008 | 0.112 | 0.125 | 0.025 | 0.588 | 0.063 | 0.407 |
| Number of children | -0.034 | 0.532 | 0.026 | 0.653 | 0.030 | 0.664 | -0.001 | 0.990 | 0.045 | 0.527 | 0.030 | 0.689 | 0.041 | 0.392 | 0.025 | 0.752 |
| Education level | -0.023 | 0.654 | -0.140 | 0.012 | 0.016 | 0.813 | -0.034 | 0.598 | 0.043 | 0.529 | 0.070 | 0.325 | -0.051 | 0.264 | 0.087 | 0.240 |
| Mean VAS during last month | -0.147 | 0.287 | -0.163 | 0.264 | -0.541 | 0.002 | -0.329 | 0.056 | -0.342 | 0.059 | -0.480 | 0.012 | -0.536 | <0.001 | -0.124 | 0.529 |
| BDI-II score | -0.178 | 0.006 | -0.239 | <0.001 | -0.352 | <0.001 | -0.174 | 0.030 | -0.407 | <0.001 | -0.175 | 0.046 | -0.120 | 0.033 | -0.237 | 0.010 |
| r2 | 0.566 | | 0.515 | | 0.304 | | 0.333 | | 0.263 | | 0.187 | | 0.67 | | 0.117 | |
| Model significance | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | <0.001 | | 0.019 | |

*Standardized coefficient β; VAS = visual analog scale; BDI-II = Beck Depression Inventory-II

was investigated using the Spearman's correlation coefficient. The potential correlates investigated were BDI-II, LANSS, current mean VAS, previous month mean VAS, duration of OFP, and patient age (Table 4).

Depression, as expressed by the BDI-II value, was found to have a statistically significant correlation with the SF-36 domains of physical functioning, bodily pain, general health perceptions, vitality, social functioning, role limitation due to emotional problems, and mental health. There was no significant correlation between BDI-II results and role limitation due to physical problems or health transitions.

The mean intensity of pain at the time of testing as measured by VAS was found to statistically significantly correlate with the BDI-II score. There was also a statistically significant correlation between pain intensity at the time of testing and the SF-36 scales of physical functioning, bodily pain, vitality, role limitation due to emotional problems, and mental health. In contrast, pain intensity in the prior month only had a statistically significant correlation to the bodily pain scale.

Patient age was statistically significantly correlated with the domains of physical functioning, role limitation due to physical problems, bodily pain, and general health perception. Disease duration lacked any statistical correlation with SF-36 or BDI-II results. LANSS scores were also found to be statistically unrelated to all SF-36 categories.

Table 5 shows multivariate linear regression models for prediction of each SF-36 QoL domain. All regression models were statistically significant, with explained variance of dependent variable ($r^2$) from 11.7% (general health perception) to 67.0% (pain). Significant predictor(s) (controlled for all other predictor variables used in the model) were as follows:

1) for higher physical functioning score, belonging to healthy group, younger age and lower BDI-II score;
2) for higher role limitation due to physical problems score, younger age, lower educational level and lower BDI-II score;
3) for higher role limitation due to emotional problems score, lower mean VAS and lower BDI-II score;
4) for higher social functioning score, lower BDI-II score;
5) for higher mental health, belonging to patient group, lower BMI, living with partner and lower BDI-II score;
6) for higher energy vitality score, belonging to patient group, lower mean VAS score and lower BDI-II score;
7) for higher pain score, lower mean VAS score and lower BDI-II score; and
8) for higher general health perception, the only predictor was lower BDI-II score.

In conclusion, BDI-II score was a common significant predictor for all HRQoL domains with highest β coefficient for mental health.

## Discussion

The main objective of any healthcare treatment is to improve the quality of life. This goal is attained primarily through slowing down and reversing the pathophysiological processes but can also be achieved through lasting relief from severe symptoms such as pain. Measurements of HRQoL outcomes can provide an insight into the impact of disease and its treatment on daily lives of those affected. Such measures are key elements in the evaluation of health care, and may be used as outcomes in clinical trials.

Through this cross-sectional controlled study, we wanted to explore the category of patients who complained of pain with neuropathic characteristics in the orofacial region. Our study analyzed data on 100 patients with OFP and 119 healthy controls. The patient group consisted mostly of elderly adults, predominated by women[31]. Such a tendency towards increasing incidence and prevalence of chronic pain in the elderly can be expected to continue and grow. As the population ages and life expectancy increases, an ever greater number of individuals will be living with chronic conditions. Another factor that can contribute to an increased prevalence of chronic pain is the growing use of therapeutic methods such as chemotherapy that can lead to the development of neuropathic pain[32]. The known risk factors for the development of NOFP include chronic physical pain, patient age, gender, and other psychosocial factors[33-37]. Gender in particular has proved important in a number of epidemiological studies on chronic pain. Women have been shown to experience a higher prevalence of chronic pain syndromes[38-40], and perceive more pain over longer time periods than men[41]. Gender differences have also appeared when assessing the efficacy of analgesic therapy. Animal models have demonstrated that a given dose of opioids produces a

greater analgesic effect in female than in male animals. At this point, however, it is not known whether the same conclusion can be made regarding gender differences in the human response to this important class of pain-relieving drugs[42].

***Measurement of pain***

Pain is a complex experience that includes a myriad of sensory and emotional factors. Despite this, the most common method of measuring pain while working with patients is simply asking "Do you feel better?" Although medical science has developed advanced methods of pain control, that progress has not been accompanied by improved methods for objective pain measurement[43-45]. Understanding the underlying etiology is the foundation of the traditional classification of neuropathic pain prevalent in clinical, experimental and pharmacological studies. While this approach remains commonplace, further research is needed on this topic. Although questionnaires are included in the diagnostic criteria in a number of clinical studies on pain[46,47], validated diagnostic criteria are notably lacking from the process of identifying and treating pain in clinical settings. This lack of clear guidelines likely explains the poor recognition of neuropathic pain, and its subsequently improper treatment. While a small number of practicing physicians do use questionnaires to help identify possible neuropathic pain, these tools often do not provide information regarding etiology. As such, complete diagnostic evaluation remains essential to complete the clinical picture of chronic pain.

Despite significant progress in the identification of pathophysiological mechanisms underlying acute and chronic pain, this knowledge has not led to the development of more efficient, safer, or better tolerated analgesics. For most conditions that cause chronic pain, opioid and NSAIDs are currently the most commonly recommended therapies[48]. Although focused only on neuropathic pain, our study found that patients were most often treated using just these therapies (Table 2). The biggest reason for this failure is the incongruity between treatment algorithms recommended by professional societies and medications that are (not) covered by insurance providers. The socioeconomic crisis is taking a toll even in this sensitive area.

***Mental health***

Depression, anxiety, and other affective disorders are often associated with pain and can alter its intensity. Chronic pain is a disorder with physical, mental, social and spiritual components, as well as one of the best examples of the interconnectedness of body and mind in clinical medicine[14]. Mood disorders may contribute directly to the experience of chronic pain but can also exacerbate painful, pre-existing physical ailments. These comorbid conditions can have a significant impact on the diagnosis and treatment of pain disorders. In our study, approximately equal percentages of subjects in both the patient and control groups met the diagnostic criteria for mild depression. The only participants whose scores identified them as having either moderate or severe depression were subjects with OFP. According to the criteria of the Croatian version of the BDI-II, a person scoring 0 to 11 points is not depressed and is included in the category of minimal depression[30]. More than 70% of the healthy controls in our study fell into this category. Having scored between 12 and 19 points, slightly less than 30% of healthy controls were categorized as suffering from mild depression. Conversely, only 28% of subjects with OFP had minimal depression and 27% had mild depression. Another 27% of patients had moderate depression, while 18% suffered from severe depression. No relationship was found between any of the qualitative characteristics of neuropathic pain and the severity of depressive symptoms.

The most frequent reports of life dissatisfaction in our study were found in those individuals with either mild or severe depression. Only half of the subjects with OFP, irrespective of depression category, reported having a satisfactory quality of life associated with the area of physical functioning. In contrast, all subjects in the control group had either minimal or mild depression and rated their quality of life as satisfactory. Our results support the growing body of evidence that chronic pain is related to the development of depression and deteriorates the quality of life.

***Health-related quality of life***

The HRQoL is a concept that extends beyond direct manifestation of illness. It takes into account the various effects that disease and treatment can have on daily activities, important contributors to a sense of satisfaction with life. The interrelated nature of health and quality of life is well captured by one of the most commonly used questionnaires to measure quality of life, the SF-36 health status questionnaire. In each of the areas measured by the SF-36, Mann-Whitney U test revealed statistically significant differences between the patient and control groups of subjects in

our study (Table 3). With the exception of vitality, all scales showed higher mean index scores in the control group as compared with the patient group. Notably, those in the control group obtained a score equal to or greater than 60% SM in six of nine categories, while the patient group did not exceed 60% in any category. These results suggest that OFP negatively affects the quality of life in all aspects measured by the SF-36 questionnaire.

The quality of life results found in our study are consistent with findings of a large survey conducted in our country little more than a decade before[26]. The large Croatian survey was conducted in a post-war period of transition from 1997 to 1999 and found that respondents rated their quality of life as unsatisfactory in the areas of vitality, general health perceptions, and health transitions. Similarly, subjects in the control group in our study, which was conducted more than ten years later, reported an unsatisfactory quality of life in relation to the areas of vitality, general health perceptions, and mental health (Fig. 1). These results suggest that low ratings in some areas may be a characteristic of the general population.

The area of vitality deserves particular attention before drawing any conclusions from SF-36 results. The respondents to the large Croatian survey reported a mean vitality score of 51.85% SM, whereas our study found a 31.64% SM vitality score for healthy controls and 38.50% SM for patients. Thus, all three groups reported their quality of life related to vitality as unsatisfactory with a trend towards decreasing vitality after the post-transition period. Interpretation of these and other findings in relation to the area of vitality may be confounded by several important factors. That of main concern is that vitality lacks an unambiguous definition. Some interpretations of vitality describe it as a mood or subjective state. The term vitality denotes the presence of energy, enthusiasm, and the lack of fatigue or exhaustion. This definition makes vitality reliant on energy[49], another term that currently lacks an appropriate definition for research purposes. One example attempting to expound on vitality and energy comes from Selye who described individuals as having a limited reservoir of 'adaptation energy'. This energy is used to cope with environmental stressors and disease[50,51] in a manner differing from calorically derived metabolic energy. While the nature of this adaptive energy remains unknown, its working definition supports a conclusion that both our subjects and the respondents to the large Croatian survey lack sufficient adaptive energy. It may be that illness, poverty, unemployment, injustice, sedentary lifestyle, poor diet, or other environmental stressors exhaust the coping mechanisms of this population and deplete their vitality.

Several questionnaires have been developed in an attempt to better measure vitality, the most common being isolated use of the vitality subscale from the SF-36 questionnaire[52]. Another potentially confounding factor is that no questionnaires currently distinguish between physical and psychological forms of vitality. Therefore, a state of exhaustion may represent a sense of physical effort in the context of poor physical fitness or psychological demands and stressors in individuals with poor coping mechanisms[53]. Differentiation between poor physical fitness and other types of exhaustion could become important in understanding the role of vitality in health research. While it is quite likely that poor physical health reduces vitality, most studies related to this topic are cross-sectional and are therefore unable to assess causality. In order to unravel any corollaries or causation between vitality and health, it is necessary to conduct longitudinal studies predicting health outcomes based on well-defined vitality measures.

## Conclusion

Our research has shown that NOFP is related to development of depression but not the severity of depression. NOFP also significantly affects the HRQoL as measured by the SF-36 questionnaire. There is a significant association between depression and low quality of life in patients with OFP. In the absence of exact methods, screening questionnaires can be used as the first step in the diagnosis of neuropathic pain but these findings must be combined with the results of clinical examination and other diagnostic methods as part of a comprehensive effort to discover the etiology of neuropathic pain.

Success of diagnosis and treatment of chronic neuropathic pain can only be achieved by multidisciplinary approach taking into account all aspects of the biopsychosocial model of pain. Future research should establish a comprehensive, sensitive and specific diagnostic classification scheme for all types of OFP. An integral part of this work should be the quality of life indicators, which would provide additional data on clinical outcomes.

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Sažetak

## MULTIDIMENZIONALNOST I MULTIDISCIPLINARNOST KRONIČNE NEUROPATSKE NEODONTOGENE OROFACIJALNE BOLI

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Cilj istraživanja bio je usporediti procijenjenu sa zdravljem povezanu kvalitetu života i stupanj depresije ispitanika s kroničnom neuropatskom neodontogenom orofacijalnom boli (NOFP) s rezultatima zdravih ispitanika kontrolne skupine. U studiju je uključeno 100 ispitanika srednje dobi od 56,95±13,58 godina s kliničkom dijagnozom NOFP u trajanju od najmanje šest mjeseci i 119 zdravih ispitanika srednje dobi od 57,21±13,87 godina koji su bili kontrolna skupina. Primijenjen je standardni dijagnostički protokol: 1) određivanje intenziteta boli vizualno numeričkom ljestvicom u trenutku ispitivanja te tijekom proteklоga mjeseca; 2) procjena prisutnosti neuropatske boli Leedskim upitnikom neuropatskih znakova i simptoma (LANSS); 3) procjena emocionalnog statusa Beckovim inventarom depresije II (BDI-II); 4) procjena o zdravlju ovisne kvalitete života (HRQoL) upitnikom SF-36. Prosječan rezultat LANSS za skupinu oboljelih iznosio je 17,18, a za kontrolnu skupinu 0. Prosječan rezultat BDI-II u skupini oboljelih bio je 18,31 prema 5,87 u kontrolnoj skupini. Mann-Whitneyjevim U testom svaka od devet kategorija koje mjere SF-36 statistički se značajno razlikovala između bolesnih i zdravih ispitanika. U svim kategorijama osim jedne (vitalnost) kontrolna skupina imala je viši indeks u odnosu na skupinu s NOFP. Rezultat kontrolne skupine bio je veći od 60% u šest od devet kategorija, dok skupina oboljelih nije prelazila granicu od 60% niti u jednoj kategoriji. Kronična NOFP uzrokuje depresiju i utječe na gotovo sve odrednice kvalitete života mjerene upitnikom SF-36. Nije dokazan utjecaj na stupanj depresije. Postoji jaka povezanost između depresije i snižene kvalitete života oboljelih od NOFP.

Ključne riječi: *Neuropatska bol; Orofacijalna bol; Neodontogena bol; Kvaliteta života; Depresija*