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Prognostic factors, symptom evolution, and quality of life of posttraumatic trigeminal neuropathy

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Abstract

Neurosensory disturbances (NSDs) caused by injury to the trigeminal nerve can affect many aspects of daily life. However, factors affecting the persistence of NSDs in patients with posttraumatic trigeminal neuropathies (PTTNs) remain largely unknown. The identification of such risk factors will allow for the phenotyping of patients with PTTNs, which is crucial for improving treatment strategies. We therefore aimed to identify the prognostic factors of NSD persistence, pain intensity, and quality of life (QoL) in patients with PTTNs and to use these factors to create a prognostic prediction model. We first performed a bivariate analysis using retrospective longitudinal data from 384 patients with NSDs related to posttraumatic injury of the trigeminal nerve (mean follow-up time: 322 ± 302 weeks). Bivariate and multivariate analyses were performed. The multivariable prediction model to predict persistent NSDs was able to identify 76.9% of patients with persistent NSDs, with an excellent level of discrimination (area under the receiver operating characteristic curve: 0.84; sensitivity: 81.8%; specificity: 70.0%). Furthermore, neurosensory recovery was significantly associated with sex; injury caused by local anesthesia, extraction, third molar surgery, or endodontic treatment; and the presence of thermal hyperesthesia. Pain intensity and QoL analysis revealed several factors associated with higher pain levels and poorer QoL. Together, our findings may aid in predicting patient prognosis after dental, oral, and maxillofacial surgery and might lead to personalized treatment options and improved patient outcomes.

Keywords: Posttraumatic trigeminal nerve injury, Neuropathic pain, Prognosis, Predictive factors, Neurosensory profile

1. Introduction

The trigeminal nerve has the largest representation in the human sensory cortex, reflecting the disproportionate sensory input that comes from the orofacial region. The reception of sensory input from trigeminal dermatomes protects vital processes that underpin our survival.[34] Pain in the trigeminal nerve area interferes with eating, speaking, sleeping, applying makeup, shaving, kissing, tooth brushing, and drinking—just about every daily routine that we take for granted. As a result, this has a significant negative effect on patients' self-image, QoL, and psychology.[9] Renton et al. reported that 36% of patients with posttraumatic trigeminal neuropathic pain (PTNP) show signs of depression and a similar proportion of patients have a clinically significant anxiety level.[26,41] Apart from patient morbidity, there is also a societal and economic burden caused by reduced labor force participation and absenteeism.[23]

Posttraumatic neuropathies can be painful or nonpainful and are an increasingly recognized postsurgical issue for patients.[20] In the orofacial region, these conditions have been defined by the International Classification of Orofacial Pain (ICOP), which is endorsed by both the International Headache Society and the International Association for the Study of Pain.[18] Posttraumatic trigeminal neuropathic pain may arise after injury to the sensory nerves. It can cause sensory abnormalities associated with hyposensitivity or hypersensitivity, with allodynia and hyperalgesia. When no neuropathic area is evident, patients may fit the criteria of chronic postsurgical pain (CPSP). This is a well-recognized complication after routine surgery, with significant rates of pain affecting patients who have undergone limb amputation, breast surgery, thoracotomy, and cardiac surgery.[20] However, questions remain as to whether CPSP and PTNP are different phenotypes of the same condition.[15]

Risk factors for CPSP are well-established and include both patient-related and surgery-related factors.[19] To date, there is limited evidence regarding the presentation and outcome of patients with posttraumatic trigeminal neuropathies (PTTNs), and potential prognostic predictors have not been thoroughly investigated.[3,4] Likely predictors for chronification can be identified

in the preoperative, intraoperative, and postoperative periods and cover 6 broad domains: genetic, demographic, psychosocial, pain, clinical, and surgical factors.[6,37] Most studies have focused on the preoperative risk factors of trigeminal neurosensory disturbances (NSDs).[10,11,33,47] The identification of these risk factors is important because they may allow the phenotyping of patients in the future. This phenotyping is crucial if we wish to improve treatment outcomes.[14] As yet, there have been no large longitudinal studies investigating the outcomes of posttraumatic trigeminal nerve injuries. Furthermore, prognostic prediction models are lacking.

The aim of this study was to identify prognostic factors in patients with PTTNs by running a multivariable analysis based on the retrospective longitudinal data of a large patient cohort from a tertiary referral center in Belgium (University Hospitals Leuven) and to build a prognostic prediction model using these data. We aimed to determine if and when NSDs persist and how symptoms evolve over time. In addition, we aimed to predict quality of life (QoL) and compare clinical features, pain quality, and characteristics between low and high pain intensity cohorts.

2. Methods

2.1. Source of data

The data used in this study originated from the TrigNerVeBeUK (TNVBUK) registry. The study protocol was approved by the institute's ethical committee (S62333, ClinicalTrials.gov identifier NCT04612855). The study was conducted according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.[8] Data were retrieved from patient charts at the Department of Oral and Maxillofacial Surgery and the Orofacial Pain Clinic between October 2018 and January 2019.

2.2. Patient selection

The charts of patient visiting between January 2010 and October 2018 were screened for posttraumatic (including iatrogenic) injury to branches of the trigeminal nerve. No age restrictions were made. Inclusion criteria were as follows: presentation with a posttraumatic injury of the trigeminal nerve or its branches and a clinical neurological diagnosis of a neurosensory deficit in the distribution of the trigeminal nerve according to previously described methods,[34] which are summarized in section 2.3. Patients were excluded if the deficit presented in a region outside of the innervation zone of the trigeminal nerve or if the follow-up time was less than 3 months. Patients diagnosed with neurosensory disturbances (NSDs) after orthognathic surgery were excluded. Orthognathic surgery patients are tracked in a different care pathway at the authors' clinic. Including these patients would result in introducing selection bias.

2.3. Clinical assessment method

The neuro-assessment protocol was conducted according to previously reported algorithms[28,34] and included qualitative sensory testing by mapping the neurosensory disturbance over the affected dermatome using blunt forceps (intraorally and/or extraorally, depending on the affected nerve). This was performed using a running needle technique from normal towards neuropathic area. The patient was asked to raise their hand as soon as the sensation was not perceived normal. The

borders were marked with a pen to allow the next assessments to be conducted within the neuropathic area vs the contralateral side. In case of bilateral involvement, the adjacent dermatome served as control. Light touch assessment was performed using a cotton bud (to assess subjective function and the presence of mechanical allodynia) and sharp or blunt discrimination by using a dental probe (to assess mechanical hyperalgesia and hyperpathia). Each stimulus was presented 5 times and 2 scores of 5 were noted if the patient correctly identified the presence of light touch and discriminated correctly between sharp or blunt. It was noted whether mechanical allodynia or hyperalgesia was present. Two-point discrimination to assess mechanoperception was conducted using a staircase method of levels starting with closed calipers and stepwise increasing separation of 1 mm until a reliable level was reached. If a thermal component (hot or cold allodynia or hyperalgesia) was described, this was also recorded. In addition, hyperesthesia (allodynia, hyperalgesia, and hyperpathia) or hypoesthesia (reduced sensation or anesthesia) was recorded. An NSD was defined as abnormal according to the algorithm proposed by Miloro.[28] This meant an abnormal or absent response to any of the conducted sensory tests compared with the contralateral side or the adjacent trigeminal dermatome in case of bilateral involvement. Two-point discrimination was considered abnormal if it exceeded 15 mm.[35] Neuropathic pain was diagnosed in accordance with a study by Finnerup et al.[12]

Patients were categorized into painful PTTN and nonpainful PTTN groups based on the recent ICOP criteria for PTNP.[18] Patients with nonpainful PTTN fulfilled all ICOP criteria except criterion A: pain in a neuroanatomically plausible area within the trigeminal distribution.

Based on the symptoms reported during history taking and the clinical findings, including qualitative neurosensory testing, patients were further stratified into the following sensory profiles: sensory loss, thermal hyperalgesia or allodynia (hereafter referred to as "thermal hyperesthesia"), mechanical hyperalgesia or allodynia (hereafter referred to as "mechanical hyperesthesia"), and combinations (hereafter referred to as "mixed").

2.4. Predictors

Preoperative predictor variables included age, sex, and smoker status. The number of other pain diagnoses in a patient's history was considered a separate variable.

Perioperative variables included the different affected trigeminal nerve branches (the inferior alveolar nerve, the maxillary nerve or its infraorbital and superior alveolar terminal branches, or the lingual nerve) and the initiating event (local anesthesia, third molar surgery, tooth extraction, endodontic treatment, or dental implant placement).

Postoperative variables were the duration of symptoms (constant or intermittent), presence of pain (yes/no), pain visual analog scale (VAS) score (Likert scale ranging from 0 to 10, with 0 meaning no pain and 10 meaning the most severe pain imaginable), and sensory profile (sensory loss, thermal hyperesthesia, mechanical hyperesthesia, or mixed). Only treatments initiated for their condition were considered, and these were further categorized into any treatment (yes/no), systemic (yes/no), topical (yes/no), and surgical (yes/no). Finally, QoL was assessed at the end of the follow-up period using the EQ-5D-5L questionnaire, which considers 5 domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a

5-point ordinal scale (0: no problems; 1: slight problems; 2: moderate problems; 3: severe problems; and 4: extreme problems). These domains were dichotomized into no problems (score 0) and any problems (scores 1-4). Patients also indicated their self-rated health on a VAS, from 0 (worst) to 100 (the best health they could imagine).

2.5. Prediction models of outcome variables

Three regression models were constructed. First, time to complete symptom resolution was predicted. For this outcome, the duration of symptoms (in weeks) since the initiating event was calculated. Patients who continued to experience NSDs 3 months postsurgery were considered to have persistent NSDs; if not, they were considered to have temporary NSDs, as suggested by the International Association for the Study of Pain and International Headache Society criteria.[17,38] Patients were seen on a regular basis until symptom resolution. If no symptom resolution occurred, most patients were followed up on a three-month basis until the end of data accrual. Improvements were recorded from the last follow-up visit on a categorical scale as worse, same, some improvement, improved a lot but still has symptoms, or improved a lot with no more symptoms. No differentiation was made between improvement in pain or in NSD. All clinical observations were made by the clinical staff, who were independent from the investigators.

In a second model, we predicted QoL using the EQ-5D-5L self-rated health VAS score at final follow-up. The third model aimed to predict pain intensity at the final follow-up moment.

2.6. Comparison of low vs moderate to severe pain intensity cohorts

Based on the pain VAS score (ranging from 0 to 10) assessed during the last follow-up moment, patients were categorized into low (<5) or moderate to severe (≥5) pain intensity cohorts. This allowed for a comparison of clinical features, pain quality, and pain characteristics between both cohorts.

2.7. Sample size and missing data

No similar studies have been conducted to be able to estimate the incidence and frequency of persistent NSDs in our study population. However, based on simulation studies, a minimum of 10 events per variable are required, rendering a sample size of 230 patients.[31,46] Missing data were handled by listwise exclusion to build the logistic regression model after verifying the randomness and frequency of missing values.

2.8. Statistical analysis

All data were handled by a certified statistician using SPSS version 25.0 (IBM Corp, Armonk, NY).

The exploratory data analysis consisted of 5 steps. (1) Descriptive data analysis by calculating the means, SDs, counts, and frequencies. (2) Bivariate analysis, for which the Kendall tau-b correlation was used to determine the relationship between continuous variables and the outcome variables: persistence of NSD and pain intensity. A chi-squared test for association was conducted between binomial variables. If expected cell counts were less than 5, a Fisher exact test was used. Strength of association was evaluated using the Cramér V test. (3) Multivariable modeling by performing binomial logistic

regression to ascertain the effects of age, sex, initiating event, injured nerve branch, VAS pain score, and sensory profile on the likelihood that participants had a persistent trigeminal nerve injury. Similarly, the effects of age, sex, initiating event, injured nerve branch, sensory profile, and persistence of NSDs were assessed on the likelihood that participants reported moderate to severe pain intensities. Variables were selected based on the bivariate analysis ($P < 0.05$), strength of correlation, and after discussion by the investigators. Treatment effects were simulated in both bivariate and multivariable models. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed through the Box–Tidwell procedure.[5] A Bonferroni correction was applied using all terms in the model.[43] Sensitivity, specificity, and positive predictive value (PPV) and negative predictive value (NPV) were determined, as well as the area under the receiver operating characteristic curve (AUC).[16] Based on this assessment, all continuous independent variables were linearly related to the logit of the dependent variables. (4) A point-biserial correlation analysis was used to determine the relationship between the dichotomous predictors and the self-perceived health-related QoL after evaluation of normality (visual inspection of Q–Q plots) and equality of variances using the Levene test. In case assumptions were not met, the Kendall tau-b correlation test was used. For continuous independent variables, a Spearman correlation test was performed. (5) Multiple regression analysis was performed to predict the QoL from the above-mentioned predictors. Linearity was assessed by inspection of partial regression plots and a plot of studentized residuals against predicted values. Independence of residuals was verified using a Durbin–Watson test. Multicollinearity was set at tolerance values greater than 0.2. The assumption of normality was assessed on a Q–Q plot.

We used a bootstrap method for internal validation of the selected variables. A random selection with replacement of 1000 samples was derived. The β coefficient and 95% confidence intervals were then calculated for each variable.

Finally, Kaplan–Meier curves were constructed to assess the effects of risk factors on persistent NSDs over time. In consultation with the investigators, the following factors were withheld for the Kaplan–Meier analysis: age, sex, painful vs nonpainful PTTNs, initiating event, injured branch, and sensory profile. A correction for multiple comparisons was applied, and censoring percentages were analyzed. The pairwise log-rank test was used to detect any significant differences between the constructed curves. P values smaller than 0.05 were considered statistically significant.

3. Results

3.1. Population characteristics

A total of 384 patients were included, with a mean follow-up time of 322 ± 302 weeks. **Table 1** summarizes patient characteristics and the considered variables. Sixty percent of patients had a persistent trigeminal nerve injury. There were more females than males (66% vs 34%), and the mean age of patients was 50.1 ± 16.6 years. The inferior alveolar nerve was most frequently damaged (45%), followed by the maxillary nerve and its terminal branches (35%). Third molar surgery was the causative procedure in 34% of all cases, followed by tooth extraction (29%) and dental implant placement (19%). Most patients had sensory loss (40%) and pain (24%), with a mean pain VAS score of 2.3 of 10. Treatments were variable and included over-the-counter

analgesics in 65% of patients, followed by antidepressants (45%). Opioids were used in 14% of patients. Eighteen percent of patients had some sort of topical treatment. In 8% of cases, a surgical intervention was performed. Improvement was seen in 42% of patients. In about half of the patients, symptoms remained the same or showed only some improvement. Half of the patients indicated some health-related problems on the EQ-5D-5L QoL questionnaire. The overall mean self-perceived health state was 70 ± 20.

3.2. Bivariate analysis between temporary and persistent neurosensory disturbances

Several patient-related and surgery-related predictors were significantly associated with persistent NSDs (**Table 2**). Bivariate analysis revealed that females had more persistent NSDs compared with males (odds ratio [OR] 2.23, 95% confidence interval [CI] 1.39-3.58, $P < 0.0001$). Older age was associated with significantly higher rates of persistent NSDs (OR 1.03, 95% CI 1.02-1.05, $P < 0.0001$). Lingual nerve injuries were associated with significant lower rates of persistent NSDs (OR 0.48, 95% CI 0.27-0.85, $P < 0.0001$). Maxillary nerve lesions were more associated with persistent NSDs (OR 3.05, 95% CI 1.80-5.18) than with temporary NSDs.

If the cause of NSD was the administration of local anesthesia, the OR for persistent NSDs was 0.08 (95% CI 0.02-0.36, $P < 0.0001$), meaning that patients were less likely to sustain persistent NSDs. Likewise, third molar surgery had an unadjusted OR of 0.36 (95% CI 0.22-0.61, $P < 0.0001$).

A persistent NSD was also associated with the presence of pain and higher pain VAS scores (OR 3.39, 95% CI 1.82-6.30, $P < 0.0005$ and OR 1.35, 95% CI 1.19-1.53, $P < 0.0005$, respectively). In addition, the presence of thermal hyperesthesia was more frequent in the persistent NSD group (OR 5.10, 95% CI 1.97-13.25, $P < 0.0005$). Patients with mechanical hyperesthesia were twice as likely to have a persistent NSD (OR 2.10, 95% CI 1.24-3.54, $P < 0.005$).

A higher number of pain diagnoses were also associated with the persistence of NSD (OR 26.20, 95% CI 1.58-434.99, $P < 0.0005$). Moreover, lower QoL (a lower self-perceived health state, scored as a lower VAS score) was associated with persistent NSDs (OR 0.94, 95% CI 0.92-0.97, $P < 0.0005$). Patients with persistent NSDs scored their current health state as 65 ± 1.9 of 100, compared with 80 ± 1.4 in the cohort with temporary NSDs ($P < 0.0005$).

Presence of any treatment did not have a significant correlation with persistence. Yet, topical treatment did correlate (OR 7.73, 95% CI 3.01-19.85, $P < 0.0005$).

3.3. Multivariable prediction model of persistent neurosensory deficits

After the bivariate analysis of 23 variables (**Table 2**), 15 were entered into the logistic regression model. The logistic regression model was statistically significant ($\chi^2(15) = 69.9$, $P < 0.0005$). The model explained 46% (Nagelkerke R^2) of the variance in persistent trigeminal nerve injuries and correctly classified 76.9% of cases. The sensitivity was 81.8%, specificity was 70.0%, PPV was 79.4%, and NPV was 73.1%.

Of the 15 predictor variables, 6 were statistically significant: sex; pain caused by local anesthesia, extraction, third molar surgery, or endodontic treatment; and the presence of thermal hyperesthesia (**Table 3**). The model showed an excellent level of

discrimination (according to Hosmer et al.)[16] with an overall AUC of 0.84 (95% CI 0.79-0.90).

An individual risk of persistent NSDs may be calculated using the supplemental calculator (Supplemental Table 1, available at http://links.lww.com/PAIN/B435). The risk is calculated by the following formula:

Table 1

Characteristics of 384 patients with posttraumatic trigeminal neuropathy.

Characteristic (N)	N	Count (%)	Mean (SD)
Gender	373		
Male		126 (33.8)	
Female		247 (66.2)	
Age	373		50.1 (16.6)
Injured nerve			
Inferior alveolar nerve	367	166 (45.2)	
Lingual nerve	367	53 (14.4)	
Maxillary nerve	367	127 (34.6)	
Mandibular nerve	367	10 (2.7)	
Inferior alveolar and maxillary nerve	367	11 (3.0)	
Initiating event			
Local anesthesia	252	15 (6.0)	
Third molar surgery	252	86 (34.1)	
Tooth extraction	252	74 (29.4)	
Endodontic treatment	252	30 (11.9)	
Dental implant placement	252	47 (18.7)	
Clinical findings			
Pain VAS score	185		2.3 (3.4)
Sensory profile	367		
Pain		87 (23.7)	
Sensory loss		145 (39.5)	
Thermal hyperesthesia		14 (3.8)	
Mechanical hyperesthesia		55 (15.0)	
Mixed		66 (18.0)	
Treatment			
Any treatment	384		
Yes		339 (88.3)	
No		45 (11.7)	
Systemic treatment	384		
Over the counter analgetics		252 (65.6)	
Antiepileptics		104 (27.1)	
Antidepressants		174 (45.3)	
Benzodiazepines		66 (17.2)	
Opioids		54 (14.1)	
Topical treatment	384	68 (17.7)	
Surgical treatment	384	30 (7.8)	
Prognosis			
Duration	343		
Temporary injury		111 (28.9)	
Persistent injury		232 (60.4)	
Improvement	287		
Worse		4 (1.4)	
Same		69 (24.0)	
Some improvement		92 (32.1)	
A lot of improvement, still symptoms		77 (26.8)	
A lot of improvement, no more symptoms		45 (15.7)	
Follow-up time in weeks	322		302 (358)
Quality of life (EQ-5D-5L)			
Dimensions			
No problems	384	190 (49.5)	
Any problem	384	194 (50.5)	
Health state	190		70.4 (19.8)

SD, standard deviation; VAS, visual analog scale.

Table 2

Comparison of variables between patients with temporary and persistent neurosensory disturbances and the results of bivariate analyses assessing the relationship between patient-related and surgery-related factors and NSD cohorts.

Characteristic	Temporary	Persistent	Test of independence	Odds ratio	95% CI for odds ratio	
					Lower	Upper
Age, mean (SD)	44 (1.7)	52 (1.0)	$\tau b = 0.186$ $P < 0.0001$ $n = 343$	1.03	1.02	1.05
Gender n (%)						
Male	51 (45.9)	64 (27.6)	$\chi^2(1) = 11.355$			
Female	60 (54.1)	168 (72.4)	$P = 0.001$ $\varphi = 0.182$ $n = 343$	2.23	1.39	3.58
Smoker n (%)						
No	34 (65.4)	66 (62.3)	$\chi^2(1) = 0.146$			
Yes	18 (34.6)	40 (37.7)	$P = 0.702$ $\varphi = 0.030$ $n = 158$	1.15	0.57	2.29
Injured nerve						
Inferior alveolar nerve n (%)						
No	49 (44.1)	122 (52.6)	$\chi^2(1) = 2.140$			
Yes	62 (55.9)	110 (47.4)	$P = 0.143$ $\varphi = 0.079$ $n = 343$	0.71	0.45	1.12
Lingual nerve n (%)						
No	84 (75.7)	201 (86.6)	$\chi^2(1) = 6.421$			
Yes	27 (24.3)	31 (13.4)	$P = 0.011$ $\varphi = -0.137$ $n = 343$	0.48	0.27	0.85
Maxillary nerve n (%)						
No	88 (79.3)	129 (55.6)	$\chi^2(1) = 18.109$			
Yes	23 (20.7)	103 (44.4)	$P < 0.0001$ $\varphi = 0.230$ $n = 343$	3.06	1.80	5.18
Initiating event						
Local anesthesia n (%)						
No	100 (90.1)	230 (99.1)	FET(1)			
Yes	11 (9.9)	2 (0.9)	$P < 0.0001$ $\varphi = -0.222$ $n = 343$	0.08	0.02	0.36
Third molar surgery n (%)						
No	72 (64.9)	194 (83.6)	$\chi^2(1) = 15.171$			
Yes	39 (35.1)	38 (16.4)	$P < 0.0001$ $\varphi = -0.210$ $n = 343$	0.36	0.22	0.61
Tooth extraction n (%)						
No	90 (81.1)	189 (81.5)	$\chi^2(1) = 0.007$			
Yes	21 (18.9)	43 (18.5)	$P = 0.932$ $\varphi = -0.005$ $n = 343$	0.98	0.55	1.74
Endodontic treatment n (%)						
No	102 (91.9)	212 (91.4)	$\chi2(1) = 0.025$			
Yes	9 (8.1)	20 (8.6)	$P = 0.873$ $\varphi = 0.009$ $n = 343$	1.07	0.47	2.43
Dental implant placement n (%)						
No	101 (91.0)	196 (84.5)	$\chi2(1) = 2.739$			
Yes	10 (9.0)	36 (15.5)	$P = 0.098$ $\varphi = 0.089$ $n = 343$	1.86	0.89	3.89
Clinical findings						
Duration n (%)			$\chi^2(1) = 0.510$			
Constant	73 (90.1)	161 (87.0)	$P = 0.475$			
Intermittent	8 (9.9)	24 (13.0)	$\varphi = 0.044$ $n = 266$	1.36	0.58	3.17

Table 2 (*continued*)

Characteristic	Temporary	Persistent	Test of independence	Odds ratio	95% CI for odds ratio	
					Lower	Upper
Pain VAS score, mean (SD)	0.8 (0.3)	3.6 (0.4)	$\tau b = 0.367$ $P<0.0005$ $n = 169$	1.35	1.19	1.53
Pain n (%)						
No	28 (25.2)	21 (9.1)	$\chi^2(1) = 16.039$			
Yes	83 (74.8)	211 (90.9)	$P< 0.0005$ $\varphi = 0.216$ $n = 343$	3.39	1.82	6.30
Sensory loss n (%)						
No	32 (28.8)	134 (57.8)	$\chi^2(1) = 25.160$			
Yes	79 (71.2)	98 (42.2)	$P<0.0005$ $\varphi = -2.71$ $n = 343$	0.30	0.18	0.48
Thermal hyperesthesia n (%)						
No	106 (95.5)	187 (80.6)	$\chi^2(1) = 13.371$			
Yes	5 (4.5)	45 (19.4)	$P<0.0005$ $\varphi = 0.197$ $n = 343$	5.10	1.97	13.25
Mechanical hyperesthesia n (%)						
No	87 (78.4)	147 (63.4)	$\chi^2(1) = 7.809$			
Yes	24 (21.6)	85 (36.6)	$P = 0.005$ $\varphi = 0.151$ $n = 343$	2.10	1.24	3.54
Number of other pain diagnoses, mean (SD)	0 (0.0)	0.2 (0.04)	$\tau b = 0.188$ $P<0.0005$ $n = 343$	26.20	1.58	434.99
Treatment						
Any treatment n (%)						
No	13 (11.7)	19 (8.2)	$\chi^2(1) = 1.101$			
Yes	98 (88.3)	213 (91.8)	$P = 0.294$ $\varphi = 0.057$ $n = 343$	1.50	0.71	3.13
Systemic treatment n (%)						
No	16 (14.4)	25 (10.8)	$\chi^2(1) = 0.944$			
Yes	95 (85.6)	207 (89.2)	$P = 0.331$ $\varphi = 0.052$ $n = 343$	1.40	0.71	2.73
Topical treatment n (%)						
No	106 (95.5)	170 (73.3)	$\chi^2(1) = 23.583$			
Yes	5 (4.5)	62 (26.7)	$P<0.0005$ $\varphi = 0.262$ $n = 343$	7.73	3.01	19.85
Surgical treatment n (%)						
No	107 (96.4)	209 (90.1)	$\chi^2(1) = 4.122$			
Yes	4 (3.6)	23 (9.9)	$P = 0.042$ $\varphi = 0.110$ $n = 343$	2.94	0.99	8.73
Quality of life (EQ-5D-5L)						
Dimensions n (%)						
No problems	52 (46.8)	101 (43.5)	$\chi^2(1) = 0.333$			
Any problem	59 (53.2)	131 (56.5)	$P = 0.564$ $\varphi = 0.031$ $n = 343$	1.41	0.73	1.80
Health state, mean (SD)	80 (1.4)	65 (1.9)	$\tau b = -0.306$ $P<0.0005$ $n = 343$	0.94	0.92	0.97

Persistent means present for more than 3 months after the injury was inflicted.

φ, phi coefficient or Cramer V; τb, Kendall tau-b correlation coefficient; CI, confidence interval; FET, Fisher exact test.; NSD, neurosensory disturbance

$$\text{risk of persistent NSD} = \frac{e^{risk\ score}}{1 + e^{risk\ score}}$$

Where *risk score* is calculated as the sum of the intercept and the sum of the multiplication of the regression coefficients and their respective values.

3.4. Bivariate and multivariable analyses of pain intensity

After dichotomizing pain intensity into low and moderate to high pain levels, we found a significant correlation with age, sex, injured nerve (lingual and maxillary nerve), and initiating event (third molar surgery) (**Table 4**). The presence of NSDs, thermal or

Table 3

Multivariable binomial regression model assessing the relationship between patient-related and surgery-related factors and the presence of persistent neurosensory disturbances.

Characteristic	B	SE	Wald	df	P	Odds ratio	95% CI for odds ratio		95% CI after bootstrap resampling	
							Lower	Upper	Lower	Upper
Gender	1.02	0.41	6.28	1	0.012	2.78	1.25	6.20	0.85	1.22
Age	0.01	0.01	0.40	1	0.530	1.01	0.98	1.04	0.01	0.01
Injured nerve										
Inferior alveolar nerve	1.09	0.96	1.29	1	0.255	2.99	0.45	19.67	1.03	1.17
Lingual nerve	1.69	1.03	2.70	1	0.100	5.41	0.72	40.47	1.48	2.00
Maxillary nerve	1.21	1.08	1.24	1	0.266	3.34	0.40	27.99	1.14	1.28
Initiating event										
Local anesthesia	−3.21	1.27	6.33	1	0.012	0.04	0.00	0.49	−3.36	−3.10
Third molar surgery	−1.25	0.55	5.09	1	0.024	0.29	0.10	0.85	−1.38	−1.11
Extraction	−2.00	0.68	8.53	1	0.003	0.14	0.04	0.52	−2.03	−1.98
Endodontic treatment	−2.84	1.24	5.24	1	0.022	0.06	0.01	0.67	−2.90	−2.79
Implant placement	−1.06	0.82	1.66	1	0.197	0.35	0.07	1.73	−1.13	-0.99
Clinical findings										
Pain VAS score	0.11	0.14	0.62	1	0.430	1.11	0.85	1.45	0.10	0.12
Pain	-0.14	0.46	0.09	1	0.767	0.87	0.35	2.16	0.37	0.15
Sensory loss	−1.23	1.01	1.50	1	0.221	0.29	0.04	2.10	−1.41	−1.10
Thermal hyperesthesia	2.75	1.35	4.15	1	0.042	15.66	1.11	220.69	2.62	2.88
Mechanical hyperesthesia	0.43	0.63	0.46	1	0.498	1.54	0.44	5.31	0.34	0.51
Constant	-0.18	1.51	0.01	1	0.905	0.83				

Gender is for females compared with males. AUC = 0.84, $\chi^2(15)$ = 69.9, $P < 0.0001$. A total of 1000 bootstrap subsamples were run.
CI, confidence interval; VAS: visual analog scale (0-10).

mechanical hyperesthesia, increased the odds of having a moderate to severe pain intensity. Logically, patients who received some treatment were more likely to experience moderate to severe pain (OR 4.69, 95% CI 1.06-20.76, P = 0.026). On the other hand, third molar surgery was less likely to be associated with moderate to severe pain (OR 0.23, 95% CI 0.10-0.52, $P < 0.0005$). A lower HrQoL was associated with moderate to severe pain intensity.

A logistic regression model was significant ($P < 0.0001$) with an AUC of 0.987 and Nagelkerke R^2 = 87.3% (**Table 5**). The sensitivity and specificity were 96.2% and 98.3%, respectively. Positive predictive value and NPV were 96.2% and 98.4%, respectively. We used the same input variables as in the previous regression model (replacing the pain variables by persistent NSDs). None of the individual features showed a significant contribution to the model except sensory loss (P = 0.002). In addition, we noted bootstrap confidence intervals that were largely different from the sample distribution. A risk score can be calculated using our tool given in Supplemental Table 1 (available at http://links.lww.com/PAIN/B435).

3.5. Bivariate and multivariable analyses of QoL

Bivariate analysis revealed that the following variables were significantly associated with the QoL health state: age, sex, injured nerve (lingual and maxillary nerve), initiated by third molar surgery, persistence of NSD, sensory loss phenotype, and number of other pain diagnoses (**Table 6**). Quality of life was adversely affected when maxillary nerve lesions were present, when an NSD was persistent, or when multiple pain diagnoses were present.

The multiple regression model to predict QoL was statistically significant $F(15, 77)$ = 4.47, $P < 0.0005$. The adjusted R^2 was 0.361. Following variables were significant to the prediction: initiating event (third molar surgery and implant-related injury), VAS pain score, and presence of any treatment, $P < 0.05$. Multicollinearity was present between any treatment and systematic treatment. After backwards regression analysis, only *any treatment* and the previously mentioned predictors (age, sex, injured nerve, initiating events, sensory profiles, and pain VAS score) were taken forward into the regression model. The results are summarized in **Table 7**. An individual QoL health state prediction may be calculated using the supplemental calculator (Supplemental Table 1, available at http://links.lww.com/PAIN/B435).

3.6. Kaplan–Meier distributions

Pairwise comparisons of Kaplan–Meier distributions revealed a statistically significant difference in NSD frequency over time between sex, age, painful and nonpainful PTTNs, initiating event, injured nerve, and sensory profile (**Fig. 1**). All survival distributions were significantly different (log-rank test $P < 0.0005$). Older age, female gender, and a diagnosis of painful PTTNs all negatively affected the time to symptom resolution. Most improvement was observed during the first 20 weeks after injury. Little improvement was seen after 60 weeks. Painful PTTNs showed less tendency for recovery of NSDs, with 86.2% of patients still complaining of NSDs after 2 years. However, improvement continued to be observed even when symptoms were long-standing.

Patients with lingual nerve injuries had the best long-term outcomes, with only 44% still experiencing NSDs after 2 years; again, most improvement was seen in the first 20 weeks. By contrast, patients with a maxillary nerve lesion reported almost no improvement of NSDs over time (92% still experienced NSDs

Table 4

Bivariate correlation analysis between cohorts with low pain intensity and moderate to severe pain intensity.

Characteristic	Low pain intensity (VAS < 5)	Moderate to severe pain intensity (VAS ≥ 5)	Test of independence	Odds ratio	95% CI for odds ratio	
					Lower	Upper
Age, mean (SD)	41.39 (15.69)	57.87 (14.98)	$\tau b = 0.345$ $P<0.0005$ $n = 185$	1.07	1.04	1.09
Gender n (%)			$\chi^2(1) = 6.557$ $P = 0.010$ $\varphi = 0.188$ $n = 185$	2.43	1.22	4.84
Male	66 (49.6)	15 (28.8)				
Female	67 (50.4)	37 (71.2)				
Smoker n (%)			$\chi^2(1) = 0.108$ $P = 0.742$ $\varphi = -0.034$ $n = 94$	0.85	0.32	2.28
No	43 (59.7)	14 (63.6)				
Yes	29 (40.3)	8 (36.4)				
Injured nerve						
Inferior alveolar nerve n (%)			$\chi^2(1) = 3.477$ $P = 0.062$ $\varphi = -0.137$ $n = 185$	0.54	0.28	1.04
No	54 (40.6)	29 (55.8)				
Yes	79 (59.4)	23 (44.2)				
Lingual nerve n (%)			$\chi^2(1) = 7.339$ $P = 0.007$ $\varphi = -0.199$ $n = 185$	0.29	0.12	0.74
No	92 (69.2)	46 (88.5)				
Yes	41 (30.8)	6 (11.5)				
Maxillary nerve n (%)			$\chi^2(1) = 29.872$ $P<0.0005$ $\varphi = 0.402$ $n = 185$	7.28	3.39	15.65
No	118 (88.7)	27 (51.9)				
Yes	15 (11.3)	25 (48.1)				
Initiating event						
Local anesthesia n (%)			FET(1) $P = 0.675$ $\varphi = -0.061$ $n = 185$	0.42	0.05	3.53
No	127 (95.5)	51 (98.1)				
Yes	6 (4.5)	1 (1.9)				
Third molar surgery n (%)			$\chi^2(1) = 13.588$ $P<0.0005$ $\varphi = -0.271$ $n = 185$	0.23	0.10	0.52
No	74 (55.6)	44 (84.6)				
Yes	59 (44.4)	8 (15.4)				
Tooth extraction n (%)			$\chi^2(1) = 3.524$ $P = 0.061$ $\varphi = 0.138$ $n = 185$	2.13	0.96	4.74
No	115 (86.5)	39 (75.0)				
Yes	18 (13.5)	13 (25.0)				
Endodontic treatment n (%)			FET(1) $P = 0.403$ $\varphi = 0.065$ $n = 185$	1.97	0.43	9.14
No	129 (97.0)	49 (94.2)				
Yes	4 (3.0)	3 (5.8)				
Dental implant placement n (%)			$\chi^2(1) = 1.582$ $P = 0.208$ $\varphi = 0.092$ $n = 185$	1.91	0.69	5.33
No	123 (92.5)	45 (86.5)				
Yes	10 (7.5)	7 (13.5)				
Clinical findings						
Duration n (%)			FET(1) $P = 0.508$ $\varphi = 0.055$ $n = 185$	1.67	0.36	7.81
Constant	96 (96.0)	43 (93.5)				
Intermittent	4 (4.0)	3 (6.5)				

Table 4 (*continued*)

Characteristic	Low pain intensity (VAS < 5)	Moderate to severe pain intensity (VAS ≥ 5)	Test of independence	Odds ratio	95% CI for odds ratio	
					Lower	Upper
Persistency n (%)						
Temporary	64 (53.8)	6 (12.0)	$\chi^2(1) = 25.330$	8.53	3.38	21.54
Persistent	55 (46.2)	44 (88.0)	$P < 0.0005$			
			$\varphi = 0.387$			
			n = 169			
Sensory loss n (%)						
No	12 (9.0)	41 (78.8)	$\chi^2(1) = 89.162$	0.03	0.01	0.07
Yes	121 (91.0)	11 (21.2)	$P < 0.0005$			
			$\varphi = -0.694$			
			n = 185			
Thermal hyperesthesia n (%)						
No	126 (94.7)	39 (75.0)	$\chi^2(1) = 15.103$	6.00	2.24	16.09
Yes	7 (5.3)	13 (25.0)	$P < 0.0005$			
			$\varphi = 0.286$			
			n = 185			
Mechanical hyperesthesia n (%)						
No	120 (90.2)	24 (46.2)	$\chi^2(1) = 42.092$	10.77	4.89	23.74
Yes	13 (9.8)	28 (53.8)	$P = 0.005$			
			$\varphi = 0.477$			
			n = 185			
Number of other pain diagnoses, mean (SD)	0.09 (0.42)	0.15 (0.61)	$\tau b = 0.047$	1.29	0.69	2.40
			$P = 0.522$			
			n = 185			
Treatment						
Any treatment n (%)						
No	21 (15.8)	2 (3.8)	FET(1)	4.69	1.06	20.76
Yes	112 (84.2)	50 (96.2)	$P = 0.026$			
			$\varphi = 0.163$			
			n = 185			
Systemic treatment n (%)						
No	25 (18.8)	3 (5.8)	FET(1)	3.78	1.09	13.12
Yes	108 (81.2)	49 (94.2)	$P = 0.038$			
			$\varphi = 0.163$			
			n = 185			
Topical treatment n (%)						
No	125 (94.0)	35 (67.3)	$\chi^2(1) = 22.764$	7.59	3.02	19.05
Yes	8 (6.0)	17 (32.7)	$P < 0.0005$			
			$\varphi = 0.351$			
			n = 185			
Surgical treatment n (%)						
No	125 (94.0)	50 (96.2)	FET(1)	0.63	0.13	3.05
Yes	8 (6.0)	2 (3.8)	$P = 0.728$			
			$\varphi = -0.043$			
			n = 185			
Quality of life (EQ-5D-5L)						
Dimensions n (%)						
No problems	65 (48.9)	25 (48.1)	$\chi^2(1) = 0.009$	1.03	0.54	1.96
Any problem	68 (51.1)	27 (51.9)	$P = 0.923$			
			$\varphi = 0.007$			
			n = 185			
Health state, mean (SD)	79.31 (12.66)	59.77 (24.88)	$\tau b = -0.339$	0.94	0.91	0.97
			$P < 0.0005$			
			n = 185			

φ, phi coefficient or Cramer V; τb, Kendall tau-b correlation coefficient; CI, confidence interval; FET, Fisher exact test; VAS, visual analogue scale.

after 2 years). For inferior alveolar nerve lesions, a persistent NSD was reported in 64% of cases after 2 years.

When comparing the most frequent initiating injury events, most NSDs after local anesthesia administration injury resolved within 40 weeks, although 25% of patients still experienced NSDs after 2 years. For injuries after third molar surgery, 47% of patients still reported NSDs after 2 years. Endodontic-related, implant-related, or extraction-related injuries had a worse course of symptoms, with around 80% of patients still experiencing NSDs after 2 years. Implant-related injuries were considered the worst

Table 5

Multivariable binomial regression model predicting moderate to severe pain intensity based on predetermined patient-related and surgery-related factors.

Characteristic	B	SE	Wald	df	P	Odds ratio	95% CI for odds ratio		95% CI after bootstrap resampling	
							Lower	Upper	Lower	Upper
Gender	1.66	1.49	1.24	1	0.266	5.27	0.28	98.50	−96.64	155.48
Age	−0.02	0.05	0.17	1	0.684	0.98	0.90	1.08	−2.65	3.58
Injured nerve										
Inferior alveolar nerve	3.67	2.51	2.15	1	0.143	39.33	0.29	5356.36	−116.35	268.61
Lingual nerve	0.19	3.10	0.00	1	0.951	1.21	0.00	521.74	−172.87	205.49
Maxillary nerve	4.23	2.91	2.11	1	0.146	68.64	0.23	20,561.07	−121.30	391.54
Initiating event										
Local anesthesia	−23.12	17,828.28	0.00	1	0.999	0.00	0.00	0.00	−315.92	261.90
Third molar surgery	1.87	2.49	0.56	1	0.453	6.47	0.05	842.36	−42.09	277.56
Extraction	2.39	2.48	0.93	1	0.335	10.94	0.09	1413.70	−95.41	163.33
Endodontic treatment	−0.34	2.54	0.02	1	0.893	0.71	0.01	102.56	−129.69	324.02
Implant placement	1.20	2.10	0.33	1	0.569	3.31	0.05	203.96	−92.38	223.41
Clinical findings										
Persistent NSD	1.04	2.87	0.13	1	0.717	2.83	0.00	780.63	−105.61	128.41
Sensory loss	−6.36	2.07	9.45	1	0.002	0.00	0.33	0.10	−422.31	−4.01
Thermal hyperesthesia	2.01	1.58	1.61	1	0.205	7.42	0.03	164.90	−84.15	117.93
Mechanical hyperesthesia	2.05	2.78	0.54	1	0.462	7.74	0.03	1797.92	−92.20	165.55
Any treatment	8.79	6.27	1.96	1	0.161	6553.60	0.03	1,43E+12	−40.56	550.21
EQ-5D Health state	−0.13	0.09	2.33	1	0.127	0.88	0.74	1.04	−16.71	0.25
Constant	−2.58	7.52	0.12	1	0.732	0.08				

Gender is for females compared with males. AUC = 0.987, $\chi^2(16) = 83.221$, $P < 0.0001$. A total of 1000 bootstrap subsamples were run.
CI, confidence interval; NSD, neurosensory disturbance.

of these, with little improvement in NSDs over time; 86% of patients still had symptoms after 2 years.

When comparing sensory profiles, mechanical and thermal hyperesthesia and mixed profiles had the worst outcome, with higher rates of long-term NSDs (ranging around 80%). Approximately 40% of patients with a sensory loss profile had persistent NSDs after 2 years.

4. Discussion

4.1. Main findings

After the occurrence of trigeminal nerve injury, there was a high tendency toward persistent NSDs in this study. Sixty percent of patients who visited our tertiary center had symptoms that persisted for more than 3 months. This is in line with findings by Bagheri and Meyer, who reported permanent inferior alveolar injury in 78% of nerve injury patients after third molar surgery and persistent lingual nerve injury in 46% of such patients.[1,2,21,27] Furthermore, Libersa et al.[24] evaluated insurance records and reported a permanent injury in 22% of nerve injury cases after third molar surgery, 15% of cases after endodontic-related injury, and 75% of cases after implant-related injury. Although high variance exists, there seems to be a relatively high conversion rate to permanent NSDs after nerve injury has occurred.

4.2. Patient profiles and predictors

As clinicians and researchers, we know that not every nerve injury presents or evolves in the same way. Increasing numbers of studies have demonstrated the usefulness of phenotyping patients based on multiparametric data.[40] In the future, it is

hoped that this phenotyping will allow cost-effective treatment strategies to be tailored to each patient.[14]

The reported multivariable prediction model based on preoperative and perioperative factors was able to identify 77% of patients with long-term NSDs. The following clinical predictors were statistically significant: (1) sex, (2) initiating event (all except implant placement), and (3) presence of thermal hyperesthesia.

Females were almost 3 times more likely than males to have persistent NSDs. Similarly, a study by Selvi et al. reported a fivefold increase in NSDs in females compared with males.[39] These authors also reported that older age and a close relationship between the third molar and the inferior alveolar nerve are associated with PTTNs after third molar surgery.

We also reported that patients with thermal hyperesthesia were 16 times more likely to have persistent NSDs. A recent report of PTNP demonstrated that increased patient age and an allodynia signature are significant factors that predict permanency of neuropathy.[36] The importance of sensory phenotyping is further supported by the finding of different treatment outcomes according to the nociceptor phenotype.[40] This study could not reveal unequivocal associations between treatment or nontreatment and outcome measures being persistence of NSD or final QoL.

One follow-up study by Pigg et al. evaluated 37 patients with persistent dentoalveolar pain, which is likely to be a neuropathic pain.[32] These authors illustrated a similar symptom course as in this report. However, they were unable to detect predictive factors, including sensory profiles, for persistent pain after 7 years of follow-up. A low baseline pain score was the only predictor for symptom resolution, although no stratification was performed for etiology or injured nerve branch.

Table 6

Bivariate correlation analysis between patient-related and surgery-related factors and QoL measured by the EQ-5D-5L VAS health state.

Characteristic	Mean QoL health state (SD)	Test of correlation
Age	—	$r_s = -0.299$ $P < 0.0005$ n = 190

Gender n (%)
  Male
  Female
	
	74.36 (17.60)
	68.30 (20.70)
		$r_{pb} = -0.146$
		$P = 0.044$
		n = 190

Smoker n (%)
  No
  Yes
	
	75.24 (16.65)
	66.29 (21.54)
		$\tau b = -0.156$
		$P = 0.078$
		n = 93

Injured nerve
  Inferior alveolar nerve n (%)
    No
    Yes
	
	71.16 (19.72)
	69.77 (20.01)
		
		$r_{pb} = -0.035$
		$P = 0.629$
		n = 190

Lingual nerve n (%)
    No
    Yes
	
	68.61 (19.93)
	81.00 (15.78)
		$r_{pb} = 0.222$
		$P = 0.002$
		n = 190

Maxillary nerve n (%)
    No
    Yes
	
	72.64 (19.23)
	66.82 (20.40)
		$r_{pb} = -0.143$
		$P = 0.049$
		n = 190

Initiating event
  Local anesthesia n (%)
    No
    Yes
	
	70.35 (20.06)
	73.60 (8.20)
		
		$r_{pb} = 0.026$
		$P = 0.719$
		n = 190

Third molar surgery n (%)
    No
    Yes
	
	67.36 (19.57)
	80.66 (17.24)
		$r_{pb} = 0.284$
		$P < 0.0005$
		n = 190

Tooth extraction n (%)
    No
    Yes
	
	70.59 (20.08)
	69.73 (18.89)
		$r_{pb} = -0.016$
		$P = 0.822$
		n = 190

Endodontic treatment n (%)
    No
    Yes
	
	70.43 (19.89)
	70.50 (19.80)
		$r_{pb} = 0.001$
		$P = 0.989$
		n = 190

Dental implant placement n (%)
    No
    Yes
	
	70.48 (19.72)
	70.13 (21.08)
		$r_{pb} = -0.006$
		$P = 0.937$
		n = 190

Clinical findings
  Duration n (%)
    Constant
    Intermittent
	
	69.14 (19.99)
	77.48 (15.72)
		
		$r_{pb} = 0.154$
		$P = 0.060$
		n = 150

Persistency n (%)
    Temporary
    Persistent
	
	80.86 (10.84)
	65.68 (21.31)
		$\tau b = -0.306$
		$P < 0.0005$
		n = 187

Pain VAS score	—	$r_s = -0.446$ $P < 0.0005$ n = 93

Pain n (%)
    No
    Yes
  Sensory loss n (%)
	
	—
	70.44 (19.83)
		
		—

Table 6 (*continued*)

Characteristic	Mean QoL health state (SD)	Test of correlation
No	64.53 (21.79)	$\tau b = 0.246$
Yes	76.53 (15.66)	$P < 0.0005$
		$n = 190$
Thermal hyperesthesia n (%)		
No	71.04 (19.95)	$r_{pb} = -0.067$
Yes	67.55 (19.31)	$P = 0.358$
		$n = 190$
Mechanical hyperesthesia n (%)		
No	71.70 (19.30)	$r_{pb} = -0.099$
Yes	67.41 (20.90)	$P = 0.175$
		$n = 190$
Number of other pain diagnoses	—	$r_s = -0.296$
		$P < 0.0005$
		$n = 190$
Treatment		
Any treatment n (%)		
No	66.68 (24.66)	$r_{pb} = 0.063$
Yes	70.85 (19.26)	$P = 0.386$
		$n = 190$
Systemic treatment n (%)		
No	67.14 (23.48)	$r_{pb} = 0.060$
Yes	70.87 (19.34)	$P = 0.408$
		$n = 190$
Topical treatment n (%)		
No	71.62 (20.13)	$r_{pb} = -0.124$
Yes	65.36 (17.86)	$P = 0.088$
		$n = 190$
Surgical treatment n (%)		
No	70.94 (19.26)	$r_{pb} = -0.087$
Yes	64.53 (25.69)	$P = 0.231$
		$n = 190$

(1) Where both dependent and independent variables were continuous, only the Spearman correlation coefficient is given. (2) No valid cases were available in the category of "no pain" to assess correlation with their health state.

SD, standard deviation; VAS, visual analogue scale; r_{pb}, point-biserial correlation; r_s, Spearman correlation; τ_b, Kendall tau-b correlation.

4.3. Pain intensity

This study further confirms age-related and gender-related associations with more severe pain.[4] Third molar surgery was less likely to be associated with moderate to severe pain. Other initiating events were not statistically significant associated with moderate to severe pain. Small numbers per variable may explain why most variables did not contribute significantly to the analysis.

It was striking that PTTN at the level of the maxilla was 7 times more likely to be associated with moderate to severe pain. Lingual and inferior alveolar nerve-related injuries were less likely to result in moderate to severe pain. This strengthens the clinical suspicion that the degree of nerve damage does not necessarily correlate with the final pain intensity.[25] It even seems that PTTN at the level of the maxilla, where one finds mainly submillimetric peripheral nerve branches and usually undergoes less extensive surgery, poses a higher risk than mandibular wisdom tooth surgery, which is considered more invasive, and takes place at the level of a 2- to 3-mm thick lingual or inferior alveolar nerve. It is true that even minimal interventions such as root canal treatment may result in persistent pain.[30]

More research will be needed to assess the role of nerve injury classifications in prediction models.[13] One interesting follow-up study would be to investigate the role of nerve fiber distributions and density in relation to PTNP and its triggering mechanisms.

different between certain patient groups, based on the previously discussed variables. For example, a patient who had lingual nerve damage after wisdom tooth surgery with a sensory loss phenotype had a better chance of spontaneous recovery compared with a patient who had inferior alveolar nerve damage after endodontic treatment and complained of thermal hyperesthesia. The Kaplan–Meier distributions highlight the different clinical course, and perhaps different underlying pathophysiology, between cohorts.

Other studies have reported a similar cut-off for spontaneous recovery.[7,29] Time to recovery is an important factor to consider. For example, there is support for the theory that faster systemic treatment of postsurgical neuropathies or CPSP can lead to better outcomes or even avoid the development of CPSP or neuropathic pain.[45] Furthermore, in the case of severe nerve injury, microsurgical neural repair should be performed within 3 months of the injury occurrence to improve outcomes.[22] Another study, by Tabrizi et al.,[44] revealed a significant association between time to treatment and neurosensory recovery after mandibular body fractures. This finding illustrates the importance of early diagnosis in patients with nerve injury. Nevertheless, further research is needed to identify the most cost-effective treatments for the different phenotypes of patients with nerve injury.

4.4. Course of symptoms

Most global improvement occurred within the first 3 months after trauma was inflicted. Notably, the evolution was markedly

4.5. Quality of life

In the end, the QoL is what matters most to our patients. We identified a significant difference between patients who sustained

Table 7

Multiple regression model assessing the relationship between patients' quality of life health state and patient-related and surgery-related factors.

Characteristic	B	SE B	P	95% CI for B		β	R^2	ΔR^2
				Lower	Upper			
Model							0.520	0.415
Gender	2.30	11.48	0.508	−4.59	9.20	0.06		
Age	−0.15	−0.13	0.209	−0.39	0.09	−0.13		
Injured nerve								
Inferior alveolar nerve	−5.29	6.35	0.407	−17.95	7.37	−0.14		
Lingual nerve	1.61	6.71	0.811	−11.76	14.99	0.04		
Maxillary nerve	−7.30	7.23	0.316	−21.72	7.11	−0.17		
Initiating event								
Local anesthesia	−1.43	10.00	0.887	−21.36	18.51	−0.01		
Third molar surgery	8.37	4.67	0.077	−0.94	17.67	0.22		
Extraction	7.63	5.74	0.188	−3.80	19.07	0.14		
Endodontic treatment	11.53	8.46	0.177	−5.32	28.38	0.13		
Implant placement	16.74	6.15	0.008	4.49	28.99	0.25		
Clinical findings								
Persistent NSD	−8.54	4.07	0.039	−16.65	−0.43	−0.22		
Pain VAS score	−2.98	1.01	0.004	−4.99	−0.97	−0.54		
Sensory loss	−12.90	7.16	0.076	−27.17	1.38	−0.32		
Thermal hyperesthesia	−5.84	5.37	0.281	−16.54	4.86	−0.11		
Mechanical hyperesthesia	−2.64	4.84	0.587	−12.28	7.00	−0.05		
Any treatment	10.60	5.00	0.037	0.64	20.57	0.20		
Constant	91.22	11.48	<0.0005	68.35	114.09			

Gender is for females compared with males.
B, unstandardized regression coefficient; NSD, neurosensory disturbance SE B, standard error of the coefficient; CI, confidence interval; VAS, visual analog scale (0-10); R^2, coefficient of determination; ΔR^2, adjusted R^2.

transient nerve injuries (EQ-5D VAS 80 ± 1.4) and patients with persistent injuries (65 ± 1.9). When this was put into perspective with national population data, we noticed a worse QoL in the patients with persistent symptoms. Szende et al. reported that the mean Belgian EQ-5D VAS score for the 45 to 54 year age group is 77.2.[42] We also observed that approximately half of all patients with temporary or persistent nerve damage reported health problems. This proportion is markedly higher than the average national figures, which are approximately 30%.[42]

Previous studies have identified a significant psychosocial burden in patients with trigeminal nerve injuries.[9,41] Smith et al. also reported that the severity of pain is related to poorer QoL in such patients.[41] These results support our finding of higher quality-of-life scores in patients with transient damage. Indeed, in
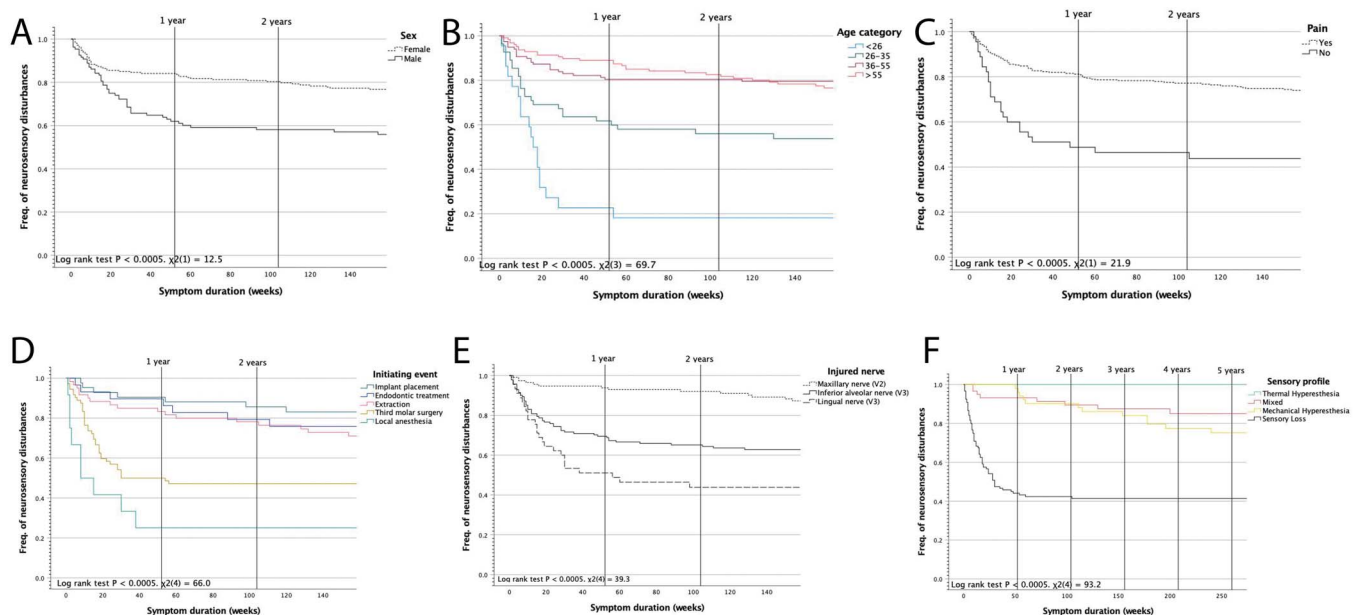

Figure 1. Kaplan–Meier analysis of neurosensory disturbances (NSDs) over time comparing sex (A), age (B), painful and nonpainful posttraumatic trigeminal neuropathies (PTTNs) (C), initiating event (D), injured nerve branch (E), and sensory profile (F). Between-group pairwise comparisons were all statistically significant (P < 0.0005, pairwise log-rank test).

these patients, pain was present less frequently and was also less severe. Together, these findings demonstrate the importance of paying attention to psychosocial impacts and improving patients' QoL.

4.6. Strengths and limitations

To the best of our knowledge, this study is the first to investigate a large population of patients with PTTN and PTNP with a long follow-up. For the first time, risk factors for developing persistent PTTNs were identified and quantified. In addition, the course of symptoms was plotted to compare cohorts based on sex, etiology, injured nerve, presence of pain, and sensory profile. Such longitudinal data are unique in the current literature. However, the different symptom courses of patients with PTNP hide an underlying pathophysiology that remains insufficiently understood. In addition, the lack of universally accepted treatment protocols makes it difficult to understand treatment effects on outcome.

Limitations of this study included its retrospective nature and its tertiary setting, which may have led to selection bias. Sensory testing was mainly qualitative in nature, which comes with its own limitations. In addition, psychosocial measures were limited. Because of the large number of variables, some variables had few events per predictor, which may explain the contradictory results of some of the bivariate and multivariate predictions. Moreover, the data-driven approach that we used on the retrospective data should be externally validated.

4.7. Implications

After a trigeminal nerve injury was inflicted, there was a high tendency toward persistent NSDs in patients in our tertiary center. This is an alarming finding considering that dental, oral, and maxillofacial surgery is one of the most frequently performed procedures. Thus, investigating preventive strategies and educating clinicians about PTTNs should be on the top of the academic agenda.

Most global improvement was observed within the first 3 months after trauma was inflicted. Multiple patient-related and surgery-related factors played a role in neurosensory recovery. The proposed multivariable prediction model may aid in predicting an individualized estimate of neurosensory recovery, but further prospective validation is needed. Important factors were identified that might aid the design of a future prospective registry study for patients with NSDs.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Acknowledgments

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B435.

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