The validation of pain index extracted from electroencephalogram in chronic pain patients

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Abstract

Purpose

A non-invasive tool is needed to help objectively assess pain. We aimed to validate the pain index (PI) extracted from electroencephalograms (EEG) to detect moderate-to-severe pain.

Methods

The participants were 18- to 80-year-old outpatients with moderate-to-severe chronic pain (NRS ≥ 4) who were eligible to receive injection therapy or shockwave therapy. The numerical rating scale (NRS) and PI extracted from the EEG signals were recorded before and 30 minutes after treatments. Anxiety and depression statuses were evaluated by the Hospital Anxiety and Depression Scale before treatments. The association between NRS and PI was evaluated using Pearson's correlations and regression analysis. The sensitivity and specificity of PI were analyzed using the area under the receiver operating characteristic (ROC) curves. Multiple regression analysis was used to analyze the associations of PI with anxiety and depression.

Results

A total of 111 patients were enrolled. A positive correlation was found between PI and NRS and between the changes in NRS (ΔNRS) and the changes in PI (ΔPI) before versus after treatments. The sensitivity and specificity of PI for moderate and severe pain were 80.4% and 86.5%, respectively, and the diagnostic threshold was 10.65. The area under the ROC curves of PI was 0.912. PI appeared to be slightly affected by anxiety or depression.

Conclusion

PI extracted from EEG appears to be a feasible objective tool to assess moderate-to-severe pain.

Introduction

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [1]. However, patients sometimes cannot properly understand commonly used subjective pain assessment methods, such as numerical rating scale (NRS) or visual analogue scale (VAS). Other patients may be too nervous and, thus, tend to rate the pain unreliably [2, 3]. There are also patients who have trouble communicating, such as trachea-intubated patients. In light of this, pain experts have been trying to explore objective pain assessment methods. Current researches mostly focus on five main strategies [4]: (1) autonomic nervous system changes (changes in blood pressure and heart rate, heart rate variability, the analgesia nociception index (ANI), and the surgical

stress index [5–8]); (2) biopotentials, such as the nociception flexion reflex threshold, evoked potentials, magnetoencephalography, and electroencephalography (EEG); (3) neuroimaging and related methods, including positron emission tomography, magnetic resonance imaging, and near-infrared spectroscopy; (4) biological markers such as assays, noxious stimulation response index, serum lipid levels, and immunoassays; and (5) composite algorithms. However, these objective methods are either invasive, expensive, affected by emotions, or not well-validated. Therefore, there is a need for a non-invasive, objective and validated method to assess pain and to guide the treatments of chronic pain.

As pain reflects the perception of a stimulus by the brain, it may be possible to assess pain by monitoring electroencephalographic signals. A wireless wearable monitor was designed to measure brain waves from the prefrontal cortex, and the pain index (PI) was extracted from the EEG signals. Jianxiong and colleagues [9] found that PI of pain patients was higher than that of healthy volunteers and that PI and NRS were independently related. However, the study did not confirm if PI changes were related to changes in pain scores or if PI was affected by other factors, such as anxiety and depression. In our study, we observed the changes of PI of the same individual while he was in pain and when he was relieved of pain. We also evaluated whether PI was affected by anxiety and depression, which is quite common in chronic pain patients.

Methods

Participants

This study was a nonrandomized, single-blind, observational study approved by the Medical Ethics Committee of Peking University People's Hospital in accordance with the Declaration of Helsinki (Date:2016.5/Number: 2016PHB030-01) and registered in ClinicalTrials.gov (NCT03613012). The study was conducted at the clinic of the Department of Pain Medicine. Data were collected between August 2018 and November 2018. Informed consent was obtained from all individual participants included in the study.

The participants were 18- to 80-year-old outpatients with diagnoses such as lumbar disc herniation and osteoarthritis, with chronic pain and NRS $\geq$4, and who were eligible to receive injection therapy or shockwave therapy. The exclusion criteria were central nervous system disorders, such as epilepsy, cerebral infarction, cerebral hemorrhage, and mental disorders, or a history of long-term use of psychotropic drugs. Patients who could not understand NRS were also excluded.

Main equipment and measures

A multifunctional monitor, HXD-1 (Beijing Easymonitor Technology Co., Ltd.®, Beijing, China), was used to record the EEG of the participants. The monitor collected and directed prefrontal brain EEG signals to a pre-processing circuit. This was followed by multistage amplification, smoothing, and A/D modulus to transform EEG signals to digital signals. Time-domain brain wave signals were obtained. EEG units with specific time windows were subjected to wavelet analysis, spectral analysis, pattern recognition analysis,

and other methods to obtain regular characteristic change “metadata” in the brain waves, which were used as variables indicating the brain’s functional status. Statistical algorithms were used to confirm the objective quantitative metadata from the brain waves with associated states corresponding to features of an index group. A total of 24 brain function indicators were developed, including PI, sedation index, and stress index, which were preliminarily verified to be clinically relevant [10]. The value of PI ranged from 0 to 100.

NRS was used as a subjective measure of pain. Anxiety and depression levels were measured by the Hospital Anxiety and Depression Scale (HADS).

Procedures

A sample size calculation was performed based on the sensitivity and specificity of the diagnostic test (allowing for a minimum sensitivity and a minimum specificity of 80%), a significance level (α) of 0.01, and an error of 0.1. The estimated sample size was 107 patients. Given a predicted dropout rate of 10%, 118 patients needed to be enrolled.

After the informed consent forms were signed, clinical data, including age, sex, dominant hand, and HADS, were recorded. Patients had their EEG recorded by the HXD-1 for eight minutes after sitting quietly for 2 minutes in a quiet room, and rated their pain with NRS (recorded as NRS_{before}). After that, the patients underwent either injection（intra articular injection, paravertebral injection, nerve block, et al.）or shockwave therapy. After the treatments, the patients rested for 30 minutes and received a second EEG monitoring session, after which they rated their pain with NRS (recorded as NRS_{after}).

To reduce environmental effects, the same examination room was used throughout the study. As EEG is affected by body movements, talking, and electrode sites, the EEG data collected in this study were reanalyzed to exclude relevant interference in order to obtain more accurate values. To reduce the researchers’ bias, all data were obtained and recorded by the same person, and all PI were calculated by the same researcher. The EEG analysts were blinded to NRS. The mean PI before the treatments was recorded as PI_{before} and the mean PI after the treatments was recorded as PI_{after}.

Statistical methods

SPSS 20.0 statistical software (International Business Machines Corporation, New York, United States) was used to analyze the data. All quantitative data were expressed as the mean ± standard deviation ($\bar{x}\pm s$). Pearson’s correlations were used to determine associations between variables. Regression analysis was used to plot the trend line.

Receiver operating characteristic (ROC) curves were used to analyze the sensitivity and specificity of PI to assess moderate-to-severe chronic pain. A NRS score of 0 was classified as no pain, 1–3 was classified as mild pain, and ratings of 4 or more were classified as moderate-to-severe pain. NRS ratings of 0–3 were considered negative, and ratings of 4 or more were considered positive.

Using PI_{before} as the dependent variable and anxiety and depression scores as the independent variables, multiple regression was used to analyze the associations of PI with anxiety and depression.

Results

Participant characteristics

Of the 113 patients enrolled in the study, two dropped out because they were not willing to wait for the second EEG monitoring session after treatments. Considering the small dropout rate, recruitment was terminated with a sample of 111 patients, including 106 right-handed persons. The sex ratio was 36 men to 75 women. Among the 111 patients, 67 had significant pain relief after treatments (more than 50% decrease in NRS after treatments).

The average age of the 111 patients was 63±13 years, and their average BMI was 24.77±3.58 kg/m^2. Table 1 shows the basic descriptive data and Table 2 shows the principal diagnoses of the patients.

Table 1 Basic descriptive data (n = 111)

	Patients
Characteristics	Mean (SD)
Gender (M/F)	36/75
Age (y)	63(13)
Right-handed	106
BMI	24.77(3.58)

F, female; M, male; SD, standard deviation; BMI, body mass index.

Table 2 Principal diagnoses of the patients (n = 111)

Diagnoses	Number of patients
Osteoarthritis	38
Lumbar disc herniation	24
Postherpetic neuralgia	9
Other pain [1]	40

[1] Other pain included cervical spondylosis, tendinitis, back pain, cervicogenic headache and myofascitis.

Correlations between NRS and PI

Pearson's correlations found a significant positive association ($r = 0.800$, $p < 0.05$) between the 222 pairs of NRS (including NRS_{before} and NRS_{after}) and PI (including PI_{before} and PI_{after}) of the 111 patients before and after treatments (Table 3). Figure 1 shows the scatter plot of the data and the linear trend line for the association between NRS and PI ($R^2 = 0.64$).

Table 3 Pearson's correlations between NRS and PI

	Pearson's correlations
NRS and PI (n = 111)	0.800*
ΔNRS and ΔPI (n = 111)	0.721*
NRS-R and PI-R (n = 67)	0.840*
ΔNRS-R and ΔPI-R (n = 67)	0.664*
NRS-NR and PI-NR (n = 39)	0.782
ΔNRS-NR and ΔPI-NR (n = 39)	0.630

* $p < 0.05$. PI, pain index; NRS, numerical rating scale; PI-R, PI of patients with significant relief after treatments (NRS scores decreased ≥ 50%); NRS-R, NRS scores of patients with significant relief after treatments (NRS scores decreased ≥ 50%); ΔNRS, the changes of NRS before and after treatments; ΔPI, the changes of PI before and after treatments; ΔNRS-R, the changes of NRS before and after treatments in patients with significant relief after treatments (NRS scores decreased ≥ 50%); ΔPI-R, the changes of PI before and after treatments in patients with significant relief after treatments (NRS scores decreased ≥ 50%); ΔNRS-NR, the changes of NRS in patients with no significant relief after treatments (NRS scores decreased < 50%); ΔPI-NR, the changes of PI in patients with no significant relief after treatments (NRS scores decreased < 50%).

A significant positive association was also found between the changes in NRS (ΔNRS) and the changes in PI (ΔPI) of the 111 patients ($r = 0.721$, $p < 0.05$) (Table 3). Figure 2 shows the scatter plot and the positive linear trend for the association between ΔPI and ΔNRS ($R^2 = 0.52$).

Association between PI and NRS in patients with significant pain relief after treatments

To determine whether PI was affected when pain changed significantly (as shown by NRS decreasing ≥50%), we analyzed the association between NRS and PI in patients with significant pain relief after treatments (NRS-R and PI-R, respectively). There was a significant positive association between NRS-R and PI-R ($r = 0.840$, $p < 0.05$) (Table 3). The scatter plot of NRS-R and PI-R (Fig. 3) shows the linear trend for the relationship ($R^2 = 0.71$).

A Pearson correlation of the changes in NRS and the changes in PI in patients with significant pain relief after treatments (ΔNRS-R and ΔPI-R, respectively) revealed a correlation coefficient of 0.664 (n = 67, $p < 0.05$) (Table 3), indicating a strong positive association. The scatter plot of ΔNRS-R and ΔPI-R (Fig. 4) shows the linear trend for the relationship ($R^2 = 0.44$).

Association between PI and NRS in patients with no significant pain relief after treatments

We found a significant positive association between NRS in patients with no significant pain relief (NRS decreasing <50%) after treatments (NRS-NR) and PI after treatments (PI-NR) ($r = 0.782$, $p < 0.05$) (Table 3). The scatter plot of PI-NR and NRS-NR (Fig. 3) shows the linear trend for the relationship ($R^2 = 0.61$).

The Pearson correlation of the changes of NRS-NR (ΔNRS-NR) and the changes of PI-NR (ΔPI-NR) before and after treatments revealed a correlation coefficient of 0.630 (n = 39, $p < 0.05$), indicating a strong positive association. The scatter plot of ΔNRS-R and ΔPI-R (Fig. 4) shows the linear trend for the relationship ($R^2 = 0.40$).

Furthermore, in order to determine whether the pain relief treatments affected PI in assessing pain, we compared the 95% confidence intervals of the R values of difference in NRS and PI in the significant pain relief group (0.6308 and 0.6972, respectively) and the no significant pain relief group (0.5985 and 0.6615, respectively). There was an overlap for these two intervals, indicating that there is no significant difference between the two correlation coefficients.

ROC analysis

The data from the 111 participants included 222 pairs of PI and NRS. NRS <4 were considered negative and NRS ≥4, positive. There were a total of 74 pairs in the negative group and 148 pairs in the positive group. We used ROC curves to analyze the sensitivity and specificity of PI to assess moderate-to-severe chronic pain (Fig. 5). The best fit with NRS categories was found with the following cut-off points based on the ROC curves: mild pain (NRS <4, PI <10.65), moderate pain ($4 \leq$ NRS < 7, $10.65 \leq$ PI < 22.7), and severe pain (NRS >7, PI ≥22.7). From the ROC analysis, we found that the sensitivity of PI to NRS ≥4 was

80.4%, and the specificity was 86.5%, while the sensitivity of PI to NRS ≥7 was 100%, and the specificity was 93.9%. Table 4 shows the results of the ROC analysis.

Table 4 ROC analysis of PI and NRS

	AUC (95% CI)	Cut-off value	Sensitivity	Specificity
NRS ≥ 4	0.912 (0.875, 0.948)	10.65	0.804	0.865
NRS ≥ 7	0.988 (0.973, 1)	22.7	1	0.939

AUC, area under the curve.

Associations of age, anxiety, and depression with PI

In this study, 63 patients completed the HADS. Multiple regression was conducted using PI_{before} as the dependent variable (y) and using age and the anxiety (ANX) and depression (DEP) scales of the HADS as independent variables; age was x_1, ANX was x_2, and DEP was x_3. The resulting model was $y = 13.053 - 0.014x_1 + 0.541x_2 + 0.23x_3$, with an adjusted R^2 of 0.138. Although the model (i.e., Model 1) was statistically significant ($p < 0.05$), the low R^2 indicated that the model was not a good fit, accounting for only a small proportion of the variance in PI_{before}, and that PI_{before} was significantly related to anxiety but not depression or age.

Given the results of Model 1, Model 2 tested the association of anxiety as the sole independent variable, with PI as $y = 13.114 + 0.735x_1$. The adjusted R^2 of Model 2 was 0.15, and it was not statistically significant. The results of the two models suggest that PI may be influenced more by anxiety than by depression, but the influence is small.

Discussion

Our study used PI extracted from EEG signals to objectively quantify pain levels. According to our results, (a) PI had a significant positive correlation with NRS, (b) PI had good sensitivity and specificity to identify moderate-to-severe pain, and (c) PI appeared to be only slightly affected by anxiety or depression.

In recent years, EEG has become one of the main techniques for exploring pain mechanisms [11 – 14]. Pain can activate the brain's reticular formation [15, 16], including the somatosensory cortex, insular lobe, cingulate gyrus, prefrontal cortex, subcortex, and brainstem regions, leading to changes in brain waves, which makes EEG a useful measure of pain [17 – 20].

Chronic pain has been correlated with a wide spectrum of EEG and magnetoencephalography, and patients with chronic pain exhibit hyperpolarization of thalamic interneurons [21 – 26]. For chronic pain patients, the α wave activity of EEG may be reduced and confined to the insular or the frontal lobe [27, 28]. Chronic pain is often accompanied by emotional problems and sleep disorders, which can also lead

to changes in brain waves. A recent study of EEGs from 103 conscious patients with chronic pain found that both the degree of pain and sleep disorders were associated with decreased α waves in the frontal and parietal cortices [29]. However, there is no generally accepted objective, quantitative EEG PI.

PI is a quantitative index that was developed in 2015, which is obtained by analyzing and processing cerebral cortical EEG signals. It has been confirmed that PI was higher in pain patients than in healthy volunteers [9]. The HXD-1, which is a dual-lead EEG acquisition system, collects the EEG signals of the left and right prefrontal lobes and uses wavelet calculation technology to decompose the pain components in the brain waves. According to the brain atrioventricular model,the potential changes at any point on the scalp are the combined effects of the electrical signals accompanied by the activity of all neuronal cells, and the activity of neuronal cells forms the performance of brain function. Therefore, any potential on the scalp contains all the information about the brain functions and the working information of neurons in the cerebral cortex. The only difference is the shape and intensity of the signal. The wavelet calculation algorithm used in this monitor can separate the weak components of different parts and decompose the pain components in the brain waves.

To exclude the effects of variables such as age, sex, and type of disease, and to reduce systemic errors due to intra-individual differences, we compared the changes of PI and NRS before and after treatments (ΔPI and ΔNRS, respectively) for patients with chronic pain. We found that ΔPI was positively related to ΔNRS, indicating that changes in PI were associated with pain intensity.

As the intensity of a painful stimulus is negatively related to α and β brain waves and is stimulus-position dependent [30], the power of specific EEG frequency, included in PI, is lower in the moderate-intense pain group compared to mild pain group. The results of our study showed that the more severe the pain, the better the specificity and sensitivity of EEG. In our study, we found that the sensitivity of PI to NRS ≥ 4 was 80.4% and the specificity, 86.5%; and that the sensitivity of PI for NRS ≥ 7 was 100% and the specificity, 93.9%. These data suggested the feasibility of PI to assess both moderate and severe pain.

A correlation analysis in patients with significant pain relief after treatments (NRS score decrease ≥ 50%) found that PI-R and NRS-R were highly correlated (r = 0.840), and the correlation of PI and NRS was 0.800. The correlation coefficient did not change significantly. This may be due to noxious stimulation activating the reticular formation of the brain [15, 16]. These brain regions produce neuronal responses in different frequency ranges, from θ (4–7 Hz) through α (8–13 Hz) and β (14–29 Hz) to γ (30–100 Hz), and these responses vary with the intensity of the stimulus and pain. This brain wave response may make the patients more sensitive to pain. Therefore, when the pain was significantly relieved, the correlation between PI and NRS did not change significantly, indicating that PI was a relatively objective and accurate method to assess the degree of pain.

In both the significant pain relief group and the no significant pain relief group, the changes in NRS and the changes in PI had a strong positive association (r = 0.664 and r = 0.630, respectively). There is no significant difference between the two correlation coefficients of the two groups, indicating that the treatments did not affect PI in detecting the patients' chronic pain.

Chronic pain is often associated with anxiety, depression, and other psychiatric problems [31 – 34], and emotions are known to affect the pain perception of patients. However, the results of this study suggest that PI was only slightly affected by anxiety or depression, which makes it a more objective, accurate, and comprehensive indicator than other measures.

Limitations

The EEG data could be collected from within 10 minutes in a quiet room. But PI was not determined in real time and needed to be calculated by a technician later.

A single-dimensional scale or a simple analysis of pain intensity may have some limitations in assessing chronic pain. In this study, only a single measure, NRS, was selected as the gold standard for pain assessment. In future studies, the feasibility and stability of PI should be evaluated for different degrees and different properties of pain, as well as the relationship to sleep quality.

This study only examined PI in conscious patients with chronic pain. Our conclusions may not apply to patients with acute pain or patients under general anesthesia.

Conclusion

This study found that PI extracted from EEG had a moderate-to-high positive correlation with NRS in chronic pain patients, and PI appeared to be only slightly affected by anxiety or depression. Therefore, it is feasible to use PI to assess moderate-to-severe chronic pain.

Declarations

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Figures

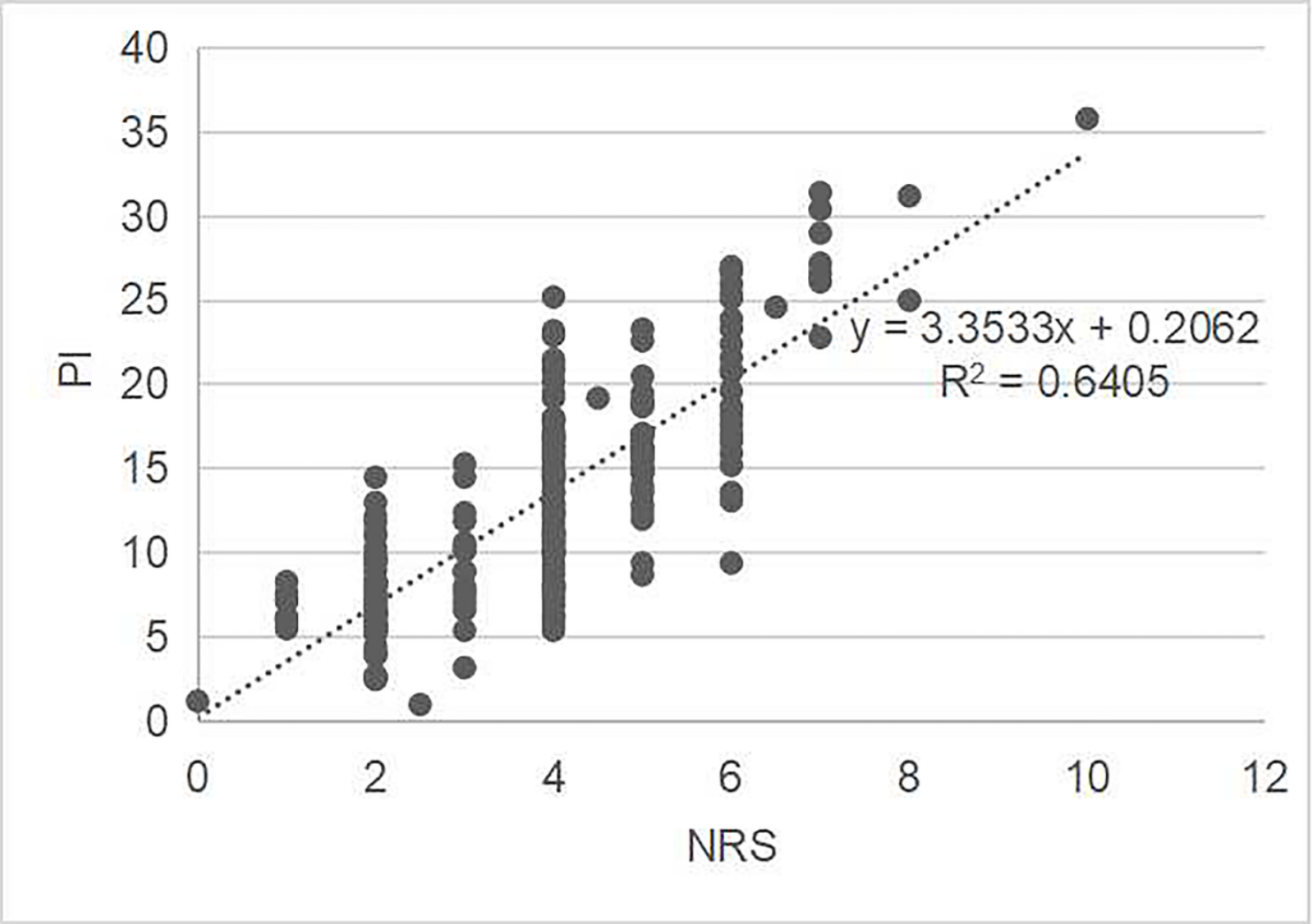

Figure 1

Scatter plot and trend line for the association between the pain index (PI) and the numerical rating scale (NRS) score. The figure shows that PI had a significant positive correlation with NRS (R^2 = 0.6405, n = 111).

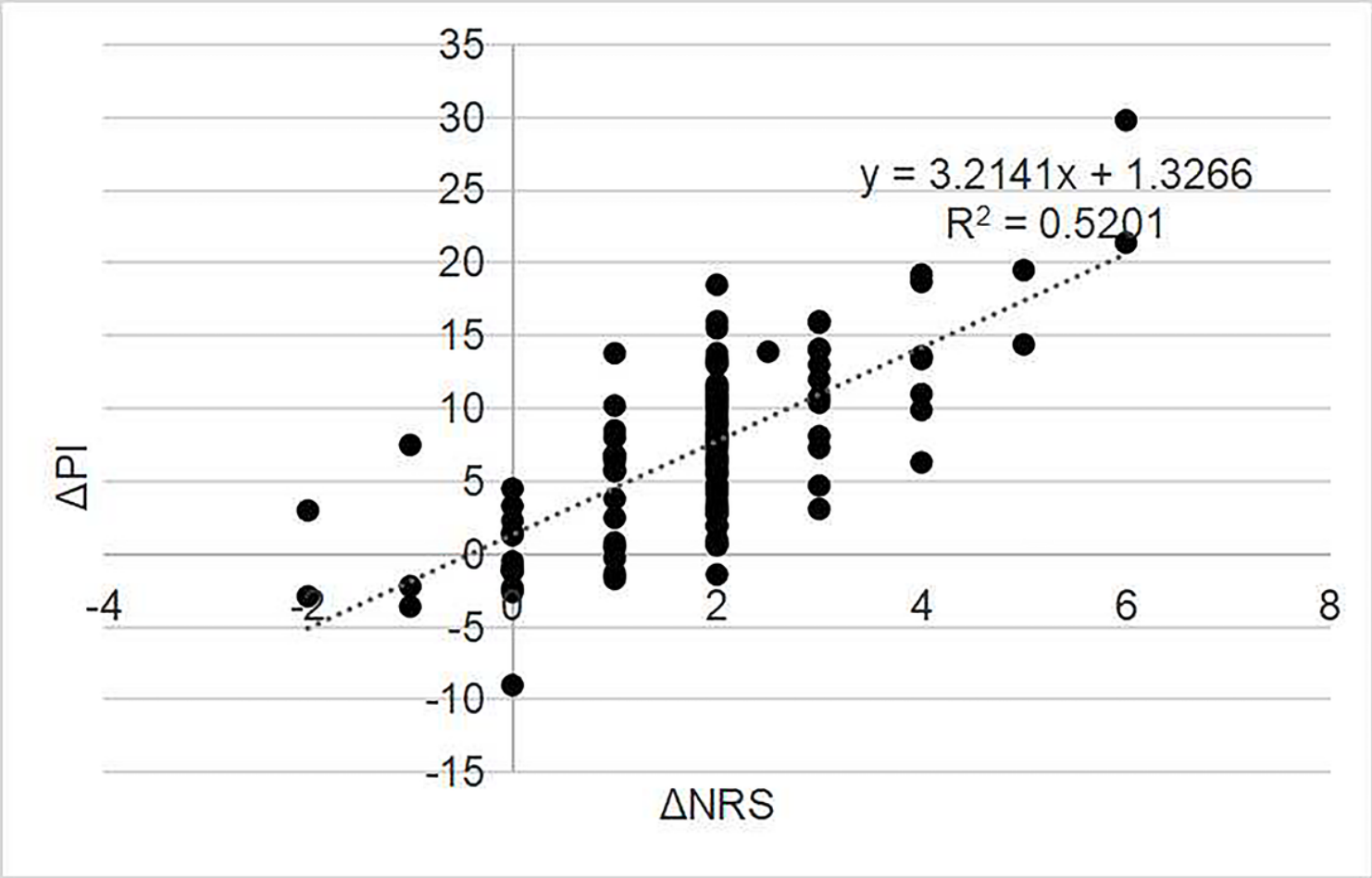

Figure 2

Scatter plot and trend line for the association between the change in the pain index (ΔPI) and the change in the numerical rating scale (ΔNRS) of pain before and after treatments. ΔPI had a significant positive correlation with ΔNRS (R^2 = 0.5201, n = 111).

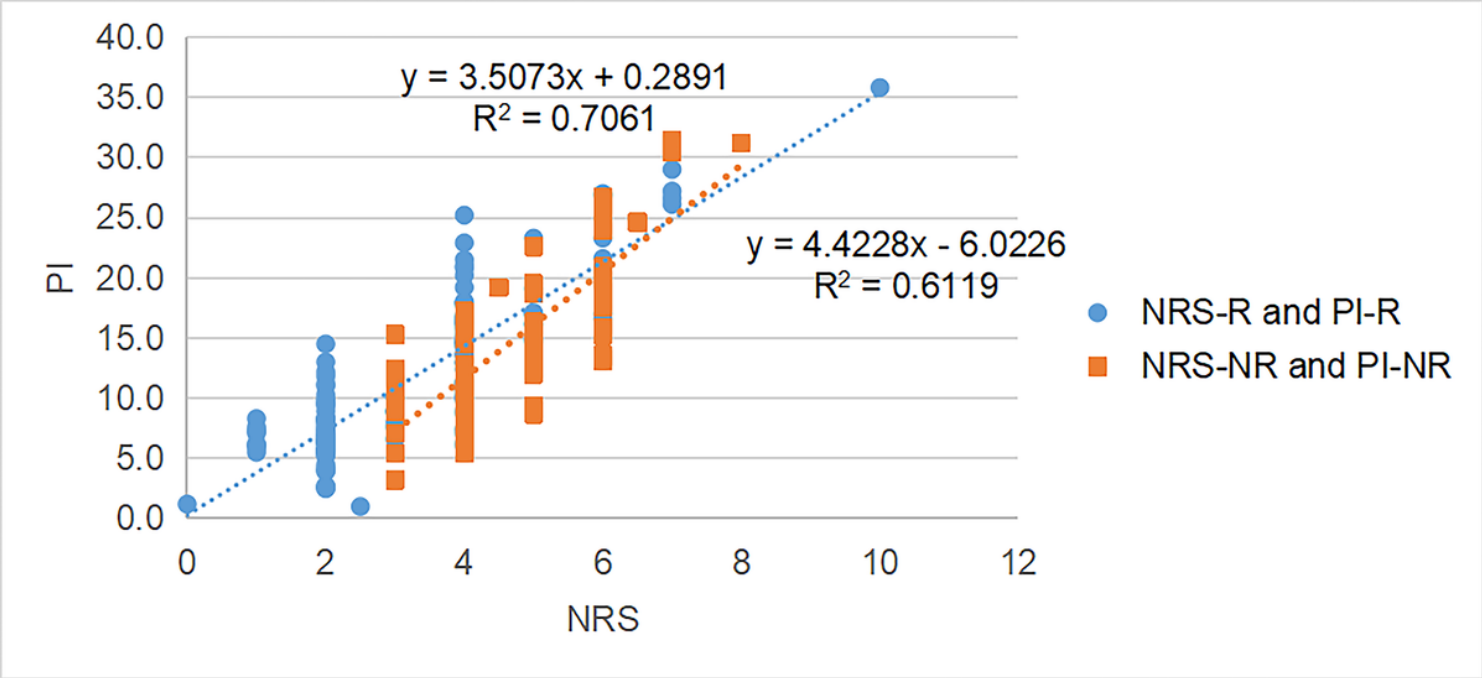

Figure 3

The orange scatter plot and trend line refers to the association between the pain index (PI-R) and the numerical rating score (NRS-R) in patients with significant pain relief after treatments (NRS decreased ≥50%). The blue scatter plot and trend line refers to the association between the pain index (PI-NR) and the numerical rating scale (NRS-NR) score in patients with no significant pain relief after treatments. This figure shows that PI-R had a significant positive correlation with NRS-R in the significant pain relief group (R^2 = 0.7061, n = 67), and that PI-NR and NRS-NR were positively correlated (R^2 = 0.6119, n = 39).

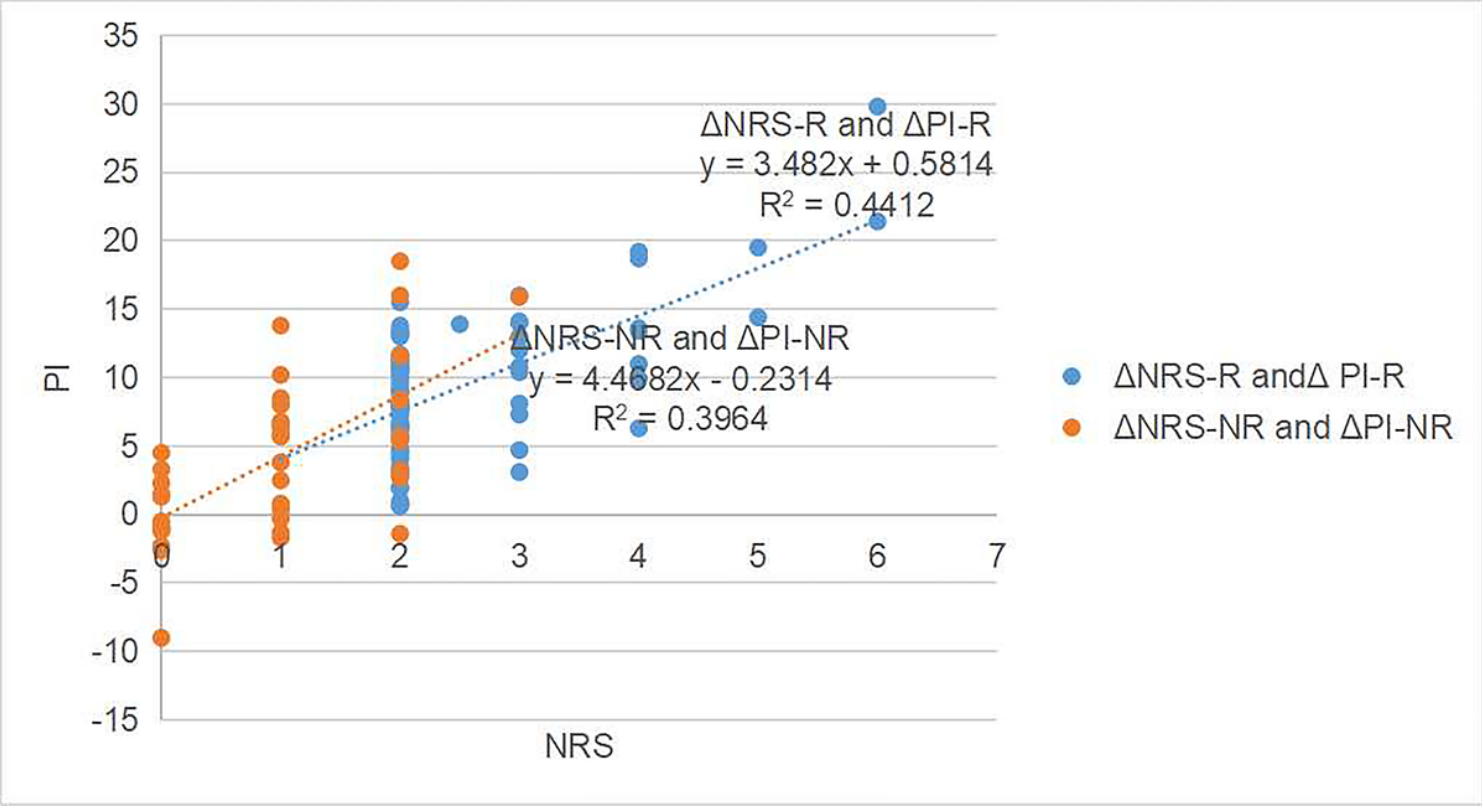

Figure 4

The orange scatter plot and trend line refers to the association between the changes in the pain index (ΔPI-R) and the changes in the numerical rating score (ΔNRS-R) in patients with significant pain relief after treatments (NRS decreased ≥50%). The blue scatter plot and trend line refers to the association between the changes in the pain index (ΔPI-NR) and the changes in the numerical rating scale (ΔNRS-NR) in patients with no significant pain relief after treatments. The figure shows that the ΔPI-R had a positive correlation with the ΔNRS-R in the significant pain relief group (R^2 = 0.4412, n = 67), and that the ΔPI-NR and the ΔNRS-NR were positively correlated (R^2 = 0.3964, n = 39).

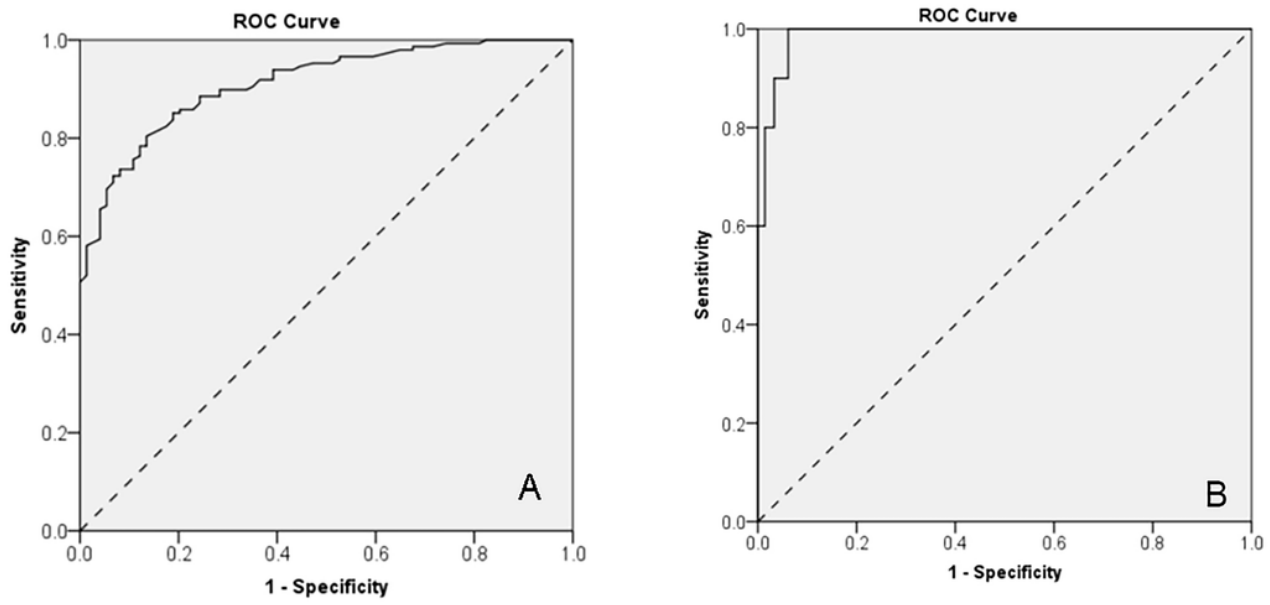

Figure 5

Receiver operating characteristic curve (ROC) curves for the pain index (PI) and the numeric rating scale (NRS). A shows the ROC analysis of PI and NRS for moderate and severe pain (NRS ≥4), and B shows the ROC analysis of PI and NRS for severe pain (NRS ≥7).