

Association Between Non-spinal Comorbid Medical Conditions and Neuropathic Low Back Pain. – A Further Unravelling of Pain Complexities in the Context of Back Pain

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Abstract

Study Design: Prospective cohort study.

Objective: Understanding the complex nature of low back pain (LBP) is crucial for effective management. The PainDETECT questionnaire is a tool that distinguishes between neuropathic (NeP) and nociceptive (NoP) low back pain. Traditionally NeP and NoP have been primarily attributed to patho-anatomical abnormalities within the lumbar spine. However, increasing evidence points to multifaceted involvement, encompassing a range of physical, biomechanical, chemical, and psychosocial factors. The study aimed to determine the independent relationship between NeP as assessed by the PainDETECT questionnaire and non-spinal comorbid medical conditions.

Methods: A prospective cohort study was conducted involving 400 patients suffering from chronic LBP (>6months), aged >18 years, who complete the PainDETECT questionnaire and provided responses regarding the presence of any comorbid conditions. A binary logistic regression model was used to analyse the confounding status of comorbid medical conditions and pain severity measured by NRS to determine independent relationships between specific conditions and neuropathic pain.

Results: The study included 143 and 257 patients suffering from NeP and NoP, respectively. The NeP group had a 38% higher mean numerical rating scale score compared to the NoP group (8.10 ± 1.55 vs 5.86 ± 2.26 , $P < 0.001$). The odds of developing NeP were 2.9 $\text{Exp(B)} = 2.844$, 95%C.I. [1.426-5.670], $P < 0.01$, 2.7 ($\text{Exp(B)} = 2.726$, 95%C.I. [1.183-6.283], $P < 0.05$) and 2.8 ($\text{Exp(B)} = 2.847$, 95%C.I. [1.473-5.503], $P < 0.05$) times higher in patients suffering from gastrointestinal conditions, rheumatoid arthritis, and depression, respectively.

Conclusion: NeP as determined by the PainDETECT questionnaire, is associated with gastrointestinal conditions, rheumatoid arthritis, and depression. This pioneering study has shed light on the potential involvement of the gut microbiome as a common factor connecting non-spinal comorbidities and NeP. These findings underscore the importance of formulating personalized management plans tailored to individual pain and medical profiles, rather than relying on a blanket approach to pain management.

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Keywords

neuropathic pain, low back pain, PainDETECT questionnaire, comorbidities, gut microbiome

Introduction

Low back pain (LBP) is the leading cause of work absenteeism and has profound effects on physical, psychological, social, and functional wellbeing of patients.¹ The consequences of LBP vary among individuals and is complex at a systems level. Pain has been traditionally studied using a scalar measurement for its “intensity”, however, the nature of pain incorporates various descriptors and current research postulates LBP is a linear spectrum consisting of predominantly nociceptive on one end and neuropathic on the other.² Nociceptive LBP (NoP) results from the activation of nociceptors which innervates many structures in the lumbar spine. It is thought to be a protective mechanism against actual or potential tissue damage.³ Neuropathic LBP (NeP) is caused by a ‘lesion or disease of the somatosensory nervous system’.⁴ It predominantly effects the radicular nerve tissues through mechanical compression or the action of chronic inflammatory mediators originating from the degenerated disk.^{5,6}

The PainDETECT questionnaire consists of 7 questions measuring various sensory aspects associated with neuropathic LBP, such as burning sensations, tingling, numbness, sensitivity to touch and pressure, and the occurrence of sudden pain attacks. Scores from each section are summed to obtain an overall PainDETECT score (≤ 12 = NoP, 13-18 = ambiguous, ≥ 19 = NeP) (Supplemental 1).⁷ It was developed by Freynhagen et al and serves as the only validated tool for distinguishing NeP in an LBP setting.⁸

Traditionally, NeP and NoP have been regarded as discrete entities, primarily attributed to patho-anatomical abnormalities within the lumbar spine.^{6,9} However, it is increasingly evident that the nature of both pain classifications is multifaceted, encompassing a range of physical, biomechanical, chemical, and psychosocial factors.¹⁰ Notably, epidemiological investigations have consistently revealed a higher prevalence of comorbid musculoskeletal disorders, cardiovascular disease, depression, gastrointestinal conditions, etc. among individuals with chronic LBP in comparison to their non-LBP counterparts.¹¹ While this underscores the possibility that specific classifications of LBP may not exclusively originate from lumbar spinal pathology, our understanding of the intricate interplay between comorbidities and NeP/NoP remains limited.

The presence of comorbidities bears substantial consequences for patients’ disability and quality of life, posing multifaceted challenges to clinical management.^{12,13} Consequently, it becomes pertinent to contemplate whether NeP is solely attributable to lumbar spinal anatomical alterations or if it represents but one facet of a broader spectrum of symptoms associated with compromised health. Delving into these

associations promises to augment our comprehension of NeP’s pathophysiology, with a particular focus on discerning its potential link to systemic inflammatory conditions vis-à-vis its localized spinal manifestation. Furthermore, this study offers the prospect of informing primary care physicians to incorporate neuropathic pain screening and consider these associated conditions before contemplating referrals to specialized spine centres.

Current literature provides limited analysis on the relationship between non-spinal comorbid medical conditions and NeP. Previous published studies have only focused on chronic LBP and did not account for the confounding nature of various co-morbid conditions. Therefore, it is interesting to ponder whether some comorbid conditions in patients with chronic LBP are independently associated with NeP. By elucidating these associations, clinicians can provide tailored treatment plans to manage individual patient’s pain conditions. A secondary cohort study of a prospectively collected database was used to explore associations between non-spinal comorbid conditions and pain classifications assessed by the PainDETECT questionnaire to allow for an improved understanding into the development of NeP and further guide treatment.

Materials and Methods

Study Design and Population

The study was IRB approved for an analysis of an ongoing prospectively collected database. Written approval for the use of an electronic format PainDETECT questionnaire was granted by the original developer for the purpose of this study.⁷ All patients provided inform consent prior to enrolling

Table 1. Patient Initial Intake Assessment. Patient Reported Past Medical History Categories.

Comorbid Medical Conditions	
Past medical history	Have you had or have Hypertension (high blood pressure) Diabetes Cardiovascular (heart) disease Lung disease Depression Other mental health disorder Rheumatoid arthritis Gastrointestinal conditions Kidney disease Liver disease Peripheral vascular disease Cancer Other all recorded [Yes/No]

into the study. The study was conducted as a cohort study of adult patients (over 18 years of age) suffering from chronic (over 6 months) low back and/or leg pain who presented to a tertiary spine clinic. Patients were included if they completed the PainDETECT questionnaire used to assess the nature of pain and a comorbidity questionnaire (Table 1) used to gather information about non-spinal comorbid conditions that the patient may have. This information was used to perform a binary logistic regression with the overall objective to investigate the relationship between NeP and non-spinal comorbid conditions. Patients were excluded if they had a history of lumbar spinal surgery, were diagnosed with specific pathologies spinal pathologies (i.e. vertebral fracture, malignancy, infection, axial spondylarthritis, cauda equina syndrome etc.), or if they had spinal deformities.

Data Collection

PainDETECT scores, numerical rating scale (NRS) scores and demographic information encompassing patient gender age were extracted from the tertiary spine clinic's PainDETECT RedCap database. PainDETECT score was dichotomized into the NoP, and NeP groups as defined by the PainDETECT questionnaire. Patient's comorbid conditions were evaluated through a multiple choice questionnaire divided into fourteen different categories (Table 1).

Statistical Analysis

Numerical variables were presented as mean $\pm$ standard deviation (SD). Categorical variables were summarized using counts (n) and percentages (%). Independent *t* test was used to analyse the difference in continuous parameters between the two groups. A binary logistic regression model was used to analyse the confounding status of comorbid medical conditions and pain severity as measured by NRS to determine independent relationships between specific conditions and neuropathic pain. The exponentiation of the B coefficient (Exp(B)) with 95% confidence intervals (95%CI) was calculated to estimate risk. Statistical analyses were conducted using the commercially available software SPSS (version 27, IBM Corporation, New York, USA). The level of statistical significance was set at 5% ($p = 0.05$).

Results

Demographics

A flowchart depicting patient inclusion, exclusion and separation into pain classification groups is shown in Figure 1. Out of the 400 patients included in the study 257 and 143 had nociceptive and neuropathic low back pain, respectively. The neuropathic group had a 38% higher mean NRS compared to the nociceptive group (8.10 ± 1.55 vs 5.86 ± 2.26 , $P < 0.001$).

There was no significant difference in age and gender between the groups (Table 2).

Association Between Comorbid Conditions and NeP

The binary logistic regression model to ascertain the effects of comorbid medical conditions on the likelihood of the presence of neuropathic pain was statistically significant ($\chi^2(13) = 47.118$, $P < 0.001$). The model explained 15.3% (Nagelkerke $R^2 = 0.153$) of the variance in neuropathic pain and correctly classified 69.5% of cases. Patients with depression, rheumatoid arthritis (RA) and gastrointestinal disorders were 2.844 (Exp(B) = 2.844, 95%CI [1.426-5.670], $P < 0.01$), 2.726 (Exp(B) = 2.726, 95%CI [1.183-6.283], $P < 0.05$) and 2.847 (Exp(B) = 2.847, 95%CI [1.473-5.503], $P < 0.05$) times more likely to suffer neuropathic pain than nociceptive pain respectively. Hypertension, diabetes, cardiovascular disease, lung disease, other mental health disorders, kidney disease, liver disease, peripheral vascular disease, cancer, and other conditions were not associated with an increased likelihood of neuropathic pain (Table 3).

Discussion

This study demonstrated that in chronic LBP patients who suffer from gastrointestinal disorders, RA, or depression, they were 2.85, 2.73 and 2.84 times more likely to have NeP compared to NoP, respectively. The study used a retrospective cohort analysis based on data from an ongoing, prospectively collected database. The aim of the analysis was to examine the association between NeP and NoP as described by the PainDETECT questionnaire with patient self-reported comorbid conditions. Of the 400 patients included, 143 had NeP and 257 had NoP. Patients in the NeP had a 38% higher mean NRS compared to those in NoP. This can be attributed to the perception of NeP by patients as distressing, unfamiliar and unpleasant in nature, resulting in more severe pain intensity, disability, and quality of life.¹⁴

For the first time a binary logistic regression was performed to determine the independent associated comorbid medical conditions with NeP, improving on previous published results which do not address the confounding status if patients suffer from multiple conditions. In seeking a putative common factor that may explain NeP's association with RA, depression and gastrointestinal disorders, our attention was drawn to the microbiome.

Gastro-intestinal disorders generally related to abdominal discomfort and include an entire spectrum of well, poorly and ill-defined abdominal conditions involving the upper, middle and lower gut. The human gut microbiome refers to the collective genomes of 10-100 trillion bacterial cells residing primarily within the colon. A perturbation of microbiome parameters, such as loss of diversity or overgrowth of pathobiont bacteria has been indicated in the pathogenesis of gut inflammation and bowel disorders.¹⁵ In contrast to the past-

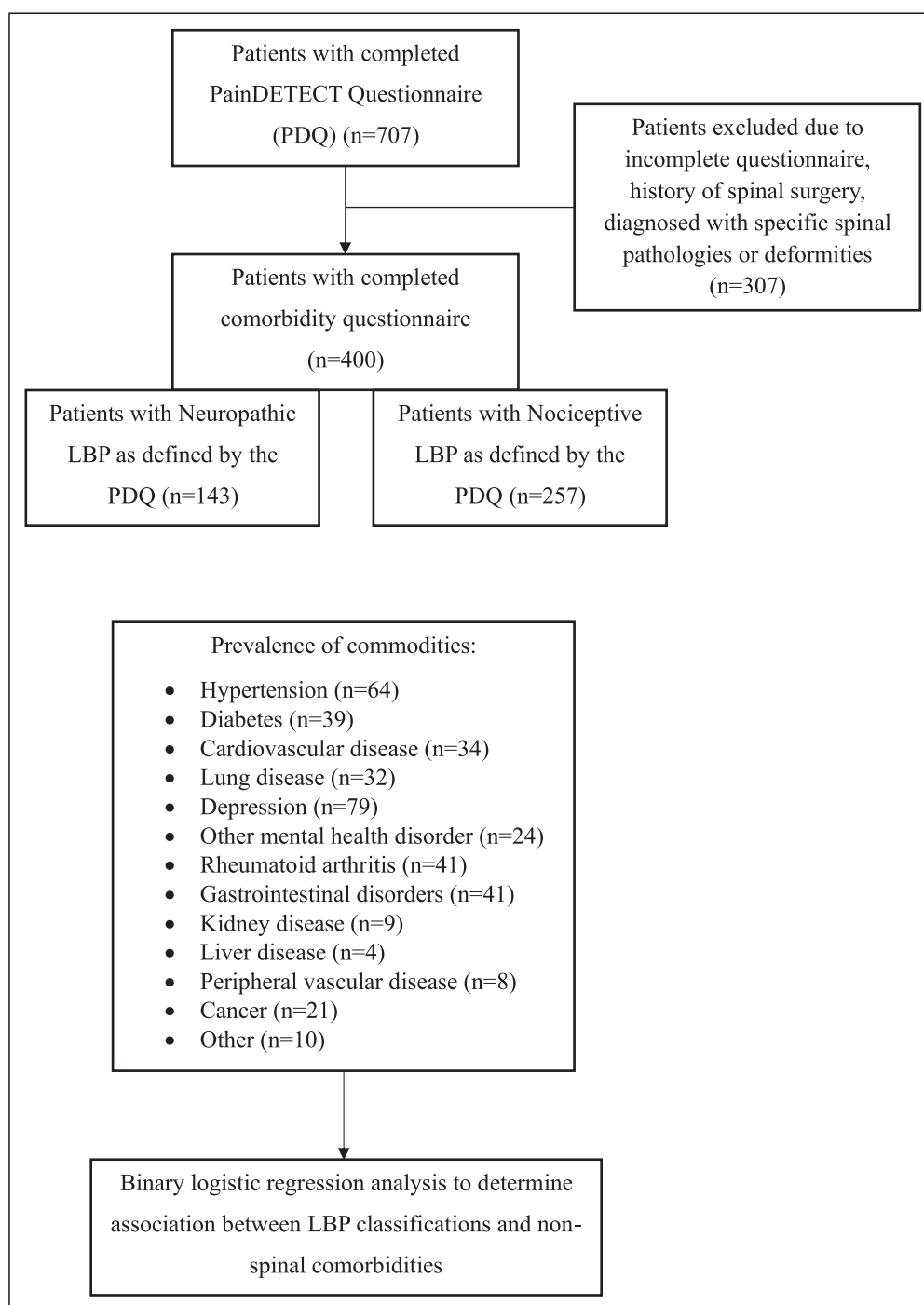


Figure 1. Flowchart depicting the inclusion of participants in the study. Flowchart representing the process of patient inclusion and exclusion into the study with the specific data on the number of patients included/excluded at each step. It illustrates how the patients in the study were divided into nociceptive and neuropathic low back pain as described by the PainDETECT questionnaire, the prevalence of comorbidities and how the data was interpreted to obtain the overall results.

held dogma of intervertebral disk (IVD) sterility, 58 bacterial species have recently been found to correspond between the IVD and the gut. Specifically, an increase in proteobacteria taxa and decrease in firmicutes have been shown in patients with irritable bowel syndrome/disease. Proteobacteria

overgrowth is implicated in the release of pro-inflammatory cytokines IL-8, TNF- α and IL-1 β and firmicutes has been found to abundantly populate IVDs in healthy states.¹⁶ Unsurprisingly, our study found chronic LBP patients with gastrointestinal disorders to be 2.85 times more likely to

Table 2. Patient Demographics and Clinical Data are Categorized Into Different Treatment Groups and Pain Classifications.

Parameter	NoP (n = 257)	NeP (n = 143)	P-Value	Total (n = 400)
Age (mean $\pm$ SD)	56.95 $\pm$ 20.17	55.76 $\pm$ 15.46	0.542	56.99. $\pm$ 18.06
Gender (m/f)	126/131	62/81	0.276	188/212
NRS (mean $\pm$ SD)	5.86 $\pm$ 2.26	8.10 $\pm$ 1.55	<0.001	6.76 $\pm$ 2.14

Pearson chi-square test and analysis of variance (ANOVA) were used to assess association and compare differences between the nociceptive, ambiguous, and neuropathic low back pain as defined by the PainDETECT questionnaire. M: male, F: female, %: percentage, SD: standard deviation.

Table 3. Binary Logistic Regression Model to Determine Associations Between Comorbid Medical Conditions and Neuropathic Pain.

Comorbid Condition (n = 350)	Total, n (%)	Nociceptive, n (%)	Neuropathic, n (%)	Odds Ratio, Exp(B) [95% C.I.]	P-Value
Nil	64 (12.9)	47 (17.2)	17 (7.7)		
Hypertension	89 (18.0)	55 (20.1)	34 (15.3)	1.017 [0.485-2.133]	0.963
Diabetes	39 (7.9)	24 (8.8)	15 (6.8)	0.774 [0.298-2.007]	0.598
Cardiovascular disease	34 (6.9)	23 (8.4)	11 (5.0)	1.311 [0.418-4.108]	0.642
Lung disease	32 (6.5)	15 (5.5)	17 (7.7)	1.048 [0.414-2.651]	0.921
Depression	79 (16.0)	29 (10.6)	50 (22.5)	2.844 [1.426-5.670]	<0.01
Other mental health disorder	24 (4.8)	8 (2.9)	16 (7.2)	1.129 [0.405-3.145]	0.817
Rheumatoid arthritis	41 (8.3)	18 (6.6)	23 (10.4)	2.726 [1.183-6.283]	<0.05
Gastrointestinal conditions	41 (8.3)	17 (6.2)	24 (10.8)	2.847 [1.473-5.503]	<0.05
Kidney disease	9 (1.8)	7 (2.6)	2 (0.9)	0.267 [0.036-1.992]	0.199
Liver disease	4 (0.8)	3 (1.1)	1 (0.5)	8.195 [0.603-114.175]	0.114
Peripheral vascular disease	8 (1.6)	3 (1.1)	5 (2.3)	2.458 [0.302-19.984]	0.400
Cancer	21 (4.2)	17 (6.2)	4 (1.8)	0.259 [0.062-1.076]	0.063
Other	10 (2.0)	7 (2.6)	3 (1.4)	0.470 [0.091-2.436]	0.368

Exp(B): exponentiation of the B coefficient (odds ratio), 95% C.I.: 95% confidence interval for Exp(B), n: count, %: percentage.

present with NeP compared to NoP. NeP is hypothesized to be a result of chronic hyperinflammation persisting after neuronal injury of adjacent nervous structures (e.g. nerve roots, dorsal root ganglion etc.).¹⁷ Nerve endings of the sinuvertebral nerve in degenerated disks have been found to penetrate into the deeper layers of the AF and can even extend into the NP. This is pathoanatomically correlated to discogenic LBP, however, a chronic increase in levels of inflammatory mediators in the IVD can lead to NeP. Degeneration of the IVD may also result in direct mechanical nerve compression via spinal and foraminal canal narrowing. Upregulation of proinflammatory cytokines and morphological changes to the lumbosacral nerve roots can occur, which aids in the pathogenesis of NeP.^{5,6}

Pain processing in inflammatory arthritis may be augmented by a range of factors driven by chronic inflammation and its interactions with other risk factors, including genetic background, comorbidities, and psychological status.¹⁸ Chronic inflammation due to synovitis generates various bioactive lipids, kinins, cytokines (e.g., tumour-necrosis-factor alpha [TNF- α], interleukin-1 [IL-1], interleukin-6 [IL-6]), neuropeptides (e.g., calcitonin-gene related peptide) and neurotrophins, which may lead to local sensitisation of peripheral nerves within the affected joint, pathologically increasing nociceptive input. As such, sustained nociceptive

input may lead to changes in central pain processing pathways via central sensitisation leading to NeP.¹⁹ This mechanism was corroborated by our study which found chronic LBP patients suffering from RA to be 2.73 times more likely to have NeP compared to NoP. Furthermore, due to the systemic nature of inflammation in RA, circulating cytokines may gain access to the CNS in instances where the blood-brain barrier is compromised by such inflammation. Immune cells within the CNS may also directly release various cytokines. Ultimately, the release of proinflammatory cytokines in both instances may also directly contribute to the development of central sensitisation.²⁰ Associations have also been established between synovitis and pathologic central/peripheral pain processing, both of which may precipitate the development and exacerbation of NeP.²¹ A cohort study by Ahmed et al. substantiates these findings, establishing one third of RA patients to suffer possible or likely neuropathic pain as quantified by the PD-Q.²²

Several associations are present between the neurobiology of depression and pathophysiological mechanisms underpinning the development of NeP, as both disorders share multiple biological and environmental bases. Dysregulation of stress and inflammatory pathways promotes alterations in neural circuitry that modulates mood, pain, and the stress response. Over time, functional changes are likely to promote

disruptions in neurotrophic support and glial-neuronal communication, processes that have both been implicated in the pathogenesis of NeP and depression.²³ An imaging study by Apkarian et al found significantly reduced grey matter volume in the dorsolateral prefrontal cortex (DLPFC) and thalamus of chronic LBP patients when compared to controls. Decreased DLPFC grey matter density was correlated with increased pain intensity, duration, and negative emotional affect.²⁴ Considering the established role of the DLPFC in top-down regulation of limbic and paralimbic prefrontal areas, it is conceivable that morphological changes within the DLPFC may contribute to compromised emotional and pain modulation apparent in both depression and NeP. Our study corroborated these findings, demonstrating patients diagnosed with moderate or severe depression to be 2.84 times more likely to experience neuropathic compared to nociceptive LBP.

In addition to gastrointestinal disorders, rheumatoid arthritis and depression have also been found to be associated with dysbiosis of the gut microbiome, specifically via elevated levels of pathognomonic bacteria and the gut-brain axis, respectively.^{25,26} The role of the gut microbiome in the pathogenesis of NeP remains debated. While studies have reported associations between gut microbiome dysbiosis, infiltration of gut-specific bacteria, IVD degeneration, and NeP, a definitive causal pathway has yet to be established.¹⁶ Furthermore, conflicting findings exist, with some studies failing to detect differences in bacterial profiles between degenerative and normal IVDs.²⁷ The gut disk axis has been hypothesized as a pathway for intestinal microbes to gain access to the IVD and a possible pathological mechanism for NeP.²⁸

Future prospective cohort studies are needed to incorporate advanced analytical techniques, such as next-generation sequencing for RNA expression analysis of gut and IVD microbiomes. These studies are essential for conducting cluster analyses and constructing causal decision trees, which will significantly advance our comprehension of the intricate interactions between comorbid medical conditions and NeP. Understanding the precise role of the gut microbiome in pain modulation is crucial for developing innovative treatment strategies, including dietary interventions, prebiotics, probiotics, and faecal transplantation, tailored to patients with NeP.

The results of this study were impacted by certain limitations. Firstly, imaging studies were not conducted to rule out other causes of low back pain. Duration of comorbidity was also not documented, which limited the studies ability to determine causal links. Additionally, the study only included patients presenting to a tertiary spine clinic, limiting the generalisability of the results to the wider population. In addition to more complex analysis of the gut and IVD microbiome, the establishment of a prospective registry of patients with NeP will allow for longitudinal tracking of individual patients. This initiative aims to elucidate the natural

history of NeP and investigate whether comorbid conditions predispose individuals to NeP or vice versa.

Conclusion

Patients with chronic LBP who suffer from gastrointestinal conditions, RA and depression were 2.9, 2.7 and 2.8 times more likely to present with NeP compared to NoP, respectively. NeP was also associated with a higher NRS compared to NoP. Ultimately, NeP is an intricate and multifaceted clinical phenomenon characterized by a myriad of complex components. Continued exploration into understanding these associated comorbidities and unravelling the intricate interconnected pathophysiology represents a critical endeavour in LBP management. The anticipated outcome is to individualize treatment for LBP by addressing its multifaceted nature with the potential to significantly enhance patient outcomes.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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IRB Statement

IRB approval was obtained from the Human Research Ethics Committee of the University of Wollongong (HREC No. 2020/329) and the University of New South Wales (HC210096) for collection of anonymized patient's initial intake forms including past medical history and PainDETECT data from digital archives.

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Supplemental Material

Supplemental material for this article is available online.

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