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3 Suicidal thoughts and behaviors in Patients with Chronic Pain, with and without co-
4 occurring Opioid Use Disorder
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41

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44 Running Title: Chronic pain, Opioid Use Disorder and Suicide
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ABSTRACT

Background: Individuals with chronic pain and a co-occurring substance use disorder present higher risk of suicide, but the individual and joint impacts of chronic pain and substance use disorders on suicide risk are not well defined. The objective of this study was to exam the factors associated with suicidal thoughts and behaviors in a cohort of patients with chronic non-cancer pain (CNCP), with or without concomitant opioid use disorder (OUD).

Design: Cross sectional cohort design

Setting: Primary care clinics, pain clinics, and substance abuse treatment facilities in Pennsylvania, Washington, and Utah

Subjects: 609 adults with CNCP treated with long-term opioid therapy (≥ 6 months) who either developed an OUD (cases, $n = 175$) or displayed no evidence of OUD (controls, $n = 434$).

Methods: The predicted outcome was elevated suicidal behavior in patients with CNCP as indicated by a Suicide Behavior Questionnaire-Revised (SBQ-R) score of 8 or above. The presence of CNCP and OUD were key predictors. Covariates included demographics, pain severity, psychiatric history, pain coping, social support, depression, pain catastrophizing and mental defeat.

Results: Participants with CNCP and co-occurring OUD had an increased odds ratio of 3.44 in reporting elevated suicide scores as compared to participants with chronic pain only. Multivariable modeling revealed that mental defeat, pain catastrophizing, depression, and having chronic pain, and co-occurring OUD significantly increased the odds of elevated suicide scores.

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Conclusions: Patients with CNCP and co-morbid OUD are associated with a 3-fold increase in risk of suicide.

Key Words: Chronic pain, suicide risk, opioid use disorders

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Introduction

Death by suicide has become a global epidemic. The World Health Organization published, "Suicide Worldwide 2019" which highlighted the magnitude of this problem: more than 700,000 people die due to suicide every year; every 40 seconds someone in the world dies of suicide; for every suicide there are many more people who attempt suicide; 77 % of suicides occur in low and middle-income countries, experiencing conflict, disaster, violence, abuse or loss and a sense of isolation are strongly associated with suicidal ideation; and suicide rates are also high amongst vulnerable groups who experience discrimination [1]. In 2019, suicide was the 10th leading cause of death in the United States among all ages [2].

Certain patient populations are at higher risk for suicide and suicidal behaviour including patients that suffer from chronic pain and individuals with substance use disorders (SUD). Extant literature reveals that the prevalence of suicidal ideation in patients with chronic pain ranges from 18%-50% [3-6]. A systematic review by Tang and Crane [6] discovered that the risk of death by suicide was doubled in patients with chronic non-cancer pain (CNCP) as compared to non-pain controls. Data from a national household survey of 8841 individuals in Australia found that the odds of a lifetime and past 12-month suicidality were two to three times greater in individuals with chronic pain as compared to patients with no history of chronic pain and 65% of people who engaged in suicidal behaviour in the previous 12 months had a history of chronic pain [7]. A more recent national study by Campbell and colleagues [8] evaluated 2590 closed cases of intentional deaths in Australia in 2014. CNCP was identified in 14.6 %

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3 of the cases. Decedents with CNCP were more likely to be older, have more mental and
4
5 physical health problems, and were more likely to die from an overdose of drugs.
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8 Another population vulnerable to suicide are patients with SUDs. Approximately
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10 40% of patients seeking treatment for SUDs report a history of suicidal attempts [9-11].
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12 Individuals with an alcohol use disorder are almost 10 times more likely to die by suicide
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14 and those who inject drugs are approximately 14 times more likely to die by suicide, as
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16 compared to the general population [12]. Persons with SUD have multiple risk factors
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18 for suicidal ideation/suicidal behavior including experiencing co-morbid depression and
19
20 enduring a myriad of severe stressors such as loss of relationships, jobs, financial
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22 problems, and other health conditions related to their SUD. Notably, persons with
23
24 chronic pain have similar stressors putting them at risk for suicidal ideation/suicidal
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26 behavior [13] and approximately 10% of patients with chronic pain exposed to
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28 prescription opioids develop an OUD, which is not inconsequential [14,15]. Thus,
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30 patients with co-occurring pain and OUD may be at high risk for attempting and/or
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32 ending their lives by suicide, but there is scant literature on the prevalence and unique
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34 risk factors for this patient population.
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40 The objective of this cross-sectional study was to evaluate risk of suicide and
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42 identify factors associated with elevated suicide scores in a cohort of patients with
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44 CNCP on prescription opioid therapy with no evidence of OUD and identify independent
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46 factors associated with the effect of concomitant OUD.
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49 **Methods**

50 Participant Eligibility and Recruitment

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3 This study presents a secondary analysis of data collected for a larger parent
4 study assessing phenotypic and genotypic characteristics of patients with CNCP who
5 developed an OUD [16]. In this study, cases (n = 175) were patients with CNCP who
6 met DSM-IV [17] criteria for OUD following the initiation of long-term opioid therapy
7 (LTOT) defined as being prescribed opioid analgesia for \geq 6 months. Control
8 participants (n = 434) were patients with CNCP on LTOT who had no evidence of OUD
9 or meeting established criteria for OUD. Controls were recruited from primary care and
10 pain clinics in Pennsylvania (University of Pennsylvania), Washington (University of
11 Washington), and Utah (Lifetree Pain Center). Cases were recruited from SUD
12 treatment facilities associated with all three recruitment sites. Participants entered the
13 study between November 2012 and September 2018. The University of Pennsylvania,
14 the University of Washington and the Lifetree Institutional Review Boards approved and
15 monitored the protocol. Participants provided written consent before beginning the study
16 and were reimbursed for participation.

35 Inclusion/Exclusion Criteria

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37 Inclusion criteria included adult patients (age 18 or older) who were Caucasian
38 and of European descent; have CNCP of musculoskeletal or neuropathic origin for at
39 least 6 months; without a history of SUD (other than nicotine) before initiating LTOT and
40 either developed an OUD (cases) or did not (controls). The genotypic aims of the parent
41 study excluded the inclusion of patients of non-Caucasian races and ethnicities.

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43 Exclusion criteria included individuals with severe psychiatric conditions preventing the
44 provision of informed consent or questionnaire completion. Pain disorders due to
45 cancer, gynecologic, abdominal, visceral, dental, trigeminal neuralgia, post-stroke
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3 syndrome, migraine-related pain; or neuropathic pains due to metabolic disease were
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5 excluded due to the more diverse etiologies of these pain conditions [18].
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7 Eligibility Determination

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10 To establish eligibility including OUD and non-OUD status in patients with CNCP
11 we utilized the Electronic Medical Record (EMR) (controls) and corroboration of clinical
12 staff (nurses, counselors, physicians) from the cases recruitment sites. For controls, the
13 EMR was systematically reviewed by a trained research technician for each subject
14 from 6 months before the date of study consent. Criteria for eligibility and having no
15 evidence of having an OUD included: The patient was on LTOT (\geq 6 months); all urine
16 drug screens (UDS) obtained as part of standard care were appropriate (presence of
17 prescribed opioid metabolite and absence of non-prescribed opioids or illicit drugs); the
18 patient had no record (both in-office notes and diagnostic codes) of current or past SUD
19 (excluding nicotine); and no evidence of aberrant drug-related behaviors (ADRB) which
20 was assessed utilizing an expert developed checklist [19]. To ensure that control
21 participants did not develop an OUD each control subject was monitored by the trained
22 research technician by reviewing EMR records each month for 12 months after
23 completing the baseline assessments.
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42 Eligibility for the OUD (cases group) included: patients with CNCP with no
43 previous history of SUD (except nicotine) as defined by DSM-IV [17] criteria before
44 commencing LTOT; at the time of enrolment meeting DSM-IV criteria for “opioid
45 dependence” (OUD in current DSM-5 terminology) determined by completing the Mini-
46 International Neuropsychiatric Interview (MINI) [20] and DSM-IV checklist obtained
47 during the initial eligibility interview; and actively receiving treatment or had been in
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3 formal treatment for an OUD. Following patient consent, research staff conferred with a
4 contact person at each substance use treatment recruitment site, who corroborated that
5 each enrolled case subject was receiving treatment for a prescription OUD and based
6 on records of the facility's initial assessment had no previous history of any SUD
7 (excluding nicotine) before beginning LTOT.
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10 All baseline assessments were conducted over the phone during a single
11 interview for cases and controls. As noted above, controls were re-evaluated at 6 and
12 12 months following the baseline assessments to confirm that controls did not develop
13 an OUD during the follow-up period.
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15 Measures

16 Measures were limited to those available in the parent study and variables were
17 selected for analysis based on the known risk factors for suicide in both the general
18 population and the population of patients with CNCP.
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20 *Demographics:* Demographic characteristics included: age, gender, socio-economic
21 status, and education level.
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23 *MINI International Neuropsychiatric Interview (MINI):* The MINI based on DSM-IV
24 criteria are used to establish psychiatric diagnoses including major depression-lifetime;
25 and drug and alcohol dependence (current and lifetime) relevant to this study [20].
26

27 *Brief Pain Inventory (BPI):* The BPI includes 2 dimensions: pain intensity and pain
28 interference. Average pain intensity experienced over the past 24 hours was utilized in
29 this study [21].
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31 *Coping Strategies Questionnaire (CSQ):* The CSQ is a validated measure of coping with
32 pain. The CSQ consists of six cognitive and one behavioral pain-coping scales. For this
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3 study, only the catastrophizing subscale was used in the analysis as it is the one
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5 subscale that has been found to be a significant risk factor for suicide in the CNCP
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7 population [5].
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10 The catastrophizing subscale score ranges from 0 to 36. Normative data from a sample
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12 of patients in an inpatient pain center revealed a mean score of 17.1 and a standard
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14 deviation of 8.78 [22].
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17 *DSM checklist for abuse or dependence:* Based on the MINI interview, a checklist of
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19 the DSM items for substance abuse and dependence was administered at each
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21 assessment. This checklist was used to define OUD throughout the study.
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24 *Duke Social Support Index (DSSI):* A 14-item, self-administered, multidimensional,
25
26 functional social support questionnaire. Construct, concurrent, and discriminant validity
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28 have been demonstrated for the two subscales (confidant support--5 items and affective
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30 support--3 items) [23].
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33 *Pain Self Perception Scale (PSPS):* The PSPS assesses the sense of mental defeat
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35 associated with the experience of pain. It is comprised of 24 items that describe
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37 negative thoughts and feelings people may have about themselves due to pain. Total
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39 score ranges from 0 to 96, with higher scores indicating higher levels of mental defeat.
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41 The PSPS demonstrated excellent internal consistency (Cronbach $\alpha=0.98$) and test-
42
43 retest reliability ($r=0.92$) when used with patients with chronic pain [24].
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47 *Patient Health Questionnaire-4 (PHQ-4):* The PHQ-4 [25] is an ultra-brief 4-question
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49 screening tool for depression and anxiety. It is both a valid and reliable measure of
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51 psychological distress in the general population [25].
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3 *Suicide Behavior Questionnaire-Revised (SBQ-R)*: The SBQ-R is a validated 4-item
4 assessment tool that taps into different dimensions of suicidality including lifetime
5 suicidal ideation and/or attempts; frequency of suicidal ideation over the past 12
6 months; the threat of suicide attempt and self-reported likelihood of suicidal behavior in
7 the future. The SBQ-R has been validated across several clinical and non-clinical
8 populations and the receiver operating characteristic (ROC) analyses revealed that the
9 most predictive cut-off scores on the SBQ-R were 7 for non-suicidal samples, and 8 for
10 clinical samples [26].
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21 Statistical Analysis

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24 In a sample of persons with CNCP the independent variable for this study was
25 the presence of co-occurring chronic pain and OUD at baseline. The dependent
26 variable, risk of suicide was operationalized as SBQ-R score, dichotomized with a cut-
27 off score of ≥ 8 to differentiate the higher risk for suicide in clinical samples [26].
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33 Bivariate tests evaluated associations between covariate sample characteristics and
34 SBQ-R score (0-7 vs. ≥ 8). Effects sizes were computed for all differences and
35 magnitude interpreted based on established criteria [27].
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40 Logistic regression models were constructed to examine the association between
41 the independent variable and covariate demographic and clinical characteristics and an
42 SBQ-R score of ≥ 8 . A multivariable logistic regression model was constructed by adding
43 only factors that were observed to have a significant association in the simple logistic
44 regression models. Variance inflation factor (VIF) was computed to assess for potential
45 multicollinearity. Model fit was assessed using the Akaike information criterion (AIC) [28]
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54 and the Hosmer–Lemeshow goodness of fit test. All analyses were conducted in R 3.6.1
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3 [29]. The final sample size (n= 609) achieved sufficient power (97%) to detect an
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5 adjusted odds ratio (AOR) of 2.3 between those with and without OUD and an SBQ-R
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7 score ≥ 8 , at an alpha level of 0.05 [30]. A ROC curve was constructed to examine
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9 differences in covariates to accurately classify patients presenting with an SBQ-R score
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11 of ≥ 8 [31].
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14 **Results**

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17 Of the 609 patients, 18% reported a score of 8 or greater on the SBQ-R. Those
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19 in this group reported SBQ-R scores that were over 6 points higher than patients with
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21 SBQ-R scores less than 8, on average (95% Confidence Interval [CI]: 5.9-6.9).
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23 Compared to patients with lower suicide scores, individuals with an SBQ-R score of ≥ 8
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25 were slightly younger and made up a larger proportion of the sample that were not
26
27 married, not working, and financially could not make ends meet (Table 1). Further, more
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29 than half (51.8%) of the 110 patients reporting an SBQ-R of ≥ 8 had co-occurring OUD
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31 (p<.001).
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36 Patients with SBQ-R scores of ≥ 8 reported significantly higher mean mental
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38 defeat scores and pain catastrophizing scores than patients reporting SBQ-R <8.
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40 Specifically, mental defeat scores were an average of 29 points higher in the highly
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42 symptomatic group compared to the other study patients (95% CI: 23.9-58.8; p<.001).
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44 Similarly, catastrophizing scores were over 7 points higher among patients reporting an
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46 SBQ-R of ≥ 8 , with a mean of 20.9, compared to those reporting scores <8, who
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48 reported a mean of 13.3 (p<.001). Patients with SBQ-R scores ≥ 8 also reported having
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50 significantly less social support based on the DSSI domains.
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3 In the univariate logistic regression models, several factors were protective
4 against higher SBQ-R scores while other factors were found to increase the odds of
5 higher SBQ-R scores (Table 2). Older age, being married, working, making enough
6 money “to get along” or “to be comfortable”, and more social support were all found to
7 be associated with a lower odds ratio of reporting an SBQ-R score of ≥ 8 ($p < .01$).
8 Alternatively, both elevated mental defeat and pain catastrophizing scores were
9 associated with an increased odds ratio (OR) for reporting higher SBQ-R scores
10 ($p < .001$). As hypothesized, participants with co-occurring CNCP and OUD were found
11 to have significantly increased odds (OR = 3.44) for reporting SBQ-R scores ≥ 8 (95%
12 CI: 2.26-5.33). With respect to the effects of psychiatric symptoms on risk of suicide,
13 each additional point on the PHQ-4 was associated with an increased OR of reporting
14 an SBQ-R score of ≥ 8 (OR: 1.30; 95% CI: 1.22-1.39; $p < .001$). Similarly, patients with a
15 depression diagnosis were observed to have a higher OR of increased SBQ-R scores
16 (OR: 4.52; 95% CI: 2.50-8.14; $p < .001$).
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35 Multivariable modeling indicated that mental defeat, pain catastrophizing, lifetime
36 major depression, and OUD together significantly increased the odds of reporting higher
37 suicidality scores on the SBQ-R (Table 3). Each 1-point increase on the mental defeat
38 scale was associated with a 2% increase in the adjusted odds ratio (AOR) of having an
39 SBQ-R score of 8 or greater (95% CI: 1.01-1.04; $p < .001$). For example, a 10-point
40 increase in mental defeat score (score range: 0-96) corresponds to a 20% increase in
41 the AOR of high suicide risk. A 1-point increase in pain catastrophizing scores (score
42 range: 0-36) was observed to increase the AOR of suicide risk by 6% (95% CI: 1.02-
43 1.11; $p < .001$). In the multivariable model, the association between an SBQ-R score of
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3 ≥8 and OUD was reduced to an AOR of 2.40 but remained statistically significant (95%
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5 CI: 1.36-4.29; p=0.003). Patients presenting with a diagnosis of lifetime major
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7 depression had twice as high an AOR of reporting an SBQ-R score of ≥8 than those
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9 without a diagnosis (AOR=2.04; 95% CI: 1.01-4.12; p=0.047). PHQ-4 scores were not
10
11 statistically significantly associated with SBQ-R scores in the final adjusted model.
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13 While not statistically significant, the inclusion of age, marital status, work status,
14
15 financial situation, and social support subscale items did improve overall model fit
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17 (Hosmer-Lemeshow Goodness of Fit $\chi^2= 5.27$, p-value = 0.73). All variance inflation
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19 factor (VIF) values in the final model were acceptable (e.g. <2.00), suggesting that
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21 multicollinearity among the independent variables is not an issue.
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27 Given the statistically significant findings of mental defeat and pain
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29 catastrophizing in the multivariable model, a ROC curve was constructed to examine
30
31 the performance of the two scales in independently classifying SBQ-R scores ≥8.
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33 Subsequent ROC analyses indicated that the mental defeat measure performed
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35 comparably to pain catastrophizing for classifying patients presenting with SBQ-R
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37 scores of ≥8. A mental defeat cut-off score of 40 provided a sensitivity value of 0.69 and
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39 a specificity value of 0.70. As presented in Table 4, this cut-off score demonstrated an
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41 acceptable ability to predict participant classification as SBQ-R scores ≥8. As seen in
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43 Figure 1, the area under the curve (AUC) was 0.77 (95% Confidence Interval: 0.72,
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45 0.82) and statistically significant (p<0.001). A pain catastrophizing cut-off score of 16
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47 provided a sensitivity value of 0.78 and a specificity value of 0.68. As presented in Table
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49 5, this cut-off score demonstrated an acceptable ability to predict participant
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51 classification as at high risk for suicide. As seen in Figure 2, the AUC was 0.75 (95%
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3 Confidence Interval: 0.71, 0.81) and statistically significant ($p < 0.001$). However, the
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5 difference between the AUC between the two curves was not statistically significantly
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7 different ($p = 0.582$). This indicates that a mental defeat score of 40 and a pain
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9 catastrophizing score of 16 are comparable in estimating an SBQ-R score of ≥ 8 .

14 **Conclusions**

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17 Suicidality is a highly sensitive topic and not a focus of routine clinical
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19 assessment in patients with CNCP. Using validated measures, we assessed 609
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21 patients with CNCP, with and without OUD, and found that 18% of these patients
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23 scored above the clinical cut-off for risk of suicide and that having an OUD increased
24
25 the odds of meeting the cut-off by >3 fold. This was significant even after considering
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27 other sociodemographic and health variables and is in line with previous studies
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29 showing that SUD presents an independent risk factor for predisposing individuals to
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31 attempt suicide [32]. Identifying individuals with SUD, and specifically OUD, and
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33 elevated suicide scores in a chronic pain population is an important finding that
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35 substantiates the growing concern around fatal prescription opioid overdose in patients
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37 with chronic pain [13, 33]. With the increased risk for suicide and easy access to means
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39 (prescription of opioids), a concern is that intentional self-harm by overdose has been
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41 overlooked in this population [13, 33].

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43 When examining patient demographics, those with elevated suicide
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45 scores in this sample tended to be younger, not married, not working, and with financial
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47 challenges. Conversely, older age, being married, working, financially secure, and
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49 higher levels of social support were all found to correlate with lower suicide risk scores.
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51 Unlike other reports [34], our results showed that sex did not influence the odds of
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3 suicide in this cohort of patients with CNCP. In both sexes, substance abuse was
4 associated with elevated suicide scores, The number of male patients in our sample
5 was small relative to female patients, which may have limited the stability of our
6 estimates [35], however, the findings are consistent with recent studies examining the
7 association between sociodemographic characteristics in various types of chronic pain
8 conditions showing no consistent association between gender and suicidality [36].
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17 Several psychosocial variables investigated in the current study map on to major
18 theories of suicidal thoughts and behaviors including the Interpersonal Theory of
19 Suicide [37]. The Interpersonal Theory of Suicide provides a conceptual framework for
20 understanding the prevalence and correlates of suicidality and proposes the
21 combination of thwarted belongingness (an unmet need for connectedness) and
22 perceived burdensomeness (a sense of burden to others) precede suicidal ideation. In
23 line with this theory, our study shows that both subjective and instrumental social
24 support, as well as social interaction, are protective factors associated with suicidal
25 behavior.
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38 Pain intensity was not a significant factor associated with elevated suicide scores
39 in this sample when other psychosocial factors were accounted for. This is in line with
40 some [4, 38], but not all of the extant cross-sectional studies [39-41]. Although pain
41 intensity was not significant in our study, it has been proposed as part of the
42 motivational-volitional model of suicidal behavior [42], that increased physical pain may
43 lead to acquired capability for suicide through habituation to pain, fear, and death in the
44 general population. More recent theories, rooted in the “ideation-to-action” framework,
45 propose that acquired capability in combination with other factors, such as access to
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3 means, increases the likelihood that suicidal ideation transitions to suicidal behavior [42,
4 43]. This notion is particularly relevant in patients with a long pain duration who have
5 access to prescription opioids for pain management and individuals with OUD that use
6 illicit opioids especially opioids with fentanyl which accounts for the majority of drug
7 overdose deaths recorded in the United States [44]; having easy access to lethal means
8 is an important risk factor for suicide [42]. It should be pointed out, however, that
9 patients with CNCP on LTOT often present with a reduced pain threshold compared to
10 the general population [eg, 45], thus inconsistent with the tenets of the motivational-
11 volitional model of suicide. Experimental studies have specifically shown decreased
12 tolerance to both heat and cold pain in patients with CNCP receiving opioid therapy
13 compared to healthy individuals [45, 46]. Future empirical research is warranted to
14 further test pain tolerance in individuals with chronic pain with and without OUD and
15 how this relates to suicidal behavior.
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33 Our findings highlight the importance of careful monitoring of the benefits and
34 risks of opioid prescriptions and their association with suicidal behavior in this patient
35 group, especially patients with CNCP and history of an OUD. Although widely used,
36 clinical scales that directly assess suicide risk are prone to a high number of false-
37 positive and tend to overcategorize low-risk patients as being at high-risk bringing into
38 question their clinical utility [47]. Instead, it has been suggested that the use of indirect
39 measures through multiple self-report clinical scales and socio-demographics may have
40 a stronger predictive value for suicide attempts [48]. Our findings provide support for the
41 use of several self-report clinical scales, such as the CSQ-CAT and PSPS as significant
42 predictors of elevated suicide risk scores The benefit of using these psychological
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3 measures is that in addition to having predictive value, they provide a specific target for
4 intervention. Future validation of the clinical utility of using these measures with patients
5 with CNCP with and without SUD in different clinical settings would be informative.
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10 Following the diagnosis of OUD, a diagnosis of depression was the next
11 strongest factor associated with elevated suicide risk scores in our cohort. This is
12 consistent with studies showing the role of depression in augmenting the risk of suicide
13 in patients living with chronic pain [6]. Examining the characteristics of the higher and
14 lower symptom severity groups based on SBQ-R scores, a diagnosis of depression was
15 significantly more prevalent in the high-symptom group. Indeed, a diagnosis of
16 depression was associated with an almost five-fold increase in the odds of reporting
17 SBQ-R scores ≥ 8 , this was reduced to an AOR of 2.04 when considering other factors
18 in our multivariable model which highlights the multifactorial nature of suicide.
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31 In line with previous research, pain catastrophizing was a significant factor
32 associated with elevated suicide scores in our study [5]. Although controversies exist
33 around the definition and effectiveness of interventions aimed at reducing pain-related
34 catastrophizing [49], catastrophizing screening still has value in predicting risk of
35 suicidal behavior. Our findings further support the value of screening for catastrophizing
36 in determining the odds of elevated suicide scores.
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45 Patients with CNCP tend to report significantly higher levels of mental defeat
46 compared to other groups including non-treatment-seeking individuals with similar
47 chronic or acute pain [24]. From the perspective of the Schematic Appraisals Model of
48 Suicide the likelihood of suicidality increases when stressful events are appraised as
49 defeating [50]. However, the concept of defeat in this context has not been fully defined.
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3 Our findings are consistent with the prevailing literature on the role of mental defeat in
4 suicide demonstrating the value of assessing defeat (described as “a sense of a loss of
5 autonomy, agency, and human integrity” [51] in patients living with chronic pain and its
6 predictive capacity for identifying suicide risk. Improving an individual’s self-appraisal
7 through cognitive reframing and developing resilience to mental defeat using adaptative
8 coping strategies may therefore be an important treatment target in the prevention of
9 suicidality [50]. Consistent with previous research, mental defeat and pain
10 catastrophizing each made a significant independent contribution to the multivariable
11 model predicting risk of suicide. The fact that both are significant contributors with
12 acceptable VIF values suggests there are no apparent issues of multicollinearity
13 between the two constructs. This is a theoretically important observation as provides
14 support for the notion that they represent overlapping but distinct concepts [51].

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31 Our study had some methodological limitations that require consideration. One of
32 the major limitations is its cross-sectional design thereby precluding claims of causality.
33 Prospective longitudinal studies are needed to ascertain the temporal relationships
34 between the factors highlighted. Another limitation is that suicidal behavior was
35 assessed using the SBQ-R which was developed for research contexts and is not a
36 recommended tool to assess the risk of future suicide attempts in clinical populations
37 [52]. Unexamined due to the nature of the secondary data analysis was the role of a
38 history of suicidal ideation and a family history of suicide, both of which are known risk
39 factors [37] as well as other variables that have been demonstrated to be associated
40 with risk of suicide in patients with CNCP such as burdensomeness [53]. Furthermore,
41 the genotypic objectives of the parent study precluded the inclusion of patients of non-

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3 Caucasian races and ethnicities which importantly limits the generalizability. Another
4 important limitation to this study is lack of consideration on smoking status in both cases
5 and controls. There is a robust literature on the association between smoking and
6 substance use disorders [eg,54] and future studies evaluating risk factors for suicide in
7 patients with CNCP and SUD should include smoking status as a substance of abuse.
8 Finally, the split in the high-and-low suicide risk group based on SBQ-R scores resulted
9 in unequal group sizes. However, the study sample was sufficiently powered for using
10 logistic regression modeling, which can be used to detect far rarer events occurring with
11 much smaller odds than those observed in this study [55].
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24 In contrast, the strengths of the current study are the presence of OUD validated
25 through formal treatment for OUD, the use of a rigorous identification procedure, having
26 an adequately powered analysis to investigate the psychosocial factors associated with
27 suicide in patients with CNCP and concomitant OUD using measurements that were
28 theoretically driven, and identifying a clinically useful cut-off for identifying individuals
29 with elevated suicide scores using ROC analysis.
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38 In conclusion, these findings have potentially important theoretical and clinical
39 implications for suicide prevention and intervention in patients with CNCP and co-
40 morbid OUD. It shows that, consistent with previous reports, several psychosocial
41 factors, such as mental defeat, pain catastrophizing, and depression were associated
42 with elevated risk of suicide scores in individuals with CNCP and co-morbid OUD in this
43 patient population. The identified abovementioned factors hold a clinically meaningful
44 predictive value in that they are possible targets of preventative interventions and
45 management to mitigate the escalation of the risk of suicide
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31 **Tables and figures:**

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35 **Table 1:** Sample Characteristics based on SBQ-R Score Cutoff of ≥ 8 (N=609)

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37 **Table 2:** Single Variable Logistic Regression Score of Estimating Odds Ratio of SBQ-R
38 Score of ≥ 8 or greater (N=609)
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41 **Table 3:** Multivariable Model Estimating Odds Ratio of SBQ-R Score of ≥ 8 or greater with
42 Variables from Significant Single Variable Regression Output (N=609)
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45 **Table 4:** ROC Curve Cut-offs – PSPS

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47 **Table 5:** ROC Curve Cut-Offs – CSQ Pain Catastrophizing
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52 **Figure 1:** ROC Curve and AUC - PSPS

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54 **Figure 2:** ROC Curve Cut-offs and AUC – CSQ Pain Catastrophizing
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Table 1: Sample Characteristics based on SBQ-R Score Cutoff of ≥ 8 (N=609)

		No/Lower Risk (0-7 SBQ-R) N=499	Higher Risk (≥ 8 SBQ-R) N=110	P	Effect Size
Sex, n (%)	Male	199 (39.9)	41 (37.3)	0.690	0.02
	Female	300 (60.1)	69 (62.7)		
Age, mean (SD)		39.3 (11.7)	34.5 (10.9)	<0.001	0.42
Education, n (%)	High School or Less	170 (34.1)	44 (40.0)	0.285	0.05
	Secondary Education	329 (65.9)	66 (60.0)		
Marital Status, n (%)	Not Married or Never Married	218 (43.7)	67 (60.9)	0.002	0.13
	Married	281 (56.3)	43 (39.1)		
Living Situation, n (%)	Live Alone	85 (17.0)	15 (13.6)	0.466	0.04
	Live with others	414 (83.0)	95 (86.4)		
Working, n (%)	No	359 (71.9)	92 (83.6)	0.016	0.11
	Yes	140 (28.1)	18 (16.4)		
Financial Situation, n (%)	Cannot make ends meet	114 (22.8)	46 (41.8)	<0.001	0.17
	Just enough to get along/ Comfortable	385 (77.2)	64 (58.2)		
Chronic Pain and Opioid Use	Chronic Pain	381 (76.4)	53 (48.2)	<0.001	0.24
	Chronic Pain + Opioid Use	118 (23.6)	57 (51.8)		
SBQ-R, mean (SD)		3.9 (1.3)	10.3 (2.4)	<0.001	4.11
PSPS, mean (SD)		29.1 (26.3)	58.8 (28.4)	<0.001	1.11
Catastrophizing, mean (SD)		13.3 (7.7)	20.9 (7.8)	<0.001	0.99
Social Interaction Scale, mean (SD)		5.2 (2.4)	4.5 (2.4)	0.008	0.28
Subjective Social Support, mean (SD)		17.8 (3.3)	15.5 (3.6)	<0.001	0.71
Instrumental Social Support, mean (SD)		8.3 (2.9)	7.6 (3.4)	0.018	0.25
PHQ 4, mean (SD)		4.8 (3.6)	8.2 (3.2)	<0.001	0.98
Depression, n (%)		29 (5.8)	24 (21.8)	<0.001	0.22
Average Pain		5.6 (1.8)	5.6 (2.0)	0.988	0.001

Note: Categorical variables' effect size computed using Cramer V, continuous variables' effect size computed using Cohen's d

Table 2: Single Variable Logistic Regression Score of Estimating Odds Ratio of SBQ-R Score of ≥ 8 or greater (N=609)

	Odds Ratio	95% Confidence Interval		P
Age	0.97	0.94	0.98	<.001
Male	0.89	0.58	1.37	NS
College Education	0.97	0.51	1.89	NS
Married	0.49	0.34	0.75	0.001
Live with others	1.31	0.73	2.43	NS
Working	0.46	0.17	0.99	0.02
Just enough to get along/ Comfortable	0.81	0.27	0.64	<.001
PSPS	1.03	1.02	1.05	<.001
Catastrophizing	1.14	1.02	1.17	<.001
Social Interaction	0.89	0.81	0.96	0.007
Subjective Social Support	0.90	0.83	0.98	<.001
Instrumental Social Support	0.92	0.86	0.98	0.012
Chronic Pain and Opioid Use	3.44	2.26	5.33	<.001
PHQ-4	1.30	1.22	1.39	<.001
Depression Diagnosis	4.52	2.50	8.14	<.001
Average Pain	1.14	1.02	1.28	0.023

Table 3: Multivariable Model Estimating Odds Ratio of SBQ-R Score of ≥ 8 or greater with Variables from Significant Single Variable Regression Output (N=609)

	Adjusted Odds Ratio	95% Confidence Interval		P	VIF
PSPS	1.02	1.01	1.03	<.001	1.55
Catastrophizing	1.06	1.01	1.10	0.013	1.64
Social Interaction	0.99	0.89	1.11	0.905	1.20
Subjective Social Support	0.99	0.91	1.08	0.974	1.65
Instrumental Social Support	1.00	0.91	1.09	0.881	1.33
Have enough money to get by/ Comfortable	1.17	0.67	2.05	0.577	1.29
Working	0.76	0.39	1.42	0.400	1.11
Married	0.78	0.46	1.35	0.378	1.28
Age	0.99	0.97	1.02	0.793	1.45
Case and Controls					
Chronic Pain (reference)	-	-	-	-	-
Chronic Pain and Opioid Use	2.40	1.36	4.29	0.003	1.46
PHQ-4	1.05	0.95	1.16	0.298	1.88
Depression	2.04	1.01	4.12	0.047	1.16
Average Pain	0.96	0.84	1.10	0.593	1.24

Note: AIC 466.1; Hosmer-Lemeshow Goodness of Fit $\chi^2 = 5.27$, p -value = 0.73

Table 4: ROC Curve Cut-offs – PSPS

PSPS Score	Sensitivity	Specificity	True Positive	False Positive	True Negative	False Negative
90	13%	99%	19	6	459	125
80	22%	95%	31	22	443	113
70	38%	91%	55	43	422	89
60	48%	84%	69	74	391	75
50	58%	75%	84	116	349	60
45	65%	73%	93	127	338	51
40*	69%	70%	100	140	325	44
35	72%	64%	103	167	298	41
30	74%	60%	106	187	278	38

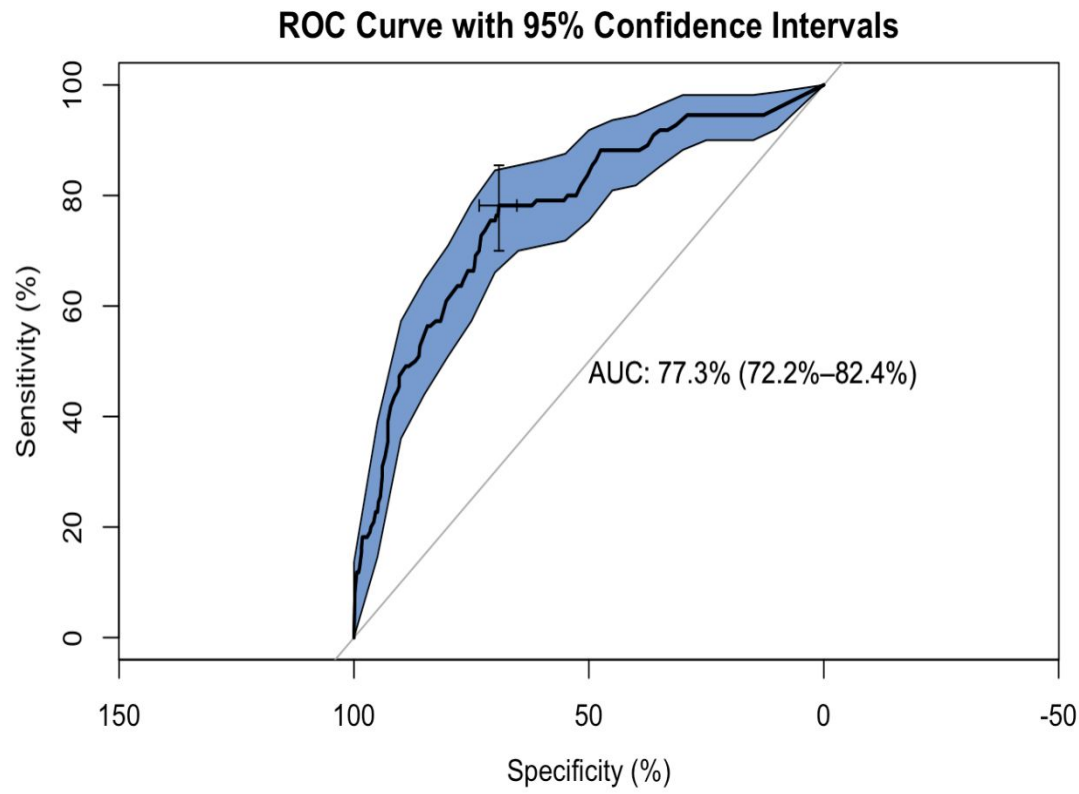
Table 5: ROC Curve Cut-Offs – CSQ Pain Catastrophizing

Pain Catastrophizing Score	Sensitivity	Specificity	True Positive	False Positive	True Negative	False Negative
28	17%	96%	19	18	481	91
24	45%	89%	50	55	444	60
20	60%	76%	66	122	377	44
16*	78%	63%	86	187	312	24
12	89%	44%	98	281	218	12
8	95%	26%	104	370	129	6
4	97%	12%	107	437	62	3

*Optimal cut-off score for sensitivity and specificity

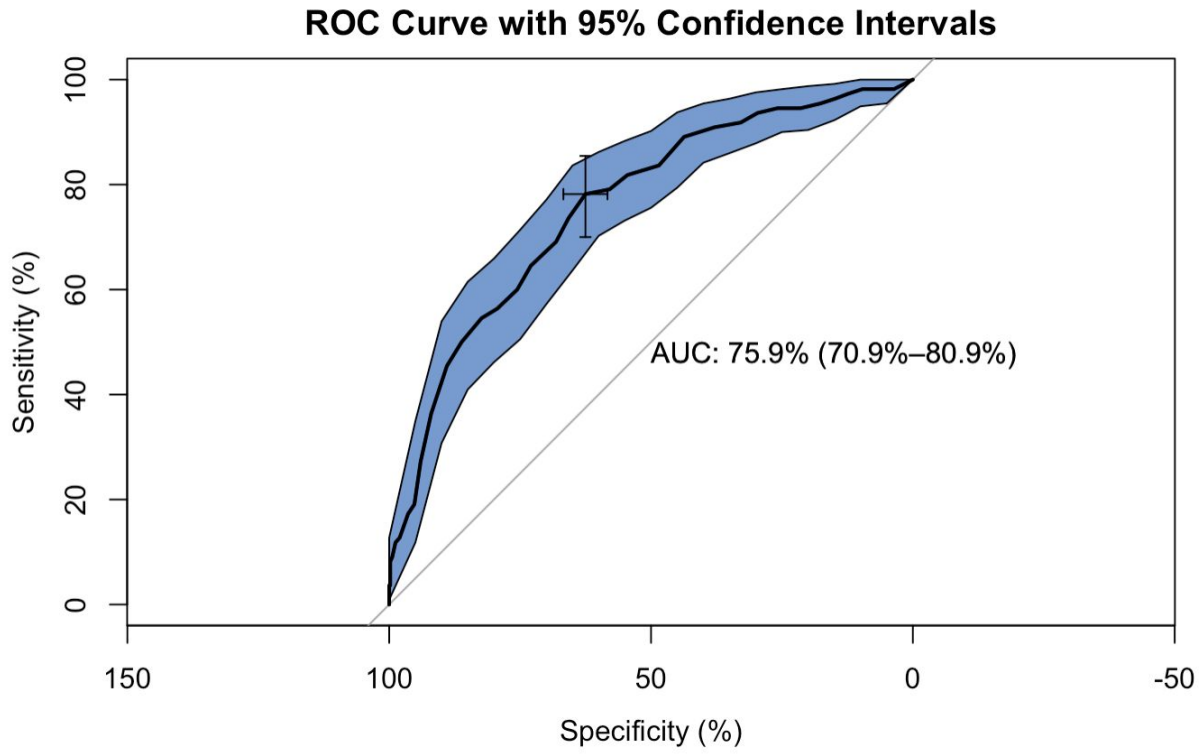
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Figure 1: ROC Curve and AUC - PSPS



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Figure 2: ROC Curve Cut-offs and AUC – CSQ Pain Catastrophizing



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