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Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities

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Quality of Life in Chronic Pancreatitis is Determined by Constant Pain, Disability/Unemployment, Current Smoking, and Associated Co-Morbidities

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OBJECTIVES: Chronic pancreatitis (CP) has a profound independent effect on quality of life (QOL). Our aim was to identify factors that impact the QOL in CP patients.

METHODS: We used data on 1,024 CP patients enrolled in the three NAPS2 studies. Information on demographics, risk factors, co-morbidities, disease phenotype, and treatments was obtained from responses to structured questionnaires. Physical and mental component summary (PCS and MCS, respectively) scores generated using responses to the Short Form-12 (SF-12) survey were used to assess QOL at enrollment. Multivariable linear regression models determined independent predictors of QOL.

RESULTS: Mean PCS and MCS scores were 36.7±11.7 and 42.4±12.2, respectively. Significant ($P<0.05$) negative impact on PCS scores in multivariable analyses was noted owing to constant mild–moderate pain with episodes of severe pain or constant severe pain (10 points), constant mild–moderate pain (5.2), pain-related disability/unemployment (5.1), current smoking (2.9 points), and medical co-morbidities. Significant ($P<0.05$) negative impact on MCS scores was related to constant pain irrespective of severity (6.8–6.9 points), current smoking (3.9 points), and pain-related disability/unemployment (2.4 points). In women, disability/unemployment resulted in an additional 3.7 point reduction in MCS score. Final multivariable models explained 27% and 18% of the variance in PCS and MCS scores, respectively. Etiology, disease duration, pancreatic morphology, diabetes, exocrine insufficiency, and prior endotherapy/pancreatic surgery had no significant independent effect on QOL.

CONCLUSIONS: Constant pain, pain-related disability/unemployment, current smoking, and concurrent co-morbidities significantly affect the QOL in CP. Further research is needed to identify factors impacting QOL not explained by our analyses.

INTRODUCTION

Chronic pancreatitis (CP), a chronic inflammatory disorder of the pancreas, is characterized by irreversible morpho- logical changes of the pancreas, abdominal pain—which is often chronic and debilitating, episode(s) of acute pancreati- tis (AP), impairment of endocrine and exocrine function, and

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in a small subset of patients, development of pancreatic cancer (1).

In previous single-center studies, quality of life (QOL) in patients with CP was noted to be significantly impaired when compared with historical population controls (2,3). In a large, multicenter study, we demonstrated a profound effect of CP on physical and a modest effect on mental QOL when compared with subjects without pancreatitis, independent of demographics, risk factors, etiology, and common medical conditions (4). Although these data document the poor QOL in CP patients, they do not provide an explanation for the factors responsible for this observation. Understanding these factors is of importance in the clinical management of patients, especially if they can be modified by behavioral changes, treatment of disease, or its complications.

Studies evaluating independent factors associated with low QOL in CP patients have consistently reported abdominal pain to be an important predictor (3,5–10). Treatment of pain by surgical or endoscopic therapy has documented effect not only in achieving pain relief but also in improving QOL (11–14). Etiology of CP has not been found to affect QOL (3,5,8). Younger age, female sex, smoking, alcohol consumption, low body mass index, diabetes, exocrine pancreatic insufficiency, pancreatic morphology, and disease duration lower QOL, but their association has been inconsistent across studies (3,5,7,8,10). The reasons for this inconsistency include variability in the instruments used to determine QOL, small sample size of studies, and the lack of use of uniform predictor variables. The effect of pain-related disability or unemployment on QOL has not been adequately studied.

The North American Pancreatitis Study 2 (NAPS2) studies have prospectively ascertained over 1,000 well-phenotyped patients with CP from several US centers. Systematically collected data on QOL and several potential predictor variables provided us with an opportunity to determine which factors may affect QOL in this cohort.

METHODS

Study population

We utilized data from the NAPS2 studies for this analysis. NAPS2 consists of a series of three studies (original NAPS2, NAPS2-CV, and NAPS2-AS) from 27 centers in the United States that prospectively ascertained 1,195 CP, 569 recurrent AP and 1,109 controls from 2000 to 2014. One of the participating centers only enrolled control subjects. Detailed methodology for the NAPS2 studies has been published (15–17). CP was defined by definitive changes on imaging studies (primarily endoscopic retrograde cholangiopancreatography or computed tomography scan or equivalent changes on magnetic resonance cholangiopancreatography or endoscopic ultrasound) or histology. The study was approved by the Institutional Review Board of each center and all subjects provided written informed consent prior to enrollment.

The present study includes 1,024/1,195 (85.6%) CP patients from the three NAPS2 studies who provided complete responses for determination of QOL, disability/unemployment, and pain characteristics (pain pattern and severity).

Data collection

Study subjects completed a detailed questionnaire, including information on demographics, family and personal history, exposure to smoking and alcohol, pain experience, disability/unemployment related to pain from pancreatitis, and QOL. Self-reported alcohol use during the maximum drinking period of life was used to create drinking categories (abstainers: no alcohol use or <20 drinks in a lifetime; light drinkers: ≤3 drinks per week; moderate drinkers: 4–7 drinks per week for females and 4–14 drinks per week for males; heavy drinkers: 8–34 drinks per week for females and 15–34 drinks per week for males; very heavy drinkers: ≥35 drinks per week for both sexes) and smoking (status: never, past, current; amount: <1 packs per day or ≥1 packs per day; and <12, 12–35, and ≥35 pack-years) as described previously (15).

The enrolling physician investigator completed a separate questionnaire consisting of information on etiology, TIGAR-O ((i) Toxic-metabolic (ii) Idiopathic (iii) Genetic (iv) Autoimmune (v) Recurrent and severe AP or (vi) obstructive) risk factors, phenotypic characteristics (history of AP, age at AP, age at the onset of CP symptoms, age at CP diagnosis, presence of diabetes, exocrine insufficiency, imaging features), and treatments received (medications, surgical and endoscopic interventions), and their perceived effectiveness.

QOL evaluation

The Short Form-12 (SF-12) version 2 was used to assess QOL in the NAPS2-CV and NAPS2-AS studies. In the original NAPS2 study, QOL was assessed using the SF-12 version 1, and scores were transformed to version 2 for interpretation (18). SF-12 is a multipurpose generic QOL questionnaire that was derived from the SF-36 Health Survey (18,19). The SF-36 and SF-12 have been validated in several languages and disease conditions, including CP (2,3,20). The SF-12 is comprised of 12 questions that measure 8 domains (role physical, role emotional, physical function, social function, mental health, vitality, bodily pain, and general health) and can be summarized into the physical component summary (PCS) and mental component summary (MCS) scores. SF-12 questionnaire takes approximately 2 min to complete without a significant loss of information and is based on a standard recall of 4 weeks (18). The summary scores for each domain are then transformed to z-scores using the SF-12 scale means and s.d. from the 1998 general US population to produce a normally distributed population score. PCS and MCS scores range from 0 to 100 with a score of 50±10 representing the mean±s.d. for the general population. These scores provide a direct comparison of the distribution in the population of interest when compared with the general population and between groups. A difference of three points in the PSC or MCS scores between groups has been suggested to be clinically relevant (4).

Pain and disability/unemployment assessment

We used patient-reported pain experience for all comparisons in this study. In the NAPS2-CV and NAPS2-AS studies, there was a leading question on the presence of pain (i.e., Have you

experienced abdominal pain related to pancreatitis in the past year?). Patients who reported "yes" were asked to choose from one of the five predefined pain patterns (episodes of mild-to-moderate pain; constant mild-to-moderate pain; usually pain free with episodes of severe pain; constant mild pain plus episodes of severe pain; and constant severe pain that does not change). For this study, we incorporated the presence, severity, and temporal nature of pain to classify patients into the following five categories: (i) No pain; (ii) Intermittent mild-to-moderate episodes of pain; (iii) Intermittent severe episodes of pain; (iv) Constant mild-to-moderate pain; and (v) Constant mild-to-moderate pain with episodes of severe pain or constant severe pain that does not change. In the original NAPS2 study, a leading question on the presence of pain was not asked and patients were directly asked to complete the question in the five pain patterns (15). Therefore, patients in the original NAPS2 study who did not identify with a pain pattern were excluded from the final analysis (*n*=126) as it is impossible to distinguish those patients without pain and those with pain who simply left their pain category blank. In addition, patients from the three NAPS2 studies were asked for the presence of pain-related disability or unemployment.

Statistics

The PCS and MCS scores were computed using the scoring method system provided in the SF-12 version 2 reference manual and presented as mean±s.d. (18). Descriptive analyses are presented as proportions for categorical data and as mean±s.d. for continuous data. Comparison between the PCS and MCS scores within each group variable was carried out using Kruskal–Wallis test. All variables with a *P*-value of <0.2 on univariate analysis comparing the PCS and MCS scores were considered for potential inclusion in the multivariable models.

Multivariable linear regression models were used to determine the independent predictors of physical and mental QOL. A backwards selection technique was used to determine significant independent predictors. Age and gender were included in both final models because of clinical significance. Other variables were removed one by one in order of the magnitude of the *P*-value for the type III F-test, with the exception of diabetes which was removed from the PCS model owing to its small effect size compared with the other variables remaining. Models were then re-run until a final model was reached containing only the variables with *P*<0.05. For the MCS final model, history of liver disease was borderline significant and was included in the final model. There were missing data in some variables, but in no case did they exceed ~6%. The PCS model was not examined for interactions to maintain easier interpretation and out of concern of including too many variables in the final model. Significant interactions were examined for the MCS model. For easier interpretation, the final models were centered at the age of 50 years. As the original NAPS2 study used an earlier version of SF12 and the presence of pain was not assessed by a leading question, a sensitivity analysis was performed after excluding these patients and using the same variables included in the final models. Data analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Demographics, risk factors, and clinical characteristics

Of the 1,024 CP patients who formed the final study cohort, 381 (37.2%) were enrolled in the original-NAPS2 study, 510 (49.8%) in the NAPS2-CV study, and 133 (13.0%) in the NAPS2-AS study. The distribution of baseline socio-demographic and clinical characteristics is shown in **Table 1**.

Overall, patients had a mean age of 50.4±14.6 years, 54.6% were male, 74.8% were white, 19.6% were current drinkers, and the majority had a normal/low body mass index (57.6%). Heavy or very heavy drinking during the maximum drinking period of life was reported by 15.1% and 34.9% and past or current smoking by 25.3% and 50.1% patients, respectively. Physicians considered alcohol as the main etiological factor in about half of (50.2%) patients. In >50% patients (54.6%), the duration of CP was ≥4 years.

In our final study cohort, abdominal pain in the year preceding enrollment was present in 91.6%. The most common pattern of abdominal pain identified was constant mild-to-moderate pain with episodes of severe pain or constant severe pain (48.5%). Less frequently patients identified intermittent episodes of severe pain (24%), intermittent episodes of mild-to-moderate pain (12.8%), and constant mild-to-moderate pain (6.3%). Pain-related disability/unemployment was reported by 27.1% of patients. About one-third of patients had exocrine insufficiency (38.1%) or diabetes (33.1%). Although 40.3% received only medical management, a prior history of pancreatic endotherapy was noted in 37.7% and pancreatic surgery in 21.5% patients. Almost half of the patients (44.3%) had history of gallstones or cholecystectomy. The most commonly reported co-morbidities noted were heart disease/heart attack/stroke (11.8%), liver disease (9%), renal disease (6.1%), or prior history of cancer (3.7%).

Predictors of physical QOL

Univariable analysis. Mean PCS score for the study cohort was 36.7±11.7. Univariable analysis for PCS scores based on demographics, risk factors, and clinical characteristics are shown in **Table 1**. A significantly lower physical QOL was noted with younger age, female sex, black race, extremes of alcohol consumption, current smoking, disability/unemployment, pain, and diabetes. A medical history of heart disease/heart attack/stroke, cancer, liver disease, renal disease, gallstones, or cholecystectomy was also significantly associated with lower PCS scores. Interestingly, the association was only borderline with disease duration, and no association was noted with body mass index, etiology, exocrine insufficiency, pancreatic morphology, prior endotherapy, or pancreatic surgery.

Multivariable analysis. Results for multivariable regression analyses for physical QOL are shown in **Table 2**. Temporal nature and severity of pain had the greatest impact on physical QOL. Compared with patients with no pain, constant mild-to-moderate pain with episodes of severe pain or constant severe pain reduced the PCS score by 10 points, while constant mild-to-moderate pain alone decreased it by 5.2 points. Presence of severe pain that was intermittent was also important but the impact of this (2.6 points)

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Table 1. Predictors of physical and mental QOL for CP patients in the NAPS2 study

Variable (n=1,024)	N (%)	Physical QOL score		Mental QOL score	
		Mean±s.d.	*P*-value	Mean±s.d.	*P*-value
Study type					
NAPS2-Original	381 (37.2)	37.4±11.2	0.07	43.4±11.6	0.06
NAPS2-CV	510 (49.8)	36.9±12.1		42.2±12.7	
NAPS2-AS	133 (13.0)	34.5±10.9		40.6±11.9	
Age, years					
<45	344 (33.5)	36.5±11.3	<0.001	41.1±12.2	<0.001
45–60	427 (41.7)	35.6±11.5		40.7±11.9	
>60	253 (24.8)	39.1±12.2		47.2±11.7	
Gender					
Male	559 (54.6)	37.5±12.0	0.02	42.9±12.1	0.15
Female	465 (45.4)	35.8±11.2		41.8±12.3	
Race (n=1,023)					
Black	228 (22.3)	35.0±11.2	0.06	40.9±12.0	0.03
Caucasian	765 (74.8)	36.2±10.8		43.0±12.3	
Other	30 (2.9)	37.2±11.8		40.6±12.4	
Body mass index (n=1,017)					
Normal/low	586 (57.6)	36.5±11.7	0.5	42.5±12.4	0.8
Overweight	275 (27)	37.4±11.9		42.1±12.2	
Obese	156 (15.4)	36.1±11.1		42.6±11.8	
Smoking (n=1,022)					
Never	251 (24.6)	39.2±12.0	<0.001	45.1±10.7	<0.001
Past	259 (25.3)	38.5±12.1		45.1±11.6	
Current	512 (50.1)	34.6±10.9		39.7±12.6	
Current drinking					
Yes	201 (19.6)	39.0±12.3	0.003	43.7±12.0	0.1
No	823 (80.4)	36.2±11.4		42.1±12.3	
Drinking category (n=998)					
Abstainer	171 (17.1)	35.5±11.0	<0.001	43.2±12.1	<0.001
Light	170 (17.0)	37.4±11.6		44.9±11.7	
Moderate	159 (15.9)	40.2±12.2		44.2±11.2	
Heavy	151 (15.1)	37.2±12.0		42.2±12.0	
Very heavy	347 (34.9)	35.3±11.4		40.0±12.6	
Alcohol etiology					
Yes	510 (49.8)	36.0±11.2	0.06	40.9±12.3	<0.001
No	513 (50.2)	37.4±12.1		44.0±12.0	
Disease duration, years (n=968)					
≤1	103 (10.7)	37.4±12.6	0.06	45.1±11.6	0.008
1–<2	122 (12.6)	38.2±12.5		43.9±12.9	
2–<3	117 (12.1)	35.8±11.3		40.9±12.4	
3–<4	97 (10.0)	39.5±11.1		40.3±12.8	
≥4	529 (54.6)	36.2±11.4		42.2±11.9	
Pain pattern					
No pain	86 (8.4)	43.7±11.9	<0.001	48.7±11.8	<0.001

Table 1. Continued

Variable (n=1,024)	N (%)	Physical QOL score		Mental QOL score	
		Mean±s.d.	P-value	Mean±s.d.	P-value
Intermittent mild-to-moderate episodes of pain	131 (12.8)	43.0±11.1		46.1±11.1	
Intermittent severe episodes of pain	246 (24.0)	40.6±11.2		47.0±10.8	
Constant mild-to-moderate pain	64 (6.3)	37.2±10.7		39.3±10.7	
Constant mild-to-moderate pain with episodes of severe pain or constant severe pain	497 (48.5)	31.9±9.9		38.5±11.9	
Disability/unemployment					
Yes	277 (27.1)	30.6±8.6	<0.001	37.1±12.1	<0.001
No	747 (72.9)	39.0±11.8		44.4±11.7	
Exocrine insufficiency					
Yes	390 (38.1)	36.1±12.0	0.11	41.5±12.3	0.05
No	634 (61.9)	37.2±11.5		43.0±12.2	
Endocrine insufficiency					
Yes	339 (33.1)	35.3±11.9	0.004	41.9±12.1	0.2
No	685 (66.9)	37.5±11.5		42.7±12.3	
Pseudocysts					
Yes	309 (30.2)	36.0±11.6	0.12	41.4±12.4	0.06
No	715 (69.8)	37.1±11.7		42.9±12.1	
Pancreatic surgery					
Yes	210 (21.5)	35.8±11.5	0.12	41.6±11.8	0.19
No	814 (79.5)	37.0±11.7		42.7±12.3	
Endoscopic therapy					
Pancreatic endotherapy	386 (37.7)	36.2±11.0	0.58	41.9±11.9	0.31
Other endotherapy	126 (12.3)	36.9±12.3		43.9±11.7	
None	512 (50.0)	37.1±12.0		42.5±12.6	
History of heart disease/heart attack/stroke					
Yes	121 (11.8)	32.9±11.2	<0.001	42.4±13.2	0.9
No	903 (88.2)	37.3±11.6		42.4±12.1	
History of cancer					
Yes	38 (3.7)	32.7±10.3	0.03	41.5±13.4	0.7
No	986 (96.3)	36.9±11.7		42.5±12.2	
History of liver disease					
Yes	92 (9.0)	33.3±10.7	0.002	39.6±12.0	0.03
No	932 (91.0)	37.1±11.7		42.7±12.2	
History of gallstones/cholecystectomy					
Yes	454 (44.3)	35.4±11.1	0.002	42.3±11.8	0.6
No	570 (55.7)	37.8±12.0		42.6±12.5	
History of renal disease					
Yes	62 (6.1)	33.3±10.7	0.02	41.8±11.5	0.6
No	962 (93.9)	37.0±11.7		42.5±12.3	

CP, chronic pancreatitis; NAPS2, North American Pancreatitis Study 2; QOL, quality of life.
Numbers are provided in parenthesis for variables where the number of patients was less than the total sample size.
Body mass index categories: Normal/low—≤25 kg/m²; Overweight—>25–≤30 kg/m²; Obese—>30 kg/m².
Drinking category definition: Abstainers: no alcohol use or <20 drinks in a lifetime; Light drinkers:≤3 drinks/week; Moderate drinkers: 4–7 drinks/week for females, 4–14 drinks/week for males; Heavy drinkers: 8–34 drinks/week for females, 15–34 drinks/week for males; Very heavy drinkers:≥35 drinks/week for both sexes.
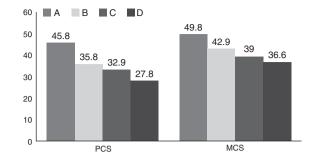
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Table 2. Multivariable regression model showing significant determinants for physical quality of life in chronic pancreatitis

Variable	Reference category	Parameter estimate	s.e.	*P*-value
Intercept	—	45.8	1.5	<0.001
Age 50 years[a]	—	−0.04	0.02	0.1
Female	Male	−1.2	0.7	0.09
Pain				
Intermittent mild-to-moderate episodes of pain	No pain	−0.8	1.5	0.6
Intermittent severe episodes of pain		−2.6	1.4	0.05
Constant mild-to-moderate pain		−5.2	1.8	0.003
Constant mild-to-moderate pain with episodes of severe pain or constant severe pain		−10	1.3	<0.001
Disabled or unemployed	Not disabled or unemployed	−5.1	0.8	<0.001
Smoking status				
Past	Never smoker	−1	0.9	0.3
Current		−2.9	0.9	0.002
Drinking category				
Light	Abstainer	2.1	1.1	0.06
Moderate		4.3	1.2	<0.001
Heavy		2.5	1.2	0.04
Very heavy		1.6	1.1	0.2
History of cancer	No cancer	−4.4	1.7	0.01
History of heart disease/heart attack/stroke	No heart disease/heart attack/stroke	−3.3	1	0.001
History of renal failure	No renal failure	−2.8	1.4	0.04
History of gallstones/cholecystectomy	No gallbladder disease/cholecystectomy	−1.6	0.7	0.02

R^2—27%.
For drinking category definition, refer to Methods section.
[a]Age variable centered at 50 years.

Figure 1. Each column represents a clinical scenario with additive attributes: (A) A 50-year-old man with CP who is non-smoker, has no pain, disability/unemployment, or co-morbidities. (B) Subject in A with constant mild-to-moderate pain with episodes of severe pain or constant severe pain that does not change. (C) Subject in B who is also a current smoker. (D) Subject in C with disability/unemployment.

of co-morbid conditions also had a significant negative impact—a history of cancer, heart disease/heart attack/stroke, and renal failure reduced the PCS score by 4.4, 3.3, and 2.8 points, respectively. Other factors associated with lower PCS scores on the univariable analysis were not significant after adjusting for other variables and were not included in the final regression model. Variables in the final multivariable model explained 27% of the variance in PCS.

To illustrate the impact of individual factors and incremental effect of predictive factors, representative PCS score for a 50-year-old man with CP and progressive addition of select attributes are shown in **Figure 1**. By adding constant mild-to-moderate pain with episodes of severe pain or constant severe pain, current smoking, and pain-related disability/unemployment, the PCS score would decrease from 45.8 to 27.8.

Predictors of mental QOL
Univariable analysis. The mean MCS score for the study cohort was 42.4±12.2. Univariable analysis for MCS scores based on demographics, risk factors, and clinical characteristics is shown in **Table 1**. A significantly lower mental QOL was noted with younger age, very heavy drinking, current smoking, disability/unemployment, and pain. In contrast to physical QOL, mental QOL was significantly lower in patients with physician-defined alcohol etiology and the duration of disease. Race, presence of pseudocysts, and exocrine insufficiency showed borderline association with MCS score, while sex, body mass index, diabetes, other features on pancreatic morphology, and prior endotherapy or pancreatic surgery showed no association.

Multivariable analysis. The results of multivariable regression analyses for mental QOL are shown in **Table 3**. Similar to physical QOL, presence of pain had the most impact on mental QOL. Interestingly, compared with those patients with no pain, a negative impact was seen only for constant pain irrespective of its severity. The impact of constant mild-to-moderate pain (6.8 points) was almost similar to constant mild-to-moderate pain with episodes of severe pain or constant severe pain (6.9 points). Intermittent pain irrespective of severity did not signifi-

was less than constant pain. Moreover, a history of gallstones or cholecystectomy, which likely reflects an indirect impact of pain, also had a negative impact (1.6 points). Other disease-related factors with a negative impact included disability/unemployment (5.1 points) and current smoking (2.9 points). The effect of self-reported drinking history was interesting in that, when compared with lifetime abstainers, the PCS score was significantly higher in patients who reported moderate (4.3 points) or heavy (2.5 points) drinking during their heaviest period of drinking in life. Presence

Table 3. Multivariable regression model showing significant determinants for mental quality of life in chronic pancreatitis

Variable	Reference category	Parameter estimate	s.e.	*P*-value
Intercept	—	49.81	1.4	<0.001
Age 50 years[a]	—	0.04	0.03	0.16
Female	Male	−0.3	0.8	0.7
Pain				
Intermittent mild-to-moderate episodes of pain	No pain	−1.3	1.6	0.41
Intermittent severe episodes of pain		−0.2	1.4	0.87
Constant mild-to-moderate pain		−6.8	1.9	<0.001
Constant mild-to-moderate pain with episodes of severe pain or constant severe pain		−6.9	1.4	<0.001
Disabled or unemployed	Not disabled or unemployed	−2.4	1.1	0.03
Smoking status				
Past	Never smoker	−0.3	1	0.79
Current		−3.9	0.9	<0.001
Liver disease	No liver disease	−2.4	1.2	0.052
Female×disability/ unemployment[b]	—	−3.7	1.6	0.02

R^2=17.9%.

[a]Age variable centered at 50 years.

[b]A significant interaction was found for female gender and disability/unemployment.

cantly impact MCS score compared with those patients with no pain. Current smoking (3.9 points) and pain-related disability/unemployment (2.4 points) also significantly reduced the MCS score. An interaction was noted between gender and disability/unemployment—the effect of disability/unemployment on MCS was an additional 3.7 points lower for women than for men. Other factors associated with lower MCS scores on the univariable analysis were not significant after adjusting for other variables and were not included in the final regression model. Variables in the final multivariable models explained 17.9% of the variance in MCS score.

To illustrate the impact of individual factors and incremental effect of predictive factors, representative MCS score for a 50-year-old CP man are shown in **Figure 1**. Progressive addition of select attributes, such as constant mild-to-moderate pain with episodes of severe pain or constant severe pain, current smoking, and disability/unemployment, would decrease the MCS score from 49.8 to 36.6.

Sensitivity analysis. Sensitivity analysis after excluding patients from the original NAPS2 study showed slight differences in the estimated effect sizes but were overall consistent with the main analyses (data not shown).

DISCUSSION

In this largest prospective study to date, we found that pain—especially constant, pain-related disability/unemployment, current smoking, and concurrent co-morbidities, to have a significant negative impact on the QOL of CP patients. Interestingly, physician-defined alcohol etiology, disease duration, pancreatic morphology, and prior endoscopic or surgical treatments did not independently affect QOL. These data underscore the need to better understand factors driving pain and to develop effective strategies to address them. Facilitating behavioral modification will also have an impact on QOL in these patients. As only a fraction of variance in PCS and MCS scores was explained by our analyses, future studies should focus on identifying other factors affecting the QOL of CP patients.

Pain occurs in up to 90% of CP patients, and about half of them have constant pain (9). Although the association of pain with poor QOL is consistent across studies (3,5–10), whether the effect is greater with severity or temporal nature of pain is debatable. A small single-center Polish study of 69 patients revealed that pain intensity correlates with QOL scores more often than frequency (8). More recently, Olesen *et al.* (10) assessed the association between the intensity and temporal pattern of pain with the QOL of 106 CP patients from two tertiary medical centers in the Netherlands and Denmark. In addition to measuring pain severity by the modified brief pain inventory short form (21), the authors used this scale to indirectly classify pain frequency into three patterns: intermittent, constant, and constant with acute exacerbations. After adjustment for confounders, they found that pain severity but not pain pattern was significantly correlated with global health status, all functional subscales, and most symptom subscales.

In 414 CP patients enrolled in the original NAPS2 study, we reported that constant pain was associated with lower physical and mental QOL scores when compared with those who had intermittent pain (9). The present study extends those findings using multivariable analyses in a larger cohort and provides a numeric estimate of the effect of each pain type on QOL. We found that, compared with those patients with no pain, constant mild-to-moderate pain with episodes of severe pain or constant severe pain to be the strongest predictor of poor physical (10 points reduction) and mental QOL (6.9 points reduction), followed by constant mild-to-moderate pain (5.2 and 6.8 points reduction, respectively). The effect of constant pain on QOL was statistically significant, clinically relevant, and independent of other covariates such as demographics, risk factors, and co-morbidities. Intermittent severe pain had no effect on the mental QOL but had a borderline significant effect on physical QOL. These data suggest that both temporal nature and severity of pain are important to consider when designing pain management strategies and clinical

trials in CP patients. The relevance of constant nature of symptoms was aptly demonstrated in the classic study of the natural history of alcoholic CP by Ammann *et al.*, (22) where the temporal nature of pain was the primary determinant for the need for surgical intervention. Interestingly, constant pain has also been shown to have a significant impact on QOL in many other health conditions (23–25).

The effect of smoking on QOL in CP differs between studies. In two Italian studies, current smoking (3) and the amount and duration of smoking did not affect QOL (7). In contrast, we previously had shown and this study confirmed that current smoking had a significant impact on both physical and mental QOL (4). Similarly, Han *et al.* (26) reported smokers to have a significantly worse physical QOL when compared with nonsmokers. A Polish study found the duration of smoking to be associated with lower physical functioning and insomnia and the amount of smoking with worse fear of future health (8). The mechanism by which smoking has an effect on QOL is unclear. One possible explanation may be the effect of smoking on disease-related manifestations such as worsening of morphology (e.g., calcifications, exocrine and/or endocrine function)—however, it is interesting to note that morphological or functional derangements by themselves did not impact QOL. Other possible explanations would be indirect, similar to the effect of current smoking on general QOL in conditions related or unrelated to smoking (27–31). Prevalence of affective spectrum disorders in CP patients is high and patients may smoke to relieve anxiety, depression, or stress that is preexisting or develops after diagnosis of CP or to cope with the need to abstain from drinking (32–35). Smoking cessation by counseling and/or pharmacological measures should be an important component of the management of CP, not only owing to its association with QOL but also for its impact on disease progression (36,37). Although smoking cessation strategies show good results in many conditions, its results in CP can be challenging and fail in the majority of patients (26).

The independent effect of disability/unemployment on QOL has not been adequately studied. We found disability/unemployment related to CP to have a significant negative impact on physical as well as mental QOL. Wehler *et al.* (5) reported an independent reduction of PCS score caused by CP-related unemployment or early retirement. Disability/unemployment can lead to heavy psychological burden, financial distress, and disruption in social and family relationships, which can limit the ability to cope with the disease (38,39). Future strategies should focus to prevent work disability and to help disabled patients to get back into the labor force (40).

Strengths of our study include a large, well-phenotyped cohort of patients and a comprehensive analysis of multiple relevant variables. This approach overcomes important limitations of prior work in this area. Our study also has limitations. First, this was a one-time assessment of QOL in patients with a chronic condition. Therefore, we are unable to evaluate for temporal changes in QOL, as well as the direct impact of interventions, such as pancreatic endotherapy or surgery, pain management, medical management of exocrine insufficiency or diabetes, etc. on QOL. We did not find a significant difference in QOL based on whether a patient had prior pancreatic endotherapy or surgery. This observation merely represents a cross-sectional assessment and does not address the question of whether performance of endotherapy or surgery improves QOL. Such a question can best be answered by studies specifically designed to evaluate changes in QOL before and after an intervention—in fact, several such studies have concluded the benefit of these interventions on QOL (11–14). A previous study of 83 CP patients (87% alcoholic) found the QOL to be stable over a 2-year period (41)—however, larger studies in patients with diverse etiologies with a longer follow-up period are needed to better assess temporal trends and determinants of QOL. Second, we excluded 126 patients in the original NAPS2 study who did not identify a pain pattern, and given the large sample size in the final cohort, we feel the impact of excluding these patients is likely small and would not affect the conclusions. Third, recruitment of patients mainly from referral centers and under-representation of racial groups (e.g., Hispanics, Asians, etc.) despite the multicenter effort may limit the generalizability of our findings.

Finally, even after an exhaustive evaluation of multiple factors, we only explain 27% variance in physical and 17.9% variance in mental QOL, leaving several unmeasured variables. Future studies should assess the role of factors not included in our analyses, examples of which include bowel habits (e.g., diarrhea, steatorrhea, opioid-induced constipation), malnutrition (e.g., weight loss, micronutrient deficiencies, metabolic bone disease), psychological factors (e.g., depression, anxiety, stress, sleep disturbance, substance abuse), social factors (e.g., work absenteeism, financial status, social support), health-care utilization (e.g., frequency and duration of hospitalizations), adherence to medical care, and genetics. The impact of behavioral (e.g., smoking or alcohol cessation strategies, relaxation techniques), medical (e.g., narcotics, neuromodulating agents, antidepressants, pancreatic enzyme replacement, micronutrient supplementation), endoscopic (e.g., pancreatic or biliary stenting, endoscopic shock wave lithotripsy, celiac plexus block) and surgical (e.g., drainage and resection techniques, total pancreatectomy and islet auto transplantation) interventions, and physical therapy needs further assessment. Management of CP by an interdisciplinary team with expertise in primary care, behavioral health, gastroenterology, therapeutic endoscopy, pancreatic surgery, endocrinology, and radiology has been recommended. The impact of such an approach on QOL should be empirically evaluated.

In summary, this large multicenter study demonstrated that constant pain, pain-related disability/unemployment, current smoking, and concurrent co-morbidities significantly impair the QOL of CP. These data expand our understanding that both temporal nature and severity of pain are important to consider when designing clinical trials in CP. Developing treatment strategies aimed to target modifiable factors may help in improving the QOL of CP patients. Future research is needed to identify factors that were not included in this study.

CONFLICT OF INTEREST

Guarantor of the article: Dhiraj Yadav, MD, MPH.

Specific author contributions: Study design: Jorge D. Machicado, Judah N. Abberbock, and Dhiraj Yadav. Data acquisition: C. Mel Wilcox, Bimaljit S. Sandhu, Vikesh K. Singh, Andres Gelrud, Stuart Sherman, Gregory A. Cote, Samer Al-Kaade, Michelle A. Anderson, Timothy B. Gardner, Michele D. Lewis, Christopher E. Forsmark, Nalini M. Guda, Joseph Romagnuolo, John Baillie, Stephen T. Amann, Thiruvengadam Muniraj, Darwin L. Conwell, Peter A. Banks, Randall E. Brand, Adam Slivka, and Dhiraj Yadav. Statistical analysis: Judah N. Abberbock and Gong Tang. Drafting of the manuscript: Jorge D. Machicado and Dhiraj Yadav. Data interpretation, review of manuscript for important intellectual content, final approval of the manuscript: all authors.

Potential competing interests: Dr Whitcomb is an inventor of intellectual property that is licensed to Ambry Genetics, which has been evaluated in this study. He also has an ownership interest in Ambry Genetics. The other authors declare no conflict of interest.

Study Highlights

WHAT IS CURRENT KNOWLEDGE
✓ Chronic pancreatitis has a profound effect on quality of life.
✓ Factors that determine quality of life in chronic pancreatitis patients are not well established.

WHAT IS NEW HERE
✓ Constant pain had the most impact on quality of life of chronic pancreatitis patients.
✓ Other independent factors were disability/unemployment related to pain, current smoking, and co-morbid conditions.
✓ Prior endoscopic or surgical pancreatic interventions had no impact on the quality of life.
✓ Alcohol etiology, disease duration, and pancreatic morphology had no effect on the quality of life.

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