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Psychometric performance of the PAncreatic CAncer disease impact (PACADI) score

Turid Heiberg [a, b, *, 1], Bart Baekelandt [c], Tore K. Kvien [c, d], Trond Buanes [c, e]

[a] Regional Research Support, Oslo University Hospital, Oslo, Norway
[b] Østfold University College, Halden, Norway
[c] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[d] Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[e] Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, Oslo, Norway

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ABSTRACT

Background/Objective: Pancreatic Cancer Disease Impact (PACADI) score measures the impact of pancreatic cancer (PC) on important health dimensions, selected by patients. The aim of this single center study was to test the psychometric performance of the Pancreatic Cancer Disease Impact (PACADI) score.
Methods: Patients with suspected pancreatic cancer (PC) completed PACADI, the EuroQol-5D (EQ-5D index) and Edmonton Symptom Assessment System (ESAS) in this longitudinal observational study. Measures were compared across patients with PC (n = 210), other malignant lesions (OML) (n = 109) and non-malignant lesions (NML) (n = 41). Associations, test-retest and internal consistency reliability, longitudinal changes, sensitivity to change and prediction of mortality during the first year were examined in patients with PC.
Results: The three measures discriminated between PC and OML. The PACADI score correlated strongly at baseline (n = 199)/after three months (n = 85) with the EQ-5D index and ESAS "sense of well-being" (0.64 and 0.66/0.73 and 0.69, $p < 0.001$, respectively), showed high test-retest reliability (ICC 0.84) and very good internal consistency reliability (Cronbach's alpha 0.81–0.85) across all visits. Scores improved over time at 3, 6, 9 and 12 months for survivors, and standardized response mean (SRM) for improvement between 2 and 3 months (n = 44) was 0.80 (PACADI), −0.59 (EQ-5D index) and 0.69 (ESAS "sense of well-being"). The PACADI score significantly predicted mortality within the first year ($p = 0.02$) in contrast to the EQ-5D index and ESAS "sense of well-being".
Conclusion: This study showed satisfactory psychometric performance of the PACADI score. The results support its use in clinical practice and intervention trials.

1. Introduction

In spite of progress in the treatment of some cancer diagnoses in terms of decreased mortality [1], pancreatic cancer (PC) remains a major health problem, both regarding disease course and survival [2]. Challenges, among others, are late diagnosis and relative paucity of research funding for PC. These challenges are shared among less survivable malignant diseases and should be addressed to hopefully double the 5-year survival by 2029 [3]. However, some recent studies have indicated progress in the treatment and prognosis of PC [4–6]. These progresses are dependent on valid measures to capture improvement.

Valid measures may also raise the awareness of symptoms and increase the detection of diagnosis and treatment. The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend researchers to provide evidence of benefit in Patient Reported Outcome Measures (PROM) to achieve approval of new medications [7]. However, extensive questionnaires with limited perceived relevance to the informants may negatively affect completion and respondent rates [8]. Assessing PROM in PC has unfortunately been rarely reported and appraised in trials, compared to survival as an outcome measure [9].

* Corresponding author. Regional Research Support, Oslo University Hospital, Klaus Torgårds vei 3, Sogn Arena, Pb 4950 Nydalen, NO-0424 Oslo, Norway.
E-mail addresses: uxtuhe@ous-hf.no, turid.heiberg@hiof.no (T. Heiberg).
[1] Turid Heiberg, Professor, Faculty of Health and Welfare, Kobberslagerstredet 5, P.O.Box 700, NO-1757 Halden, Norway.

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Disease specific PROM are usually more sensitive in capturing changes than generic PROM [10]. Furthermore, it is still an open question which dimensions to include in PROM questionnaires, and there is a diversity of PROM dimensions in use for patients with PC [11,12].

Lack of concordance in reporting symptoms between patients and clinicians [13] indicates a need for questionnaires that ask questions which primarily reflects relevance and importance to the patients.

We have previously reported the development of a brief, fully patient-derived, disease specific questionnaire that can be expressed with a score, the PAncreatic CAncer Disease Impact (PACADI) score [14].

A preliminary validation has been performed [14]. However, we are now able to provide a more complete study on the full psychometric performance of the PACADI score. Thus, the aim of this study was to examine the psychometric performance of the PACADI score, both in a cross-sectional and longitudinal perspective with simultaneous examination of EuroQol-5D (EQ-5D) index [15] and the global question "sense of well-being" in Edmonton Symptom Assessment System (ESAS) [16].

2. Patients and methods

A couple of purely patient derived PROM have been developed for patients with rheumatic diseases [17–19] and the methodological approach was also a model for the development of the PACADI score.

Adult (>18 years) patients with suspected PC (n = 360) who were referred to a tertiary hepato-pancreato-biliary (HPB) center, were included in this study from 2012 to 2016. The patients were categorized into three diagnostic groups; PC (n = 210), other malignant lesions (OML) (n = 109), and non-malignant lesions (NML) (n = 41) (Table 1). Our aim was to include 200 patients with confirmed diagnoses of PC (i.e. ICD10 C25.0–3) [20].

Data on the confirmation of diagnoses by imaging modalities, cytology, histology or histology in combination with surgery as well as stage, were collected after enrollment (Table 2).

2.1. Design and data collection

Two authors (TB, MD, surgeon/TH, RN, researcher) recruited patients during their diagnostic appointments to take part in a study to select dimensions for a PROM to assess PC. Data were collected at inclusion (baseline) and after 1, 2, 3, 6, 9 and 12 months follow-up. Age, gender as well as body weight and height to calculate body mass index (BMI) were recorded in the case report form (CRF) at baseline. Since weight loss is a recognized symptom in PC [21], regular body weight prior to disease onset was also recorded.

2.2. Instruments

The CRF included the PACADI questionnaire which consists of 8 dimensions prioritized by patients (Pain/discomfort, Anxiety, Loss of appetite, Itchiness, Fatigue, Nausea, Dry mouth, Bowel/digestive problems), without further subscales [14]. Responses were given for each dimension on a numeric rating scale (NRS) 0–10 at every visit. Past week was the time frame for the responses [14]. Anchors were "not at all" (0) and "worst possible" [10]. According to patients' rankings for priority, we calculated a relative weight for each dimension [(14]. The PACADI score (range 0–10) was calculated by multiplying NRS values (range 0–10) by the final weight of each dimension and sum up the products [14]: NRS pain/discomfort value x 0.16 + NRS fatigue value x 0.16 + NRS bowel/digestion value x 0.15 + NRS loss of appetite value x 0.14 + NRS anxiety value x

Table 1
Baseline characteristics across three diagnostic groups (n = 360) (discriminatory validity).

	PC n = 210 (58.7%)	OML n = 109 (30.0%)	NML n = 41 (11.3%)	p-value[b]	Total (n = 360)
Age	67.5 (10.4)	65.8 (11.1)	65.8 (11.3)	0.35	66.8 (10.7)
Females (%)	49.3	38.9	39.0	0.15	45.0%
Weight	71.7 (14.9)	76.0 (13.9)	75.5 (15.0)	0.037	73.5 (14.7)
Weight loss[a]	7.7 (8.7)	6.4 (6.5)	6.3 (8.2)	0.34	7.1 (8.0)
BMI	24.1 (4.3)	25.1 (4.0)	25.1 (4.0)	0.11	24.5 (4.2)
BMI change[a]	2.6 (3.0)	2.1 (2.1)	2.2 (2.8)	0.29	2.4 (2.7)
PACADI dimensions					
Pain/discomfort	3.0 (2.9)	2.4 (2.7)	3.0 (3.0)	0.14	2.8 (2.8)
Anxiety	4.0 (3.1)	3.4 (2.7)	3.3 (2.5)	0.14	3.7 (2.9)
Loss of appetite	3.6 (3.4)	2.7 (2.9)	3.0 (3.3)	0.06	3.2 (3.3)
Itchiness	2.4 (3.6)	2.8 (3.6)	1.9 (2.7)	0.39	2.4 (3.59
Fatigue	4.4 (2.9)	3.5 (2.9)	3.6 (3.1)	0.039	4.0 (3.0)
Nausea	2.1 (2.9)	1.7 (2.8)	2.0 (2.7)	0.64	2.0 (2.8)
Dry mouth	3.4 (3.1)	2.9 (2.9)	3.5 (3.6)	0.35	3.3 (3.1)
Bowel and/or digestive problems	3.6 (3.1)	2.7 (3.0)	3.1 (3.0)	0.05	3.3 (3.1)
PACADI score	3.4 (2.1)	2.8 (2.0)	3.0 (2.3)	0.045	3.2 (2.1)
EQ-5D index	0.60 (0.30)	0.70 (0.26)	0.66 (0.33)	0.045	0.64 (0.29
ESAS dimensions					
Pain at rest	2.0 (2.5)	1.4 (2.2)	2.0 (2.5)	0.09	1.8 (2.5)
Pain at movement	2.2 (2.6)	1.5 (2.5)	2.4 (2.7)	0.07	2.0 (2.6)
Fatigue	3.9 (3.00)	3.2 (2.9)	3.2 (3.1)	0.07	3.6 (3.0)
Nausea	1.6 (2.7)	1.5 (2.7)	1.4 (2.4)	0.89	1.6 (2.7)
Dyspnea	1.3 (2.3)	1.6 (2.4)	2.3 (3.2)	0.043	1.5 (2.5)
Dry mouth	3.0 (3.0)	2.6 (2.8)	3.2 (3.6)	0.49	2.9 (3.0)
Loss of appetite	3.3 (3.3)	2.1 (2.6)	2.6 (3.1)	0.004	2.9 (3.1)
Anxiety	3.3 (3.1)	2.9 (2.7)	3.3 (3.0)	0.52	3.2 (3.0)
Depression	2.6 (3.0)	2.0 (2.3)	2.6 (3.0)	0.20	2.4 (2.8)
Sense of well-being	3.7 (2.9)	3.1 (2.7)	3.2 (2.8)	0.17	3.4 (2.8)

PC=Pancreatic cancer. OML= Other malignant lesions. NML= Non malignant lesions.
[a] From disease onset to baseline.
[b] ANOVA/chi-square, as appropriate.

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Table 2
Description of the stage, performed surgery and diagnostic methods in the three diagnostic groups.

	PC n = 210 (58.7%)	OML n = 109 (30.0%)	NML n = 41 (11.3%)	p-value[a]
Stage				
Localized	43.5	68.5	100.0	0.000
Locally advanced	35.4	20.4	0	
Metastatic	21.1	11.1	0	
Surgery	72.3	89.9	73.2	0.001
Main diagnostic tool for confirmation of diagnoses				
Imaging modality	9.2	3.9	10.3	0.054
Cytology	9.7	1.0	7.7	
Histology	62.8	72.8	66.7	
Histology and surgery	18.4	22.3	15.4	

PC=Pancreatic cancer. OML= Other malignant lesions. NML= Non malignant lesions.
[a] Chi-square.

0.13 + NRS dry mouth value x 0.11 + NRS itchiness value x 0.08 + NRS nausea value x 0.07. This algorithm emphasizes the relative importance of each dimension to the patients [14].

We used a one-dimensional anchor for the patients' subjective perception of change in health condition, over the last month, i.e. since last visit. Response options were improved, unchanged or worse [22].

Other questionnaires in the CRF included EQ-5D index [15] with five dimensions (three dimensions addressing physical function, and the two last items addressing anxiety and pain), each with 3 levels of response options (none/minor, moderate or major problem). Calculation of the EQ-5D index utility score was based on the original algorithm (better health with increasing values), ranging from below zero to 1.0 (perfect health) [15]. Furthermore, the ESAS [16] with 10 items was included also with responses on NRS 0–10 but with regard to the current day as the time frame [16]. ESAS "sense of well-being" (question 10) was considered as a disease-specific global PROM for PC to enable reasonable comparisons. ESAS has been developed to assess PC with a special emphasize on the palliative phase [16].

3. Statistical analyses

Baseline characteristics and other descriptive data are presented as mean (SD) for continuous variables and counts/percentages for categorical variables. ANOVA was used to compare the three diagnostic groups (PC, OML and NML) and to examine the discriminant validity of PACADI, EQ-5D index and ESAS "sense of well-being".

We also compared PC versus OML, PC versus NML and OML versus NML, using independent samples t-tests. The differences at baseline and corresponding 95% CI are presented (Table 3).

We included gender and age as covariates in univariate analyses of variance to check for bias of covariates in the examination of the discriminatory strength of the PACADI score across diagnostic groups. Body weight as a disease manifestation [23] was not included as a covariate.

We used independent samples *t*-test to examine differences in variables at baseline between patients who completed and patients who did not complete all follow-ups.

No imputation for missing data was used. All analyses were conducted from baseline to each time point on the remaining responding sample, using paired sample t-tests.

As the data according to histograms and comparing mean versus median were not normally distributed, Spearman's correlation was used in cross-sectional analyses to examine validity at baseline and at the 3-month follow-up examination. The levels of correlation based on Spearman's rho were defined as very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59, strong (0.60–0.79) or very strong (0.80–1.00). Significant correlations were recorded as either $p < 0.05$ or $p < 0.001$.

The Intraclass Correlation Coefficient (ICC) was calculated for examination of test-retest reliability. The test-retest was performed with an interval from baseline to 1 month in patients reporting to be unchanged, i.e. with stable disease status on the global anchor question for patients' subjective perception of change in health condition. Values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.90, and greater than 0.90 were considered indicative of poor, moderate, good, and excellent reliability, respectively [24].

To check for internal consistency, we also calculated Cronbach's alpha across dimensions for the two composite measures PACADI score and EQ-5D index at baseline and at 3-, 6-, 9- and 12-month follow-up.

Paired samples T-tests were applied to examine longitudinal changes in PROM (PACADI score, EQ-5D index and ESAS) for patients with PC over time at all visits.

These data were also used to examine standardized response mean (SRM for the PACADI score, EQ-5D index and ESAS "sense of well-being" in the subset of patients who reported disease improvement during the last month at three months, since this is the time with potential improvement after surgery [12]. SRM was

Table 3
Within-group tests of the diagnostic groups.

PROM	Comparisons	Sig. (2-tailed)	Mean difference	95% CI Lower	95% CI Upper
PACADI score	PC vs OML	0.012	0.654	0.147	1.160
	PC vs NML	0.318	0.350	−0.339	1.039
	OML vs NML	0.414	−0.304	−1.036	0.429
EQ-5D index	PC vs OML	0.013	−0.939	−0.168	−0.198
	PC vs NML	0.334	−0.540	−0.164	0.056
	OML vs NML	0.466	0.399	−0.068	0.148
ESAS "Sense of well-being"	PC vs OML	0.054	0.665	−0.110	1.341
	PC vs NML	0.426	0.370	−0.545	1.285
	OML vs NML	0.542	−0.294	−1.246	0.657

Two samples t-tests (Equal variance assumed).

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calculated as the change in outcome measures from month 2 to month 3 divided by the SD of the change. Cohen definitions for effect size (ES) can also be used for SRM: 'trivial' ES < 0.20, 'small' ES ≥ 0.20 < 0.50, 'moderate' ES ≥ 0.50 < 0.80, or large ES ≥ 0.80 [25].

Finally, we used separate Cox Regression analyses to examine prediction of early (before 12 months) mortality for the PACADI score, EQ-5D index and ESAS "sense of well-being" with adjustment for age and gender.

Data were stored with a numeric identifier in a separate, secured central hospital research server. The code list was securely stored, only accessible for the principal investigators. The regional ethical committee approved the protocol and patient information/consent form (REK no.265-08412c). The privacy protection supervisor evaluated and accepted the data-handling procedures. All patients signed a written informed consent before inclusion.

4. Results

4.1. Patients

Patients with suspected PC (n = 360, mean (SD) age 66.8 (10.7), 45.0% females) were consecutively included between 2012 and 2016. Longitudinal follow-up was performed from May 2013. The number of patients at baseline with PC was 210 (58.7%), OML 109 (30.0%) and NML 41 (11.3%). Three patients declined to be enrolled in the study. Eleven patients did not complete PACADI at baseline, but they completed PACADI at later time points.

The groups were comparable for clinical characteristics except for body weight, stage and performance of surgery (Table 1). The results of adjusted univariate analyses of variance were similar to the ANOVA analyses. Gender was a significant covariate to the PACADI score (p = 0.007), whereas age was not (p = 0.40).

Stage, performed surgery and diagnostic methods used in our material showed that surgery was less frequent in patients with PC than in the other two groups, with the highest percentage of locally advanced and metastatic disease. Most patients were diagnosed with histology or a combination of surgery and histology (Table 2).

4.2. Discrimination

The PACADI score at baseline was significantly higher (p = 0.045) in the patients with PC compared to the other two groups. The EQ-5D index also discriminated significantly between the diagnostic groups (Table 1). PACADI single dimensions showed significant discrimination between the diagnostic groups for "fatigue" and "bowel/digestive problems" (p = 0.039/0.005) and borderline for "loss of appetite" (p = 0.06). ESAS "sense of well-being" (global) did not significantly discriminate between the diagnostic groups. However, ESAS single dimensions showed significant discriminatory trait for "loss of appetite" (p = 0.004) (Table 1).

Within-group comparisons across the three diagnostic groups, using the three main measures (PACADI score, EQ-5D index and ESAS "sense of well-being") showed that PACADI and EQ-5D index discriminated significantly between PC vs OML, whereas ESAS "Sense of well-being" showed a borderline significance between PC and OML. Differences between PC and NML were not statistically significant (Table 3).

The two variables that were significantly different at baseline between patients who completed the study to the 12-month follow-up and those who did not, were "bowel and/or digestive problems" (p = 0.02) and EQ-5D (p = 0.001).

4.3. Correlations

Correlations between PACADI score, EQ-5D index and ESAS "sense of well-being" as global measures at baseline/after three months were significant (p < 0.001) and were strong to EQ-5D index (−0.64/-0.73) and to ESAS "sense of well-being" (0.66/0.69) (Table 4). Most of the six overlapping dimensions between PACADI and ESAS correlated very strongly both at baseline and at the 3-month visit. Correlations between other dimensions varied from moderate to very weak (Table 4).

4.4. Reliability

Test-retest reliability testing in patients with stable condition (n = 14), using an interval from baseline to one month, showed ICC 0.84 for PACADI score in patients with PC and 0.74 for all patients with stable condition (n = 34) (Table 5). ICC for EQ-5D index were in patients with PC/all patients 0.88/0.83 and for ESAS "sense of well-being" 0.85/0.72 (Table 5). The ICC of the three global measures is regarded as good in patients with PC [24].

Internal consistency reliability assessed by Cronbach's alpha for patients with PC was consistently very high across visits at baseline/3/6/9/12 months for the PACADI score (0.83/0.85/0.81/0.84/0.84, respectively). For the EQ-5D index, Cronbach's alpha showed moderate to very high internal consistency reliability at the same time points (0.58/0.82/0.66/0.70/0.72, respectively.

4.5. Longitudinal changes

Longitudinal examinations showed significant improvement (p < 0.05 - p < 0.001) in PACADI score for patients with PC from baseline (n = 199) to 3 (n = 85), 6 (n = 76), 9 (n = 61) and 12 (n = 51) months (Table 6). The EQ-5D index did not significantly improve, and ESAS "sense of well-being" had improved significantly after 9 and 12 months. For two single dimensions in PACADI, "anxiety" and "itchiness", the improvement was significant from baseline to all other time points (p < 0.001). Also "loss of appetite", "fatigue" and "dry mouth" improved during the 12-month follow-up. For the single dimensions in ESAS, "loss of appetite", "fatigue" and "anxiety" improved (Table 6).

Responsiveness of PACADI score was examined in patients who reported improvement at three months since the previous visit at 2 months, because this is the time when patients usually return to preoperative values after surgery [26]. SRM was large for PACADI score (0.80, n = 44), moderate for EQ-5D index (−0.59, n = 43) as well as for ESAS "sense of well-being" (0.69, n = 42).

4.6. Prediction of mortality

Out of the three global measures, only PACADI score significantly (p = 0.02) predicted mortality during the first year follow-up of patients with PC, adjusted for age and gender in the analyses (Table 7). The three dimensions of the PACADI score that contributed significantly to this psychometric property, were "pain/discomfort" (p = 0.004), "fatigue" (p = 0.034) and "bowel and/or digestive problems" (p = 0.02).

5. Discussion

The PACADI score is a disease-specific patient-reported outcome measure for patients with PC. We have previously reported on the development of the score and presented some preliminary data on the psychometric performance [14]. PACADI is intended for use both in clinical practice and in science. However, we expect that the individual dimensions will be more important for clinical practice,

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Table 4
Spearman's correlations between PACADI score, EQ-5D index and ESAS at baseline/3 months in patients (n = 199/85) with pancreatic cancer (concurrent validity).

Baseline	EQ-5D index	ESAS									
		Pain at rest	Pain at movement	Fatigue	Nausea	Dyspnea	Dry mouth	Loss of appetite	Anxiety	Depression	Sense of well-being
PACADI score	−0.64**/-0.73**	0.50**/0.57**	0.48**/0.60**	0.73**/0.83**	0.53**/0.57**	0.21**/0.41**	0.54**/0.43**	0.64**/0.68**	0.40**/0.55**	0.48**/0.64**	0.66**/0.69**
Pain/discomfort	−0.48**/−0.76**	0.74**/0.74**	0.69**/0.71**	0.38*/0.63**	0.36**/0.55**	0.29**/0.28*	0.28**/0.24*	0.36**/0.53**	0.20**/0.41**	0.30**/0.53**	0.39**/0.69**
Anxiety	−0.49**/−0.62**	0.15*0.44**	0.16*/0.47**	0.25**/0.60**	0.16*/0.42**	0.02/0.24*	0.22**/0.23*	0.23**/0.37**	0.81**/0.83**	0.64**/0.73**	0.47**/0.58**
Loss of appetite	−0.47**/−0.49**	0.38**/0.39**	0.37**/0.40**	0.53**/0.64**	0.46**/0.45**	0.14*/0.24*	0.37**/0.21*	0.80**/0.90**	0.23**/0.36**	0.25**/0.37**	0.52**/0.56**
Itchiness	−0.12/−0.21	0.10/0.21	0.13/0.27*	0.34**/0.25*	0.23**/0.26*	0.08/0.38**	0.26**/0.16	0.22**/0.31**	0.15*/0.09	0.23**/0.17	0.21**/0.18
Fatigue	−0.51**/-0.65**	0.33**/0.42**	0.30**/0.50**	0.80**/0.93**	0.44**/0.46**	0.12/0.40**	0.44**/0.27*	0.57**/0.57**	0.20**/0.45**	0.29**/0.57**	0.52**/0.59**
Nausea	−0.42**/-0.52**	0.43**/0.51**	0.44**/0.57**	0.53**/0.50**	0.82**/0.86**	0.25**/0.32**	0.39**/0.24*	0.57**/0.47**	0.15*/0.34**	0.25**/0.37**	0.39**/0.43**
Dry mouth	−0.42**/−0.27*	0.26**/0.23*	0.22**/0.28*	0.47**/0.36**	0.36**/0.42**	0.17*/0.28*	0.85**/0.92**	0.34**/0.25*	0.26**/0.26*	0.33**/0.34**	0.38**/0.37**
Bowel and/or digestive problems	0.40**−0.40**	0.33**/0.36**	0.35**/0.38**	0.50**/0.55**	0.29**/0.39**	0.17*/0.10	0.26**/0.27*	0.26**/0.40**	0.23**/0.27*	0.34**/0.36**	0.44**/0.37**

*p < 0.05.
**p < 0.001.

Table 5
Intraclass correlation coefficient (ICC) at baseline and during follow-up after one month in patients with pancreatic cancer/all patients who reported stable disease (test-retest reliability).

	Pancreatic cancer n = 14			All patients n = 34		
	Mean baseline	Mean after one month	ICC	Mean baseline	Mean after one month	ICC
PACADI score	2.64 (2.25)	2.94 (1.70)	0.84*	2.42 (2.24)	2.78 (1.88)	0.74**
EQ-5D index	0.69 (0.32)	0.65 (0.28)	0.88*	0.75 (0.26)	0.67 (0.27)	0.83**
ESAS Pain at rest	0.85 (2.23)	1.85 (2.70)	0.74*	1.03 (2.10)	1.78 (2.47)	0.79**
ESAS Pain at movement	1.08 (2.29)	1.54 (2.26)	0.87*	1.22 (2.23)	1.59 (2.30)	0.67*
ESAS Fatigue	2.92 (2.93)	3.54 (3.23)	0.82*	2.61 (2.96)	2.65 (2.70)	0.63*
ESAS Nausea	1.00 (2.24)	0.15 (1.68)	0.19	1.16 (2.49)	1.25 (1.88)	0.02
ESAS Dyspnea	0.62 (2.22)	1.46 (1.90)	−0.16	1.16 (2.46)	1.44 (1.87)	0.67*
ESAS Dry mouth	1.85 (2.44)	3.38 (2.93)	0.85*	2.00 (2.61)	2.55 (2.73)	0.71*
ESAS Loss of appetite	3.00 (3.49)	3.08 (3.69)	0.90**	2.03 (3.02)	2.75 (3.36)	0.81**
ESAS Anxiety	2.92 (3.59)	2.38 (2.57)	0.81*	2.59 (2.89)	1.97 (2.29)	0.71**
ESAS Depression	2.00 (2.97)	1.46 (1.94)	0.67*	1.34 (2.48)	1.31 (2.04)	0.64*
ESAS Sense of well-being	2.54 (3.02)	2.62 (2.60)	0.85*	2.28 (2.64)	2.44 (2.38)	0.72**

*p < 0.05.
**p < 0.001.

and that the sum score will be more relevant for research.

5.1. Patients

The sample size target of 200 was based on the recommendation from the Women's Cancer Program at the Mayo Clinic, Rochester, USA [20], indicating that sample sizes for testing should include at least 200 cases and results should be replicated in at least one additional sample. We have received a request from Sweden to include the PACADI score into the Swedish National Pancreas Registry which may provide an opportunity for the suggested replication of our findings.

None of the patients or investigators knew the exact diagnoses at baseline. Patients were all referred because of suspicion of PC. It was only, mainly after histology (Table 2), that the exact diagnoses were known. The awareness of a possible malignant disease could have influenced the level of anxiety at baseline. A significant reduction in anxiety was seen in the longitudinal data when the patients eventually knew more about the exact diagnoses and the disease impact (Table 6). Itchiness was another dimension that changed significantly after baseline, which probably was caused by surgery or stenting, to remove the blockage of lesions in the biliary duct, and not by awareness of the diagnoses.

5.2. Discrimination

Discriminant validity between disease groups as shown in this study is another indicator of a strong disease specific feature of PACADI. Significant differences between groups were also found in “Fatigue” and “Bowel and/or digestive problems” as well as “loss of appetite”. These dimensions showed the highest discriminant property, which supports that they are highly relevant disease specific measures.

The within group analyses revealed that the discriminant property was only between PC and OML, i.e. between malignant diseases. One explanation why the PACADI score was significantly different between patients with PC and OML but was not significant between patients with PC and NML, may be because many of the patients with NMLs had pancreatitis which initially has a clinical picture similar to PC [27], and tissue examination and/or imaging is needed to confirm the correct diagnoses.

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Table 6
Longitudinal data of PACADI score, EQ-5D index and ESAS over 12 months (baseline, after 1, 2, 3, 6, 9 and 12 months) in patients with pancreatic cancer (n's are based on complete PACADI score at each measurement).

	Baseline n = 199	1 month n = 94	2 months n = 81	3 months n = 85	6 months n = 76	9 months n = 61	12 months n = 51
PACADI score	3.38 (2.22)	3.41 (1.70)	3.06 (1.87)	2.72 (1.90)*	2.43 (1.66)**	2.24 (1.72)**	2.13 (1.75)*
PACADI dimensions							
Pain/discomfort	2.89 (2.74)	3.70 (2.32)*	3.13 (2.29)	3.05 (2.49)	2.90 (2.36)	2.43 (2.60)	2.36 (2.10)
Anxiety	4.31 (3.23)	3.42 (2.50)**	3.14 (2.74)**	2.73 (2.62)**	2.57 (2.56)**	2.48 (2.67)**	2.30 (2.55)**
Loss of appetite	3.54 (3.50)	4.12 (2.99)	3.32 (2.95)	2.63 (2.86)*	2.00 (2.50)**	2.07 (2.59)*	1.78 (2.67)*
Itchiness	2.58 (3.77)	0.80 (1.91)**	1.10 (2.16)**	1.12 (2.20)**	0.88 (1.92)**	1.12 (2.04)**	1.00 (1.92)**
Fatigue	4.21 (2.94)	4.47 (2.81)	3.56 (2.77)	3.66 (2.79)	3.19 (2.55)*	2.78 (2.35)**	2.89 (2.44)*
Nausea	2.22 (2.84)	1.98 (2.37)	1.95 (2.42)	2.05 (2.44)	1.25 (2.01)	1.27 (2.09)	1.23 (1.82)
Dry mouth	3.04 (2.90)	3.24 (2.85)*	2.34 (2.54)*	2.34 (2.45)**	2.08 (2.38)**	2.19 (2.66)	1.70 (2.30)**
Bowel and/or digestive problems	3.27 (3.14)	3.52 (2.75)	3.35 (2.61)	3.49 (2.60)	3.06 (2.76)	3.17 (2.74)	2.57 (2.39)
EQ-5D index	0.62 (0.28)	0.57 (0.29)	0.64 (0.24)	0.64 (0.29)	0.73 (0.22)	0.73 (0.27)	0.75 (0.20)
ESAS dimensions							
Pain at rest	1.82 (1.40)	1.89 (2.14)	1.80 (2.10)	1.72 (2.10)	1.74 (2.03)	1.30 (2.12)	1.30 (1.96)
Pain at movement	1.93 (2.48)	2.40 (2.30)	2.34 (2.24)	2.11 (2.45)	1.82 (2.09)	1.56 (2.28)	1.72 (2.26)
Fatigue	3.97 (3.14)	4.02 (2.83)	3.72 (2.55)	3.43 (2.63)	2.95 (2.28)	2.62 (2.55)	2.62 (2.31)*
Nausea	1.66 (2.66)	1.72 (2.36)	1.70 (2.44)	1.48 (2.14)	1.10 (1.96)	1.08 (1.93)	0.86 (1.68)
Dyspnea	1.26 (2.20)	1.48 (2.01)	1.82 (2.30)*	1.70 (2.32)*	1.14 (1.78)	1.46 (2.21)	0.92 (1.37)
Dry mouth	2.67 (2.98)	2.54 (2.72)	2.56 (2.76)	2.18 (2.57)*	1.92 (2.30)	1.97 (2.68)	1.50 (2.28)
Loss of appetite	3.66 (3.48)	3.33 (2.85)	3.87 (2.87)	2.69 (2.93)	2.13 (2.68)*	2.77 (2.56)*	1.29 (2.03)**
Anxiety	3.57 (3.20)	2.57 (2.47)**	2.67 (2.72)*	2.42 (2.58)*	2.27 (2.36)*	2.08 (2.49)*	1.79 (2.24)
Depression	2.71 (3.01)	2.31 (2.48)	2.24 (2.56)	2.33 (2.51)	1.90 (2.42)	2.03 (2.63)	1.51 (2.12)
Sense of well-being	3.56 (3.03)	3.41 (2.52)	3.09 (2.49)	2.89 (2.37)	2.61 (2.28)	2.20 (2.23)*	2.02 (2.02)**

Paired samples t-tests.
*$p < 0.05$.
**$p < 0.01$.

Table 7
Predictive validity of PACADI score, EQ-5D index and ESAS "sense of well-being" for mortality within the first year after baseline in the three diagnostic groups (predictive validity).

	PC n = 210		OML n = 109		NML n = 41	
	HR[a]	p-value	HR[a]	p-value	HR[a]	p-value
PACADI score	1.09	0.02	1.05	0.47	1.20	0.18
EQ-5D index	0.68	0.17	0.42	0.10	0.29	0.18
ESAS sense of well-being	1.01	0.78	1.01	0.73	0.99	0.79

[a] Hazard Ratio from separate cox regression analyses adjusted for age and gender.

5.3. Correlations and reliability

The PACADI score correlated more strongly to EQ-5D index and ESAS "sense of well-being" than to the different components of ESAS, which also supports that the PACADI score performs as a global measure in patients with PC (Table 4).The ICC values for the PACADI score were similar to EQ-5D index and ESAS "sense of well-being". The higher ICC in patients with PC versus all patients without PC further supports that the PACADI score performs well as a disease specific measure for PC. One can question whether n = 14 is sufficient for a calculation of ICC. However, the minimum sample size required to estimate the magnitude of the agreement between observations is dependent on the actual value of ICC and the number of observations of each subject. This means that for all of our three global measures with two measurements, the n of 14 is well beyond the minimum sample size required to calculate ICC [28]. The number of patients reporting stable condition during the first 3 months was low, explained by the high frequency of comprehensive surgical procedures shortly after baseline, with an expected initial decline in the proportion of patients with stable condition [12].

The internal reliability of the scale of EQ-5D index was moderate to very strong across visits, but very strong at all time points for PACADI, indicating that the PACADI score possess high internal consistency reliability.

5.4. Longitudinal changes and prediction of mortality

Multiple t-tests were used to assess the changes over time. We acknowledge that an adjustment for multiple testing could meet the challenge with false positive findings. However, the use of such adjustments in observational studies, where the number of tests both presented and not presented are considerable, is controversial [29]. We have thus chosen to keep the multiple t-tests without adjustments, keeping in mind that the interpretation of the p-values is not confirmatory but indicative of change.

The difference that was found at baseline between those who completed the study and those who did not, may, not surprisingly, reflect a better general health at baseline in those who completed. Survivors with improved health status during follow-up have also been observed in other studies [30]. "Bowel and/or digestive problems" that worsens over time for patients with PC can potentially be explained by all the digestion regulating hormones that are produced in the pancreas.

The PACADI score and five of the eight dimensions improved significantly in the longitudinal examinations. With an inflicting disease like PC, an improvement over time may appear surprising. The main explanation may be that curative and palliative interventions impact PROMs positively [4]. An additional explanation may be that those who would report worsening PROM were mostly deceased, supported by the decline in respondents from baseline (n = 199) to 12 months (n = 51). The improvement appeared mostly at the 3-month visit at which time patients are expected to have recovered after surgery [31].

The subsample at 12 months (n = 51) may seem small, however it is 25.6% of the patients with PC who participated at baseline (n = 199). Still this is a limitation. However, other longitudinal studies of patients with PC have observed similar or lower retention rates, influenced by the high mortality in these patients [12,26].

The significant high baseline levels and longitudinal improvement in "Anxiety" and "Itchiness" in the PACADI score indicate that these two dimensions play a clinically relevant role at an early stage of the disease.

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The SRM values for PACADI score performed well compared to EQ-5D index and ESAS "sense of well-being" supporting that the PACADI score could be a valuable instrument in future intervention trials in patients with PC.

Further, the PACADI score significantly predicted mortality unlike EQ-5D index and ESAS "sense of well-being" (Table 7). Thus, the PACADI score may be useful to identify patients who may benefit from early and progressive intervention.

5.5. PACADI and ESAS

The two questionnaires PACADI score and ESAS have similar features, sharing 6 dimensions which, not surprisingly, correlated strongly with each other: "pain", "anxiety", "fatigue", "nausea", "dry mouth", "loss of appetite". "Dyspnea" in ESAS is a complimentary dimension to the PACADI score dimensions, with significant discriminatory property between the groups. However, contrary to the other measures, the mean value was significantly higher with non-malignant diseases than the two other groups. ESAS "dyspnea" and "depression" were not included dimensions in the PACADI score, since they were not given sufficient priority by the patients.

The two PACADI dimensions that were complementary to ESAS dimensions were "Bowel and/or digestive problems" as well as "itching". Not all patients are affected by itching, but those who are, reported that it should have high priority for improvement [14].

One other difference between the two instruments is the time frame. ESAS focuses on "today", whereas PACADI asks for the perception during the last week. Symptoms may vary from one day to the next. We used last week as time frame for PACADI to obtain a report over more time than a single day, but recall bias may be an issue. However, data from other studies have shown that daily and 7-day time frame scores correlate strongly, even though somewhat influenced by the day of recording [32]. Thus, past week time frame may contribute to highlight a more general disease experience.

5.6. Other PROM

Another disease specific PROM for PC has been developed by the European Organization for Research and Treatment of Cancer (EORTC) and contains 26 questions (QLQ-PAN26) divided into 17 scales, in addition to the basic cancer module with 30 questions, divided into 15 scales. The extensive number of questions has caused return rates too low to be included in analyses at follow-up after one year [8]. Questions of sexuality in QLQ-PAN26 are less frequently completed [8]. In the PACADI score, dimensions of highest priority to patients were included, and sexuality was never mentioned by the patients, potentially caused by lower relevance [8,14].

Psychometric properties for QLQ-PAN26 (23 scales out of 26 questions) showed some variation in internal consistency measured with Cronbach's alpha, which may indicate that some of the questions were not conceptually consistent [33]. The PACADI score had consistently very strong internal consistency reliability (>0.8) across all visits. Convergent validity between QLQ PAN26 and QLQ-C30 also showed variable values, but were generally strong ($r > 0.6$).

Patient-Reported Outcomes Measurement Information System (PROMIS) has now been developed for several cancer diagnoses, but up to now, PC is not one of them [34]. Several advantages are linked to PROMIS, like electronic versions and computer adaptive testing (CAT) [34].

Clinical Benefit Response (CBR) is a measure that has frequently been used in trials [11]. It has an algorithm that includes pain intensity, analgesic consumption, residual pain, Karnofsky Performance to measure physical function and weight loss over at least 4 consecutive weeks [35]. CBR responders and non-responders to treatment are calculated. CBR has recently been suggested to be replaced by PROM [11] in evaluations, since PROM has been shown to gain complementary information and a higher response rate without losing substantial information. CBR requires several time consuming measurements, whereas PROM questionnaires is completed by the patients and represent dimensions with relevance and meaning based on the importance to the patients [11].

5.7. The patient perspective

Some questionnaires include questions about health care performance [36]. One issue may be whether such questions are sensitive to the effect of new therapeutic agents. Development of PROM usually has input from high impact professionals alongside patients [8,37,38], providing a mixed message from different perspectives in one PROM. However, multiple studies have shown discrepancies between opinions and responses between clinicians and patients [13]. Thus, the validity of PROM from a patient perspective would potentially increase by using patients rather than health professionals as the main source for identification of items to be included in the PROM.

Advantageous feasibility features of PROM include brevity and relevance, which may influence the amount of missing data and respondent rates [8]. Relevance to the target population (content validity) is inherent when patients are the only source for selecting dimensions of PROM and how many questions to ask. For scientific comparisons on a group level a weighted score reflecting the relative importance of different dimensions to patients to express a composite measure is informative and easy to communicate.

5.8. Weaknesses and strengths

One potential weakness in this study is the single-center design, which means that the findings need to be validated in other centers, preferably in other countries. One benefit with a single center versus multicenter approach can be reduced variability in trial conduct and data collection by a consistent team and environment [39]. A PACADI web site was established in 2013 [40] with an increasing number of international visitors. Using Google analytics at this web site since October 2017, we found that main stakeholders abroad representing USA, China, Canada and Sweden have expressed an interest in using PACADI for scientific purposes. Importantly, some tools require a payment when used, which may be a challenge for less affluent research groups and for use in daily clinical practice. PACADI is freely available for academic purposes, similar to the RAID and PsAID questionnaires [17–19].

One major strength in this psychometric study is the full range of analyses that we were able to apply in this longitudinal observational study, with coherently supporting findings across methods, eventually ending up with a feasible, valid, brief, patient derived and disease specific measure for PC.

6. Conclusion

The current study examines both cross-sectional and longitudinal psychometric properties across an extensive variety of analyses and demonstrates that the PACADI score keeps satisfactory psychometric performance, also in comparison with the generic EQ-5D index as well as the disease-specific ESAS "sense of well-being". We suggest that PACADI is eligible for use in clinical practice as well as in scientific studies in the international community caring about patients with PC.

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Conflicts of interest

None of the authors declare any conflict of interest related to this work.

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