Clinical Gastroenterology and Hepatology 2017;15:1435–1443

PANCREAS, BILIARY TRACT, AND LIVER

Acute Pancreatitis Has a Long-term Deleterious Effect on Physical Health Related Quality of Life

Jorge D. Machicado,[*] Amir Gougol,[*] Kimberly Stello,[*] Gong Tang,[‡] Yongseok Park,[‡] Adam Slivka,[*] David C. Whitcomb,[*] Dhiraj Yadav,[*] and Georgios I. Papachristou[*,§]

[*]Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [‡]Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania; [§]Division of Gastroenterology, Veterans Affairs Pittsburgh Health System, Pittsburgh, Pennsylvania

BACKGROUND & AIMS: **It is not clear how acute pancreatitis (AP) affects health related quality of life (HRQOL). We aimed to determine the long-term independent effect of AP on physical and mental HRQOL.**

METHODS: **We analyzed data from 91 patients (mean 52 years of age, 54% women) admitted with AP to the University of Pittsburgh Medical Center from 2011 to 2015 who responded to telephone surveys at a median of 14 months after hospital discharge (interquartile range, 12–16 months). Individuals who did not answer the telephone survey were sent a questionnaire by regular mail. Patients answered questions from the 12-Item Short-Form Survey, and answers were used to calculate mental component summary (MCS) and physical component summary (PCS) scores with norm-based scoring (normal ≥50). HRQOL for these subjects was compared with that of age- and sex-matched individuals without pancreatitis (1:2) identified from the North American Pancreatitis Study. We controlled for other covariates using multivariable regression analysis.**

RESULTS: **At follow-up, individuals with AP had a significantly lower PCS score (46.2 ± 11.8) than did control subjects (51.1 ± 9.5; $P < .01$), but a similar MCS score. A 4-point reduction of the PCS was attributed to AP after controlling for sociodemographic factors and medical comorbidities. The only pancreatitis-related factor associated with low PCS score was multisystem organ failure. Presence of abdominal pain, analgesic use, disability, and current smoking at the time of follow-up were also associated with lower PCS scores. Etiology of AP, disease severity (by Revised Atlanta classification), use of nutritional support, and performance of pancreatic interventions did not affect HRQOL at follow-up.**

CONCLUSIONS: **In a 14-month follow-up of patients hospitalized with AP, we found a meaningful, independent, and deleterious effect of AP in the physical HRQOL of these patients, compared to individuals without AP. Further research is needed to determine the duration of this impairment and to evaluate the effects of modifying risk factors.**

Keywords: Disease Progression; Natural History; Pancreas; Patient-Reported Outcomes.

The management of acute pancreatitis (AP) has evolved over the last 2 decades likely resulting in reduction of case fatality.[1] As more patients with AP survive, increased attention has been directed toward long-term outcomes following an AP attack. Whether AP plays an independent role in the health related quality of life (HRQOL) of those who survive an AP attack is of clinical importance so as to better understand the natural history of AP, counsel patients and families of what to expect, and adequately implement rehabilitation strategies.

Given the difficulty to obtain baseline HRQOL measurements before AP onset, previous studies have compared HRQOL during or after AP with historical control subjects from the general population. Using this approach there seems to be significant reduction in both the mental and physical HRQOL during an AP attack.[2] This effect appears to be temporal, as the physical and mental HRQOL scores are comparable to control subjects after more than 3 years of AP attack.[3–6] The impact of AP on physical and mental HRQOL in studies with shorter

Abbreviations used in this paper: **AP, acute pancreatitis; BMI, body mass index; CP, chronic pancreatitis; ICU, intensive care unit; IQR, interquartile range; MCS, mental component summary; NAPS2, North American Pancreatitis Study 2; OF, organ failure; PCS, physical component summary; HRQOL, health related quality of life; RAC, Revised Atlanta classification; SF-12, 12-Item Short Form Survey.**

Most current article

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2017.05.037

follow-up intervals has been inconsistent.[2,7,8] Reasons for these inconsistencies include small sample size ($n \leq 30$), use of different AP phenotypes, inability to control for pre-existent factors, and variability in the use of HRQOL assessment tools.

The factors that determine the HRQOL after AP have not been well studied. Alcoholic etiology and severe AP defined by the original Atlanta classification have been associated with poor HRQOL subdomains following AP.[2,9] The role in HRQOL of other pancreatitis related factors (eg, severity by Revised Atlanta classification [RAC], multisystem organ failure, treatment strategies) and other patient outcomes (eg, abdominal pain, analgesic use, disability) have not been previously studied. Understanding these factors is important to delineate strategies that may help to improve the HRQOL of AP survivors.

First, our primary objective was to assess the independent long-term effect of AP on physical and mental HRQOL, by comparing a prospectively enrolled cohort of AP patients with nondisease control subjects. Second, we aimed to determine the factors associated with impaired HRQOL following AP. Third, we assessed the changes of physical and mental HRQOL scores between short- and long-term follow-up after an AP attack.

Methods

Study Population

All consecutive patients admitted with AP at the University of Pittsburgh Medical Center between September 2011 and May 2015 were prospectively enrolled. Patients with chronic pancreatitis (CP), based on a previously established diagnosis or on abnormalities detected on cross-sectional imaging (eg, calcifications), were excluded. Survivors were contacted for short- and long-term follow-up HRQOL assessments. These were obtained through a telephone survey performed by a research coordinator as early as 2 months for short-term follow-up and 12 months for long-term follow-up. If a participant did not answer the phone, a voicemail was left with instructions to call back. If this phone call was not returned within 2 weeks, the research coordinator called back and repeated the same method for up to 5 occasions. For those who did not answer the telephone surveys, a questionnaire was subsequently sent by regular mail. Ethical approval was obtained from the Institutional Review Board at the University of Pittsburgh (protocol ID PRO08010374).

In the present study, only AP survivors who responded to long-term follow-up surveys were analyzed. Among 174 patients enrolled during pancreatitis attack, 10 died during the index hospital admission and 9 died during follow-up period. Additionally, 5 patients older than 85 years of age were excluded because age-matched control subjects were not available. From 150 eligible AP patients contacted for long-term follow-up, 91 (61%) completed the survey at a median of 14 months (interquartile range [IQR], 12–16 months). Among respondents, 57 (63%) also provided short-term follow-up information at a median of 4 months (IQR, 3–5 months). From nonrespondents, 26 had responded to short-term follow-up surveys only (data not shown), whereas 33 provided no follow-up data at all.

HRQOL Assessment

The 12-Item Short Form Survey (SF-12) version 2 was used to assess HRQOL in AP patients (see Supplement). This is a multipurpose generic HRQOL questionnaire that was derived from the 36-Item Short Form Survey,[10,11] which has been the most used tool to assess HRQOL after AP.[4,5,7,8] The SF-12 has been validated in CP,[12,13] and has been previously used to assess HRQOL after AP.[2] This tool comprises 12 questions that measure 8 subdomains, which can be summarized into the physical component summary (PCS) and mental component summary (MCS) scores. The questionnaire takes approximately 2 minutes to complete and is based on a standard recall of 4 weeks.[11] The obtained scores for each domain are then transformed to z-scores using the SF-12 scale mean $\pm$ SD from the 1998 U.S. population to produce a normally distributed population score. PCS and MCS scores range from 0 to 100 with a score below 50 indicating a HRQOL below average. A difference of 3 points in the PCS or MCS scores between groups has been suggested to be clinically meaningful.[10]

Control Population

The North American Pancreatitis Study 2 (NAPS2) consists of 3 studies (original NAPS2, NAPS2 Continuation and Validation, and NAPS2 Ancillary Study) which prospectively enrolled patients with recurrent AP and CP, in addition to nonpancreatitis control subjects from 27 U.S. centers from 2000 to 2014.[14,15] Control subjects ($n = 1109$) included spouses, willing family members, accompanying friends, or unrelated subjects, who completed a detailed questionnaire that included the SF-12 and information on demographics, risk factors, and comorbidities.[14] PCS and MCS scores from the NAPS2 control population are comparable with historical control subjects from the 1998 U.S. population.[12,13]

To study the impact of AP on long-term HRQOL, we matched the NAPS2 control subjects (139 from NAPS2 and 43 from NAPS2 Continuation and Validation studies) to the AP patients with long-term follow-up ($n = 91$) in a 1:2 ratio and by age ($\pm$ 2 years) and gender.

Data Collection

Demographic data including age, gender, race, and body mass index (BMI), was recorded from AP cases and

NAPS2 control subjects. BMI was classified as normal or low (<25 kg/m^2), overweight (25–29.9 kg/m^2), or obesity (≥30 kg/m^2). Current smoking and current alcohol consumption were reported at time of enrollment in NAPS2 control subjects, and during long-term follow-up in AP patients. Common comorbidities such as diabetes, cardiovascular disease (heart disease or heart attack or stroke), cancer, renal disease, and liver disease, were obtained at enrollment in AP patients and control subjects, and could be compared. AP patients were asked for the presence of new-onset diabetes during follow-up assessments. Available outpatient medical records (n = 53) of those without diabetes at baseline (n = 70) were retrospectively reviewed to ascertain for diagnosis of new-onset diabetes at the time of long-term follow-up. Coexistent diabetes was defined as diabetes at follow-up.

To evaluate pancreatitis-related factors affecting long-term HRQOL, well-phenotyped data on etiology, clinical course, management, and hospital outcomes were prospectively recorded in AP patients. RAC was used to group AP severity into mild, moderately severe, and severe. Multisystem organ failure (OF) refers to involvement of at least 2 organs (renal, pulmonary, or cardiovascular).[16]

During follow-up HRQOL assessments, patients were also asked whether they were experiencing abdominal pain subjectively attributed to pancreatitis, and if they were using analgesics on a regular basis to control it. Presence of disability at follow-up was also obtained.

Statistics

In descriptive analyses, PCS and MCS scores are presented as mean ± SD. Categorical variables are presented as proportion of study subjects. Age and length of stay are presented as median and IQR. Comparisons of AP patients who responded to long-term follow-up surveys and those who did not were done using the Pearson chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables.

To compare HRQOL between AP and their NAPS2 control subjects, the mean PCS and MCS scores for the 2 control subjects of each case set were calculated, and then compared with the scores of the matched case using Wilcoxon signed rank test for paired comparisons. Comparison of categorical variables between cases and control subjects was performed via the Pearson chi-square test. Determination of independent predictors of PCS was done using linear regression models. History of renal disease and liver disease were not included in the models, as they occurred in <2% of cases and control subjects. History of cancer had no significant effect on initial models and was subsequently removed. Variables that were used in final models other than AP included demographics (age, sex, race, BMI category), current smoking, current alcohol consumption, coexistent diabetes, and history of heart disease or heart attack or stroke. All first-degree interactions between the presence of AP and other variables were also investigated. For easier interpretation, age was centered at 50 years in the final models.

To evaluate factors associated with PCS and MCS, we performed univariable analysis using Wilcoxon rank sum test and Kruskal-Wallis test for groups with 2 or more than 2 attributes respectively to provide more robust assessment. The change between short- and long-term PCS and MCS is presented using mean delta change ± SD. Comparison of the scores change over time was assessed using Wilcoxon signed rank test for pairs.

Data analysis was performed using Stata/IC version 12.1 (StataCorp, College Station, TX) and SAS/STAT 9.4 (SAS Institute, Cary, NC). Statistical tests or covariates in regression models with P values <.05 are called statistically significant.

Results

Characteristics of AP Cohort

Data at enrollment. The distribution of baseline demographics, comorbidities, and clinical profile of the final AP cohort is shown in Table 1.

Respondents to long-term follow-up surveys (n = 91) had a median age of 52 years (interquartile range, 36–69 years), 54% were women, 93% were white, and 36% were obese. Diabetes (23%), cardiovascular disease (15%), and cancer (8%) were common comorbidities among respondents. About half (51%) had been transferred from another institution.

The majority of respondents had a sentinel attack (64%), biliary etiology (43%), and mild disease (59%). Moderately severe AP was present in 24%, severe in 17%, and multisystem OF in 14%. In terms of treatment, 30% received intensive care unit (ICU) care, 22% underwent pancreatic drainage or debridement interventions, and 29% had nutritional support (enteral 26%, parenteral 7%). Median length of hospital stay was 7 days (interquartile range, 4 to 13 days).

Baseline characteristics were similarly distributed between respondents and nonrespondents, except for higher rates of obesity in nonrespondents ($P < .01$).

Data at long-term follow-up. At long-term follow-up, abdominal pain was present in 23%, and 9% were using analgesics regularly. Current alcohol consumption was reported by 19%, current smoking by 20%, and new-onset disability by 7%. Excluding those with baseline history of diabetes (n = 21), new-onset diabetes was diagnosed in 5 of 70 patients (7%), 2 by self-report and review of outpatient records and 3 by review of outpatient records only. Seventeen patients had no outpatient medical records by the time of follow-up, but denied new-onset diabetes during telephone surveys.

Table 1. Demographics, Risk Factors, and Clinical Profile at the Time of Acute Pancreatitis Based on Availability of Long-Term Follow-Up

Variable	Respondents of long-term follow-up (n = 91)	Nonrespondents of long-term follow-up (n = 59)	*P* value
Age group			
<45 y	35 (38.4)	27 (45.8)	.29
45–60 y	25 (27.5)	19 (32.2)	
>60 y	31 (34.1)	13 (20.0)	
Female	49 (53.8)	33 (55.9)	.80
Race			
Caucasian	85 (93.4)	52 (88.1)	.31
Black	6 (6.6)	7 (11.9)	
BMI			
Normal/low	29 (31.9)	10 (17.0)	.003
Overweight	29 (31.9)	11 (18.6)	
Obese	33 (36.2)	38 (64.4)	
Comorbidities			
History of diabetes	21 (23.1)	16 (27.1)	.57
History of heart disease/heart attack/stroke	14 (15.4)	7 (11.9)	.54
History of cancer	7 (7.7)	3 (5.1)	.53
History of renal disease	1 (1.1)	3 (5.1)	.14
History of liver disease	1 (1.1)	1 (1.7)	.76
History of AP			
Sentinel AP attack	58 (63.7)	36 (61.0)	.74
Prior AP attack(s)	33 (36.3)	23 (39.0)	
Transferred	42 (46.2)	33 (55.9)	.24
Etiology			
Biliary	39 (42.9)	30 (50.8)	.06
Alcoholic	4 (4.4)	9 (15.2)	
Hypertriglyceridemic	9 (9.9)	6 (10.2)	
Idiopathic	12 (13.2)	5 (8.5)	
Other	27 (29.7)	9 (15.3)	
Severity by RAC			
Mild	54 (59.3)	37 (62.7)	.55
Moderately severe	22 (24.2)	16 (27.1)	
Severe	15 (16.5)	6 (10.2)	
Multisystem OF	13 (14.3)	3 (5.1)	.08
ICU admission	27 (29.7)	14 (23.7)	.42
Drainage/debridement	20 (21.9)	9 (15.3)	.31
Nutritional support	26 (28.6)	18 (30.5)	.79
Median LOS, days	7 (4–13)	5 (4–10)	.16

Values are n (%) or median (interquartile range).
AP, acute pancreatitis; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; OF, organ failure; RAC, Revised Atlanta classification.

HRQOL in Control Subjects and AP Patients With Long-Term Follow-Up

Univariable analysis. The demographics, comorbidities, and HRQOL scores of AP patients who responded to long-term follow-up surveys compared with age- and sex-matched control subjects are presented in Table 2. Compared with control subjects, AP patients at follow-up were more likely to have coexistent diabetes (29% vs. 14%; $P < .01$) and less likely to consume alcohol (19% vs. 51%; $P < .001$).

In univariable analyses, PCS score at long-term follow-up of patients with AP was significantly impaired compared with age- and sex-matched control subjects (46.2 ± 11.8 vs. 51.1 ± 9.5; $P < .01$). In contrast, MCS score was not significantly different between AP subjects with long-term follow-up and control subjects (51.6 ± 10.4 vs. 53.1 ± 7.6; $P = .4$) (Figure 1).

In a subgroup analysis based on the number of prior attacks of AP, both sentinel (46.7 ± 12.2 vs. 51.3 ± 6.5; $P = .03$) and recurrent (45.5 ± 11.5 vs. 50.8 ± 7.3; $P = .01$) attacks had a negative impact on the PCS score. No impact on MCS score was found following either a sentinel (53.4 ± 9.4 vs. 53.9 ± 4.9; $P = .9$) or recurrent (48.6 ± 11.6 vs. 51.8 ± 6.5; $P = .2$) AP attack.

Multivariable analysis of physical HRQOL. Data from multivariable regression analysis for PCS are provided in Table 3. After controlling for demographics, current smoking, current alcohol consumption, and comorbidities, the effect of AP on physical HRQOL remained substantial at long-term follow-up (4 points reduction). Other significant predictors of impaired PCS in order of magnitude included history of cardiovascular disease, obesity, coexistent diabetes, gender, and age. A significant interaction was seen for AP patients at long-term follow-up with age, smoking, and alcohol consumption.

Table 2. Sociodemographic Characteristics and Quality of Life Scores for Control Subjects From Patients With Long-Term Follow-Up After AP and NAPS2 Control Populations

Variable	AP patients with long-term follow-up (n = 91)	Age- and sex-NAPS2 control populations (n = 182)	*P* value
PCS score	46.2 ± 11.8	51.1 ± 9.5	.002
MCS score	51.6 ± 10.4	53.1 ± 7.6	.40
Race			
White	85 (93.4)	157 (86.3)	.07
Black	6 (6.6)	16 (8.8)	
Other	0	9 (4.9)	
Current smoking	18 (19.8)	33 (18.1)	.74
Current alcohol consumption	17 (18.7)	93 (51.1)	<.001
BMI			
Normal/low	29 (31.9)	64 (35.6)	.31
Overweight	29 (31.9)	67 (37.2)	
Obesity	33 (36.2)	49 (27.2)	
Comorbidities			
Coexistent diabetes,	26 (28.6)	25 (13.7)	.003
History of heart disease/ heart attack/stroke	14 (15.4)	19 (10.4)	.23
History of cancer	7 (7.7)	12 (6.6)	.74
History of renal disease	1 (1.1)	1 (0.6)	.62
History of liver disease	1 (1.1)	3 (1.6)	.72

Values are mean ± SD or n (%).
AP, acute pancreatitis; BMI, body mass index; MCS, mental component summary; NAPS2, North American Pancreatitis Study 2; PCS, physical component summary.

Although an increase in 1 year of age after 50 years in a control subject resulted in a decrease of PCS score by 0.1 points, for an AP patient the effective change for 1-year increase in age was an increase by 0.1 points (−0.1 + 0.2). Moreover, current alcohol consumption and current smoking had no significant independent effect in control subjects, but had a significant increase of 7 points (−0.2 + 7.2) and borderline reduction of 7.3 points

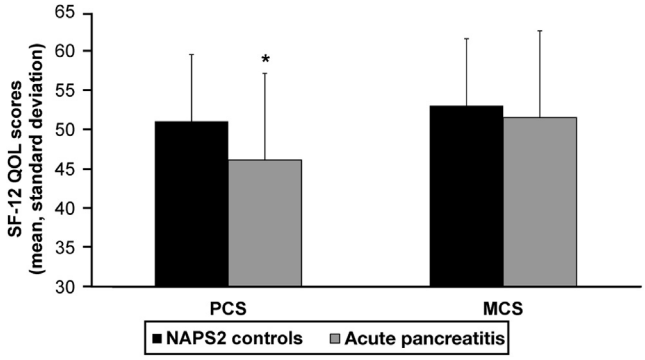

Figure 1. Physical and mental quality of life scores for North American Pancreatitis Study 2 (NAPS2) control subjects and acute pancreatitis (AP) patients with long-term follow-up available. Comparisons performed using Wilcoxon matched-pairs signed rank test. *$P < .05$.

Table 3. Multivariate Regression Model Showing Significant Determinants for PCS in Control Subjects and AP Patients

Variable	Reference category	Parameter estimate	SE	*P* value
Intercept	—	50.60	2.10	<.001
AP	Control subjects	−4.00	1.60	.01
Age 50 y[a]	—	−0.10	0.1	<.01
Female	Male	−2.80	1.20	.02
White	Other	2.90	2.10	.16
Current smoking	No current smoking	−1.70	1.80	.35
Current alcohol consumption	No current alcohol consumption	−0.20	1.40	.88
Obese	No obese	−5.50	1.20	<.001
Coexistent diabetes	No diabetes	−4.00	1.50	<.01
History of heart disease/heart attack/stroke	No history of heart disease, heart attack, or stroke	−7.10	1.80	<.001
AP and age 50 y[b]	—	0.20	0.1	.01
AP and current smoking[b]	—	−5.60	3.10	.07
AP and current alcohol consumption[b]	—	7.20	2.90	.01

Final sample size: control subjects, n = 182; acute pancreatitis (AP), n = 91.
Adjusted $R^2 = 29.6\%$.
PCS, physical component summary.
[a]Age variable centered at 50 years.
[b]A significant interaction is noted.

(−1.7 + −5.6) of PCS in patients following AP respectively. The model explained almost a third of the variance in the PCS score (adjusted $R^2 = 29.6\%$).

Associations With Long-Term HRQOL After AP

Univariable analysis for PCS and MCS scores at long-term follow-up of AP based on demographics, comorbidities, and clinical profile of AP are shown in Table 4. Comparisons of PCS and MCS scores based on abdominal pain, disability, smoking, and alcohol consumption at long-term follow-up are shown in Table 5.

A significantly lower PCS score at long-term follow-up was seen in AP patients with obesity ($P < .05$), coexistent diabetes ($P < .01$), and history of cardiovascular disease ($P < .05$). Multisystem OF was the only AP-related factor associated with impaired PCS ($P < .05$). A borderline association with poor PCS was seen in those AP patients with ICU admission ($P = .07$). Abdominal pain ($P < .001$), analgesic use ($P < .01$), new disability ($P < .01$), and current smoking ($P < .05$) at long-term follow-up were significantly associated with lower PCS score. Interestingly, current alcohol consumption at long-term follow-up was associated with higher PCS ($P < .01$).

MCS score at long-term follow-up was significantly lower with prior AP attacks ($P < .05$). A borderline association with impaired MCS score was noted in

Table 4. PCS and MCS at Long-Term Follow-Up Based on Demographics, Comorbidities, and Clinical Profile of AP

Variable (n = 91)	PCS Mean ± SD	PCS *P* value	MCS Mean ± SD	MCS *P* value
Age, y				
<45	46.8 ± 11.4	.88	49.3 ± 12.1	.27
45–60	45.4 ± 14.3		50.7 ± 11.4	
>60	46.3 ± 10.6		55.0 ± 6.3	
Gender				
Male	46.4 ± 11.4	.73	52.6 ± 10.8	.22
Female	46.2 ± 12.4		50.7 ± 10.2	
Race				
Caucasian	46.4 ± 12.1	.36	51.5 ± 10.4	.36
Black	44.4 ± 9.2		53.1 ± 12.0	
BMI category				
Normal/low	49.1 ± 11.0	.03	51.0 ± 8.8	.62
Overweight	48.6 ± 9.6		51.2 ± 12.1	
Obese	41.8 ± 13.4		52.5 ± 10.5	
Coexistent diabetes				
Yes	40.3 ± 13.6	.003	52.4 ± 10.1	.93
No	48.7 ± 10.3		51.3 ± 10.6	
History of heart disease/ heart attack/stroke				
Yes	38.8 ± 14.1	.02	50.7 ± 12.6	.94
No	47.7 ± 11.0		51.8 ± 10.1	
History of cancer				
Yes	45.8 ± 12.1	.16	51.4 ± 12.0	.72
No	52.3 ± 7.1		51.6 ± 10.4	
Transferred from another center				
Yes	46.2 ± 12.1	.91	51.8 ± 7.9	.41
No	46.3 ± 11.8		51.4 ± 12.3	
Etiology				
Biliary	46.7 ± 13.2		54.3 ± 9.4	
Alcoholic	46.3 ± 12.7	.59	40.6 ± 18.6	.08
HyperTG	42.4 ± 10.7		51.6 ± 8.7	
Idiopathic	44.0 ± 13.6		47.3 ± 9.5	
Other	48.2 ± 9.8		50.8 ± 10.6	
History of AP				
Sentinel AP attack	46.7 ± 12.1	.56	53.3 ± 9.4	.03
Prior AP attack(s)	45.5 ± 11.5		48.6 ± 11.6	
Severity by RAC				
Mild	46.8 ± 11.9		51.9 ± 11.0	
Moderately severe	48.3 ± 11.5	.12	48.8 ± 10.6	.13
Severe	41.5 ± 11.9		54.3 ± 7.3	
Multisystem OF				
Yes	40.6 ± 12.1	.04	53.9 ± 7.4	.52
No	47.2 ± 11.6		51.2 ± 10.9	
ICU admission				
Yes	44.0 ± 10.7	.07	53.1 ± 7.7	.67
No	47.3 ± 12.3		51.0 ± 11.4	

AP, acute pancreatitis; BMI, body mass index; HyperTG, hypertriglyceridemia; ICU, intensive care unit; MCS, mental component summary; OF, organ failure; PCS, physical component summary; RAC, Revised Atlanta classification.

alcoholic and idiopathic etiologies ($P = .08$). Significantly impaired MCS score was seen in AP patients with abdominal pain ($P < .001$), analgesic use ($P < .01$), new disability ($P < .01$), and current smoking ($P < .05$) at long-term follow-up.

Comparison of HRQOL Scores Between Short- and Long-Term Follow-Up

A total of 57 subjects responded to both short- and long-term follow-up surveys after AP. Overtime, PCS increased 2 points (SD, 10.5), and MCS increased 0.5 points (SD, 10.3). However, neither of these changes was statistically significant.

Discussion

To our knowledge, this is the largest prospective study evaluating HRQOL following AP. Our results indicate a clinically and statistically significant long-term impact of AP on patients' physical HRQOL, but not mental HRQOL, when compared with control subjects. This effect was independent of sociodemographic factors and comorbidities. Development of multisystem organ failure during the AP attack was associated with lower long-term physical HRQOL. Abdominal pain, regular analgesic use, current smoking and disability at follow-up, were also associated with this effect.

Previous studies have tried to evaluate the 1-year effect of AP on HRQOL by using historical control subjects.[2,8] However, these studies were small ($n \leq 30$), had inconsistent results, and did not control for additional attributes to assess the independent impact of AP. By comparing a larger, well-phenotyped population of AP patients from a single U.S. center cohort with non-pancreatitis control subjects from a large multicenter U.S. cohort, we demonstrated that the physical HRQOL after 14 months of AP was significantly impaired compared with control subjects. The effect of AP in physical HRQOL was independent of age, gender, race, current smoking, current alcohol consumption, BMI, and comorbidities. The 4-point reduction attributed to AP was statistically and clinically meaningful.[10] Similar impairment of HRQOL has been described in critically ill patients with acute respiratory distress syndrome, sepsis, and trauma, which can last for at least a year and normalizes over several years.[17] The impairment of mental HRQOL during an AP attack appears to normalize within the first year of follow-up. This may be related to early recovery of vitality, activity level, functioning, and mental health, which ultimately leads to the return of the ability to work. Interestingly, the presence of recurrent AP or alcoholic etiology was associated with lower mental HRQOL scores at long-term follow-up. These may represent 2 vulnerable subgroups of AP patients that could have impaired mental HRQOL for more than a year, or a subgroup with undetected progression to CP, which is known to impair both the physical and mental HRQOL.[13]

The presence of obesity, coexistent diabetes, and history of cardiovascular disease shared an equal independent negative impact on the physical HRQOL of both AP patients and control subjects in final multivariable models, which suggests a direct effect of these

Table 5. PCS and MCS at Long-Term Follow-Up of AP, Based on Pain, Disability, Smoking, and Alcohol Consumption at Follow-Up

		PCS		MCS	
Variable at follow-up (n = 91)	n (%)	Mean ± SD	*P* value	Mean ± SD	*P* value
Abdominal pain					
Yes	21 (23.0)	36.4 ± 10.3	<.001	43.2 ± 12.6	<.001
No	70 (77.0)	49.3 ± 10.3		54.2 ± 8.3	
Analgesic use					
Yes	8 (8.9)	31.7 ± 12.8	.002	37.14 ± 15.7	.005
No	83 (91.1)	47.7 ± 10.9		53.0 ± 8.7	
New disability					
Yes	6 (6.6)	31.7 ± 4.9	.002	37.9 ± 11.6	.004
No	85 (93.4)	47.3 ± 11.6		52.6 ± 9.7	
Current alcohol consumption					
Yes	17 (18.7)	52.9 ± 9.4	.001	51.2 ± 9.2	.71
No	74 (81.3)	44.8 ± 11.9		51.7 ± 10.8	
Current smoking					
Yes	18 (19.8)	41.1 ± 11.7	.03	47.7 ± 9.1	.01
No	73 (80.2)	47.6 ± 11.7		52.6 ± 10.6	

AP, acute pancreatitis; MCS, mental component summary; PCS, physical component summary.

comorbidities in HRQOL rather than mediated by AP.[18,19] In contrast, current smoking at follow-up was associated with a 7.3 points decrement in the physical HRQOL of AP patients, but did not cause a significant change in control subjects. This could be explained by the higher risk for developing recurrent AP or progressing into CP with ongoing smoking.[20] Another possible explanation is a direct effect of smoking on HRQOL.[21] Therefore, smoking cessation strategies appear to be important for improving the physical HRQOL of AP survivors.

Multisystem organ failure during AP was the only disease-related factor associated with poor physical HRQOL at long-term follow-up. This has been noticed as the major independent determinant of poor physical HRQOL of ICU survivors at 6 and 12 months of follow-up, but has not been previously evaluated as a predictor of HRQOL after AP.[22,23] Possible explanations may include cognitive impairment, sleep disturbance, post-traumatic stress disorder, prolonged rehabilitation process, unemployment, and disability in those who survive multisystem OF.[17] Interestingly, we found that etiology, severity RAC, need for nutritional support, and pancreatic interventions were not associated with impaired physical or mental HRQOL at follow-up. This does not mean that multisystem OF is the only disease related factor to impact the physical HRQOL of AP survivors, but that the effect of other possible disease-related factors might not persist at long-term follow-up.

The presence of abdominal pain, analgesic use, and disability at follow-up were important factors associated with impaired physical and mental HRQOL after AP. Causality for these factors was not explored and cannot be directly attributed to AP. Possible mechanisms of pain include smoldering pain from the index pancreatitis attack, recurrent subclinical AP attacks, visceral hyperalgesia, or progression to CP. Disability may be caused by the psychological burden, financial distress, and social disruption that follows AP, or could indirectly reflect other debilitating factors (eg, deconditioning, chronic pain).[24]

Even though this is the largest prospective study evaluating HRQOL after AP, it has several limitations. First, a heterogeneous group of patients with sentinel and recurrent AP attacks was used. To tease out whether our results were driven by the number of prior attacks of AP, we performed a subgroup analysis that demonstrated that both sentinel and recurrent AP had a negative impact in physical but not mental HRQOL. Second, HRQOL before the pancreatitis attack could not be evaluated in this cohort. To overcome this, we used NAPS2 nonpancreatitis control subjects as an approximation to HRQOL before AP to control for several covariates. This approach might have limited a more comprehensive assessment of comorbidities, as only some diseases for which information was collected in both studies could be controlled in our analysis. Third, despite the efforts of trying to contact the study participants several times and by different methods, the follow-up response rate was 61%. This is lower compared with response rates reported in other HRQOL studies following critical illness (~80%),[17] but may correspond to an overall decline in the response rate to surveys seen in recent years especially in the absence of financial incentives.[25] As nonrespondents were as healthier as respondents, except for a higher rate of obesity in the former group, it is likely that most nonrespondents had a satisfactory recovery and considered HRQOL questionnaires trivial. Other potential explanations include that nonrespondents may have been too ill to respond to surveys or wanted to avoid memories of their AP attack—which could have translated into lower response rates at short-term follow-up in those with long-term follow-up available. Fourth, patients were

enrolled at a large tertiary-care center in the United States with expertise in pancreatic disorders, introducing a risk for referral bias. For example, this may explain why the distribution of etiologies in our cohort (biliary 43%, miscellaneous 30%, idiopathic 13%, alcoholic 4%) was similar compared with reports from other international expert centers, but different from those at a population level.[26,27] Fifth, in the absence of a disease specific instrument to measure HRQOL in AP patients, we used a generic HRQOL tool (SF-12) that has been previously used in other HRQOL studies following AP and critical illness. Sixth, only patients with previous diagnosis of established CP or with morphologic abnormalities on cross-sectional imaging consistent with CP were excluded at enrollment. Adding currently available biochemical, structural, and functional biomarkers was not possible due to the observational design of the study. Therefore, it is possible that a small fraction of AP subjects enrolled in our cohort had undiagnosed early CP or less likely established CP at diagnosis. Seventh, important subgroups were under-represented in our cohort (eg, African-Americans, Hispanics, alcoholic etiology). Thus, our results are mostly representative of white AP patients at large referral centers where alcohol is a relatively rare etiology. Finally, additional factors at follow-up that may have negatively affected the HRQOL of this cohort were not objectively measured (eg, recurrent episodes of AP, progression to CP, new-onset exocrine pancreatic insufficiency).

In summary, AP demonstrated an independent substantial negative impact on physical HRQOL of subjects at long-term follow-up of 14 months. Multisystem OF during the AP attack, and the presence at follow-up of abdominal pain, analgesic use, disability and current smoking, were important factors associated with this decrement. Future large-scale multicenter studies need to validate our findings at a population level. Specific interventions toward modifiable factors that affect the HRQOL of AP survivors (eg, smoking cessation, physical therapy, behavioral changes, pain management) are likely important in improving physical HRQOL following AP and need further evaluation.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2017.05.037.

References

1. Munigala S, Yadav D. Case-fatality from acute pancreatitis is decreasing but its population mortality shows little change. Pancreatology 2016;16:542–550.
2. Pezzilli R, Morselli-Labate AM, Campana D, et al. Evaluation of patient-reported outcome in subjects treated medically for acute pancreatitis: a follow-up study. Pancreatology 2009;9:375–382.
3. Halonen KI, Pettila V, Leppaniemi AK, et al. Long-term health-related quality of life in survivors of severe acute pancreatitis. Intensive Care Med 2003;29:782–786.
4. Broome AH, Eisen GM, Harland RC, et al. Quality of life after treatment for pancreatitis. Ann Surg 1996;223:665–670, discussion 670–672.
5. Andersson B, Pendse ML, Andersson R. Pancreatic function, quality of life and costs at long-term follow-up after acute pancreatitis. World J Gastroenterol 2010;16:4944–4951.
6. Soran A, Chelluri L, Lee KK, et al. Outcome and quality of life of patients with acute pancreatitis requiring intensive care. J Surg Res 2000;91:89–94.
7. Hochman D, Louie B, Bailey R. Determination of patient quality of life following severe acute pancreatitis. Can J Surg 2006; 49:101–106.
8. Wright SE, Lochan R, Imrie K, et al. Quality of life and functional outcome at 3, 6 and 12 months after acute necrotising pancreatitis. Intensive Care Med 2009;35:1974–1978.
9. Winter Gasparoto RC, Racy Mde C, De Campos T. Long-term outcomes after acute necrotizing pancreatitis: what happens to the pancreas and to the patient? J Pancreas 2015; 16:159–166.
10. Ware JE Jr, Kosinski M, Keller SD. SF-36 Physical and Mental Summary Scales: A User's Manual. Boston, MA: The Health Institute, 1994.
11. Ware JE KM, Turner-Bowker DM, Gandek B. How to score version 2 of the SF 12 Health Survey with a supplement documenting version 1. QualityMetric Incorporated (Rhode Island) and Health Assessment Lab (Boston, Massachusetts), 2002.
12. Machicado JD, Amann ST, Anderson MA, et al. Quality of life in chronic pancreatitis is determined by constant pain, disability/unemployment, current smoking, and associated co-morbidities. Am J Gastroenterol 2017;112:633–642.
13. Amann ST, Yadav D, Barmada MM, et al. Physical and mental quality of life in chronic pancreatitis: a case-control study from the North American Pancreatitis Study 2 cohort. Pancreas 2013; 42:293–300.
14. Whitcomb DC, Yadav D, Adam S, et al. Multicenter approach to recurrent acute and chronic pancreatitis in the United States: the North American Pancreatitis Study 2 (NAPS2). Pancreatology 2008;8:520–531.
15. Wilcox CM, Sandhu BS, Singh V, et al. Racial differences in the clinical profile, causes, and outcome of chronic pancreatitis. Am J Gastroenterol 2016;111:1488–1496.
16. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638–1652.
17. Oeyen SG, Vandijck DM, Benoit DD, et al. Quality of life after intensive care: a systematic review of the literature. Crit Care Med 2010;38:2386–2400.
18. Muller-Nordhorn J, Muckelbauer R, Englert H, et al. Longitudinal association between body mass index and health-related quality of life. PLoS One 2014;9:e93071.
19. Schunk M, Reitmeir P, Schipf S, et al. Health-related quality of life in subjects with and without Type 2 diabetes: pooled analysis of five population-based surveys in Germany. Diabet Med 2012;29:646–653.
20. Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. Clin Gastroenterol Hepatol 2016; 14:738–746.

21. Goldenberg M, Danovitch I, IsHak WW. Quality of life and smoking. Am J Addict 2014;23:540–562.
22. Wehler M, Geise A, Hadzionerovic D, et al. Health-related quality of life of patients with multiple organ dysfunction: individual changes and comparison with normative population. Crit Care Med 2003;31:1094–1101.
23. Pettila V, Kaarlola A, Makelainen A. Health-related quality of life of multiple organ dysfunction patients one year after intensive care. Intensive Care Med 2000;26:1473–1479.
24. Milner A, LaMontagne AD, Aitken Z, et al. Employment status and mental health among persons with and without a disability: evidence from an Australian cohort study. J Epidemiol Community Health 2014;68:1064–1071.
25. Kelly BJ, Fraze TK, Hornik RC. Response rates to a mailed survey of a representative sample of cancer patients randomly drawn from the Pennsylvania Cancer Registry: a randomized trial of incentive and length effects. BMC Med Res Methodol 2010;10:65.
26. Papachristou GI, Machicado JD, Stevens T, et al. Acute pancreatitis patient registry to examine novel therapies in clinical experience (APPRENTICE): an international, multicenter consortium for the study of acute pancreatitis. Ann Gastroenterol 2017;30:106–113.
27. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas 2006;33:323–330.

Reprint requests
Address requests for reprints to: Georgios I. Papachristou, MD, PhD, Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh Medical Center, 200 Lothrop Street, M2, C-Wing, Pittsburgh, Pennsylvania 15213. e-mail: papachri@pitt.edu.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by Veterans Affairs Merit Review Award No. I01CX000272-01A2 (to GIP).

Supplement: Short Form-12 (SF-12), version 2

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	Not limited at all
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
3. Climbing several flights of stairs	☐	☐	☐

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
4. Accomplished less than you would like	☐	☐	☐	☐	☐
5. Were limited in the kind of work or other activities	☐	☐	☐	☐	☐

During the past 4 weeks, how much of the time you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
6. Accomplished less than you would like	☐	☐	☐	☐	☐
7. Did work or other activities less carefully than usual	☐	☐	☐	☐	☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm and peaceful?	☐	☐	☐	☐	☐
10. Did you have a lot of energy?	☐	☐	☐	☐	☐
11. Have you felt downhearted and blue?	☐	☐	☐	☐	☐

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐