

# Patient-caregiver dyads in pancreatic cancer: Identification of patient and caregiver factors associated with caregiver well-being

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# Abstract

**Background:** There is a paucity of studies that address the stressors and associated risk factors amongst pancreatic cancer patients and their caregivers. We aimed to examine the psychosocial well-being in the patient-caregiver dyad, and to determine pancreas cancer patient and caregiver characteristics that predict caregiver distress.

**Methods:** Demographics and caregiving characteristics were gathered from patient and patient-caregiver dyads. Primary caregivers completed validated instruments investigating anxiety, depression, perceived stress and caregiver burden. Both caregivers and patients completed the National Comprehensive Cancer Network Distress Thermometer. Chi-square test or Fisher's exact test was used to compare categorical variables. Continuous variables per group were reported as mean (standard deviation). Demographics, patient and caregiving characteristics were analyzed as predictors of caregiver distress using *t*-tests, Kruskal-Wallis, and regression analyses.

**Results:** A total of 128 patient-caregiver dyads were enrolled over a period of eleven consecutive months. Patient and caregiver distress scores were not affected by patient clinical disease burden. Patient distress was a significant predictor of caregiver distress, anxiety, depression, and perceived caregiver burden. Younger caregiver age was also associated with higher caregiver anxiety and perceived burden. Additional predictors of caregiver depression and perceived stress included number of "other" caregiving activities (e.g., provision of emotional support, decision-making support) and overall health status.

**Conclusion:** We identified particular patient and caregiver variables which negatively impact the well-being of pancreatic cancer caregivers. Future efforts should focus on development and implementation of more comprehensive caregiver support programs for those at highest risk for psychosocial distress.

## Background

There is a persistent rise in the yearly incidence and mortality of pancreatic cancer in the United States; in 2022, there are an estimated 62,210 new cases and 49,830 deaths [1]. Surgery remains the only treatment option for curative intent and prolonged survival, yet 80% of patients are unresectable at presentation [2]. Despite worsened prognosis with advanced stage, randomized controlled trials have demonstrated improved response and survival in patients across all spectrums of presentation with the adoption of new regimens [3–6]. The American Cancer Society reported in 2022 that the five-year survival rate for pancreas cancer increased to 11%, a 5% increase in the past decade [7].

As patients with pancreas cancer are living longer across all disease stages, there has been a renewed focus on addressing quality of life (QOL), both pre- and post- multimodal therapy. The Massachusetts General Hospital group initially reported on QOL amongst pancreatic cancer patients with resected disease, locally advanced, and metastatic disease burden [8]. This was later surveyed in a larger cohort of five-year survivors after pancreaticoduodenectomy, which demonstrated improved QOL compared to a matched sample [9]. In a larger cohort, Allen et al. reported that QOL improved over time and surpassed

preoperative measurements at six months to one year after pancreatic surgery [10]. Deng et al. found that QOL in patients with pancreas cancer was a significant predictor of poor prognosis, and emphasized the need to focus on interventions to alleviate symptom burden [11].

Despite a myriad of studies focused on improving QOL for patients with pancreatic cancer, there is limited data on the psychological toll the diagnosis of pancreas cancer has not only on patients, but their caregivers as well. Caregivers are individuals who provide short or long-term care that is typically uncompensated, involves significant time and energy, and requires the performance of tasks that may be physically, emotionally, socially, and/or financially straining. Tasks may include monitoring treatment side effects; helping to manage pain, nausea, and fatigue; assisting with treatment decision-making; administering medication; providing transportation to doctors' appointments; and assisting with nutrition. As cancer care becomes more outpatient focused and the complexity of care increases, there is expected to be more demands on the caregiver. Several studies have demonstrated a significant, reciprocal relationship between cancer patients and caregiver emotional distress [12–14]. In an analysis of patients and caregivers with newly diagnosed incurable cancers, Jacobs et al. showed there was significant crossover between patient anxiety and partner depression, and vice versa, confirming a bidirectional and interdependent association of distress [15].

While many recent studies suggest that screening for and addressing distress not only enhances QOL but also may be associated with improved cancer treatment outcomes [16, 17], there are few studies addressing the impact that the diagnosis of pancreatic cancer has on the caregiver. More specifically, there is a lack of identification of proposed factors placing those caregivers at greatest risk for distress. Given that pancreatic cancer is different from other cancer diagnosis due to the high symptom burden coupled with rapidly progressive disease, it is important that we recognize the impact on caregiver well-being and identify opportunities for intervention and emotional support.

Due to the significant gap in literature identifying specific stressors and associated risk factors amongst pancreatic cancer patients and their caregivers, our study aimed to examine the psychosocial well-being in the patient-caregiver dyad, and to determine patient and caregiver characteristics that predict caregiver distress in this population. Our goal was to identify factors associated with increased risk of caregiver distress which may afford future opportunities for intervention, and ultimately increase the well-being of the caregiver and improve patient-centered outcomes.

## **Methods**

### **Participants and Procedure**

This was a cross-sectional, observational study of the psychosocial well-being of pancreatic cancer patients and their primary caregivers. All participating patients were consented to an institutional protocol with permitted access to medical record information for research purposes. This study received institutional review board approval (Advarra Pro00040381). Patients were screened for eligibility through

chart review and consultation with the patient's treatment team in Moffitt Cancer Center (MCC) Gastrointestinal Oncology Clinic.

Eligibility criteria for patients included: (1) a primary diagnosis of pancreatic cancer (any stage and at any time after diagnosis); (2) at least one consultation visit with a MCC provider; (3) at least 18 years old; (4) able to communicate in English; and (5) able to provide informed consent. Eligibility criteria for primary caregivers included: (1) individual self-identifies as a current primary caregiver of an eligible patient; (2) at least 18 years old; (3) able to communicate in English; and (4) able to provide informed consent. A maximum of one primary caregiver per patient was enrolled in the study. If multiple primary caregivers were identified, the caregiver who identified as providing the *most* hands-on care was enrolled, irrespective of marital status, habitation, or financial arrangements of caregiving.

Potential participants were approached either in person during a regularly scheduled clinic appointment, or via a mailed letter and subsequent telephone call. Patients and primary caregivers who met all eligibility criteria were given verbal and written information about the nature, purpose, and possible risks and benefits of the study. Participants then independently completed a one-time self-report questionnaire either electronically or on paper, depending on their preferences. For the electronic version, the participant was provided with a link to the online questionnaire, which they completed on their own device. For the paper version, they were either given the questionnaire in person or the questionnaire was sent via mail, along with a prepaid return envelope. All caregiver data and patient well-being data were collected via these questionnaires; corresponding patient demographic and clinical data were collected via abstraction of data from the patient's electronic medical record.

## Measures

**Primary caregivers** reported on **demographics and caregiving characteristics** using investigator-designed items assessing gender, age, race/ethnicity, relationship status, ZIP code of residence, education, employment status, household income, comorbid medical conditions, relationship to the patient, and total length and hours/week of caregiving. Primary caregivers also reported the types of caregiving activities they engaged in, including personal care activities (e.g., feeding, toileting), daily life activities (e.g., transportation, medication management), and "other" caregiving activities (e.g., provision of emotional support, decision-making support). **Distress** was assessed using the National Comprehensive Cancer Network (NCCN) Distress Thermometer (DT), a one-page screening instrument that includes one item assessing subjective distress on a scale of 0–10 [11]. Majority of studies have proposed cut-off scores of 4 or 5 for this item, with most recent guidelines from NCCN suggesting a score of  $\geq 4$  to indicate elevated distress [18–21]. Global levels of **perceived stress** were assessed using the 4-item Perceived Stress Scale 4 (PSS-4) [22]. Total scores range from 0–16, with higher scores indicative of more perceived stress; no specific cut-offs have been established for the PSS-4, but normative data have indicated that mean score among the general population is 6.11 (Standard deviation [SD] = 3.14) [23]. **Anxiety and depression symptoms** were assessed with the 4-item Patient Reported Outcomes Measurement Information System-

Anxiety Short Form 4a (PROMIS-Anxiety) and the 4-item Patient Reported Outcomes Measurement Information System-Depression Short Form 4a (PROMIS-Depression), respectively [24]. Both PROMIS measures produce a T-score (i.e., range = 0-100, general population mean = 50, SD = 10), with T-scores of 55–59 representing mild symptoms, 60–69 representing moderate symptoms, and  $\geq 70$  representing severe symptoms [25]. **Caregiver burden** was assessed with the 12-item Zarit Caregiver Burden Interview (CBI-12): scores range from 0–48, with scores  $\geq 17$  representing high burden [26].

**Patients** reported only on **distress** using the NCCN DT, which was administered on paper as part of usual clinical care during a regularly scheduled clinic appointment. As noted above, patient **demographic and clinical information** was collected from patient medical records and included: patient gender, age, race/ethnicity, relationship status, ZIP code of residence, comorbid medical conditions, and information related to the patient's pancreatic cancer, including date of diagnosis, stage at diagnosis, and whether the cancer was resectable.

Per institutional policy, all patients who score  $\geq 5$  on the NCCN DT are automatically referred to social work for further evaluation and management [27]. Distressed primary caregivers who participated in the current study were also given the option to receive a referral to social work by investigators.

## Data Analysis

Patients and their caregivers' sociodemographic characteristics, depressions related variables were summarized using descriptive statistics. Continuous variables per group were reported as mean (SD) and categorical variables were reported with frequency and percentage. Patient and caregiver DT scores were stratified by disease stage and compared using Kruskal-Wallis test. Patient and primary caregiver demographic characteristics, as well as patient disease stage and time since diagnosis were analyzed as predictors of caregiver distress using univariate and multivariate linear regression analyses. The predictors were kept in multivariate linear models when  $p$ -value  $< 0.05$  in univariate linear models. Our sample size of at least 128 patient-caregiver dyads provides 80% power to detect a medium-sized effect ( $d = .50$ ) using a  $t$ -test to examine mean differences between two groups with equal sample sizes, at a significance level of .05 (2-tailed).  $P$ -values were two-sided and  $p$ -values  $< 0.05$  were considered statistically significant. All statistical analyses were performed using R version 4.1.2.

## Results

A total of 128 patient-caregiver dyads were enrolled over a period of eleven consecutive months. Demographics and clinical characteristics are shown in Table 1. Mean patient and caregiver ages were 67.5 and 63.6 years, respectively. Slightly more than half (53.6%) of patients were male, while the majority (64.8%) of caregivers were female. Most caregivers (82.0%) were the patient's spouse; 69.0% of caregivers were the primary and sole caregiver for the patient. A mean of 44.4 hours/week was spent performing caregiving tasks, and in 94.5% of the dyads the care was performed by the primary caregiver without paid assistance. Treatment with palliative intent was offered to 57.9% of the study group (22.7%

locally advanced and 35.2% metastatic), while 42.2% were treated with curative intent (10.2% resected, 7.81% resectable and 24.2% borderline resectable). Additional patient and caregiver demographic and clinical characteristics are described in Table 1.

**Table 1.** Demographics and characteristics of patients and caregivers

	Patient	Caregiver
	N = 128	N = 128
Age	67.5 (9.17)	63.6 (11.5)
Race		
Asian	3 (2.34%)	3 (2.34%)
Black	4 (3.12%)	3 (2.34%)
Native Hawaiian/Pacific Islander	1 (0.78%)	0 (0.00%)
White/Caucasian	120 (93.8%)	122 (95.3%)
Hispanic		
No	117 (93.6%)	118 (92.2%)
Yes	8 (6.40%)	10 (7.81%)
Gender		
Female	59 (46.1%)	83 (64.8%)
Male	69 (53.9%)	45 (35.2%)
Marital Status		
Married or cohabiting	102 (79.7%)	115 (89.8%)
Partnered	1 (0.78%)	0 (0.00%)
Separated/divorced	19 (14.8%)	7 (5.47%)
Single, never married	1 (0.78%)	1 (0.78%)
Widowed	5 (3.91%)	5 (3.91%)
Education		
College graduate (bachelor degree or equivalent)	28 (26.2%)	22 (17.6%)
Graduate or professional degree	22 (20.6%)	24 (19.2%)
High school graduate or GED	29 (27.1%)	22 (17.6%)
Some graduate or professional school	0 (0.00%)	11 (8.80%)
Vocational school or some college (associate degree)	28 (26.2%)	46 (36.8%)
Patient Clinical Stage		
Borderline resectable	31 (24.2%)	
Locally advanced	29 (22.7%)	



Metastatic	45 (35.2%)	
Resectable	10 (7.81%)	
Resected	13 (10.2%)	
Time since diagnosis (months)	0.50 (1.02)	
Age adjusted Charlson Comorbidity Score	5.66 (3.11)	
ECOG score		
0	55 (44.7%)	
1	63 (51.2%)	
2	4 (3.25%)	
3	1 (0.81%)	
Caregiver Overall Health		
Excellent		19 (14.8%)
Very good		58 (45.3%)
Good		41 (32.0%)
Fair/Poor		10 (7.81%)
Relationship to Patient		
Child		11 (8.59%)
Non-relative		4 (3.12%)
Other relative		6 (4.69%)
Parent		2 (1.56%)
Spouse/Partner		105 (82.0%)
Lives with patient?		
No		17 (13.3%)
Yes		111 (86.7%)
Years of relationship with patient		34.7 (16.0)
Months of caregiving		25.6 (87.5)
Caregiving arrangement		
Primary and only caregiver		87 (69.0%)
Primary caregiver, with some help from others		28 (22.2%)

Secondary caregiver		5 (3.97%)
Split caregiving equally with others (multiple caregivers)		6 (4.76%)
Caregiver paid help		
No		121 (94.5%)
Yes		7 (5.47%)
Caregiver Household Income		
Less than \$10,000		1 (1.16%)
\$10,000–24,999		7 (8.14%)
\$25,000–39,999		12 (14.0%)
\$40,000–49,999		11 (12.8%)
\$50,000–74,999		20 (23.3%)
\$100,000 or more		35 (40.7%)
Caregiver Employment Status		
Employed full-time		38 (30.4%)
Employed part-time		13 (10.4%)
Not employed		74 (59.2%)
Caregiving hours/week		44.4 (55.8)
Caregiving Personal Care, # tasks		1.30 (2.09)
Caregiving Daily Activities, # tasks		4.13 (2.11)
Caregiving Other Activities, # tasks		6.41 (2.04)
NCCN DT Score	3.88 (2.61)	4.50 (2.64)
PROMIS-Anxiety Score		55.4 (9.68)
PROMIS-Depression Score		50.9 (8.53)
PSS-4 Score		4.83 (2.87)
CBI-12 Score		10.1 (7.02)
Abbreviations: <i>ECOG</i> , Eastern Cooperative Oncology Group; <i>NCCN DT</i> , National Comprehensive Cancer Network Distress Thermometer; <i>PROMIS</i> , Patient Reported Outcomes Measurement Information System; <i>PSS-4</i> , Perceived Stress Scale 4; <i>CBI-12</i> , Caregiver Burden Interview.		

The mean patient and caregiver NCCN DT scores were 3.88 (SD = 2.61) and 4.50 (SD = 2.64), respectively. A higher proportion of caregivers (n = 69, 53.9%) than patients (n = 58, 45.3%) scored in the “severe distress” range and were referred to social work for further evaluation. Patient (p = 0.91) and caregiver (p = 0.24) NCCN DT scores were not significantly associated with patient clinical disease burden (Fig. 1). The mean caregiver PROMIS-Anxiety, PROMIS-Depression, PSS-4, and CBI-12 scores were 55.4 (SD = 9.68), 50.9 (SD = 8.53), 4.83 (SD = 2.87) and 10.1 (SD = 7.02) respectively. The proportion of caregivers with PROMIS-Anxiety scores reflecting mild, moderate, and severe symptoms were 31.3% (n = 40), 21.9% (n = 28), and 5.5% (n = 7), respectively. The proportion of caregivers with PROMIS-Depression scores reflecting mild, moderate, and severe symptoms were 25.8% (n = 33), 5.5% (n = 7), and 3.9% (n = 5), respectively. Nearly half, 43.8% (n = 56) of caregivers had PSS-4 scores reflective of perceived stress greater than the general population. High burden was reported in 18% (n = 23) of caregivers.

### **Distress (Table 2)**

No significant predictors of patient NCCN DT score on univariate analysis were identified (all p > 0.05, data not shown). Predictors of caregiver NCCN DT score on univariate analysis were *patient* NCCN DT score (p < .001), more caregiver daily activities (p = .021) and other activities (p = .039), and caregiver’s overall health status (p = .050). In particular, caregivers who described their health status as fair/poor had the highest NCCN DT scores compared to caregivers who described their health status as excellent, very good or good. On multivariate analysis, only patient NCCN DT score persisted as a predictor of caregiver NCCN DT score ( $\beta=0.39$ ; 95% confidence interval [CI]=0.23, 0.56; p<.001).

**Table 2.** Univariate and multivariate linear regression models on Caregiver NCCN DT, PROMIS-Anxiety, PROMIS-Depression, PSS-4 and CBI-12 scores

Variable	Univariate model		Multivariate model	
	$\beta$ (95% CI)	p-value	$\beta$ (95% CI)	p-value
NCCN DT score:				
Caregiver Daily Activities	0.26 (0.038, 0.47)	0.021	0.19 (-0.056, 0.43)	0.13
Caregiver Other Activities	0.24 (0.012, 0.46)	0.039	0.055 (-0.20, 0.32)	0.67
Patient NCCN DT Score	0.44 (0.28, 0.60)	< 0.001	0.39 (0.23, 0.56)	<b>&lt; 0.001</b>
Caregiver Overall Health		0.050		0.18
Excellent	3.53 (2.34, 4.71)		1.0 (Reference)	
Very good	4.21 (3.47, 4.94)		0.21 (-1.10, 1.52)	0.75
Good	5.02 (4.26, 5.79)		1.09 (-0.29, 2.47)	0.12
Fair/Poor	5.90 (4.34, 7.46)		1.23 (-0.69, 3.14)	0.21
PROMIS-Anxiety score:				
Caregiver Age	-0.26 (-0.41, -0.12)	< 0.001	-0.18 (-0.36, -0.004)	<b>0.045</b>
Caregiver Daily Activities	0.93 (0.14, 1.73)	0.022	0.51 (-0.36, 1.38)	0.25
Caregiver Other Activities	1.35 (0.53, 2.18)	0.0016	0.79 (-0.16, 1.73)	0.1
Patient NCCN DT Score	1.20 (0.58, 1.82)	< 0.001	0.83 (0.22, 1.43)	<b>0.008</b>
Caregiver Employment Status		0.003		0.27
Employed full-time	59.4 (56.6, 62.3)		1.0 (Reference)	
Employed part-time	50.6 (44.9, 56.3)		-4.98 (-11.18, 1.22)	0.11
Not employed	54.1 (51.9, 56.3)		-1.55 (-6.16, 3.06)	0.51
PROMIS-Depression score:				
Caregiver Daily Activities	0.81 (0.099, 1.51)	0.026	-0.008 (-0.77, 0.75)	0.98
Caregiver Other Activities	1.19 (0.46, 1.92)	0.0016	1.15 (0.31, 1.99)	<b>0.0076</b>
Patient NCCN DT Score	1.00 (0.46, 1.55)	< 0.001	0.58 (0.051, 1.10)	<b>0.032</b>
Caregiver Overall Health		< 0.001		<b>&lt; 0.001</b>
Excellent	46.3 (43.1, 49.5)		1.0 (Reference)	
Very good	49.6 (47.5, 51.7)		3.87 (-0.25, 7.98)	0.065
Good	52.7 (50.3, 55.1)		7.18 (2.84, 11.51)	<b>0.0014</b>
Fair/Poor	61.0 (52.8, 69.3)		13.44 (7.23, 19.66)	<b>&lt; 0.001</b>

	Univariate model		Multivariate model	
PSS-4 score:				
Caregiver Age	-0.054 (-0.097, -0.011)	0.014	-0.035 (-0.088, 0.018)	0.19
Caregiver Daily Activities	0.39 (0.16, 0.62)	0.001	0.23 (-0.07, 0.53)	0.13
Caregiver Other Activities	0.33 (0.082, 0.58)	0.001	0.16 (-0.14, 0.46)	0.28
Caregiver Personal Care	0.32 (0.087, 0.56)	0.008	0.058 (-0.21, 0.33)	0.67
Patient NCCN DT Score	0.28 (0.093, 0.47)	0.004	0.13 (-0.058, 0.31)	0.18
Caregiver Employment Status		0.010		0.14
Employed full-time	5.71 (4.7, 6.72)		1.0 (Reference)	
Employed part-time	3.00 (1.35, 4.65)		-1.73 (-3.57, 0.12)	0.066
Not employed	4.69 (4.08, 5.31)		-0.29 (-1.65, 1.08)	0.68
Caregiver Overall Health		0.001		<b>0.012</b>
Excellent	3.58 (2.26, 4.9)		1.0 (Reference)	
Very good	4.43 (3.72, 5.14)		0.76 (-0.66, 2.19)	0.29
Good	5.35 (4.44, 6.26)		1.66 (0.16, 3.16)	<b>0.031</b>
Fair/Poor	7.78 (6.16, 9.4)		3.16 (1.01, 5.31)	<b>0.004</b>
CBI-12 score:				
Caregiver Age	-0.13 (-0.23, -0.02)	0.020	-0.11 (-0.21, -0.009)	<b>0.036</b>
Caregiver Daily Activities	1.01 (0.45, 1.57)	< 0.001	0.61 (-0.11, 1.33)	0.096
Caregiver Other Activities	0.98 (0.37, 1.59)	0.002	0.22 (-0.49, 0.93)	0.54
Caregiver Personal Care	1.01 (0.44, 1.58)	< 0.001	0.48 (-0.19, 1.14)	0.16
Patient NCCN DT Score	0.70 (0.24, 1.16)	0.003	0.53 (0.088, 0.98)	0.019
$\beta$ is the slope of the linear model for continuous variables, and mean for categorical variables.				
Abbreviations: <i>NCCN DT</i> , National Comprehensive Cancer Network Distress Thermometer; <i>PROMIS</i> , Patient Reported Outcomes Measurement Information System; <i>PSS-4</i> , Perceived Stress Scale 4; <i>CBI-12</i> , Caregiver Burden Interview.				

### Anxiety Symptoms (Table 2)

Higher patient NCCN DT score ( $p < .001$ ), younger caregiver age ( $p < .001$ ), more caregiver daily ( $p = .022$ ) and other ( $p = .002$ ) activities, and caregiver full-time employment status ( $p = .003$ ) were significantly

correlated with higher caregiver PROMIS-Anxiety scores. On multivariate analysis, the patient NCCN DT score ( $\beta=0.83$ ; 95% CI = 0.22, 1.43;  $p = .008$ ) and caregiver age ( $\beta=-0.18$ ; 95% CI=-0.36, -0.004;  $p=.045$ ) persisted as predictors of caregiver PROMIS-Anxiety scores.

### **Depression Symptoms (Table 2)**

On univariate analysis, higher patient NCCN DT score ( $p < .001$ ), more caregiver daily ( $p = .026$ ) and other ( $p = .002$ ) activities, and worse caregiver overall health status ( $p < .001$ ) were statistically correlated with higher PROMIS-Depression scores. Caregivers who described their health status as fair/poor had the highest PROMIS-Depression scores compared to those who described their health status as excellent, very good, or good. On multivariate analysis, the patient NCCN DT score ( $\beta=0.58$ ; 95% CI = 0.05, 1.10;  $p=.032$ ), caregiver overall health status (overall  $p<.001$ ) and caregiver other activities ( $\beta=1.15$ ; 95% CI = 0.31, 1.99;  $p=.008$ ) were significant predictors of caregiver PROMIS-Depression scores.

### **Perceived Stress (Table 2)**

Higher patient NCCN DT score ( $p = .004$ ), younger caregivers ( $p = .014$ ), more personal care ( $p = .008$ ), daily ( $p = .001$ ), and other ( $p = .010$ ) caregiving activities, full-time employment status ( $p = 0.010$ ) and caregiver health status ( $p = .001$ ) were correlated with higher caregiver PSS-4 scores. Particularly, caregivers who described their health status as fair/poor had the highest PSS-4 scores compared to those who described their health as excellent, very good, or good ( $p = 0.001$ ). On multivariate analysis, only the caregiver's health status ( $p = .012$ ) persisted as a predictor of PSS-4 score. Compared to the reference group of excellent health, caregivers with fair/poor health had higher PSS-4 scores ( $\beta=3.16$ ; 95% CI = 1.10, 5.31;  $p=.004$ ).

### **Caregiver Burden (Table 2)**

Higher patient NCCN DT score ( $p = .003$ ), younger caregiver age ( $p = .020$ ), and more personal care ( $p < .001$ ), daily ( $p < .001$ ), and other ( $p = .002$ ) caregiving activities were significantly correlated with higher caregiver CBI-12 scores. On multivariate analysis, only the patient NCCN DT score ( $\beta=0.53$ ; 95% CI = 0.09, 0.98;  $p = .019$ ) and caregiver age ( $\beta=-0.11$ ; 95% CI=-0.21, -0.01;  $p=.036$ ) demonstrated a significant relationship with caregiver CBI-12 score.

## **Discussion**

Results of this cross-sectional, observational study of pancreas cancer patient-caregiver dyads showed that patient distress was a significant predictor of caregiver distress, anxiety, depression, and perceived caregiver burden. Younger caregiver age was also associated with higher caregiver anxiety and perceived burden. Additional predictors of caregiver depression and perceived stress included number of "other" caregiving activities (e.g., provision of emotional support, decision-making support) and overall health status. These findings suggest that the burden endured by the caregiver population may be significantly under-recognized, as much of the focus in the medical community continues to be on the screening of

depression and stress in patients. We have identified particular patient and caregiver variables which negatively impact the well-being of pancreatic cancer caregivers.

Our findings are consistent with previous studies that have described a significant, interdependent relationship between cancer patients and caregiver emotional distress, calling to attention the need to address the patient-caregiver dyad as a unit of care [14, 28]. Prior longitudinal studies indicated that not only does caregiver distress negatively impact optimal patient care, but it also has a negative impact on patients' long-term adjustment [29, 30]. A meta-analysis of 21 studies with a combined sample of 1,098 patient and caregiver dyads concluded that emotional responses to a cancer diagnosis were interrelated and dependent on the phase of the illness [31]. Although there was a trend towards higher patient and caregiver distress with progressive clinical stage in the present sample, we did not find stage was a significant predictor of caregiver distress, perceived burden, anxiety, or depression. In contrast to other studies that examined a heterogeneous population cancer diagnoses, our study focused solely on caregivers for, and patients diagnosed with pancreas cancer.

In 2015, Pancreatic Cancer Action Network (PanCAN) surveyed 184 patients and 213 caregivers and reported differences in perceptions on the role of and psychological burden on caregivers [32]. Interestingly, patients reported a more hopeful outlook than caregivers. Furthermore, patients with pancreas cancer underappreciated the degree to which caregivers were assisting with their activities. Similarly, in an Australian population of patients with pancreatic cancer and their caregivers, there was a higher proportion of caregivers than patients with elevated levels of anxiety [33]. This may be secondary to unrecognized demands of not only caring for patients but also managing activities of daily of living and the personal disruption that occurs with being a caregiver, caregiver health issues and navigating an increasingly complex and specialized healthcare system [34]. Our findings support this theory: caregivers with more activities/responsibilities other than caregiving and poorer personal health status ("Good" or "Fair/Poor" as opposed to "Excellent" or "Very Good") demonstrated an increased likelihood of depression. Therefore, when the demands of caregiving exhaust resources, there is an increased risk of distress and depression, particularly amongst less healthy caregivers.

A prior study from the University of Copenhagen highlighted that caregivers had a higher risk of depression and anxiolytic and hypnotic use than pancreas cancer patients, especially 2–5 years from the time of diagnosis [35]. In addition, Janda et al. postulated that younger caregivers may have their own inherent coping challenges, as they may not have had the degree of life experiences as their older counterparts, given the nature and typical epidemiology of pancreas cancer, in coping with a cancer diagnosis [33]. This correlates with our finding that younger caregiver age was a predictor of greater anxiety and burden. More so than their older peers, younger caregivers are at increased risk for distress and burnout while fulfilling the caregiver role.

In a recent analysis of the Surveillance, Epidemiology, and End Results database, Gaddam et al. described a significant increase in annual percentage change in patients less than 55 years of age diagnosed with pancreas cancer among women (1.93%) and men (0.77%) between 2000–2018 [36]. This demographic

data raises the important idea that as pancreas cancer increasingly impacts a working-age demographic, the potential risk for financial toxicity is obvious and alarming [37, 38]. Emphasizing this point, in the 2015 PanCAN study, 40% percent of caregivers with a mean age of 46.8 years (89% women) reported giving up their jobs in order to fulfill the caregiver role [32]. Taken cumulatively, caregivers who are increasingly younger and most often women, are at increased risk of distress in multiple facets. As the burden of pancreas cancer care increasingly impacts a younger demographic, it is critical for behavioral researchers and clinicians alike to apply diagnostic tools to recognize distress in patients and their caregiver support systems as well as implement meaningful interventions to mitigate this distress.

Our study has several limitations. Patient-caregiver dyads were enrolled and data was collected at one time point within the patients' clinical care. This may not fully depict the evolution of distress and psychosocial symptom burden within the patient-caregiver dyad that occurs longitudinally during the cancer care process. However, our cross-sectional strategy is similar to many other studies in the literature and does represent the spectrum of disease encountered in a large tertiary referral center. Our sample was also relatively homogeneous with regard to race/ethnicity. Coping strategies may be significantly influenced by cultural and societal factors, and therefore, the results of our study may not be as applicable to patients and caregivers who identify as racial or ethnic minorities, and/or in a non-United States population.

Finally, we add to a growing body of literature describing a limitation within the current medical practice. The NCCN Guidelines for Distress Management outlines that, "distress should be recognized, monitored, documented, and treated promptly at all stages of disease and in all settings" [19]. Our study examined the performance of the NCCN DT in the largest population to date of patients with pancreas cancer and their caregivers. Specifically, the NCCN DT correlated well with validated behavioral measures including PROMIS-Depression, PROMIS-Anxiety, and CBI-12 assessment tools. In addition, caregiver-centered factors including the caregiver's own health, younger age, and the extent of needed caregiving activities were key contributors to distress. Healthcare providers and health systems are designed to diagnose and care for patients. Unfortunately, it is clear that while caregivers are vital to the patient's well-being and their adherence to treatment, they are shouldering this burden at the cost of personal/family-unit distress. Addressing caregiver related factors is important because the health of the surrounding support system directly and reciprocally influences cancer specific outcomes for patients [39, 40]. While practicing clinicians will clearly acknowledge the vital role to which family and caregiver support structures add to patient care, few resources have traditionally been available to directly support these caregivers, and thereby indirectly support patient care. Distress is a complex dynamic with multiple contributors that exert physical and emotional tolls. The findings of this study support directed efforts towards interventions that address caregiver distress, particularly supportive strategies aimed towards younger caregivers, and providing resources to offset the time demands of caregiving.

## Declarations



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Conflicts of interest/Competing interests: Not applicable.

Availability of data and material: I have full control of all primary data and agree to allow the journal to review the data if requested.

Code availability: I agree to allow the journal to review the code if requested.

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Kevin Allenson, Amy K. Otto, Maria Kocab, Brent T. Xia, and Pamela J. Hodul. The first draft of the manuscript was written by Brent T. Xia, Kelvin Allenson and Amy K. Otto, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Consent to participate: All participating patients were consented to an institutional protocol with permitted access to medical record information for research purposes.

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## References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A (2022) Cancer statistics, 2022 *CA Cancer J Clin* 72: 7-33
2. Xia BT, Ahmad SA (2016) Clinical Considerations for Pancreatic Cancer *Semin Roentgenol* 51: 74-81
3. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M, Groupe Tumeurs Digestives of U, Intergroup P (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer *N Engl J Med* 364: 1817-1825
4. Katz MH, Shi Q, Ahmad SA, Herman JM, Marsh Rde W, Collisson E, Schwartz L, Frankel W, Martin R, Conway W, Truty M, Kindler H, Lowy AM, Bekaii-Saab T, Philip P, Talamonti M, Cardin D, LoConte N, Shen P, Hoffman JP, Venook AP (2016) Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101 *JAMA Surg* 151: e161137

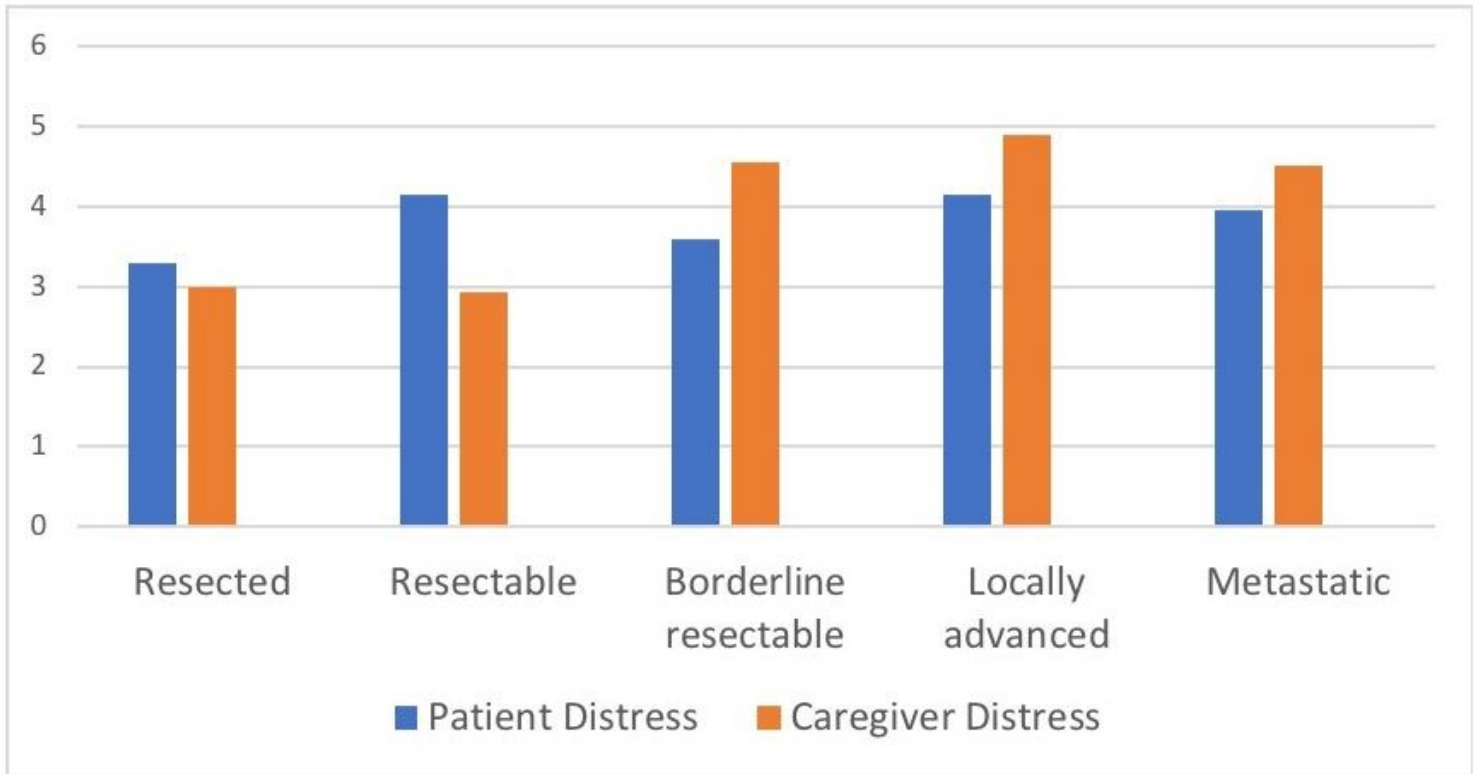
5. Neoptolemos JP, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluyi O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherriff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Buchler MW, European Study Group for Pancreatic C (2017) Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial *Lancet* 389: 1011-1024
6. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine *N Engl J Med* 369: 1691-1703
7. (2022) *Cancer Facts and Figures 2022* American Cancer Society
8. Crippa S, Dominguez I, Rodriguez JR, Razo O, Thayer SP, Ryan DP, Warshaw AL, Fernandez-del Castillo C (2008) Quality of life in pancreatic cancer: analysis by stage and treatment *J Gastrointest Surg* 12: 783-793; discussion 793-784
9. Fong ZV, Alvino DM, Castillo CF, Nipp RD, Traeger LN, Ruddy M, Lubitz CC, Johnson CD, Chang DC, Warshaw AL, Lillemoe KD, Ferrone CR (2017) Health-related Quality of Life and Functional Outcomes in 5-year Survivors After Pancreaticoduodenectomy *Ann Surg* 266: 685-692
10. Allen CJ, Yakoub D, Macedo FI, Dosch AR, Brosch J, Dudeja V, Ayala R, Merchant NB (2018) Long-term Quality of Life and Gastrointestinal Functional Outcomes After Pancreaticoduodenectomy *Ann Surg* 268: 657-664
11. Deng Y, Tu H, Pierzynski JA, Miller ED, Gu X, Huang M, Chang DW, Ye Y, Hildebrandt MAT, Klein AP, Zhao R, Lippman SM, Wu X (2018) Determinants and prognostic value of quality of life in patients with pancreatic ductal adenocarcinoma *Eur J Cancer* 92: 20-32
12. Andrews SC (2001) Caregiver burden and symptom distress in people with cancer receiving hospice care *Oncol Nurs Forum* 28: 1469-1474
13. Hagedoorn M, Sanderman R, Bolks HN, Tuinstra J, Coyne JC (2008) Distress in couples coping with cancer: a meta-analysis and critical review of role and gender effects *Psychol Bull* 134: 1-30
14. Northouse LL, Katapodi MC, Schafenacker AM, Weiss D (2012) The impact of caregiving on the psychological well-being of family caregivers and cancer patients *Semin Oncol Nurs* 28: 236-245
15. Jacobs JM, Shaffer KM, Nipp RD, Fishbein JN, MacDonald J, El-Jawahri A, Pirl WF, Jackson VA, Park ER, Temel JS, Greer JA (2017) Distress is Interdependent in Patients and Caregivers with Newly Diagnosed Incurable Cancers *Ann Behav Med* 51: 519-531
16. Andersen BL, Thornton LM, Shapiro CL, Farrar WB, Mundy BL, Yang HC, Carson WE, 3rd (2010) Biobehavioral, immune, and health benefits following recurrence for psychological intervention participants *Clin Cancer Res* 16: 3270-3278
17. Giese-Davis J, Collie K, Rancourt KM, Neri E, Kraemer HC, Spiegel D (2011) Decrease in depression symptoms is associated with longer survival in patients with metastatic breast cancer: a secondary

analysis J Clin Oncol 29: 413-420

18. Jacobsen PB, Donovan KA, Trask PC, Fleishman SB, Zabora J, Baker F, Holland JC (2005) Screening for psychologic distress in ambulatory cancer patients Cancer 103: 1494-1502
19. National Comprehensive Cancer Network (2022) NCCN Guidelines - Distress Management (Version 1.2022). In: Editor (ed)^(eds) Book NCCN Guidelines - Distress Management (Version 1.2022), City.
20. Martinez P, Galdon MJ, Andreu Y, Ibanez E (2013) The Distress Thermometer in Spanish cancer patients: convergent validity and diagnostic accuracy Support Care Cancer 21: 3095-3102
21. Grassi L, Johansen C, Annunziata MA, Capovilla E, Costantini A, Gritti P, Torta R, Bellani M, Italian Society of Psycho-Oncology Distress Thermometer Study G (2013) Screening for distress in cancer patients: a multicenter, nationwide study in Italy Cancer 119: 1714-1721
22. Cohen S, Kamarck T, Mermelstein R (1983) A global measure of perceived stress J Health Soc Behav 24: 385-396
23. Warrtig SL, Forshaw MJ, South J, White AK (2013) New, normative, English-sample data for the Short Form Perceived Stress Scale (PSS-4) J Health Psychol 18: 1617-1628
24. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D, Group PC (2011) Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger Assessment 18: 263-283
25. Jensen RE, Potosky AL, Moinpour CM, Lobo T, Cella D, Hahn EA, Thissen D, Smith AW, Ahn J, Luta G, Reeve BB (2017) United States Population-Based Estimates of Patient-Reported Outcomes Measurement Information System Symptom and Functional Status Reference Values for Individuals With Cancer J Clin Oncol 35: 1913-1920
26. Bedard M, Molloy DW, Squire L, Dubois S, Lever JA, O'Donnell M (2001) The Zarit Burden Interview: a new short version and screening version Gerontologist 41: 652-657
27. Schenker Y, Bahary N, Claxton R, Childers J, Chu E, Kavalieratos D, King L, Lembersky B, Tiver G, Arnold RM (2018) A Pilot Trial of Early Specialty Palliative Care for Patients with Advanced Pancreatic Cancer: Challenges Encountered and Lessons Learned J Palliat Med 21: 28-36
28. Matthews B, Baker F, Spillers R (2003) Family caregivers and indicators of cancer-related distress Psychol Health Med 8: 46-56
29. Northouse L, Templin T, Mood D (2001) Couples' adjustment to breast disease during the first year following diagnosis J Behav Med 24: 115-136
30. van Ryn M, Sanders S, Kahn K, van Houtven C, Griffin JM, Martin M, Atienza AA, Phelan S, Finstad D, Rowland J (2011) Objective burden, resources, and other stressors among informal cancer caregivers: a hidden quality issue? Psychooncology 20: 44-52
31. Hodges LJ, Humphris GM, Macfarlane G (2005) A meta-analytic investigation of the relationship between the psychological distress of cancer patients and their carers Soc Sci Med 60: 1-12
32. Engebretson A, Matrisian L, Thompson C (2015) Pancreatic cancer: Patient and caregiver perceptions on diagnosis, psychological impact, and importance of support Pancreatology 15: 701-

33. Janda M, Neale RE, Klein K, O'Connell DL, Gooden H, Goldstein D, Merrett ND, Wyld DK, Rowlands IJ, Beesley VL (2017) Anxiety, depression and quality of life in people with pancreatic cancer and their carers *Pancreatology* 17: 321-327
34. Sherman DW, McGuire DB, Free D, Cheon JY (2014) A pilot study of the experience of family caregivers of patients with advanced pancreatic cancer using a mixed methods approach *J Pain Symptom Manage* 48: 385-399 e381-382
35. Dengso KE, Thomsen T, Andersen EW, Hansen CP, Christensen BM, Hillingso J, Dalton SO (2021) The psychological symptom burden in partners of pancreatic cancer patients: a population-based cohort study *Support Care Cancer* 29: 6689-6699
36. Gaddam S, Abboud Y, Oh J, Samaan JS, Nissen NN, Lu SC, Lo SK (2021) Incidence of Pancreatic Cancer by Age and Sex in the US, 2000-2018 *JAMA* 326: 2075-2077
37. Collado L, Brownell I (2019) The crippling financial toxicity of cancer in the United States *Cancer Biol Ther* 20: 1301-1303
38. Desai A, Gyawali B (2020) Financial toxicity of cancer treatment: Moving the discussion from acknowledgement of the problem to identifying solutions *EClinicalMedicine* 20: 100269
39. Davis RE, Trickey AW, Abrahamse P, Kato I, Ward K, Morris AM (2021) Association of Cumulative Social Risk and Social Support With Receipt of Chemotherapy Among Patients With Advanced Colorectal Cancer *JAMA Netw Open* 4: e2113533
40. Ikeda A, Kawachi I, Iso H, Iwasaki M, Inoue M, Tsugane S (2013) Social support and cancer incidence and mortality: the JPHC study cohort II *Cancer Causes Control* 24: 847-860

## Figures



**Figure 1**

NCCN Dyad Distress Scores by Clinical Stage

Patient distress:  $p=0.91$

Caregiver distress:  $p=0.24$