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

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Received: 4 May 2022 / Accepted: 27 July 2022 / Published online: 20 August 2022 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract We aimed to examine the psychosocial well-being in the pancreas cancer patient-caregiver dyad, and determine patient and caregiver characteristics that predict caregiver distress. This was a cross-sectional, observational study. Demographics and caregiving characteristics were gathered from patients and caregivers. Caregivers completed validated instruments investigating anxiety, depression, perceived stress and caregiver burden. Over a period of eleven months, 128 patient-caregiver dyads were enrolled. Patient and caregiver distress scores were not associated with patient clinical disease burden. Patient distress was a significant predictor of concurrent caregiver distress, anxiety, depression, and perceived burden. Younger caregivers were also associated with higher caregiver anxiety and perceived burden. Additionally, number of caregiving activities and caregiver overall health status were predictors of concurrent caregiver depression and perceived stress. Certain pancreatic cancer patient and caregiver variables may negatively impact the well-being of caregivers. Future efforts should focus on development and implementation of comprehensive caregiver support programs for those at risk for psychosocial distress.

Keywords Pancreas cancer · Caregiver distress · Caregiver burden

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 (Siegel et al., 2022). Surgery remains the only treatment option for curative intent and prolonged survival, yet 80% of patients are unresectable at presentation (Xia & Ahmad, 2016). 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 (Desseigne et al., 2011, Von Hoff et al., 2013; Katz et al., 2016, Palmer et al. 2017). 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 (American Cancer Society, 2022).
As patients with pancreas cancer are living longer across all disease stages, there has been a renewed focus on addressing quality of life, both pre- and post- multimodal therapy. The Massachusetts General Hospital group initially reported on quality of life amongst pancreatic cancer patients with resected disease, locally advanced, and metastatic disease burden (Crippa et al., 2008). This was later surveyed in a larger cohort of five-year survivors after pancreaticoduodenectomy, which demonstrated improved global quality of life compared to an age and gender-adjusted normal population sample (Fong et al., 2017). In a larger cohort, Allen et al. reported that emotional and physical domains of quality of life improved over time and surpassed preoperative measurements at six months to one year after pancreatic surgery (Allen et al., 2018). Deng et al. found that physical and mental health quality of life in patients with pancreas cancer was a significant predictor of poor prognosis, and emphasized the need to focus on interventions to alleviate symptom burden (Deng et al., 2018).

Despite a myriad of studies focused on improving quality of life 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. Meta-analyses of patients and their caregivers of breast, gynecologic, prostate and gastrointestinal cancers have suggested a reciprocal relationship between patients and caregiver emotional distress (Andrews, 2001; Hagedoorn et al., 2008; Northouse et al., 2012). In an analysis of patients and caregivers with newly diagnosed, advanced incurable lung and non-colorectal gastrointestinal cancers, Jacobs et al. reported crossover between patient anxiety and partner depression, and vice versa, suggesting a bidirectional and interdependent association of distress (Jacobs et al., 2017).

While many recent studies suggest that screening for and addressing distress not only enhances quality of life but also may be associated with improved cancer treatment outcomes, there are few studies addressing the impact that the diagnosis of pancreatic cancer has on the caregiver (Andersen et al., 2010). More specifically, there is a lack of identification of proposed factors placing those caregivers as 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 cross-sectional, observational study aimed to examine the psychosocial well-being in the patient-caregiver dyad, and to determine patient and caregiver characteristics that predict concurrent 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 was in accordance with the ethical standards of the institutional review committee and with the 1964 Helsinki Declaration and its later amendments, and 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 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 MC 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. This assessment was created by the authors, and included three questions (with 8–9 options for the caregiver to select all that applied) regarding 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 (Deng, Tu et al.), a one-page validated screening instrument that includes one item assessing subjective distress on a scale of 0–10 represented on a visual graphic of a thermometer that ranges from no distress to extreme distress. (Deng, Tu et al.). It has shown good convergent validity with various other measures of psychosocial distress in cancer survivors, including self-reported measures of depression and anxiety (Jacobsen et al., 2005; Mitchell, 2010, Johansen et al. 2013). 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 ≥ 4 to indicate elevated distress (Jacobsen et al., 2005; Grassi, Johansen et al. 2013. Martinez et al., 2013, National Comprehensive Cancer Network, 2022). Global levels of perceived stress were assessed using the 4-item Perceived Stress Scale 4 (PSS-4) (Cohen et al., 1983). Total scores range from 0 to 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) (Warttig et al., 2013). The PSS-4 is expedient in its ease of use and time to complete, and has been previously shown to be reliable with internal consistency as a screening tool to measure stress from disease and behavioral disorders (Cohen et al., 1983; Lee, 2012). 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 (Choi et al. 2011). 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 ≥ 70 representing severe symptoms (Jensen et al., 2017). The PROMIS measures were crafted and calibrated using a comprehensive protocol that involved literature review, patient feedback, expert consensus and psychometric analyses (Choi et al., 2011). These measures are the product of an extensive validation, have been used extensively in cancer and other clinical populations, and the anxiety and depression 4-item scales have demonstrated excellent internal reliability and convergent validity with other screening instruments for anxiety and depression (Cella et al., 2019; Kroenke et al., 2014).

Caregiver burden was assessed with the 12-item Zarit Caregiver Burden Interview (CBI-12): scores range from 0 to 48, with scores ≥ 17 representing high burden (Bedard et al., 2001). This was developed from caregivers of cognitively impaired older adults referred to a memory clinic, and the short 12-item version was found to correlate well with the 22-item version, which demonstrated excellent internal consistency and convergent validity with measures of perceived stress, depression, health-related quality of life, and patient dependence/caregiving needs (Bedard et al., 2001; Gratao et al., 2019; Hagell et al., 2017).

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 ≥ 5 on the NCCN DT are automatically referred to social work for further evaluation and management (Schenker et al., 2018). 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 (standard deviation [SD]) and categorical variables were reported with frequency and percentage. Validated screening questionnaire continuous scores were used as dependent variables in all analyses. Patient and caregiver DT scores were stratified by disease stage and compared using Kruskal–Wallis test, and the level of correspondence between patient DT scores and caregiver DT, PSS-4, PROMIS-Anxiety, PROMIS-Depression and CBI-12 scores were calculated. Patient and primary caregiver demographic characteristics, as well as patient disease stage and time since diagnosis were analyzed as predictors of concurrent patient distress, caregiver distress, caregiver perceived stress, caregiver anxiety, caregiver depression, and caregiver burden using univariate and multivariate linear regression analyses, and the unstandardized regression coefficients are reported. The predictors were kept in multivariate linear models when p-value < 0.05 in univariate linear models. 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 h/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. Of the 144 patients approached, a minority, 16 (11.1%) patients declined participation in the study. Demographics and clinical characteristics of the patients who declined participation, in comparison to those who agreed to the study, are shown in Supplementary Table A. Patients who declined participation, compared to their counterparts that agreed to participate, had a significantly longer time since diagnosis (p = 0.026) and higher age-adjusted Charlson Comorbidity Score (p < 0.001).

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 “elevated 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. The mean CBI-12 score was 10.12 (SD = 7.02), and the percentage of patients who scored ≥ 17 (high burden) was 18% (n = 23) of caregivers. There was a significant correlation between patient DT scores and caregiver DT score (R = 0.45, p < 0.001), caregiver PSS-4 score (R = 0.25, p = 0.004), caregiver PROMIS-Anxiety score (R = 0.35, p < 0.001), caregiver PROMIS-Depression score (R = 0.34, p < 0.001), and caregiver CBI-12 score (R = 0.28, p = 0.001) [Supplementary Figure A].

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 < 0.001), more caregiver daily activities (p = 0.021) and assistance with other activities in addition to daily life and personal care help (p = 0.039), and caregiver’s overall health status (p = 0.050). 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 concurrent caregiver NCCN DT score (β = 0.39; 95% confidence interval [CI] = 0.23, 0.56; p < 0.001).

Anxiety symptoms (Table 2)

Higher patient NCCN DT score (p < 0.001), younger caregiver age (p < 0.001), more caregiver daily (p = 0.022) and other (p = 0.002) activities, and caregiver full-time employment status (p = 0.003) were significantly correlated with higher caregiver PROMIS-Anxiety scores. On
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 (91.4%) | 118 (92.2%) |           |            |
| Yes                            | 11 (8.6%) | 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%)  |           |            |
| Widowed                        | 5 (3.91%) | 5 (3.91%)  |           |            |
| Single, never married          | 1 (0.78%) | 1 (0.78%)  |           |            |
| Education                      |         |            |           |            |
| High school graduate or GED    | 29 (27.1%) | 22 (17.6%)  |           |            |
| Vocational school or some college (associate degree) | 28 (26.2%) | 46 (36.8%) |           |            |
| College graduate (bachelor degree or equivalent) | 28 (26.2%) | 22 (17.6%) |           |            |
| Some graduate or professional school | 0 (0.00%) | 11 (8.80%) |           |            |
| Graduate or professional degree | 22 (20.6%) | 24 (19.2%) |           |            |
| 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%) |           |           |            |
| Treatment status               |         |            |           |            |
| Curative—active treatment      | 16 (12.5%) |           |           |            |
| Curative—inactive treatment    | 40 (31.2%) |           |           |            |
| Palliative—active treatment    | 39 (30.5%) |           |           |            |
| Palliative—inactive treatment  | 33 (25.8%) |           |           |            |
| Time since diagnosis (months)  | 10.5 (13) |           |           |            |
| 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%) |           |           |            |
multivariate analysis, the patient NCCN DT score ($\beta=0.83$; 95% CI = 0.22, 1.43; $p=0.008$) and caregiver age ($\beta=-0.18$; 95% CI = −0.36, −0.004; $p=0.045$) persisted as predictors of concurrent caregiver PROMIS-Anxiety scores.

**Table 1** (continued)

|                        | Patient | Caregiver |
|------------------------|---------|-----------|
| Parent                 | 2 (1.56%) | 2 (1.56%) |
| Spouse/Partner         | 105 (82.0%) | 105 (82.0%) |
| Other relative         | 6 (4.69%) | 6 (4.69%) |
| Non-relative           | 4 (3.12%) | 4 (3.12%) |
| *Lives with patient?*  |         |           |
| No                     | 17 (13.3%) | 17 (13.3%) |
| Yes                    | 111 (86.7%) | 111 (86.7%) |
| *Years of relationship with patient* |         |           |
| 1–3 years              | 24 (18.7%) | 24 (18.7%) |
| 4+ years               | 104 (81.3%) | 104 (81.3%) |
| *Months of caregiving* |         |           |
| 1–6 months             | 20 (15.6%) | 20 (15.6%) |
| 7+ months              | 108 (84.4%) | 108 (84.4%) |
| *Caregiving arrangement* |         |           |
| Primary and only caregiver | 87 (69.0%) | 87 (69.0%) |
| Primary caregiver, with some help from others | 28 (22.2%) | 28 (22.2%) |
| Secondary caregiver     | 5 (3.97%) | 5 (3.97%) |
| Split caregiving equally with others (multiple caregivers) | 6 (4.76%) | 6 (4.76%) |
| *Caregiver paid help*  |         |           |
| No                     | 121 (94.5%) | 121 (94.5%) |
| Yes                    | 7 (5.47%) | 7 (5.47%) |
| *Caregiver household income* |         |           |
| Less than $10,000      | 1 (1.16%) | 1 (1.16%) |
| $10,000–24,999         | 7 (8.14%) | 7 (8.14%) |
| $25,000–39,999         | 12 (14.0%) | 12 (14.0%) |
| $40,000–49,999         | 11 (12.8%) | 11 (12.8%) |
| $50,000–74,999         | 20 (23.3%) | 20 (23.3%) |
| $100,000 or more       | 35 (40.7%) | 35 (40.7%) |
| *Caregiver employment status* |         |           |
| Employed full-time     | 38 (30.4%) | 38 (30.4%) |
| Employed part-time     | 13 (10.4%) | 13 (10.4%) |
| Not employed           | 74 (59.2%) | 74 (59.2%) |
| Caregiving hours/week  | 44.4 (55.8) | 44.4 (55.8) |
| Caregiving Personal Care, # tasks | 1.30 (2.09) | 1.30 (2.09) |
| Caregiving Daily Activities, # tasks | 4.13 (2.11) | 4.13 (2.11) |
| Caregiving Other Activities, # tasks | 6.41 (2.04) | 6.41 (2.04) |
| NCCN DT Score (range 0–10, ≥ 4 indicates elevated distress) | 3.88 (2.61) | 3.88 (2.61) |
| PROMIS-Anxiety Score (range 0–100; 55–59 mild, 60–69 moderate, ≥ 70 severe symptoms) | 55.4 (9.68) | 55.4 (9.68) |
| PROMIS-Depression Score (range 0–100; 55–59 mild, 60–69 moderate, > 70 severe symptoms) | 50.9 (8.53) | 50.9 (8.53) |
| PSS-4 Score (range 0–16, general population mean score 6.11) | 4.83 (2.87) | 4.83 (2.87) |
| CBI-12 Score (range 0–48, ≥ 17 indicates high burden) | 10.1 (7.02) | 10.1 (7.02) |

ECOG, Eastern Cooperative Oncology Group; NCCN DT, National Comprehensive Cancer Network Distress Thermometer; PROMIS, Patient Reported Outcomes Measurement Information System; PSS-4, Perceived Stress Scale 4; CBI-12, Caregiver Burden Interview

**Depression symptoms (Table 2)**

On univariate analysis, higher patient NCCN DT score ($p<0.001$), more caregiver daily ($p=0.026$) and other ($p=0.002$) activities, and worse caregiver overall health status ($p<0.001$) 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 ($\beta=0.58; 95\% CI=0.05, 1.10; p=0.032$), caregiver overall health status (overall $p<0.001$) and caregiver other activities in addition to daily life and personal care help ($\beta=1.15; 95\% CI=0.31, 1.99; p=0.008$) were significant predictors of concurrent caregiver PROMIS-Depression scores.

Perceived stress (Table 2)

Higher patient NCCN DT score ($p=0.004$), younger caregivers ($p=0.014$), more personal care ($p=0.008$), daily ($p=0.001$), and other ($p=0.010$) caregiving activities, full-time employment status ($p=0.010$) and caregiver health status ($p=0.001$) 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 ($p=0.012$) persisted as a predictor of concurrent PSS-4 score. Compared to the reference group of excellent health, caregivers with fair/poor health had higher PSS-4 scores ($\beta=3.16; 95\% CI=1.10, 5.31; p=0.004$).

Caregiver burden (Table 2)

Higher patient NCCN DT score ($p=0.003$), younger caregiver age ($p=0.020$), and more personal care ($p<0.001$), daily ($p<0.001$), and other ($p=0.002$) caregiving activities were significantly correlated with higher caregiver CBI-12 scores. On multivariate analysis, only the patient NCCN DT score ($\beta=0.53; 95\% CI=0.09, 0.98; p=0.019$) and caregiver age ($\beta=-0.11; 95\% CI=-0.21, -0.01; p=0.036$) demonstrated a significant relationship with caregiver CBI-12 score.

Full results of all univariate findings are included in Supplementary Table B.

Discussion

Results of this cross-sectional, observational study of pancreas cancer patient-caregiver dyads showed that patient distress significantly correlated with all five validated screening measures, and was a significant predictor of four of five validated screening measures utilized: concurrent caregiver distress, anxiety, depression, and perceived caregiver burden. Younger caregiver age was also associated with higher caregiver anxiety and perceived burden. Additional predictors of concurrent 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 proposed an 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 (Matthews et al., 2003; Northouse et al., 2012). 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 (Northouse et al., 2001; van Ryn et al., 2011). 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 (Hodges et al., 2005). 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 concurrent predictor of caregiver distress, perceived burden, anxiety, or depression.
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 | β (95% CI) | p-value | R²     | β (95% CI) | p-value |
|---------------------------|------------------|--------------------|------------|---------|--------|------------|---------|
|                           |                  |                    |            |         |        |            |         |
| **NCCN DT score**         |                  |                    |            |         |        |            |         |
| Caregiver daily activities| 0.26 (0.038, 0.47)| 0.021              | 0.041      |         | 0.19 (-0.056, 0.43) | 0.13 |
| Caregiver other activities| 0.24 (0.012, 0.46)| 0.039              | 0.033      |         | 0.055 (-0.20, 0.32) | 0.67 |
| Patient NCCN DT score     | 0.44 (0.28, 0.60) | < 0.001            | 0.028      |         | 0.39 (0.23, 0.56) | < 0.001 |
| Caregiver overall health  |                  | 0.050              | 0.061      |         |        |            |         |
| Excellent                 | 3.53 (2.34, 4.71) |                    | 1.0 (Reference) | |        |            |         |
| Very good                 | 4.21 (3.47, 4.94) |                    | 0.21 (-1.10, 1.52) | |        |            |         |
| Good                      | 5.02 (4.26, 5.79) |                    | 1.09 (-0.29, 2.47) | |        |            |         |
| Fair/Poor                 | 5.90 (4.34, 7.46) |                    | 1.23 (-0.69, 3.14) | |        |            |         |
| **PROMIS—anxiety score**  |                  |                    |            |         |        |            |         |
| Caregiver age             | -0.26 (-0.41, -0.12) | < 0.001        | 0.099      |         | -0.18 (-0.36, -0.004) | 0.045 |
| Caregiver daily activities| 0.93 (0.14, 1.73) | 0.022             | 0.041      |         | 0.51 (-0.36, 1.38) | 0.25 |
| Caregiver other activities| 1.35 (0.53, 2.18) | 0.0016            | 0.078      |         | 0.79 (-0.16, 1.73) | 0.1 |
| Patient NCCN DT score     | 1.20 (0.58, 1.82) | < 0.001            | 0.01       |         | 0.83 (0.22, 1.43) | 0.008 |
| Caregiver employment status| 0.003             |                    | 0.091      |         |        |            |         |
| 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) | |        |            |         |
| Not employed              | 54.1 (51.9, 56.3) |                    | -1.55 (-6.16, 3.06) | |        |            |         |
| **PROMIS—depression score**|                  |                    |            |         |        |            |         |
| Caregiver daily activities| 0.81 (0.099, 1.51) | 0.026             | 0.039      |         | -0.008 (-0.77, 0.75) | 0.98 |
| Caregiver other activities| 1.19 (0.46, 1.92) | 0.0016            | 0.078      |         | 1.15 (0.31, 1.99) | 0.0076 |
| Patient NCCN DT score     | 1.00 (0.46, 1.55) | < 0.001            | 0.002      |         | 0.58 (0.051, 1.10) | 0.032 |
| Caregiver overall health  | < 0.001           |                    | 0.17       |         |        |            |         |
| Excellent                 | 46.3 (43.1, 49.5) | 1.0 (Reference)   |            |         |        |            |         |
| Very good                 | 49.6 (47.5, 51.7) |                    | 3.87 (-0.25, 7.98) | |        |            |         |
| Good                      | 52.7 (50.3, 55.1) |                    | 7.18 (2.84, 11.51) | |        |            |         |
| Fair/Poor                 | 61.0 (52.8, 69.3) |                    | 13.44 (7.23, 19.66) | |        |            |         |
| **PSS—4 score**           |                  |                    |            |         |        |            |         |
| Caregiver age             | -0.054 (-0.097, -0.011) | 0.014           | 0.048      |         | -0.035 (-0.088, 0.018) | 0.19 |
| Caregiver Daily Activities| 0.39 (0.16, 0.62) | 0.001             | 0.084      |         | 0.23 (-0.07, 0.53) | 0.13 |
| Caregiver Other Activities| 0.33 (0.082, 0.58) | 0.001             | 0.053      |         | 0.16 (-0.14, 0.46) | 0.28 |
| Caregiver Personal Care   | 0.32 (0.087, 0.56) | 0.008             | 0.056      |         | 0.058 (-0.21, 0.33) | 0.67 |
| Patient NCCN DT Score     | 0.28 (0.093, 0.47) | 0.004             | 0.014      |         | 0.13 (-0.058, 0.31) | 0.18 |
| Caregiver Employment Status| 0.010             |                    | 0.074      |         |        |            |         |
| 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) | |        |            |         |
| Not employed              | 4.69 (4.08, 5.31) |                    | -0.29 (-1.65, 1.08) | |        |            |         |
| Caregiver overall health  |                    | 0.001             | 0.13       |         |        |            |         |
| Excellent                 | 3.58 (2.26, 4.9)  | 1.0 (Reference)   |            |         |        |            |         |
| Very good                 | 4.43 (3.72, 5.14) |                    | 0.76 (-0.66, 2.19) | |        |            |         |
| Good                      | 5.35 (4.44, 6.26) |                    | 1.66 (0.16, 3.16) | |        |            |         |
| Fair/Poor                 | 7.78 (6.16, 9.4)  |                    | 3.16 (1.01, 5.31) | |        |            |         |
| **CBI—12 score**          |                  |                    |            |         |        |            |         |
| Caregiver age             | -0.13 (-0.23, -0.02) | 0.020           | 0.043      |         | -0.11 (-0.21, -0.009) | 0.036 |
| Caregiver daily activities| 1.01 (0.45, 1.57) | < 0.001           | 0.093      |         | 0.61 (-0.11, 1.33) | 0.096 |
| Caregiver other activities| 0.98 (0.37, 1.59) | 0.002             | 0.076      |         | 0.22 (-0.49, 0.93) | 0.54 |
| Caregiver personal care   | 1.01 (0.44, 1.58) | < 0.001           | 0.091      |         | 0.48 (-0.19, 1.14) | 0.16 |
| Patient NCCN DT score     | 0.70 (0.24, 1.16) | 0.003             | 0.015      |         | 0.53 (0.088, 0.98) | 0.019 |

All multivariate p-values < 0.05 are bolded

β is the slope of the linear model for continuous variables, and mean for categorical variables. R² is the coefficient of determination

NCCN DT, National Comprehensive Cancer Network Distress Thermometer; PROMIS, Patient Reported Outcomes Measurement Information
Similarly, there was no significant correlation of caregiver distress, perceived burden, anxiety or depression with treatment intent (curative versus palliative) and if the patient was on active treatment. 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 surveyed 184 patients and 213 caregivers and reported differences in perceptions on the role of and psychological burden on caregivers (Engelbrecht et al., 2015). 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 sample of patients with pancreatic cancer and their caregivers, there was a higher proportion of caregivers than patients with elevated levels of anxiety (Janda et al., 2017). This may be secondary to unrecognized demands of not only caring for patients and addressing their personal needs such as activities of daily living, but also personal disruption that occurs with being a caregiver, caregiver health issues and navigating an increasingly complex and specialized healthcare system (Sherman et al., 2014). Our findings support this theory: caregivers with additional caregiving activities/responsibilities in addition to patient personal care and daily life activities and poorer personal health status (“Good” or “Fair/Poor” as opposed to “Excellent” or “Very Good”) demonstrated an increased likelihood of concurrent 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 (Dengso et al., 2021). 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 (Janda et al., 2017). This correlates with our finding that younger caregiver age was a predictor of concurrent greater anxiety and burden. More so than their older peers, younger caregivers may be 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 diagnosed with pancreas cancer who are less than 55 years of age, especially amongst women (+1.93%), between 2000 and 2018 (Gaddam et al., 2021). 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 (Collado & Brownell, 2019; Desai & Gyawali, 2020). Emphasizing this point, in the 2015 Pancreatic Cancer Action Network 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 (Engelbrecht et al., 2015). 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. Inherent to the nature of this observational study, we did not generate specific hypotheses prior to study execution. In addition, we found significant differences in comorbidity scores and time from diagnosis to study recruitment amongst patients who agreed and declined to the study, which may affect potential caregiver screening results. However, the differences between patients who accepted and refused study enrollment should be interpreted with caution given the sample mismatch, as only a minority of patients declined participation. There may be differences in interpretation and responses as our questionnaires contained fill-in as well as multiple choice questions. 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. Lastly, our study did not include prior patient and caregiver clinical mental health diagnoses, although our comprehensive questionnaires did encompass screening for symptoms that may be associated with unrecognized mental distress.

**Table 2 (continued)**

| System | PSS-4, Perceived Stress Scale | CBI-12, Caregiver Burden Interview |
|--------|-------------------------------|-----------------------------------|

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 diagnosed with pancreas cancer who are less than 55 years of age, especially amongst women (+1.93%), between 2000 and 2018 (Gaddam et al., 2021). 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 (Collado & Brownell, 2019; Desai & Gyawali, 2020). Emphasizing this point, in the 2015 Pancreatic Cancer Action Network 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 (Engelbrecht et al., 2015). 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.

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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” (National Comprehensive Cancer Network, 2022). Our study examined the performance of the NCCN DT in the largest population to date of patients with pancreas cancer and their caregivers. Specifically, higher NCCN DT scores were concurrently associated with four out of five validated screening measures: elevated PROMIS-Depression, PROMIS-Anxiety, and CBI-12 scores. In addition, caregiver-centered factors including the caregiver’s own health, younger age, and the extent of needed caregiving activities were more likely to be associated with psychological 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 may have an influence on cancer specific outcomes such as survival and patient compliance with multimodal therapy. A prospective Japanese cohort study demonstrated worse survival amongst men with colorectal cancer with poor social support (Ikeda et al., 2013). 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 if a complex dynamic with multiple contributors that exert physical and emotional toils.

Additional research is needed to validate the association of variables correlated to caregiver psychosocial distress and burden, including longitudinal data collection at different time points after diagnosis and treatment modalities to examine if there is a temporal association. In addition, multi-institutional cooperation and data is necessary to address at-risk patients-caregivers that may be underrepresented in our sample. 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.

Acknowledgements A thank you to the Canopy Collective; Fisher Family; as well as the Moffitt Pancreas Research Fund, supported by patients/families, who are inspirational in helping the medical community identify opportunities for more comprehensive and compassionate care.

Authors’ contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by KA, AKO, MK, BTX, and PJH. The first draft of the manuscript was written by BTX, KA and AKO, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This study was supported by the Junior Scientist Research Partnership Award through Moffitt Cancer Center.

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.

Declarations

Conflicts of interest Not applicable.

Ethics approval This study received institutional review board approval (AdvarraPro00040381).

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

Consent for publication Not applicable.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study received institutional review board approval (AdvarraPro00040381).

Informed Consent Informed consent was obtained from all individual participants included in the study.

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