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Lifetime stressor exposure and depression among patients with pancreatic cancer: insights from the Florida Pancreas Collaborative

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Abstract

Background Although depression is reported to be higher among patients with pancreatic cancer than in the general population, research on depression and stress levels in this population is limited.

Methods To address this gap, we investigated the prevalence of self-reported depression and lifetime stressor exposure in a cohort of treatment-naïve patients with pancreatic ductal adenocarcinoma (PDAC) or other types of pancreatic tumors such as pancreatic neuroendocrine tumors and intraductal papillary mucinous neoplasms who received care at one of 15 institutions participating in the multi-institutional study Florida Pancreas Collaborative. Depression severity was assessed using the Edmonton Symptom Assessment System-revised (ESAS-r) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC), and acute and chronic stressor exposure was assessed with the Stress and Adversity Inventory (STRAIN).

Results PDAC patients reported higher average depression symptom severity at the time of diagnosis and after 6 months compared to non-PDAC patients ($p=0.027$ and $p=0.063$, respectively). On the other hand, non-PDAC patients experienced a higher mean number and severity of lifetime stressors ($p=0.021$ and $p=0.039$, respectively) than PDAC patients. Across the sample, greater stressor exposure (measured by stressor count, severity, and event type) was associated with higher odds of clinically significant depressive symptoms. We also observed that chronic stressors were significantly associated with lower odds of advanced disease (OR = 0.896, $p=0.002$). Among PDAC patients who completed both STRAIN and ESAS-r ($n=52$), greater severity of acute life events was associated with a significant increase in ESAS-r depression scores between baseline and 6-month follow-up ($p=0.015$).

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Conclusions These findings highlight distinct patterns of depression and stress across pancreatic tumor types and reveal a robust association between lifetime stress exposure and depressive symptoms. Together, they underscore the need for systematic screening and integrated psychosocial support for patients with pancreatic cancer.

Keywords Depression, Pancreatic cancer, Lifetime stress, Adversity

Introduction

Cancer and mental health burden

The association between cancer and mental health is complex and dynamic, with physical and emotional challenges arising at each step of a patient's journey [1]. For cancer patients, feelings of worry, sadness, and hopelessness can arise and contribute to an increased risk for depressive symptoms compared to the general population [2]. Depression can develop due to a combination of factors, including genetic predisposition, major life events, and the stress of a cancer diagnosis. This psychological burden can, in turn, negatively impact both a patient's prognosis and overall well-being [3–6].

Pancreatic cancer and depression

Of all cancer types, pancreatic cancer is the most lethal, with a 5-year survival rate of only 13%[4]. Despite advances in detection and treatment, most patients with pancreatic cancer present at an advanced stage. Depression is one of the most common mental health conditions experienced by patients with pancreatic cancer, with prevalence estimates reported to be as high as 30 to 50%[2], a burden attributed to its poor prognosis [5, 6]. Several studies have also suggested that depression and anxiety may be prodromal symptoms, occurring before the diagnosis of pancreatic cancer. For instance, Seoud et al. (2020) analyzed depression rates among 62,450 pancreatic cancer patients from 26 major integrated health systems across the United States using the healthcare database Explorys, and found that 16.4% were diagnosed with depression in the 3 years prior to their cancer diagnosis whereas 13% of patients received a depression diagnosis after they were diagnosed with pancreatic cancer [7]. More recently, Davis et al. (2022) found that of the 14% of 856 pancreatic cancer patients diagnosed with depression, 2.5% had a depression diagnosis preceding their pancreatic cancer diagnosis, whereas 11.5% were diagnosed with depression after their pancreatic cancer diagnosis [8]. These findings demonstrate the importance of examining depression both before and after a pancreatic cancer diagnosis and underscore that psychological distress may not only be a consequence of cancer but also a potential early indicator, reinforcing the need for timely screening and intervention in this population.

Notably, pre-existing depression has been associated with worse survival rates among pancreatic cancer patients [9]. Additionally, depression and cancer can share similar symptoms, including fatigue, loss of appetite, and weight loss, potentially leading to delayed diagnosis and treatment. Indeed, patients with pre-existing mental health conditions have been shown to have higher odds of advanced stage cancer at the time of diagnosis [10]. Furthermore, patients with depression have been shown to be less likely to receive appropriate treatments, such as chemotherapy or surgical resection [8, 9].

A pancreatic cancer diagnosis also has a significant impact on physical, psychological, and social function quality-of-life domains. For example, Jia et al. [11] found that pancreatic cancer patients with depression ($n = 39/50$, or 78%) had a significantly lower quality of life in every functional scale of several validated questionnaires. This effect was greater than in patients with other cancers who also had depression ($n = 76/212$ or 35.8%), including liver, esophageal, gastric, and colorectal cancers. In a cross-sectional study, Clark et al. [12] examined 304 patients with pancreatic cancer and 7,749 patients with other cancer diagnoses. They found that 28.8% of pancreatic cancer patients reporting elevated depression after diagnosis across each subscale of the Brief Symptom Inventory and Brief Symptom Inventory-Shortened Version when compared to 18.5% of those diagnosed with other cancer diagnoses. Together, these findings suggest that depression may more negatively impact quality of life and symptom burden among patients with pancreatic cancer compared to other malignancies, exemplifying the need for targeted psychosocial support in this uniquely vulnerable population. Providing comprehensive care and support to pancreatic cancer patients is therefore crucial in maximizing their quality of life and minimizing the burden of the disease [13, 14].

Disparities in pancreatic cancer and mental health

Importantly, the burden of pancreatic cancer does not affect all patients equally. Racial and ethnic disparities in both pancreatic cancer outcomes and mental health must be considered. Non-Hispanic Black patients face higher incidence and mortality rates for pancreatic cancer than non-Hispanic White and Hispanic/Latinx patients [15, 16]. However, in the general population, non-Hispanic Black and Hispanic/Latinx individuals appear to have a lower prevalence of depression and psychiatric disorders than non-Hispanic White individuals [17, 18]. Despite these disparities, most existing studies on the topic of depression and PDAC have not explored differences by race and ethnicity [19–21]. Among cancer survivors, non-Hispanic Black and Hispanic/Latinx groups

are more likely to report poor mental health than non-Hispanic White survivors after cancer diagnosis. Specifically, Hispanic/Latinx survivors are 1.42 times (95% CI 1.30–1.55) as likely to report a diagnosis of depression relative to non-Hispanic White survivors [22]. These findings suggest that the intersection of race, ethnicity, cancer, and mental health is complex and may contribute to disparities in both diagnosis and treatment outcomes.

Role of stress and life stressors

Life stressors can also play a significant role in the development and severity of depression. Stressors are events or conditions causing psychological or physical strain, and they can be characterized as acute or chronic in nature [23, 24]. Acute stressors include immediate events like receiving a cancer diagnosis, the sudden onset of severe symptoms, or undergoing invasive procedures such as surgery or chemotherapy. Chronic stressors encompass ongoing difficulties such as prolonged treatment regimens, financial burdens, or strained personal relationships. Comprehensive tools can assess these stressors across different life domains and stages, capturing their severity, frequency, timing, and duration to better understand their impact on an individual's well-being [25, 26].

Prior research on depression in pancreatic cancer: gaps to fill

Most prior studies of pancreatic cancer and depression [19–21] have focused on patients with pancreatic ductal adenocarcinoma (PDAC), the most common malignant histologic subtype affecting > 90% of all pancreatic cancer cases [27]. Other studies have not specified the histologies evaluated [11, 12]. Only a few studies have evaluated depression among patients with other types of malignant or pre-malignant pancreatic tumors. For example, among 44 patients with pancreatic neuroendocrine tumors, 38.8% reported mild or moderate depressive symptoms after diagnosis [28]. In a study of 101 patients with intraductal papillary mucinous neoplasms, a commonly-detected pre-malignant pancreatic cyst, Pezilli and Calculli found no changes over time in Beck Depression Inventory-II scores at diagnosis and at two annual follow-up timepoints [29]. In a third study of patients with pre-malignant pancreatic cysts under surveillance, depression scores were found to be low and clinically insignificant prior to diagnosis [30].

Study rationale and objectives

To date, no prior studies of PDAC [19–21] have included individuals with other types of malignant, pre-malignant, or benign pancreatic tumors as a comparison group or examined how lifetime stressor exposure relates to depressive symptoms in this population. In the present study, we therefore investigated the prevalence of self-reported depressive symptoms and cumulative lifetime stressor exposure among patients with PDAC compared to other pancreatic tumors enrolled in a multi-institutional prospective cohort study. We also examined whether greater lifetime stressor exposure predicts higher depressive symptom severity over time. By integrating descriptive and predictive analyses, we aimed to characterize the psychological burden across pancreatic tumor types and provide insights that can guide targeted supportive care and future interventions.

Methods

Study population

Participants were those newly diagnosed with pancreatic tumors between April 2019 and September 2021 at one of fifteen institutions participating in the state-wide multi-institutional prospective longitudinal cohort study and biorepository known as the Florida Pancreas Collaborative (FPC) [31]. Eligible individuals were adults (≥ 18 years) who self-identify as non-Hispanic Black, Hispanic/Latinx, or non-Hispanic White, presented with a suspected or confirmed treatment-naïve pancreatic tumor at one of the participating sites, and were willing to provide informed consent, complete study questionnaires, and donate biospecimens and medical images obtained at the time of standard of care procedures. All diagnoses were histologically confirmed by participating institutions. To comprehensively assess participant characteristics and experiences, data collection involved the use of standardized self-administered questionnaires.

Data collection

As described in our whitepaper [31]self-administered questionnaires were employed to obtain data on demographic, epidemiologic, clinical, and social characteristics at enrollment/baseline, six months post-enrollment (follow-up 1), and 12 months post-enrollment (follow-up 2). These questionnaires ascertained information about a personal medical history of depression and included validated instruments including a revised version of the Edmonton Symptom Assessment System (ESAS-r) [32] the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ30) [33]and the Stress and Adversity Inventory (STRAIN) [34].

The ESAS-r assesses depression symptoms on a scale of 0 to 10, with higher scores indicating greater symptom burden [32]. The ESAS-r has one question about "depression (feeling sad)", which asks respondents to "select the number that best describes how you feel now." Depression severity was categorized as none-to-mild (scores from 0 to 3) and moderate-to-severe (scores from 4 to 10) [35]. The EORTC-QLQ30 assesses the health-related

quality of life of cancer patients over the past week across physical, psychological, and social dimensions [33]. Each item is scored on an ordinal scale from 1 to 4 (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). The responses to the question "did you feel depressed?" were specifically analyzed from this survey. Finally, the questionnaire also asked if the patient had ever been diagnosed with depression, anxiety, or other mental health problems. The STRAIN is a comprehensive tool that assesses an individual's exposure to acute and chronic stressors across the entire life course, considering the severity, frequency, exposure timing, and duration of stressors across different life domains [34] (see https://www.strainsetup.com). Based on a dynamic interview, the system generates numerous distinct variables reflecting an individual's exposure to both acute life events and chronic difficulties in addition to early-life stressors.

With regard to psychometric properties, the ESAS-r demonstrates a moderate correlation with concurrent psychological assessment tools and exhibits high test-retest reliability; however, its validity is variable, influenced by differences in administration format and symptom presentation [36]. The EORTC-QLQ30 demonstrates high content validity and moderate reliability [37, 38]. The STRAIN has excellent test-retest reliability, as well as strong concurrent, discriminate, and predictive validity in relation to a variety of psychological, biological, and cancer outcomes [34, 39–42].

Finally, in an effort to identify participants with depression or related mental health concerns before their pancreatic cancer diagnosis, the study questionnaire specifically asked about prior counseling for mental health conditions with the following question: "During the past 12 months, have you seen a professional provider, licensed practitioner, or therapist for your own health for counseling regarding depression, anxiety, or other issues?" Collectively, these instruments provided a multifaceted understanding of the participants' mental health, stress levels, and quality of life, with focused questions related to depression *prior to* and *after* their diagnosis of a pancreas tumor.

Statistical analysis

For purposes of analysis, participants were classified into two groups according to confirmed histology: PDAC and non-PDAC pancreatic tumors. Categorical variables were analyzed with Pearson chi-square tests and are presented as frequencies and percentages. Z-tests with Bonferroni corrections were performed for post-hoc analysis following significant chi-square tests. Continuous variables were compared using Mann-Whitney U tests, which were chosen due to non-normal distributions, and are presented as mean ± standard error of the mean. Additionally, at each timepoint, a Mann-Whitney U test was used to compare the distribution of ESAS-r depression scores between PDAC patients and non-PDAC patients. Ordinal logistic regression was used to evaluate the relationship between a patient's stressor exposure (measured using the STRAIN) and tumor stage. Ordinal logistic regression was used because the outcome variable, tumor stage, is an ordinal categorical variable. This approach enabled us to model the odds of being in a higher tumor stage as a function of stressor exposure, as measured by the STRAIN, while preserving the ordinal nature of the outcome. Correlations between stressor severity and count were analyzed with Spearman tests, which are appropriate for non-parametric data. A p-value of < 0.05 was considered statistically significant.

Statistical analyses were performed using SPSS v28 (IBM Corp., Armonk, NY) for most analyses, whereas R (R Core Team, 2024, Vienna, Austria) was specifically used for the Cochrane-Armitage trend test, which is not directly available in SPSS.

Results

Study population characteristics

A total of 500 participants enrolled in the FPC study, consisting of 318 (63.6%) PDAC cases and 182 non-PDAC cases. The non-PDAC cases primarily comprised patients with pancreatic neuroendocrine tumors ($n = 58$; 11.6%) and pre-malignant precursor lesions including intraductal papillary mucinous neoplasms ($n = 52$; 10.4%) and mucinous cystic neoplasm ($n = 8$; 1.6%). The remaining non-PDAC cases had other less common histologies. Select characteristics of the study cohort are presented in Table 1. Compared to non-PDAC cases, PDAC cases were significantly older at the time of diagnosis ($p = 0.006$). No significant associations were found between PDAC diagnosis and patient biological sex ($p = 0.736$), race ($p = 0.334$), marital status ($p = 0.272$), income ($p = 0.162$), or education ($p = 0.241$).

Evaluation of depression burden by diagnosis

Approximately 95% of PDAC cases (303 of 318) and 92% of non-PDAC cases (167 of 182) completed the ESAS-r survey in the health screen at baseline, with the number of respondents decreasing slightly at each of the two follow-up timepoints (Table 2; Fig. 1). At the 6-month follow-up time-point (follow-up 1), 100 PDAC and 54 non-PDAC patients completed the survey. By the 12-month follow-up time-point (follow-up 2), a similar modest decline in survey completion was observed, with 54 PDAC and 42 non-PDAC respondents. Overall, 21.5% of PDAC patients reported moderate-to-severe depressive symptoms on the ESAS-r survey (a score of 4–10) at baseline compared to only 13.18% of non-PDAC patients ($p = 0.027$). Additionally, symptoms did not vary by racial or ethnic group. At baseline, 11.8% of non-Hispanic Black

Table 1 Select demographic and socioeconomic characteristics of the Florida Pancreas Collaborative study cohort

Variable	PDAC (*n* = 318)	Non-PDAC (*n* = 182)	Total (*N* = 500)	*p*-value
Age (*n*, %)				
< 50	13 (4.09%)	20 (10.99%)	33 (6.6%)	0.006
50–59	37 (11.64%)	23 (12.64%)	60 (12.0%)	
60–69	92 (28.93%)	61 (33.52%)	153 (30.6%)	
70–79	133 (41.82%)	65 (35.71%)	198 (39.6%)	
> 79	43 (13.52%)	13 (7.14%)	56 (11.2%)	
Mean ± SEM	69.56 ± 0.55	65.62 ± 0.86	68.13 ± 0.48	< 0.001
Gender (n, %)				
Female	161 (50.63%)	95 (52.20%)	256 (51.2%)	0.736
Male	157 (49.37%)	87 (47.80%)	244 (48.8%)	
Race (n, %)				
Non-Hispanic White	236 (74.21%)	124 (68.13%)	360 (72.0%)	0.334
Hispanic/Latinx	47 (14.78%)	32 (17.58%)	79 (15.8%)	
Non-Hispanic Black	35 (11.01%)	26 (14.29%)	61 (12.2%)	
Marital Status (n, %)				
Married	135 (70.68%)	85 (64.89%)	220 (68.3%)	0.272
Not Married	56 (29.32%)	46 (35.11%)	102 (31.7%)	
Income Level (n, %)				
< 40 K	55 (28.50%)	27 (20.93%)	82 (25.5%)	0.162
40 K-<80 K	47 24.35%)	30 (23.26%)	77 (23.9%)	
80 K-<100 K	15 (7.77%)	14 (10.85%)	29 (9.0%)	
100 K-<150 K	17 (8.81%)	19 (14.73%)	36 (11.2%)	
150 K-<200 K	10 (5.18%)	10 (7.75%)	20 (9.3%)	
> 200 K	6 (3.11%)	7 (5.43%)	13 (4.0%)	
Prefer not to answer	38 (19.69%)	22 (17.05%)	60 (18.6%)	
Unknown	5 (2.59%)	0	5 (1.6%)	
Education (n, %)				
Some high school or less than high school	18 (9.28%)	3 (2.27%)	21 (6.4%)	0.241
Completed high school or GED equivalent	39 (20.10%)	24 (18.18%)	63 (19.3%)	
Technical or trade school	18 (9.28%)	13 (9.85%)	31 (9.5%)	
2-year college	40 (20.62%)	24 (18.18%)	64 (19.6%)	
4-year college or university	34 (17.53%)	34 (25.76%)	68 (20.9%)	
Graduate or professional school	42 (21.65%)	30 (22.73%)	72 (22.1%)	
Attended school outside the USA	3 (1.55%)	4 (3.03%)	7 (2.1%)	

Some variables do not add to the total due to missing values

patients reported moderate to severe depressive symptoms, compared to 17.2% of Hispanic/Latinx patients and 19.9% of non-Hispanic White patients ($p = 0.596$). Similarly, at follow-up 1, 22.2% of non-Hispanic Black patients, 22.8% of Hispanic/Latinx patients, and 15% of non-Hispanic White patients reported moderate to severe depressive symptoms ($p = 0.535$). Compared to non-PDAC cases, PDAC cases also had marginally greater depression severity at the 6-month follow-up timepoint ($p = 0.063$).

A total of 305 patients (181 PDAC and 124 non-PDAC cases) completed the EORTC depression rating survey at baseline (Table 3; Fig. 2A and B). Both PDAC and non-PDAC patients reported similar rates of depression at the baseline timepoint, whereas depression rates were slightly higher for the PDAC cases (50.7%) than non-PDAC cases (42.3%) at the follow-up 1 timepoint ($p = 0.090$).

Finally, when specifically asked in the baseline study questionnaire if they had ever been diagnosed with depression, anxiety, or another mental health problem *prior* to their current diagnosis of a pancreatic tumor, only 25 (7.9%) PDAC patients and 20 (10.9%) non-PDAC patients answered affirmatively.

Evaluation of life events and stressors by diagnosis

A subset of 94 PDAC patients and 81 non-PDAC patients completed the STRAIN at baseline (Table 4; Fig. 3). There was a relatively similar distribution of demographic and socioeconomic characteristics among this subset of patients compared to the entire cohort, although non-Hispanic Black and Hispanic/Latinx patients were underrepresented, limiting generalizability (Supplementary Table 1). Data from the STRAIN revealed that compared to PDAC patients, non-PDAC patients experienced a higher mean number of total lifetime stressors ($p = 0.021$). PDAC patients also experienced a greater severity of total lifetime stressors ($p = 0.039$). The number of both acute life events and chronic difficulties was also higher among non-PDAC patients, with statistically significant differences evident for chronic difficulties ($p = 0.003$; see Table 4). Additionally, the severity of both acute life events and chronic difficulties were also higher among non-PDAC patients. There was a notable positive correlation between the severity and count of stressors, suggesting that as patients report a higher number of stressors, they also rated the severity of each stressor higher (Table 5). Notably, a significantly higher percentage of non-PDAC cases than PDAC cases (13.7% versus 5.5%) reported using mental health counseling services prior to being diagnosed with a pancreatic tumor ($p = 0.011$).

Of the 54 PDAC patients who completed both STRAIN and ESAS-r, we found that greater severity of acute life events was associated with a significant increase in

Table 2 ESAS-r frequency and severity of depression symptoms, by diagnosis

	Baseline		Follow Up 1		Follow Up 2	
Frequency Collective Percentage	**PDAC**	**Non-PDAC**	**PDAC**	**Non-PDAC**	**PDAC**	**Non-PDAC**
Total (*n*)	303	167	100	54	54	42
0–3 (None to mild depressive symptoms) (n, %)	238 (78.55%)	145 (86.82%)	79 (79%)	49 (90.74%)	46 (85.19%)	38 (90.48%)
4–10 (Moderate to severe depressive symptoms) (n, %)	65 (21.45%)	22 (13.18%)	21 (21%)	5 (9.26%)	8 (14.81%)	4 (9.52%)
p-value	0.027		0.063		0.437	

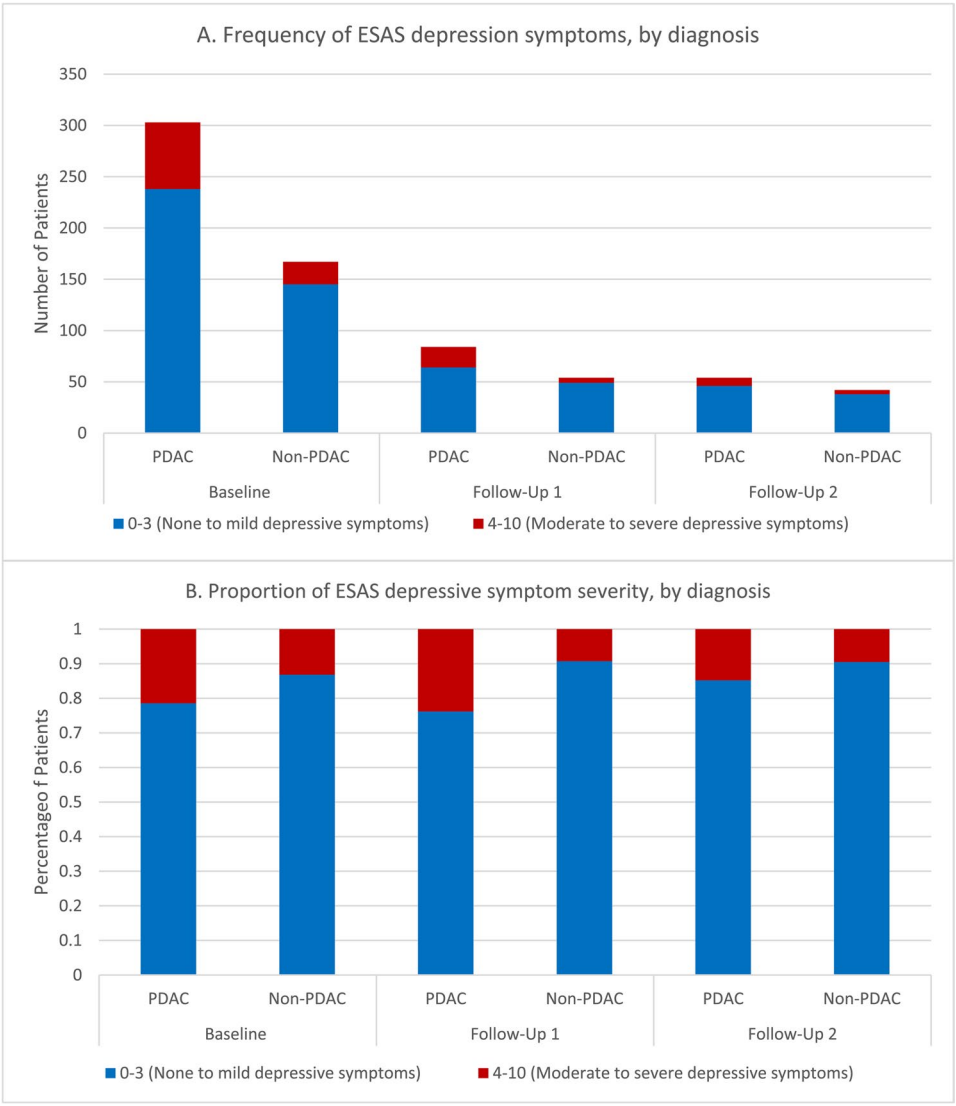

Fig. 1 Frequency and proportion of ESAS-r depression symptoms, by diagnosis

ESAS-r depression scores between baseline and follow-up 1 ($p = 0.015$) (Table 6). Total count and severity of lifetime stressors—as well as count of acute life events—exhibited a similar but not- statistically significant association with ESAS-r scores between baseline and follow-up 1 ($p = 0.464$). These findings suggest that recent acute stressors may exacerbate depressive symptoms in patients with PDAC, demonstrating the need for timely psychosocial assessment and support in the clinical setting.

An ordinal logistic regression was performed to examine the association between different facets of lifetime stressor exposure (assessed using the STRAIN) and tumor stage (Table 7). Patients with higher overall stressor

Table 3 Frequency of depression symptoms in Florida Pancreas Collaborative patients using the EORTC questionnaire, by diagnosis

"Did you feel depressed" (*n*, %)	PDAC (181)	Non-PDAC (124)	Total (305)
Baseline			
No	97 (53.6%)	51 (58.9%)	170 (55.7%)
A little	66 (36.5%)	41 (33.1%)	107 (35.1%)
Quite a bit	12 (6.6%)	8 (6.5%)	20 (6.6%)
Very much	6 (3.3%)	2 (1.6%)	8 (2.6%)
p-value	0.699		
Follow-Up 1			
	PDAC (71)	Non-PDAC (71)	Total (142)
No	35 (49.3%)	41 (57.7%)	76 (53.5%)
A little	28 (39.4%)	29 (40.8%)	57 (40.1%)
Quite a bit	5 (7.0%)	0	5 (3.5%)
Very much	3 (4.2%)	1 (1.4%)	4 (2.8%)
p-value	0.090		
Follow-Up 2			
	PDAC (9)	Non-PDAC (21)	Total (30)
No	5 (55.6%)	11 (52.4%)	16 (53.3%)
A little	3 (33.3%)	6 (28.6%)	9 (30.0%)
Quite a bit	0	3 (14.3%)	3 (10.0%)
Very much	1 (11.1%)	1 (4.8%)	2 (6.7%)
p-value	0.631		

Quality of Life Questionnaire

EORTC European Organization for Research and Treatment of Cancer

exposure, whether indexed by total stressor count, severity, or the number of acute and chronic events, tended to have lower odds of being diagnosed with a more advanced tumor stage. Among the specific domains, chronic difficulties (both count and severity) showed the strongest and most consistent associations with tumor stage. Higher total stressor count was significantly associated with lower odds of being diagnosed with a more advanced tumor stage ($OR = 0.949$, $p = 0.002$). Similarly, higher total lifetime stressor severity was also associated with reduced odds of advanced tumor stage ($OR = 0.984$, $p = 0.015$). Total count of acute life events and chronic difficulties count were both significantly associated with lower odds of more advanced tumor stage ($OR = 0.934$, $p = 0.007$; OR = 0.896, $p = 0.002$; respectively). However, the severity of acute life events was not significantly associated with tumor stage ($OR = 0.982$, $p = 0.136$). Chronic difficulties severity, on the other hand, was significantly associated with lower odds of advanced tumor stage ($OR = 0.967$, $p = 0.003$). Figure 4 shows the distribution of the total lifetime count and severity of stressors by tumor stage.

Discussion

The objective of this study was to examine the prevalence of self-reported depressive symptoms and lifetime stressor exposure among patients with PDAC and to investigate how stressor exposure predicts depressive symptom severity and relates to clinical and demographic factors. This study is the first to compare these measures among patients with PDAC and other types of pancreatic tumors over time. Through our data analysis, we found that PDAC patients had greater depression severity at diagnosis and afterward than those with other pancreatic tumors. This finding suggests that the unique biological, prognostic, and treatment-related aspects of PDAC may place patients at heightened psychological risk compared to individuals with other tumor types. The particularly aggressive nature of PDAC, coupled with its limited therapeutic options and rapid disease trajectory, may exacerbate depressive symptoms. These results are consistent with Ji et al., who found that major depressive disorder occurred in 51.8% of 114 PDAC patients over 6 months after diagnosis [43]. One proposed explanation for this finding is the prevalence of abdominal pain. Abdominal pain, secondary to perineural invasion, presents in about 60% of PDAC patients, developing in nearly all patients as the disease progresses [44]. This pain can be debilitating and challenging to manage, and prior studies have shown that it, along with related symptoms such as nausea and fatigue, can negatively influence psychological well-being in PDAC patients [44, 45].

The prognosis, severity, and rapid progression of PDAC relative to pancreatic neuroendocrine tumors and intraductal papillary mucinous neoplasms may also contribute to these differences in depression frequency. For instance, the ESAS-r scale in our sample indicated PDAC patients reported moderate to severe depressive symptoms at a similar rate between the baseline (21.4%) and first follow-up (21%) questionnaires, whereas non-PDAC patients reported a decrease in moderate-to-severe depressive symptoms between baseline (13.2%) and follow-up 1 (9.3%). PDAC patients typically require intensive interventions such as surgery, chemotherapy, and radiation, whereas non-PDAC patients often do not require these aggressive treatments [46]. Treatment-related complications and toxicities are known to impact patient well-being and may contribute to increased stress and depression symptoms in PDAC patients [47]. These differences highlight that tumor type and disease trajectory may play a crucial role in the persistence or resolution of depressive symptoms, emphasizing the need for

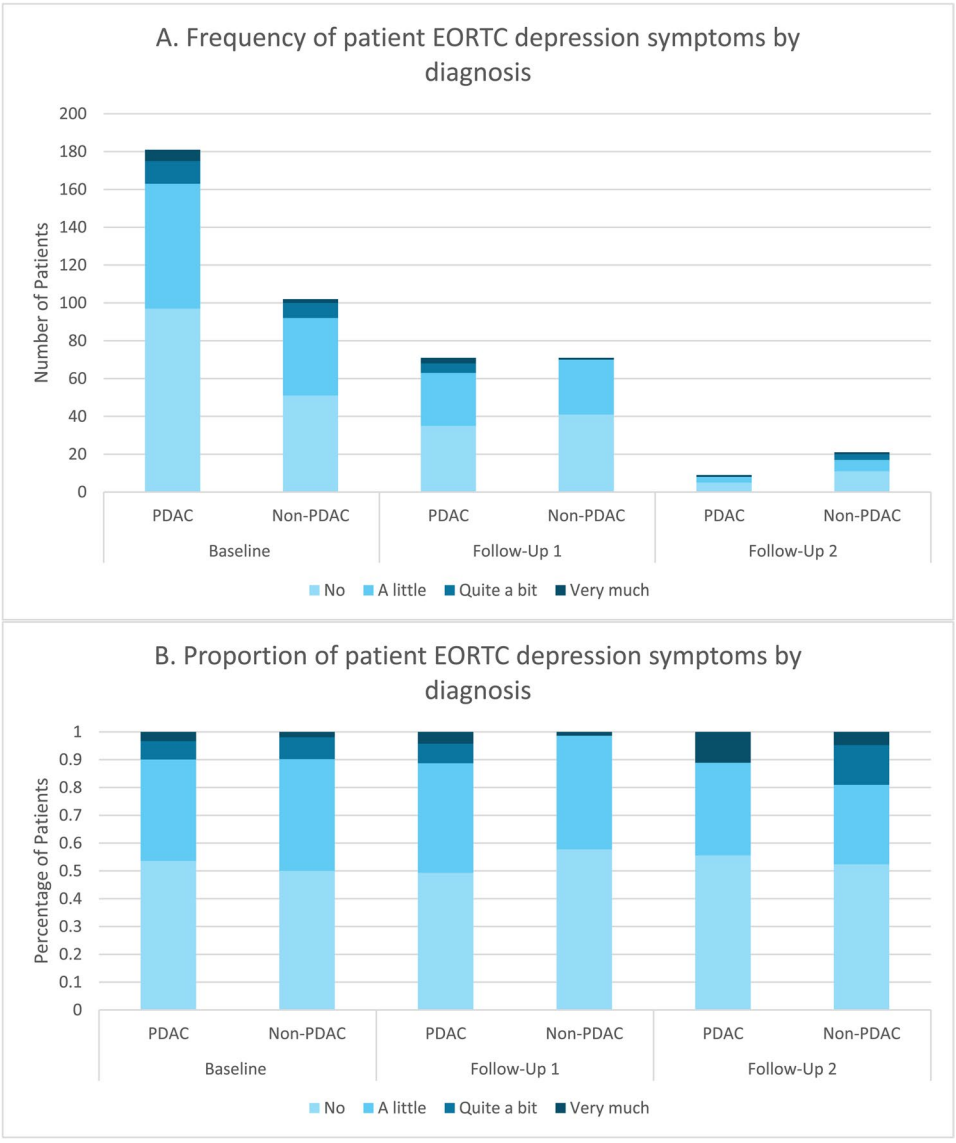

Fig. 2 Frequency and proportion of depression symptoms among Florida Pancreas Collaborative patients using EORTC, by diagnosis

continuous monitoring and tailored psychosocial interventions, particularly for patients facing more aggressive disease.

We also assessed participants' lifetime stressor exposure using the STRAIN, which quantified both the number and severity of stressors experienced by patients over the lifetime, given prior evidence that greater stressor exposure is related to greater depression severity [40]. To our surprise, we found that PDAC patients reported an average of 4 fewer total stressors than non-PDAC patients and rated their stressors as 18.52% less severe on average than non-PDAC patients. In our analysis of the association between stressor exposure and tumor stage, we employed ordinal logistic regression to explore how total stressor count and various dimensions of stress (including severity and specific types of stressors) relate to tumor progression. Across multiple models, we observed a trend suggesting that higher exposure to stressors was associated with a less advanced tumor stage. This counterintuitive finding may reflect survival bias, as patients with later-stage tumors and higher stressor exposure could have been less likely to survive or participate in the study, potentially leading to an underrepresentation of high-stress, advanced-stage cases in our sample. In addition, psychosocial factors such as more robust coping strategies or stronger social support networks among long-term survivors could contribute to lower reported stressor exposure [48]. These alternative explanations highlight the need for further research to clarify how psychological stress interacts with pancreatic cancer progression.

Table 4 Stress and adversity inventory multivariate analysis, by diagnosis

		Total Count of Lifetime Stressors ($p=0.021$*)	Total Severity of Lifetime Stressors ($p=0.039$*)	Count of Acute Life Events ($p=0.111$*)	Count of Chronic Difficulties ($p=0.003$*)	Severity of Acute Life Events ($p=0.142$*)	Severity of Chronic Difficulties ($p=0.017$*)
PDAC ($n=94$)	Mean	19.64	42.94	13.76	5.88	25.27	17.67
	Median	17.00	38.50	12.00	4.00	23.00	14.00
	Std. Error of Mean	1.20	2.76	0.77	0.53	1.38	1.59
	Std. Deviation	11.67	26.73	7.46	5.14	13.38	15.39
Non-PDAC ($n=81$)	Mean	23.51	51.47	15.33	8.17	28.20	23.27
	Median	22.00	48.00	15.00	7.00	25.00	20.00
	Std. Error of Mean	1.36	3.33	0.84	0.64	1.60	1.94
	Std. Deviation	12.27	29.95	7.52	5.72	14.37	17.45
Total ($n=175$)	Mean	21.43	46.89	14.49	6.94	26.62	20.26
	Median	20.00	41.00	14.00	6.00	25.00	16.00
	Std. Error of Mean	0.913	2.15	0.57	0.48	1.05	1.25
	Std. Deviation	12.07	28.51	7.51	5.52	13.88	16.56

p-values were calculated using a Mann-Whitney U test to compare the distribution of the STRAIN responses between PDAC and Non-PDAC patients

Taken together, these findings suggest that the association between stressor exposure and tumor stage is complex and may reflect both biological and psychosocial processes. Clinically, understanding how stress and coping interact with disease progression could help identify patients at higher risk for adverse outcomes and guide interventions aimed at stress reduction and psychosocial support to potentially improve quality of life and overall prognosis. Additionally, the correlation between severity and count of stressors was significant and positive, indicating that when patients reported experiencing more lifetime stressors, they reported those stressors as being more severe. This suggests that a higher burden of stress not only increases the frequency of adverse life events but may also amplify the perceived intensity or impact of each stressor, which could have further implications for understanding cumulative stress exposure and its potential influence on psychological and physical health outcomes.

The significant association we found between lifetime severity of acute life events and ESAS-r depression scores suggests a potential association between psychosocial stressor exposure and depressive symptoms in PDAC patients. This finding is consistent with prior studies that highlighted the impact of psychosocial factors on mental health outcomes in cancer patients [42, 49–51]. The non-significant relations with total count and severity of stressors, as well as count of acute life events, could be attributed to true differences in stress-depression associations but we cannot rule out other possibilities, such as sample size limitations or other unmeasured variables that may influence these effects. Importantly, these results can guide future research by highlighting the need for larger cohorts and more detailed assessment of stressor characteristics. They also suggest that screening strategies should continue to consider both acute and chronic stressors when evaluating psychosocial risk for patients with pancreatic cancer. Additionally, the decreased odds of patients reporting a higher count and severity of stressors and having an advanced tumor stage suggest a potential inverse relationship between stress exposure and tumor progression. This finding is consistent with the idea that patients with more advanced cancer stages may not be present in our sample due to survival bias, possibly leading to a lower observed stress burden in advanced stages.

Above all, our findings suggest that the association between lifetime stressor exposure and the presence of depressive symptoms among pancreatic cancer patients may be specific to particular stressor types and patient groups. This highlights the importance of systematic screening for stressor exposure in cancer populations to evaluate depression. The news of a cancer diagnosis and poor prognosis may also play a role in the development of depressive symptoms. Notably, the non-PDAC patients in our study also reported utilizing mental health counseling prior to diagnosis at higher rates than pancreatic cancer patients, which may correspond with the greater frequency and severity of stressors reported by these patients. This pattern could indicate that individuals with non-PDAC tumors had a pre-existing vulnerability or ongoing psychosocial burden that prompted them to seek professional support even before their cancer diagnosis. The greater reliance on counseling may reflect heightened awareness of mental health needs or better access to resources, but it may also suggest that cumulative life stressors in this group created a sustained demand for psychological care. Differences in access to or utilization of mental health services could influence both the prevalence and severity of depression, indicating the importance of integrating psychosocial support into cancer care.

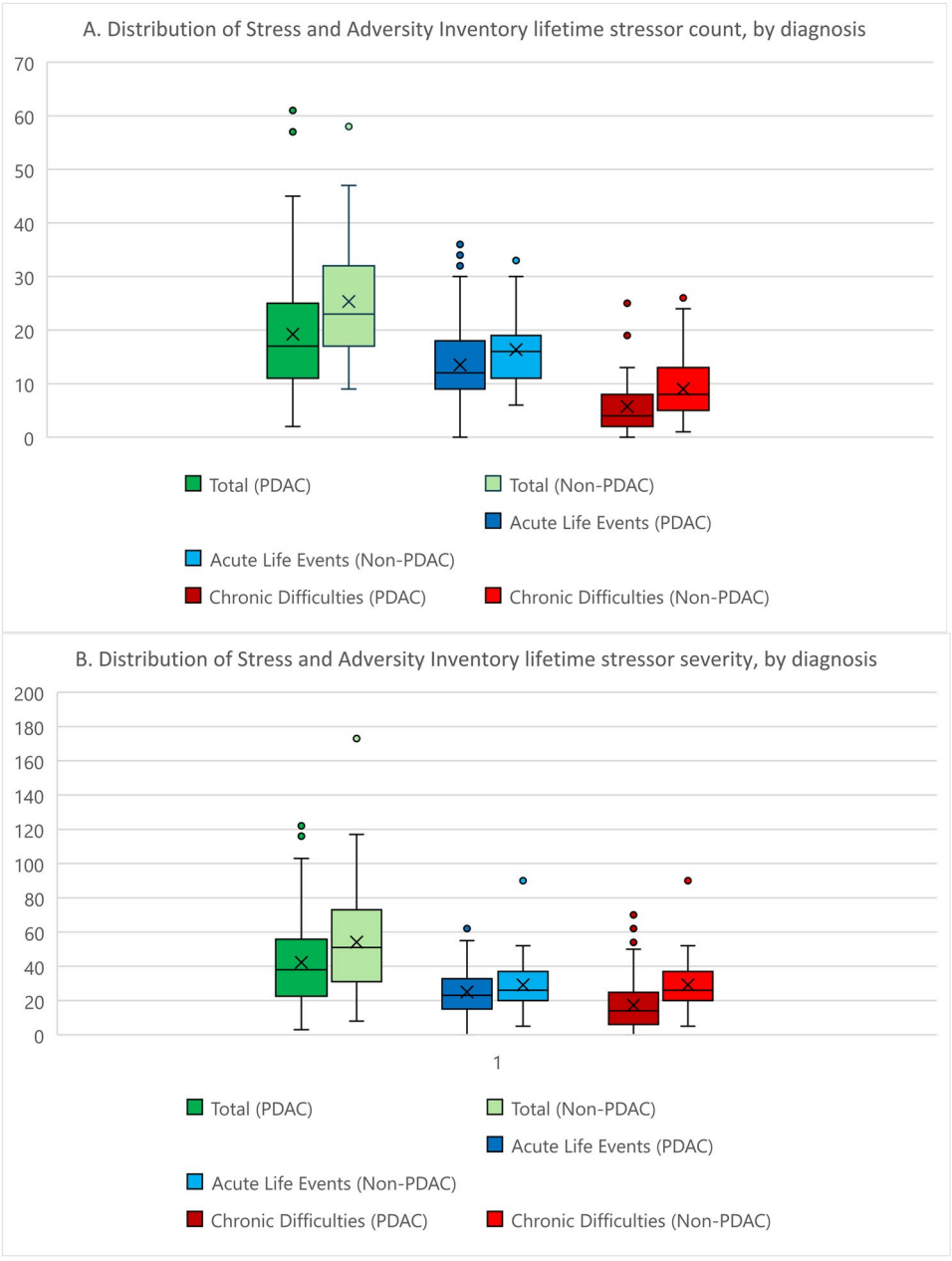

Fig. 3 Distribution of stress and adversity inventory lifetime stressor count and severity, by diagnosis

Implications

The results of this study further advance existing research highlighting a complex association between PDAC, depression, and stressor exposure. This information can significantly impact the quality of life for pancreatic cancer patients by ensuring they receive comprehensive support that addresses all aspects of their disease tailored to the specific psychosocial patterns identified. For example, patients exhibiting high lifetime stressor exposure and depressive symptoms may benefit from individual counseling to address personal coping strategies, while support groups and online communities can help mitigate social isolation and provide peer support [52]. Telephone and email helplines offer timely assistance for patients experiencing acute stress, and cancer-specific resources for patients and families can help address stress related to disease management and treatment planning [52]. Screening depression and stress levels in pancreatic cancer patients allows providers and case managers to connect patients to these resources early, potentially mitigating the aggravation of depression and physical symptoms.

Table 5 Correlation between the lifetime count and severity of stressors among patients with PDAC

		PDAC Diagnosis	Total Count of Lifetime Stressors	Total Severity of Lifetime Stressors	Count of Acute Life Events	Count of Chronic Difficulties	Severity of Acute Life Events	Severity of Chronic Difficulties
PDAC Diagnosis	Correlation Coefficient	1.000	−0.175*	−0.157*	−0.121	−0.228**	−0.111	−0.181*
	Sig. (2-tailed)	--	0.021	0.038	0.111	0.002	0.143	0.017
	N	500	175	175	175	175	175	175
Total Count of Stressors	Correlation Coefficient	−0.175*	1.000	0.853**	0.934**	0.862**	0.756**	0.818**
	Sig. (2-tailed)	0.021	--	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
	N	175	175	175	175	175	175	175
Total Severity of Stressors	Correlation Coefficient	−0.157*	0.853**	1.000	0.728**	0.836**	0.911**	0.925**
	Sig. (2-tailed)	0.038	< 0.001	--	< 0.001	< 0.001	< 0.001	< 0.001
	N	175	175	175	175	175	175	175
Count of Acute Life Events	Correlation Coefficient	−0.121	0.934**	0.728**	1.000	0.638**	0.738**	0.621**
	Sig. (2-tailed)	0.111	< 0.001	< 0.001	--	< 0.001	< 0.001	< 0.001
	N	175	175	175	175	175	175	175
Count of Chronic Difficulties	Correlation Coefficient	−0.228**	0.862**	0.836**	0.638**	1.000	0.614**	0.924**
	Sig. (2-tailed)	0.002	< 0.001	< 0.001	< 0.001	--	< 0.001	< 0.001
	N	175	175	175	175	175	175	175
Severity of Acute Life Events	Correlation Coefficient	−0.111	0.756**	0.911**	0.738**	0.614**	1.000	0.699**
	Sig. (2-tailed)	0.143	< 0.001	< 0.001	< 0.001	< 0.001	--	< 0.001
	N	175	175	175	175	175	175	175
Severity of Chronic Life Events	Correlation Coefficient	−0.181*	0.818**	0.925**	0.621**	0.924**	0.699**	1.000
	Sig. (2-tailed)	0.017	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	--
	N	175	175	175	175	175	175	175

*Correlation is significant at the 0.05 level (2-tailed)

**Correlation is significant at the 0.01 level (2-tailed)

Table 6 Trend analysis of STRAIN and ESAS-r depression changes from baseline to follow-up in PDAC patients

STRAIN Variables	Statistic	*P*-value
Total Count of Lifetime Stressors	0.5350859	0.464
Total Severity of Lifetime Stressors	0.5350859	0.464
Count of Acute Life Events	0.8124233	0.367
Severity of Acute Life Events	5.9466462	0.0147

Table 7 Association between stressor factors and tumor stage odds ratios

Variable	Estimate (B)	Standard Error	t value	Odds Ratio (OR)	*p* value
Total Lifetime Stressor Count	−0.052	0.017	−3.133	0.949	0.0017
Total Lifetime Stressor Severity	−0.016	0.006	−2.444	0.984	0.0145
Acute Life Events Count	−0.068	0.025	−2.694	0.934	0.0071
Chronic Difficulties Count	−0.110	0.035	−3.159	0.896	0.0016
Acute Life Events Severity	−0.018	0.012	−1.492	0.982	0.1357
Chronic Difficulties Severity	−0.034	0.012	−2.946	0.967	0.0032

Strengths and limitations

This study has several strengths, including a well-characterized sample, use of a state-of-the-art system for assessing lifetime stressor exposure, and longitudinal assessment of patients. Similar to other studies, one limitation of ours is that a majority (72%) of patients identified as non-Hispanic White, resulting in a lack of representation for underserved populations [7, 8, 12]. This underrepresentation may limit the generalizability of our findings and could lead to bias if stress–depression associations differ by race, ethnicity, or other sociodemographic factors. A second limitation of our study was that survey participation was lower at the follow-up visits, limiting data availability for longitudinal analyses; this can be attributed, in part, to some patients passing away during the study duration. Future studies could address this issue by implementing more structured follow-up protocols, using multiple modes of contact, or incorporating proxy reporting from caregivers to ensure more complete longitudinal data. In addition, as with all self-administered study questionnaires, implicit reporting biases or unanticipated communication barriers from question design or method of questionnaire administration could have influenced the results [53]. Finally, given the study design, causality and directionally of effects cannot be assumed.

Conclusions

In conclusion, this study is among the first to integrate both depressive symptoms and lifetime stressor exposure in patients with pancreatic tumors, offering new

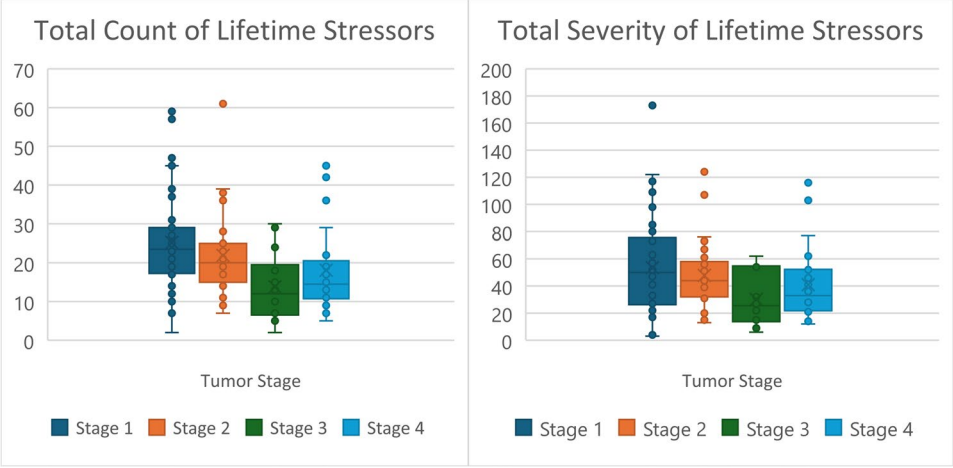

Fig. 4 Distribution of the total count and total severity of lifetime stressors by tumor stage

insights into the psychological burden faced by this population. By demonstrating that PDAC patients experience greater depression severity after diagnosis compared to those with non-PDAC tumors, our findings highlight a subgroup at elevated risk for persistent psychological distress. At the same time, the higher rates of counseling utilization and stressor exposure among non-PDAC patients demonstrate the heterogeneity of psychosocial needs across tumor types. These distinctions suggest that a uniform approach to psychosocial care may be insufficient. Instead, tailored interventions that account for both tumor biology and individual psychosocial histories may better address patient well-being. With a better understanding of the prevalence of depression among patients with pancreatic tumors of different etiologies, support systems and management of emotional symptoms can be implemented to improve the quality of life of pancreatic cancer patients. By mitigating the aggravation of depressive symptoms associated with the diagnosis, such systems may also result in improved survival. Future studies should evaluate how integrating systematic stressor assessments with symptom screening can inform early, targeted psychosocial support strategies in the clinical setting.

Abbreviations

ESAS-r	revised Edmonton Symptom Assessment System
EORTC	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
STRAIN	stress and adversity inventory
PDAC	pancreatic ductal adenocarcinoma
FPC	Florida Pancreas Collaborative

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
AD: Conceptualization, Data curation, Analysis, Methodology, Writing, original draft; SM: Data curation, Analysis, Methodology, Writing, original draft; RM: Writing, original draft; MAP: Conceptualization, Data curation, Analysis, Writing, original draft; GSS: Analysis, Methodology, Writing; GMS: Writing, original draft; JBP: Conceptualization, Funding Acquisition, Data curation, Methodology, Writing, original draft; Review and editing of final draft, all authors.

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Data availability
The datasets presented in this article are not publicly available because de-identified data may be shared only after requirements are met by the Florida Pancreas Collaborative Data Sharing Committee. Reasonable requests to access datasets should be directed to the corresponding author.

Declarations

Ethics approval and consent to participate
In accordance with the Declaration of Helsinki, informed consent was obtained from all participants and approved by the Institutional Review Board at Advarra, Inc (protocol MCC 19717/IRB Pro00029598 version 1.4, approved February 12, 2019).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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