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The Impact of Pre-Existing Psychiatric Disorders on Outcomes After Pancreatic Cancer Surgery

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Abstract

Objectives: Comorbid psychiatric illness has been associated with worse outcomes following some major surgical procedures. We hypothesized that patients with pre-existing mood disorders would have worse postoperative and oncologic outcomes after pancreatic cancer resection.

Methods: This retrospective cohort study analyzed Surveillance, Epidemiology, & End Results patients with resectable pancreatic adenocarcinoma. A pre-existing mood disorder was classified if a patient was diagnosed and/or treated with medication approved for depression/anxiety within 6 months before surgery.

Results: Of 1305 patients, 16% had a pre-existing mood disorder. Mood disorders had no impact on hospital length of stay (12.9 vs 13.2 days, $P = 0.75$), 30-day complications (26% vs 22%, $P = 0.31$), 30-day readmissions (26% vs 21%, $P = 0.1$), or mortality (30 days: 3% vs 4%, $P = 0.35$); only an increased 90-day readmissions rate (42% vs 31%, $P = 0.001$) was observed. No effect on adjuvant chemotherapy receipt (62.5% vs 69.2%, $P = 0.06$) or survival (24-months, 43% vs 39%, $P = 0.44$) was observed.

Conclusions: Pre-existing mood disorders influenced 90-day readmissions after pancreatic resection, but not other postoperative or oncologic outcomes. These findings suggest that affected patients should be expected to have outcomes similar to patients without mood disorders.

Keywords

pancreatic cancer; depression; anxiety; complications; survival

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Introduction

For patients with early-stage pancreatic cancer, surgery offers the best chance for cure. However, these complex operations have substantial postoperative morbidity and mortality, requiring careful and accurate prediction of each patient's perioperative risk.[1,2] Depression and its related disorders have the potential to negatively impact postoperative recovery through decreased engagement and participation.[3] Feelings of hopelessness and apathy associated with a poor prognosis are especially applicable to pancreatic cancer patients. A recent study demonstrated that patients with cancers known to have a poor prognosis have a 3.5-fold increase in suicide mortality risk compared to the general population, which underscores the importance of recognizing comorbid depression or anxiety in pancreatic cancer patients.[4] Furthermore, depression has been linked with increased complications, hospital length of stay, 30-day readmissions, and mortality among surgical patients.[5–8]

According to the National Institute of Health, depression and anxiety affect 10–20% of all US adults and these disorders often occur concurrently.[9–11] Despite their prevalence, no clinical risk prediction tools include these disorders as patient-related risk factors. Pancreatic cancer patients specifically are known to develop symptoms of anxiety and depressive symptoms prior to their cancer diagnosis and have been shown to have higher rates of these disorders than the general population[12–14] Furthermore, a pre-existing diagnosis of depression has been shown as an independent predictor of worse overall survival in a study of pancreatic cancer at all stages, likely related to decision-making around the receipt of systemic therapy.[15] While pre-existing depression has been studied in pancreatic cancer as a whole, there is limited data on the impact of depression or anxiety on postoperative outcomes for patients with early-stage disease. Of all potential psychiatric disorders, we sought to focus on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) classification of mood disorders, which consists of depression and anxiety-related disorders rather than psychoses, substance use disorders, or personality disorders.[16] Mood disorders were chosen given their high prevalence in the United States and prior recognition of their potentially negative impact on active participation in recommended medical care, including perioperative treatments and systemic adjuvant therapies. The objective of this study was to determine whether pre-existing mood disorders influence postoperative outcomes or survival for patients undergoing pancreatic resection. We hypothesized that mood disorders would be associated with worse postoperative and oncologic outcomes after pancreatic cancer resection.

MATERIALS AND METHODS

We performed a retrospective cohort analysis of patients diagnosed with resectable pancreatic adenocarcinoma from the Surveillance, Epidemiology, and End Results (SEER) database merged with Medicare data from January 1, 2009, to December 31, 2013. The SEER program is sponsored by the National Cancer Institute and collects information regarding demographic characteristics, site and extent of disease, clinical and pathological stage, and date and cause of death. Medicare is the primary health insurer for 97% of the US population aged 65 and older and covers inpatient hospital care (Part A), outpatient care (Part B), and prescription drug coverage (Part D).[17] This research protocol was approved

by the institutional review board of the University of California Davis with a waiver of consent granted for the use of deidentified data. This study followed the Reporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines.[18]

Study Population

A total of 1305 patients with stage I or II pancreatic adenocarcinoma underwent pancreatic resection, had with complete Medicare A/B/D coverage, and were diagnosed between January 1, 2009, to December 31, 2013. Diagnosis was based on the *International Classification of Diseases (ICD) for Oncology, Third Revision* codes for site (C250–259) and histology (8000, 8010, 8020, 8050, 8140, 8141, 8144, 8210, 8211, 8255, 8260, 8261, 8262, 8263, 8490, 8500, and 8560).[19] Pancreatic resection included pancreaticoduodenectomy, distal, total, and other pancreatectomy based on *ICD, Ninth Edition (ICD-9)* procedure codes (525, 5251, 5252, 5253, 5259, 526, and 527).[20] Continuous Medicare A/B/D coverage was required at least 6 months prior to the admission date and 1 month after the discharge date for the index surgical hospitalization.

Patient demographic, clinicopathologic and treatment characteristics were abstracted from SEER, including patient age, sex, race, tumor grade, T and N staging, composite American Joint Committee on Cancer stage (sixth and seventh editions), and chemotherapy.[21,22] Chemotherapy was considered neoadjuvant if received within 6 months prior to surgery and adjuvant if received within 6 months after surgery. The Elixhauser comorbidity index was used to measure risk associated with comorbid health conditions and created using *ICD-9* codes. This validated method for creating a weighted index score to represent the severity of comorbidity burden ranges from −11 to 62, with higher scores indicating greater comorbidities.[23–26]

Patients were designated as having a pre-existing mood disorder if they had a diagnosis of a depressive or anxiety disorder or were prescribed any medication used for the treatment of depressive or anxiety disorders within 6 months before their surgery date. Mood disorder diagnoses were classified according to the DSM-IV guidelines that were representative of the study period and were captured with *ICD-9* diagnostic codes for depression (293, 296, 298, 301, and 311) and anxiety (300, 308, 309). Prescription drugs with Food and Drug Administration-approved indications for depression or anxiety were included and captured medications from the following drug classes: selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, atypical antipsychotics, norepinephrine-dopamine reuptake inhibitors, tetracyclic antidepressants, and serotonin antagonist and reuptake inhibitors.

The primary outcomes were related to the postoperative clinical course and included hospital length of stay, 30-day postoperative complications, readmissions within 30 and 90 days, and mortality within 30 and 90 days. The secondary oncologic outcomes were the receipt of adjuvant chemotherapy (either neoadjuvant or adjuvant) and overall survival after pancreatic cancer resection between comparison groups. Postoperative complications were derived from *ICD-9* codes, and included standard complications (pulmonary failure, pneumonia, myocardial infarction, cardiac arrest, pulmonary embolism, deep vein thrombosis, gastrointestinal tract hemorrhage, surgical site and organ space

infections, systemic shock, acute kidney injury, delayed gastric emptying, gastrointestinal or enterocutaneous fistula, and bile leak). Overall survival was calculated from the date of diagnosis to the date of death or last follow-up. Variables with 10 or fewer observations are not presented with the exact value in accordance with SEER-Medicare guidelines regarding patient confidentiality.

Statistical Analysis

Patient demographic, clinicopathologic, and treatment differences were compared between treatment groups using χ^2 and Fisher's exact tests for categorical variables, Student's t-test for normally distributed continuous variables, and Mann-Whitney U test for non-normally distributed continuous variables. Survival was estimated using the Kaplan-Meier method and log-rank test to compare groups. Statistical analyses were performed with SAS software (version 9.4, SAS Institute, Cary, NC). All tests were two-sided and p-values <0.05 were considered significant.

RESULTS

Demographic, clinicopathologic, and treatment characteristics for patients by treatment group are shown in Table 1. Of 1305 patients, 208 (16%) met criteria for a pre-existing mood disorder while 1097 (84%) did not have a mood disorder at the time of pancreatic cancer resection. The overall average patient age at diagnosis was 74.2 years (standard deviation, 5.7). Most patients presented with moderately differentiated (43%) and larger tumors (T3, 80%), with evidence of nodal spread (N1, 61%). The majority of patients received chemotherapy (68%), with only a small proportion receiving neoadjuvant treatment (10%). No group differences were identified regarding patient age, tumor grade, or tumor or nodal stage when comparing patients with and without mood disorders. There were distinct differences between treatment groups when considering sex, race, Elixhauser comorbidity index score, stage, and pancreatic resection type. Patients with a mood disorder were more likely to be female (71% vs 53%, $P < 0.0001$) and white (94% vs 2% Black vs 4% Asian/other, $P = 0.01$) consistent with the national epidemiology of these mood disorder diagnoses. From a disease standpoint, patients with a mood disorder had higher mean Elixhauser comorbidity index scores (3.63 vs 3.08, $P < 0.0001$) which is likely related to the mood disorder diagnosis. For disease-related variables, there was a smaller proportion of stage II disease (81% vs 87%, $P = 0.01$) and a slightly higher fraction of patients who underwent distal pancreatectomy (23% vs 17%, $P = 0.04$) though no other group differences relating to pancreatic resection type were noted.

Shown in Table 2 are the results for postoperative outcomes by treatment group. The mean hospital length of stay for all patients after pancreatic resection was 13.2 days (standard deviation, 10.3). A total of 297 patients (23%) developed a serious complication within 30 days of surgery, while 283 patients (22%) and 428 (33%) required a hospital readmission within 30 or 90 days of surgery, respectively. Of 1305 patients, 53 (4%) died within 30 days of surgery, while 113 (9%) died within 90 days. When stratifying by treatment group, patients with a pre-existing mood disorder had similar postoperative length of stay (12.9 vs 13.2 days, $P = 0.75$), 30-day complications (26% vs 22%, $P = 0.31$), 30-day readmissions

(26% vs 21%, $P = 0.1$), 30-mortality (3% vs 4%, $P = 0.35$), and 90-day mortality (8% vs 9%, $P = 0.79$); only greater 90-day readmissions rates (42% vs 31%, $P = 0.001$) were observed. This finding of increased 90-day readmissions was confirmed by multivariate logistic regression analysis, which demonstrated greater odds of 90-day readmission among patients with comorbid mood disorders (odds ratio, 1.63; 95% confidence interval, 1.19–2.23).

Regarding oncologic treatment and outcomes, there was no difference in receipt of chemotherapy between groups. For those patients with mood disorders, 62.5% received chemotherapy whereas 69.2% of patients without mood disorders received systemic chemotherapy ($P = 0.06$). Overall survival estimates were consistent with typical outcomes for pancreatic cancer with an observed overall median survival time of 17 months (interquartile range [IQR], 10–29). There was no difference in median survival time between groups ($P = 0.99$, Fig. 1), when comparing patients with mood disorders (survival time, 18 months; IQR, 10–30) and without mood disorders (survival time, 17 months; IQR, 10–29). The 2-year survival incidence was 43% in patients with a mood disorder and 39% in patients without a mood disorder ($P = 0.44$); overall, there were no survival differences at any timeframe among treatment groups (log-rank $P > 0.05$, Table 2).

DISCUSSION

In this large retrospective analysis of national data, we examined the relationship between pre-existing mood disorders with postoperative outcomes and survival among patients with stage I-II pancreatic cancer who underwent surgical resection. Our analysis showed that concurrent mood disorders did not significantly influence short-term postoperative outcomes such as hospital length of stay or complication rates; similarly, oncologic outcomes such as receipt of adjuvant chemotherapy or overall survival were not impacted. Our analysis showed that only 90-day hospital readmissions were increased in patients with pre-existing mood disorders compared to those patients without these psychiatric illnesses.

The published research examining the impact of mood disorders after major surgery are limited and contradictory.[7,27,28] For example, Rumalla et al[8] demonstrated that a prior existing diagnosis of major depressive disorder was associated with increased complications after undergoing craniotomy for malignant brain tumor resection. Furthermore, Ali et al[7] and Browne et al[29] showed patients with pre-existing depression undergoing joint arthroplasty had increased risk of specific complications such as infection. In contrast, Olive at al[28] found no effect of psychiatric comorbidities on outcomes among patients with non-small cell lung cancers undergoing resection. An important consideration is that some of this contradiction may be related to the definition of mood disorders. While most studies have used similar methodology to our analysis (ie, prior diagnosis or receipt of medical treatment), other studies have relied on depression screening questionnaires at the time of admission to delineate subgroups.[5] This heterogeneity in classification expectedly yields varying results in an already difficult-to-study disease.

The impact of comorbid mood disorders on long-term oncologic outcomes has also shown significant variability in the reported literature. For instance, Goodwin et al[30] and Shim et

al[31] demonstrated that breast cancer patients with comorbid depression had an increased mortality risk, even when difference in treatment choice was taken into account. In contrast, Sheibani-Rad et al[32] found no difference in treatment choice or survival among pancreatic cancer patients with pre-existing depression. However, a larger, more recent study of the SEER database by Boyd et al[15] demonstrated that among patients with pancreatic cancer at any stage, comorbid depression decreased overall survival, which was partially mediated by less frequent receipt of appropriate oncologic treatment. Among those with locoregional disease, patients with depression were less likely to see a surgeon (36.3% vs 48.5%, P <0.0001) and less likely to undergo surgical resection. (15.0% vs 24.4%, P < 0.0001). Notably, our analysis also utilized the SEER database, but included only early-stage patients undergoing surgery. These data suggest that either: 1) patients who follow through with surgical referrals and treatment may represent a less debilitated cohort of patients; 2) surgeons may preferentially select patients with well-compensated mood disorders for operative intervention; or 3) the embedded perioperative support services are sufficient to allow co-management of mood disorders along with effective pancreatic cancer treatment administration.

There are several important limitations to our study inherent to the analysis of administrative data. The first aspect relates to the identification of mood disorders, which is inherently difficult to measure accurately. We observed a 16% disease prevalence based on diagnostic and treatment data. While our study prevalence closely matches the national prevalence for mood disorders for all adults in the United States (approximately 20%), estimates are more challenging in pancreatic cancer patients given that the prevalence of depression or anxiety reportedly ranges between from 14–55% in this patient population.[1,2,6,33] Despite our best efforts, some patients still may be misclassified since mild symptoms may not lead to diagnosis or may be well-managed with non-pharmacologic treatment. Furthermore, the severity of mood disorders in this cohort may have been milder than the overall adult population as severe, or poorly managed conditions may not have been offered surgery as noted in the study by Boyd et al.[15] Additionally, we are unable to assess any differences of perioperative psychologic support services between groups, which may have impacted the receipt of recommended treatment.

Within these limitations, our study suggests that among patients receiving surgery for early-stage pancreatic cancer, pre-existing mood disorders do not have a significant impact on short-term postoperative outcomes or long-term oncologic outcomes. While there may be concerns that psychiatric illnesses adversely affect postoperative outcomes from high-risk procedures based on literature in other diseases, we were unable to determine a similar association. Therefore, patients with pre-existing mood disorders may not need additional risk stratification and should be expected to have outcomes similar to patients without mood disorders.

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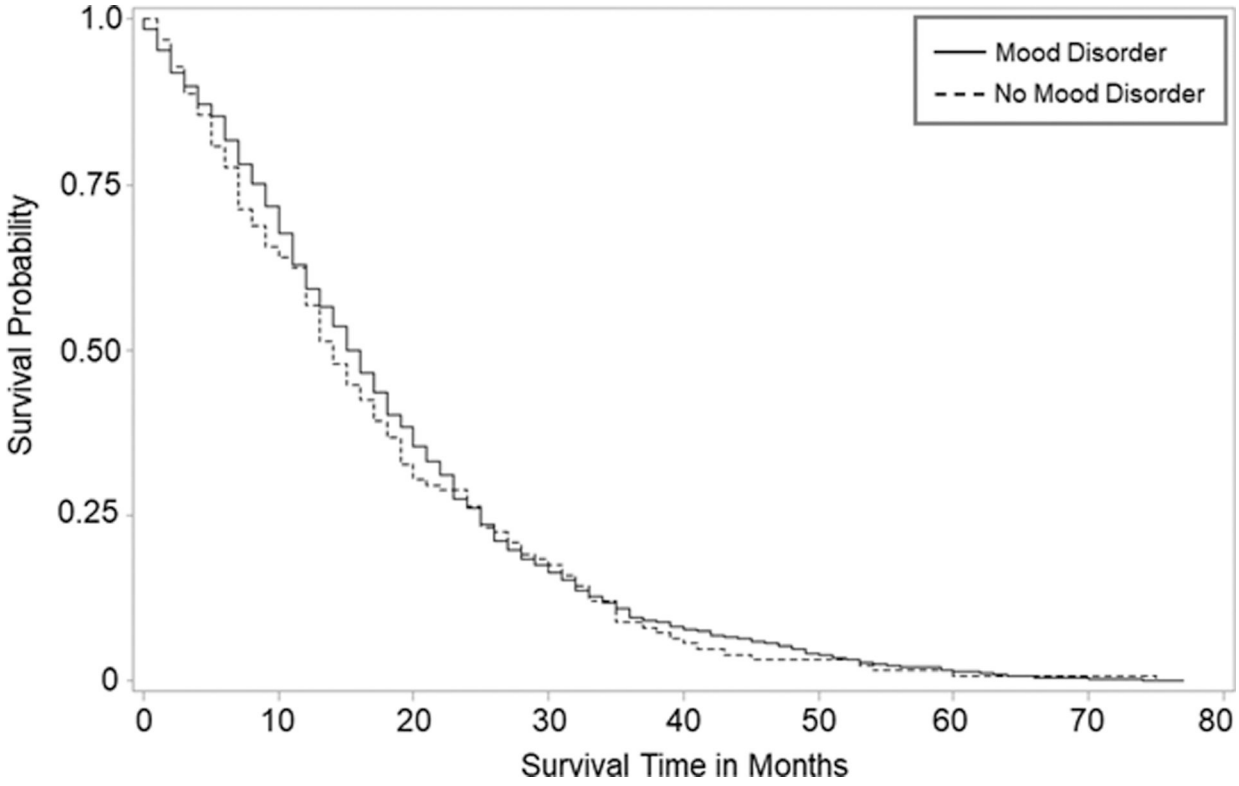

FIGURE 1.

Kaplan-Meier survival analysis comparing survival probabilities for patients with and without a pre-existing mood disorder who underwent pancreatic cancer resection.

TABLE 1.

Patient Demographic and Clinicopathologic Differences by Treatment Group Among Patients With Early-Stage Pancreatic Cancer

Characteristic	Overall	Mood Disorder	No Mood Disorder	*P*
Total, n (%)	1305 (100)	208 (16.0)	1097 (84.0)	
Age, mean (SD), y	74.2 (5.7)	73.5 (5.5)	74.3 (5.7)	0.07
Sex, male, n (%)	572 (43.8)	61 (29.3)	511 (46.6)	<0.0001
Race, n (%)				0.01
White	1148 (88.0)	196 (94.2)	952 (86.8)	
Black	54 (4.1)	≤10*	50 (4.6)	
Asian or other	103 (7.9)	≤10*	95 (8.7)	
Elixhauser comorbidity index score,† (mean, SD)	3.17 (1.66)	3.63 (1.81)	3.08 (1.61)	<0.0001
Tumor grade, n (%)				0.99
Well-differentiated	141 (10.8)	23 (11.1)	118 (10.8)	
Moderately differentiated	564 (43.2)	91 (43.8)	473 (43.1)	
Poorly differentiated or undifferentiated	483 (37.0)	76 (36.5)	407 (37.1)	
Unknown	117 (9.0)	18 (8.7)	99 (9.0)	
Tumor stage, n (%)				0.19
T1	84 (6.4)	17 (8.2)	67 (6.1)	
T2	182 (14.0)	35 (16.8)	147 (13.4)	
T3	1039 (79.6)	156 (75.0)	883 (80.5)	
Nodal stage, n (%)				0.45
N0	511 (39.2)	86 (41.6)	425 (38.8)	
N1	792 (60.7)	121 (58.5)	671 (61.2)	
Stage, n (%)				0.01
I	179 (13.8)	40 (19.2)	139 (12.7)	
II	1122 (86.2)	168 (80.8)	958 (87.3)	
Pancreatic resection, n (%)				
Pancreaticoduodenectomy	975 (74.7)	147 (70.7)	828 (75.5)	0.14
Distal pancreatectomy	235 (18.0)	48 (23.1)	187 (17.1)	0.04
Total pancreatectomy	46 (3.5)	≤10*	40 (3.7)	0.59
Other	51 (3.9)	≤10*	44 (4.0)	0.66
Chemotherapy, n (%)	889 (68.1)	130 (62.5)	759 (69.2)	0.06
Neoadjuvant	127 (9.7)	13 (6.3)	114 (10.4)	0.07
Adjuvant	841 (64.4)	126 (60.6)	715 (65.2)	0.20

*Presented as ≤10 observations per SEER-Medicare guidelines regarding patient confidentiality.

†Elixhauser comorbidity index score: ranges from −11 to 62; higher scores indicate greater comorbidities.

SD indicates standard deviation.

TABLE 2.

Clinical Outcomes and Overall Survival by Treatment Group Among Patients With Early-Stage Pancreatic Cancer

Characteristic	Overall (N = 1305)	Mood Disorder (n = 208)	No Mood Disorder (n = 1097)	*P*
Hospital length of stay, mean (SD), d	13.2 (10.3)	12.9 (10.4)	13.2 (10.2)	0.75
30-day complications, n (%)	297 (22.8)	53 (25.5)	244 (22.2)	0.31
Readmissions, n (%)				
30-day	283 (21.7)	54 (26.0)	229 (20.9)	0.10
90-day	428 (32.8)	88 (42.3)	340 (31.0)	0.001
Mortality				
30-day	53 (4.1)	≤10 *	47 (4.3)	0.35
90-day	113 (8.7)	17 (8.2)	96 (8.8)	0.79
Survival time estimates, HR (95% CI)				
6 mo	0.85 (0.83–0.87)	0.85 (0.80–0.90)	0.85 (0.83–0.88)	0.89
12 mo	0.68 (0.65–0.70)	0.68 (0.62–0.74)	0.68 (0.65–0.70)	0.75
18 mo	0.52 (0.49–0.55)	0.53 (0.46–0.60)	0.52 (0.49–0.55)	0.46
24 mo	0.39 (0.37–0.42)	0.43 (0.36–0.50)	0.39 (0.36–0.42)	0.44

* Presented as ≤10 observations per SEER-Medicare guidelines regarding patient confidentiality.

SD indicates standard deviation; HR, hazard ratio, CI, confidence interval.