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ORIGINAL RESEARCH

Can Symptom Clusters Predict Stage, Resectability, and Survival in Pancreatic Cancer?

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Background: Pancreatic cancer is most often diagnosed at an advanced stage because it develops silently, and its early symptoms are vague and nonspecific. Grouping patients by their primary symptom clusters could provide valuable prognostic insights, enabling more accurate predictions of the stage at diagnosis, the likelihood of surgical resection, and expected survival.

Methods: Single-center retrospective cohort study of 164 adults with histologically confirmed pancreatic adenocarcinoma. Patients were grouped by primary symptom cluster: obstructive (jaundice/dark urine/pruritus/steatorrhea), systemic (anorexia, fatigue, weight loss, or dyspnea/neurologic), pain-predominant (abdominal/back/epigastric pain or acute pancreatitis), or control (asymptomatic/incidental).

Results: The study included 164 patients with a median age of 69 years (range 57–81); 56.7% were male. At diagnosis, the overall stage distribution was as follows: stage I, 11%; stage II, 15.9%; stage III, 24.4%; and stage IV, 48.8%. Patients in the obstructive, systemic, and pain-predominant groups were more likely to present with advanced disease than those in the control group ($p<0.05$). Among the symptomatic groups, the systemic cluster had a higher proportion of advanced-stage cases compared with both the obstructive and pain-predominant groups ($p<0.05$). In contrast, no difference was found between the obstructive and pain-predominant groups ($p>0.05$). In Cox proportional hazards analysis, symptom cluster category, stage at diagnosis, surgical resection status, treatment rate, treatment type, and localization were identified as independent predictors of overall survival ($p<0.05$). Median survival was longest in the control group (37.6 months), followed by the obstructive (16.0 months), pain-predominant (11.8 months), and systemic (7.8 months) groups, with all between-group comparisons reaching significance ($p<0.05$).

Conclusion: Presenting symptom clusters are strongly associated with disease stage, surgical resectability, and survival outcomes in pancreatic cancer. Early recognition of high-risk symptom profiles may improve surgical opportunities and outcomes.

Keywords: pancreatic cancer, symptom clusters, surgical resection, survival, prognosis

Introduction

Pancreatic cancer is a highly aggressive tumor type that often progresses without clear early signs and shows resistance to current treatments. This contributes to its status as one of the leading causes of cancer-related death worldwide.[1] Because diagnosis frequently happens at an advanced stage, when surgery intended to cure the disease is no longer an option, the five-year survival rate stays below 10%.[1,2] Even in cases where the cancer can be surgically removed, median survival ranges from 20 to 28 months, and the five-year survival rate rarely exceeds 20%.[3] These bleak outcomes result from a lack of effective screening, the tumor's tendency to spread early within the local area and to distant sites, and the nonspecific nature of early symptoms.[4]

Pancreatic head lesions often cause obstructive symptoms such as jaundice, pruritus, and dark urine due to early bile duct involvement.[5] In contrast, tumors in the body or tail may remain silent longer, presenting with systemic complaints or pain from retroperitoneal nerve invasion.[6] While imaging is the gold standard for assessing resectability, the type and combination of symptoms can offer indirect clues to tumor stage and operability, leading to interest in grouping related symptoms into clusters.[7] Several studies have connected symptom clusters with resectability and prognosis. Jaundice at presentation in pancreatic head tumors was linked to a higher likelihood of surgical resection, likely indicating earlier detection.[8] Back pain signals celiac plexus invasion, a finding associated with unresectable disease in over 80% of cases.[9] In individuals over 50, new-onset diabetes combined

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with rapid weight loss was linked to more advanced disease and a lower chance of resection.[10] Obstructive symptoms without vascular invasion often indicated resectable disease, while pain, weight loss, and diabetes predicted advanced, unresectable tumors.[11] Paraneoplastic syndromes doubled the risk of metastasis and decreased resectability.[12]

In gastrointestinal cancers, anorexia, nausea, fatigue, and weight loss are linked to decreased survival regardless of stage.[13] In end-stage disease, clusters dominated by dyspnea, appetite loss, fatigue, and nausea doubled short-term mortality.[14] This study aimed to investigate whether presenting symptom clusters can predict both surgical resectability and survival outcomes in patients with pancreatic cancer. The four symptom clusters (obstructive, systemic, pain-predominant, and control) were predefined based on previously reported associations between specific symptoms and prognosis, representing a novel, integrative grouping designed by the authors to systematically test their predictive value.

Materials and Methods

Study Design

This was a retrospective single-center cohort conducted at the Department of Medical Oncology, Van Training and Research Hospital. The study protocol was reviewed and approved by the Van Training and Research Hospital Ethics Committee (Approval No: GOKAEK/2025-06-12). All procedures were performed in line with the principles of the Declaration of Helsinki. For each patient, we recorded demographic information (age, sex), tumor localization (head, body, tail), stage at diagnosis (according to the 8th edition of the AJCC), treatment type, surgical resection status, and survival data.

Patient Population

We retrospectively examined the medical records of all patients diagnosed with pancreatic cancer between January 2015 and December 2023. Eligibility for inclusion required a histologically confirmed pancreatic adenocarcinoma in individuals aged 18 years or older. Only patients with complete clinical, radiological, and pathological records available at the time of initial presentation were considered. Furthermore, the presence of a documented symptom profile at the time of first admission was mandatory for entry. Patients were excluded if they had pancreatic neuroendocrine tumors, cystic neoplasms, secondary metastatic involvement of the pancreas, or incomplete clinical data (Figure 1).

Symptom Cluster Definition

At the time of presentation, each patient was categorized into one of four predefined symptom clusters according to their predominant clinical features. Symptom classification was based on the dominant manifestation that prompted medical attention. In cases with overlapping presentations (eg, jaundice accompanied by weight loss), patients were assigned according to the primary reason for their hospital admission. The four clusters were defined as follows: an obstructive cluster, characterized by jaundice, dark urine, pruritus, or steatorrhea; a systemic cluster, including anorexia, fatigue, weight loss, vomiting, nausea, dyspnea, confusion, or diarrhea; a pain-predominant cluster, encompassing abdominal, back, or epigastric pain, as well as acute pancreatitis; and a control group, consisting of asymptomatic patients or those incidentally diagnosed. Two oncologists independently performed symptom classification, and any discrepancies were resolved through consensus.

Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the associations between symptom clusters and survival outcomes. Separate models were re-estimated after excluding (a) patients with missing data on treatment type, (b) those who received best supportive care only, and (c) the control group due to its exclusively stage I composition. The direction and significance of results remained consistent across all analyses.

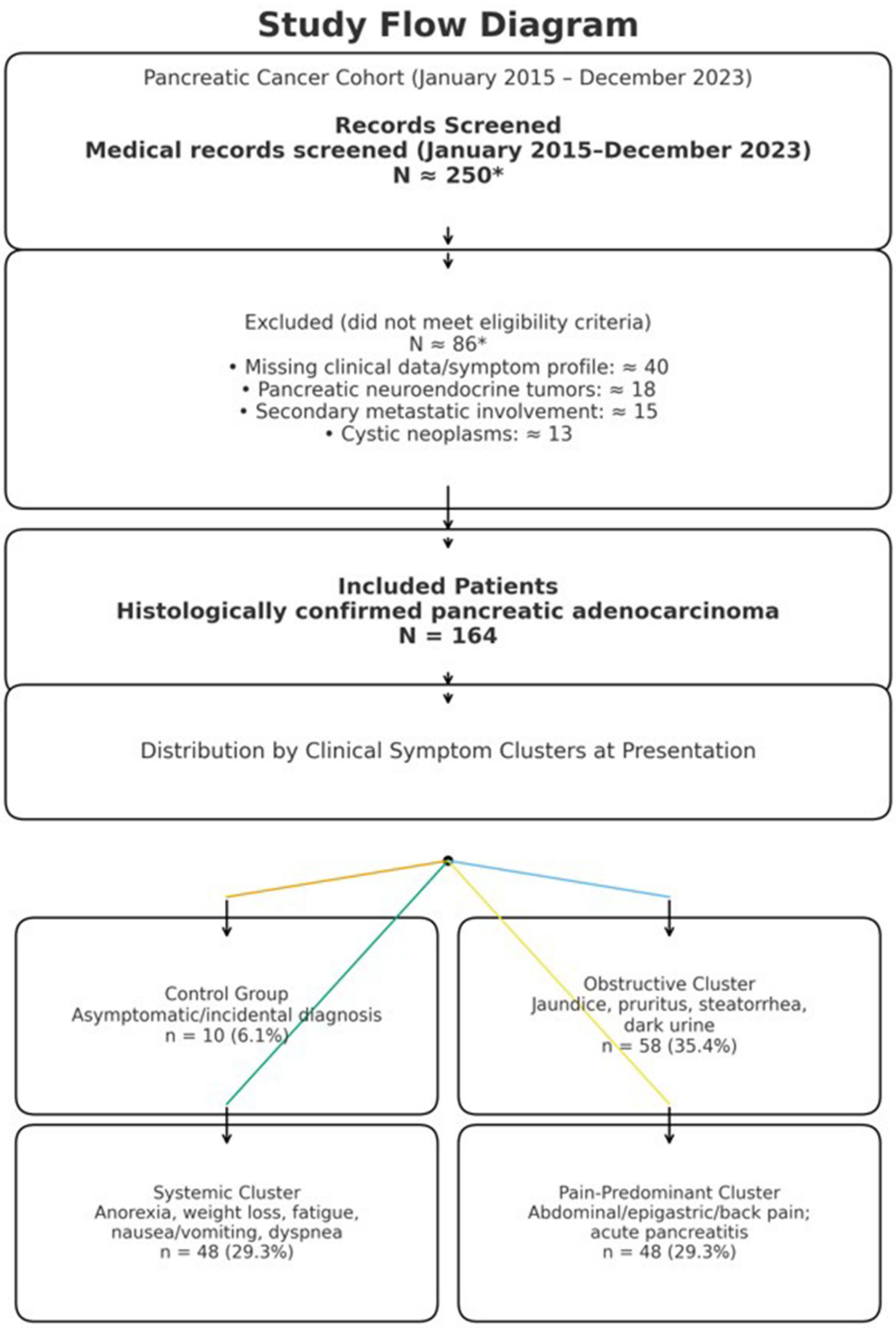

Figure 1 Study design flowchart.

Statistical Analysis

Continuous variables were summarized as the mean ± standard deviation (SD) or median (with minimum and maximum values), and categorical variables were presented as counts and percentages. The distribution of continuous variables was assessed with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Group comparisons for categorical data were made using the Chi-square test or Fisher's exact test, where appropriate. Survival curves were generated using the Kaplan-Meier method and compared with the Log rank test. Variables with $p<0.05$ in univariate Cox regression analysis were entered into a multivariable Cox proportional hazards model to identify independent predictors of OS. Results are

presented as hazard ratios (HR) with 95% confidence intervals. Treatment rate was defined as a binary variable indicating whether the patient received any cancer-directed therapy (chemotherapy, chemoradiotherapy, or surgery) versus best supportive care alone. Tumor localization was included as a covariate in multivariable analysis based on clinical relevance. All analyses were performed using SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). P values <0.05 were considered significant.

Results

A total of 164 patients were included in the study. Median age was 69.0 years (57–81), 56.7% male. Tumors were predominantly in the pancreatic head (63.4%). At presentation, 10 patients (6.1%) were in the control group, while the others were categorized as obstructive (35.4%), systemic (29.3%), or pain-predominant (29.3%) (Table 1). Treatment

Table 1 Baseline Demographic, Clinical, and Tumor Characteristics of Patients with Pancreatic Cancer

	Mean ± sd/n-%	
Age (med:69: min:57-max:81)	**69.1**	**5.6**
Gender		
Female	71	43.3%
Male	93	56.7%
Tumor Localization		
Head	104	63.4%
Corpus	32	19.5%
Tail	28	17.1%
Symptom		
Others		
Incidental	8	4.9%
Asymptomatic	2	1.2%
Obstructive Symptoms		
Jaundice	31	18.9%
Pruritus	11	6.7%
Dark Urine	8	4.9%
Steatorrhea	8	4.9%
Systemic Symptoms		
Fatigue	11	6.7%
Weight Loss	9	5.4%
Vomiting	7	4.2%
Nausea	9	5.4%
Anorexia	6	3.7%

(*Continued*)

Table 1 (Continued).

	Mean ± sd/n-%	
Age (med:69: min:57-max:81)	**69.1**	**5.6**
Dyspnea	2	1.2%
Confusion	2	1.2%
Diarrhea	2	1.2%
Pain-Predominant Symptoms		
Abdominal Pain	21	12.8%
Pain	9	5.4%
Back Pain	6	3.7%
Acute Pancreatitis	6	3.7%
Epigastric Pain	3	1.8%
Pancreatitis	3	1.8%
Stage		
I	18	11.0%
II	26	15.9%
III	40	24.4%
IV	80	48.8%
Surgery	44	26.8%

patterns included palliative chemotherapy (34.1%), adjuvant chemotherapy (23.2%), and best supportive care (14.6%), which were the most common. At follow-up end, 146 patients (89.0%) had died (Table 2).

Disease stage varied significantly between clusters (Table 3). 18 patients (11.0%) presented with stage I disease. Of these, 10 patients belonged to the control group, while 8 patients were in the obstructive symptom cluster. Advanced

Table 2 Distribution of Treatment Modalities and Outcomes in Pancreatic Cancer

	N	%
Treatment		
Treatment Rejection	4	2.4%
Best Supportive Care	24	14.6%
Adjuvant CT	38	23.2%
Definitive Chemoradiation	20	12.2%
Neoadjuvant CT	22	13.4%
Palliative KT	56	34.1%

(*Continued*)

Table 2 (Continued).

	N	%
Gemcitabine/Cisplatin	30	18.8%
Adjuvant Folfirinox	24	15.0%
Palliative Care	24	15.0%
Neoadjuvant Folfirinox	20	12.5%
Folfirinox+Radiotherapi	18	11.3%
Folfirinox	16	10.0%
Adjuvant Gemcitabine/Capecitabine	14	8.8%
Gemcitabine/Nab-Paclitaxel	6	3.8%
Neoadjuvant Gemcitabine/Cisplatin	4	2.5%
Gemcitabine	2	1.3%
Gemcitabine/Capecitabine	2	1.3%
Death (Exitus)	146	89.0%

Notes: "Best Supportive Care" refers to non-chemotherapy supportive measures; "Palliative Care" indicates symptom-focused interventions in advanced disease.

Table 3 Stage at Diagnosis and Surgical Resection Rates According to Symptom Clusters in Pancreatic Cancer

		Control Group (n:10)		Obstructive Symptoms (n:58)		Systemic Symptoms (n:48)		Pain-Predominant Symptoms (n:48)		P
		N	%	n	%	N	%	n	%	
Stage	I	10	100%	8	13.8%	0	0.0%	0	0.0%	<0.001
	II	0	0.0%	14	24.1%	2	4.2%	10	20.8%	
	III	0	0.0%	10	17.2%	8	16.7%	22	45.8%	
	IV	0	0.0%	26	44.8%	38	79.2%	16	33.3%	
Surgical	(-)	0	0.0%	36	62.1%	48	100%	36	75.0%	<0.001
	(+)	10	100%	22	37.9%	0	0.0%	12	25.0%	

Notes: Chi-square test (Fisher test)/Difference from Control Group p<0.05. Difference from Obstructive Symptoms p<0.05, Difference from Systemic Symptoms p<0.05. 18 patients (11.0%) presented with stage I disease. Of these, 10 patients (6%) belonged to the control group, while 8 patients were in the obstructive symptom cluster.

disease (III–IV) occurred in 62.0% (obstructive), 95.9% (systemic), and 79.1% (pain-predominant) (Figure 2). Stage IV was most prevalent in the systemic group (79.2% vs 44.8% obstructive, 33.3% pain-predominant; p<0.05). Resection rates: 100% (control), 37.9% (obstructive), 25% (pain-predominant), 0% (systemic) (p<0.05).

In univariate Cox regression analysis, age, symptom cluster, stage, surgical resection status, treatment rate, and treatment type were associated with OS (p<0.05), whereas gender was not. Tumor localization showed borderline significance (p=0.056) (Table 4). Multivariable Cox analysis identified symptom cluster, stage, resection status, treatment rate, treatment type, and tumor localization as independent OS predictors (Table 4). Sensitivity analyses excluding

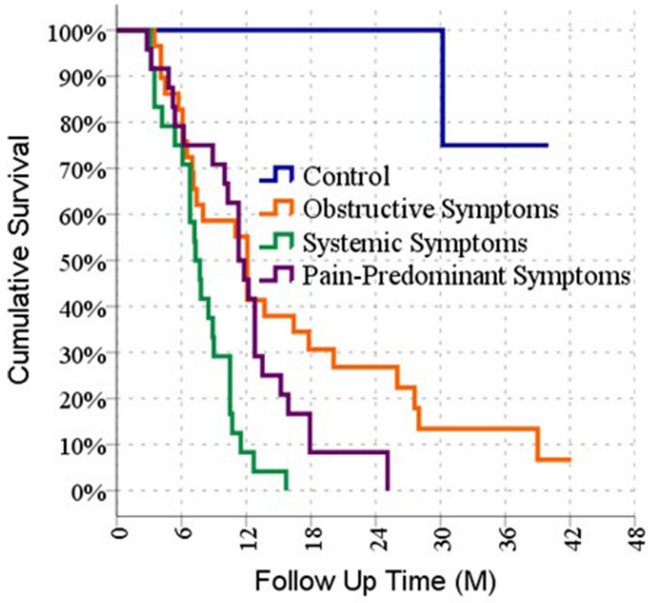

Figure 2 Kaplan–Meier survival curves by symptom cluster. (Curves show significant separation: control> obstructive> pain-predominant> systemic; log-rank p<0.05).

patients treated with best supportive care or the control group (stage I only) did not materially change the hazard ratios or their significance levels, confirming the robustness of the findings.

Tail tumors had significantly worse survival compared to head tumors (HR, 1.92; 95% CI, 1.15–3.20; p=0.013). Median OS: 37.6 months (control), 16.0 (obstructive), 11.8 (pain-predominant), 7.8 (systemic); all pairwise p<0.05 after Bonferroni correction (Figure 3). A Summary of prior studies evaluating symptom profiles or prognostic factors in PC was given in Table 5.

Table 4 Univariate and Multivariable Cox Regression Analyses of Factors Associated with Overall Survival

	Univariate Model			Multivariable Model		
	HR	%95 GA	p	HR	%95 GA	P
Age	1.051	1.017–1.087	0.003			
Gender	1.034	0.741–1.441	0.846			
Tumor Localization	1.018	0.829–1.250	0.863			
Symptom	1.465	1.238–1.733	<0.001	1.452	1.151–1.832	0.002
Stage	7.397	5.303–10.317	<0.001	3.144	1.635–6.046	0.001
Surgical	92.99	22.24–388.77	<0.001	5.183	1.050–25.575	0.043
Treatment	1.999	1.772–2.255	<0.001	1.607	1.103–2.341	0.013
Type of Treatment	1.267	1.203–1.334	<0.001	1.109	1.005–1.224	0.040

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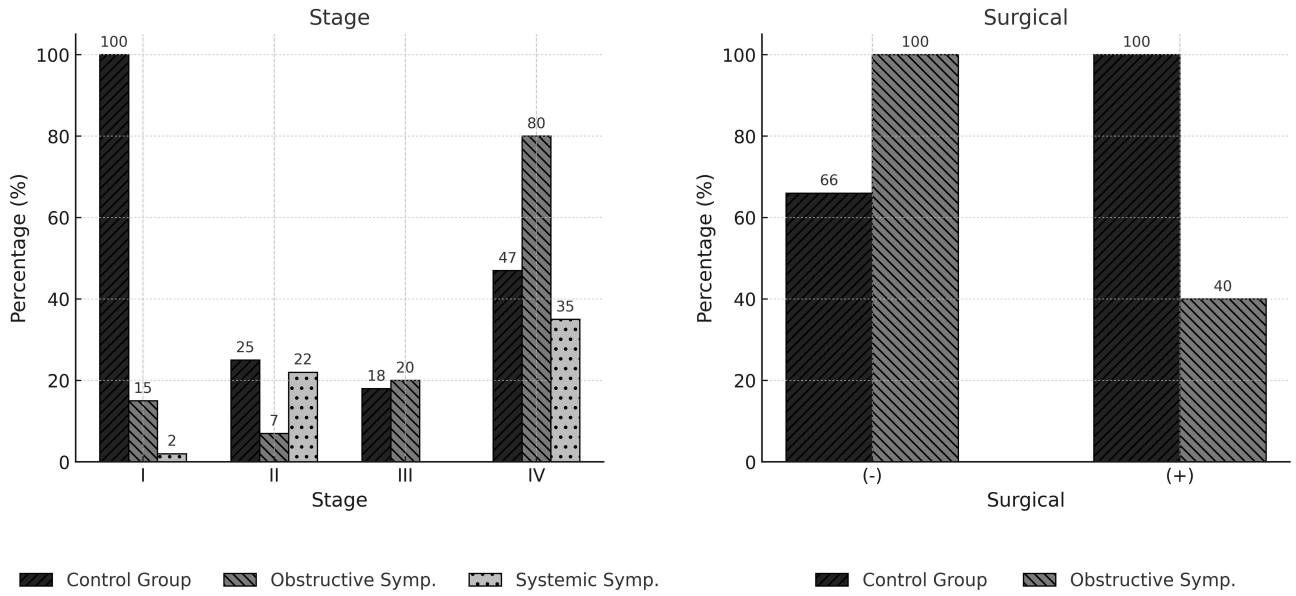

Figure 3 Distribution of Disease Stage and Surgical Resection Rates by Symptom Cluster.

Discussion

This retrospective cohort study demonstrates that the symptom cluster at initial presentation is a strong, independent predictor of disease stage, surgical resectability, and overall survival in patients with pancreatic cancer. Dividing patients into obstructive, systemic, pain-predominant, and control groups revealed striking differences in outcomes. The systemic

Table 5 Summary of Prior Studies Evaluating Symptom Profiles or Prognostic Factors in Pancreatic Cancer

Author (Year)	Design / Population	Symptoms, Stage, and Prognosis
Bilimoria et al 2007[8]	Retrospective, 246 patients with pancreatic head adenocarcinoma	Obstructive symptoms such as jaundice were linked to higher resectability and improved survival, indicating earlier detection.
Hartwig et al 2013[9]	Prospective, patients with pancreatic cancer presenting with pain	Back pain reflected celiac plexus invasion and was associated with unresectable, advanced disease.
Pannala et al 2011[10]	Clinical study of new-onset diabetes in pancreatic cancer	The combined presence of diabetes and weight loss predicted advanced stage and poor surgical outcomes.
Hidalgo et al 2015[11]	Review of pancreatic cancer management	Obstructive symptoms without vascular invasion suggested resectable disease, while pain and weight loss indicated advanced tumors.
Lee et al 2018[12]	Retrospective multicenter analysis	Paraneoplastic syndromes doubled the risk of metastasis and decreased resectability in pancreatic cancer.
Barsevick et al 2007[13]	Review of cancer symptom clusters	Clusters including fatigue, anorexia, and weight loss were associated with decreased survival regardless of cancer stage.
Hui et al 2015[14]	Cohort of advanced cancer patients	Dyspnea, fatigue, and appetite loss clusters significantly increased short-term mortality.
Bachmann et al 2008[15]	Retrospective, resected pancreatic cancer patients	Cachexia and systemic symptoms negatively affected prognosis despite surgical resection.
Burrell et al 2018[16]	Surgical cohort study (Part I/II)	Identified perioperative symptom clusters (pain, fatigue, weakness) related to postoperative quality of life and recovery, consistent with the present concept.
Present Study (2025)	Retrospective, 164 patients (Van Training and Research Hospital)	Symptom clusters (obstructive, systemic, pain-predominant, control) independently predicted stage, resectability, and overall survival. Systemic symptoms were linked to advanced disease and the shortest survival.

Notes: Summary of representative prior studies evaluating the relationship between presenting symptoms and clinical outcomes in pancreatic cancer. The current study integrates these findings by grouping symptoms into four clusters predictive of disease stage, resectability, and survival.

symptom cluster had the highest proportion of stage IV disease (79.2%) and the shortest median survival (7.8 months). By contrast, the control group comprising asymptomatic or incidentally diagnosed patients presented exclusively with stage I disease, achieved a 100% resection rate, and had the most extended median survival (37.6 months). Multivariable Cox regression confirmed that symptom cluster, stage at diagnosis, surgical resection status, treatment rate, treatment type, and tumor localization were all independent predictors of survival.

The link between systemic symptoms and advanced stage aligns with previous reports that constitutional complaints such as weight loss, fatigue, and anorexia often reflect higher tumor burden and more widespread disease.[15,17] Such manifestations are believed to be mediated by tumor-related inflammatory cytokines, including IL-6 and TNF-α, which promote cachexia and a catabolic metabolic profile.[18,19] In contrast, obstructive symptoms such as jaundice—seen in 44.8% of our obstructive group—tend to appear earlier, especially in pancreatic head tumors where bile duct obstruction occurs before distant spread. This likely explains why the obstructive group presented with earlier-stage disease and had a more prolonged survival than the systemic group (16.0 vs 7.8 months). Similar trends have been reported by Bilimoria et al[8] and Hidalgo et al,[11] who noted that obstructive features can indicate earlier disease if major vascular invasion is absent.

We also found a strong association between symptom cluster and surgical resectability. While large population-based series report resection rates under 20%,[20] every patient in the control group of our study underwent successful surgery, most likely because their cancers were detected incidentally during imaging for unrelated reasons. In contrast, none of the systemic groups were candidates for surgery. Obstructive presentations had significantly higher resection rates than systemic ones (37.9 vs 0%), consistent with prior observations that jaundice prompts earlier referral and assessment.[8,11,21] Survival rates displayed a distinct hierarchy—control group highest, followed by obstructive, pain-predominant, and systemic—paralleling multi-center evidence that patients without systemic symptoms at diagnosis generally experience better outcomes.[22,23] The poor prognosis of the systemic group likely reflects both advanced stage and an inflammatory, cachectic state that reduces tolerance to chemotherapy and overall physiological reserve.[18,19,24] The pain-predominant group, with a median survival of 11.8 months, likely represents patients with locally advanced disease and perineural invasion, a well-known adverse prognostic factor.[25]

Tumor localization emerged as a novel independent predictor in multivariable analysis, with tail tumors conferring nearly twice the mortality risk of head tumors (HR: 1.92, p=0.013). This finding aligns with Hartwig et al, who reported delayed diagnosis in tail tumors due to absent biliary obstruction.[9] Obstructive symptoms often indicate localized disease involving the bile duct. Systemic symptoms suggest widespread inflammation and metabolic disruption.[18,19] Pain-predominant presentations frequently accompany retroperitoneal spread and nerve invasion.[25] In clinical practice, recognizing these clusters could provide a quick, non-invasive method for estimating prognosis and prioritizing diagnostic workup and treatment planning. These findings complement NCCN guidelines, which focus on stage and performance status as the main drivers of management decisions.[26] Adding symptom cluster assessment to the initial evaluation may improve prognostication and help guide the urgency of diagnostic and treatment steps. Our results suggest that patients with systemic symptoms should be prioritized for rapid multidisciplinary evaluation, given their high risk of advanced disease.

Formal cluster analyses focused on pancreatic cancer are emerging. Burrell et al identified perioperative symptom clusters among surgical pancreatic cancer patients (two linked Part I/II studies), reporting recurring groups that included pain–fatigue–weakness and psycho-emotional subclusters, and relating them to quality-of-life and recovery trajectories—conceptually concordant with our finding that different presenting clusters map onto distinct clinical courses.[16] Beyond clustering, hallmark symptom-focused pancreatic cancer studies reinforce elements of our framework: jaundice often signals earlier, potentially operable disease; back pain can reflect locally advanced or posteriorly invasive disease and poorer prognosis; and new-onset diabetes may be a paraneoplastic harbinger that, when recognized, can lead to earlier detection in a subset.[27,28] Our results indicate different priorities for rapid evaluation by cluster, without implying that expedited care necessarily equates to curative intent in all cases.

Gu et al highlighted that integrating patient-derived models with single-cell omics provides unprecedented insights into intratumoral heterogeneity, immune components, and signaling networks within the pancreatic cancer milieu.[29] Such approaches may help explain the biological underpinnings of clinical symptom clusters, for example, how inflammatory activity and cytokine signaling in the tumor microenvironment contribute to systemic manifestations such as cachexia or fatigue. In parallel, growing evidence supports a bidirectional "crosstalk" between tumor cells and the nervous system.

As summarized by Huang et al, neurotransmitters and neurotrophic factors not only modulate tumor growth and invasion but also influence tumor-derived secretions that promote neural remodeling and perineural invasion.[31] This neural–tumor interaction is particularly relevant to pancreatic cancer, where perineural invasion is typical and often associated with pain-predominant or systemic symptom profiles. Within this framework, the poor prognosis observed in our systemic symptom cluster may not be solely attributable to advanced disease stage.

Our study is limited by the small number of patients in the control group, all of whom were diagnosed at stage I. This limitation, inherent to the retrospective design and the rarity of incidental early-stage detection, may restrict generalizability. Another limitation is the reliance on subjective clinical documentation of symptoms, which introduces potential recall bias. Incorporating standardized symptom evaluation tools or patient-reported outcome measures could provide more objective and reproducible data. Additionally, while the time interval between diagnosis and initiation of treatment may influence outcomes, this parameter was not systematically available in our dataset. Future research should examine this variable to refine prognostic assessments. Radiological staging categories (resectable, borderline resectable, metastatic), which are widely used in clinical practice, were not systematically available in our retrospective dataset; therefore, AJCC TNM staging was applied.

Conclusions

Symptom clusters independently predict stage, resectability, and survival in pancreatic cancer. Tumor localization emerges as an additional prognostic factor in multivariable analysis. While systemic symptoms signal dismal outcomes requiring palliative focus, obstructive presentations may benefit from accelerated pathways to surgery. The exclusively stage I composition of our control group necessitates validation in larger cohorts with diverse early-stage presentations. Future research should investigate whether symptom cluster-based triage can reduce the time to diagnosis and enhance resection rates.

Data Access Statement

The data supporting the findings are available from the corresponding author Mehmet Salim Demir upon reasonable request.

Ethical Statement

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Van Training and Research Hospital (Approval ID: GOKAEK/2025-06-12). Informed consent was obtained from all participants for the use of their data in anonymized research.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no potential conflicts of interest.

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