Original Article

# Predicting Early Mortality in Resectable Pancreatic Adenocarcinoma: A Cohort Study

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**BACKGROUND:** Survival after surgical resection for pancreatic cancer remains poor. A subgroup of patients die early (<6 months), and understanding factors associated with early mortality may help to identify high-risk patients. The Khorana score has been shown to be associated with early mortality for patients with solid tumors. In the current study, the authors evaluated the role of this score and other prognostic variables in this setting. **METHODS:** The current study was a cohort study of patients who underwent surgical resection for pancreatic cancer from January 2006 through June 2013. Baseline (diagnosis ±30 days) parameters were used to define patients as high risk (Khorana score ≥3). Statistically significant univariable associations and a priori prognostic variables were tested in multivariable models; adjusted hazard ratios (HR) were calculated. **RESULTS:** The study population comprised 334 patients. The median age was 67 years, 50% of the study population was female, and 86% of the patients were white. The pancreatic head was the primary tumor site for 73% of patients; 67% of tumors were T3 and 63% were N1. The median Khorana score was 2; 152 patients (47%) were determined to be high risk. Adjunctive treatment included chemotherapy (70%) and radiotherapy (40%). The postoperative (30-day) mortality rate was 0.9%. The 6-month mortality rate for the entire cohort was 9.4%, with significantly higher rates observed for high-risk patients (13.4% vs 5.6%; $P=.02$). On multivariable analyses (examining a total of 326 patients), the Khorana score (HR for high risk, 2.31; $P=.039$) and elevated blood urea nitrogen (HR, 4.34; $P<.001$) were associated with early mortality. **CONCLUSIONS:** Patients at high risk of early mortality after surgical resection of pancreatic adenocarcinoma can be identified using simple baseline clinical and laboratory parameters. Future studies should address preoperative interventions in these patients at high risk of early mortality. ***Cancer* 2015;000:000-000.** © *2015 American Cancer Society.*

**KEYWORDS:** pancreatic cancer, early mortality, Khorana score, predictors.

## INTRODUCTION

Despites advances in the understanding of the pathogenesis of pancreatic adenocarcinoma, outcome after treatment remains poor. Even when it presents as early, resectable disease, the median overall survival after surgery and adjuvant therapy is <2 years.[1,2] Although perioperative mortality has improved considerably (currently <1% at 30 days), a subgroup of patients experience disease recurrence early (within 6 months).[3] These patients may not benefit from the current standard of care but to our knowledge little is known regarding how best to identify such patients at high risk of early mortality. Surgical resection margin has been shown to be associated with survival outcomes,[4] although there are some contradictory reports owing to nonstandardized pathologic margin assessment.[5,6] CA 19-9 is another marker reported to have varying associations with survival.[7,8] Of possible baseline clinical parameters, a high body mass index (BMI) has been shown to be associated with inferior outcomes after the development of pancreatic cancer.[9] A venous thromboembolism risk score, the Khorana score, also has been shown to be associated with early mortality in patients with solid tumors,[10] but has not been tested specifically in individuals with pancreatic cancer. The score comprises simple baseline clinical parameters and allows for the early risk stratification for patients with various malignancies (Table 1). We evaluated this score as well as other demographic and clinical parameters in relation to early mortality in patients undergoing potentially curative surgical resection of pancreatic adenocarcinoma.

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## MATERIALS AND METHODS

We conducted a retrospective cohort study of consecutive patients who underwent surgical resection of pancreatic adenocarcinoma from January 2006 through June 2013 who were followed at the Cleveland Clinic. Data regarding demographic, clinical, pathologic, and laboratory variables were extracted from electronic medical charts. These included age, sex, race, marital status, tobacco and alcohol use status, height, weight, calculated BMI, serum hemoglobin, white blood cell count, platelet count, blood urea nitrogen (BUN), creatinine, calcium, protein, albumin, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, CA 19-9, pathologic descriptors (including location, histology, T classification, N classification, M classification, and surgical resection margin), details regarding therapy including chemotherapy and radiotherapy use, and timelines (including dates of diagnosis, surgical resection, last follow-up, and death, if applicable). For serial clinical and laboratory data, values closest to the date of the definitive diagnosis of pancreatic adenocarcinoma were chosen; all values selected for the final data set were within ±30 days of the diagnosis.

The Khorana score was calculated as reported previously and is summarized in Table 1.[10] A high-risk score was defined as a score ≥3. Postoperative mortality was defined as death within 30 days from the date of surgical resection of pancreatic adenocarcinoma. Early mortality was interpreted as death within 180 days (6 months) from the date of a definitive diagnosis of pancreatic adenocarcinoma. For analysis of early mortality, we censored patients who were lost to follow-up before 180 days from diagnosis and those alive >180 days from diagnosis. For analysis of overall survival, we censored patients who were alive at the date of last follow-up.

Descriptive results were provided using median (range) and percentage values. Survival analyses were performed using the Kaplan-Meier method. Hazard ratios (HR) for univariable and multivariable models of predictors were calculated using Cox regression; 95% confidence intervals (95% CIs) and 2-sided *P* values are presented. For continuous laboratory variables found to be significant on univariable tests, standard laboratory cutoff values at the study institution were used to categorize these variables into normal and elevated for the multivariable models. The final models were constructed using a stepdown approach. Data regarding CA 19-9 were missing for 87 patients. Therefore, CA 19-9 values were not included in the multivariable models. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Cleveland Clinic.[11] All analyses were performed using SAS statistical software (version 9.3; SAS Institute Inc, Cary, NC). The study was approved by the Institutional Review Board of the Cleveland Clinic.

**TABLE 1.** Khorana Score

| Characteristic | Score Points |
|---|---|
| Site of cancer | |
| Very high risk (pancreas, stomach) | 2 |
| High risk (lung, gynecologic, bladder, testicular, lymphoma) | 1 |
| Baseline hemoglobin <10 g/dL | 1 |
| Baseline white blood cell count >11,000/mm$^3$ | 1 |
| Baseline platelet count ≥350,000/mm$^3$ | 1 |
| Body mass index ≥35 kg/m$^2$ | 1 |
| Add all score points above for a total score | |
| Total Points | Score Category |
| 0 | Low |
| 1-2 | Intermediate |
| ≥3 | High |

## RESULTS

### *Baseline Characteristics*

The study population comprised 334 patients. Baseline demographic and clinical characteristics are shown in Table 2. The median age of the patients was 67 years, 50% of the patients were female, and 86% were white. The pancreatic head was the primary tumor site for 73% of patients. Pathologic staging was T3 for 225 cases (67%) and N1 for 211 cases (63%). An R0 surgical resection was achieved in 217 patients (65%). The median Khorana score was 2; 152 patients (46%) were determined to have a high-risk score. Comorbidities were present in 196 patients (59%). Adjuvant treatment included chemotherapy (approximately 70% of patients) and radiotherapy (approximately 40% of patients). Eighteen patients (5%) received preoperative radiotherapy for borderline resectable disease. Khorana score values were derived from baseline variables; 8 patients had data missing regarding ≥1 component variables, thereby precluding a score calculation. The median baseline CA 19-9 level was 80 U/mL (range, 0-9343 U/mL).

### *Survival Outcomes*

With a median follow-up of 39.4 months for all 334 patients, there were 205 deaths reported in the study cohort (61%). The median overall survival was 21.3 months. The actual overall survival rates at 1, 2, 3, and 5 years were 84%, 68%, 59%, and 28%, respectively. There were 3 deaths (0.9%) occurring within 30 days of surgical resection of the pancreatic cancer. At 180 days after diagnosis, there were 29 deaths (8.7%).

**TABLE 2.** Baseline Demographic and Clinical Characteristics of the Study Population (N=334)[a]

| Characteristic | Value |
|---|---|
| Age, y | 67 (35-88) |
| Male sex | 168 (50%) |
| White race | 287 (86%) |
| Current or prior smoker | 204 (61%) |
| Current or prior alcohol use | 145 (43%) |
| Pancreatic head tumor | 244 (73%) |
| pT3 tumor | 225 (67%) |
| pN1 tumor | 211 (63%) |
| R0 surgical resection | 217 (65%) |
| Adjunctive chemotherapy | 241 (72%) |
| Adjunctive radiotherapy | 136 (41%) |
| Body mass index, kg/m$^2$ | 26.4 (11.3-69.5) |
| Hemoglobin, g/dL | 12.3 (6.3-16.2) |
| White blood cell count, ×1000/mm$^3$ | 7.7 (3.2-22) |
| Platelet count, ×1000/mm$^3$ | 282 (60-1460) |
| Blood urea nitrogen, mg/dL | 14 (1-83) |
| Creatinine, mg/dL | 0.8 (0.3-8) |
| Total protein, g/dL | 6.7 (2.6-8.4) |
| Albumin, g/dL | 3.8 (1.5-4.9) |
| Total bilirubin, mg/dL | 0.8 (0.1-26.8) |
| Alkaline phosphatase, U/L | 141 (27-2313) |
| No comorbidities | 138 (41%) |
| 1 comorbidity | 39 (12%) |
| ≥2 comorbidities | 157 (47%) |
| Khorana score | 2 (2-6)[b] |
| Khorana score, high | 152 (46%)[b] |

[a] Continuous variables are presented as the median (range) and discrete variables are presented as the number (%).
[b] Khorana score values were missing for 8 patients due to missing values on component variables.

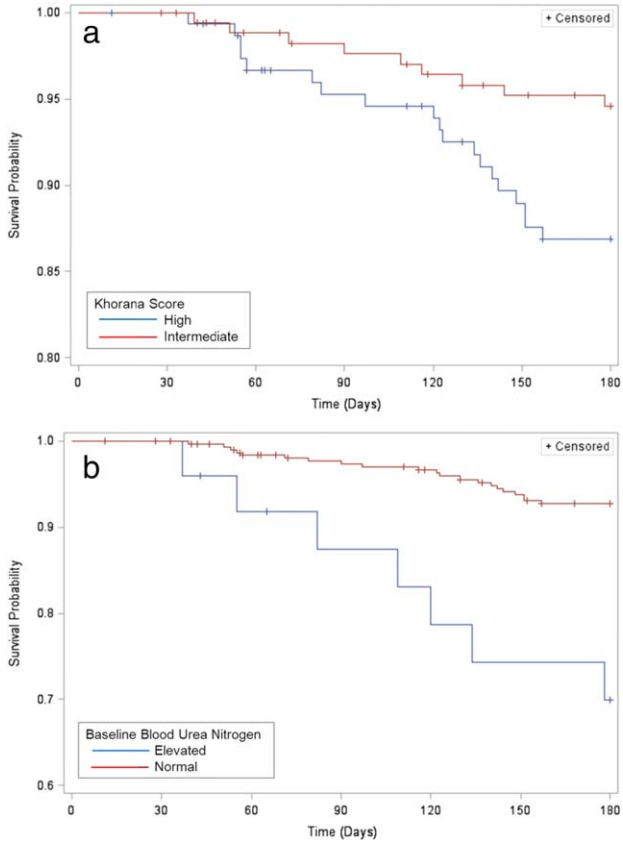


**Figure 1.** (*Top*) Early (6-month) mortality by baseline Khorana score in 326 patients. Data regarding 8 patients were excluded due to missing values. Note that the y-axis was modified for visualization. (*Bottom*) Early (6-month) mortality by baseline blood urea nitrogen level in 329 patients. Data regarding 5 patients were excluded due to missing values. Note that the y-axis was modified for visualization.

On univariable analyses, 6-month mortality was found to be statistically significantly associated with hemoglobin (HR per unit increase, 0.76; 95% CI, 0.63-0.92 [$P = .005$]), BUN (HR per unit increase, 1.05; 95% CI, 1.02-1.07 [$P < .001$]), continuous Khorana score (HR per unit increase, 1.53; 95% CI, 1.11-2.10 [$P = .009$]), and high-risk Khorana score category (HR, 2.49; 95% CI, 1.13-5.51 [$P = .02$]). Other key variables, including pathologic TNM staging, were not found to be associated with 6-month mortality. Accounting for correlations between hemoglobin and the Khorana score, in the final multivariable model (total was 326 patients due to missing data concerning some Khorana score components), Khorana score category and elevated BUN (>25 mg/dL) were found to be statistically significantly associated with 6-month mortality (Table 3) (Fig. 1).

For overall mortality, univariable analyses demonstrated statistically significant associations with BUN (HR per unit increase, 1.02; $P = .008$), creatinine (HR per unit increase, 1.33; $P = .003$), bilirubin (HR per unit increase, 1.03; $P = .024$), and positive resection margin (HR vs negative margin, 1.45; $P = .013$). Using laboratory cutoff values and factoring for correlation between BUN and creatinine, a final multivariable model included surgical resection margin, elevated BUN at baseline, and elevated bilirubin at baseline as factors associated with overall survival (Table 4).

## DISCUSSION

In the current cohort study, we identified a simple set of baseline parameters that may help to identify patients at high risk of early mortality after surgical resection of pancreatic adenocarcinoma. These parameters are collected routinely among all patients undergoing clinical care for pancreatic cancer, allowing for easy targeting of high-risk patients for specific interventions aimed at improving clinical outcomes.

There are limited and varying data regarding a definition of early mortality in patients with pancreatic cancer.[12-14] We focused on the 6-month mark because it allows for the capture of physiologic and pathologic

**TABLE 3.** Multivariable Model for Early (6-Month) Mortality (N=326)[a]

| Variable | HR (95% CI) | *P* |
|---|---|---|
| High-risk Khorana score (vs intermediate) | 2.32 (1.04-5.13) | .039 |
| Elevated blood urea nitrogen (>25 mg/dL vs ≤25 mg/dL) | 4.34 (1.84-10.25) | <.001 |

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio.
[a] Determined using stepwise removal of nonstatistically significant variables, including hemoglobin.

**TABLE 4.** Multivariable Model for Overall Mortality (N=316)[a]

| Variable | HR (95% CI) | *P* |
|---|---|---|
| Positive surgical resection margin (vs negative) | 1.57 (1.17-2.11) | .003 |
| Elevated blood urea nitrogen (>25 mg/dL vs ≤25 mg/dL) | 2.29 (1.40-3.73) | <.001 |
| Elevated bilirubin (>1.5 mg/dL vs ≤1.5 mg/dL) | 1.57 (1.17-2.12) | .003 |

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio.
[a] Determined using stepwise removal of nonstatistically significant variables, including creatinine and Khorana score.

characteristics that render our current therapeutic approaches largely ineffective because most patients at the 6-month mark are still receiving or have only recently completed curative-intent therapy. The predictors identified in the current study reflect the pathologic process as well as the individual's physiologic response to that process. Elevated BUN as observed in the current study as a prognostic factor for early mortality is a novel finding in patients with resectable pancreatic cancer. A study among patients with all stages of pancreatic cancer demonstrated that elevated BUN was associated with increased mortality in a final multivariable model, although not in the univariable analyses.[15] Elevated BUN has also been associated with worse prognosis in patients with non-small cell lung cancer,[16] and advanced malignancies in patients receiving palliative care.[17,18] In one study from Japan, a low BUN (<8 mg/dL) was found to be associated with higher 30-day mortality after pancreatoduodenectomy, although indications for surgery in the study population included various cancers as well as nonmalignant lesions.[19] It is unlikely that elevated BUN in the patient population in the current study was an indicator of major renal dysfunction. There were only 13 patients (4%) with a known diagnosis of chronic kidney disease, compared with 25 patients (7.5%) with elevated BUN. The results of the current analysis indicated that subtle baseline elevations in BUN may indicate subclinical renal dysfunction or a surrogate for other comorbidities that may be associated with poorer overall prognosis.

Anemia is well known as an adverse prognostic factor in general; low hemoglobin at baseline has been associated with inferior clinical outcomes in patients with various malignancies.[20-24] The results of the current study add to this literature in pancreatic cancer. Leukocytosis and thrombocytosis are likely reflective of aggressive disease biology or even micrometastatic disease eliciting a physiologic response. Cancer-related inflammation is a well-described phenomenon,[25-27] and elevated white blood cell and platelet counts are established markers of inflammation. Studies in colorectal,[24] endometrial,[28] anal,[29] cervical,[30] and non-small cell lung[31] cancers using definitions of abnormal blood counts similar to those in the current study have demonstrated that these variables are adverse prognostic factors. To the best of our knowledge, there are limited similar data in patients with pancreatic cancer. A study of 4945 patients undergoing pancreatoduodenectomy demonstrated that leukocytosis was associated with increased perioperative morbidity but there was no association noted with perioperative mortality.[32] Another study indicated that preoperative thrombocytosis is associated with poorer disease-free survival in patients with pancreatic cancer who are undergoing surgical resection.[33] These studies have slightly varying results depending on the individual relationship of anemia, leukocytosis, and thrombocytosis with clinical outcomes, as well as the exact definition of each criterion; the Khorana score has the advantage of capturing all these variables into a universal model that can be replicated easily across studies.

Findings related to BMI are noteworthy. Although, similar to anemia, a high BMI is associated with adverse clinical outcomes in a variety of settings, a peridiagnostic BMI in patients with cancer may be falsely low due to a majority of patients experiencing cancer-induced weight loss. In a study similar to the current one of patients who underwent surgical resection of pancreatic cancer, a baseline BMI >35 $kg/m^2$ was associated with decreased disease-free and overall survival.[34] A large population-based study established that an elevated prediagnostic BMI (using 35 $kg/m^2$ as the cutoff definition, identical to the current study) is associated with decreased survival after a diagnosis of pancreatic adenocarcinoma. This association was found to be strongest between BMI values collected 18 to 20 years before diagnosis.[9] Similar results were observed in a large case-control study that demonstrated a higher incidence of and lower overall survival

from pancreatic cancer in individuals with a high BMI several years before diagnosis.[35] In another study, a decrease in BMI due to cancer-associated weight loss during follow-up was associated with poorer overall survival.[36] This is further highlighted by a study in patients with pancreatic cancer that demonstrated a trend toward inferior overall survival in patients with high BMI, despite an improved median survival in such patients, indicating a time-dependent association.[37] However, in another study of patients with advanced pancreatic cancer, increased BMI was associated with poorer overall survival.[38] In the current study, baseline BMI was not associated with either early mortality or overall survival. Therefore, the role of BMI as a prognostic factor may be affected by the timing of BMI measurement, stage of disease at the time of diagnosis, and comorbidities. Because the Khorana score incorporates BMI, it is likely that any effect will be captured in our model.

For overall survival, adverse prognostic factors were surgical resection margin status and elevated BUN or bilirubin at baseline. The surgical resection margin is most likely associated with inferior long-term outcomes, although data are controversial.[4-6] A possible reason for these discrepant findings is that the surgical resection margin status is an amalgam of various factors, such as patient selection for surgery, surgical volume and technique of pathologic assessment, disease biology, and the effect of any preoperative chemotherapy or radiotherapy. Nonetheless, it is to be noted that surgical resection margin status was not associated with early mortality, which is more likely related to patient factors, but was found to be associated with overall survival, which is likely related to tumor as well as patient factors. Elevated BUN and bilirubin likely reflect subclinical organ dysfunction or serve as surrogates for other comorbid conditions, such as cardiac disease.

The current study certainly has some limitations. It is a retrospective analysis and patient selection bias and missing data are potential problems. To minimize these issues, we focused on patients with adequate follow-up at the study institution. CA 19-9 level, a useful prognostic factor in patients with pancreatic cancer, was missing for several patients, thereby limiting our ability to factor it into final analyses. Another limitation is that some patients had received preoperative cancer-directed therapy, making it a somewhat heterogeneous population. In addition, treatment approaches for resectable and borderline resectable pancreatic cancer continue to evolve, with more focus on preoperative therapies, whereas the current study cohort had only a small minority of patients receiving such therapies. Nonetheless, chemotherapy and radiotherapy were not found to be associated with early mortality, and the final model was applicable across the study population, making it a robust finding.

The results of the current study demonstrate that a simple set of parameters available on every patient undergoing routine clinical care may help to identify patients at high risk of early mortality from resectable pancreatic adenocarcinoma. With a growing trend toward preoperative therapies for resectable and borderline resectable pancreatic cancer at the study institution as well as others, there is an opportunity for prospective studies focusing on this subgroup of high-risk patients to validate these findings. Calculation of this score at baseline may be used to stratify patients, and ultimately may be used to select high-risk patients for more aggressive therapies in prospective studies. At our multidisciplinary pancreatobiliary tumor board, there is growing emphasis on preoperative variables in addition to standard pathologic variables, and future interventional studies are planned to incorporate these findings for prospective validation. Furthermore, the data from the current study suggest a need to attempt to better understand the relation between urea and bilirubin with outcome, because interventions to optimize these variables may be possible and could allow for the modification of outcomes.

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## CONFLICT OF INTEREST DISCLOSURES

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