Original Article

# Baseline Hemoglobin-A1c Impacts Clinical Outcomes in Patients With Pancreatic Cancer

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**Abstract**

An association between diabetes mellitus and pancreatic ductal adenocarcinoma (PDA) has long been recognized. This article assesses the effect of the baseline hemoglobin-A1c (HbA1c) value on the clinical outcomes of patients with PDA. HbA1c values were prospectively collected on 656 consecutive patients presenting to a pancreas multidisciplinary cancer clinic from 2009 to 2012. Patients were diagnosed with benign pancreatic disease (BPD) or biopsy-confirmed resectable (R), borderline/locally advanced (BL), or metastatic (M) PDA. Excluded were those with prior treatment for PDA or a history of chronic diabetes mellitus (>1-year or unknown duration), resulting in a final cohort of 284 patients. Of 284 patients, 44 had benign disease, 62 had R-PDA, 115 had BL-PDA, and 63 had M-PDA. Patients with malignant disease (R-, BL-, and M-PDA) collectively had a higher average HbA1c value than patients with BPD (6.1% vs 5.6%; *P*<.001). Among patients with PDA (n=240), HbA1c values of 6.5% or greater were significantly associated with inferior overall survival (OS) compared with patients with HbA1c values less than 6.5% (hazard ratio [HR], 1.74; OS, 10.2 vs 13.0 months; *P*=.007), along with other known prognostic factors, such as age of 65 years or older, ECOG performance status of 1 or greater, carbohydrate antigen 19-9 level greater than 90, tumor size larger than 3 cm, and disease stage. HbA1c values of 6.5% or greater remained in the final predictive model using backward elimination (HR, 1.46; *P*=.097), indicating that HbA1c values of 6.5% or greater influence OS of patients with PDA even when accounting for other known prognostic factors. HbA1c level at presentation is significantly higher in patients with PDA than patients with BPD and seems to affect survival. (*J Natl Compr Canc Netw* 2014;12:50–57)

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An association between diabetes mellitus (DM) and pancreatic ductal adenocarcinoma (PDA) has been recognized for more than half a century,[1] yet diagnostic and therapeutic applications of this relationship remain limited. Increasing epidemiologic evidence suggests that patients with DM are at significantly greater risk for PDA. In a population-based study of 2122 patients with DM, the incidence of pancreatic cancer within 3 years of DM diagnosis was nearly 8 times that of the general nondiabetic population.[2]

Although long-standing DM may be a risk factor for developing PDA, new-onset DM may, conversely, be a manifestation of the cancer. Patients with PDA are significantly more likely to have new-onset DM (<2-year duration) than noncancer controls[3] and to have a significantly higher prevalence of DM than patients with other types of cancer, such as lung, breast, prostate, and colorectal cancers, and patients without cancer.[4]

Moreover, dysglycemia itself may have a negative impact on outcomes of hospitalized patients with cancer in terms of infection, mortality, length of stay, and toxicities. The risk of cancer death (from stomach, liver, lung cancers) has been noted to be significantly higher among those with a high fasting plasma glucose ( ≥5.6 mmol/L), after adjustment for potentially confounding factors.[5]

This article directly evaluates the relationship between glycosylated hemoglobin (HbA1c), an objective and quantifiable measure of glucose intolerance, and pancreatic cancer in patients without a history of chronic DM presenting with suspected PDA. Specifically, this article examines the potential utility of HbA1c level to discriminate between benign pancreatic disease (BPD) and stages of PDA, and investigates the effect of impaired glucose tolerance on patient survival outcomes.

## Materials and Methods

### Study Population and Data Collection

All patients included in this study were seen at a pancreatic multidisciplinary cancer clinic. The purpose of the clinic is to provide a comprehensive multispecialist evaluation for patients with suspected pancreatic cancer. With Institutional Review Board approval, HbA1c values were prospectively collected on patients seen at the clinic between January 2009 and October 2012. Patients were required to provide written informed consent before study enrollment. A total of 656 patients presented to the clinic during the study period. Based on multidisciplinary review, patients were diagnosed as having resectable (R), borderline resectable/locally advanced (BL), or metastatic (M) pancreatic cancer, or BPD. Diagnoses considered to be benign disease included autoimmune pancreatitis, intraductal papillary mucinous neoplasm, or pancreatic cyst. Exclusion criteria included prior treatment with surgical resection or nonsurgical antineoplastic therapies (n=306) and a self-reported history of type 1 DM (n=6) or type 2 DM (n=60) for longer than 1 year or of unknown duration. The final study cohort included 284 patients.

All patients underwent a pancreatic protocol 3-dimensional (3D) CT scan and routine laboratory tests, including CBC count, complete metabolic profile, carbohydrate antigen 19-9 (CA19-9) level, and HbA1c level, on the morning of the clinic visit. All 3D CT studies were performed with a Definition Dual Source CT scanner (Siemens Medical Solutions, Malvern, NJ, USA) according to a standard protocol.[6] Demographics, medical history, and clinical information were obtained from the initial consult note recorded at the clinic visit. Self-reported race, family history of pancreatic cancer (up to second-degree relative), performance status (PS; as previously defined by Oken et al[7]), and use of antihyperglycemic medication were also recorded to assess for interaction with HbA1c. Survival was determined and cross-checked through review of clinical follow-up information and the Social Security Death Index.

### Statistical Analysis

All demographic and baseline data were summarized using descriptive statistics. Differences in HbA1c values among patients with BPD and R-PDA, BL-PDA, and M-PDA were assessed for significance using the Student *t* test. All *P* values are reported as 2-sided, and the a priori level of significance was set at 0.05 or less. Kaplan-Meier analysis was used to estimate time-to-event curves and survival rates. Univariate Cox regression analyses were performed to assess for an association between clinical factors/laboratory values and overall survival (OS). Characteristics that showed a univariate association with survival at a significance level of 0.05 or less were entered as covariates into a multivariate proportional hazards regression model for OS, and backward elimination was performed to generate the final model. The final proportional hazards regression model was used to estimate the hazard ratio (HR) for death attributable to each covariate. Analyses were performed using R software, version 2.15.2.

## Results

### Study Cohort

The final study cohort included 284 patients seen at the clinic who met the following criteria: 1) newly diagnosed with no prior history of anti-PDA treatment (including surgery); 2) either no prior history of DM or first diagnosed with DM less than 1 year before clinic visit; 3) available HbA1c level from day of clinic visit; and 4) follow-up survival data available. Classified by disease stage, 44 patients (15%) had BPD, 62 had R-PDA (22%), 115 had BL-PDA (40%), and 63 had M-PDA (22%). The demograph-

ic and baseline characteristics of the study population are shown in Table 1.

### Disease Stage and HbA1c

A plot of mean HbA1c values for each disease stage is shown in Figure 1. Mean HbA1c was 5.6% (standard deviation [SD], 0.5) for patients with BPD; 5.9% (SD, 1.0) for R-PDA; 6.2% (SD, 1.1) for BL-PDA; and 6.1% (SD, 0.8) for M-PDA. Patients with malignant disease (including R-, BL-, and M-PDA) collectively had higher HbA1c values became on average at presentation than patients with BPD (6.1% vs 5.6%; *P*<.001). When each stage of PDA was compared separately with the BPD group, the difference in mean HbA1c values more significant as stage increased (R-PDA: 5.9% vs 5.6%, *P*=.048; BL-PDA: 6.2% vs 5.6%, *P*=.00043; M-PDA: 6.1% vs 5.6%, *P*<.0001). A trend was seen toward higher HbA1c at presentation in patients with advanced PDA (BL and M) compared with patients with R-PDA (6.2% vs 5.9%; *P*=.100). The proportion of patients with HbA1c levels in the diabetic range (>6.4%) increased with more advanced stage of disease (4.5% of BPD, 11.3% of R-PDA, 16.5% of BL-PDA, and 28.6% of M-PDA).

### HbA1c Prognostic Value

Using univariate Cox regression analysis, inferior OS was found to be significantly associated with 6 factors (Table 2): 1) HbA1c level of 6.5% or greater (HR, 1.74; 95% CI, 1.2–2.6; *P*=.007); 2) age category of 65 or greater (HR, 1.57; 95% CI, 1.13, 2.20; *P*=.008); 3) ECOG PS 2 compared with ECOG PS 0 (HR, 2.28; 95% CI, 1.09–5.25; *P*=.030); 4) CA19-9 level of 90 U/mL or greater (HR, 1.45; 95% CI, 1.14–1.85; *P*=.004); 5) tumor diameter of 3 cm or greater (HR, 1.60; 95% CI, 1.16–2.20; *P*=.004); and 6) advanced disease stages BL-PDA compared with R-PDA (HR, 1.71; 95% CI, 1.12–2.64; *P*=.014) and M-PDA compared with R-PDA (HR, 2.70; 95% CI, 1.70–4.29; *P*<.001). These factors were used as covariates to construct the multivariable proportional hazards model for survival. Using a multivariate analysis with backward elimination, the following factors were independently related to inferior OS (Table 3): HbA1c value of 6.5% or greater (HR, 1.46; 95% CI, 0.93–2.27; *P*=.097); age of 65 years or greater (HR, 1.64; 95% CI, 1.11–2.41; *P*=.012); CA19-9 level of more than 90 U/mL (HR, 1.98; 95% CI, 1.32–12.97; *P*=.001); ECOG PS 1 compared with ECOG PS 0 (HR, 1.35; 95% CI, 0.92–1.99; *P*=.131); ECOG PS 2 compared with ECOG PS 0 (HR, 2.39; 95% CI, 1.04–5.51; *P*=.041); and advanced disease stages BL-PDA compared with R-PDA (HR, 1.36; 95% CI, 0.84–2.21; *P*=.217) and M-PDA compared with R-PDA (HR, 1.93; 95% CI, 1.14–3.27; *P*=.014).

Median OS for all patients with PDA (n=240) was 12.4 months (95% CI, 11.1–13.6 months). Patients with HbA1c values less than 6.5% had a significantly greater median OS at 13.0 months (95% CI, 8.5–17.5 months) compared with those with HbA1c values of 6.5% or greater at 10.2 months (95% CI, 7.3–13.1 months; *P*<.001).

To evaluate the effect of HbA1c level on overall survival in each disease stage, the separate Kaplan-Meier analyses were performed for patients with R-PDA, BL-PDA, and M-PDA with HbA1c values of 6.5% or greater or less than 6.5% (Figure 2). Median OS was 20.5 months (95% CI, 9.9–31.1) in patients with R-PDA, 13.0 months (95% CI, 9.3–16.8 months) in patients with BL-PDA, and 8.2 months (95% CI, 7.1–9.3) in patients with M-PDA. OS was superior in patients with R-PDA with HbA1c values less than 6.5% (21.9 months; 95% CI, 14.0–29.8 months) compared with patients with R-PDA with HbA1c values of 6.5% or greater (10.9 months; 95% CI, 3.4–18.4 months; *P*=.041). Patients with BL-PDA with HbA1c values less than 6.5 (16.4 months; 95% CI, 11.3–21.5 months) compared with patients with BL-PDA with HbA1c values of 6.5% or greater (11.7 months; 95% CI, 8.9–14.6 months) had improved OS; however, this did not approach significance (*P*=.101). No difference in survival was seen between patients with M-PDA with baseline HbA1c values less than 6.5% and those with baseline HbA1c values of 6.5% or greater (*P*>.05).

## Discussion

This study evaluates how the HbA1c level measured at presentation among patients with newly diagnosed PDA affects their clinical outcomes. Patients with pancreatic cancer often do not exhibit disease-specific symptoms until the cancer is at an advanced stage. Only 15% to 20% of patients are diagnosed early enough to qualify for surgical resection, whereas the remainder present with locally advanced or metastatic disease.[8,9] DM, especially of new onset (<2-year duration), has previously been noted

**Table 1 Demographic and Baseline Characteristics of Patients Presenting to Clinic With HbA1c Values and No Prior Treatment for Pancreatic Diseases**

| Characteristic | Value | | | | |
|---|---|---|---|---|---|
| | Total (N=284) | Benign (n=44) | Resectable (n=62) | Locally Advanced (n=115) | Metastatic (n=63) |
| Median age, y (IQR) | 66 (58–73) | 58 (46–68) | 66 (59–73) | 66 (60–73) | 67 (79–73) |
| Age ≥65 y, n (%) | 153 (53.9) | 15 (34.1) | 37 (59.7) | 65 (56.5) | 36 (57.1) |
| Age <65 y, n (%) | 131 (46.1) | 29 (65.9) | 25 (40.3) | 50 (43.5) | 27 (42.9) |
| Sex, n (%) | | | | | |
| Female | 136 (47.9) | 22 (50.0) | 27 (43.5) | 53 (46.1) | 34 (54.0) |
| Male | 148 (52.1) | 22 (50.0) | 35 (56.5) | 62 (53.9) | 29 (46.0) |
| Race/ethnicity, n (%) | | | | | |
| White | 245 | 34 (77.3) | 54 (87.1) | 102 (88.7) | 55 (87.3) |
| Asian | 10 | 5 (11.4) | 1 (1.6) | 2 (1.7) | 2 (3.2) |
| Black | 19 | 3 (6.8) | 5 (8.1) | 7 (6.1) | 4 (6.3) |
| Hispanic | 4 | 0 (0) | 2 (3.2) | 1 (0.9) | 1 (1.6) |
| Other | 6 | 2 (4.5) | 0 (0) | 3 (2.6) | 1 (1.6) |
| ECOG, n (%) | | | | | |
| 0 | 128 (45.0) | 31 (70.4) | 30 (48.4) | 47 (40.9) | 20 (31.7) |
| 1 | 95 (33.5) | 6 (13.6) | 20 (32.3) | 41 (35.7) | 28 (44.4) |
| 2 | 12 (4.2) | 0 (0) | 1 (1.6) | 6 (5.2) | 5 (7.9) |
| Not available | 49 17.2) | 7 (15.9) | 11 (17.7) | 21 (18.3) | 10 (15.9) |
| Family history | | | | | |
| Pancreatic cancer | 40 (14.1) | 6 (13.6) | 9 (14.1) | 17 (14.8) | 8 (12.7) |
| Diabetes | 29 (10.2) | 6 (13.6) | 8 (14.1) | 9 (7.8) | 6 (9.5) |
| CA19-9, U/mL | | | | | |
| ≥90 | 151 (56.7) | 0 (0.0) | 33 (53.2) | 86 (74.8) | 42 (66.7) |
| <90 | 133 (43.3) | 44 (100.0) | 29 (46.8) | 29 (25.2) | 21 (33.3) |
| HbA1c category | | | | | |
| <6.5% | 238 (83.8) | 42 (95.5) | 55 (88.7) | 96 (83.5) | 45 (71.4) |
| ≥6.5% | 46 (16.1) | 2 (4.5) | 7 (11.3) | 19 (16.5) | 18 (28.6) |

Abbreviations: CA19-9, carbohydrate antigen 19-9; HbA1c, hemoglobin-A1c; IQR, interquartile range.

to be significantly more prevalent among patients with PDA than among age-matched controls.[3] Lee et al[10] recently reported that PDA-associated DM could be discriminated from benign new-onset type 2 DM with 80.8% sensitivity and 67.6% specificity using the clinical factors of age, weight loss, body mass index, and family history of DM. The present study highlights the significant relationship between HbA1c, which is an objective, quantifiable, and readily available marker of hyperglycemia, and PDA among a cohort of patients presenting with either BPD or PDA and no chronic history of DM. Results show that, although patients with benign pancreatic lesions, such as intraductal papillary mucinous neoplasms or pancreatic cysts, or benign conditions, such as autoimmune pancreatitis, are more likely to present with a mean HbA1c value in the normal range (<5.7%), patients with PDA are more likely to present with a mean HbA1c in the prediabetic range (5.7%–6.4%), and that the proportion of patients with diabetic-range HbA1c levels (>6.4%) increases with more advanced disease stages. The present

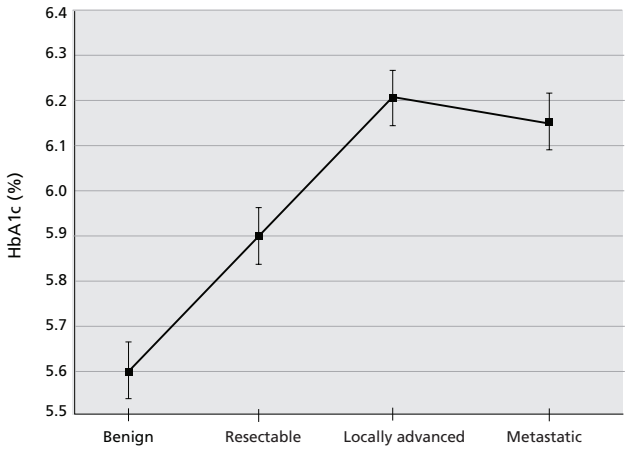


**Figure 1** Plot of mean hemoglobin-A1c (HbA1c) based on disease status.

study also shows that HbA1c has an important impact on survival in patients with pancreatic cancer: HbA1c values of 6.5% or greater were significantly associated with inferior OS (HR, 1.74; OS, 10.2 vs 13.0 months; *P*=.007) in the univariate model, and remained an important factor in multivariate model analysis with backward elimination through providing unique contributions to the fitting that could not be explained by the other variables. Importantly, although HbA1c level contributed to the final multivariate model, it did not reach statistical significance. Still, given the unique impact of HbA1c on this model, hyperglycemia may indicate a different, more aggressive tumor biology that leads to worse survival outcomes in patients with PDA. A diabetic-range serum HbA1c may serve as an initial marker of this difference.

PDA-associated DM presents a unique interface between endocrine regulation and tumorigenesis. Insulin and C-peptide measurements during glucose tolerance tests in patients with pancreatic cancer suggest abnormal beta-cell function and possible insulin resistance.[11] When comparable physiologic insulin levels were achieved in patients with pancreatic cancer and age/weight-matched healthy controls via insulin infusion, Cersosimo et al[12] observed that total body glucose use was consistently lower in patients with pancreatic cancer, consistent with a state of insulin resistance. To evaluate beta-cell function in patients with pancreatic cancer, Basso et al[13] performed a glucagon stimulation test in patients with PDA, type 1 DM, and type 2 DM, and in healthy controls. After glucagon stimulation, no significant increase was observed in C-peptide values among patients with type 1 DM and those with pancreatic cancer, whereas significant increases occurred in controls and patients with type 2 DM. These results suggest that insulin resistance and altered beta-cell function found in patients with pancreatic cancer likely lead to hyperglycemia, supporting the finding of elevated HbA1c in patients with PDA compared with BPD.

Although the association between DM and PDA has been of interest to the medical community for some time, the pathophysiology of PDA-associated DM is not well understood. Emerging evidence suggests that insulin and insulin-like growth factor 1 (IGF-1) may be involved in tumorigenesis through its role in producing high energy intake, increased cell proliferation, and suppression of apoptosis.[14] In vitro, insulin stimulates the growth of cancer cells through interaction with IGF-1 receptors and its own receptors.[15] Observational studies on type 2 DM show that insulin therapy is associated with an increased incidence of several forms of cancer, although the effect of confounders is difficult to discriminate from that of insulin itself, and randomized trials do not confirm the increased risk associated with insulin therapy.[16]

On the other hand, PDA-associated DM has been postulated to be a paraneoplastic phenomenon caused by a tumor-secreted diabetogenic product.[3] Conditioned medium from PDA cell lines not only inhibits insulin release from beta-cell lines[17,18] but also impairs glucose metabolism in peripheral tissues.[19–21] Using matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) analysis, rat hepatocytes incubated with PDA cell line–conditioned media were compared with rat hepatocytes incubated with unconditioned media and sera of patients with PDA, and a low-molecular-weight, potential diabetogenic factor was identified.[20,21] Aggarwal et al[22] recently proposed this factor to be adrenomedullin, a 52–amino acid peptide that is upregulated in PDA cell lines, impairs insulin secretion from beta cells, and contributes to the insulin inhibitory effect of PDA cells in vitro and in vivo. In humans, adrenomedullin is upregulated at the gene level, at the protein level, and in the plasma of patients with PDA, especially those with DM.[22]

Independent studies have shown resolution of new-onset DM in PDA after tumor resection,[3,23–26] consistent with the hypothesis that PDA-associated

**Table 2 Associations Between Clinical Factors/Laboratory Values and OS for 240 Patients With PDA**

| Characteristic | N | Median OS[a] (mo) | | HR[b] (95% CI) | *P*[b] |
|---|---|---|---|---|---|
| All patients with cancer | 240 | 12.4 | (11.1, 13.6) | | |
| HbA1c category | | | | | |
| <6.5 % | 196 | 13.02 | (8.54, 17.50) | 1.00 | |
| ≥6.5% | 44 | 10.22 | (7.31, 13.13) | 1.74 (1.17, 2.60) | .007 |
| Age category | | | | | |
| <65 y | 102 | 18.1 | (14.5, 21.8) | 1.00 | |
| ≥65 y | 138 | 10.3 | (7.5, 13.0) | 1.57 (1.13, 2.20) | .008 |
| Sex | | | | | |
| Male | 126 | 12.4 | (11.3, 13.5) | 1.00 | |
| Female | 114 | 12.7 | (7.6, 18.0) | 0.99 (0.72, 1.38) | .981 |
| Race | | | | | |
| White | 211 | 12.4 | (9.3, 15.4) | 1.00 | |
| Non-White | 29 | 11.5 | (9.7, 13.3) | 1.19 (0.74, 1.91) | .476 |
| ECOG | | | | | |
| 0 | 97 | 16.2 | (12.0, 20.3) | 1.00 | |
| 1 | 89 | 10.9 | (9.2, 12.5) | 1.40 (0.99, 2.00) | .059 |
| 2 | 12 | 5.1 | (1.5, 8.6) | 2.28 (1.09, 5.25) | .030 |
| CA19-9 | | | | | |
| <90 U/mL | 87 | 18.2 | (11.6, 24.8) | 1.00 | |
| ≥90 U/mL | 152 | 10.9 | (11.1, 13.7) | 1.45 (1.14, 1.85) | .002 |
| Current treatment for DM | | | | | |
| None | 228 | 12.4 | (11.0, 13.7) | 1.00 | |
| Oral medication | 7 | 10.4 | (5.2, 15.6) | 2.38 (0.59, 9.66) | .224 |
| Insulin | 5 | 23.2 | (17.3, 29.1) | 2.54 (0.46, 13.97) | .284 |
| Family history of PDA | | | | | |
| No | 205 | 12.4 | (11.3, 13.5) | 1.00 | |
| Yes | 32 | 10.7 | (3.6, 17.8) | 1.00 (0.67, 1.48) | .957 |
| Family history of DM | | | | | |
| No | 226 | 12.4 | (11.1, 13.7) | 1.00 | |
| Yes | 11 | 18.1 | (3.1, 32.9) | 0.83 (0.59, 1.17) | .263 |
| Tumor diameter | | | | | |
| <3 cm | 77 | 18.2 | (10.6, 25.8) | 1.00 | |
| ≥3 cm | 143 | 11.2 | (9.9, 12.53) | 1.60 (1.16, 2.20) | .004 |
| Disease stage | | | | | |
| R-PDA | 62 | 20.5 | (9.9, 31.1) | 1.00 | |
| BL-PDA | 115 | 13.0 | (9.2, 16.8) | 1.72 (1.12, 2.64) | .014 |
| M-PDA | 63 | 8.2 | (7.1, 9.3) | 2.70 (1.70, 4.29) | <.001 |

[a]Median survival is shown in months with a 95% CI.
[b]All hazard ratios and *P* values are derived from univariate models.
Abbreviations: BL, borderline/locally advanced; CA19-9, carbohydrate antigen 19-9; DM, diabetes mellitus; HbA1c, hemoglobin-A1c; HR, hazard ratio; M, metastatic; OS, overall survival; PDA, pancreatic ductal adenocarcinoma; R, biopsy-confirmed resectable.

DM is caused by a diabetogenic tumor-secreted product. After pancreaticoduodenectomy, although DM resolved in 57% of patients with new-onset DM, its prevalence was unchanged in patients with long-standing DM.[4] These observations further support the notion that new-onset DM in patients with pancreatic cancer may be driven by a tumor-secreted product.

This study shows that HbA1c has an important impact on survival in patients with pancreatic cancer. Glycemic control has been said to reduce morbidity and mortality in specific groups of patients, such as critically ill patients. On the controversial subject of the mortality and morbidity benefits of glycemic control, Van den Berghe et al[27] showed that intensive insulin therapy to maintain blood glucose at or below 110 mg/dL reduced morbidity and mortality among patients in the surgical intensive care unit, and that the risk of subsequent death and disease was reduced in patients on tight glycemic control treated for 3 or more days in the medical intensive care unit.[28] Dysglycemia may also have a negative impact on outcomes of hospitalized patients with cancer in terms of infection, mortality, length of stay, and toxicities.[29] A 31% reduction in overall relative risk of cancer (0.69; 95% CI, 0.61–0.79) was found in subjects taking metformin compared with other antidiabetic drugs; this association was significant for pancreatic and hepatocellular cancers, and nonsignificant for colon, breast, and prostate cancers.[30] Enhanced glycemic control may improve outcomes of patients with pancreatic cancer, although this hypothesis must be tested in a prospective randomized fashion before any definitive conclusions can be drawn.

A notable limitation of this study is that the HbA1c level was obtained only at each patient's initial visit to the clinic, therefore only providing a snapshot of glycemic control at one point throughout the disease course. To further elucidate the role played by glycemic control in improving survival in patients with PDA, it would be worthwhile to obtain HbA1c levels at regular intervals both during cancer treatment and at regular posttreatment follow-up visits.

## Conclusions

Patients with PDA have higher HbA1c levels at presentation than patients with BPD, suggesting impaired glucose tolerance among patients with PDA. Severity of glucose intolerance seems to correlate with more advanced disease stage at presentation and, moreover, to be independently related to survival.

**Table 3 Independent Predictors for Overall Survival Identified by the Final Multivariable Proportional Hazards Model After Backwards Elimination[a]**

| Characteristic | HR (95% CI) | *P* |
|---|---|---|
| HbA1c ≥6.5% | 1.46 (0.93, 2.27) | .097 |
| Age ≥65 y | 1.64 (1.11, 2.41) | .012 |
| CA19-9 >90 U/mL | 1.98 (1.32, 12.97) | .001 |
| ECOG 0 vs 1 | 1.35 (0.92, 1.99) | .131 |
| ECOG 0 vs 2 | 2.39 (1.04, 5.51) | .041 |
| Disease stage: R-PDA vs BL-PDA | 1.36 (0.84, 2.21) | .217 |
| Disease stage R-PDA vs M-PDA | 1.93 (1.14, 3.27) | .014 |

[a]All factors showing a significant relationship to overall survival on univariate analysis were included in the initial model (HbA1c ≥6.5%, age ≥65 y, ECOG ≥1, CA19-9 >90 U/mL, tumor diameter ≥3cm, and disease stage; see Table 2).
Abbreviations: BL, borderline resectable/locally advanced; CA19-9, carbohydrate antigen 19-9; HbA1c, hemoglobin-A1c; HR, hazard ratio; M, metastatic; PDA, pancreatic ductal adenocarcinoma; R, resectable.

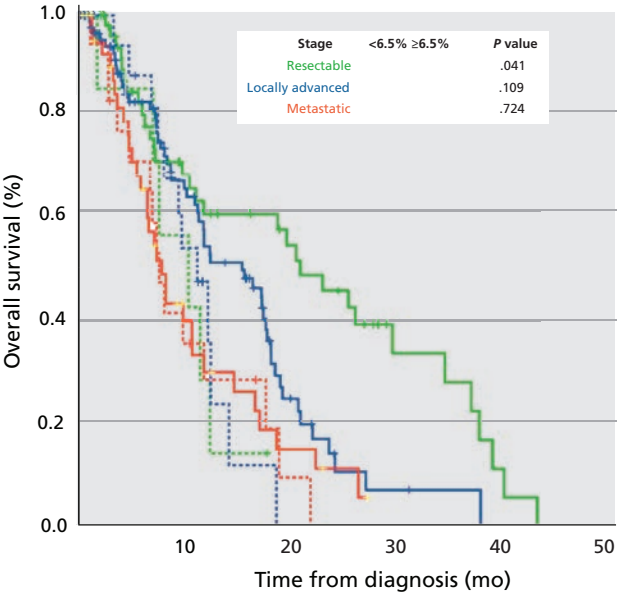


**Figure 2** Kaplan-Meier curves for patients with resectable (green), locally advanced (blue), and metastatic (red) pancreatic ductal adenocarcinoma. Patients are stratified based on HbA1c level <6.5% (solid line) or ≥6.5% (dashed line) at initial diagnosis.

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