The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer

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Background. *Although operative resection represents the only hope for cure in pancreatic cancer, it is associated with significant morbidity and mortality. Furthermore, in some patients disease progression occurs very early postoperatively and no tangible benefit is seen from the operation. Identification of preoperative predictors of death within the first year of surgery could help in the counseling of patients diagnosed with pancreatic cancer.*

Methods. *We studied retrospectively patients who underwent resection for pancreatic adenocarcinoma from 2002 to 2012. We calculated the age-adjusted Charlson Age Comorbidity Index (CACI) and used logistic regression models to determine predictors of mortality within 1 year of surgery. Kaplan–Meier curves and Cox proportional hazards models were developed to determine hazard ratios on survival.*

Results. *Surgery with curative intent was performed in 497 patients; 136 (27%) died within the first year. A CACI score of >4 was predictive of increased duration of stay (P < .001), postoperative complications (P = .042), and mortality within 1 year of pancreatic resection (P < .001). A CACI score of ≥6 increased 3-fold the odds of death within the first year.*

Conclusion. *CACI is useful to predict outcome after pancreatectomy for pancreatic cancer. Patients with a high CACI score have a <50% likelihood of being alive 1 year postoperatively. This information should be used when considering the appropriateness of pancreatic resection in patients with multiple comorbidities. (Surgery 2015;157:881-7.)*

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PANCREATIC DUCTAL ADENOCARCINOMA is the fourth leading cause of adult cancer death and has a rising incidence in the United States; the National Cancer Institute estimates 48,960 new cases in 2015.[1-3] Operative resection remains the only potentially curative treatment,[4-6] but even after surgery with a curative intent, ≤30% of patients die within the first year.[7-10]

Although limited, advances in chemotherapy for pancreatic cancer translate into longer survival and a potentially better quality of life. For all stages of disease, the traditional use of gemcitabine has a median overall survival of 6.7 months,[1,3,11] the combination gemcitabine with nab-paclitaxel, 8.5 months,[4,6,12] and FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil and leucovorin), 11.1 months.[7,9,11]

Given the morbidity associated with surgery, selecting patients for the most appropriate therapeutic strategy is of paramount relevance. Better outcome prediction will allow for better preoperative counseling and guidance on the best treatment in an era of multidisciplinary and personalized medicine.

The aims of this study were to identify the subpopulation of pancreatic cancer patients at high risk of death within the first year postoperatively and to evaluate the effect of comorbidities on patient's outcome using a statistically validated tool, the Charlson Age Comorbidity Index (CACI).[11,13] Ultimately, we seek to determine preoperative factors that correlate with early mortality after resection for pancreatic cancer.

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METHODS

This is a retrospective, single-institution study and data were collected between 2002 and 2012. After obtaining the Massachusetts General Hospital (MGH) Institutional Review Board approval, patients who underwent surgery for pancreatic adenocarcinoma were identified from a manual filing system based on common operative procedure codes created by MGH department of Medical Records and Health Information Systems. We then reviewed manually the electronic medical records for clinical information, operative and pathology reports, as well as laboratory values and radiographic images. Date of death was obtained either from the medical records or the Social Security Death Index. Only patients with confirmed date of death were included in the study; those lost to follow-up were excluded.

Pancreatic surgery at MGH has been performed on the pancreatic unit since 2000; 77% of these surgeries were performed by the same 2 surgeons, accounting for consistency of the surgical technique for the duration of this study.[12,14] Early mortality was defined as death between 3 and 12 months after surgery and we evaluated preoperative and postoperative factors that could predict patient's outcome during this time frame. Comorbidity score was classified according to the Charlson index,[7,9,11] as calculated at the time of pancreatic cancer diagnosis based on clinical history. Age adjusted comorbidity index (CACI) was calculated by weighing individual comorbidities and adding 1 point per decade to ages >40 years. The index was modified not to weight points for any tumor, because our cohort only contains patients with cancer. As an example, a patient with a score ≥4 would be ≥ 50 years old, diabetic, and would have congestive heart failure and chronic obstructive pulmonary disease.

We looked at 2 cutoff values for CACI (<4 or ≥4) and (<6 or ≥6), based on receiver operating characteristic sensitivity/specificity studies and median value for our cohort.

Information on patients' comorbidities was retrieved retrospectively from patient's chart by manual review of patient's clinical history, as described in the chart by the appointed physician at the time. Total bilirubin levels were measured at time of diagnosis and intraoperative loss of blood was retrieved from the operative anesthesia records. Postoperative complications were classified according to the standard morbidity and mortality scoring system described by Clavien-Dindo.[8,10,13,15,16] Additionally, we analyzed predictors of duration of stay and type of discharge (home/home with visiting nurse vs rehabilitation facility). Patients who died within 90 days of surgery were analyzed separately as a perioperative mortality group, because we inferred that their death was most likely related to surgical complications.[14,17-20]

Continuous variables were compared using the Student *t* test, and Chi-square tests were used to compare categorical variables. Mortality was calculated from date of surgery to date of death. Early mortality and perioperative mortality were dichotomized and logistic regression models (univariate and multivariable) were used to determine the association between predictor variables and outcome variables. Relative risks were expressed as odds ratios with a 95% confidence interval (CI). Predictor variables were chosen based on their statistical significance. Receiver operating characteristic curves were built to determine the best sensitivity/specificity results for CACI scores as predictors of early mortality.

Kaplan–Meier curves and Cox proportional hazards models were also built to analyze overall survival in months for the full cohort. We used a direct enter fashion (univariate inclusion criteria of $P < .25$ by the Wald statistic) to determine the hazard of death. Relative risks were expressed as hazard ratios with a 95% CI. All tests were 2-sided. All data analyses were performed with STATA 12.1 software (StataCorp, College Station, TX).

RESULTS

Between 2002 and 2012, 497 patients underwent surgery for pancreatic ductal adenocarcinoma. The demographics of the study population are depicted in Table I and the Charlson index in Table II. The median age at time of surgery was 67 years (range, 35–93); 92% of the patients were white and 81% of the patients underwent a pancreatoduodenectomy. The mean operative time was 347 minutes for the Whipple procedure and 186 minutes for distal resection. One hundred thirty-six patients (27%) died within the first year after surgery. These patients were more likely to be older, have higher CACI scores, higher mean operative blood loss, longer duration of stay, more postoperative complications, higher American Joint Committee on Cancer (AJCC) stage, higher rate of lymphovascular invasion, and more likely to have positive lymph nodes and to have been discharged to a rehabilitation facility.

Mortality within 3 and 12 months (early mortality). Of 497 patients, 122 (25%) died between 3 and 12 months (Fig 1), with a median survival of 7 months. Nearly half of the early mortality patients received either gemcitabine (23%) or

Table I. Patient demographics, and operative and tumor pathologic characteristics by early mortality status

Characteristic	*Total* (n = *497*)	*Early mortality*		P *value*
		Yes (n = *136*)	*No* (n = *361*)	
Preoperative				
Age (y), *n* (%)				
0–<50	23 (4)	5 (22)	18 (78)	.04
50–<70	277 (56)	65 (23)	212 (77)	
≥70	197 (40)	66 (34)	131 (66)	
Gender, *n* (%)				.73
Male	246 (49)	69 (28)	177 (72)	
Female	251 (51)	67 (27)	184 (73)	
Body mass index category (kg/m^2), *n* (%)				.08
<18.5 (underweight)	7 (2)	0	7	
18.5–<25 (normal)	196 (43)	61 (31)	135 (69)	
25–35 (obese)	221 (48)	51 (23)	170 (77)	
>35 (morbidly obese)	34 (7)	11 (32)	23 (68)	
CACI				<.001
<6	444 (89)	110 (25)	334 (75)	
≥6	53 (11)	26 (49)	27 (51)	
CA 19-9, category (U/mL), *n* (%)				.06
<200	153 (36)	48 (31)	105 (69)	
>200	272 (64)	63 (23)	209 (77)	
Total bilirubin category (mg/dL), *n* (%)				.06
≤1.5	272 (57)	60 (22)	212 (78)	
≤1.5–10	137 (29)	44 (32)	93 (68)	
>10	66 (14)	20 (30)	46 (70)	
Size on CT (cm), *n* (%)				.67
1–2	119 (32)	29 (24)	90 (76)	
>2–4	219 (59)	61 (28)	158 (72)	
>4	35 (9)	8 (23)	27 (77)	
Intraoperative				
Type of operation, *n* (%)				.37
Whipple procedure	400 (81)	115 (29)	285 (71)	
Distal pancreatectomy	88 (18)	19 (22)	69 (78)	
Total pancreatectomy	5 (1)	1 (20)	4 (80)	
EBL (L), mean (SD)	0.6 (0.6–15)	1.8 (1.4)	0.7 (0.6)	.02
Operative time (min), mean (SD)	361 (121–1,124)	359 (2.3)	363 (1.9)	.42
Postoperative				
Duration of stay (d), *n* (%)				.003
≤10	380 (77)	92 (24)	288 (76)	
>10	111 (23)	43 (39)	68 (61)	
Disposition, *n* (%)				<.001
Home/home with visiting nurse	406 (84)	92 (23)	314 (77)	
Rehab	76 (16)	35 (46)	41 (54)	
Complications, *n* (%)				.02
0	343 (73)	84 (24)	259 (76)	
I	46 (10)	7 (15)	39 (85)	
II	39 (8)	15 (38)	24 (62)	
III	30 (7)	13 (43)	17 (57)	
IV	10 (2)	3 (30)	7 (70)	
Pathology report				
Histologic grade, *n* (%)				.17
Well differentiated	28 (6)	5 (17)	24 (83)	
Moderately differentiated	305 (61)	76 (25)	229 (75)	
Poorly differentiated	158 (32)	54 (34)	104 (66)	
Undifferentiated	5 (1)	1 (20)	4 (80)	

(*continued*)

Table I. (*continued*)

Characteristic	*Total* (n = *497*)	*Early mortality*		P *value*
		Yes (n = *136*)	*No* (n = *361*)	
Tumor size (cm), *n* (%)				.07
1–2	83 (17)	9 (10)	74 (89)	
>2–4	314 (63)	80 (26)	225 (74)	
>4	100 (20)	33 (35)	62 (65)	
Stage, *n* (%)				.004
I	41 (8)	6 (15)	35 (85)	
IIa	102 (21)	18 (18)	84 (82)	
IIb	353 (71)	111 (31)	242 (69)	
Resection margins status, *n* (%)				.06
Positive	107 (22)	37 (35)	70 (65)	
Negative	389 (78)	99 (25)	290 (75)	
Lymph nodes metastases, *n* (%)				.005
Positive	344 (69)	102 (30)	242 (70)	
Negative	144 (31)	25 (17)	119 (83)	
Lymphovascular invasion, *n* (%)				.002
Yes	206 (41)	95 (33)	196 (67)	
No	291 (59)	41 (20)	165 (80)	
Perineural invasion, *n* (%)				.09
Yes	450 (91)	95 (33)	196 (67)	
No	47 (9)	41 (20)	165 (80)	

CA, Carcinoembryonic antigen; *CACI*, Charlson Age Comorbidity Index; *EBL*, estimated blood loss; *SD*, standard deviation.

Table II. Charlson index

Weight	*Conditions*
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic obstructive disease
	Ulcer disease
	Mild liver disease
	Diabetes mellitus
2	Hemiplegia
	Moderate/severe renal disease
	Diabetes with end-stage organ damage
	Leukemia
	Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumor
	AIDS

Age index adds 1 point for each decade >40 years.

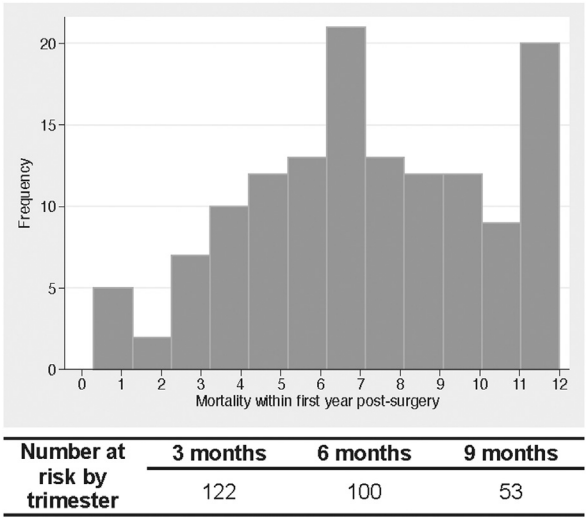

Fig 1. Mortality in the first year after surgery, and total number of patients in the early mortality group in each trimester (number at risk).

gemcitabine and chemoradiation (26%) after surgery. Of those who did not, one-half (30 patients) had received neoadjuvant treatment and the remaining 32 patients (26%) received no treatment at all. The proportion of patients who received chemotherapy and/or radiotherapy in the early mortality group was 74%, slightly lower than the proportion of patients in the late mortality (survival > 12 months) group (84%), but this difference was not significant.

The median CACI score was 4 in the early mortality group and 3 for the full cohort (range, 0–14). Neither age nor single comorbidities were predictive of early mortality. In the multivariable analysis a CACI of ≥4 doubled the odds of early mortality (odds ratio [OR], 2.04; 95% CI, 1.35–3.09; $P = .001$),

Table III. Predictors of early mortality by logistic regression

	Univariate analysis		*Multivariate analysis*	
Predictor	*OR (95% CI)*	P *value*	*OR (95% CI)*	P *value*
CACI ≥ 4	2.04 (1.35–3.09)	.001	2.17 (1.31–3.53)	.001
LVI	1.93 (1.25–3.00)	.003	1.29 (0.78–2.15)	NS
PNI	2.34 (1.00–5.68)	.060	2.49 (0.82–7.56)	NS
pN	2.12 (1.28–3.50)	.004	1.77 (1.00–3.18)	.058
R1	1.60 (1.00–2.57)	.052	1.75 (1.02–3.00)	.041

CACI, Charlson Age Comorbidity Index; *LVI*, lymphovascular invasion; *NS*, nonsignificant; *pN*, presence of metastatic lymph nodes in the histologic specimen (American Joint Committee on Cancer classification); *PNI*, perineural invasion.

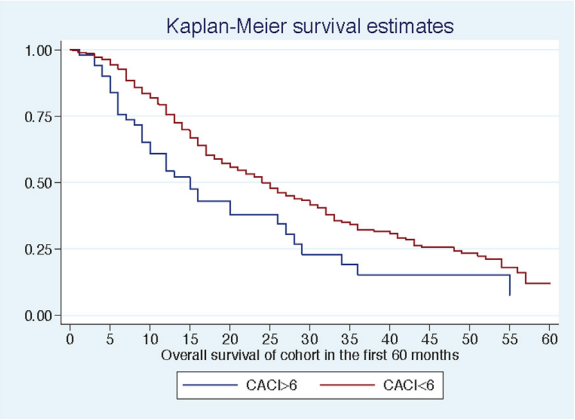

Fig 2. Kaplan–Meier curve according to Charlson Age Comorbidity Index (CACI) score depicts survival advantage for patients with lower scores. (Color illustration of the figure appears online.)

and a CACI of ≥6 tripled the odds (OR, 2.89; 95% CI, 1.56–5.30; P = .001), with 27 of 53 patients (51%) with a CACI of ≥6 dying within the 1 year.

From a pathologic standpoint, even though patients in the early mortality group were more likely to have higher AJCC stage, lymphovascular invasion, and positive lymph nodes, only a positive resection margin (OR, 1.75; 95% CI, 1.02–3.00; P = .041) and positive lymph nodes (OR, 1.77; 95% CI, 1.00–3.18; P = .058) were predictors of early mortality in the multivariable analysis (Table III).

Mortality within the first 90 days (perioperative mortality). Fourteen patients (2.8%) died within the first 90 days after surgery, 8 from septic and/or hemorrhagic shock, 2 from pulmonary embolism, 1 from myocardial infarction, 2 from unknown causes, and 1 from disease progression. Age alone was not predictive of perioperative mortality, but a CACI of ≥4 increased 4-fold the risk of death within 3 months of surgery (OR, 3.96; 95% CI, 1.22–12.80; P = .022).

CACI score and patient outcome. In addition to increasing perioperative mortality, a CACI of ≥4 increased the odds of postoperative complications by 52% (OR, 1.52; 95% CI, 1.01–2.28; P = .042). For patients who underwent a Whipple procedure, the median duration of stay was 7 days (range, 3–77) and a CACI of ≥4 doubled the odds of a duration of stay of ≥10 days (OR, 2.21; 95% CI, 1.44–3.40; P < .001).

Regarding disposition at discharge, 84% of patients were able to return either home or home with visiting nurse, and the remaining went to a rehabilitation facility. A CACI of ≥4 increased the odds of discharge to a rehabilitation facility by 6-fold (OR, 5.75; 95% CI, 3.31–9.97; P < .001).

When looking at overall survival in the Cox proportional hazards analysis a CACI score of ≥4 reduced overall survival by 37% (hazard ratio, 1.37; 95% CI, 1.04–1.79; P = .023) and a CACI score of ≥6 reduced it by 74% (hazard ratio, 1.74; 95% CI, 1.11–2.72; P = .016). The Kaplan–Meier survival curve is shown on Fig 2.

DISCUSSION

A clinician counseling a patient with potentially resectable pancreatic cancer on the appropriateness of care is weighing not only the risk of death or significant complications from a major operation, but also the likelihood that the patient will have a survival benefit from the intervention. Although data on survival of patients with resectable pancreatic cancer who do not undergo surgery are lacking, we can extrapolate from the survival of patients with either locally advanced or metastatic pancreatic cancer treated with chemotherapy. Newer regimes, like FOLFIRINOX, have increased survival to >11 months,[7,9] and patients with earlier stages would presumably do better. It would, therefore, be reasonable to expect ≥1 year of survival after surgery for pancreatic cancer and to consider less than that a failure. The problem is that predicting mortality in pancreatic cancer has always relied heavily on pathologic

data, which, by definition, are only available after resection. We currently lack tools to properly advise patients before surgery on their individual likelihood of surviving beyond 1 year.

Our data show that 27% of patients undergoing operative resection (mostly pancreaticoduodenectomies) for pancreatic cancer died within the first 12 months after the operation. About 10% of these deaths (2.8%) occurred within the first 90 days of the operation, and for the most part these deaths were derived from postoperative complications. The remaining 25%, which we defined as the "early mortality" group, died within months 3 and 12 (median, 7). This early demise occurred despite the fact that 74% of patients had received adjuvant or neoadjuvant treatment, a proportion that was not different from that of resected patients who survived >12 months. Other large series have also shown that the proportion of pancreatic cancer patients who are no longer alive 1 year after surgery is quite significant, with numbers ranging from 14 to 30%.[8,10,15,16]

Our goal was to identify factors predicting early death after surgery for pancreatic cancer. Not surprisingly, we found that positive lymph nodes and lymphovascular invasion were both independent predictors in the multivariable model, but the strongest predictor was a CACI of ≥6, which nearly tripled the odds of death within the first year. An example of a patient with a score 6 would be one ≥70 years, diabetic, and with a prior history of congestive heart failure and chronic obstructive pulmonary disease.

The Charlson comorbidity index is a statistically validated tool that assigns different weights to patients' comorbidities to predict mortality, and that can be adjusted to the age of the patient. It has been used extensively in studies on cancer and other medical conditions to predict outcome.[17-20] In our study, unlike age alone, the CACI was able to predict not only mortality at 1 year, but also duration of stay, postoperative complications, and disposition. When looking only at patients who died in the immediate postoperative period, a CACI of ≥4 was associated with a 4-fold increase in the odds of death within 90-days. This finding is similar to that described by Hill et al,[16] who used a CACI of ≥3 to build an integer-based risk score to predict in-hospital mortality after pancreatic resection.

Mortality at 9 and 12 months after surgery for pancreatic cancer was previously evaluated in a study by Hsu et al[8] involving 740 patients. Those authors found age >75 years, tumor size ≥ 3 cm, poor differentiation, and presence of comorbidities (diabetes mellitus, cardiovascular disease and chronic obstructive pulmonary disease) to be significant predictors of early mortality. They did not, however, use a scoring system to classify comorbidities, and used tumor differentiation, which is typically only available after resection, as one of their variables. Another study found operative blood loss of >2 L to be associated with death within 6 months after surgery.[21] In our study, we found that patients who died within 1 year had an average estimated blood loss of 1.8 L compared with 0.7 L in patients who survived >1 year. Although this difference was significant, the variable did not hold in the multivariable analysis. To our knowledge, the CACI has not been evaluated as a tool to analyze early mortality after pancreatic cancer resection. In addition to its simplicity, it has the advantage of not including pathologic variables, and therefore being applicable before the operation is undertaken.

It is, of course, impossible to determine what would have been the course of these patients who died within the first year of surgery had they had not undergone the operation. Because the majority of patients received either adjuvant or neoadjuvant treatment, we cannot argue that not undergoing an operation and giving chemotherapy instead would have been better in terms of survival or quality of life.

Taken together, our findings indicate that the CACI can be useful to predict increased duration of stay, postoperative complications, disposition, and mortality within 1 year of pancreatic resection. Its use may be relevant to refocus appropriateness of care in some circumstances. The knowledge that a CACI of ≥6 is associated with a <50% likelihood of survival beyond 1 year may allow patients and their families to make a more informed decision regarding surgery, and for patients who do undergo surgery and have a high CACI, the perioperative team can anticipate a higher likelihood of complications and consequently a longer duration of stay and recovery. Additional studies are needed to confirm these observations and clarify the usefulness of CACI and other scores in the management of patients with pancreatic cancer.

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