ORIGINAL ARTICLE

Recognition of Complications After Pancreaticoduodenectomy for Cancer Determines Inpatient Mortality

Evan S Glazer[1], Albert Amini[1], Tun Jie[1], Rainer WG Gruessner[1], Robert S Krouse[1,2], Evan S Ong[1]

[1]Department of Surgery, The University of Arizona;
[2]Surgical Care Line, The Southern Arizona Veterans Affairs Healthcare System. Tucson, AZ, USA

ABSTRACT

Context While perioperative mortality after pancreaticoduodenectomy is decreasing, key factors remain to be elucidated. **Objective** The purpose of this study was to investigate inpatient mortality after pancreaticoduodenectomy in the Nationwide Inpatient Sample (NIS), a representative inpatient database in the USA. **Methods** Patient discharge data (diagnostic and procedure codes) and hospital characteristics were investigated for years 2009 and 2010. The inclusion criteria were a procedure code for pancreaticoduodenectomy, elective procedure, and a pancreatic or peripancreatic cancer diagnosis. Chi-square test determined statistical significance. A logistic regression model for mortality was created from significant variables. **Results** Two-thousand and 958 patients were identified with an average age of 65±12 years; 53% were male. The mean length of stay was 15±12 days with a mortality of 4% and a complication rate of 57%. Eighty-six percent of pancreaticoduodenectomy occurred in teaching hospitals. Pancreaticoduodenectomy performed in teaching hospitals in the first half of the academic year were associated with higher mortality than in the latter half (5.5% *vs*. 3.4%, P=0.005). On logistic regression analysis, non-surgical complications are the largest predictor of death (P<0.001) while operations in the latter half of the academic year are associated with decreased mortality (P<0.01). **Conclusions** The timing of pancreaticoduodenectomy for cancer remained more predictive of mortality than age or length of stay; only complications were more predictive of death than time of year. This suggests that there remains a clinically and statistically significant learning curve for trainees in identifying complications; further study is needed to prove that identification of complications leads to a decrease in mortality rate by taking corrective actions.

INTRODUCTION

Elective pancreaticoduodenectomy in patients with primary pancreatic cancer provides the only hope for long-term cure in patients even though the 5-year survival is less than 10% even when curative resection are performed [1, 2]. Other modalities for treatment of pancreatic and peripancreatic cancers, such as radiotherapy and chemotherapy, are associated with significantly worse long term survival causing patients to accept higher rates of perioperative morbidity and mortality in the hopes of resectability and long term cure [3, 4]. Likewise, advances in cross sectional imaging with MRI and CT have resulted in fewer non-therapeutic operations [5]. While centralization of this procedure has decreased morbidity and mortality, pancreaticoduodenectomy remains one of the most morbidly elective operations with relatively high mortality.

There remains a significant variability to the quality and quantity of pancreaticoduodenectomy performed based on surgeon experience, patient health, hospital location, patient referral patterns, and volume of complex operations performed in a given institution [6, 7, 8]. Many of these factors are uncontrollable, and patient may choose not to travel for an operation for many reasons. Likewise, increased mortality associated with a low volume surgeon may be ameliorated in high volume centers [7]. In addition, some patients with resectable pancreatic cancer may not be referred to a surgeons resulting in patient selection difficulties outside of the surgeon's control.

Received July 27th, 2013 – Accepted September 27th, 2013
Keywords Intraoperative Complications; Morbidity; Mortality; Pancreaticoduodenectomy
Abbreviations ICD: International Classification of Diseases; NIS: Nationwide Inpatient Sample
Correspondence Evan Ong
Arizona Health Science Center; 1501 N. Campbell Ave.; Box 245131; Tucson, AZ 85724-5131;USA
Phone: +1-520.626.6664; Fax: +1-520.626.7785
E-mail: eong@surgery.arizona.edu

The Nationwide Inpatient Sample (NIS) is an inpatient administrative database representing 20% of hospitalizations in the USA [9]. It collects diagnostic and procedural patient discharge data as well as hospital data. Only inpatient data elements exist in this database, so no information regarding medium- or long-term survival can be elucidated. Likewise, this is an administrative database based on coding by expert coders in each hospital.

The purpose of this study was to investigate recent inpatient mortality after pancreaticoduodenectomy utilizing the NIS database's two most recent years. We hypothesized that modifiable factors, such as teaching status or time of year, contribute to inpatient mortality after pancreaticoduodenectomy. A secondary endpoint of this study was to investigate contributing factors that are associated with complications after elective pancreatico-duodenectomy for cancer.

METHODS

Data source

The NIS is a database of patient-discharges only contained data elements for that inpatient hospitalization. It represents approximately 20% of all inpatient admissions in the USA, and it is a representative sample maintained by the Healthcare Cost and Utilization Project (Agency for Healthcare Research and Quality). The NIS contains over 100 patient level data elements (demographic, diagnostic, and procedural) as well as hospital data such as location, median income of patients by zip code, teaching status, etc. Data in the NIS is de-identified. In addition, expected payer data is contained for each admission/discharge as well. Data from January 1, 2009 to December 31, 2010 (most recent available) were investigated. The academic year is defined as July 1 through June 30 with the early academic year July 1 through December 31 and the latter academic year January 1 through June 30. The institutional review board deemed this research exempt from review.

Patient Characteristics

Patient discharge data (International Classification of Diseases 9th edition, ICD-9, diagnostic and procedure codes) and hospital characteristics were investigated in two recent years of the NIS database (2009 and 2010). The inclusion criteria were an ICD-9 procedure code for pancreatico-duodenectomy, an elective procedure, and a pancreatic or peripancreatic cancer diagnosis.

In addition, the NIS also contains clinical classification codes that categorize data representing multiple ICD-9 codes. For example, diabetes mellitus has numerous ICD-9 codes depending on clinical sequelae, but only two classification codes (complicated or uncomplicated diabetes mellitus). NIS data elements for each patient discharge contain each of the appropriate ICD-9 codes as well as the overall classification code. Likewise, surgical complications as well as any inpatient complication have unique clinical classification codes used to identify these diagnoses. Finally, certain terms are defined by the NIS and uniform throughout the data set such as chronic medical conditions (number of conditions requiring ongoing medical attention), surgical complications (complications directly related to surgical technique), urban/rural location, etc.

STATISTICS

Data are reported as mean and standard deviation values or frequencies. Data analysis was performed with STATA version 11 (College Station, TX, USA). Proportions were analyzed for categorical or ordinal data. Univariate analysis was performed by means of the chi-square test in order to determine statistical significance with a two-tailed alpha level of 0.05. Multivariate logistic regression models for mortality and inpatient complications were created from statistically significant or near statistically significant variables on univariate analysis ($P<0.1$); odds ratios (ORs) and 95% confidence intervals (95% CIs) were reported.

RESULTS

Patient Characteristics

Of the 2,958 patients who underwent pancreatico-duodenectomy with complete data, the average age was 65±12 years while 53% were male. Seventy-six percent of patients were Caucasian while 9% were African Americans, 8% were Hispanic, 3% were Asian, 0.5% were Native American, and the rest were identified as 'Other.' Six percent of patients were coded as obese (or morbidly obese). The mean length of stay was 15±12 days with an inpatient mortality of 4% and a complication rate of 57%. Eighty-six percent of pancreaticoduodenectomy occurred in teaching hospitals while 97% were performed in urban hospitals. Ninety-six percent of hospitals in the Northeast are teaching hospitals, 86% of hospitals in the Midwest and South are teaching hospitals and 79% percent of hospitals are teaching hospitals in the West (overall $P<0.001$).

Inpatient Mortality

On univariate analysis, inpatient mortality after elective pancreaticoduodenectomy for cancer was significantly associated with age, time during academic year, number of chronic medical diagnoses, complications, and length of stay (Table 1). Patients undergoing pancreaticoduodenectomy in the latter half of the academic year have decreased odds of inpatient mortality (Figure 1,

Table 1. Univariate and multivariate analysis for inpatient mortality after pancreaticoduodenectomy. Univariate and multivariate analysis for inpatient mortality after pancreaticoduodenectomy for cancer demonstrate that a non-surgical complication is the largest predictor of death while chronic pancreatitis and operations in the latter half of the academic year are associated with decreased mortality.

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.04	1.02-1.06	<0.001	1.03	1.02-1.05	<0.001
Female gender	0.91	0.64-1.29	0.645	-	-	-
Ethnicity	0.97	0.81-1.16	0.740	-	-	-
Obesity	0.58	0.24-1.44	0.239	-	-	-
Non-private insurance	1.54	0.83-2.83	0.169	-	-	-
Household income [a]	0.89	0.77-1.05	0.194	-	-	-
Transfer patient	1.30	0.73-2.29	0.373	-	-	-
Urban hospital	0.85	0.30-2.35	0.332	-	-	-
Teaching hospital	0.68	0.43-1.07	0.098	0.83	0.52-1.32	0.441
Latter half of academic year	0.60	0.42-0.86	0.005	0.61	0.42-0.88	0.008
Hospital region [b]	1.34	1.12-1.60	0.001	1.22	1.02-1.47	0.030
Chronic medical diagnoses	1.11	1.10-1.80	0.001	1.03	0.96-1.1	0.839
Chronic pancreatitis	0.24	0.09-0.65	0.005	0.20	0.06-0.63	0.006
Diabetes mellitus	0.78	0.53-1.14	0.299	-	-	-
Non-surgical complications	12.4	6.00-25.4	<0.001	10.2	4.7-22.3	<0.001
- Myocardial infarction	1.70	0.96-3.02	0.074			
- Venous thromboembolism	2.42	1.46-4.02	0.001			
disease	5.07	3.47-7.40	<0.001			
- Pneumonia	16.3	11.2-23.7	<0.001			
- Acute renal injury	0.94	0.49-1.82	0.864			
- Urinary tract infection						
Surgical complications	3.35	2.30-4.90	<0.001	1.08	0.72-1.63	0.712
- Fistula	0.33	0.05-2.45	0.283			
- Abscess	2.20	1.30-3.50	0.001			
Length of stay	1.03	1.02-1.04	<0.001	1.02	1.01-1.03	<0.001

[a] Patients with income over the median value *vs.* those under the median value

[b] Patients outside the Northeast region *vs.* those of Northeast region

P=0.005). Likewise, chronic pancreatitis was protective of mortality (OR=0.24, univariate P=0.005).

Hospital and community level economic data elements such as rural location, hospital owner, and median home income were not significantly related to mortality. Interestingly, there was significant variation in mortality across the USA with patients in the South having the highest inpatient mortality (6.3%) and patients in the Northeast having the lowest mortality rate (2.3%, Figure 2, P=0.001).

Non-surgical complication had the largest effect on mortality based on univariate analysis (OR=12.4, P<0.001). Of the non-surgical complications, acute renal injury had the largest effect on mortality (OR=16.3, P<0.001). Likewise, surgical

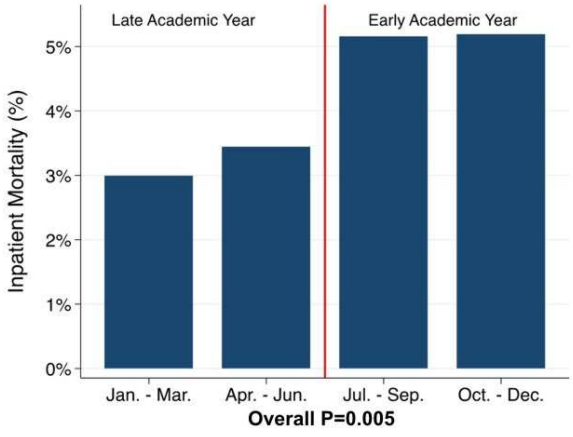

Figure 1. When divided into calendar quarters, inpatient mortality after pancreaticoduodenectomy decreases in the latter half of the academic year (P=0.005; chi-square test).

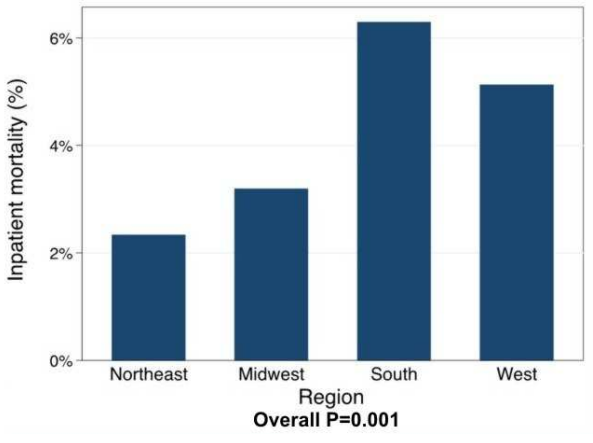

Figure 2. Mortality varies by region across the USA (P=0.001; chi-square test).

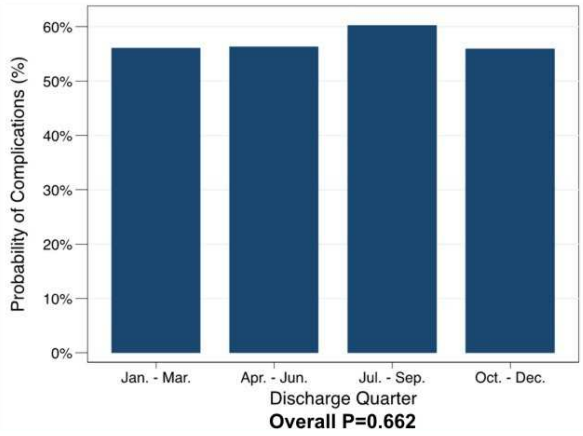

Figure 3. The overall inpatient complication rate after pancreaticoduodenectomy remains unchanged throughout the year (P=0.662; chi-square test).

complications were associated with a 3-fold odds having died while in the hospital (P<0.001). Intra-abdominal abscess had the highest surgery specific association with mortality (OR=2.2, P=0.001).

Teaching hospital status was not associated with inpatient mortality after pancreaticoduodenectomy (4% mortality in teaching hospitals *vs*. 6% mortality in non-teaching hospitals, P=0.098). However, pancreaticoduodenectomy performed in teaching hospitals in the first half of the academic year were associated with a higher mortality than in the latter half (5.5% *vs*. 3.4%, P=0.005). Likewise, for all patients in all hospitals, operations in the latter half of the academic year were associated with a lower likelihood of mortality (OR=0.6, P=0.006).

On multivariate logistic regression analysis, non-surgical complications are the largest predictor of death (OR=10.2, P<0.001) while chronic pancreatitis and operations in the latter half of the academic year are associated with decreased mortality (Table 1). On multivariate analysis, surgical complications were not associated with mortality (P=0.712). While length of stay and age were both associated with mortality (each multivariate P<0.001) the overall effect was minimal (OR=1.03 per year and OR=1.02 per day, respectively). On multivariate analysis, patients outside of the Northeast region were associated with a higher mortality rate (OR=1.22, P=0.030). Secondary non-surgical complications, such as pneumonia or acute renal injury, had the largest associations with mortality (Table 1).

Complications

The overall complication rate was 57%. Surgical specific complications (i.e., fistula, abscess, infection, reaction to blood transfusion, etc.) occurred in 39% of patients. All patients who had surgical complications also had at least one unrelated non-surgical complication. The time of academic year was not associated with complications (Figure 3, P=0.662). The Northeast region had the lowest complication rate (52%) while the West region had the highest (62%); the complication rate was 60% in the South and 53% in the Midwest (overall P<0.001).

On univariate analysis (Table 2), there was a small but statistically significant relationship between age and complications (OR=1.01 per year, P<0.001) while there was a larger association (protective effect) between being female and developing complications (OR=0.81, P=0.004). In addition, it

Table 2. Univariate and multivariate analysis of predictor associated with inpatient complications after pancreaticoduodenectomy for cancer. On multivariate analysis, chronic medical conditions and length of stay were both associated with a higher probability of inpatient complications after pancreaticoduodenectomy for cancer.

Variable	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.01	1.00-1.02	<0.001	1.01	0.99-1.01	0.098
Female gender	0.81	0.70-0.93	0.004	0.86	0.73-1.00	0.072
Ethnicity	0.99	0.92-1.06	0.812	-	-	-
Obesity	1.28	0.94-1.74	0.113	-	-	-
Non-private insurance	1.29	0.95-1.76	0.099	1.22	0.87-1.69	0.252
Household income [a]	1.01	0.94-1.07	0.878	-	-	-
Transfer patient	1.08	0.81-1.42	0.610	-	-	-
Urban hospital	1.11	0.71-1.76	0.632	-	-	-
Teaching hospital	0.77	0.62-0.96	0.021	0.85	0.67-1.08	0.184
Hospital region [b]	1.16	1.08-1.24	<0.001	1.05	0.97-1.13	0.247
Latter half of academic year	0.92	0.80-1.07	0.292	-	-	-
Chronic medical diagnoses	1.14	1.11-1.18	<0.001	1.10	1.07-1.14	<0.001
Chronic pancreatitis	1.01	0.80-1.27	0.926	-	-	-
Diabetes mellitus	1.01	0.87-1.18	0.889	-	-	-
Length of stay	1.11	1.10-1.12	<0.001	1.11	1.10-1.12	<0.001

[a] Patients with income over the median value *vs*. those under the median value
[b] Patients outside the Northeast region *vs*. those of Northeast region

was found that teaching hospitals were protective of complications (OR=0.77, P=0.022). Furthermore, the number of chronic diagnoses was associated with inpatient complications (OR=1.14 per diagnosis, P<0.001). Finally, length of stay was associated with complications as well (OR=1.11 per day, P<0.001).

On multivariate analysis, the number of chronic medical diagnoses (OR=1.10, P<0.001) and length of stay were associated with complications (OR=1.11 per day, P<0.001). Specifically, age was not significantly associated with complications on multivariate analysis (Table 2, P=0.098), as well gender and insurance status were not associated with complications on multivariate analysis.

DISCUSSION

The results herein describe mortality after elective pancreaticoduodenectomy for cancer as being associated with both modifiable and non-modifiable factors. The greatest variable associated with mortality is the presence of non-surgical complications (OR=12.4) while the second largest association is time of operation during the academic year (OR=0.60, favoring the latter half of the academic year). Since no events can occur after death, these two variables are powerful predictors of inpatient death. Age is associated with increasing mortality, albeit a small association (OR=1.03). However, complications remain steady throughout the year suggesting that there was no direct link between complications and inpatient mortality. Hospital teaching status alone is not associated with mortality on multivariate analysis, but the vast majority of pancreaticoduodenectomy are performed at teaching hospitals limiting the utility of this factor. Finally, length of stay is associated with inpatient mortality. This is likely a secondary measure of the complications and not a contributing factor.

A causative link between complications and death has been well described [10, 11, 12]. In this case, the limitations of the NIS do not permit us to prove that recognition of complications, and correction thereof, prevents inpatient death. However, the data is convincing that most pancreaticoduodenectomy are performed in teaching hospitals and complications are associated with mortality. Since trainees are promoted each summer, a new set of individuals take on primary identification of complications each July. Furthermore, a learning curve associated with complications is established in the literature, especially regarding trainees [13, 14, 15]. This learning curve seems to be between 30 and 50 cases and take as long as 4 months of regular training to master a single set of learning/operative objectives. Therefore, it is reasonable to theorize that there is link between trainees recognizing complications sooner as the academic year progresses. Since the rate of complications did not change throughout the year, we suppose that recognition of complications is primary means of decreasing mortality as individual trainees may take action sooner. Of course, it is difficult to prove this. However, we suggest that since non-surgical complications remains predictive of mortality, it is the recognition of these complications that leads to decrease mortality later in the academic year. Likewise, intraoperative factors not recorded in the NIS data set, such as intraoperative blood loss and operative time, may be associated with complications and mortality; these factors, likely, would also change latter in the academic year.

Overall, the difference in mortality seen between teaching and non-teaching hospitals did not reach statistical significance (P=0.098 at univariate analysis). However, complications were less likely in teaching hospitals (56% *vs*. 62%; P=0.021, chi-square test). Taken together, despite a learning curve for trainees in teaching hospitals, teaching hospitals appear to be safer given the significantly lower inpatient complication rate. Furthermore, there was no significant difference in surgical complications between teaching and non-teaching hospitals (39% *vs*. 43%, P=0.184, chi-square test). Therefore, we suppose that teaching hospitals not only start the academic year safer than non-teaching hospitals, but that difference increases throughout the academic year as trainees refine their diagnostic skills and continue to recognize complications. Of course, teaching hospitals are often larger centers with multiple resources, so it is not necessarily the case that trainees *per se* are the cause of improved outcomes.

The largest association with complications is the number of chronic medical diagnoses (OR=1.11, P<0.001 at univariate analysis). The NIS defines chronic medical diagnoses as those conditions limiting activities, lasting longer than one year, and requiring ongoing medical interventions. Given that the median number of chronic medical diagnoses is 5, it is likely clinically significant that an increase of one chronic medical diagnosis increases the odds of a complication by more than 10%. However, the current literature is lacking regarding pre-operative medical diagnoses and inpatient complications as described herein after pancreaticoduodenectomy. Interestingly, we have found that a diagnosis of chronic pancreatitis is associated with decreased odds of mortality. The NIS does not discern whether this diagnosis is known prior to surgery or identified after surgery, but we theorize that chronic pancreatitis often leads to dilated pancreatic duct that may be easier to anastomose to small intestine.

Interestingly, the inpatient mortality rate varied by the region in the USA where the operation occurred (Figure 2). The Northeast had the lowest mortality rate (2%), while the South had the highest (6%; P=0.001). Likewise, complication rates were lowest in the Northeast and highest in the South, suggesting that the higher complication rate is not only correlated with mortality but leads to it.

Unfortunately, neither nutritional status nor functional status is routinely recorded as part of the NIS. While poor nutrition and poor function prior to pancreaticoduodenectomy should remain relative contraindications, we suggest that more than 5 chronic medical conditions places the patient at above average risk of complications while an inpatient. This is quite concerning since complications have the largest association with mortality. We believe that the high density of hospitals in the Northeast contributes to more centralized care that leads lower complications as has been reported previously.

The major limitations of this study relate to it being an administrative databases. First, the quality of the data is limited by the coding recorded at the individual patient level. Likewise, the NIS limits diagnosis and procedures to 25 codes and 15 codes, respectively. Taking this together, we may be missing critical data that was either not coded at all or coded beyond the scope of the NIS. Furthermore, a limitation of ICD-9 codes relates to the severity of disease. While some diseases such as diabetes have unique ICD-9 codes for sequelae of the primary disease, this is not always the case. Finally, we have no data concerning mortality or complications after discharge. Furthermore, re-admissions data is not possible in the NIS.

In conclusion, the timing of elective pancreaticoduodenectomy for cancer remained more predictive of mortality than age, length of stay, or comorbidities; only complications were more predictive of death than time of academic year. Since the vast majority of pancreatico-duodenectomy are performed in teaching hospitals, this suggests that there remains a clinically and statistically significant learning curve for trainees in identifying medical complications in post operative patients that leads to inpatient mortality.

Conflicts The authors have no conflicts or disclosures

Previous dissemination Portions of this work were presented at the Society of Surgical Oncology's Annual Cancer Symposium in March 2013 (National Harbor, MD, USA)

Acknowledgments The authors would like to acknowledge Mary Knatterud for assistance with manuscript preparation

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