The Effect of Atrial Fibrillation on Perioperative Outcomes in Patients With Pancreatic Cancer Undergoing Open Pancreaticoduodenectomy: Analysis of the National Inpatient Sample

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Abstract

Background: To assess the role of atrial fibrillation (AF) on perioperative outcomes in patients with pancreatic cancer undergoing open pancreaticoduodenectomy (OPD).

Methods: We investigated patients with pancreatic cancer undergoing OPD during 2012-2014 within National Inpatient Sample (NIS) database. The study population was divided into two groups based on the presence of AF. In-hospital mortality, length of stay (LOS), cost of hospitalization, and in-hospital complications were compared between the two groups. Logistic regression models and linear regression were used to adjust for potential confounders.

Results: Of the 12,785 patients aged ≥ 18 years undergoing OPD during years 2012-2014, 11,469 (90%) had no AF and 1,316 (10%) had AF. Patients with AF were found to have significantly higher cost (coefficient 0.35, 95% CI 0.06-0.64, $P = 0.02$), but similar mortality (OR 3.57, 95% CI 0.86-14.87, $P = 0.08$) and LOS (coefficient 0.16, 95% CI 0-0.33, $P = 0.052$) compared to those without AF. The risk of gastrointestinal anastomotic leakage (OR 22.11, 95% CI 3.25-150.22, $p = 0.002$), cardiac complications (OR 17.88, 95% CI 5.32-60.11, $p < 0.001$), respiratory complications (OR 2.38, 95% CI 1.23-4.60, $p = 0.01$), pulmonary embolism (OR 18.53, 95% CI 2.67-128.62, $p = 0.003$), and perioperative shock (OR 5.16, 95% CI 1.03-25.72, $p = 0.045$) were found to be significantly higher in AF group than non-AF group. In elderly patients (> 65 y), AF was found to be associated with a significantly higher cost (coefficient 0.38, 95% CI 0.05-0.71, $P = 0.023$), longer LOS (coefficient 0.21, 95% CI 0.03-0.39, $P = 0.023$), higher incidence of cardiac complications (OR 17.38, 95% CI 3.42-88.43, $p = 0.001$), respiratory complications (OR 2.93, 95% CI 1.31-6.53, $p = 0.009$) and postoperative shock (OR 27.06, 95% CI 2.35-311.15, $p = 0.008$), yet similar mortality (OR 3.35, 95% CI 0.58-19.37, $P = 0.177$).

Conclusions: AF was found to be associated with higher cost in pancreatic cancer patients undergoing OPD, as well as increased occurrence of cardiac complications, respiratory complications, pulmonary embolism and perioperative shock. Surgeons should pay special attention to these patients and formulate an appropriate perioperative evaluation plan.

Background

Pancreatic cancer is one of the most deadly neoplasm in the United States and it is the fourth leading cause of death from cancer[1]. A pancreaticoduodenectomy (PD), pancreatoduodenectomy, Whipple procedure, or Kausch-Whipple procedure is reference surgical option for the resection of pancreatic tumors[2]. During a PD, pancreatic head, common bile duct, gallbladder, and duodenum along with some part of the proximal jejunum need to be removed, and partial gastrectomy might be conducted[3]. The approach of PD includes open pancreaticoduodenectomy (OPD), laparoscopic pancreaticoduodenectomy (LPD) and robot-assisted pancreaticoduodenectomy (RPD).

Atrial fibrillation (AF) is the most common arrhythmia (1–2% in the general population)[4], and it is associated with increased perioperative mortality and morbidity[5]. Several studies have proved that AF is

related to bad outcomes and more perioperative complications[6, 7]. However, there is limited literature evaluating the impact of AF on outcomes of patients with pancreatic cancer undergoing OPD, especially through large-scale studies. The purpose of this study was to investigate the effect of AF on perioperative outcomes in patients with pancreatic cancer undergoing OPD.

Methods

1 Data Source

Supported by the Healthcare Cost and Utilization Project (HCUP), the National Inpatient Sample (NIS) is one of the largest inpatient administrative databases in the U.S. It represents approximately 20% of hospitalization in the USA, and it extracts data of nearly 8 million hospital discharges from more than 1,000 hospitals per year. The diagnosis and procedure codes in NIS database are based on the International Classification of Diseases, Ninth Revision, and Clinical Modification, Ninth Revision (ICD-9-CM). 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 from 2012 to 2014 were investigated. As NIS data are de-identified, this study was exempt from institutional review board evaluation.

2 Study Population

We searched for patient discharge data (ICD-9-CM) and hospital characteristics of patients ≥ 18 -year-old during years 2012-2014. The population of interest in this study was patients who underwent OPD, identified by ICD-9-CM procedure code 52.7. Robotic assisted procedures (ICD-9 procedure code 17.4) and laparoscopic procedures (ICD-9 procedure code 54.21) were excluded. Non-elective procedures were also excluded. Patients were then stratified into 2 groups based on the presence of AF (ICD-9-CM code 427.3). Patient demographics (age, sex, race, income, insurance status), hospital characteristics (location, teaching status and size) and common comorbidities were identified with ICD-9-CM codes (Supplement Table 1). Patients with missing data were excluded from our analyses.

3 Study endpoints

The primary endpoint of this study included (1) in-hospital mortality; (2) length of stay (LOS); (3) cost and (4) in-hospital complications, including gastrointestinal (GI) anastomotic leakage, GI bleeding, acute kidney injury (AKI), gastroparesis, blood transfusion, cardiac complications, respiratory complications, pneumonia, pulmonary embolism (PE), urinary tract infection (UTI), cardiac arrest, postoperative sepsis, postoperative shock and wound complications.

4 Statistical Analysis

We used a survey-specific method, with commands `svyset` and `svy` with `pweight` using `DISCWT` for 2012 to 2014 to generate nationwide estimates for each year. The `stratum` statement specifies `NIS_STRATUM` as the stratum identifier and the `cluster` statement specifies `HOSP_NIS` as the cluster identifier.

Descriptive statistics was used to compare demographic characteristics and outcomes between OPD patients with and without AF. The baseline characteristics were compared between the AF group and control group using the Chi-square test for categorical variables and Student's t-test for continuous variables. In our multivariable regression model, we assessed differences in binary outcomes by using logistic regression (logistic command in Stata [StataCorp]) and in continuous outcomes by using linear regression (Stata command regress). All above were carried out in weighted samples.

Analyses were performed using Stata version 14 (StataCorp, College Station, TX). All statistical tests were two-sided, and P values less than 0.05 were considered statistically significant.

Results

1 Patient and hospital characteristics

A total of 12,785 patients aged ≥ 18 years underwent OPD during years 2012-2014 (Figure 1). Among them, 11,469 (90%) had no AF and 1,316 (10%) had AF. There were significantly more male, more Caucasian, older and Medicaid patients in AF group. There was no statistically significant difference in median annual income, hospital bed size, region, location and teaching status. As for comorbidities, history of myocardial infarction (MI), hypertension, diabetes mellitus, history of stroke, peripheral vascular disease (PVD), congestive heart failure (CHF), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), valvular heart disease (VHD), coronary artery disease (CAD) and cirrhosis were more prevalent in the AF group. There was no significant difference in thrombocytopenia, chronic liver disease and obesity between the AF and non-AF group (Table 1).

2 Mortality

The in-hospital mortality rate for all patients was 3.17%. Mortality in AF group was higher than that in non-AF group (7.60% versus 2.66%). Multivariable regression analysis revealed that there is a trend that AF was associated with higher mortality in patients with pancreatic cancer undergoing OPD (adjusted OR 3.57, 95% CI 0.86-14.87, $P = 0.08$). We further focused on elder patients (age > 65). However, results of multivariable regression analysis still showed no significant difference (adjusted OR 3.35, 95% CI 0.58-19.37, $P = 0.177$) (Table 2, Figure 2).

3 Length of stay

The in-hospital mean LOS for all patients with OPD was 12.1 days. Unadjusted analysis showed patients with AF had longer LOS (14.6 days versus 11.8). However, after multivariate regression we didn't get significant result (adjusted coefficient 0.16, 95% CI 0-0.33, $P = 0.052$). Significant difference was found in the subgroup analysis in patients older than 65 years (adjusted coefficient 0.21, 95% CI 0.03-0.39, $P = 0.023$) (Table 2, Figure 2).

4 Cost of hospitalization

The in-hospital mean cost for all patients with OPD was 40,450.05 US dollars. Unadjusted analysis showed patients with AF had a significantly higher cost of hospitalization (54,601.47 dollars versus 38,812.80 dollars). After multivariate regression we still got significant result (adjusted coefficient 0.35, 95% CI 0.06-0.64, $P = 0.02$). Among elder patients (> 65 years old), there was still significant difference between AF group and non-AF group on cost of hospitalization (adjusted coefficient 0.38, 95% CI 0.05-0.71, $P = 0.023$) (Table 2, Figure 2).

5 In-hospital complications

We also focused on in-hospital complications using univariate screening and multivariate regression. Patients in AF group has significantly higher incidence of GI anastomotic leakage (OR 22.11, 95% CI 3.25-150.22, $p = 0.002$), cardiac complications (OR 17.88, 95% CI 5.32-60.11, $p < 0.001$), respiratory complications (OR 2.38, 95% CI 1.23-4.60, $p = 0.01$), PE (OR 18.53, 95% CI 2.67-128.62, $p = 0.003$), postoperative shock (OR 5.16, 95% CI 1.03-25.72, $p = 0.045$) than non-AF group. While no difference in GI bleeding, AKI, gastroparesis, blood transfusion, pneumonia, UTI, cardiac arrest, postoperative sepsis and wound complications was observed. Among patients older than 65 years, significantly higher incidence of cardiac complications (OR 17.38, 95% CI 3.42-88.43, $p = 0.001$), respiratory complications (OR 2.93, 95% CI 1.31-6.53, $p = 0.009$) and postoperative shock (OR 27.06, 95% CI 2.35-311.15, $p = 0.008$) was found in AF group (Table 2, Figure 2).

Discussion

PD is the reference standard surgical method for the treatment of tumors in the head of the pancreas, the lower end of the common bile duct, the duodenal papilla, and certain benign lesions. The current perioperative mortality of PD is less than 5%[8], but the incidence of perioperative complications is up to 27.1% or even higher[9]. The prognosis of PD is poor, and the 5-year survival rate after surgery is only 16%-20%[10, 11]. Common complications of PD include pancreatic fistula, bile leakage, GI anastomotic leakage, GI bleeding, AKI, gastroparesis, cardiac complications, respiratory complications, UTI, postoperative sepsis, postoperative shock, wound complications, etc.[12, 13] Previous studies have shown that perioperative complications have an adverse effect on survival and prognosis in various tumor types including esophageal cancer[14], gastric cancer[15] and colorectal cancer[16]. Similarly, in pancreatic cancer, the occurrence of perioperative complications also adversely affects survival and prognosis.

AF is the most common type of arrhythmia[4], accounting for 1–2% of the overall population. Patients with AF are at higher risk of thrombo-embolic disease and often require regular anticoagulation therapy[17]. It has been reported that AF can significantly promote the occurrence of perioperative complications of various surgical operations including urinary system surgery and liver transplantation, etc.[6, 7, 18]

To the best of our knowledge, this is the first population-based study that investigated the impact of AF on the outcomes of pancreatic cancer patients with OPD. The reports on mortality of PD varies in various

studies. Cameron et al. summarized 1,000 consecutive PD and found that only 10 postoperative deaths, for a mortality of 1%[19]. Kneuert et al. reported that the 30-day mortality after PD was 2.9%[20]. Our study found that during three-year time from 2012 to 2014, the overall in-hospital mortality was 3.17%. The in-hospital mortality was 7.6% and 2.66% in the AF group and non-AF group, respectively, without significant difference (adjusted OR 3.57, 95% CI 0.86–14.87, $P = 0.08$). Kumar et al.[21] found that pulmonary complications were the leading cause for mortality after PD. Other causes of death include bile sepsis, liver failure, MI, pancreatic leak, etc. Narayanan et al.[22] showed that the most common cause of death after PD within 90 days is multisystem organ failure, followed by post-pancreatectomy hemorrhage, and cardiopulmonary arrest from myocardial infarction or pulmonary embolus. LOS was longer in AF group, but no significant difference was found (14.6 days versus 11.8, adjusted coefficient 0.16 (0-0.33), $P = 0.052$). There was a significant difference in cost between the two groups (54601.47 dollars versus 38812.80 dollars, adjusted coefficient 0.35 (0.06–0.64), $P = 0.02$). The need of more thorough evaluation of cardiac function and more complex management of perioperative complications might be a possible reason.

Our study found that the AF group had more perioperative complications than the non-AF group, including GI anastomotic leakage, cardiac complications, respiratory complications, PE and postoperative shock. Among all complications, the incidence of GI anastomotic leakage in the AF group was approximately 22 times higher than that in the non-AF group. Although AF may affect the stability of hemodynamics and thus affect the blood supply of the anastomosis, the number of occurrences in both groups is small (5 patients versus 30), so further study is needed to confirm the conclusion.

Botwinick et al.[23] reported that patients with AF are more likely to experience gastroparesis, but our study did not find the adverse effect of AF on gastroparesis. There were 249 patients included in Botwinick's study, of which only 13 had atrial fibrillation, so further research may be needed to confirm the relationship between atrial fibrillation and gastroparesis. In addition, no differences were found in GI bleeding, AKI, gastroparesis, blood transfusion, pneumonia, UTI, cardiac arrest, postoperative sepsis, wound complications, etc.

With the advancement of surgical techniques, more and more elderly pancreatic cancer patients with complex comorbidities receive PD. Several studies have shown that age has an important adverse effect on the occurrence of perioperative complications and survival after PD[24, 25]. So, we further analyzed patients aged > 65 years. No significant difference was found in mortality, while there was significant difference between the two groups in LOS and cost. As for complications, the differences in various complications between the AF group and the non-AF group in the elderly population are similar to the overall population. It can be seen that although age will increase complications and mortality, it will increase evenly between the two groups. Further studies are needed to reveal the influence of age on perioperative complications and death after whipple's surgery.

There are several limitations of the present study. First of all, our study is a retrospective study based on the NIS database with all inherent shortcomings. Secondly, because NIS is an inpatient database coding

with ICD-9-CM, complications without ICD-9 code, such as pancreatic fistula, bile leakage, cannot be analyzed. In addition, tumor information such as tumor type, stage, and neoadjuvant chemotherapy is absent in the NIS database, which may have an impact on the outcomes of OPD. Finally, as the follow-up information is not included within the NIS database, the postoperative outcomes is not discussed in this study. Despite these limitations, this is the first population-based study that investigated the impact of AF on the outcomes of pancreatic cancer patients undergoing OPD, providing surgeons data and serving as a basis for future prospective studies.

Conclusions

AF increases the cost of pancreatic cancer patients undergoing OPD, also increases the occurrence of cardiac complications, respiratory complications, PE, and postoperative shock. Surgeons should pay special attention to these patients and develop an appropriate preoperative evaluation plan.

Abbreviations

PD: pancreaticoduodenectomy

OPD: open pancreaticoduodenectomy

AF: atrial fibrillation

NIS: National Inpatient Sample

LOS: length of stay

ICD-9-CM: International Classification of Diseases, Ninth Revision, and Clinical Modification, Ninth Revision

Declarations

Ethics approval and consent to participate

This study was exempt from institutional review board evaluation of Beijing Friendship Hospital, Capital Medical University and informed consent was not required because this study was based on the NIS database, which includes fully anonymized and de-identified data.

Consent for publication

Not applicable.

Availability of data and materials

The HCUP dataset utilized for this study is publicly available for approved research studies. Further details and instructions for application can be found at: <https://www.hcup-us.ahrq.gov/nisoverview.jsp>.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZZ and WG provided administrative support. PH and YY contributed to the concept design and the draft of the manuscript. YH, HW, DW, KL participated in the acquisition of the data. PH, YY, CG and XZ conducted statistical analysis. All authors contributed to manuscript writing and approved the final version of the manuscript.

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Tables

Table 1
Characteristics of included patients

	No AF	AF	P value
Patient characteristics			
No. (%) of patients	11469 (90%)	1316 (10%)	
Female	5467 (47.67%)	495 (37.64%)	0.002
Race			0.023
White	8806 (76.85%)	1134 (85.48%)	
Black	1032 (9.01%)	48 (3.63%)	
Hispanic	845 (7.37%)	64 (4.84%)	
Asian or Pacific Islander	364 (3.17%)	32 (2.42%)	
Native American	43 (0.37%)	0 (0%)	
Other	369 (3.23%)	48 (3.63%)	
Median age, y	65.1	71.9	< 0.001
Median annual income in patient's zip code, US\$, no. (%)			0.347
\$1 - \$38,999	2416 (21.07%)	229 (17.44%)	
\$39,000 - \$47,999	2799 (24.40%)	326 (24.81%)	
\$48,000 - \$62,999	2957 (25.78%)	398 (30.23%)	
\$63,000 or more	3299 (28.75%)	362 (27.52%)	
Insurance type, no. (%)			< 0.001
Medicaid	6015 (52.58%)	1032 (76.72%)	
Medicare	780 (6.82%)	26 (1.91%)	
Private	4445 (38.85%)	272 (20.23%)	
Uninsured	200 (1.75%)	15 (1.14%)	
Hospital characteristics			
Hospital region, no. (%)			0.274
Northeast	2496 (21.75%)	270 (20.53%)	
Midwest	2436 (21.23%)	340 (25.86%)	

AF, atrial fibrillation.

	No AF	AF	P value
South	4210 (36.70%)	480 (36.50%)	
West	2329 (20.32%)	225 (17.11%)	
Hospital bed size, no. (%)			0.538
Small	950 (8.28%)	90 (6.84%)	
Medium	2125 (18.53%)	270 (20.53%)	
Large	8395 (73.19%)	955 (72.63%)	
Location of hospital			0.444
Rural hospital	95 (0.83%)	5 (0.38%)	
Urban hospital	11375 (99.17%)	1310 (99.62%)	
Teaching status of hospital			0.069
Rural and urban non-teaching hospital	1140 (9.94%)	85 (6.46%)	
Urban teaching hospital	10330 (90.06%)	1230 (93.54%)	
Comorbidity			
History of myocardial infarction	430 (3.75%)	105 (7.98%)	0.001
Chronic liver disease	1385 (12.07%)	165 (12.55%)	0.821
Hypertension	6555 (57.15%)	935 (71.10%)	< 0.001
Diabetes mellitus	3745 (32.65%)	535 (40.68%)	0.009
History of stroke	60 (0.52%)	20 (1.52%)	0.038
Peripheral vascular disease	390 (3.40%)	90 (6.84%)	0.004
Obesity	1190 (10.37%)	145 (11.03%)	0.738
Congestive heart failure	220 (1.92%)	175 (13.31%)	< 0.001
Chronic kidney disease	475 (4.14%)	125 (9.51%)	< 0.001
Chronic obstructive pulmonary disease	810 (7.06%)	160 (12.17%)	0.003
Thrombocytopenia	470 (4.10%)	65 (4.94%)	0.516
Valvular heart disease	290 (2.53%)	105 (7.98%)	< 0.001
Coronary artery disease	1385 (12.07%)	415 (31.56%)	< 0.001
Cirrhosis	147 (1.27%)	29 (2.41%)	0.401
AF, atrial fibrillation.			

Table 2
In-hospital outcomes

In-Hospital Outcomes	Overall population		Patients > 65 years	
	Adjusted Odds ratio	p Value	Adjusted Odds ratio	p Value
Mortality	3.57(0.86–14.87)	0.080	3.35(0.58–19.37)	0.177
Length of stay (day, coefficient)	0.16(0-0.33)	0.052	0.21(0.03–0.39)	0.021
Total cost (US dollar, coefficient)	0.35(0.06–0.64)	0.020	0.38(0.05–0.71)	0.023
GI anastomotic leakage	22.11(3.25-150.22)	0.002	NA	NA
GI bleeding	0.54(0.06–4.84)	0.581	NA	NA
AKI	1.86(0.80–4.29)	0.147	1.98(0.87–4.49)	0.102
Gastroparesis	0.41(0.10–1.61)	0.200	0.34(0.05–2.42)	0.284
Blood transfusion	0.87(0.46–1.64)	0.669	0.93(0.45–1.89)	0.831
Cardiac complications	17.88(5.32–60.11)	< 0.001	17.38(3.42–88.43)	0.001
Respiratory complications	2.38(1.23–4.60)	0.010	2.93(1.31–6.53)	0.009
Pneumonia	0.39(0.07–2.31)	0.299	0.13(0.01–1.89)	0.134
PE	18.53(2.67-128.62)	0.003	16.76(0.67–417.50)	0.086
UTI	1.47(0.65–3.31)	0.353	1.65(0.67–4.06)	0.272
Cardiac arrest	5.50(0.61–49.46)	0.128	2.52(0.18–34.92)	0.490
Post-operative sepsis	0.87(0.29–2.64)	0.808	0.89(0.30–2.69)	0.842
Post-operative shock	5.16(1.03–25.72)	0.045	27.06(2.35-311.15)	0.008
Wound complications	0.70(0.33–1.50)	0.359	0.62(0.26–1.49)	0.287
GI, gastrointestinal; AKI, acute kidney injury; PE, pulmonary embolism; UTI, urinary tract infection;				

Figures

Figure 1

Flow chart of the study population selection process

Figure 2

Forest plot of in-hospital outcomes

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementTable1.docx](#)