# The Potential Impact of Aortic Stenosis on in-Hospital Mortality in Patients With Pancreatic Cancer Undergoing Pancreaticoduodenectomy: A Nationwide Analysis

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# Abstract

Background:

Patients with aortic stenosis (AS) undergoing non-cardiac surgery, poses a management dilemma to physicians as they are at an increased risk for complications. This study aims to investigate the potential effect of AS on in-hospital mortality and other complications in patients with pancreatic cancer undergoing pancreaticoduodenectomy (PD).

Methods:

In this retrospective study, we investigated patients with pancreatic cancer undergoing PD between 2016 to 2019 using the National Inpatient Sample (NIS) database. The study population was divided into two groups based on the presence and absence of AS. Multivariate logistic regression analyses were performed to determine factors associated with in-hospital mortality, mechanical ventilation, cardiac arrest, vasopressor use, and intensive care unit (ICU) admission. Odds ratio (OR) at 95% confidence interval (CI) was used to describe the association between the study and outcome variables.

Results:

Of the 16,150 patients with pancreatic cancer underwent PD, 165 patients were diagnosed with AS. The mean age of patients with AS underwent PD was significantly higher than patients without AS. Patients with AS had a significantly higher in-hospital mortality, cardiac arrest, and ICU admission compared to patients without AS. There was no difference in the mechanical ventilation usage, hospital charges, and length of stay between the two groups.

Conclusion

AS was found to be associated with higher in-hospital mortality and worse outcomes in pancreatic cancer patients undergoing PD. A multidisciplinary team involving surgeons, cardiologists, anaesthesiologists, and physician should work together to jointly develop an appropriate preoperative and postoperative approach and management for these patients.


# Introduction

Pancreatic cancer is the fourth most common cause of cancer death in the United States (US), with a 5-year survival rate of 8% despite the advancement in medical care [1, 2]. It is most commonly prevalent in males and the elderly [3]. Pancreaticoduodenectomy (PD), also known as the Whipple procedure, is a complex surgical procedure indicated for the management of both resectable and borderline resectable pancreatic cancer [4]. It is considered a high-risk procedure due to the complex anatomy and blood supply of the area, difficult intra-abdominal dissection, and reconstruction of the digestive system. Previous reports have shown higher mortality and perioperative morbidity due to the complex nature of the procedure [5, 6].

Aortic stenosis (AS) is the most common valve disease in the elderly, and the prevalence of AS is rising among the aging population [7]. The mortality rates depend on the severity of the AS, with the highest mortality seen in patients with symptomatic severe AS [8]. Patients with AS are at increased risk for complications after non-cardiac surgeries, including intraoperative hypotension, myocardial ischemia or infarction, heart failure, stroke, arrhythmias and death. These patients require a detailed preoperative assessment and risk stratification in order to decide which AS patients can undergo a non-cardiac surgery, and which patients require further evaluation and management before [9].

Previous studies have shown that patients undergoing PD who have a history of coronary artery disease (CAD) or congestive heart failure (CHF), had almost three times the risk of developing major complications [10]. However, to the best of our knowledge, there is no data on patients with AS undergoing PD. In this retrospective nationwide study, we aim to evaluate the potential effect of AS on in-hospital mortality and other in-hospital complications in patients with pancreatic cancer undergoing PD.

# Methodology

Data source

This is a retrospective cohort study of patients who were admitted to hospitals in the US in the period between 2016 to 2019. The data was extracted from the Healthcare Cost and Utilization Project National Inpatient Sample (NIS) database. The NIS is sponsored by the Agency for Healthcare Research Quality (AHRQ) and is considered the largest publicly available inpatient health care database in the US. The database includes data from at least 46 states and covers more than 97% of the US population [11]. A 20% probability sample was collected and subsequently weighted to ensure that the selected population was nationally representative. Each admission in the database was assigned one principal diagnosis, up to 40 secondary diagnoses, and 25 procedures. These variables are defined via the International Classification of Disease, 10th revision, and Clinical Modification (ICD-10-CM) codes.

Study variables

The target population age was 18 years old and older. Using ICD-10-CM codes, we were able to identify patients who carry a diagnosis of pancreatic cancer and underwent a PD during admission. Patient’s age (in years), gender, race (white, black, Hispanic and others), and hospital information (region and bed size) were collected and considered as baseline characteristics. The comorbidities included hypertension (HTN), chronic kidney disease (CKD), CHF, CAD, atrial fibrillation (Afib), smoking, and obesity (defined as body mass index (BMI) of more than 24.9). The population was divided into AS and non-AS groups. The intensive care unit (ICU) admission was defined as any patient who had a cardiac arrest, required vasopressor administration or mechanical ventilation.

# Statistical analysis

The statistical analysis was done using the STATA software, version 17.0 (StataCorp., College Station, TX, USA). The characteristics of patients in the AS group and the non-AS group were described using descriptive statistics. In this study, multivariate logistic regression analysis was performed to determine factors associated with in-hospital mortality, mechanical ventilation, cardiac arrest, vasopressor use, and ICU admission. Variables that were not statistically significant (p-value < 0.05) on the univariate analysis were excluded from the multivariate analysis. The odds ratio (OR) at 95% confidence interval (CI) was used to describe the association between study and outcome variables. Statistical significance was defined as a two-tailed p-value of < 0.05.

# Results

Demographics and clinical characteristics

Out of 16,150 patients carrying the diagnosis of pancreatic cancer who underwent PD during the same admission, it was found that 165 patients (1.02%) were diagnosed with concurrent AS. The mean age of pancreatic cancer patients who underwent PD during the same admission and had a concurrent diagnosis of AS was significantly higher than patients without AS (74.51 years vs 66.41 years, p-value < 0.001). There was no difference in gender, race, and hospital characteristics between both groups. The prevalence of HTN, CHF, CAD, and Afib was higher in the AS group. However, no difference was noted in the prevalence of CKD, smoking, and obesity between both groups (Table 1).

Table 1
Demographic and clinical characteristics of patients in the AS group vs the non-AS group

| Variable | Non-AS | AS | P |
|---|---|---|---|
| Age (mean, year) | 66.41 | 74.51 | < 0.001 |
| Gender (%) | | | 0.0964 |
| Male | 51.49% | 66.67% | |
| Female | 48.51% | 33.33% | |
| Race (%) | | | 0.5627 |
| White | 72.29% | 75.76% | |
| Black | 8.45% | 6.06% | |
| Hispanic | 8.51% | 3.03% | |
| Others | 10.76% | 15.15% | |
| Hospital region (%) | | | 0.66 |
| Northeast | 20.49% | 18.18% | |
| Midwest | 22.24% | 15.15% | |
| South | 36.07% | 45.45% | |
| West | 21.21% | 21.21% | |
| Hospital bed size (%) | | | 0.716 |
| Small | 6.19% | 9.09% | |
| Medium | 18.74% | 21.21% | |
| Large | 75.07% | 69.7% | |
| Comorbidities (%) | | | |
| HTN | 60.59% | 84.85% | 0.0025 |
| CKD | 6.91% | 15.15% | 0.0684 |
| CHF | 4.1% | 18.18% | 0.0001 |
| CAD | 15.08% | 36.36% | 0.0012 |
| Afib | 10.38% | 35.38% | < 0.001 |
| Smoking | 40.1% | 42.42% | 0.7819 |

Abbreviations: AS: aortic stenosis; HTN: hypertension; CKD: chronic kidney disease; CHF: congestive heart failure; CAD: coronary artery disease; Afib: atrial fibrillation

| Variable | Non-AS | AS | P |
|---|---|---|---|
| Obesity | 14.61% | 15.15% | 0.9313 |
| Abbreviations: AS: aortic stenosis; HTN: hypertension; CKD: chronic kidney disease; CHF: congestive heart failure; CAD: coronary artery disease; Afib: atrial fibrillation | | | |

Inpatient outcomes

# Comparison of total hospital charges, length of stay (LOS), and in-hospital mortality

Total hospital charges were not significantly different in the AS group compared to the non-AS group ($205,231 vs $176,265, p-value 0.680). The mean LOS in AS group and the non-AS group was not significantly different as well (12.3 days vs 11.45 days, p-value 0.596). On the other hand, in-hospital mortality (7.69% vs 1.99%, p-value 0.001), cardiac arrest (9.09% vs 1.03%, p-value < 0.001), and ICU admission (18.18% vs 6.26%, p-value .006) were significantly higher in the AS group compared to the non-AS group. There was no significant difference in the chance of mechanical ventilation both groups (Table 2).

Table 2
Clinical outcomes in pancreatic cancer patients underwent pancreaticoduodenectomy in AS vs non-AS groups

| **Total hospital charges ($)** | **176,265** | **205,231** | **0.309** |
|---|---|---|---|
| LOS (days) | 11.45 | 12.3 | 0.596 |
| In-hospital mortality (%) | 2.28% | 12.12% | 0.0003 |
| Mechanical ventilation | 20.03% | 0.01% | 0.4967 |
| Cardiac arrest | 1.03% | 9.09% | < 0.001 |
| ICU admission | 6.26% | 18.18% | 0.0065 |
| Abbreviations: AS: aortic stenosis; LOS: length of stay; ICU: intensive care unit | | | |

# In-hospital mortality

After adjusting for age, gender, race, and comorbidities, patients with AS had a significantly higher chance for in-hospital mortality compared to patients without AS (OR 3.86, p-value 0.025). CHF was associated with a higher chance of death as well. Patients with Afib had a higher chance on in-hospital mortality on the univariate analysis only, but that was not evident on the multivariate analysis. Interestingly, smoking was associated with a statistically significant decrease in the chance of in-hospital mortality on both univariate and multivariate analyses (Table 3).

Table 3
Univariate and Multivariate analysis of potential factors affecting the in-hospital mortality in the AS vs non-AS groups

| In-Hospital mortality | Univariate (CI 95%) | P | Multivariate (CI 95%) | P |
|---|---|---|---|---|
| AS | 5.89 (1.99–17.40) | 0.001 | 3.86 (1.18–12.63) | 0.025 |
| Age < 65 years | - | - | - | - |
| Age ≥ 65 years | 1.37 (0.84–2.24) | 0.195 | 1.16 (0.69–1.93) | 0.563 |
| Male | - | - | - | - |
| Female | 0.67 (0.42–1.07) | 0.095 | 0.67 (0.42–1.08) | 0.103 |
| White | - | - | - | - |
| Non-white | 1.42 (0.88–2.28) | 0.144 | 1.5 (0.92–2.44) | 0.104 |
| HTN | 1.066 (0.67–1.69) | 0.785 | - | - |
| CKD | 1.78 (0.87–3.64) | 0.109 | - | - |
| CHF | 3.55 (1.77–7.1) | < 0.001 | 2.65 (1.78–3.93) | < 0.001 |
| CAD | 1.46 (0.83–2.56) | 0.178 | - | - |
| Afib | 2.424 (1.27–3.95) | 0.005 | 1.67 (0.86–3.23) | 0.126 |
| Smoking | 0.55 (0.33–0.92) | 0.023 | 0.56 (0.33–0.94) | 0.03 |
| Obesity | 1.08 (0.57–2.01) | 0.809 | - | - |
| Note: Variables that were not statistically significant (p-value < 0.05) on univariate analysis were excluded from the multivariate analysis | | | | |
| Abbreviations: OR: odds ratio; CI: confidence interval; AS: aortic stenosis; HTN: hypertension; CKD: chronic kidney disease; CHF: congestive heart failure; CAD: coronary artery disease; Afib: atrial fibrillation | | | | |

Mechanical Ventilation, cardiac arrests, and ICU admissions

AS was significantly associated with increased chance of mechanical ventilation (OR 2.93, CI 95% 1.07–7.98; p-value 0.035), and cardiac arrest (OR 3.29, CI 95% 1.09–9.98; p-value 0.035). There was an increased chance for ICU admission in patients with AS, however this was not statistically significant (OR 2.19, CI 95% 0.82–5.81; p-value 0.115) (Tables 4, 5, 6).

Table 4
Univariate and Multivariate analysis of potential factors affecting mechanical ventilation in the AS vs non-AS groups

| Mechanical ventilation | Univariate (CI 95%) | P | Multivariate (CI 95%) | P |
|---|---|---|---|---|
| AS | 4.51 (1.8-11.27) | 0.001 | 2.93 (1.07–7.98) | 0.035 |
| Age < 65 years | - | - | - | - |
| Age ≥ 65 years | 1.55 (1.08–2.22) | 0.015 | 1.28 (0.88–1.86) | 0.189 |
| Male | - | - | - | - |
| Female | 0.93 (0.67–1.29) | 0.69 | 1 (0.71–1.4) | 0.998 |
| White | - | - | - | - |
| Non-white | 1.36 (0.97–1.92) | 0.074 | 1.44 (1.01–2.05) | 0.039 |
| HTN | 1 (0.72–1.39) | 0.987 | - | - |
| CKD | 1.67 (1-2.8) | 0.05 | 1.19 (0.83–2.26) | 0.542 |
| CHF | 4.22 (2.59–6.86) | < 0.001 | 2.86 (1.61–5.08) | < 0.001 |
| CAD | 1.91 (1.31–2.79) | 0.001 | 1.42 (0.91–2.23) | 0.118 |
| A.Fib | 1.99 (1.29–3.06) | 0.002 | 1.37 (0.83–2.26) | 0.215 |
| Smoking | 0.63 (0.44–0.88) | 0.008 | 0.66 (0.46–0.93) | 0.02 |
| Obesity | 1.48 (0.99–2.2) | 0.053 | - | - |

Note: Variables that were not statistically significant (p-value < 0.05) on univariate analysis were excluded from the multivariate analysis

Abbreviations: OR: odds ratio; CI: confidence interval; AS: aortic stenosis; HTN: hypertension; CKD: chronic kidney disease; CHF: congestive heart failure; CAD: coronary artery disease; Afib: atrial fibrillation

Table 5
Univariate and Multivariate analysis of potential factors affecting the chance of cardiac arrest in the AS vs non-AS groups

| Cardiac arrest | Univariate (CI 95%) | P | Multivariate (CI 95%) | P |
|---|---|---|---|---|
| AS | 9.58 (2.77–33.18) | < 0.001 | 3.29 (1.09–9.98) | 0.035 |
| Age < 65 years | - | - | - | - |
| Age ≥ 65 years | 2.74 (1.19–6.29) | 0.017 | 1.42 (0.79–2.54) | 0.23 |
| Male | - | - | - | - |
| Female | 0.466 (0.22–0.95) | 0.036 | 0.59 (0.35-1) | 0.05 |
| White | - | - | - | - |
| Non-white | 1.15 (0.56–2.34) | 0.39 | 1.28 (0.77–2.13) | 0.328 |
| HTN | 1.94 (0.91–4.14) | 0.086 | - | - |
| CKD | 2.7 (1.11–6.55) | 0.028 | 2.16 (1.18–3.96) | 0.012 |
| CHF | 4.67 (1.9-11.45) | 0.001 | 1.38 (0.61–3.12) | 0.432 |
| CAD | 3.18 (1.59–6.35) | 0.001 | 0.85 (0.44–1.63) | 0.628 |
| A.Fib | 4.87 (2.45–9.68) | 0.001 | 4.84 (2.71–8.66) | < 0.001 |
| Smoking | 0.84 (0.42–1.67) | 0.624 | - | - |
| Obesity | 0.94 (0.36–2.43) | 0.902 | - | - |

Note: Variables that were not statistically significant (p-value < 0.05) on univariate analysis were excluded from the multivariate analysis

Abbreviations: OR: odds ratio; CI: confidence interval; AS: aortic stenosis; HTN: hypertension; CKD: chronic kidney disease; CHF: congestive heart failure; CAD: coronary artery disease; Afib: atrial fibrillation

Table 6
Univariate and Multivariate analysis of potential factors affecting the chance of ICU admission in the AS vs non-AS groups

| ICU admission | OR (CI 95%) | P | aOR (CI 95%) | P |
|---|---|---|---|---|
| AS | 3.33 (1.32–8.34) | 0.01 | 2.19 (0.82–5.81) | 0.115 |
| Age < 65 years | - | - | - | - |
| Age ≥ 65 years | 1.39 (1.03–1.86) | 0.028 | 1.19 (0.87–1.63) | 0.261 |
| Male | - | - | - | - |
| Female | 0.9 (0.68–1.2) | 0.506 | 0.99 (0.73–1.33) | 0.951 |
| White | - | - | - | - |
| Non-white | 1.19 (0.87–1.62) | 0.269 | 1.28 (0.77–2.12) | 0.323 |
| HTN | 1.01 (0.75–1.35) | 0.92 | - | - |
| CKD | 1.65 (1.03–2.62) | 0.034 | 1.28 (0.77–2.12) | 0.323 |
| CHF | 3.59 (2.29–5.61) | < 0.001 | 2.56 (1.52–4.3) | < 0.001 |
| CAD | 1.75 (1.25–2.45) | 0.001 | 1.29 (0.87–1.92) | 0.198 |
| A.Fib | 2 (1.38–2.89) | < 0.001 | 1.5 (0.98–2.29) | 0.061 |
| Smoking | 0.79 (0.58–1.05) | 0.116 | - | - |
| Obesity | 1.39 (0.98–1.98) | 0.06 | - | - |

Note: Variables that were not statistically significant (p-value < 0.05) on univariate analysis were excluded from the multivariate analysis

Abbreviations: OR: odds ratio; CI: confidence interval; AS: aortic stenosis; HTN: hypertension; CKD: chronic kidney disease; CHF: congestive heart failure; CAD: coronary artery disease; Afib: atrial fibrillation

# Discussion

In this nationwide study, we found that patients with a history of AS who had pancreatic cancer and were admitted for PD had a higher in-hospital mortality than patients without AS. Patients with AS who need a non-cardiac surgery present a tough clinical challenge. AS is a fixed obstruction of left ventricular emptying that results in left ventricular hypertrophy, poor compliance, and increased end-diastolic pressures due to alterations in the left ventricular myocardium [12]. Therefore, these patients are more sensitive to any alterations in hemodynamics as a result of these modifications. Thus, patients with AS have a higher chance of clinical deterioration during anesthesia and surgery [13]. Moreover, previous studies showed that patients with AS who undergo a non-cardiac surgery had a higher rate of

postoperative cardiovascular complications [14–17]. This can result in increased intraoperative and postoperative complications and possibly increased mortality.

In our study, patients with AS who underwent PD had more comorbidities than patients without AS. This could have contributed to the increased in-hospital mortality in these patients. In a study done by Kelly et al., patients with preoperative cardiac comorbidities were found to have a higher rate of perioperative mortality and morbidity when undergoing pancreatic resection. However, this study only looked at patients with CAD and heart failure, but not at patients with valvular heart disease [18]. Therefore, we recommend that in patients with AS, it is important to do a detailed preoperative evaluation prior to undergoing PD, as these patients may have a high operative risk and may potentially have worse clinical outcomes. Another potential factor that may contributed to the increased in-hospital mortality in AS patients undergoing PD is age. In our study, we found that patients in the AS group were significantly older than patients in the non-AS group. Generally, clinical outcomes are poor in elderly patients due to multiple reasons including poor functional status, frailty, more medical comorbidities, and a higher preoperative risk than younger patients [19, 20].

Our study showed that patients with AS had a statistically significant higher chance of cardiac arrest, which is one of the common complications seen in patients with AS undergoing a non-cardiac surgery as demonstrated by previous studies [21, 22]. Moreover, patients in the AS group had a significant higher chance of requiring mechanical ventilation during hospitalization, however, there was no difference in ICU admissions between both groups. Furthermore, our study demonstrated no significant difference in the LOS and hospital charges between the two groups.

There are several limitations of this study. Due to the nature of the NIS database, our observations reflect admissions and not individual patients. Therefore, the unit of analysis is admission. Given the inability to account for multiple admissions for a given patient in the NIS, our conclusions may be confounded by the risk of repeat hospitalization. Thus, our reported rates may be viewed as over-estimates of a per-patient admission rate. Mortality rates, however, are unlikely to be affected. Under-or over-coding can lead to misclassification, although a large number of patients in the database strongly mitigates against substantial misclassification bias. NIS undergoes data quality assessment annually to ensure the internal validity of the data. Moreover, patients in the AS group were not classified based on the severity of stenosis, as this can potentially affect the outcome. Additionally, observational studies may not be able to fully adjust for unmeasured confounding factors that might affect our estimates for the reported associations between in-hospital mortality and included covariates. Therefore, conclusions based on these observational data should be viewed as associational and not causal in nature. Finally, these observations pertain to the AS population in the US and may not be generalizable to other AS populations in other countries.

As a conclusion, patients with AS had an increased hospital mortality, cardiac arrest and ICU admissions compared to non-AS patients. Therefore, patients with concurrent diagnosis of AS and pancreatic cancer undergoing PD might warrant a closer observation. A multidisciplinary approach involving oncologists,

surgeons, cardiologists and anaesthesiologists should be done to jointly develop an appropriate preoperative and postoperative evaluation and management for these patients in order to prevents such complications.

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# Declarations

Regarding the statement of ethics approval: IRB approval was not obtained as this study was done using a public database (National Inpatient Sample database). Competing interests: All authors have no competing interests to declare.