

Risk Factors for Post-Pancreaticoduodenectomy Mortality: Identification and Mitigation

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Abstract: Historically, postoperative mortality rates were high after pancreaticoduodenectomy (PD), but in recent times those rates have improved, and Whipple procedures are safely performed. Multiple factors have contributed to the improvement of postoperative mortality rates after PD over time. Known risk factors leading to postoperative mortality after PD are based on patient factors, surgeon/hospital factors, and postoperative factors. These factors can be attributed to improvements in patient selection and optimization, operative techniques and regionalization to high volume centers, and better understanding and standardization of postoperative care and management of common complications. Further studies should investigate preoperative optimization using prehabilitation and explore early diagnosis of postoperative complications and interventions to prevent mortality after PD.

Keywords: pancreaticoduodenectomy, mortality, risk assessment, operative volume, failure to rescue, PD, FTR

Introduction

Pancreaticoduodenectomy (PD) is a major oncologic procedure reserved for periampullary lesions and those located in the head of the pancreas. Historically, from the popularization of the operative procedure by Allen Oldfather Whipple and into the 1970s, PD was performed infrequently because of high hospital mortality rates of 25–30%.^{1–5} During the 1980s and 1990s, high volume centers were developed where complex gastrointestinal operative procedures were performed in greater numbers and mortality rates improved.^{2–5} In the contemporary era, PD has become a safe procedure performed with mortality rates <5%.^{2,5–7}

Multiple factors have contributed to the improvement of postoperative mortality rates after PD over time. These factors can be attributed to improvements in patient selection and optimization, operative techniques and regionalization to high volume centers, and better understanding and standardization of postoperative care and management of common complications.^{2,5,6}

To mitigate postoperative mortality after PD, it is essential to identify and understand risk factors that contribute to it. In this article, we summarize and discuss the known risk factors leading to postoperative mortality after PD based on patient factors, surgeon/hospital factors, and postoperative factors.

Patient Factors

Identification of patient risk factors for postoperative mortality after PD is an essential component for patient selection and optimization before the operative procedure. This has prompted the creation of multiple validated risk models to better predict mortality after PD.^{8–12} These models have been derived from both institutional and large national databases (Table 1).

In a single institution, 1, 976 patients who underwent PD or total pancreatectomy between 1998 and 2009 were reviewed and age, sex, preoperative serum albumin level, tumor size, total pancreatectomy, and a high Charlson index predicted 90-day mortality (area under the curve [AUC], 0.78; 95% CI, 0.71–0.85).⁹ All factors except for Charlson index also predicted 30-day mortality. Other scoring systems have been derived from large national databases and have focused on 30-day and in hospital mortality risk models. Greenblatt et al assessed the American College of Surgeons

Table I Validated Risk Models to Better Predict Mortality After PD

Reference	Year	Period	Data Source	Risk Factors
Greenblatt et al ¹²	2011	2005–2009	ACS NSQIP	30-day mortality: COPD, hypertension, neoadjuvant radiation, elevated serum creatinine, hypoalbuminemia
Venkat et al ⁹	2011	1998–2009	Institutional (Johns Hopkins)	30-day mortality: Age, male sex, preoperative serum albumin level, tumor size, total pancreatectomy 90-day mortality: Age, male sex, preoperative serum albumin level, tumor size, total pancreatectomy, high Charlson index
Gleeson et al ¹¹	2016	2005–2012	ACS NSQIP	30-day mortality: (Whipple-ABACUS) Hypertension with medications + history of cardiac surgery + age >62 + 2 (bleeding disorder) + Albumin <3.5 g/dL + 2 (disseminated cancer) + 2 (use of steroids) + 2 (preoperative SIRS criteria met)
Hill et al ⁸	2010	1998–2006	NIS	30-day mortality: Age group, Charlson score, sex, type of pancreatectomy, hospital volume status
Ragulin-Coyne et al ¹⁰	2012	1998–2006	NIS	30-day mortality: Age group, Charlson index, sex, diagnosis, pancreatectomy type, hospital volume

Abbreviations: ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program; NIS, Nationwide Inpatient Sample.

National Surgical Quality Improvement Program (ACS NSQIP) database between 2005 and 2009 for patients who underwent elective PD. Of 4,945 patients, chronic obstructive pulmonary disease (COPD), hypertension (HTN), neoadjuvant radiation, elevated serum creatinine, and hypoalbuminemia were significant predictors of 30-day mortality.¹² In a further assessment of PD from ACS NSQIP database between 2005 and 2012 with a larger patient population of 14,993 patients, Gleeson et al created and validated the Whipple-ABACUS as a risk score for 30-day mortality after PD (AUC = 0.71, $p < 0.001$).¹¹ Eight variables were found to be independently significant including: HTN requiring medication, history of cardiac operation, age >62 years, bleeding disorder, albumin <3.5 g/dL, disseminated cancer, chronic steroid use, and meeting SIRS criteria. Two additional studies identified preoperative risks of in hospital mortality after pancreatectomy using the Nationwide Inpatient Sample (NIS) between 1998 and 2006.^{8,10} They had similar findings demonstrating that age group, Charlson score, sex, type of pancreatectomy, and hospital volume status were factors associated with in hospital mortality. Although there is some heterogeneity in these risk models, there are several factors that are consistent in all the models. Age, sex, albumin levels, and certain cardiopulmonary comorbidities, are independent factors that have been found to influence postoperative mortality and are consistent in these models. Although these models are based on retrospective data, they provide an additional adjunct for preoperative evaluation of patients undergoing PD based on curated databases with large patient populations that would be hard to obtain in a prospective study.

In addition to preoperative risk assessment tools, other patient risk factors have been extensively investigated, yet have yielded conflicting results. One such risk factor is age and performing PD in the elderly. As was previously stated, age has been included in risk assessment models and shown to influence mortality.^{8–11} Large studies have been recently performed in the United States, Sweden, and Korea with conflicting results.^{13–15} In an evaluation of patients undergoing PD from the ACS NSQIP database from 2005–2010, those patients aged greater than or equal to 80 years old were associated with an increased likelihood of 30-day mortality compared to those less than 80.¹⁴ Additionally, on subgroup analysis those greater than or equal to 70 years old also had a similar increased risk of mortality compared to those less than 70.¹⁴ Contrary to these findings, a group from Korea performed a retrospective cohort study between 2000 and 2014 of patients who underwent PD for periampullary cancers and found no difference in 30-day mortality between those 75 years and older compared to those younger than 75.¹³ Although, the group did report a lower 5 year overall survival in the older group.¹³ Most recently, the Swedish National Registry was queried between 2010 and 2018 for patients who underwent PD.¹⁵ Patients were divided into those less than 70, 70–79, and greater than or equal to 80 years old.¹⁵ There was no significant difference in hospital 30-day or 90-day mortality amongst the groups.¹⁵ In a systematic review and meta-analysis of 45 studies of older patients versus younger patients undergoing PD, older patients had a higher risk of death (4.54% [older] vs. 2.26% [younger]; RR: 2.23; 95% CI 1.74–2.87).¹⁶

Although chronological age is an important factor in assessing operative risk, frailty, which involves the progressive loss of physical and mental function with or without coexistence of disease, has been shown to be an independent predictor of postoperative mortality.^{17,18} In a query of 9,986 patients undergoing PD from the NSQIP database between 2005 and 2016, the modified frailty index (mFI) was used to predict postoperative outcomes after PD.¹⁸ The NSQIP mFI contains eleven variables including diabetes, functional status, COPD or pneumonia, congestive heart failure, history of myocardial infarction, HTN requiring medication, peripheral vascular disease or rest pain, impaired sensorium, history of either transient ischemic attack or cerebrovascular accident, history of cerebrovascular accident with neurologic deficit, prior percutaneous coronary intervention, previous coronary surgery, or angina.¹⁸ Of the total patients, 6.4% had increase mFI, defined as a score >0.27 . Increasing mFI was associated with increased 30-day mortality on univariate analysis (odds ratio: 2.45; 95% CI 1.74–3.45; $p < 0.001$) and multivariate analysis (odds ratio: 1.536; 95% CI 1.049–2.248; $p = 0.027$).¹⁸ Similarly, in a recent analysis of patients undergoing PD from 2011–2020 from a high volume tertiary care hospital, the mFI was used to evaluate the impact of frailty on postoperative complications following PD.¹⁷ Twelve percent of the 554 patients had a high mFI (defined as mFI >0.27). High mFI patients had a higher 90-day mortality rate (11% vs. 4.1%, $p = 0.017$).¹⁷

There are several other patient populations that have been considered high risk surgical candidates when it comes to major oncologic procedures such as PD. Patients with renal dysfunction and end stage kidney disease have been associated with increased mortality after PD.^{19,20} In a study to assess the impact of preoperative eGFR levels on outcomes after PD, the ACS NSQIP was queried between 2014 and 2017.¹⁹ Of 21,148 patients, 12% had low eGFR (defined as <60 mL/min/1.73m²).¹⁹ On logistic multivariable regression, lower preoperative eGFR was associated with increased 30-day mortality after PD (aOR: 2.064 [1.523–2.797]).¹⁹ Another query of the ACS-NSQIP database between 2015 and 2019 who underwent PD investigated the effects of chronic kidney disease on postoperative outcomes.²⁰ Kidney function was stratified according to the Kidney Disease: Improving Global Outcomes classification.²⁰ Findings suggested that worsening preoperative renal dysfunction correlated with increased risk of 30-day mortality.²⁰

Liver disease, specifically cirrhosis, is another comorbidity commonly associated with poor outcomes in patients undergoing major surgical procedures. In a single institution study looking into surgical outcomes in patients with liver cirrhosis undergoing PD between January 2002 and December 2011, El Nakeeb et al demonstrated that in hospital mortality was higher in cirrhotic patients (11.9% vs. 1.6%, $p = 0.001$).²¹ The cirrhotic patients involved in the study had Child Pugh classes of A and B. The study included 442 patients, 15.2% of whom had cirrhosis. These findings were also supported by Enderes et al in another single institutional study of 275 patients with liver cirrhosis and advanced liver fibrosis between January 2012 and December 2020.²² In this study, patients with liver cirrhosis and advanced liver fibrosis demonstrated higher mortality rates compared to patients with no pre-existing liver pathology (20% vs. 3%, $p = 0.021$).²²

Obesity has been another extensively studied risk factor in relation to postoperative mortality after PD with inconsistent results.^{23–25} A BMI >30 in patients undergoing PD is associated with increased incidence of morbidity, but not mortality in most studies.^{23–25} In a study which stratified the classification of obesity, patients with class III obesity (BMI >40) were associated with higher risk of 30-day mortality after undergoing PD.²⁵ Similarly, in an analysis of patients undergoing PD from the ACS NSQIP database between 2014 and 2018, our group demonstrated that patients with Metabolic Syndrome (obesity, diabetes, and HTN) have an increased associated risk of 30-day mortality.²⁶

The influence of benign vs. malignant pathology on postoperative surgical outcomes after PD has been studied, yet postoperative mortality has not been found to be influenced by pathology.^{27–29} In a study evaluating 6,085 patients in the NSQIP database between 2005 and 2011 for patients undergoing PD, outcomes were compared between benign/premalignant pathology and malignant pathology.²⁷ Twelve percent of patients had benign/premalignant pathology and 88% had malignant neoplasms.²⁷ 30-day mortality did not differ between the two groups (3% vs. 2%, $p = 0.128$).²⁷ In a single institution retrospective study, patients with unexpected benign disease was compared to those with malignant disease undergoing PD.²⁸ The incidence of benign disease was 29 out of 446 patients (6.5%).²⁸ There was interestingly a higher trend in mortality for those with benign disease yet there was no significant difference statistically.²⁸ Most recently, Mavroeidis et al performed a retrospective single institution paired case matched controlled study for patients who underwent PD for suspected malignancy, yet had nonmalignant pathology.²⁹ There was no difference in 30-day or 90-day mortality between those with benign vs. malignant pathology.²⁹ These findings are curious as one would believe that patients with malignant pathology would have worse outcomes. What is apparent and should be considered is the

follow-up of these patients. The outcomes of mortality of these patients are only for 30 and 90 days postoperatively and do not provide long term data of overall survival, which would most likely differ between patients with benign and malignant final pathology.

When comparing adjuvant and neoadjuvant therapy (chemotherapy/chemoradiation), neoadjuvant therapy has a theoretical benefit of assessing chemosensitivity, increasing control of micrometastases and circulating tumor cells, ensuring a higher rate of systemic therapy completion, potentially downstaging disease, and reducing pancreatic leak after PD.³⁰ Most of the data regarding neoadjuvant therapies and outcomes after PD have come from analyses of patients with pancreatic ductal adenocarcinoma given the increase in neoadjuvant therapy utilization.^{30–33} There have been several studies using NSQIP and the National Cancer Database (NCDB) studying the association between neoadjuvant therapy and postoperative outcomes after PD.^{30–33} The NSQIP database was queried between 2014 and 2015,³² 2015 to 2019,³⁰ and 2014–2019.³¹ In all three studies, there was no difference in 30-day mortality between those undergoing PD who received preoperative neoadjuvant therapy and those who did not.^{30–32} Furthermore, a study which compared outcomes of patients receiving neoadjuvant chemotherapy alone, concurrent chemoradiation, and chemotherapy followed by radiation amongst patients with pancreatic adenocarcinoma undergoing PD was performed using the NCDB between 2006 and 2011.³³ The odds of 30-day and 90-day mortality were not influenced by delivery of any neoadjuvant therapy type.³³ Multivariate analysis did suggest that delivery of concurrent chemoradiation compared to neoadjuvant therapy with full dose systemic chemotherapy is associated with shortened survival.³³

Surgeon, Hospital, and Operative Factors

There have been many studies that have analyzed the outcomes of hospital and provider volume for major surgical procedures. The relationship between volume and surgical outcomes in pancreatic surgery has been well demonstrated.^{34–37} Hospital volume is strongly and inversely associated with postoperative mortality rates.^{34–37} Sosa et al originally analyzed hospital discharge data from all nonfederal acute care hospitals in Maryland for patients who underwent a pancreatic resection, palliative bypass, or stent procedure between 1990 and 1995, and found that increased hospital volume was associated with markedly decreased in-hospital mortality.³⁴ In this study, 48 hospitals were included and categorized as high-volume (performed more than or equal to 20 procedures per year), medium-volume (performed 5–19 procedures per year), or low-volume (performed <5 procedures per year). On behalf of the Signaling Committee Cancer of the Dutch Cancer Society, Gooiker et al performed a systematic review and meta-analysis to identify all primary studies examining the effects of hospital or surgeon volume on postoperative mortality and survival after pancreatic surgery up to February 2010.³⁷ There were 14 eligible studies, 11 included with hospital volume as the independent factor, 2 with surgeon volume as the independent factor, and 1 study had hospital and surgeon volume as independent factors.³⁷ Nine studies were from the United States, two from Canada, and one each from Taiwan, Italy, and Finland.³⁷ The results demonstrated a significant association between hospital volume and postoperative mortality (odds ratio 0.32 [0.16–0.64]) and between hospital volume and survival (hazard ratio 0.79 [0.70–0.89]), while the effect on surgeon volume postoperative mortality was not significant.³⁷ Significant heterogeneity was seen in the analysis of hospital volume and mortality. In a more contemporary systematic review and meta-analysis, Hata et al specifically looked at the influence of hospital volume on various outcomes after PD.³⁵ Of the 13 studies, four studies were from the United States or Canada, six from Europe.³⁵ The overall pooled odds ratio for mortality favoring the high-volume hospitals was 2.37 (95% confidence interval [1.95–2.88] with high heterogeneity [$I^2 = 63\%$]).³⁵

The first laparoscopic PD was described in 1994 and first robotic PD approach was described in 2003.³⁸ Minimally invasive PD (MIPD) account for about 4.4% to 14% of all PD cases performed.³⁸ Most studies have reported data from small institutional studies, but there have also been several larger database studies, of which have had conflicting results regarding surgical outcomes after MIPD compared to open PD.^{38–45} There have been several systematic reviews with meta-analyses of the smaller institutional studies, which demonstrate no significant difference in mortality between MIPD and open PD.^{39,40,44,45} However, in one of the systematic reviews and meta-analyses, mortality after MIPD was increased in low-volume hospitals (7.5% vs. 3.4%, $p = 0.003$).⁴⁵ Two studies queried the NCDB between 2010 and 2011.^{42,43} Both had similar findings that on unadjusted comparison, there was no difference in 30-day mortality between MIPD and open PD, yet on multivariable analysis, 30-day mortality was higher in patients undergoing MIPD.^{42,43}

However, one of the studies also found that institutions that performed >10 MIPD, had equal 30-day mortality than that of the open approach.⁴³ Another study used the NSQIP database between 2014 and 2015 to compare patients who underwent MIPD and open PD.³⁸ MIPD and open PD patients were compared using a 3:1 matched propensity score and the 30-day mortality for both groups was similar (MIPD 1.8% vs. open PD 1.3%, $p = 0.52$).³⁸ There has been one randomized controlled Phase 2/3 trial that was performed by four centers in the Netherlands (each performed twenty or more PDs annually), which compared laparoscopic PD to open PD referred to as the LEOPARD-2 trial.⁴⁶ The trial prematurely terminated because of increased complication related 90-day mortality in the laparoscopic PD arm (10% vs. 2%) on interim analysis.⁴⁶ They believed that experience, learning curve, and annual volume may have influenced the outcomes.

The impact of vascular reconstruction on morbidity and mortality after PD is widely debated.^{47–49} The effects of vascular reconstruction on short-term outcomes after PD remain unclear with multiple studies reporting conflicting results.^{47–49} Most of the published literature is based upon institutional studies that are limited by small sample size. In a metaanalysis performed to evaluate studies comparing PD with venous resection vs. those without venous resection, 22 retrospective studies were used which included 2,890 patients who were eligible for analysis of perioperative morbidity, mortality, and long-term survival.⁴⁷ There was no difference in mortality and 1-year and 3-year survival between the two groups.⁴⁷ Patients with venous resection with R0 resection (microscopically negative margins) had significantly better survival compared to those with R1 resection (removal of all macroscopic disease but microscopic margins are positive) both at 2 years and 5 years.⁴⁷ In histopathology subgroup analysis, those with venous resection who had true tumor infiltration had significantly worse survival compared to those with inflammation pathology.⁴⁷ From an initial study from the NSQIP database between 2005 and 2009, outcomes associated with vascular resection during PD were analyzed.⁴⁸ Of 3,582 patients included, 7.8% underwent vascular reconstruction during PD.⁴⁸ Vascular resection was associated with greater risk-adjusted 30-day mortality (5.7% vs. 2.9%, aOR: 2.1 [1.22–3.73], $p = 0.008$).⁴⁸ In a more recent study with inclusion of more specific data from the NSQIP database between 2014 and 2015, outcomes of both arterial and venous reconstruction during PD were analyzed, which was previously unable to be differentiated in the prior analysis.⁴⁹ A total of 3,002 patients were included, with 12.8% venous reconstruction, 1.7% with arterial reconstructions, and 2.7% had both.⁴⁹ On multivariable analysis, there was no difference in 30-day mortality following venous reconstruction, while arterial reconstruction was associated with increased 30-day mortality.⁴⁹

Postoperative Factors

There have been several studies that demonstrate the association of accumulation of major morbidities after PD being responsible for postoperative mortality,^{6,7} while more recently, differences in failure to rescue (FTR) have been associated with mortality rates after PD.^{50–52}

In a large single institution study designed to compare the differences between early (as defined as 90-day mortality) and late (defined as mortality between 91 and 365 days of operation) mortality in patients after PD from 2007 to 2016, Narayanan et al found that early mortality was associated with postoperative complications including multi organ failure (45%), post-pancreatectomy hemorrhage (25%), and cardiopulmonary arrest from myocardial infarction or pulmonary embolism (15%).⁶ Deaths in the late period were a result of prolonged postoperative malnutrition, debility, or recurrence of cancer.⁶

A Pancreatic Surgery Mortality Study Group comprised of 36 pancreatic surgeons from 15 institutions in 4 countries used root-cause analysis to analyze mortalities (30-day and 90-day) after pancreatectomy from 2000 to 2010.⁷ They found that 77% of patients who died had a variety of major complications before death, almost half expired between 31 and 90 days, and operative-related complications contributed to 40% of deaths.⁷ Of the operative-related complications leading to death, postoperative pancreatic fistula was the most evident at 14%.⁷

Most recently, it has been suggested that mortality rates after major surgery between centers is driven by the ability to successfully treat morbidities, not the incidence of morbidities.⁷ In order to further understand this relationship, Del Valle et al reviewed the ACS NSQIP database from 2006 to 2016 for patients undergoing PD.⁵⁰ They found that there was a decrease in mortality attributed to FTR on both univariable (9.8% to 4.1%, $p < 0.001$) and multivariable analysis (odds ratio 3.65, 95% CI 2.07–6.76, $p < 0.001$), while the decrease was independent of preoperative variables and major

morbidity.⁵⁰ FTR is an important hospital quality metric and patient safety indicator defined as death after the development of a complication.^{50,53} FTR was initially described by Silber et al in 1992, with a hypothesis that factors that prevent complications may differ from those that promote rescue.⁵⁴ When hospitals have similar major complication rates but differ in mortality, those with higher mortality rates are most likely attributed to failing to rescue their patients. However, other factors have been shown to be associated with FTR, specifically after PD, such as patient, postoperative, surgeon, and hospital factors.⁵²

Discussion

In this review article, we discuss risk factors associated with increased mortality after PD. We have summarized factors contributing to improvements in patient selection and optimization, operative techniques and regionalization to high volume centers, and better understanding and standardization of postoperative care and management of common complications which have contributed to the improved postoperative mortality after PD from the historically high rates. By identifying and recognizing the patient, surgeon/hospital, and postoperative risk factors associated with postoperative mortality after PD, interventions and optimization of these known risk factors are imperative to mitigation of negative outcomes.

As discussed earlier in the manuscript, using standardized preoperative risk scores in patients undergoing PD are important in identifying high risk populations. Factors such as age, albumin levels, frailty, and certain medical comorbidities have demonstrated a correlation to increased morbidity and mortality after PD.

Although certain risk factors are not modifiable, there has been a recent emphasis on preoperative interventions for optimization, patient health, and lifestyle to enable patients to better withstand the postoperative stress response known as prehabilitation.^{55,56} Prehabilitation focuses on three main elements including exercise and preconditioning, nutrition, and psychological wellbeing. Prehabilitation programs in patients undergoing major surgeries, including pancreatic resection, have shown positive effects of the intervention on aerobic capacity and physical activity resulting in significant reduction of both postoperative complications and length of stay.^{55,56} A randomized blinded controlled study which sought to assess the impact of prehabilitation on postoperative complications in high risk patients undergoing elective major abdominal surgery supported these findings.⁵⁷ In the study, 71 patients were randomized to the control group and 73 to the prehabilitation group with findings demonstrating that the intervention group had enhanced aerobic capacity, reduced number of patients with postoperative complications, and also reduced the rate of complications as compared with controls.⁵⁷ Although such data is promising, there have been few studies investigating patients specifically undergoing pancreatic resection and the effect of prehabilitation on postoperative outcomes. The data available demonstrate heterogeneity amongst prehabilitation regimens, inability to accurately record adherence to prehabilitation programs, and small patient populations.⁵⁵ Further well-designed trials are needed to understand the relationship between prehabilitation and patients undergoing pancreatic resection.

A key intervention in the mitigation and reduction of mortality after PD is centralization and referral to high volume centers. High volume centers and the implementation of regionalization and centralization for PD has demonstrated improved postoperative mortality rates.^{34–37} On a national level, centralization initiatives were based on mutual agreement between surgeons, and demonstrated that centers had increased resection rates, and these high volume centers had significantly better survival rates.³⁶

In accordance with this principle, early identification and appropriate intervention of PD postoperative major complications are key in rescuing patients and preventing mortality.⁵² Interventions such as this have been demonstrated on a national level in the Netherlands with the PORSCHE trial. This was an open-label, nationwide, stepped-wedge cluster randomized trial that included all patients having pancreatic resection during a 22-month period who were allocated to usual care (control) or a multimodal, multidisciplinary algorithm for early recognition and minimally invasive management of postoperative complications.⁵⁸ The algorithm demonstrated an improved 90-day mortality compared to usual care (3% vs. 5%; odds ratio 0.42; $p = 0.029$).⁵⁸ Demonstrating that centralization of care to high volume centers can be successfully executed on a national level and improve outcomes.

Conclusion

Mortality after PD has improved significantly and is safely performed at high volume centers with low mortality rates. Further studies should investigate the optimization of patients with known preoperative risk factors for mortality using prehabilitation. Additionally, further studies are also needed to explore early diagnosis of postoperative complications and interventions to prevent mortality after PD.

Disclosure

The authors report no conflicts of interest in this work.

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