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Preoperative Risk Assessment of Pancreatic Fistula Impact on Adjuvant Chemotherapy Delivery After Pancreatoduodenectomy

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Abstract

Background Up to 40% of patients undergoing pancreatoduodenectomy (PD) for resectable pancreatic ductal adenocarcinoma do not receive adjuvant chemotherapy (aCT). This study aimed to evaluate the impact of postoperative pancreatic

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fistula (POPF) on aCT delivery and timing and to explore how preoperative variables influence these outcomes according to the occurrence of a POPF.

Methods This multicenter retrospective study included patients from 25 pancreatic centers. Propensity score matching was performed based on anatomical, biological, and conditional variables. Multivariable regression analyses were used to identify independent predictors of aCT omission and delay.

Results Among 1590 patients, 267 (16.8%) developed a POPF. Overall, aCT was administrated in 1,146 patients (72.1%) with a median time to first dose delivery of 56 days (26). After matching, POPF was associated with a significantly lower likelihood of aCT delivery ($p < 0.001$) and a significant delay in its initiation ($p < 0.001$). Independent predictors of aCT omission were age ≥ 70 (odds ratio [OR] 2.480, 95% confidence interval [CI] 1.439–4.274; $p < 0.001$), chronic renal failure (OR 4.554, 95% CI 1.320–15.708; $p = 0.016$), and chronic obstructive pulmonary disease (OR 2.775, 95% CI 1.021–7.546; $p = 0.045$) when POPF occurred. In the absence of POPF, apart from age ≥ 70, venous contact (OR 1.574, 95% CI 1.114–2.224; $p = 0.010$) and tumor size > 20 mm (OR 0.713, 95% CI 0.523–0.972; $p = 0.032$) were predictors of aCT delivery.

Conclusions Postoperative pancreatic fistula is a key driver of aCT delivery after pancreatoduodenectomy. Its interaction with patient frailty highlights the need for preoperative risk assessment to better select candidates for upfront surgery in resectable pancreatic ductal adenocarcinoma.

Keywords Pancreatic fistula · Pancreatoduodenectomy · Adjuvant chemotherapy · Pancreatic cancer · Conditional status

Surgical resection for pancreatic cancer is burdened by a high morbidity with postoperative complications occurring in approximately 60–70% of the cases.[1] This is particularly true for pancreatic head resections, where postoperative pancreatic fistula (POPF) represents undoubtedly the most significant event influencing patients outcome and hospital stay. Beyond its direct impact on patient recovery and mortality, POPF may have an indirect effect by delaying the initiation of a systemic adjuvant chemotherapy (aCT) or entirely preventing its administration.[2–4] This last event is rather frequent in literature, with aCT omission rate up to 25–50%.[5–9] Older patients or with important comorbidities are, in fact, considered as "conditional" borderline according to the proposed ABC criteria, although this status is difficult to be clearly defined.[10,11] Performance status of some patients can deteriorate after a pancreatoduodenectomy (PD) with a consequent failure of a proper aCT administration and an increased risk of disease recurrence and mortality.[7,12,13] These concerns are particularly relevant in patients with upfront resected pancreatic ductal adenocarcinoma (PDAC), who are generally exposed to a higher rate of POPF and, more importantly, who have not received any systemic treatment prior to surgery, placing them at oncologic risk.[14] Beyond the challenges in objectively defining patient frailty and the borderline conditional status (BR-C) prior to a PD, it may be essential to stratify the risk of aCT omission based on the development of a POPF, which is likely a major determinant of CT administration.[15] A POPF may in fact destabilize the delicate balance of a patient's comorbidities, while initiation of a systemic therapy may be

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feasible in the same frail patient when the POPF does not occur. This complication can often be predicted based on preoperative features, such as pancreas aspect and Wirsung caliber on imaging, or patients body mass index (BMI), and estimated nowadays with always more accurate tools known as Fistula Risk Scores.[16–19]

The purpose of this study is to confirm the potentially detrimental impact of a POPF on the administration, protocol strategy, and timing of aCT based on patients and tumour status at surgery, in patients with a resectable PDAC undergoing PD. Simultaneously, the study seeks to evaluate on a large scale the preoperative predictors for failure of systemic treatment initiation in relation to the confirmed onset or not of a POPF. The result could help to refine the concept of patient frailty and BR-C status and its relevance in preoperative risk assessment in this specific clinical context.

Methods

Study Design

This is an international multicenter retrospective study built within the Pancreatoduodenectomy Adjuvant Chemotherapy Failure (PANACHEF) study project. Data from 25 pancreatic centers across five countries were collected in a common database. Patients older than 18 years undergoing upfront PD from January 1, 2015 to October 31, 2023 for a histologically confirmed PDAC were enrolled. Only tumors classified as anatomically resectable according to the National Comprehensive Cancer Network (NCCN) classification were included.[20] Borderline biological and conditional criteria for resectability were not considered for this inclusion phase. Exclusion criteria were (1) tumors classified as anatomically borderline resectable, locally advanced or metastatic, (2) no oncologic follow-up with lack of data regarding aCT administration, (3) 30-day or in-hospital postoperative mortality, (4) no data on postoperative course and specifically on POPF ang its grading, and (5) other final histology than PDAC. All sensitive data of the enrolled patients were protected in accordance with Ministerial Decree No. 162 of July 15, 1997, Legislative Decree No. 196/2003 (as amended) and the applicable European regulations (Regulation EU 679/2016—GDPR). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed to conduct the study and report the outcomes.[21] The study was aligned to the Helsinki declaration, and the original protocol was approved by the ethical committee of the Eastern Piedmont University on the October 30, 2024 (Registration number n° 1331).

Definitions and Outcomes

All potential influent preoperative variables were included in the analysis. Among baseline data, BMI, age, gender, and weight loss were recorded. Age was evaluated as a dichotomous variable with the cutoff of 70 years chosen after ROC curve analysis. Weight loss was confirmed in case of loss of ≥10% of the baseline weight at surgery.[22,23] The threshold used for differentiating medium- and high-volume centers for PD was 35 cases per year.[24] Use of preoperative biliary drainage was considered in the analysis, as well as baseline CA 19-9 value as a dichotomous variable with a cutoff of 500 mg/dL.[25] Preoperative tumor size, at last CT scan or MRI, and main portal vein (MPV) or superior mesenteric vein (SMV) contact, assessed at last CT scan before pancreatic resection, were registered for each patient among the different centers. Separately assessing the most relevant comorbidities was preferred over the inclusion of the American Society of Anesthesiologists score or Charlson comorbidity index, due to the high variability of the former and the lack of pancreas-specific applicability of the latter.[26,27] History of medical treatment for diabetes, previous deep venous thrombosis or pulmonary embolism, chronic obstructive pulmonary disease (COPD), and cerebrovascular events were evaluated. Chronic renal failure (CRF) was defined as a preoperative estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2, known or persisting for 3 months or more.[28] With regard to cardiac function, a history of ischemic heart disease and heart failure, defined by an ejection fraction below 50%, were included among the conditional variables.[29] Decision of type of operative approach was recorded and assessed as open or minimally invasive. Among postoperative data, POPF was defined according to the latest classification of the international study group for pancreatic surgery and did not included what is now classified as a biochemical leak.[30] The administration of aCT was recorded, along with the type of regimen, when available. Chemotherapy administered within 4 months after PD and in the absence of early recurrence was considered adjuvant treatment. The timing of aCT delivery, defined as the interval between surgery and the first administration, was calculated when data was available. Follow-up protocol was chosen by the local oncologists but always included a physical examination, serum tumour markers measurement, and routine imaging.[31]

The primary outcome was the rate of aCT administration, its timing and type of regimen delivered according to the onset of POPF, Subsequently, patients at risk of aCT administration failure or delay according to the occurrence of this complication were identified by the analysis of preoperative tumoral and patient features.

Statistical Analysis

Categorical data were reported as absolute number with relative proportions (%) and compared by the χ^2 test with Yates correction if necessary. Continuous data were expressed as median and interquartile range and compared by using Mann-Whitney *U* test. Best cutoff for age was chosen by assessing ROC curve analysis for aCT deliverance through Youden index method.[32] Two-side *p*-value < 0.05 was considered as statistically significant. Propensity score matching was performed to reduce the bias of preoperative patient status and tumoral extension when assessing the impact of POPF on aCT. A nearest neighbor matching without replacement was chosen to create the largest sample size as possible preserving, at the same time, the homogeneity of all the remaining variables and the reliability of the comparison. Preoperative baseline, anatomical and conditional variables of patients experiencing or not a POPF were balanced in a 1:2 ratio. Covariates used to create the model included were those significantly different at the primary outcome analysis. Wirsung diameter was not assessed concurrently with POPF for the obvious collinearity bias in the regression analyses. Considering the introduction of the FOLFIRINOX based and, more generally of the polychemotherapy regimen, after the PRODIGE-24 trial in 2019,[33] as well as the international nature of this study with the consequent heterogeneity in the CT protocol decision, a sensitivity analysis was performed when assessing the type of regimen administrated, including only patients resected after June 1, 2019, which was 6 months after the publication of the trial. Kaplan-Meier analysis between the two matched groups were performed and survival outcomes compared by using log-rank test. Correlation between all preoperative variables and the failure of CT administration was assessed through a multivariable binary logistic regression. Results were shown with odds ratio (OR), 95% confidence interval (CI), and *p*-value. Similarly, the association between timing of CT administration and all factors was investigated by using a multiple linear regression analysis, with adjusted R^2 used as a measure of the goodness of fit of the model. Both models were repeated in the two groups with or without a POPF to determine which patients are at risk in each group. Regression imputation was used for CA 19-9 missing values during the creation of these lasts models.

All statistical analyses were performed by using SPSS software (version 29.0, IBM Corp., Armonk, NY) and R (R Project for statistical computing, version 4.2.2, R Core Team) while Forest plots for binary logistic regression made with Excel (Microsoft 365, Microsoft Corporation).

Results

A total of 2,125 patients were enrolled across the different centers following the study proposal. After applying inclusion and exclusion criteria set for this specific study, 1,590 patients were finally included for the analysis (Supplementary Fig. 1). Of these patients, 862 were male (54.2%), and the median age was 70 years.[14] Overall rate of POPF and biochemical leak in the cohort was 29% (n = 461), while a true POPF occurred in 267 patients (16.8%). Baseline characteristics according to the occurrence of a POPF are shown in Table 1. Factors significantly different between the two groups were sex ($p = 0.014$), age ($p = 0.007$), pancreatic center volume ($p = 0.012$), tumor size ($p = 0.048$), venous contact ($p = 0.006$), and approach ($p = 0.025$). After matching, a total of 534 patients with no POPF were matched to the 267 patients developing this type of complication, balancing all the preoperative variables (Table 1). As regards survival analysis, 16 patients were lost to FU, all without a POPF.

Effect of POPF on aCT Administration, Regimen, and Timing

aCT was administrated in 1,146 patients in the whole cohort (72.1%). This treatment was started more often in younger patients ($p < 0.001$), with larger Wirsung diameter ($p < 0.029$) in open resections ($p < 0.001$) and in the absence of some comorbidities (Supplementary Table 1). Rate of aCT delivery was significantly reduced in presence of a POPF (61% vs. 74.3% in patients with and without POPF, respectively; $p < 0.001$) (Table 2). The onset of this complication was also an independent predictor of the failure of aCT administration at multivariate analysis (OR 2.051, 95% CI 1.458–2.885; $p < 0.001$) (Supplementary Table 2). aCT protocol was known in 1,034 of the 1,146 patients (90.2%). Type of adjuvant regimen chosen did not differ according to the onset of a POPF ($p = 0.946$; Table 2). Among the 1,146 patients receiving an aCT, time from pancreatic resection to first administration was available in 948 cases (82.7%). Of these patients, median time to first CT was 56 days (26). Timing of CT administration significantly differs according to the onset of a POPF (62 days [27.5] vs. 55 days [26] in patients with or without a POPF, respectively; $p < 0.001$).

Matched Cohort

In the matched cohort, aCT administration remained significantly associated with the occurrence of a POPF (61% vs. 76% in patients with and without POPF, respectively; $p < 0.001$) (Table 2). Type of regimen administrated was

Table 1 Comparison of preoperative baseline, surgical/anatomical and conditional variables, before and after propensity score matching

Variables	*Before matching*			*After matching*		
	No POPF n = 1323	POPF n = 267	*p*	No POPF n = 534	POPF n = 267	*p*
	No. (%)			No. (%)		
Baseline variables						
Sex ratio (M/F)	699 (624)	163 (104)	***0.014***	314 (220)	163 (104)	0.541
Age (years), median (IQR)	70 (14)	67 (15)	***0.007***	66.9 (15)	67 (15)	0.399
BMI (Kg/m^2), median (IQR)	24 (5)	24.5 (6.2)	0.072	24.2 (5.1)	24.5 (6.2)	0.499
Weight loss[a]						
No	891 (67.3)	170 (63.7)	0.245	357 (66.9)	170 (63.7)	0.371
Yes	432 (32.7)	97 (36.3)		177 (33.1)	97 (36.3)	
Anatomical/surgical criteria						
Pancreatic center volume						
Medium	248 (18.7)	68 (25.5)	***0.012***	137 (25.7)	68 (25.5)	0.954
High	1075 (81.3)	199 (74.5)		397 (74.3)	199 (74.5)	
Biliary drainage						
No	636 (48.1)	112 (41.9)	0.067	247 (46.3)	112 (41.9)	0.248
Yes	687 (51.9)	155 (58.1)		287 (53.7)	155 (58.1)	
CA 19-9 > 500 U/mL[a]						
No	799 (79.6)	172 (83.5)	0.199	315 (81.8)	172 (83.5)	0.610
Yes	205 (20.4)	34 (16.5)		70 (18.2)	34 (16.5)	
Tumor size (mm), median (IQR)	25 (10)	22 (13)	***0.048***	24 (10)	22 (13)	0.253
MPV/SMV contact						
No	1119 (84.6)	243 (91)	***0.006***	481 (90.1)	243 (91)	0.672
Yes	204 (15.4)	24 (9)		53 (9.8)	24 (9)	
Approach						
Open	1003 (75.8)	185 (69.3)	***0.025***	374 (70)	185 (69.3)	0.828
MI	320 (24.2)	82 (30.7)		160 (30)	82 (30.7)	
Conditional criteria						
Dyslipidemia						
No	1023 (77.3)	199 (74.5)	0.544	414 (77.5)	199 (74.5)	0.346
Yes	299 (22.6)	68 (25.5)		120 (22.5)	68 (25.5)	
Diabetes						
No	955 (72.7)	206 (77.2)	0.237	391 (73.2)	206 (77.2)	0.484
Oral therapy	264 (20)	45 (16.9)		106 (19.9)	45 (16.9)	
Insulin therapy	104 (7.9)	16 (6)		37 (6.9)	16 (6)	
Arterial hypertension						
No	691 (52.2)	148 (55.4)	0.339	299 (56)	148 (55.4)	0.880
Yes	632 (47.8)	119 (44.6)		235 (44)	119 (44.6)	
DVT/PE						
No	1293 (97.7)	260 (97.4)	0.726	524 (98.1)	260 (97.4)	0.488
Yes	30 (2.3)	7 (2.6)		10 (1.9)	7 (2.6)	
Atrial fibrillation						
No	1225 (92.6)	248 (92.9)	0.868	501 (93.8)	248 (92.9)	0.612
Yes	98 (7.4)	19 (7.1)		33 (6.2)	19 (7.1)	
Chronic renal failure						
No	1260 (95.2)	254 (95.1)	0.940	512 (95.9)	254 (95.1)	0.625
Yes	63 (4.8)	13 (4.9)		22 (4.1)	13 (4.9)	
COPD						
No	1228 (92.8)	247 (92.5)	0.858	498 (93.3)	247 (92.5)	0.695
Yes	95 (7.2)	20 (7.5)		36 (6.7)	20 (7.5)	

Table 1 (continued)

Variables	*Before matching*			*After matching*		
	No POPF n = 1323	POPF n = 267	*p*	No POPF n = 534	POPF n = 267	*p*
Ischemic heart disease						
No	1206 (91.2)	249 (93.3)	0.261	494 (92.5)	249 (93.3)	0.700
Yes	117 (8.8)	18 (6.7)		40 (7.5)	18 (6.7)	
Cardiac Failure						
No	1293 (97.7)	260, (97.4)	0.726	519 (97.2)	260 (97.4)	0.879
Yes	30 (2.3)	7 (2.6)		15 (2.8)	7 (2.6)	
Cerebrovascular events						
No	1274 (96.3)	253 (94.8)	0.239	514 (96.3)	253 (94.8)	0.321
Yes	49 (3.7)	14 (5.2)		20 (3.7)	14 (5.2)	

Statistically significant values are given in bold italic

[a]Missing data in 380 patients

POPF postoperative pancreatic fistula; *IQR* interquartile range; *BMI* body mass index; *MPV* main portal vein; *SMV* superior mesenteric vein; *MI* minimally invasive; *DVT* deep venous thrombosis; *PE* pulmonary embolism; *COPD* chronic obstructive pulmonary disease

Table 2 Adjuvant chemotherapy administration, timing and regimen according to the onset of a POPF, before and after propensity score matching

Outcomes	*Before matching*			*After matching*		
	No POPF, n = 1,323	POPF, n = 267	*p*	No POPF, n = 534	POPF n = 267	*p*
	No. (%)			No. (%)		
Adjuvant CT administration						
No	340 (25.7)	104 (39)	***<0.001***	128 (24)	104 (39)	***<0.001***
Yes	983 (74.3)	163 (61)		406 (76)	163 (61)	
Type of adjuvant CT[a]						
Multiagent chemotherapy	438 (86.1)	71 (13.9)	0.946	195 (54.5)	71 (49)	0.279
Gemcitabine or other single agents	451 (85.9)	74 (14.1)		163 (45.5)	74 (51)	
Type of adjuvant CT[b]						
Multiagent chemotherapy	316 (63.6)	49 (61.3)	0.388	141 (70.5)	49 (61.3)	0.088
Gemcitabine or other single agents	181 (36.4)	31 (38.8)		59 (29.5)	31 (38.8)	
Timing to first CT (days), median (IQR)[c]	55 (26)	62 (27.5)	***<0.001***	56 (27)	62 (27.5)	***<0.001***
Overall survival (months), median (95% CI)	28 (25.8-30.2)	25 (20.5-29.5)	0.128	31 (27.1-34.9)	25 (20.5-29.5)	***0.013***

Statistically significant values are given in bold italic

[a]112 and 66 patients not included before and after matching, respectively, because adjuvant regimen was unknown

[b]Sensitivity analysis, including only patients resected from June 1, 2019

[c]198 and 105 patients not included before and after matching, respectively, because timing of adjuvant CT was unknown

*POPF*postoperative pancreatic fistula; *CT* chemotherapy; *IQR* interquartile range; *CI* confidence interval

once more not influenced by POPF ($p = 0.279$). The sensitivity analysis revealed that even after the introduction of the multiagent CT as a standard of care in the adjuvant setting, POPF did not influence the rate of systemic therapy regimen ($p = 0.088$). The association between timing of CT administration after surgery and development of POPF was still significative after the propensity score matching, with a median time of 56 days [27] before

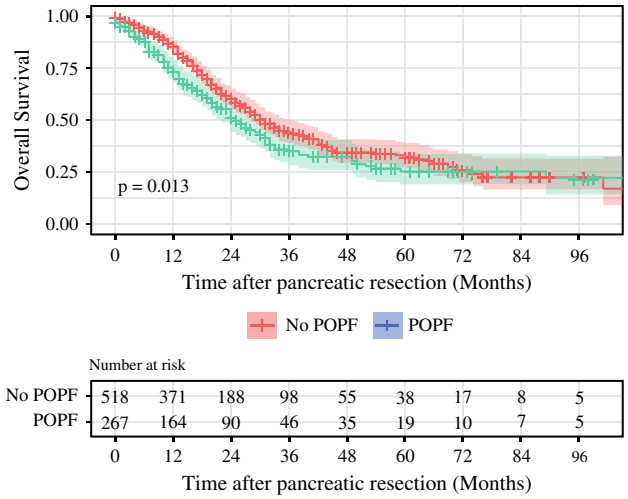

Fig. 1 Kaplan-Meier curves estimating the survival probability according to the onset of a POPF in the matched cohort. POPF: postoperative pancreatic fistula

the first CT cycle in the no POPF group, against 62 days [27.5] in patients experiencing this complication ($p < 0.001$). Finally, median OS of patients developing this type of complication (25 months, 95% CI 20.4–29.6) was significantly shorter compared with those patients without a POPF in the matched cohort (31 months, 95% CI 27.1–34.9; log-rank test, $p = 0.013$) (Fig. 1).

Variables Predicting CT Administration and Timing According to POPF

In the binary logistic model built in the main cohort, covariates independently associated with the administration of an aCT in the no POPF group were age ≥70 (OR 2.685, 95% CI 2.039–3.535; $p < 0.001$), MPV/SMV contact (OR 1.574, 95% CI 1.114–2.224; $p = 0.010$), and tumor size > 20 mm (OR: 0.713, 95% CI 0.523–0.972; $p = 0.032$) (Fig. 2A). Conversely, when a POPF occurred, age ≥70 (OR 2.480, 95% CI 1.439–4.274; $p < 0.001$), renal failure (OR 4.554, 95% CI 1.320–15.708; $p = 0.016$) and COPD (OR 2.775, 95% CI 1.021–7.546; $p = 0.045$) were the only independent predictors for the delivery of an aCT (Fig. 2B). When building the multivariable linear model for predicting the delay of CT initiation (Table 3), model failed to predict the CT timing in patients without a POPF (adjusted R^2 of the model: −0.015, $p = 0.966$), indicating a very poor fit. When this complication occurred, only chronic renal failure was associated with a delay of CT ($p < 0.001$).

Discussion

Surgical resection followed by aCT currently represents the standard of care for curative treatment in resectable PDAC, with multiagent regimens preferred based on patient's general condition.[20,33–36] Patient fitness is often suboptimal due to the advanced median age at diagnosis or for the frequent related morbidity.[37] It is well established that postoperative complications adversely affect oncologic outcomes of these patients, primarily for aCT omission.[4,13,38] More than a quarter of patients in fact do not receive systemic therapy after PD, as confirmed by these findings. Although several postoperative events have been considered as predictors of impaired oncologic outcomes, such as infectious complications or organ failure, many of these are directly related to the occurrence of a POPF.[39–41] This study confirms that in patients with similar baseline tumoral, surgical and, above all, conditional factors, this specific complication severely reduces the likelihood of receiving aCT or significantly delays its initiation. Conversely, even after sensitivity analysis, type of regimen was not influenced by the presence of this complication. Although limited by the absence of pathological data and other prognostic factors that may differ between the groups, the development of a POPF was associated in this series with poorer survival. Given the extensive availability of tools to predict POPF risk,[16,18,19,42] this event should therefore be considered preoperatively as a potential indicator of adjuvant therapy omission. Nevertheless, generalizing this finding to all clinical scenarios may be inappropriate, as patient frailty remains a key determinant of failure to rescue after PD.[10] Defining frailty in this setting is extremely challenging. Performance status has several limitations, as most patients undergoing PD have a score of 0 or 1.[25,43] Other parameters, such as American Society of Anesthesiologists, Charlson comorbidity index, or Charlson's age-comorbidity index, suffer from high interobserver variability or lack specificity in pancreatic cancer, limiting their utility in reliably assessing preoperative risk.[5,26,43] Some authors evaluated existing frailty indices or developed new ones to predict adverse outcomes in pancreatic resections or, more importantly, predict completion of aCT in resectable PDAC.[44,45] Funamizu et al. proposed a modified frailty index based on six preoperative variables which demonstrated predictive value for postoperative complications and survival.[45] However, the small cohort used to develop this score, the inclusion of different type of pancreatic resections, and the absence of interaction with other key preoperative variables, such as tumor-specific factors and predictors of POPF, represents a significant limitation and potential source of bias. As previously discussed, a comprehensive preoperative assessment must incorporate all relevant features—including patient-related, tumor-related, and technical factors—to

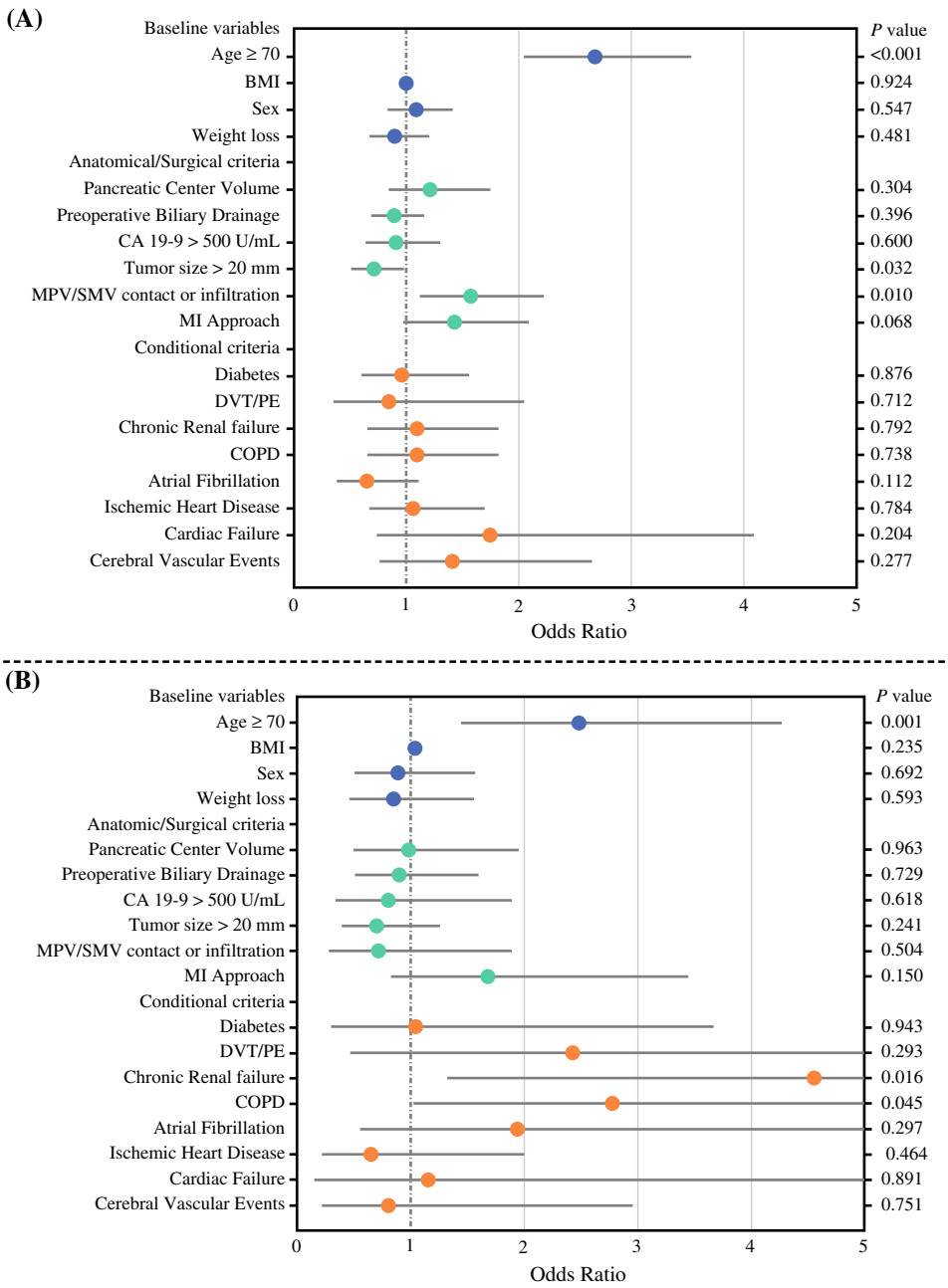

Fig. 2 Forest-plots showing the association between different variables and the likelihood of receiving an adjuvant chemotherapy at multivariable binary logistic regression model. The x-axis represents the odds ratio (OR) obtained in the analysis with the relative 95% CI, identified by the horizontal line of each dot. **A** The first image shows results of the multivariate analysis in patients not developing a POPF. An OR > 1 identifies a higher risk of aCT administration failure, while an OR lower than 1 is associated with a higher probability of undergoing CT. **B** Results of the multivariate logistic regression analysis in patients experiencing a POPF. *BMI* body mass index; *CA* carbohydrate antigen; *POPF* postoperative pancreatic fistula; *MPV* main portal vein; *SMV* superior mesenteric vein; *MI* minimally invasive; *DVT* deep venous thrombosis; *PE* pulmonary embolism; *COPD* chronic obstructive pulmonary disease

determine whether the BR-C status consistently contributes to aCT omission. Furthermore, these outcomes could potentially be mediated by the occurrence of POPF, which underscores the need for a multidimensional approach to preoperative risk stratification. Age is undoubtedly one of the most important key factors in aCT delivery, but while most of the trials on perioperative CT in PDAC ideally include patients up to 75 years old, analysis coming from real scenario found a cutoff of 70 years to be predictive of systemic therapy administration.[33,37,46] These findings corroborate this data, with a cutoff of 70 years independently associated with CT delivery. While all older patients seem to be affected by this risk independently from POPF onset, concurrent factors interact with patient's age according to this complication. Conditional factors for instance, such as CRF or COPD, significantly affect aCT delivery or timing only when a POPF occurred. Renal toxicity remains a major concern for oncologists and is a known source of severe treatment-related morbidity. Adjuvant systemic therapies have in fact shown an increased rate of adverse events in patients with CRF, often leading to dose reductions or treatment discontinuation, which could be potentially be exacerbated in the setting of a PD.[47,48] Conversely, in the absence of POPF, tumor-related factor, as venous contact and smaller

Table 3 Multivariable linear regression predicting the delay of chemotherapy administration

Variables		No POPF, n = 818			POPF, n = 130		
		B	95% CI	*p*	B	95% CI	*p*
Baseline variables							
Sex	Female vs. male	− 16.69	− 59.47-62.44	0.447	3.94	− 14.47-22.35	0.672
Age	>70 vs. ≤70	28.73	− 14.82-72.27	0.196	5.42	− 15.43-26.27	0.535
BMI	Continuous data	− 3.13	− 8.5-2.23	0.252	− 0.87	− 2.85-1.17	0.387
Weight loss	Yes vs. no	− 30.4	− 75.68-14.88	0.188	− 8.11	− 26.71-10.49	0.388
Anatomical/Surgical criteria							
Biliary drainage	Yes vs. no	16.69	− 26.03-59.41	0.443	− 5.23	− 23.4-12.94	0.569
Pancreatic center volume	High vs. medium	1.48	− 59.47-62.4	0.962	6.07	− 21.01-33.16	0.657
CA 19-9 > 500	Yes vs. no	− 18.43	− 73.27-36.41	0.510	0.32	− 24.73-25.37	0.980
Tumor size (mm)	>20 vs. ≤20	18.36	− 25.92-62.64	0.814	− 1.08	− 20.98-17.37	0.852
MPV/SMV contact	Yes vs. no	1.08	− 60.04-62.19	0.972	− 1.15	− 27.7-25.4	0.932
Approach	MI vs. open	− 10.21	− 67.20-46.87	0.725	15.67	− 11.88-43.22	0.261
Conditional criteria							
Diabetes	Yes vs. no	− 11.56	− 46.55-23.43	0.517	− 1.61	− 18.59-15.37	0.851
Atrial fibrillation	Yes vs. no	− 19.84	− 109.16-69.48	0.663	2.93	− 35.07-40.93	0.878
DVT/PE	Yes vs. no	− 9.02	− 173.9-155.86	0.914	5.27	− 70.36-80.9	0.890
Chronic renal failure	Yes vs. no	− 4.21	− 122.48-114.07	0.944	208.6	118.3-298.85	*<0.001*
COPD	Yes vs. no	8.4	− 80.86-97.65	0.853	11.01	− 41.85-63.88	0.680
Ischemic heart disease	Yes vs. no	− 13.13	− 94.81-68.55	0.752	− 15.75	− 57.75-26.25	0.458
Cardiac failure	Yes vs. no	67.5	− 115.53-250.54	0.472	− 3.52	− 95.45-88.42	0.932
Cerebrovascular events	Yes vs. no	− 15	− 134.32-104.32	0.790	4.27	− 36.29-44.86	0.834

CI confidence interval; *POPF* postoperative pancreatic fistula; *BMI* body mass index; *MPV* main portal vein; *SMV* superior mesenteric vein; *MI* minimally invasive; *DVT* deep venous thrombosis; *PE* pulmonary embolism; *COPD* chronic obstructive pulmonary disease

tumor size, were independent predictors of adjuvant treatment initiation, outweighing the influence of conditional factors. While the need for vascular resection is a well-recognized predictor of treatment initiation or discontinuation, likely due to its association with increased morbidity,[9] the influence of tumor size may reflect the occurrence of other complications, as biliary leak or cholangitis, which are more frequently observed following resection for smaller lesions. These findings should be interpreted with caution. Although a high risk of adjuvant chemotherapy (aCT) omission might support consideration of a neoadjuvant strategy, especially in older patients, this approach may be poorly tolerated. In the worst-case scenario, treatment-related decline in performance status could preclude subsequent curative resection, with dropout rates reported to range from 20% to 30% in recent randomized controlled trials.[49,50]

Some limitations should be acknowledged. First, despite the inclusion of many centers and a robust sample size that reflect real-world clinical practice, the retrospective design inherently carries a risk of selection bias. Second, while a broad range of preoperative comorbidities was considered to explore potential interactions, other important factors—particularly nutritional status and specific biochemical parameters—were not included but should be accounted for in an ideal model of patient frailty. Lastly, data regarding CT discontinuation, treatment-related adverse events and cause for its omission, which could provide further insight into patient outcomes, were not consistently available across all participating centers and therefore not assessed.

Conclusions

The omission rate of aCT after PD for pancreatic cancer remains considerably high and POPF is an independent and strong determinant of treatment initiation and timing. Conditional factors, significantly impact these two events only when a POPF occurs, suggesting a synergistic effect. These findings support the need to selectively incorporate patient frailty into preoperative decision-making according to POPF risk, to better select candidates for upfront surgery and optimize the oncologic pathway in potentially resectable PDAC.

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Disclosure None

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