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Association between chronic pancreatitis and pancreatic cancer at a central hospital in KwaZulu-Natal, South Africa

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Background: The frequency of histological chronic pancreatitis (CP) evidence in the resident pancreas of resected periampullary cancers (PACs) has never been studied in Africa. This study aims to describe the spectrum of pathology and outcomes of pancreatic surgeries and address this deficit from a South African central hospital cohort.
Methodology: A retrospective audit of patients undergoing pancreatic surgery at Inkosi Albert Luthuli Central Hospital (IALCH) between 2003 and 2023 was conducted. The patient demographics, human immunodeficiency virus (HIV) status, histological subtypes, type and extent of surgery, and 30-day and overall mortality were captured from medical records. The presence of CP in the resident pancreas of patients resected for pancreatic and PAC was obtained from the pathology reports.
Results: Of the cohort, 72% were Africans, presenting at an earlier average age than other races. Surgery was performed on 126 (107 for cancer, 19 for CP) patients. Of these, 77 were pancreaticoduodenectomy (PD), of which 34 were for pancreatic ductal adenocarcinoma (PDAC). The prevalence of CP in the resident pancreas was 29.9%, and 55.9% in PDAC. Age was the only factor significantly associated with 30-day mortality, as well as long-term survival amongst patients with pancreatic and PAC. The overall median survival for patients with PAC was seven months; 11 patients are alive.
Conclusion: In a predominantly African cohort undergoing pancreatic surgery, PDAC presents at a younger age. The high perioperative mortality and low overall survival (OS) in the setting of high CP prevalence in the resident pancreas requires further investigation of its role in the aetiopathogenesis and prognosis in PDAC.
Keywords: chronic pancreatitis, pancreatic cancer, pancreaticoduodenectomy, pancreatic ductal adenocarcinoma, periampullary carcinoma

Introduction

Pancreatic cancer (PC) is the seventh most lethal cancer in the world, with a mortality-to-incidence ratio of 98% and a five-year OS rate of only 9%.[1,2,3] This lethality, also observed in the most common subtype of adenocarcinoma, is mainly due to the retroperitoneal location of the pancreas and non-specific clinical signs of PC, resulting in late diagnosis when it is locally advanced and amenable, in the main, to palliative therapy.[3,4,5] There is a lack of data on the burden of PC in South Africa (SA). In 2020, the SA National Cancer Registry reported PC rates of 0.62% to 0.64% of all cancers.[6] In Africa, the age-standardised rate of PC was reported to be 2.2 per 100 000 compared to 7.7 per 100 000 in Europe.[7] A study in the Free State province found a discordantly higher incidence of PC when contrasted with the national registry reports, possibly reflecting underdiagnosis or under-reporting nationally.[8]

Sub-Saharan African (SSA) countries face additional hurdles in managing PC. These include late-stage disease presentation, limited diagnostic capabilities, restricted access to surgical interventions, and constraints in providing adjuvant therapies. The lack of specialised healthcare professionals and limited capacity for postoperative care further exacerbate these challenges.[9] In a Zambian study, 90% of patients with PC were managed palliatively, with 100% (24) presenting with stage 4 disease.[10] In Malawi, the reported number of PC patients treated with curative intent was also low, with 94% managed palliatively.[11] Only three publications on the outcomes of PD have been published, and two are in abstract form only.[5,12,13]

A study from Groote Schuur Hospital, reviewing 32 patients accrued over two decades from 1973, reported an in-hospital mortality rate of 9.4%, with a 46% five-year survival following PD for ampullary carcinoma.[12] Another study reviewing data from 2017 reported that out of 90 patients discussed over 12 months with the multidisciplinary team, only one-third were resectable, with a longer waiting time for surgery significantly associated with irresectability of curatively-intended pancreatic malignancies.[5] A recent abstract from Sudan also reported on 184 patients, of which 58% were PDAC treated with PD despite the challenge of

late presentation, though they did not report their 30-day mortality.[13]

CP is a known risk factor for the development of PC. Clinical diagnosis of CP is commonly based on morphological ductal changes on cross-sectional imaging like computed tomography (CT), magnetic resonance pancreatography (MRP), or endoscopic ultrasound (EUS). Histologically, it is characterised by chronic inflammation of the pancreas, resulting in fibrosis of the pancreatic parenchyma, acinar atrophy, and ductal changes.[14] However, there is scarce CP data in SSA, especially in relation to PDAC. The only data in SSA on CP incidence based on clinical and imaging-based criteria in the PC cohort comes from the Free State study, which reported CP as associated with 1.7% of their cohort.[8]

This retrospective study in a cohort of CP, pancreatic, and PAC patients undergoing surgery aims to describe the spectrum of pathology and the outcomes of pancreatic surgeries and establish any association between PC and CP in the resident pancreas.

Methods

Study setting

The study was conducted at IALCH in Durban, one of only two main referral centres for complex or high-risk surgical care in the public sector in the KwaZulu-Natal (KZN) province of SA. KZN is a largely rural province, with the second largest population in SA of 11.5 million.

Study design and population

This is a retrospective, descriptive cohort study of adult patients who underwent elective surgery with curative intent for PC, PAC, and symptomatic CP from 2003 to 2023. The patient demographics, HIV status, histological subtypes, type and extent of surgery, and 30-day mortality were captured from the medical records. The life status of PC and PAC patients for survival analysis was confirmed using the www.verifyid.co.za website and the Department of Home Affairs helpdesk.

The histopathological prevalence of CP in the resident pancreas of patients undergoing surgery for PC and PAC was obtained from the histopathological reports. The triad of fibrosis, atrophy of acinar tissue, and duct distortion and dilatation on an adequate histopathology specimen were used as central features of CP.[15] Original slides of reports not detailing the presence of CP on the resident pancreas from the last decade were reviewed by a histopathologist and 20 supplementary reports were added to the data for analysis.

Statistical analysis

The data was analysed using IBM SPSS (Statistical Package for the Social Sciences) version 28. Frequency tables and percentages were used to describe categorical variables. The mean and standard deviation (SD) were used to summarise normally distributed continuous variables, and the median and interquartile range (IQR) were used to summarise not normally distributed variables. Associations between categorical variables were tested using Pearson's chi-square test or Fisher's exact test, while the student's t-test was used to compare means between two independent groups.

A p-value < 0.05 was considered statistically significant. Kaplan-Meier (KM) survival analysis was used to univariately assess the association between several risk factors for time to mortality in a subgroup of patients. Logrank tests were used to compare time to mortality between groups. Cox proportional hazard models were used to assess the association of factors that showed statistical significance or trends in the KM analysis to adjust for confounding. Hazard ratios (HR) and 95% confidence intervals (CI) were reported.

Results

Patient characteristics

The study cohort comprised 126 patients who underwent pancreatic surgery. Table I details their demographics and surgical pathologies. The overall median age was 55 years, with an even sex distribution. Most patients had pancreatic surgery for cancers (n = 107). The surgical procedures are detailed by pathology in Figure 1.

Various surgical interventions were conducted based on the diagnosis and location or stage of the pancreatic condition. Table II shows the surgical spectrum of final histopathology and the status of the resident pancreas.

The overall prevalence of CP in the resident pancreas of patients undergoing pancreatic surgery for cancer was 29.9%, and a further 6.5% with chronic inflammation not meeting the threshold for CP diagnostic criteria. We found a significant association between the type of cell line and the presence of CP, with CP being more common within the

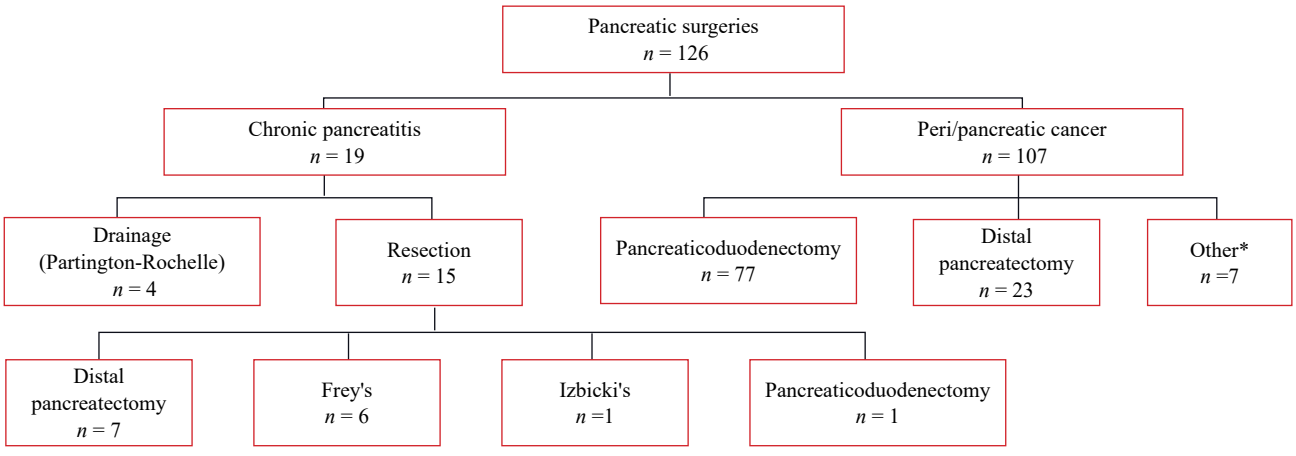

Figure 1: Pathology of surgical procedures

Table I: Demographics of cases by pathology and race

	All pancreatic surgeries			Chronic pancreatitis			Periampullary and pancreatic cancers			Pancreatic ductal adenocarcinoma		
	n	Median age (IQR)	M : F	*n*	Median age (IQR)	M : F	*n*	Median age (IQR)	M : F	*n*	Median age (IQR)	M : F
Overall	126	55 (43–63)	66 : 60	19	47 (40–56)	13 : 6	107	56 (44–65)	53 : 54	34	61 (41–85)	22 : 12
African	91	49 (39–63)	44 : 47	12	44 (34–53)	7 : 5	79	50 (41–64)	37 : 42	20	59. (41–79)	13 : 7
Indian	20	58 (56–63)	10 : 10	4	56 (51–57)	3 : 1	16	61 (56–66)	7 : 9	6	66.(46–85)	3 : 3
Mixed race	5	62 (61–64)	5 : 0	1	51	1 : 0	4	63 (62–67)	4 : 0	3	62 (61–70)	3 : 0
White	10	58 (46–67)	7 : 3	2	51 (46–56)	2 : 0	8	60 (49–69)	5 : 3	5	59 (42–70)	3 : 2

M : F – male-to-female ratio, IQR – interquartile range

Table II: Type of surgery and histology related to disease category.

	Disease category			
	Periampullary and pancreatic cancers (*n* = 107)		Chronic pancreatitis (*n* = 19)	
Resection	***n***	**%**	***n***	**%**
Pancreaticoduodenectomy	77	72.0	1	5.3
Distal pancreatectomy	23	21.5	7	36.8
Frey's	0	0.0	6	31.6
Drainage and (Izbicki's × 1)**	0	0.0	5	26.4
Other	7	6.5	0	0.0
Histology of main pathology				
No specimen	0	0.0	4	21.1
PDAC	34	31.7	0	0.0
SPN	14	13.1	0	0.0
Non-Hodgkin's B lymphoma	1	0.9	0	0.0
NET	21	19.6	0	0.0
No tumour	0	0.0	13	68.4
Cholangiocarcinoma	15	14.0	0	0.0
Duodenum adenocarcinoma	5	4.7	0	0.0
Ampulla adenocarcinoma	7	6.5	0	0.0
Chronic pancreatitis	0	0.0	1	5.3
Intraepithelial neoplasia	0	0.0	1	5.3
Others***	10	9.2	0	0.0
Resident pancreas histology				
Normal	25	23.4	0	0.0
Chronic pancreatitis	32	29.9	15	78.9*
Chronic inflammation	7	6.5	0	0.0
Not reported	41	38.3	0	0.0
No specimen	0	0.0	4	21.1
PanIEN – IPMN	1	0.9	0	0.0
Acute pancreatitis	1	0.9	0	0.0

* 15/19 patients with chronic pancreatitis (4 were drainage procedures)
** One case of Izbicki's added to 4 drainage procedures
*** Others: liposarcoma, MANEC, GIST, MCN
PDAC – pancreatic ductal adenocarcinoma, SPN – solid pseudopapillary neoplasm, NET –neuroendocrine tumour, PanIEN – pancreatic intraepithelial neoplasm, IPMN – intraductal papillary mucinous neoplasm, MANEC – mixed adenocarcinoma neuroendocrine carcinoma, GIST – gastrointestinal stromal tumour, MCN – mucinous cystic neoplasm

resident pancreas from PDAC resections (55.9%) versus other cancers (17.8%) ($p < 0.001$) (Table III).

Table III: Cell lineage relationship to the presence of chronic pancreatitis in the resident pancreas

Cancer cell lineage	CP in resident pancreas					
	No		Yes		Total	
	n	%	n	%	n	%
Pancreatic						
PDAC	15	44.1	19	55.9	34	100
Other cancers	60	82.1	13	17.8	73	100
Total	**75**	**70.1**	**32**	**29.9**	**107**	**100**

CP – chronic pancreatitis, PDAC – pancreatic ductal adenocarcinoma
Pearson's chi-square = 16.04, $p < 0.001$

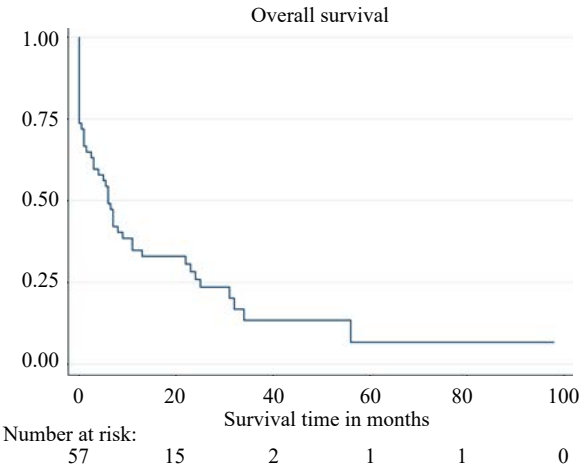

Figure 2: Overall survival

Only age was significantly associated with 30-day mortality ($p = 0.040$), with those who died being slightly older than those who did not die (odds ratio [OR] = 1.039 [95% CI 1.001–1.079]). Other variables (HIV status, presence of CP in the resident pancreas, pancreatic cell line, and extent of surgery) tested showed similar rates between those who died and those who did not die (Table IV).

There were 57/61 patients with PAC who underwent PD whose life status could be ascertained, which represents an attrition rate of 6.6%. Of the patients, 46 (80.7%) had died, and the remaining 11 were still alive at the time of analysis and thus considered censored. The overall median time to mortality from surgical intervention was six months (95% CI IQR 4.15–7.85 months) and seven months (95% CI IQR 1.5–26 months) from presumptive diagnosis. The OS curve of the 57 patients is shown in Figure 2.

Factors associated with time to mortality were analysed in the subgroups of patients using KM survival analysis

Table IV: 30-day mortality related to HIV status, extent of resection, and cancer cell line

	30-day mortality				*p*-value
	No (*n* = 89)		Yes (*n* = 18)		
	Mean	SD	Mean	SD	
Age (years)	52.3	± 15.3	60.5	± 14.4	0.040
	n	%	*n*	%	
HIV status					
Negative	26	29.2	3	16.7	
Positive	18	20.2	6	33.3	0.365
Unknown	45	50.6	9	50.0	
Extent of resection					
Pancreaticoduodenectomy	62	67.7	15	83.3	
Distal pancreatectomy	20	22.5	3	16.7	0.361
Other	7	7.9	0	0	
Cancer cell line					
PDAC	27	30.3	7	38.9	
Other cancers	62	69.7	11	61.1	
SPN	14	15.7	2	11.1	0.477
NET	21	23.6	1	5.56	
CholangioCa	15	16.9	5	27.8	
Ampulla/Duodenum	12	13.5	3	16.7	

SD – standard deviation, HIV – human immunodeficiency virus, PDAC – pancreatic ductal adenocarcinoma

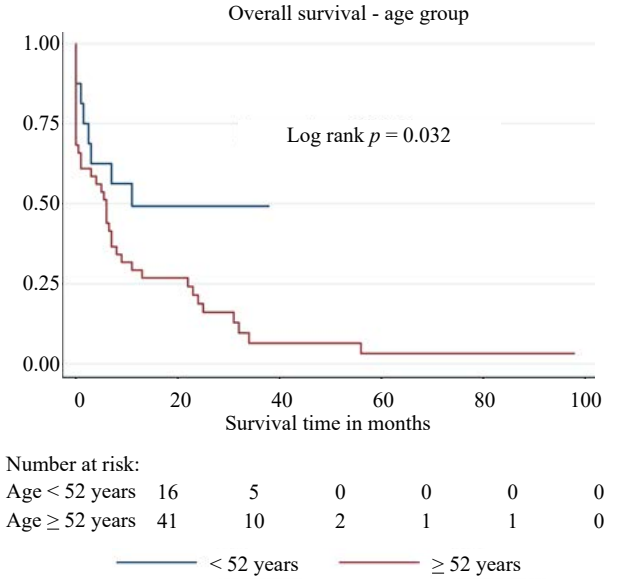

Figure 3

and Cox proportional hazard models. For KM analysis, age was subdivided into two groups based on receiver operating characteristic curve (ROC) classification of optimum differentiation between alive and dead patients at 52 years. There was a statistically significant difference in survival between those ≥ 52 years (see Figure 3) and those below that age ($p = 0.032$). While HIV status and cancer cell line lineage (see Figure 4) show trends in association with time to mortality, only age remained a significant predictor after adjusting for confounders.

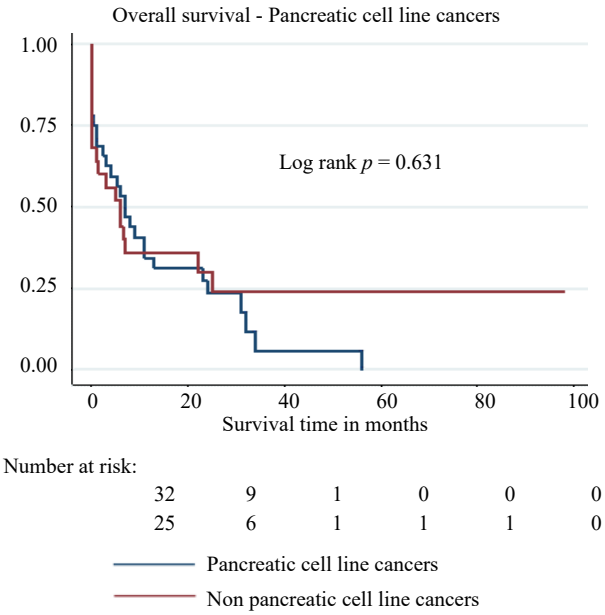

Figure 4: Overall survival per pancreatic cell line

Discussion

Our study examines the surgical outcomes and histopathology of patients undergoing pancreatic surgery for PC and PACs in KZN, SA. Our patient cohort's demographic characteristics, predominantly African ancestry, is, on average, a decade younger compared to cohorts in high-income countries (HIC).[10,16] Close to three-quarters (72%) of the resections for cancers were PD, similar to the general frequency of malignancies involving the head of the pancreas as reported in the Zambian study where the location of PC was reported to be in the head of the pancreas in 83% of cases.[10]

On average, PC presents in the mid-sixties and CP in the mid-forties.[17] Less than 10% of PC patients are below 55 years, with the median age at onset of 71.[16] Compared to HIC, pancreatic and PACs presented at an earlier median age of 56 (IQR 44–65) in our cohort, despite the similar mean age of presentation for CP. The median age for a subset of PDAC is 59.5 (IQR 41–79). Africans presented with CP and PC at an earlier mean age than other races. A retrospective study in Zambia ($n = 27$) had similar findings, with the mean age of PC diagnosis at 55.7 for an African ancestry cohort, which is still a decade younger than the median age in the African-American cohort (66.7 years) in the Surveillance, Epidemiology, and End Results (SEER) database.[10] Significantly, according to the SEER registry, African-Americans present with PC earlier than other races, with poorer prognosis and higher rates of PC.[18,19]

A systematic review focusing on the burden of PC in Europe, including 91 studies, found 12 papers that reported a median survival from diagnosis ranging from 1 to 6.1 months and an OS of 4.6 months.[20] The same review found five papers that reported a median survival following resection or radical surgery ranging from 11 to 25.7 months.[20] In our study, the 30-day mortality was 16.8%, with age being the only predictor of mortality; those who died were eight years older than the survivors (60.5 vs. 52.3 years). The risk of 30-day mortality increased by 3.9% for each additional year of age (OR = 1.039 [95% CI 1.001–1.079]). The rates for 30-day mortality between PDAC and other PACs were similar, with

an overall median time to death from surgical intervention of six months and seven months from presumptive diagnosis.

We are cognisant that the literature has shown significant improvements in the perioperative mortality in PC and PA, with rates under 5% in high-volume centres, and that the rate of 16.8% in this study from 107 PCs over 20 years was higher than expected. This is an experience of just over five cases per year, below the threshold of 11–20 cases per year according to the current consensus definition of high-volume centres, with low-volume centres < 5 per annum in the Netherlands having a mortality of 14.7%.[21]

The only paper that has reported perioperative mortality in SSA is the 1999 study from Cape Town on 32 ampullary carcinomas treated by PD accrued over two decades with a rate of 9.4%.[12] Hence, with such a paucity of SA and SSA survival data, we believe that despite its limitations, this study provides a reference point for studies in this region and a stimulus for others to report on their practice.

Overall mortality is related to the availability of chemotherapy and other modalities of treatment that have become the standard of care for PC in HIC.[22,23] None of our patients received neoadjuvant therapy, and not all patients received adjuvant treatment for different reasons not explored in this paper. Our data only looked at patients treated with curative intent and excluded the metastatic or unresectable cohorts. The OS is expected to be even worse had the latter cohort of patients been considered. Multidisciplinary oncology meetings were only introduced in the latter decade of the study. In addition, several low-risk patients are still managed at regional hospitals and are not referred to central hospitals. This may have led to a selection bias of higher risk; poor prognosis patients referred to a central hospital contribute to the high mortality in our cohort.

The interplay between PC and CP is well-documented in the literature. Korpela et al.[24] found features of CP in 38.8% of histopathological specimens following surgery for PC. Another study from Helsinki University Hospital showed that disease-specific survival (DFS) is shorter in patients with CP in the resident pancreas who had surgery for PDAC (median 20.6 months, 95% CI 10.3–30.9) than for patients without CP (median 41.8 months, 95% CI 26.0–57.6) (logrank test $p = 0.001$).[14] In our cohort, the overall prevalence of histopathological CP in the resident pancreas of patients undergoing surgery for pancreatic/PAC is 29.9%. However, the prevalence is even higher in a subset of PDAC (55.9%) compared to other PACs (17.8%). Due to the retrospective nature of our study, there was no data to establish whether CP was an antecedent to or a result of the development of PC.

Some prospective studies on PC in the setting of CP exclude PC cases diagnosed in the first two years following diagnosis with CP because PC can lead to pancreatitis through tumour-related ductal obstruction.[25,26] The presence of CP stromal reaction in resected PC has been linked to a poorer DFS than those without it.[14] The mechanism of the poorer prognosis may be due to a pro-inflammatory state, as evidenced in a Japanese study that found resectable PC patients with high C-reactive protein to albumin ratio (CAR) due to inflammation and poor nutritional state have a significantly worse OS and DFS than those with a low ratio.[27] They also showed a high CAR with an insignificant association with portal vein resection and adjuvant therapy.[27] A systematic review of 10 articles showed C-reactive protein, modified Glasgow Prognostic Score (mGPS), and neutrophil-lymphocyte ratio (NLR) in PC to be inversely proportional to survival.[28]

An Italian group studied a cohort of 16 cases of HIV-infected patients and found that these patients were diagnosed with PC a decade earlier than in the control group (49 vs. 59.5 years).[28] They also found that HIV-infected patients have a significantly worse survival rate than uninfected patients.[29] The potential adverse effect of HIV positivity on prognosis is important, as 22.4% of the cancers in our cohort were found in those living with HIV but could not be effectively addressed in our study as more than half of the patients did not have documentation of their HIV status.

Acute pancreatitis (AP) may be the initial symptom of patients with PC.[30] We found only one patient with AP (0.9%) in a cohort of 107 surgeries for PC. AP carries a five-year absolute risk of developing PC of 0.87% compared to 0.13% in matched controls.[31,32] The risk of developing PC is greater in smokers and males than females. It is dependent on the duration of AP and decreases with time until it disappears beyond ten years.[30,33]

Pancreatic intraepithelial neoplasias (PanINs) are the most common precursor lesions predisposing to PDAC. PanIN is relatively common, affecting 16% of healthy adults and 60% of people with CP. However, only 1% will eventually lead to malignant transformation, resulting in PC.[34-36] We found only one premalignant lesion (PanIN) in the CP arm of pancreatic surgeries, representing 6.6% of the resections for CP and 5.3% of overall procedures for CP.

Conclusion

Although staging was not included in the analysis, this study has benchmarked outcomes of major pancreatic surgery in an under-resourced health system setting. The high 30-day mortality and poor OS underscore the need for a thorough evaluation of all factors involved in the risk of death. This includes the association of CP in the resident pancreas in PC. A better-designed prospective, longitudinal study that measures both antecedent CP diagnosed on clinical and radiological grounds and histopathological CP in the resident pancreas will better delineate the significance of CP as either a risk factor for developing PC or a prognostic factor for survival.

Conflict of interest

The authors declare no conflict of interest.

Funding source

The study was self-funded.

Ethical approval

Ethical approval was obtained from the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00004931/2022), and the site approval from IALCH and the KZN Department of Health (NHRD Ref: KZ_202212_010). The study was registered with the National Health Laboratory Services (NHLS) Academic Affairs and Research Management System (AARMS) (Ref# PR2345418) to review histopathology reports and samples or slides.

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