HPB

ORIGINAL ARTICLE

Outcomes of patients undergoing elective liver and pancreas cancer surgery during the SARS-CoV-2 pandemic: an international, multicentre, prospective cohort study

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Abstract

Background: The effect of SARS-CoV-2 infection upon HPB cancer surgery perioperative outcomes is unclear. Establishing risk is key to individualising treatment pathways.

We aimed to identify the mortality rate and complications risk for HPB cancer elective surgery during the pandemic.

Methods: International, prospective, multicentre study of consecutive adult patients undergoing elective HPB cancer operations during the initial SARS-CoV-2 pandemic. Primary outcome was 30-day perioperative mortality. Secondary outcomes included major and surgery-specific 30-day complications. Multilevel cox proportional hazards and logistic regression models estimated association of SARS-CoV-2 and postoperative outcomes.

Results: Among 2038 patients (259 hospitals, 49 countries; liver n = 1080; pancreas n = 958) some 6.2%, n = 127, contracted perioperative SARS-CoV-2. Perioperative mortality (9.4%, 12/127 vs 2.6%, 49/1911) and major complications (29.1%, 37/127 vs 13.2%, 253/1911) were higher with SARS-CoV-2 infection, persisting when age, sex and comorbidity were accounted for (HR survival 4.15, 95% CI 1.64 to 10.49; OR major complications 3.41, 95% CI 1.72 to 6.75). SARS-CoV-2 was associated with late postoperative bleeding (11.0% vs 4.2%) and grade B/C postoperative pancreatic fistula (17.9% vs 8.6%).

Conclusion: SARS-CoV-2 infection was associated with significantly higher perioperative morbidity and mortality. Patients without SARS-CoV-2 had acceptable morbidity and mortality rates, highlighting the need to protect patients to enable safe ongoing surgery.

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Introduction

Cancer pathways within healthcare systems worldwide have been severely impacted by the SARS-CoV-2 pandemic. Widespread

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Abbreviations: STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; HCC, Hepatocellular carcinoma; CCA, Cholangiocarcinoma; CRLM, Colorectal liver metastasis; ARDS, Acute respiratory distress syndrome; ISGLS, International Study Group of Liver Surgery; ISGPS, International Study Group on Pancreatic Surgery; qRT-PCR, Quantitative reverse transcription polymerase chain reaction; CT, Computed tomography; REDCap, Research Electronic Capture Database; ASA, American Association of Anesthesiologists; TACE, Transarterial chemoembolization; RFA, Radiofrequency ablation.

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cancellation of elective surgery led to an estimated 28.4 million cancelled or postponed operations, including cancer surgery, in part due to a scarcity of intensive care capacity.[1–3] Fear of perioperative mortality among patients undergoing major liver and pancreas cancer surgery in the setting of SARS-CoV-2 has also affected allocation of surgery. Early studies reporting 30-day mortality from perioperative SARS-CoV-2 as high as 23.8% have been a key driver for this.[4–7] Patients undergoing surgery for pancreatic and liver cancers are already at higher risk of poor peri-operative outcomes compared to other cancers.[8] They also have particularly time critical disease where treatment delays are

associated with disease progression.[9–15] As the pandemic continues and new variants emerge, a better understanding of how SARS-CoV-2 infection impacts peri-operative outcomes is especially important for this group of patients.

With the SARS-CoV-2 pandemic ongoing, and the continued threat of the development of new variants of the virus, it is vital that the risk of perioperative SARS-CoV-2 for patients with resectable liver and pancreas cancer is better understood. Firstly, this will enable risk stratification of elective patients prior to elective surgery.[5] Secondly, clinicians will be better equipped to inform patients of the risk of perioperative infection, and subsequently balance that with the risk of cancer progression with non-operative and/or bridging management strategies.[16,17] Finally, this may provide evidence to maintain funding and provision of measures to prevent nosocomial SARS-CoV-2 transmission such preoperative screening and COVID-19 'free' surgery pathways, or increased use of nonoperative and neoadjuvant treatment strategies.[18–20]

This study aimed to identify the mortality rate and risk of complications for patients undergoing elective surgery for liver and pancreas cancer during the initial phase of the SARS-CoV-2 pandemic.

Methods

Study design
This international, multicentre, observational cohort study included consecutive elective patients with liver and pancreas cancer who underwent surgery with curative intent during the COVID-19 pandemic. Local principal investigators were responsible for obtaining clinical audit, institutional review board, or ethical approval in line with local and national regulations. In the United Kingdom the study did not require research ethics approval and was registered as a clinical audit as only routinely collected anonymized data were recorded. The study was conducted according to guidelines set by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies.[21]

Site inclusion criteria
Hospitals performing elective liver and pancreas cancer surgery in areas affected by the COVID-19 pandemic were eligible for participation. Patient enrolment at each site commenced from the date of admission of the first patient with SARS-CoV-2 to the participating hospital or, in the case of COVID-19–free surgical pathways in hospitals where no cases had been recorded, admission of the first patient with SARS-CoV-2 to the nearest hospital treating patients with SARS-CoV-2.

Patient eligibility criteria
Consecutive adult patients, aged 18 and over, undergoing an elective operation between the first emergence of SARS-CoV-2 at each centre, up to 3 months from this date, were eligible for inclusion, with a follow-up period up to 31st August 2020. Patients who underwent surgery with curative intent for pancreatic or liver cancer (including hepatocellular carcinoma (HCC), intrahepatic/hilar cholangiocarcinoma (CCA), and colorectal liver metastasis (CRLM)) were eligible for inclusion and were followed-up until 30-days after surgery, with the day of surgery as day 0. Patients undergoing operations for gallbladder cancer or liver transplantation were excluded as gallbladder cancer is rare and liver transplantation comes with different COVID-19 risks associated with iatrogenic immunosuppression.

Outcome measures
The primary outcome measure was 30-day perioperative survival, defined as time to death from any cause within 30 days from the date of surgery. The secondary outcome measures included major complications (Clavien-Dindo grade ≥ III, including death), pulmonary complications and liver or pancreas specific surgical complications. Pulmonary complications were defined as pneumonia, acute respiratory distress syndrome (ARDS), or unexpected postoperative ventilation. Unexpected postoperative ventilation was defined as the use of non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation after initial extubation, or the patient could not be extubated as planned after surgery. Surgical complications included postoperative bleeding (divided into early [<24 h] and late [>24 h]), bile leak, postoperative pancreatic fistula (for pancreatic surgery only) and posthepatectomy liver failure. We defined bile leak and posthepatectomy liver failure according to the International Study Group of Liver Surgery (ISGLS) criteria and postoperative pancreatic fistula according to the International Study Group on Pancreatic Surgery (ISGPS) criteria.

Diagnosis of SARS-CoV-2 infection
This was defined either by laboratory, radiological or clinical diagnosis. Laboratory diagnosis was by SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (qRT-PCR) testing. Radiological diagnosis was by thorax computed tomography (CT) scanning with reporting according to local protocols. Clinical diagnosis was by a senior clinician documenting signs and symptoms consistent with SARS-CoV-2 infection, by the WHO COVID-19 case definition,[22] including cough, fever, and myalgia. Clinical diagnosis was included owing to the status of SARS-CoV-2 as an emergent pathogen in the early period of the pandemic, and the inclusion of centres in healthcare systems where testing could have been limited.

Data collection and explanatory variables
Data was collected by teams of clinicians according to a prespecified protocol and uploaded into a secure online Research Electronic Capture Database (REDCap).[23] Explanatory variables to account for perioperative risk and SARS-CoV-2 risk included; patient demographics (age, biological sex, comorbidities,

American Association of Anesthesiologists (ASA) grade), operative characteristics (procedure performed, location of cancer, urgency, approach, extent of resection), tumour characteristics and treatment, national comprehensive cancer network stage, suspected diagnosis and timing of diagnosis, use of preoperative biliary drainage, transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). National level of SARS-CoV-2 was defined according to publicly available data from John Hopkins University Coronavirus Research Center. SARS-CoV-2 rate was divided into peak and post-peak (post-peak defined as a sustained fall to below 20% of the maximum number of cases).[24]

Statistical analysis

Frequencies and percentages were used to summarize categorical data. Continuous data were summarized using mean (standard deviation) or median (interquartile range) depending on distribution. We used Cox-proportional hazards models for the primary survival outcome and multilevel logistic regression models for secondary outcomes to adjust for other explanatory variables on the outcome of interest. For time to death, day of surgery was taken as day zero. Discharge from hospital was considered an absorbing state (once discharged, patients were considered no longer at risk of death). Discharged patients were not censored and included in the risk set until the end of follow-up, thus discharge did not compete with death. Multilevel logistic regression models were specified with level 1 fixed effects (patient and disease characteristics) and level 2 random effects (centre level). Clinically plausible factors were entered into these models and final model selection was guided through minimization of the Akaike information criterion (AIC). Models were checked for any relevant first order interactions and any significant interactions were retained. Effect estimates are presented as hazard ratios for the primary time-to-event outcome (HR) and odds ratios for binary outcomes (OR). Effect estimates are presented alongside their corresponding 95% confidence intervals (95% CI). As a sensitivity analysis to help healthcare planners decide when elective surgery for hepatopancreatobiliary cancer may be safe, we compared risk of death andSARS-CoV-2 at during the first peak and after the first peak.

All analyses were performed in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, AUT) using the *tidyverse* and *finalfit* packages.

Results

Between the emergence of SARS-CoV-2 and 31st August 2020, 2038 adult patients undergoing elective surgery for liver (1080/2,038, 53.0%) and pancreas cancer (958/2,038, 47.0%) were enrolled across 259 hospitals in 49 countries (Fig. 1). Two patients without survival outcomes were excluded. Most patients were from United Kingdom (15.0%, n = 306), Italy (14.6%, n = 298), Spain (8.3%, n = 170), and Germany (7.9%, n = 161) (Supplementary Table S1). Patient demographic data is described

in Table 1, disease characteristics of patients with pancreatic or liver cancers in Tables 2 and 3 respectively.

Overall mortality and complications

The overall 30-day mortality was 3.0% (61/2038), being higher among patients undergoing pancreatic resection (4.1% 39/958) compared to liver resection (2.0% 22/1080) (Table 4). Mortality rates by extent of liver surgery are described in Supplementary Table S2. Major complications occurred in 14.2% (290/2038) of patients; grade B/C post-hepatectomy liver failure (PHLF) affecting 3.0% (32/1080) and grade B/C postoperative pancreatic fistula (POPF) affecting 9.4% (90/958) of patients undergoing liver and pancreatic surgery, respectively.

Development of SARS-CoV-2 and subsequent outcomes

Some 6.2% (127/2038) of patients developed perioperative SARS-CoV-2, being more prevalent among those undergoing pancreatic surgery (8.1%, 78/958 vs 4.5%, 49/1080; p < 0.001). After adjusting for age, sex, comorbidities and cancer location there were no independent predictors for the development of perioperative SARS-CoV-2 infection (Supplementary Fig. S1).

Postoperative outcomes were worse among patients who developed SARS-CoV-2 (Table 4). The 30-day postoperative mortality rate was over three times higher for patients with SARS-CoV-2 than those without (9.4%, 12/127 vs 2.6%, 49/1911; p < 0.001). Following adjustment for explanatory variables, development of SARS-CoV-2 infection remained associated with significantly worse survival (Fig. 2). Performance status of 2 or greater was the only explanatory variable found to have an independent association with 30-day survival. SARS-CoV-2 infection was associated with higher rates of major complications, unplanned critical care admission, postoperative bile leak, late postoperative bleeding, all grades of POPF and longer length of stay (Table 4). After adjustment for explanatory variables, SARS-CoV-2, male gender, higher performance status and pancreatic surgery were independently associated with higher rates of major complications (Fig. 3). As expected, patients who tested positive for SARS-CoV-2 had a higher rate of respiratory complications (40.9%, 52/127 vs 5.8% 110/1911; adjusted OR 13.98, 95%CI 6.60 to 29.63, Table 4 and Supplementary Fig. S2).

Temporal patterns of SARS-CoV-2

SARS-CoV-2 diagnoses occurred most frequently between March and April 2020, when most countries had reached a peak number of infections or were building up to their peak (6.9% peak, 124/1797 versus 0.8% after peak 22/240, Fig. 4). 11.8% (240/2038) of patients had their operation after the peak and had equivalent demographics (including age, sex, performance status and BMI) to those during the peak (Supplementary Tables S3 and S4). Higher mortality rates were seen during national peaks when compared to after the peak (3.2% vs 0.8%, Fig. 4b).
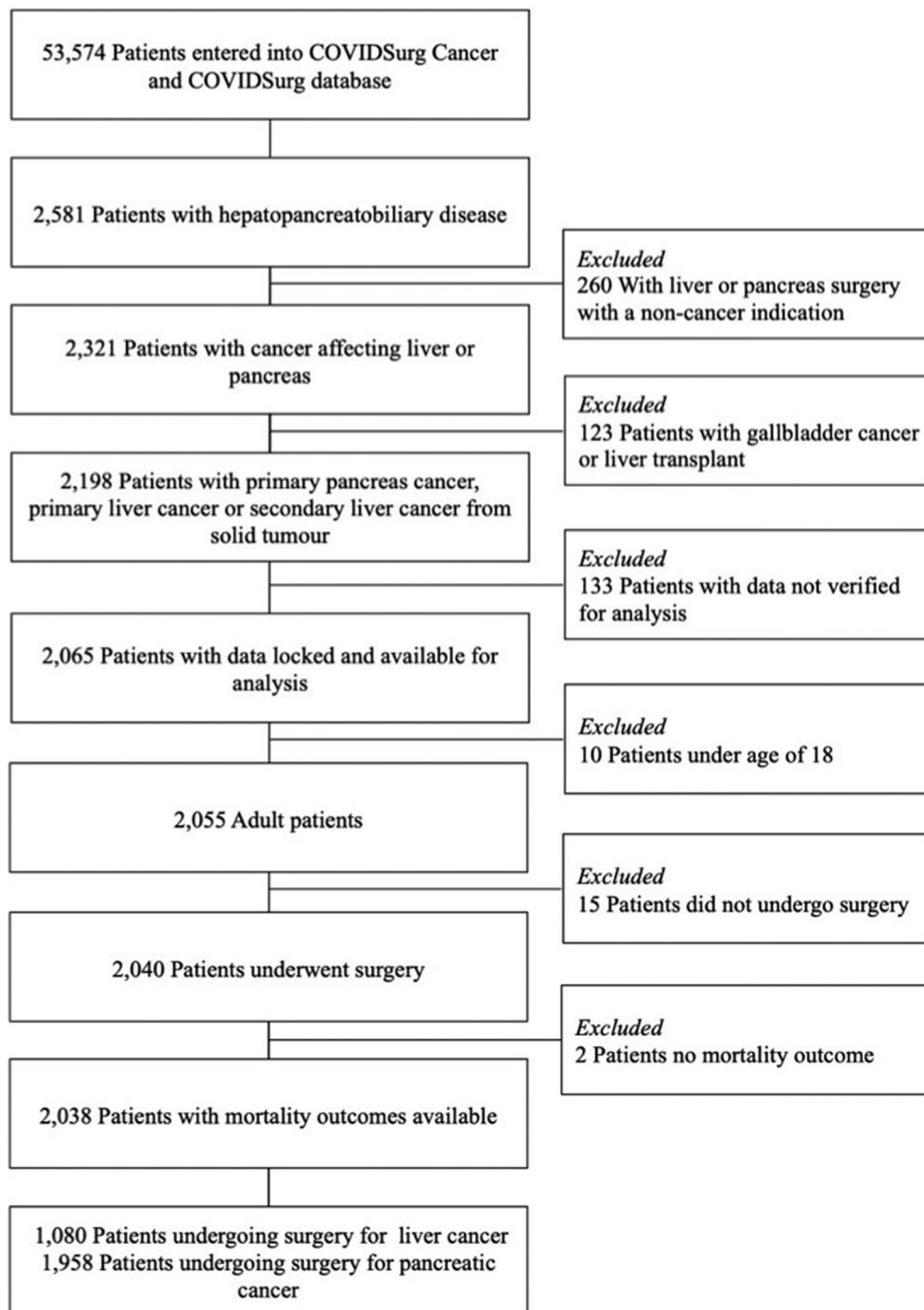
Figure 1 Patient flowchart

These rates were primarily driven by patients with SARS-CoV-2 (8.8% mortality in peak time, versus 2.8% in those who did not have SARS-CoV-2 during same time period). In people who sustained a major complication at times of peak infection rates, the mortality rate was 22.7% (58/256) compared with 6.0% (2/33) after the peak.

Discussion

Elective operating during the SARS-CoV-2 pandemic has been a source of concern for patients and clinicians. To our knowledge, this is the largest study of elective major liver and pancreas surgery undertaken during the pandemic, with 2038 patients

Table 1 Patient demographics

		Total N (%)	No SARS-CoV-2 N (%)	SARS-CoV-2 N (%)	p-value
Total		2038	1911 (93.8%)	127 (6.2%)	
Age (years)	Under 50	235 (11.5)	215 (11.3)	20 (15.7)	0.238
	50 to 69	1077 (52.8)	1007 (52.7)	70 (55.1)	
	70 to 79	582 (28.6)	554 (29.0)	28 (22.0)	
	Over 80	144 (7.1)	135 (7.1)	9 (7.1)	
Sex	Female	810 (39.7)	757 (39.6)	53 (41.7)	0.705
	Male	1228 (60.3)	1154 (60.4)	74 (58.3)	
WHO/ECOG Performance Score	0	716 (35.1)	679 (35.5)	37 (29.1)	**0.022**
	1	148 (7.3)	132 (6.9)	16 (12.6)	
	≥2	28 (1.4)	25 (1.3)	3 (2.4)	
	Missing	1146 (56.2)	1075 (56.3)	71 (55.9)	
ASA	I	247 (12.1)	230 (12.0)	17 (13.4)	0.278
	II	943 (46.3)	876 (45.8)	67 (52.8)	
	III	806 (39.5)	764 (40.0)	42 (33.1)	
	IV	41 (2.0)	40 (2.1)	1 (0.8)	
	Missing	1 (0.0)	1 (0.1)	0 (0.0)	
BMI	Underweight	68 (3.3)	58 (3.0)	10 (7.9)	0.086
	Normal	923 (45.3)	868 (45.4)	55 (43.3)	
	Overweight	679 (33.3)	636 (33.3)	43 (33.9)	
	Moderately obese	257 (12.6)	244 (12.8)	13 (10.2)	
	Severely obese	62 (3.0)	57 (3.0)	5 (3.9)	
	Very severely obese	27 (1.3)	26 (1.4)	1 (0.8)	
	Missing	22 (1.1)	22 (1.2)	0 (0.0)	
Number of comorbidities	Mean (SD)	2.0 (1.3)	2.0 (1.4)	2.0 (1.3)	0.838
Final surgical intention	Curative	1890 (92.7)	1782 (93.2)	108 (85.0)	**0.001**
	Palliative	148 (7.3)	129 (6.8)	19 (15.0)	

[a]ECOG – Eastern Cooperative Oncology Group, WHO – World Health Organization, ASA: American Society of Anesthesiology, BMI: Body Mass Index, Underweight: BMI <18.5, Normal (healthy weight): BMI 18.5–24.9, Overweight: BMI 25–29.9, Moderately obese: BMI 30–34.9, Severely obese: BMI 35–39.9, Very severely obese: BMI ≥40.

undergoing liver and pancreas surgery, including 127 patients with perioperative SARS-CoV-2. This prospective international cohort study undertaken during the first wave of the SARS-CoV-2 pandemic demonstrates that perioperative SARS-CoV-2 infection in patients undergoing elective surgery for liver and pancreas cancer is associated with significantly poorer postoperative outcomes. One in every 16 patients undergoing elective surgery for liver and pancreas cancer had perioperative SARS-CoV-2 infection. Perioperative SARS-CoV-2 infection was associated with higher rates of postoperative complications and mortality, with 1 in every 11 patients with SARS-CoV-2 dying within 30-days of their operation.

Early studies during the pandemic reported significant mortality rates associated with perioperative SARS-CoV-2 infection. One study found an overall mortality rate of 23.8%, however, of the 294 patients undergoing elective surgery in the study, including a small cohort of 30 undergoing major liver or pancreas resections, the mortality rate was 19.8%.[4] This was corroborated by meta-analysis of 2947 patients with perioperative SARS-CoV-2, which reported a mortality rate of 20%, although these were mixed specialty emergency and elective procedures of varying operative complexity.[25] Prior to our study, data on mortality rates of perioperative SARS-CoV-2 in liver and pancreas surgery was lacking, as was data pertaining to the risk of operating on patients without SARS-CoV-2 during the pandemic. It has therefore proven challenging for clinicians and patients to fully understand the perioperative risk of major liver and pancreas surgery during the pandemic. The mortality rate for those with SARS-CoV-2 was 9.4% compared to 2.6% without. Although this is considerably lower than previous reports, it remains unacceptably high, highlighting the need to protect elective surgery patients from contracting SARS-CoV-2,

Table 2 Disease characteristics for patients with pancreatic cancer

		Total N (%)	No SARS-CoV-2 N (%)	SARS-CoV-2 N (%)	p-value
Total N (%)		958	880 (91.9)	78 (8.1)	
Resectability (NCCN Classification)	Resectable	759 (79.2)	703 (79.9)	56 (71.8)	0.235
	Borderline resectable (vein)	101 (10.5)	92 (10.5)	9 (11.5)	
	Borderline resectable (artery)	30 (3.1)	26 (3.0)	4 (5.1)	
	Locally advanced	67 (7.0)	58 (6.6)	9 (11.5)	
	Missing	1 (0.1)	1 (0.1)	0 (0.0)	
Operative approach	Open	846 (88.3)	778 (88.4)	68 (87.2)	0.630
	MIS	99 (10.3)	91 (10.3)	8 (10.3)	
	MIS-Open	13 (1.4)	11 (1.2)	2 (2.6)	
Resection margin status	R0	716 (74.7)	655 (74.4)	61 (78.2)	**0.048**
	R1	117 (12.2)	113 (12.8)	4 (5.1)	
	R2	32 (3.3)	27 (3.1)	5 (6.4)	
	Missing	93 (9.7)	85 (9.7)	8 (10.3)	

NCCN: National Comprehensive Cancer Network, MIS: minimally invasive surgery, MIS-Open: minimally invasive surgery converted to open, R0: no microscopic or macroscopic disease within 1 mm of margin, R1: microscopic disease within 1 mm of margin, R2: macroscopic disease at margin.

Table 3 Disease characteristics for patients with liver cancers

		Total N (%)	No SARS-CoV-2 N (%)	SARS-CoV-2 N (%)	p-value
Total N (%)		1080	1031 (95.5)	49 (4.5)	
Liver: Tumour type	Colorectal liver metastasis	499 (46.2)	481 (46.7)	18 (36.7)	0.108
	Hepatocellular carcinoma	325 (30.1)	305 (29.6)	20 (40.8)	
	Intrahepatic CC	112 (10.4)	109 (10.6)	3 (6.1)	
	Hilar CC	85 (7.9)	78 (7.6)	7 (14.3)	
	Other	58 (5.4)	57 (5.5)	1 (2.0)	
	Missing	1 (0.1)	1 (0.1)	0 (0.0)	
Extent of resection	Minor resection	556 (51.5)	536 (52.0)	20 (40.8)	0.079
	Major resection	474 (43.9)	450 (43.6)	24 (49.0)	
	Extra major resection	49 (4.5)	44 (4.3)	5 (10.2)	
	Missing	1 (0.1)	1 (0.1)	0 (0.0)	
Peri-COVID Operative approach performed	Open	782 (72.4)	746 (72.4)	36 (73.5)	0.985
	MIS	275 (25.5)	263 (25.5)	12 (24.5)	
	MIS-Open	21 (1.9)	20 (1.9)	1 (2.0)	
	(Missing)	2 (0.2)	2 (0.2)	0 (0.0)	
Resection margin status	R0	829 (76.8)	791 (76.7)	38 (77.6)	0.359
	R1	110 (10.2)	108 (10.5)	2 (4.1)	
	R2	33 (3.1)	31 (3.0)	2 (4.1)	
	Unknown	108 (10.0)	101 (9.8)	7 (14.3)	
	Missing	829 (76.8)	791 (76.7)	38 (77.6)	

CC: cholangiocarcinoma, MIS: minimally invasive surgery, MIS-Open: minimally invasive surgery converted to open, R0: no microscopic or macroscopic disease within 1 mm of margin, R1: microscopic disease within 1 mm of margin, R2: macroscopic disease at margin.
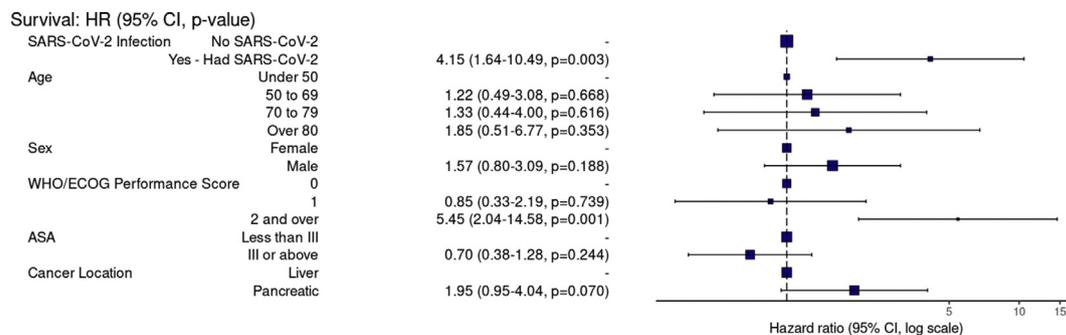
Survival: HR (95% CI, p-value)

		HR (95% CI, p-value)
SARS-CoV-2 Infection	No SARS-CoV-2	-
	Yes - Had SARS-CoV-2	4.15 (1.64-10.49, p=0.003)
Age	Under 50	-
	50 to 69	1.22 (0.49-3.08, p=0.668)
	70 to 79	1.33 (0.44-4.00, p=0.616)
	Over 80	1.85 (0.51-6.77, p=0.353)
Sex	Female	-
	Male	1.57 (0.80-3.09, p=0.188)
WHO/ECOG Performance Score	0	-
	1	0.85 (0.33-2.19, p=0.739)
	2 and over	5.45 (2.04-14.58, p=0.001)
ASA	Less than III	-
	III or above	0.70 (0.38-1.28, p=0.244)
Cancer Location	Liver	-
	Pancreatic	1.95 (0.95-4.04, p=0.070)

Hazard ratio (95% CI, log scale)

Figure 2 Adjusted survival and effect of SARS-CoV-2

Table 4 Postoperative outcomes

			All N (%)	No SARS-CoV-2 N (%)	SARS-CoV-2 N (%)	p-value
	Total N (%)		2038	1911 (93.8)	127 (6.2)	
Overall complications	Mortality (CD V)		61 (3.0)	49 (2.6)	12 (9.4)	**<0.001**
	Mortality: pancreas surgery (CD V)		39 (4.1)	30 (3.4)	9 (11.5)	**0.001**
	Mortality: Liver surgery (CD V)		22 (2.0)	19 (1.8)	3 (6.1)	0.120
	Unplanned Critical Care Admission (CD IV)		54 (2.6)	44 (2.3)	10 (7.9)	**<0.001**
	Any major complication (CD III-V)		290 (14.2)	253 (13.2)	37 (29.1)	**<0.001**
	Postoperative Pulmonary Complication		162 (7.9)	110 (5.8)	52 (40.9)	**<0.001**
	Length of stay (days)	Mean (SD)	11.6 (9.9)	11.2 (9.1)	18.0 (16.3)	**<0.001**
HPB complications	Postoperative bleeding	No	1895 (93.0)	1786 (93.5)	109 (85.8)	**0.002**
		Early (≤24 h)	46 (2.3)	43 (2.3)	3 (2.4)	
		Late (>24 h)	94 (4.6)	80 (4.2)	14 (11.0)	
		Missing	3 (0.1)	2 (0.1)	1 (0.8)	
	Bile leak	No	1893 (92.9)	1791 (93.7)	102 (80.3)	**<0.001**
		Grade A	41 (2.0)	29 (1.5)	12 (9.4)	
		Grade B	65 (3.2)	59 (3.1)	6 (4.7)	
		Grade C	36 (1.8)	30 (1.6)	6 (4.7)	
		Missing	3 (0.1)	2 (0.1)	1 (0.8)	
Pancreatic specific complications	Postoperative pancreatic fistula	No	714 (74.5)	669 (76.0)	45 (57.7)	**0.002**
		Grade A	152 (15.9)	134 (15.2)	18 (23.1)	
		Grade B/C	90 (9.4)	76 (8.6)	14 (17.9)	
		Missing	2 (0.2)	1 (0.1)	1 (1.3)	
Liver specific complications	Post-hepatectomy liver failure	No	912 (88.5)	42 (85.7)	954 (88.3)	0.693
		Grade A	85 (8.2)	5 (10.2)	90 (8.3)	
		Grade B	25 (2.4)	1 (2.0)	26 (2.4)	
		Grade C	7 (0.7)	1 (2.0)	8 (0.7)	
		Missing	2 (0.2)	0 (0.0)	2 (0.2)	

CD – Clavien Dindo.

to ensure safe surgery can continue for this rapidly progressive cancer. Although vaccination rates are increasing globally, at the time of writing, the majority of the global population have not received a dose thus far. Therefore, our data remain relevant to help plan services, inform patients fully of the risks and deliver safe hepatopancreatobiliary surgery amidst the ongoing pandemic.

The overall 30-day mortality rate for patients undergoing elective surgery for liver or pancreas cancer during the pandemic was 3.0%. This is in keeping with recent national studies of
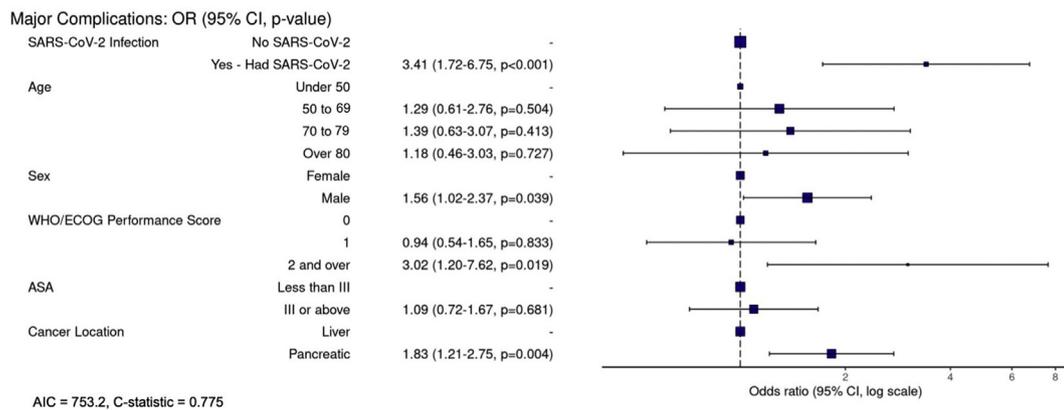
Figure 3 Adjusted odds of major complications with elective liver and pancreas cancer surgery during the SARS-CoV-2 pandemic

unselected hospitals reporting in-hospital mortality rates after pancreatic surgery, ranging from 3.2 to 8.6%[26,27] and 3.4−5.8% for liver surgery.[28,29] However, when mortality rates were stratified by peak and post-peak pandemic time periods, there was considerable variation in mortality (peak of first wave 3.1% compared with 0.8% after the first wave). This is surprising as there were no significant differences in reported patient demographics between groups and is likely multi-factorial. It is possible that there was greater patient selection post-peak with lower risk patients undergoing surgery not reflected in the observed variables, explaining the lower mortality rate. This observation was identified by a UK study, showing one third of pancreatic centres changes their management strategy for patients with borderline-resectable venous disease from a surgery-first approach to neo-adjuvant therapy at the beginning of the pandemic.[7] When resources are constrained, operating upon patients more likely to have a good outcome reduces the strain on precious critical care resources and risk stratification should be considered. It is also possible that the higher peak mortality rate was related to a failure to rescue patients following complications due to resource constraints caused by the pandemic, also seen in a Spanish study of emergency general and gastro-intestinal surgery patients.[30]

Patients with SARS-CoV-2 infection had significantly higher rates of major complications including late postoperative bleeding, POPF and bile leak. However, our study lacks the temporal data around time of SARS-CoV-2 infection to definitively attribute complications to SARS-CoV-2 infection, we therefore can report the association between the factors, but not definitive causality. Patients sustaining complications are more likely to require longer hospital stays, therefore increasing the risk of developing nosocomial SARS-CoV-2 infection, thus potentially giving the appearance of a higher rate of surgical complications in the SARS-CoV-2 group. Similarly, the development of complications frequently shares common risk factors with development of severe SARS-CoV-2 infection (i.e., being male, high BMI).[31] Coagulopathy and massive activation of the fibrinolytic system

is frequently observed in patients with SARS-CoV-2, which could explain the higher rate of late onset bleeding we identified in those with SARS-CoV-2 infection.[32] Although rare, these bleeding complications can be devastating for patients with liver and pancreas cancers. Particularly if these occur at home, or at healthcare facilities with limited capacity to rescue severe complications which could be a concern if critical care resources are already stretched by SARS-CoV-2. Greater research in this area would prove clinically useful, as preventative interventions for those at risk of developing complications could be deployed, strict SARS-CoV-2 free pathways used or even implementation of ambulatory care or telemedicine to avoid exposure to SARS-CoV-2 in patients who do develop complications.

The low perioperative morbidity and mortality for patients without SARS-CoV-2 infection supports the view that surgery for liver and pancreas cancer during the pandemic can be safely performed. It is clearly desirable to ensure SARS-CoV-2 free hospital pathways reduce the likelihood of perioperative SARS-CoV-2 infection, and the optimal perioperative pathway is yet to be determined.[33] Different approaches are likely to work in different settings and will depend on a variety of local factors including flexible staffing, critical care availability, local immunisation rates and local rates of SARS-CoV-2. However, the effectiveness of complete segregation of the operating theatre, critical care, and inpatient ward areas in reducing perioperative SARS-CoV-2 infection has been demonstrated on a global scale.[18,34,35]

Worldwide, liver and pancreas cancer surgery has been impacted by availability of postoperative ICU support, with only 5%−14% units reporting normal operative during pandemic the peak of the pandemic.[7,36] Providing safe pathways to protect patients from perioperative SARS-CoV-2 infection and providing ICU care where needed is a clear priority. When these pathways cannot be provided, alternative cancer management strategies are essential as liver and pancreas cancers are rapidly progressive.[9,37,38] Initial advice suggested moving away from surgery-first treatment to reduce caseload of critically stretched ICUs, and due
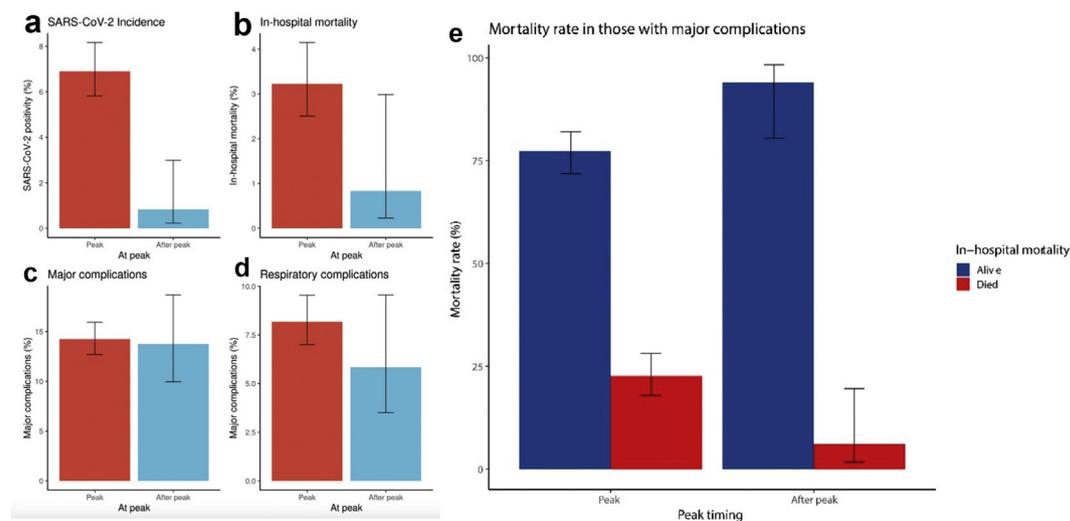
Figure 4 Relationship between length of stay, surgical complications and developing SARS-CoV-2. a – SARS-CoV-2 incidence in surgical patients undergoing liver or pancreas cancer surgery by first wave country peak; b – In-hospital mortality at times of first wave country peaks in surgical patients undergoing liver or pancreas cancer surgery; c – Major complication rates at times of first wave country peaks in surgical patients undergoing liver or pancreas cancer surgery; d – Respiratory complication rates at times of first wave country peaks in surgical patients undergoing liver or pancreas cancer surgery; e – Mortality in patients with major complications at times of first wave country peaks in surgical patients undergoing liver or pancreas cancer surgery

to concerns that patients with cancer were at higher risk of severe SARS-CoV-2 infection due to cancer-related immunosuppression.[39–42] However, non-operative pathways such as neoadjuvant FOLFIRINOX in pancreatic cancer, have also been compromised as they represent a risk to patients through immunosuppression and multiple healthcare institution visits where the burden of SARS-CovV-2 infection may be high.[43,44] Anecdotally, this led to delivery of less intensive treatment regimens, often those that could be delivered orally.[45]

This study acknowledges several limitations. Firstly, only patients who had an operation were included, and previous work has identified that large numbers of elective operations were cancelled.[7,46,47] Our data may focus on those representing either low SARS-CoV-2 infection incidence areas, or those prioritized for surgery owing to their underlying disease.[1] The effect of delays in surgery on long-term outcomes in patients with liver and pancreas cancers remains unknown, and the balance of reduced deaths from SARS-CoV-2 infection against the cancer-related deaths arising from delays to surgery, needs characterising fully.[48] Secondly, timing of complications in relation to SARS-CoV-2 infection diagnosis was not collected, due to unfeasibility at scale. Therefore, whether patients who went on to develop SARS-CoV-2 infection postoperatively had a complication before or after infection remains unknown. This data would help assign causality to whether SARS-CoV-2 infection alone causes increased surgical complications, or whether patients with surgical complications are more likely to develop nosocomial SARS-CoV-2 infection. Furthermore, we did not capture precise timing of diagnosis and whether this was done at a point where

symptoms were present. As access to testing varied over the course of the pandemic, by country and by testing strategy adopted by each country, comparing the different modalities for SARS-CoV-2 diagnosis would likely be highly confounded. Future studies should also establish whether immunisation provides good protection to this vulnerable patient group following surgery, as it is currently unclear as to their effectiveness in the surgical population.

For clinicians and policy makers involved in the planning and delivery of liver and pancreas cancer services, the present data shows that patients undergoing elective procedures remain at risk from SARS-CoV-2 infection. We did not identify any hospital level measures which altered this significantly. In lieu of strong evidence demonstrating robust, system level approaches to prevention, taking precautions such as separating patients of different levels of SARS-CoV-2 infection risk into different clinical areas or hospitals (such as use of COVID-19 free pathways), enforcing preoperative isolation, rigorous preoperative testing and ensuring good infection prevention measures, all have an important role. Healthcare planners should consider adapting services to respond to SARS-CoV-2 fluctuations, by ensuring the presence of robust COVID-19 free surgical pathways for all patients undergoing major cancer surgery and/or by conducting operations at times where circulating virus is at its lowest and halting all but the most urgent cases when infection rates increase again. Due to the increased risk in patients with long hospital stays, clinicians should consider whether patients who are at higher risk of complications should have operations delayed or whether there are mitigating strategies (i.e., COVID-

19 free pathways, immunisations, enhanced testing) that could prevent nosocomial transmission in the postoperative period.

Role of the funding source

Data sharing

Data sharing requests will be considered by the management group upon written request to the corresponding author. If agreed, de-identified participant data will be available, subject to a data sharing agreement.

Presentations

This study has not previously been presented at an academic meeting or conference.

Conflicts of interest

Nil to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2022.03.002.