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

Siobhan C. McKay1,2 COVIDSurg Collaborative*

1Liver Unit, Queen Elizabeth Hospital Birmingham, UK, and 2Department of Academic Surgery, University of Birmingham, UK

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.

Received 8 December 2021; accepted 10 March 2022

Correspondence
Siobhan C McKay, Liver Unit, Queen Elizabeth Hospital Birmingham, UK. E-mail: siobhan.mckay1@nhs.net

Introduction

Cancer pathways within healthcare systems worldwide have been severely impacted by the SARS-CoV-2 pandemic. Widespread 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. As the pandemic continues and new variants emerge, a better understanding of how SARS-CoV-2 infection impacts perioperative 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. 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. Finally, this may provide evidence to maintain funding and provision of measures to prevent nosocomial SARS-CoV-2 transmission such as preoperative screening and COVID-19 ‘free’ surgery pathways, or increased use of nonoperative and neoadjuvant treatment strategies.

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.

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, 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). Explanatory variables to account for perioperative risk and SARS-CoV-2 risk included; patient demographics (age, biological sex, comorbidities, 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.

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, 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). 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, ur-
genity, 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
tfall 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 pri-
mary 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 in-
teractions 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 and SARS-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 pa-
tients 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 vari-
ables, development of SARS-CoV-2 infection remained asso-
ciated 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, pa-
tients 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).
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...
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 for liver and pancreas cancer was 19.8%. 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. 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 1 Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>No SARS-CoV-2</th>
<th>SARS-CoV-2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2038</td>
<td>1911 (93.8%)</td>
<td>127 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 50</td>
<td>235 (11.5)</td>
<td>215 (11.3)</td>
<td>20 (15.7)</td>
<td>0.238</td>
</tr>
<tr>
<td>50 to 69</td>
<td>1077 (52.8)</td>
<td>1007 (52.7)</td>
<td>70 (55.1)</td>
<td></td>
</tr>
<tr>
<td>70 to 79</td>
<td>582 (28.6)</td>
<td>554 (29.0)</td>
<td>28 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Over 80</td>
<td>144 (7.1)</td>
<td>135 (7.1)</td>
<td>9 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>810 (39.7)</td>
<td>757 (39.6)</td>
<td>53 (41.7)</td>
<td>0.705</td>
</tr>
<tr>
<td>Male</td>
<td>1228 (60.3)</td>
<td>1154 (60.4)</td>
<td>74 (58.3)</td>
<td></td>
</tr>
<tr>
<td>WHO/ECOG Performance Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>716 (35.1)</td>
<td>679 (35.5)</td>
<td>37 (29.1)</td>
<td>0.022</td>
</tr>
<tr>
<td>1</td>
<td>148 (7.3)</td>
<td>132 (6.9)</td>
<td>16 (12.6)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>28 (1.4)</td>
<td>25 (1.3)</td>
<td>3 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1146 (56.2)</td>
<td>1075 (56.3)</td>
<td>71 (55.9)</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>247 (12.1)</td>
<td>230 (12.0)</td>
<td>17 (13.4)</td>
<td>0.278</td>
</tr>
<tr>
<td>II</td>
<td>943 (46.3)</td>
<td>876 (45.8)</td>
<td>67 (52.8)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>806 (39.5)</td>
<td>764 (40.0)</td>
<td>42 (33.1)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>41 (2.0)</td>
<td>40 (2.1)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.0)</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>68 (3.3)</td>
<td>58 (3.0)</td>
<td>10 (7.9)</td>
<td>0.086</td>
</tr>
<tr>
<td>Normal</td>
<td>923 (45.3)</td>
<td>868 (45.4)</td>
<td>55 (43.3)</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>679 (33.3)</td>
<td>636 (33.3)</td>
<td>43 (33.9)</td>
<td></td>
</tr>
<tr>
<td>Moderately obese</td>
<td>257 (12.6)</td>
<td>244 (12.8)</td>
<td>13 (10.2)</td>
<td></td>
</tr>
<tr>
<td>Severely obese</td>
<td>62 (3.0)</td>
<td>57 (3.0)</td>
<td>5 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Very severely obese</td>
<td>27 (1.3)</td>
<td>26 (1.4)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>22 (1.1)</td>
<td>22 (1.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>Mean (SD)</td>
<td>2.0 (1.3)</td>
<td>2.0 (1.4)</td>
<td>0.838</td>
</tr>
<tr>
<td>Final surgical intention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curative</td>
<td>1880 (92.7)</td>
<td>1782 (93.2)</td>
<td>108 (85.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Palliative</td>
<td>148 (7.3)</td>
<td>129 (6.8)</td>
<td>19 (15.0)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2 Disease characteristics for patients with pancreatic cancer

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

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

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

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.
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.
unselected hospitals reporting in-hospital mortality rates after pancreatic surgery, ranging from 3.2 to 8.6% and 3.4–5.8% for liver surgery. 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.

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 gastrointestinal surgery patients.

 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). 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. 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. 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.

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. 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. Initial advice suggested moving away from surgery-first treatment to reduce caseload of critically stretched ICUs, and due...
to concerns that patients with cancer were at higher risk of severe SARS-CoV-2 infection due to cancer-related immunosuppression. 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-CoV-2 infection may be high. Anecdotally, this led to delivery of less intensive treatment regimens, often those that could be delivered orally.

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. 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. 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.

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

Role of the funding source
This report was funded by a National Institute for Health Research (NIHR) Global Health Research Unit Grant (NIHR 16/136.79) using UK aid from the UK Government to support global health research; Association of Coloproctology of Great Britain and Ireland; Bowel & Cancer Research; Bowel Disease Research Foundation; Association of Upper Gastrointestinal Surgery; British Association of Surgical Oncology; British Gynaecological Cancer Society; European Society of Coloproctology; NIHR Academy; Sarcoma UK; Vascular Society for Great Britain and Ireland; Yorkshire Cancer Research. The funders had no role in study design, data collection, analysis and interpretation, or writing of this report. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR, or the UK Department of Health and Social Care.

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.

References


Appendix A. Supplementary data

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