




# Global overview of the management of acute cholecystitis during the COVID-19 pandemic (CHOLECOVID study)

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Presented to the annual meeting of the Association of Surgeons of Great Britain and Ireland, Glasgow, UK, May 2021 (virtual presentation) and at the International Congress of the European–African Hepato-Pancreato-Biliary Association (E-AHPBA), Bilbao, Spain, September 2021 (virtual presentation).

## Abstract

**Background:** This study provides a global overview of the management of patients with acute cholecystitis during the initial phase of the COVID-19 pandemic.

**Methods:** CHOLECOVID is an international, multicentre, observational comparative study of patients admitted to hospital with acute cholecystitis during the COVID-19 pandemic. Data on management were collected for a 2-month study interval coincident with the WHO declaration of the SARS-CoV-2 pandemic and compared with an equivalent pre-pandemic time interval. Mediation analysis examined the influence of SARS-CoV-2 infection on 30-day mortality.

**Results:** This study collected data on 9783 patients with acute cholecystitis admitted to 247 hospitals across the world. The pandemic was associated with reduced availability of surgical workforce and operating facilities globally, a significant shift to worse severity of disease, and increased use of conservative management. There was a reduction (both absolute and proportionate) in the number of patients undergoing cholecystectomy from 3095 patients (56.2 per cent) pre-pandemic to 1998 patients (46.2 per cent) during the pandemic but there was no difference in 30-day all-cause mortality after cholecystectomy comparing the pre-pandemic interval with the pandemic (13 patients (0.4 per cent) pre-pandemic to 13 patients (0.6 per cent) pandemic;  $P = 0.355$ ). In mediation analysis, an admission with acute cholecystitis during the pandemic was associated with a non-significant increased risk of death (OR 1.29, 95 per cent c.i. 0.93 to 1.79,  $P = 0.121$ ).

**Conclusion:** CHOLECOVID provides a unique overview of the treatment of patients with cholecystitis across the globe during the first months of the SARS-CoV-2 pandemic. The study highlights the need for system resilience in retention of elective surgical activity. Cholecystectomy was associated with a low risk of mortality and deferral of treatment results in an increase in avoidable morbidity that represents the non-COVID cost of this pandemic.

## Introduction

Acute cholecystitis is inflammation of the gallbladder, typically due to gallstones<sup>1</sup>. Management of patients with this condition is a major global healthcare burden<sup>2</sup>. International guidelines provide information on standards for diagnosis and treatment<sup>3,4</sup>. In patients without major co-morbidity, laparoscopic cholecystectomy during index admission is the recommended treatment for acute cholecystitis<sup>3–5</sup>. Globally, laparoscopic cholecystectomy is among the most frequently undertaken general surgical procedures with an estimated 115 performed per 100 000 of the world's population every year.<sup>6</sup>

In those who are unfit for surgery, treatment with antibiotics may be used as a temporizing option or as an attempt to control symptoms<sup>1</sup>. Radiologically guided percutaneous cholecystostomy can also be used in patients who are unfit for surgery or if operative treatment is not feasible<sup>4,7,8</sup>.

The outbreak due to the novel coronavirus, severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2),

presented a significant challenge to healthcare systems across the world<sup>9</sup>. With the WHO declaration of a global pandemic on 12 March 2020, healthcare resources were re-directed to care for patients with COVID-19<sup>10</sup>. Subsequently, healthcare organizations across the world published guidelines for the management of cholecystitis during the pandemic<sup>11–14</sup>. Patients requiring elective cholecystectomy had their treatment deferred where possible, with only those with the most urgent presentations undergoing surgery. In parallel there was emerging evidence of high rates of postoperative pulmonary complications in patients with perioperative SARS-CoV-2 infection<sup>15</sup>. This led to recommendations that thresholds for surgery during the COVID-19 pandemic should be higher and that consideration should be given to postponing elective cholecystectomy together with utilization of non-operative treatment for acute cholecystitis.

Although deferral or avoidance of treatment for acute cholecystitis was thus necessary during the initial stages of the SARS-CoV-2 pandemic, the consequences for these patients are

**Received:** December 14, 2021. **Revised:** January 22, 2022. **Accepted:** March 03, 2022

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not well understood. The present study examines global changes in the management and clinical outcomes of patients with acute cholecystitis during the SARS-CoV-2 pandemic. The CHOLECOVID study places emphasis on how management was changed during the pandemic, the consequences of these changes, and seeks to identify themes which may help clinicians address the management of acute cholecystitis in the ongoing pandemic setting.

## Methods

### Design

CHOLECOVID is an international, multicentre, observational comparative study of patients admitted to hospital with acute cholecystitis during the COVID-19 pandemic. Data on presentation and outcome were collected for a 2-month study interval coincident with the WHO declaration of the SARS-CoV-2 pandemic. These data are compared with a 2-month time interval from before the pandemic.

### Setting

The study was open to any hospital globally that managed patients with acute cholecystitis.

### Participants

Data were collected retrospectively for patients admitted with acute cholecystitis at participating centres in two 8-week time intervals. The index time interval was the 2 months from the WHO declaration of a SARS-CoV-2 pandemic (12 March 2020 to 12 May 2020). The comparator time interval was the 2 months from 12 September 2019 to 12 November 2019 before the pandemic. Consecutive adult patients (older than 18 years) with a clinical diagnosis of acute cholecystitis constituted the study population.

### Definitions of acute cholecystitis and SARS-COV-2 used in this study

Acute cholecystitis was defined according to the Tokyo criteria (2018), with at least one local sign of inflammation (Murphy's sign positive or right upper quadrant mass/pain/tenderness), at least one systemic sign of inflammation (fever or elevated C-reactive peptide (CRP) or elevated white cell count, and imaging findings characteristic of acute cholecystitis by at least one imaging modality (transabdominal ultrasonography, CT or magnetic resonance cholangiopancreatography (MRCP))<sup>1</sup>.

SARS-CoV-2 infection in the peri-admission interval (positivity 7 days before admission to 30 days from day of admission) was defined as a positive quantitative reverse transcriptase PCR (RT-PCR) test, including nasopharyngeal swab or bronchoalveolar lavage (BAL) performed according to local protocols. As quantitative RT-PCR testing was not available at all participating hospitals in the early stages of the COVID-19 pandemic, patients were also classed as positive if they had a radiological (chest X-ray or CT thorax) or a clinical diagnosis (cough, fever, and loss of sense of smell/taste) of COVID-19<sup>16</sup>.

### Study data set

Descriptive data are provided on global patient cohorts from the pre-pandemic and pandemic time intervals.

### Participating site profiles

Each participating site completed a site profile questionnaire for each data collection interval to describe local processes and resource provision. This specifically assessed the number of

consultants/attending surgeons routinely performing cholecystectomy and the availability of daily urgent dedicated operating lists for cholecystectomy (termed 'hot' lists in some healthcare systems), together with operating list availability for cholecystectomy during the index admission with acute cholecystitis. In addition, the questionnaire assessed onsite interventional radiology and endoscopic retrograde cholangiopancreatography (ERCP) provision. Records with more than 5 per cent incomplete variables were excluded from the analyses. Hospitals submitting data to the study were included in analyses if at least one eligible patient record was uploaded per time interval. International health settings were categorized as either low/middle-income country (LMIC) or high-income country (HIC) according to the Human Development Index (HDI) of the United Nations Development programme<sup>17</sup>.

### Demographic data and diagnosis of acute cholecystitis

Demographic variables collected included age at time of admission, sex, BMI, and Charlson co-morbidity index (CCI)<sup>18</sup>. Admission blood tests were recorded including leucocyte count (WCC), CRP, haemoglobin, platelet count, and enzymatic liver function tests. Acute kidney injury was also recorded where present, graded according to Kidney Disease Improving Global Outcomes guidance<sup>19</sup>. Data were collected for imaging modality utilized and timing of these tests following admission. Data were also collected for Tokyo grade of acute cholecystitis, use of critical care support on admission, and SARS-COV-2 status.

### Management and outcome of acute cholecystitis

Data were collected on management of acute cholecystitis including non-operative (conservative) management, the use of cholecystostomy, and cholecystectomy. SARS-CoV-2 infection in the peri-admission interval is reported for the pandemic cohort. Duration of hospital stay, 30-day re-admission rates, and 30-day all-cause mortality after conservative management, cholecystostomy and cholecystectomy are provided. Data were collected on complication profiles after laparoscopic cholecystectomy.

### Global overview of the management of acute cholecystitis

Global patterns in the management of acute cholecystitis are reported with further analysis by continent and HDI.

### Data collection procedure

Data collection followed a previously validated collaborative research methodology<sup>15</sup>. Anonymized data were submitted and stored online via the Research Electronic Data Capture (REDCap) web application, hosted on secure servers at the University of Manchester (Manchester, UK).

### Statistical analysis

Continuous data were assessed for distribution, summarized as mean (s.d.) or median (interquartile range; i.q.r.) with appropriate parametric or non-parametric tests performed. Categorical data were expressed as counts and percentages with differences tested with chi-squared or Fisher's exact tests.

Multiple logistic regression was used to investigate mortality from cholecystitis during the two time intervals. Covariates included in the model were age, sex, CCI<sup>18</sup>, WCC, acute kidney injury<sup>19</sup>, and Tokyo grade of cholecystitis<sup>1</sup>. Hospitals nested within country were added as random effects and final model selection was performed by minimizing the Akaike information criterion and maximizing the c statistic. After adjustment for

case mix, variation in intervention for acute cholecystitis between the pre-pandemic and pandemic intervals was explored with Bland–Altman plots<sup>20</sup>.

The influence of SARS-CoV-2 infection on 30-day mortality was explored through mediation analysis with a natural-effects model<sup>21</sup>. The total effect underwent two-way decomposition into the effect of the time interval of surgery (direct effect) and the effect mediated by SARS-CoV-2 infection (indirect effect). This model was based around an *a priori* hypothesis that SARS-CoV-2 infection would significantly increase the 30-day mortality.

For all analyses, the threshold of two-sided statistical significance was set at  $P < 0.05$ . Effect estimates were summarized as OR with 95 per cent confidence interval (c.i.). All analyses were performed with R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Ethics

Each study centre was required to comply with their appropriate institutional research board or audit committee and a statement confirming that this was in place was required before data acceptance. For the UK's National Health Service, the National Research Ethics Service decision tool (<http://www.hra-decisiontools.org.uk/research/>) confirmed that the study did not require research registration.

## Results

### Overview

This study collected data on 10 065 patients with acute cholecystitis admitted to 254 hospitals during the two study intervals (Fig. 1). After exclusions for incomplete data, 9783 patients from 247 hospitals from 40 countries constitute the study population. Of these, 5505 (56.3 per cent) were admitted with acute cholecystitis before the COVID-19 pandemic (the pre-pandemic cohort), and 4278 (43.7 per cent) were admitted during the pandemic (pandemic cohort). Data from 60 hospitals

(24.3 per cent) and 1743 patients (17.8 per cent) were from LMICs; the remaining 187 (75.7 per cent) hospitals and 8040 patients (82.2 per cent) were from HICs. In terms of type of healthcare facility, 97 (39.3 per cent) were secondary care centres, and 150 (60.7 per cent) were tertiary care centres.

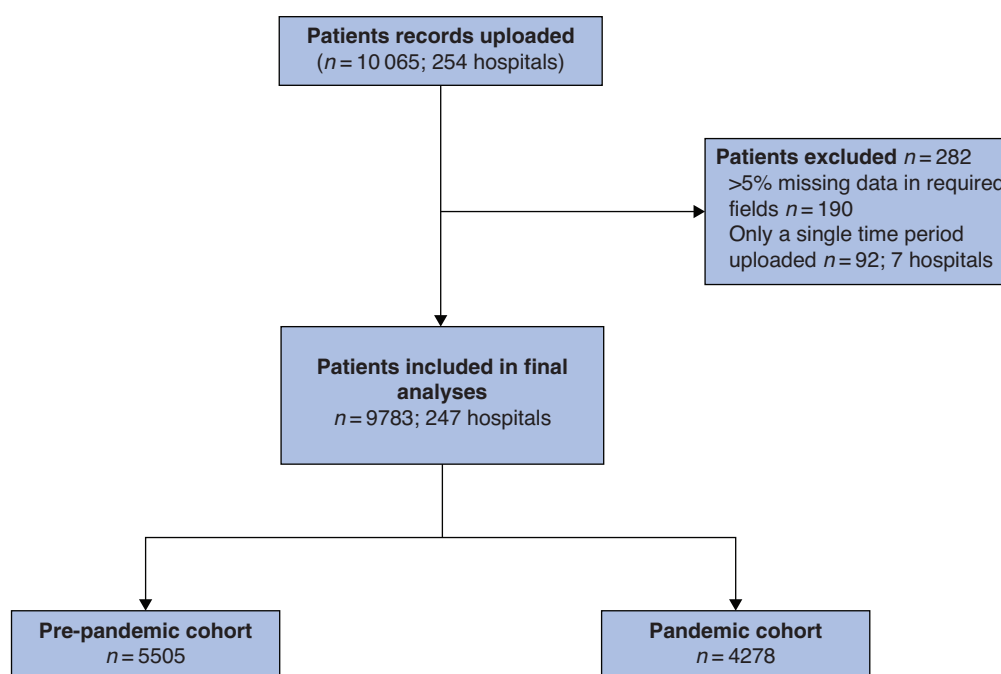
## Profile of participating sites

Fewer sites (38 per cent compared with 45.4 per cent,  $P = 0.117$ ) had urgent cholecystectomy list availability during the pandemic, with an increase in the number of sites providing either no sessions or more than one session per week ( $P = 0.002$ ) (Table 1). There was no significant difference in the availability of either onsite interventional radiology or ERCP services.

**Table 1** Profile of participating clinical sites

	Pre-pandemic	Pandemic	P
<b>Total number of sites</b>	242	242	NA
Number of consultants/ attendings routinely performing cholecystectomy			
1	6 (2.5)	11 (4.5)	0.069
2	11 (4.5)	16 (6.6)	
3	8 (3.3)	15 (6.2)	
4	27 (11.2)	32 (13.2)	
5	13 (5.4)	22 (9.1)	
≥6	177 (71.7)	146 (60.3)	
<b>Daily urgent gallbladder operating list</b>	110 (45.5)	92 (38.0)	0.117
Urgent gallbladder list frequency			
No sessions	132 (54.5)	150 (62.0)	0.002
Less than 1 session per week	7 (2.9)	18 (7.4)	
1–2 sessions per week	29 (12.0)	33 (13.6)	
3–4 sessions per week	35 (14.5)	23 (9.5)	
5 or more sessions per week	39 (16.1)	18 (7.4)	
<b>Onsite interventional radiology</b>	206 (85.1)	201 (83.1)	0.619
<b>Onsite ERCP service</b>	214 (88.4)	208 (86.0)	0.496

Participating site details are available for 242 hospitals. Values in parentheses are percentages. NA, not available; ERCP, endoscopic retrograde cholangiopancreatography.



**Fig. 1** Flow chart of patients in CHOLECOVID study.

Table 2 Baseline characteristics of patients with cholecystitis

	Pre-pandemic	Pandemic	P
<b>Total number of patients</b>	5505	4278	NA
Age, years			
Median (i.q.r.)	60.0 (45.0–74.0)	60.0 (44.0–74.0)	0.865
Sex			
Male (%)	2456 (44.6)	2011 (47.0)	0.019
BMI (%)			
<18.5	64 (1.2)	57 (1.3)	0.088
18.5–24.9	1251 (22.7)	890 (20.8)	
25–29.9	1559 (28.3)	1238 (28.9)	
30–39.9	1064 (19.3)	907 (21.2)	
≥40	218 (4.0)	164 (3.8)	
Unknown	1349 (24.5)	1022 (23.9)	NA
Charlson co-morbidity index			
Median (i.q.r.)	2.0 (0–4.0)	2.0 (0–4.0)	0.948
White cell count			
Mean(s.d.)	12.4(5.3)	12.9(5.6)	<0.001
C-reactive peptide			
Median (i.q.r.)	39.3 (8.6–145.4)	39.0 (7.8–160.0)	0.908
ALP			
Median (i.q.r.)	100.0 (73.0–161.0)	101.0 (74.0–170.0)	0.294
ALT			
Median (i.q.r.)	31.0 (18.0–91.8)	36.0 (20.0–102.0)	<0.001
Bilirubin			
Median (i.q.r.)	15.0 (8.0–27.0)	15.0 (8.3–28.0)	0.019
Acute kidney injury (%)			
None	5011 (91.0)	3795 (88.7)	0.001
Stage I	336 (6.1)	330 (7.7)	
Stage II/III	158 (2.9)	153 (3.6)	
Tokyo severity grade (%)			
Grade I (mild)	3644 (66.2)	2604 (60.9)	<0.001
Grade II (moderate)	1653 (30.0)	1499 (35.0)	
Grade III (severe)	208 (3.8)	175 (4.1)	
Critical care on admission (%)			
No	5381 (97.7)	4207 (98.3)	0.045
Yes	124 (2.3)	71 (1.7)	
<b>SARS-CoV-2 (pandemic interval only)</b>			
<b>Total SARS-CoV-2 positivity (%)</b>			197 (4.5)
SARS-CoV-2 infection 7 days before admission (%)			
Positive			35 (0.8)
Negative			1093 (25.6)
Unknown			3150 (73.6)
Method of diagnosis pre-admission (%)			
Nasopharyngeal swab			33 (94.3)
X-ray			9 (25.7)
CT			6 (17.1)
Clinical diagnosis			11 (31.4)
SARS-CoV-2 infection during admission (%)			
Positive			180 (4.2)
Negative			3179 (74.3)
Unknown			919 (21.5)
Positive tests during admission (% of cohort)			
Nasopharyngeal swab			127 (2.9)
X-ray			47 (1.1)
CT			57 (1.3)
Clinical diagnosis			78 (1.8)

Values in parentheses are percentages unless otherwise specified. ALP, alkaline phosphatase; ALT, alanine transaminase; i.q.r., interquartile range; NA, not available. Note that the total number of SARS-Cov-2 positive results of 197 includes patients who tested positive in the 7 days before surgery in addition to patients diagnosed as inpatients. Eighteen patients who tested positive in the 7 days before admission were also positive on admission tests. Note also that more than one method of diagnosis of SARS-Cov-2 was reported thus patients could have a combination of nasopharyngeal swab, X-ray, CT, and clinical diagnosis.

Table 3 Diagnosis of acute cholecystitis

	Pre-pandemic	Pandemic	Total	P
<b>Total number performed (% of patients in cohort)</b>				
Ultrasound	4525 (82.2)	3152 (73.7)	7677 (78.5)	<0.001
CT	2014 (36.6)	1976 (46.2)	3990 (40.7)	<0.001
MRCP	858 (15.6)	714 (16.7)	1572 (16.1)	0.179
<b>First-line imaging modality utilized (%)</b>				
US	4013 (72.9)	2742 (64.1)	6755 (69.0)	<0.001
CT	1409 (25.6)	1450 (33.9)	2859 (29.3)	
MRCP	83 (1.5)	86 (2.0)	169 (1.7)	
<b>Mean (s.d.) timing of imaging modality in days</b>				
Ultrasound	0.8 (3.2)	0.6 (1.6)	0.7 (2.7)	0.001
CT	0.9 (2.7)	0.8 (2.5)	0.9 (2.6)	0.153
MRCP	3.4 (3.9)	2.7 (3.1)	3.1 (3.6)	<0.001

MRCP, magnetic resonance cholangiopancreatography; US, transabdominal ultrasound scan.

Note that more than one diagnostic test could be used.

### Characteristics of patients with acute cholecystitis

There was no significant difference in age, BMI, or CCI between the pre-pandemic and pandemic cohorts (Table 2). During the pandemic there was a significant shift in severity of acute cholecystitis with more grade II (1653 patients (30 per cent) pre-pandemic compared with 1499 patients (35 per cent) pandemic) and more grade III disease (208 patients (3.8 per cent pre-pandemic) compared with 175 patients (4.1 per cent pandemic);  $P < 0.001$ ).

Fewer patients were admitted directly to critical care during the pandemic (71 patients (1.7 per cent) versus 124 patients (2.3 per cent),  $P = 0.045$ ). Of patients admitted during the pandemic, 197 patients (4.5 per cent) tested positive for SARS-CoV-2 infection of whom 35 patients (0.8 per cent) tested positive in the 7-day interval before admission, with 94.3 per cent of these diagnosed by nasopharyngeal swab.

### Diagnosis of acute cholecystitis

There was reduced utilization of transabdominal ultrasonography during the pandemic (82.2 per cent pre-pandemic versus 73.7 per cent pandemic;  $P < 0.001$ ), with an increase in CT imaging (36.6 per cent pre-pandemic versus 46.2 per cent pandemic;  $P < 0.001$ ) (Table 3). The use of CT as a first-line imaging modality increased during the pandemic with a concomitant reduction in first-line transabdominal ultrasonography. The delay from admission to ultrasound scan was shorter during the pandemic (pre-pandemic mean(s.d.) 0.8(3.2) days versus pandemic 0.6(1.6) days;  $P < 0.001$ ).

### Management of acute cholecystitis

There was a significant increase in the proportion of patients with grade II or grade III cholecystitis being managed conservatively during the pandemic with fewer undergoing cholecystectomy (960 undergoing cholecystectomy pre-pandemic compared with 720 during the pandemic;  $P < 0.001$ ) (Table 4). Forty-six patients who were positive for SARS-CoV-2 underwent cholecystectomy during the pandemic interval.

Table 4 Management and overall outcome of acute cholecystitis

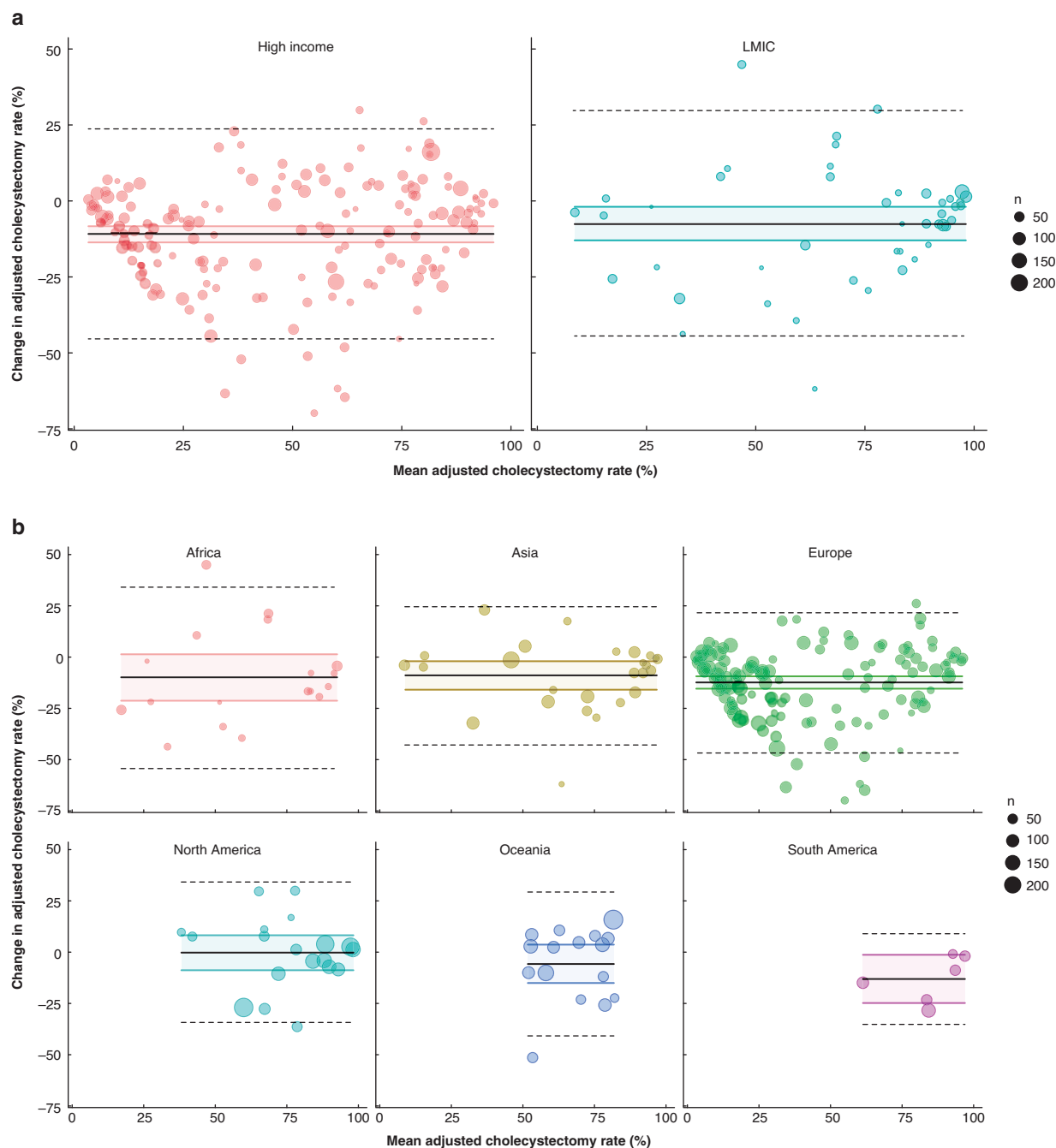
	Pre-pandemic				Pandemic			
	Conservative management	Cholecystostomy	Cholecystectomy	P	Conservative management	Cholecystostomy	Cholecystectomy	P
<b>Tokyo severity grade (per cent)</b>								
Grade I (mild)	1430 (68.2)	89 (27.6)	2125 (68.9)	<0.001	1231 (64.5)	95 (25.7)	1278 (63.9)	<0.001
Grade II (moderate)	598 (28.5)	171 (53.1)	885 (28.7)		612 (32.0)	216 (58.4)	671 (33.6)	
Grade III (severe)	70 (3.3)	62 (19.3)	75 (2.4)		67 (3.5)	59 (15.9)	49 (2.5)	
<b>SARS-CoV-2 infection in the peri-admission interval (per cent)</b>								
Positive	NA	NA	NA	NA	107 (5.6)	44 (11.9)	46 (2.3)	<0.001
Negative	NA	NA	NA	NA	1803 (94.4)	326 (88.1)	1952 (97.7)	
<b>Median (i.q.r.) duration of hospital stay, days</b>	5.0 (3.0–8.0)	11.0 (7.0–17.0)	4.0 (3.0–6.0)	<0.001	5.0 (3.0–7.0)	9.0 (6.0–15.0)	4.0 (2.0–6.0)	<0.001
<b>30-Day re-admission (per cent)</b>	268 (12.8)	121 (37.6)	223 (7.2)	<0.001	227 (11.9)	143 (38.6)	137 (6.9)	<0.001
<b>30-day all-cause mortality (per cent)</b>	60 (2.9)	31 (9.6)	13 (0.4)	<0.001	63 (3.3)	33 (8.9)	13 (0.6)	<0.001

Conservative management, cholecystostomy, and cholecystectomy before and during the pandemic are compared. i.q.r., interquartile range; NA, not available.

Table 5 Complication profiles and peri-procedural outcomes of cholecystostomy and cholecystectomy

	Pre-pandemic	Pandemic	Total	P
<b>Cholecystostomy</b>				
Total (n)	322	370	692	NA
Complication	51 (15.8)	68 (18.4)	119 (17.2)	0.434
Bleeding	9 (2.8)	12 (3.2)	21 (3.0)	0.904
Bile leak	5 (1.6)	9 (2.4)	14 (2.0)	0.583
Intra-abdominal collection	6 (1.9)	6 (1.6)	12 (1.7)	0.990
Occlusion	7 (2.2)	12 (3.2)	19 (2.7)	0.532
Dislodgement	27 (8.4)	37 (10.0)	64 (9.2)	0.549
Perforation	1 (0.3)	1 (0.3)	2 (0.3)	0.990
Re-intervention	79 (24.6)	83 (22.4)	162 (23.4)	0.559
Discharged with cholecystostomy <i>in situ</i>	248 (77.0)	298 (80.5)	546 (78.9)	0.299
Pulmonary complication	34 (10.6)	57 (15.4)	91 (13.2)	0.077
Pulmonary complication (by SARS-CoV-2)				
Negative	NA	39 (10.5)	NA	NA
Positive	NA	18 (4.9)	NA	
Pneumonia	22 (6.8)	38 (10.3)	60 (8.7)	0.142
ARDS	8 (2.5)	13 (3.5)	21 (3.0)	0.572
Unexpected ventilation	10 (3.1)	12 (3.2)	22 (3.2)	0.990
Pulmonary embolus	2 (0.6)	2 (0.5)	4 (0.6)	0.990
<b>Cholecystectomy</b>				
Total (n)	3085	1998	5083	NA
Clavien–Dindo grade				
Minor (I–II)	434 (14.0)	370 (18.5)	804 (15.8)	<0.001
Major (III–V)	165 (5.3)	112 (5.6)	277 (5.4)	
30-Day postoperative mortality	13 (0.4)	13 (0.6)	26 (0.5)	0.355
Post-cholecystectomy biliary complications				
Bile leak	85 (2.7)	54 (2.7)	139 (2.7)	0.127
Bile duct injury	12 (0.4)	7 (0.4)	19 (0.4)	0.651
Pulmonary Complications	85 (2.7)	54 (2.7)	139 (2.7)	0.992
Pulmonary complications (by SARS-CoV-2)				
Yes (negative)	NA	42 (2.1)	NA	NA
Yes (positive)	NA	12 (0.6)	NA	
Pneumonia	46 (1.5)	28 (1.4)	74 (1.5)	0.896
ARDS	12 (0.4)	13 (0.6)	25 (0.5)	0.270
Unexpected ventilation	27 (0.9)	10 (0.5)	37 (0.7)	0.174
Pulmonary embolus	4 (0.1)	4 (0.2)	8 (0.2)	0.794

Figures in parentheses represent percentages. ARDS, adult respiratory distress syndrome; i.q.r., interquartile range; NA, not available. Unexpected ventilation refers to unplanned urgent (emergency) intubation. Clavien–Dindo grades relate to all complications pre-pandemic compared with post-pandemic.



**Fig. 2** Bland–Altman plots of change in cholecystectomy rate during the pandemic compared with pre-pandemic

**a** Data stratified by high-income versus low/middle-income countries. **b** Data stratified by continent. Each plot is expressed as percentages of the difference in adjusted cholecystectomy rates on the y axis (pandemic rate – pre-pandemic rate) versus the mean of the two rates across the two intervals ((pandemic rate + pre-pandemic rate)/2). Mean change is represented as a solid black line with 95 per cent confidence intervals for the mean represented as shaded areas. The limits of agreement, represented as dashed black lines, are defined as the mean difference with 1.96 s.d. of differences.

Median (i.q.r.) duration of hospital of stay was greatest after cholecystectomy (11 (7–17) days before the pandemic and 9 (6–15) days during the pandemic), with no change in inpatient stay after cholecystectomy before or during the pandemic (4 (3–6) days and 4 (2–6) days) respectively.

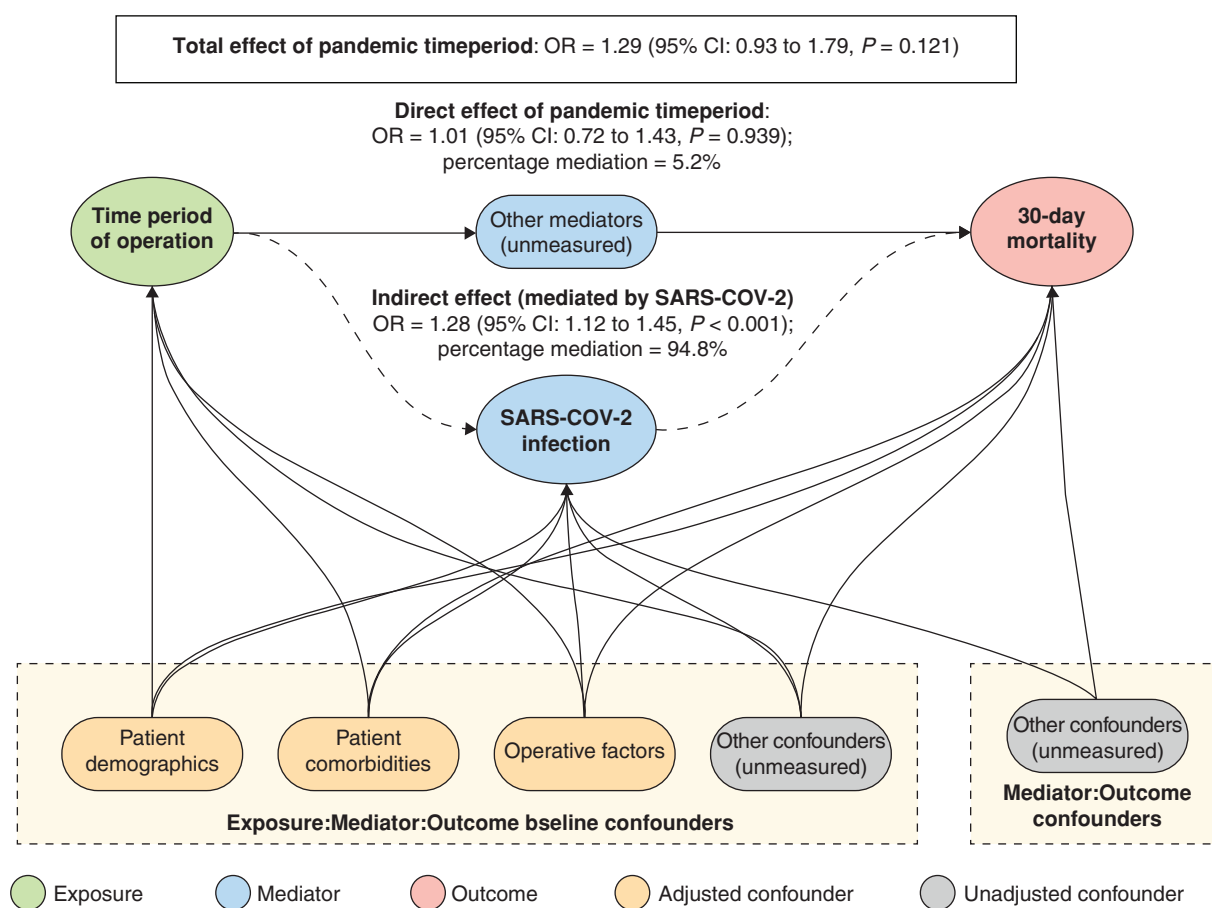
There was a reduction (both absolute and proportionate) in the number of patients undergoing cholecystectomy from 3095 patients (56.2 per cent) pre-pandemic to 1998 patients (46.2 per cent) during the pandemic but there was no difference in 30-day all-cause mortality after cholecystectomy comparing the

pre-pandemic interval to the pandemic (13 patients (0.4 per cent) pre-pandemic to 13 patients (0.6 per cent) pandemic;  $P=0.355$ ).

## Complication profiles of cholecystectomy and cholecystectomy

### Cholecystectomy

Overall, 119 (17.2 per cent) of patients experienced procedure-related complications from cholecystectomy (Table 5). There was no difference in the frequency of complications



**Fig. 3** Mediation analysis of excess odds of death in patients with acute cholecystitis during the SARS-CoV-2 pandemic by SARS-CoV-2 infection

The model used patient and disease characteristics and SARS-CoV-2 infection as covariates. The proportion of the total effect mediated by SARS-CoV-2 infection for mortality in patients with acute cholecystitis during the pandemic with bootstrapped 95 per cent confidence intervals is reported.

before and during the pandemic. Re-intervention was required in 162 cases (23.4 per cent). Once placed, 78.9 per cent of patients were discharged home with a cholecystostomy tube *in situ*. Median duration of hospital stay for patients with cholecystitis was longest for the group undergoing cholecystostomy (Table 4).

### Cholecystectomy

Cholecystectomy complications were assessed by Clavien–Dindo grade. Although there were significantly more complications after cholecystectomy during the pandemic interval, this was mainly due to differences in minor complications (Clavien–Dindo grade I–II, 14.0 per cent pre-pandemic versus 18.5 per cent during pandemic; Clavien–Dindo grade III–V, 5.3 per cent pre-pandemic versus 5.6 per cent during pandemic;  $P < 0.001$ ). There was no difference in the post-cholecystectomy complications of bile leak, bile duct injury, or overall pulmonary complications.

### Management of cholecystitis comparing HICs with LMICs

There was a significant increase in conservative management of acute cholecystitis during the pandemic. In HICs this was from 1915 patients (42.9 per cent) to 1743 patients (48.7 per cent) ( $P < 0.001$ ). In LMICs this was from 183 patients (17.5 per cent) to 167 patients (24.0 per cent) ( $P < 0.002$ ). Proportionately more patients underwent conservative management in HICs in both time intervals (1915 patients (42.9 per cent) before the pandemic and 1743 patients (48.7 per cent) during the pandemic).

In relation to cholecystectomy, 2764 procedures (89.2 per cent) were undertaken laparoscopically before the pandemic and 1760 procedures (87.9 per cent) were undertaken during the pandemic. This difference was not significant ( $P = 0.173$ ). The Bland–Altman plots (Fig. 2) show that HICs showed a negative difference in adjusted cholecystectomy rates compared with LMICs with the pandemic rate being lower than the pre-pandemic rate. By continent, the reduction in adjusted cholecystectomy rates was greatest for Europe, South America, and Oceania.

### Effect of SARS-CoV-2

Following adjustment with a natural-effects mediation analysis, an admission with acute cholecystitis during the pandemic was associated with a non-significant increased risk of death (OR 1.29, 95 per cent c.i. 0.93 to 1.79,  $P = 0.121$ ) (Fig. 3). In the absence of SARS-CoV-2 infection, there was no difference in the mortality rate between the time intervals (OR 1.01, 95 per cent c.i. 0.72 to 1.43,  $P = 0.939$ ). The indirect effect of excess odds of death due to SARS-CoV-2 infection was a significant increase in 30-day mortality (OR 1.28, 95 per cent c.i. 1.12 to 1.45,  $P < 0.001$ ).

### Discussion

CHOLECOVID is the largest global observational cohort study to date comparing the management of patients with acute cholecystitis during the initial stages of the SARS-CoV-2 pandemic with a similar time interval before this. Although

studies have examined the effects of the pandemic on surgery in general and on specific aspects such as surgical oncology<sup>22</sup>, CHOLECOVID provides a unique perspective on the spectrum of outcomes for patients with acute cholecystitis.

What can be learnt from this large study of 9783 patients with acute cholecystitis admitted to 247 hospitals in 40 countries during the two study intervals? The surgical workforce was disrupted by the pandemic with a reduction in the number of centres with six or more consultants/attending surgeons performing cholecystectomy.

In parallel, there was a significant shift in the severity of acute cholecystitis. CHOLECOVID did not collect information on delay from onset of symptoms to admission, and declined or avoided hospital admission rates. However, it is possible to speculate that the shift in admission severity reflects at least in part, delayed presentation<sup>23,24</sup> and/or increased difficulty (or avoidance) of hospital admission<sup>25</sup>. The reduction in admission directly to critical care is thought to represent re-prioritization of bed use with greater resource being diverted to care for patients with COVID-19<sup>26</sup>. Note that the 4.5 per cent (197 of 4278) positive rate for SARS-CoV-2 infection is likely to reflect scarcity of testing in the early stages of the pandemic. The shift in diagnostic modality for acute cholecystitis, away from transabdominal ultrasound and towards CT is possibly reflective of pressures to undertake social distancing and may relate to guidance on the use of thoracic CT in the early stages of the pandemic<sup>27</sup>.

In terms of management, there was a shift to a greater proportion of grade II and grade III cholecystitis patients being treated conservatively during the pandemic and fewer undergoing cholecystectomy. This finding is similar to the experience reported from a national overview study of 4035 patients undergoing cholecystectomy in Germany during the initial stages of the pandemic<sup>28</sup>.

Although cholecystostomy may provide a useful temporizing procedure, it was associated with a 17.2 per cent incidence of procedure-related complications; 23.4 per cent of patients required re-intervention and 78.9 per cent went home with the cholecystostomy tube *in situ*. While this may facilitate hospital discharge, it creates an additional burden of workload for community care.

In relation to cholecystectomy, there was no significant difference in the frequency of pulmonary complications, and although there was an increase in the overall complication profile this did not translate into increased 30-day mortality. Thus a key theme to emerge from CHOLECOVID is that while temporizing manoeuvres may get patients out of hospital quickly, the lack of provision of definitive treatment leads to ongoing problems.

The comparison of the management of cholecystitis in different parts of the world during the pandemic is interesting. Conservative management was more frequently employed in HICs before and during the pandemic. This may reflect availability of other treatment modalities such as interventional radiology facilities. Laparoscopic cholecystectomy was maintained throughout the pandemic. The Bland–Altman plot (Fig. 2) shows a greater change in adjusted cholecystectomy rates in HICs compared with LMICs. By continent, the greatest reductions were seen in Europe, Oceania, and South America and the least in North America, Africa, and Asia. It is important to avoid over-interpretation from these data, but the greater change in adjusted cholecystectomy rates in HICs may be a genuine finding due to the availability of other treatment options in these healthcare systems or may represent

limitations in data capture. The role of socioeconomic status is also important as this can impact the use of cholecystectomy<sup>29</sup>.

Natural-effects mediation analysis showed that an admission with acute cholecystitis during the pandemic was associated with an overall non-significant increase in risk of death (OR 1.29, 95 per cent c.i. 0.93 to 1.79,  $P=0.121$ ) (Fig. 3). The indirect effect of excess odds of death due to SARS-CoV-2 infection was a significant increase in 30-day mortality (OR 1.28, 95 per cent c.i. 1.12 to 1.45,  $P<0.001$ ). Mediation analysis is routinely used to assess the effect of multiple factors on an outcome. Its limitations relate to the accuracy with which an individual contributing factor can be quantified.

When interpreting the findings, limitations of the study must be borne in mind. First, there was no independent validation of data. Thus, the data set could be influenced by acquisition bias and the allocated treatments influenced by allocation bias. Reporting could also have been influenced by sampling and attrition bias. However, previous data verification in national and international observational studies has shown acceptable accuracy in reporting when utilizing this method of data collection<sup>6</sup>. Second, the study interval was short and the pandemic interval encompassed the time of likely maximal disruption. Third, the choice of the early interval of the pandemic pre-dated mass population testing for SARS-CoV-2. Fourth, although CHOLECOVID was open to recruitment from centres across the globe there were more replies from HICs and from tertiary care facilities.

In summary, CHOLECOVID provides an overview of the treatment of patients with cholecystitis across the globe during the first months of the SARS-CoV-2 pandemic. The study shows that although healthcare priorities may need to reflect the pressing needs of patients with SAR-CoV-2, it must be appreciated that reallocation of resources occurs at a cost to patients with common surgical conditions, such as cholecystitis. The definitive and better outcomes from cholecystectomy shown here provide support for enhancing system resilience to retain activity during the ongoing pandemic. Deferral of treatment or change in treatment results in an increase in avoidable morbidity that represents the non-COVID cost of this pandemic.

## Collaborators

### CHOLECOVID Collaborative

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## Funding

There was no funding support for this study.

Disclosure. The authors declare no conflict of interest.

## Supplementary material

Supplementary material is available at BJS Open online.

## Data availability

Anonymized source data can be made available on request.

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