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Original Article

Death following pulmonary complications of surgery before and during the SARS-CoV-2 pandemic

STARSurg Collaborative and COVIDSurg Collaborative *
Correspondence to: James Glasbey, NIHR Global Health Research Unit on Global Surgery, Institute of Translational Medicine, University of Birmingham, Birmingham B15 2TH, UK (e-mail: j.glasbey@bham.ac.uk; collaborate@starsurg.org)

Abstract

Background: This study aimed to determine the impact of pulmonary complications on death after surgery both before and during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

Methods: This was a patient-level, comparative analysis of two, international prospective cohort studies: one before the pandemic (January–October 2019) and the second during the SARS-CoV-2 pandemic (local emergence of COVID-19 up to 19 April 2020). Both included patients undergoing elective resection of an intra-abdominal cancer with curative intent across five surgical oncology disciplines. Patient selection and rates of 30-day postoperative pulmonary complications were compared. The primary outcome was 30-day postoperative mortality. Mediation analysis using a natural-effects model was used to estimate the proportion of deaths during the pandemic attributable to SARS-CoV-2 infection.

Results: This study included 7402 patients from 50 countries; 3031 (40.9 per cent) underwent surgery before and 4371 (59.1 per cent) during the pandemic. Overall, 4.3 per cent (187 of 4371) developed postoperative SARS-CoV-2 in the pandemic cohort. The pulmonary complication rate was similar (7.1 per cent (216 of 3031) *versus* 6.3 per cent (274 of 4371); $P = 0.158$) but the mortality rate was significantly higher (0.7 per cent (20 of 3031) *versus* 2.0 per cent (87 of 4371); $P < 0.001$) among patients who had surgery during the pandemic. The adjusted odds of death were higher during than before the pandemic (odds ratio (OR) 2.72, 95 per cent c.i. 1.58 to 4.67; $P < 0.001$). In mediation analysis, 54.8 per cent of excess postoperative deaths during the pandemic were estimated to be attributable to SARS-CoV-2 (OR 1.73, 1.40 to 2.13; $P < 0.001$).

Conclusion: Although providers may have selected patients with a lower risk profile for surgery during the pandemic, this did not mitigate the likelihood of death through SARS-CoV-2 infection. Care providers must act urgently to protect surgical patients from SARS-CoV-2 infection.

*Members of the STARSurg Collaborative and COVIDSurg Collaborative are co-authors of this article and are listed under the heading Collaborators

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Lay summary

This study compared death rates in patients who developed pulmonary complications of surgery before and during the pandemic in two large, international studies. Patients who underwent surgery during the pandemic tended to be younger and fitter. Overall, 4.3 per cent were diagnosed with SARS-CoV-2 infection after surgery in the pandemic cohort. Deaths within 30 days after surgery tripled during the first wave of the pandemic (from 0.7 to 2.0 per cent), whereas the rate of pulmonary complications remained the similar (7.1 to 6.3 per cent). Over half of these excess deaths (54.8 per cent) were estimated to be related to SARS-CoV-2 infection.

Introduction

Pulmonary complications are a common sequelae of abdominal cancer surgery, with an incidence of around 8 per cent in prospective data sets[1–3]. Pulmonary sequelae include pneumonia, acute respiratory distress syndrome (ARDS), and/or unexpected ventilation, linked by a common pathophysiological mechanism of pulmonary collapse and airway contamination[4]. Before coronavirus disease 2019 (COVID-19), existing data linked pulmonary complications with a moderate risk of death and critical care use[5,6].

Early in the pandemic, it was recognized that patients faced an increased risk of death from pulmonary complications if they became infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the perioperative phase[7]. To reduce in-hospital transmission, health providers around the world

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postponed many elective operations, and cut diagnostic and outpatient services[8]. This had a major collateral impact on those requiring surgery, including patients with cancer facing long delays and associated morbidity[9,10]. Yet in some areas, operations for time-critical conditions such as cancer were continued even during periods with high community SARS-CoV-2 infection rates. Now, during pandemic recovery, surgery must be urgently upscaled to address a growing backlog of elective surgery[8]. However, measures to protect patients from infection, including service reconfiguration to provide COVID-19-free surgical pathways[11] and routine preoperative testing[12], have major financial, logistical, and staffing implications. Data are needed to support shared decision-making and justify investment in protective measures.

Understanding of the relationship between pulmonary complications and postoperative mortality in the pandemic era remains incomplete. In an international study[12] of patients infected with SARS-CoV-2 in the perioperative phase, 51.2 per cent developed a pulmonary complication and 23.8 per cent died. Pulmonary events accounted for 82.6 per cent of deaths in infected patients. These rates were higher than any reported before the pandemic, even for the highest-risk patient groups[2,3,5]. However, this study has been criticized for a lack of comparison with uninfected patients, and a risk of selection bias in identifying the most severely affected patients[13,14]. The effect of the collateral impact on critical care and support services during the pandemic on capacity to rescue patients after surgical complications also remains unmeasured[15,16].

This study aimed to compare mortality after pulmonary complications before and during the pandemic in two international cohort studies of patients undergoing planned cancer surgery, and to explore the mediators of any differences observed.

Methods

This study was a comparative analysis of combined patient-level data from two, international, multicentre, prospective observational cohort studies. Both collected routine, anonymized data with no change to clinical care pathways. Confirmation of appropriate local or national regulatory approval was required before patient enrolment. This study was performed according to STROBE reporting guidelines for observational studies[17].

Participants and settings

Data from two international cohort studies from collaborative groups were combined. Definitions of cases, operations, and outcomes were harmonious in both studies, allowing and robust interpretation of the combined study data set. The RECON study[18] collected data on consecutive adult patients who underwent major abdominal surgery between 21 January 2019 and 23 March 2019 in the UK and Ireland, and between 22 September 2019 and 19 October 2019 in Australia (prepandemic cohort). The COVIDSurg cancer study collected data on consecutive adult patients who underwent cancer surgery with curative intent from the local emergence of COVID-19 (22 February onwards) up to an interim censoring date of 19 April 2020 (pandemic cohort)[19]. Any centre around the world performing cancer surgery was eligible to enrol patients.

Patients undergoing elective (planned) resection of one of five intra-abdominal cancer types with curative intent were included in this combined analysis. Eligible surgical oncology disciplines were colorectal, oesophagogastric, hepatopancreatobiliary (liver, pancreatic), urological (prostate, bladder, renal), and gynaecological (uterine, ovarian, cervical) surgery. Participating centres could contribute data about one or more cancer sites based on local services and capacity. There was an absolute requirement to include all eligible patients during the study inclusion window. Patients with a confirmed SARS-CoV-2-positive test or suspected COVID-19 (with no test result available) at the time of surgery were excluded from the pandemic cohort study.

Outcome measures

The primary outcome was death within 30 days after surgery. The secondary outcome measures were postoperative pulmonary complication and SARS-CoV-2 infection rates.

Postoperative pulmonary complications were defined as a composite of three outcomes plausibly associated with SARS-CoV-2 infection: pneumonia, defined according to US Centre for Disease Control criteria[4]; ARDS, defined according to Berlin consensus criteria[4]; and unexpected postoperative ventilation (defined as failure of planned postoperative extubation, or subsequent requirement for non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation[20]). This outcome definition has been used previously in defining complications of surgery in the context of COVID-19 and major randomized trials[11,20,21].

Reflecting variable access to testing around the world during the early phase of the pandemic, SARS-CoV-2 infection was defined pragmatically. SARS-COV-2 testing was performed according to policy and availability at the participating centre. The primary method of identification was nasopharyngeal swab testing with quantitative reverse transcriptase–polymerase chain reaction (RT–qPCR) used to detect the RNA signature of SARS-CoV-2. Where RT–qPCR testing was not available, radiological and clinical diagnosis with features suggestive of COVID-19 were accepted within the outcome definition[22]. Patients who were initially suspected of having COVID-19 using either clinical or radiological methods, and who subsequently received a negative laboratory test, were classified as uninfected. Patients with unknown SARS-COV-2 infection status were combined with those who were negative for SARS-COV-2 infection to form a variable describing whether or not patients had a SARS-COV-2 diagnosis. In the prepandemic data set, all patients were considered uninfected.

Study procedures and definitions

Data in both studies were collected using a collaborative research methodology[23], engaging clinicians, medical students, and allied healthcare professionals at sites around the world to collect data according to prepublished study protocols[18,19]. Anonymized data were submitted and stored on secure Research Electronic Data Capture (REDCap) servers at the University of Birmingham (Birmingham, UK)[24]. The data sets were homogenized and combined based on variables that shared a common definition and a complementary data structure[18,19].

Clinically relevant co-variables were selected for the purpose of adjustment for case mix. Sociodemographic and operative data recorded included: age, sex, ASA physical status classification, obesity (body mass index (BMI) at least 30 kg/m^2), smoking status, co-morbidities (chronic lung disease, cardiovascular disease, diabetes mellitus), operative approach (open or minimally invasive), operative incision (thoracoabdominal, upper abdominal, or lower abdominal), and operative complexity (complex major or intermediate/major according to the British United Provident Association Schedule of Procedures[25]). Operative incision was classified as the highest extent to which the incision reached; for example, an incision crossing the upper and lower

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abdomen was classified as upper abdominal). Patients for whom the primary outcome (mortality) was missing were excluded from the analysis.

Statistical analysis

Characteristics and postoperative outcomes of patients who underwent surgery in the prepandemic and pandemic cohorts were compared. The phenotype of pulmonary complications, and investigated differences in each component of the composite measure were analysed. Continuous data were summarized as mean(s.d.) or median (i.q.r.) based on visual and statistical evaluation for normality, with testing using appropriate parametric or non-parametric tests. Categorical data were cross-tabulated, and differences tested using χ^2 or Fisher's exact test.

The overall impact of pulmonary complications and death on surgical systems before and during the pandemic was estimated by comparing the fraction of mortality attributable to pulmonary complications—the population attributable fraction[26]. In the present context, this can be interpreted as the estimated percentage of all deaths that would not have occurred if no patients in the cohort had a pulmonary complication.

The influence of timing of surgery (before pandemic *versus* pandemic) and SARS-COV-2 infection on the primary outcome measure (death) was explored in mediation analysis using a natural-effects model[27]. A classical approach was used with two-way decomposition of total effect into the effect of the time interval of surgery (direct effect), and the proportion of this effect that was mediated by SARS-COV-2 infection (indirect effect). Associations between exposure (timing of surgery) and outcome (death), and then the mediator (SARS-COV-2 infection) and both exposure (timing of surgery) and outcome (death) were characterized using logistic regression models. The mediation effect estimate therefore represents the proportion of any difference in death rates between the prepandemic and pandemic cohorts that can be explained by SARS-COV-2 infection. Bootstrapping of estimates was performed to provide 95 per cent confidence intervals. Models were adjusted for all clinically relevant co-variables described above. To explore the effect of inclusion of different hospitals and countries in the cohort studies and differences in operative approach, sensitivity analyses were conducted by including only patients from high-income countries and only open procedures respectively.

Finally, multivariable, mixed-effects (multilevel) logistic regression models were constructed to identify factors associated with mortality. To explore the association between postoperative pulmonary complications and SARS-CoV-2 infection and death these were included as the key explanatory variables, grouped into three categories: no pulmonary complication; pulmonary complication, no SARS-CoV-2; or pulmonary complication, SARS-CoV-2 infection. Again, the model was adjusted for the clinically relevant co-variables described above, with hospital and country included as random effects. First-order interactions were investigated, and final model selection was informed by the Akaike information criterion and C-statistic.

For all analyses, the threshold for two-sided statistical significance was set at $P < 0{\cdot}050$. Effect estimates were summarized as adjusted odds ratios (ORs) with 95 per cent confidence intervals. Data were analysed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), with packages including tidyverse, finalfit, medflex, and collaboratoR[28].

Results

Some 7402 patients were included in this analysis; 3031 (40.9 per cent) underwent surgery before and 4371 (59.1 per cent) during the pandemic (*Fig. 1*). Overall, the surgical case mix was 45.5 per cent (3368 patients) colorectal, 8.5 per cent (631) oesophagogastric, 11.5 per cent (852) hepatopancreatobiliary, 19.9 per cent (1475) gynaecological, and 14.5 per cent (1076) urological cancers. Some 49.0 per cent of patients (3629) underwent open surgery and a minimally invasive approach was attempted in 51.0 per cent (3770).

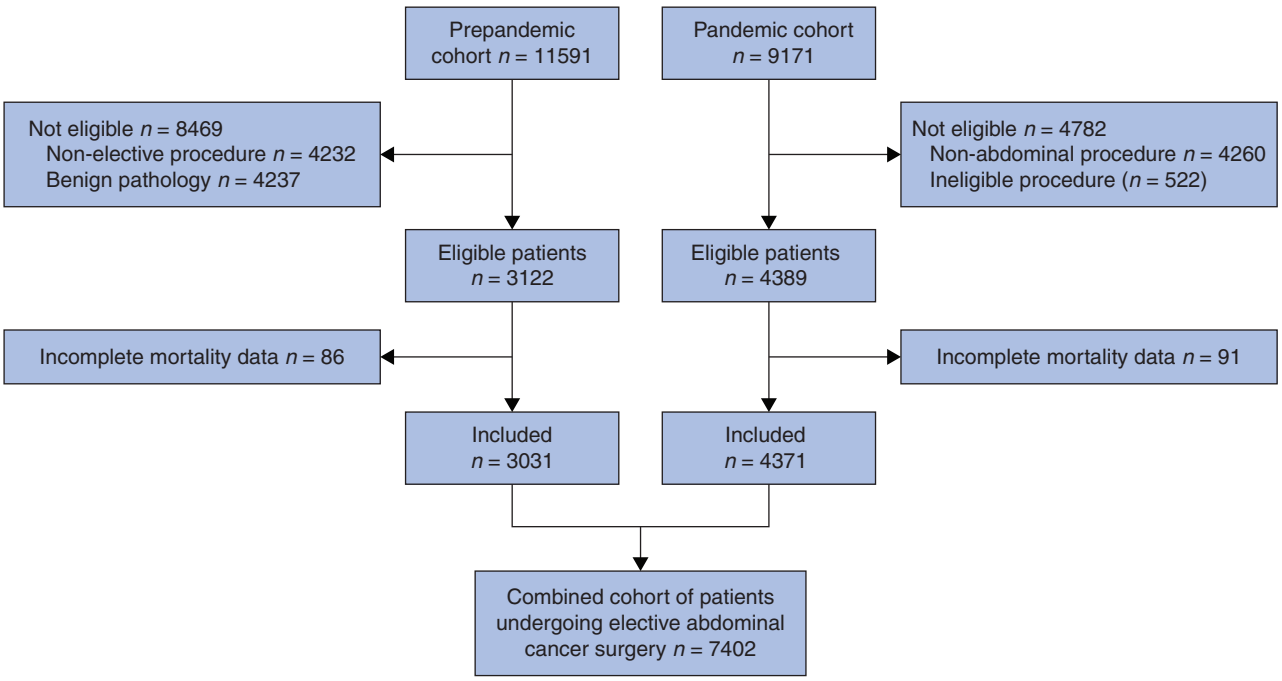


Fig. 1 Study flow diagram

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Comparison of case mix in prepandemic and pandemic data

There were differences between patient groups who had surgery before and during the pandemic (*Table 1*). Patients undergoing surgery during the pandemic had a lower baseline risk than those treated during the pandemic across most risk factors. However, there was a higher proportion of patients undergoing open procedures during than before the pandemic (52.8 and 43.6 per cent respectively). There were some differences in cancer types included in the two cohorts, with a higher rate of colorectal and lower rate of urological cancers in the pandemic cohort. All patients in the prepandemic cohort were from high-income countries. In the pandemic cohort, 12.4 per cent of patients (541 of 4371) were from low- and middle-income countries.

Comparison of outcomes in prepandemic and pandemic data

Despite selection of patients with a lower baseline risk for surgery during the pandemic, there was no reduction in pulmonary complications (7.1 per cent (216 of 3031) before *versus* 6.3 per cent (274 of 4371) during the pandemic; $P = 0.158$), but the mortality rate was significantly higher during the pandemic (0.7 per cent (20 of 3031) and 2.0 per cent (87 of 4371) respectively; $P < 0.001$). In the pandemic cohort, 4.3 per cent of patients (187 of 4371) were found to be positive for SARS-CoV-2 in the postoperative period.

Different phenotypes of pulmonary complications were registered before and during the pandemic (*Fig. 2a*), with a more severe pattern of disease in the pandemic cohort; ARDS was more common (0.2 per cent before *versus* 1.2 per cent during pandemic; $P < 0.001$), whereas pneumonia was less common (6.0 *versus* 4.6 per cent; $P = 0.013$). Postoperative SARS-CoV-2 infection was strongly associated with pulmonary complications on multivariable analysis of combined data (OR 24.95, 95 per cent c.i. 16.75 to 37.17; $P < 0.001$) (*Table 2*).

Before the pandemic, 11 of 20 patients who died had a pulmonary complication. During the pandemic, 45 of 87 patients who died had a pulmonary complication, of whom 31 had a SARS-CoV-2 infection (*Fig. 2b*). The population fraction of mortality that was attributable to pulmonary complications increased from 37.0 (95 per cent c.i. 14.6 to 64.1) per cent before the pandemic to 66.0 (48.6 to 79.3) per cent during the pandemic.

Differences in mortality rates

Having surgery during the pandemic was associated with threefold higher adjusted odds of mortality than expected if these patients had undergone surgery in the prepandemic period (OR 2.72, 95 per cent c.i. 1.58 to 4.67; $P < 0.001$) (*Fig. 3* and *Table S1*). This increase in postoperative mortality was largely explained by SARS-CoV-2 (OR 1.73, 1.40 to 2.13; $P < 0.001$), with 54.8 per cent of excess deaths mediated through SARS-CoV-2 infection (indirect effect). The direct effect of timing of surgery was not significant (OR 1.57, 0.91 to 2.73; $P = 0.108$). This was reproduced in a sensitivity analysis for patients from high-income countries only and those who underwent only open surgical operations (*Table S2*).

In the combined data set, pulmonary complications in the presence SARS-CoV-2 infection had higher odds of death (OR 53.74, 23.33 to 123.80; $P < 0.001$) than pulmonary complications in patients without COVID-19 (OR 6.91, 3.71 to 12.89; $P < 0.001$) (*Table 3*). When SARS-COV-2 infection was discounted from the multilevel model, there was no significant change in the associations observed except for pulmonary complications (OR 13.11, 7.53 to 22.82; $P < 0.001$), and discrimination remained consistent (*Table S3*). This indicates that death associated with SARS-COV-2 infection was being mediated through pulmonary complications.

Table 1 Sociodemographic and operative differences between the prepandemic and pandemic cohorts

	Before pandemic ($n = 3031$)	Pandemic ($n = 4371$)
Age (years)		
< 60	890 (29.4)	1391 (31.8)
60–69	926 (30.6)	1287 (29.4)
> 70	1215 (40.1)	1693 (38.7)
Sex		
F	1430 (47.2)	2214 (50.7)
M	1601 (52.8)	2157 (49.3)
ASA grade		
I–II	1956 (68.9)	3005 (69.0)
III–V	883 (31.1)	1347 (31.0)
Obese (BMI ≥ 30 kg/m^2)		
No	1823 (68.3)	3167 (76.6)
Yes	848 (31.7)	970 (23.4)
Smoker		
Not current	2699 (89.0)	3962 (90.6)
Current	332 (11.0)	409 (9.4)
Chronic lung disease		
No	2541 (83.8)	3912 (89.5)
Yes	490 (16.2)	459 (10.5)
Cardiovascular disease		
No	1804 (59.5)	2238 (51.2)
Yes	1227 (40.5)	2133 (48.8)
Diabetes mellitus		
No	2586 (85.3)	3582 (81.9)
Yes	445 (14.7)	789 (18.1)
Operative approach		
Minimally invasive	1709 (56.4)	2061 (47.2)
Open	1321 (43.6)	2308 (52.8)
Operative site		
Lower abdominal	2457 (81.1)	3400 (77.8)
Upper abdominal	451 (14.9)	856 (19.6)
Thoracoabdominal	123 (4.1)	115 (2.6)
Operative complexity		
Intermediate/major	1970 (65.0)	3124 (71.5)
Complex major	1061 (35.0)	1247 (28.5)
Surgical specialty		
Lower gastrointestinal	1180 (38.9)	2188 (50.1)
Upper gastrointestinal	257 (8.5)	374 (8.6)
Hepatopancreatobiliary	279 (9.2)	573 (13.1)
Urology	719 (23.7)	357 (8.2)
Gynaecology	596 (19.7)	879 (20.1)
Country World Bank classification		
Low and middle income	0 (0)	541 (12.4)
High income	3031 (100)	3830 (87.6)
30-day pulmonary complication		
No	2821 (93.1)	4097 (93.7)
Yes	216 (7.1)	274 (6.3)
30-day mortality		
No	3011 (99.3)	4284 (98.0)
Yes	20 (0.7)	87 (2.0)
SARS-COV-2 diagnosis		
No	3031 (100)	4147 (94.9)
Yes	0 (0)	187 (4.3)

Values in parentheses are percentages. SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

Discussion

This study compared mortality after pulmonary complications following elective cancer surgery both before and during the SARS-CoV-2 pandemic, and postulated mechanisms underlying

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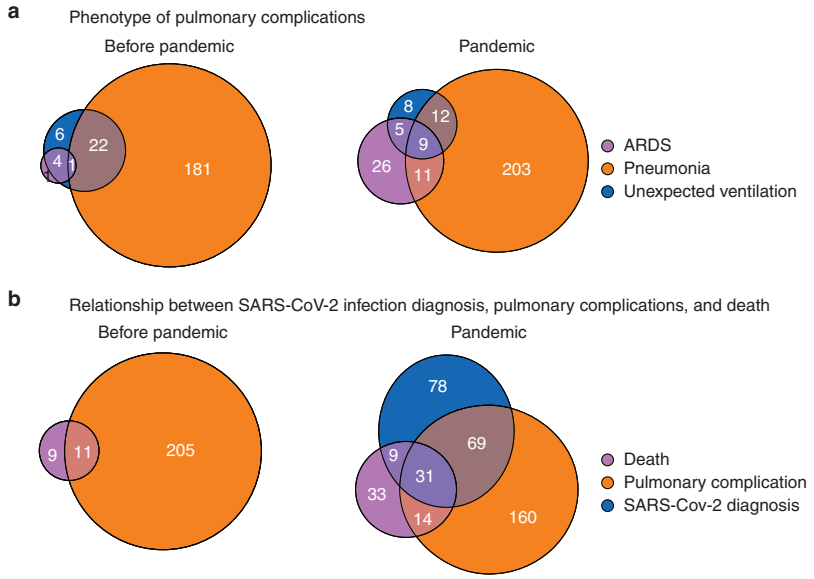


Fig. 2 Comparison of outcomes across prepandemic and pandemic cohorts

a Phenotype of pulmonary complications and **b** relationship between severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) infection diagnosis, pulmonary complications, and death.

Table 2 Multilevel model of association between SARS-COV-2 infection and pulmonary complications in elective abdominal cancer surgery

Postoperative SARS-COV-2 diagnosis	30-day postoperative pulmonary complications		Univariable analysis		Multilevel analysis	
	Yes	No	Odds ratio*	P	Odds ratio*	P
No	390 (5.4)	6825 (94.6)	1.00 (reference)		1.00 (reference)	
Yes	100 (53.5)	87 (46.5)	20.11 (14.84, 27.33)	< 0.001	24.95 (16.75, 37.17)	< 0.001
Age (years)						
< 60	92 (4.0)	2189 (96.0)	1.00 (reference)		1.00 (reference)	
60–69	136 (6.1)	2077 (93.9)	1.56 (1.19, 2.05)	0.001	1.26 (0.92, 1.74)	0.153
> 70	262 (9.0)	2646 (91.0)	2.36 (1.85, 3.02)	< 0.001	1.96 (1.44, 2.66)	< 0.001
Sex						
F	162 (4.4)	3482 (95.6)	1.00 (reference)		1.00 (reference)	
M	328 (8.7)	3430 (91.3)	2.06 (1.70, 2.50)	< 0.001	1.75 (1.38, 2.22)	< 0.001
ASA grade						
I–II	244 (4.9)	4717 (95.1)	1.00 (reference)		1.00 (reference)	
III–V	232 (10.4)	1998 (89.6)	2.24 (1.86, 2.71)	< 0.001	1.60 (1.26, 2.04)	< 0.001
Obese (BMI ≥ 30 kg/m^2)						
No	314 (6.3)	4676 (93.7)	1.00 (reference)		1.00 (reference)	
Yes	128 (7.0)	1690 (93.0)	1.13 (0.91, 1.39)	0.268	1.20 (0.93, 1.54)	0.152
Smoker						
Not current	418 (6.3)	6243 (93.7)	1.00 (reference)		1.00 (reference)	
Current	72 (9.7)	669 (90.3)	1.61 (1.23, 2.08)	< 0.001	1.59 (1.16, 2.19)	0.004
Chronic lung disease						
No	393 (6.1)	6060 (93.9)	1.00 (reference)		1.00 (reference)	
Yes	97 (10.2)	852 (89.8)	1.76 (1.38, 2.21)	< 0.001	1.47 (1.10, 1.95)	0.009
Cardiovascular disease						
No	226 (5.6)	3816 (94.4)	1.00 (reference)		1.00 (reference)	
Yes	264 (7.9)	3096 (92.1)	1.44 (1.20, 1.73)	< 0.001	1.08 (0.85, 1.38)	0.512
Diabetes mellitus						
No	391 (6.3)	5777 (93.7)	1.00 (reference)		1.00 (reference)	
Yes	99 (8.0)	1135 (92.0)	1.29 (1.02, 1.61)	0.030	0.94 (0.70, 1.25)	0.648
Operative approach						
Minimally invasive	194 (5.1)	3576 (94.9)	1.00 (reference)		1.00 (reference)	
Open	296 (8.2)	3333 (91.8)	1.64 (1.36, 1.98)	< 0.001	1.37 (1.09, 1.74)	0.008
Operative site						
Lower abdominal	295 (5.0)	5562 (95.0)	1.00 (reference)		1.00 (reference)	
Upper abdominal	114 (8.7)	1193 (91.3)	1.80 (1.43, 2.25)	< 0.001	1.62 (1.14, 2.30)	0.007
Thoracoabdominal	81 (34.0)	157 (66.0)	9.73 (7.24, 13.00)	< 0.001	10.56 (6.74, 16.54)	< 0.001
Operative complexity						
Intermediate/aajor	270 (5.3)	4824 (94.7)	1.00 (reference)		1.00 (reference)	
Complex major	220 (9.5)	2088 (90.5)	1.88 (1.56, 2.26)	< 0.001	0.86 (0.63, 1.19)	0.360

Values in parentheses are percentages unless indicated otherwise. *Values in parentheses are 95 per cent confidence intervals. SARS-COV-2, severe acute respiratory syndrome coronavirus 2. Number in model = 6644, number of groups = 493, Akaike information criterion = 2646.2, C-statistic = 0.852.

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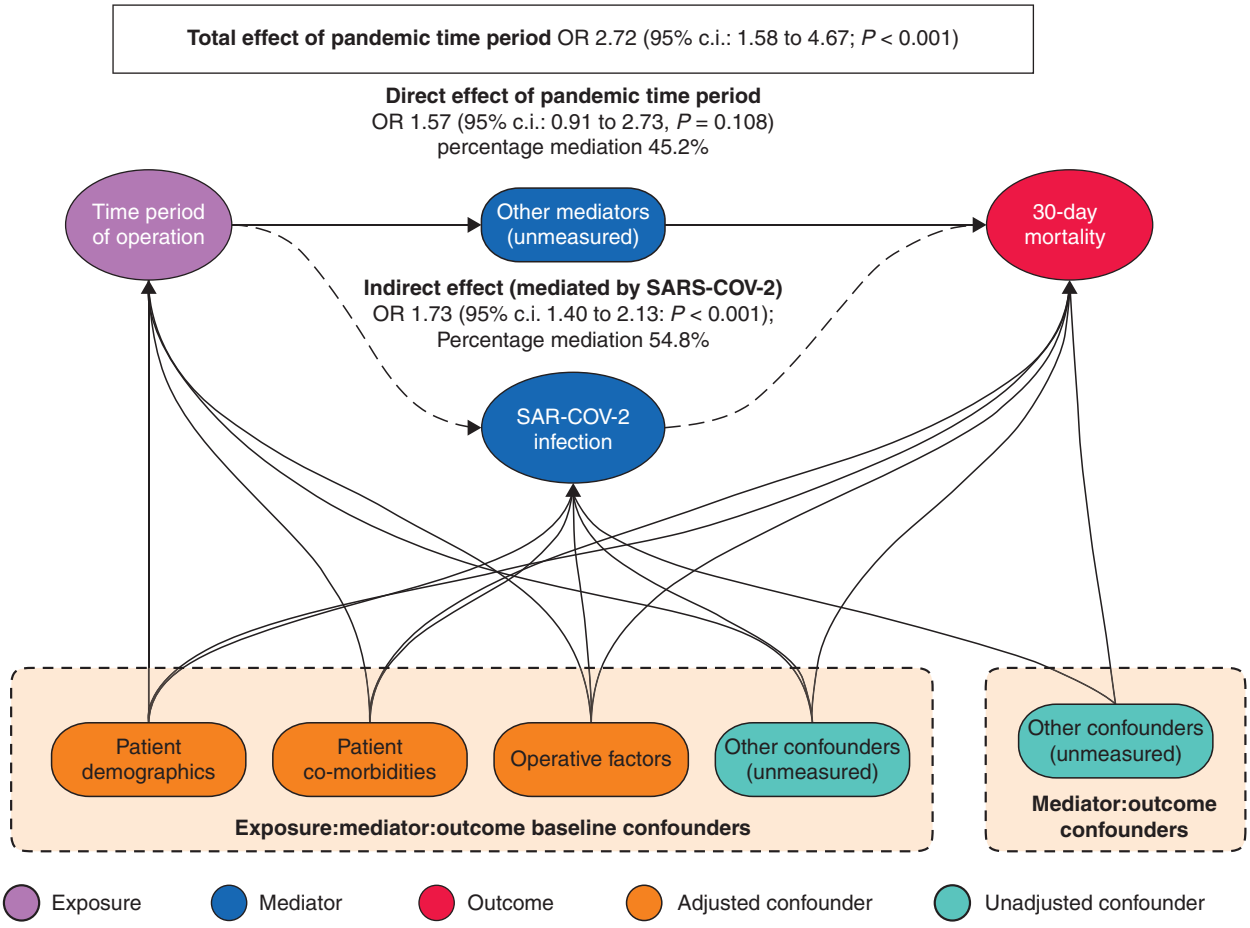


Fig. 3 Multivariable natural-effects model of postoperative death associated with time interval, mediated by SARS-COV-2 infection

OR, odds ratio; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

the differences. Two cohort studies were combined to allow direct comparison. Despite attempts to maintain safety during the pandemic by selecting lower-risk patients for surgery, a threefold increase in the adjusted odds of death was noted. This effect was largely explained by postoperative SARS-CoV-2 infection, which was associated with a more severe and lethal pattern of pulmonary events. It is also notable that the rate of pulmonary complications was similar between time intervals (7.1 per cent before *versus* 6.3 per cent during pandemic; $P = 0.158$). Given that SARS-COV-2 infection showed a significant association with the development of postoperative pulmonary complications (*Table 2*), this may be in part due to changes in overall case mix, or more proactive surveillance and prophylaxis of postoperative pulmonary complications in the pandemic cohort. Additional variability in the adjusted odds of death between periods may be associated with the collateral impact on hospitals, and a reduction in capacity to rescue. The overall fraction of deaths after surgery attributable to pulmonary complications doubled between the study periods (from 37.0 to 66.0 per cent). This has major implications for health systems around the world. To safely upscale surgery and address growing backlogs, providers must urgently invest in measures to reduce the risk of SARS-CoV-2 exposure for surgical patients. Until vaccination has been implemented universally, avoiding pulmonary complications is the major research and practice priority in surgery.

The severe phenotype of pulmonary complications of SARS-CoV-2 has now been well described in observational data[29]. However, there remains a lack of comparative data for the severity of pulmonary complications in infected and uninfected patients, fuelling debates around the overall impact on surgical health systems. Reports of low rates of nosocomial infection have promoted a narrative around minimal overall impact of SARS-CoV-2 on the safety of elective surgery. The present study has demonstrated that SARS-CoV-2-associated pulmonary complications are associated with higher odds of death than pulmonary complications in uninfected patients. Although the absolute proportion of patients with a SARS-CoV-2 infection has been small (below 5 per cent), it has had a devastating overall effect. During the pandemic, pulmonary complications have been the major driver of death in elective surgical patients, implicated in an estimated 70 per cent of all early mortality. This has important policy implications. Previous data demonstrated that just 20 per cent of patients undergoing surgery during the first pandemic wave underwent care in a protected COVID-19-free surgical pathway, and under 40 per cent underwent routine screening[11]. Although this proportion is likely to have increased over time, these data support the urgent need for hospital-network realignment in providing COVID-19-protected pathways for all patients undergoing elective surgery. This represents the most important strategy to reduce avoidable deaths until universal vaccination is available.

Death after surgery (accepting caveats) is the third leading cause of death worldwide[30]. There have been global concerns about the safety of surgery during the pandemic because of the collateral impact on hospital services such as critical care,

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Table 3 Multilevel model of association between pulmonary complications, SARS-COV-2 infection, and 30-day postoperative mortality in elective abdominal cancer surgery

	30-day postoperative mortality		Univariable analysis		Multilevel analysis	
	Died	Alive	Odds ratio*	P	Odds ratio*	P
30-day pulmonary complication						
No	51 (0.7)	6861 (99.3)	1.00 (reference)		1.00 (reference)	
Yes (Non-COVID)	25 (6.4)	365 (93.6)	9.21 (5.56, 14.89)	< 0.001	6.91 (3.71, 12.89)	< 0.001
Yes (COVID)	31 (31.0)	69 (69.0)	60.44 (36.24, 99.91)	< 0.001	53.74 (23.33, 123.80)	< 0.001
Age (years)						
< 60	11 (0.5)	2270 (99.5)	1.00 (reference)		1.00 (reference)	
60–69	26 (1.2)	2187 (98.8)	2.45 (1.24, 5.19)	0.013	2.39 (0.99, 5.78)	0.052
> 70	70 (2.4)	2838 (97.6)	5.09 (2.81, 10.18)	< 0.001	3.77 (1.60, 8.86)	0.002
Sex						
F	34 (0.9)	3610 (99.1)	1.00 (reference)		1.00 (reference)	
M	73 (1.9)	3685 (98.1)	2.10 (1.41, 3.20)	< 0.001	1.38 (0.81, 2.34)	0.241
ASA grade						
I–II	48 (1.0)	4913 (99.0)	1.00 (reference)		1.00 (reference)	
III–V	59 (2.6)	2171 (97.4)	2.78 (1.90, 4.10)	< 0.001	2.11 (1.23, 3.64)	0.007
Obese (BMI ≥ 30 kg/m^2)						
No	73 (1.5)	4917 (98.5)	1.00 (reference)		1.00 (reference)	
Yes	20 (1.1)	1798 (98.9)	0.75 (0.44, 1.21)	0.255	0.68 (0.37, 1.24)	0.203
Smoker						
Not current	92 (1.4)	6569 (98.6)	1.00 (reference)		1.00 (reference)	
Current	15 (2.0)	726 (98.0)	1.48 (0.82, 2.48)	0.167	1.40 (0.69, 2.85)	0.353
Chronic lung disease						
No	92 (1.4)	6361 (98.6)	1.00 (reference)		1.00 (reference)	
Yes	15 (1.6)	934 (98.4)	1.11 (0.62, 1.87)	0.709	0.76 (0.38, 1.54)	0.453
Cardiovascular disease						
No	38 (0.9)	4004 (99.1)	1.00 (reference)		1.00 (reference)	
Yes	69 (2.1)	3291 (97.9)	2.21 (1.49, 3.32)	< 0.001	1.32 (0.77, 2.28)	0.317
Diabetes mellitus						
No	73 (1.2)	6095 (98.8)	1.00 (reference)		1.00 (reference)	
Yes	34 (2.8)	1200 (97.2)	2.37 (1.55, 3.54)	< 0.001	1.94 (1.10, 3.40)	0.021
Operative approach						
Minimally invasive	21 (0.6)	3749 (99.4)	1.00 (reference)		1.00 (reference)	
Open	86 (2.4)	3543 (97.6)	4.33 (2.74, 7.18)	< 0.001	5.40 (2.85, 10.25)	< 0.001
Operative site						
Lower abdominal	66 (1.1)	5791 (98.9)	1.00 (reference)		1.00 (reference)	
Upper abdominal	27 (2.1)	1280 (97.9)	1.85 (1.16, 2.87)	0.008	0.55 (0.25, 1.23)	0.144
Thoracoabdominal	14 (5.9)	224 (94.1)	5.48 (2.92, 9.62)	< 0.001	1.53 (0.55, 4.31)	0.416
Operative complexity						
Intermediate/major	55 (1.1)	5039 (98.9)	1.00 (reference)		1.00 (reference)	
Complex major	52 (2.3)	2256 (97.7)	2.11 (1.44, 3.10)	< 0.001	1.65 (0.83, 3.31)	0.155

Values in parentheses are percentages unless indicated otherwise. *Values in parentheses are 95 per cent confidence intervals. SARS-COV-2, severe acute respiratory syndrome coronavirus 2. Number in model = 6644, number of groups = 493, Akaike information criterion = 756.6, C-statistic = 0.961.

diagnostic and interventional radiology, and medical staffing[13]. This could reduce health systems' capacity to rescue in the perioperative setting[15]. However, there are no existing high-quality comparative data that have measured this effect to date. The present data have demonstrated a higher adjusted likelihood of death for patients undergoing surgery during the pandemic. The analysis suggests that this was largely mediated by the sequelae of SARS-CoV-2 infection rather than collateral effects. This may demonstrate the capacity of included hospitals to compensate for system-level stress for patients who underwent surgery. It cannot, however, provide evidence about overall resilience of surgical systems to maintain surgical capacity, nor the impact on higher-risk patients who may not have undergone surgery and faced delays[9,10].

This study was able to compare case selection and outcomes of global elective cancer surgery in two large prospective data sets collected before and during the pandemic. Both cohorts adopted the same definitions of pulmonary complications and measured this a primary outcome measure within the original studies. However, there were several limitations. First, the data suggest that some patients at higher baseline risk were not offered surgery; it has not been possible to estimate the impact of delayed treatment on longer-term outcomes for this group. Second, complete case ascertainment or complete ascertainment of SARS-COV-2 infection status cannot be ensured, and it is possible that selection bias was introduced. Any unmeasured SARS-COV-2 infections would have likely inflated pulmonary complications and deaths in the comparison group, so would have led to underestimation of the association between SARS-COV-2 diagnosis and death. However, previous work[15] has been validated for both case ascertainment and data accuracy across a wide range of settings, and all centres that did not self-report complete-case inclusion were excluded. Third, it was not possible to collect data for all possible risk factors implicated in the aetiology of pulmonary complications; for example, the specific chronic respiratory pathology and all risk factors from validated scoring systems such as duration of procedure were not included[3]. Data points selected were chosen to be practical and pragmatic in the context of frontline clinical practice during a time of severe systemic stress. Finally, there were differences in the settings in which data were collected in the two cohort studies; for example, the prepandemic cohort included data from three high-income countries, compared with 50 mixed-income countries in the pandemic cohort. Discrepancies in access to care and clinical practice exist

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even between high-income countries; however, this study adopted the same approach to account for these as in previous similar analyses[15,31] . Some 12.4 per cent of patients in the pandemic cohort study were also from a low- or middle-income country, and hospitals in these settings are known to have significantly higher rates of postoperative morbidity related to inequities in access to care[15]. However, the primary findings of the multivariable analyses were robust in a sensitivity analysis including high-income country data only.

Collaborators

KA McLean, SK Kamarajah, D Chaudhry, RR Gujjuri, K Raubenheimer, I Trout, E AlAmeer, B Creagh-Brown, EM Harrison, D Nepogodiev, AC Roslani, E Li, F Pata, A Ramos-De la Medina, GH van Ramshorst, R Sayyed, J Simoes, N Smart, A Bhangu, JC Glasbey, RA Khaw, W Ahmed, M Akhbari, D Baker, A Borakati, E Mills, V Murray, R Thavayogan, I Yasin, J Glasbey, W Ridley, M Sarrami, G Zhang, N Egoroff, P Pockney, T Richards, M Edwards, M Lee, T Pinkney, R Pearse, R Vohra, C Sohrabi, A Jamieson, M Nguyen, A Rahman, C English, L Tincknell, P Kakodkar, I Kwek, N Punjabi, J Burns, S Varghese, M Erotocritou, S McGuckin, S Vayalapra, E Dominguez, J Moneim, S Bhatia, O Kouli, M Salehi, HL Tan, A Yoong, L Zhu, B Seale, Z Nowinka, N Patel, B Chrisp, J Harris, I Maleyko, F Muneeb, M Gough, C.E. James, O Skan, A Chowdhury, N Rebuffa, H Khan, B Down, Hussain Q Fatimah, K Siaw-Acheampong, RA Benson, E Bywater, BE Dawson, JP Evans, E Heritage, CS Jones, C Khatri, JM Keatley, A Knight, S Lawday, HS Mann, EJ Marson, SC Mckay, EC Mills, G Pellino, M Picciochi, EH Taylor, A Tiwari, JFF Simoes, IM Trout, ML Venn, RJW Wilkin, NJ Smart, A Minaya-Bravo, G Gallo, S Moug, S Di Saverio, A Vallance, D Vimalchandran, EA Griffiths, RPT Evans, P Townend, K Roberts, S McKay, J Isaac, S Satoi, J Edwards, AS Coonar, A Marchbank, EJ Caruana, GR Layton, A Patel, A Brunelli, S Ford, A Desai, A Gronchi, M Fiore, M Almond, F Tirotta, S Dumitra, A Kolias, SJ Price, DM Fountain, MD Jenkinson, P Hutchinson, HJ Marcus, RJ Piper, L Lippa, F Servadei, I Esene, C Freyschlag, I Neville, G Rosseau, K Schaller, AK Demetriades, F Robertson, A Alamri, R Shaw, AG Schache, SC Winter, M Ho, P Nankivell, J Rey Biel, M Batstone, I Ganly, R Vidya, A Wilkins, JK Singh, D Thekinkattil, S Sundar, C Fotopoulou, E Leung, T Khan, L Chiva, J Sehouli, A Fagotti, P Cohen, M Gutelkin, R Ghebre, T Konney, R Pareja, R Bristow, S Dowdy, STS Rajkumar, J Ng, K Fujiwara, GD Stewart, B Lamb, K Narahari, A McNeill, A Colquhoun, J McGrath, S Bromage, R Barod, V Kasivisvanathan, T Klatte, TEF Abbott, S Abukhalaf, M Adamina, AO Ademuyiwa, A Agarwal, M Akkulak, E Alameer, D Alderson, F Alakaloko, M Albertsmeiers, O Alser, M Alshaar, S Alshryda, AP Arnaud, KMagne Augestad, F Ayasra, J Azevedo, BK Bankhead-Kendall, E Barlow, D Beard, R Blanco-Colino, A Brar, KA Breen, C Bretherton, I Lima Buarque, J Burke, M Chaar, S Chakrabortee, P Christensen, D Cox, M Cukier, MF Cunha, GH Davidson, SDi Saverio, TM Drake, JG Edwards, M Elhadi, S Emile, S Farik, EJ Fitzgerald, T Garmanova, D Ghosh, G Mendonça Ataíde Gomes, G Grecinos, M Gründl, C Halkias, I Hisham, PJ Hutchinson, S Hwang, A Isik, P Jonker, HMA Kaafarani, D Keller, S Kruijff, I Lawani, H Lederhuber, S Leventoglu, A Litvin, A Loehrer, MW Löffler, MAguilera Lorena, MMarta Modolo, P Major, J Martin, HN Mashbari, D Mazingi, S Metallidis, HM Mohan, R Moore, D Moszkowicz, JS Ng-Kamstra, M Maimbo, I Negoi, M Niquen, F Ntirenganya, M Olivos, K Oussama, O Outani, M Parreno-Sacdalanm, C Jose Perez Rivera, TD Pinkney, W van der Plas, A Qureshi, D Radenkovic, M Rutegård, JJ Segura-Sampedro, I Santos, A Schache, AA Schnitzbauer, JO Seyi-Olajide, N Sharma, S Shu, K Soreide, A Spinelli, M Sund, S Tabiri, G Tsoulfas, D Vimalachandran, OJ Warren, D Wedderburn, N Wright, EuroSurg, European Society of Coloproctology, Global Initiative for Children's Surgery, GlobalSurg, GlobalPaedSurg, ItSURG, PTSurg, SpainSurg, Italian Society of Colorectal Surgery, Association of Surgeons in Training, Irish Surgical Research Collaborative, Transatlantic Australasian Retroperitoneal Sarcoma Working Group, Italian Society of Surgical Oncology, C Allemand, L Boccalatte, M Figari, M Lamm, J Larrañaga, C Marchitelli, F Noll, D Odetto, M Perrotta, J Saadi, L Zamora, C Alurralde, EL Caram, D Eskinazi, JP Mendoza, M Usandivaras, R Badra, A Esteban, JS García, PM García, JI Gerchunoff, SM Lucchini, MA NIgra, L Vargas, T Hovhannisyan, A Stepanyan, T Gould, R Gourlay, B Griffiths, S Gananadha, M McLaren, J Cecire, N Joshi, S Salindera, A Sutherland, JH Ahn, G Charlton, S Chen, N Gauri, R Hayhurst, S Jang, F Jia, C Mulligan, W Yang, G Ye, H Zhang, M Ballal, D Gibson, D Hayne, J Moss, P Viswambaram, UG Vo, J Bennetts, T Bright, M Brooke-Smith, R Fong, B Gricks, YH Lam, BS Ong, M Szpytma, D Watson, K Bagraith, S Caird, E Chan, C Dawson, D Ho, E Jeyarajan, S Jordan, A Lim, GJ Nolan, A Oar, D Parker, H Puhalla, A Quennell, L Rutherford, Papen M Von, M Wullschleger, A Blatt, D Cope, M Fenton, J Gani, N Lott, N Shugg, M Elliott, D Phung, D Phan, D Townend, C Bong, J Gundara, A Frankel, S Bowman, GR Guerra, J Bolt, K Buddingh, NN Dudi-Venkata, S Jog, HM Kroon, T Sammour, R Smith, C Stranz, K Lah, W McGahan, D Mitchell, A Morton, A Pearce, M Roberts, G Sheahan, B Swinson, N Alam, S Banting, L Chong, P Choong, S Clatworthy, D Foley, A Fox, MW Hii, B Knowles, J Mack, M Read, A Rowcroft, S Ward, G Wright, M Lanner, I Königsrainer, M Bauer, M Kafka, F Messner, D Öfner, I Tsibulak, K Emmanuel, M Grechenig, R Gruber, M Harald, L Öhlberger, J Presl, A Wimmer, İ Namazov, E Samadov, D Barker, R Boyce, S Corbin, A Doyle, A Eastmond, R Gill, A Haynes, S Millar, M O'Shea, G Padmore, N Paquette, E Phillips, John S St, K Walkes, N Flamey, P Pattyn, W Oosterlinck, den Eynde J Van, den Eynde R Van, A Gatti, C Nardi, R Oliva, Cicco R De, I Cecconello, P Gregorio, Lima L Pontual, Junior U Ribeiro, F Takeda, RM Terra, M Sokolov, B Kidane, S Srinathan, M Boutros, N Caminsky, G Ghitulescu, G Jamjoum, J Moon, J Pelletier, T Vanounou, S Wong, A Kouyoumdjian, B Johnston, C Russell, S Demyttenaere, R Garfinkle, J Abou-Khalil, C Nessim, J Stevenson, F Heredia, A Almeciga, A Fletcher, A Merchan, LO Puentes, Quevedo J Mendoza, G Bačić, D Karlović, D Kršul, M Zelić, I Luksic, M Mamic, B Bakmaz, I Čoza, E Dijan, Z Katusic, J Mihanovic, I Rakvin, K Frantzeskou, N Gouvas, G Kokkinos, P Papatheodorou, I Pozotou, O Stavrinidou, A Yiallourou, L Martinek, M Skrovina, I Szubota, J Žatecký, V Javurkova, J Klat, T Avlund, JL Harbjerg, LH Iversen, DW Kjaer, HØ Kristensen, M Mekhael, AL Ebbehøj, P Krarup, N Schlesinger, H Smith, A Abdelsamed, AY Azzam, H Salem, A Seleim, A Abdelmajeed, M Abdou, NE Abosamak, Sayed M AL, F Ashoush, R Atta, E Elazzazy, M Elhoseiny, M Elnemr, MS Elqasabi, Hewalla ME Elsayed, I Elsherbini, E Essam, M Eweda, I Ghallab, E Hassan, M Ibrahim, M Metwalli, M Mourad, MS Qatora, M Ragab, A Sabry, H Saifeldin, Mesbah Mohamed Elkaffas M Saleh, A Samih, Abdelaal A Samir, S Shehata, K Shenit, D Attia, N Kamal, N Osman, AM Abbas, Elazeem HAS Abd, MM Abdelkarem, S Alaa, AK Ali, A Ayman, MG Azizeldine, H Elkhayat, S Melghazaly, FA Monib, MA Nageh, MM Saad, M Salah, M Shahine, EA Yousof, A Youssef, A Eldaly, M ElFiky, A Nabil, G Amira, I Sallam, M Sherief, A Sherif, A Abdelrahman, H Aboulkassem, G Ghaly, R Hamdy, A Morsi, G Sherif, H Abdeldayem, Salama I Abdelkader, M Balabel, Y Fayed, AE Sherif, A Bekele, J Kauppila, E Sarjanoja, O Helminen, H Huhta, JH Kauppila, C Beyrne, L Jouffret, L Lugans, L Marie-

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Macron, E Chouillard, Simone B De, J Bettoni, S Dakpé, B Devauchelle, N Lavagen, S Testelin, S Boucher, R Breheret, A Gueutier, A Kahn, J Kün-Darbois, A Barrabe, Z Lakkis, A Louvrier, S Manfredelli, P Mathieu, A Chebaro, V Drubay, amrani M El, C Eveno, K Lecolle, G Legault, L Martin, G Piessen, FR Pruvot, S Truant, P Zerbib, Q Ballouhey, B Barrat, J Laloze, H Salle, A Taibi, J Usseglio, D Bergeat, A Merdrignac, Roy B Le, LO Perotto, A Scalabre, A Aimé, A Ezanno, B Malgras, P Bouche, S Tzedakis, E Cotte, O Glehen, V Kepenekian, J Lifante, G Passot, A D'Urso, E Felli, D Mutter, P Pessaux, B Seeliger, J Bardet, R Berry, G Boddaert, S Bonnet, E Brian, C Denet, D Fuks, D Gossot, M Grigoroiu, A Laforest, Y Levy-Zauberman, C Louis-Sylvestre, A Moumen, G Pourcher, A Seguin-givelet, E Tribillon, E Duchalais, F Espitalier, C Ferron, O Malard, U Bork, M Distler, J Fritzmann, J Kirchberg, C Praetorius, C Riediger, J Weitz, T Welsch, P Wimberger, K Beyer, C Kamphues, J Lauscher, FN Loch, C Schineis, M Albertsmeier, M Angele, A Kappenberger, H Niess, T Schiergens, J Werner, R Becker, J Jonescheit, I Pergolini, D Reim, C Boeker, I Hakami, J Mall, P Liokatis, W Smolka, K Nowak, T Reinhard, F Hölzle, A Modabber, P Winnand, M Knitschke, P Kauffmann, S Wolfer, J Kleeff, K Lorenz, C Michalski, U Ronellenfitsch, R Schneider, E Bertolani, A Königsrainer, M Quante, C Steidle, L Überrück, C Yurttas, CS Betz, J Bewarder, A Böttcher, S Burg, C Busch, M Gosau, A Heuer, J Izbicki, TO Klatte, D Koenig, N Moeckelmann, C Nitschke, M Priemel, R Smeets, U Speth, S Thole, FG Uzunoglu, T Vollkommer, N Zeller, MJ Battista, K Gillen, A Hasenburg, S Krajnak, V Linz, R Schwab, K Angelou, D Haidopoulos, A Rodolakis, P Antonakis, K Bramis, L Chardalias, I Contis, N Dafnios, D Dellaportas, G Fragulidis, A Gklavas, M Konstadoulakis, N Memos, I Papaconstantinou, A Polydorou, T Theodosopoulos, A Vezakis, MI Antonopoulou, DK Manatakis, N Tasis, N Arkadopoulos, N Danias, P Economopoulou, P Kokoropoulos, A Larentzakis, N Michalopoulos, J Selmani, T Sidiropoulos, V Tsaousis, P Vassiliu, K Bouchagier, S Klimopoulos, D Paspaliari, G Stylianidis, K Baxevanidou, K Bouliaris, P Chatzikomnitsa, M Efthimiou, A Giaglaras, C Kalfountzos, G Koukoulis, AM Ntziovara, K Petropoulos, K Soulikia, I Tsiamalou, K Zervas, S Zourntou, I Baloyiannis, A Diamantis, E Gkrinia, J Hajiioannou, C Korais, O Koukoura, K Perivoliotis, A Saratziotis, C Skoulakis, D Symeonidis, K Tepetes, G Tzovaras, D Zacharoulis, V Alexoudi, K Antoniades, I Astreidis, P Christidis, D Deligiannidis, T Grivas, O Ioannidis, I Kalaitsidou, L Loutzidou, A Mantevas, D Michailidou, K Paraskevopoulos, S Politis, A Stavroglou, D Tatsis, I Tilaveridis, K Vahtsevanos, G Venetis, I Karaitianos, T Tsirlis, A Charalabopoulos, T Liakakos, E Mpaili, D Schizas, E Spartalis, A Syllaios, C Zografos, C Anthoulakis, C Christou, V Papadopoulos, A Tooulias, D Tsolakidis, D Zouzoulas, E Athanasakis, E Chrysos, J Tsiaoussis, S Xenaki, E Xynos, K Futaba, MF Ho, SF Hon, TWC Mak, SSM Ng, CC Foo, B Banky, N Suszták, M Aremu, A Canas-Martinez, O Cullivan, C Murphy, P Owens, L Pickett, L Akmenkalne, J Byrne, M Corrigan, C Cullinane, A Daly, C Fleming, P Jordan, S Killeen, N Lynch, A McCarthy, H Mustafa, S O'Brien, P O'Leary, WAS Syed, L Vernon, D Callanan, L Huang, A Ionescu, P Sheahan, I Balasubramanian, M Boland, K Conlon, D Evoy, N Fearon, T Gallagher, J Geraghty, H Heneghan, N Kennedy, D Maguire, D McCartan, EW McDermott, RS Prichard, D Winter, D Alazawi, C Barry, T Boyle, W Butt, EM Connolly, N Donlon, C Donohue, BA Fahey, R Farrell, C Fitzgerald, J Kinsella, JO Larkin, P Lennon, PJ Maguire, P Mccormick, BJ Mehigan, H Mohan, T Nugent, H O'Sullivan, N Ravi, JV Reynolds, A Rogers, P Shokuhi, J Smith, LA Smith, C Timon, Y Bashir, G Bass, T Connelly, B Creavin, H Earley, JA Elliott, A Gillis, D Kavanagh, P Neary, J O'riordan, IS Reynolds, D Rice, P Ridgway, M Umair, M Whelan, P Carroll, C Collins, K Corless, L Finnegan, A Fowler, A Hogan, M Kerin, A Lowery, P McAnena, K McKevitt, K Nizami, É Ryan, A Samy, JC Coffey, R Cunningham, M Devine, D Nally, C Peirce, S Tormey, N Hardy, S O'Malley, M Ryan, S Macina, NM Mariani, E Opocher, Ceretti A Pisani, F Ferrari, F Odicino, E Sartori, C Cotsoglou, S Granieri, F Bianco, A Camillo', M Colledan, S Tornese, MF Zambelli, G Bissolotti, S Fusetti, F Lemma, MV Marino, A Mirabella, G Vaccarella, C Agostini, G Alemanno, I Bartolini, C Bergamini, A Bruscino, C Checcucci, Vincenti R De, Bella A Di, M Fambrini, L Fortuna, G Maltinti, P Muiesan, F Petraglia, P Prosperi, MN Ringressi, M Risaliti, F Sorbi, A Taddei, R Tucci, C Bassi, L Bortolasi, T Campagnaro, L Casetti, Pastena M De, A Esposito, M Fontana, A Guglielmi, L Landoni, G Malleo, G Marchegiani, S Nobile, S Paiella, C Pedrazzani, S Rattizzato, A Ruzzenente, R Salvia, G Turri, M Tuveri, P Bellora, G D'Aloisio, M Ferrari, E Francone, S Gentilli, H Nikaj, M Bianchini, M Chiarugi, F Coccolini, Franco G Di, N Furbetta, D Gianardi, S Guadagni, L Morelli, M Palmeri, D Tartaglia, G Anania, P Carcoforo, M Chiozza, Troia A De, Radica M Koleva, M Portinari, MG Sibilla, A Urbani, N Fabbri, CV Feo, S Gennari, S Parini, E Righini, L Ampollini, L Bellanti, M Bergonzani, G Bertoli, G Bocchialini, G D'Angelo, D Lanfranco, L Musini, T Poli, GP Santoro, A Varazzani, L Aguzzoli, G Borgonovo, Ruiz C Castro, S Coiro, G Falco, VD Mandato, V Mastrofilippo, MT Montella, V Annessi, M Zizzo, U Grossi, S Novello, M Romano, S Rossi, G Zanus, G Esposito, F Frongia, A Pisanu, M Podda, C Belluco, A Lauretta, G Montori, L Moras, M Olivieri, F Bussu, AG Carta, ML Cossu, P Cottu, A Fancellu, CF Feo, GC Ginesu, G Giuliani, M Madonia, T Perra, A Piras, A Porcu, D Rizzo, AM Scanu, A Tedde, M Tedde, P Delrio, D Rega, G Badalamenti, G Campisi, A Cordova, M Franza, G Maniaci, G Rinaldi, F Toia, M Calabrò, F Farnesi, EG Lunghi, A Muratore, Federico NS Pipitone, F Bàmbina, G D'Andrea, P Familiari, V Picotti, Palma G De, G Luglio, G Pagano, FP Tropeano, L Baldari, GA Beltramini, L Boni, E Cassinotti, A Gianni', L Pignataro, S Torretta, C Abatini, M Baia, D Biasoni, G Bogani, P Cadenelli, V Capizzi, SPB Cioffi, D Citterio, LV Comini, M Cosimelli, S Folli, M Gennaro, L Giannini, M Guaglio, A Macchi, F Martinelli, V Mazzaferro, A Mosca, S Pasquali, C Piazza, F Raspagliesi, L Rolli, R Salvioni, G Sarpietro, C Sarre, L Sorrentino, A Agnes, S Alfieri, F Belia, A Biondi, V Cozza, A D'Amore, D D'Ugo, Simone V De, G Gasparini, L Gordini, F Litta, CP Lombardi, L Lorenzon, AA Marra, F Marzi, A Moro, A Parello, E Perrone, R Persiani, C Ratto, F Rosa, G Saponaro, G Scambia, O Scrima, G Sganga, R Tudisco, A Belli, V Granata, F Izzo, R Palaia, R Patrone, FM Carrano, MM Carvello, Virgilio A De, Candido F Di, F Ferreli, F Gaino, G Mercante, V Rossi, G Spriano, DM Donati, T Frisoni, E Palmerini, A Aprile, F Barra, P Batistotti, S Ferrero, P Fregatti, S Scabini, M Sparavigna, E Asti, D Bernardi, L Bonavina, A Lovece, L Adamoli, M Ansarin, S Cenciarelli, F Chu, Berardinis R De, Romario U Fumagalli, F Mastrilli, G Pietrobon, M Tagliabue, E Badellino, A Ferrero, R Massobrio, Manzoni Garberini A De, P Federico, P Maida, E Marra, G Marte, A Petrillo, T Tammaro, A Tufo, M Berselli, G Borroni, E Cocozza, L Conti, M Desio, L Livraghi, V Quintodei, A Rizzi, A Zullo, C Baldi, C Corbellini, GM Sampietro, P Cellerino, E Baldini, P Capelli, SM Isolani, M Ribolla, A Bondurri, F Colombo, L Ferrario, C Guerci, A Maffioli, T Armao, M Ballabio, P Bisagni, A Gagliano, M Longhi, M Madonini, P Pizzini, AM Baietti, M Biasini, P Maremonti, F Neri, GM Prucher, S Ricci, F Ruggiero, AG Zarabini, R Barmasse, S Mochet, A Usai, P Incollingo, S Mancini, Cosentino L Marino, A Sagnotta, R Fruscio, T Grassi, LC Nespoli, N Tamini, A Anastasi, B Bartalucci, A Bellacci, G Canonico, L Capezzuoli, Martino C Di, P Ipponi, C Linari, M Montelatici, T Nelli, G Spagni, L Tirloni, A Vitali, E

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Supplementary material

Supplementary material is available at *BJS* online.

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