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Impact of SARS-CoV-2 infection on short-term postoperative outcomes after gastroenterological cancer surgery using data from a nationwide database in Japan

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Abstract

Background: Due to the coronavirus disease 2019 (COVID-19) pandemic, cancer screening, diagnosis, and treatment have changed. This study aimed to investigate the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection prior to gastroenterological cancer surgeries on postoperative complications using data from a nationwide database in Japan.

Methods: Data on patients who underwent surgery for cancer including esophageal, gastric, colon, rectal, liver, and pancreatic cancer between July 1, 2019, and September 300, 2022, from real-world sources in Japan were analyzed. The association between preoperative SARS-CoV-2 infection and short-term postoperative outcomes was evaluated. A similar analysis stratified according to the interval from SARS-CoV-2 infection to surgery (<4 vs. >4 weeks) was conducted.

Results: In total, 60 604 patients were analyzed, and 227 (0.4%) patients were diagnosed with SARS-CoV-2 infection preoperatively. The median interval from

SARS-CoV-2 infection to surgery was 25 days. Patients diagnosed with SARS-CoV-2 infection preoperatively had a significantly higher incidence of pneumonia (odds ratio: 2.05; 95% confidence interval: 1.05–3.74; $p = 0.036$) than those not diagnosed with SARS-CoV-2 infection based on the exact logistic regression analysis adjusted for the characteristics of the patients. A similar finding was observed in patients who had SARS-CoV-2 infection <4 weeks before surgery.

Conclusions: Patients with a history of SARS-CoV-2 infection had a significantly higher incidence of pneumonia. This finding can be particularly valuable for countries that have implemented strict regulations in response to the COVID-19 pandemic and have lower SARS-CoV-2 infection-related mortality rates.

KEYWORDS
gastroenterological cancer surgery, nationwide database, SARS-CoV-2 infection

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected in Wuhan, China. COVID-19 caused a pandemic. In relation to this, a significant number of surgeries had to be canceled or postponed. This phenomenon resulted in restrictions on the provision of standard medical care to several patients with cancer requiring surgery.[1,2] This health crisis had repercussions on cancer screening, diagnosis, and treatment.[2–4] Because of limitations in endoscopic screening, there has been an increase in the number of cancer cases diagnosed at advanced stages during the pandemic.[5] In response to the need to allocate medical resources for COVID-19 treatment and prevent hospital-acquired infections, the Japanese Surgical Society, which comprises 10 major surgical societies in Japan, emphasized the importance of surgical triage based on the severity of the patients' conditions on April 1, 2020. Nonurgent surgeries, such as those for benign conditions, were postponed. Due to this recommendation, the number of surgeries significantly reduced. In particular, the rate of gastroenterological surgeries decreased by approximately 15% during the COVID-19 pandemic, based on an analysis of nationwide data in Japan.[5]

To assess surgical outcomes in this unusual situation, we investigated the trends in complication and mortality rates for gastroenterological cancer surgeries, including esophagectomy and distal gastrectomy, before and during the COVID-19 pandemic.[6,7] Our findings revealed that surgical safety can be maintained even in cases in which healthcare resources are constrained. However, the association between SARS-CoV-2 infection and the development of postoperative complications remains unknown.

To date, several reports have shown that prior SARS-CoV-2 infection has a negative impact on postoperative outcomes, particularly the development of pulmonary complications, after elective surgeries.[8–14] The COVIDSurg Collaborative first showed that an increased risk of surgical mortality lasted for 7 weeks after an acute SARS-CoV-2 infection.[11] Moreover, Verhagen et al. showed that a previous history of COVID-19 infection is an independent risk factor for adverse surgical outcomes. Moreover, the risk remains elevated for 12 weeks after SARS-CoV-2 infection based on the N3C Data Enclave, which is a health data platform comprising >18 000 000 patients in the United States.[15] Although these studies have obtained important findings regarding surgical management during the COVID-19 pandemic, they encompass various surgical specialties, such as neurosurgery, plastic surgery, general surgery, and urological surgery, each differs in terms of invasiveness. To date, no studies have focused on the impact of COVID-19 infection on patients awaiting gastroenterological cancer surgeries. Patients with cancer are generally immunocompromised. Patients with COVID-19 infection may present with more severe diseases than those who are not immunocompromised, which could significantly affect postoperative outcomes.[16,17] Furthermore, the measures taken in response to the COVID-19 pandemic varied significantly between Western and East Asian countries, which can lead to different outcomes. Therefore, a detailed examination at the national level is required.

This study aimed to investigate the impact of SARS-CoV-2 infection on short-term outcomes after gastroenterological cancer surgeries using data from a nationwide database in Japan. This evidence could be particularly valuable for countries that have implemented strict regulations in response to the COVID-19 pandemic and have lower SARS-CoV-2 infection-related mortality rates.

2 | METHODS

2.1 | Database and patient selection

This retrospective cohort study utilized the Japan Medical Data Center database, which is one of the most frequently used real-world data sources in Japan and provides access to insurance data for over 16 million individuals.[18] Each patient was assigned with a unique and anonymized identification number, thereby allowing for the chronological tracking of data related to their visits to facilities.

Information on outcomes, such as mortality and morbidity, can be obtained from these anonymized personal identification numbers. The researchers were provided with data containing these unique identification numbers. However, no personal information about the patients, such as their names or addresses, was accessible.

In this study, data on patients who underwent surgery for primary cancer including esophageal (International Classification of Diseases, Tenth Revision (ICD-10): C15), gastric (C16), colon (C18), rectal (C20, C21), liver (C22), and pancreatic (C25) cancer between July 1, 2019, and September 30, 2022, were collected and analyzed. To maintain the quality of the dataset, we included data that had a 1-year (365 days) look-back period, did not include cancer-related treatment (surgery, chemotherapy, radiation, or nonsurgical management; File S1) for the target condition during the look-back period, and had a tracking period of no less than 90 days. The date of cancer diagnosis for the target condition was defined as the entry point (index time) into the cohort. Data on the background characteristics of the patients, clinical cancer stage using TNM classification, and short-term outcomes stratified according to preoperative SARS-CoV-2 infection were compared.[19] The association between preoperative SARS-CoV-2 infection and short-term outcomes was analyzed based on the interval from SARS-CoV-2 infection to surgery (<4 vs. >4 weeks).[8]

Data on the primary outcomes, which included the rates of overall complications, pneumonia, anastomotic leakage, surgical site infection, pulmonary embolism, deep vein thrombosis, respiratory failure, kidney injury, arrhythmia, hemorrhage, cardiac infarction, cerebral infarction, pancreatic fistula, and biliary fistula were extracted from the database (File S1). Cancer stage was determined according to the TNM classification.[19] The Institutional Review Board of the School of Medicine, Keio University, approved the study protocol, and the need for an individual written informed consent was waived (ID: 20221157).

2.2 | Statistical analysis

Ordinal variables were analyzed using the Wilcoxon's rank-sum test, and categorical variables were examined using the chi-square test or the Fisher's exact test, as appropriate. Moreover, exact logistic regression analyses of primary outcomes were conducted after adjusting for sex, age, smoking status, body mass index, Barthel index (during hospitalization), TNM stage, and cancer type. Two-sided p-values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using R version 4.2.3 (2023; R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Background characteristics of the participants

In total, 60 604 patients who underwent surgery for primary cancer were analyzed. Among them, 1181 (1.9%) underwent surgery for esophageal cancer, 15 456 (25.5%) for gastric cancer, 27 019 (44.6%) for colon cancer, 10 521 (17.4%) for rectal cancer, 2070 (3.4%) for liver cancer, and 2684 (4.4%) for pancreatic cancer. The patient population comprised 36 627 (60.4%) men and 23 977 (39.6%) women, with a median age of 73 (interquartile range [IQR]: 66–80) years. Table 1 shows the other clinicopathological characteristics of the participants.

Further, 227 (0.4%) patients were diagnosed with SARS-CoV-2 infection preoperatively. Meanwhile, 60 377 (99.6%) patients did not develop SARS-CoV-2 infection preoperatively. The background characteristics of patients who had SARS-CoV-2 infection and those who did not were compared. Results showed a significant difference in terms of Barthel index ($p < 0.001$), T stage ($p < 0.001$), N stage ($p < 0.001$), and M stage ($p < 0.001$). However, there was no significant difference in terms of other factors such as age and sex.

3.2 | Association between complications and SARS-CoV-2 infection

In total, 6278 (10.4%) patients developed complications. Pneumonia ($n = 1362$, 2.25%) was the most common complication, followed by respiratory failure ($n = 1333$, 2.20%), anastomotic leakage ($n = 1084$, 1.79%), and surgical site infection ($n = 1020$, 1.68%). The association between the development of complications and preoperative SARS-CoV-2 infection was investigated using the Fisher's exact test. Patients diagnosed with SARS-CoV-2 infection preoperatively had a significantly higher incidence of pneumonia than those who were not diagnosed ($p = 0.002$). Pneumonia was also considered a significant complication based on the exact logistic regression adjusted for sex, age, smoking status, body mass index, Barthel index (during hospitalization), TNM stage, and cancer type (odds ratio: 2.05; 95% confidence interval: 1.05–3.74; $p = 0.036$) (Table 2, Figure 1). Furthermore, anastomotic leakage was also a related factor (odds ratio: 1.84; 95% confidence interval: 0.81–3.73; $p = 0.131$). Table S1 showed a multivariable analysis for the occurrence of pneumonia and anastomotic leakage. In addition to SARS-CoV-2 infection, age, sex, and cancer type were identified as related factors for pneumonia. Whereas sex and cancer type were identified as related factors for anastomotic leakage.

The median interval from infection onset to surgery in patients diagnosed with SARS-CoV-2 infection was 25 (IQR: 6–70) days. Among them, 118 (52.0%) patients were diagnosed with SARS-CoV-2 infection <4 weeks before surgery. Only five (2.2%) patients had severe infection, and one patient received ventilator management. Four patients were admitted to the intensive care unit (Table 3). A subgroup analysis of the interval from SARS-CoV-2 infection to surgery was also performed. Patients ($n = 118$) who had SARS-CoV-2 infection <4 weeks before surgery were more likely to present with overall complications (odds ratio: 1.57; 95% confidence interval: 0.92–2.59; $p = 0.095$) and pneumonia (odds ratio: 2.31; 95% confidence interval: 0.92–5.09; $p = 0.071$) than patients who did not present with SARS-CoV-2 infection <4 weeks before surgery. Conversely, patients who did not have SARS-CoV-2 infection <4 weeks before surgery were

TABLE 1 Characteristics of the patients.

Characteristics	All patients N = 60 604	Patients without SARS-CoV-2 infection n = 60 377	Patients with SARS-CoV-2 infection n = 227	p-value
Female sex	23 977 (39.6%)	23 895 (39.6%)	82 (36.1%)	0.320
Age, median (IQR)	73 (66–80)	73 (66–80)	74 (68–81)	0.253
Smoker				
No	31 076 (51.3%)	30 960 (51.3%)	116 (51.1%)	0.568
Yes	22 292 (36.8%)	22 213 (36.8%)	79 (34.8%)	
Unknown	7236 (11.9%)	7204 (11.9%)	32 (14.1%)	
BMI, kg/m^2				
<25	40 773 (67.3%)	40 631 (67.3%)	142 (62.6%)	0.256
≥25	11 601 (19.1%)	11 554 (19.1%)	47 (20.7%)	
Unknown	8230 (13.6%)	8192 (13.6%)	38 (16.7%)	
Barthel index				
<100	7116 (11.7%)	7081 (11.7%)	35 (15.4%)	0.001
100	50 513 (83.3%)	50 342 (83.4%)	171 (75.3%)	
Unknown	2975 (4.9%)	2954 (4.9%)	21 (9.3%)	
T				
T0	95 (0.2%)	95 (0.2%)	0 (0.0%)	<0.001
Tis	746 (1.2%)	742 (1.2%)	4 (1.8%)	
T1	11 322 (18.7%)	11 285 (18.7%)	37 (16.3%)	
T2	8467 (14.0%)	8436 (14.0%)	31 (13.7%)	
T3	20 231 (33.4%)	20 171 (33.4%)	60 (26.4%)	
T4	11 018 (18.2%)	10 978 (18.2%)	40 (17.6%)	
TX	3310 (5.5%)	3300 (5.5%)	10 (4.4%)	
Unknown	5415 (8.9%)	5370 (8.9%)	45 (19.8%)	
N				
N0	31 082 (51.3%)	30 984 (51.3%)	98 (43.2%)	<0.001
N1	12 463 (20.6%)	12 422 (20.6%)	41 (18.1%)	
N2	6286 (10.4%)	6259 (10.4%)	27 (11.9%)	
N3	1907 (3.1%)	1902 (3.2%)	5 (2.2%)	
N4	8 (0.0%)	8 (0.0%)	0 (0.0%)	
NX	3444 (5.7%)	3433 (5.7%)	11 (4.8%)	
Unknown	5414 (8.9%)	5369 (8.9%)	45 (19.8%)	
M				
M0	47 398 (78.2%)	47 244 (78.2%)	154 (67.8%)	<0.001
M1	4737 (7.8%)	4718 (7.8%)	19 (8.4%)	
MX	3056 (5.0%)	3047 (5.0%)	9 (4.0%)	
Unknown	5413 (8.9%)	5368 (8.9%)	45 (19.8%)	
Esophageal cancer	1181 (1.9%)	1175 (1.9%)	6 (2.6%)	0.605
Gastric cancer	15 456 (25.5%)	15 401 (25.5%)	55 (24.2%)	0.715
Colon cancer	27 019 (44.6%)	26 917 (44.6%)	102 (44.9%)	0.968
Rectal cancer	10 521 (17.4%)	10 481 (17.4%)	40 (17.6%)	0.987
Liver cancer	2070 (3.4%)	2064 (3.4%)	6 (2.6%)	0.646
Pancreatic cancer	2684 (4.4%)	2668 (4.4%)	16 (7.0%)	0.078

Abbreviations: BMI, body mass index; IQR, interquartile range.

more likely to exhibit respiratory failure compared with patients who had SARS-CoV-2 infection <4 weeks before surgery based on the exact logistic analysis (odds ratio: 0.28; 95% confidence interval: <0.001–0.96; $p = 0.046$) (Table 4). The difference in background and outcome for patients who had SARS-CoV-2 infection <4 weeks before surgery and that of >4 weeks before surgery was summarized in Tables S2 and S3.

4 | DISCUSSION

This study showed that patients with a history of SARS-CoV-2 infection had a significantly higher incidence of pneumonia. Moreover, this finding was observed in patients who were infected with SARS-CoV-2 <4 weeks before surgery. To the best of our knowledge, this study first assessed the association between preoperative SARS-CoV-2 infection and the risk of postoperative complications in patients with gastroenterological cancer using data obtained from a nationwide database in Japan.

To date, several reports have shown that SARS-CoV-2 infection has a negative impact on perioperative outcomes.[8,14,20,21] In the early period of the COVID pandemic, an international cohort study revealed that postoperative pulmonary complications were observed in half of patients with perioperative SARS-CoV-2 infection. Further, this research found that these complications are associated with high mortality rates.[22] The COVIDSurg Collaborative, which is a platform of studies aiming to explore the impact of COVID-19 in surgical patients and services, revealed that patients with perioperative COVID-19 had worse short-term outcomes, which included mortality, longer length of hospitalization, and morbidities such as septic shock.[11] Other studies, including ours, have also reached a similar conclusion. That is, perioperative SARS-CoV-2 infection is associated with the development of complications, particularly pulmonary complications. However, this is the only study that focused on gastroenterological cancer surgery, which is a highly invasive procedure with high complication rates. Patients with gastroenterological cancer have a weak immune system; hence, they are more susceptible to viral infections than those with benign diseases.[16,17] We hypothesized that these patients are more likely to exhibit severe outcomes and complications due to preoperative COVID-19 infection. Moreover, previous studies focused on specific populations from Europe and the United States, which had higher infection rates in different types of surgeries than Asian countries. Our results can provide important data on countries that have implemented strict regulations in response to the COVID-19 pandemic.

In the current study, in addition to pulmonary complications, anastomotic leakage was also frequently observed in patients with SARS-CoV-2 infection. The increase in the rates of pulmonary complications due to preoperative SARS-CoV-2 infection is reasonable. A previous study revealed that >60% of patients who had infection had persistent lung abnormalities, such as subtle ground-glass opacities, and 20% had overt fibrotic lesions.[23] These abnormalities may also have a negative impact on pulmonary function even after surgery, resulting in the development of pneumonia. Furthermore, SARS-CoV-2 infection has a negative impact on multiple organ function. That is, it causes not only pulmonary but also cardiovascular, endocrine, gastrointestinal, and renal damage, which are risk factors for anastomotic leakage.[24–26] In previous reports, the incidence of other non-pulmonary complications such as acute renal failure, septic shock, thromboembolic complications, and ischemic stroke significantly increased due to SARS-CoV-2 infection.[8,13] Based on these findings, these complications are associated with adverse effects on multiple organs. Therefore, surgeries must be performed cautiously because of the increased risk of various complications, including pulmonary complications.

Recent studies have investigated the optimal interval from SARS-CoV-2 infection to surgery. First, the result from the COVIDSurg Collaborative, which showed that SARS-CoV-2 infection had a negative impact on mortality after surgery, focused on patients who had SARS-CoV-2 infection diagnosed within 7 days before or 30 days after surgery.[22] Based on this report, the Japanese Surgical Society recommends that patients with risk factors such as old age, smoking history, multiple comorbidities, and preexisting respiratory dysfunction should be managed with caution, with consideration of surgical indications. Moreover, Deng et al. showed that surgery performed within 8 weeks after SARS-CoV-2 infection is related to the development of pneumonia. Meanwhile, surgery performed 8 weeks after infection is not associated with an increased incidence of complications, including pneumonia.[8] They concluded that patients can safely undergo elective, nonemergent surgery after at least 8 weeks from the first date of confirmed recent SARS-CoV-2 infection. Our result is consistent with these results. That is, an interval of 4 weeks from SARS-CoV-2 infection to surgery may lead to poor short-term outcomes. Surgical procedures can be safely performed from an interval of at least 4 weeks after the diagnosis of infection. Conversely, our study showed that patients who were not infected with SARS-CoV-2 were more likely to develop respiratory failure compared with those who had been infected with SARS-CoV-2 at least 4 weeks prior to surgery. Although the reason for this finding remains unclear, this result supports the fact that an interval of 4 weeks after infection may relieve the negative impact of SARS-CoV-2 infection on surgical outcomes. This finding is rather important for the patients who have malignant tumors that need to be treated as quickly as possible.

The severity of SARS-CoV-2 infection is associated with the development of complications, particularly respiratory failure. Due to the implementation of severe regulations during the pandemic, the number of patients with severe infection in Japan was lower than that in Western countries. That is, only five patients with severe infection were observed in the current analysis. Thus, the association between the severity of infection and the short-term outcomes

TABLE 2 Association between complications and SARS-CoV-2 infection.

Complications	All patients $N = 60604$	Patients without SARS-CoV-2 infection $n = 60377$	Patients with SARS-CoV-2 infection $n = 227$	*p*-value (Fisher's exact test)	*p*-value (exact logistic regression)[a]
All complications	6278 (10.36%)	6249 (10.35%)	29 (12.78%)	0.230	0.701
Pneumonia	1362 (2.25%)	1349 (2.23%)	13 (5.73%)	0.002	0.036
Anastomotic leakage	1084 (1.79%)	1076 (1.78%)	8 (3.52%)	0.069	0.131
SSI	1020 (1.68%)	1017 (1.68%)	3 (1.32%)	1.000	0.593
PE	41 (0.07%)	41 (0.07%)	0 (0.00%)	1.000	0.878
DVT	491 (0.81%)	489 (0.81%)	2 (0.88%)	0.707	0.757
Respiratory failure	1333 (2.20%)	1327 (2.20%)	6 (2.64%)	0.645	0.902
Kidney injury	242 (0.40%)	242 (0.40%)	0 (0.00%)	1.000	0.669
Arrhythmia	301 (0.50%)	299 (0.50%)	2 (0.88%)	0.311	0.619
Hemorrhage	848 (1.40%)	848 (1.40%)	0 (0.00%)	0.082	0.515
Cardiac infarction	39 (0.06%)	39 (0.06%)	0 (0.00%)	1.000	0.938
Cerebral infarction	203 (0.33%)	203 (0.34%)	0 (0.00%)	1.000	0.688
Pancreatic fistula	455 (0.75%)	454 (0.75%)	1 (0.44%)	1.000	0.542
Biliary fistula	81 (0.13%)	81 (0.13%)	0 (0.00%)	1.000	0.873

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; SSI, surgical site infection.

[a]These analyses were adjusted for sex, age, smoking status, BMI, Barthel index (during hospitalization), TNM stage, and cancer type.

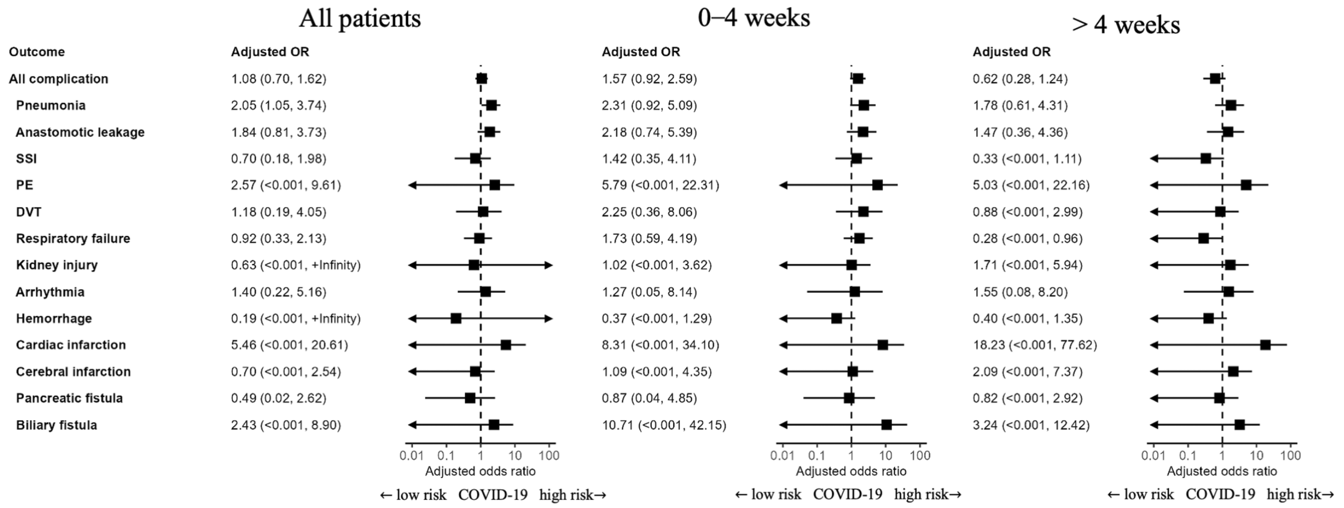

FIGURE 1 Adjusted odds ratio of the incidence of each complication in all patients and patients with an interval from SARS-CoV-2 infection to surgery of <4 or >4 weeks.

TABLE 3 Detailed information about SARS-CoV-2 infection.

Variables	Patients with SARS-CoV-2 infection (+) $n=227$
Duration from SARS-CoV-2 infection to surgery (days), median (IQR)	25 (6, 70)
Duration from SARS-CoV-2 infection to surgery, no. (%)	
≤4 weeks	118 (52.0%)
>4 weeks	109 (48.0%)
Severe cases, no. (%)	5 (2.2%)
Ventilator management, no. (%)	1 (0.4%)
ICU admission, no. (%)	4 (1.8%)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

could not be evaluated. Nevertheless, more studies with a larger number of patients should be performed.

This study had several limitations. First, not only viral infection itself but also other factors can be related to the development of complications in patients who had SARS-CoV-2 infection. These patients might not have undergone sufficient preoperative assessment and rehabilitation due to the infection, which could have led to complications. Since several studies have reported an association between preoperative infection and postoperative outcome, it remains unclear whether the adverse effect of infection on postoperative outcome is only observed in SARS-CoV-2 infection.[27–29] However, in this century when surgery has become the standard of care for malignancies, no other infection is as prevalent as SARS-CoV-2 infection, and this finding is important for many people. Second, we cannot confirm whether the preoperative pneumonia caused by SARS-CoV-2 infection was indeed cured by the time of surgery. However, we speculate that Japanese surgeons may not perform surgery if there is residual pneumonia caused by SARS-CoV-2 infection. This is because we always check the infectious status and X-rays to examine the patient's condition before surgery as a routine. In addition, the results can be beneficial in the gastroenterological field. However, due to the limited number of patients with SARS-CoV-2 infection, the impact of infection on each surgical procedure such as gastrectomy and esophagectomy was not evaluated. Therefore, the exact logistic regression analysis adjusted for cancer type was performed to confirm the validity of our findings. Third, the effect of vaccination in inhibiting the development of complications is unknown because information on vaccination history could not be obtained from the database. Moreover, the number of patients with SARS-CoV-2 infection was extremely small. Hence, comparisons according to strain or wave could not be performed. The look-back period was set at 90 days to maintain the quality of the dataset. This resulted in a lack of data on operative mortality. Fourth, the change in surgical indications could not be analyzed. Several treatment options, including chemotherapy, radiotherapy, chemoradiotherapy, and endoscopic resection, could be considered for patients with cancer. Thus, the change in the number of patients who had undergone nonsurgical treatment should also be investigated. Fifth, the only data for patients who were admitted to the ICU or used ventilators was available as a breakdown of severity. However, we did not focus on the analysis of the association between complications and severity of SARS-CoV-2 infection in the present study. In addition, the use of steroids is important to evaluate the short-term outcome after surgery. However, we did not pick up data on steroid use because our database could not determine the purpose of steroid use, whether steroids were used to treat SARS-CoV-2 infection or comorbidities. Finally, the negative impact of the pandemic on cancer treatment, not only short- but also long-term outcomes, which are important limitations, should be assessed.

In conclusion, patients with a history of SARS-CoV-2 infection had a significantly higher incidence of pneumonia. Moreover, this finding was observed in patients who were infected with SARS-CoV-2 <4 weeks before surgery. To the best of our knowledge, this study first showed the association between preoperative SARS-CoV-2 infection and the risk of postoperative complications in patients with gastroenterological cancer using data obtained from a

TABLE 4 Association between complications and SARS-CoV-2 infection stratified according to the duration from infection to surgery.

Subgroup	Complications	All patients	Patients without SARS-CoV-2 infection	Patients with SARS-CoV-2 infection	*p*-value (Fisher's exact test)	*p*-value (exact logistic regression)[a]
Duration from SARS-CoV-2 infection to surgery ≤4 weeks[a]	All complications	6269 (10.36%)	6249 (10.35%)	20 (16.95%)	0.032	0.095
	Pneumonia	1356 (2.24%)	1349 (2.23%)	7 (5.93%)	0.017	0.071
	Anastomotic leakage	1081 (1.79%)	1076 (1.78%)	5 (4.24%)	0.061	0.142
	SSI	1020 (1.69%)	1017 (1.68%)	3 (2.54%)	0.455	0.539
	PE	41 (0.07%)	41 (0.07%)	0 (0.00%)	1.000	0.941
	DVT	491 (0.81%)	489 (0.81%)	2 (1.69%)	0.249	0.301
	Respiratory failure	1332 (2.20%)	1327 (2.20%)	5 (4.24%)	0.192	0.274
	Kidney injury	242 (0.40%)	242 (0.40%)	0 (0.00%)	1.000	0.754
	Arrhythmia	300 (0.50%)	299 (0.50%)	1 (0.85%)	0.444	0.778
	Hemorrhage	848 (1.40%)	848 (1.40%)	0 (0.00%)	0.419	0.582
	Cardiac infarction	39 (0.06%)	39 (0.06%)	0 (0.00%)	1.000	0.957
	Cerebral infarction	203 (0.34%)	203 (0.34%)	0 (0.00%)	1.000	0.763
	Pancreatic fistula	455 (0.75%)	454 (0.75%)	1 (0.85%)	0.590	0.985
	Biliary fistula	81 (0.13%)	81 (0.13%)	0 (0.00%)	1.000	0.967
Duration from SARS-CoV-2 infection to surgery >4 weeks[a]	All complications	6258 (10.35%)	6249 (10.35%)	9 (8.26%)	0.635	0.193
	Pneumonia	1355 (2.24%)	1349 (2.23%)	6 (5.50%)	0.036	0.249
	Anastomotic leakage	1079 (1.78%)	1076 (1.78%)	3 (2.75%)	0.448	0.507
	SSI	1017 (1.68%)	1017 (1.68%)	0 (0.00%)	0.269	0.563
	PE	41 (0.07%)	41 (0.07%)	0 (0.00%)	1.000	0.929
	DVT	489 (0.81%)	489 (0.81%)	0 (0.00%)	1.000	0.727
	Respiratory failure	1328 (2.20%)	1327 (2.20%)	1 (0.92%)	0.736	0.046
	Kidney injury	242 (0.40%)	242 (0.40%)	0 (0.00%)	1.000	0.832
	Arrhythmia	300 (0.50%)	299 (0.50%)	1 (0.92%)	0.419	0.624
	Hemorrhage	848 (1.40%)	848 (1.40%)	0 (0.00%)	0.412	0.589
	Cardiac infarction	39 (0.06%)	39 (0.06%)	0 (0.00%)	1.000	0.979
	Cerebral infarction	203 (0.34%)	203 (0.34%)	0 (0.00%)	1.000	0.857
	Pancreatic fistula	454 (0.75%)	454 (0.75%)	0 (0.00%)	1.000	0.717
	Biliary fistula	81 (0.13%)	81 (0.13%)	0 (0.00%)	1.000	0.900

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; SSI, surgical site infection.

[a]These analyses were adjusted for sex, age, smoking status, BMI, Barthel index (during hospitalization), TNM stage, and cancer type.

nationwide database in Japan. Our findings can be valuable for countries that have implemented strict regulations in response to the COVID-19 pandemic and have lower SARS-CoV-2 infection-related mortality rates.

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

Approval of the research protocol: The protocol of this study was reviewed and adopted by the Japanese Society of Gastrointestinal Surgery Committee and approved by Institutional Review Board of Keio University. The need for an individual written informed consent was waived (ID: 20221157).

Informed Consent: N/A.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382:727–33.
2. COVIDSurg Collaborative. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. Br J Surg. 2020;107:1440–9.
3. Maeda H, Endo H, Yamamoto H, Miyata H, Munekage M, Taketomi A, et al. Effects of the COVID-19 pandemic on gastroenterological surgeries in 2020: a study using the national clinical database of Japan. Ann Gastroenterol Surg. 2023;7:407–18.
4. Driessen MLS, Sturms LM, Bloemers FW, Duis HJT, Edwards MJR, den Hartog D, et al. The detrimental impact of the COVID-19 pandemic on major trauma outcomes in the Netherlands: a comprehensive nationwide study. Ann Surg. 2022;275:252–8.
5. Ikeda N, Yamamoto H, Taketomi A, Hibi T, Ono M, Niikura N, et al. The impact of COVID-19 on surgical procedures in Japan: analysis of data from the national clinical database. Surg Today. 2022;52:22–35.
6. Takeuchi M, Endo H, Hibi T, Seishima R, Nakano Y, Yamamoto H, et al. The impact of COVID-19 for postoperative outcomes using a nationwide Japanese database of patients undergoing distal gastrectomy for gastric cancer. Ann Gastroenterol Surg. 2023;7:887–95.
7. Takeuchi M, Endo H, Hibi T, Seishima R, Nakano Y, Yamamoto H, et al. Analysis of the short-term outcomes after esophagectomy for esophageal cancer during the COVID-19 pandemic using data from a nationwide Japanese database. Esophagus. 2023;20:617–25.
8. Deng JZ, Chan JS, Potter AL, Chen YW, Sandhu HS, Panda N, et al. The risk of postoperative complications after major elective surgery in active or resolved COVID-19 in the United States. Ann Surg. 2022;275:242–6.
9. Zheng Z, Gao B, Luo G, Wang L, Lei C. Impact of SARS-CoV-2 infection on postoperative complications of patients undergoing surgery after general outbreak in China: a protocol for multicentre prospective cohort study. BMJ Open. 2023;13:e072608.
10. de Graaff MR, Hogenbirk RNM, Janssen YF, Elfrink AKE, Liem RSL, Nienhuijs SW, et al. Impact of the COVID-19 pandemic on surgical care in the Netherlands. Br J Surg. 2022;109:1282–92.
11. Argandykov D, Dorken-Gallastegi A, El Moheb M, Gebran A, Proaño-Zamudio JA, Bokenkamp M, et al. Is perioperative COVID-19 really associated with worse surgical outcomes? A nationwide COVIDSurg propensity-matched analysis. J Trauma Acute Care Surg. 2023;94:513–24.
12. Prasad NK, Mayorga-Carlin M, Sahoo S, Englum BR, Turner DJ, Siddiqui T, et al. Mid-term surgery outcomes in patients with COVID-19: results from a nationwide analysis. Ann Surg. 2023;277:920–8.
13. Lal BK, Prasad NK, Englum BR, Turner DJ, Siddiqui T, Carlin MM, et al. Periprocedural complications in patients with SARS-CoV-2 infection compared to those without infection: a nationwide propensity-matched analysis. Am J Surg. 2021;222:431–7.
14. COVIDSurg Collaborative. Outcomes and their state-level variation in patients undergoing surgery with perioperative SARS-CoV-2 infection in the USA: a prospective multicenter study. Ann Surg. 2022;275:247–51.
15. Verhagen NB, SenthilKumar G, Jaraczewski T, Koerber NK, Merrill JR, Flitcroft MA, et al. Severity of prior coronavirus disease 2019 is

associated with postoperative outcomes after major inpatient surgery. Ann Surg. 2023;278:e949–e956.
16. Bakouny Z, Labaki C, Grover P, Awosika J, Gulati S, Hsu CY, et al. Interplay of immunosuppression and immunotherapy among patients with cancer and COVID-19. JAMA Oncol. 2023;9:128–34.
17. Kumagai S, Togashi Y, Sakai C, Kawazoe A, Kawazu M, Ueno T, et al. An oncogenic alteration creates a microenvironment that promotes tumor progression by conferring a metabolic advantage to regulatory T cells. Immunity. 2020;53:187–203.e8.
18. Ishida Y, Maeda K, Murotani K, Shimizu A, Ueshima J, Nagano A, et al. Body mass index and weight change are associated with mortality in chronic kidney disease: a retrospective cohort study using a Japanese medical claims database. Nutrition. 2023;116:112147.
19. Sobin LH, Gospodarowicz MK, Wittekind C. International Union Against Cancer (UICC): TNM classification of malignant tumours. Oxford: Wiley-Blackwell; 2017.
20. Knisely A, Zhou ZN, Wu J, Huang Y, Holcomb K, Melamed A, et al. Perioperative morbidity and mortality of patients with COVID-19 who undergo urgent and emergent surgical procedures. Ann Surg. 2021;273:34–40.
21. Prasad NK, Lake R, Englum BR, Turner DJ, Siddiqui T, Mayorga-Carlin M, et al. Increased complications in patients who test COVID-19 positive after elective surgery and implications for pre and postoperative screening. Am J Surg. 2022;223:380–7.
22. COVIDSurg Collaborative. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. Lancet. 2020;396:27–38.
23. Writing Committee for the COMEBAC Study Group, Morin L, Savale L, Pham T, Colle R, Figueiredo S, et al. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA. 2021;325:1525–34.
24. Takeuchi M, Ishii K, Seki H, Yasui N, Sakata M, Shimada A, et al. Excessive visceral fat area as a risk factor for early postoperative complications of total gastrectomy for gastric cancer: a retrospective cohort study. BMC Surg. 2016;16:54.
25. Kim SH, Son SY, Park YS, Ahn SH, Park DJ, Kim HH. Risk factors for anastomotic leakage: a retrospective cohort study in a single gastric surgical unit. J Gastric Cancer. 2015;15:167–75.
26. Marano L, Porfidia R, Pezzella M, Grassia M, Petrillo M, Esposito G, et al. Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study. Ann Surg Oncol. 2013;20:3912–8.
27. Kunisaki C, Miyata H, Konno H, Saze Z, Hirahara N, Kikuchi H, et al. Modeling preoperative risk factors for potentially lethal morbidities using a nationwide Japanese web-based database of patients undergoing distal gastrectomy for gastric cancer. Gastric Cancer. 2017;20:496–507.
28. Takeuchi H, Miyata H, Gotoh M, Kitagawa Y, Baba H, Kimura W, et al. A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database. Ann Surg. 2014;260:259–66.
29. Takeuchi M, Takeuchi H, Kawakubo H, Booka E, Mayanagi S, Fukuda K, et al. Perioperative risk calculator predicts long-term oncologic outcome for patients with esophageal carcinoma. Ann Surg Oncol. 2018;25:837–43.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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