



# OPEN The COVID-19 pandemic and clinical characteristics of colorectal cancer: a multicenter retrospective study

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The spread of COVID-19 has led to numerous hospitals prioritizing case management and to delays in diagnosis and treatment. Consequently, many cancer patients have developed life-threatening complications during the COVID-19 pandemic. The aim of this study was to investigate the impact of COVID-19 pandemic on colorectal cancer (CRC), including its clinical and pathologic characteristics. This multicenter cohort study was performed at six institutions in Korea and included a total of 3871 patients with CRC treated between March 2019 and February 2021. After exclusion of 211 patients who did not undergo surgery, the data of 3660 patients were compared 1 year before and after the COVID-19 pandemic. The patients' baseline characteristics, CRC-related complications, perioperative outcomes including emergency surgery, R0 resection rates, stoma formations, postoperative complications, and pathologic outcomes were assessed. The number of patients decreased during the pandemic (−18.0%, from 2127 to 1744), but the baseline characteristics did not differ. The pandemic group had greater disease severity given the presence of bleeding, perforation, and obstruction as complications (9.8% vs. 12.7%,  $P=0.033$ ). The proportion of patients who had open surgery (15.9% vs. 17.6%,  $P=0.049$ ), stoma formation (11.9% vs. 15.4%,  $P<0.001$ ), early postoperative complications (13.5% vs. 17.5%,  $P=0.001$ ), and adjuvant chemotherapy increased in the pandemic group (45.5% vs. 50.1%,  $P=0.003$ ). The clinical and pathologic features of CRC partly worsened during the pandemic. Healthcare providers and governments should prepare to encounter patients with CRC having poor clinical features for years and encourage people to participate in cancer screening programs. The Clinical Research Information Service (No. KCT0008063), January 2, 2023, retrospectively registered.

**Keywords** Colon cancer, Coronavirus, COVID-19, Pandemic, Multicenter

The spread of the SARS-CoV-2 virus that causes COVID-19 has affected the healthcare systems worldwide over the last 2 years. COVID-19 is mainly characterized by severe respiratory problems with high infectivity and mortality; however, it also negatively influences new-onsets or aggravates pre-existing medical conditions, such as cardiovascular, hematological, endocrine, and malignant diseases<sup>1–4</sup>. Regarding surgery, several reports have shown that patients with COVID-19 had poorer postoperative outcomes, including pulmonary problems, than those without COVID-19 infection<sup>1,5,6</sup>.

Apart from the direct effect of the viral infection, the rapid increase in patients with COVID-19 under limited resources has led to several governments and hospitals prioritizing management of patients and to delays in diagnosis and treatment of other diseases<sup>7–9</sup>. The severity of urgent diseases, regardless of COVID-19 infection, increased, with worse clinical outcomes during the COVID-19 pandemic relative to the severity in the prepandemic period<sup>10–12</sup>. Moreover, the priority for treating malignancy was adjusted during the COVID-19

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era as suggested by the World Health Organization that recommended postponement of nonurgent procedures, although malignancy is a life-threatening condition that may progress into an emergency situation<sup>8</sup>.

Colorectal cancer (CRC) has been ranked 3rd among various malignancies worldwide<sup>13</sup>. It has been strongly associated with progression to emergency situations, such as obstruction, perforation, and bleeding, which would need radiological, endoscopic, or surgical interventions. Due to the prioritization of CRC management, some patients with CRC have developed life-threatening complications during the pandemic<sup>14</sup>. Therefore, assessing the clinical manifestations and treatment of CRC is crucial during the pandemic to evaluate relevant strategies, such as prioritization and distribution, to establish progressive policies after the end of the COVID-19 era<sup>15</sup>.

Because COVID-19 patients were treated at government-designated hospitals in South Korea, owing to the unique healthcare system, most university hospitals could focus on their primary roles in the early period. However, some obstacles, such as mandatory COVID-19 testing, decreased accessibility, and phobia of visiting hospitals, emerged as the virus spread, leading to changes in cancer diagnosis and treatment indirectly. Our multicenter, retrospective study investigated the impact of the COVID-19 pandemic on CRC, including clinical and pathologic characteristics, using databases from tertiary institutions across South Korea.

## Materials and methods

### Study design and population

This is a multicenter retrospective study that compared the clinical and pathologic characteristics of patients with CRC 1 year before and after the COVID-19 pandemic. Six tertiary hospitals throughout the Republic of Korea participated after obtaining approval from each institution's review board (Human Research Protection Center of Ajou University Hospital, Suwon, Korea, AJIRB-MED-MDB-21-425). This study was conducted in compliance with the Declaration of Helsinki and approved by the committee of an Office of Human Research Protections-certified institution (Federal Wide Assurance 00002740). Between March 2019 and February 2021, we collected data from consecutive patients with primary colorectal cancer following the study's registration at the Clinical Research Information Service (KCT0008063). Written informed consent requirements for enrolling patients were waived due to the retrospective study design. Patients with recurrent CRC and non-adenocarcinoma, such as a gastrointestinal stromal tumor, neuroendocrine tumor, and sarcoma, were excluded. Patients with colorectal metastasis from other organs (stomach, ovary, pancreas, etc.) were also excluded.

The cohort was divided into two groups for comparison: 1 year before and after the COVID-19 pandemic. This period was established according to when the COVID-19 test had been made mandatory for all admitted patients in each institution. Despite the differences in start dates among the institutions, the study was conducted within a few weeks around March 2020. Any type of COVID-19 test was considered valid, including the polymerase chain reaction or rapid antigen test. Patients with a positive COVID-19 test result were transferred to one of the hospitals designated for the treatment of COVID-19 by the Korean government.

### Clinical and pathologic outcomes

The baseline characteristics of the patients, including sex, age, body mass index (BMI), The American Society of Anesthesiologists (ASA) physical status class, previous abdominal surgery, preoperative tumor markers (CEA and CA19-9), tumor location, and complications caused by the primary CRC, including bleeding, perforation, and obstruction, were extracted from the collected data. When the CRC was obstructive, data on stent insertion or stoma formation before surgery were assessed.

Perioperative outcomes were also compared: operative time, emergency surgery, surgical method (open, laparoscopy, robot, and conversion), surgical type, radical resection, combined resection of other organs, stoma formation, intraoperative and postoperative complications, length of hospital stay, and postoperative tumor markers. Postoperative complications were recorded as early and late when they occurred within 30 days after surgery. The severity of complications was recorded following the Clavien–Dindo classification<sup>16</sup>.

Variables for pathologic outcomes included tumor differentiation, tumor diameter, Tumor–Node–Metastasis (TNM) stage, number of harvested lymph nodes, proximal and distal resection margins, lymphatic/vascular/perineural invasions, and adjuvant chemotherapy. TNM staging was based on the American Joint Committee on Cancer guidelines, 8th edition<sup>17</sup>. Oncologic outcomes were analyzed from surveillance data at the outpatient clinic until February 2024, the last follow-up date.

### Statistical analysis

A sample-size calculation was not performed due to the retrospective nature of this study. Continuous variables were represented as the mean with standard deviations and compared using Student's *t*-tests, whereas categorical variables were compared using  $\chi^2$  tests or Fisher's exact tests. *P* values < 0.05 were considered to be indicative of statistical significance. Kaplan–Meier graph and log-rank test were applied to analyze recurrence and survival. All statistical analyses were performed using Statistical Package for the Social Sciences software (IBM SPSS Statistics for Windows version 20.0, Armonk, NY, USA).

## Results

### Study population

A total of 3871 patients with CRC were enrolled between March 2019 and February 2021 from six institutions across the Republic of Korea (Table 1). Among them, 211 patients did not undergo surgery for various reasons, including unresectable status, poor performance, and patient refusal (prepandemic, 119 vs. pandemic, 92). After excluding these patients, a total of 3660 patients underwent surgery and were divided into the prepandemic (*n* = 2008) and pandemic groups (*n* = 1652).

Variable	Pre-pandemic	Pandemic	P-value
	(n = 2008)	(n = 1652)	
Male Sex	1196 (59.6%)	932 (56.4%)	0.055
Age (years)	64.0 (16–95)	64.0 (14–94)	0.505
BMI (kg/m <sup>2</sup> )	23.5 (14.6–48)	23.5 (13.9–46)	0.551
Race/Ethnicity	Asian/Korean	Asian/Korean	
ASA physical status class			0.032
I	903 (45.0%)	717 (43.4%)	
II	621 (30.9%)	514 (31.1%)	
III	398 (19.8%)	314 (19.0%)	
IV	54 (2.7%)	58 (3.5%)	
V	32 (1.6%)	49 (3.0%)	
Previous abdominal surgery	370 (18.4%)	383 (23.2%)	<0.001
Preoperative CEA (ng/mL)	3.5 (0.5–7877)	3.7 (0.1–8021)	0.115
Preoperative CA19-9 (U/mL)	10.8 (0.2–8443)	12.5 (0.5–10000)	0.195
Tumor location			0.135
Appendix	19 (0.9%)	11 (0.7%)	
Cecum	68 (3.4%)	60 (3.6%)	
Ascending colon	310 (15.4%)	277 (16.8%)	
Hepatic flexure	70 (3.5%)	39 (2.4%)	
Transverse colon	92 (4.6%)	76 (4.6%)	
Splenic flexure	20 (1.0%)	10 (0.6%)	
Descending colon	85 (4.2%)	65 (3.9%)	
Sigmoid colon	567 (28.2%)	467 (28.3%)	
Rectosigmoid junction	193 (9.6%)	149 (9.0%)	
Rectum	568 (28.3%)	470 (28.5%)	
Anus	0 (0%)	2 (0.1%)	
Synchronous	16 (0.8%)	26 (1.6%)	
Complication	196 (9.8%)	210 (12.7%)	0.033
Bleeding	7 (0.3%)	4 (0.2%)	
Fistula	1 (0.1%)	2 (0.1%)	
Intussusception	5 (0.2%)	4 (0.2%)	
Perforation	23 (1.1%)	35 (2.1%)	
Obstruction	160 (8.0%)	165 (10.0%)	
Stent insertion	81 (50.6%)	73 (44.2%)	0.268
Stoma formation	29 (18.1%)	29 (17.6%)	>0.999

**Table 1.** Baseline characteristics of the patients. All values are represented as mean  $\pm$  SD. ASA, The American Society of Anesthesiologists; BMI, Body mass index; CEA, Carcinoembryonic antigen.

The number of patients with CRC decreased during the COVID-19 pandemic (–18.0%, 2127 to 1744). The baseline characteristics such as sex, age, and BMI did not differ between the two groups; however, the ASA physical status class 5 significantly worsened (1.6% vs. 3.0%  $P=0.032$ ), and there was an increase in the number of patients with a history of prior abdominal surgery (18.4% vs. 23.2%,  $P<0.001$ ). There were no differences in the preoperative levels of tumor markers (CEA: 3.5 ng/mL vs. 3.7 ng/mL,  $P=0.115$  and CA19-9: 10.8 U/mL vs. 12.5 U/mL,  $P=0.195$ , respectively) and tumor location. The number of CRC-related complications, including bleeding, fistula formation, intussusception, perforation, and obstruction, increased in the pandemic group (9.8% vs. 12.7%,  $P=0.033$ ). In addition, complicated cancer tended to increase by the advanced stage in both groups (Stage 0, 1.4%; Stage 1, 1.2%; Stage 2, 12.2%; and Stage 3, 11.8%; and Stage 4, 27.2%; Supplementary Table 1).

### Clinical and pathologic outcomes

More emergency surgeries were performed in the pandemic group than in the prepandemic group, although the difference was not significant (3.3% vs. 4.6%,  $P=0.059$ , Table 2). However, significantly more open surgeries and stoma formation surgeries were performed during the pandemic (15.9% vs. 17.6%,  $P=0.049$ ; 11.9% vs. 15.4%,  $P<0.001$ , respectively). Surgical type, R0 resection rates, and combined resection did not differ between the two groups. Early postoperative complication rates were higher in the pandemic group than in the prepandemic group (13.5% vs. 17.5%,  $P=0.001$ ), although no significant difference in severity was noted (Clavien–Dindo classification 3b/4/5; 13.3% vs. 13.5%,  $P>0.999$ ). In contrast, the late postoperative complication rates and severities did not differ between the two groups.

Variable	Pre-pandemic	Pandemic	P-value
	(n = 2008)	(n = 1652)	
Operation time (min)	205.0 ± 112.7	205.9 ± 111.0	0.8
Emergent operation	67 (3.3%)	76 (4.6%)	0.059
Surgical method			0.049
Open	320 (15.9%)	290 (17.6%)	
Laparoscopy	1461 (72.8%)	1157 (70.0%)	
Robot	189 (9.4%)	164 (9.9%)	
Conversion	17 (0.8%)	29 (1.8%)	
Surgical type			0.245
Right colectomy	534 (26.6%)	433 (26.2%)	
Left colectomy	113 (5.6%)	88 (5.3%)	
Anterior resection	563 (28.0%)	452 (27.4%)	
Low anterior resection	639 (31.8%)	527 (31.9%)	
Hartmann operation	33 (1.6%)	37 (2.2%)	
Abdominoperineal resection	30 (1.5%)	43 (2.6%)	
Pelvic exenteration	2 (0.1%)	0 (0%)	
Total/Subtotal colectomy	29 (1.4%)	29 (1.8%)	
Transanal excision	22 (1.1%)	12 (0.7%)	
Bypass/ileostomy/colostomy	43 (2.1%)	31 (1.9%)	
R0 resection	1846 (91.9%)	1052 (90.6%)	0.174
Combined resection	257 (12.8%)	243 (14.7%)	0.1
Stoma formation	238 (11.9%)	254 (15.4%)	< 0.001
Intraoperative complications	23 (1.1%)	26 (1.6%)	0.312
Postoperative hospital stay (days)	9.4 ± 7.7	9.0 ± 6.3	0.078
Postoperative CEA (ng/mL)	2.5 (0.6–1762)	2.9 (0.5–442)	0.333
Postoperative CA19-9 (U/mL)	10.7 (2–311)	11.4 (2–117)	0.719
Early postoperative complications <sup>a</sup>	271 (13.5%)	289 (17.5%)	0.001
Clavien-Dindo classification			> 0.999
1/2/3a	235 (86.7%)	250 (86.5%)	
3b/4/5	36 (13.3%)	39 (13.5%)	
Late postoperative complications <sup>b</sup>	64 (3.2%)	36 (2.2%)	
Clavien-Dindo classification			0.302
1/2/3a	39 (60.9%)	18 (50%)	
3b/4/5	25 (39.1%)	18 (50%)	

**Table 2.** Perioperative outcomes. All values are represented as mean ± SD. CEA, Carcinoembryonic antigen.

<sup>a</sup>Within 30 days after surgery. <sup>b</sup>From 30 days after surgery to February 2024 (the final follow-up date).

Pathologic outcomes, including tumor differentiation, tumor diameter, and TNM stage, did not significantly differ between the two groups (Table 3). Harvested lymph nodes and surgical resection margins, which reflect the quality of radical surgery, were not different between the two groups. However, more patients received adjuvant chemotherapy following surgery in the pandemic group than in the prepandemic group (45.5% vs. 50.1%,  $P=0.003$ ). Although some patients' follow-up data were missing (20%), overall and recurrence-free survival rates were not different between the groups (90.8% vs. 91.8%,  $P=0.23$  and 84.8% and 84.9%,  $P=0.78$ , respectively, Fig. 1).

## Discussion

Although our study found that fewer patients were diagnosed with CRC during the COVID-19 pandemic than before the pandemic, their diseases were more advanced and complicated, which consequently increased the number of emergency surgeries, open surgeries, stoma formations, and postoperative complications. Despite the lack of significant differences in the pathologic results, more patients should have received adjuvant chemotherapy following surgery.

The survival rates of CRC in Korea have been reported to be the highest worldwide; the 5-year survival rates are 71.8% for colon cancer and 71.1% for rectal cancer<sup>18</sup>. Although the CONCORD-3 study group did not discuss the reasons in detail, a possible explanation is that the Korean healthcare system, which started its national cancer screening program in 1999 and expanded it to include CRC in 2004, is responsible<sup>19</sup>. Easy access to medical services based on low costs contributes to better survival rates given that Koreans aged ≥ 50 years can receive fecal occult blood tests at no cost. Moreover, Koreans with positive fecal occult blood test results are recommended to undergo colonoscopy at no cost. The number of doctor consultations per person and average

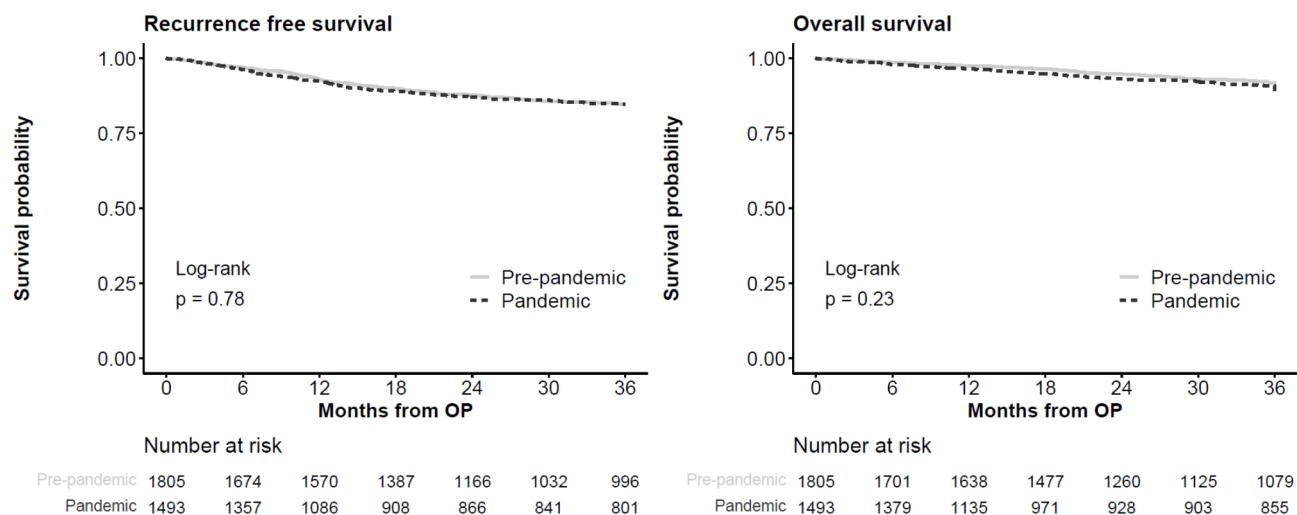
Variable	Pre-pandemic (n = 2008)	Pandemic (n = 1652)	P-value
Differentiation			0.549
Well-	163 (8.1%)	150 (9.1%)	
Moderately-	1705 (84.9%)	1379 (83.5%)	
Poorly-	63 (3.1%)	55 (3.3%)	
Mucinous	57 (2.8%)	50 (3.0%)	
Signet ring cell	14 (0.7%)	8 (0.5%)	
Others	6 (0.3%)	10 (0.6%)	
Tumor diameter (cm)	3.6 (0-18.3)	3.7 (0-20.7)	0.06
Tumor stage			0.861
Tis	84 (4.2%)	83 (5.0%)	
T1	312 (15.5%)	251 (15.2%)	
T2	274 (13.6%)	225 (13.6%)	
T3	1050 (52.3%)	855 (51.8%)	
T4	245 (12.2%)	207 (12.5%)	
No data	43 (2.1%)	31 (1.9%)	
Nodal stage			0.261
N0	1140 (56.8%)	915 (55.4%)	
N1	552 (27.5%)	460 (27.8%)	
N2	248 (12.4%)	233 (14.1%)	
No data	68 (3.4%)	44 (2.7%)	
TNM stage			0.103
0	70 (3.5%)	75 (4.5%)	
I	480 (23.9%)	382 (23.1%)	
II	554 (27.6%)	417 (25.2%)	
High risk stage II	312 (56.3%) <sup>a</sup>	216 (51.8%) <sup>a</sup>	
III	647 (32.2%)	531 (32.1%)	
IV	257 (12.8%)	247 (15.0%)	
Harvested lymph nodes	17 (0-207)	18 (0-150)	0.065
PRM (cm)	9.5 (0-133)	10.0 (0-135)	0.178
DRM (cm)	4.0 (0-106)	4.0 (0-95.5)	0.894
Lymphatic invasion	499 (24.9%)	439 (26.6%)	0.169
Vascular invasion	362 (18.0%)	299 (18.1%)	0.268
Perineural invasion	427 (21.3%)	339 (20.5%)	0.172
Adjuvant chemotherapy	914 (45.5%)	828 (50.1%)	0.003
High risk stage II	177 (19.4%)	121 (14.6%)	
- Drop rate <sup>b</sup>	43.20%	44.00%	
Stage III	510 (55.8%)	486 (58.7%)	
- Drop rate <sup>b</sup>	21.20%	14.10%	

**Table 3.** Pathologic outcomes. All values are represented as mean  $\pm$  SD. DRM, Distal resection margin; PRM, Proximal resection margin. <sup>a</sup>Among the patients with stage II cancer. <sup>b</sup>Proportion of the patients who were indications for chemotherapy but did not received it.

length of hospital stay in Korea have been among the highest in the Organization for Economic Co-operation and Development countries<sup>20</sup>. Individuals who do not meet the CRC screening criteria but wish to undergo colonoscopy can do so for only US\$ 80.

Despite the better accessibility and lower prioritization of CRC management than in other countries, fewer patients were diagnosed with CRC during the COVID-19 pandemic in this study. Similar findings have been observed from other countries<sup>15,21,22</sup>. Miyo et al. reported reductions in surgeries and colonoscopies of 10.4% and 14%, respectively, in Japan in their retrospective study<sup>23</sup>. Two other single-center studies in Korea showed 5.4% and 24.3% decreases in CRC patients between 2019 and 2021, respectively<sup>24,25</sup>. The nationwide database showed an increase in CRC patients from 1999 to 2011, followed by a decrease owing to the aforementioned cancer screening program<sup>26</sup>. However, our study found an 18% decrease over the last 2 years, which is much larger than the average decrease between 2015 and 2019 (i.e., 2% per year). This finding indicated a delay in the diagnosis of CRC due to reduced medical screening rather than decreased CRC incidence.

The inevitable delays in the diagnosis of CRC could affect not only a large number of patients but also patients with more advanced and complicated diseases. The higher complication rate in the pandemic group might



**Fig. 1.** Oncologic outcomes (3-year overall and recurrence-free survival).

be due to a decline in cancer screening and a rise in delayed hospital visits until symptoms onset. Although most patient characteristics did not differ in this study, delays in the diagnosis and treatment have resulted in a significant reduction in CRC survival rates from previous studies<sup>27–29</sup>. When potential patients become the “real” patients due to diagnostic delays, the age at diagnosis also increases. Subsequently, other related factors, such as the ASA physical status class, medical and surgical history, and advanced tumor complications, could worsen and easily lead to postoperative morbidity and mortality. In comparison to the prepandemic group, the pandemic group had more preoperative tumor-related problems and postoperative complications within 30 days after surgery. A few reports have shown similar results<sup>15,22,30</sup>, whereas others have shown no difference in tumor-related complications, including perforation and obstruction, unlike our findings<sup>21,24,25,30</sup>. This difference reflects the limitations of a single-center study, small number of cases, or lack of detailed data. The difference in the rate of emergency surgeries reached a borderline *P*-value (3.3 vs. 4.6%,  $P = 0.059$ ), despite the fact that the pandemic group had higher rates of complicated symptoms. Contrary to perforation, which nearly always required emergency surgery, patients with obstruction had a variety of alternatives: stent insertion followed by elective surgery or emergency surgery, depending on the severity of their symptoms, preference of surgeons, and available healthcare devices.

The pathologic outcomes did not differ between the prepandemic- and pandemic groups, as indicated in several studies<sup>21,23</sup>. However, complicated cancer tended to relate to the advanced stage in both groups (Supplementary Table 1). Healthcare providers should pay attention to it, although the TNM stage did not differ in our study. Adjuvant chemotherapy increased, albeit it is unclear why (drop rate 21.2% vs. 14.1%), not because the stages were advanced but rather because patients with stage 3 cancer were more compliant with chemotherapy. Some studies have revealed advanced pathologic results, including lymphatic invasion, lymphovascular invasion, and lung metastasis, which could have an impact on the prognosis of patients with CRC<sup>24,25,30</sup>. However, because these results were analyzed from the early pandemic period database, they potentially could become aggravated within the near future unless the COVID-19 pandemic ends soon. Further assessment for pathologic variables, including tumor diameter, TNM stage, and lymphatic/vascular/perineural invasion is required.

Apart from delays in diagnosis and treatment, screening delays can also affect the prognosis<sup>31</sup>. Despite the gradual increase in CRC screening rates between 2012 and 2019, screening of identified individuals decreased by 6.1% in 2020, the year COVID-19 emerged<sup>32</sup>. Although the rate slightly increased in 2021, it did not return to the levels observed during 2018. This decline should not be ignored because it may lead to lower overall adenoma detection rates as well as the diagnosis of malignancy. Unlike the effects of delayed CRC patient visitation, the effects of omitting screening would not be reflected over a short period considering the progression rates of adenoma to adenocarcinoma. Encouraging people to participate in the national cancer screening program and promptly visit their care provider when suspicious symptoms emerge will reduce future socioeconomic costs.

In preparation for similar crises in the future, our study could provide some recommendations. Rapid establishment of infection control guidelines should be the top priority. During non-pandemic periods, efforts should focus on increasing CRC screening rate to enable early diagnosis and treatment, leading to nationwide downstaging. The potential for reducing social costs through early intervention can be considered as part of a comprehensive approach to formulating infection control and public health policies during crises.

To the best of our knowledge, this study—which was based on a comprehensive database—is the largest multicenter study to reflect the effects of the COVID-19 pandemic on various aspects of CRC. The six hospitals participating in this study are all tertiary referral hospitals in Korea, and the colorectal surgeons involved are all experts in standardized surgical procedures. However, due to the study’s retrospective design, one of the limitations was selection bias. No stratification of the participating institutions, surgeons, surgical techniques, and treatment policies was possible. Even though all the participating institutions were tertiary, large-volume centers in Korea with secured multidisciplinary teams for CRC management, we excluded the clinical stages determined

by preoperative imaging studies due to the possibility of inter-observer difference and the discrepancy between the clinical stages and the pathologic ones. Another limitation is the insufficient information on the prognosis of participants. Although we depicted three-year survival outcomes, approximately 20% of the patients' follow-up data was missing due to retrospective nature; however, these data will be examined in a few years through regular surveillance. Lastly, our results cannot be applied to the general population given the differences in healthcare systems and situations among countries.

## Conclusion

Real-world data revealed that the clinical and pathologic features of CRC partly worsened during the pandemic. We believe that our findings can help our global colleagues in their fight against COVID-19, aid in the recovery of their healthcare systems, prepare them for encounters with patients having poor clinical features, and encourage people to participate in screening programs.

## Data availability

Data were generated by the authors and deposited in a repository. However, you can contact the corresponding author for data sharing based on the guidelines of Ministry of Health and Welfare of the Korean government.

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## Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by YD Han, SU Bae, WR Kim, DR Lim, and CW Kim. The first draft of the manuscript was written by YD Han and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Declarations

### Competing interests

The authors declare no competing interests.

## Additional information

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