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ORIGINAL ARTICLE

Implementation of pre- and post-COVID pandemic outcomes of colon cancer patients undergoing colectomies

Aplicación de los resultados pre- y pospandemia de COVID-19 en pacientes con cáncer de colon sometidos a colectomía

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Abstract

Objective: *Colectomy is a standard surgical technique for colon cancer, but the prognostic indexes are limited. We aimed to evaluate clinicopathology of colectomies under emergency and elective conditions due to colon cancer, and correlate prognostic indexes with these outcomes collected before and during COVID-19 pandemic.* **Method:** *Clinicopathological and laboratory findings of 250 patients underwent colectomies under elective and emergency conditions for left and right colon cancer between 2017 and 2021 were retrospectively analyzed. Prognostic markers, including Clavien-Dindo Classification (CDC), Frailty index (FI), hemoglobin, albumin, lymphocyte, and platelet (HALP) score, and Charlson Comorbidity Index (CCI) were used.* **Results:** *CDC Grade 2 was the most common grade in both periods for all patients (p = 0.014) and for elective cases (p = 0.006), but not FI and HALP scores. Frequency of perineural invasion was significantly higher during COVID-19 among elective cases (19.8% vs. 40.6%; p = 0.032). Increase in CDC (OR: 0.123; 95%CI: 0.331-1.393; p = 0.007) and in CCI (OR: 0.067; 95% CI: 0.147-1.158; p = 0.028) primarily affected mortality rate during pandemic.* **Conclusions:** *Our analyses revealed short-term influences of COVID-19 pandemic on patients' surgical care of the colon cancer patients. The operative management of comorbidities, CDC for complications, and CCI for comorbidities might be helpful tools to identify post-operative mortality of colectomies.*

Keywords: *Colon cancer. Colectomy. Morbidity. Frailty index.*

Resumen

Objetivo: *Evaluar la clínica y la patología de las colectomías electivas y de urgencia por cáncer de colon, correlacionando los índices pronósticos con los resultados pre- y pospandemia de COVID- 19.* **Método:** *Se analizaron 250 casos de colectomía entre 2017 y 2021, incluyendo marcadores pronósticos como la clasificación de Clavien-Dindo (CDC), el índice de fragilidad (FI), el índice HALP y el índice de comorbilidad de Charlson (CCI).* **Resultados:** *La CDC de grado 2 predominó en ambos periodos para los pacientes (p = 0.014) y los casos electivos (p = 0.006), no así para el FI y el HALP. Se observó una mayor invasión perineural durante la COVID-19 en los casos electivos (19.8% frente a 40.6%; p = 0.032). El aumento de CDC (OR: 0.123; IC 95%: 0.331-1.393; p = 0.007) y CCI (OR: 0.067; IC 95%: 0.147-1.158; p = 0.028) afectó a la tasa de mortalidad pandémica.* **Conclusiones:** *Los análisis revelaron influencias a corto plazo de la pandemia de COVID-19 en la atención quirúrgica de los pacientes con cáncer de colon. El tratamiento quirúrgico de la comorbilidad, la CDC para las complicaciones y el CCI para la comorbilidad podrían ser herramientas útiles para identificar la mortalidad posoperatoria de las colectomías.*

Palabras clave: *Cáncer de colon. Colectomía. Morbilidad. Índice de fragilidad.*

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Date of reception: 23-08-2023
Date of acceptance: 08-11-2023
DOI: 10.24875/CIRUE.M23000919

Cir Cir (Eng). 2026;94(1):79-89
Contents available at PubMed
www.cirugiaycirujanos.com

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Introduction

The World Health Organization (WHO) has classified the ongoing global pandemic of viral pneumonia that has been caused by the rapid spread of the novel coronavirus 2019-nCov (COVID-19) – designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a public health emergency[1,2]. Mortality rate for patients with severe or critical new coronavirus pneumonia increased with age and with the presence of more comorbid conditions, such as diabetes, cardiovascular disease, and cerebrovascular illness[2,3]. Notably, the systemic immunosuppressive state brought on by cancer puts patients at higher risk for serious infections and in a worse prognosis.

For colon cancer patients with coronavirus pneumonia, a number of conservative therapy approaches are currently advised, although surgery for individuals with surgical reasons is typically postponed[3]. For the majority of patients with SARS-CoV-2 infection, it is advised to stop cancer treatment if the infection worsens. Due to this, cancer patients had a comparatively high chance of tumor progression, which raised questions about the efficacy of tumor therapy[4]. Safe implementation of colorectal cancer surgery during the pandemic is challenging due to safety issues of the operating rooms and surgery team members, the restrictions of a limited number of hospital services and health staff, and the concerns of post-operative COVID-19-associated complications and mortality[5]. Therefore, there is a need to minimize the risk of COVID-19 positive patients for elective surgery and to introduce prioritization and additional safety measures in clinical practice.

Cancer initiation, progression, and metastasis are not only dependent on the type of cancer, but the systemic inflammation and nutritional status play important roles. The prognosis screening in colon cancer is crucial due to high morbidity and mortality rates. There are several indexes and classification of colon cancer patients. One of these indexes, hemoglobin, albumin, lymphocyte, and platelet (HALP) score, is an inflammation index that has been reported to be beneficial in showing the prognosis of stomach, colorectal, kidney, bladder, and prostate cancers[6]. Other indexes are the pre-operative Frailty index (FI) and Clavien Dindo Classification (CDC), which are valuable indicators of mortality and morbidity, respectively. Another index is the Charlson comorbidity index (CCI), which is the most used comorbidity index[7,8]. CCI categorizes the comorbidities of patients based on the International Classification of Diseases diagnosis codes found in administrative data, such as hospital abstracts data. Each comorbidity category has an associated weight[1-6], based on the adjusted risk of mortality or resource use, and the sum of all the weights results in a single comorbidity score for a patient (CCI; < 4 and ≥ 4). CCI has been adapted and verified as applicable and valid for predicting the outcome and risk of death from the colon cancer[9]. Regarding various studies based on all these indexes in colon cancer patients during the COVID period are limited.

Considering the prognostic indices, we aimed to compare the findings before and after COVID-19 to predict the pre- and post-operative prognostics of the colon cancer patients based on the elective and emergency colectomies.

Method

Patient selection

The patients who underwent surgical treatment within elective and emergency conditions for colon cancer in the Department of General Surgery, Bagcilar Hospital, aculty of Medicine, Health Sciences University between March 2017 and May 2021 were included in this retrospective study. The patients who had coexisting inflammatory bowel diseases (ulcerative colitis and Crohn's disease) or benign diseases (plastron appendicitis, diverticulitis, etc.), rectal cancer, and emergency cases were excluded from the study.

The study protocol was approved by the Ethical Committee of Istanbul Medipol University (Decision No: GOKAEK-Decision No: E-10840098-772.02-4012 on 24/08/2021).

Data collection

Demographical and clinical characteristics were reported from patients' files. These characteristics included the gender, age, body mass index (BMI), American Society of Anesthesiology (ASA) classification, comorbidities (hypertension [HT], congestive heart failure [CHF], diabetes mellitus [DM], albumin [mg/dL], platelet [PLT, $10^3/mm^3$], white blood cells [WBC] count [$10^9/L$], C-reactive protein [CRP], neutrophil [cells/mm^3], lymphocyte [cells/mm^3] and hemoglobin [g/dL]) level. Colonoscopy was performed in only elective cases, and computed tomography was

performed in all cases. Metastatic disease was diagnosed by using computed tomography.

Surgery treatment protocol

All patients were operated on with an open technique. An operative report was used to define right- sided lesions (tumor proximal to splenic flexure) and left-sided lesions (tumor distal to splenic flexure). Other pre-operative data were reported, such as main operative procedure time, complications, stoma formation, and closure. Complications were divided as minor; wound infection, ileus, wound dehiscence, urinary tract infection, and major; anastomotic leak, intra- abdominal abscess, sepsis, pneumonia, pulmonary embolism, acute renal failure, myocardial infarction, cardiac arrest, cerebrovascular disease, intubation, and need for reoperation. Surgical materials were sent to the pathology department for both macroscopic and microscopic examination and tumor staging.

Pathological examination

As clinicopathological features; tumor grades (Grade I; well-differentiated, Grade II; moderately differentiated, Grade III; severe), tumor diameter, total number of resected lymph nodes (LN), and number of patients with positive LN involvement was examined. The 8th edition of TNM staging, accepted by the American Cancer Committee (AJCC) and the Union for International Cancer Control, was used for cancer staging in pathology reports.

Scoring system

Pre-operative evaluation of the patients' HALP score from medical archives, which is an inflammatory and nutritional marker, was evaluated. HALP score was calculated by the formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)/platelets (/L). HALP scores of patients were categorized according to data review.

Post-operative data included 30-day morbidity, mortality, and length of hospital stay. Prognostic markers that are important for morbidity and mortality in gastrointestinal surgery clinical outcomes were used. These were the CDC and the pre-operative FI, respectively. All complications were graded according to the CDC[10], and patients were classified according the highest CDC grade for complication they developed (1-5), allowing patients with multiple complications to be represented by a single severity grade[11].

The comorbidities were also stratified by modified FI, which included five features as 5-mFI: CHF, chronic obstructive pulmonary disease, HT requiring medication, diabetes, and non-independent functional status. The 5-mFI score was measured by multiplying each number of frailty features (1 point per each existence; 0-5 points). Patients were categorized into three groups (mFI = 0, mFI = 1, and mFI $\geq$ 2)[12].

The last scoring system we used in this study was CCI, which contains 19 issues, including diabetes with diabetic complications, CHF, peripheral vascular disease, chronic pulmonary disease, mild and severe liver disease, hemiplegia, renal disease, leukemia, lymphoma, metastatic tumor, and acquired immunodeficiency syndrome, each of which was weighted according to their potential influence on mortality.

Statistical analysis

Descriptive data of quantitative variables were presented as mean with standard deviation for continuous ones. The Chi-square test or Fisher's exact test, where appropriate, was performed for categorical variables. The student's t-test was used for continuous variables. Parametric methods were used for measurement suitable for a normal distribution. According to parametric methods, "ANOVA" test was used in the comparison with the measurement values of three or more independent groups. Non-parametric methods were used for non-normal distribution measurements. In accordance with non-parametric methods, "Mann-Whitney U" test was used to compare the measurement values of two independent groups, and "Kruskal-Wallis" test was used to compare the measurement values of three or more independent groups. Optimal cut-off values of HALP score were calculated according to the review of data. Kaplan-Meier method with log- rank test was used to draw the survival curve for the HALP tested. Multivariate Cox proportional hazard regression models were used to analyze the independent prognostic factors for overall survival. R version 4.0.5 (1.0.143 – ©2009-2016 RStudio, Inc.) package program was used for statistical analysis. Significance level was determined as $p < 0.05$.

Results

Demographic and baseline features of patients are presented in table 1. There were 188 patients who

Table 1. Demographic and baseline features of patients

Findings of patients	All colon cancer patients			p	Emergency cases		p	Elective cases		p
	Total (n = 250)	Pre-COVID (n = 188)	Post-COVID (n = 62)		Pre-COVID (n = 87)	Post-COVID (n = 30)		Pre-COVID (n = 101)	Post-COVID (n = 32)	
Age, year (X ± SD)	63.02 ± 12.48	63.46 ± 12.87	61.68 ± 11.20	0.330	65.08 ± 14.15	62.23 ± 9.02	0.305	62.07 ± 11.55	61.16 ± 13.04	0.706
Gender, n (%)										
Male	144 (57.6)	111 (59.0)	33 (53.2)	0.512	52 (59.8)	13 (43.3)	0.177	59 (58.4)	20 (62.5)	0.839
Female	106 (42.4)	77 (41.0)	29 (42.8)		35 (40.2)	17 (56.7)		42 (41.6)	12 (37.5)	
ASA, n (%)										
1	32 (12.8)	28 (14.9)	4 (6.5)		12 (13.8)	2 (6.7)		16 (15.8)	2 (6.2)	
2	97 (38.8)	65 (34.6)	32 (51.6)	0.018	28 (32.2)	17 (56.7)	0.057	37 (36.6)	15 (46.9)	0.304
3	109 (43.6)	83 (44.1)	26 (41.9)		39 (44.8)	11 (36.7)		44 (43.6)	15 (46.9)	
4	12 (4.8)	12 (6.4)	0 (0.0)		8 (9.2)	0 (0.0)		4 (4.0)	0 (0.0)	
BMI, n (%)										
1	80 (32.0)	52 (27.7)	28 (45.2)	0.025	29 (33.3)	3 (43.3)	0.369	23 (22.8)	15 (46.9)	0.049
2	123 (49.2)	95 (50.5)	28 (45.2)		38 (43.7)	14 (46.7)		57 (56.4)	14 (43.8)	
3	38 (15.2)	32 (17.0)	6 (9.7)		15 (17.2)	3 (10.0)		17 (16.8)	3 (9.4)	
4	38 (15.2)	9 (4.8)	0 (0.0)		5 (5.7)	0 (0.0)		4 (4.0)	0 (0.0)	
Complications, n (%)										
Major	25 (10.0)	20 (10.6)	5 (8.1)	0.153	20 (23.0)	4 (13.3)	0.360	3 (3.0)	2 (6.2)	0.751
Minor	36 (14.4)	31 (16.5)	5 (8.1)	0.733	17 (19.5)	3 (10.0)	0.386	11 (10.9)	1 (3.1)	0.326
Frailty index										
mFI = 0	95 (38.0)	72 (38.3)	23 (37.1)	0.897	39 (44.8)	9 (30.0)	0.360	33 (32.7)	14 (43.8)	0.393
mFI = 1	63 (25.2)	46 (24.5)	17 (27.4)		19 (21.8)	8 (26.7)		27 (26.7)	9 (28.1)	
mFI ≥ 2	92 (36.8)	70 (37.2)	22 (35.5)		29 (33.3)	13 (43.3)		41 (40.6)	9 (28.1)	
CDC, n (%)										
1	78 (31.2)	58 (30.9)	20 (32.3)		12 (13.8)	9 (30.0)		46 (45.5)	11 (34.4)	
2	108 (43.2)	76 (40.4)	32 (51.6)	0.014	36 (41.4)	14 (46.7)	0.006	40 (39.6)	18 (56.2)	0.329
3	38 (15.2)	33 (17.6)	5 (8.1)		22 (25.3)	4 (13.3)		11 (10.9)	1 (3.1)	
4	4 (1.6)	1 (0.5)	3 (4.8)		0 (0.0)	2 (6.7)		1 (1.0)	1 (3.1)	
5	22 (8.8)	20 (10.6)	2 (3.2)		17 (19.5)	1 (3.3)		3 (3.0)	1 (3.1)	
CCI (X ± SD)	3.49 ± 1.88	3.11 ± 1.56	3.62 ± 1.97	0.067	3.80 ± 2.00	3.23 ± 1.59	0.159	3.46 (1.93)	3.00 (1.55)	0.226

ASA: American society of anesthesiologists; BMI: body mass index; CDC: clavien-dindo classification; CCI: charlson comorbidity index.

underwent surgery before the pandemic and 62 patients during pandemic due to the diagnosis of colon cancer. In pre-pandemic period, 87 patients (46.3%) were operated in emergency conditions and 101 (53.7%) were operated in elective conditions. However, during pandemic, 30 patients were emergency cases, and 32 were elective cases (48.4% vs. 51.6%, respectively, p = 0.820).

Before the pandemic, 31 patients in 2017, 62 patients in 2018, 81 patients in 2019, and 14 in March 2020, a total of 188 patients were operated. During the pandemic, 32 patients were operated after March 2020, and 30 patients were operated until 19 August 2021. Most of colon cancer patients were male (57.6%), 65 were emergency cases, and 119 were elective cases. Mean age of all patients was 63.02 ± 12.48 years. No statistical significance was found for the distribution of age and gender for total (p > 0.05) (Table 1).

Majority of pre-COVID patients were at ASA III (44.1%), and of post-COVID patients were at ASA II (51.6%). Since the number of emergency surgeries in the pre-pandemic period was more than those in the post-pandemic period, the ASA score of pre-COVID patients was found as higher and statistically significant compared to that of post-COVID patients (p = 0.018). However, comparison of ASA scores on the basis of emergency and elective condition, there was no significant difference between the scores of pre-pandemic and pandemic period (p = 0.057 vs. 0.304, respectively) (Table 1).

Table 2. Laboratory findings of patients

Laboratory findings	All colon cancer patients			p	Emergency cases		p	Elective cases		p
	Total (n = 250)	Pre-COVID (n = 188)	Post-COVID (n = 62)		Pre-COVID (n = 87)	Post-COVID (n = 30)		Pre-COVID (n = 101)	Post-COVID (n = 32)	
Albumin	3.77 ± 0.62	3.72 ± 0.61	3.89 ± 0.63	0.064	3.66 ± 0.68	3.84 ± 0.78	0.243	3.78 ± 0.54	3.94 ± 0.45	0.120
CRP	43.16 ± 60.85	44.66 ± 63.16	38.60 ± 53.47	0.498	62.26 ± 80.93	53.36 ± 68.31	0.591	29.5036 ± 42	24.77 ± 29.17	0.505
WBC	9.88 ± 3.91	9.68 ± 3.67	10.48 ± 4.52	0.163	10.43 ± 4.41	12.41 ± 4.82	0.040	9.04 ± 2.77	8.67 ± 3.38	0.536
Lymphocyte	1.90 ± 0.98	1.86 ± 0.92	2.01 ± 1.14	0.271	1.63 ± 0.84	2.03 ± 1.44	0.064	2.05 ± 0.94	2.00 ± 0.79	0.759
Neutrophil	7.05 ± 3.62	6.92 ± 3.39	7.43 ± 4.27	0.339	7.94 ± 3.83	9.23 ± 4.72	0.137	6.04 ± 2.67	5.74 ± 2.98	0.587
Platelets (X ± SD)	330.6 ± 109.3	329.6 ± 106.5	333.7 ± 118.1	0.797	334.9 ± 99.2	366.1 ± 115.6	0.157	325.0 ± 112.6	303.3 ± 114.0	0.346
MPV	9.97 ± 1.23	10.01 ± 1.29	9.85 ± 1.02	0.367	10.09 ± 1.37	9.81 ± 1.10	0.315	9.94 ± 1.22	9.88 ± 0.97	0.800
Hemoglobin	11.67 ± 2.29	11.71 ± 2.20	11.56 ± 2.55	0.654	12.05 ± 2.37	11.82 ± 2.91	0.672	11.42 ± 2.00	11.32 ± 2.18	0.800
HALP score (X ± SD)	28.58 ± 19.71	27.73 ± 19.68	31.14 ± 19.73	0.238	22.63 ± 13.11	28.89 ± 20.24	0.055	32.12 ± 23.12	33.26 ± 19.32	0.802

All values are presented as mean ± standard deviation.
CRP: C-reactive protein; WBC: white blood cells; MPV: mean platelet volume; HALP: hemoglobin, albumin, lymphocyte, and platelet score.

BMI of all colon cancer patients and that of elective cases significantly differed between pre- and post-pandemic periods (p = 0.025 vs. 0.049, respectively), but BMI of emergency cases did not differ significantly (p = 0.369). No statistical significance was found in major/minor complications for all patients and different conditions (p > 0.05). Most emergency cases in pre- COVID period had FI score 0, while most during the pandemic had score over 2 (44.8% vs. 43.3%, respectively; p = 0.360). Most of the elective cases in pre-COVID period had FI score over 2, while most during pandemic had score 0 (40.6% vs. 43.8%, respectively, p = 0.393). Most of all cancer patients and of emergency cases were classified at CDC II (43.2% and 41.4%, respectively), and there was a significant difference in the distribution of CDC classification of pre- and post-COVID patients (p = 0.014 and 0.006, respectively). However, CDC classification of elective cases did not significantly differ (p = 0.329). No significance was found in the mean CCI values of all patients independent of the operation conditions (p > 0.05) (Table 1).

The laboratory findings of all patients were presented in table 2. The mean albumin, CRP, WBC, lymphocyte, neutrophil, thrombocyte, hemoglobin, MPV, and HALP score, which showed no significant difference between periods for all patients and also for emergency and elective cases (p > 0.05), except that there was a significance in WBC values of the emergency cases (p = 0.040).

Considering the clinicopathology of patients (Table 3), the tumor was most commonly located in the left colon in pre-COVID period among all patients (59.0%), the emergency cases (62.1%), and elective cases (56.4%), which did not differ compared to post-COVID patients (p > 0.05). However, the most frequently performed operation was right hemicolectomy in patients who could be operated in both periods (41.0% vs. 46.8%, respectively, p = 0.743). Type of procedure did not differ significantly among all patients and based on the operation conditions (p > 0.05). Most patients did not need a stoma (75.0% vs 86.9%, respectively, p = 0.107). Rate of ileus formation did not differ significantly among all patients and based on the operation conditions (p > 0.05). 16.1% of the emergency cases before the pandemic had ascites, while none of those in post- pandemic period had ascites (p = 0.044). No difference was observed for the rate of ascites formation among all patients and elective cases (p > 0.05) (Table 3).

Mean tumor diameter and distribution of lymphatic invasion and adjacent organ invasion did not differ among all patients and patients operated under elective conditions (p > 0.05); however, the rate of perineural invasion among patients operated under elective conditions was significantly higher during

Table 3. Clinicopathological features of patients

Surgical findings	All colon cancer patients			p	Emergency cases		p	Elective cases		p
	Total (n = 250)	Pre-COVID (n = 188)	Post- COVID (n = 62)		Pre-COVID (n = 87)	Post- COVID (n = 30)		Pre-COVID (n = 101)	Post- COVID (n = 32)	
Location, n (%)										
Right	108 (43.2)	77 (41.0)	31 (50.0)	0.272	33 (37.9)	13 (43.3)	0.76	44 (43.6)	18 (56.2)	0.294
Left	142 (56.8)	111 (59.0)	31 (50.0)		53 (62.1)	17 (56.7)		57 (56.4)	14 (43.8)	
Procedure, n (%)										
Left Hemicolectomy	106 (42.4)	38 (20.2)	9 (14.5)		22 (25.3)	8 (26.7)		16 (15.8)	1 (3.1)	
Right Hemicolectomy	47 (18.8)	77 (41.0)	29 (46.8)	0.743	33 (37.9)	13 (43.3)	0.8	44 (43.6)	16 (50.0)	0.308
Subtotal colectomy	5 (2.0)	4 (2.1)	1 (1.6)		2 (2.3)	0 (0.0)		2 (2.0)	1 (3.1)	
Anterior resection	92 (36.8)	69 (36.7)	23 (37.1)		30 (34.5)	9 (30.0)		39 (38.6)	14 (43.8)	
Stoma, n (%)										
None	194 (77.9)	141 (75.0)	53 (86.9)	0.107	48 (55.2)	22 (75.9)	0.059	93 (92.1)	31 (96.9)	0.439
Ileostomy	15 (6.0)	14 (7.4)	1 (1.6)		11 (12.6)	0 (0.0)		3 (3.0)	1 (3.1)	
Colostomy	40 (16.1)	33 (17.6)	7 (11.5)		28 (32.2)	7 (24.1)		5 (5.0)	0 (0.0)	
Ileus, n (%)	118 (47.2)	90 (47.9)	28 (45.2)	0.823	84 (96.6)	27 (90.0)	0.356	6 (5.9)	1 (3.1)	0.867
Ascites, n (%)	19 (7.6)	18 (9.6)	1 (1.6)	0.076	14 (16.1)	0 (0.0)	0.044	4 (4.0)	1 (3.1)	1.000
Diameter (X ± SD)	5.59 (2.72)	5.49 (2.27)	5.89 (3.79)	0.319	5.66 (1.95)	6.62 (4.80)	0.128	5.35 (2.51)	5.21 (2.40)	0.788
Perineural invasion, n (%)	104 (41.6)	73 (38.8)	31 (50.0)	0.162	53 (60.9)	18 (60.0)	1	20 (19.8)	13 (40.6)	0.032
Lymphatic invasion, n (%)	175 (70.0)	131 (69.7)	44 (71.0)	0.975	77 (88.5)	26 (86.7)	1	54 (53.5)	18 (56.2)	0.943
Adjacent organ invasion, n (%)	45 (18.0)	34 (18.1)	11 (17.7)	1	24 (27.6)	9 (30.0)	0.986	10 (9.9)	2 (6.2)	0.784
Grade, n (%)										
1	29 (11.6)	23 (12.2)	6 (9.7)	0.408	7 (8.0)	3 (10.0)	0.59	16 (15.8)	3 (9.4)	0.498
2	186 (74.4)	136 (72.3)	50 (80.6)		61 (70.1)	23 (76.7)		75 (74.3)	27 (84.4)	
3	35 (14.0)	29 (15.4)	6 (9.7)		19 (21.8)	4 (13.3)		10 (9.9)	2 (6.2)	
T stage, n (%)										
0	2 (0.8)	2 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)		2 (2.0)	0 (0.0)	0.854
1	5 (2.0)	4 (2.1)	1 (1.6)	0.783	0 (0.0)	0 (0.0)	0.715	4 (4.0)	1 (3.1)	
2	14 (5.6)	11 (5.9)	3 (4.8)		2 (2.3)	1 (3.3)		9 (8.9)	2 (6.2)	
3	103 (41.2)	80 (42.6)	23 (37.1)		30 (34.5)	8 (26.7)		50 (49.5)	15 (46.9)	
4	126 (50.4)	91 (48.4)	35 (56.5)		55 (63.2)	21 (70.0)		36 (35.6)	14 (43.8)	
N stage, n (%)										
0	95 (38.0)	69 (36.7)	26 (41.9)	0.525	16 (18.4)	10 (33.3)	0.191	53 (52.5)	16 (50.0)	0.865
1	98 (39.2)	73 (38.8)	25 (40.3)		40 (46.0)	13 (43.3)		33 (32.7)	12 (37.5)	
2	57 (22.8)	46 (24.5)	11 (17.7)		31 (35.6)	7 (23.3)		15 (14.9)	4 (12.5)	
M stage, n (%)										
0	206 (82.4)	151 (80.3)	55 (88.7)	0.046	56 (64.4)	26 (86.7)	0.039	88 (87.1)	30 (93.8)	0.477
1	44 (17.6)	37 (19.7)	7 (11.3)		31 (35.6)	4 (13.3)		13 (12.9)	2 (6.2)	
Stage, n (%)										
0	2 (0.8)	2 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)		2 (2.0)	0 (0.0)	
1	15 (6.0)	11 (5.9)	4 (6.5)	0.24	1 (1.1)	1 (3.3)	0.168	10 (9.9)	3 (9.4)	0.711
2	71 (28.4)	50 (26.6)	21 (33.9)		11 (12.6)	7 (23.3)		39 (38.6)	14 (43.8)	
3	110 (44.0)	80 (42.6)	30 (48.4)		44 (50.6)	17 (56.7)		36 (35.6)	13 (40.6)	
4	52 (20.8)	45 (23.9)	7 (11.3)		31 (35.6)	5 (16.7)		14 (13.9)	2 (6.2)	
LN, n (%)										
Total	26.04 (14.40)	26.73 (15.32)	23.94 (10.97)	0.186	24.14 (13.40)	21.70 (10.06)	0.364	28.96 (16.55)	26.03 (11.53)	0.353
Positive	2.73 (5.66)	2.85 (5.45)	2.35 (6.28)	0.55	4.31 (7.06)	2.27 (3.11)	0.129	1.59 (3.03)	2.44 (8.28)	0.39

LN: lymph node.

the pandemic compared to pre-pandemic (40.6% vs. 19.8%, p = 0.032). Grade 2 tumors and T4 tumors predominated in both periods (72.3% vs. 80.6% and 48.4% vs. 56.5%, respectively) without any significant difference among groups (p > 0.05). moreover, the most common stage of tumor among all patients

was Stage 3, observed in both periods (42.6% vs. 48.4%, respectively) without any significant difference (p = 0.284). N1 tumors (38.8%) were in the majority in pre-pandemic period, while number of N0 tumors (41.9%) was higher during COVID, without any significant difference (p = 0.525). The distribution of grade, TN stage, and overall stages of the emergency cases and elective cases did not differ significantly between pre-pandemic and pandemic period (p > 0.05). However, the rate of solid organ metastasis (M) of all patients was significantly higher in pre-pandemic period compared to that during pandemic (19.7% vs. 11.3%, p = 0.046). Emergency cases was also significantly higher in pre-pandemic period (35.6% vs. 13.3%, p = 0.039), but the rate of LN metastasis did not differ among periods (p > 0.05) (Table 3).

The mortality rate was 30.4% (n = 76) among all 250 patients; 36 of 117 emergency cases (30.8%) and 40 of 133 elective cases (30.1%) died due to the pulmonary issues, anastomosis leakage, myocardial infarcts, multiple organ failure, etc. The mortality rate was 37.2% before the pandemic, but 9.7% during the pandemic, which was significantly lower than the pre-pandemic rate (n = 70 vs. n = 6, respectively, p < 0.001). The mean survival duration was 20.39 ± 14.81 months for all patients; 24.39 ± 14.74 months before the pandemic and 8.24 ± 5.51 months during the pandemic, which was significantly lower than the mean of pre-pandemic survival duration (p < 0.001). According to Kaplan-Meier estimation results, there was no significant association between pandemic period as an independent prognostic factor for survival rates of the colon cancer patients (HR=0.965, 95% CI: 0.417-2.568, p = 0.94) (Fig. 1).

The Multivariate Cox regression analysis of clinicopathological factors showed that an increase in CDC (OR: 0.123; 95% CI: 0.331-1.393; p = 0.007) and in CCI (OR: 0.067; 95% CI: 0.147-1.158; p = 0.028) primarily affected the mortality rate during COVID-19 (Table 4). However, other clinicopathological factors, including age, BMI, HALP, grade, and stage of colon cancer, location of tumor, FI, ASA score, type of procedure, and surgery did not affect the mortality rate significantly during pandemic (Table 4).

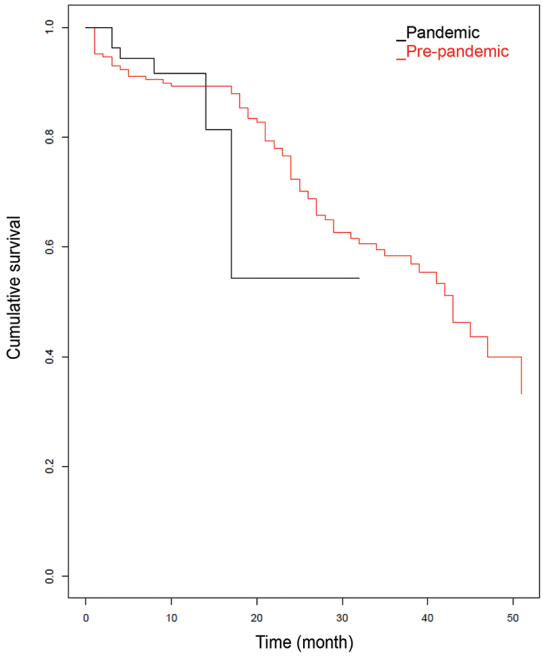

Figure 1. *Cancer-specific survival curve (Kaplan-Meier curve) for patients with colon cancer during COVID-19 pandemic period.*

Discussion

During COVID-19, both elective and emergency surgeries have been canceled or postponed in cancer patients[2,13,14]. The current study included patients with colon cancer that underwent elective or emergency surgeries before and during the pandemic. We found that FI and HALP scores did not differ among periods, while CDC grade was significantly higher among all patients and especially in elective cases before COVID-19. Frequency of ascites and tumors at M stage was significantly higher among emergency cases before COVID-19, while the frequency of perineural invasion was significantly higher during COVID-19 among elective cases. CDC and CCI scores primarily affected the mortality rate during COVID-19.

During COVID-19, the risks and benefits between the protection of patients and health care providers and the adverse outcomes resulting from delayed surgery need to be balanced. Particularly consistent criteria for “emergent” colorectal surgery should be established that could help to simplify surgeons’ decisions to operate in their practices[15,16]. Consistency with the reports, there has been an increase in the number of urgent surgeries at hospitals where elective activity was reduced[17,18], as in our practices.

Age and gender, as patient-level factors, along with overall health status and comorbidities, are included in clinical risk scores associated with worse outcomes of SARS-CoV-2 infection[19]. The evaluation of Kuzuu

Table 4. Multivariate cox regression analysis of Clinicopathological factors affecting the mortality during COVID-19 pandemic

Clinicopathological factors	Hazard ratio (95% CI)	p
Pandemic	0.468 (0.169-1.184)	0.717
Age	0.012 (0.002-1.002)	0.823
BMI	0.150 (-0.053-0.948)	0.724
HALP	0.005 (0.001-1.001)	0.805
FI	0.169 (0.065-1.067)	0.700
CDC	0.123 (0.331-1.393)	0.007
ASA	0.149 (0.278-1.321)	0.061
CCI	0.067 (0.147-1.158)	0.028
Procedure	0.116 (–0.043-0.957)	0.707
Surgery	0.267 (–0.298-0.741)	0.264
Location	0.272 (–0.110-0.895)	0.685
Grade	0.235 (–0.040-0.960)	0.862
Stage	0.163 (0.154-1.167)	0.344

BMI: body mass index; HALP: hemoglobin, albumin, lymphocyte, and platelet score; FI: frailty index; CDC: clavien dindo classification; CCI: charlson comorbidity index; CI: confidence interval.

et al. in pre-COVID-19 and during pandemic reported without significant differences between two periods in terms of the proportions of gender and age according to cancer[20]. In the current study, most of colon cancer patients in pre-COVID and post-COVID period were male, and the mean age in post-COVID period was slightly lower without a significant difference between periods and ineffective for mortality rates during pandemic.

Studies indicated that the numbers of elective colorectal surgeries during the pandemic did not differ in age, gender, and BMI between the number of elective surgeries in two years before pandemic[21,22]. Inconsistently, BMI of 250 colon cancer patients and that of 133 elective cases significantly differed between pre- and post-pandemic periods, but BMI of 117 emergency cases did not differ significantly, suggesting that BMI did not compromise a bias for surgeries for emergency cases but may be important point of view in the elective surgeries. Similar to the literature, we eventually reported that BMI was not an effective factor for the mortality during COVID-19 pandemic.

The diagnostic, prognostic factors and indexes in colon cancer patients have become more apparent during pandemic. Effects of COVID-19 on some outcomes for some cancer types in 2019 and 2020 were investigated and reported that more patients presented with ASA level 3 in the COVID-19 year versus 2019[23]. Similarly, ASA score 3 was mostly reported in pre-COVID period, while ASA score 2 was seen promptly in post-COVID period. However, the evaluation of emergency and elective surgeries regarding ASA scores between two periods showed no any significant correlation in the mortality rate during pandemic.

Studies have indicated higher mortality and complications suffered by patients undergoing surgery during pandemic, particularly those with SARS-CoV-2 infection[24]. Moreover, it was reported that some patients avoided visiting the hospital unless it was an emergency because they feared contracting COVID-19[25]. The need for this group was motivated by widespread concern among surgical patients about the unanticipated consequences of COVID-19, which had an impact on morbidity and mortality rates[26]. It was reported that the cancer, cardiac disease, chronic immunosuppression, chronic anticoagulation, reoperation, intraoperative and post-operative blood transfusion, or the duration of surgery were significantly associated with complications. In addition, a significant correlation between complications and other relative risk variables was found in the post-operative infection[27]. In another study, colorectal cancer patients showed no significant differences in comorbidities, CCI, and mortality rate determined in pre-COVID vs. during COVID[28]. According to our study, the minor complications, including wound infection, ileus, wound dehiscence, urinary tract infection, and major complications including anastomotic leakage, intra-abdominal abscess, sepsis, pneumonia, pulmonary embolism, acute renal failure, myocardial infarction, cardiac arrest, cerebrovascular disease, the need for intubation and reoperation were less likely higher in pre-COVID period without a statistical significance. During the pandemic, there were also no differences in post-operative recovery and incidence of post- operative complications. Surgical duration, amount of intraoperative bleeding, and length of post- surgical hospital stay did not change substantially. This could be attributed to a combination of enhanced recovery after surgery (ERAS) guidelines and laparoscopic minimally invasive surgery, which has a slight impact on post-operative nutritional status and shortens the length of post- operative hospital stay, especially in older patients with colorectal

cancer, as in literature[29,30]. Consistently, CDC Grade 2 was promptly seen in both periods in patients with morbidity. These differences were eventually apparent for all colon cancer patients and specifically for emergency cases. Interestingly, CDC was a significant factor affecting the mortality during pandemic, suggesting that CDC is as a promising feature to be predicting the prognosis of colon cancer patients.

Colorectal cancer is largely diagnosed at old age, when comorbidities and frailty are common and might be important prognostic factors of this cancer, which are strong prognostic factors of survival in colorectal patients apart from commonly considered sociodemographic and tumor characteristics. In a meta-analysis for the impact of comorbidity and frailty on prognosis in colorectal cancer patients, compared to colorectal cancer patients without comorbidity, those with mild/moderate and severe comorbidity were found to have a higher risk of 30-day, overall, and CRC-specific mortality. In addition, frail CRC patients showed higher overall mortality than non-frail patients[31]. In some recent studies, the relationship between the mFI-5, malnutrition, body composition, systemic inflammation, and short-term clinical outcomes in patients undergoing surgery for colorectal cancer was investigated and found that the male gender elevated inflammation, and mFI-5 score remained significantly associated with the incidence of post- operative complications. They reported that mFI-5 frailty score was significantly associated with age, systemic inflammation, and post-operative outcomes in patients undergoing potentially curative resections for colorectal cancer[12]. We also did not find a significant difference in both CCI and frailty indexes between pre- and post-COVID periods, but CCI was found to be correlated with increased mortality during pandemic.

Current coronavirus evolution models and prognosis scores have used in evaluation, including HALP scoring and management of severe cases to predict the prognosis of disease[32,33]. In a very recent review, the prognostic role of HALP score on survival outcomes in patients with solid tumors was investigated. Low HALP score was associated with decreased overall survival, cancer-specific survival, and progression/disease/recurrence-free survival. The prognostic value of HALP on overall survival was observed across various tumor types and tumor stages. They concluded that a low pretreatment HALP score is a reliable and negative prognostic biomarker for survival outcomes in patients with cancer[34]. Therefore, we investigated HALP score between pre- and post- COVID periods unlikely with a significant difference for emergency and elective cases.

Various cancer screening programs for colorectal cancer have been suspended in many countries after the onset of the COVID-19, such as the completion of colonoscopies with declines[35]. Therefore, we compared the survival duration during the pandemic, which was significantly lower than the mean of pre-pandemic survival duration. However, the results of survival analysis showed a less likely an association between pandemic period as an independent prognostic factor for survival rates of colon cancer patients. There are controversy findings whether an appropriate delay in the surgery date among patients with Stage I to III colorectal cancer has an influence on survival time. A study concluded that an appropriate delay of surgical date did not affect survival[36]. In fact, any delay in treatment may lead to tumor progression and an increased risk of transformation from a resectable to an unresectable tumor. Some researches predicted that delays in diagnosis brought about by the pandemic would shorten the long-term survival time of colorectal cancer patients, potentially increase in mortality within 5 years of diagnosis[30]. Including the stages at diagnosis among patients with gastrointestinal cancer during COVID-19 was evaluated with a significant decrease in numbers of patients with stage 0 or I colorectal cancer[20]. Considering post-operative clinicopathology of our cohort, even though the distributions of patients according to the grade, TN stage and overall stage of cancer were comparable before and during pandemic, the proportion of patients with perineural invasion (a feature of adverse prognosis) among elective cases significantly increased during pandemic, suggesting that clinical diagnosis and treatment of colorectal cancer may proceed following the epidemic prevention[36]. Clinically, our patients had more likely slight increases in tumoral extension and staging.

There are some limitations based on the data; (1) nested regression models to generate some imputations for missing values < 30 % of laboratory results, (2) retrospective analysis including measurement and recall biases, (3) without stepwise or any other machine learning models. However, this is the first and largest study to identify the factors to predict mortality and post-operative complications in early settings for elective and emergency colon cancer

surgery. This makes it a distinctively proficient tool that can guide surgeons primarily to distinguish the patients to prompt surgical interventions regarding physiological and pre-operative assessments.

Conclusions

We investigated the effective factors for mortality of patients who underwent colonic resection for cancer during pandemic. The operative management of comorbidities, CDC for the complications, and CCI for comorbidities might be a helpful clinical tool to better identify the post-operative mortality regarding pandemic, priorly. In addition, the prediction of post-operative outcomes when accounting for patient comorbidities and patient acuity might add value to current challenges during the pandemic to improve the quality of care and decrease the mortality. In the future, incorporation of systemic screening tools in clinics may help to improve the prognosis of colon cancer patients.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the World Medical Association and the Declaration of Helsinki. The procedures were authorized by the Institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely collected and anonymized clinical data; therefore, individual informed consent was not required. Relevant ethical recommendations have been followed. The study protocol was approved by the Ethical Committee of Non-invasive Clinical Research (Decision No: GOKAEK-Decision No: 19.08.2021/868).

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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