Impact of the Covid-19 Pandemic on Colorectal Cancer Surgery in Madrid

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Abstract

Introduction   The Covid-19 pandemic has had an important impact on colorectal cancer surgery, for hospital resources had to be redistributed in favour of Covid-19 patients. The aim of the present study is to analyze our results in colorectal oncologic surgery during the Covid-19 pandemic in patients with and without perioperative SARS-CoV-2 infection.

Methods   In total, 32 patients (19 male and 13 female patients), with a mean age of 64 years (range: 57.2 to 69.5 years) with colorectal cancer underwent surgery under the recommendations of surgical societies included in a protocol. Data collection included clinical characteristics (gender, age, body mass index, American Society of Anesthesiologists score, tumor location, preoperative staging, lymphopenia), data related to SARS-CoV-2 infection (postoperative symptoms, diagnostic tests), operative details (surgical procedure, approach, duration, stoma), pathological outcomes (tumor stage, number of lymph nodes harvested, distal and circumferential radial margins, quality of the total mesorectal excision), and surgical outcomes (morbidity, mortality, hospital stay, and the rates of reoperation and readmission).

Results   A total of 3 (9.4%) patients who underwent colorectal surgery during the Covid-19 pandemic were infected by SARS-CoV-2 in the postoperative period. Chronic obstructive pulmonary disease was associated with Covid-19 (6.2% versus 33.3%; $p = 0.042$), and surgical morbidity was higher among Covid-19 patients (100% versus 37.9%; $p = 0.039$). There were not significant differences between COVID-19 patients and non-COVID-19 patients in relation to the rest of the analyzed outcomes.

Conclusion   During the Covid-19 pandemic, colorectal cancer surgery should be performed according to the recommendations of surgical societies. However, Covid-19 patients could present a higher morbidity rate.

Keywords
► colorectal cancer surgery
► Covid-19 pandemic
► SARS-CoV-2 infection
► surgical patients
► oncological surgery

Introduction

On March 11, 2020, the SARS-CoV-2 infection was declared a pandemic by the World Health Organization (WHO).[1] The coronavirus disease 2019 (Covid-19) pandemic has caused an unprecedented impact on healthcare systems worldwide. Globally, more than 20 million confirmed cases of Covid-19 and more than 700,000 deaths have been reported.[2] By August 10, 2020, the total number of confirmed Covid-19 cases in Spain had reached 322,980 cases, with the death of 28,576 patients.[3]

The rapid and dramatic spread of the Covid-19 pandemic in Spain from March to May 2020 has forced to cancel elective surgeries. During the most aggressive period of the pandemic, the cancellation of elective surgical interventions enabled the conversion of operating rooms into intensive care units to treat cases of COVID-19, and the occupation of beds from surgical departments by COVID-19 patients. Although these strategies were implemented under rigorous prioritization rules and could facilitate the care for COVID-19 patients, they delayed the surgical treatment of patients with colorectal cancer.[4,5] In Spain, colorectal cancer is the third most frequent neoplasia; therefore, the COVID-19 crisis has particular effects on colorectal oncologic surgery.[6]

The delay of surgeries in cases of colorectal cancer could increase the likehood of developing metastatic disease, and tumors could progress from being resecable to non-resecable.[7] For colorectal cancer, a delay of six months could have a significant impact on survival rates and this effect could be worse in younger patients with advanced tumours.[8] So the delivery of healthcare resources should be reviewed regularly according to the percentage of COVID-19 patients hospitalized and the hospital capacity.

During the COVID-19 pandemic, there was a potential high risk of acquiring the of SARS-CoV-2 infection in the perioperative period among patients who underwent surgery. Moreover, postoperative pulmonary complications, which are associated with a high mortality rate, could occur in half of the patients with perioperative SARS-CoV-2 infection.[9] Therefore, it is extremely necessary to balance individually the increased risk associated with SARS-CoV-2 infection during the postoperative period and the risk of delaying surgery in patients with colorectal cancer.

The aim of the present study is to analyze the outcomes of oncologic colorectal surgery during the COVID-19 pandemic in patients with and without perioperative SARS-CoV-2 infection.

Material and Methods

The present is an observational, retrospective and unicentric study performed at the Unit of Colorectal Surgery, General and Digestive Surgery Department, Hospital Universitario 12 de Octubre,in Madrid, the city in Spain most seriously affected by the SARS-CoV-2 infection. In total, 32 patients with colorectal cancer who had undergone surgery from March 14, 2020 to May 25, 2020, the period of transition from Phase 0 the State of Alarm in Madrid, were included. We described the surgical outcomes of colorectal cancer surgery during the pandemic, and compared the results obtained from confirmed COVID-19 patients (included in COVID-19 group) with the outcomes from the non-COVID-19 group.

A protocol to manage surgical patients during the COVID-19 pandemic was elaborated and implemented in our hospital by a multidisciplinary team according to the recommendations of national and international societies.[10] Thus, since April 28, 2020, when the protocol was approved, every patient undergoing surgery has been tested preoperatively for COVID-19 using epidemiological surveys 7 days before surgery, and viral RNA detection by quantitative real-time polymerase chain reaction (RT-PCR) on samples from nasal swabs 72 hours before surgery. In case of clinical suspicion and negative samples, the performance of chest radiographs or computed tomography (CT) scans were recommended. If a patient was diagnosed preoperatively with COVID-19 by clinical, microbiological or radiological findings, the COVID-19 multidisciplinary committee and the board of surgical planning decided case by case if the the elective surgery should be postponed. The surgical team was properly trained to use personal protection equipment (PPE).

The patients were considered positive for COVID-19 if they had SARS-CoV-2 infection confirmed by clinical, laboratory (positive RT-PCR for SARS-CoV-2 nucleic acid in the nasal swab), and/or radiological findings (chest radiograph or CT scan) within 7 days before or 30 days after surgery.

Data collection included: patient features (gender, age, comorbidities, body mass index [BMI], American Society of Anesthesiologists [ASA] score, tumor location, preoperative staging, neoadjuvant chemoradiotherapy); laboratory findings (white-blood-cell count, lymphopenia, hemoglobin, and level of carcinoembryonic antigen); details regarding the surgical procedure (elective versus emergency surgery, open versus laparoscopic approach, type of surgical intervention, stoma creation, operative time); pathological outcomes (pathological tumor stage, number of lymph nodes harvested, positive distal and circumferential margins, quality of the total mesorectal excision); surgical outcomes (morbidity rate, grade of complication according to the Clavien-Dindo classification,[11] mortality rate, hospital stay, and rates of reoperation and readmission); and data related to the SARS-CoV-2 infection (preoperative and postoperative symptoms, RT-PCR and radiological findings, cross-infection between patients and staff).

In the statistical analysis, the quantitative data were reported as means (with their respective ranges), and the qualitative data were reported as the number (and percentage) of patients. The Shapiro-Wilk test was used to check for data with normal distribution. The dichotomous and categorical variables were analyzed using the Chi-squared (χ^2) or Fisher exact tests, as appropriate. The continuous variables were compared using the independent Student t-test for normally-distributed data, and the Mann-Whitney test for

non-normally-distributed data. All variables that were significant in the univariate analyses and those considered clinically relevant were inserted in a multivariate stepwise regression model to determine which variables were independent risk factors with statistical significance. Values of $p < 0.05$ were considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics IBM Corp., Armonk, NY, US) software, version 23.0.

Results

Patient Characteristics and Details Regarding the Surgical Procedure

A total of 32 patients (19 male and 13 female patients) with colorectal cancer underwent surgery during the COVID-19 pandemic. Overall, seven patients with colorectal cancer, who were not included in the present study, were transferred to a private hospital to undergo surgery, because of the collapse of our hospital. At this moment our hospital had more than 80% of its beds occupied by COVID-19 patients. Covid-19 was diagnosed in 3 (9.4%) patients during the

postoperative period. Patient features and laboratory findings are presented in ►Table 1.

Covid-19 was associated with chronic obstructive pulmonary disease (COPD) (33.3% versus 6.2%; $p = 0.042$).

A total of 10 patients with locally-advanced rectal cancer were treated with neoadjuvant therapy followed by delayed surgery, 6 (60%) of them with short-course radiotherapy (25 Gy in fractions of 5 Gy), and 4 (40%) with long-course radiotherapy (50.4 Gy to 54 Gy in fractions of 1.8 Gy) combined with concurrent chemotherapy. These patients underwent delayed surgery 8 weeks (range: 6.7 to 9.2 weeks) after the end of the neoadjuvant therapy.

The details regarding the surgical procedure are shown in ►Table 2. Most patients underwent elective surgery, and only one patient underwent emergency surgery due to an intestinal obstruction secondary to rectal cancer.

Data Related to SARS-CoV-2 Infection

In total, 3 (9.4%) patients acquired COVID-19 in the postoperative period, and 2 of them had dyspnea and 1 had fever as the first symptom. All COVID-19 patients developed bilateral pneumonia confirmed by chest CT scan, but none of them

Table 1 Characteristics of the study sample

	Total (n = 32)	Covid-19 group (n = 3)	Non-Covid-19 group (n = 29)	p
Age (years)	64(57.2–69.5)	77 (57–80)	64(56–67.5)	0.157
Male gender	19 (59.4%)	2 (66.7%)	17 (58.6%)	0.787
Female gender	13 (40.6%)	1 (33.3%)	12 (41.4%)	
Comorbidities				
Hypertension	15 (46.9%)	1 (33.3%)	14 (48.3%)	0.621
Diabetes mellitus	10 (33.2%)	1 (33.3%)	9 (31%)	0.935
Chronic obstructive pulmonary disease	2 (6.2%)	1 (33.3%)	1 (3.4%)	**0.042***
Obesity (body mass index > 30 kg/m^2)	7 (21.9%)	0	7 (24.1%)	0.336
ASA III-IV	17 (53.1%)	1 (33.3%)	16 (55.2%)	0.471
Tumor location				0.765
Right colon	4 (12.5%)	1 (33.3%)	3 (10.3%)	
Transverse colon	3 (9.4%)	0	3 (10.3%)	
Sigmoid colon	8 (25%)	1 (33.3%)	7 (24.1%)	
Rectum	16 (50%)	1 (33.3%)	15 (51.7%)	
Ileum	1 (3.1%)	0	1 (3.4%)	
Tumor stage III-IV	7 (21.8%)	0	7 (24.1%)	0.888
Laboratory findings				
Lymphopenia (< 1.200 cells/ml)	9 (28.1%)	1 (33.3%)	8 (27.6%)	0.833
White blood cells (l/mL)	6.5 (5.1–8.7)	7.1 (6.7–7.7)	6.3 (5.1–9.4)	0.680
Lymphocites (l/mL)	1.4 (0.9–2.1)	1.3 (0.6–2.4)	1.5 (0.9–2.1)	0.758
Hemoglobin (g/dl)	14.1 (11.9–14.6)	14 (11.9–15.3)	14.7 (11.5–14.6)	0.696
Carcinoembryogenic antigen (ng/ml)	2.9 (1.8–4.7)	3.2 (1.6–4.8)	2.9 (1.8–4.8)	0.726
Neoadjuvant therapy	10 (62.5%)	0	10 (34.5%)	0.451

Note: *Statistically significant difference.

Table 2 Details regarding the surgical procedure

	Total (n = 32)	Covid-19 group (n = 3)	Non-Covid-19 group (n = 29)	P
Surgical procedure				0.195
Right-sided hemicolectomy	3 (9.4%)	0	3 (10.3%)	
Extended right hemicolectomy	3 (9.4%)	0	3 (10.3%)	
Sigmoidectomy	8 (25%)	1 (33.3%)	7 (24.1%)	
Low anterior resection	7 (21.9%)	0	7 (24.1%)	
Abdominoperineal excision	3 (9.4%)	0	3 (10.3%)	
Hartmann procedure	1 (3.1%)	1 (33.3%)	0	
Transanal minimally-invasive surgery	4 (12.5%)	0	4 (13.8%)	
Colostomy	2 (6.2%)	1 (33.3%)	1 (3.4%)	
Closure of Ileostomy	3 (9.4%)	0	1 (3.4%)	
Laparoscopic approach	20 (62.5%)	1 (33.3%)	19(65.5%)	0.540
Stoma creation	9 (28.1%)	1 (33.3%)	2 (6.9%)	0.833
Operative time (minutes)	180 (120–207)	180 (150–180)	180 (120–215)	0.973

required admission to the intensive care unit (ICU) or invasive mechanical ventilation. In every patient confirmed with COVID-19, the preoperative SARS-CoV-2 detection by RT-PCR on samples of the respiratory tract was negative. However, the postoperative RT-PCRs were positive for two of them, and one Covid-19 patient with negative postoperative RT-PCR was diagnosed by the findings on a postoperative CT scan.

Before surgery, 24 (75%) patients underwent viral RNA detection by RT-PCR to rule out SARS-CoV-2 infection.

During the postoperative period, 11 patients underwent RT-PCR and chest radiography because 8 of them presented symptoms of Covid-19 (5 had fever and 3 had dyspnea). And 3 patients had come into close contact with patients with confirmed Covid-19 in the hospital, but none of them were diagnosed with infection by SARS-CoV-2. Fever (33.3% versus 13.8%; $p = 0.001$) and dyspnea (66.6% versus 3.4%, $p = 0.001$) after colorectal cancer surgery were statistically associated with Covid-19 in the postoperative period.

Pathological and Surgical Outcomes

The pathological and surgical outcomes were described in ►**Table 3**. The morbidity rate was of 43.8%, and it was higher among Covid-19 patients (100% versus 37.9%; $p = 0.039$). In the Covid-19 group, the postoperative complications were: ileus, anastomotic leak, and hematoma; and, in the non-Covid-19 group, the complications were: 2 cases of wound infections, 2 cardiovascular events, 1 case of renal failure, 5 anastomotic leaks, and 2 hematomas.

One patient with postoperative SARS-CoV-2 infection was readmitted because of intestinal occlusion, and four patients from the non-Covid group were readmitted because of pros-

tatic abscess, hematoma, anastomotic leak and surgical-site infection. Two patients without SARS-CoV-2 infection were reoperated due to anastomotic leak. No deaths occurred.

In the multiple logistic regression analyses, no independent association was found between Covid-19 after colorectal cancer surgery and COPD (odds ratio [OR] = 14; 95% confidence interval [95%CI]: 0.618–31.737; $p = 0.097$), age >70 years (OR = 7.667; 95%CI: 0.519–9.482; $p = 0.119$), and lymphopenia (OR = 1.312; 95%CI: 0.104–16.556; $p = 0.883$).

Discussion

The results of the present study describe the effects of the spread of the Covid-19 pandemic regarding colorectal oncologic surgery; 32 patients with colorectal cancer underwent surgery, and 3 (9.4%) were diagnosed with SARS-CoV-2 infection postoperatively. None of them needed UCI care, but the morbidity rate was significantly higher among the Covid-19 group.

All health and safety measures included in the protocol to manage surgical patients during the pandemic were applied according to the recommendations of medical societies and associations.[12–18] Most of these recommendations are based on expert opinions, which should be continuously updated in order to adapt to the evolution of the pandemic. According to our results, 3 patients came into close contact with Covid-19 patients in the hospital during the postoperative period. They were tested for SARS-CoV-2 infection by detection of viral RNA by RT-PCR on samples from nasopharyngeal swabs and chest radiographs, and all of them resulted negative. The early detection of SARS-CoV-2 infection during the postoperative period is an

Table 3 Pathological and surgical outcomes

	Total (n = 32)	Covid-19 group (n = 3)	Non-Covid-19 group (n = 29)	P
Pathological outcomes				
pT3-4	11 (34.4%)	3 (100%)	9 (31%)	0.174
pN+	9 (28.1%)	1 (33.3%)	8 (27.6%)	0.841
Number of lymph nodes harvested	16.5 (15.7–23.5)	16 (8–21)	17 (16–25)	0.332
Positive distal margin	1 (3.1%)	0	1 (3.4%)	0.843
Positive circumferential radial margin	0	0	0	–
Total mesorectal excision (n = 16)	16	1 (33.3%)	14 (48.3%)	0.876
Surgical outcomes				
Morbidity rate	14 (43.8%)	3 (100%)	11 (37.9%)	**0.039**[*]
Clavien-Dindo classification > 3	2 (6.2%)	0	2 (6.9%)	0.639
Hospital stay (days)	8 (7–10.7)	14 (9–17)	8 (6.5–10)	0.256
Readmission rate	15.6%	1 (33.3%)	4 (13.8%)	0.410
Reoperation rate	6.2%	0	2 (6.9%)	0.639
Mortality rate	1 (3.1%)	0	1 (3.4%)	0.744

Note: [*]Statistically significant difference.

essential rule to identify, isolate and treat Covid-19 patients. Therefore, it is extremely necessary to include tests to rule out SARS-CoV-2 infection for every person who came into contact with confirmed Covid-19 patients in the hospital and for those who present symptoms.

Postoperative fever should be considered a main symptom of Covid-19, which requires that physicians rule out SARS-CoV-2 infection in these patients. Fever occurs at the onset of the illness in about 50% of the patients with Covid-19.[19] In the present study, 5 patients had postoperative fever, and one of them was diagnosed with Covid-19; therefore, postoperative fever is statistically associated with Covid-19 (33.3% versus 13.8%; $p = 0.001$). Other symptoms such as dyspnea, fatigue, myalgia, dry cough, anorexia, diarrhea and smell or taste disorders should be considered suggestive of postoperative SARS-CoV-2 infection.[20]

Lymphopenia is a particular laboratory feature of Covid-19, and it has been associated with severe cases of the disease.[19,21] However, we did not find any significant relationship between lymphopenia and SARS-CoV-2 infection in patients who underwent colorectal surgery. This result could be explained because inmunosupression is associated with cancer patients, and lymphopenia could be present in patients with and without Covid-19 who underwent colorectal cancer surgery. Other laboratory findings like hiperleukocytemia and increased levels of D-dimer, reactive C protein (RCP), procalcitonine Q15 and lactate dehydrogenase (LDH) are frequently observed in cases of Covid-19, and during the postoperative period. Therefore, the positive predictive value of these laboratory findings for the diagnosis of Covid-19 could decrease in series including surgical patients.

We have already mentioned that COPD was associated with postoperative SARS-CoV-2 infection (33.3% versus 6.2%; $p = 0.042$) among patients who underwent colorectal cancer surgery. Thus, physicians should be alert and highly suspicious if patients with COPD during the postoperative period show any signs or symptoms of Covid-19. Higher rates of mortality and admission to the ICU have been described among Covid-19 patients with COPD who underwent surgery.[9,22,23]

The present series reported a global morbidity rate of 43.8% during the Covid-19 crisis, higher in Covid-19 patients with a significant association (37.9% versus 100%; $p = 0.0339$). However, we did not find significant differences between the groups with or without Covid-19 in relation to the Clavien-Dindo classification of surgical complications and the rate of admission to the ICU. One of the first studies[23] on Covid-19 from Wuhan, China, included 34 surgical patients with SARS-CoV-2 infection, and described a mortality rate of 20.5% and rate of admission to the ICU of 44.1%, which was higher among patients with comorbidities and those who underwent more difficult surgeries. An international multicentre cohort study[9] including 1,128 surgical patients with perioperative SARS-CoV-2 infection during pandemic reported a similar mortality rate (23.8%), and pulmonary complications occurred in 51.2% of the patients. The high mortality rate among surgical patients with perioperative Covid-19 should make surgeons balance the risks and benefits of elective surgeries for Covid-19 patients

during the pandemic. In cases of colorectal cancer, we should weigh the risk of a higher morbidity rate the pandemic against the benefits of not delaying elective cancer surgery.

It is difficult to quantify the impact of delaying colorectal cancer surgery on the prognosis of oncological patients. Sud et al.[8] developed a complex model based on reported surgical outcomes to quantify the impact on survival of delayed cancer treatment, and they estimated that a six-month delay could reduce between 2.1% and 28.8% of the the 5-year survival of colorectal cancer patients. This reduction could be higher among patients with advanced tumurs and younger patients.

Although the rate of surgeries performed by our colorectal surgery unit decreased, we tried to follow the recommendations of the European Society for Medical Oncology (ESMO) to not postpone surgical treatment for colorectal cancer for more than six weeks.[15] Thus, oncological surgical interventions were prioritized, non-oncological surgeries were delayed, and we transferred seven patients to a private hospital to undergo surgery during the worst week of the pandemic. When the pressure on hospital resources was extremely high because there were too many Covid-19 patients hospitalized and the capacity of the ICU and ventilators was limited, surgical societies recommended redistributing hospital resources and introducing challenges on elective surgery.[24,25] Under these extreme circumstances, the priorities for colorectal cancer surgical treatment include cases of: nearly obstructed colon and rectal cancer, cancers with high transfusion requirements, cancers with evidence of local perforation and sepsis, and rectal cancer after neo-adjuvant chemoradiation with no response to therapy. Cases of malignant polyps, prophylactic indications for hereditary conditions, and large benign asymtomatic polyps could be postponed until a decrease in the severity of the Covid-19 crisis. All decisions should be supported by Covid-19 multi-disciplinary and ethics committees.[26] Another adequate option to lower the pressure for health care when the situation is critical is the transfer of patients in need of colorectal cancer surgery to a hospital with capacity, as we did. The collaboration between different (public or private) hospitals within the national health care system has been essential in the fight against the Covid-19 pandemic in Madrid. The establishment of instant messaging groups linking different hospitals enabled the quick identification of the regional availability of beds to facilitate the rapid patient transfer.[24,25]

In the present series, on average surgery was performed 8 weeks (range: 6.7 to 9.2 weeks) after the end of the neoadjuvant therapy for locally advanced rectal cancer (LARC). The ESMO does not recommend delaying surgery after neoadjuvant therapy for LARC, except in extreme circumstances, and postponement should only be considered in patients who respond to the therapy, adding another cycle of the neoadjuvant therapy.[15] However, Ren et al.[27] stated that the surgery could be delayed for 16 to 24 weeks after the neoadjuvant treatment during the

Covid-19 pandemic based on the results of the GRECCAR-6 randomized trial,[28] which showed that a delay of up to 11 weeks from the end of the neoadjuvant therapy to surgery did not have any consequence in the three-year overall survival and disease-free survival, but it was associated with a significant increase in the rate of postoperative morbidity.

In cases of LARC during the pandemic, short-course radiotherapy (SCRT) is preferred instead of long-course radiotherapy (LCRT), because it could decrease the risk of acquiring SASR-CoV-2 infection and provides quality oncological care for the patients. The Stockholm III trial[29] did not find differences in locoregional recurrence, distant metastasis and overall survival among ptients who underwent SCRT with immediate surgery, SCRT with delayed surgery, and LCRT with delayed surgery. In the present series, in which these recommendations were follwed, 60% of the patients with LARC underwent SCRT followed delayed surgery during the pandemic. This percentage was higher than before the pandemic, when SCRT was reserved for older and fragile patients.

During the pandemic, 62.5% of the colorectal cancer surgeries were performed by laparoscopy at our unit. Before the pandemic, this percentage was higher. We performed laparoscopy and transanal minimally-invasive surgery (TAMIS) for colorectal cancer following the recommendations regarding the advantages for patients of minimally-invasive procedures during the pandemic. The laparoscopic approach for colorectal cancer patients is especially important during the pandemic because it would diminish the hospital stay, reduce the risk of acquiring SARS-CoV-2 infection, and quickly free hospital beds for Covid-19 patients.

Laparoscopy in confirmed Covid-19 patients may include aerosolization of SARS-CoV-2 favored positive intra-abdominal pressure during pneumoperitoneum, but there is not strong evidence suggesting transmission of viral diseases through surgical smoke during laparoscopy.[30] Protective measures have been recommended by surgical societies to avoid the accidental exposure of health professionals to toxic aerosol during laparoscopic surgery. These safety measures include: the use of appropriate PPE by the surgical team, the reduction, as much as possible, in the number of trocars used, the use of self-sealing trocars, the performance of port incisions as small as practicable to reduce leakage around the ports, the use of a safe surgical smoke evacuation system and high-efficiency particulate air (HEPA) filter, the lowest possible pneumoperitoneum pressure settings to maintain an adequate working space for surgery, the use of cautery settings at their minimum voltages, evacuation all gases for safety before extracting specimens.[31–34]

The main limitations of the present study are the fact that it is unicentric, the small sample, and the low percentage of Covid-19 patients operated, which could create biases regarding our conclusions.

Conclusion

Colorectal cancer surgery should be performed during the Covid-19 pandemic under safe conditions and according to the recommendations of surgical societies. However, the rate of morbidity was higher among patients with confirmed Covid-19 who underwent surgery for colorectal cancer.

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Ethical Approval

Ethical approval is not required due to retrospective character of the study.

Conflict of Interests

The authors have no conflict of interests to declare.

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