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ORIGINAL RESEARCH

COPD is a clear risk factor for increased use of resources and adverse outcomes in patients undergoing intervention for colorectal cancer: a nationwide study in Spain

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Background: We hypothesized that patients undergoing surgery for colorectal cancer (CRC) with COPD as a comorbidity would consume more resources and have worse in-hospital outcomes than similar patients without COPD. Therefore, we compared different aspects of the care process and short-term outcomes in patients undergoing surgery for CRC, with and without COPD.

Methods: This was a prospective study and it included patients from 22 hospitals located in Spain – 472 patients with COPD and 2,276 patients without COPD undergoing surgery for CRC. Clinical variables, postintervention intensive care unit (ICU) admission, use of invasive mechanical ventilation, and postintervention antibiotic treatment or blood transfusion were compared between the two groups. The reintervention rate, presence and type of complications, length of stay, and in-hospital mortality were also estimated. Hazard ratio (HR) for hospital mortality was estimated by Cox regression models.

Results: COPD was associated with higher rates of in-hospital complications, ICU admission, antibiotic treatment, reinterventions, and mortality. Moreover, after adjusting for other factors, COPD remained clearly associated with higher and earlier in-hospital mortality.

Conclusion: To reduce in-hospital morbidity and mortality in patients undergoing surgery for CRC and with COPD as a comorbidity, several aspects of perioperative management should be optimized and attention should be given to the usual comorbidities in these patients.

Keywords: COPD, colorectal cancer, in-hospital mortality, reintervention, complications

Introduction

Colorectal cancer (CRC), one of the most common cancers in developed countries, has a 5-year survival rate of about 60%.[1–3] Most patients are diagnosed at a relatively advanced age, when chronic comorbidities are often present. COPD is prevalent and commonly associated with other diseases.[4,5]

Surgery is essential in many cases of CRC and is associated with considerable mortality (up to 11% at 30 days) and a high rate of complications.[6,7] Many factors are associated with outcomes after different types of surgery, and COPD has been associated with increased short-term mortality. However, few studies of postoperative outcomes in patients with COPD focus on patients with CRC or on postoperative outcomes other than mortality, such as reintervention, complications, or length of stay (LOS).[8] Recently, Platon et al[9] found COPD was a strong predictor of intensive care unit (ICU) admission and 30-day mortality after CRC surgery.[9]

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Poorer outcomes after surgery in patients with COPD are related to respiratory failure or other postoperative complications, which can lead to higher short-term mortality. In patients undergoing abdominal surgery, the most common short-term complications include not only infection or other complications involving the site of surgery but also organ failure, including respiratory failure or ventilator problems. In patients with COPD, respiratory complications are probably even more common, adding complexity to immediate postoperative management and increasing the likelihood of worse outcomes.

Despite the prevalence and importance of COPD, few studies have analyzed the overall impact of COPD on postoperative (in-hospital) outcomes or on the use of resources in oncologic surgery in general or CRC surgery in particular. We hypothesized that patients undergoing surgery for CRC with COPD as a comorbidity would consume more resources and have worse in-hospital outcomes than similar patients without COPD. To test this hypothesis, we compared some aspects of the care process and short-term outcomes in two cohorts of patients (with and without COPD) undergoing surgery for CRC in diverse hospitals in Spain.

Methods

Design and patients

This prospective multicenter cohort study of patients from 22 hospitals located in nine regions of Spain was done in the framework of the REDISSEC-CARESS/CCR (Results and Health Services Research in Colorectal Cancer) study, which addressed diverse research objectives in hospitals treating CRC in Spain for the national health system.[10] The hospitals' size and technological resources varied widely. The Clinical Research Ethics Committees of the Parc Taulí Sabadell-University Hospital; Hospital del Mar; Fundació Unio Catalana d'Hospitals; Gipuzkoa Health Area; Basque Country; Hospital Galdakao-Usansolo; Hospital Txagorritxu; La Paz University Hospital; Fundación Alcorcón University Hospital; Hospital Universitario Clínico San Carlos (formerly Clinical Research Ethics Committee of Area 7 – Hospital Clínico San Carlos); and the Regional Clinical Research Ethics Committee of Andalusia approved the study. All patients provided written informed consent.

We included patients undergoing scheduled or urgent surgery for primary invasive CRC in the period from June 2010 through December 2012, whether the goal of surgery was to excise the tumor or to palliate symptoms.

The REDISSEC-CARESS/CCR study excluded patients with only cancer in situ, those with relapsed tumors, those with cancer not located in the colon or rectum, those who died before surgery, those with inoperable cancer, and those transferred for surgery in another center.

Variables and data collection

Appropriately trained reviewers used a structured questionnaire and a manual to collect data from clinical records and interviews with surgeons about the following clinical variables: age, categorized as <80 years or ≥ 80 years; sex; smoking habit; chronic alcoholism; body mass index (BMI), calculated from the weight and height recorded in the clinical history, with BMI <18.5 considered low, 18.5–25 normal, and BMI >25 overweight/obese; baseline comorbidities included in the Charlson Index, with Charlson scores classified in three categories (0, 1–2, ≥ 3); tumor location (colon or rectum); American Society of Anesthesiologists (ASA) score (I–IV); urgency of the intervention; type of surgery (laparoscopic or open); and staging according to the AJCC.[11]

COPD (eg, emphysema and chronic bronchitis) was considered present when the diagnosis was mentioned in patients' clinical charts. Asthma or other acute or chronic inflammatory diseases of the airways resulting in bronchospasm alone were not considered COPD. Likewise, diffuse interstitial fibrosis or sarcoidosis was not considered COPD.

We recorded the following process variables: postintervention ICU admission, use of invasive mechanical ventilation, and postintervention antibiotic treatment or blood transfusion.

Outcome variables were reintervention, major complications during the intervention, complications during the hospital stay (as described in Quintana et al[10]), and the LOS after the intervention grouped into four ranges (1–7 days, 8–15 days, 16–30 days, >30 days). For the purposes of this study, complications were classified by severity into three mutually exclusive categories (none, minor, major) according to the clinical judgment of the surgeons participating in the study, with major complications classified by type (infectious, hemorrhagic, surgical, vascular, or medical). In-hospital mortality was defined as any death occurring before discharge from hospital, independently of the duration of the hospital LOS.

Data analyses

A descriptive analysis of all variables was carried out. To compare patients with COPD versus those without COPD, we used chi-square tests or Fisher's exact test for categorical variables. For process and outcome variables, we also estimated crude odds ratios (OR) with 95% confidence

intervals (CI). We used logistic regression techniques, incorporating statistically or clinically significant variables in the bivariate analysis to estimate the adjusted risk of death during the hospital stay. To adjust for comorbidities, we took the Charlson scores into account. Thus, in addition to the variable COPD, the final regression model included the other significant variables that enabled the maximum discriminatory capacity of the model estimated by the area under the receiver operating characteristic curve with good calibration according to the Hosmer–Lemeshow test.

To estimate the probability of in-hospital death in function of the presence of COPD, we used Kaplan–Meier survival analysis, in which discharge was considered a censoring event. We compared the survival curves of patients with COPD versus those without COPD by log-rank test. We used Cox regression models to estimate the hazard ratio (HR) for hospital mortality, adjusted for the same factors or variables as in the logistic regression model.

We defined statistical significance as $P<0.05$, and we used IBM Statistical Package for the Social Sciences (SPSS) Statistics 23 and R statistical package 2.15.3 for the analyses.

Results

We analyzed a total of 2,748 patients with CRC (mean age, 68 years); of these, 472 (17.2%) had COPD. Table 1 compares the sociodemographic and clinical variables in patients with COPD versus those without COPD. The COPD group had higher proportions of men (80.5% vs 60.1%, $P<0.001$), patients aged ≥80 years (25.8% vs 14.7%, $P<0.001$), patients with chronic alcoholism (22.1% vs 11%, $P<0.001$), and patients with smoking habit (18.6% vs 12.2%, $P<0.001$). Moreover, Charlson scores were higher in patients with COPD because comorbidities were more common. Specifically, the following comorbidities were more common in patients with COPD than in those without COPD: heart failure (20% vs 7.6%, $P<0.001$), diabetes (26% vs 18%, $P<0.001$), peripheral vascular disease (10.9% vs 4%, $P<0.001$), peptic ulcers (11.4% vs 4.8%, $P<0.001$), and primary malignant tumors other than CRC (11.3% vs 6.7%, $P<0.001$). The most common comorbidities in patients with COPD were diabetes mellitus (25.8%), moderate to severe heart failure (20.3%), peptic ulcer (11.5%), malignant primary tumors other than CRC (11.3%), and peripheral vascular disease (10.9%).

No differences were observed between patients with COPD and those without COPD in the urgency of the intervention, CRC location, or CRC stage. Laparoscopic surgery

Table 1 Sociodemographic and clinical variables in patients with COPD versus in those without, 2010–2012

Variable	COPD				*P*-value
	No (N=2,276)		Yes (N=472)		
	n	%	n	%	
Sex					<0.001
Male	1,368	60.1	380	80.5	
Female	908	39.9	92	19.5	
Age (years)					<0.001
<80	1,937	85.3	350	74.2	
≥80	335	14.7	122	25.8	
Chronic alcoholism					<0.001
No	1,915	89.0	352	77.9	
Yes	237	11.0	100	22.1	
Smoking habit					<0.001
No	1,980	87.8	376	81.4	
Yes	275	12.2	86	18.6	
BMI (kg/m^2)					0.846
Low	12	0.7	3	0.8	
Normal	522	30.1	108	28.6	
Overweight/obesity	1,202	69.2	266	70.6	
Comorbidities					
Charlson Index					<0.001
0	1,913	84.1	322	68.7	
1–2	299	13.1	124	26.4	
≥3	64	2.8	23	4.9	
Ischemic heart disease					0.004
No	2,166	95.3	431	92.1	
Yes	106	4.7	37	7.9	
Heart failure (moderate/severe)					<0.001
No	2,104	92.4	376	79.7	
Yes	172	7.6	96	20.3	
Peripheral vascular disease					<0.001
No	2,186	96.0	418	89.1	
Yes	90	4.0	51	10.9	
Cerebrovascular disease					0.299
No	2,175	95.6	443	94.5	
Yes	101	4.4	26	5.5	
Dementia					0.301
No	2,258	99.2	463	98.7	
Yes	18	0.8	6	1.3	
Peptic ulcer					<0.001
No	2,165	95.2	415	88.5	
Yes	110	4.8	54	11.5	
Connective tissue disease					1.000
No	2,267	99.6	467	99.6	
Yes	9	0.4	2	0.4	
Liver disease					<0.001
No	2,226	97.8	443	94.5	
Yes	50	2.2	26	5.5	
Diabetes					<0.001
No	1,866	82.0	348	74.2	
Yes	410	18.0	121	25.8	
Renal failure (moderate/severe)					0.079
No	2,225	97.8	452	96.4	
Yes	51	2.2	17	3.6	

(*Continued*)

Table 1 (*Continued*)

Variable	COPD				*P*-value
	No (N=2,276)		Yes (N=472)		
	n	%	n	%	
Hemiplegia					0.305
No	2,265	99.5	465	99.1	
Yes	11	0.5	4	0.9	
Leukemia, lymphoma, or any other tumor (past 5 years)					0.001
No	2,124	93.3	416	88.7	
Yes	152	6.7	53	11.3	
Metastatic solid tumor (different from colorectal cancer)					0.238
No	2,256	99.1	468	99.8	
Yes	20	0.9	1	0.2	
AIDS					–
No	2,276	100.0	469	100.0	
Yes	0	0.0	0	0.0	
ASA score					<0.001
I–II	1,402	63.4	145	31.5	
III	751	34.0	269	58.5	
IV	59	2.7	46	10.0	
Tumor and intervention					
Location					0.554
Colon	1,633	71.7	345	73.1	
Rectum	643	28.3	127	26.9	
Stage					0.193
I	501	22.1	125	26.7	
II	798	35.2	156	33.3	
III	749	33.1	143	30.6	
IV	216	9.5	44	9.4	
Urgency of intervention					0.302
No	2,197	96.5	451	95.6	
Yes	79	3.5	21	4.4	
Type of surgery					0.001
Laparoscopic	1,342	59.6	237	50.9	
Open	910	40.4	229	49.1	

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

was less common in patients with COPD (50.9% vs 59.6%, $P<0.001$). A greater proportion of patients with COPD were classified under ASA III (58.5% vs 34%, $P<0.001$) and IV (10% vs 2.7%, $P<0.001$) risk categories.

Table 2 compares the process and outcome variables in patients with COPD versus those without COPD.

A greater proportion of patients with COPD developed complications during the hospital stay (62.5% in patients with COPD vs 47.5% in those without, $P<0.001$); likewise, a greater proportion of patients with COPD developed more severe complications (38.3% in patients with COPD vs 26.4% in those without, $P<0.001$). Major infectious, surgical, vascular, and medical complications were more common in patients with COPD. Table 3 reports the frequencies of specific major complications in patients with COPD

Table 2 Process and outcome variables in patients with COPD versus in those without, 2010–2012

Variable	COPD				*P*-value	OR (95% CI)
	No (N=2,276)		Yes (N=472)			
	n	%	n	%		
Complications						
Severity of complications					<0.001	
No	1,193	52.4	177	37.5		
Minor	481	21.1	114	24.2		1.597 (1.234–2.068)
Major	602	26.4	181	38.3		2.027 (1.611–2.549)
Infectious (major)					<0.001	
No	2,021	88.8	388	82.2		
Yes	255	11.2	84	17.8		1.716 (1.311–2.246)
Hemorrhagic (major)					0.286	
No	2,159	94.9	442	93.6		
Yes	117	5.1	30	6.4		1.252 (0.828–1.895)
Surgical (major)					<0.001	
No	2,004	88.0	380	80.5		
Yes	272	12.0	92	19.5		1.784 (1.375–2.315)
Vascular (major)					0.035	
No	2,166	95.2	438	92.8		
Yes	110	4.8	34	7.2		1.529 (1.027–2.276)
Medical (major)					<0.001	
No	2,141	94.1	409	86.7		
Yes	135	5.9	63	13.3		2.443 (1.779–3.355)
Use of resources						
Intensive care unit admission					<0.001	
No	1,743	76.6	325	68.9		
Yes	533	23.4	147	31.1		1.479 (1.190–1.839)
Invasive mechanical ventilation					0.027	
No	2,221	97.6	452	95.8		
Yes	55	2.4	20	4.2		1.787 (1.061–3.011)
In-hospital antibiotic treatment (postintervention)					0.001	
No	1,274	56.0	223	47.2		
Yes	1,002	44.0	249	52.8		1.420 (1.164–1.732)
Blood transfusion					0.444	
No	1,702	74.8	345	73.1		
Yes	574	25.2	127	26.9		1.092 (0.872–1.366)
Reintervention					0.010	
No	2,106	92.5	420	89.0		
Yes	170	7.5	52	11.0		1.534 (1.105–2.129)
Postintervention LOS (days)					<0.001	
1–7	1,104	48.5	164	34.7		
8–15	799	35.1	194	41.1		1.634 (1.303–2.051)
16–30	278	12.2	78	16.5		1.889 (1.399–2.549)
>30	93	4.1	36	7.6		2.606 (1.715–3.959)
In-hospital death					<0.001	
No	2,256	99.1	451	95.6		
Yes	20	0.9	21	4.4		5.252 (2.824–9.770)

Abbreviations: LOS, length of stay; OR, odds ratio; 95% CI, 95% confidence interval.

and in those without. The infectious complications that were more common in patients with COPD than in those without were pneumonia and other respiratory tract infections, intravenous catheter infections, and septic shock. The main surgical complications that were more common in patients

Table 3 Major complications in patients with COPD versus in those without COPD

Type of complication	COPD				*P*-value
	No (N=2,276)		Yes (N=472)		
	N	%Col	N	%Col	
Infectious					<0.001
No	2,021	88.8	388	82.2	
Yes	255	11.2	84	17.8	
Pneumonia					0.018
No	2,250	98.9	460	97.5	
Yes	26	1.1	12	2.5	
Catheter infection					0.006
No	2,235	98.2	454	96.2	
Yes	41	1.8	18	3.8	
Sepsis					0.158
No	2,266	99.6	467	98.9	
Yes	10	0.4	5	1.1	
Septic shock					0.030
No	2,224	97.7	453	96.0	
Yes	52	2.3	19	4.0	
Localized intra-abdominal infection (abscess)					0.341
No	2,204	96.8	453	96.0	
Yes	72	3.2	19	4.0	
Peritonitis					0.036
No	2,212	97.2	450	95.3	
Yes	64	2.8	22	4.7	
Deep surgical infection					0.705
No	2,211	97.1	457	96.8	
Yes	65	2.9	15	3.2	
Respiratory tract infection					0.001
No	2,266	99.6	462	97.9	
Yes	10	0.4	10	2.1	
Hemorrhagic complication					0.286
No	2,159	94.9	442	93.6	
Yes	117	5.1	30	6.4	
Bleeding wound					0.905
No	2,225	97.8	461	97.7	
Yes	51	2.2	11	2.3	
Internal bleeding of other organs					0.074
No	2,222	97.6	454	96.2	
Yes	54	2.4	18	3.8	
Hemoperitoneum					0.309
No	2,255	99.1	465	98.5	
Yes	21	0.9	7	1.5	
Surgical complication					<0.001
No	2,004	88.0	380	80.5	
Yes	272	12.0	92	19.5	
Wound leakage					0.007
No	2,214	97.3	448	94.9	
Yes	62	2.7	24	5.1	
Anastomotic leakage					0.022
No	2,193	96.4	444	94.1	
Yes	83	3.6	28	5.9	
Evisceration					0.003
No	2,250	98.9	458	97.0	
Yes	26	1.1	14	3.0	
Necrosis (abdominal wall)					0.390
No	2,269	99.7	469	99.4	
Yes	7	0.3	3	0.6	
Enterocutaneous fistula					0.110
No	2,249	98.8	462	97.9	
Yes	27	1.2	10	2.1	
Biliary fluid in peritoneum					0.530
No	2,273	99.9	471	99.8	
Yes	3	0.1	1	0.2	
Urological injuries					1.000
No	2,266	99.6	470	99.6	
Yes	10	0.4	2	0.4	
Vascular injuries					0.010
No	2,272	99.8	467	98.9	
Yes	4	0.2	5	1.1	
Neurological injuries					
No	2,276	100.0	472	100.0	
Yes	0	0.0	0	0.0	
Other organ laceration					0.099
No	2,246	98.7	461	97.7	
Yes	30	1.3	11	2.3	
Vascular					0.035
No	2,166	95.2	438	92.8	
Yes	110	4.8	34	7.2	
Transient ischemic attack					0.530
No	2,273	99.9	471	99.8	
Yes	3	0.1	1	0.2	
Pulmonary embolism					0.038
No	2,274	99.9	469	99.4	
Yes	2	0.1	3	0.6	
Angor or acute myocardial infarction					0.075
No	2,171	95.4	441	93.4	
Yes	105	4.6	31	6.6	
Medical complication					<0.001
No	2,141	94.1	409	86.7	
Yes	135	5.9	63	13.3	
Cardiac arrest					<0.001
No	2,273	99.9	465	98.5	
Yes	3	0.1	7	1.5	
Heart failure					0.016
No	2,244	98.6	458	97.0	
Yes	32	1.4	14	3.0	
Kidney failure					<0.001
No	2,224	97.7	447	94.7	
Yes	52	2.3	25	5.3	
Respiratory problems/failure					<0.001
No	2,215	97.3	438	92.8	
Yes	61	2.7	34	7.2	
Intestinal obstruction					0.166
No	2,254	99.0	464	98.3	
Yes	22	1.0	8	1.7	
Multiorgan failure					0.076
No	2,267	99.6	467	98.9	
Yes	9	0.4	5	1.1	

Abbreviation: %Col, column percentage.

with COPD than in those without were the dehiscence of the surgical wound or anastomosis, evisceration, and vascular damage. The main medical complications that were more common in patients with COPD than in those without were cardiac arrest, heart failure, respiratory failure, and renal failure; the risk of major medical complications was 78%–235% higher in patients with COPD (OR 2.443; 95% CI 1.779–3.355).

The greater incidence of complications in patients with COPD was also associated with greater consumption of resources during the hospital stay, longer LOS, and higher in-hospital mortality (Table 2). Greater proportions of patients with COPD were admitted to the ICU (31.1% vs 23.4%; OR 1.5), received invasive mechanical ventilation (4.2% vs 2.4%; OR 1.8), and received antibiotics after the intervention (53% vs 44%; OR 1.4). Moreover, a greater proportion of patients with COPD required reintervention (11% vs 7.5%; OR 1.5). However, no differences in hemorrhagic complications or blood transfusions were observed between the two groups.

The overall mean LOS after the intervention was 12.4±11.1 days (median 9, range 1–213). COPD was associated with longer LOS. Only 35% of the patients with COPD spent less than a week in hospital after the intervention compared to 48.5% of those without COPD. There was also a trend in the strength of the association between COPD and longer LOS, being especially strong for LOS >30 days (OR 2.606; 95% CI 1.715–3.959).

A total of 41 (1.5%) patients died in hospital. The risk of death was higher in patients with COPD (OR 5.252; 95% CI 2.824–9.770); after adjustment for the significant variables (age, sex, tumor location, ASA risk, and reintervention), the OR was 3.514 (95% CI 1.662–7.429) and the HR was 2.480 (95% CI 1.228–5.006).

The survival curves (Figure 1) show that death occurred earlier in patients with COPD than in those without (log-rank test 14.458; *P*=0.000). The most common causes of death in patients with COPD were septic shock and medical complications.

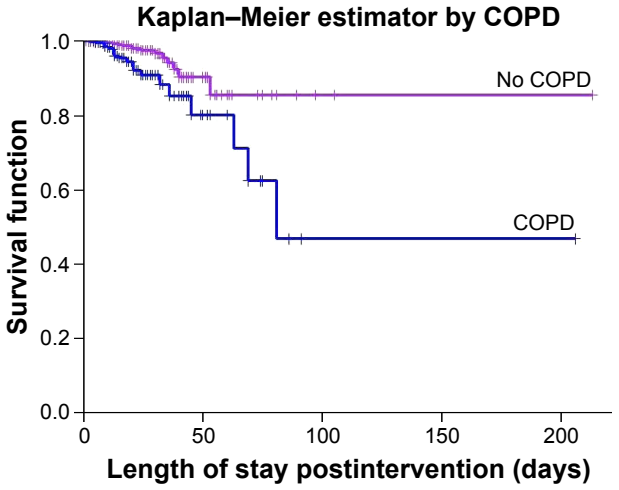

Figure 1 In-hospital survival function in patients with and without COPD.

Discussion

In this nationwide study of patients undergoing surgery for CRC, we found that COPD was associated with higher rates of postoperative complications, ICU admission, antibiotic treatment, reinterventions, and mortality during hospitalization. Moreover, after adjusting for other factors, COPD remained clearly associated with higher and earlier in-hospital mortality.

Previous nationwide studies in the USA found that even after adjusting for other clinical factors, COPD clearly increases postoperative morbidity and mortality (up to 30 days) and LOS in patients undergoing all types of surgery and in patients undergoing all types of abdominal surgery.[8,12] Our results show that these findings are also valid for the more specific group of patients undergoing surgery for CRC in a nationwide sample in Spain.

The prevalence of COPD in our cohort (17%) is similar to that reported in other settings, although differences in important factors make comparisons among studies difficult. A previous study in our setting reported 19% prevalence of COPD in patients undergoing surgery for rectal cancer;[13] however, the prevalence of COPD was lower in the aforementioned studies in more general surgical populations: 5% in Gupta et al's cohort and 3.8% in Fields and Divino's cohort. COPD is more common in cancer patients, in part, due to the history of smoking habit. In our study, COPD patients were identified concurrently with data collection. Despite the difficulties inherent in this design, it does not seem that the prevalence of COPD has been underestimated.

The only study published to date that focuses on COPD in CRC interventions reported 13% 30-day mortality in patients with COPD, about 70% higher than in those without COPD; these figures varied with different clinical variables.[9]

The in-hospital mortality rate in our study was low, but it was four times higher in patients with COPD than in those without, remaining significant after adjusting for sex, age, ASA risk, tumor location, and reintervention. Furthermore, patients with COPD died earlier after the intervention, underlining the importance of optimizing pulmonary function when

possible and maintaining closer postoperative surveillance in these patients.

The most common causes of death in patients with COPD are respiratory disease and cardiovascular disease.[14,15] As reported in other studies,[16–18] the prevalence of heart failure and respiratory insufficiency were higher in patients with COPD than in those without. This clinically important difference could explain the higher rates of ICU admission and invasive mechanical ventilation in COPD patients. On the other hand, our COPD patients also had a higher rate of infectious complications after surgery than patients without COPD, which explains, in part, their higher rate of postoperative antibiotic treatment. Among infectious complications, septic shock, pneumonia, and other respiratory tract infections were especially prevalent.

Interestingly, COPD patients in our study had higher rates of wound or anastomosis dehiscence, and even evisceration, partially explaining their higher rate of reintervention. Platon et al[9] reported similar findings. The higher rates of these surgical complications in patients with COPD are not surprising: coughing is both a frequent symptom of COPD and a common cause of wound dehiscence; many COPD patients receive oral glucocorticoids that delay wound healing; and many lack good nutritional status essential for wound healing.[19] All these factors explain the longer LOS in patients with COPD.

Conclusion

In conclusion, to reduce morbidity and mortality in patients with COPD undergoing surgery for CRC, several aspects of perioperative management are important: bronchodilator therapy, postoperative analgesia, and respiratory physiotherapy should be optimized and attention should be given to the usual comorbidities in these patients.

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Disclosure

The authors report no conflicts of interest in this work.

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