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The Impact of an Enhanced Recovery Protocol in a High-Risk Population Undergoing Colon Cancer Surgery

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Abstract

Objective: Enhanced Recovery ERP protocols (ERP) have improved surgical outcomes in patients undergoing elective colon cancer (CC) surgery; however, efficacy in different populations may vary. We examined the impact of an ERP in a population with high rates of obesity and multiple comorbidities.

Methods: We performed a retrospective analysis of factors associated with postoperative complications (PoC) and length of stay (LOS) following CC surgery from 2011 to 2019 in a 5-hospital healthcare system which serves a population with higher rates of obesity (body mass index ≥30kg/m^2) and multi-comorbidities, as compared to published studies. Univariable and multivariable analyses were performed.

Results: A total of 408 elective CC surgery patients with complete oncologic surgical data were identified. Of these, 191 (46.81%) were under ERP. Factors independently associated with PoC included obesity (OR=1.66, P=.029), laparoscopic (OR=.52, P=.020), and hybrid (OR=.38, P=.012) versus open surgery and ASA (American Society of Anesthesiologists) class ≥3 (OR=1.98, P=.006). ERP did not impact PoC but was associated with a reduction in LOS (β=−1.02 days, 95%CI: −1.75 – -.30, P=.006). ERP had an impact on LOS in both the non-obese and obese groups (P<.001 and P=.034, respectively). PoC significantly increased LOS (β=6.67 days, 95%CI: 5.41-7.03, P<.001).

Conclusions: Following elective CC surgery, obesity and medical comorbidities were associated with increased PoC and in turn, as expected, increased LOS. ERP was associated with a reduction in LOS in both obese and non-obese patients. In high-risk populations, application of ERP may be particularly important to optimize surgical outcomes following CC surgery.

Keywords

ERP, colon cancer, obesity, comorbidities, surgical outcomes

Key Takeaways

- Efficacy of ERP in high-obesity/comorbidity populations remains undefined.
- In our population, ERP was associated with a reduction in length of stay, but was not associated with any impact on perioperative morbidity
- Minimally invasive surgery was associated with a reduction in postoperative morbidity.

Introduction

Enhanced Recovery Protocols (ERP) have been shown to be effective in improving short term operative outcomes such as postoperative complication rates and length of stay in colorectal surgery.[1,2] ERP use standardized evidence–based peri- and postoperative strategies to improve clinical practice

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and reduce the physiologic stress associated with surgery.[2] Reductions in complication rates of up to 50% have been reported.[1] Notably, the postoperative components of ERP, including multimodal pain management, have been reported to be the most important in improving postoperative outcomes.[3,4] However, there are data that ERP are not equally effective in all patient populations.[5]

Obesity and patient comorbidities are factors that increase the risk of adverse postoperative events. In colorectal surgery, studies have shown increased rates of postoperative complication in obese patients.[6] Patients with more comorbidities, such as defined by the American Society of Anesthesiologist (ASA) physical status classification system, also have worse short term surgical outcomes. While ERP have been shown to be safe in the obese population, the efficacy of ERP in a population with high rates of obesity and medical comorbidities remains unclear.

The Mid-South area of the United States has high rates of both obesity and chronic medical conditions.[7] This area is also known to have poor colorectal cancer outcomes; for this paper, we chose to focus on patients with colon cancer. We examined the impact of an ERP on short term colon cancer surgical outcomes in a population with high rates of obesity and medical comorbidities. The primary outcomes of this study were postoperative complications (PoC) and length of stay (LOS).

Materials and Methods

Approval for this study was obtained from The University of Tennessee Health Science Center (UTHSC) Institutional Review Board. We performed a retrospective electronical medical record (EMR) chart review of patients receiving elective surgery for colon cancer in the Methodist LeBonheur Healthcare (MLH) System in Memphis, TN. This system consists of 5 hospitals, 4 of which provide care in medically underserved areas (as defined by the Health Resource & Services Administration, https://data.hrsa.gov) across 3 states (TN, MS, and AK). A list of all patients treated for colon cancer at MLH between 2011 and 2019 was obtained through the Commission on Cancer-compliant cancer registry. This specific study period was chosen due the fact that an ERP was introduced to MLH in 2014 (once available, it was optional for surgeons, and thus not mandatory); the years 2011-2013 were included to ensure a non-ERP cohort large enough for meaningful analysis, as most elective colorectal cancer surgery patients were on the ERP after 2014. The institutional ERP was modeled and implemented in concordance with the clinical practice guidelines available at the time. The key components included pre-operative patient counseling/nutritional optimization, peri- and postoperative fluid management, multimodal (non-narcotic) pain regimen, and early postoperative mobilization and enteral nutrition. Patients with pathologic stage I–III colon cancer, as identified by the cancer registry, who received elective colon cancer surgery were included in this study. Patients with rectal cancer were excluded from this analysis. Patients were also excluded if they had non-elective or unplanned surgeries, unknown pathologic stage, or unknown location of their colon cancer/type of surgery received.

Data Collection

Demographic, clinicopathologic, and outcome data were collected for all patients with pathologic stage I-III (non-metastatic) colon cancer. Race was categorized as "White," "Black," or "Other/Unknown" (which included "Hispanic," "Asian," and "Other"). Date of diagnosis and age at diagnosis were defined from the date that colon cancer was first identified by biopsy. Body Mass Index (BMI) was calculated from the patient's height (in cm) and weight (in kg) at time of primary hospital admission. Obesity was defined as BMI $\geq$30 kg/m^2. Insurance status was obtained from the EMR, where it is recorded in the patient face sheet. Medicare/Medicaid was defined as "public" insurance and any commercial insurance was defined as "private." ASA (American Society of Anesthesiologist) class was determined by review of anesthesia records, where it is documented as part of the pre-anesthesia evaluation note. Comorbidities were determined by chart review (specifically defined as hypertension, diabetes, hyperlipidemia, or other chronic systemic disease). Details of the surgery performed were derived from the operative report. Surgery was classified by approach (open, laparoscopic, or hybrid—which includes planned procedures with open and minimally invasive elements but not converted procedures) and by side (right vs. left; as defined by resection proximal or distal to the splenic flexure, respectively). PoC was identified by thorough chart review and graded by the Clavien-Dindo Classification (CDC) of surgical complications; furthermore, CDC 1-3 were considered mild/moderate complications and CDC 4-5 were considered severe complications. LOS was defined as days from admission to discharge during the primary hospital encounter.

Patients were classified as being on the ERP if chart review demonstrated that they had 1) an ERP preoperative counseling appointment and 2) standardized pre- and post-operative ERP order sets initiated. Per intention-to-treat analyses, patients remained in the ERP cohort even if there was evidence of deviation from the pathway during hospital course. The main elements of the specific ERP order set are detailed in Supplement 1. The use of multimodal pain management (defined as non-narcotic pain medication ordered in the immediate postoperative period) was the most accurately documented and reliably accessible ERP parameter in our EMR and was thus collected to estimate protocol compliance.

Statistical Analysis

Categorical variables were reported as counts with relative frequency, while continuous variables of age and LOS were reported as median with interquartile range (IQR). BMI was reported as mean with standard deviation (SD). Baseline univariable comparisons were performed by chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables (Student's t-test for BMI). A *P*-value was considered significant at level of $\alpha<.05$. PoC was treated as a categorical outcome variable and analyzed as both binary (yes/no) and ordinal (none/mild-moderate/severe). Variables with P<.2 by univariable analysis were entered into a multiple logistic regression model. Backwards elimination was used as a variable selection approach to arrive at the most parsimonious model. LOS was treated as a continuous outcome variable. Predictors with P<.2 by simple correlation analysis were placed into a multiple linear regression model, and the final model was attained by backwards elimination. Multivariable models were tested for interaction effects, and an interaction term was included in the model if found to be statistically significant. All analyses were performed using SAS 9.4® (SAS institute Inc., Cary, NC).

Results

Baseline Demographics

Four hundred and eight patients receiving elective surgery for non-metastatic colon cancer with complete surgical and oncologic data were identified. Of these, 191 (46.8%) were on an ERP protocol. Median age at diagnosis was 65 years (IQR 56-73.5), 51.7% (n = 211) of patients were white, 52.0% (n = 212) were male, 39.7% (n = 162) were obese, 51.2% (n = 209) had 2 or more comorbidities, while 56.9% (n=232) were classified as ASA class ≥3 (n=14 were ASA class 4, none were ASA class 5). The mean BMI in the non-obese cohort was 25.04 kg/m^2 (±3.18) and in the obese cohort was 36.04 kg/m^2 (±5.68). The majority had public (Medicare/Medicaid) insurance (58.87%, n = 239). The open approach was slightly more common (54.9%, n = 224). Overall, 29.4% (n=120) of patients experienced a PoC, a majority of which (100/120=83%) were mild or moderate (CDC 1–3). The median LOS was 5 days (IQR 4–7) (Table 1).

ERP vs. non-ERP

The ERP vs. non-ERP cohorts were analyzed to determine baseline comparability (Table 1). Type of surgery was found to be significantly different, with open approach being more common in the non-ERP cohort, and laparoscopic and hybrid approach being more common in the ERP cohort. Further analysis showed that by simple logistic regression, both laparoscopic and hybrid surgery were positively correlated with ERP status, which is expected given the ERP recommendation for use of minimally invasive techniques when possible.[8] Year of treatment was a significant positive predictor of ERP application (OR =2.18, 95%CI =1.90-2.49, P < .001), again as expected. ERP patients were significantly more likely to have multimodal pain management (P < .001), which is supportive of this variable as a reasonable indicator of overall ERP compliance.

Postoperative Complication

The results of the univariate analysis for the outcome of PoC are detailed in Table 2. ASA class≥3 was found to be associated with development of PoC. Occurrence of PoC was also predictive of 30-day readmission and longer LOS (both P < .0001). By multivariable analysis, factors found to be independently predictive of development of PoC include obesity, open (vs. laparoscopic or hybrid) surgery, and ASA class ≥3 (Table 3). ERP was not predictive of PoC. Further analysis of PoC as an ordinal variable showed that these same variables were significantly predictive of the development of mild to moderate grade PoC, while age was the only variable independently predictive of the development of severe grade complications (Table 3).

Subgroup multivariable analyses by type of operation (open/laparoscopic/hybrid; Table 4) showed that for open and hybrid surgery, there were no significant predictors of PoC, although in both groups ASA ≥3 trended towards significance (P<.1). For laparoscopic surgery, obesity was independently predictive of PoC (OR=4.23, P = .002). In all three subgroups, ERP was not associated with PoC (P>.1).

Subgroup analysis by obesity (Table 5) found no significant predictors of PoC in the obese group, while in the non-obese group, ASA class ≥3 increased the risk of PoC (OR=2.35, P=.0096). Laparoscopic (vs. open) surgery and hybrid (vs. open) surgery were both associated with decreased PoC (OR=.30 P = .004, OR=.35 P = .040, respectively).

Length of Stay

By simple correlation analysis, factors significantly correlated with increased LOS included male gender, public insurance status, non-white race, PoC, non-ERP, and higher ASA class. By simple linear regression, laparoscopic and hybrid surgeries were correlated with reduced LOS compared to open surgery (β=−1.42 days ±.49, P = .004 and β=−1.41 days ±.61, P = .020, respectively).

By multiple linear regression (Table 6), patients with PoC were found to have increased LOS (β=6.67 days, 95%CI= 5.41–7.93, P < .001) and being on ERP protocol was associated with decreased LOS (β= −1.02 days, 95%

Table 1. Basic Patient Demographics: overall and by ERP.

	Overall N(%)	Non-ERP	ERP	p	Non-obese	Obese	p
n	408	217	191		246 (60.29)	162 (39.71)	
Age at diagnosis (years, median, IQR)	65 (56–73.5)	65 (57–74)	65 (56–72)	.391	67 (58–75)	62 (54–69)	**<.001**
Gender							
Male	212 (51.96)	112 (51.61)	100 (52.36)	.881	132 (53.66)	80 (49.38)	.340
Female	196 (48.04)	105 (48.39)	91 (47.64)		114 (46.34)	82 (50.62)	
Race							
White	211 (51.72)	107 (49.31)	104 (54.45)	.051	137 (55.69)	74 (45.68)	**.050**
Black	185 (45.34)	107 (49.31)	78 (40.84)		100 (40.65)	85 (52.47)	
Other/Unknown	12 (2.94)	3 (1.38)	9 (4.71)		9 (3.66)	3 (1.85)	
BMI							
Underweight (≤18.5 kg/m^2)	12 (2.94)	7 (3.23)	5 (2.62)	.920	Mean BMI (SD)= 25.04 (3.18)	Mean BMI (SD)= 36.04 (5.68)	**<.001**
Normal weight (18.5–30 kg/m^2)	234 (57.35)	125 (57.60)	109 (57.07)				
Obese (30+ kg/m^2)	162 (39.71)	85 (39.17)	77 (40.31)				
Comorbidities							
None	81 (19.85)	45 (20.74)	36 (18.85)	.140	57 (23.17)	24 (14.81)	**.001**
1	118 (28.92)	70 (32.26)	48 (25.13)		78 (31.71)	40 (24.69)	
2	119 (29.17)	63 (29.03)	56 (29.32)		72 (29.27)	47 (29.01)	
3+	90 (22.06)	39 (17.97)	51 (26.70)		39 (15.85)	51 (31.48)	
ASA class							
<3	160 (39.22)	90 (41.47)	70 (36.65)	.319	113 (45.93)	47 (29.01)	**.001**
≥3	232 (56.86)	121 (55.76)	111 (58.12)		121 (49.19)	111 (68.52)	
unknown	16 (3.92)	6 (2.76)	10 (62.50)		12 (4.88)	4 (2.47)	
Insurance (n = 406)							
Public	239 (58.87)	128 (59.53)	111 (58.12)	.610	147 (60.00)	92 (57.14)	.243
Private	150 (36.95)	80 (37.21)	70 (36.65)		85 (34.69)	65 (40.37)	
Uninsured	17 (4.19)	7 (3.26)	10 (5.24)		13 (5.31)	4 (2.48)	
Tumor Location							
Cecal/Right/ Transverse	278 (68.14)	147 (67.74)	131 (68.59)	.855	175 (71.14)	103 (63.58)	.109
Left/Sigmoid	130 (31.86)	70 (32.26)	60 (31.41)		71 (28.86)	59 (36.42)	
Type of Surgery							
Open	224 (54.90)	152 (70.05)	72 (37.70)	**<.001**	133 (54.07)	91 (56.17)	.572
Laparoscopic	119 (29.17)	42 (19.35)	77 (40.31)		70 (28.46)	49 (30.25)	
Hybrid	65 (15.93)	23 (10.60)	42 (21.99)		43 (17.48)	22 (13.58)	

(Continued)

Table 1. Continued

	Overall N(%)	Non-ERP	ERP	p	Non-obese	Obese	p
Surgical Segment							
Right Colon	264 (64.71)	140 (64.52)	124 (64.92)	.932	164 (66.67)	100 (61.73)	.307
Left Colon	144 (35.29)	77 (35.48)	67 (35.08)		82 (33.33)	62 (38.27)	
Pathologic Stage							
I	153 (37.5)	76 (35.02)	77 (40.31)	.527	90 (36.59)	63 (38.89)	.756
II	114 (27.94)	62 (28.57)	52 (27.23)		72 (29.27)	42 (25.93)	
III	141 (34.56)	79 (36.41)	62 (32.46)		84 (34.15)	57 (35.19)	
ERP							
No	217 (53.19)		—	—	132 (53.66)	85 (52.47)	.814
Yes	191 (46.81)	—			114 (46.34)	77 (47.53)	
Postop Complications (binary)							
No	228 (70.59)	154 (70.97)	134 (70.16)	.858	185 (75.20)	103 (63.58)	**.012**
Yes	120 (29.41)	63 (29.03)	57 (29.84)		61 (24.80)	59 (35.42)	
Clavien Dindo Grade	(n=288)		28 (23.33)	.061			.684
I	46 (38.33)	18 (28.57)			25 (40.98)	21 (35.59)	
II	35 (29.17)	24 (38.10)	11 (19.30)		19 (31.15)	16 (27.12)	
III	19 (15.83)	8 (12.70)	11 (19.30)		7 (11.48)	12 (20.34)	
IV	17 (14.17)	11 (17.46)	6 (10.53)		9 (14.75)	8 (13.56)	
V	3 (2.5)	2 (3.17)	1 (1.75)		1 (1.64)	2 (3.39)	
Postop Complications (ordinal)							
None	288 (70.59)	154 (70.07)	134 (70.16)	.463	185 (75.20)	103 (63.58)	**.042**
Mild/moderate (grade 1-3)	100 (24.51)	50 (23.04)	50 (26.18)		51 (20.73)	49 (30.25)	
Severe (grade 4-5)	20 (4.9)	13 (5.99)	7 (3.66)		10 (4.07)	10 (6.17)	
Multimodal Pain Management (available immediately postop)							
No	137 (33.58)	129 (59.45)	8 (4.19)	**<.001**	87 (35.37)	50 (30.86)	.346
Yes	271 (66.42)	88 (40.55)	183 (95.81)		159 (64.63)	112 (69.14)	
Length of Stay (days, median, IQR) 30-day Readmission							
No	5 (4–7)	6 (5–7)	4 (3–6)	**<.001**	5 (4-7)	5 (4-7)	.458
	369 (90.44)	197 (90.78)	172 (90.05)	.802	224 (91.06)	145 (89.51)	.602
Yes	39 (9.56)	20 (9.22)	19 (9.95)		22 (8.94)	17 (10.49)	

CI= −1.75 – -.30, P = .006). Furthermore, several variables had significant interactions with PoC. In the presence of PoC, females were found to have decreased LOS compared to males (β= −3.81 days, 95%CI= −5.19 – -2.44, P < .001) and patients with private insurance had decreased LOS compared to patients with public insurance (β= −3.23 days, 95%CI= −4.70 – -1.76, P < .001). Patients with no insurance were also found to have decreased LOS compared to patients with public insurance (β= −3.34 days, 95%CI= −6.43 – -.25, P = .034).

Patients treated by open surgery experienced a reduction in LOS with ERP (β=−1.19 days, 95%

Table 2. Univariable analysis for outcome Postoperative Complication.

	No	Mild/Moderate (Clavien Dindo 1-3)	Severe(Clavien Dindo 4-5)	p
n	288	100	20	—
Age (years, median, IQR)	64.0 (56.0–73.0)	64.0 (56.5–73.0)	71.0 (65.0–76.5)	.0618
Gender				
Male	139 (48.26)	61 (61.00)	12 (60.00)	.0683
Female	149 (51.74)	39 (39.00)	8 (40.00)	
Race				
White	145 (50.35)	55 (55.00)	11 (55.00)	.8591
Black	134 (46.53)	43 (43.00)	8 (40.00)	
Other/Unknown	9 (3.13)	2 (2.00)	1 (5.00)	
BMI				
Underweight (≤18.5 kg/m^2)	9 (45.00)	10 (50.00)	1 (5.00)	.1015
Non-obese (18.5-30 kg/m^2)	175 (60.76)	103 (35.76)	10 (3.47)	
Obese (30+ kg/m^2)	50 (50.00)	49 (49.00)	1 (1.00)	
Comorbidities				
None	63 (21.88)	15 (15.00)	3 (15.00)	.0920
1	87 (30.21)	29 (29.00)	2 (10.00)	
2	84 (29.17)	28 (28.00)	7 (35.00)	
3+	54 (18.75)	28 (28.00)	8 (40.00)	
ASA class				
<3	127 (45.85)	29 (30.53)	4 (20.00)	**.0049**
≥3	150 (54.15)	66 (69.47)	16 (80.00)	
Insurance				
Public	162 (56.45)	61 (61.00)	16 (84.21)	.1279
Private	114 (39.72)	34 (34.00)	2 (10.53)	
Uninsured	11 (3.83)	5 (5.00)	1 (5.26)	
Type of Surgery				
Open	146 (50.69)	65 (65.00)	13 (65.00)	.1160
Laparoscopic	90 (31.25)	24 (24.00)	5 (25.00)	
Hybrid	52 (18.06)	11 (11.00)	2 (10.00)	
Pathologic Stage				
I	111 (38.54)	31 (31.00)	11 (55.00)	.1865
II	79 (27.43)	33 (33.00)	2 (10.00)	
III	98 (34.03)	36 (36.00)	7 (35.00)	
Tumor Location				
Cecal/Right/Transverse	200 (69.44	63 (63.00)	15 (75.00)	.3914
Left/Sigmoid	88 (30.56)	37 (37.00)	5 (25.00)	
Surgical Segment				
Right Colon	195 (67.71)	55 (55.00)	14 (70.00)	.0637
Left Colon	93 (32.29)	45 (45.00)	6 (30.00)	
ERP				
No	154 (53.47)	50 (50.00)	13 (65.00)	.4634
Yes	134 (46.53)	50 (50.00)	7 (35.00)	
30-day Readmission				
No	273 (94.79)	82 (82.00)	14 (70.00)	**<.0001**
Yes	15 (5.21)	18 (18.00)	6 (30.00)	
Length of Stay (days, median, IQR)	4.0 (4.0-6.0)	7.0 (5.0-8.5)	11.5 (7.5-21.0)	**<.0001**

CI= −2.25 – -.12, P = .029). This effect of ERP was not observed in patients treated by laparoscopic or hybrid surgical approaches. PoC was significantly correlated with increased LOS in all 3 types of surgery (P < .001). In the laparoscopic subgroup, an additional interaction effect was observed, in which females with PoC had shorter LOS compared to males with PoC (β= −4.26 days, 95% CI= −6.83 – -1.69, P = .001) (Table 7).

Both obese and non-obese patients on the ERP protocol had significantly decreased LOS compared to patients not on ERP (Tables 8). PoC was significantly associated with increased LOS in both groups. In the

Table 3. Multivariable analysis for outcome Postoperative Complication.

	Overall Sample (yes PoC: n=115 vs no PoC: n=277)			Mild/Moderate PoC (n=95) vs no PoC (n=277)			Severe PoC (n=20) vs no PoC (n=277)		
Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
BMI									
Obese vs non-obese	1.66	1.05–2.62	**.0289**	1.73	1.05–2.86	**.0320**	2.09	.77–5.65	.1468
Type of Operation:									
Laparoscopic vs open	.52	.30–.90	**.0196**	.50	.28–.90	**.0210**	.61	.20–1.92	.4013
Hybrid vs open	.38	.18–.81	**.0116**	.37	.16–.82	**.0142**	.47	.10–2.27	.3456
ASA class (≥3 vs <3)	1.98	1.22–3.21	**.0056**	1.77	1.04–3.00	**.0344**	2.54	.80–8.04	.1135
ERP	1.38	.85–2.23	.1906	1.56	.94–2.61	.0880	.82	.30–2.30	.7113
Age (per 1 yr)	-	-	-	-	-	-	1.05	1.01–1.10	**.0307**

Table 4. Multivariable analysis for outcome Postoperative Complication in Type of Surgery subgroups.

	Open subgroup (n=140 no PoC, 75 yes PoC)			Laparoscopic subgroup (n=88 no PoC, 29 yes PoC)			Hybrid subgroup (n=49 no PoC, 11 yes PoC)		
Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
BMI									
Obese vs non-obese	1.22	.68–2.18	.5026	4.23	1.72–10.42	**.0017**	-	-	-
ASA class (≥3 vs <3)	1.72	.95–3.12	.0736	-	-	-	4.43	.86–22.94	.0762
ERP	1.05	.57–1.94	.8652	2.24	.83–6.06	.1123	2.59	.49–13.82	.2659

Table 5. Multivariable analysis for outcome Postoperative Complication in high-risk subgroups.

	Obese subgroup (N=99 no PoC, 59 yes PoC)			Non-obese subgroup (N=178 no PoC, 56 yes PoC)			ASA≥3 subgroup (N=161 no PoC, 87 yes PoC)			ASA<3 subgroup (N=138 no PoC, 38 yes PoC)		
Variable	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Type of Operation												
Lap vs open	.91	43–1.94	.802	.30	.13–.68	**.004**				.30	.11–.83	**.021**
Hybrid vs open	.44	.14–1.34	.148	.35	.13–.95	**.040**	-	-	-	.31	.10–1.00	**.051**
ASA class (≥3 vs <3)	1.66	.79–1.34	.181	2.35	1.23–4.49	**.010**	-	-	-	-	-	-
ERP	1.60	.80–3.17	.182	1.22	.61–2.41	.577	.87	.51–1.47	.595	1.81	.83–4.00	.138
Obesity	-	-	-	-	-	-	1.40	.82–2.37	.217	-	-	-
Sex (F vs M)	-	-	-	-	-	-	.60	.35–1.03	.065	-	-	-
Age	-	-	-	-	-	-	-	-	-	1.03	1.00–1.07	**.033**

Table 6. Multivariable analysis for outcome LOS (multiple linear regression) (n = 406).

Variable	β	P-val	95% CI
ERP (Y vs N)	−1.0237	**.0055**	−1.7453 – -.3020
Postop complication (Y vs N)	6.6673	**<.0001**	5.4081 – 7.9265
Postop complication (Y)*Gender (F)	−3.8133	**<.0001**	−5.1898 – -2.4368
Postop complication (Y)* Insurance (Private vs Public)	−3.2300	**<.0001**	−4.6975 – -1.7625
Postop complication (Y)* Insurance (Uninsured vs Public)	−3.3378	**.0343**	−6.4270 – -.2486

*β= parameter estimate

obese group, in the presence of PoC, female gender was correlated with decreased LOS compared to male gender. In the non-obese group, left-sided surgery was predictive of decreased LOS compared to right-sided colon surgery.

Regardless of ASA classification (<3 vs. ≥3), PoC was associated with increased LOS (Tables 8). ERP had a more significant impact on reducing LOS in the ASA<3 subgroup. In the ASA ≥3 subgroup, in the presence of

Table 7. Multivariable analysis for outcome LOS in Type of Surgery Subgroups.

	Open subgroup (n = 224)			Laparoscopic subgroup (n = 119)			Hybrid subgroup (n = 65)		
Variable	β	p	95% CI	β	p	95% CI	β	p	95% CI
ERP (Y vs N)	−1.19	**.029**	−2.25 −.12	−.69	.297	−1.99 – .61	−.07	.953	−2.58 – 2.43
PoC (Y vs N)	3.86	**<.001**	2.81 – 4.90	5.87	**<.001**	3.99 – 7.74	4.74	**.002**	1.75 – 7.74
PoC (Y)*	-	-	-	−4.26	**.001**	−6.83	-	-	-
Gender (F)						−1.69			

*Par.Est. = Parameter Estimate

Table 8. Multivariable analysis for outcome LOS by high-risk subgroups.

	Obese subgroup (n = 161)			Non-Obese subgroup (n = 221)			ASA≥3 subgroup (N = 248)			ASA<3 subgroup (N = 159)		
Variable	β	p	95% CI	β	p	95% CI	β	p	95% CI	β	p	95% CI
ERP	−1.40	**.034**	−2.70 −.10	−1.53	**<.001**	−2.1 −1.0	−1.02	.079	−2.15 – .12	−1.25	**.001**	−1.6−.54
PoC (Y vs N)	5.47	**<.001**	3.62 – 7.33	1.02	**<.001**	2.28-3.76	5.56	**<.001**	4.01 – 7.11	2.97	**<.001**	2.10 – 3.84
PoC (Y)*	−3.59	**.002**	−5.84	-	-	-	−2.99	**.003**	−4.96 −1.01	-	-	-
Gender (F)			−1.34									
Segment (L vs R)	-	-	-	-	-	-	-	-	-	.98	**.013**	.21 – 1.75

PoC, female gender once again was correlated with reduced LOS compared to male gender. In the ASA<3 subgroup, left-sided surgery was correlated with decreased LOS compared to right-sided surgery.

Discussion

Although there is significant evidence suggesting that ERP is beneficial in colon cancer surgery, its efficacy in a population with high rates of obesity and medical comorbidities has not been specifically studied or defined by previous reports. In fact, a recent review of current literature identified no studies that included subgroup analyses of an ERP pathway in patients with specific comorbidities, and identified this as a need for future studies.[5] In the current study, we have demonstrated that the application of ERP, in a population with high rates of obesity and multiple medical comorbidities, was associated with reduced LOS, but with neither positive nor negative effect on overall post-operative morbidity. Our study population was comprised of patients from a healthcare system located in the Mid-South region of the United States, where rates of obesity and chronic medical conditions are significantly elevated compared to the rest of the nation.[7] The mean BMI of patients in this study was higher than in previously published large randomized controlled trials on ERP outcomes.[9,10] The national prevalence of obesity increased from 34.9% to 42.4% between 2011 and 2018. In our sample population, 39.7% of patients were obese; in 2019, 43.6% of our cohort was obese. The majority of our patients were ASA class ≥3 (56% in the non-ERP cohort and 58% in the ERP cohort), which also stands in contrast to previously published studies where the majority of the populations were classified as ASA<3.[9,10] The high rates of obesity and chronic medical conditions in this area allowed a unique opportunity to study the impact of ERP in this patient population, and to our knowledge, represents the first study to specifically do so.

We observed an increased risk of postoperative morbidity in patients with obesity and ASA class ≥3. More specifically, these factors were independent predictors of mild/moderate PoC (CDC 1–3), but not severe PoC (CDC 4–5). Notably, the analysis for severe complications lacked power, as there were only 20 events. Our findings suggest that obesity and multiple comorbidities confer a level of increased operative risk that is not completely mitigated by ERP. Iranmanesh et al observed no difference in postoperative outcomes between obese and non-obese patients, but this study had a relatively fewer number of obese patients (n = 86, only 23% of whom had BMI ≥35) and their obese cohort was generally healthier (mean ASA class 2.19 vs. 2.69 for our study).[11]

In the study of obesity, there is emerging evidence that there may be important distinctions between BMI, visceral obesity and sarcopenic obesity (referring to obesity in the setting of low muscle mass).[12] Increased visceral fat volume may be a better marker of poor surgical outcomes than BMI. A recent study by Pedrazzani et al examining the effect of visceral fat on surgical outcomes after

colorectal resection found that while only 12.6% of their cohort were obese by BMI, 68.6% had visceral obesity. Furthermore, a high Sarcobesity Index (defined using the visceral adipose tissue/skeletal muscle area ratio) was a better predictor of postoperative complications after laparoscopic resection for colorectal cancer than BMI.[13] However, in this study, only 33 subjects were BMI obese, and 2/3 of those were ASA class <3, which is a much smaller and overall healthier obese population as compared to that of our study.[13] An important future direction of investigation would be to examine the effect of ERP on a population with high rates of known visceral obesity and sarcopenic obesity.

Laparoscopic and hybrid surgeries (vs. open) were more common in our ERP cohort, were associated with a reduction in overall PoC, and conferred a protective effect against mild/moderate PoC but not severe PoC (although as acknowledged, the analysis for severe PoC lacked sufficient power). These findings are concordant with previous studies demonstrating the advantages of a minimally invasive approach in patients undergoing colorectal surgery, and with the American Society of Colon and Rectal Surgeons (ASCRS) ERP clinical guidelines, which strongly recommend using laparoscopic surgery.[8,10] Interestingly, we demonstrated obesity to be a significant predictor of PoC in the laparoscopic cohort, suggesting that while laparoscopy is overall effective in decreasing postoperative morbidity, obesity does confer additional risk for patients undergoing minimally invasive surgery. This is in agreement with some published studies showing that obesity is associated with worse operative outcomes after laparoscopic colorectal resection,[14] although findings of this association remain inconsistent.[15] ERP was not found to be protective against PoC regardless of type of surgery, once again suggesting that its benefit may be overshadowed by the deleterious effects of obesity and multiple comorbidities in this population.

ERP was independently associated with a significant reduction in LOS for the overall cohort, as well as for the open surgery subgroup, although not in the laparoscopic or hybrid subgroups. Both the obese and non-obese subgroups experienced a reduction in LOS for ERP patients; however, the effect was more pronounced in the non-obese group. ERP was also correlated with decreased LOS in patients with both high and low ASA class, although this effect was more significant in the ASA<3 subgroup. These findings suggest that obesity and multiple medical comorbidities attenuate the benefit of ERP in decreasing LOS.

A large meta-analysis demonstrated a mean overall reduction of 2.28 days in LOS with ERP implementation for patients undergoing colorectal surgery.[1] We observed estimated LOS reductions of 1.02 days in the overall model, with 1.4 days and 1.5 days in the obese and non-obese subgroups, respectively. This suggests that in our cohort, the effect of ERP was not as strong as in other studies, likely due, in part, to the high prevalence of patient comorbidities. Another factor to consider is that the effect of ERP has been shown to be "dose-dependent" by rate of compliance to individual components.[16] It is possible that the actual compliance to ERP components was lower than defined, as compliance to individual ERP components was not reliably recorded in the EMR. Pain management is one of the most important cornerstones of ERP protocols and is also the most reliably accessible and recorded aspect of ERP in our EMR. As previously stated, there is evidence that adherence to postoperative ERP components highlighted by pain management is the most effective in improving surgical outcomes.[3] There is also evidence that ERP compliance is lowest in the postoperative period, so although it is not a perfect surrogate, the high adherence observed here is indicative of compliance to the overall protocol .[4,16]

In concordance with other studies in the literature reporting that operative complications are the main drivers of LOS, we also observed that PoC was strongly associated with increased LOS (overall and in all subgroups).[17] Several interactions with PoC affecting LOS were also observed. In the presence of PoC, females had shorter LOS than males (interestingly, this held true in the obese but not in the non-obese subgroup), and holders of public insurance had longer LOS than those with private insurance as well as those without insurance. Patients with private insurance may generally be healthier than holders of public insurance, or may have more post-discharge resources, leading to a decreased LOS. It is possible that for uninsured patients, there is monetary incentive from both the patients' and the hospitals' standpoint for earlier discharges. Lee et al identified subjective pain and fatigue as factors affecting a patient's decision to refuse discharge despite being deemed medically ready, and although neither insurance status nor gender made a significant difference in this study (possibly due to small sample size, with only 17 patients out of 91 refusing discharge), it is conceivable that insurance and gender may affect subjective readiness for discharge.[18]

In two subgroups (non-obese and ASA <3), left-sided surgery was associated with decreased LOS compared to right-sided surgery. This is consistent with existing literature demonstrating that patients undergoing left-sided surgery for colon cancer have decreased hospital stay vs. right-sided surgery, even while on ERP protocol.[19] Increased LOS for right-sided surgery has been attributed to slower return of bowel function as compared to left-sided procedures.[20]

In the overall cohort, the year of surgery was positively predictive of ERP; however, this was largely due to the relative lack of patients on ERP protocol during the beginning of the study. From 2014 to 2015, 60–80% of patients were on ERP, and from 2016 onwards, greater than 80% of patients were consistently on ERP. Analysis of years 2014–2019 did not demonstrate an association

with ERP status. This suggests that after its introduction, use of the ERP protocol was not significantly time-dependent, and therefore minimizes the confounding effects of time-related factors.

This study has several limitations. A common issue with retrospective ERP studies is the inability to reliably quantitate subsequent medically significant compliance to the different components of ERP.[3,16] Compliance to each of the ERP components (such as restrictive intravenous fluids, postoperative nasogastric tube usage, and early ambulation) is not deducible from our EMR, which limits our ability to assess the effects of degree of compliance on surgical outcomes. This is a limitation of many retrospective ERP studies.[16] However, our healthcare system's ERP protocol was modeled and implemented in concordance with the existing clinical practice guidelines and compiled into a standardized order set, which we feel improves adherence.[8] Another limitation is that several subgroups (such as the severe complications group) are comprised of sample sizes too small to allow for meaningful analyses.

Conclusion

In conclusion, in a population with high rates of obesity and concomitant medical comorbidities, ERP neither increases nor decreases postoperative morbidity, but is effective at reducing length of stay following elective colon cancer surgery. However, the impact of ERP appears to be attenuated in the presence of obesity and medical comorbidities. Choice of operative approach is important in decreasing postoperative complications, with minimally invasive approaches conferring an overall protective effect. Postoperative complication remains a significant contributor to increased length of stay, and interactions with factors such as insurance status and gender were also observed. Further research is warranted to fully elucidate how to best care for this unique patient population.

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Supplemental Material

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