



# Laparoscopic versus open colectomy: the impact of frailty on outcomes

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## Abstract

Frailty in the elderly population is an important predictor of surgical outcomes. It has been quantified by several models, including the modified frailty index, which has demonstrated applicability in many surgical subspecialties. We aim to conduct the first decade-long retrospective analysis of frailty and complications between open and laparoscopic colectomy. We used the American College of Surgeons National Surgical Quality Improvement Program database to identify colectomies performed between 2005 and 2014. Our primary outcome was 30-day mortality. Secondary outcomes were grouped into five categories: wound, hematologic, pulmonary, renal, or cardiac/vascular complications. Chi-square and multivariate logistic regression were used to identify significant predictors of outcomes. Of the 244,639 colectomies identified in our data set, 117,064 cases were included after exclusion criteria were applied. 42,192 (36%) cases were laparoscopic. Mortality rates among open colectomies in mFI cohorts 0, 1, 2, 3, and  $\geq 4$  were 1.2, 3.4, 7.9, 14.3, and 20.3%, respectively, while rates in laparoscopic colectomies 0.2, 0.7, 2, 3.5, and 5.4%, respectively ( $p < 0.05$ ). Logistic regression showed increase likelihood of mortality with open colectomies in all mFI cohorts ( $p < 0.05$ ). The open approach also had statistically significant higher rates of secondary outcomes in nearly all frailty levels. Our study analyzed the relationship of frailty, approach to colectomy, and postoperative complications. Laparoscopic colectomies resulted in lower mortality rates as well as less wound, hematologic, pulmonary, renal, and cardiovascular complications.

**Keywords** Frailty · Colectomy · Laparoscopic · Open

## Introduction

Frailty has emerged as a significant predictor of surgical complications, particularly in the elderly. Defined as a decrease in physiologic reserve, it has been quantified by several models, including the modified frailty index (mFI). Based on the Canadian Study of Health and Aging, Velanovich et al. developed the mFI as a means to rapidly evaluate perioperative risk of surgical complications [1] and has been validated among several general surgery procedures [2, 3]. This model of frailty is based on the theory of accumulating comorbidities, which generally reach higher levels in the elderly.

Frailty has been associated with increased morbidity and mortality in emergency general surgery [4]. Colon resection, which continues to have a high general incidence (14.8–80%, depending on underlying condition) [5, 6], is commonly performed in the elderly population [7]. Surgery in the elderly, however, carries significant perioperative risk factors unique to their age cohort [8, 9].

In recent years, minimally invasive laparoscopic and robotic surgery has emerged as an increasingly utilized alternative to open colectomy [10]. The rate of minimally invasive colectomy has increased from 2.2% in 1996 to 31.4% in 2009. Minimally invasive surgery is known to provide several advantages compared to open procedures, particularly in regards to oncological and non-malignant morbidity, return of normal bowel function, shorter hospital stay, and less pain [11, 12]. Despite this, utilization of laparoscopy is significantly reduced in patients aged 80 years or more [10]. To better understand this trend, it is important to determine the outcomes of a laparoscopic approach to colectomy in frail patients.

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A recent study using national data up to 2012 showed that patients undergoing laparoscopic colectomy had lower rates of morbidity, mortality, and shorter length of stay compared to open surgery [13]. While this demonstrates the general advantages provided by a laparoscopic approach in frail patients, the general literature is lacking in the analysis of specific subsets of complications. Our goal is to conduct the first decade-long retrospective analysis to describe the relationship between frailty, complication rate, mortality, and specific organ system and surgical site complications. We aim to support the conclusions that assessment of frailty will augment informed decision-making between patients and their surgeons.

## Methods

### Data source

The data used in this study were obtained from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), a collection of de-identified data regarding surgical cases obtained from voluntarily participating hospitals. NSQIP provides HIPAA-compliant

patient-level information such as risk factors and comorbidities as well as 30-day morbidity and mortality outcomes, collected by trained specialists from over 500 hospitals. It provides an aggregate sample that does not identify patients, medical-care providers, or hospitals involved in each case. NSQIP is routinely audited and demonstrates overall inter-rater disagreement rates of less than 2% [14]. Our study is a retrospective analysis of data gathered by NSQIP from 2005 to 2014. IRB approval exemption was obtained.

### Population

Inclusion criteria for selection were age 18 and above and occurrence of a laparoscopic or open colectomy identified by current procedural terminology (CPT) code (Table 1). To ensure that all cases involving colectomy were included, we selected cases associated with colectomy as the primary CPT code as well as those associated with colectomy as a secondary CPT code. Of these patients, we excluded those missing any of the 15 variables needed to calculate the modified frailty index (mFI) (Table 2). Thus, the inclusion criteria for this study are colectomy cases with information regarding the following variables: COPD or recent pneumonia, myocardial infarction, congestive heart failure, angina/

**Table 1** Colectomy CPT<sup>a</sup> code descriptions

Colectomy type	CPT	Description
Open	44141	Colectomy, partial; with skin-level cecostomy or colostomy
	44144	Colectomy, partial; with resection, with colostomy or ileostomy and creation of mucofistula
	44145	Colectomy, partial; with coloproctostomy (low pelvic anastomosis)
	44146	Colectomy, partial; with coloproctostomy (low pelvic anastomosis), with colostomy
	44147	Colectomy, partial; abdominal and transnasal approach
	44143	Colectomy, partial; with end colostomy and closure of distal segment (Hartmann type procedure)
	44155	Colectomy, total, abdominal, with proctectomy; with ileostomy
	44156	Colectomy, total, abdominal, with proctectomy; with continent ileostomy
	44160	Colectomy, partial, with removal of terminal ileum with ileocolostomy
	44139	Mobilization (take-down) of splenic flexure performed in conjunction with partial colectomy (List separately in addition to primary procedure)
Laparoscopic	44140	Colectomy, partial; with anastomosis
	44205	Laparoscopy, surgical; colectomy, partial, with removal of terminal ileum with ileocolostomy
	44207	Laparoscopy, surgical; colectomy, partial, with anastomosis, with coloproctostomy (low pelvic anastomosis)
	44208	Laparoscopy, surgical; colectomy, partial, with anastomosis, with coloproctostomy (low pelvic anastomosis) with colostomy
	45395	Laparoscopy, surgical; proctectomy, complete, combined abdominoperineal, with colostomy
	45397	Laparoscopy, surgical; proctectomy, combined abdominoperineal pull-through procedure (e.g., colo-anal anastomosis), with creation of colonic reservoir (e.g., J-pouch), with diverting enterostomy, when performed
	44204	Laparoscopy, surgical; colectomy, partial, with anastomosis
	44206	Laparoscopy, surgical; colectomy, partial, with end colostomy and closure of distal segment (Hartmann type procedure)
	44212	Laparoscopy, surgical; colectomy, total, abdominal, with proctectomy, with ileostomy
	44213	Laparoscopy, surgical, mobilization (take-down) of splenic flexure performed in conjunction with partial colectomy (List separately in addition to primary procedure)

<sup>a</sup>Current procedural terminology

**Table 2** NSQIP<sup>a</sup> variables to calculate mFI<sup>b</sup>

COPD <sup>c</sup> or recent pneumonia
Myocardial infarction
Congestive heart failure
Angina, previous coronary intervention, or previous coronary surgery
Diabetes mellitus
Transient ischemic attack or cerebrovascular accident
Cerebrovascular accident with neurological deficit
Hypertension requiring medication
Functional status (totally or partially dependent)
Impaired sensorium
Peripheral vascular disease or ischemic rest pain

<sup>a</sup>National Surgical Quality Improvement Program

<sup>b</sup>Modified frailty index

<sup>c</sup>Chronic obstructive pulmonary disease

previous coronary intervention/previous coronary surgery, diabetes mellitus, transient ischemic attack or cerebrovascular accident, hypertension requiring medication, functional status, impaired sensorium, and peripheral vascular disease or ischemic rest pain. Next, we generated a secondary variable to identify whether a patient had undergone a laparoscopic or open colectomy based on CPT codes (Table 1).

**Modified frailty index**

A modified frailty index was determined for each patient based on risk factors and comorbidities listed in NSQIP. Though multiple methods have been used to calculate mFI

in the past, our study uses the mFI [1], which includes 15 NSQIP variables. To calculate the modified frailty index, each contributing variable was given a value of 1 if the patient was positive for it or 0 if negative. We used the sum of these values to assign each patient an mFI. Thus, the mFI is a sum representing the total number of health deficits for a given patient. Because several of the 15 variables share a common pathophysiology or nature, these variables were combined into one to prevent accounting for the same variable twice. Therefore, each patient was assigned an mFI from 0 to 11 (Table 2). Patients were then grouped into cohorts based on their mFI from 0 to  $\geq 4$ . Patients with an mFI score  $\geq 4$  were categorized into a single cohort to allow for meaningful comparison, since they collectively represented only 4.3% of the population.

**Outcomes of interest**

Our primary outcome of interest was 30-day mortality rate. Secondary outcomes included morbidity related to various organ systems or wounds occurring within 30 days of surgery. Outcome variables were then organized into one of five groups: wound, hematologic, pulmonary, renal, and cardiac/vascular complications (Table 3). These categories were established to determine if laparoscopy provides an advantage in reducing the likelihood of a complication occurring within a particular organ system or category. In addition, the rate of having at least one complication within 30 days of surgery was also evaluated (30-day morbidity).

**Table 3** Secondary outcomes

Category	NSQIP <sup>a</sup> variable name	NSQIP variable definition
Wound	SUPINFEC	Superficial surgical site infection
	WNDINFD	Occurrences deep incisional SSI
	ORGSPCSSI	Occurrences organ space SSI
	DEHIS	Occurrences wound disrupt
Hematologic	OTHBLEED	Occurrences bleeding transfusions
	OTHDVT	Occurrences DVT/thrombophlebitis
	OTHSYSEP	Occurrences sepsis
	OTHSESHOCK	Occurrences septic shock
Pulmonary	OUPNEUMO	Occurrences pneumonia
	REINTUB	Occurrences unplanned intubation
	PULEMBOL	Occurrences pulmonary embolism
	FAILWEAN	Occurrences ventilator > 48 h
Renal	RENAINSF	Occurrences progressive renal insufficiency
	OPRENAFL	Occurrences acute renal fail
	URNINFEC	Occurrences urinary tract infection
Cardiovascular	CNSCVA	CVA/Stroke with neurological deficit
	CDARREST	Occurrences cardiac arrest requiring CPR
	CDMI	Occurrences myocardial infarction

<sup>a</sup>National Surgical Quality Improvement Program

## Statistical analysis

Chi-square analysis was used to determine the predictor variables in NSQIP significantly associated with each outcome after colectomy. Chi-square analysis was also used to assess significance of laparoscopic vs. open approach ( $p < 0.05$  for mortality and morbidity in all mFI groups). Multivariate logistic regression was then used to determine the impact of open compared to laparoscopic colectomy in patients of each mFI cohort on the 30-day mortality and five categories of morbidities (wound, hematologic, pulmonary, renal, and cardiovascular complication) while controlling for factors such as age, race, gender, and various comorbidities. Results were reported as odds ratio (OR) with 95% confidence interval for the each of the aforementioned outcomes (Tables 5 and 6). Statistical Package for the Social Science (SPSS) was used to enter and analyze the data (International Business Machines, Corp., Armonk, NY).

## Results

### Demographics

Of the 244,639 colectomies identified based on CPT codes listed in NSQIP from 2005 to 2014, 117,064 laparoscopic and open colectomies were included after application of the exclusion criteria. Demographics including age (18–40, 41–60, 61–80,  $\geq 80$ ), gender (male or female), race (white, black, hispanic, Asian, unknown), emergent vs elective status, and mFI cohort (0, 1, 2, 3,  $\geq 4$ ) were recorded (Table 4). Of the cases included in the study, 16.6% of colectomies were done in an emergent setting and 7.9% of emergent colectomies were done laparoscopically. Laparoscopy accounted for only 36% (42,192 cases) of all of the colectomies identified. Incidence of laparoscopy decreased as mFI increased, with laparoscopy accounting for only 15.9% of all colectomies done in the mFI  $\geq 4$  cohort. This indicates that a vast majority of colectomies in this high frailty group were done via an open, non-laparoscopic approach. The size of the mFI cohorts also decreased with increasing frailty, the smallest being the mFI  $\geq 4$  cohort consisting of only 4.3% of the total study population, suggesting that fewer colectomies were performed in more frail patients, as would be expected.

### Thirty-day mortality

The overall 30-day mortality rate within this study population is 3.9%, with laparoscopic approach accounting for 23.4% of the 30-day mortality in the population. 0.9% of laparoscopic colectomies and 3.0% of open colectomies resulted in death within 30 days. Laparoscopic and open colectomy resulted in death in 4.7 and 14.7% of emergent cases, respectively,

**Table 4** Demographics

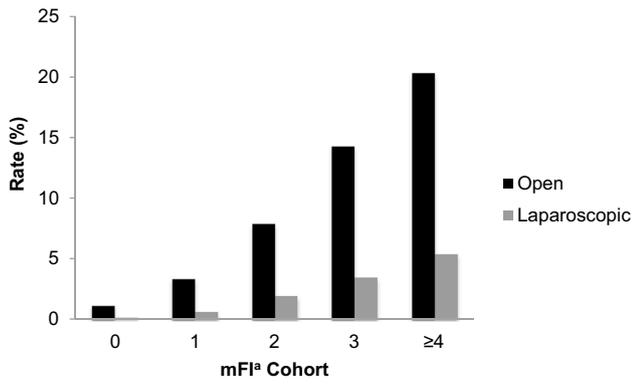
	All	Laparoscopic	Open
Age			
18–40	9774 (8.3%)	3662 (8.7%)	6112 (8.2%)
41–60	40453 (34.6%)	15630 (37%)	24823 (33.2%)
61–80	51688 (44.2%)	18553 (44%)	33135 (44.3%)
$\geq 80$	15149 (12.9%)	4347 (10.3%)	10802 (14.4%)
Gender			
Male	55492 (47.4%)	20156 (47.8%)	35336 (47.2%)
Female	61327 (52.4%)	21900 (51.9%)	39427 (52.7%)
Missing	245 (0.2%)	136 (0.3%)	109 (0.1%)
Race			
White	87566 (74.8%)	32137 (76.2%)	55429 (74%)
Black	10934 (9.3%)	3174 (7.5%)	7760 (10.4%)
Hispanic	5209 (4.4%)	2007 (4.8%)	3202 (4.3%)
Asian	3352 (2.9%)	1461 (3.5%)	1891 (2.5%)
Unknown	9805 (8.4)	3317 (7.9%)	6488 (8.7%)
Missing	198 (.2%)	96 (0.2%)	102 (0.1%)
mFI <sup>a</sup>			
0	46466 (39.7%)	19070 (45.2%)	27396 (36.6%)
1	37243 (31.8%)	13978 (33.1%)	23265 (31.1%)
2	20076 (17.1%)	6393 (15.2%)	13683 (18.3%)
3	8299 (7.1%)	1961 (4.6%)	6338 (8.5%)
$\geq 4$	4980 (4.3%)	790 (1.9%)	4190 (5.6%)
Type			
Laparoscopic	42192 (36%)		
Open	74872 (64%)		
Emergent status			
Emergent	19396 (16.6%)	1541 (3.7%)	17855 (23.8%)
Non-emergent	97667 (83.4%)	40651 (96.3%)	57016 (76.2%)

<sup>a</sup> Modified frailty index

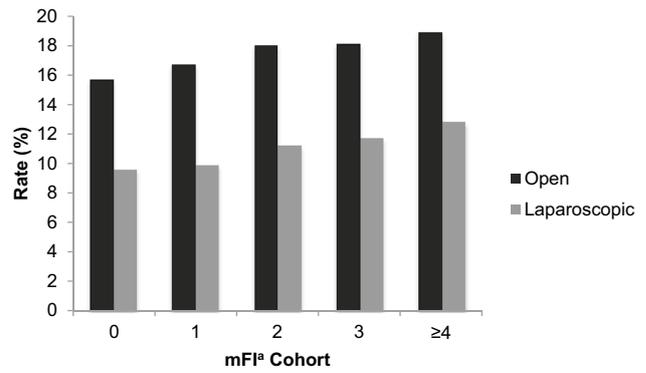
and 0.8 and 2.6% of elective cases, respectively. Patients in the mFI cohort of 0, 1, 2, 3, and  $\geq 4$  who had undergone open colectomy had a mortality rate of 1.2, 3.4, 7.9, 14.3, and 20.3%, respectively. Patients in mFI cohort 0, 1, 2, 3, and  $\geq 4$  who had undergone laparoscopic colectomy had a mortality rate of 0.2, 0.7, 2, 3.5, and 5.4%, respectively (Fig. 1). Logistic regression revealed that odds of 30-day mortality were significantly higher for open compared to laparoscopic colectomies in all five mFI cohorts ( $p < 0.05$ , Table 5).

### Thirty-day morbidity outcomes

Overall 30-day morbidity rates were significantly higher in patients undergoing open compared to laparoscopic colectomies across all mFI cohorts (Fig. 2). The rate of overall morbidity increased with mFI index in open (26.5% in mFI 0–59.1% in mFI  $\geq 4$ ) and laparoscopic (13.9% in mFI 0–35.5% in mFI  $\geq 4$ ) colectomy groups, as did the rate of wound, hematological, pulmonary, renal, and cardiac/



**Fig. 1** Bar graph of 30-day mortality rates by <sup>a</sup>mFI cohort in patients undergoing open and laparoscopic colectomy. Created using Microsoft Excel 2011. <sup>a</sup>Modified frailty index

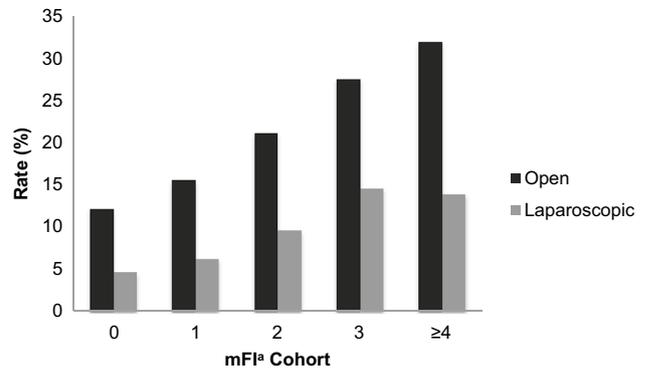


**Fig. 3** Bar graph of 30-day wound complication rates by <sup>a</sup>mFI cohort in patients undergoing open and laparoscopic colectomy. Created using Microsoft Excel 2011. <sup>a</sup>Modified frailty index

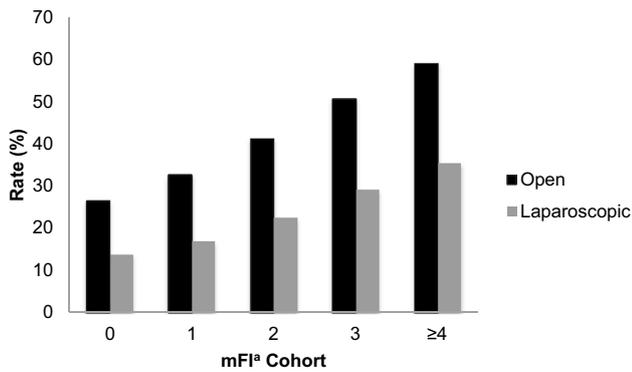
**Table 5** Odds ratio of 30-day mortality with open surgery (reference group: laparoscopic surgery) with 95% confidence intervals

mFI <sup>a</sup>	Death
0	2.904 (1.978–4.263)*
1	2.144 (1.693–2.716)*
2	1.717 (1.391–2.119)*
3	1.819 (1.367–2.421)*
≥4	1.508 (1.112–2.044)*

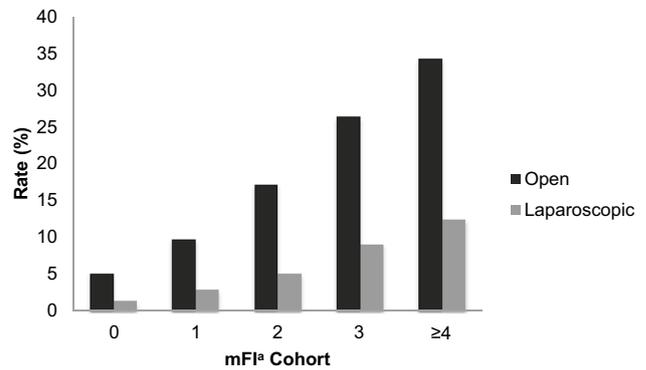
<sup>a</sup>Modified frailty index  
\**p* value < 0.05



**Fig. 4** Bar graph of 30-day hematologic complication rates by <sup>a</sup>mFI cohort in patients undergoing open and laparoscopic colectomy. Created using Microsoft Excel 2011. <sup>a</sup>Modified frailty index



**Fig. 2** Bar graph of 30-day morbidity rates by <sup>a</sup>mFI cohort in patients undergoing open and laparoscopic colectomy. Created using Microsoft Excel 2011. <sup>a</sup>Modified frailty index



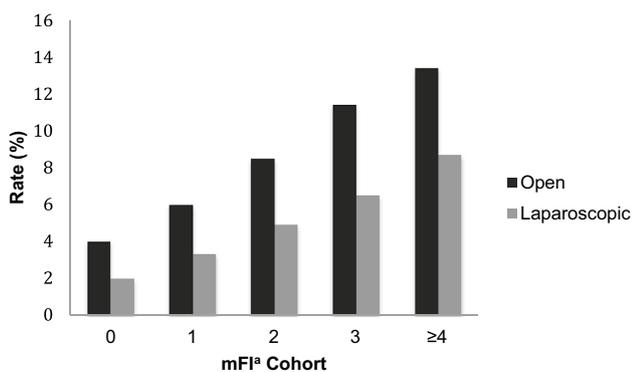
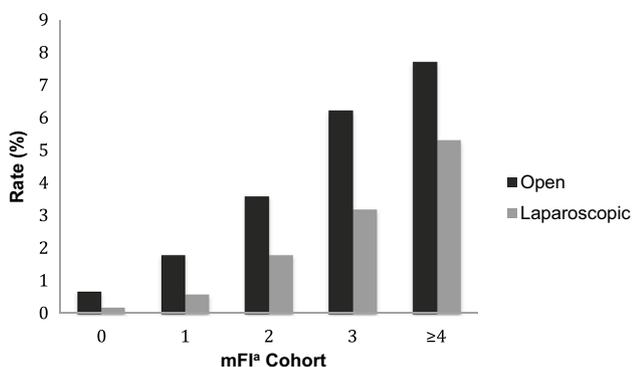
**Fig. 5** Bar graph of 30-day pulmonary complication rates by <sup>a</sup>mFI cohort in patients undergoing open and laparoscopic colectomy. Created using Microsoft Excel 2011. <sup>a</sup>Modified frailty index

vascular complication. Rates of wound, hematological, and pulmonary complications were significantly higher in patients undergoing open colectomy across all mFI categories (Figs. 3, 4, 5). Renal and cardiac/vascular complication rates were also significantly higher in open colectomies across all mFI categories except for patients with an mFI ≥ 4 (Table 6) (Figs. 6, 7). The most common complications in high risk (mFI ≥ 4) patients undergoing open colectomy

were hematologic (32.0%) and pulmonary (34.2%). The rate of hematologic and pulmonary complications in the mFI ≥ 4 group that underwent laparoscopic surgery was 14 and 12.5%, respectively.

**Table 6** Odds ratio of secondary outcomes with open surgery (reference group: laparoscopic surgery) with 95% confidence intervals

mFI <sup>a</sup>	Morbidity	Wound complication	Hematologic complication	Pulmonary complication	Renal complication	Cardiac/vascular complication
	Odds ratio	Odds ratio	Odds ratio	Odds ratio	Odds ratio	Odds ratio
0	1.779 (1.686–1.877)*	1.545 (1.45–1.647)*	2.104 (1.936–2.286)*	2.213 (1.923–2.546)*	1.91 (1.678–2.175)*	1.929 (1.332–2.795)*
1	1.801 (1.701–1.907)*	1.716 (1.598–1.843)*	1.874 (1.722–2.04)*	1.993 (1.77–2.244)*	1.606 (1.429–1.806)*	2.077 (1.608–2.683)*
2	1.645 (1.526–1.774)*	1.614 (1.463–1.779)*	1.635 (1.475–1.813)*	1.839 (1.611–2.098)*	1.47 (1.277–1.691)*	1.404 (1.115–1.768)*
3	1.556 (1.378–1.758)*	1.591 (1.347–1.878)*	1.411 (1.211–1.644)*	1.541 (1.282–1.852)*	1.399 (1.127–1.735)*	1.352 (1.004–1.821)*
≥4	1.55 (1.298–1.851)*	1.628 (1.271–2.084)*	1.667 (1.338–2.076)*	1.742 (1.37–2.216)*	1.438 (1.079–1.917)	0.954 (0.68–1.339)

<sup>a</sup>Modified frailty index\**p* value < 0.05**Fig. 6** Bar graph of 30-day renal complication rates by <sup>a</sup>mFI cohort in patients undergoing open and laparoscopic colectomy. Created using Microsoft Excel 2011. <sup>a</sup>Modified frailty index**Fig. 7** Bar graph of 30-day cardiac/vascular complication rates by <sup>a</sup>mFI cohort in patients undergoing open and laparoscopic colectomy. Created using Microsoft Excel 2011. <sup>a</sup>Modified frailty index

## Discussion

Frailty is associated with adverse outcomes following surgery across many subspecialties. Many studies in recent years have reported an increase in adverse outcomes following surgery in this vulnerable population, including

prolonged length of stay, increased morbidity, and increased mortality [15, 16]. In a study including 201 patients, Robinson and colleagues reported that frail patients had an increase in postoperative complications in both colorectal and cardiac procedures [17]; a study with 226 patients conducted by Saxton and colleagues similarly reported that frail patients had an increase in severe Clavien–Dindo complication rates for general surgery procedures [18]; Makary and colleagues analyzed 594 elderly patients undergoing elective surgery, and reported that frail patients had an increase in postoperative complications, length of stay, and discharge destination to a skilled or assisted living facility [19]. We acknowledge the authors' similar conclusions that an assessment of frailty can promote informed decision-making between patients and their physicians. To our knowledge, the assessment of frailty between open and laparoscopic colectomy has not been thoroughly explored. We present the first decade-long retrospective study to analyze the relationship between frailty and approach to colectomy.

The laparoscopic approach to colon resection is associated with lower complication rates and shorter length of stay compared to open resection [20, 21]. In the largest trial to date, the United States Intergroup Clinical Outcomes of Surgical Therapy (COST) trial analyzed outcomes in 872 patients with colonic adenocarcinoma assigned to either open or laparoscopic colectomy. Although operative time was longer in laparoscopic cases (150 vs. 95 min), length of stay was decreased and long-term outcomes were similar [12]. In the multicenter Colon Cancer Laparoscopic or Open Resection (COLOR) trial, the laparoscopic approach resulted in earlier recovery of bowel function, need for fewer analgesics, and shorter length of stay [22].

As a result, the laparoscopic approach has been increasingly utilized among general surgeons for benign and malignant conditions [23, 24]. Despite the effectiveness of the approach, the elderly population and those with more comorbidities remain particularly vulnerable populations [25]. Due to increasing size of the elderly population, understanding pertinent risk factors is becoming increasingly important.

As such, numerous studies have analyzed the effectiveness of comorbidity indexes in this cohort [26, 27].

Despite such advantages, the open approach constitutes the majority of cases; within our study population, which includes data from 2005 to 2014, 74,872 (64%) underwent open, while only 42,192 (36%) underwent laparoscopic. Open was also more frequent across all mFI cohorts. Studies exploring incidence of either approach likewise report underutilization of minimally invasive surgery, ranging from 6.7 to 40% [21]. Patients undergoing laparoscopic surgery also tended to be younger [28]. Thus, further investigation into the surgical considerations for the elderly is warranted.

Our study provides further validation of the mFI in colon surgery. A recent study suggests that the rate of having a complication with open procedures in this population is, indeed, higher and results in longer length of hospital stay [13]. Our work corroborates with these findings, and elucidates the effect on specific organ system and wound complications. In particular, we report the association between frailty and mortality and wound, hematological, pulmonary, renal, and cardiac/vascular complications.

Our aim was to better elicit the effects of surgical approach to colon resection in the frail. While a recent study concluded that the rate of having any complication with open procedures in this population was, indeed, higher [13], we aim to target the effect on specific organ system and wound complications while using a larger data set (22,253 additional cases). This information is thus applicable to individualized management in patients with system-specific comorbidities.

Mortality was significantly increased among patients undergoing open procedures (3.0%) compared to patients undergoing laparoscopic colectomy (0.9%) consistent with the existing literature (Table 5) [29]. Within each frailty cohort, laparoscopic colectomy provides better outcomes compared to an open approach in all domains, including cardiac/vascular, pulmonary, renal, hematologic, and wound complications. In addition, the rates of mortality and each secondary outcome increased with increasing frailty.

Although laparoscopy has been underutilized in the past, it is becoming increasingly implemented in colorectal surgery [30]. Our data lend support to this trend across all levels of frailty. Concerns about operating on the vulnerable elderly and frail population may have historically hindered utilization of minimally invasive surgery, but our data suggest that it is safer than previously thought. Further investigations may confirm this.

The retrospective nature of our analysis limits our ability to unequivocally provide a cause-and-effect relationship between open and laparoscopic surgery in frail patients. This can only be accomplished through another study design, such as a randomized-controlled trial. In addition, the NSQIP database also only contains data up to 30 days

after surgery, limiting our ability to apply these data beyond 30 days postoperatively.

## Conclusion

Our study analyzed the relationship of frailty, approach to colectomy, and postoperative complications. Laparoscopic procedures had statistically significant lower rates of all primary and secondary outcomes, across all but two frailty levels. We propose further research to investigate the relationship between frailty and approach for different indications, as well as randomized trials in vulnerable populations. This may further highlight the differences between laparoscopic and open colectomies, and provide a more individualized plan of care to improve outcomes.

**Author contributions** All authors listed above contributed to the manuscript and have met all of the authorship guidelines as per the International Committee of Medical Journal Editors (ICMJE).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no potential conflict of interest.

**Research involving human participants and/or animals** Our research was approved and exempted by the Institutional Review Board at Rutgers-New Jersey Medical School.

**Informed consent** For this type of study informed consent is not required.

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