Role of Enhanced Recovery Protocols in Postoperative Morbidity and Mortality in Frail Patients Undergoing Colorectal Cancer Surgery

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ABSTRACT

Introduction: Our goal was to analyze the postoperative outcomes of colorectal oncologic surgeries, as well as the impact of enhanced recovery (ER) protocols, on frail patients.

Material and Methods: Patients underwent surgery between 2018 and 2021. We compared the morbidity and mortality rates of frail and non-frail patients of all ages. Patients with a five-variable Modified Frailty Index ≥ 2 were considered frail. Complications, hospital readmissions within 30 days of surgery, and mortality at 30, 90, and 365 days were analyzed. Morbidity, mortality, reoperations, hospital readmissions, and length of hospitalization were also assessed according to inclusion in an ER protocol.

Results: Three hundred thirty-four patients were included (66 (19.8%) frail). Frail patients had a higher risk of 30-day complications (p=0.005), longer hospital stay (p=0.001), and a higher mortality rate than non-frail patients. Frailty was associated with higher mortality after adjusting for age, sex, and the American Society of Anesthesiologists classification. No significant associations with morbidity or mortality were found among frail patients, regardless of whether they were included in ER protocols. However, those who followed these protocols had shorter hospital stays.

Conclusions: Frailty is an independent risk factor for postoperative morbidity and mortality in patients of all ages undergoing colorectal oncologic surgery. Incorporating these patients into ER protocols is safe and reduces the length of stay.

***Keywords**: frailty; colorectal surgery; postoperative; adults; morbidity and mortality*

INTRODUCTION

Colon cancer is one of the most prevalent malignancies worldwide, with an estimated 1.4 million cases and 700,000 deaths per year. The incidence of this disease increases with age, with the diagnosis being made more frequently in individuals over 50 years of age. The primary treatment approach entails surgical interventions, necessitating meticulous care to optimize outcomes.[1-4]

Traditionally, age and systems such as the American Society of Anesthesiologists (ASA) or the Revised Cardiac Risk Index (LEE) are used.5,6 However, chronological age correlates imprecisely with postoperative outcomes, and these instruments do not adequately measure a patient's functional reserve. Thus, the concept of "frailty" emerges as a vital source of information for surgical decision-making. [7]

Frailty is defined as a state of decreased physiological reserve and increased vulnerability to external stressors, which can result in suboptimal postoperative outcomes. While this condition is more frequently observed in elderly patients, it can also affect young patients with comorbidities.[8,9]

Frailty can be quantified using scales such as the five-variable Modified Frailty Index (5-mFI), which considers arterial hypertension, chronic obstructive pulmonary disease (COPD), pneumonia, diabetes mellitus, mobility impairments, and heart failure. The 5-mFI predicts post-surgical complications, length of hospital stay, and mortality in elderly patients. Numerous advances in colorectal oncologic surgery aim to improve outcomes. These include enhanced recovery (ER) protocols, which have improved the incidence of complications and reduced hospital stays.[10,11] However, these protocols are not routinely applied to frail or elderly patients in our setting.

The impact of frailty on younger patients is unclear; however, given the rising prevalence of chronic diseases, they may experience similar adverse outcomes as older patients.[9]

The objective of this study is to analyze the postoperative outcomes of colorectal oncologic surgeries and the impact of applying ER protocols to frail patients.

MATERIALS AND METHODS

The objective of the study was to compare the incidence of morbidity and mortality at 30, 90, and 365 days in patients who were either frail or non-frail and underwent colorectal oncologic surgery. The length of stay, the occurrence of unscheduled hospital readmission, and 30-day reoperations were evaluated in both groups. Furthermore, a comparative analysis was conducted between the morbidity and mortality of frail patients included in ER protocols and those under conventional postoperative care.

Design

A retrospective cohort study was conducted on patients older than 18 years who underwent laparoscopic oncologic colorectal resections between 2018 and 2021, performed by the same surgical service at two sites of a tertiary hospital.

The following laparoscopic procedures were considered: right and left colectomy, low anterior resection, abdominoperineal resection, Hartmann's, and pull-through. Patients with a follow-up period of less than one year, those with stage IV oncologic disease, and those undergoing multi-organ resection, emergency surgery, conventional surgery, or palliative procedures were excluded from the study.

According to the 5-mFI, patients were divided into two groups: frail and non-frail. Patients with two or more positive variables in the index were considered frail. Complications were defined according to the Clavien-Dindo classification as follows: minor complications (grades I and II), major complications (grades III and IV), and mortality (grade V).

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Furthermore, patients were evaluated according to the ER protocols employed in our medical centers, which are based on the ERAS® (Enhanced Recovery After Surgery) protocol guidelines.[12,13] All patients in the ER group received the same standardized treatment. In contrast, patients receiving conventional care were treated based on medical judgment without structured implementation of the ER protocol.
All patients in the ER group were treated under the same standardized protocol. In contrast, patients receiving conventional care were treated according to the attending physician's medical judgment, without a structured protocol.

Database

We collected familial data and baseline characteristics from internal databases of the surgical service and the patients' electronic medical records. We analyzed age, sex, ASA grade, and inclusion in ER protocols. We recorded the type of surgery performed, including usual colorectal surgical procedures in oncologic diseases. Only comorbidities included in the 5-mFI risk calculation were considered.

Statistical analysis

T-tests and x2 tests were performed to compare continuous and categorical variables, respectively. The Mann-Whitney U test was employed for variables exhibiting abnormal distribution. To assess the relationship between frailty and adverse outcomes, a comprehensive multivariate analysis was conducted. This analysis included all potentially confounding covariates, ensuring the robustness of the findings.
Survival analysis was conducted using Kaplan-Meier curves at one year, comparing frail and non-frail patients. Patients who survived beyond 365 days were administratively censored at day 365, ensuring that subsequent follow-ups did not influence the annual survival estimate. Cox regression analysis was conducted to evaluate the correlation between frailty and mortality at 30, 90, and 365 days postoperatively, incorporating variables with a p-value less than 0.05 in the univariate analysis, and recognized risk factors.
The statistical calculations were performed using SPSS V26. (Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).
A bilateral significance level of $p < 0.05$ was established.

RESULTS

A total of 334 patients were included in the study (Fig. 1), with a frailty prevalence of 19.8% (n = 66). Their baseline characteristics are shown in Table 1. The median follow-up period was 19 (interquartile range [IQR] 15-26) months for frail patients and 18 (IQR 15-25) months for non-frail patients. Data were collected for up to one year, given the scope of this study.

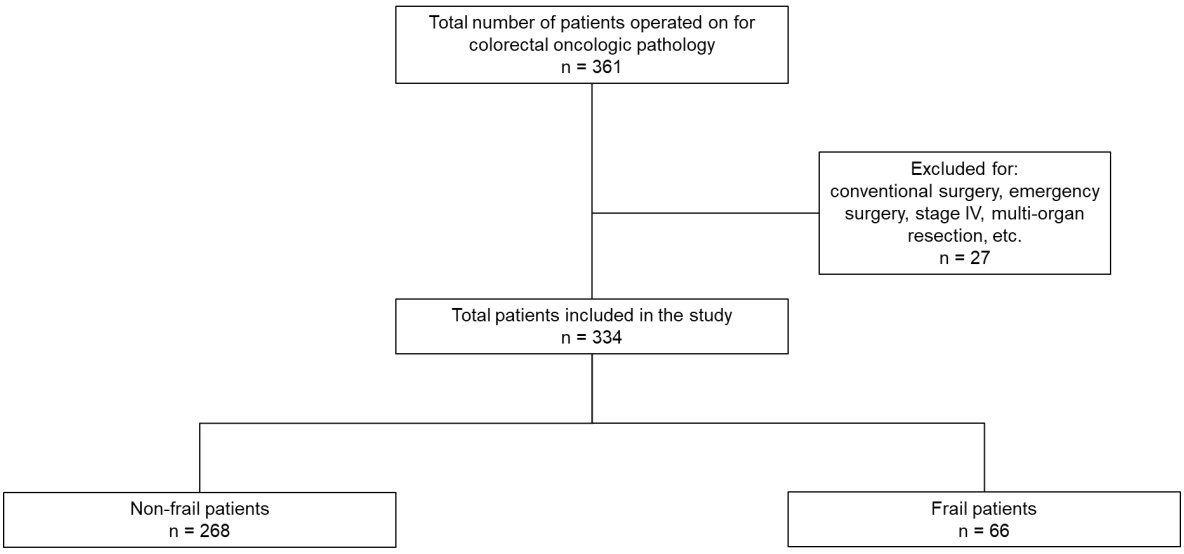

Figure 1. *Patient selection and distribution flow chart.*

Frail patients had a significantly higher risk of complications within 30 days when compared to non-frail patients (74.2 vs. 54.4%, odds ratio [OR] 2.32, confidence interval [CI]: 1.27-4.23; p=0.005). The total number of complications was found to be significantly higher in frail patients (median 2 vs. 1, p<0.01). However, no statistically significant difference was observed in the occurrence of any major complication (24.4 vs. 16.4%, OR 1.6, 95% CI: 0.8-3.1; p=0.14). Additionally, there were no significant differences in the rate of reoperations; however, frail patients exhibited a higher incidence of unscheduled readmissions (21.5 vs. 10.9%, OR 2.23, 95% CI; 1.1-4.53; p=0.02) (Table 2).

Table 1. Demographic characteristics.

Variable	Non-frail n = 268	Frail n = 66	p-value
Age, mean ± SD	63 ± 12.6	69.8 ± 8	0.002
Men (%)	145 (54)	47 (71)	0.01
ASA III (%)	63 (23.5)	41 (62)	0.0001
HT (%)	108 (63)	64 (37)	0.0001
Diabetes (%)	18 (27)	48 (73)	0.0001
COPD (%)	6 (37.5)	10 (62.5)	0.0001
CHF (%)	1 (11)	8 (89)	0.0001
ADLD (%)	3 (16)	16 (84)	0.0001
Included in ER protocol (%)	63 (23.5)	8 (12)	0.063
Surgeries performed (%) RC (n = 107) LC (n = 137) LAR (n = 69)	 82 (76.6) 113 (82.5) 58 (84)	 25 (23) 24 (17.5) 11 (16)	0.383

SD: standard deviation. ER: enhanced recovery. HT: hypertension. CHF: Congestive heart failure. ADLD: activities of daily living dependency. RC: right colectomy. LC: left colectomy. LAR: low anterior resection.

Table 2. Comparison of complications between frail and non-frail patients.

Complications	Non-frail n = 268	Frail n = 66	OR (CI95%)	p-value
Any complication, n (%)	148 (55.4)	49 (74.2)	2.3 (1.3–4.2)	0.005
Complications III - V, n (%)	44 (16.4)	16 (24.2)	1.6 (0.8–3.1)	0.14
Number of complications, mean (IQR)	1 (0 – 2)	2 (0 – 4)	-	< 0.001
Reoperations, n (%)	27 (10.2)	9 (13.6)	1.4 (0.6–3.1)	0.4
Readmissions, n (%)	29 (10.9)	14 (21.5)	2.2 (1.1–4.4)	0.02
Length of stay, days Median (IQR)	6 (4 – 8)	8 (5 – 11)	-	< 0.001

OR: odds ratio. IQR: interquartile range. CI95%: 95% confidence interval.

Frail patients had a significantly longer length of stay than non-frail patients (median 8 vs. 6 days; p=0.001). Frail patients demonstrated a higher risk of mortality at 30 days (6.1 vs. 0.4%, OR 17.35; 95% CI: 1.91-157.99; p=0.006), 90 days (9.1 vs. 2.2%, OR 4.47; 95% CI: 1.4-14.36; p=0.01), and 365 days (13.6 vs. 3.7%, OR 4.18; 95% CI: 1.62-10.76; p=0.004) (Table 3).

In a multivariate analysis that controlled for age, sex, and ASA, frailty remained the only independent risk factor for survival at 30 days (adjusted OR 12.3; 95% CI: 1.23-123.1; p=0.03) and 365 days (adjusted OR 2.8; 95% CI: 1.07-7.51; p=0.03). However, frailty was not statistically significant in any of these variables for 90-day mortality (Table 4).

Table 3. Univariate analysis for mortality at 30, 90, and 365 days.

Mortality	Frail	Non-frail	OR (CI95%)	p-value
30 days	1 (0.4 %)	4 (6.1 %)	17.2 (1.9 – 156.8)	< 0.001
90 days	6 (2.2 %)	6 (9.1 %)	4.4 (1.4 – 14)	0.007
365 days	10 (3.7 %)	9 (13.6 %)	4.1 (1.6 – 10.56)	0.002

OR: odds ratio. CI95%: 95% confidence interval.

Table 4. Multivariate analysis for 30-day and 365-day mortality.

Mortality	30 days			365 days		
	AOR	CI95%	p-value	AOR	CI95%	p-value
Fragility	12.3	1.23 – 123.1	0.03	2.8	1.07 – 7.51	0.04
Age	1.1	0.96 – 1.22	0.17	1.03	0.98 – 1.25	0.1
Sex	2.38	0.25 – 22.3	0.45	0.82	0.31 – 2.18	0.7
ASA	0.98	0.14 – 6.9	0.98	1.5	0.54 – 4.3	0.98

AOR: Adjusted Odds Ratio. CI95%: 95% confidence interval.

Regarding survival at 365 days, a Kaplan-Meier curve of frail and non-frail patients revealed a significant decrease among the former (Fig. 2). In the multivariate Cox regression analysis, adjusting for age, sex, and ER protocols, frailty demonstrated a significant association with lower survival (adjusted HR 3.22; 95% CI: 1.28-8.1; p=0.013) (Figs. 3 and 4).

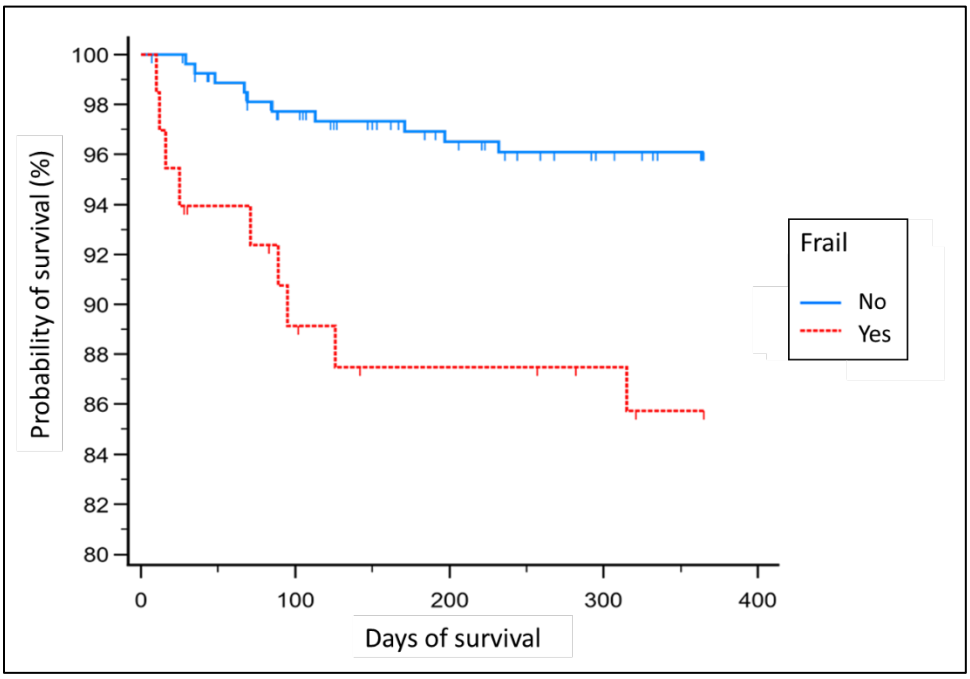

Figure 2. *Survival analysis. Kaplan-Meier curve. Difference in survival between frail and non-frail patients (Log-rank test: p=0.006).*

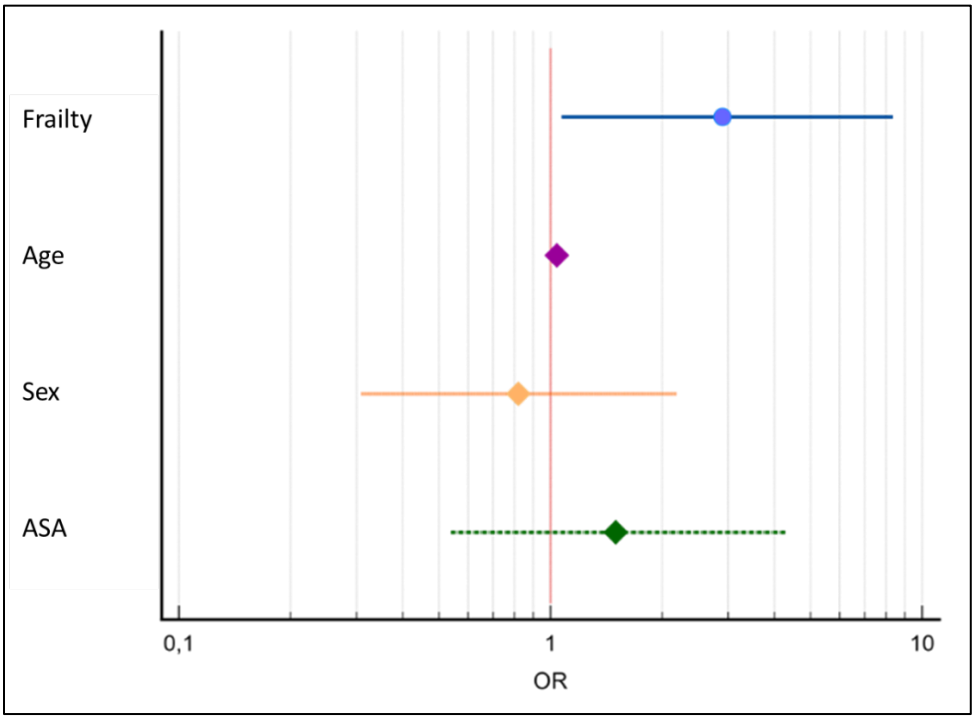

Figure 3. *Forest-plot. Adjusted risks for 365-day mortality in all patients.*

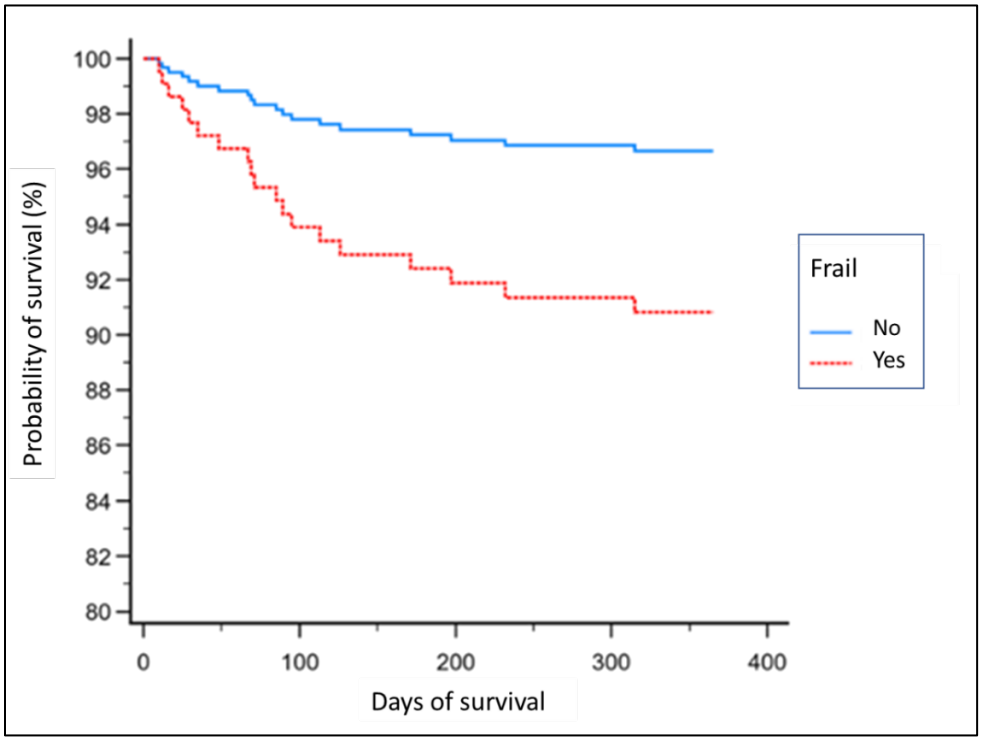

Figure 4. *Graph of 1-year survival of frail vs. non-frail patients, adjusting for age, sex, frailty, inclusion in enhanced recovery protocol, and ASA. Adjusted Hazard Ratio: 2.8 (95%CI: 1.1-7.5; p=0.04).*

A subsequent analysis of the results of frail patients included in ER protocols revealed no significant associations with the occurrence of any complications (p=0.3), major complications (p=0.7), or mortality at 30 (p=1), 90 (p=1) or 365 days (p=1) when compared to frail patients submitted to conventional care. Additionally, there were no statistically significant differences in the incidence of reoperations (p=0.2) or unscheduled readmissions (p=0.3). However, the length of stay in frail patients with ER was significantly lower than that in patients without ER (median of 3 days [minimum-maximum range: 2-5] vs. 9 days [6-14]; p=0.002) (Table 5).

Frail patients within the ER group were then compared to non-frail patients receiving conventional care. Frail patients within the ER group (n=8) experienced a median reduction in hospitalization length of stay from 6 to 3 days (p<0.001), with no significant difference observed in 30-day mortality (0.5 vs. 0%; p=1) or major complications (12.5 vs. 18%; p=0.50) when compared to non-frail patients within the conventional care group (Table 6).

Table 5. Univariate analysis comparing mortality, length of stay, and complications in frail patients outside and inside the enhanced recovery protocol.

	Conventional protocol n=58	Enhanced recovery n=8	OR (CI95%)	p-value
Mortality 30 days	4 (7)	0	0,7 (0,03 – 13,9)	1
Mortality 365 days	9 (15)	1 (12,5)	0,8 (0,08 – 7,1)	1
Length of stay, days	9 (6 – 14)	3 (2,5 – 5)	-	< 0,001
Complications	44 (76)	5 (63)	2,5 (0,5 – 12,1)	0,3
Major complications	15 (26)	1 (12)	0,4 (0,05 – 3,6)	0,7
Unscheduled readmissions	11 (19)	3 (38)	2,5 (0,5 – 12,1)	0,3

OR: odds ratio. CI95%: 95% confidence interval.

Table 6. Univariate analysis for comparison of mortality, length of stay, and complications in frail patients in enhanced recovery protocol and non-frail patients in conventional care protocol.

	Non-frail Conventional protocol n = 202 (%)	Frail Enhanced recovery n = 8 (%)	OR (IC95%)	p-valor
Mortality 30 days	1 (0.5)	0	0.9 (0.98 – 1)	1
Mortality 365 days	10 (5)	1 (12.5)	2.7 (0.3 – 24)	0.3
Length of stay, days	6 (3 – 24)	3 (2 – 5)	-	< 0.001
Complications	116 (57)	5 (62)	1.2 (0.3 – 5.3)	0.5
Major complications	36 (18)	1 (12.5)	0.6 (0.8 – 5.5)	0.5
Unscheduled readmissions	25 (12.4)	3 (38)	2.5 (0.5 – 12.1)	0.07

OR: odds ratio. CI95%: 95% confidence interval.

DISCUSSION

This study aimed to compare the postoperative outcomes of frail and non-frail patients of all ages undergoing oncologic colorectal surgery, whether or not they were included in ER protocols.

Given the complexity of colorectal and oncologic surgery, a comprehensive preoperative evaluation is imperative to identify and optimize high-risk patients.[8,14] Patients deemed fragile have been shown to have an elevated risk of postoperative complications.[8,15,16] However, few studies in our environment have examined this association.

The systems employed in identifying frail patients are often extensive, not very objective, and occasionally inadequate for implementation in daily clinical practice.[17] Consequently, there is a need to ascertain the postoperative morbidity and mortality in our frail patients, and the selection of the 5-mFI as a tool to identify them in our study is warranted. This instrument has been validated in multiple similar studies, allowing for a simple and effective assessment of frailty in the surgical context.[9,15]

The present study indicated a significant association between frailty and adverse postoperative outcomes. Frail patients exhibited a higher probability of experiencing 30-day complications, a greater total number of complications, a prolonged length of hospital stay, and a higher rate of unscheduled readmissions when compared with non-frail patients. This finding is consistent with the reviewed literature.[8,15-19]As shown in the study by Al-Khamis et al.,[15] even in high-volume surgical centers, frail patients (5-mFI ≥ 2) had significantly higher rates of total and severe morbidity compared to patients without comorbidities (5-mFI = 0) and those with a single comorbidity factor (5-mFI = 1).

In our study, frail patients did not exhibit a higher incidence of major complications (Clavien-Dindo III-IV) or reoperations compared to patients without frailty. This finding contrasts with the results reported in the reviewed literature.[8,15,16,18]

However, frail patients had a higher risk of 30-day and one-year mortality after surgery. Frailty remained as the sole risk factor for mortality after adjusting for age, sex, and ASA classification. These differences may be attributable to the reduced responsiveness of frail patients to surgical stress or its complications.[8,15,16,20]

Notably, age was not an independent risk factor for mortality at 30 or 365 days postoperatively, indicating that frailty is a determining factor in patients of all ages. This is even more significant when considering that approximately one-third of the frail patients were younger than 65 years of age.

Similar results have been reported in several studies where age did not directly correlate with frailty. For instance, as demonstrated in the research conducted by Al-Khamis et al.,[15] frail patients younger than 50 years old exhibited comparable outcomes to those observed in older frail patients.

The incorporation of frail patients into the ER protocol did not increase complication rates. Conversely, these patients had a significant reduction in the length of stay compared to non-protocolized frail patients. Similarly, Hampton et al.[10] found no differences in length of hospitalization, readmission rates, or major complications between frail and non-frail patients undergoing ER protocols. The identification of patients with frailty who are to undergo colorectal oncologic surgery facilitates proactive management of these patients, with the intention to reduce surgical risk.

Another analysis was performed that compared frail patients under the ER protocol with non-frail patients under the conventional protocol. Frail patients managed with the AR protocol were discharged three days earlier than non-frail patients receiving conventional care. There was no increase in 30-day mortality or major complications.

The observed trend toward more readmissions and higher annual mortality in the frail ER group was not significant. Nevertheless, given that the group included only eight patients, the analysis is likely underpowered. A larger sample size would be required to confirm the late safety of early discharge and better delineate its clinical benefit in these patients.

The present study is not without its limitations. The primary constraint pertains to its retrospective nature. Moreover, the limited sample size and single-center design limit generalizability. Larger, prospective, multicenter studies are needed to validate and expand upon our results.

CONCLUSION

Frailty is an independent risk factor for postoperative complications and mortality in patients of all ages undergoing laparoscopic oncologic colorectal surgery. Including frail patients in enhanced recovery protocols is safe and can lead to shorter length of stay. It is essential to identify frail patients to optimize their management and postoperative outcome.

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