


Multidimensional Prognostic Index (MPI) score has the major impact on outcome prediction in elderly surgical patients with colorectal cancer: The FRAGIS study

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Abstract

Background: This study aims (I) to evaluate whether the Multidimensional Prognostic Index (MPI) score is associated with postoperative outcomes and (II) to develop a prognostic model for individual complication-risk prediction following colorectal cancer (CRC) surgery.

Method: This is a prospective multicentric cohort study. Consecutive ≥ 75 -year-old candidates for elective CRC surgery were enrolled from October 2017 to August 2019. Patients underwent standardized preoperative geriatric assessment including the MPI. Patients with MPI score > 0.33 were classified as frail. Logistic regression models were employed to evaluate variables associated with major postoperative complications and mortality, using 10-fold cross-validated LASSO (least absolute shrinkage and selection operator) for model selection.

Results: In all, 104 patients were included, 34 (33%) had MPI score > 0.33 . Major postoperative complications occurred in 52% of frail versus 16% of fit (MPI score ≤ 0.33) patients ($p < .01$). Both 30-day (9% vs. 0%; $p = .033$) and 90-day mortality (18% vs. 1%; $p < .01$) were higher among frail patients. In multivariate analysis, MPI score was associated with adverse outcomes. A final postoperative complication predictive model was created, including MPI score, gait-speed test, ASA (American Society of Anesthesiology) score, surgical approach, and stoma creation.

Conclusion: MPI score is strongly associated with postoperative major complications in CRC elderly patients and it is a primary component of an individual prediction model.

KEYWORDS

colorectal surgery, complication, frailty, geriatric assessment, multidimensional

1 | INTRODUCTION

The prevalence of colorectal cancer (CRC) increases with age. Approximately 60% of patients with newly diagnosed CRC are over 75 years of age,¹ a proportion that is expected to rise over the next years.² Aging reduces the physiological reserves making patients more susceptible to postoperative complications.³ Older people represent a heterogeneous group and discrepancies between chronological and biological age are frequent, due to differences in cognitive and functional status, social resources, prevalence of comorbidities, and polypharmacy.

Among elderly patients, colon resections conducted in the elective setting have low mortality (around 3%⁴), but show non-negligible postoperative morbidity, with rates up to 60% in some subjects.^{5,6} As such, it is important to distinguish “fit” patients, who have preserved physiological reserve and can benefit from standard therapeutic strategies, from “frail” patients, who are vulnerable and at increased risk of complications. They could benefit from tailored surgery and pre-habilitation (or even palliative strategies if physical reserve cannot be improved preoperatively).⁶

Risk scores commonly used for surgical patients (i.e., ASA, APACHE, P-POSSUM) have substantial limitations when applied to elderly patients: (I) they were built and validated in past decades mainly on young adults; (II) they consider one single organ function at a time, and (III) they do not estimate the patient's physiologic reserve, functional, cognitive, and social factors, which are all recognized as relevant outcome determinants in geriatric medicine.⁷ Thus, despite the widespread adoption of these scores, their ability to predict complications appears low among elderly CRC patients scheduled for surgery.⁸

The comprehensive geriatric assessment (CGA) is the “evidence-based” reference tool to assess the overall health of elderly patients.^{9,10} CGA is usually delivered by a multidisciplinary team led by a geriatrician alongside specialist nurses, physiotherapists, occupational therapists, and social workers.¹¹ Despite being recommended by several geriatric oncology societies,¹² CGA is rarely performed on surgical elderly patients. A recent survey showed that CGA is adopted by only 6.4% of cancer surgeons,¹³ mainly because it is a time and resource-consuming procedure, often difficult to perform in a busy surgical clinic.¹⁴

The Multidimensional Prognostic Index (MPI; Pilotto et al.¹⁵) is a practical and prognostic tool, allowing to predict short- and long-term mortality in elderly subjects.

It is based on the CGA and includes the assessment of social, functional, cognitive, and nutritional status, pressure sore risk, comorbidities, and polytherapy. MPI is derived from validated scales which are commonly used in geriatric medicine.¹⁵ When compared to other frailty instruments, the MPI had demonstrated higher predictive power of short- and long-term all-cause mortality in hospitalized elderly patients.^{16,17}

The primary goal of the FRAGIS (Frailty Assessment by Geriatric Investigation in Surgery) study was to evaluate the association

between the MPI score and the occurrence of major postoperative complications within 30 days of CRC surgery.

The secondary goal was to develop a model to predict the individual risk of postoperative complications, allowing the appropriate patient selection for surgery.

2 | METHODS

2.1 | Study design, study population, and inclusion criteria

The FRAGIS study is a prospective multicentric cohort study involving three surgical wards of different hospitals in Northern Italy: *Chirurgia Generale 2 of Spedali Civili of Brescia* (leading center), *Chirurgia Generale of Ospedali Riuniti—University of Trieste*, and *Chirurgia Generale of Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico of Milan*.

All CRC patients aged ≥ 75 years, who were scheduled for elective surgery and able to express their consent to treatment, were considered. The study was carried out from October 2017 to August 2019.

Patients who met the inclusion criteria underwent geriatric evaluation within 2 weeks before surgery. Patients previously diagnosed with cognitive impairment were interviewed together with their caregivers or next of kin. Information on functional status was confirmed by the nursing staff.

The surgical treatment was planned before and regardless of the geriatric evaluation.

The multidimensional assessment was performed by residents in Geriatric Medicine and took about 30 min.

It was comprehensive of the eight CGA domains included in the MPI (Table S1):

- Functional status: Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL)^{18,19};
- Cognitive function: Short Portable Mental Status Questionnaire (SPMSQ)²⁰;
- Nutritional status: Mini Nutritional Assessment (MNA)²¹;
- Risk of developing Pressure Lesion: Exton-Smith Scale (ESS)²²;
- Physical health and comorbidities: Cumulative Index Rating Scale—Comorbidity Index (CIRS-CI)²³;
- Polypharmacy: number of drugs used;
- Social status: cohabitation status.

Each domain was scored using a tripartite hierarchy (0, no problems; 0.5, minor problems; and 1, major problems) according to Pilotto et al.¹⁵ The sum of the scores from the eight domains was then divided by 8 to obtain the final MPI score ranging between 0 and 1.

Patients were then divided into three groups: MPI class 1 (MPI score up to 0.33), MPI class 2 (MPI score > 0.33 up to 0.66), and MPI class 3 (MPI score > 0.66) according to previously validated cut-off points.¹⁵ In this study, all patients categorized MPI class 2–3 were

classified as “frail.” This classification predicted length of stay and survival below the median in older patients hospitalized in an acute ward.¹⁵⁻¹⁷

Additionally, the patient's physical performance was assessed by the 5-Meter Walk Test (5MWT).²⁴ This gait speed test measured the time (in seconds) the patient took to complete 5-m walking at his/her usual pace. The test was performed three times and the best result was recorded. The use of walking aids was not an exclusion criterion for the test; individuals who required assistance to walk were excluded from the 5MWT.

The American Society of Anesthesiology (ASA) score calculation was part of standardized clinical assessment.

Any deviation from a regular postoperative course was considered a postoperative complication and scored according to Clavien–Dindo classification²⁵: surgical site infection and anastomotic leak; bleeding; ileus; stroke; any respiratory, renal, cardiovascular, hepatic impairment. Complications were recorded throughout the hospitalization and up to 30 days after surgery.

Follow-up visits were conducted 30 and 90 days after surgery. When in person follow-up visits were not possible, patients were interviewed by phone.

2.2 | Sample size

The sample size was estimated on the primary outcome. The literature reports a mean incidence rate of major postoperative complications after CRC surgery of 20%–40% in patients aged ≥ 75 years.^{6,26-28} We anticipated a lower complication rate (estimated around 15%) in the group of patients with MPI class 1 and a higher complication rate (estimated around 45%) in MPI class 2–3 patients.

According to the literature, we expected that about three-quarters of surgical patients aged ≥ 75 years could enter MPI class 1 and only a quarter could enter MPI class 2, or MPI class 3.¹⁶ Assuming a level of significance of 5%, a power of 80%, and MPI class 1/MPI class 2–3 ratio of 3:1, 104 patients would have to be enrolled (78 MPI class 1 vs. 26 MPI class 2–3).

2.3 | Statistical analysis

Patients were grouped according to the frailty status defined through MPI score and according to the presence of major postoperative complications (Clavien–Dindo grades ≥ 3). If a patient experienced more than one complication, only the “highest ranking” complication was included. Categorical variables were summarized using frequencies and compared across groups through the χ^2 test or Fisher's exact test in case of expected frequencies < 5 . Continuous variables were described in terms of the median and interquartile range (IQR) and compared through the Mann–Whitney test.

The thresholds for the MPI, 5MWT, and ASA scores were defined through the point-closest-to-(0,1) approach within the receiver operating characteristic (ROC) curve.²⁹

Concordance between definitions of frailty was evaluated with the kappa statistics.

Univariate logistic regression models were fitted to assess the association between major postoperative complications and MPI score, ASA score and 5MWT value, as well as selected socio-demographic and clinical variables. Each of the three scores were included in the models as categorical variables using the threshold identified through the ROC curve analysis.

The most predictive multivariate model for major postoperative complications was then identified by means of a 10-fold cross-validated least absolute shrinkage and selection operator (LASSO)³⁰ regression technique. Briefly, cross-validated LASSO allowed to find the optimal shrinkage parameter λ and, thus, define the set of independent predictors. The selected model was then cross-validated to avoid overfitting, and model discrimination evaluated through the area under the ROC curve (AUC). Model results have been graphically presented through a nomogram, an intuitive tool allowing to find the predicted probability model of postoperative major complications based on selected prognostic variables.

Analyses have been carried out using R version 3.6.1 (R Core Team, 2019). The package “glmnet” was used for the LASSO regression and the package “rms” for drawing the nomogram.

2.4 | Ethical aspects

The study was conducted in accordance with the general clinical practices, the ethical principles deriving from the Helsinki Declaration and the current legislation on observational studies. The informed consent for personal/clinical data management and surgical treatment was obtained from all patients enrolled in the study.

The study was approved by the Ethical Committees of all the three hospitals involved.

3 | RESULTS

A total of 121 patients were selected. Among these, 13 (11%) refused to participate and 4 (3%) were unable to give their consent, leaving 104 patients eligible for the study. No one was lost at follow-up. The median age was 81 years (range 75–95 years), 53% of patients were males. Demographic and clinical characteristics of the patients according to MPI class cut-offs are reported in Table 1. A total of 34 (33%) patients were classified as frail (MPI class 2–3).

Comparison between frail and fit patients found the former to be older (84 vs. 80 years; $p = .028$) and to have higher ASA score (ASA 4 in 21% vs. 1% of cases; $p < .01$), higher CIRS-CI (≥ 3 in 97% vs.

TABLE 1 Demographics of 104 elderly colorectal cancer patients by Multidimensional Prognostic Index (MPI) classification

	MPI class		p value
	1 (fit patients) n = 70	2-3 (frail patients) n = 34	
Age (years)	80 (IQR 78-84; range 75-95)	84 (IQR 80-88; range 75-95)	.03
Sex (male, %)	44 (63%)	11 (32%)	<.01
ASA score			<.01
1	0 (0%)	0 (0%)	
2	31 (44%)	1 (3%)	
3	38 (54%)	26 (76%)	
4	1 (1%)	7 (21%)	
CIRS-CI			<.01
0	0 (0%)	0 (0%)	
1-2	23 (33%)	1 (3%)	
≥3	47 (67%)	33 (97%)	
MNA			<.01
≥24	54 (77%)	5 (15%)	
17-23.5	16 (23%)	25 (74%)	
<17	0 (0%)	4 (12%)	
5MWT (m/s)	0.95 (IQR 0.79-1.12; range 0.42-1.71)	0.65 (IQR 0.28-0.83; range 0-1.1)	<.01

Note: Due to rounding, the sum of the percentages may not be 100%. Abbreviations: ASA, American Society of Anesthesiologists; CIRS-CI, Cumulative Illness Rating Scale—Comorbidity Index; IQR, interquartile range; MNA, Mini Nutritional Assessment; 5MWT, 5-Meter Walk Test.

67% of cases; $p < .01$) and lower MNA score (<17 in 12% vs. 0% of cases; $p < .01$). The prevalence of women was higher among frail patients (68% vs. 37%; $p < .01$). Comparison of gait speeds obtained through the 5MWT revealed poorer physical performance among frail patients (median speed 0.65 m/s vs. 0.95 m/s; $p < .01$).

3.1 | Operative and postoperative treatment

No significant differences were found in terms of surgical approach, colon resection types, stoma creation, and epidural catheter employment among fit and frail patients. Also, neo- or adjuvant chemoradiotherapy use was similar (Table 2).

3.2 | Postoperative outcomes

Major postoperative complications were significantly more frequent among frail patients: 52% versus 16% ($p < .01$), including need for transfusions (53% vs. 30%; $p = .04$). The hospital stay after surgery was significantly longer among frail patients (13 vs. 8.5 days; $p = .03$).

TABLE 2 Intra- and postoperative factors by Multidimensional Prognostic Index (MPI) classification

	MPI class		p value
	1 (fit patients) n = 70	2-3 (frail patients) n = 34	
Neoadjuvant therapy	8 (11%)	1 (3%)	.29
Adjuvant therapy	10 (14%)	1 (3%)	.16
Operative approach (laparoscopy, %)	41 (59%)	14 (41%)	.14
Epidural catheter (POD 1-3)	33 (47%)	13 (38%)	.52
Resection type			.74
Right colectomy	32 (46%)	19 (56%)	
Left colectomy	15 (21%)	7 (21%)	
Rectal resection	17 (24%)	7 (21%)	
APR	4 (6%)	1 (3%)	
Total colectomy	2 (3%)	0 (0%)	
Stoma creation	13 (19%)	4 (12%)	.55

Note: Due to rounding, the sum of the percentages may not be 100%. Abbreviations: APR, abdominoperineal resection (Miles' procedure); POD, postoperative day.

Both 30 and 90 days postoperative mortality (POM) were significantly higher among frail patients (9% vs. 0%; $p = .03$ and 18% vs. 1%; $p = .005$, respectively; Table 3).

Univariate analysis showed strong associations between MPI score and major postoperative complications (Table 4). At the ROC curve analysis, the best cut-off was 0.33 (Figure 1A). More in detail, patients with MPI score > 0.33 (i.e., MPI class 2-3) had sixfold higher risk of complications. Further variables associated with major postoperative complications were gait speed ≤ 0.75 m/s as assessed through 5MWT and ASA score ≥ 3 . The ROC curve analysis is shown in Figure 1A. The interaction between MPI score and 5MWT value on postoperative outcomes is shown in Table S2.

The best multivariable predictive model, selected through a logistic cross-validated LASSO multivariate analysis, includes as predictors of major postoperative complications: (I) MPI score > 0.33, (II) 5MWT value ≤ 0.75 m/s, (III) ASA score ≥ 3 , (IV) laparotomic operative approach, and (V) stoma creation (Table 4). No significant interactions were selected. The cross-validated model AUC was 0.69, representing a fair model discrimination (Figure 2A).

The nomogram we created allows to predict the probability of major postoperative complications according to the aforementioned characteristics (Figure 2B).

The 90-day POM was strongly associated with MPI score > 0.375, ASA score > 3, and 5MWT value ≤ 0.49 m/s (Figure 1B), as well as with patients age and resection type at univariate analyses (Table S3).

However, there were no statistically significant predictors of 90-days POM selected through a logistic cross-validated LASSO multivariate analysis.

TABLE 3 Postoperative outcomes by Multidimensional Prognostic Index (MPI) classification

	MPI class		p value
	1 (fit patients) n = 70	2-3 (frail patients) n = 34	
RBC transfusion	21 (30%)	18 (53%)	.04
Major postoperative complication (Clavien-Dindo grade ≥3)	11 (16%)	18 (52%)	<.01
Minor postoperative complication (Clavien-Dindo grade 1-2)	34 (49%)	11 (32%)	.18
Postoperative LoS (days) ^a	8.5 (IQR 7-12; range 4-48)	13 (IQR 7-20; range 5-36)	.03
30-day POM	0/70 (0%)	3/34 (9%)	.03
90-day POM	1/70 (1%)	6/34 (18%)	<.01

Abbreviations: IQR, interquartile range; LoS, length of stay; POM, postoperative mortality; RBC: red blood cells.

^aExcludes patients who died postoperatively (n = 3).

4 | DISCUSSION

In our study population, one-third of patients were classified as frail by MPI evaluation. The typical “frail” phenotype was female sex, age > 80 years, ASA score ≥ 3, CIRS-CI ≥ 3, MNA < 24, and low walking speed (<0.8 m/s) at the 5MWT.

In the studies by Giantin et al.^{31,32} 60% of patients were classified as MPI class 1, 30% as MPI class 2, and 10% as MPI class 3. Several other studies have tried to estimate the prevalence of frailty in elderly cancer patients. A recent systematic review³³ including 22 studies from 20 cohorts found that the median prevalence of frailty is 42% (range 6%–86%), and the median prevalence of pre-frailty is 43% (range 13%–79%) in that population.

This substantial variation among studies can be partially explained by the different settings of investigation (surgical clinic vs. medical/geriatric ward vs. nursing home) and by different definitions of frailty, as the number of impaired CGA domains used to diagnose frailty varied from 1 to 4.

To our knowledge, the FRAGIS study is the first to evaluate the predictive value of the MPI score on ≥75-year-old patients scheduled for CRC surgery. A review addressing frailty on CRC surgical patients aged ≥65 years was recently published by Fagard et al.³⁴ Although no consensus was reached on the most appropriate tools for frailty diagnosis, the study found that frailty assessment helps clinicians determine operative risks/benefits and perioperative management.

TABLE 4 Univariable and multivariable analysis of potential determinants for major complications after surgery

	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
5MWT value ≤ 0.75 m/s	4.82 (1.94-12.02)	<.01	2.50 (0.84-7.38)	.09
MPI score > 0.33	6.03 (2.38-15.32)	<.01	3.33 (1.04-11.40)	.05
ASA score ≥ 3	3.72 (1.17-11.81)	.03	1.54 (0.41-6.51)	.53
Age (×10 years)	1.22 (0.53-2.79)	.64	–	
Sex (male)	0.77 (0.33-1.83)	.56	–	
Hb < 10 g/dl	1.21 (0.46-3.19)	.71	–	
Operative approach (open)	2.32 (0.96-5.60)	.06	2.11 (0.79-5.83)	.14
Resection type		.61	–	
Right colectomy	1 (Reference)			
Left or total colectomy	1.62 (0.56-4.72)			
Rectal/APR	1.46 (0.53-4.05)			
Stoma creation	1.52 (0.50-4.57)	.46	2.16 (0.56-8.26)	.25

Abbreviations: APR, abdominoperineal resection (Miles' procedure); ASA, American Society of Anesthesiologists; CI, confidence interval; MPI: Multidimensional Prognostic Index; OR, odds ratio; POM, postoperative mortality; 5MWT, 5-Meter Walk Test.

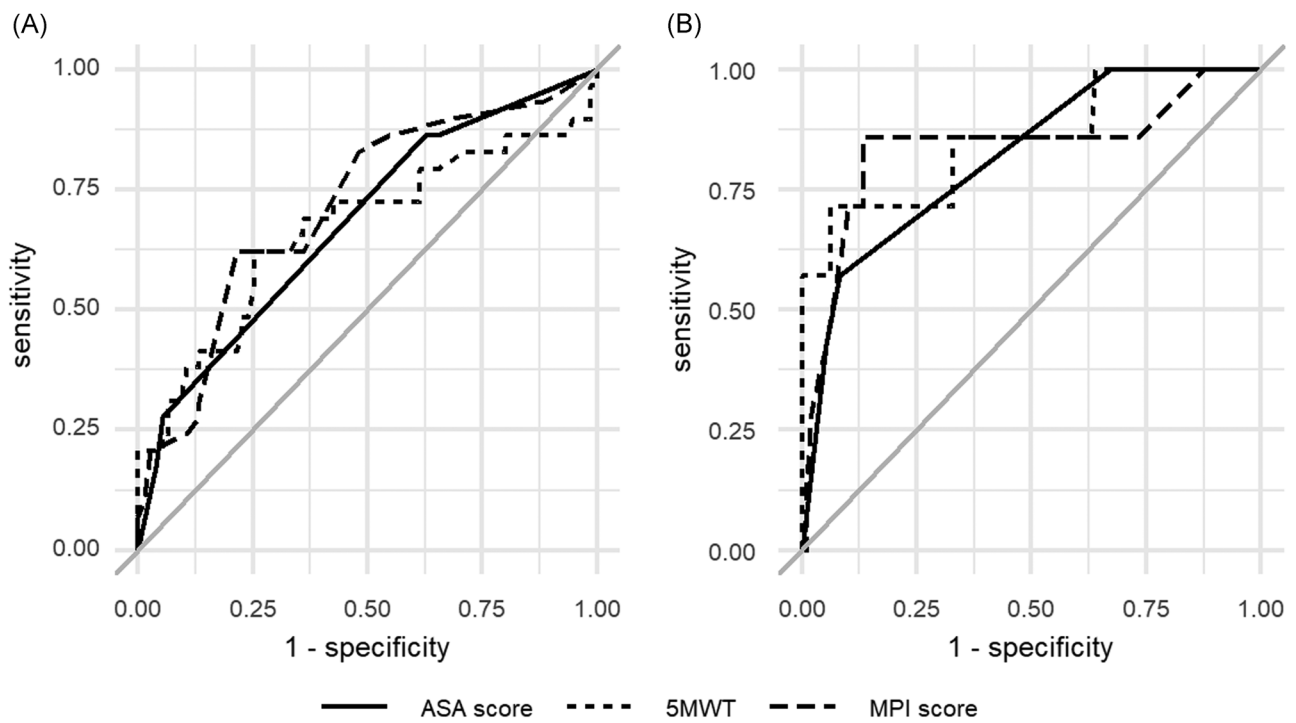


FIGURE 1 Receiver operating characteristic (ROC) curve for the Multidimensional Prognostic Index (MPI) score, the gait speed test measured by the 5-Meter Walk Test (5MWT), and the ASA score for major postoperative complications (A) and 90-day mortality (B). (A) Cut-offs and unvalidated AUC values: MPI score > 0.33, AUC 0.72; 5MWT value \leq 0.75 m/s, AUC 0.67; ASA score \geq 3, AUC 0.68. (B) Cut-offs and unvalidated AUC values: MPI score > 0.375, AUC 0.84; 5MWT value \leq 0.49 m/s, AUC 0.85; ASA score > 3, AUC 0.82. ASA, American Society of Anesthesiologists; AUC, area under the ROC curve; ROC, receiver operating characteristic

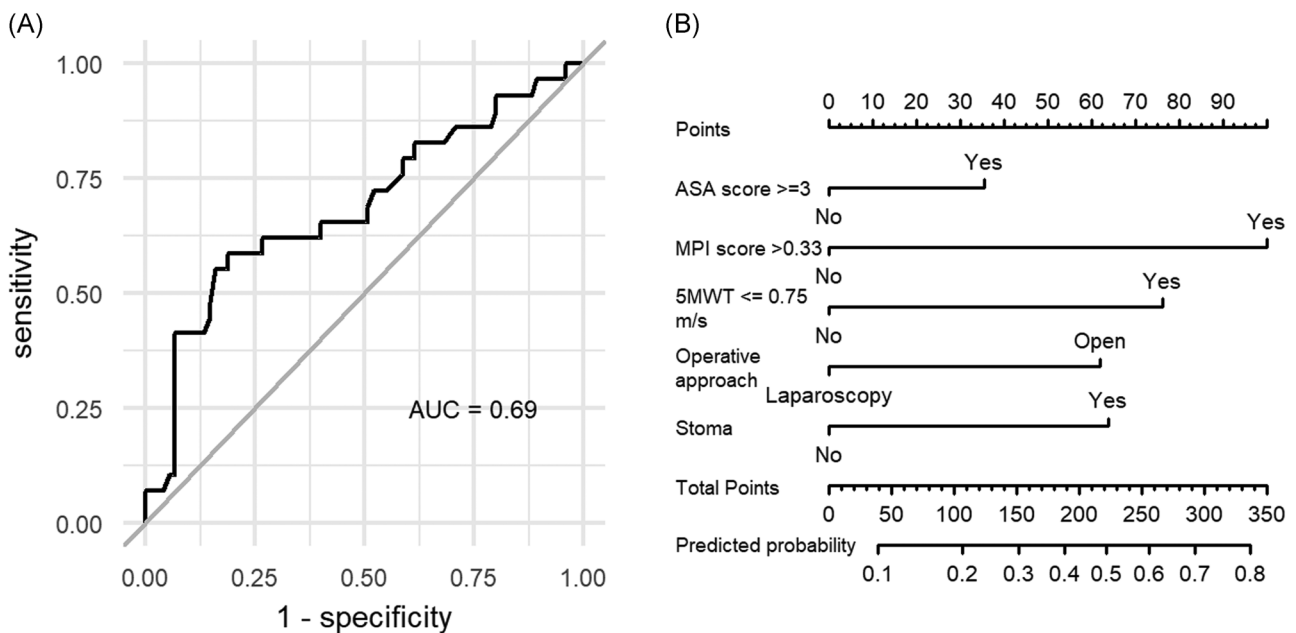


FIGURE 2 ROC curve for the best multivariable predictive model of major postoperative complications selected through cross-validated LASSO (A) and model nomogram (B). ASA, American Society of Anesthesiologists; AUC, area under the ROC curve; LASSO, least absolute shrinkage and selection operator; MPI: Multidimensional Prognostic Index; ROC, receiver operating characteristic; 5MWT, 5-Meter Walk Test

More recently, the association between “frail” phenotype—assessed by the modified Fried Index (mFI) and the Clinical Frailty Scale (CFS)—and outcomes after noncardiac (mostly orthopedic) surgery has been described.³⁵ Neither mFI nor CFS demonstrated adequate sensitivity or specificity as a screening tool (about 60%). Comparable conclusions on mFI were drawn by a meta-analysis by Panayi et al.³⁶

4.1 | MPI as a tool to assess frailty in surgical patients

The MPI score has shown good prognostic value in different cohorts of elderly patients hospitalized for acute diseases (heart failure,³⁷ pneumonia,³⁸ or acute intestinal bleeding³⁹).

In the context of geriatric oncology, MPI classes have shown adequate predictive value for mortality. In a study by Giantin et al.³¹ on 160 elderly patients with locally advanced or metastatic solid cancer, the hazard ratios (HRs) for all-cause mortality were 4.36 at 6 months and 3.57 at 12 months for MPI class 2 versus MPI class 1 subjects, respectively. HRs were 8.09 at 6 months and 5.66 at 12 months for MPI class 3 versus MPI class 1 subjects, respectively. The same authors recently compared the prognostic value of the MPI versus the Multidimensional Geriatric Assessment (MGA).³² The MGA is a more complex and time-consuming tool. Despite that, MPI (AUC of 0.73, 95% CI 0.65–0.81) performed better than MGA (AUC 0.65, 95% CI 0.56–0.73) in predicting 12-month mortality risk.

Our study found a statistically significant association between the MPI score and the incidence of major postoperative complications. Frail patients also had increased postoperative length of stay. The longer hospitalization could be due to the higher morbidity, but also to the greater likelihood of discharge to a skilled care facility, which can delay discharge. The best MPI cut-off value for major complications was 0.33 at the ROC curve analysis. This cut-off corresponds exactly to that previously validated by Pilotto et al.¹⁵ to distinguish patients at low risk of mortality (MPI class 1 = MPI score \leq 0.33).

The overall 90-day POM among frail subjects was 18% in our study. It increased up to 32% among patients with MPI score $>$ 0.375 and reached 50% if associated with a walking speed $<$ 0.49 m/s.

The MPI score was strongly associated with 90-days POM in the univariate logistic model (OR 38.78). However, the limited sample size hampered any significant correlation at the multivariate analysis. Adequately powered studies on postoperative mortality outcome in geriatrics patients affected by CRC are needed.

4.2 | Predictive model of major postoperative complications

Our study showed that MPI score represents the most important variable associated with adverse postoperative outcomes among elderly CRC patients. Furthermore, some surgical aspects (laparoscopic/open approach and stoma creation) together with clinical parameters

(ASA score and 5MWT speed) contributed to define the postoperative individual risk profile.

We adopted the 5MWT because physical performance has been acknowledged to play a central role in characterizing frailty. Physical performance is only indirectly evaluated by some domains (i.e., ADL, IADL, ESS) in the MPI. Gait speed represents a reliable measure to assess balance, coordination, and strength, and is inversely associated with the presence of sarcopenia.^{40,41} Studenski et al.⁴² reported that gait speed above 0.8 m/s as measured by 5MWT predicts a higher life expectancy, regardless of age and sex.⁴¹ According to our ROC curve analysis, the best cut-off value that could be used for frailty definition was \leq 0.75 m/s, hence not exceedingly different from 0.8 m/s reported by Studenski et al.⁴²

The results of our multivariate model on postoperative major complications were graphically translated into a model nomogram. We believe that this graphical representation could be useful in clinical practice, as it provides the clinician with an immediate visualization of the risk through the simple sum of the variables. Compared to other previously validated risk calculators (such as the ACS NSQIP surgical risk calculator⁴³), our model is the result of an in-depth evaluation of the patient's nutritional and functional status, parameters that are now believed to be crucial in addition to comorbidities in the definition of frailty. Surely the comparison between different evaluation tools could provide interesting results in future publications.

We recognize that the use of LASSO is not so common in a regression framework, and that readers may not be familiar with model selection unrelated to the statistical significance of single regressors, as for stepwise or backward methods. Conversely, LASSO shifts the paradigm to identify highly predictive rather than highly significant variables.

Our study shows that frailty is not uncommon among elderly patient affected by CRC, and a simple tool as the MPI can be useful to assess this condition. In our opinion frail patients, particularly when frailty is associated with high ASA scores and low 5MWT speeds (one-fifth of our study population), could benefit from a full CGA to specifically assess their strengths and resources alongside their weakness and needs. The best course of action for these patients is still not well established. Some might benefit from tailored surgery preceded by pre-habilitation^{44,45} while an exclusively palliative treatment (endoscopic or surgical) could be deemed adequate for other patients.

4.3 | Limitations

We must acknowledge some limitations of the present study. The study size was determined to evaluate only the association between the MPI score and the occurrence of postoperative morbidity. Thus, we must point out that the multivariate prognostic model developed using LASSO selection may lack adequate power, especially for revealing potential interactions among prognostic factors. In terms of model discrimination, while the AUC of the cross-validated

categorical MPI score was equal to 0.61, the AUC of the identified multivariate model was only slightly higher, being equal to 0.69.

In addition, the low rate of 90-days POM in the enrolled patients hampered the identification of mortality risk factors in a multivariate analysis.

Larger prospective multicenter studies are therefore needed to confirm our findings, particularly to externally validate the model nomogram for postoperative complications.

5 | CONCLUSIONS

Old age is not an absolute contraindication to CRC radical treatment, but frailty should be detected preoperatively because it increases morbidity. We provided a nomogram to address risk stratification of elderly patients undergoing surgery. In this process, the MPI score has the major impact on outcome prediction.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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REFERENCES

1. Cronin Kathleen A, Lake Andrew J, Scott S, et al. Annual Report to the Nation on the Status of Cancer, part I: national cancer statistics. *Cancer*. 2018;124(13):2785–2800. <http://doi.org/10.1002/cncr.31551>
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49:1374–1403.
3. Partridge JS, Harari D, Dhisi JK. Frailty in the older surgical patient: a review. *Age Ageing*. 2012;41:142–147.
4. Janssen-Heijnen ML, Houterman S, Lemmens VE, Louwman MW, Maas HA, Coebergh JW. Prognostic impact of increasing age and comorbidity in cancer patients: a population-based approach. *Crit Rev Oncol Hematol*. 2005;55:231–240.
5. Alves A, Panis Y, Mathieu P, Kwiatkowski F, Slim K, Association Française de Chirurgie. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. *Arch Surg*. 2005;140:278–283; discussion 284.
6. Audisio RA, Pope D, Ramesh HS, et al. Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study. *Crit Rev Oncol Hematol*. 2008;65:156–163.
7. Leung E, McArdle K, Wong LS. Risk-adjusted scoring systems in colorectal surgery. *Int J Surg*. 2011;9(2):130–135.
8. Hill BL, Brown R, Gabel E, et al. An automated machine learning-based model predicts postoperative mortality using readily-extractable preoperative electronic health record data. *Br J Anaesth*. 2019;123(6):877–886.
9. Ellis G, Langhorne P. Comprehensive geriatric assessment for older hospital patients. *Br Med Bull*. 2004;71:45–59.
10. Clegg A, Rogers L, Young J. Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review. *Age Ageing*. 2015;44:148–152.
11. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. *J Am Geriatr Soc*. 1991;39:8S-16S; discussion 17S–18S.
12. Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg*. 2012;215:453–466.
13. Ghignone F, van Leeuwen BL, Montroni I, et al. The assessment and management of older cancer patients: a SIOG surgical task force survey on surgeons' attitudes. *Eur J Surg Oncol*. 2016;42:297–302.
14. Audisio RA. Preoperative evaluation of the older patient with cancer. *J Geriatr Oncol*. 2016;7:409–412.
15. Pilotto A, Ferrucci L, Franceschi M, et al. Development and validation of a Multidimensional Prognostic Index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. *Rejuvenation Res*. 2008;11:151–161.
16. Pilotto A, Rengo F, Marchionni N, et al. Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. *PLOS One*. 2012;7:e29090.
17. Pilotto A, Sancarlo D, Pellegrini F, et al. The Multidimensional Prognostic Index predicts in-hospital length of stay in older patients: a multicentre prospective study. *Age Ageing*. 2016;45:90–96.
18. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914–919.
19. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179–186.
20. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23:433–441.
21. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*. 1999;15:116–122.
22. Bliss MR, McLaren R, Exton-Smith AN. Mattresses for preventing pressure sores in geriatric patients. *Mon Bull Minist Health Public Health Lab Serv*. 1966;25:238–268.
23. Conwell Y, Forbes NT, Cox C, Caine ED. Validation of a measure of physical illness burden at autopsy: the Cumulative Illness Rating Scale. *J Am Geriatr Soc*. 1993;41:38–41.
24. Wilson CM, Kostsura SR, Boura JA. Utilization of a 5-Meter Walk Test in evaluating self-selected gait speed during preoperative screening of patients scheduled for cardiac surgery. *Cardiopulm Phys Ther J*. 2013;24:36–43.
25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
26. Pirrera B, Vaccari S, Cuicchi D, et al. Impact of octogenarians on surgical outcome in colorectal cancer. *Int J Surg*. 2016;35:28–33.
27. Kennedy GD, Heise C, Rajamanickam V, Harms B, Foley EF. Laparoscopy decreases postoperative complication rates after abdominal colectomy: results from the national surgical quality improvement program. *Ann Surg*. 2009;249:596–601.
28. Longo WE, Virgo KS, Johnson FE, et al. Risk factors for morbidity and mortality after colectomy for colon cancer. *Dis Colon Rectum*. 2000;43:83–91.

29. Rota M, Antolini L. Finding the optimal cut-point for Gaussian and Gamma distributed biomarkers. *Comput Stat Data Anal.* 2014;69:1-14.
30. Tibshirani R. Regression shrinkage and selection via the LASSO. *J R Stat Soc Ser B.* 1996;58:267-288.
31. Giantin V, Valentini E, Iasevoli M, et al. Does the Multi-dimensional Prognostic Index (MPI), based on a Comprehensive Geriatric Assessment (CGA), predict mortality in cancer patients? Results of a prospective observational trial. *J Geriatr Oncol.* 2013;4:208-217.
32. Giantin V, Falci C, De Luca E, et al. Performance of the Multi-dimensional Geriatric Assessment and Multidimensional Prognostic Index in predicting negative outcomes in older adults with cancer. *Eur J Cancer Care.* 2018;27:e12585.
33. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol.* 2015;26:1091-1101.
34. Fagard K, Leonard S, Deschodt M, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: a systematic review. *J Geriatr Oncol.* 2016;7:479-491.
35. McIsaac DI, Taljaard M, Bryson GL, et al. Frailty as a predictor of death or new disability after surgery: a prospective cohort study. *Ann Surg.* 2020;271:283-289.
36. Panayi AC, Orkaby AR, Sakthivel D, et al. Impact of frailty on outcomes in surgical patients: a systematic review and meta-analysis. *Am J Surg.* 2019;218:393-400.
37. Pilotto A, Addante F, Franceschi M, et al. Multidimensional Prognostic Index based on a comprehensive geriatric assessment predicts short-term mortality in older patients with heart failure. *Circ Heart Fail.* 2010;3:14-20.
38. Pilotto A, Addante F, Ferrucci L, et al. The multidimensional prognostic index predicts short- and long-term mortality in hospitalized geriatric patients with pneumonia. *J Gerontol A Biol Sci Med Sci.* 2009;64:880-887.
39. Pilotto A, Ferrucci L, Scarcelli C, et al. Usefulness of the comprehensive geriatric assessment in older patients with upper gastrointestinal bleeding: a two-year follow-up study. *Dig Dis.* 2007;25:124-128.
40. Peel NM, Kuys SS, Klein K. Gait speed as a measure in geriatric assessment in clinical settings: a systematic review. *J Gerontol A Biol Sci Med Sci.* 2013;68:39-46.
41. Vetrano DL, Rizzuto D, Calderón-Larrañaga A, et al. Walking speed drives the prognosis of older adults with cardiovascular and neuropsychiatric multimorbidity. *Am J Med.* 2019;132:1207-1215.
42. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA.* 2011;305:50-58.
43. Bilimoria KY, Liu Y, Paruch JL, et al. Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons. *J Am Coll Surg.* 2013;217:833-842.
44. Milder DA, Pillinger NL, Kam PCA. The role of prehabilitation in frail surgical patients: a systematic review. *Acta Anaesthesiol Scand.* 2018;62:1356-1366.
45. Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation before major abdominal surgery: a systematic review and meta-analysis. *World J Surg.* 2019;43:1661-1668.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.