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Frailty assessment in elective gastrointestinal oncogeriatric surgery: Predictors of one-year mortality and functional status

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ABSTRACT

Objectives: Perioperative frailty assessment is still a challenge, especially in oncogeriatrics. We aimed at assessing the diagnostic accuracy of the 40 items Frailty Index (FI) as compared to the comprehensive geriatric assessment (CGA) for the prediction of one-year mortality and functional status after colorectal surgery in old-age subjects. **Material and methods:** Ninety-nine consecutive patients aged 65 years or older who were candidate for elective gastrointestinal cancer surgery, with G8 score ≤ 14 were enrolled and subjected to CGA and to frailty stratification according to the 40-items FI. Long-term outcomes including one-year mortality and functional decline were collected.

Results: Mean patient age was 80.3 ± 5.6 years. Colorectal cancer was the most common diagnosis. The most prevalent clinical phenotype was pre-frail. CGA and FI showed similar predictive accuracy in identifying one-year mortality after surgery and patient functional status. Our multivariate analysis indicated the pre-morbid functional status (IADL) and cancer stage as the most significant predictors of one-year mortality.

Conclusions: This is the first study to investigate the prognostic accuracy of the 40-items FI as compared to CGA in a vulnerable octogenarian cancer population. Its results are consistent with patient functional status being a mediator of frailty and with both serving as intertwined markers of clinical vulnerability. In addition, according to our results, cancer and specific environmental stressors, such as surgery, are likely to affect the frailty trajectory.

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1. Introduction

Due to the aging of populations worldwide and to the rising incidence of cancer with age, the surgical management of older patients is becoming more and more a key issue [1].

Surgery is the most efficient treatment for several solid cancers and recent technical advances with improved perioperative care have led to an increased number of older adults eligible for oncogeriatric surgery [2,3].

Postoperative mortality is a key outcome measure after cancer surgery, especially for high-risk older populations. However, while most studies considered 30-day postoperative mortality as a clinical end point, there is increasing evidence for a high mortality beyond 30 days [4].

Indeed, the exceeding postoperative mortality, up to 1 year after surgery, has been indicated as the most discriminant factor for long-term survival in elderly patients with colorectal cancer [5,6].

Abbreviations: CGA, Comprehensive Geriatric Assessment; SIOG, International Society of Geriatric Oncology; NCCN, National Comprehensive Cancer Network; EORTC, European Organization for Research and Treatment of Cancer; FI, Frailty Index; SF36, Short Form 36; MNA, Mini Nutritional Assessment; GA, geriatric assessment; MMSE, Mini Mental State Examination; CDT, Clock Drawing Test Shulman; GDS, Geriatric Depression Scale; I-ADL, Instrumental Activities of Daily Living; TUG, Timed "Up & Go" test; CIRS, Cumulative Illness Rating Scale; SI, Illness Severity Index; CI, Co-morbidity Index; NRS, Numeric Rating Scale; SVI, social vulnerability index; SD, standard deviation; IQR, median and inter-quartile range; AUC, Area under the curves; ROC, Receiver operating characteristic.

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The heterogeneity of biological aging mandates the accurate identification of a patient's vulnerability in order deliver individualized treatments [7,8]. Chronological age alone can no longer be considered the sole exclusion criterion for cancer surgery [2]. The presence of comorbidity [9], functional decline, and older age [10] were reported to play an important role in postoperative outcomes in elderly patients with gastrointestinal malignancies.

The inability of traditional risk assessment tools to estimate older patients' physiologic reserve after surgery has resulted in a growing interest in preoperative geriatric assessment [11].

The International Society for Geriatric Oncology (SIOG) recommended a two-step diagnostic assessment in patients aged 65 or older, consisting of an initial screening to identify vulnerable patients (e.g. G8 or VES-13) and of a comprehensive geriatric assessment (CGA) in those patients who score positive at the initial screen [12].

In line with these recommendations, the American College of Surgeons and the American Geriatrics Society also recommended a preoperative frailty assessment for all older adults who are candidates for surgical procedures [13].

Growing evidence indicates a role for CGA in the perioperative prediction of adverse clinical outcomes, including morbidity [14–17], short-term mortality [15,18] and mortality [19] in elderly cancer patients undergoing surgical interventions.

So far [20–24], progression-free survival and overall survival still represent the most commonly reported clinical outcomes for older adults, while long-term functional status, physical performance and frailty trajectories should represent the mainstay instead [17,25,26].

Given this scenario, we sought to compare the accuracy of CGA vs. Rockwood's 40-items Frailty Index (FI) in predicting one-year mortality and functional status after surgery in elderly patients with gastrointestinal cancer. In addition, we aimed at defining the clinical variables that best predict one-year mortality after surgery.

2. Materials and Methods

2.1. Study Design and Patients' Selection

This is a prospective study performed at the oncological gastrointestinal surgery ward of the IRCCS Ospedale Policlinico San Martino, Genoa, Italy.

From January 2015 to December 2017, 123 older cancer patients, candidate for elective gastrointestinal surgery were consecutively enrolled.

The study was approved by the Local Ethical Committee and met the guidelines of the local Governmental Agency. The study has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Patients were included if they were >65 years old, had a diagnosis of solid gastrointestinal tumour, were candidate for surgery, had a G8 questionnaire [27] score ≤ 14 , had adequate understanding of the Italian language and the ability to sign an informed consent.

Patients were excluded if they were younger than 65 years, had any clinical instability, received emergency surgery, had advanced dementia or pre-existing major neurological and/or psychiatric disorders.

2.2. Geriatric Assessment

The pre-operative clinical assessment was performed within 0–14 days before elective surgery at the hospital geriatric outpatient office by an expert trained geriatrician.

Patients with a score ≤ 14 on the G8 screening tool [27] received the comprehensive geriatric assessment (CGA) (Appendix A) [28–38] and the frailty assessment [39], based on FI [40] (FI). Patients were defined as frail if they had a score of 3 or more altered domains to the CGA [41]. Namely, Tinetti scale [31] was meant to assess postural instability, Morse scale was meant to assess the risk of falls [31], whilst Gijon scale

[38] to assess social vulnerability. On the basis of the FI assessment, a score of ≤ 0.08 defined patients as fit; a score of ≥ 0.25 as frail and a score between 0.08 and 0.25 defined patients as pre-frail [39].

Timed up & go test [42] (TUG) was used to assess the physical performance.

2.3. Data Collection

Demographic data (age, gender), tumour characteristics (site, local or metastatic) and the prevalence and types of geriatric recommended clinical interventions were collected.

Post-operative complications were recorded on the basis of Clavien–Dindo classification scale [43].

After twelve months from surgery, Barthel Index telephone interview (BII) was administered to assess long-term functional status [44]. Functional decline was defined as mild (BII > 80), moderate (BI: 21 to 79) and severe (BI ≤ 20). One-year mortality was also recorded.

2.4. Statistical Analysis

The descriptive analysis for quantitative variables was expressed as mean and standard deviation (SD).

Receiver operating characteristic (ROC) curves were used to compare CGA and FI and to compare their ability in predicting short-term mortality and post-operative complications. Area under the curves (AUC) with 95% CI were reported.

Receiver operating characteristic (ROC) curves were used to compare CGA and FI and to compare their ability in predicting 1-year mortality and 1-year functional status. Area under the curves (AUC) with 95% CI were reported.

The association between categorical data was performed with the two-tailed χ^2 or the Fisher exact test, when appropriate.

The non-parametric Mann–Whitney *U* test was used to compare patients on quantitative measures.

Spearman correlation coefficient was used to assess the correlation between two clinical variables, when appropriate.

All measures that were found to be significant at univariate analysis were included into the multivariable model according to a stepwise approach after adjustment for age and gender. Specifically, a *p* value of 0.10 was used as threshold for inclusion into the multivariate model and a *p* < 0.05 was considered as statistically significant.

Graph Pad v.5.0b and Stata (v.14; StataCorp) were used for the computation.

3. Results

3.1. Patients' Clinical Characteristics

Between January 2015 and December 2017, one-hundred and twenty-three gastrointestinal cancer patients, who were candidate for elective surgery, were consecutively enrolled. All patients underwent a two steps oncogeriatrics assessment (i.e. G8 screening test and CGA assessment). At 12 months, 24 patients (19.5%) had missing data and were excluded from the study. Thus, a total of ninety-nine patients were ultimately enrolled in the study (Fig. 1).

Mean patient age was 80.1 years ± 5.88 (range, 65–93 years). 47.5% of the patients were aged 85 years or older. 62% were male. All patients were community-dwelling.

Colorectal cancer was the most prevalent cancer diagnosis (88% of the cases) while gastric cancer represented 12% of the cases. Patients had surgery for colon carcinoma in 64% of the cases and for rectal carcinoma in 36.5% of the colorectal cancer cases.

Patients with a diagnosis of colorectal cancer were classified as stage I (10%), stage II (49%), stage III (31%) and stage IV (9%) according to TNM V classification (Fig. 2).

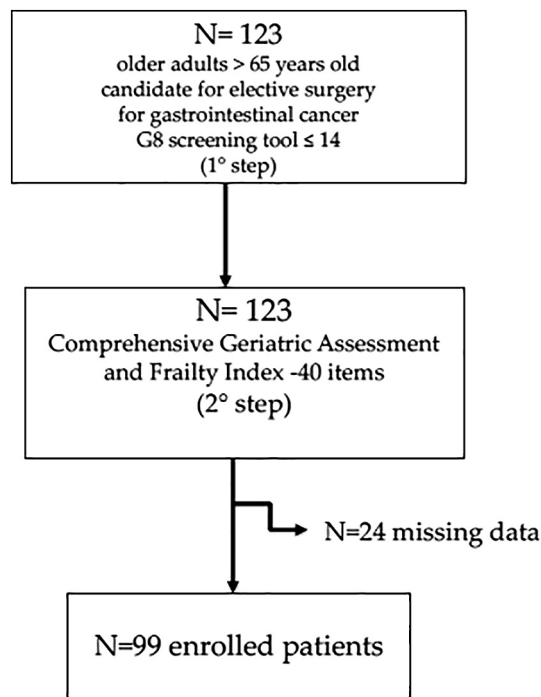


Fig. 1. Study design: patient's selection and two step oncogeriatric assessment.

Patients' clinical phenotype was characterized by multimorbidity, initial functional decline and malnutrition risk (Table 1).

Overall, 63 out of 99 patients (63,6%) had deficits in more than three CGA clinical domains, which was indicative of a frail phenotype (Fig. 3).

According to the FI, 9 patients were fit (9%), 50 were pre-frail (50,5%) and 40 patients were frail (40,5%) (Fig. 3).

Based on our CGA assessment, seventy patients received clinical therapeutic recommendations, with an average of 1.6 interventions per patient (range: 0–6). The most frequent recommendations were nutritional interventions (56%) and therapeutic interventions for pain (36%) and mood (39%) (Fig. 4).

The mean length of in-hospital stay was 8.8 ± 1.2 days.

3.2. Short-Term Outcomes: 30 Days Mortality and Post-Operative Complications (Clavien-Dindo Classification)

3.2.1. Short-Term Post-Operative Complications

FI was the clinical variable that we found to be most closely associated with post-operative complications (OR = 1.52 (95% CI: 1.05–2.22); $p = 0.027$), with an increase in post-operative complications by 52% corresponding to any FI increase by 0.1 points.

An impaired physical performance (as detected by time-up-and-go -TUG-test) was the clinical variable that showed the strongest

Table 1
Patients' clinical characteristics (N = 99).

Clinical variables	%	
Demographics		
Gender:		
Female	38	
Male	62	
Mean age (sd)	80.18 ± 5.88 (range 65–93 years)	
Age groups		
< 70	5	
71–75	17	
76–80	31	
81–85	29	
86–90	13	
> 91	5	
Screening tool, Cga assessment, Frailty assessment		
G8 screening tool	≤14	12.4 ± 2.3
Mmse	<24	27.10 ± 3.49
Cdt (schulman)	≥3	2.53 ± 1.44
Mna	<23	23.12 ± 3.31
Iadl	≤7	7.08 ± 1.73
Barthel index	<50	97.48 ± 6.54
Cirs severity		2.01 ± 0.34
Cirs comorbidity	>3	4.46 ± 1.79
N° of drugs	≥ 3	4.74 ± 2.83
Gds	≥ 5	3.92 ± 3.34
Tinetti scale	≤ 18	24.33 ± 5.35
Morse scale	≥ 25	21.10 ± 15.77
Gijon scale	≥ 10	8.80 ± 2.44
Cut off cga	≥ 3	3.49 ± 2.28
Fi		0.22 ± 0.13

association with post-operative complications (OR = 1.15 (95% CI: 1.00–1.33); $p = 0.048$).

3.2.2. Short-Term (30 Days) Mortality

Short-term mortality rate was of 0.8% (8/96 patients). FI (AUC = 0.72; 95% CI: 0.53–0.90) and CGA (AUC = 0.70; 95% CI: 0.51–0.89) showed similar predictive accuracy for short-term mortality ($p = 0.73$).

IADL was the clinical scored exhibiting the strongest association with short-term mortality (OR = 1.67; 95% CI: 1.20–2.27; $p = 0.002$). Specifically, an increase in mortality risk was demonstrated for any decline by 1-point of IADL.

3.3. Long-Term Outcomes: One-Year Mortality

One year after surgery for a gastrointestinal cancer, the mortality rate was 19% (19/99). In this group, 40% of the patients had stage IV cancer and 56% had reported major post-operative complications (Fig. 5). A pair-wise analysis of the ROC curves of CGA ($n = 99$; AUC = 0.72; 95% CI: 0.58–0.86) and FI ($n = 99$; AUC = 0.70; 95% CI: 0.54–0.89) showed a similar accuracy for the two scores in identifying one-year mortality after cancer surgery ($p = 0.61$) (Fig. 6). The FI cut-off value of 0.19

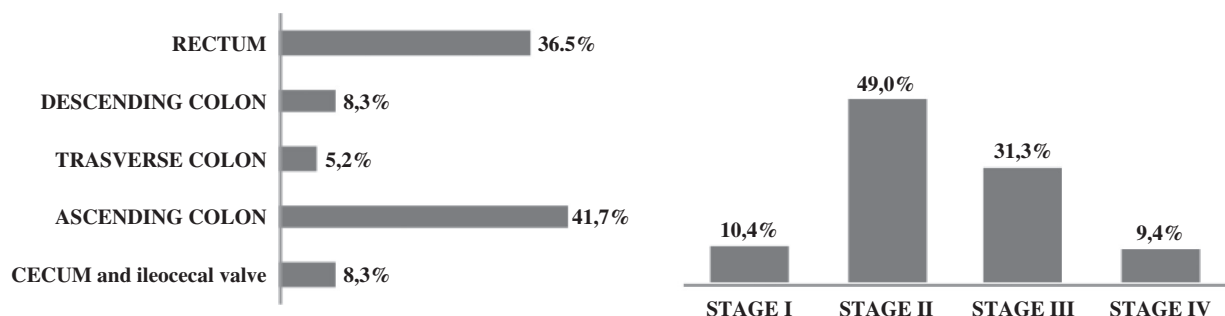


Fig. 2. Colorectal cancer distribution and stage.

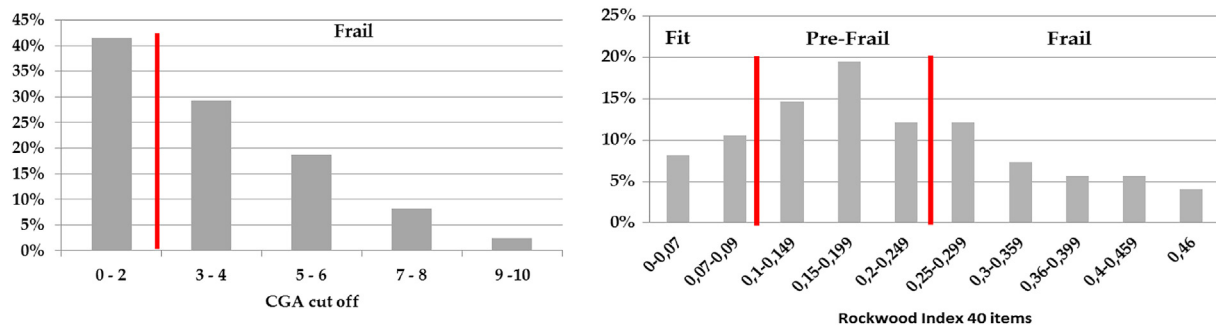


Fig. 3. Distribution of patients' clinical phenotype according to Comprehensive Geriatric Assessment and 40-Item Frailty Index IF.

(sensitivity:87.5%; specificity: 51.1%) showed the best predictive threshold for one-year mortality, whilst in the case of CGA, the best threshold predictive of one-year mortality was the value of 3 (sensitivity: 87.5%; specificity: 44.3%).

Our multivariate logistic regression analysis adjusted for age showed that functional decline in IADL (OR = 1.45; 95% CI: 1.03–2; $p = 0.033$) and cancer stage (OR = 3.28; 95% CI: 0.91–11.8; $p = 0.069$) were the clinical variables with the strongest association with one-year mortality. In particular, for each sub-item decrease in the IADL score, the mortality risk was found to increase by 45%. For each increase in cancer stage, the mortality risk was found to increase by >3 times. For the univariate analysis before stepwise logistic regression analysis see the [Appendix B](#).

3.4. Long-Term Outcomes: Functional Status After One Year From Gastrointestinal Surgery

As compared to pre-morbid functional status, at one year after surgery for gastrointestinal cancer, a functional decline in basic activities of daily living was observed in 23% of patients, with an average loss of 5.6 ± 15.8 points on the Barthel Index, between the two-points assessment.

The pair-wise comparison of the ROC curves of CGA ($n = 99$; AUC = 0.65; 95% CI: 0.50–0.80) and FI ($n = 99$; AUC = 0.69; 95% CI: 0.54–0.85), showed similar accuracy in predicting patients' functional status at one year after surgery ($p = .45$) (Fig. 7).

A FI cut off score between 0.15 (sensitivity: 76.5%; specificity: 43.6%) and 0.18 (sensitivity: 70.6%; specificity: 52.7%) showed the best predictive threshold for one-year functional decline. Similarly, a CGA cut off score of 3 (sensitivity: 64.7%; specificity: 50.9%) showed the best predictive threshold for one-year functional decline.

4. Discussion

The present study shows that, as compared to the gold standard CGA, the FI is very accurate in predicting the one-year mortality and functional status in a real-world population of elderly patients undergoing surgery for a gastrointestinal cancer. Furthermore, we also show that IADL and cancer stage are the key predictors of one-year mortality, with a decreased in mortality risk by 32% for each increase of sub items in the IADL score, adjusted for age and gender.

Functional status (IADL), physical performance (TUG) and FI also accurately predicted short-term outcomes, such as 30 days mortality and post-operative complications [45–50].

To date, few studies have investigated long-term outcomes, especially in very old oncological patients. Some of these studies have identified comorbidity, ASA classification, TNM stage and post-operative complications as key predictors of one-year mortality [19,26,51].

Previously, older patients with gastrointestinal cancer were reported to experience immediate post-operative functional decline, while about 11% of these old-age patients had permanent functional decline after 6 months from surgery [52].

The vast majority of elderly patients who are residents in nursing home were reported to have significant functional decline as a result of colon cancer surgery, although the lack of pre-operative frailty assessment prevented the generalization of the clinical findings [53].

A functional decline in IADL after colorectal cancer surgery was observed in a two-years observational follow up of octogenarian patients [26]. However, in this study, the perioperative CGA did not show any predictive role on long-term mortality and functional outcomes, due to the small sample size. In keeping with previous findings [18], comorbidity, functional decline in IADL, depression, and impaired nutrition, were the variables with the strongest ability to predict post-operative complications and early mortality.

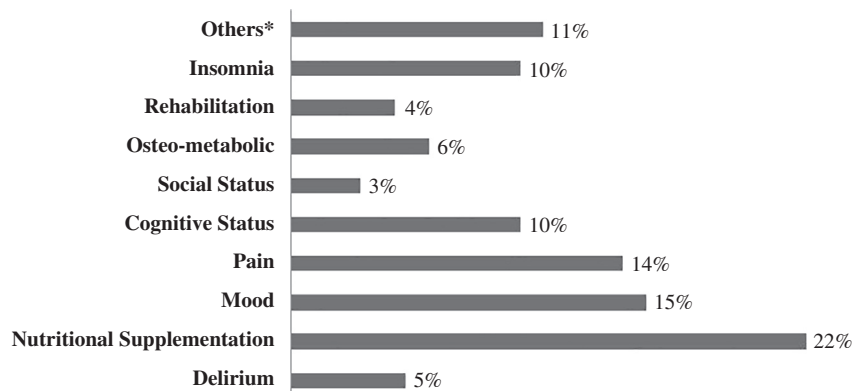


Fig. 4. Preoperative therapeutic recommendations based on CGA impaired clinical domains.

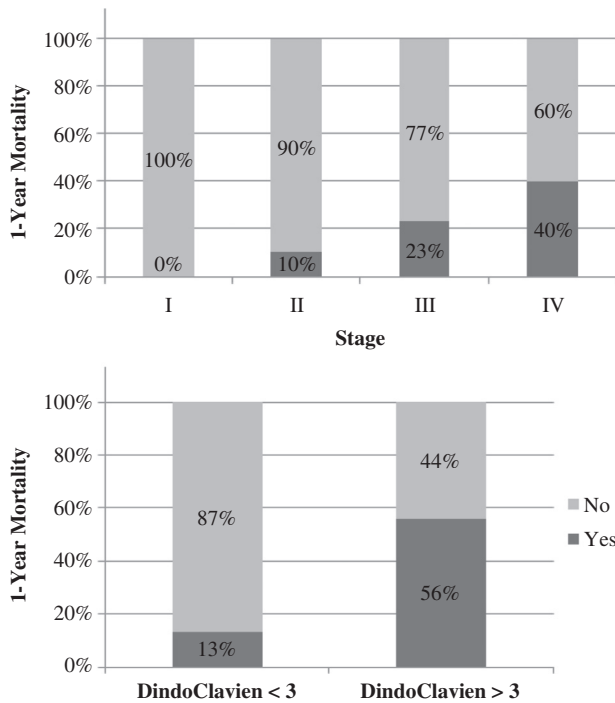


Fig. 5. One-year mortality patients' status on the basis of cancer stage (TNM 1–4 staging system) and post-operative complications (Clavien-Dindo Classification; < 2 minor complications; > 3 major complications), respectively.

In the study by Ommundsen et al. [19], which also enrolled elderly patients with colorectal cancer, IADL, nutritional status and comorbidity were the most predictive variables for both short-term (1-year) and long-term (5-year) survival after surgery.

Hamaker et al. [54] observed a worsening functional trajectory after three months from colorectal cancer surgery (with a mean functional decline of 18% - range: 2%–39%) and up to the first-year of follow-up, with permanent functional decline in older and frail patients.

The results of these studies indicate how patient-centered outcomes still receive poor attention as compared to traditional complications of surgery and to survival, whereas patient functional status and physical capacity should also be outcomes of primary interest, particularly in the older patient population [55].

Consistent with this notion, incorporating a perioperative frailty assessment of older cancer patients as a way to effectively predict immediate (30-day) post-operative complications and long-term mortality outcomes is now considered a priority [56].

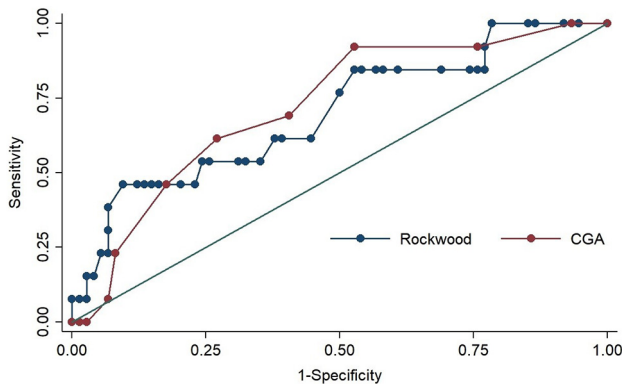


Fig. 6. ROC curve diagnostic accuracy comparison between CGA and 40-Item Frailty Index IF to predict one-year mortality.

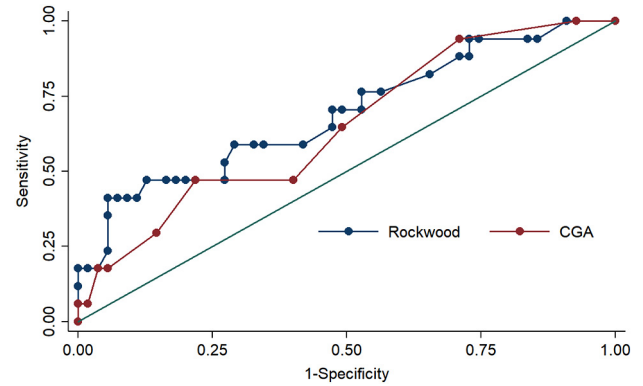


Fig. 7. ROC curve diagnostic accuracy comparison between CGA and 40-Item Frailty Index IF to predict functional status after one year from surgery.

In addition, obtaining more information on trajectories of frailty, functional decline, physical performance and cognitive status after major surgery for solid tumors has also become highly necessary, primarily for a more rationally planning of patient care and for conceiving and designing interventional studies. With this in mind, our study clearly indicates that the early preoperative assessment of functional status might unmask initial frailty trajectories that may reflect into short-term and long-term clinical outcomes as well.

Although the study was aimed at assessing the non-inferiority of FI as compared to CGA, it is noteworthy that measuring frailty allowed us to identify frailty cut-offs for the prediction of long-term outcomes. Namely, the FI cut off of 0.19 turned out to be the threshold for predicting mortality, while the cut off of 0.15 turned out to be the threshold for irreversible one-year functional decline. Indeed, also in our study, the frailty model based on the notion of accumulating clinical deficit seemed to better distinguish fit patients from vulnerable patients, thus delineating individualized clinical trajectories.

In addition, the identification of a frailty threshold, pointed out, at the same time, how frailty is a dynamic and potentially reversible syndrome at least at the initial stages.

These findings could lay the foundation for the implementation of systematic geriatric interventions in cancer older patients, as a way to reverse the homeostatic loss, recovering vulnerable patients to full oncological treatments.

The main limitations of our study are the single point preoperative frailty assessment and the single-centre population, that may represent a potential selection bias. In addition, intraoperative parameters, cancer disease progression/relapse, chemotherapy (changes or discontinuance) and re-hospitalizations were not systematically recorded during the observational period. However, they are part of ongoing research to assess patients' functional trajectories over time (2 years and more).

The strengths of our study are its prospective nature with long-term outcomes measurement, including functional status, in old age patients with gastrointestinal cancer. The systematic assessment of frailty, by virtue of the FI assessment, moved a step forward the understanding of long-term clinical outcomes after cancer surgery in the old age patients.

Although preliminary in nature, our definition of predictors of homeostatic loss is meant to help identify older subject with cancer, who are at the highest risk of seeing their vulnerability/frailty exacerbated by surgery. Based on our data, we propose that a severely impaired functional status may reflect the inability to react to treatment and/or act synergistically with cancer (especially if advanced in stage), leading to a failure-to-thrive status.

Studies that prioritize long-term outcomes related to functional status, rather than survival, are important for providing patients with reliable information on what to expect after cancer surgery. In line with this notion, the perioperative assessment of functional status and its clinical

trajectory over time should be a key focus of disease-management teams dealing with elderly cancer patients.

Moreover, a better knowledge of old patients' functional trajectories will help tailoring surgical, medical and geriatric interventions in fit vs. vulnerable patients, potentially allowing a return to the pre-morbid functional status.

Systematic preoperative assessment of frailty in elderly cancer patients may help estimating surgical risk and identifies patients who might benefit from perioperative interventions designed to enhance physiologic reserve and to improve long-term clinical trajectories.

Eventually, frailty assessment in the surgical setting may become the ultimate framework for the decision-making process of disease management teams, guiding choices of surgical, medical and radiotherapy approaches based on a truly comprehensive vision of the elderly patient by virtue of their high biological heterogeneity.

Author Contributions

Chiara Giannotti (CG), Silvia Sambuceti (SS1), Alessio Signori (AS), Stefano Scabini (SS2), Emanuele Romairone (ER), Irene Caffa (IC), Alessio Nencioni (AN), Alberto Ballestrero (AB), Patrizio Odetti (PO), Fiammetta Monacelli (FM).

Study concepts: FM, CG, SS1, AN

Study design: FM, CG, SS

Data acquisition: CG, SS2, ER, SS1, IC

Quality control of data and algorithms: FM, AS
Data analysis and interpretation: FM, CG, AN; IC
Statistical analysis: AS, FM, CG
Manuscript preparation: FM, CG
Manuscript editing: FM, CG, PO, AB
Manuscript review: FM, PO, AN, AB

Disclosures and Conflict of Interest Statements

The authors have no conflicts of interest to disclose.

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None to declare.

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Appendix A. Comprehensive Geriatric Assessment (CGA), Clinical Domain and Cut-Offs

Tool	Clinical domain	Number of items	Range	Cut-offs ^a
Iadl [28]	Functional status	8	0–8	≤ 7
Barthel index [29]	Functional status	10	0–100	< 50
Morse scale [30]	Risk of fall	6	0–125	≥ 25
Tinetti scale [31]	Postural stability	16	0–28	≤ 18
Cirs [32]	Comorbidity	19	0–37	>3
Severity			0–5	
Comorbidity			0–13	
Mmse [33]	Cognitive status	7	0–30	<24
Cdt [34]	Cognitive status	1	1–6	≥ 3
Gds [35]	Psychological status	15	0–15	≥ 5
Mna [36]	Nutritional status	18	0–30	< 23
Nrs [37]	Pain	1	0–10	≥ 3
Gijon scale [38]	Social status	5	5–25	≥ 10
Cga [41]	–	–	–	≥ 3

Abbreviations: I-ADL: Instrumental Activities of Daily Living; CIRS: Cumulative Illness Rating Scale; SI: Illness Severity Index; CI: Co-morbidity Index; MMSE: Mini Mental State Examination; CDT: Clock Drawing Test Shulman; GDS: Geriatric Depression Scale; MNA: Mini Nutritional Assessment; NRS: Numeric Rating Scale; CGA: Comprehensive Geriatric Assessment.

^a Cut-off score.

Appendix B. Supplementary Table for Univariate and Multivariate Analysis

Clinical domain and tool mean score (±sd)	1-Year mortality		Univariate Analysis P value ^a	Multivariate analysis OR (95% CI; P value)
	Patients Who survived N 80	Patients Who died N 19		
Age	80.2 ± 5.604	80.68 ± 5.841	0.032	1.12 (0.98–1.30); p = 0.10
MMSE	27.03 ± 3.594	27.47 ± 2.951	0.63	
CDT	2.540 ± 1.473	2.438 ± 1.209	0.65	
Barthel Index	98.46 ± 4.519	92.11 ± 11.70	P < 0.001	
IADL	7.279 ± 1.517	6.021 ± 2.405	P < 0.001	1.45 (1.03–2); p = 0.033
TUG	10.16 ± 4.371	11.71 ± 5.417	0.22	
Tinetti Scale	24.78 ± 4.568	21.72 ± 8.266	0.046	
Morse Scale	19.86 ± 13.30	27.89 ± 24.79	0.037	
MNA	23.46 ± 3.120	21.74 ± 3.773	0.12	
GDS	4.45 ± 3.70	4.54 ± 3.62	0.24	

(continued)

Clinical domain and tool mean score (\pm sd)	1-Year mortality		Univariate Analysis P value ^a	Multivariate analysis OR (95% CI; P value)
	Patients Who survived N 80	Patients Who died N 19		
Gijon Scale	8.721 \pm 2.427	9.263 \pm 2.535	0.83	
CIRS comorbidity	4.337 \pm 1.760	5.105 \pm 1.853	0.085	
CIRS severity	1.996 \pm 0.326	2.074 \pm 0.391	0.30	
N° of drugs	4.606 \pm 2.844	5.5 \pm 2.728	0.047	
FI	0.204 \pm 0.116	0.296 \pm 0.169	0.012	
CGA cut off	3.279 \pm 2.262	4.632 \pm 2.060	0.0044	
Clavien-Dindo	1.152 \pm 1.173	1.722 \pm 1.904	0.0017	
Stage of disease, n (%)			0.076	3.28 (0.91–11.8); p = 0.069
1	11/11 (100)	0/11		
2	37/41 (90.2)	4/41 (9.8)		
3	27/35 (77.1)	8/35 (22.9)		
4	3/5 (60)	2/5 (40)		

Abbreviations: MMSE, Mini-Mental State Examination – cognitive status; CDT, Clock drawing test Shulman 1 – visuospatial impairment; Barthel Index, functional status; IADL, Instrumental Activities of Daily Living – functional status; TUG, Timed up & go; Tinetti Scale – risk of falls; MNA, Mini-Nutritional Assessment – nutritional status; GDS, Geriatric Depression Scale – depression; Gijon scale – social frailty; CIRS, Cumulative Illness Rate Scale for Geriatrics – multimorbidity; FI, Rockwood 40-Item Frailty Index; CGA, comprehensive geriatric assessment; Clavien-Dindo – postoperative complications.

^a Non-parametric Mann-Whitney *U* test.

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