European Journal of Cancer 177 (2022) 112–119

Available online at www.sciencedirect.com

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journal homepage: www.ejcancer.com

Original Research

The oncological multidimensional prognostic index is a promising decision-making tool: A real-world analysis in older patients with metastatic colorectal cancer☆

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Received 11 July 2022; received in revised form 15 September 2022; accepted 22 September 2022
Available online 7 October 2022

KEYWORDS
Older patients;
Metastatic colorectal cancer;
Oncological multidimensional prognostic index;
Comprehensive geriatric assessment;
Real-world analysis;
Chemotherapy intensity

Abstract ***Background:*** Approximately 50% of colorectal cancers occur in older patients. International societies recommend geriatric tools to optimise treatment of older patients. Comprehensive Geriatric Assessment (CGA) is a multidimensional assessment used to classify patients as fit, vulnerable, or frail. The CGA-based oncological multidimensional prognostic index (onco-MPI) also classifies patients as high-, intermediate-, or low-risk based on tumour characteristics. We investigated the role of CGA and onco-MPI in older patients with metastatic colorectal cancer (mCRC) in a real-world setting.

Methods: Data for consecutive mCRC patients aged ≥70 years were retrieved from a prospectively maintained database from 2010 to 2020. We analyzed patients' and tumours' characteristics, and the CGA domains. Onco-MPI was calculated by a validated algorithm derived from CGA domains. Pearson's test was used to verify whether onco-MPI scores and chemotherapy administration were correlated.

☆ The present study was previously presented as abstract (#e11552), and poster at the ASCO (#e244) on June 3rd, 2019 and at the ESMO (#399P) on September 11th, 2022.

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https://doi.org/10.1016/j.ejca.2022.09.023

Results: The study included 488 mCRC patients with a mean age of 76.1 years. According to CGA, 52% of patients were fit, 28% vulnerable, and 20% frail. According to onco-MPI, 9% were low, 54% intermediate, and 37% high-risk. The median OS was 22.7 months. The following factors improved OS: 0–1 ECOG PS, low onco-MPI, fit based on CGA, chemotherapy administration, and doublet regimen. Chemotherapy administration significantly correlated with onco-MPI scores, leading to a survival gain regardless of the risk subgroups. First-line regimen had no impact on survival across the CGA and onco-MPI categories.
Conclusion: CGA and onco-MPI scores confirmed their prognostic impact in older mCRC patients and may aid in decision-making and subgroup stratification in dedicated trials.

1. Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related death worldwide, and its incidence increases with age: more than half of patients with metastatic (m)CRC are aged 70 years or older [1]. This population will increase in future decades, making its management an important part of daily practice for oncologists.

Despite this group's growing requirements, oncologists are scarcely prepared to meet the challenge of making decisions for older patients – a heterogeneous population in terms of comorbidities and physical reserve. At present, there is a lack of evidence on the risk-to-benefit ratio of treatments for older mCRC patients since they are underrepresented in randomised trials [2,3] establishing the standard of care.

The International Society of Geriatric Oncology recommends a comprehensive geriatric assessment (CGA) [4,5] to inform oncologists' decisions, but there is still no consensus regarding the best tool to use [5–7]. As CGA is poorly standardised and perceived as time-consuming, its use in oncological settings is limited.

Several scoring systems have been developed to estimate short- and long-term mortality. Among the short-term predictors, Pilotto *et al.* validated a multidimensional prognostic index (MPI) for one-year mortality based on CGA, which is used in older hospitalised patients with acute illnesses [8]. Similarly, MPI accuracy was maintained in hospitalised cancer patients [9].

Brunello *et al.* recently set up an oncological MPI (onco-MPI) applicable in outpatient setting to predict one-year mortality in older patients with different types and stages of cancer [10]. Onco-MPI was developed by a validated algorithm as a weighted combination of the following domains: age, sex, basal and instrumental activities of daily living (ADL and IADL), Eastern Cooperative Oncology Group Performance Status (ECOG PS), Mini-Mental State Examination (MMSE), Body Mass Index (BMI), Cumulative Illness Rating Scale (CIRS), the number of drugs, and caregiver presence (Supplementary Materials, Table A). Onco-MPI compiled these data into a single score ranging from 0 to 1, with good discriminatory power [10].

The aim of this study was to investigate the prognostic role of CGA and onco-MPI in older patients with mCRC in a real-world outpatient setting.

2. Materials and methods

A database was prospectively maintained for patients aged ≥70 years who were referred to the Veneto Institute of Oncology from 2010 to 2020.

All consecutive patients having histological diagnosis of mCRC and ability to provide informed consent were included.

On their first visit, patients aged 70 years and older were assessed through a CGA as per institutional policy. An oncologist and a psychologist conducted a clinical interview investigating the following items: ADL and IADL, MMSE, Geriatric Depression Scale, BMI and Mini Nutritional Assessment, medications, and comorbidities based on CIRS.

Patients were classified as fit, vulnerable, or frail according to Balducci's criteria [11].

The following variables were also collected: age, gender, ECOG PS, pain, and caregiver presence.

The onco-MPI derived from the CGA was calculated using a raw formula, as previously reported [10]. The following tumour characteristics were recorded: primary tumour location, *RAS*/*BRAF* mutational status, number of metastases, and treatment regimens.

Given the paucity of CGA-based guidelines for older patients with mCRC, the final treatment decision was based on the oncologist's expertise, the patient's preference, CGA results, and general guidelines.

First-line regimens were classified according to the chemotherapy backbone as follows: monotherapy (fluoropyrimidine, anti-EGFR, irinotecan, anti-*BRAF*, checkpoint inhibitors), doublet (oxaliplatin or irinotecan-based chemotherapy ± monoclonal antibodies [moAbs]), and triplet (FOLFOXIRI ± moAbs).

This study was conducted in accordance with the Declaration of Helsinki; the administered CGA was

approved by the Veneto Institute of Oncology's Ethical Board.

Overall survival (OS) was defined as the period from the mCRC diagnosis until death or last follow-up. Survival curves were reported using the Kaplan-Meyer method, and these were compared using the long-rank test.

Pearson's chi-squared test was used to verify the correlation between onco-MPI scores and first-line administration. A p value of <0.05 was deemed statistically significant.

All analyses were conducted using R for Windows software (Italy, Windows version 4.1.2).

3. Results

Out of 679 mCRC patients $\geq$70 years, a geriatric assessment with full data to calculate onco-MPI was available for 488 (72%) subjects (Fig. 1).

Patient characteristics are reported in Table 1. Mean age at first visit was 76.1 years.

According to CGA, 52% of patients were classified as fit, 28% vulnerable, and 20% frail. According to onco-MPI score, 9%, 54%, and 37% of patients, respectively, were low-, intermediate- (or medium-), and high-risk.

Overall, 24.6% of patients did not receive any treatment. Among those treated, two lines of chemotherapy were administered in 18.8% of cases, with doublet being the most prevalent regimen (55.7%).

Median OS after mCRC diagnosis was 22.7 months in the whole population (Supplementary Materials, Fig. A).

As summarised in Table 2, the following variables were significantly associated with OS in univariate analysis: ECOG PS $\leq$ 1, single site of metastasis, at least one line of chemotherapy, doublet regimen, and CGA and onco-MPI scores (Table 2 and Fig. 2).

Cox regression analysis (Supplementary Materials, Table B) failed to establish correlation between survival and any of the significant variables identified by univariate analysis. ECOG PS was excluded from multivariate analysis since its weighting was already accounted in onco-MPI score.

CGA and onco-MPI categories were significantly associated with treatment administration, with high-

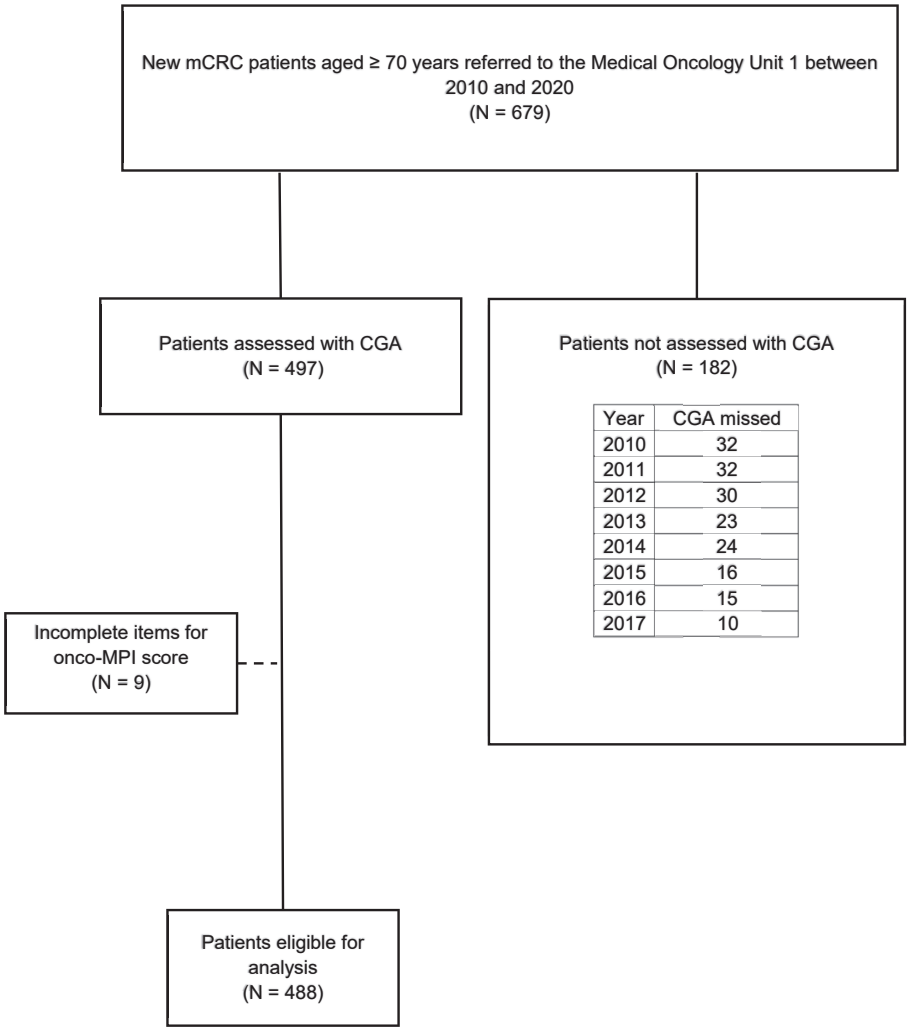

Fig. 1. Consort flow diagram.

Table 1
Major clinical-pathological features.

Characteristic		n (%)
ECOG Performance Status	0–1	410 (84)
	≥2	78 (16)
Basal Activities of Daily Living	<6	137 (28)
	6	351 (72)
Instrumental ADL	<8	232 (47.5)
	8	256 (52.5)
Mini-Mental State Examination	<24	85 (17.4)
	≥24	403 (82.6)
CAREGIVER	Yes	480 (98.4)
	No	8 (1.6)
Onco-MPI scores	Low	43 (9)
	Medium	263 (54)
	High	180 (37)
CGA-based categories	Fit	254 (52)
	Vulnerable	102 (28)
	Frail	96 (20)
Primary tumour location	Rectum	103 (21.1)
	Left	181 (37.1)
	Right	186 (38.1)
	NAS or multiple	18 (3.7)
RAS	Wild-type	272 (55.7)
	Mutated	216 (44.3)
BRAF	Wild-type	437 (89.6)
	Mutated	51 (10.4)
1st diagnosis of metastasis	Synchronous	311 (63.7)
	Metachronous	177 (36.3)
Total lines of treatment for metastatic disease	0	120 (24.6)
	1	140 (28.7)
	2	92 (18.8)
	≥3	134 (27.5)
	Missing	2 (0.4)
Regimen	Monotherapy ± Monoclonal Antibody	132 (35.9)
	Doublet ± Monoclonal Antibody	205 (55.7)
	Triplet +/- Monoclonal Antibody	26 (7.1)
	Missing	5 (1.3)

risk/frail patients receiving less chemotherapy (Pearson's test $p < 0.0001$) (Table 3).

According to CGA subgroups, median OS was 32.5 months (95% CI 20–36) in fit patients, 20.3 months (95% CI 15–22) in vulnerable patients, and 13 months (95% CI 6.9–22) in frail ones. According to onco-MPI categories, median OS was 30 months (95% CI 23.3–42.9) in low-, 28.6 months (95% CI 25.5–32.8) in intermediate-, and 14 months (95% CI 12.3–17.6) in high-risk patients.

Despite the OS disparities resulting from CGA and onco-MPI categories, chemotherapy improved survival in all risk-score subgroups. In fact, high-risk patients receiving chemotherapy had a median OS of 15.9 versus 11.2 months for those not treated. Due to the small sample size, low-risk patients (9% of study population) were grouped with intermediate-risk patients for further analysis. Patients at low-/intermediate-risk had a median OS of 26.6 months if treated and 12.3 months if untreated, as shown in Fig. 3. Similar results were recorded in CGA categories (Supplementary Materials, Fig. B.1 and Fig. B.2).

Table 3 summarises chemotherapy administration based on CGA and onco-MPI risk subgroups in terms of the impact of geriatric assessment on regimen choice. In detail, all low-risk subjects underwent at least one line of chemotherapy, with doublet being the most offered regimen (62.2%). Patients with high onco-MPI score received monotherapy and doublet in 76.7% and 23.3% of cases, respectively; none of them received triplet.

As shown in Fig. 4, first-line regimen did not significantly impact survival in onco-MPI and CGA subgroups (Supplementary Materials, Fig. C).

4. Discussion

Therapeutic decisions are difficult in older cancer patients, given the need to also consider the heterogeneity of their ageing and functional status.

An increasing number of studies are demonstrating the prognostic role of CGA in older patients with various tumours [12–15]. According to current guidelines, a geriatric assessment is recommended to estimate life expectancy and to develop tailored programs [16–18].

This is the first study to evaluate CGA and onco-MPI concurrently in a homogeneous and large cohort of older mCRC patients.

In addition to the main MPI elements, onco-MPI takes tumour site and stage into account due to their relevance for predicting mortality [9], and it is applicable in both clinical and research settings. Onco-MPI is user-friendly in clinical settings since it can be easily calculated through an Excel file by multiplying the value of each domain by the coefficient. Moreover, its one-year time horizon facilitates decision-making in advanced cancers [10].

Due to its standardisation, which classifies homogeneous subgroups, onco-MPI could be applied more effectively than conventional CGA in trials.

In univariate analysis, both CGA and onco-MPI correlated with OS of the global population. As illustrated in Fig. 2, patients with high onco-MPI scores had worse outcome than those with low and medium scores. This finding supports the importance of geriatric assessment in oncology, as it demonstrates that prognosis in older patients, including those with metastatic cancer, is not just determined by the oncological characteristics, but also by functional reserves included in onco-MPI. These conclusions are consistent with those reported by Giantin and Basso *et al.*, who demonstrated that the presence of advanced cancer may not impair the prognostic role of geriatric assessment *per se* [9,19].

Focussing on mCRC, the present analysis strengthens the prognostic role of onco-MPI by overcoming biases

Table 2
Univariate analysis for OS from diagnosis of mCRC.

Variable	Factor	HR	Confidence Interval		*p* value
ECOG PS	0-1 versus > 1	2.451	1.911	3.132	**0.004**
Gender	Male versus Female	0.978	0.781	1.342	0.8950
CGA	fit versus vulnerable	1.419	1.135	1.775	**0.0021**
	fit versus frail	2.441	1.908	3.123	**<0.00001**
Onco-MPI	low versus medium	1.010	0.724	1.409	0.9537
	low versus high	1.700	1.207	2.395	**0.0024**
KRAS	mut versus wt	3.109	0.986	9.804	0.0529
NRAS	mut versus wt	0.768	0.407	1.449	0.4150
BRAF	mut versus wt	0.951	0.683	1.323	0.7640
Chemotherapy	No versus Yes	0.629	0.504	0.785	**<0.00001**
Number of metastases	1 versus > 1	2.141	1.759	2.607	**<0.00001**
Chemotherapy regimen	monotherapy versus doublet	0.713	0.056	0.907	**0.0057**
	monotherapy versus triplet	0.697	0.444	1.094	0.1168

observed in the original study which included tumors in various sites and stages [10].

Among the other variables significantly associated with survival, ECOG PS and the number of metastases confirmed their well-known prognostic value.

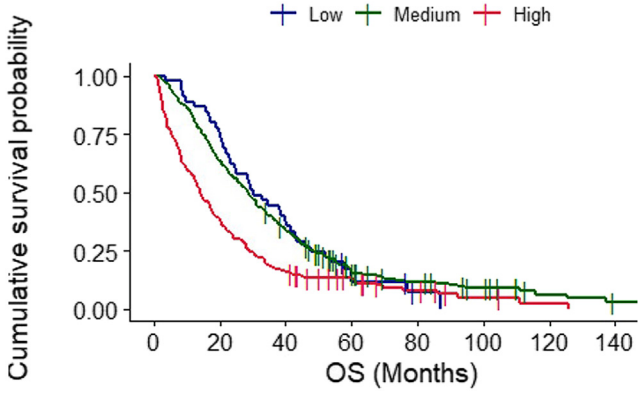

Fig. 2. Analysis of overall survival since the diagnosis of metastatic colorectal cancer according to the onco-MPI risk scores (low, medium, and high).

Notably, the chemotherapy administration significantly reduced mortality by 37.1%. Chemotherapy improved survival in all categories of CGA and onco-MPI, with a striking effect on medium-risk patients, where median OS is 26.6 months for treated patients compared to 12.3 months for untreated ones. Our findings are in line with the DISCO study [20], which demonstrated the significance of first-line in terms of longer survival, including in older mCRC patients.

A growing body of evidence indicates that biological age, as measured by geriatric assessment, should be used to decide whether a patient is eligible for chemotherapy [20–22]. The GERICO study concluded that CGA-based interventions boosted the number of older patients completing scheduled chemotherapy with survival gain [21].

Our analysis showed poorer survival in untreated patients, irrespective of the onco-MPI group; this is potentially due to poor conditions. In our opinion, onco-MPI could enhance a personalised up-front strategy that avoids undertreatments of low- and medium-

Table 3
Chemotherapy administration according to CGA and onco-MPI risk scores.

Chemotherapy	Fit	CGA vulnerable	Frail	low-risk	Onco-MPI medium-risk	high-risk
None	14%	25%	50%	0%	4%	59%
Monotherapy	27%	41.2%	64.6%	15.5%	30.2%	76.7%
Doublet	62%	54%	35.4%	62.2%	63.3%	23.3%
Triplet	11%	4.8%	0%	22.3%	6.5%	0%

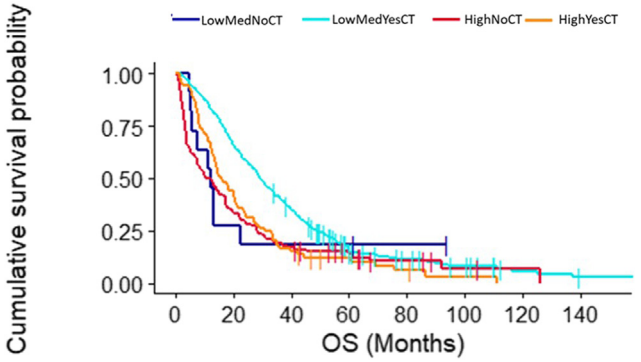

Fig. 3. Analysis of overall survival since the diagnosis of metastatic colorectal cancer according to chemotherapy administration (yes, no) and onco-MPI risk scores (low, medium, and high).

risk patients, with all low-risk patients receiving chemotherapy, as indicated in our study.

Moreover, our data add relevant insights on the role of chemotherapy in high-risk subjects. Unlike the GERICO trial [21], in which frail patients were excluded and only 29 patients presented metastatic disease, the present study confirmed the survival benefit of treatment even in the high-risk subgroup, with a median OS of 16 months in treated high-risk patients compared to 11 months in untreated high-risk individuals. Similar results were recorded in CGA-based analysis, where frail patients, if treated, had a median OS of 19 months compared to 8 months for untreated ones.

Clearly, oncologists can select high-risk/frail patients for chemotherapy despite their frailty. In the absence of details on which elements triggered decisions in our high-risk population, eligibility for chemotherapy could be based on other factors, irrespective of onco-MPI score, and this may have affected its prognostic role in multivariate analysis. Some frail patients would receive only best supportive care in a real-world setting, but they could also benefit from chemotherapy if their functional impairment was caused by symptomatic mCRC. In this scenario, the aim of first-line chemotherapy is the palliation of symptoms through tumour debulking.

In our opinion, the confirmed survival benefit of chemotherapy in high-risk/frail patients is an unexpected finding, suggesting that geriatric assessment should not be interpreted as an '*absolute dogma*', but rather should incorporate other decision-making elements, particularly for high-risk/frail patients for whom the benefit-risk ratio of chemotherapy must be carefully weighed.

In our analysis, oncologists appropriately used CGA and onco-MPI to determine whether to prescribe chemotherapy as shown by the Pearson's test. Secondly, these tools were useful for selecting the optimal regimen, as shown in Table 3: the intensity of chemotherapy was distributed coherently across CGA and onco-MPI categories.

Observation of high-risk patients receiving chemotherapy yielded intriguing insights: monotherapy was the prevalent regimen (76.7%), including anti-EGFR (24%), which could be a convenient option for older patients unsuitable for combination regimens, thus reducing toxicities. Although high-risk/frail patients mostly received monotherapy treatment, their survival was comparable to that expected in older population, indicating that oncologists were adept at extracting information from CGA and onco-MPI.

Analysis of the survival impact of different regimens is more complex. Globally, doublet or triplet correlated with better survival compared to monotherapy, reducing mortality by 27% and 30%, respectively. However, when homogeneous subgroups based on CGA and onco-MPI were considered, no significant impact of regimen was observed. While this may be due to the low number of patients in fit/low-risk categories, we were unable to formulate well-founded hypotheses for other risk subgroups.

Due to the paucity of evidence, the optimal upfront treatment for older mCRC patients remains debatable. In daily practice, therapeutic options rely on retrospective studies or meta-analyses [22,23]. Based on the AVEX trial [24], capecitabine monotherapy plus bevacizumab is reasonable for older mCRC patients, irrespective of *RAS* status. Moreover, the PANDA trial concluded that 5-fluorouracil monotherapy plus panitumumab may be effective in older patients with *RAS*/*BRAF* wild-type mCRC, with outcome similar to FOLFOX plus panitumumab [25,26]. In our opinion, both well-tolerated

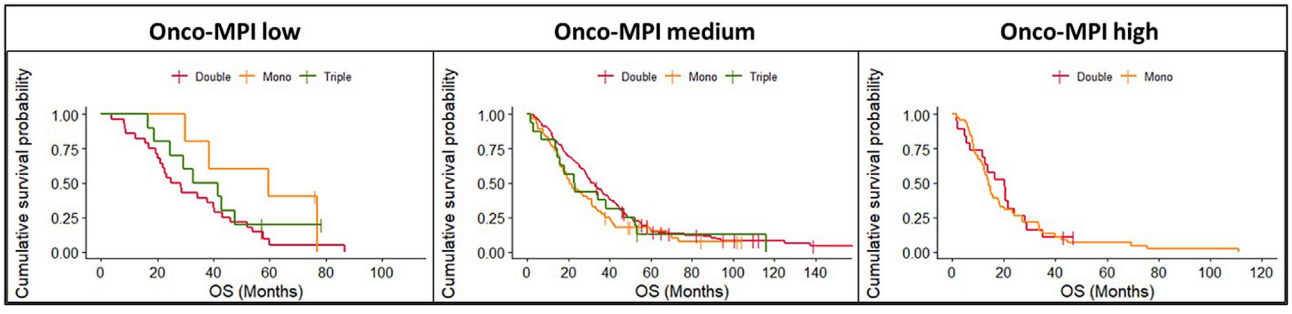

Fig. 4. Analysis of overall survival since the diagnosis of metastatic colorectal cancer according to the chemotherapy regimen (monotherapy [mono], doublet [double], triplet [triple]) and onco-MPI risk scores (low, medium, and high).

regimens may be a viable option for high-risk/frail patients prior to excluding them from any treatment.

Given the controversial results of multivariate analysis, the observational nature of data, and the absence of a head-to-head comparison between onco-MPI and CGA, our analysis is unable to answer the long-standing question of the optimum form of geriatric assessment. Nonetheless, we can still draw certain conclusions.

As indicated by earlier research, performance variability was apparent across various forms of CGA [27,28]. Ferrat *et al.* demonstrated a weaker discrimination of CGA in CRC [27] suggesting that cut-offs of CGA domains require adjustment according to tumour site. For instance, the absence of nutritional status in Balducci classification contributes to its inferior performance in mCRC, where malnutrition correlates with a poor prognosis.

Moreover, onco-MPI could facilitate patients recruitment for clinical trials due to its standardisation. From a practical standpoint, a 74-year-old man with 0 ECOG PS, 8/8 IADL, 29 BMI, and one moderate comorbidity would be classified as fit by CGA and low-risk by onco-MPI. A second patient with the same functional reserve but three moderate comorbidities and a BMI of 17 would receive medium score. The first patient was enrolled in trial receiving triplet whereas monotherapy was proposed for the second patient. Both patients resulted fit according to Balducci's classification, thus confirming that onco-MPI adds information for therapy.

This study has some limitations such as retrospective nature and selection bias. We may have included a lower number of frail subjects because of outpatient setting. Furthermore, the onco-MPI time horizon of only one year may explain why many established prognosticators in mCRC were not associated with OS.

Despite these limitations, the information provided by our analysis may assist oncologists in correctly applying the CGA and onco-MPI tools in the right context.

5. Conclusion

Our study confirms the prognostic role of CGA and onco-MPI by adding valuable information for older cancer patients management. In treatment-eligible patients, first-line intensity has been modulated by CGA and onco-MPI categories, resulting in a survival benefit for all subgroups, including frail/high-risk category predominantly receiving monochemotherapy.

As real-world analysis, this study cannot address the question of the optimal geriatric assessment, but it can support the incorporation of onco-MPI in first-line decision-making.

The external validation and demonstration of onco-MPI's potential to predict mortality with a longer follow-up are currently underway to improve its accuracy and feasibility.

Funding

This research was partially funded by the Regione Veneto Grant RP-2014-00000395, the Italia Ministero della Salute Grant GR-2009-1606663, the Ricerca Sanitaria Finalizzata Grant 2011-02352137, and Ricerca Corrente 2022 CDC 099183, COMM.SCI: ZAGO-8779/22.

Author's contribution

Procaccio: Conceptualisation, Data curation, Investigation, Methodology, Project administration, Resources, Validation, Visualisation, Roles/Writing-original draft, Writing-review & editing.

Bergamo: Data curation, Investigation, Methodology, Project administration, Resources, Validation, Visualisation, Writing-review & editing.

Gatti: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualisation.

Chiusole, Tierno, Bergo: Data curation, Investigation, Methodology, Resources, Visualisation.

Daniel, Nappo, Maddalena, Rasola, Barsotti, De Grandis, Piva, Rizzato: Data curation, Investigation, Resources, Visualisation.

Sergi: Data curation, Investigation, Methodology, Resources, Visualisation.

Brunello, Zagonel, Lonardi: Conceptualisation, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualisation, Writing-review & editing.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.09.023.

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