Journal of Geriatric Oncology 15 (2024) 101639

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

journal homepage: www.elsevier.com/locate/jgo

Systematic Review

Effect of frailty on postoperative complications, mortality, and survival in older patients with non-metastatic colon cancer: A systematic review and meta-analysis

Mª. Rosario Moreno-Carmona [a], Mateu Serra-Prat [b,c,*], Stephanie A. Riera [d,e], Oscar Estrada [f], Tarsila Ferro [g], Rosa Querol [h]

[a] Department of Oncology, Hospital de Mataró, Consorci Sanitari del Maresme, 08304 Mataró, Catalunya, Spain
[b] Research Unit, Fundació Salut del Consorci Sanitari del Maresme (Mataró), Barcelona, Spain
[c] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain
[d] Gastrointestinal Motility Laboratory, Hospital de Mataró, Consorci Sanitari del Maresme, 08304 Mataró, Catalunya, Spain
[e] Department of Surgery and Morphological Sciences, University Autonomous of Barcelona, 08193 Cerdanyola del Vallès, Catalunya, Spain
[f] Department of Surgery, Hospital of Mataró, Consorci Sanitari del Maresme, 08304 Mataró, Catalunya, Spain
[g] Department of Oncology, Hospital Duran i Reynals. Institut Català d'Oncologia (ICO), 08908 L'Hospitalet de Llobregat, Catalunya, Spain
[h] Department of Oncology, Consorci Corporació Sanitària Parc Taulí de Sabadell, 08208 Sabadell, Catalunya, Spain

ARTICLE INFO

Keywords:
Frailty
colon neoplasms
Frail older adults
Mortality
Toxicity
Postoperative complications

ABSTRACT

Introduction: New evidence has emerged on the impact of frailty on prognosis in colon cancer, but the findings are not always consistent and conclusive. The aim of this systematic review was to assess the effect of frailty on postoperative complications and mortality in patients with non-metastatic colon cancer (CC) aged 65 years and older.

Materials and Methods: We systematically searched for original studies published in the PubMed and Web of Science databases up to June 2021. Two independent reviewers selected the studies and extracted predefined data. A meta-analysis was performed using the random effects model to assess the effect of frailty on 30-day, 3- to 6-month and 1-year mortality, survival, and postoperative complications.

Results: The search yielded 313 articles, of which 14 were included in this systematic review. The meta-analysis showed an effect for frailty on 30-day, 3- to 6-month, and 1-year mortality with respective pooled odds ratios (ORs) of 3.67 (95% confidence interval [CI] 1.53–8.79, $p = 0.004$), 8.73 (95% CI 4.03–18.94, $p < 0.0001$), and 3.99 (95% CI 2.12–7.52, $p < 0.0001$). Frailty also had an effect on survival, with a pooled hazard ratio of 2.99 (95% CI 1.70–5.25. $p < 0.0001$), and on overall and severe postoperative complications with pooled ORs of 2.34 (95% CI 1.75–3.15; $p < 0.0001$) and 2.43 (95% CI 1.72–3.43; $p < 0.0001$), respectively.

Discussion: Frailty in older patients with CC is a risk factor for postoperative complications and mortality in the short term (30 days), medium term (3–6 months), and long term (1 year).

1. Introduction

Cancer is a disease associated with aging. Colorectal cancer (CRC) is the most common cancer in adults, the second most common cancer among females, and the third most common cancer in males [1]. Most new cases (58%) occur in people aged 65 years or older. As life expectancy increases, so does the number of older patients with CRC [2]. Surgery is the primary curative-intent treatment, and pathological staging is the best indicator of recurrence risk. The main prognostic factors are the degree of local tumor infiltration and metastatic infiltration of regional lymph nodes. Other predictors of poor prognosis are the number of affected lymph nodes in relation to total number of nodes removed (lymph node ratio), lymph node micrometastases, tumor nests in the mesentery, angiolymphatic or perineural invasion, positive margins, elevated preoperative carcinoembryonic antigen, poorly differentiated histology, bowel obstruction or perforation, and resection of

* Corresponding author at: Research Unit, Hospital de Mataró, Carretera de Cirera 230, Mataró, 08304 Barcelona, Spain.
E-mail addresses: mmorenocarm@csdm.cat (Mª.R. Moreno-Carmona), mserra@csdm.cat (M. Serra-Prat), oestrada@csdm.cat (O. Estrada), tferro@iconcologia.net (T. Ferro).

https://doi.org/10.1016/j.jgo.2023.101639
Received 9 March 2023; Received in revised form 28 August 2023; Accepted 27 September 2023
Available online 6 October 2023

PubMed with the following Medical Search Headings (MesH):
((((((((((Frail Scale) OR "clinical frailty scale") OR "clinical frailty index") OR "clinical frailty score") OR frail y[MeSH Terms]) AND "geriatric intervention") AND "geriatric assessment") OR frail elderly[MeSH Terms]) OR geriatric assessment[MeSH Terms])))) AND ((((((((((((((((Colorectal Neoplasms[MeSH Terms]) OR Colorectal Neoplasm) OR Neoplasm, Colorectal) OR Colorectal Tumors) OR Colorectal Tumor) OR Tumor, Colorectal) OR Colorectal Carcinomas) OR Colorectal Cancer) OR Cancers, Colorectal)) NOT (((metastases) OR metastasis) OR METASTAS*)))))))).

WOS: TS=(assessment OR evaluation OR screening) AND
TS=(elderly OR old* OR geriatri* OR ageing OR aging) AND
TS=(prognos* OR pronostic) AND
TS=(colorectal adenocarcinoma OR colon cancer OR colon-cancer OR colorectal carcinoma OR colorectal cancer OR colorectal-cancer OR colorectal-adenocarcinoma OR colorectal-carcinoma) NOT TS=(metasta*)

Fig. 1. Literature search strategy.

fewer than 12 lymph nodes [3]. There is evidence that adjuvant chemotherapy reduces the risk of recurrence and improves overall survival in patients who have undergone surgery for stage II or III colon cancer (CC) [4].

Aging is associated with a decline in the function of different organs and systems, which is accompanied by an increased risk of surgical complications and chemotherapy toxicity. Curative surgery and adjuvant chemotherapy are less likely to be performed in older patients, and decisions regarding the treatment of CRC in older members of the population are often influenced by chronological age, with little account taken of intrinsic capacity, frailty status, or biological age [5]. There is, however, increasing evidence that patients aged 65 years or older can benefit from adjuvant chemotherapy similarly to younger patients, and whether or not chemotherapy results in greater toxicity in this population remains to be established [6]. For all these reasons, there is growing consensus that chronological age alone should not determine whether a given treatment should be pursued or rejected and that decisions should be accompanied by a comprehensive, individualized assessment that considers, among other factors, frailty status as an indicator of biological age. Frailty has been proposed as a potential marker of worse health outcomes after surgery, including intra- and postoperative complications, length of hospital stay, and mortality [7]. Given that frailty is defined as a state of vulnerability due to a decrease in the functional capacity of different organs and systems, including the inflammatory-immune system, it is reasonable to speculate that it has a vital role in the prognosis of CRC and the risk of complications from aggressive treatments such as surgery and chemotherapy. In such cases, a decreased repair response and/or ability to recover homeostasis would lead to a higher risk of complications in the short, medium, and long term, greater toxicity and less tolerance of chemotherapy, and increased readmissions, hospital stays, and mortality. Frailty may also contribute to a late diagnosis of CRC by masking warning signs such as fatigue, weakness, and weight loss. It can also favor rapid disease progression and decrease the likelihood of patients receiving standard treatments or doses [6,8,9]. For all these reasons, scientific oncology societies recommend screening for frailty in older patients with cancer. Although several tools have been developed to identify frailty in patients with cancer, such as the Balducci criteria, the Vulnerable Elders Survey-13 (VES-13), and the Geriatric 8 (G8) [10–12], systematic evaluation of older patients in oncological clinical practice is largely lacking.

Studies evaluating the impact of frailty on CRC prognosis have not consistently shown conclusive or concordant results. We are aware of just three systematic reviews investigating the prognostic value of frailty in CRC: two focused on surgical outcomes in patients of all ages and stages [2,13], while the third included just two original papers evaluating frailty [6]. Determining the effects of frailty in older patients with non-metastatic CC is important, since the presence of metastasis influences treatment decisions, disease course, and prognosis and can also act as a confounding factor when evaluating outcomes. Understanding and quantifying how frailty impacts prognosis in older patients with CC is useful for patient management and clinical decision-making. It can help plan, adjust, or individualize treatments according to the risk of toxicity or complications, inform preventive and/or recovery interventions, and, ultimately, improve quality of life and prognosis [6,8,9]. The aim of this study was to assess the effect of frailty on mortality and postoperative complications in patients with non-metastatic CC aged 65 years and older.

2. Methods

We conducted a systematic review guided by the recommendations set forth in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA statement) (www.prisma-statement.org).

2.1. Search Strategy

A literature search was performed in the PubMed and Web of Science (WOS) databases using the following keywords: “frailty,” “colorectal neoplasm,” “aged,” “mortality,” “toxicity,” and “postsurgical complications.” The search strategy is presented in Fig. 1. It covered articles published up to June 2021 and placed no language or other restrictions. A manual search of the references of selected articles was also conducted.

2.2. Selection Criteria

Studies that met all the inclusion criteria and none of the exclusion criteria were included. The inclusion criteria were original observational and prospective studies that evaluated the prognostic effect of frailty in patients aged 65 years or older with CC. The exclusion criteria were studies of patients with metastatic CC only, studies of patients younger than 65 years, and duplicate studies. In the case of studies with multiple publications, the article containing the most up-to-date data was selected. Two reviewers (MRM and MSP) independently selected the initial studies. Disagreements were resolved by discussion.

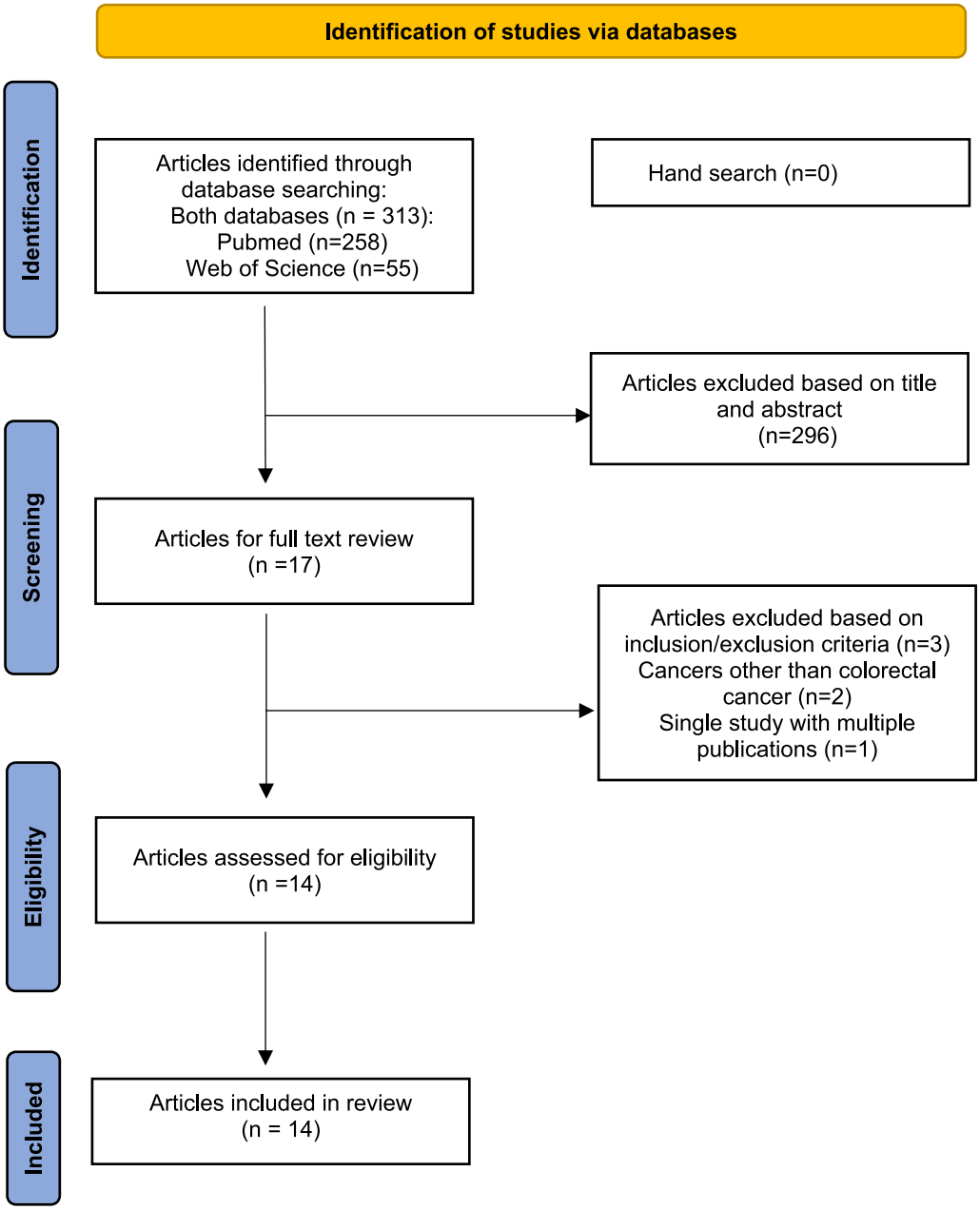

Fig. 2. PRISMA Flowchart of search results and study selection.

2.3. Data Extraction and Quality Assessment

The same researchers (MRM and MSP) independently extracted data from the selected studies using a predesigned form including items on study identification (author, journal, year); methodological and sample characteristics (sample size, mean age, TNM stage, frailty criteria, primary outcome measures, and follow-up time); methodological quality; and main results (30-day, 3- to 6-month-, and 1-year mortality, survival, and postoperative complications according to the Clavien-Dindo criteria). To assess methodological quality, an ordinal 3-point scale (0, minimum quality; 0.5, intermediate quality; and 1, highest quality) was used to rate the following aspects: (a) representativeness of the study sample; (b) definition of the assessment criteria for the main study factor (frailty); (c) definition and specification of primary outcome measures; (d) loss to follow-up and consideration of this in the statistical analysis; and (e) consideration of confounding variables and/or adjustment for age, sex, and cancer stage in multivariate models. An overall score for methodological quality was obtained from the sum of scores for the five domains (total possible score, 0–5). The higher the score, the higher the methodological quality. Initial disagreements about aspects of the data extraction and methodological quality assessment processes were resolved by further review and discussion among the reviewers.

2.4. Data Synthesis

The results of the studies are presented in the form of evidence tables. Quantitative synthesis of outcome measures for which sufficient and/or necessary data were available was performed using meta-analysis techniques. The degree of heterogeneity among the studies was evaluated using the Tau^2 test. Regardless of the result of this test, the random effects model was used in all cases due to the heterogeneous study designs. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs), except for survival results, which are presented as hazard ratios (HRs) with 95% CIs. Six meta-analyses were performed, one for

Table 1
Characteristics of included studies.

Study	N No. (%) of frail older adults	Mean age (y)	CC stage	Frailty criteria	Follow-up	Main outcome measures	Quality score
Okabe H (Am J Surg 2019)	269 78 (29.0%)	71.7	I-II: 70.6% III-IV: 29.4%	Clinical Frailty Scale ≥4	During hospitalization	• Mortality • Postoperative complicacions (Clavien-Dindo)	3.5
Giannotti Ch (J Geriatr Oncol 2019)	99 40 (40.4%)	80.2	I: 10%, II: 49% III: 31% IV: 9%	Rockwood Frailty Index	1 year	• Mortality (30 day and 1 year) • Postoperative complicacions (Clavien-Dindo)	4
Ommundsen N (Eur J Surg Oncol 2018)	114 114 (100%)	79	0-III: 91% IV: 9%	VES-13 ≥ 3	30 days	• Postoperative complicacions (Clavien-Dindo)	3.5
Vermillion S (J Surg Oncol 2017)	41,455 4203 (10.1%)	72.4	Not specified	Modified frailty index >0.27	30 days	• Mortality (30 days) • Postoperative complicacions (Clavien-Dindo)	4.5
Souwer E (Ann Surg Oncol 2019)	550 27 (4.9%)	76.5	I: 30% II: 39% III: 31%	VMS ≥ 3	Median 870 days	• Survival • Postoperative complications (Clavien-Dindo)	4.5
Ramsdale E (JAGS 2013)	38 -	72	III: 21% IV: 79%	VES ≥ 13	Not specified	• Survival	3
Ronning B (J Geriatr 2016)	180 73 (40.5%)	80	I: 47 (26%) II: 57 (32%) III: 38 (21%) IV: 17 (9%)	Barthel Index, NEADL, comorbidities, MNA, CIRS, GDS, MMSE, and polypharmacy	Median 22 months (range 16–28)	• Quality of life EORTC	3.5
Aaldriks Ab (J Geriatr Oncol 2013)	143 34 (24%)	75	II-III: 38% IV: 62%	GFI ≥ 4	Median 15 months	• Tolerance of adjuvant and palliative chemotherapy • Mortality	4.5
Kristjansson S (Crit Rev. Onc 2010)	178 76 (42.7%)	79.6	0: 8 (5%) I: 43 (24%) II: 57 (32%) III: 37 (25%) IV: 21 (12%)	CGA	30 days 3 months (telephone)	• Readmissions • Mortality (30 days) • Postoperative complications (Clavien-Dindo)	4.5
Yang Tan K (Am J Surg 2012)	83 23(27.7%)	81.2	Not specified	Fried frailty phenotype criteria	30 days	• Mortality (30 days) • Postoperative complicacions (Clavien-Dindo)	4
Souwer E (J Geriatr Oncol 2018)	139 32(23%)	77.7	I: 33 (24%) II: 57 (41%) III: 49 (35%)	ISAR-HP	30 days 6 months	• Readmissions • Mortality (30 days and 6 months) • Postoperative complications (Clavien-Dindo)	3.5
Reisinger K (Ann Surg 2015)	153 39 (24.6%)	69	Not specified	Groningen Frailty Indicator (GFR) ≥5	30 days	• Mortality (30 days) • Postoperative complicacions (Clavien-Dindo)	4
Pata G (J Surg Oncol 2020)	104 34 (33%)	81	Not specified	Multidimensional Prognostic Index >0.33	30 days 90 days	• Mortality (30 and 90 days) • Postoperative complicacions (Clavien-Dindo)	5
Ommundsen N (The Oncologist 2014)	178 76 (43%)	80	0: 8 (5%) I: I43 (24%) II: 57 (32%) III: 45 (25%) IV: 21 (12%)	Modified version of Balducci criteria	5 years or until death	• Mortality (1 and 5 years) • Survival	5

CC, colon cancer; VES-13, Vulnerable Elders Survey; VMS, Dutch National Patient Safety Program; NEADL, Nottingham Extended Activities of Daily Living Scale; MNA, Mini Nutritional Assessment; CIRS, Cumulative Illness Rating Scale; GDS, Geriatric Depression Scale; MMSE, Mini Mental State Examination; GFI, Groningen Frailty Indicator; CGA, Comprehensive Geriatric Assessment; ISAR-HP, Identification of Seniors At Risk-Hospitalized Patients.

Table 2
Survival and 30-day, 3- to 6-month, and 1-year-mortality.

Study	30-day mortality		3–6 month mortality		1-year mortality		Survival
	Frail older patients n (%)	Non-frail older patients n (%)	Frail older patients n (%)	Non-frail older patients n (%)	Frail older patients n (%)	Non-frail older patients n (%)	HR
Giannotti Ch (J Geriatr Oncol 2019)	8 (8.3%) in total (both groups)		–	–	17 (30.3%)	2 (4.6%)	–
Ommundsen N (Eu J Surg Oncol 2018)	5 (4.4%)	–	–	–	–	–	–
Vermillion S (J Surg Oncol 2017)	235 (5.6%)	915 (2.5%)	–	–	–	–	–
Souwer E (Ann Surg Oncol 2019)	5 (18.5%)	9 (1.7%)	7 (25.6%)	18 (3.4%)	7 (25.6%)	24 (4.6%)	HR: 1.9 for intermediate risk ($p = 0.03$) HR: 8.7 for high risk ($p < 0.001$)
Ramsdale E (JAGS 2013)							Adjusted HR: 15.6 ($p = 0.02$)
Aaldriks Ab (J Geriatr Oncol 2013)	–	–	–	–	E II-III: 1 (9.1%) E IV: 16 (69.5%)	E II-III: 5 (11.6%) E IV: 28 (42.4%)	HR: 1.7 (ns)
Yang Tan K (Am J Surg 2012)	0 (0%)	0 (0%)	–	–	–	–	–
Souwer E (J Geriatr Oncol 2018)	3 (9.4%)	3 (2.8%)	4 (12.5%)	3 (2.8%)	–	–	–
Reisinger K (Ann Surg 2015)	3 (7.7%)	8 (7.0%)	–	–	–	–	–
Pata G (J Surg Oncol 2020)	3 (8.8%)	0 (0%)	6 (17.6%)	1 (1.4%)	–	–	
Ommundsen N (The Oncologist 2014)	–	–	–	–	- 80%	- 92%	Adjusted HR: 3.6 ($p < 0.001$)

HR, hazard ratio; ns, non-significant.
HR*: adjusted HR, ns: non-significant.

each of the outcome measures considered: 30-day mortality, 3- to 6-month mortality, 1-year mortality, survival (HR), postoperative complications, and severe postoperative complications (Clavien-Dindo grade > III). Subgroup analyses were not performed due to the small number of studies. A sensitivity analysis to test the robustness of results was performed by removing the selected studies one by one. Statistical significance was established at a p value <0.05. Analyses were performed using the Cochrane ReviewManager (RevMan) software.

3. Results

3.1. Study Selection

The literature search identified 313 articles: 258 in PubMed and 55 in the Web of Science. After excluding duplicate articles, multiple publications, and studies that did not meet the selection criteria during title and abstract screening, 17 eligible articles remained [14–30]. Three [28–30] were excluded during the full-text review for not meeting the selection criteria (they dealt with different types of cancers and one was from a study with multiple publications). This left 14 articles [14–27], one of which was a letter to the editor [19]. The flow chart summarizing the search results and selection process is depicted in Fig. 2.

3.2. Study Design and Sample Characteristics

Of the 14 selected studies, two had been conducted in the United States [17,19], one in Japan [14], one in Singapore [23], four in the Netherlands [18,21,24,25], four in Norway [16,20,22,27], and two in Italy [15,26]. The main characteristics of the study population and methodology are presented in Table 1. The Vermillion et al. [17] study stood out with a sample of 41,455 patients. The sample sizes of the other studies ranged from 83 to 550 patients. The mean participant age ranged from 69 to 81 years. The criteria used to assess frailty constituted a significant source of heterogeneity between the studies. Overall, methodological quality was satisfactory, with a mean score of 4.1 out of 5.

3.3. Effect of Frailty on Mortality and Survival

The mortality and survival results reported by each of the selected studies are summarized in Table 2. The results of the meta-analysis for the effect of frailty on 30-day-, 3- to 6-month, and 1-year mortality (ORs) and survival (HR) are depicted in Fig. 3. Eight studies reported 30-day mortality, but just six of these were included in the meta-analysis because one did not specify mortality according to frailty [18] and in another, all the patients were frail [16], precluding analysis of the association between mortality and frailty. The OR could not be calculated for one of the studies included in the meta-analysis because no events (deaths) were observed. The effect of frailty on 30-day mortality was not statistically significant in three of the five remaining studies, but the meta-analysis showed an OR of 3.67 (95% CI 1.53–8.79, $p = 0.004$). Three studies reported 3- to 6-month mortality, and the meta-analysis showed a significant effect for frailty with an OR of 8.73 (95% CI 4.03–18.94, $p < 0.0001$). Finally, 1-year mortality was reported in four studies. In this case, the OR was 3.99 (95% CI 2.12–7.52, $p < 0.0001$). The effects remained statistically significant each time a study was removed in the sensitivity analysis, with ORs ranging from 2.35 to 5.11, 7.19 to 10.53, and 3.10 to 5.13 for mortality at 30 days, 3 to 6 months, and one year, respectively. Survival was reported in four studies

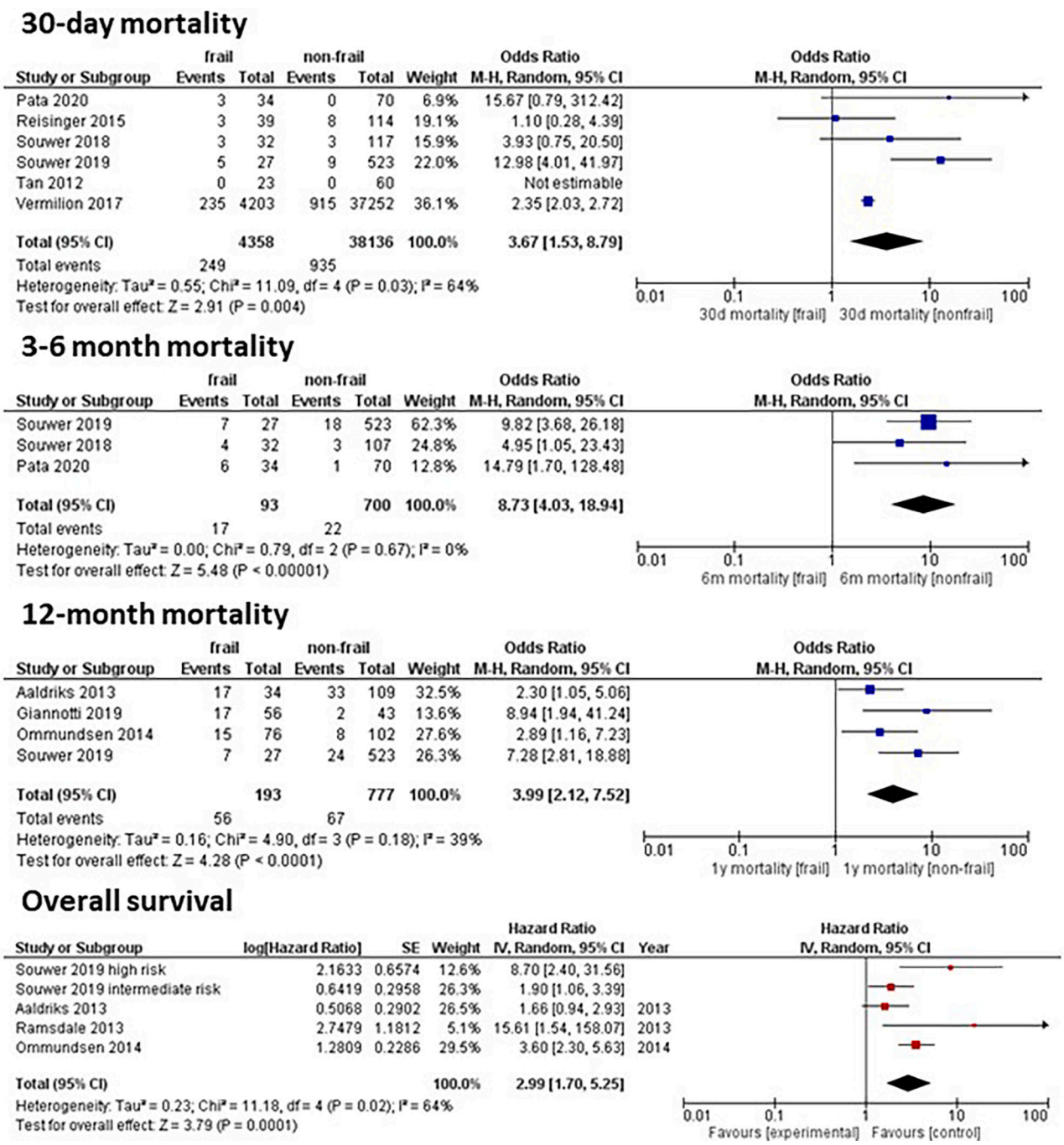

Fig. 3. 30-day, 3–6-month- and 1-year mortality meta-analysis results.

[16,18,19,21]. Because the 2019 study by Souwer et al. [18] distinguished between patients with an intermediate and a high risk of frailty, these results were treated as two separate studies in the meta-analysis. The meta-analysis of survival data showed an HR of 2.99 (95% CI 1.70–5.25, $p < 0.0001$). The results remained robust in the sensitivity analysis, with a statistically significant HR ranging between 2.16 and 3.18 in all cases. Five-year survival rates in the only study to report these data [16] were 24% for frail patients and 66% for non-frail patients ($p < 0.001$).

3.4. Effect of Frailty on Postoperative Complications and Chemotherapy Tolerance

The results reported by each of the selected studies for postoperative complications are shown in Table 3. Ten studies reported complications, but just eight were included in the meta-analysis [14,17,18,22–26]. The association between frailty and postoperative complications could not be analyzed in the other two because one did not report the results according to frailty [15]. In the other, all the patients were frail [16]. In two of the eight studies, frailty had a non-significant effect on postoperative complications [18,25], but in the rest it was a significant risk factor. The meta-analysis showed frailty to be a risk factor for postoperative complications in CC with an OR of 2.34 (95% CI 1.75–3.15, $p < 0.0001$) (Fig. 4). Five articles reported results for severe postoperative complications (Clavien-Dindo grade > III). Four showed that frailty was a risk factor, and the meta-analysis identified an effect with an OR of 2.43 (95% CI 1.72–3.43, $p < 0.0001$). The effect remained significant in the sensitivity analysis, with ORs ranging between 2.20 and 2.80 for all

Table 3
Overall and severe postoperative complications.

Study	Postoperative complications		Severe postoperative complications	
	Frail older patients n (%)	Non-frail older patients n (%)	Frail older patients n (%)	Non-frail older patients n (%)
Okabe H (Am J Surg 2019)	Clavien-Dindo III/IV 18 (23%)	Clavien-Dindo III/IV 16 (8%)	Hemorrhage: 1 (1.3%) Infection: 20 (25.6%) Suture failure: 8 (10.2%)	Hemorrhage: 0 (0%) Infection: 28 (14.6%) Suture failure: 2 (1.0%)
Giannotti Ch (J Geriatr Oncol 2019)	OR = 1.52 (95% CI 1.05–2-22, $p = 0.027$ Non-disaggregated data available		–	–
Ommundsen N (Eu J Surg Oncol 2018)	93 (81.6%)	–	–	–
Vermillion S (J Surg Oncol 2017)	1548 (36.8%)	9296 (24.9%)	1223 (29.1%)	6668 (17.9%)
Souwer E (Ann Surg Oncol 2019)	14 (51.8%)	177 (33.8%)	–	–
Kristjansson S (Crit Rev. Oncol Hematology 2010)	58 (76.3%)	49 (48.0%)	47 (61.8%) Readmissions 13 (17.1%)	(35.3%) Readmissions 7 (6.8%)
Yang Tan K (Am J Surg 2012)	11 (47.8%)	11 (18.3%)	–	–
Souwer E (J Geriatr Oncol 2018)	17 (53.0%)	34 (13.0%)	9 (28.1%) Readmissions 6 (18.7%)	16 (14.9%) Readmissions 7 (6.5%)
Reisinger K (Ann Surg 2015)	5 (16.7%)	12 (13.0%)	–	–
Pata G (J Surg Oncol 2020)	29 (85.3%)	45 (64.3%)	18 (52.9%)	11 (15.7%)

postoperative complications and 1.90 and 2.86 for severe ones. The most common postoperative complications were hemorrhage, infection, and suture failure. Just one article analyzed the effect of frailty on chemotherapy tolerance [21] and concluded that both malnutrition and frailty were associated with a lower tolerance for palliative chemotherapy.

4. Discussion

In this systematic review of 14 studies involving 43,683 patients with non-metastatic CC aged 65 years and older, frailty was clearly associated with a higher rate of overall and severe postoperative complications, a higher risk of postoperative mortality at 30 days, 3 to 6 months, and 1 year, as well as worse survival.

Postoperative complications were reported in 10 of the 14 articles. Seven used the Clavien-Dindo grading system [14–17,22,23,26]; the other three used different systems but reported similar results. Although the results are somewhat heterogeneous between studies, with ORs ranging from 1.3 to 4, most showed a statistically significant association between frailty and postoperative complications. The present meta-analysis confirmed this association, which has also been reported in previous systematic reviews [2,6,13]. We therefore believe that the effect of frailty on postoperative complications is well established and has potential consequences for clinical practice. One is the likely need for systematic screening for frailty using standard, validated instruments and subsequent confirmation with a comprehensive geriatric assessment in the case of a positive result. Determination of frailty status should contribute to decision-making on clinical management and treatment and improve the planning of care. Prehabilitation programs for patients who undergo surgery could minimize complications. Although most studies classify patients as frail or non-frail, the specification of the level of frailty (robust, pre-frail, frail, or very frail) makes a difference, as it allows for more targeted interventions [31–33]. Interventions should aim to prevent, delay, or reverse the various states of frailty, as well as prevent or reduce complications in patients with advanced frailty that is no longer reversible [34]. An ongoing randomized clinical trial is evaluating the efficacy of a multimodal prehabilitation program based on physical exercise, nutritional and psychological status assessment, and smoking cessation in the four weeks before CC surgery [35]. Multimodal prehabilitation is expected to improve functional capacity and reduce postoperative complications in older patients with CC. There is, in fact, evidence suggesting that the best time to intervene is during the preoperative phase [36]. Additional benefits of multimodal prehabilitation are empowerment of patients, enabling them to play a more active role in their disease, and earlier initiation of adjuvant chemotherapy, which could improve survival and quality of life [37,38].

This systematic review also shows that frailty is a clear risk factor for worse survival and increased 30-day, 3- to 6-month, and 1-year mortality. Mortality was 3 to 8 times higher in frail patients, confirming previous systematic review findings showing that older patients with CC who are frail (or have multiple comorbidities) have higher mortality [2] and worse survival [6] than their non-frail counterparts. The systematic review by Boakye et al. [6] included 37 studies, but just two of these specifically assessed frailty. In the present review, all 14 studies assessed frailty in CC. Another systematic review of five studies, of which just two reported 30-day mortality data, did not show significant differences between frail and non-frail patients [13]. It is important to highlight that the study by Vermillion et al. [17] had considerable weight in the meta-analysis (even using a random effects model) because of its much larger sample size. Nonetheless, the effect it detected for frailty on mortality is similar to that detected by the meta-analysis for the rest of the studies. Thus, the meta-analysis results do not seem very sensitive to the study by Vermillion et al. We found just one study that evaluated five-year survival in older patients with CC [30], and it reported respective rates of 24% and 66% for frail and non-frail patients ($p < 0.001$). Taken together, the evidence presented clearly and conclusively shows that frailty is a risk factor for increased mortality in the short, medium, and long term in older patients with CC, once again reinforcing the need for frailty screening accompanied by multimodal interventions based on pain control, underlying disease control, appropriate use of medication, diet, physical exercise, and psychological and social support [39]. Interventions of this nature have been shown to improve or reverse frailty [40] and should increase the chances of treatment success with fewer adverse effects in CC.

The main strengths of this systematic review lie in the design of the selected studies (all prospective and observational), their high methodological quality, the range of settings in which they were performed (improved external validity), and the reporting of data amenable to meta-analysis, which affords a more objective interpretation of results. This review, however, also has some limitations. First, there is a risk, albeit slight in our opinion, of selection bias due to publication bias or an incomplete literature search. Second, we were unable to perform subgroup analyses due to the relatively small number of studies ($n = 14$) and, in some cases, the reporting of outcome measure data in a form incompatible with meta-analysis. Thirdly, the studies used heterogeneous follow-up times and frailty measurements (the primary study outcome). The comprehensive geriatric assessment is the most appropriate way to assess frailty, but only 1 out of 14 studies used it. All other instruments are screening tools with limited diagnostic accuracy and poor concordance among them. They do not measure precisely the same concept (some are limited to physical frailty, others to a more comprehensive frailty concept, etc.). Still, they all aim to identify those who suffer from some degree of vulnerability that makes them more prone to

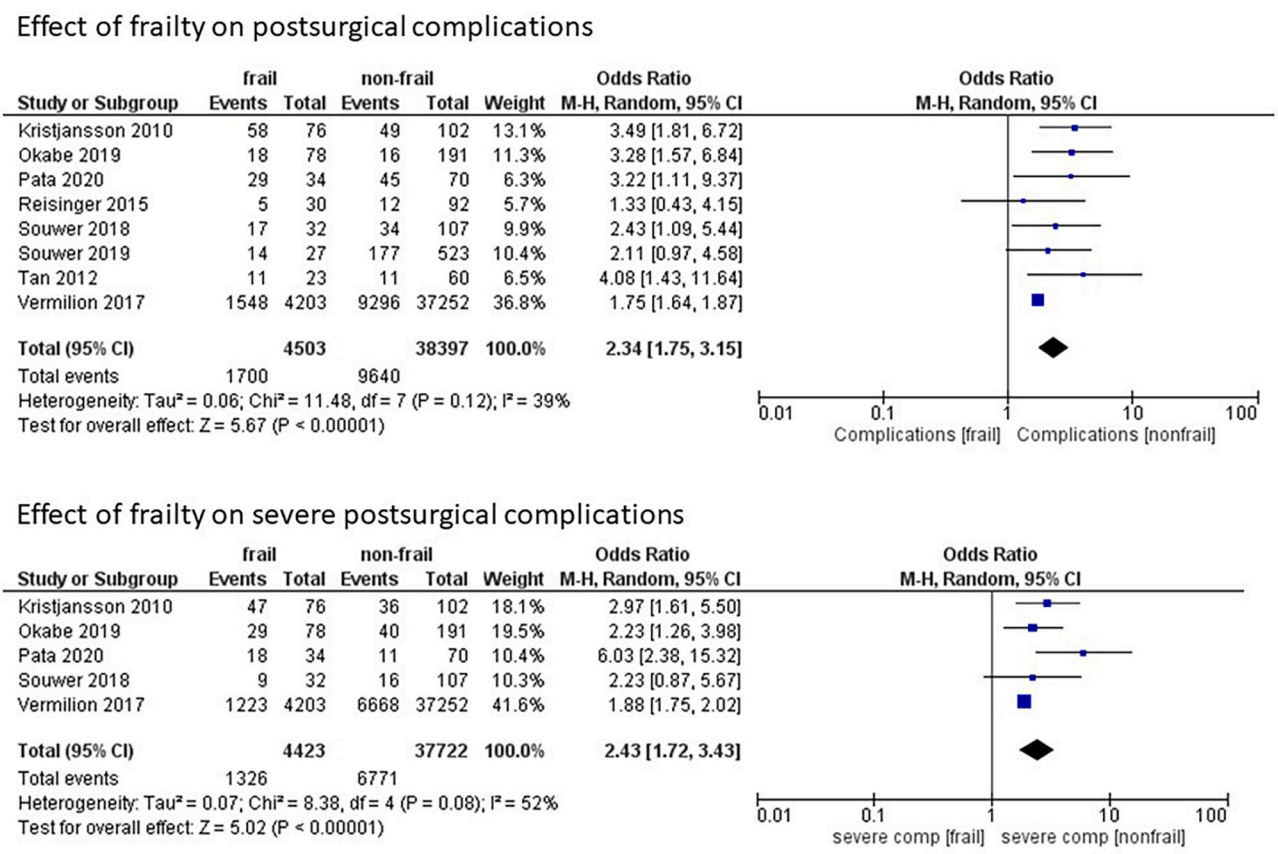

Fig. 4. Post-surgical complications meta-analysis results.

disease and adverse health outcomes, so it is worth to obtain a measure of the join effect of all them. Although frailty is a well-accepted concept and clinical condition among most geriatricians, its diagnosis is still a matter of debate and research. Finally, the study by Vermillion et al. [17] had a greater weight in the meta-analysis due to its much larger sample size. Nonetheless, it had a somewhat higher methodological quality than the mean, and the sensitivity analyses showed very robust, similar results when this study was excluded from the meta-analysis.

In conclusion, frailty in older patients with non-metastatic CC is a risk factor for postoperative complications, severe postoperative complications, mortality in the short (30 days), medium (3–6 months), and long-term (1 year), and poor survival. Implementing frailty screening programs and more exhaustive monitoring and prehabilitation programs could minimize complications in this setting. However, randomized clinical trials would be needed to assess the safety and efficacy of these interventions.

Author Contributions

MR and MSP contributed to the conception and design of the research, extracted data, and drafted the article; SR contributed to the data analysis; OE, TF, and RQ contributed to the interpretation of the data. All authors critically revised the article, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final article.

This study is part of the doctoral thesis of Maria del Rosario Moreno Carmona (*Universitat de Barcelona*, Doctoral program in nursing and health).

Declaration of Competing Interest

All authors declare that they have no conflicts of interest in relation to this study.

Acknowledgments

This study was partially funded by a grant from the Spanish Ministry of Health - *Instituto de Salud Carlos III* (ISCIII), with reference code PI19/00500.

References

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011 Mar-Apr;61(2):69–90. https://doi.org/10.3322/caac.20107 (Epub 2011 Feb 4. Erratum in: CA Cancer J Clin. 2011 Mar-Apr;61(2):134. PMID: 21296855).

[2] Michaud Maturana M, English WJ, Nandakumar M, Li Chen J, Dvorkin L. The impact of frailty on clinical outcomes in colorectal cancer surgery: a systematic literature review. ANZ J Surg 2021;91:2322–9 (John Wiley and Sons Inc).

[3] Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000 Jul;124(7):979–94. https://doi.org/10.5858/2000-124-0979-PFICC (PMID: 10888773).

[4] American Cancer Society. La sociedad Americana contra el cáncer 2010. 2010.

[5] Kim JH. Chemoterapy for colorrectal cancer in the elderly. World J Gastroenterol 2015;21(7):5158–66.

[6] Boakye D, Rillmann B, Walter V, Jansen L, Hoffmeister M, Brenner H. Impact of comorbidity and frailty on prognosis in colorectal cancer patients: a systematic review and meta-analysis. Cancer Treat Rev 2018;64:30–9. https://doi.org/10.1016/j.ctrv.2018.02.003. Epub 2018 Feb 10, 29459248.

[7] Lacas ARK. Frailty in primary care: a review of its conceptualization and implications for practice. BMC Med 2012;10:4.

[8] Lund CM, Vistisen KK, Dehlendorff C, Rønholt F, Johansen JS, Nielsen DL. The effect of geriatric intervention in frail elderly patients receiving chemotherapy for colorectal cancer: a randomized trial (GERICO). BMC Cancer 2017 Jun 28;17(1):448. https://doi.org/10.1186/s12885-017-3445-8. PMID: 28659138; PMCID: PMC5490215.

[9] Mohile SG, Dale W, Somerfield MR, Schonberg MA, Boyd CM, Burhenn PS, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. J Clin Oncol 2018 Aug 1;36

(22):2326–47. https://doi.org/10.1200/JCO.2018.78.8687 (Epub 2018 May 21. PMID: 29782209; PMCID: PMC6063790).
[10] González-Senac NM, Mayordomo-Cava J, Macías-Valle A, Aldama-Marín P, González SM, Arnés MLC, et al. Colorectal cancer in elderly patients with surgical indication: state of the art, current management, role of frailty and benefits of a geriatric liaison. Int J Environ Res Public Health 2021;18(11):1–22.
[11] Molina-Garrido MJ, Guillén-Ponce C. Métodos de evaluación de fragilidad en el adulto mayor oncológico. Gac Med Bilbao 2017;114(3):124–31.
[12] Molina-Garrido MJGPC. Oncogeriatría: una forma de optimizar la atención global del paciente anciano con cáncer. Nutr Hosp 2016;33(Suple 1):31–9.
[13] Fagard K, Leonard S, Deschodt M, Devriendt E, Wolthuis A, Prenen H, 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(6):479–91.
[14] Okabe H, Ohsaki T, Ogawa K, Ozaki N, Hayashi H, Akahoshi S, et al. Frailty predicts severe postoperative complications after elective colorectal surgery. Am J Surg 2019;217(4):677–81.
[15] Giannotti C, Sambuceti S, Signori A, Ballestrero A, Murialdo R, Romairone E, et al. Frailty assessment in elective gastrointestinal oncogeriatric surgery: predictors of one-year mortality and functional status. J Geriatr Oncol 2019;10(5):716–23.
[16] Ommundsen N, Nesbakken A, Wyller TB, Skovlund E, Bakka AO, Jordhøy MS, et al. Post-discharge complications in frail older patients after surgery for colorectal cancer. Eur J Surg Oncol 2018;44(10):1542–7.
[17] Vermillion SA, Hsu FC, Dorrell RD, Shen P, Clark CJ. Modified frailty index predicts postoperative outcomes in older gastrointestinal cancer patients. J Surg Oncol 2017;115(8):997–1003.
[18] Souwer ETD, Hultink D, Bastiaannet E, Hamaker ME, Schiphorst A, Pronk A, et al. The prognostic value of a geriatric risk score for older patients with colorectal cancer. Ann Surg Oncol 2019;26(1):71–8.
[19] Ramsdale E, Polite B, Hemmerich J, Bylow K, Kindler HL, Mohile S, et al. The vulnerable elders Survey-13 predicts mortality in older adults with later-stage colorectal cancer receiving chemotherapy: a prospective pilot study. J Am Geriatr Soc 2013 Nov;61(11):2043–4. https://doi.org/10.1111/jgs.12536. 24219208.
[20] Rønning B, Wyller TB, Nesbakken A, Skovlund E, Jordhøy MS, Bakka A, et al. Quality of life in older and frail patients after surgery for colorectal cancer-a follow-up study. J Geriatr Oncol 2016;7(3):195–200.
[21] Aaldriks AA, van der Geest LGM, Giltay EJ, le Cessie S, Portielje JEA, Tanis BC, et al. Frailty and malnutrition predictive of mortality risk in older patients with advanced colorectal cancer receiving chemotherapy. J Geriatr Oncol 2013;4(3):218–26.
[22] Kristjansson SR, Nesbakken A, Jordhøy MS, Skovlund E, Audisio RA, Johannessen HO, et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: a prospective observational cohort study. Crit Rev Oncol Hematol 2010;76(3):208–17.
[23] Tan KY, Kawamura YJ, Tokomitsu A, Tang T. Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. Am J Surg 2012;204(2):139–43.
[24] Souwer ETD, Verweij NM, van den Bos F, Bastiaannet E, Slangen RME, Steup WH, et al. Risk stratification for surgical outcomes in older colorectal cancer patients using ISAR-HP and G8 screening tools. J Geriatr Oncol 2018;9(2):110–4.
[25] Reisinger KW, Van Vugt JLA, Tegels JJW, Snijders C, Hulsewé KWE, Hoofwijk AGM, et al. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. Ann Surg 2015;261(2):345–52.
[26] Pata G, Bianchetti L, Rota M, Marengoni A, Chiesa D, Cassinotti E, et al. Multidimensional prognostic index (MPI) score has the major impact on outcome prediction in elderly surgical patients with colorectal cancer: the FRAGIS study. J Surg Oncol 2021;123(2):667–75.
[27] Ommundsen N, Wyller TB, Nesbakken A, Jordhøy MS, Bakka A, Skovlund E, et al. Frailty is an independent predictor of survival in older patients with colorectal cancer. Oncologist. 2014;19(12):1268–75.
[28] Ørum M, Gregersen M, Jensen K, Meldgaard P, Marie E, Damsgaard S. Frailty status but not age predicts complications in elderly cancer patients: a follow-up study. Acta Oncol 2018;57(11):1458–66.
[29] Massa E, Madeddu C, Astara G, Pisano M, Spiga C, Tanca FM, et al. An attempt to correlate a «multidimensional geriatric assessment» (MGA), treatment assignment and clinical outcome in elderly cancer patients: results of a phase II open study. Crit Rev Oncol Hematol 2008;66(1):75–83.
[30] Armstrong JJ, Stolee P, Hirdes JP, Poss JW. Examining three frailty conceptualizations in their ability to predict negative outcomes for home-care clients. Age Ageing 2010;39(6):755–8.
[31] Rockwood K, Theou O, Mitnitski A. What are frailty instruments for? Age Ageing 2015;44(4):545–7.
[32] Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2015;26(6):1091–101.
[33] Decoster L, Van Puyvelde K, Mohile S, Wedding U, Basso U, Colloca G, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. Ann Oncol 2015;26(2):288–300.
[34] Chen X, Mao G, Leng SX. Frailty syndrome: an overview. Clin Interv Aging 2014;9:433–41.
[35] Van Rooijen S, Carli F, Dalton S, Thomas G, Bojesen R, Le Guen M, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC Cancer 2019;19(1):1–11.
[36] Mayo NE, Feldman L, Scott S, Zavorsky G, Kim DJ, Charlebois P, et al. Impact of preoperative change in physical function on postoperative recovery: argument supporting prehabilitation for colorectal surgery. Surgery 2011;150(3):505–14.
[37] van Rooijen SJ, Engelen MA, Scheede-Bergdahl C, Carli F, Roumen RMH, Slooter GD, et al. Systematic review of exercise training in colorectal cancer patients during treatment. Scand J Med Sci Sports 2018;28(2):360–70.
[38] De Backer IC, Van Breda E, Vreugdenhil A, Nijziel MR, Kester AD, Schep G. High-intensity strength training improves quality of life in cancer survivors. Acta Oncol 2007;46(8):1143–51.
[39] Sternberg SA, Schwartz AW, Karunananthan S, Bergman H, Mark Clarfield A. The identification of frailty: a systematic literature review. J Am Geriatr Soc 2011;59(11):2129–38.
[40] Serra-Prat M, Sist X, Domenich R, Jurado L, Saiz A, Roces A, et al. Effectiveness of an intervention to prevent frailty in community-dwelling older people consulting in primary care. A randomized controlled trial. Age Ageing 2017;46(3):401–7.