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Systematic Review

Associations between outcome variables of nutritional screening methods and systemic treatment tolerance in patients with colorectal cancer: A systematic review

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ABSTRACT

Introduction: Multiple screening methods for malnutrition are available, but a systematic review of evidence in patients with colorectal cancer (CRC) is lacking. The aim of this study is to systematically investigate which outcome variables of nutritional screening methods are associated with treatment tolerance in patients with CRC.
Material and Methods: A systematic review was performed with respect to outcome variables of nutritional screening methods and their association with systemic treatment tolerance in patients with CRC. The Cochrane guidelines for systematic reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Two authors independently assessed the risk of bias and quality of each included study.
Results: A total of sixteen studies were included. The following screening methods for malnutrition were assessed in the included studies: serum albumin, body mass index, C-reactive protein/albumin ratio, modified version of the Glasgow prognostic score, mini nutritional assessment, nutritional risk index, patient-generated subjective global assessment, sarcopenia and weight loss.
Discussion: Sarcopenia tended to be associated with treatment tolerance more often than other screening methods but the current review suggests that there are ample screening methods rendering meaningful outcomes regarding a patient's nutritional status and associated risk for treatment intolerance. This grants practitioners the flexibility to choose from a variety of different nutritional screening methods. Nutritional screening can thus be tailored to the individual patient. Importantly, nutritional screening may help identify those patients at risk for chemotoxicity thus allowing for the implementation of targeted prehabilitation programs in order to prevent (severe) chemotoxicity.

1. Introduction

Worldwide, colorectal cancer (CRC) is the second most common malignancy in females and the third in males with approximately 1.8 million new patients in 2018. Among those, one-third had a tumor located in the rectum [1]. Currently, chemotherapy after surgical resection is indicated for patients with high-risk stage II, III and IV CRC [2–4]. High-risk is defined according to current guidelines, since 2016, by pathological T4 and according to former guidelines by fewer than twelve harvested lymph nodes, perforation or obstruction, poorly differentiated histology and/or lymphatic/perineural invasion in addition to pathologic T4 [4]. In case of distant metastases (stage IV), systemic therapy is given in almost 50% of patients with a palliative treatment intention [5]. As a result of improvements in both diagnostics

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and treatment, five-year survival rates have increased from 54% in the period 1991–2000 to 67% in the period 2011–2018 [5]. The developments in oncologic care are partially due to an increased use of novel chemotactic agents which simultaneously leads to an increased incidence of chemotoxicity [6].

Due to the direct effects of the underlying disease as well the indirect effects of chemotherapy, patients with cancer have an increased risk of malnutrition with an overall prevalence about 40% [7,8]. Patients with colorectal malignancies are particularly at risk of malnutrition because the pathology interferes directly with digestion and absorption [9,10]. The presence of malnutrition has been associated with poor tolerance of chemotherapy in patients with CRC, which often leads to loss of (instrumental) activities, in particular among older patients, and may have substantial impact on quality of life [11–13]. Therefore, identification of malnutrition before start of oncological treatment is recommended in order to select patients who are at risk for chemotoxicity and to achieve better treatment tolerance in those patients by nutritional interventions and/or dietary counseling as this is an important part of multimodal prehabilitation.

Multiple screening methods for malnutrition are available. In 2016, a systematic review provided an overview of nutritional screening methods in older patients with cancer and assessed their content validity based on internationally accepted definitions for malnutrition. Among 37 screening methods utilized for patients with cancer, the mini nutritional assessment (MNA) scored highest for the calculated content validity [14]. This suggests that the MNA may be the best method to assess nutritional status in older patients. Another, more recent systematic review investigated the prognostic significance of nutritional status by the MNA regarding health and treatment outcomes in patients with cancer [15]. The results indicated that the MNA predicts survival, treatment maintenance, and quality of life (but not adverse treatment outcomes). The large heterogeneity of included studies in this review, however, obfuscates the potential differences in the clinical value of the MNA for the various types and stages of cancer and treatment modalities (e.g., chemotherapy and/or surgery) [15].

The predictive value of malnutrition for systemic treatment tolerance has been suggested by several studies [12,15,16], but a systematic review investigating the association between outcome variables of nutritional screening methods and treatment tolerance in patients with CRC is not available yet. The goal of this study is therefore to systematically investigate which outcome variables of nutritional screening methods are associated with systemic treatment tolerance in patients with stage II-IV CRC.

2. Methods

A systematic review was performed with respect to outcome variables of nutritional screening methods and their association with systemic treatment tolerance in patients with colorectal cancer. The Cochrane guidelines for systematic reviews [17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] were followed (Supplementary Table 2). The PRISMA 2020 template is shown in the supplemental material. The study protocol was registered at PROSPERO (CRD42020220679).

2.1. Systematic Literature Search

A systematic literature search using database-specific search strategies was conducted in PubMed, Embase, and CINAHL for studies published in English up to March 2021. The search strategies included a combination of keywords and MeSH−/Emtree terms. Key terms were defined according to the patient, exposure, comparison, outcome (PECO) strategy [19] by using the following terms: colorectal cancer combined with chemotherapy, nutritional screening method, and chemotoxicity. Additionally, reference lists of retrieved studies and published systematic reviews were screened. Details on the search strategy are shown in Supplementary Table 1.

2.2. Study Selection

All prospective and retrospective cohort studies that operationalized outcome variables of nutritional screening methods and their association with systemic treatment tolerance in patients with stage II-IV CRC who underwent adjuvant and/or palliative chemotherapy were included. All types of screening methods (i.e., functional or biochemical tests, anthropometric measurements, or questionnaires) were included. Case studies, conference papers, qualitative research or reviews were excluded. After removal of duplicates, titles and abstracts of studies obtained by the literature search were screened by two authors (K.B. and M.V.) independently for judging eligibility. Assessment of full-texts was performed independently by these two authors. Any disagreements on inclusion or exclusion of studies were discussed and/or resolved by consulting a third author (M.J.) who independently decided.

2.3. Data Extraction

Two authors (K.B. and M.V.) independently extracted data from each of the included studies by using a standardized data collection file. The following information was collected from each study: name of the first author, year of publication, type of cohort, sample size, age, performance status according the Eastern Cooperative Oncology Group (ECOG) [20] and sex of the participants, cancer stage, type of chemotherapy, used nutritional screening method and corresponding cut-off values, and outcome variables of systemic treatment tolerance (chemotoxicity and treatment duration). Outcome variables of treatment tolerance were categorized as chemotoxicity (i.e., adverse events) or changes in treatment plan (i.e., treatment duration/early termination). Adverse events were defined as chemotoxicity when these occurred during chemotherapy and/or within six months after the last treatment cycle, depending on which systemic therapy was given. Chemotoxicity was categorized by hematological and non-hematological toxicities in case this information was available.

2.4. Risk of Bias Assessment

The quality of included studies was assessed using the Newcastle Ottawa Scale (NOS) [21]. Good-quality studies were defined by scoring 3 or 4 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain. Fair-quality studies were defined by scoring 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain. Poor-quality studies were defined by scoring 0 or 1 stars in the selection domain or 0 stars in the comparability domain or 0 or 1 stars in the outcome/exposure domain. Two authors (K.B. and M.V.) independently assessed the risk of bias and quality of each included study. Conflicts were discussed and/or resolved by consulting a third author (M.J.).

2.5. Data Synthesis

Associations between outcome variables of nutritional screening methods and treatment tolerance defined by chemotoxicity and/or treatment duration were considered statistically significant when p-values were < 0.05. Prevalence of malnutrition and cut-off values for outcomes of nutritional screening methods for an increased risk of chemotoxicity were reported in case of a significant association.

3. Results

3.1. Study Selection

After removing duplicates, 1005 studies based on title/abstract and

22 full-text studies were screened for potential eligibility. Finally, sixteen studies [12,22–36] were included. Main reasons for exclusion were alternative study design (i.e., nutritional intervention), alternative population or alternative outcome (e.g., postoperative complications). A flow diagram for the selection of studies is shown in Fig. 1.

3.2. Study and Patient Characteristics

An overview of characteristics of the included studies is shown in Table 1. Eleven studies [12,22–30,32] were prospective observational and five studies [31,33–36] had a retrospective observational design. Year of publication ranged from 2011 to 2021. Median sample size was 136 patients (ranging from 36 to 523 with a total of 2439) and the mean age of the included patients ranged from 48 to 80 years. The mean percentage of patients with an ECOG-PS score ≥ 2 was 15% (range 0% to 61%). The percentage of males ranged from 38% to 75%. Two studies [22,33] included only patients with a curative treatment intention, four studies [12,27,32,36] included both patients with a curative and palliative treatment intention and ten studies [23–26,28–31,34,35] included only patients with a palliative treatment intention. Definitions and cut-off values of each nutritional screening method are shown in Table 2. Definitions of treatment tolerance are shown in Table 3.

3.3. Risk of Bias

The results of the quality assessment are shown in Table 4. Twelve studies [12,22,23,25–27,30–35] were ranked with a good quality based on the NOS. Four studies [24,28,29,36] were ranked with a poor quality based on the fact that follow-up periods were too short. For all studies, there was consensus between the two reviewers.

3.4. Associations between Pretreatment Nutritional Screening Method and Treatment Complications

The included studies assessed the following nutritional screening methods (see Table 1): weight loss, body mass index (BMI), serum albumin, C-reactive protein (CRP)/albumin ratio (CAR), the modified version of the Glasgow prognostic score (mGPS) and the nutritional risk index (NRI) as clinical and biochemical tests; the MNA and the patient-generated subjective global assessment (PG-SGA) as questionnaires; and sarcopenia and the psoas muscle index (PMI). The associations between outcome variables of nutritional screening methods and treatment tolerance with regard to chemotoxicity and treatment duration, as were found in the included studies, are shown in Table 5. In seven studies [27–32,34], chemotoxicity was categorized as hematological and non-hematological toxicity.

3.4.1. Screening by Clinical and Biochemical Tests

Seven studies [22,24,25,28–30,32] assessed the association between weight loss and treatment tolerance. In one study [24], overall toxicity was more frequent in patients with a weight loss >10%: 78% versus 56% ($p = 0.02$). Five studies [23,25,28–30] assessed the association between BMI and chemotoxicity. A significant association between underweight measured with the BMI <25 kg/m^2 and non-hematological toxicity was found in one of these five studies ($p = 0.01$) [30].

Five studies [28–32] assessed the association between serum albumin and treatment tolerance, of which two [30,31] reported a significant association between low levels of serum albumin and a higher risk of chemotoxicity ($p < 0.01$ [30] and $p = 0.03$ [31] for non-hematological toxicity, and $p = 0.03$ [30] and $p < 0.01$ [31] for hematological toxicity). In one [31] out of five studies, low serum albumin was significantly associated with a reduced treatment duration ($p < 0.01$).

One study [33] assessed the association between CAR and treatment tolerance. A high level of CAR tended to be associated with chemotoxicity and discontinuation of adjuvant chemotherapy ($p < 0.01$ and $p = 0.02$ respectively). Multivariate analysis identified CAR ≥ 0.1 (HR: 7.06, 95% confidence interval [CI]: 2.51–19.88, $p < 0.01$) as a significant determinant of chemotoxicity.

One study [34] assessed the association between the mGPS and chemotoxicity. No difference in the frequency of chemotoxicity between

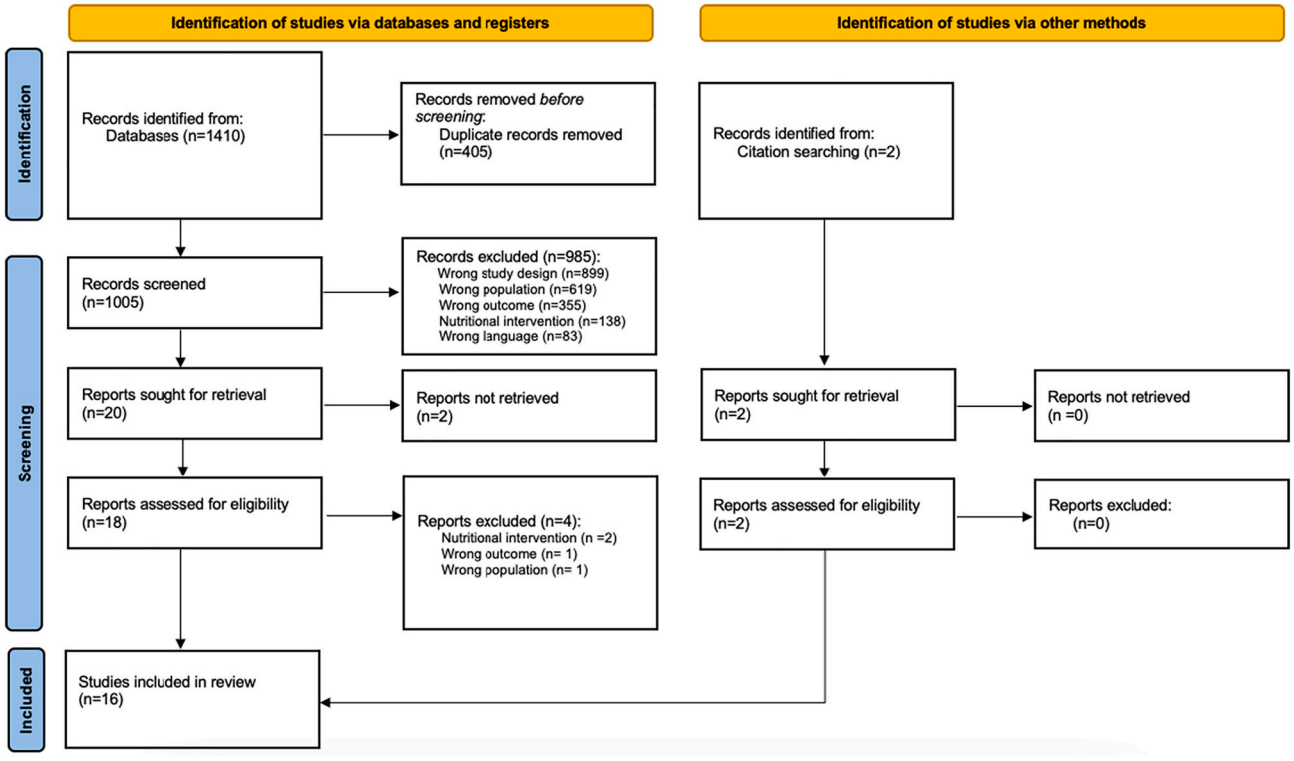

Fig. 1. Flow diagram for the selection of included studies according the PRISMA 2020 statement [18].

Table 1
Characteristics of included studies that evaluated the association between nutritional screening methods and systemic treatment intolerance.

Author/year	Type of observational cohort[a]	Sample size (n)	Mean age (range)	PS ≥2 (%)	Male (%)	Cancer stage	Type of chemotherapy (%)	Nutritional screening method[d]	Outcome
Aaldriks et al. 2013	Prospective	143	75 (70–92)	2	59	Mixed	Capecitabine, CapOx, FOLFOX4, 5FU/LV, bevacizumab	MNA	Treatment duration
Antonio et al. 2017	Prospective	193	80 (75–89)	22	63	II-III	Capecitabine, CapOx, FOLFOX6	Weight loss	Chemotoxicity/ treatment duration
Barret et al. 2011	Prospective	114	65[b] (22–92)	25	68	Advanced	FP, IRI, FP/Ox, FP/IRI	Albumin, NRI, weight loss	Chemotoxicity
Barret et al. 2014	Prospective	51	65[b] (22–84)	14	75	Advanced	FP, IRI, FP/Ox, FP/IRI	BMI, sarcopenia	Chemotoxicity
Chemama et al. 2016	Prospective	97	53[c] [43–58]	NA	38	Advanced	CRS-HIPEC	BMI, sarcopenia, weight loss	Chemotoxicity
Decoster et al. 2017	Prospective	193	77[b] (70–89)	61	62	Mixed	Capecitabine, 5FU, capecitabine/5FU, bevacizumab	MNA	Chemotoxicity
Decoster et al. 2018	Prospective	252	77 (69–91)	15	62	Advanced	Capecitabine, CapOx, FOLFIRI, 5FU/LV, FOLFOX	MNA	Chemotoxicity/ treatment duration
Gallois et al. 2019	Prospective	168	70[b] (33–93)	17	56	Advanced	Capecitabine, Ox, IRI, bevacizumab	Albumin, BMI, PG-SGA, NRI, weight loss	Chemotoxicity
Gallois et al. 2021	Prospective	149	70[b]	19	55	Advanced	Capecitabine, Ox, IRI, bevacizumab	Albumin, BMI, PG-SGA, sarcopenia, SMI weight loss	Chemotoxicity
Gökyer et al. 2019	Retrospective	36	62	0	61	Mixed	Regorafenib	Sarcopenia	Chemotoxicity
Karabulut et al. 2018	Prospective	137	62[b] (18–83)	0	39	Advanced	FP, FP/Ox, FP/IRI, FP/Ox/IRI	Albumin, BMI, NRI, weight loss	Chemotoxicity
Nagata et al. 2016	Retrospective	42	64	NA	52	Advanced	CapOx, FOLFOX, TS-1, SOX, IRIS	PMI	Treatment duration
Okada et al. 2017	Retrospective	108	65[b] (34–83)	1	54	Advanced	FOLFOX, FOLFIRI	Albumin	Chemotoxicity/ treatment duration
Retornaz et al. 2020	Prospective	97	79[c] (75–83)	NA	50	Mixed	5FU, cetuximab, 5FU/Ox/ bevacizumab, 5FU/Ox/ cetuximab, 5FU/IRI/ bevacizumab, 5FU/IRI/ cetuximab	Albumin, MNA, weight loss	Chemotoxicity
Tsuchihashi et al. 2018	Retrospective	523	63[b]	5	59	Advanced	Regorafenib, TFTD	mGPS	Chemotoxicity
Tominga et al. 2016	Retrospective	136	63	9	58	III	Capecitabine, CapOx, TS-1, FOLFOX, SOX	CRP/albumin ratio	Chemotoxicity/ treatment duration

Abbreviations: PS = perfomance status; NA = not available; CapOx = capecitabine/oxaliplatin; FOLFOX4 = 5-fluorouracil/leucovorin/oxaliplatin; 5FU = 5-fluorouracil; LV = leucovorin, FOLFOX6 = modified 5-fluorouracil/leucovorin/oxaliplatin; FP = 5-Fluorouracil/cisplatin; IRI = irinotecan; Ox = oxaliplatin; CRS-HIPEC = cytoreductive surgery-hyperthermic intraperitoneal chemotherapy; TFTD = trifluridine/tipiracil; TS-1 = tegafur/Gimeracil/Oteracil; SOX = S-1/oxaliplatin; IRIS = tegafur/gimeracil/oteracil.
[b] Median (range). [c] Median (interquartile range). [d] Abbreviations are defined in Table 2.

mGPS groups was found in patients treated with regorafenib and trifluridine/tipiracil (TFTD), except for hematological toxicities in patients treated with TFTD ($p = 0.03$). No information was given about odds ratios (ORs) and or 95% CIs.

Three studies [24,28,30] assessed the association between the NRI and chemotoxicity. In one study [24], all types of toxicity were more frequent in severely malnourished patients based on the NRI (NRI < 83.5) than in patients with no or moderate (NRI: 97.5–83.5) malnutrition ($p = 0.01$). In another study [30], moderate to severe malnutrition was significantly associated with both hematological toxicity ($p < 0.01$) and non-hematological toxicity ($p = 0.05$).

3.4.2. Screening by Questionnaires

Four studies [12,26,27,32] assessed the association between the MNA and treatment tolerance. One study [27] reported that patients at risk of malnutrition or who were malnourished (MNA < 24) had a significantly higher risk of grade 3 or 4 non-hematological toxicity (OR for MNA > 24: 0.33, 95% CI: 0.09–1.27, $p = 0.03$). Another study [12] reported poor MNA scores to be significantly associated with receiving fewer than 4 cycles of palliative chemotherapy ($p < 0.01$). This finding persisted in multivariate analysis (OR for ≥4 cycles vs. <4 cycles: 0.29, 95% CI: 0.11–0.81). One study [26] reported a significant association between poor MNA scores and treatment duration (4.7 months for poor MNA versus 6.7 months for normal MNA; $p = 0.02$).

Two studies [28,29] assessed the association between the PG-SGA and chemotoxicity. One study [28] categorized malnutrition into moderate and severe defined by the PG-SGA and reported a significant association between moderate malnutrition and a higher risk for non-hematological toxicity (OR: 3.7, 95% CI: 1.6–8.1, $p < 0.01$). Another study [29] also reported a significant association between moderate/severe malnutrition and a higher risk for non-hematological toxicity (OR 4.2, 95% CI 1.6–10.6, p < 0.01).

3.4.3. Screening of Sarcopenia

Four studies [23,25,29,36] assessed the association between sarcopenia and chemotoxicity. Sarcopenia was significantly associated with chemotoxicity in three studies [23,25,36] (OR: 13.55, 95% CI 1.08–169.31, $p = 0.04$ and OR: 3.97, 95% CI 1.52–10.39, $p = 0.01$ and hazard ratio (HR): 12.99, 95% CI1.25–134.80, $p = 0.03$). In one study [29], a decrease in skeletal muscle index>14% was significantly associated with non-hematological toxicity in univariate analysis (OR: 3.0, 95%CI: 1.2–7.7, $p = 0.02$).

One study [35] assessed the association between the PMI as indicator of sarcopenia and treatment duration. A low PMI was significantly associated with a shorter period of chemotherapy (p = 0.02).

Table 2
Definition and cut-off values of nutritional screening methods.

Study	Definition	Cut-off values of malnutrition as defined by the authors in the included study
Clinical and biochemical nutritional tests		
Antonio et al. 2017	Unintentional weight loss	≥10% last 6 months or 5% last 3 months
Barret et al. 2011	Weight loss	>10% last 6 months
Chemama et al. 2016	Relative weight loss	≥8% to usual weight
Gallois et al. 2019	Weight loss	>10% last 6 months
Gallois et al. 2021	Weight loss	>10% last 6 months
Karabulut et al. 2018	Weight loss	>10% last 6 months
Retornaz et al. 2020	Weight loss	>4 kg and/or loss of appetite
Barret et al. 2011	Serum albumin	<35 g/L
Gallois et al. 2019	Serum albumin	<35 g/L
Gallois et al. 2021	Serum albumin	<35 g/L
Karabulut et al. 2018	Serum albumin	<35 g/L
Okada et al. 2017	Serum albumin	<38 g/L or a decrease in serum albumin level of <10 g/L when baseline serum albumin was ≥38 g/L
Retornaz et al. 2020	Serum albumin	<32 g/L
Barret et al. 2014	Body mass index (kg/m^2)	<25 kg/m^2
Chemama et al. 2016	Body mass index (kg/m^2)	<25 kg/m^2
Gallois et al. 2019	Body mass index (kg/m^2)	<18.5 kg/m^2
Gallois et al. 2021	Body mass index (kg/m^2)	<18.5 kg/m^2
Karabulut et al. 2018	Body mass index (kg/m^2)	<25 kg/m^2
Tominga et al. 2016	CRP/albumin ratio: serum C-reactive protein level (mg/dL)/ serum albumin level (g/dL).	≥0.1 mg/d
Tsuchihashi et al. 2018	Modified version of Glasgow Prognostic Score (mGPS): a combination of C-reactive protein (CRP) and albumin levels.	mGPS 1: albumin level > 3.5 g/dL and CRP > 10 mg/L; mGPS 2: albumin<35 g/dL and CRP > 10 mg/L
Nutritional questionnaires		
Barret et al. 2011	Nutritional risk index (NRI): 1.519 x serum albumin level + 0.417 x current weight/basis weight x 100).	83–5-97.5: moderate malnutrition; <83.5: severe malnutrition
Gallois et al. 2019	Nutritional risk index (NRI): 1.519 x serum albumin level + 0.417 x current weight/basis weight x 100).	83–5-97.5: moderate malnutrition; <83.5: severe malnutrition
Karabulut et al. 2018	Nutritional risk index (NRI): 1.519 x serum albumin level + 0.417 x current weight/basis weight x 100).	83–5-97.5: moderate malnutrition; <83.5: severe malnutrition
Aaldriks et al. 2013	Mini nutritional assessment (MNA): a questionnaire comprised of two sections (screening and assessment section with respectively 7 and 18 domains)	Screening section: when the score is <12 points (indicating possibility of malnutrition), the assessment section is filled in. With the assessment section, a score of 24–30 points is indicative of being well nourished, 17–23.5 points for being at risk of malnutrition and a score <17 points for being malnourished.
Decoster et al. 2017	Mini nutritional assessment (MNA): a questionnaire with 18 domains.	<24
Decoster et al. 2018	Mini nutritional assessment (MNA): a questionnaire with 18 domains.	<24
Retornaz et al. 2020	Mini nutritional assessment-short form (MNA-SF): a questionnaire with 6 six domains.	8–11: at risk of malnutrition; 0–7 malnourished.
Gallois et al. 2019	Patient-generated subjective global assessment (PG-SGA): an overall assessment classifying the patient as category A (no malnutrition), B (moderate malnutrition) or C (severe malnutrition) and a numerical score, the values of each section (questionnaire completed by the patient and physical examination) being summed.	Malnutrition: grade B—C of PG-SGA and/or PG-SGA score ≥ 9; severe malnutrition: grade C of PG-SGA.
Gallois et al. 2021	Patient-generated subjective global assessment (PG-SGA): an overall assessment classifying the patient as category A (no malnutrition), B (moderate malnutrition) or C (severe malnutrition) and a numerical score, the values of each section (questionnaire completed by the patient and physical examination) being summed.	Malnutrition: grade B—C of PG-SGA and/or PG-SGA score ≥ 9; severe malnutrition: grade C of PG-SGA.
Sarcopenia		
Nagata et al. 2016	Psoas muscle index (PMI): the sum of bilateral psoas muscle cross-sectional areas (cm^2)/ body height (m^2).	<5.5 × 10^{-4} cm^2/m^2
Barret et al. 2014	Cross-sectional areas (cm^2) of respective tissues (muscle tissue, subcutaneous adipose tissue and visceral adipose tissue) computed by CT, normalized for height and expressed in units of cm^2/m^2 with the third lumbar vertebra (L3) as reference.	Male: <55.4 cm^2/m^2; female<38.9 cm^2/m^2
Chemama et al. 2016	Cross-sectional areas (cm^2) of respective tissues (muscle tissue, subcutaneous adipose tissue and visceral adipose tissue) computed by CT, normalized for height and expressed in units of cm^2/m^2 with the third lumbar vertebra (L3) as reference.	Male: <43 cm^2/m^2 if BMI < 25 kg/m^2 and < 53 cm^2/m^2 if BMI ≥ 25 kg/m^2; female <41 cm^2/m^2
Gallois et al. 2021	Cross-sectional areas (cm^2) of muscle at the level of the third lumbar vertebra (L3) were computed by CT, normalized for height and expressed in units of cm^2/m^2.	Male: 32.6–49.5 cm^2/m^2; female: 15.6–42.1 cm^2/m^2
Gökyer et al. 2019	Cross-sectional areas (cm^2) of muscle at the level of the third lumbar vertebra (L3) were computed by CT, normalized for height and expressed in units of cm^2/m^2.	Male: ≤ 49 cm^2/m^2; female: ≤ 31 cm^2/m^2
Gallois et al. 2021	Skeletal muscle index: variation in skeletal muscle index (measured as above-mentioned).	>14%

Table 3
Definitions/criteria and cut-off values of treatment intolerance.

Study	Outcome measure	Definition/criteria	Cut-off values for chemotoxicity and treatment duration
Aaldriks et al. 2013	Treatment duration	Number of received cycles of chemotherapy.	<4 or ≥ 4
Antonio et al. 2017	Chemotoxicity Treatment duration	CTCAE version 3.0/4.0 Completion (defined as completing initially planned chemotherapy course without later modifications or early discontinuation) of chemotherapy.	Grade ≥ 3 ≥80% of planned dose
Barret et al. 2011	Chemotoxicity	CTCAE version 3.0	Grade ≥ 2
Barret et al. 2014	Chemotoxicity	CTCAE version 4.0	Grade 3–4
Chemama et al. 2016	Chemotoxicity	CTCAE version 3.0	Grade 3–4
Decoster et al. 2017	Chemotoxicity	CTCAE version 4.0	Grade 3–4
Decoster et al. 2018	Chemotoxicity Treatment duration	3-point scale with mild: discomfort noticed but no disruption of normal daily activity; moderate: discomfort sufficient to reduce or affect daily activity; severe: inability to work or perform normal daily activity. Time interval between the first and last administration of chemotherapy.	- -
Gallois et al. 2019	Chemotoxicity	CTCAE version 4.0	Grade ≥ 2
Gallois et al. 2021	Chemotoxicity	CTCAE version 4.0	Grade ≥ 2
Gökyer et al. 2019	Chemotoxicity	CTCAE version 4.0	Dose reduction or drug withdrawal
Karabulut et al. 2018	Chemotoxicity	CTCAE version 4.0	Grade ≥ 2
Nagata et al. 2016	Treatment duration	Time interval between the first and last administration of chemotherapy.	–
Okada et al. 2017	Chemotoxicity Treatment duration	CTCAE version 5.0 Dose reduction or discontinuation of scheduled chemotherapy	Grade ≥ 2 -
Retornaz et al. 2020	Chemotoxicity	CTCAE version 2.0	Grade 3–4
Tsuchihashi et al. 2018	Chemotoxicity	CTCAE version 4.0	Grade ≥ 3
Tominga et al. 2016	Chemotoxicity Treatment duration	CTCAE version 4.0 Stopped adjuvant chemotherapy during the planning period for any reason.	Grade ≥ 3 -

CTCAE: Common Toxicity Criteria for Adverse Events [37].

4. Discussion

The aim of this systematic review was to evaluate which outcome variables of nutritional screening methods are associated with systemic treatment tolerance in patients with CRC. Results demonstrate that a wide variety of variables of nutritional screening methods seem to be associated with chemotoxicity and/or treatment duration. A comparison between studies was hampered due to a large variation in the used outcome measurements of nutritional screening methods together with often different definitions and cut-off values of these outcome measurements. Nevertheless, the overall methodological quality of the included studies was good and this systematic review provides a good overview of the available nutritional screening methods and their association with systemic treatment tolerance in patients with CRC. Below, we further discuss the value of the nutritional screening methods in the same order as these methods are presented in the Results section above: [1] clinical/biochemical tests, [2] questionnaires, [3] screening for sarcopenia.

This review noted a significant association between weight loss and overall toxicity in one [24] out of seven studies. This is in contrast to previous studies in which patients with weight loss had significantly more dose-limiting toxicities than other patients with gastrointestinal malignancies [9,38]. One study [30] reported a significant association between being underweight measured by BMI and non-hematological toxicity. However, the used cut-off values of malnutrition (<25/>25 kg/m^2) do not represent the group that is underweight (defined as <18.5 kg/m^2); only 0.4% of patients were underweight in this study. This should be kept in mind when interpreting the results. Although weight loss and BMI are objective and easy-to-perform measurements, the interpretation in the context of chemotoxicity is complex due to several influencing factors. First, the measurement of BMI includes fat and fat-free mass, both of which are known to be influenced by age and sex [39]. Second, many studies used weight loss expressed in percentages and calculated from the previous six months based on memory recall, so the risk of recall bias should be noted [40]. Third, there may be an overestimation of actual lean mass by the presence of ascites and/or edema which can result from protein depletion and/or abdominal tumor spread [24]. When the administered dose is based on body surface measurements such as BMI, the hidden loss of muscle mass may induce a drug overdose. This was also demonstrated by Prado et al. [41] in which patients with higher rates of chemotoxicity had higher doses of 5-fluorouracil per kilogram of lean body mass compared to those without chemotoxicity.

Apart from anthropometric measurements (such as body weight), serum albumin is a biomarker indicating nutritional status. In this systematic review, a low serum albumin was associated with a higher risk for chemotoxicity in two [30,31] out of five studies. Previous studies have demonstrated the role of serum albumin as prognostic marker for both systemic and surgical outcomes in patients with colorectal cancer, but the results were not consistent [42–44]. Although the measurement of serum albumin is easy to perform and relatively cheap, the biochemical relevance of this screening method in patients with cancer is dubious and difficult to interpret since the underlying disease interferes with the synthesis of albumin [45]. Due to high states of physiological stress with local tissue damage (i.e. tumor hypoxia/necrosis), a systemic release of proinflammatory cytokines and growth factors will appear, leading to production of acute phase proteins, such as CRP, and a decreased production of albumin [42]. Relative to albumin, the CAR and the mGPS have been reported as better predictors of systemic treatment outcome in the oncological setting, since these screening methods include the proinflammatory process in the interpretation of nutritional status [33,46–48]. Studies included in this systematic review showed that high levels of CAR (but not mGPS) were associated with chemotoxicity. It is important to note that although both the CAR and the mGPS use the same components (serum albumin and CRP), their outcome measures are different. The CAR is a ratio, whereas the GPS is scored on a three-point ordinal scale [33]. This might affect the interpretation of the results of these studies since continuous outcome measurements by the CAR are divided into separate groups by the mGPS and this may lead to an underestimation or overestimation of malnutrition. With respect to treatment duration, serum albumin and the CAR were also predictive for a shorter treatment duration [31,33]. Unfortunately, no information in these studies was given about the frequency and/or grading of adverse events which could provide us more insights into the relation of early discontinuation and the occurrence of adverse events.

Table 4
Quality assessment based on the Newcastle-Ottawa Scale for cohort studies.[a]

First author	Selection			Comparability			Outcome		
	Representativeness exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest present at start of the study	Comparability of cohorts on the basis of the design of analysis	Assessment of outcome	Follow-up time	Adequacy of follow-up of cohort	Quality [b]
Aaldriks et al. 2013	B*	A*	A*	A*	A*	A*	A*	A*	Good
Antonio et al. 2017	B*	A*	A*	A*	A*	A*	A*	A*	Good
Barret et al. 2011	A*	A*	A*	B	A*	A*	B	A*	Poor
Barret et al. 2014	A*	A*	A*	B	A*	A*	A*	A*	Good
Chemama et al. 2016	A*	A*	A*	B	A*	A*	A*	A*	Good
Decoster et al. 2017	B*	A*	A*	B	A*	A*	A*	A*	Good
Decoster et al. 2018	B*	A*	A*	A*	A*	A*	A*	A*	Good
Gallois et al. 2019	A*	A*	A*	B	A*	A*	A*	B	Poor
Gallois et al. 2021	B*	A*	A*	B	A*	A*	A*	B	Poor
Gökyer et al. 2019	A*	A*	A*	B	A*	A*	A*	B	Poor
Karabulut et al. 2018	A*	A*	A*	B	NR	A*	A*	A*	Good
Nagata et al. 2016	A*	A*	A*	A*	B*	A*	A*	A*	Good
Okada et al. 2017	B*	A*	A*	B	B*	A*	A*	A*	Good
Retornaz et al. 2020	B*	A*	A*	A*	B*	A*	A*	A*	Good
Tsuchihashi et al. 2018	A*	A*	A*	B	B*	A*	B	A*	Good
Tominga et al. 2016	B*	A*	A*	B	B*	A*	A*	A*	Good

Abbreviations: NR = not reported.

[a] Stars (*) are awarded on the basis of answers (A, B, C, or D) provided for each item.

[b] Thresholds for converting the Newcastle-Ottawa scale scores to Agency for Healthcare Research and Quality (AHRQ) standards (good, fair, and poor): good quality = 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; fair quality = 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain; poor quality = 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 stars in the outcome/exposure domain.

One may argue that nutritional status cannot be adequately assessed with a single outcome measure. Therefore, tools have been developed combining different measurements to more adequately assess nutritional status. The NRI is an easy-to-incorporate and objective screening tool that considers both serum albumin and weight loss. This tool has been used to assess the nutritional status of patients with head and neck cancer [49] and gastrointestinal cancer [50] and the combination of serum albumin and weight loss seems superior in its association with malnutrition to hypoalbuminemia or weight loss taken alone [24]. Two [24,30] out of the three studies included in this study reported a significant association between malnutrition assessed by the NRI and chemotoxicity. However, it should be noted that one [24] of these studies demonstrated severe malnutrition to be associated with >1 treatment line, so there may be a correlation between higher rates of chemotoxicity and impaired nutritional status due to a greater proportion of non-first-line patients in the severely malnourished subgroup.

Another method for nutritional screening concerns questionnaires, such as the PS-SGA and the MNA. One study [27] reported that malnourished patients or patients at risk for malnutrition (based on the MNA) had a significantly higher risk for grade 3 or 4 non-hematological toxicity. This finding is in line with a recent systematic review by Torbahn et al. [15]. Taking the large heterogeneity with respect to various types and stages of cancer into account, as well as differences in oncologic treatment and outcome measurements of this study by Torbahn et al. [15], only one [51] out of nine studies showed a significantly higher risk for non-hematologic toxicity in patients at risk of malnutrition or who were malnourished. Poor MNA scores were neither predictive for hematological toxicities in the current review study, nor in the review by Torbahn et al. [15]. The association between poor MNA scores and chemotoxicity is therefore not convincing, although the MNA is widely used in older patients and often a standard part of geriatric assessment [15,52]. The fact that both the MNA and the PG-SGA showed to be associated with a higher risk for non-hematological toxicities and this was not confirmed on hematological toxicities may be explained by the fact that treatment is continued for as long as it is tolerable in most patients with advanced CRC. This way, hematological toxicities may be prevented by dose reductions as a consequence of less threatening non-hematological toxicities such as diarrhea and/or hand-foot syndrome. In the present review, two studies [12,27] reported a significantly higher risk for patients at risk for malnutrition or who were malnourished (based on the MNA) to receive fewer cycles of planned chemotherapy. Again, this corroborates the results of the recent systematic review by Torbahn et al. [15].

Gallois et al. [28,29] evaluated the prognostic value of the PG-SGA for both non-hematological chemotoxicity and hematological chemotoxicity in 2019 and 2021. In both studies, a significant association between malnutrition as defined by the PG-SGA and non-hematological toxicities was found. However, since only a limited follow-up of up to two months was available in these studies [28,29], no conclusion can be drawn for the late adverse effects of chemotherapy, especially for

Table 5
Association between nutritional screening method and chemotoxicity and treatment duration.

Study	Cancer stage	Nutritional screening method	Treatment outcomes:							
			All types of toxicity		Non-hematological toxicity		Hematological toxicity		Treatment duration	
			OR/HR (95% CI)	P-value	OR/HR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Clinical and biochemical nutritional tests										
Antonio et al. 2017	II-III	Weight loss	*0.48 (0.1–2.3)*	*0.34*	–	–	–	–	*1.09 (0.4–3.3)*	*0.87*
Barret et al. 2011	Advanced	Weight loss	–	***0.02***	–	–	–	–	–	–
Chemama et al. 2016	Advanced	Weight loss	*1.49 (0.5–4.4)*	*0.46*	–	–	–	–	–	–
Gallois et al. 2019	Advanced	Weight loss	–	–	*0.8 (0.4–1.8)*	*0.6*	*0.8 (0.3–1.8)*	*0.6*	–	–
Gallois et al. 2021	Advanced	Weight loss	–	–	*1.0 (0.9–1.0)*	*0.7*	*1.0 (0.9–1.1)*	*0.8*	–	–
Karabulut et al. 2018	Advanced	Weight loss	–	–	–	0.29	–	0.27	–	–
Retornaz et al. 2020	Mixed	Weight loss	–	*0.65*	–	–	–	–	–	–
Barret et al. 2011	Advanced	Serum albumin	–	***0.04***	–	–	–	–	–	–
Gallois et al. 2019	Advanced	Serum albumin	–	–	*0.9 (0.4–1.9)*	*0.80*	*1.8 (0.8–3.7)*	*0.10*	–	–
Gallois et al. 2021	Advanced	Serum albumin	–	–	*0.9 (0.4–1.9)*	*0.80*	*1.8 (0.8–3.7)*	*0.10*	–	–
Karabulut et al. 2018	Advanced	Serum albumin	–	–	–	***0.03***	–	***<0.01***	–	–
Okada et al. 2017	Advanced	Serum albumin	–	–	–	**<0.01**[a]	–	**0.03**[a]	–	**<0.01**
Retornaz et al. 2020	Mixed	Serum albumin	3.9 (0.6–25.9)	0.10	–	–	–	–	–	–
Barret et al. 2014	Advanced	BMI	0.96 (0.1–7.2)	0.97	–	–	–	–	–	–
Chemama et al. 2016	Advanced	BMI	*1.41 (0.6–3.6)*	*0.47*	–	–	–	–	–	–
Gallois et al. 2019	Advanced	BMI	–	–	*2.1 (0.7–6.4)*	*0.2*	*0.2 (0.0–1.5)*	*0.1*	–	–
Gallois et al. 2021	Advanced	BMI	–	–	2.1 (0.7–6.4)	0.2	0.2 (0.0–1.5)	0.1	–	–
Karabulut et al. 2018	Advanced	BMI	–	–	–	***0.01***	–	*0.81*	–	–
Tominga et al. 2016	III	CAR	7.1 (2.5–19.9)	**<0.01**	–	–	–	–	–	**0.02**
Tsuchihashi et al. 2018	Advanced	mGPS	–	–	–	*0.84*[b]/ *0.27*[c]	–	*0.44*[b]/ ***0.03***[c]	–	–
Nutritional questionnaires										
Barret et al. 2011	Advanced	NRI	–	***0.01***	–	**–**	–	**<0.01**	–	–
Gallois et al. 2019	Advanced	NRI	–	–	*0.6 (0.3–1.2)*[d]	*0.10*[d]	*1.4 (0.7–3.1)*[d]	*0.3*[d]	–	–
Gallois et al. 2019	Advanced	NRI	–	–	*0.7 (0.2–2.2)*[e]	*0.50*[e]	*1.4 (0.4–4.7)*[e]	0.5[e]	–	–
Karabulut et al. 2018	Advanced	NRI	–	–	–	***0.05***	–	***<0.01***	–	–
Aaldriks et al. 2013	Mixed	MNA	–	–	–	–	–	–	0.3 (0.1–0.8)	**<0.01**
Decoster et al. 2017	Mixed	MNA	–	–	0.3 (0.1–1.3)	**0.03**	–	0.07	–	–
Decoster et al. 2018	Advanced	MNA	–	*0.12*	–	–	–	–	–	***0.02***
Retornaz et al. 2020	Mixed	MNA	–	*0.67*	–	–	–	–	–	–
Gallois et al. 2019	Advanced	PG-SGA	–	–	3.7 (1.6–8.1)[d]	**<0.01**[d]	1.1 (0.5–2.4)[d]	0.7[d]	–	–
Gallois et al. 2019	Advanced	PG-SGA	–	–	2.5 (0.9–6.8)[e]	0.07[e]	0.2 (0.0–1.4)[e]	0.6[e]	–	–
Gallois et al. 2021	Advanced	PG-SGA	–	–	4.2 (1.6–10.6)	**<0.01**	1.1 (0.5–2.4)	0.7	–	–
Sarcopenia										
Nagata et al. 2016	Advanced	PMI	–	–	–	**–**	–	–	–	***0.02***
Barret et al. 2014	Advanced	Sarcopenia	13.5 (1.1–169.3)	**0.04**	–	–	–	–	–	–
Chemama et al. 2016	Advanced	Sarcopenia	4.0 (1.5–10.4)	**<0.01**	–	–	–	–	–	–
Gallois et al. 2021	Advanced	Sarcopenia	–	–	*1.1 (0.5–2.6)*	*0.7*	*1.7 (0.7–4.0)*	*0.2*	–	–

(*continued on next page*)

Table 5 (*continued*)

Study	Cancer stage	Nutritional screening method	Treatment outcomes:							
			All types of toxicity		Non-hematological toxicity		Hematological toxicity		Treatment duration	
			OR/HR (95% CI)	P-value	OR/HR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
		SMI	–	–	*3.0 (1.2–7.7)*	***0.02***	*2.1 (0.7–5.8)*	*0.1*	–	–
Gökyer et al. 2019	Mixed	Sarcopenia	13.0 (1.25–134.8)	**0.03**	–	–	–	–	–	–

Abbreviations: OR: odds ratio; CI: confidence interval; BMI: body mass index; CAR: CRP/albumin ratio; mGPS: modified Glasgow prognostic score; NRI: nutritional risk index; MNA: mini nutritional assessment; PG-SGA: patient-generated subjective global assessment; PMI: psoas muscle index; SMI: skeletal muscle index. [a] Only grade 3 toxicity; [b] Regorafenib group; [c] TFTD group; [d] moderate based on NRI; [e] severe based on NRI. Numbers represents multivariate analysis, unless shown in italics: univariate analysis.

neurotoxicity induced by oxaliplatin. Thereby, the prognostic value in general is dubious since the PG-SGA consists of a questionnaire in which both fat and fat-free mass are included that are, as mentioned above, both known to be influenced by age and sex [53].

Considering nutritional screening methods and its relevance for predicting treatment tolerance in patients with CRC, measurements based on body composition such as sarcopenia seem preferable. It is noteworthy that, Lieffers et al. [54] noticed that almost two thirds of patients with sarcopenia had a BMI >25 kg/m^2, so loss of muscle mass may possibly be masked when using body surface measurements (also called 'sarcopenic obesity'). In the present review, all included studies that evaluated the prognostic value of sarcopenia showed a significant association between sarcopenia and systemic treatment intolerance [23,25,29,35,36]. These results are consistent with findings in studies that evaluated the prognostic value of sarcopenia in patients with advanced CRC receiving palliative chemotherapy or other solid tumors treated with capecitabine [55–57]. Determining sarcopenia therefore seems more suitable and relevant than BMI when predicting chemotoxicity. The implementation of the assessment of sarcopenia as standard care should be possible. Computed tomography (CT) images are used for cancer staging in patients with CRC and these images can be used to assess sarcopenia as well, forestalling the need for additional diagnostics [35]. However, there is still no consensus regarding the definition of sarcopenia. Eventually, the diversity in definitions and cut-off values might also increase heterogeneity between studies determining the prognostic value of sarcopenia.

It should be noted that there are some limitations to this systematic review. First, the diversity in existing nutritional screening methods with a wide variety of definitions, cut-off values, and outcomes of systemic treatment tolerance hampered a good comparison of studies. In addition, although we conducted our literature search by using MeSH/Emtree-terms according to the PECO-strategy, possible overlapping entities such as cachexia might have been missed due to the wide variety in definitions. This highlights the need for a universal definition for the diagnostic criteria of malnutrition. However, the wide variety also provides an opportunity to select an appropriate screening method (or methods) in individual cases taking age (i.e., the MNA for the older population), comorbidity, and other risk factors into account. In 2018, Cederholm et al. proposed the Global Leadership Initiative on Malnutrition (GLIM) criteria for the diagnosis of malnutrition. Recently, two studies evaluated predictive value of GLIM-defined malnutrition in patients with colorectal cancer [58,59]. Both studies showed a significant association with overall survival, but the sensitivity and specificity of the GLIM criteria were moderate compared to other nutritional assessments. Because this definition has been released recently, it is important to validate these criteria at larger scale in the context of (colorectal) cancer. Second, several studies focused only on grade 3 or 4 toxicities. Although grade 1 or 2 toxicities in general are defined as acceptable, they may impair patients' quality of life and may also influence treatment alterations. The latter was also observed in the study we recently published with approximately 66% of older patients who deviated from scheduled adjuvant chemotherapy because of relatively low grades of toxicity [60]. Third, despite our strength focusing only on one specific type of cancer, there are substantial differences in cancer stage and first-line treatment regimens across studies with potential differences in terms of toxicity. This should be kept in mind when interpreting results. Fourth, it is important to mention that most studies reported results from univariate analysis and were not able to perform multivariate analysis. Fifth, this systematic review includes mainly studies in older patients but it would have been informative to compare outcomes with younger patients. However, the mean percentage of patients with a poor performance score in this review was only 15%. This information might play a role in treatment decisions with respect to dosage and/or type of therapy. Last, chemotoxicity was often categorized in hematological and non-hematological toxicity. However, non-hematological toxicity concerns a varied group of toxicities. A hypothesis for this allocation might be the fact that hematological toxicity such as neutropenia is more related to mortality compared to non-hematological toxicity which often leads to reduced quality of life [61,62].

In sum, clinical/biochemical tests, questionnaires for nutritional assessment, and screening for sarcopenia are all viable methods for nutritional screening in patients with CRC. Furthermore, the present review emphasizes the fact that practitioners should be made aware of the difficulty interpreting laboratory tests such as albumin and body composition measurements because these assessments may be moot due to underlying inflammation and/or hidden weight loss. The results of this systematic review can also be used to select what nutritional screening method is best suited for which individual patient with CRC to identify those patients at risk for chemotoxicity. This allows for applying targeted nutritional interventions in order to prevent (severe) chemotoxicity.

This review provides a comprehensive overview of studies with good methodological quality investigating the association between outcomes of nutritional screening methods and systemic treatment tolerance in patients with colorectal cancer. Thereby, this review emphasizes the fact that practitioners should be made aware of the difficulty interpreting laboratory tests such as albumin and body composition measurements because these assessments may be moot due to underlying inflammation and/or hidden weight loss. By summarizing the existing evidence and by exploring the interpretation of the different nutritional screening methods, the results of this systematic review can be used when considering which tools are applicable (i.e., available, less invasive and targeted to risk factors such as age) to the individual patient in order to eventually identify those patients at high-risk for chemotoxicity. This way, targeted nutritional interventions can be applied in order to prevent (severe) chemotoxicity. The results of this systematic review have also shown that there is a need for further research into the validation of multiple nutritional assessments as part of standard care and this knowledge might be incorporated into prehabilitation programs.

5. Conclusion

Results of this systematic review show that a wide variety of outcomes of nutritional screening methods are associated with a higher risk for treatment intolerance in patients with CRC. However, associations of these outcomes with systemic treatment tolerance for any particular nutritional screening method are not always found. Nutritional screening in patients with CRC is relevant, but there is no current evidence suggesting a superior assessment method. Overall, assessment of sarcopenia tended to be associated more often with systemic treatment tolerance than the other screening methods in this review, but a universal definition of sarcopenia is still lacking. The absence of a gold standard for nutritional screening does not mean that such screening is unwarranted. The current review suggests that there are ample screening methods rendering meaningful outcomes regarding a patient's nutritional status and associated risk for treatment intolerance. This grants practitioners the flexibility to choose from a variety of different nutritional screening methods. Nutritional screening can thus be tailored to the individual patient with CRC, the healthcare organizational context, and/or practitioner experience. Importantly, nutritional screening – regardless of assessment method – may help identify those patients at risk for chemotoxicity thus allowing for the implementation of targeted prehabilitation programs in order to prevent (severe) chemotoxicity.

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CRediT authorship contribution statement

K. Beukers: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **M.J.J. Voorn:** Formal analysis, Investigation, Supervision, Validation, Writing – review & editing. **R. Trepels:** Supervision, Writing – review & editing. **A.J. van de Wouw:** Supervision, Writing – review & editing. **F.J. Vogelaar:** Supervision, Writing – review & editing. **R.C. Havermans:** Supervision, Writing – review & editing. **M.L.G. Janssen-Heijnen:** Supervision, Writing – review & editing.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2022.06.010.

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