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REVIEW

Risk factors for cancer-related fatigue in patients with colorectal cancer: a systematic review and meta-analysis

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Abstract

Purpose Cancer-related fatigue seriously affects the quality of life of cancer patients, yet few systematic reviews have evaluated the risk factors for cancer-related fatigue in patients with colorectal cancer. We therefore conducted a meta-analysis to assess the risk factors of cancer-related fatigue in patients with colorectal cancer.

Methods Literature databases, including PubMed, Ovid, Embase, the Cochrane Central Register of Controlled Trials, the Web of Science, the China National Knowledge Infrastructure, Wanfang, and VIP, were searched from their establishment to September 2021 to identify suitable studies. The quality of included studies was assessed using different tools and evaluated independently by two investigators. Review Manager version 5.4 (Cochrane Collaboration, London, UK) was used for statistical analysis, and sensitivity analysis was conducted.

Results In total, 2642 articles were screened, and data from 25 studies involving 8733 subjects were included in this meta-analysis. After controlling for confounding variables, the following risk factors were associated with cancer-related fatigue: younger age, female sex, low physical activity level, a clinical stage of III or IV, surgery, chemotherapy, insomnia, pain, anxiety, and depression.

Conclusion Younger age, female sex, low physical activity level, a clinical stage of III or IV, chemotherapy, pain, insomnia, anxiety, and depression were identified as risk factors for cancer-related fatigue. Future research should focus on how multidisciplinary teams adopt targeted measures according to these risk factors to better reduce the incidence of cancer-related fatigue.

Keywords Cancer-related fatigue · Colorectal cancer · Risk factors · Meta-analysis

Introduction

Fatigue is a common subjective symptom in cancer patients that seriously affects their quality of life [1]. The National Comprehensive Cancer Network (NCCN) proposed fatigue to be a cancer patient's sixth-most-prevalent life sign and defined cancer-related fatigue (CRF) as a painful, persistent, subjective physical, emotional, and/or cognitive fatigue not proportional to recent activity and which interferes with normal function [2]. The incidence of CRF ranges from 14.03 to 100% [3], and it can occur in all stages of tumorigenesis, development, and treatment. According to global cancer epidemic statistics released by the International Agency for Research on Cancer of the World Health Organization, there were 1,931,600 new cases of colorectal cancer (CRC) and 935,200 deaths worldwide in 2020, ranking CRC third and second, respectively, among all malignant tumors globally [4].

CRC may easily lead to CRF; one study reported an incidence of postoperative CRF of 91.82%, while another found that the degree of fatigue negatively correlates with quality of life [5]. At present, the pathogenesis of CRF is unclear [6]. Therefore, early identification of modifiable risk factors can help the multidisciplinary teams to identify patients

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at high risk of fatigue and carry out targeted interventions according to their unique characteristics.

Known risk factors for CRF include anemia, malnutrition, poor sleep quality, and a low level of mental flexibility [7]. However, prior studies mostly enrolled breast cancer and gastric cancer patients [8, 9]. Oxaliplatin dysregulates mitochondrial and energy homeostasis when used to treat CRC, leading to skeletal muscle fatigue [10]. Similarly, regorafenib causes reg-induced hypothyroidism when used to treat CRC, and it is strictly related to fatigue [11]. What is more, it was shown that the central nervous system (CNS) is a significant factor in the induction of CRF. Cancer cells will destroy the homeostasis of gut microbiota during development. Thus, gut microbiota can indirectly affect CNS through brain-gut axis and cause CRF further [12]. Moreover, some risk factors remain inconsistent and uncertain across different studies. For example, Tian et al. (2016) reported that age is related to CRF degree [13], and Butt et al. (2010) observed a significant negative correlation between age and CRF [14]. Some research has also suggested that those with less education tend to have more severe CRF symptoms [15], but other authors have concluded that more educated patients are more likely to have CRF [16]. There are many reasons for this discrepancy. First, CRF is a subjective feeling and can be assessed using different scales (e.g., the Brief Fatigue Inventory or the Piper Fatigue Scale), and variations in the sensitivity and specificity of these scales may lead to different fatigue and risk factor evaluation results. Second, varying study methods were used, which can lead to discordant results and reduce the accuracy of risk factor judgment. Therefore, risk factors for CRF in CRC patients must be further clarified. However, there remains a lack of meta-analyses on risk factors of CRF in patients with CRC. This study was a systematic review of risk factors of CRF that sought to provide a scientific basis for early clinical intervention by also conducting a meta-analysis of published studies on risk factors of CRF in patients with CRC.

Materials and methods

Literature search strategy

Electronic literature databases, including PubMed, Ovid, Embase, the Cochrane Central Register of Controlled Trials, the Web of Science, the China National Knowledge Infrastructure Database, Wanfang, and VIP, were searched from their establishment until September 2021. The search strategy involved a combination of MeSH terms and free words, as follows:

- Colorectal cancer OR colorectal neoplasm OR colorectal tumor OR colorectal carcinoma.
- Cancer fatigue OR cancer-related fatigue OR cancer treatment-related fatigue OR CRF.
- Risk factor* OR risk-factor* OR hazard factor* OR adverse effect* OR adverse reaction* OR effect OR influence.

According to the characteristics of each database to formulate the corresponding retrieval model, as a PubMed retrieval example, the retrieval strategy used was as follows:

#1 "cancer-related fatigue" [Title/Abstract] OR "cancer fatigue"[Title/Abstract] OR "CRF"[Title/Abstract] OR "cancer treatment related fatigue"[Title/Abstract] OR "fatigue*"[Title/Abstract].
#2 "colorectal neoplasm" [MeSH].
#3 "risk factor*" [Title/Abstract] OR "factor*" [Title/Abstract] OR "risk-factor*" [Title/Abstract] OR "hazard factor*" [Title/Abstract] OR "adverse effect*" [Title/Abstract] OR "adverse reaction*" [Title/Abstract] OR "effect" [Title/Abstract] OR "influence" [Title/Abstract].
#4 #1 and #2 and #3.

Studies of adult human subjects were identified, and the language of eligible studies was limited to either English or Chinese. The reference lists of research reviews and retrieved articles were also searched manually to identify additional relevant publications. Abstracts and unpublished reports were not considered.

Inclusion and exclusion criteria

To be included in the present systematic review, a study was required to (1) have considered patients aged ≥ 18 years with CRC diagnosed histopathologically; (2) be focused on the influencing or risk factors of CRF; (3) have evaluated CRF using relevant questionnaires, including the Cancer Fatigue Scale, the Chinese Brief Fatigue Inventory, the revised Piper Fatigue Scale, the Function Assessment of Cancer Therapy–Fatigue, and the European Organization for the Research and Treatment of Cancer's Quality of Life Questionnaire Fatigue Scale, or by using CRF diagnostic criteria (International Classification of Diseases 10th revision); and (4) be a randomized controlled trial, cross-sectional study, cohort study, or case–control study. When duplicate articles from the same institution were identified, either the better-quality study or the most recent publication was included unless the endpoints were mutually exclusive or measured at different time intervals. Other study exclusion criteria included incomplete outcome data, animal study, undetermined study type, and lack of approval from the local ethics committee. If a minimum number of studies are limited, the trials with low methodological quality are not excluded.

Data extraction and validity assessment

First, all literature was imported into the Endnote X9 software program (Clarivate Analytics, London, UK) to screen and remove duplicate studies. Two researchers (S. T. H. and X. K.) screened titles and abstracts according to the inclusion and exclusion criteria as part of an independent preliminary screening; the included articles were then screened again after their full texts were read. A third researcher (X. Y. Y.) mediated any conflicts about including a study; however, if doubt persisted, a fourth researcher (Y. X. W.) was consulted. Finally, data were extracted into Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) independently by two authors (S. T. H. and D. L.).

The quality of the included studies was evaluated independently by two investigators (S. T. H. and X. K.). The Cochrane Collaboration's tool for assessing the risk of bias was used to evaluate the risk of bias in randomized controlled trials [17], focusing on selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Each index was judged as showing a "low risk of bias," an "unclear risk of bias," or a "high risk of bias." Each included study was evaluated item by item using the above criteria. If all items were "low risk," the study's quality was "A," indicating a low overall bias risk and high research quality. When ≥ 1 items were "unclear," the study's quality was "B," indicating that the possibility of bias was moderate. Finally, if ≥ 1 items were considered "high risk," the quality was "C," indicating that the study had a high risk of bias and a low research quality. Cohort and case–control studies were evaluated using the Newcastle–Ottawa Scale [18], which is divided into two parts with eight items in three major sections covering selection, comparability, exposure, and outcome. The Newcastle–Ottawa Scale adopts the semi-quantization principle of the "star" system for literature quality evaluation; the highest possible score is nine stars, and one star is equivalent to 1 point, so the more stars, the higher the literature quality. Low-quality studies were defined by scores < 5 points, and high-quality studies were defined by scores ≥ 5 points. To evaluate cross-sectional studies, we used the Joanna Briggs Institute evaluation tool [19], which contains 10 evaluation items scored as 0–2 points each (with 20 total points possible), where 0 points means the item did not meet the requirements; 1 point is mentioned but not described in detail; and 2 points indicates a detailed, comprehensive, and correct description. Low-quality studies were defined by scores < 15 points, and high-quality studies were defined by scores ≥ 15 points.

Statistical analysis

The meta-analysis was performed using Review Manager version 5.4 (Cochrane Collaboration, London, UK). The Q test was used to determine whether there was heterogeneity among the results, and the I^2 value was used to evaluate the degree of heterogeneity. If $p \geq 0.1$ and $I^2 < 50\%$, then multiple similar studies were considered to be homogenous, and a fixed-effect model was used to calculate the combined amount. In contrast, $p < 0.1$ and $I^2 \geq 50\%$ indicated the heterogeneity of multiple similar studies, so a random-effect model was selected to combine the effect size, and sensitivity and subgroup analyses were performed to find the source of the heterogeneity. As a general rule, if $p < 0.1$ and the source of heterogeneity could not be determined, then a meta-analysis should be abandoned, and a descriptive study should be adopted. For continuous data, the weighted mean difference was used as the effect size index if the results were obtained using the same measurement tools; if the results were obtained with different measurement tools for the same variable, then the standardized mean difference was used as the effect size index. For dichotomous variables, the odds ratio (OR) was used as the effect size index. All effect sizes were expressed with a 95% confidence interval (CI). A funnel plot was used to detect publication bias. Sensitivity analyses of CRF were also performed [20].

Results

Study characteristics

A total of 2642 relevant trials were identified using the predefined search strategy. Twenty-five studies (13 published in English and 12 published in Chinese) involving 8733 patients met the criteria for inclusion in this meta-analysis (Fig. 1).

Characteristics of the studies included in the meta-analysis are presented in Table 1.

Quality assessment

Among the 25 included studies, there were 3 RCTs [21–23] with 2 "B" and 1 "A" quality grades (Table S1), respectively, and 9 cohort studies [24–32] with quality assessment scores ranging from 5 to 8 points, indicating that the papers were high-quality literature (Table S2). Additionally, among 13 cross-sectional studies [33–45], the overall quality scores ranged from 12 to 18 points; 11 of these studies with scores > 15 points were considered to be of high quality, while 2 studies [35, 37] had scores < 15 points and were considered to be of low quality (Table S3).

Synthesis of results

The identified studies reported on 36 risk factors, with 8 risk factors involved in ≥ 3 studies, 5 risk factors involved

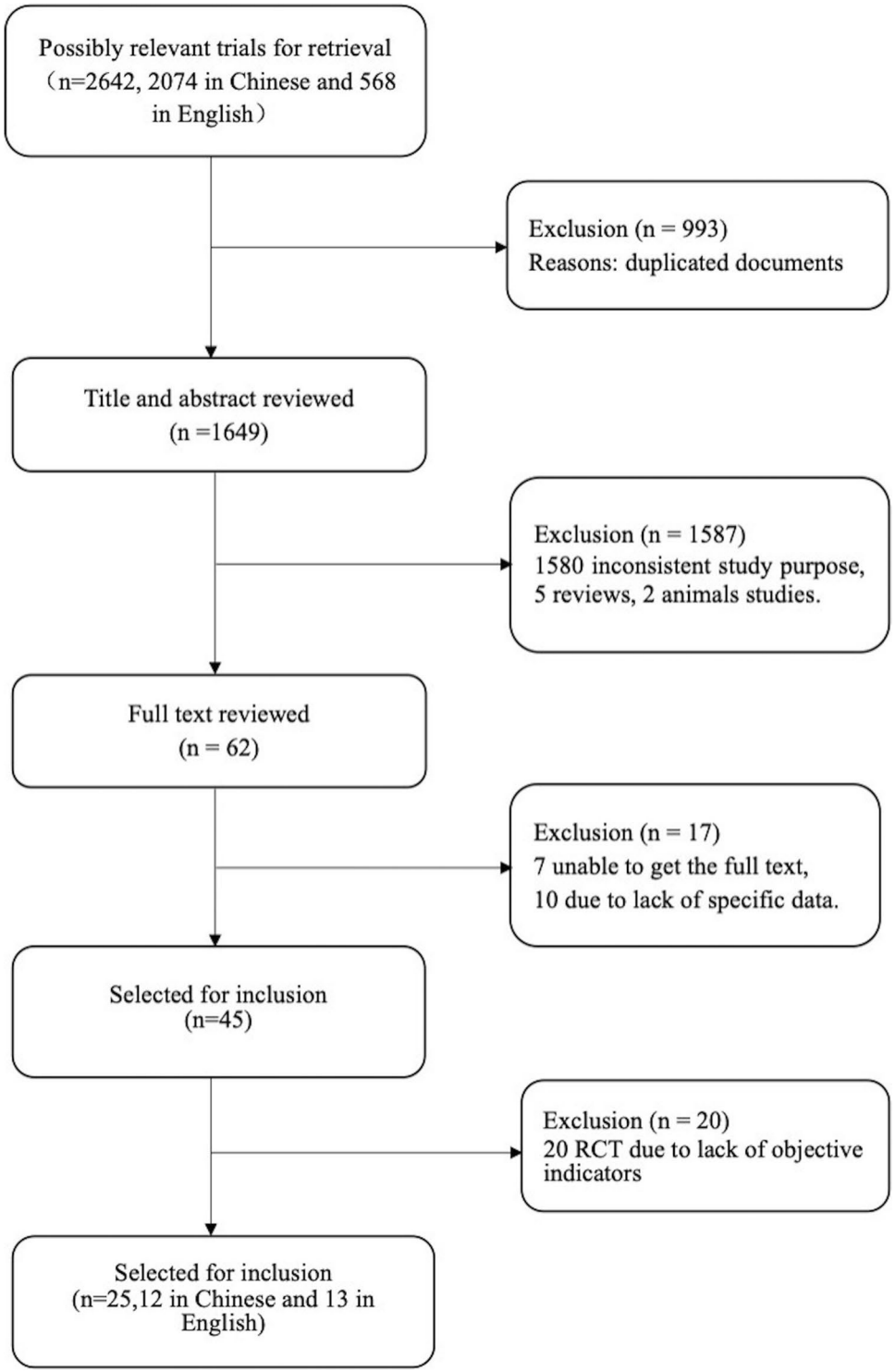


Fig. 1 Flow diagram of the study

in 2 studies, and the remaining 23 risk factors involved in a single study each; thus, a meta-analyses could only be conducted on these 13 risk factors involved in ≥ 2 studies. Among all studies in the current meta-analysis, 11 distinct instruments were used to investigate CRF. The most commonly used tools were the Brief Fatigue Inventory and the European Organization for the Research and Treatment of Cancer's Quality of Life Questionnaire Fatigue Scale.

Table 1 Clinical characteristics of the included studies

Study	Sample size	Evaluation time	Instrument for measuring CRF	Study type	Risk factors assessed	Quality assessment score
[21] Ribeiro et al. (2017)	24	Before each of the four cycles of chemotherapy	FACIT-F	RCT	Lack of zinc	B
[22] Zhang et al. (2017)	120	Pretherapy and posttreatment	RPFS-CV	RCT	Natural killer cells, CD_3^+, CD_4^+	B
[23] Yang (2019)	64	Postchemotherapy	BFI-C, RPFS-CV	RCT	Cognition function and diarrhea	A
[24] Wang et al. (2001)	72	During the period of chemotherapy	BFI	Cohort study	Pain and diarrhea	7
[25] Li (2009)	78	Preoperative and postoperative 3, 7, 14, and 30 days	VAS-F	Cohort study	Older age, male sex, and clinical stage	6
[26] Melissa et al. (2013)	338	Survival period	FAS	Cohort study	Surgery + chemotherapy, anxiety, depression	8
[27] Husson et al. (2015)	1458	Survival period	FAS	Cohort study	Female sex, younger age, partner, educational level, radiotherapy cognitive functioning, quality of life, anxiety, and depression	8
[28] Wu et al. (2016)	83	1–3 days before surgery and postoperative 4–5 weeks	RPFS-CV	Cohort study	Surgery	6
[29] Salome et al. (2019)	2059	Not mentioned	FAS	Cohort study	Male sex	5
[30] Himbert et al. (2019)	236	Before and after surgery	EORTC QLQ-C30	Cohort study	Genotypes of sICAM1 and VEGFD	6
[31] Agasi-Idenburg et al. (2020)	56	Postoperative	MFI	Cohort study	Length of hospital stay	6
[32] Wesselink et al. (2020)	1417	Postdiagnosis 6 months	EORTC QLQ-C30	Cohort study	Interleukin-6, high-sensitivity C-reactive protein	7
[33] Yan (2009)	193	Postoperative 5 and 8 days	EORTC QLQ-C30	Cross-sectional study	Pain, chemotherapy, depression, colostomy, and leukocytes	17
[34] Mota D. D. et al. (2012)	157	Not mentioned	RPFS-CV	Cross-sectional study	Sleep disturbance, depression, and physical activity	16
[35] Gao et al. (2015)	71	Chemotherapy before	RPFS-CV	Cross-sectional study	Pain, depression, and low level of social support	14
[36] Ouyang (2016)	309	Not mentioned	BFI-C, ICD-10	Cross-sectional study	Female, clinical stages, exercise, chemotherapy, smoking, and genotype of rs25531	17
[37] Deng et al. (2016)	183	Postoperative	CFS	Cross-sectional study	Female sex, family income, anxiety, coping effect	12
[38] Qiao et al. (2017)	216	Not mentioned	EORTC QLQ-C30	Cross-sectional study	Sleep disturbance, single, nausea, and vomiting	18
[39] Ou et al. (2018)	568	Not mentioned	BFI-C	Cross-sectional study	Female sex, clinical stage, exercise, chemotherapy, smoking, and genotype of rs25531	17
[40] Luo (2018)	121	During the period of chemotherapy	BFI-C	Cross-sectional study	5-HTTLPR genotype	16

Table 1 (continued)

Study	Sample size	Evaluation time	Instrument for measuring CRF	Study type	Risk factors assessed	Quality assessment score
[41] Li (2019)	160	Not mentioned	RPFS-CV, VAS-F, ICD-10	Cross-sectional study	Pain, depression, anxiety, sleep disturbance, clinical stage, weak sense of happiness, and physical activity	17
[42] Bonhof et al. (2019)	471	Not mentioned	FAS	Cross-sectional study	Anxiety and depression	17
[43] Liu et al. (2020)	132	Postoperative chemotherapy	BFI-C	Cross-sectional study	Comorbidities, clinical stages, surgery, chronic diseases, body mass index, red blood cell count, and lymphocyte count	18
[44] Si et al. (2020)	67	Convalescence	MFI, CFS	Cross-sectional study	Thyroid hormone and cortisol	15
[45] Sharour L. A. (2020)	80	Not mentioned	CFS	Cross-sectional study	Nutrition	17

BFI, Brief Fatigue Inventory; BFI-C, Brief Fatigue Inventory–Chinese version; CIS-F, fatigue severity subscale of the Checklist Individual Strength; CFS, Cancer Fatigue Score; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer's Quality of Life Fatigue Questionnaire C30; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FAS, Fatigue Assessment Scale; ICD-10, International Classification of Diseases, 10th edition; MFI, Multidimensional Fatigue Inventory; RCT, randomized controlled trial; RPFS-CV, revised Piper Fatigue Scale–Chinese Version; VAS-F, Visual Analogue Scale–Fatigue.

Meta-analysis of demographic factors

The patient factors involved in this study were sex, age, education level, monthly income, and marital status. Two studies reported the relationship between age and CRF in CRC patients, and the results showed that the combined effect size was statistically significant, with younger age being a risk factor for CRF (OR = −0.69; 95% CI = −1.20, −0.18; $p < 0.05$; $I^2 = 67\%$). Six studies reported the relationship between gender and CRF, and the pooled results showed high heterogeneity ($p < 0.05$, $I^2 = 92\%$). Sensitivity analysis revealed that the studies by Ou et al. (2018) [39] and Husson et al. (2015) [27] were sources of heterogeneity; after excluding these studies, the combined results showed that female sex was a risk factor for CRF (OR = 1.66, 95% CI = 1.33–2.08, $p < 0.05$, $I^2 = 0\%$) (Fig. 2). Educational level, monthly income, and marital status were reported by only one study each, and these results could not be combined with effect size, so only a descriptive analysis was performed.

Meta-analysis of clinical factors

Clinical factors of interest included clinical stage, radiotherapy, chemotherapy, surgery, insomnia, pain, diarrhea, cognitive function, physical activity (prior to illness), complications, chronic diseases, body mass index, nutritional status, length of hospital stay, quality of life, and other factors. Five studies reported a high level of heterogeneity between clinical stage and CRF ($p < 0.05$, $I^2 = 90\%$). Sensitivity analysis showed that the studies by Li (2019) [41] and Liu et al. (2020) [43] were sources of heterogeneity; after excluding these studies, the combined results showed that a clinical stage of III or IV was a risk factor for CRF (OR = 0.16, 95% CI = 0.09–0.28, $p < 0.05$, $I^2 = 0\%$). Two studies reported the relationship between surgery and CRF in CRC patients, and the combined results showed that the combined effect size was statistically significant, with surgery being a risk factor for CRF (OR = 3.15, 95% CI = 1.02–9.78, $p < 0.05$, $I^2 = 87\%$). Three studies reported a high level of heterogeneity between chemotherapy and CRF ($p < 0.05$, $I^2 = 90\%$). Sensitivity analysis showed that the study by Yan (2009) [33] was the source of heterogeneity; after excluding this study, the combined results showed that chemotherapy was a risk factor for CRF (OR = 2.32, 95% CI = 1.75–3.09, $p < 0.05$, $I^2 = 0\%$). Four studies reported the relationship between pain and CRF. Sensitivity analysis showed that the study by Wang et al. (2001) [24] was the source of heterogeneity; after excluding this study, the combined results showed that pain was a risk factor for CRF (OR = 1.22, 95% CI = 1.08–1.371, $p = 0$, $I^2 = 43\%$). Three studies reported the relationship between insomnia and CRF, and the combined results showed that the combined effect size was statistically significant, with insomnia being a risk factor for

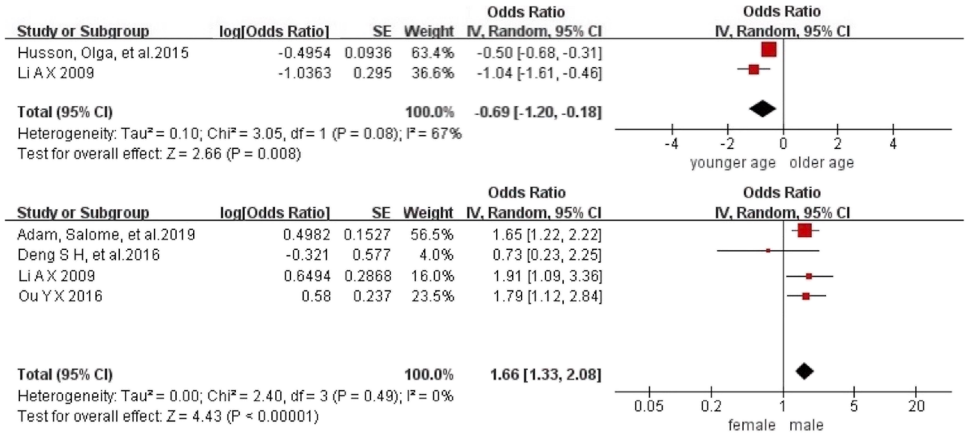


Fig. 2 Forest plot showing the odds ratios for the demographic risk factors

CRF (OR = 1.36, 95% CI = 1.02–1.81, $p < 0.05$, $I^2 = 81\%$). Two studies reported the relationship between diarrhea and CRF, and the pooled results showed that diarrhea was not a risk factor for CRF (OR = 0.25; 95% CI = − 0.94, 1.44; $p = 0.68$; $I^2 = 89\%$). Two studies reported the relationship between cognitive function and CRF, and the pooled results showed that cognitive function was not a risk factor for CRF (OR = 0.97, 95% CI = 0.60–1.59, $p = 0.92$, $I^2 = 76\%$). Four studies reported a high level of heterogeneity between physical activity level and CRF ($p < 0.05$, $I^2 = 87\%$). Sensitivity analysis showed that the study by Mota et al. (2012) [34] was the source of heterogeneity; after excluding this study, the combined results showed that a low physical activity level was a risk factor for CRF (OR = 0.63, 95% CI = 0.31–1.28, $p < 0.05$, $I^2 = 0\%$) (Fig. 3). Chronic diseases, red blood cell count, lymphocyte count, serum total protein, hemoglobin, white blood cell count, zinc level, genotype, and so on were only evaluated in single studies, respectively, and could not be combined with effect size, so they were only examined by descriptive analysis.

Meta-analysis of psychological factors

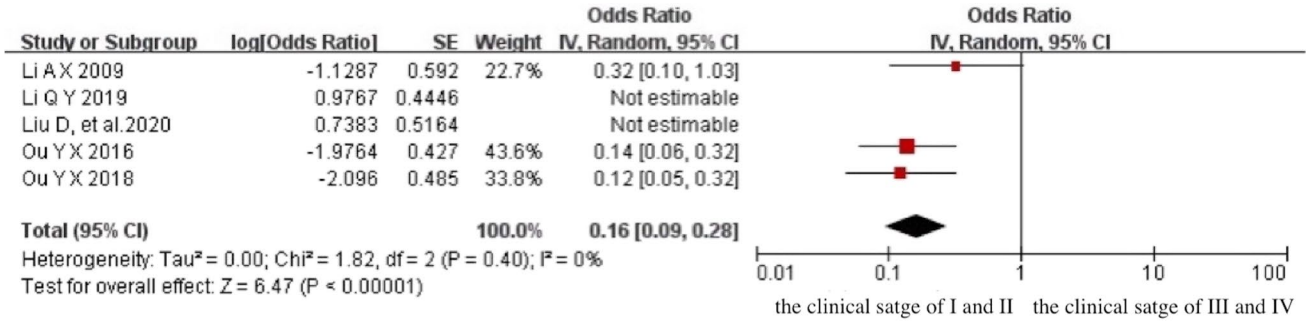
The psychological factors involved in this study included anxiety, depression, and coping style. Three studies reported the relationship between anxiety and CRF, and the results showed that anxiety was a risk factor for CRF (OR = 1.16, 95% CI = 1.12–1.20, $p < 0.05$, $I^2 = 0\%$). Five studies reported the relationship between depression and CRF, and the combined results showed that the combined effect size was statistically significant, with depression being a risk factor for CRF (OR = 2.82, 95% CI = 1.28–6.20, $p < 0.05$, $I^2 = 100\%$) (Fig. 4). Coping style could not be combined with effect size, so only a descriptive analysis was performed.

Discussion

After controlling for confounding variables, the following risk factors were associated with CRF: younger age, female sex, clinical stage of III or IV, surgery, chemotherapy, pain, insomnia, low physical activity level, anxiety, and depression.

Demographic factors

First, the meta-analysis results further strengthened the notion that the risk of CRF is higher among female individuals, which may be because women's hemoglobin levels are lower so their oxygen-carrying capacity is correspondingly lower, making them more prone to fatigue [46]. In addition, female endocrine levels tend to affect their emotions more than male endocrine levels, potentially making them appear more sensitive and vulnerable, which may also account for differences in emotional and perceptual fatigue according to sex [47]. Second, the age analysis indicated that CRF is more common in younger CRC patients, further confirming that younger patients are more likely to suffer from CRF than older patients. This finding may be related to the psychological tolerance threshold of younger patients, whose psychological tolerance is weaker than that of elderly patients, so their ability to cope with fatigue may also be reduced [14]. Moreover, this finding may also relate to heavier social and family burdens. Younger individuals shoulder most of the burden of looking after children and aging parents; if they are sick, they may also face the loss of their jobs and primary source of income. Further studies are necessary to explore the specific reasons.


Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
Li A X 2009 -1.1287 0.592 22.7% 0.32 [0.10, 1.03]
Li Q Y 2019 0.9767 0.4446 Not estimable
Liu D, et al.2020 0.7383 0.5164 Not estimable
Ou Y X 2016 -1.9764 0.427 43.6% 0.14 [0.06, 0.32]
Ou Y X 2018 -2.096 0.485 33.8% 0.12 [0.05, 0.32]
Total (95% CI) 100.0% 0.16 [0.09, 0.28]
Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 6.47 (P < 0.00001)
0.01 0.1 1 10 100
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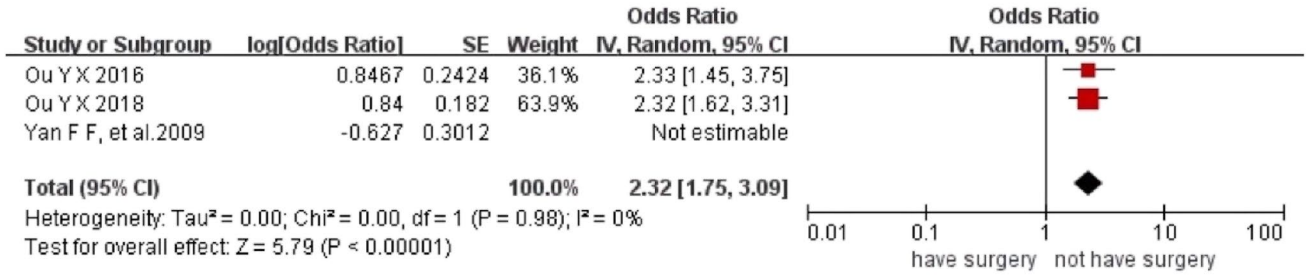
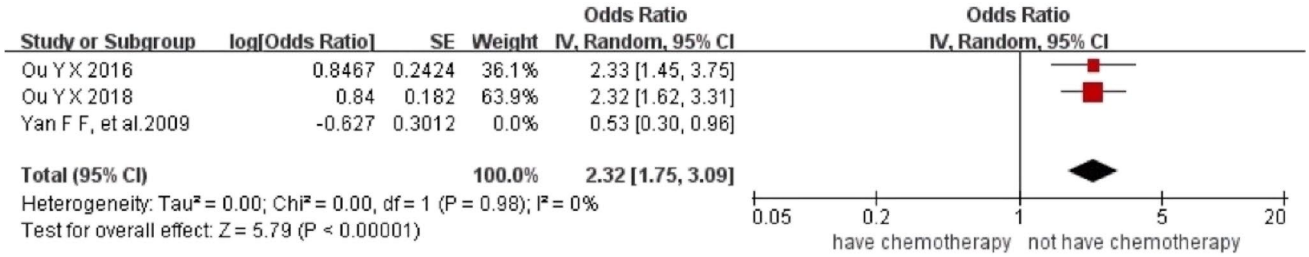
the clinical satge of III and IV


Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
Ou Y X 2016 0.8467 0.2424 36.1% 2.33 [1.45, 3.75]
Ou Y X 2018 0.84 0.182 63.9% 2.32 [1.62, 3.31]
Yan F F, et al.2009 -0.627 0.3012 Not estimable
Total (95% CI) 100.0% 2.32 [1.75, 3.09]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 5.79 (P < 0.00001)
0.01 0.1 1 10 100
have surgery
not have surgery


Odds Ratio
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Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
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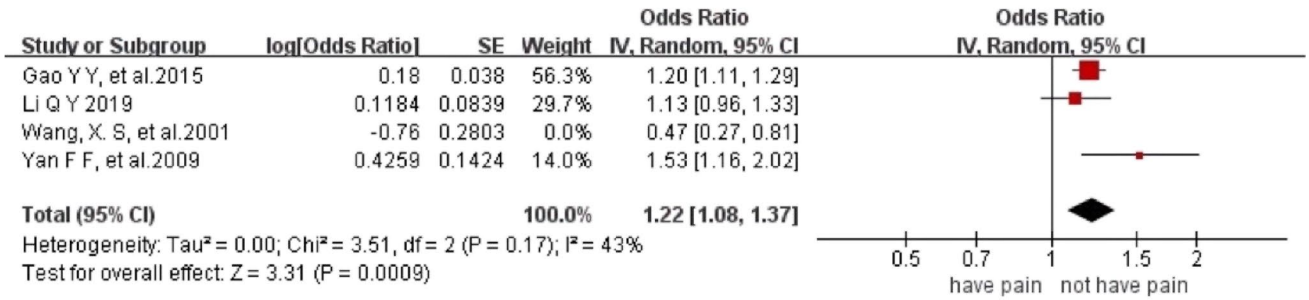
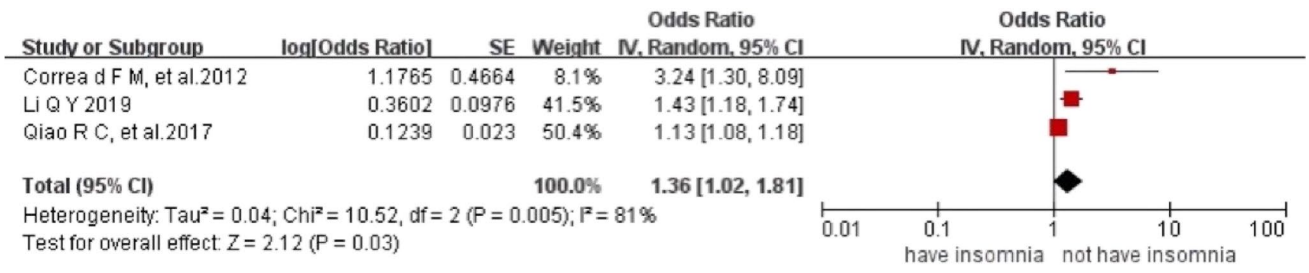
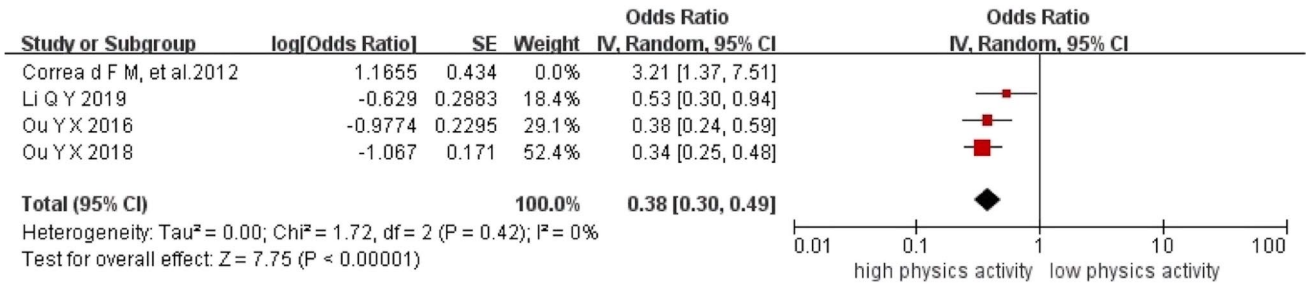
Ou Y X 2016 0.8467 0.2424 36.1% 2.33 [1.45, 3.75]
Ou Y X 2018 0.84 0.182 63.9% 2.32 [1.62, 3.31]
Yan F F, et al.2009 -0.627 0.3012 0.0% 0.53 [0.30, 0.96]
Total (95% CI) 100.0% 2.32 [1.75, 3.09]
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 5.79 (P < 0.00001)
0.05 0.2 1 5 20
have chemotherapy
not have chemotherapy


Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
Gao Y Y, et al.2015 0.18 0.038 56.3% 1.20 [1.11, 1.29]
Li Q Y 2019 0.1184 0.0839 29.7% 1.13 [0.96, 1.33]
Wang, X. S, et al.2001 -0.76 0.2803 0.0% 0.47 [0.27, 0.81]
Yan F F, et al.2009 0.4259 0.1424 14.0% 1.53 [1.16, 2.02]
Total (95% CI) 100.0% 1.22 [1.08, 1.37]
Heterogeneity: Tau² = 0.00; Chi² = 3.51, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 3.31 (P = 0.0009)
0.5 0.7 1 1.5 2
have pain
not have pain


Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
Correa d F M, et al.2012 1.1765 0.4664 8.1% 3.24 [1.30, 8.09]
Li Q Y 2019 0.3602 0.0976 41.5% 1.43 [1.18, 1.74]
Qiao R C, et al.2017 0.1239 0.023 50.4% 1.13 [1.08, 1.18]
Total (95% CI) 100.0% 1.36 [1.02, 1.81]
Heterogeneity: Tau² = 0.04; Chi² = 10.52, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 2.12 (P = 0.03)
0.01 0.1 1 10 100
have insomnia
not have insomnia


Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
Correa d F M, et al.2012 1.1655 0.434 0.0% 3.21 [1.37, 7.51]
Li Q Y 2019 -0.629 0.2883 18.4% 0.53 [0.30, 0.94]
Ou Y X 2016 -0.9774 0.2295 29.1% 0.38 [0.24, 0.59]
Ou Y X 2018 -1.067 0.171 52.4% 0.34 [0.25, 0.48]
Total (95% CI) 100.0% 0.38 [0.30, 0.49]
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 7.75 (P < 0.00001)
0.01 0.1 1 10 100
high physics activity
low physics activity

◂**Fig. 3** Forest plot showing the odds ratios for the clinical risk factors

Clinical factors

First, a significant risk factor of CRF included a clinical stage of III or IV compared to the clinical stages of I and II. Consistent with the results of this study, the risk of fatigue in patients with advanced tumors was 1.16 times higher than that in patients with early-stage tumors [48]. The reason for this result may be that patients with advanced tumors have more serious clinical manifestations, higher tumor recurrence rates, and a poorer physical condition and prognosis, further aggravating their physical fatigue. Therefore, members of multidisciplinary medical teams should pay greater attention to the physical status of patients with a clinical stage of III or IV. Second, it is well-established that the side effects of treatment significantly correlate with a worsening of CRF [2]. Consistent with these results, this study showed that surgery and chemotherapy are risk factors for CRF. As far as surgery is concerned, in addition to the direct influence of tumor removal, the operation is also related to a series of clinical symptoms, such as increased protein mobilization, gastrointestinal bleeding, body energy consumption, and aggravation of malnutrition caused by surgical stress [49]. Regarding chemotherapy, some studies have shown that the incidence of CRF at this stage can reach 75–100% [50]. As the results of this study showed that the risk of CRF was greater among patients who received chemotherapy (2.32 times) than those who did not, the trend may be associated with side effects of chemotherapy (e.g., nausea and vomiting, loss of appetite, constipation, pain, insomnia), which increase the consumption of energy and decrease the intake of sources of energy. As is known, when the body's energy demand exceeds its supply, fatigue is more likely to occur [48].

Third, pain, insomnia, and depression were also found to be risk factors of fatigue in CRC patients. To some extent, pain and insomnia can affect the psychological functioning of patients, leading to the development of depression and emotional fatigue [51]. One study showed that fatigue and sleep disturbances, pain, and depression often come in the form of symptom clusters, and they are known to correlate and share synergistic effects with each other [52], supporting the idea that different risk factors may interact with each other to affect CRF. Therefore, it is a good idea for researchers to explore how symptoms cluster among the risk factors known to affect CRF and investigate whether the number and type of symptoms in a cluster change dynamically over time. Finally, the analysis of results demonstrated that a low level of physical activity (prior to illness) is a risk factor. The reason for this result may be that patients who have ever exercised can reduce the risk of CRF perhaps because exercise can improve aerobic capacity and muscle reduction caused by skeletal muscle loss, prevent muscle reduction and atrophy, improve body immunity, and promote sleep, thus avoiding the facilitation of CRF [53]. NCCN guidelines [54] have indicated that exercise therapy can effectively relieve fatigue in patients. However, although there are many studies at present considering exercise intervention, none are individualized [55, 56]. Due to patients' varying conditions and degrees of fatigue, as international position statements suggest that doctors can prescribe exercise in oncology. Therefore, clinical exercise physiologists and physical therapists can work together to recommend targeted exercise plans to appropriate institutions [57].

Psychological factors

The present meta-analysis results also showed that anxiety and depression are risk factors of CRF in CRC, and the reason for this may be that a tumor, as a major stress event, can alter the body's positive feedback regulation system, resulting in hypothalamic–pituitary–adrenal axis dysfunction, endocrine dysfunction, and hormone level disorders, leading to abnormal psychological changes or mental disorders in cancer patients and resulting in a series of fatigue symptoms [58]. Anxiety and depression have mutual effects; these two symptoms show the same course over time, and anxiety can be masked by depression, while depression can be a further emotional evolution of anxiety [59]. Therefore, a prospective study should be performed to assess the possible causal links between both symptoms in CRF in the future. Importantly, CRF not only manifests as physical fatigue but also depression, helplessness, and other types of psychological fatigue. Therefore, improving psychological fatigue can in turn reduce the physical fatigue of patients and promote their health.

Limitations

There are some limitations to this study. First, although 25 studies were included, they were mainly cross-sectional studies, which resulted in low evidence-based strength. In addition, the limited number of studies included for each factor made it impossible to draw funnel plots in all cases, which may have led to publication bias. The included studies were also limited to only those published in English or Chinese, which limited the comprehensiveness of the included studies. Future studies will need to evaluate risk factors for CRF in a more comprehensive manner. Second, different cancer-related fatigue assessment tools are used in different studies, and the assessment time and follow-up time are different; the heterogeneity of the results may be higher. There was a lack of unified assessment tools to evaluate CRF

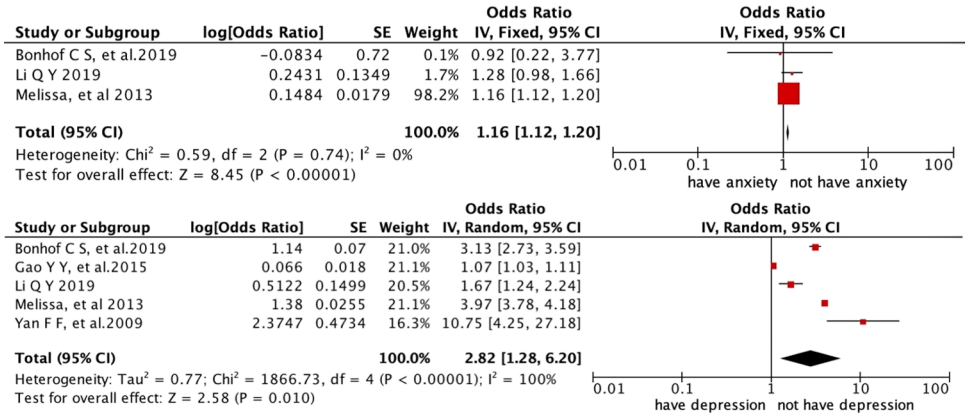


Fig. 4 Forest plot showing the odds ratios for the psychological risk factors

across the included studies. This disparity may also affect the degree of fatigue.

Conclusion

Younger age, female sex, low physical activity level, a clinical stage of III or IV, surgery, chemotherapy, pain, insomnia, anxiety, and depression are risk factors for CRF. Based on the risk factors of CRF, medical staff should identify risk factors early—especially those that are controllable—and timely introduce corresponding early interventions. As suggested by the NCCN, it is necessary to change the current standardized nursing intervention mode of intervention by a multidisciplinary team composed of doctors, nurses, nutritionists, physical therapists, and hypnotherapists. After evaluating the disease information, physiology, exercise, sleep, and other relevant indicators of patients in the cancer clinic, the cancer specialist nurses consult or refer the patient to the corresponding professionals for early guidance according to the patient's problems. For example, physical therapists can continue to develop professional rehabilitation guidance plans for cancer survivors after evaluation. Sports medicine experts can make targeted exercise plans for patients with low exercise levels. In this way, patients can be targeted for early intervention. In addition, further systematic reviews should overcome the limitations of this study and attempt to gain a more complete understanding of risk factors for CRF.

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Declarations

Competing interests The authors declare no competing interests.

Research involving human participants and/or animals This study involved the analysis of previously published papers and did not involve studies with animals or people; therefore, the approval of an ethics committee was not needed.

Informed consent N/A.

Consent for publication N/A.

Registration The review was not registered, and a protocol was not prepared.

Conflict of interest The authors declare no competing interests.

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