



Review Article

Recent Advances in Chinese and Western Medicine for Cancer-related Fatigue: A Review



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Abstract

Cancer-related fatigue is a common symptom in patients with malignant tumors, which seriously affects patient quality of life and even the progress of treatment. There have been numerous studies on various aspects of cancer-related fatigue. This review summarizes and analyzes its pathogenesis, screening, evaluation, and treatment from the perspectives of modern medicine and traditional Chinese medicine (TCM). Modern medicine believes that the pathogenesis of cancer-related fatigue is still unclear. Screening assessment scales are varied and have different focuses, so they should be selected and used comprehensively. Drug intervention for cancer-related fatigue has safety problems and is not recommended for conventional treatment. Non-drug treatment methods such as exercise, psychological intervention, diet guidance, and light therapy have good efficacy and high safety and are worthy of clinical promotion. In TCM, cancer fatigue is included as a deficiency. The syndrome of TCM is divided into two categories: deficiency syndrome and syndrome of intermingled deficiency and excess, involving the three viscera, the liver, spleen, and kidney that are closely related to the pathological products of blood stasis, toxin, phlegm, and dampness. The TCM diagnosis and evaluation scale is still in its infancy, which objectively quantifies TCM syndromes, forms a unified diagnostic standard for TCM syndrome differentiation, and standardizes TCM syndrome differentiation and treatment. The elements of syndromes open the idea of constructing a TCM scale. TCM offers various treatment and nursing methods that have high efficacy and safety. TCM, acupuncture, moxibustion, and traditional exercises are the main methods, but high-quality evidence is needed. In the future, the advantages of the combination of TCM and Western medicine should be used to overcome cancer-related fatigue.

Introduction

According to a study of 438 papers spanning nearly 20 years, cancer-related fatigue (CRF) is a common complication of malignant

tumors and occurs throughout the course of malignant tumors, with a frequency of up to 90%.¹ CRF is defined by the USA's National Cancer Network as persistent and painful fatigue in subjective awareness related to malignancy and treatment, affecting physical, emotional, role, and cognitive dimensions, and interfering with treatment and quality of life.^{2,3} In this review, we summarize the status of current CRF research in Chinese and Western medicine from three aspects, pathogenesis, screening and assessment, and treatment.

Pathogenesis of CRF

Studies of the pathogenesis of CRF (Figs. 1 and 2) mainly focus on: (1) dysregulation of inflammatory cytokines. The high metabolic activity of malignant tumors causes inflammatory responses and the synthesis, secretion, and release of various inflammatory cytokines such as interleukin (IL)-6, IL1 β , tumor necrosis factor- α , and C-reactive protein, which leads to fatigue. IL6 is an independent driver of CRF that promotes the growth of malignant tumors or the production of CRF by activating the Janus kinase/

Keywords: Cancer-related fatigue; Pathogenesis; TCM syndrome scale; Research status.

Abbreviations: ATP, adenosine triphosphate; CAT, computer adaptive test; CLOCK, clock gene; CRF, cancer-related fatigue; DRD2, dopamine receptor D2; HPA, hypothalamic-pituitary-adrenal; IFN- γ , interferon-gamma; IL, interleukin; JAK-STAT, Janus kinase/signal transducer and activator of transcription; MDASI, MD Anderson Symptom Inventory; PROMIS, patient-reported outcomes measurement information system; SNP, single nucleotide polymorphism; TCM, traditional Chinese medicine.

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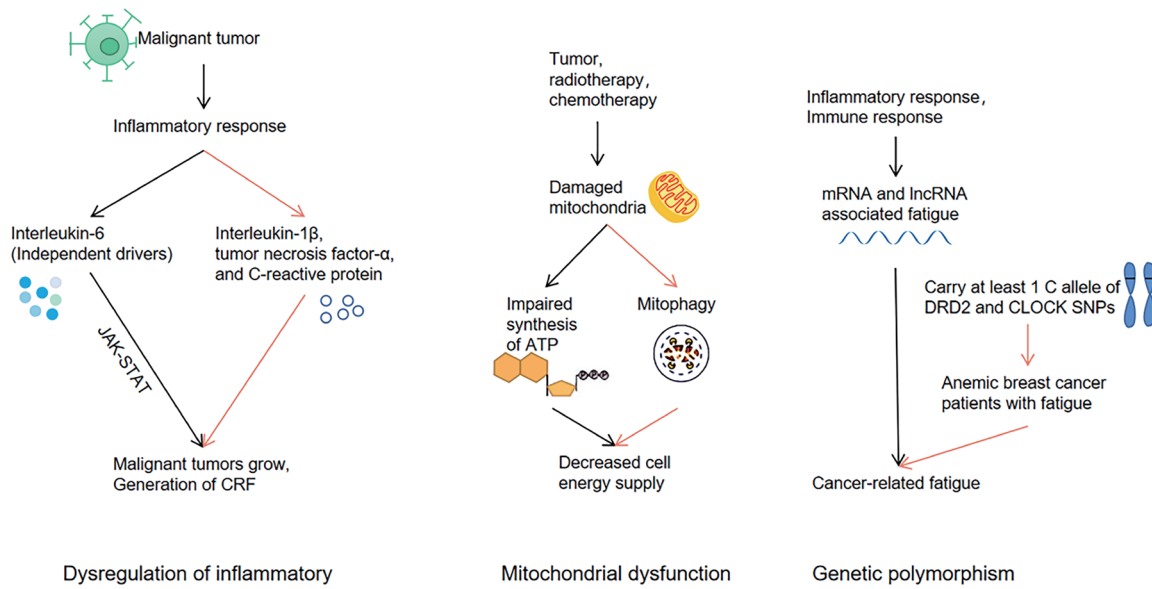


Fig. 1. Pathogenesis of CRF in dysregulation of inflammatory, mitochondrial dysfunction and genetic polymorphism. ATP, adenosine triphosphate; CLOCK, clock gene; CRF, cancer-related fatigue; DRD2, dopamine receptor D2; JAK-STAT, Janus kinase/signal transducer and activator of transcription; SNP, single nucleotide polymorphism.

signal transducer and activator of the transcription signaling pathway.^{4,5} (2) Mitochondrial dysfunction, which induces mitochondrial autophagy,⁶ decreases adenosine triphosphate and the cellular energy supply, which leads to fatigue. Physical fatigue is nega-

tively correlated with mitochondrial DNA content, suggesting that mitochondrial content and function are closely related to CRF.⁷ (3) Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, which regulates oxidative stress by controlling the secretion, syn-

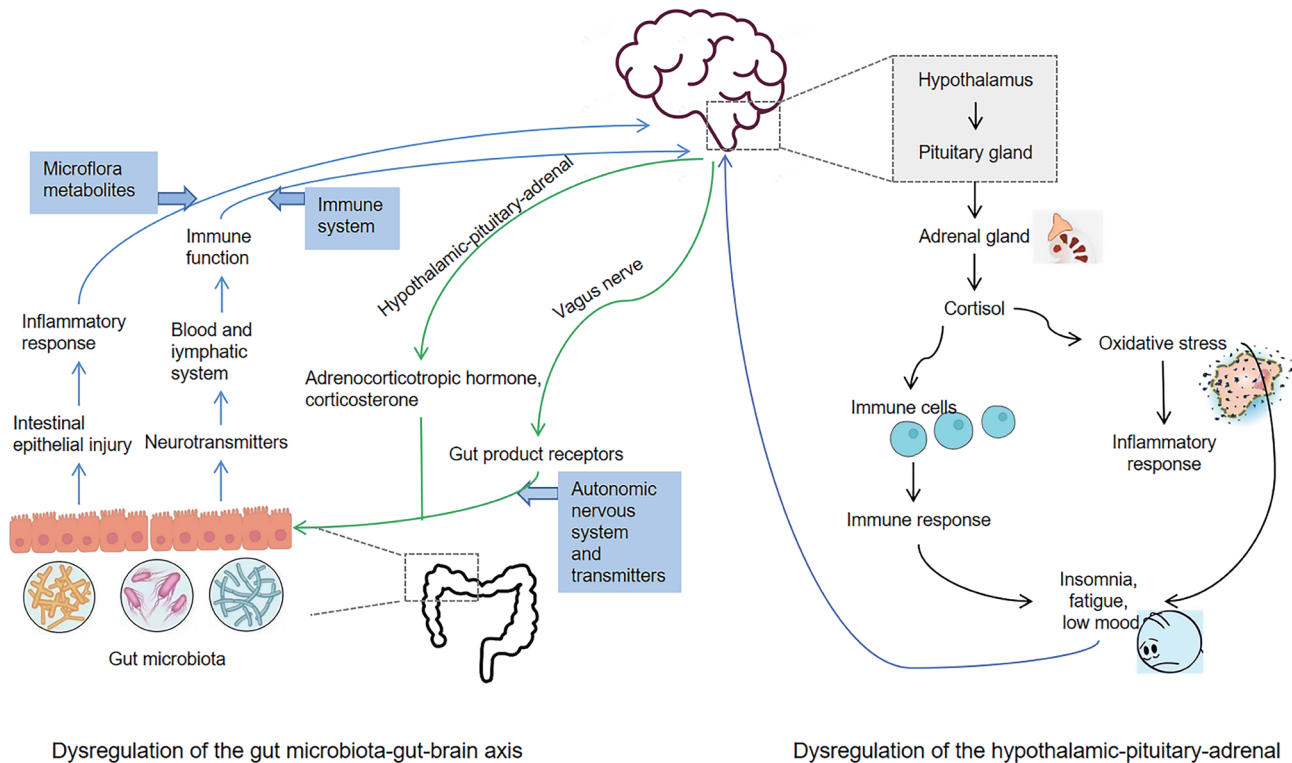


Fig. 2. Pathogenesis of CRF in dysfunction of the hypothalamic pituitary-adrenal (HPA) axis, disruption of the gut and microbiota-gut-brain axis. CRF, cancer-related fatigue; HPA, hypothalamic-pituitary-adrenal.

thesis, and release of hormones to regulate immunity and control the inflammatory response.⁸ Under stress, the HPA axis is disrupted, hormone secretion is abnormal, and immune function is impaired, leading to fatigue, insomnia, depression, and other symptoms.⁹ At the same time, the vicious cycle of insomnia, fatigue, and depression aggravates the disruption of the HPA axis.¹⁰ (4) Disruption of gut microbiota-gut-brain axis, which affects brain function by bidirectional regulation of gut microbiota and three signaling pathways (the autonomic nervous system and transmitter, the immune system, and metabolites of the gut microbiota), so as to maintain human dynamic balance.¹¹ The pro-inflammatory gut microbiota group (AD3011 of the genus XIII) is closely related to high fatigue.¹² (5) Genetic polymorphism, which is related to the development of malignant tumors and the occurrence and severity of CRF. Wu *et al.* found that mRNAs and lncRNAs related to fatigue are associated with biological processes related to inflammation and immune responses.¹³ Among them, *SEC61A2*, *ADCY6*, *LPAR5*, *COL7A1*, *SNHG1*, *GNG4*, *LMO7*, and other genes predicted the prognosis of patients with nonmetastatic prostate cancer. Aline *et al.* found that patients with malignant breast tumors, with anemia after chemotherapy, and carrying at least one C allele of the single nucleotide polymorphisms, dopamine receptor D2 and *CLOCK*, had an increased risk of fatigue.¹⁴

TCM syndrome types

There is no specific name for describing CRF in TCM books. According to its typical symptoms, CRF can be classified in the category of deficiency.¹⁵ TCM considers deficiency fatigue as a chronic weakness syndrome with five viscera asthenia as the main clinical manifestations, viscera deficiency, Qi blood deficiency and imbalance between Yin and Yang as the main pathogenesis, and mental fatigue, limb fatigue, sighing, dizziness, spontaneous sweating, and insomnia as the main syndromes.¹⁶ Spleen is the origin of acquired and the source of Qi and blood biochemistry. Splenic disorder, inability to transport the essence of the water valley, and there will be anorexia, emaciation, mental fatigue, and physical fatigue. The heart governs the mind, and the liver controls dispersion. The heart blood is sufficient, and the liver stores blood, so the Qi movement is smooth, the Qi and blood are harmonious, and the mood is stable. On the contrary, Qi and blood disharmony, emotional disorders, there will be symptoms of low mood, crying, and laughing impermanence. Asthenia pulmonary Qi, people will not easily resist the invasion of exogenous evil. There are symptoms of shortness of breath and spontaneous perspiration. Liver and kidney Yin deficiency, water failing to moisten wood, liver Yang disturbance, and dizzy symptoms appear. Qi is the leader of blood. Qi deficiency cannot push blood movement, which leads to Qi stagnancy and blood stasis. Phlegm, stasis, and toxins cement each other, cremation heat over time, further depleting the viscera of the human body and Yin and Yang of Qi and blood, and manifest as fatigue, weakness, and other typical clinical symptoms of CRF.¹⁷ TCM believes that malignant tumors are a syndrome of deficiency in origin and excess in superficiality. CRF coexists with malignant tumors. The internal causes such as lack of native endowment, tumor consumption, and emotional paralysis, and external causes such as retention of cancer toxins, treatment methods (radiotherapy, chemotherapy, surgery, *etc.*), diet, work, and rest disorders lead to an imbalance of Yin and Yang in the viscera of the body, so that blood stasis, toxin, phlegm, dampness, and other pathological products accumulate, resulting in CRF.^{18,19}

At present, the TCM syndrome differentiation of cancer-related fatigue is mainly a deficiency syndrome and a syndrome of intermingled deficiency and excess. Deficiency syndrome mainly involves the liver, spleen, and kidney. Song *et al.* summarized the TCM literature and found that the most common syndromes of CRF were Qi and blood deficiency syndrome, spleen, and kidney deficiency syndrome.²⁰ Liu *et al.* reported that the occurrence of cancer-related fatigue is closely related to weakness of the spleen and stomach and should be treated in the spleen and stomach.²¹ Wang *et al.* believed that liver dysfunction was the central link of CRF in breast cancer. Based on the dysfunction of spleen and kidney function, liver dysfunction and liver blood deficiency lead to CRF.²² The syndrome of intermingled deficiency and excess is mostly based on positive deficiency, which forms solid evil pathological products such as Qi stagnation, spittle coagulation, blood stasis, damp-heat, and so on. Li *et al.* believed that most of the patients with malignant tumors are weak in constitution, blood stasis, and phlegm were pooled in the body, coexisting with Qi stagnation, hindering the movement of Qi and blood in the zangfu, and causing the disease.²³ Liu *et al.* found that patients with advanced colorectal cancer caused by fatigue often had symptoms such as soreness and weakness of the waist and knees, hot flushes and night sweats, and concluded that the TCM syndrome type was kidney deficiency combined with damp-heat syndrome.²⁴ It can be summarized into the following six symptoms: spleen-stomach deficiency syndrome; spleen-kidney Yang deficiency syndrome; liver spleen disharmony syndrome; hepatic stagnation causing splenic deficiency combined with Qi stagnancy and blood stasis; syndrome of spleen-kidney deficiency combined with intermingled phlegm-stasis blood syndrome; and deficiency of Qi combined with retention of damp-heat.²⁵

Screening assessment scale

CRF was evaluated and screened mainly by a self-measuring scale. There are a variety of scales used to assess screening for CRF. The scales have different focuses, including different age groups and countries, different stages of disease, different numbers of items, inconsistent difficulty levels, and different reliability and validity. Scale scores may be influenced by patient culture, education, cognition, and other personal factors.²⁶ The EORTC-QLQ-C30 scale has a reliability of > 0.86 and can be used as a good indicator of the quality of life in cancer patients.²⁷ The MD Anderson Symptom Inventory (MDASI) is a multisymptom self-rating scale that includes 13 core symptoms that occur most frequently or most severely in patients with a variety of cancers and applies to patients with different types and treatments of cancer. A study validated the application of the MDASI in 309 thyroid patients, and the results showed that the content validity index scale and content validity index items of the scale were above 0.80.²⁸ Functional assessment of chronic illness therapy scales for patients undergoing cancer treatment.²⁹ The Portuguese version of the functional assessment of chronic illness-therapy fatigue scale has been verified, with an internal consistency of 0.84 and retest reliability of 0.92, which is a reliable and accurate assessment scale.³⁰ Patient-reported outcomes measurement information system (PROMIS) is an accurate, flexible, and comprehensive measurement system for the general population as well as patients with chronic diseases.³¹ The fatigue brief table and the computerized fitness test fatigue table have good internal consistency and reliability and have certain feasibility and accuracy.^{32,33} The multidimensional fatigue scale is moderately difficult to complete and has no special requirements for the

Table 1. Screening/assessment scale

Screening/assessment scale	Item	Number of dimensions/type	Degree of difficulty	Internal consistency, α	Other
European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-30 Core Questionnaire	30	15/five functional (physical, role, cognitive, emotional, social) three symptoms (fatigue, pain, nausea, and vomiting), overall, and six single entries	Moderate	0.86	Reverse scoring entries exist
MD Anderson Symptom Inventory	19	8/physiological function, physiological function, pain, wholeness, vitality, social function, emotional function, mental health	Easy	0.80	
Functional Assessment of Chronic Illness Therapy-Fatigue	13	1/fatigue	Easy	0.84	
PROMIS CAT for Fatigue	20	3/fatigue, sleep disturbance, sleep impairment	Relatively simple	0.92	
Multidimensional Fatigue Inventory-20	20	5/decrease in overall, physical, mental, activity, and motivation	Moderate	0.83–0.94	Likert scale combined with visual analog measurement
Brief Fatigue Inventory	9	1/fatigue	Easy	0.82–0.97	
Fatigue Symptom Inventory	14	4/fatigue degree, fatigue frequency, daily variation, influence	Moderate	0.92	Can distinguish fatigue changes over time
Cancer Fatigue Scale	15	3/physical fatigue, cognitive fatigue, emotional fatigue	Easy	0.806	
Piper Fatigue Scale-Revised	24	4/behavior, emotion, feeling, cognition	Easy	0.9	
PROMIS Fatigue-Short Forms V1.0	7	1/fatigue	Easy	0.87–0.92	There are four versions: 4a, 6a, 7a, and 8a

PROMIS, patient-reported outcomes measurement information system; CAT, computer adaptive test.

disease stage of the patient. Cronbach's alpha coefficient is 0.83 to 0.94, which is a useful tool for studying fatigue.³⁴ Two screening methods are currently recommended: the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire-30 Core Questionnaire (grade A evidence), and the MDASI (grade B evidence). Eight assessments are conducted: Functional assessment of chronic illness-therapy fatigue, Piper fatigue scale-revised, PROMIS fatigue-short form v1.0 fatigue scale (grade A evidence), brief fatigue inventory, fatigue symptom inventory, cancer fatigue scale, PROMIS computerized adaptive testing for fatigue, multidimensional fatigue inventory-20 (grade B evidence) (Table 1).^{35,36}

TCM diagnostic evaluation scale

Only by establishing a TCM standard diagnostic evaluation scale, objectively quantifying TCM syndromes, and forming unified diagnostic criteria for TCM syndrome differentiation can we realize the systematization and standardization of TCM syndrome differentiation and benefit more patients. At present, China has not established a standardized TCM diagnosis and treatment CRF path and has not formed an authoritative CRF TCM syndrome scale. Therefore, it is necessary to design a TCM syndrome scale rich in TCM characteristics and with high reliability and validity to fill

the gap in this field.³⁷ Zhen *et al.* stratified TCM syndromes into two syndrome items, disease location, and disease type, to screen disease.³⁸ They assigned values to each item of the TCM syndrome scale of CRF and evaluated the reliability and validity of the scale. Current research on relevant scales is in the initial stage, and the TCM diagnostic assessment scale can be developed along the idea of syndrome elements. However, the TCM syndrome is complex, and the two syndrome elements of disease location and disease nature cannot completely outline the TCM syndrome and treatment. We should constantly enrich the syndrome elements and improve the system to develop an appropriate TCM syndrome scale.

Western medicine therapy

Drug treatment of CRF is mainly symptomatic treatment, which includes the following five types: (1) Anemia correction with erythropoietin, iron supplements, red blood cell infusion, and other methods in patients with malignant tumors, increases the oxygen-carrying capacity of the blood, and reduces fatigue.³⁹ However, long-term use of erythropoietin may cause thrombosis, so it should be used with caution after contraindications are ruled out. (2) Relief of cancer pain treatment with third-order analgesics and standardized care of cancer pain can relieve pain, improve sleep quality, reduce anxiety, and alleviate fatigue.^{40,41} (3) Corticosteroids,

which are a common adjuvant for patients with end-stage malignancies and have some effect in relieving symptoms such as fatigue, anorexia, and depression. However, insufficient evidence on dose, efficacy, side effects, and hormone types limits their use.⁴² (4) Antidepressants are used because there is an association between CRF and depression.⁴³ Treatment with antidepressants is effective in alleviating fatigue. Bupropion can significantly reduce fatigue in patients with malignancies without significant side effects.⁴⁴ (5) Central nervous system stimulants are used, but there is no gold standard for methylphenidate in the treatment of CRF, and the results of efficacy evaluation and side effects are mixed. A meta-analysis summarizing studies over the past decade showed that methylphenidate significantly improved fatigue symptoms without significant side effects.⁴⁵ However, Centeno *et al.* found that long-term use of methylphenidate had no significant effect.⁴⁶

Western medicine non-drug therapy

Non-drug intervention is the most important therapy and includes four components: (1) Exercise therapy with both aerobic training and combined multimodal training (aerobic training, resistance training, and flexibility training) can effectively improve CRF.⁴⁷ Resistance training combined with aerobic training to treat CRF can regulate serum cortisol and adrenocorticotropic hormone levels and reduce fatigue by adjusting the function of the HPA axis.⁴⁸ (2) Psychological intervention is essential to improve poor psychological state and reduce fatigue in patients with CRF. Zhao's cognitive behavioral therapy has effectively improved patients' symptoms of anxiety, depression, and fatigue.⁴⁹ A meta-analysis involving 1,680 patients showed that mindfulness-based stress reduction had positive significance in alleviating CRF, improving sleep, improving positive psychology, and promoting rehabilitation.⁵⁰ (3) Diet and nutrition counseling reduces the incidence of malnutrition in patients with malignant tumors by up to 80%.⁵¹ A scientific diet plan provides patients with adequate nutritional support, which plays a positive role in reducing fatigue, improving quality of life, and improving overall health.⁵² The Mediterranean diet promotes the health of the body by improving energy metabolism to alleviate CRF.⁵³ (4) Phototherapy decreases disruption of the circadian rhythm, which affects the functioning of the body and leads to anxiety, depression, insomnia, fatigue, and other adverse effects.⁵⁴ Zhou *et al.* conducted a study treating CRF patients with simultaneous chemoradiotherapy for nasopharyngeal cancer.⁵⁵ The results showed that phototherapy effectively improved CRF and depression, thus enhancing the patient's quality of life.⁵⁵ Starreveld *et al.* used phototherapy therapy to treat CRF patients with non-Hodgkin's lymphoma, and their fatigue, sleep quality, depression, quality of life, and circadian rhythm were improved.⁵⁶

Drug intervention is mainly to treat symptoms and cannot fundamentally solve the problem of fatigue. Some drugs have the problem of poor safety and uncertain efficacy, so they should be used cautiously in clinical practice. There are various non-drug intervention methods, which have good therapeutic effects on improving the symptoms of cancer-related fatigue, sleep, depression, *etc.*, and have been widely recognized, as worthy of further promotion in clinical treatment.

TCM internal treatment

TCM internal treatment of CRF mainly focuses on tonifying the spleen and kidney. In addition, the hepatic stagnation causing splenic deficiency is treated by liver-dispersing and spleen-

strengthening methods; the intermingled phlegm-stasis blood syndrome is treated by regulating Qi, removing phlegm and eliminating blood stasis; and the damp-heat symptom is treated by eliminating heat and detoxifying. (1) The method of invigorating the spleen, supplementing Qi, and nourishing blood is used to treat spleen-stomach deficiency syndrome. When the spleen and stomach are healthy, Qi and blood are born. Cancer toxins, radiotherapy, chemotherapy, and other treatments can damage the spleen and stomach, affect muscles and limbs, and cause fatigue. Flavored Buzhongyiqi decoction,⁵⁷ Huangqi Sijunzi decoction,⁵⁸ and Ginseng tonic decoction relieve fatigue by taking care of the spleen and stomach and nourishing Qi and blood.⁵⁹ Shen Qi fu zheng injection drops exert anti-CRF effects by improving oxidative stress and mitochondrial dysfunction, regulating immune activation and inflammatory response, and regulating cytokines.⁶⁰ Xuesusheng granules can reduce the degree of bone marrow suppression, improve immune function, regulate immune inflammatory factors, reduce fatigue symptoms, and improve the quality of life of patients.⁶¹ *Astragalus membranatus* and *Atractylodes rhizome* regulate cytokines, cancer signaling pathways, and metabolism via the targets of protein kinase Ba, tumor necrosis factor and interleukin-6, and relieve fatigue.⁶² (2) Warming and tonifying the spleen and kidney are used to treat spleen-kidney Yang deficiency syndrome. Tonifying the spleen and kidney Qi is the key to treating CRF. Sanhuang Sanxian decoction can increase the levels of interferon-gamma (IFN- γ) and interleukin (IL)-2, decrease the levels of tumor necrosis factor-alpha and IL4, relieve fatigue, decrease the levels of inflammatory factors and improve immune ability.⁶³ Jianpi Shengsui Gao alleviates skeletal myoblast cell apoptosis, oxidative stress, and mitochondrial dysfunction to improve CRF in an activated protein kinase-silencing information regulator 1 and hypoxia-inducible factor 1-dependent manner.⁶⁴ *Lycium barbarum* polysaccharide regulates energy metabolism by regulating the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 signaling pathway,⁶⁵ and then improves oxidative stress response to alleviate fatigue. (3) The method of harmonizing liver and spleen is used to treat liver-spleen disharmony syndrome: The emotions of patients with malignant tumors are not regulated, which affects the function of the liver and further damages the spleen. The imbalance of the liver and spleen leads to fatigue, weakness, irritability, and other symptoms. Shugan Ji-anspi granules can increase physical strength, and improve anxiety symptoms, and sleep quality in patients with CRF.⁶⁶ Chaiqi Sanhua decoction, which has the function of calming the liver and strengthening the spleen, can effectively reduce cancer-related fatigue and relieve the symptoms of breast cancer patients without obvious side effects.⁶⁷ Angelica is a commonly used TCM to reconcile the liver and spleen. The polysaccharide of angelica can increase glycogen reserves, reduce the accumulation of lactic acid and urea nitrogen, regulate the content of ATPase in the body to improve the level of energy metabolism, and achieve the effect of antifatigue.⁶⁸ (4) The method of invigorating the spleen, calming the liver, eliminating turbidity, and removing blood stasis is used to treat hepatic stagnation causing splenic deficiency combined with Qi stagnancy and blood stasis. If the spleen and stomach are weak they cannot transport liquid and generate phlegm dampness, resulting in phlegm turbidity and accumulation. Poor emotional and Qi blood deficiency lead to blood stasis and damp pathogens. Blood stasis and damp pathogens stick to the human body and show signs of fatigue. Qi-tonifying and phlegm-removing prescriptions can lower serum carcino-embryonic antigen, neuron-specific enolase, and Cytokeratin 19-fragment levels, inhibit tumor

Table 2. Internal treatment with TCM

Internal treatment of TCM	Deficiency syndrome			Syndrome of intermingled deficiency and excess		
	Invigorating the spleen, supplementing Qi, and nourishing blood	Warming and tonifying spleen and kidney	Harmonizing liver and spleen	Invigorate spleen, calm liver, eliminate turbidity, and remove blood stasis	Strengthening body resistance to anticancer, detoxify, and disperse method	Supplementing Qi and nourishing Yin, eliminating heat, and detoxifying
Prescription	Flavored Buzhongyiqi decoction, Huangqi Sijunzi decoction, Ginseng tonic decoction	Sanhuang Sanxian decoction	Chaiqi Sanhua decoction	Qi-tonifying and phlegm-removing prescription, Fu Yuan Huo Xue decoction	Fuzheng Jianpi Jiedu decoction, Attenuated anticancer prescription	Yangyin Jiedu decoction, Yiqi Yangyin decoction
Proprietary Chinese medicine/self-pharmaceutical	Shen Qi Fu Zheng injection, Xuesusheng granule	Jianpi Shengsui Gao	Shugan Jianpi granule		Simiao Jiedu decoction	
Chinese medicine/Chinese medicine ingredient	Astragalus, Atractylodes	Lycium barbarum polysaccharide	Angelica polysaccharide			

TCM, traditional Chinese medicine.

growth, reduce toxic effects and side effects after chemotherapy, and improve fatigue.⁶⁹ Fu Yuan Huo Xue decoction, which has the effect of soothing the liver and relieving depression, promoting blood circulation, and removing blood stasis, can reduce the serum levels of CRP, IL6, and adrenocorticotrophic hormone in lung cancer patients with CRF, relieve severe CRF, and has high safety.⁷⁰ (5) The method of strengthening body resistance to cancer, the detoxify and disperse method is used to treat syndrome of spleen-kidney deficiency combined with intermingled phlegm-stasis blood syndrome: Qi deficiency of five viscera in patients with malignant tumor, combined with the invasion of cancer toxins. The vicious circle of deficiency, toxins, and blood stasis leads to the development and aggravation of fatigue. Fuzheng Jianpi Jiedu decoction can lower the levels of vascular endothelial growth factor, cyclooxygenase-2, and S intercellular cell adhesion molecule-1, and control the disease by inhibiting tumor angiogenesis and controlling the inflammatory response in the body, restore gastrointestinal function, and improve fatigue symptoms.⁷¹ Attenuated anticancer prescriptions can improve CRF and TCM syndrome in patients with advanced ovarian cancer, and reduce related tumor markers.⁷² Simiao Jiedu decoction can increase the levels of CD3+, CD4+, CD8+, and natural killer cells in patients with CRF after chemotherapy, effectively improving immune function and alleviating fatigue.⁷³ (6) The method of supplementing Qi and nourishing Yin, Eliminating heat and detoxifying method is used to treat deficiency of Qi combined with retention of damp-heat. Radiation and chemotherapy are pyretic toxicity that can consume Qi, blood, and body fluids. Therefore, during treatment, we should not only protect the Qi of the body, but also nourish the Yin, eliminate heat, and detoxify. Yangyin Jiedu decoction supplements Qi and nourishes Yin, eliminating heat and toxins in the treatment of CRF, and has a significant effect on reducing fatigue. It can also improve CD3+ and CD4+ levels, reduce CD8+ levels, and reduce immune damage.⁷⁴ Yiqi Yangyin decoction can relieve the clinical symptoms and CRF of patients with non-small cell lung cancer, and improve their quality of life (Table 2).⁷⁵

Personalized TCM syndrome differentiation treatment can ad-

just medication according to the patient’s internal factors such as syndrome constitution, and age, and external factors such as geographical location, weather, season, *etc*. It has the advantages of flexibility, convenience, clear efficacy, few side effects, and can effectively improve CRF, and improve patients’ quality of life and immunity. However, there is no unified standard for the syndrome type and treatment of this disease in TCM. As a result, TCM treatment of CRF cannot be unified, standardized, and carried out on a wide range, so there is also a lack of high-level evidence-based support for TCM treatment of CRF.

TCM external treatment

Acupuncture, moxibustion, massage, patching, auriculo acupuncture, scraping, foot baths, and other external TCM therapies are widely used because of their advantages such as fast action, low price, and high safety (Table 3). Acupuncture and moxibustion are safe and effective for treating CRF.⁷⁶ The top three points with a high frequency of use are Zusanli, Qihai, and Guanyuan. The meridians with a high frequency of use are the ren meridian, stomach meridian of foot-yangming, the kidney meridian of foot-shaoyin, the spleen channel of foot-taiyin, du mai, and the liver meridian of foot-jueyin.⁷⁷ Acupuncture treatments (selected acupoints: Baihui, Guanyuan, Qihai, Fengchi, Zusanli, and Sanyinjiao) can significantly reduce the levels of C-reactive protein, IL6, tumor necrosis factor alpha, and relieve fatigue.⁷⁸ Moxibustion (selection of acupoints: bilateral Zusanli, Sanyinjiao, Guanyuan, Shenshu, and Qihai, with a frequency of 20 m each time, 1 time/day, 6 times/week) can significantly increase the level of natural killer cells and relieve fatigue by regulating immunity.⁷⁹ Tiaoyi Sanjiao acupuncture (main points: Shanzhong, Zhongwan, Qi Hai, bilateral Zusanli; auxiliary points: Bilateral blood sea, Waiguan, and Taichong) regulates the number of CD3+, CD4+, and CD8+T cells, improving immune function, achieving the effect of relieving fatigue in patients with advanced non-small cell lung cancer, and improving the quality of life.⁸⁰ The combination of Shutiaojieyuanshen decoction containing Bupleurum, Yujin, Yinyanghuo, Atracty-

Table 3. Traditional Chinese medicine external treatment and nursing

Acupuncture	moxibustion	Acupuncture and moxibustion	Scraping along the meridians	Other/combination treatments	Emotional therapy	Diet	Healthy exercise
Select points: Zusanli, Qihai, Guanyuan, <i>etc.</i> ; meridians: ren meridian, stomach meridian of foot- yangming, the liver meridian of foot- jueyin, <i>etc.</i>	Moxibustion after acupoint selection (frequency: 20 m/time, 1 time/day, 6 times/week)	Tiaoyi Sanjiao acupuncture method	Copper bian scraping board saves the bladder meridian on both sides, scraping board and skin 45 degrees angle, from top to bottom, first light then heavy, first slow then fast, medium intensity, operation time 20 m, once a week, five times for a course of treatment	Umbilical compress combined with ear acupuncture bean pressure: Ten big Bujia Fang umbilical compress combined with ear acupuncture bean pressure (auricular point: spleen, stomach, kidney, Shenmen, sympathetic and tender point); burning mountain fire acupuncture combined decoction: burning mountain fire acupuncture (leave the needle for 30 m, treatment once a day, continuous treatment for 20 d); acupuncture Baliao combined with Wenyang Jianpi Yichang decoction oral	Mutual restraint of emotions, empathy suggestion, <i>etc.</i>	Medicinal food (including Astragalus, ginseng, Poria, <i>etc.</i>)	Tai Chi, eight infantile finger loops and whorls, Yijinjing, <i>etc.</i>

lodes, Jujube seed, Schisandrin fructus, alhuan skin, Polygala, calin stone, *etc.*, and the application of acupoint patching (selected points: Qimen, Taichong, Neiguan, Sanyinjiao, and Yongquan) for the treatment of CRF can improve sleep quality and reduce fatigue.⁸¹ The application of Qi nourishing TCM foot baths (recipe: *Scutellaria baicalensis*, Niudali, *Poria cocos*, Cohoma, Qianghuo, Duhuo, FangFeng, schizonepeta, and Perilla leaves at 37–42°C for 30 m, one dose/day, for 3 consecutive days) in the treatment of CRF can significantly reduce fatigue and improve quality of life.⁸² In addition, umbilical compress combined with ear acupuncture bean pressure,⁸³ transcutaneous electrical acupuncture stimulation,⁸⁴ burning mountain fire acupuncture combined with decoction,⁸⁵ and scraping along the meridians can alleviate fatigue and improve quality of life,⁸⁶ which is worth promoting.

TCM nursing treatment

TCM nursing can provide more comprehensive care to patients with CRF through emotions, diet, daily life, exercise, and other methods, which relieve the symptoms of fatigue, insomnia, and anxiety and improve the quality of life (Table 3). Constitutional determination can involve various care methods according to individual conditions so that the body can achieve a dynamic balance of Yin and Yang. Applying the methods of Shun Yi and five sound catharsis to patients with Yang deficiency, Yin deficiency, phlegm dampness, and stagnation, Qi stagnancy, and blood stasis can greatly improve the pathological constitution and fatigue symptoms.⁸⁷ “If you want to cure the disease, you should first treat the mind.” Regulating emotions is an important method of treating diseases. Emotional therapy such as calming the mind, emotional balance, and empathic suggestion alleviates negative patient emotions, reduces their psychological distress, and improves sleep and

fatigue.⁸⁸ A meta-analysis found that traditional Chinese health exercises (Tai Chi, eight infantile finger loops and whorls, and Yijinjing, five-animal exercises) improved fatigue, anxiety, and sleep quality.⁸⁹ An 8-week eight infantile finger loops and whorls exercise can improve fatigue and quality of life in patients with CRF.⁹⁰ Medical food homology, including astragalus, ginseng, poria, angelica, and licorice, effectively improve the levels of inflammatory factors and T lymphocytes, enhance immune function, and alleviate fatigue after being processed into medicinal food.⁹¹

Conclusions

The incidence of CRF is high, the degree is serious, and the influence is huge, which has attracted wide attention. The pathogenesis of CRF is complex and may be related to disorders of inflammatory cytokines, mitochondrial dysfunction, HPA axis disorders, intestinal microbiota-gut-brain axis disorders, and gene polymorphism. More research and data are needed to clarify its pathogenesis. The management of CRF is divided into screening, preliminary assessment, intervention, and reassessment. There are various screening and evaluation scales for CRF, each with its own emphasis. Selecting the appropriate scale can effectively and correctly evaluate the condition, adjust treatment strategy, and allow personalized treatment measures. Treatments include drug and nondrug interventions. Drug interventions mainly include symptomatic treatment that alleviates some patient symptoms, but there are safety problems. Various nondrug interventions are effective in improving sleep, diet, anxiety, depression, and fatigue. Nondrug interventions are recommended for patients with a high degree of cooperation, good economic ability, and mild disease.

TCM treatment of CRF has obvious advantages, including treatment based on syndrome differentiation, with or without the

syndrome, considering efficacy and safety, effectively improving CRF, and improving quality of life. However, the TCM diagnostic evaluation scale is still in its infancy and there is no unified standard and path for TCM syndrome differentiation, diagnosis, and treatment of CRF. This leads to difficulties in objective, comprehensive, and systematic evaluation of CRF in TCM. Many investigators continue to explore principle-method-recipe-medicine and modern technology, analyze etiology and pathogenesis, master the law of syndrome differentiation, use effective prescriptions, give full play to the advantages of TCM, and improve the treatment effect so that patients benefit.

Both TCM and Western medicine have their advantages and disadvantages in studying the pathogenesis, assessment, screening, and treatment of CRF. It is proposed to expand the research ideas in the future, fully exploit the advantages of both traditional Chinese and Western medicine, and provide more comprehensive research, a more authoritative foundation, and more effective treatment methods to alleviate CRF and improve quality of life.

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Conflict of interest

DHL has been an editorial board member of *Future Integrative Medicine* since November 2021. The other author reports no conflict of interests in this work.

Author contributions

Design of the research and writing and revision (XLD, DHL, RJJ, CLM), collecting the data, and translating the manuscript (XLD, JPZ). The final manuscript was read and approved by all authors.

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