Postprint of a Meta-Analysis of Factors Associated with Frailty in Cancer Patients

Authors: Guo Yinning, Miao Xueyi, Jiang Xiaoman, Xu Ting, Xu Qin, Xu Qin

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Abstract

Background Frailty is highly prevalent among cancer patients and severely impacts their prognosis and recovery. Objective To identify the influencing factors of frailty in cancer patients through meta-analysis, providing a scientific basis for the design and implementation of future frailty intervention strategies for this population. Methods A comprehensive and systematic search was conducted from inception to August 2022 across CNKI, VIP, Wanfang, PubMed, Web of Science, Cochrane Library, CINAHL, and Embase databases to include studies on influencing factors of frailty in cancer patients. Literature screening, quality assessment of studies meeting inclusion and exclusion criteria, and data extraction were performed. Meta-analysis was conducted using Stata 17.0 and RevMan 5.4 software. Results A total of 11 studies were included, comprising 9 cross-sectional studies and 2 cohort studies, involving 2,898 cancer patients, of whom 1,025 were frail, covering 12 influencing factors. Meta-analysis results showed that the pooled prevalence of frailty in cancer patients was 34%. Influencing factors included age [OR=1.16, 95%CI (1.05, 1.27), P=0.002], educational level [OR=0.78, 95%CI (0.68, 0.90), P=0.003], comorbidities [OR=1.46, 95%CI (1.28, 1.67), P<0.001], body mass index (BMI) [OR=1.13, 95%CI (1.05, 1.21), P<0.001], albumin [OR=0.33, 95%CI (0.12, 0.90), P=0.03], nutritional status [OR=2.77, 95%CI (1.27, 6.06), P=0.01], symptom clusters [OR=1.07, 95%CI (1.04, 1.09), P<0.001], depression [OR=1.27, 95%CI (1.12, 1.44), P<0.001], and instrumental activities of daily living (IADL) [OR=0.50, 95%CI (0.42, 0.59), P<0.001]. However, gender [OR=0.81, 95%CI (0.54, 1.21), P=0.30], marital status [OR=0.21, 95%CI (0.02, 2.31), P=0.20], and hemoglobin [OR=0.51, 95%CI (0.22, 1.22), P=0.13] were not associated with frailty in cancer patients. Conclusion Current meta-analysis results indicate that age, educational level, comorbidities, BMI, albumin, nutritional status, symptom clusters, depression, and IADL are influencing factors for frailty occurrence in cancer patients. Cancer patients with advanced age, low educational level, comorbidities, high BMI,

albumin level <35 g/L, poor nutritional status, accompanied by symptom clusters, depressive symptoms, and impaired activities of daily living are priority populations requiring attention.

Full Text

Preamble

Associated Factors of Frailty in Cancer Patients: A Meta-analysis

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Guo Yinning, Miao Xueyi, Jiang Xiaoman, Xu Ting, Xu Qin*

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Affiliation: School of Nursing, Nanjing Medical University, Nanjing 211166, Jiangsu Province, China

*Corresponding author: Xu Qin, Dean of the School of Nursing, Professor, Doctoral Supervisor; E-mail: qinxu@njmu.edu.cn

Abstract

Background: Frailty is common in cancer patients and seriously affects patient prognosis.

Objective: To identify factors associated with frailty in cancer patients through meta-analysis, and to provide a scientific basis for designing and implementing frailty intervention programs.

Methods: We systematically searched China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database (VIP), Wanfang, PubMed, Web of Science, Cochrane Library, CINAHL, and Embase databases from inception to August 2022 to collect studies on factors associated with frailty in cancer patients. Meta-analysis of included literature was performed using Stata 17.0 and RevMan 5.4.

Results: A total of 11 articles were included, comprising 9 cross-sectional studies and 2 cohort studies, with 2,898 cancer patients (including 1,025 frail patients) and involving 12 associated factors. Meta-analysis results showed the average incidence of frailty in cancer patients was 34%. Significant associated factors included age [OR=1.16, 95%CI (1.05, 1.27), P=0.002], education level [OR=0.78, 95%CI (0.68, 0.90), P=0.003], comorbidity [OR=1.46, 95%CI (1.28, 1.67), P<0.001], body mass index (BMI) [OR=1.13, 95%CI (1.05, 1.21), P<0.001], albumin [OR=0.33, 95%CI (0.12, 0.90), P=0.03], nutritional

status [OR=2.77, 95%CI (1.27, 6.06), P=0.01], symptom cluster [OR=1.07, 95%CI (1.04, 1.09), P<0.001], and depression [OR=1.27, 95%CI (1.12, 1.44), P<0.001]. Instrumental activities of daily living (IADL) [OR=0.50, 95%CI (0.42, 0.59), P<0.001] was a protective factor. Gender [OR=0.81, 95%CI (0.54, 1.21), P=0.30], marital status [OR=0.21, 95%CI (0.02, 2.31), P=0.20], and hemoglobin [OR=0.51, 95%CI (0.22, 1.22), P=0.13] were not significantly associated with frailty.

Conclusion: Current evidence suggests that age, education level, comorbidity, BMI, albumin, nutritional status, symptom cluster, depression, and IADL are associated factors of frailty in cancer patients. Elderly cancer patients with low education level, comorbidities, high BMI, albumin level <35 g/L, poor nutritional status, symptom clusters, depressive symptoms, and low IADL represent priority populations requiring attention.

Keywords: cancer; frailty; associated factors; Meta analysis

Introduction

Malignant tumors represent a major public health threat to human physical and mental health. The World Health Organization (WHO) reported that in 2020, there were 19.3 million new cancer cases and nearly 10 million cancer deaths worldwide, and projected that by 2040, the number of new malignant tumor cases will reach 28.4 million, representing a 47% increase from 2020 [1]. For these cancer patients, frailty is particularly common due to tumor invasion combined with various stressors such as surgery, chemotherapy, radiotherapy, and psychological factors, with reported prevalence rates ranging from 6% to 86% [2]. Frailty refers to a multidimensional syndrome characterized by multisystem organ dysfunction, reduced physiological reserve, increased vulnerability, and diminished stress resistance [3]. Studies have confirmed [4, 5] that frailty is an independent predictor of prognosis in cancer patients and is associated with multiple adverse outcomes (e.g., increased treatment toxicity, hospitalization rates, and mortality risk). Therefore, understanding the influencing factors of frailty in cancer patients is a critical first step for improving patient prognosis.

Currently, most studies on frailty influencing factors in cancer patients, both domestically and internationally, are small-sample cross-sectional studies focusing primarily on sociodemographic and physiological factors, with inconsistent conclusions and limited generalizability. However, frailty results from the combined effects of multiple factors, making a comprehensive, multi-level investigation of its influencing factors more meaningful for cancer patient prevention and treatment. Therefore, it is necessary to conduct a meta-analysis of frailty influencing factors in cancer patients to create a large-sample study that comprehensively and systematically summarizes relevant factors, yielding more reliable and generalizable conclusions. This will provide an evidence-based foundation for clinical healthcare providers to screen high-risk frailty populations among cancer patients and implement systematic, comprehensive preventive interventions.

Methods

1.1 Literature Search

We conducted a comprehensive systematic search of China National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database (VIP), Wanfang, PubMed, Web of Science, Cochrane Library, CINAHL, and Embase databases from inception to August 2022 to identify studies on frailty in cancer patients. The search strategy combined subject headings with free-text terms, with subject headings determined according to the MeSH thesaurus, and searches were conducted in both Chinese and English. The specific Chinese search formula was: (frailty OR frailty syndrome) AND (tumor OR cancer) AND (influencing factors OR risk factors OR related factors). The English search formula was: (frail* OR frailty OR "frailty syndrome") AND (neoplasm OR neoplas* OR cancer* OR tumor* OR malignanc* OR carcinoma OR oncology OR CA) AND (factor OR "risk factors" OR "influence factors" OR "associated factors"). Table 1 presents the detailed search strategy for the PubMed database.

1.2 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Study design: cross-sectional, cohort, or case-control studies, published in Chinese or English; (2) Participants: aged $ $18 years with pathologically confirmed malignant tumors; (3) Frailty assessed using specific measurement methods or tools; (4) Frailty as a dichotomous outcome with reported associated factors, and data providing multivariate-adjusted OR values with 95%CI or sufficient data for calculation.

Exclusion criteria: (1) Studies with incomplete data, inability to extract or convert data, or unobtainable full text; (2) Duplicate publications with identical data; (3) Articles scoring 0-3 on the Newcastle-Ottawa Scale (NOS) [6] or the Agency for Healthcare Research and Quality (AHRQ) recommended quality assessment criteria [7].

1.3 Literature Screening and Data Extraction

Two researchers independently screened study titles and abstracts according to the inclusion and exclusion criteria, excluding literature clearly irrelevant to the topic and duplicate publications. The remaining articles were then read in full text to determine final inclusion for meta-analysis.

Two researchers independently extracted data in a double-blind manner, including study characteristics, region, design type, cancer type, frailty assessment tool, participant age, number of frail individuals, total sample size, and factors included in multivariate analysis. Any disagreements were resolved through discussion with a third researcher.

1.4 Literature Quality Assessment

Literature quality assessment was also conducted independently by two researchers using NOS [6] or AHRQ-recommended quality assessment criteria [7] for the 11 included studies. Cohort and case-control studies were evaluated using NOS, which scores three domains with a maximum of 9 points: 0-3, 4-6, and 7-9 points indicate low, moderate, and high quality, respectively [6]. Cross-sectional studies were assessed using AHRQ criteria, which requires researchers to evaluate 11 items, scoring 1 point for "yes" and 0 points for "no" or "unclear," with a maximum score of 11 points: 0-3, 4-7, and 8-11 points indicate low, moderate, and high quality, respectively [7].

1.5 Data Processing

Stata 17.0 was used to calculate the pooled incidence of frailty in cancer patients and its 95% CI, with subgroup analysis performed when necessary. RevMan 5.4 software was used to analyze pooled ORs and 95%CIs for frailty influencing factors, with a significance level of α=0.05. Heterogeneity among pooled data was primarily assessed using I^2. If P$ 0.10*andI*^{2}$$ $50%, indicating no significant heterogeneity, a fixed-effects model was used for meta-analysis; otherwise, a random-effects model was employed. Sensitivity analysis was conducted by switching between fixed-effects and random-effects models to verify the robustness of pooled results. Considering that publication bias analysis is less meaningful when fewer than 10 studies are included, we specified that when the number of studies for a single outcome indicator was $ $10, funnel plots would be generated and Egger' s test performed using Stata 17.0 to assess publication bias.

Results

2.1 Literature Selection Process

The initial search retrieved 5,010 relevant articles. After preliminary screening, 24 articles were selected for full-text review, and ultimately 11 articles were included, comprising 6 Chinese-language studies [8-13] and 5 English-language studies [14-18]. The detailed literature screening process is shown in Figure 1 [Figure 1: see original paper].

2.2 Characteristics and Quality Assessment of Included Studies

This study ultimately included 11 articles comprising 2,898 cancer patients, including 9 cross-sectional studies [8-10, 12-17] and 2 cohort studies [11, 18]. Factors appearing in $ $2 studies were extracted for analysis. The 12 influencing factors extracted from all 11 articles were appropriately categorized according to their characteristics into: (1) demographic factors (including age, gender, education level, marital status); (2) physical/physiological factors (including comorbidities, BMI, hemoglobin, albumin, nutritional status, symptom clusters);

and (3) psychosocial factors (depression, activities of daily living). The 2 included cohort studies [11, 18] were both high-quality, while the cross-sectional studies [8-10, 12-17] were of moderate or high quality.

The basic characteristics of included studies are presented in Table 2 , and quality assessment results are shown in Tables 3-4 .

2.3 Pooled Effect Sizes

2.3.1 Pooled Effect Size for Frailty Incidence We performed meta-integration of frailty incidence in cancer patients using baseline data from 9 cross-sectional studies [8-10, 12-17] and 2 cohort studies [11, 18], totaling 2,898 patients, of whom 1,025 were frail. Heterogeneity testing using Stata 17.0 revealed significant heterogeneity among studies (I^2=98%, P<0.001), so a random-effects model was selected. The final pooled average incidence of frailty in cancer patients was 34% [95%CI (0.23, 0.45)], as shown in Figure 2 [Figure 2: see original paper].

2.3.2 Subgroup Analysis Subgroup analysis was performed by cancer type. Two studies [11, 12] investigated frailty in lung cancer patients, with a prevalence of 31% [95%CI (0.25, 0.36)]. Four studies [9, 10, 14, 18] reported a frailty prevalence of 42% [95%CI (0.26, 0.59)] in patients with digestive system tumors. Two studies [16, 17] reported a frailty incidence of 12% [95%CI (0.09, 0.16)] in other tumor types. Chi-square test revealed that digestive system tumor patients had the highest frailty incidence, followed by lung cancer, with relatively lower incidence in other tumors, and the difference was statistically significant (^{2}=134.88, P<0.001), as shown in Table 5 .

2.3.3 Pooled Effect Sizes for Frailty Influencing Factors We extracted and analyzed data for 12 influencing factors from the 11 included studies. Results showed that six factors (gender, education level, comorbidity, BMI, symptom cluster, and IADL) had acceptable heterogeneity across studies, so a fixed-effects model was used. The remaining factors showed substantial heterogeneity and used a random-effects model. The findings indicated that all factors except gender, marital status, and hemoglobin were statistically significant. Detailed results are presented in Table 5 . Meta-analysis revealed that advanced age, comorbidity, high BMI, poor nutritional status, high symptom cluster scores, and depression were risk factors for frailty in cancer patients, while high education level, high albumin level, and good instrumental activities of daily living (IADL) were protective factors.

2.4 Sensitivity Analysis

Sensitivity analysis was performed by sequentially excluding each study' s frailty incidence data from the 9 cross-sectional and 2 cohort studies. Meta-analysis showed that the pooled effect size did not change significantly, indicating relatively stable results. Additionally, we estimated pooled ORs and 95%CIs for

included influencing factors using both random-effects and fixed-effects models. Except for marital status and hemoglobin, other factors showed good consistency, demonstrating that our results are basically reliable (Table 6).

2.5 Publication Bias

Egger' s test was used to assess publication bias for frailty incidence across the 11 included studies, with a funnel plot shown in Figure 3 [Figure 3: see original paper]. Egger' s test revealed t=-4.12, P=0.003, indicating some publication bias, possibly related to large differences in cancer types among included studies. Additionally, since fewer than 10 studies were included for each of the 12 extracted influencing factors, publication bias analysis was not performed for these factors.

Discussion

3.1 Frailty Incidence

Multiple studies have confirmed that frailty is an independent risk factor for poor prognosis in cancer patients, often causing a series of health problems (e.g., increased complications, chemotherapy/radiotherapy toxicity, hospitalization duration, and mortality risk) [19, 20]. This study aimed to systematically investigate influencing factors of frailty in cancer patients to provide an evidence-based foundation for clinical healthcare providers to screen high-risk frailty populations and implement comprehensive interventions. Meta-analysis data showed that the average incidence of frailty among included cancer patients was 34%, significantly higher than the 12% frailty incidence in general community-dwelling older adults [21]. Subgroup analysis by cancer type revealed a frailty incidence of 31% in lung cancer, 42% in digestive system tumors, and 12% in other tumors. Digestive system tumors had the highest frailty incidence, which is consistent with Giannotti et al.' s [22] reported 40.5% frailty incidence in gastrointestinal tumors. These findings suggest that we should emphasize frailty assessment and prevention in cancer patients, particularly for those with digestive system tumors and lung cancer, to improve their prognostic quality of life.

3.2 Influencing Factors of Frailty

Our study results showed that age, education level, comorbidity, BMI, albumin, nutritional status, symptom cluster, depression, and IADL are influencing factors of frailty in cancer patients.

3.2.1 Demographic Factors The results showed that age is an important risk factor for frailty in cancer patients. A systematic review [23] also demonstrated that frailty risk increases significantly with age. This may be because older patients experience more pronounced organ function decline, lower physiological reserve, and weaker stress resistance, which combined with cancer effects

substantially increases frailty risk. Additionally, patients' education level also influences frailty occurrence. Previous research [24] has shown that higher education level is associated with lower frailty incidence, possibly because individuals with higher education generally have higher income and social status, better access to healthcare resources, and greater health awareness. In contrast, patients with lower education levels often have poorer economic status and health awareness, leading to differences in frailty occurrence. For these demographic factors that cannot be directly intervened upon, we can emphasize frailty assessment in cancer patients, particularly strengthening evaluation for older patients with lower education levels and providing timely appropriate interventions.

3.2.2 Physical and Physiological Factors Comorbidity is a major potential contributor to increased frailty risk in cancer patients. Previous research [25] has found that disease and frailty share common pathogenic mechanisms with considerable pathophysiological overlap. Many scholars believe that chronic inflammation activation plays an important role in frailty development. Elevated serum C-reactive protein and interleukin-6 are also part of the pathogenic mechanism underlying frailty-disease coexistence [26]. Physical disease can lead to frailty, and conversely, frailty can worsen physical disease, creating a vicious cycle where disease and frailty are mutually causal and reinforcing. Therefore, we need to pay special attention to cancer patients with comorbidities, actively treat and manage existing diseases to delay frailty progression.

This study also found that patients with high BMI (especially BMI$ 30.0kg/m^{2}) are more prone to frailty than those with normal BMI. Bennett et al. [17] found that each unit increase in BMI increased the odds of physical frailty by 12%. A systematic review [27] also confirmed that BMI is associated with frailty in older adults, with higher BMI associated with greater frailty risk. This study further found that abdominal obesity (waist circumference $ $102 cm in men and $ $88 cm in women) was positively correlated with frailty, with individuals having larger waist circumference havi
and abdominal obesity (waist circumference $ $102 cm in men and $ $88 cm in women) as routine screening indicators for frailty in cancer patients.

This study demonstrated that albumin level $ $35 g/L is a protective factor against frailty in cancer patients. Yamamoto et al. [31] found that albumin level is negatively correlated with frailty risk, with lower albumin associated with higher frailty risk, consistent with our results. Other studies have used albumin as a biomarker for frailty to assist in screening [32]. Cancer patients in chronic inflammatory states experience increased capillary permeability, accelerating serum albumin loss and increasing frailty risk [33]. Albumin is also a primary biochemical indicator commonly used clinically to assess nutritional status, and healthcare providers often use its level to determine nutritional risk. Our results confirm that poor nutritional status is also an important frailty risk factor. In addition to close association with decreased albumin, poor nutritional status may also relate to insufficient intake of vitamin D and trace elements [34]. Furthermore, most cancer patients are elderly with decreased taste,

chewing strength, gastrointestinal function, and enzyme activity, all contributing to malnutrition and accelerating frailty. This suggests healthcare providers need to continuously monitor albumin levels and nutritional status in cancer patients, conduct nutritional risk assessments, and increase nutritional intake when appropriate to improve nutritional status and thereby ameliorate frailty.

Symptom clusters in cancer patients also represent a major frailty-inducing factor. Common symptom clusters include neurological, digestive, and respiratory symptom clusters. Cancer treatments such as surgery, chemotherapy, and radiotherapy often cause multiple adverse effects including pain, nausea, vomiting, loss of appetite, and cough [5], which limit activity and reduce dietary intake, making frailty highly likely. Therefore, clinicians need to emphasize assessment of symptom clusters in cancer patients, conduct early screening, and provide targeted interventions to reduce symptom burden, alleviate frailty, and improve quality of life and survival.

3.2.3 Psychosocial Factors Depression is another major risk factor for frailty. Wang et al. [35] found that frailty is positively correlated with depressive symptoms, with depression having a direct path coefficient of 0.59 on frailty. Currently, the mechanisms linking frailty and depression remain unclear, but research suggests their association may be partially explained by overlapping mechanisms such as chronic inflammation, cerebrovascular disease, oxidative stress, mitochondrial dysfunction, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation [36]. Increasing evidence supports a positive correlation between frailty and inflammatory cytokines such as interleukin-6 (IL-6) [37]. Since IL-6 levels are generally elevated in patients with depression, and inflammatory cytokines are associated with reduced muscle mass and function and negatively affect central dopaminergic system function, they can cause fatigue and slowed cognition and movement, thereby inducing frailty [38]. Additionally, cancer patients are more prone to anxiety, depression, and other negative emotions due to disease diagnosis and treatments such as surgery, chemotherapy, and radiotherapy, which can further lead to passive treatment attitudes, reduced physical exercise and social activities, and social withdrawal, creating a vicious cycle. These findings suggest healthcare providers should emphasize psychological care for cancer patients, continuously monitor psychological changes, provide timely communication and counseling for patients with negative emotions, organize peer support groups to allow patients to express their true feelings, and encourage active participation in social activities and enhanced family interaction.

Finally, this study found that instrumental activities of daily living (IADL) also affect frailty. IADL is part of activities of daily living, including eight capabilities: using transportation, shopping, doing housework, laundry, cooking, making phone calls, managing finances, and taking medication. Sun et al. [39] also found that higher IADL is associated with lower frailty likelihood. Therefore, we should emphasize the development of IADL capabilities in cancer patients

and advise family members to provide patients with some autonomy in daily living, avoiding excessive arrangement of patients' lives simply because they are ill, which can create over-dependency.

3.3 Limitations and Future Directions

This meta-analysis has several limitations: (1) Most included studies were small-sample cross-sectional studies lacking large-sample prospective cohort studies, limiting the credibility of conclusions; (2) Conference papers, dissertations, and studies in languages other than Chinese and English were not included, which may introduce bias; (3) Only some influencing factors were extracted and pooled, and factors such as "gender"could not be further analyzed due to limited included studies; (4) Due to large differences in cancer types among study populations, there was some publication bias in frailty incidence.

In summary, current evidence indicates that age, education level, comorbidity, BMI, albumin, nutritional status, symptom cluster, depression, and IADL are influencing factors of frailty in cancer patients. Elderly cancer patients with low education level, comorbidities, BMI$ 30.0kg/m^{2}$, albumin level <35 g/L, poor nutritional status, symptom clusters, depressive symptoms, and low activities of daily living represent priority populations requiring attention. Therefore, in future cancer management, healthcare providers can develop a cancer frailty risk screening tool based on these factors to enable timely implementation of precision preventive treatment protocols for cancer populations identified as high-risk for frailty, thereby improving prognostic recovery in cancer patients.

Author Contributions

Guo Yinning was responsible for manuscript writing, data collection, and organization; Guo Yinning and Miao Xueyi conducted statistical processing, results analysis, and interpretation; Jiang Xiaoman and Xu Ting performed manuscript revision; Xu Qin was responsible for quality control and final approval, with overall responsibility for the article and supervision.

Conflicts of Interest

The authors declare no conflicts of interest.

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