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Research Article

Fatigue and Co-Occurring Cancer-Related Symptoms in Breast Cancer Survivors: A Systematic Review and Network Meta-Analysis

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Objective: The relative strength of risk factors for cancer-related fatigue (CRF) among breast cancer survivors (BCSs) remains unclear. This study aims to systematically evaluate and compare the strength of different risk factors for CRF using a network meta-analysis (NMA) approach.
Methods: This NMA included observational studies on female BCSs with extractable data related to risk factors for CRF. The PubMed, Cochrane Library, and Embase databases were systematically searched, and the study protocol was registered in PROSPERO (reference no. CRD42025642021). A random-effects meta-analysis was performed to estimate pooled effect sizes, and an NMA with P-scores was used to rank the relative strength of risk factors. Subgroup analyses, sensitivity analyses, and meta-regression were conducted to assess methodological quality and explore potential sources of heterogeneity.
Results: Thirty observational studies ($n = 36{,}302$ female BCSs) that were published between 2004 and 2024 were included in this NMA. Depression exhibited the strongest association with CRF (OR = 3.34, 95% CI 2.50–4.46, P-score = 0.9727), followed by insomnia (OR = 2.35, 95% CI 1.45–3.81, P-score = 0.6549), pain (OR = 1.94, 95% CI 1.33–2.84, P-score = 0.4587), and anxiety (OR = 1.85, 95% CI 1.23–2.79, P-score = 0.4132). Subgroup analysis revealed that the associations of the four risk factors with CRF remained significant at the three posttreatment time points (< 1 year, 1–5 years, and > 5 years), with the exception of anxiety and insomnia at < 1 year and pain at > 5 years. Meta-regression demonstrated that higher study quality (measured via the Newcastle–Ottawa scale [NOS]) was significantly correlated with stronger associations of anxiety and insomnia with CRF ($\beta = 0.305$ and 0.221, $p < 0.05$, respectively). Sensitivity analysis confirmed the robustness of the main findings.
Conclusion: Depression plays a central role in CRF development and should be prioritized in survivorship care. Integrating multimodal interventions for depression, sleep disturbances, and pain management may improve fatigue outcomes.

1. Introduction

Breast cancer has become the most commonly diagnosed cancer in the world, accounting for nearly 12% of all cancer cases worldwide [1]. In countries with a very high human development index, 1 in 12 women are diagnosed with breast cancer in their lifetime, and 1 in 71 women die from breast cancer [2]. Among breast cancer survivors (BCSs), cancer-related fatigue (CRF) is the most commonly reported symptom in various studies [3, 4]. CRF is a persistent, subjective feeling of physical, emotional, and/or cognitive exhaustion related to cancer or its treatment, disproportionate to recent activity and disruptive to usual daily functioning [5]. The incidence of CRF ranges from 14.03% to 100%, and this symptom can last for 5–10 years after treatment and even beyond [6–8]. Patients have reported

that fatigue is the most distressing symptom associated with cancer and its treatment—more distressing than pain or nausea and vomiting, which can generally be managed by medications [9].

The persistent burden of CRF among long-term cancer survivors is likely multifactorial, with comorbidities playing a significant role in symptom severity and progression [10]. Although previous studies have highlighted the risk factors for CRF, the presentation of CRF may vary across cancer types [11]. The unique characteristics of breast cancer, such as its predominance in females, the diverse range of treatment modalities (e.g., surgery, chemotherapy, radiotherapy, hormone therapy, targeted therapy, and immunotherapy), and the need for long-term medication such as antiestrogen drug among ER-/PR-positive breast cancer patients, contribute to the complexity of the mechanisms underlying CRF in BCSs [12].

Previous studies have demonstrated that both psychological (e.g., anxiety and depression) and physical (e.g., insomnia and pain) factors are associated with CRF [8, 12–14]. However, similar evidence for CRF in BCSs is inconsistent, and traditional meta-analysis cannot comprehensively compare multiple risk factors simultaneously. Network meta-analysis (NMA) offers a robust solution by integrating direct and indirect comparisons, thus allowing for a more precise ranking of risk factors based on the strength of their influence on CRF. According to practice guidelines, the patient is assessed for the presence of treatable factors known to contribute to fatigue. If present, factors should be treated with referral to other care professionals as appropriate [5]. As managing concurrent symptoms and treatable contributing factors is important, identifying key risk factors informs the prioritization of which psychological comorbidities warrant early intervention in survivorship care.

We hypothesized that CRF in BCSs arises from a complex interplay of demographic, psychological, biological, and behavioral factors, with psychological risk factors (e.g., depression and anxiety) exerting a greater cumulative impact than physical factors (e.g., sleep disturbances, and pain). Therefore, the aims of this study were as follows: (1) to perform a systematic review and NMA to establish a hierarchical ranking of the risk factors for CRF based on the strength of their influence and (2) to explore the relative importance of modifiable risk factors for CRF.

2. Method

2.1. Protocol and Registration. To ensure methodological rigor, this meta-analysis was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020 statement (Supporting Appendix 1) as well as the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) Checklist for meta-analyses of observational studies (Supporting Appendix 2) and the PRISMA extension statement for systematic reviews incorporating NMA (Supporting Appendix 3) [15–17]. This meta-analysis was also registered in the PROSPERO database (reference no. CRD42025642021) [18].

2.2. Literature Search Strategy. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for relevant observational studies published between January 1989 and January 2025. We chose 1989 as the starting point because breast cancer mortality rates began to decline thereafter, reflecting advances in screening and treatment [19]. The databases were searched using the Boolean operators by combining medical headings, keywords, and search filters. Additionally, we manually searched the reference lists of relevant articles and systematic reviews, and we searched several key journals to identify additional eligible studies. No language restrictions were applied in the literature search. The selection criteria were consistent with the search strategy recommended by the Cochrane Collaboration [20, 21]. The following terms were used alone or in combination with each other: "fatigue," "cancer-related fatigue," "breast neoplasms," "risk factors," "correlation," and relevant items, including "humans" and "female". We focused on study types, including "retrospective," "prospective," and "observational studies." All the above words were used as search keywords to specify longitudinal or cross-sectional population-based observational studies. A detailed search strategy is provided in Supporting Table 1.

2.3. Inclusion and Exclusion Criteria. The inclusion criteria were as follows: (1) females who were diagnosed with breast cancer; (2) BCSs who completed breast cancer treatment; (3) data that could be used to identify the risk factors for CRF (psychological distress, sleep disturbance, depression, and anxiety); and (4) cross-sectional studies, longitudinal cohort studies, or case–control studies. The exclusion criteria were as follows: (1) outcome measures could not be extracted; (2) patients were diagnosed with two or more primary cancers; (3) the study design was an animal study, protocol, conference abstract, review, or meta-analysis article; or (4) the full text could not be retrieved.

We cataloged and categorized four risk factors for CRF: anxiety vs. no anxiety, depression vs. no depression, insomnia vs. no insomnia, and pain vs. no pain. The former groups in each comparison were labeled as exposed groups, whereas the latter groups were labeled as observation groups. Finally, no direct contact with the study authors was made, as all necessary data were available in the peer-reviewed published reports, thus ensuring methodological rigor and data completeness.

2.4. Outcome Measures and Data Extraction. The study selection process was illustrated using a PRISMA 2020 flow diagram [15]. All the literature was imported into EndNote 21 software (Thomson ISI Research Soft, Philadelphia, PA) to screen and remove duplicate publications. To ensure methodological rigor and data reliability, we included only peer-reviewed publications and excluded gray literature.

Two researchers (C.C. Huang and Y.H. Liu) screened titles and abstracts in accordance with the inclusion and exclusion criteria; the included articles were then screened again after their full texts were read. A third researcher (Y.S.

Horng) was consulted in the case of disagreements regarding study inclusion. Finally, the data were extracted into Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

The following data were extracted: first author, country, year of publication, study design, total sample size, mean age, prevalence of CRF, specific posttreatment time point (in years), methods of CRF assessment, primary cancer treatments, primary cancer staging, percentage of chemotherapy, and key correlates or risk factors analyzed in the study.

2.5. Quality Assessment. The quality of the included studies was assessed via the Newcastle–Ottawa scale (NOS), which provides separate quality assessment instruments for observational studies [22]. The NOS evaluates three major domains: participant selection, comparability of exposed and observation groups, and assessment of outcomes. The scale has a maximum score of 9 points, with NOS scores of 7–9 indicating high quality, scores of 4–6 indicating moderate quality, and scores of 1–3 indicating low quality [23]. Two authors (C.C. Huang and Y.H. Liu) independently assessed each study based on the NOS criteria, and discrepancies were discussed and resolved via consensus (Y.S. Horng).

2.6. Statistical Analyses. A traditional meta-analysis was initially performed to assess the associations of each risk factor (i.e., anxiety, depression, insomnia, and pain) with CRF among BCSs. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to quantify the associations between risk factors and CRF [24]. Pooled estimates of ORs across the included studies were obtained via a DerSimonian–Laird random-effects model. An OR greater than 1 indicated that the presence of risk factors was associated with the risk of CRF. A p-value of < 0.05 indicated that the pooled OR significantly deviated from the null value. Leave-one-out sensitivity analysis was performed to evaluate the robustness of the results by excluding one study at a time. Heterogeneity was examined via Cochran's Q statistic and the I^2 value. For the Q statistic, p values < 0.10 were considered to indicate statistically significant heterogeneity. For the I^2 statistic, a value of 0% indicated no heterogeneity, whereas 100% represented extreme heterogeneity. I^2 values of 25%, 50%, and 75% were generally interpreted as indicating low, moderate, and high heterogeneity, respectively [25, 26]. Subgroup analyses were performed based on different time points or NOS scores.

Meta-regression analysis was performed to examine whether any moderators impacted the association between risk factors and CRF. Potential moderators included mean age, percentage of chemotherapy, prevalence of fatigue, and the NOS score, all of which were treated as continuous variables in our meta-regression. Publication bias was examined using funnel plots, and asymmetry of the funnel plots was detected by Egger's test ($p < 0.1$ was considered to indicate statistical significance) [27].

To enhance the analysis, an NMA was conducted to compare the relative importance and significance of various risk factors for CRF. A frequentist approach was performed using the R package "netmeta" [28]. Patients without the presence of a risk factor were considered the reference group. Cochrane's Q statistics and I^2 values were used as measures of heterogeneity and inconsistency. Additionally, a design-based decomposition of Cochran's Q was performed to divide the Q statistic into between-design inconsistency and within-design heterogeneity [29]. The rankings of the treatments were calculated using P-scores, with a relatively high probability indicating prominence, which was analogous to the surface under the cumulative ranking (SUCRA) curve method in Bayesian NMA [30]. All analyses were performed using R version 4.0.3 and Comprehensive Meta-Analysis, version 4.0 (Biostat, Englewood, NJ, USA).

3. Results

3.1. Baseline Characteristics. This study included 30 observational studies (with a total of 36,302 participants) published between 2004 and 2024 [6, 31–59] (Table 1). The data collection period spanned from 1993 to 2017. The distribution of studies by publication period was as follows: 3 (10%) studies published from 2000 to 2005, 6 (20%) studies published from 2006 to 2010, 7 (23%) studies published from 2011 to 2015, 6 (20%) studies published from 2016 to 2020, and 8 (27%) studies published from 2021 to 2024. The baseline age of the participants ranged from 40 to 79 years, with the largest proportion in the 55–59 age group (43%). The mean age across studies was 57.57 years.

The sample size varied across studies, with 16 studies (53%) including 100–1000 participants, 10 studies (33%) including 1000–5000 participants, and 1 study (3%) including 5000–10,000 participants. The follow-up duration also varied, with 14 studies (47%) reporting a follow-up duration of less than 1 year, 9 studies (30%) reporting a follow-up duration between 1 and 5 years, and 7 studies (23%) reporting a follow-up duration exceeding 5 years, with follow-up periods ranging from 0.27 to 10.5 years post-treatment (mean follow-up: 2.44 years post-treatment). In terms of study design, 18 studies (60%) were longitudinal, whereas 12 studies (40%) were cross-sectional. The reported prevalence of CRF varied widely across studies. The most common fatigue prevalence range was 30%–40% (47%), followed by 50%–60% (20%). The pooled prevalence of CRF was 40.6%.

The included studies were conducted across five continents and 11 countries, with the majority of studies conducted in Europe (15 studies, 50%), followed by North America (9 studies, 30%), Oceania (4 studies, 13%), South America (1 study, 3%), and Asia (1 study, 3%). Among the European studies, one was conducted in the Netherlands, four in France, three in Germany, one in Ireland, one in Italy, four in Norway, and one in Spain. Additionally, nine studies were conducted in the United States, one in Brazil, and one in South Korea. The study selection process is illustrated in the PRISMA flowchart (Figure 1).

Table 1: The demographic characteristics of included studies (July 2004 to November 2024).

Author, year	Nation	Subject (N)	Age (y)	Design	Extracted risk factor	Time points (y)	NOS score	Quality rating	Percentage of C/T	Prevalence of CRF
Bennett 2004	Australia	109	52.8	CS	Depression	1	8	High	79%	37%
Andrykowski 2005	USA	288	54.5	L	Depression	0.27	8	High	52%	26%
Nieboer 2005	Dutch	430	45	L	Pain	1	9	High	20%	20%
Goldstein 2006	Australia	176	56	L	Depression	0.83	8	High	49%	49%
Bower 2006	USA	763	59	L	Pain	5.6	8	High	21%	34%
Meeske 2007	USA	800	55	CS	Depression & pain	2.7	8	High	31%	41%
Kim 2008	Korea	1933	47	CS	Insomnia & pain	4.6	9	High	28.6%	66%
Andrykowski 2010	USA	304	54.8	L	Depression	0.5	9	High	48.2%	9%
Reinertsen 2010	Norway	249	55	L	Depression & pain	4	8	High	79.9%	33%
Reinertsen 2011	Norway	302	55	CS	Anxiety & depression	4	9	High	87%	33%
Noal 2011	France	294	56	L	Anxiety & depression	1	8	High	54%	40%
Myers 2012	USA	18	44	CS	Anxiety & depression & insomnia	0.8	5	Moderate	100%	55.6%
Goldstein 2012	Australia	218	52	L	Depression	1	9	High	65.1%	8%
Garabeli 2012	Brazil	202	51	CS	Insomnia & pain	4.2	8	High	66.3%	37.6%
Romito 2012	Italy	255	58	CS	Insomnia	10.5	8	High	82%	34%
Pertl 2013	Ireland	61	50.15	L	Depression	0.44	6	Moderate	100%	52.2%
Reinertsen 2017	Norway	84	50	L	Insomnia & pain	1.3	8	High	100%	36%
Kühl 2018	Germany	1389	63	L	Depression & pain	5.5	8	High	NM	33.9%
Mao 2018	USA	1103	63	CS	Insomnia & pain	1	7	High	51.5%	56%
Lee 2020	USA	2799	60	L	Anxiety	1	8	High	49%	30%
Puigpinós 2020	Spain	2235	NM	CS	Anxiety & depression	5.9	7	High	NM	83.8%
Bjerkeset 2020	Norway	834	55	CS	Anxiety & pain	4.1	6	Moderate	37%	52%
Maurer 2021	Germany	1292	62	L	Depression	5.5	7	High	NM	36.1%
Bean 2021	Australia	460	55	L	Depression & insomnia	1	7	High	53.8%	53.9%
Haque 2021	USA	315	71	CS	Depression & insomnia	5.6	5	Moderate	29.5%	38%
Di Meglio 2022	France	7902	56.2	L	Anxiety & depression	1	9	High	47.4%	36.4%
Ghannam 2022	France	3295	57	L	Anxiety & depression	0.3	8	High	52.5%	33.3%
Rosas 2023	USA	2059	58.2	L	Depression	2	8	High	30%	23.2%
Di Meglio 2024	France	4262	57.9	CS	Anxiety & depression	1.3	9	High	44.1%	34.4%
Schmidt 2024	Germany	1871	67.3	L	Depression	5.3	9	High	NM	53.9%

Note: Time points: the specific years post-treatment at which measurements were taken. Quality rating: assessed using the Newcastle–Ottawa Scale (NOS) score. CS, cross-sectional study; L, longitudinal study; C/T, chemotherapy.

Abbreviations: CRF, cancer-related fatigue; NM, not mentioned; NOS, Newcastle–Ottawa Scale.

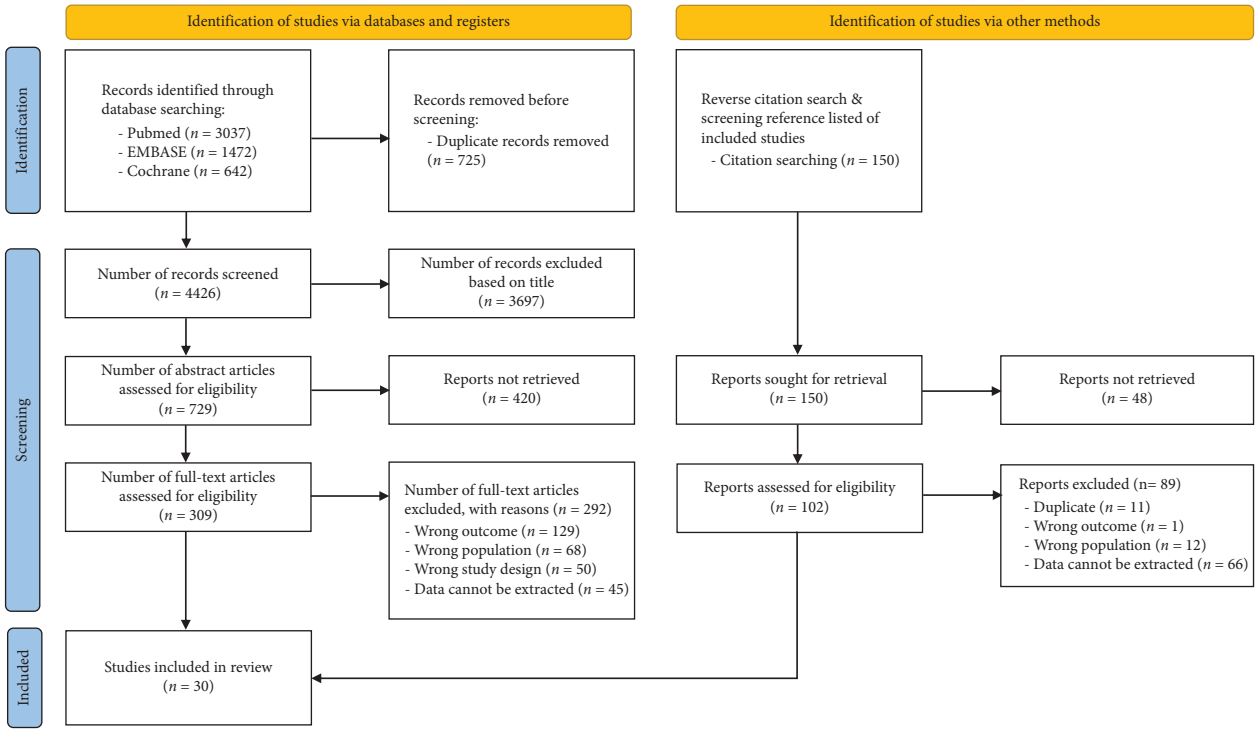


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram for the study selection process.

3.2. Assessment Results of Quality. The quality of the studies included was evaluated using the NOS score, with 26 (87%) studies classified as high quality. Most studies (73%) had high NOS scores (8–9), while 6 (20%) studies had scores of 6–7, and 3 (10%) studies had scores of 3–5. The mean NOS score was 7.8, indicating that the majority of the included studies exhibited moderate to high methodological quality. The quality of four studies was moderate due to their small sample size, lack of a control group, subjective outcome measures, and potential selection bias [43, 45, 49, 53]. Further details on the quality assessment are provided in Supporting Table 2.

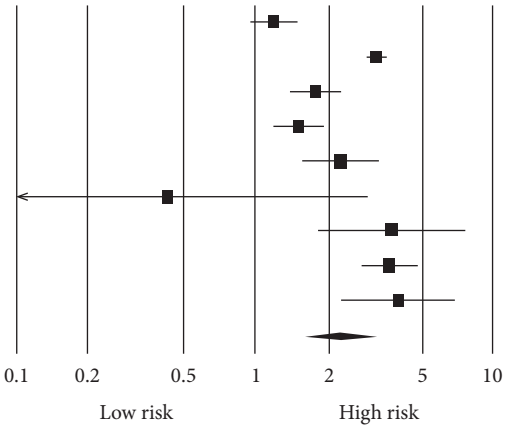
3.3. Results of the Meta-Analysis. Figure 2 presents the main effects, forest plots, and within-group heterogeneity of the 30 included studies. The analysis revealed four factors significantly associated with CRF ($p < 0.001$), with ORs greater than 1, indicating a positive relationship with CRF. Compared with the observation group, depression (OR = 3.702, 95% CI 2.609–5.251, $p < 0.001$) had the most significant effect on CRF. However, depression ($I^2 = 91.344\%$), anxiety ($I^2 = 92.120\%$), and pain ($I^2 = 86.667\%$) exhibited high heterogeneity ($I^2 > 75\%$), indicating substantial variability across studies, whereas insomnia ($I^2 = 41.837\%$) demonstrated moderate heterogeneity, suggesting greater consistency in the study results [26]. The funnel plot (Figure 3) displays the OR on the horizontal axis and the standard error on the vertical axis. Egger's weighted regression test further confirmed the symmetry of the funnel plot, indicating that there was no significant publication bias ($p > 0.10$).

3.4. Results of NMA. A network diagram (Figure 4(a)) was constructed to illustrate the direct and indirect comparisons among the included studies. Each node represented a risk factor, and the edges indicated available comparisons, with edge thickness proportional to the number of studies contributing to each comparison [60]. The pairwise comparison results are presented in Figure 4(b), and the forest plot of the NMA with the P-score rankings is shown in Figure 4(c). The results indicated that depression had the strongest association with CRF (highest P-score = 0.9727), followed by insomnia, pain, and anxiety. The tests for heterogeneity and inconsistency in the NMA revealed significant heterogeneity in terms of both within-design ($Q = 203.57$, df = 27, $p < 0.001$) and between-design heterogeneity ($Q = 182.24$, df = 13, $p < 0.001$).

3.5. Subgroup Analyses. Subgroup analysis (Tables 2 and 3) was performed based on different follow-up durations (< 1 year, 1–5 years, and > 5 years). As shown in Table 2, most ORs for the four risk factors remained significant across the three follow-up durations with the exception of anxiety at < 1 year (OR 1.775, $p = 0.058$), insomnia at < 1 year (OR 1.165, $p = 0.503$), and pain at > 5 years (OR 1.235, $p = 0.660$). These findings suggested that the effects of anxiety and insomnia on CRF were less pronounced in the early post-treatment phase, whereas the effect of pain on CRF was initially high but diminished over time.

We also performed subgroup analysis on the basis of the quality of the articles (NOS score, high quality vs. moderate quality; Table 3). The associations between the four risk

First author (year)	Statistics for each study					Odds ratio with 95% CI
	Odds ratio	Lower limit	Upper limit	*Z*-Value	*p*-Value	
Bjerkeset, 2020	1.186	0.941	1.494	1.445	0.148	
Di Meglio, 2022	3.192	2.900	3.512	23.747	< 0.001	
Di Meglio, 2024	1.770	1.370	2.287	4.371	< 0.001	
Ghannam, 2022	1.507	1.179	1.927	3.272	0.001	
Lee, 2020	2.245	1.541	3.271	4.210	< 0.001	
Myers, 2012	0.429	0.062	2.972	−0.858	0.391	
Noal, 2011	3.670	1.809	7.446	3.602	< 0.001	
Puigpinos-Riera, 2020	3.608	2.724	4.778	8.948	< 0.001	
Reinertsen, 2011	3.915	2.268	6.761	4.898	< 0.001	
Total pooled effect	2.247	1.600	3.155	4.675	< 0.001	

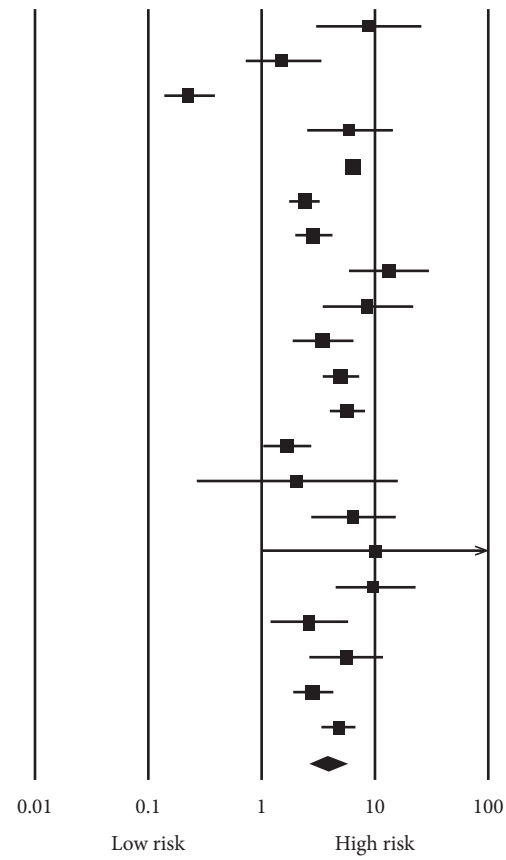


Heterogeneity test

$Q = 101.543$, df = 8, $p < 0.001$, $I^2 = 92.12\%$

(a)

First author (year)	Statistics for each study					Odds ratio with 95% CI
	Odds ratio	Lower limit	Upper limit	*Z*-Value	*p*-Value	
Andrykowski 2005	8.723	2.993	25.422	3.969	< 0.001	
Andrykowski, 2010	1.510	0.703	3.244	1.056	0.291	
Bean, 2021	0.223	0.134	0.370	−5.799	< 0.001	
Bennett 2004	5.806	2.406	14.006	3.914	< 0.001	
Di Meglio, 2022	6.134	5.415	6.949	28.510	< 0.001	
Di Meglio, 2024	2.315	1.704	3.145	5.372	< 0.001	
Ghannam, 2022	2.779	1.896	4.073	5.240	< 0.001	
Goldstein, 2006	12.848	5.842	28.256	6.350	< 0.001	
Goldstein, 2012	8.286	3.332	20.606	4.549	< 0.001	
Haque, 2021	3.400	1.850	6.249	3.940	< 0.001	
Kuhl, 2018	4.914	3.535	6.830	9.474	< 0.001	
Maurer, 2021	5.494	3.819	7.903	9.185	< 0.001	
Meeske, 2007	1.670	1.027	2.716	2.067	0.039	
Myers, 2012	2.000	0.260	15.381	0.666	0.505	
Noal, 2011	6.310	2.680	14.858	4.216	< 0.001	
Pertl, 2013	10.000	0.957	104.490	1.923	0.054	
Puigpinos-Riera, 2020	9.738	4.294	22.085	5.448	< 0.001	
Reinertsen, 2010	2.570	1.180	5.599	2.376	0.018	
Reinertsen, 2011	5.384	2.515	11.525	4,335	< 0.001	
Rosas, 2023	2.790	1.866	4.170	5.001	< 0.001	
Schmidt, 2024	4.674	3.358	6.505	9.143	< 0.001	
Total pooled effect	3.702	2.609	5.251	7.337	< 0.001	



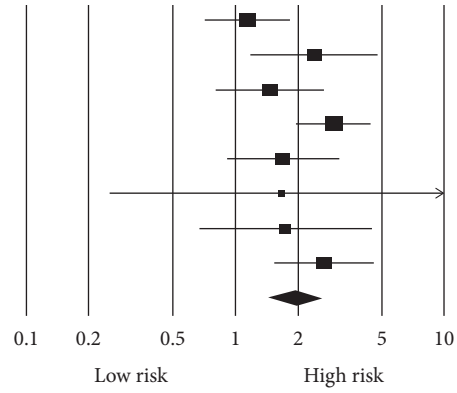
Heterogeneity test

$Q = 231.054$, df = 20, $p < 0.001$, $I^2 = 91.34\%$

(b)

Figure 2: Continued.

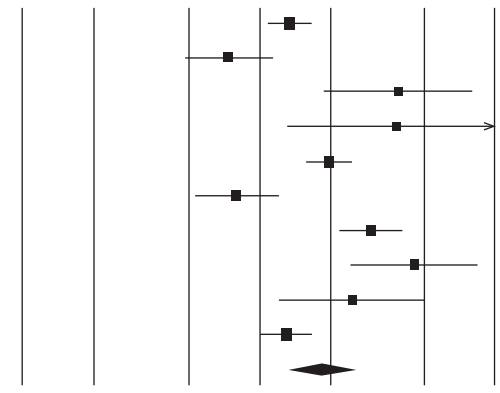
First author (year)	Statistics for each study					Odds ratio with 95% CI
	Odds ratio	Lower limit	Upper limit	*Z*-Value	*p*-Value	
Bean, 2021	1.140	0.720	1.806	0.560	0.575	
Garabeli, 2012	2.400	1.188	4.850	2.439	0.015	
Haque, 2021	1.470	0.810	2.669	1.266	0.205	
Kim, 2008	2.980	1.979	4.488	5.228	< 0.001	
Mao, 2018	1.716	0.925	3.182	1.713	0.087	
Myers, 2012	1.667	0.251	11.071	0.529	0.597	
Reinertsen, 2017	1.750	0.678	4.517	1.157	0.247	
Romito, 2012	2.664	1.542	4.601	3.513	<0.001	
Total pooled effect	1.932	1.444	2.586	4.430	< 0.001	



Heterogeneity test
$Q = 12.035$, df = 7, $p = 0.099$, $I^2 = 41.84\%$

(c)

First author (year)	Statistics for each study					Odds ratio with 95% CI
	Odds ratio	Lower limit	Upper limit	*Z*-Value	*p*-Value	
Bjerkeset, 2020	1.348	1.092	1.665	2.776	0.006	
Bower 2006	0.750	0.487	1.154	–1.309	0.191	
Garabeli, 2012	3.870	1.878	7.973	3.669	< 0.001	
Kim, 2008	3.800	1.322	10.920	2,479	0.013	
Kuhl, 2018	1.961	1.564	2.459	5.838	< 0.001	
Mao, 2018	0.805	0.534	1.214	–1.033	0.301	
Meeske, 2007	2.964	2.193	4.007	7.066	< 0.001	
Nieboer 2005	4.511	2.425	8.391	4.758	< 0.001	
Reinertsen, 2010	2.490	1.226	5.055	2.525	0.012	
Reinertsen, 2017	1.300	1.016	1.663	2.086	0.037	
Total pooled effect	1.841	1.332	2.545	3.697	< 0.001	



Heterogeneity test
$Q = 67.481$, df = 9, $p < 0.001$, $I^2 = 86.66\%$

(d)

Figure 2: Forest plots for the association between cancer-related fatigue and risk factors. (a) Anxiety. (b) Depression. (c) Insomnia. (d) Pain.

factors and CRF remained significant for high-quality studies; however, the associations of insomnia and anxiety with CRF were nonsignificant for moderate-quality studies. Findings from higher-quality studies were more consistent with established evidence, suggesting that higher methodological quality yielded more accurate and unbiased results.

3.6. Sensitivity Analysis. To examine the consistency of the findings, leave-one-out sensitivity analysis was conducted. In this approach, individual studies were removed from the meta-analysis one at a time, and the pooled effect sizes for anxiety, depression, insomnia, and pain were recalculated to determine whether the exclusion of any single study significantly altered the overall estimates. We then checked both fixed-effects and random-effects models to examine the consistency of the results. Notably, the exclusion of studies by Di Meglio 2022 (a large cohort with 7902 cases), Haque 2021 (which had the highest mean age of 71 years), and Puigpinós-Riera 2020 (which did not report participant age) had no effect on the pooled estimates, thus reinforcing the robustness of the findings. The detailed results are presented in Supporting Table 3.

3.7. Meta-Regression. The associations between each risk factor and CRF were evaluated by meta-regression to examine the moderating effects of four covariates (mean age, percentage of patients receiving chemotherapy, NOS score, and prevalence of CRF) (Table 4). Studies with higher NOS scores revealed significantly positive associations between anxiety and CRF ($\beta = 0.305$, $p = 0.010$) and between insomnia and CRF ($\beta = 0.221$, $p = 0.009$); these findings suggested that high-quality studies were more likely to

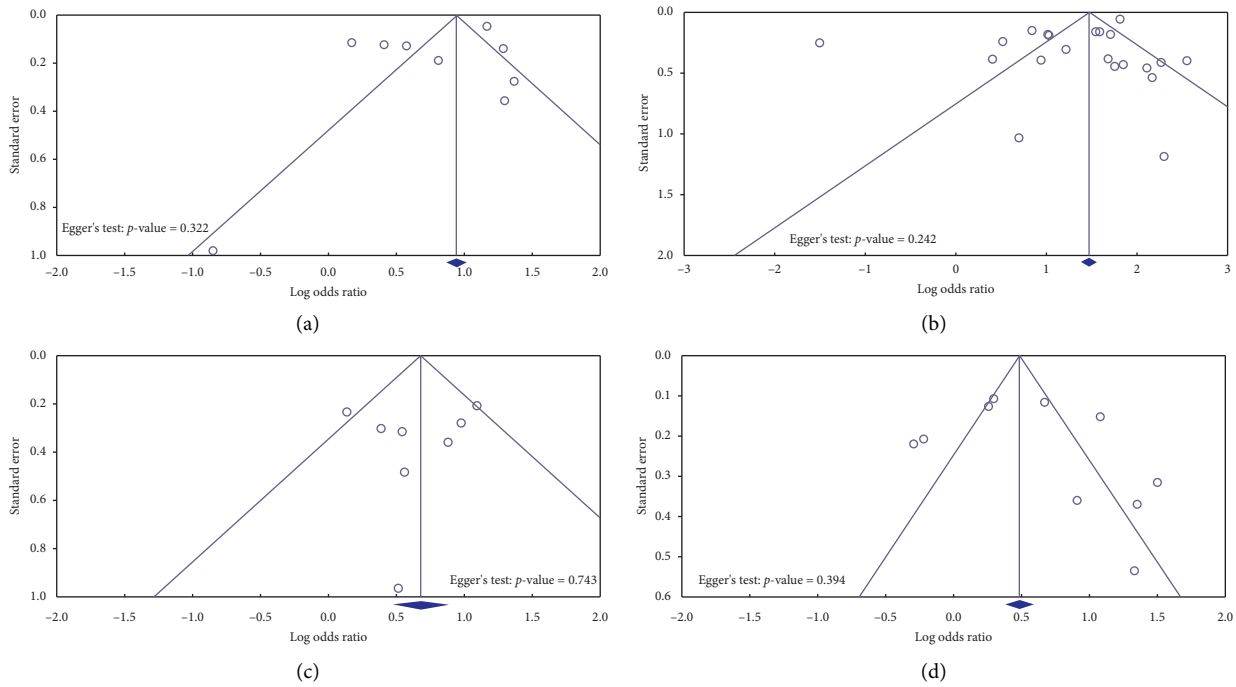


FIGURE 3: Funnel plots and Egger's test for publication bias in cancer-related fatigue risk factors. (a) Anxiety, p-value = 0.322. (b) Depression, p-value = 0.242. (c) Insomnia, p-value = 0.743. (d) Pain, p-value = 0.394.

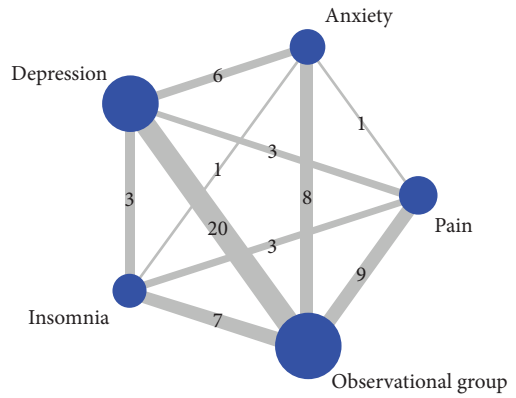
report stronger relationships between CRF and these risk factors than low-quality studies.

In contrast, the proportion of chemotherapy patients and the prevalence of CRF did not significantly influence the heterogeneity across studies (all p values > 0.05), indicating that chemotherapy status alone was not a major risk factor for CRF. The detailed size-encoded scatter plots for each covariate, which were used to visualize the associations between risk factors and CRF, are presented in Supporting Figure 1.

4. Discussion

On the basis of the 30 included studies encompassing 36,302 patients, this study demonstrated that depression, insomnia, pain, and anxiety were significantly associated with CRF among BCSs. Among these risk factors, depression had the highest OR and P-score, followed by insomnia, pain, and anxiety. These findings revealed that the mechanism underlying CRF is multifactorial, as shown in a previous meta-analysis of multiple cancer types, which identified insomnia, depression, and pain as key risk factors for CRF [8]. However, our study focused on breast cancer patients and provided a more detailed examination of the CRF within this population. Furthermore, the subgroup analyses indicated that even when the data were grouped by time points and study quality, the results were generally consistent with the main effect. High-quality studies have consistently demonstrated significant associations between CRF and four factors (depression, insomnia, pain, and anxiety), which implies that the results tend to be more significant in studies with more rigorous methodologies [61]. In contrast, the associations between anxiety/insomnia and CRF in the moderate-quality subgroups were both nonsignificant. Methodological quality might influence the statistical power for detecting the associations between CRF and risk factors [62]. This could be attributed to variations in study design, measurement tools, or unmeasured confounders, leading to misclassification biases and reduced statistical power in moderate-quality studies [62–64].

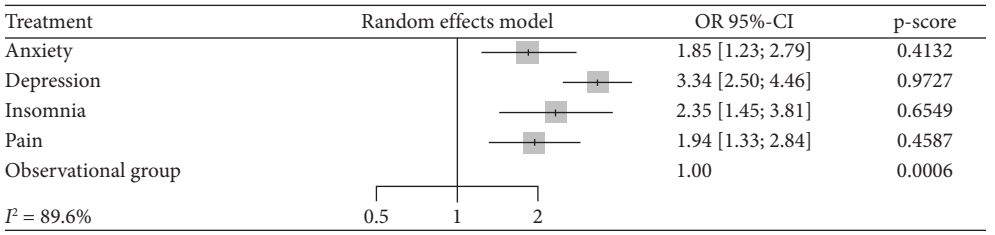
The time point-stratified subgroup analysis, which was based on different follow-up durations (0–1 year, 1–5 years, and > 5 years), further revealed time-dependent variations in the associations. As shown in Table 4, most ORs for the four risk factors remained significant at all three follow-up time points with the exception of anxiety and insomnia at < 1 year and pain at > 5 years. These findings suggested that the impact of anxiety and insomnia on CRF might be less pronounced in the early posttreatment phase, whereas the effect of pain on CRF was initially high but diminished over time. In the early posttreatment stage, the side effects of cancer treatment and short-term physiological stress might overshadow the effects of insomnia on fatigue [65, 66]. An observational study of BCSs reported that good sleepers were likely to remain good sleepers (80.0%–87.1%) at subsequent time points, whereas poor sleepers (20.6%) were likely to experience worse sleep disturbances even at 18 months posttreatment [67]. Conversely, the OR of pain on CRF was high in the < 1-year subgroup (OR 4.511, $p < 0.001$), subsequently decreased over time and became nonsignificant in the > 5-year subgroup (OR 1.235, $p = 0.660$). This finding could be attributed to improvements in pain management strategies or to long-term physiological adaptations [68, 69].



(a)

Depression				
1.42 (0.84, 2.42)	Insomnia			
1.72 (1.11, 2.67)	1.21 (0.69, 2.12)	Pain		
1.81 (1.16, 2.80)	1.27 (0.69, 2.36)	1.05 (0.62, 1.79)	Anxiety	
3.34 (2.50, 4.46)	2.35 (1.45, 3.81)	1.94 (1.33, 2.84)	1.85 (1.23, 2.79)	Observation

(b)



(c)

Figure 4: Results of network meta-analysis for the risk factors of cancer-related fatigue. (a) Network map of the included studies. Note: Direct comparisons are shown by the gray lines connecting different risk factors. Line width is proportional to the number of studies, and the node size is proportional to the sample size of patients for each risk factor in the network. (b) Relative effect sizes of risk factors for cancer-related fatigue according to network meta-analysis. Note: Risk factors are ordered in the rank of their chance of being the best risk factor. Significant pairwise comparisons are highlighted in bold. (c) The network meta-analysis examined the association between cancer-related fatigue and anxiety, depression, pain, and insomnia. Note: The table also presents the ranking of risk factors for CRF, compared to observation, based on P-scores.

Table 2: Subgroup meta-analysis stratified by post-treatment time points and study quality. Subgroup analysis—influence of post-treatment time points on the prevalence and risk factors for cancer-related fatigue.

Risk factors	Group by time point	Number of studies	Effect size				
			OR	95% CI		Z	*p* value
Anxiety	0–1 year	5	1.775	0.980	3.215	1.895	**0.058**
	1–5 year	3	1.905	1.123	3.231	2.390	0.017
	> 5 year	1	3.608	2.724	4.778	8.948	< 0.001
Depression	0–1 year	11	3.804	1.792	8.073	3.479	0.001
	1–5 year	7	4.784	2.531	9.043	4.818	< 0.001
	> 5 year	5	4.990	4.095	6.080	15.934	< 0.001
Insomnia	0–1 year	2	1.165	0.745	1.821	0.669	**0.503**
	1–5 year	4	2.412	1.801	3.231	5.909	< 0.001
	> 5 year	2	2.004	1.120	3.586	2.340	0.019
Pain	0–1 year	1	4.511	2.425	8.390	4.759	< 0.001
	1–5 year	10	2.101	1.413	3.123	3.667	< 0.001
	> 5 year	2	1.235	0.482	3.166	0.440	**0.660**

Note: The bold text indicated nonsignificant outcomes.

Table 3: Subgroup meta-analysis stratified by post-treatment time points and study quality. Subgroup analysis—Influence of study quality on the association between risk factors and cancer-related fatigue.

Risk factors	Group by quality	Number of studies	Effect size				
			OR	95% CI		Z	*P*-value
Anxiety	High	7	2.586	1.917	3.488	6.223	< 0.001
	Moderate	2	1.144	0.791	1.655	0.713	**0.476**
Depression	High	18	3.708	2.554	5.383	6.889	< 0.001
	Moderate	3	3.475	1.973	6.121	4.313	< 0.001
Insomnia	High	6	2.025	1.429	2.870	3.968	< 0.001
	Moderate	2	1.487	0.842	2.626	1.366	**0.172**
Pain	High	9	1.948	1.326	2.863	3.396	0.001
	Moderate	1	1.348	1.092	1.665	2.776	0.006

Note: The bold text indicated nonsignificant outcomes.

Table 4: Results of random-effects meta-regression models.

Risk factors	Covariates	β	SE	95% CI	95% CI	Z	*p*-value
Anxiety	Age (year)	0.077	0.073	−0.066	0.220	1.050	0.292
	Chemotherapy (%)	0.006	0.012	−0.017	0.029	0.500	0.614
	NOS	**0.305**	0.119	0.072	0.538	2.570	**0.010**
	Prevalence (%)	−0.038	0.024	−0.086	0.010	−1.540	0.123
Depression	Age (year)	−0.008	0.051	−0.107	0.091	−0.160	0.877
	Chemotherapy (%)	0.006	0.012	−0.018	0.031	0.520	0.606
	NOS	0.167	0.196	−0.217	0.551	0.850	0.394
	Prevalence (%)	−0.016	0.019	−0.053	0.021	−0.850	0.393
Insomnia	Age (year)	−0.021	0.018	−0.056	0.014	−1.190	0.232
	Chemotherapy (%)	0.0001	0.007	−0.013	0.014	0.020	0.987
	NOS	**0.221**	0.085	0.055	0.387	2.610	**0.009**
	Prevalence (%)	0.002	0.014	−0.025	0.029	0.150	0.881
Pain	**Age (year)**	**−0.093**	0.034	−0.160	−0.025	−2.700	**0.007**
	Chemotherapy (%)	−0.003	0.008	−0.018	0.013	−0.300	0.761
	NOS	0.423	0.237	−0.041	0.887	1.790	0.074
	Prevalence (%)	−0.014	0.017	−0.047	0.019	−0.850	0.394

Note: "Age" referred to the mean age of the study populations included. "Chemotherapy" represented the proportion of the population that completed chemotherapy. "Prevalence" indicated the prevalence of fatigue in the studies included. The bold text indicates significant outcomes.

Our meta-analysis revealed substantial heterogeneity ($I^2 > 75\%$) in the main effect. Meta-regression analysis revealed significant correlations between insomnia and NOS scores as well as between anxiety and NOS scores. Specifically, for each 1-point increase in the NOS score, the association between insomnia and CRF (measured by effect sizes such as the log OR) increased by 0.221. In contrast, the associations between depression and CRF were not affected by the NOS score, the prevalence of fatigue, the percentage of patients who received chemotherapy, or age. Moreover, subgroup analysis revealed that the OR of depression increased over time and remained significant across the three time points; therefore, depression was the strongest risk factor for CRF. On the other hand, the meta-analysis revealed that age was negatively associated with the log OR of pain on CRF ($\beta = -0.093$, $p = 0.007$), which indicated that older individuals might have reported lower levels of pain-related CRF. This phenomenon might be explained by the degeneration of the nervous system in old individuals, which decreases the nerve conduction velocity and increases the pain threshold [70, 71].

Despite our study showing no publication bias, as indicated by the symmetry of the funnel plot, and sensitivity analyses confirming the robustness of the main findings, the observed heterogeneity may have been due to the different measurement tools used in the 30 included studies (e.g., FACT-F, Brief Fatigue Inventory, EORTC QLQ-C30), lifestyle factors (e.g., physical activity, nutrition), socioeconomic status, and treatment histories [14, 63, 72]. Moreover, the majority of the included studies were conducted in Europe (50%) and North America (30%), whereas Asia (3%) and South America (3%) were significantly underrepresented. This geographic imbalance might limit the generalizability of the findings to populations outside Western countries, particularly in regions with different healthcare systems, cultural influences, and genetic predispositions affecting CRF.

4.1. Clinical Implications. In our study, the prevalence of fatigue was 40.6%, which was not significantly different from previous findings. A meta-analysis of 18 studies focusing on cancer survivors reported a CRF incidence of 42.2% [13].

Moreover, a meta-analysis of longitudinal studies revealed a substantial decrease in the prevalence of severe fatigue during the first half-year after treatment completion; however, fatigue levels appeared to remain relatively high when assessed approximately 5 years after cancer treatment [12]. This raised an important question of how to support patients effectively in terms of reducing long-term CRF and improving their quality of life.

Previous studies reported that the mechanism of CRF is related to the dysregulation of proinflammatory cytokines (including IL-1β, IL-6, and TNF-α) [66, 73, 74], the hypothalamic–pituitary–adrenal (HPA) axis [75], circadian rhythm desynchronization [76], skeletal muscle wasting [77], and genetic dysregulation [78]. Proinflammatory cytokines such as IL-6, TNF-α, and CRP are significantly elevated in cancer patients experiencing both depression and CRF, suggesting that systemic inflammation plays a key role in the pathogenesis of these symptoms [45]. However, fatigue is rarely an isolated symptom and most commonly occurs with other symptoms, such as pain, emotional distress, anxiety, depression, anemia, and sleep disturbances, forming symptom clusters. For example, pain and fatigue could have a synergistic effect that worsens the overall symptom experience [79, 80]. Therefore, patients should be screened for multiple symptoms during clinical assessment.

The findings from our study indicated that depression had the strongest association with CRF and should have been prioritized as a primary target for intervention. Routine assessments of depression alongside CRF and the implementation of effective treatment strategies are essential [81]. Previous evidence suggested that both antidepressants medication and psychological interventions such as music therapy during radiation treatment or psychoeducational curriculum were beneficial for alleviating CRF [82–92].

Additionally, factors associated with the development of chronic cancer-related pain include chemotherapy (e.g., painful peripheral neuropathy), radiation (e.g., brachial plexopathy), and surgery (e.g., mastectomy pain) [93]. Effective pain management strategies (e.g., palliative radiation, nerve blocks, or epidural management) and anti-inflammatory medicine have been shown to reduce the burden of fatigue [5, 94–98]. While our study revealed that pain-related CRF might diminish over time, the association between pain and CRF might be influenced by long-term physiological adaptations, which could contribute to pain reduction in BCSs [69].

For insomnia, several published studies support the conclusion that nonpharmacological interventions (e.g., cognitive behavioral therapy for insomnia [CBT-I], stimulus control, sleep restriction, and sleep hygiene) designed to optimize sleep quality in patients who complete cancer treatment may improve fatigue [82, 99–104]. CBT-I is based on a straightforward, common-sense model of relationships among cognition, emotion, and behavior, which is recommended by NCCN survivorship guidelines for fatigue [5]. Previous study revealed that a CBT-I program (6 weekly self-guided modules plus online clinician support) was effective in reducing the burden of insomnia in cancer survivors [104]. Another study also found that CBT led to a median reduction in nightly wakefulness of nearly 1 hour, while the control group showed no change [105]. As pharmacological therapy, both sedative-hypnotics (46%) and analgesics (24%) were commonly used as sleep aids among breast cancer patients [106].

Our findings highlight the critical roles of depression, pain, insomnia, and anxiety in the development and persistence of CRF. Targeting these factors through comprehensive, multidisciplinary approaches might lead to improved fatigue management and overall well-being in BCSs.

4.2. Strengths and Limitations. The major strengths of our study included the large sample size (more than 36,302 BCSs), thus leading to robust statistical power. Additionally, we employed an NMA approach to systematically compare the relative importance of various risk factors for CRF. Furthermore, the included studies were of moderate to high quality, with most studies demonstrating strong methodological rigor, as reflected by 73% of the included studies receiving NOS scores of 8–9. Finally, by incorporating the most recent literature up to 2024, with 27% of the included articles published between 2021 and 2025, our study provides a comprehensive and up-to-date synthesis of existing evidence, laying a foundation for future clinical applications.

Some limitations of this study should be noted. One of the primary limitations was the difficulty in conducting subgroup analyses based on cancer stage and treatment regimens due to several factors. The reporting of cancer stage varied significantly across studies, with some studies using the TNM (tumor, node, or metastasis) classification, others employing broader stage groupings (e.g., early-stage vs. advanced-stage cancer), and some studies not reporting staging details at all. Similarly, subgroup analysis on the basis of cancer treatment was challenging owing to the wide variability in treatment regimens, including differences in chemotherapy protocols, radiotherapy doses, surgical approaches and hormone therapy use. Additionally, many patients receive multimodal therapy, making it difficult to isolate the effects of a single treatment type on CRF. Additionally, the studies in this meta-analysis were predominantly conducted in Western countries (Europe and North America), whereas Asia and South America were significantly underrepresented.

Furthermore, the use of various fatigue assessment tools across studies might have introduced measurement bias, as differences in scale sensitivity and cutoff values could have affected CRF prevalence and risk factor associations. Only peer-reviewed articles were included to enhance reliability, but this might reduce the sample size and exclude studies with negative results, contributing to publication bias. Given that the studies spanned several decades, advancements in cancer treatment, such as immunotherapy and targeted therapy, might have influenced CRF trajectories and risk factors. Finally, our analysis was limited to female BCSs, thus limiting its generalizability to other cancer populations.

Despite these challenges, future research could compare the effects of treating depression with those of treating insomnia or pain on CRF outcomes. Combined approaches

addressing both psychological and physical factors might have offered better management, whereas larger data sets could have enabled more precise subgroup analyses.

5. Conclusion

This study identified depression as the most influential risk factor for CRF in BCSs, followed by insomnia, pain, and anxiety, with CRF persisting from 3.6 months to 10.5 years after treatment. Step-by-step management of these symptoms, including psychological interventions, pharmacological treatments, and nonpharmacological strategies, may help control CRF and improve cancer survivorship outcomes. Future studies should explore multidisciplinary interventions and long-term CRF trajectories to develop more comprehensive fatigue management strategies for cancer survivors.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure

We affirmed that we had no financial affiliation (including research funding) or involvement with any commercial organization that had a direct financial interest in any matter included in this manuscript, except as disclose. All authors had read and approved the final version of manuscript to be submitted.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

Chih-Chieh Huang and Yu-Hsu Liu were involved in literature search, data acquisition, data analysis, and manuscript preparation. Yi-Shiung Horng was involved in study concepts, study design, literature search, manuscript preparation, and article editing.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information 1. 1. Supporting Appendix 1. PRISMA 2020 abstract checklist: All items on the abstract checklist were included in the abstract.

Supporting Information 2. 2. Supporting Appendix 2. MOOSE Checklist for Meta-analyses of Observational Studies: In line with the MOOSE recommendations, eligibility criteria, search strategy, data extraction, quality assessment, and statistical methods are all presented in the manuscript.

Supporting Information 3. 3. Supporting Appendix 3. PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis: In accordance with the PRISMA recommendations, all required items for reporting a network meta-analysis are presented in the manuscript.

Supporting Information 4. 4. Supporting Table 1. Detailed search strategy: A comprehensive and systematic search strategy was implemented across the PubMed, Cochrane Library, and EMBASE databases.

Supporting Information 5. 5. Supporting Table 2. Methodological quality of the selected studies according to the NOS (Newcastle–Ottawa Scale): The methodological quality of the included studies was assessed using the Newcastle–Ottawa Scale (NOS). The NOS is a tool for evaluating the quality of observational studies, comprising three domains, including selection of study groups, comparability between groups, and outcome. The quality of studies could be classified as high, moderate, or low quality.

Supporting Information 6. 6. Supporting Table 3. Sensitivity Analysis: Assessing the stability of findings using the leave-one-out method and comparing the impact of random-effects and fixed-effects models on the association between CRF and each RFs. 6.1 Supporting Table 3a. Sensitivity test—Leave-one-out method for anxiety outcome: In this analysis, each study is removed in turn, and the overall effect size recomputed to assess whether any single study disproportionately influences the pooled estimate. This table presents the leave-one-out sensitivity analysis for the anxiety outcome. 6.2 Supporting Table 3b. Sensitivity test—Leave-one-out method for depression outcome: In this analysis, each study is removed in turn, and the overall effect size recomputed to assess whether any single study disproportionately influences the pooled estimate. This table presents the leave-one-out sensitivity analysis for the depression outcome. 6.3 Supporting Table 3c. Sensitivity test—Leave-one-out method for insomnia outcome: In this analysis, each study is removed in turn, and the overall effect size recomputed to assess whether any single study disproportionately influences the pooled estimate. This table presents the leave-one-out sensitivity analysis for the insomnia

outcome. 6.4 Supporting Table 3d. Sensitivity test—Leave-one-out method for pain outcome: In this analysis, each study is removed in turn, and the overall effect size is recomputed to assess whether any single study disproportionately influences the pooled estimate. This table presents the leave-one-out sensitivity analysis for the pain outcome. 6.5 Supporting Table 3e. Sensitivity test—Sensitivity analysis across different statistical models: In this analysis, pooled effect sizes for each outcome were recalculated using multiple modeling approaches. Consistency of point estimates and confidence intervals across these models indicates that the meta-analytic findings are robust to different analytical assumptions.

Supporting Information 7. 7. Supporting Figure 1. Size-encoded scatter plot of meta-regression: A size-encoded scatter plot of meta-regression was used to examine whether potential moderators influenced the association between risk factors and cancer-related fatigue (CRF). The *X*-axis represents continuous variables, including mean age, chemotherapy proportion, NOS score, and fatigue prevalence, while the *Y*-axis represents for the log odds ratio. A total of four risk factors (anxiety, depression, insomnia, and pain) were analyzed in the meta-regression. The size of each bubble corresponds to the study weight. 7.1. Supporting Figure 1a. Regression analysis of the mean age of the included study populations on the log odds ratio of risk factors for CRF: Figure (a) shows the odds ratio of anxiety increased with age. Figure (b) shows the odds ratio of depression decreased with age. Figure (c) shows the odds ratio of insomnia decreased with age. Figure (d) shows the odds ratio of pain decreased with age. 7.2. Supporting Figure 1b. Regression analysis of the percentage of the included population that received chemotherapy for breast cancer on the log odds ratio of risk factors for CRF. Figure (a) shows the odds ratio of anxiety increased with the percentage of chemotherapy. Figure (b) shows the odds ratio of depression increased with the percentage of chemotherapy. Figure (c) shows the odds ratio of insomnia have no changes with the percentage of chemotherapy. Figure (d) shows the odds ratio of pain decreased with the percentage of chemotherapy. 7.3. Supporting Figure 1c. Regression analysis of the NOS scores of the included studies on the log odds ratio of risk factors for CRF. Figure (a) shows the odds ratio of anxiety increases with the NOS score. Figure (b) shows the odds ratio of depression increases with the NOS score. Figure (c) shows how the odds ratio of insomnia increases with the NOS score. Figure (d) shows how the odds ratio of pain increases with the NOS score. 7.4. Supporting Figure 1d. Regression analysis of fatigue prevalence in the included studies on the log odds ratio of risk factors for CRF. Figure (a) shows the odds ratio of anxiety decreases with the prevalence of CRF. Figure (b) shows the odds ratio of depression decreases with the prevalence of CRF. Figure (c) shows the odds ratio of insomnia increases with the prevalence of CRF. Figure (d) shows how the odds ratio of pain decreases with the prevalence of CRF.

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