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Review Article

Psychoneuroimmunological Markers of Psychological Intervention in Pediatric Cancer: A Systematic Review and New Integrative Model

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SUMMARY

Purpose: Pediatric cancer is a serious problem and still becomes a global challenge today. Various complex stressors due to diagnosis, disease symptoms, and various side-effects from the treatment that children with cancer undergo will cause problems in the child's psychoneuroimmunological aspects. Psychological interventions designed to modulate the stress response include psychoneuroimmunological markers. Unfortunately, there is little evidence to support the effect of psychological interventions on psychoneuroimmunological markers. This systematic review aims to assess the effectiveness of psychological interventions on psychoneuroimmunological markers in children with cancer and to provide a new integrative model for further research.

Methods: This systematic review uses four main databases (Scopus, PubMed, ScienceDirect, and ProQuest). The guideline used Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Selecting articles used the Rayyan application. The quality study was conducted using Joanna Briggs Institute (JBI)'s critical appraisal tools. The data were analyzed using the population, intervention, comparison, outcome, and study design (PICO) Synthesis based on similarities and differences in study characteristics to interpret the results.

Results: The search results in this systematic review found 1653 articles, 21 of which matched the predetermined inclusion and exclusion criteria. Most of the designs used were randomized controlled trials (57.1%). Massage therapy was the most common type of psychological intervention (14.2%). Almost half of the studies measured psychological responses (38.0%), and psycho-physiological responses (42.9%), and only a small proportion assessed the effectiveness of psychological interventions on neuroimmunological markers in pediatric cancer.

Conclusions: We recommend the use of psychological interventions as an additional intervention in managing psychoneuroimmunological markers of pediatric cancer. This study offers a new integrative model demonstrating the interaction between stress and psychological intervention involving neuroendocrine and immune mechanisms. However, future researchers need to test all domains of these new integrative models. This will reveal the complex interactions among these components and understand their relevance to health outcomes.

Introduction

Cancer ranks as the second most prevalent cause of mortality among children aged 1 to 14 years, following accidents. According to available data, it is projected that around 1040 children below the age of 15 in the United States will experience mortality due to cancer in the year 2023 [1]. Multiple empirical studies have

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indicated that the well-being of children and their families can be adversely affected by diseases and adverse effects associated with different forms of cancer treatment, including chemotherapy, radiation therapy, surgery, and bone marrow transplants [1–4]. The administration of the treatment can exacerbate the symptoms of heightened distress that are commonly linked to the adverse effects of the treatment and its toxic properties [5]. In addition to the physical manifestations of the disease and the adverse effects of the treatment regimen, pediatric cancer patients are subjected to an extensive period of hospitalization, which may elicit a range of emotional responses including fear, anger, and sadness [6]. According to previous research, children and adolescents diagnosed with cancer often describe experiencing both physical and psychosocial transformations resulting from their therapeutic interventions. Additionally, they frequently encounter stigmatization from others and express a strong desire to regain a sense of normalcy that they had prior to their illness [4].

The majority of pediatric patients diagnosed with cancer encounter at least one distressing symptom, with a significant proportion experiencing at least one highly distressing symptom [7]. According to prior studies, a significant majority of children undergoing cancer treatment exhibit various symptoms, including reduced appetite (87.0%) and pain (86.0%) [8]. Additionally, these children commonly experience fatigue, nausea, vomiting, and sleep disturbances [5,9,10]. A range of factors can contribute to the occurrence of stressful conditions in children. This finding is consistent with prior scholarly investigations, which elucidate that children diagnosed with cancer exhibit notable indications of anxiety, stress, and depression [11]. The presence of symptoms related to anxiety, stress, and depression during the course of treatment has the potential to adversely impact the overall quality of life experienced by individuals [12].

Numerous scholarly sources elucidate the significant advancements witnessed in the domain of pediatric cancer treatment and supportive care in recent decades. As a result, the current 5-year survival rate for pediatric cancer exceeds 80.0% [13]. This assertion is corroborated by additional research studies which have documented favorable outcomes among a significant number of pediatric cancer survivors subsequent to their treatment. Nevertheless, the majority of subgroups encountered psychological distress and a decline in health-related quality of life [14]. There exists a significant body of evidence within the cancer population that establishes a correlation between psychological stress and a decline in immune function [15]. The impact of psychological distress on the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been recognized, leading to disruptions in the integration of neurohormonal and immunological processes [13,16–18]. The occurrence of psychological stress prompts communication between the brain and the immune system, thereby exerting an influence on immune function. The bidirectional communication between the immune system and the brain is facilitated through reciprocal pathways. Both directions are associated with the progression of diseases. This becomes particularly pertinent in cases where the psychological stress persists over an extended period of time, or when there is a chronic activation of the immune system. In both scenarios, there is a decrease in both physical and mental activity, which has the potential to contribute to the development and progression of illness and disease [18,19].

The psychoneuroimmunological perspective is derived from the integration of psychological distress and the body's biological conditions [19]. Psychoneuroimmunology (PNI) is a discipline that investigates the impact of the interplay between psychological, neural, and immunological mechanisms on both human health and behavior [20–22]. Additional scholarly literature elucidates that PNI is a discipline that exhibits a strong interconnection with stress regulation, the intricate interplay between human behavior, and the intricate functioning of the nervous, endocrine, and immune systems [20–23]. This discipline encompasses the comprehension of the impact that thoughts, emotions, and behaviors can exert on the immune response and overall well-being [20–22]. In the field of pediatric oncology, research on psychoneuroimmunology (PNI) aims to elucidate the interplay between psychological factors, the nervous system, and the immune response, as well as their impact on cancer pathology and therapeutic interventions [24,25].

Several interventions have been devised to assist pediatric cancer patients in managing psychoneuroimmunological markers, with psychological interventions being one such approach. Nevertheless, there exists a lack of consensus regarding the precise delineation of the terminology associated with psychological intervention. According to a meta-review conducted by Hodges et al. [26] states that the description of the terms of intervention that are often used in research are ‘psychosocial’, psychological, psychotherapy, nonpharmacological, behavioral, supportive, psychoeducational, psychosomatic, psychiatric, and noninvasive. Hoffman et al. [27] define psychological interventions as a method or strategy used to manage a person's physical, psychological, and neurocognitive response interventions. These interventions can be categorized into various approaches, including relaxation techniques, distraction techniques, cognitive behavioral therapy (CBT) strategies, mindfulness-based stress reduction, acceptance and commitment therapy, cognitive therapy functional, health coaching, biofeedback, education, and counseling.

There is a growing body of research focused on cancer survivors, which indicates that a range of psychological interventions have the potential to mitigate psychological distress, enhance coping mechanisms, and positively impact immune function by influencing the neuro-endocrine and immune systems [24]. The existing body of literature has extensively documented the correlation between psychological stress and cancer across different age groups. Nevertheless, the existing body of literature indicates a scarcity of empirical support regarding the impact of psychological interventions on psychoneuroimmunological markers, specifically within the context of pediatric cancer. The utilization of psychoneuroimmunological markers to identify the physiological reactions of the body can serve as a prospective objective measure in evaluating the efficacy of psychological interventions in the context of pediatric cancer [28].

This review aims to provide empirical evidence regarding the efficacy of psychological interventions in modulating the psychoneuroimmunological system in pediatric cancer patients. Furthermore, this review presents an integrative framework that offers a comprehensive understanding of the interplay between pediatric cancer, psychological intervention, and the intricate processes involved in nervous system development. This framework allows for the evaluation of the impact on children's psychoneuroimmunological markers as a means of assessing these novel pathways. This systematic review aims to contribute to the advancement of interventions by providing a comprehensive overview of the integration of biopsychosocial factors, psychological interventions, and PNI in the context of pediatric cancer. The objective of this systematic review is to evaluate the efficacy of psychological interventions in modulating psychoneuroimmunological markers among pediatric cancer patients.

Methods

The guideline used to conduct this systematic review is The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) [29]. This systematic review has been registered with PROSPERO with registration number CRD42023392169.

Inclusion and exclusion criteria

The selection and search criteria used inclusion and exclusion criteria. The inclusion criteria include: (1) using PICOS (population, intervention, comparison, outcome, and study design). P (Population), means the study must involve children aged 0 to 18 years who suffer from cancer, I (intervention), is the use of all types of psychological interventions (we replicate the definition provided by Hoffman et al. [27] by defining psychological intervention as one of the following approaches: all kinds of relaxation techniques, all kinds of distraction technique, cognitive behavioral therapeutic strategies, mindfulness based stress reduction, acceptance and commitment therapy, cognitive functional therapy, health coaching, biofeedback, education, and counseling), C (comparison), is the control group or comparison group that is not psychological intervention, O (outcome), means studies include an analysis of at least one psychoneuroimmunological response in the form of a psychological responses (there is a feeling that someone feels like stress level, depression level, anxiety level, fear, fatigue level, quality of sleep, and quality of life that is measured by using a questionnaire); physiological responses (an individual response physically characterized by an increase heart rate, pulse, blood pressure, pain level, appearance nausea, vomiting, and fever); and neuroimmunological response (the body's response to stimuli involving the central nervous system (CNS) and the immune system that is measured by one of the saliva, hair, blood, or urine tests such as cortisol, leukocytes, cytokines, immunoglobulins and other immune responses). Study design (S) is all types of quantitative research; (2) the year of publication is the last ten years, between 2013 and 2022; (3) the articles taken are published in English. The exclusion criteria are (1) protocol studies, conference presentations, editorials, review articles, case reports, and case series, qualitative research, applied or development designs; (2) Studies involving molecular indicators or DNA; and (3) studies combining psychological intervention therapy with pharmacological intervention (use of drugs).

Search strategy

Reviewers scanned academic databases from the study commencement date from December 2022 to February 09, 2023. Searches were performed on four databases (Scopus, PubMed, ScienceDirect, and ProQuest). The minimum standard for searching the literature in a systematic review is minimally using a combination of 4 main databases [30]. The consequence of using these four main databases is that researchers will produce fewer search results, and there is a possibility of missing relevant references. However, in this systematic review, we also use Google Scholar to minimize the possibility of missing relevant references. In general, researchers consider combining four main databases equipped with Google Scholar to provide efficient results in this systematic review.

The main search term is “psychological intervention” combined using the Boolean “AND/OR” with terms related to “psychological and physiological responses” and “neuroimmunological markers”. Then the related term “children with cancer” was added. The author defines synonyms with the keyword as follows: (“Paediatrics” OR “Child” OR “childhood” OR “Children” OR “Adolescent” OR “teen” OR “teenagers”) AND (“cancer” OR “pediatric cancer” OR “childhood cancer” OR “neoplasm”) AND (“psychology” OR “psychological” OR “Psychological programs” OR “Psychological intervention” OR “psychotherapeutic” OR “psychotherapy”) AND (“Psychoneuroimmunology” OR “Psychoneuroimmunology responses” OR “psychology” OR “Physiology” OR “neurology” OR “endocrinology” OR “immunology” OR “Biological Markers” OR “Biomarkers” OR “cortisol” OR “leukocyte” OR “Cytokines” OR “lymphocytes” OR “immunoglobulins” OR “interleukins” OR “anxiety” OR “distress” OR “stress” OR “pain” OR “Fatigue” OR “Heart rate” OR “blood pressure” OR “respiratory rate” OR “body temperature” OR “blood oxygen”). Full search strategies for all resources can be seen in supplementary Appendix 1.

Selection of study

All authors (IH, NN, IL, WFR, ZH, and TR) scanned academic databases. Then we conduct the process of selecting articles. Four reviewers (IH, WFR, ZH, and TR) used Rayyan's intelligent systematic review to select articles. Rayyan is a web and mobile app for systematic reviews. Rayyan proved effective in conducting a systematic review and has significant potential to lighten the load of reviewers [31]. Articles filtered from the four main databases were entered into the Rayyan application. The total number of studies from this initial database search found 1,652 articles (898 from the main database and 754 from the auxiliary database). These articles were then checked, and the duplicates were removed.

IH, WFR, ZH, and TR independently reviewed the titles and abstracts yielded by this comprehensive search and subsequently selected articles based on the predetermined inclusion and inclusion criteria. Titles and abstracts were screened to include articles that first referred to psychological interventions and then had any terms related to PNI responses (as listed in the search terms above). We found 34 relevant studies from the main database and independently read them in full text. Then, disagreements between reviewers were resolved by consensus or by the decision of a third independent reviewer. A level of consensus of 80.0% or higher was considered to represent strong agreement [32]. Finally, 21 studies were included in this systematic review (13 articles from the main database and eight articles from the supplementary database (Figure 1).

Data extraction, analysis, and synthesis

Data were taken from each article that met the inclusion criteria. The data extraction process uses a Microsoft Excel sheet. All articles were read, and all authors extracted the data independently. Then, any discrepancies were discussed and resolved consensually. When differences could not be resolved, a third opinion would be sought, which might prove unnecessary. Given the apparent heterogeneity among studies in the type of psychological intervention, length of intervention, and study design, a meta-analysis was impossible. Thus, we only conducted a narrative review of the findings. Analysis using PICO Synthesis. The stages of the synthesis process begin with identifying the characteristics of the study (Population, Intervention, Comparison, Outcome, and study design) in each article obtained, then grouping them based on the Cochrane Handbook for Systematic Reviews [33].

Risk of bias and study quality

The authors identified study quality by considering the risk of bias. This assessment aims to assess a study's methodological quality and determine the extent to which a study has overcome possible biases in its design, implementation, and analysis. To identify the risk of bias, this systematic review uses The Joanna Briggs Institute (JBI) Critical Appraisal tools following the research design [34]. Each research design has different questions. Researchers must assess the articles that have been selected. The scoring results come from the scoring results from the percentage, which is $\geq$ 75% = Good, 50–75% = Fair, and <50% = Poor [35].

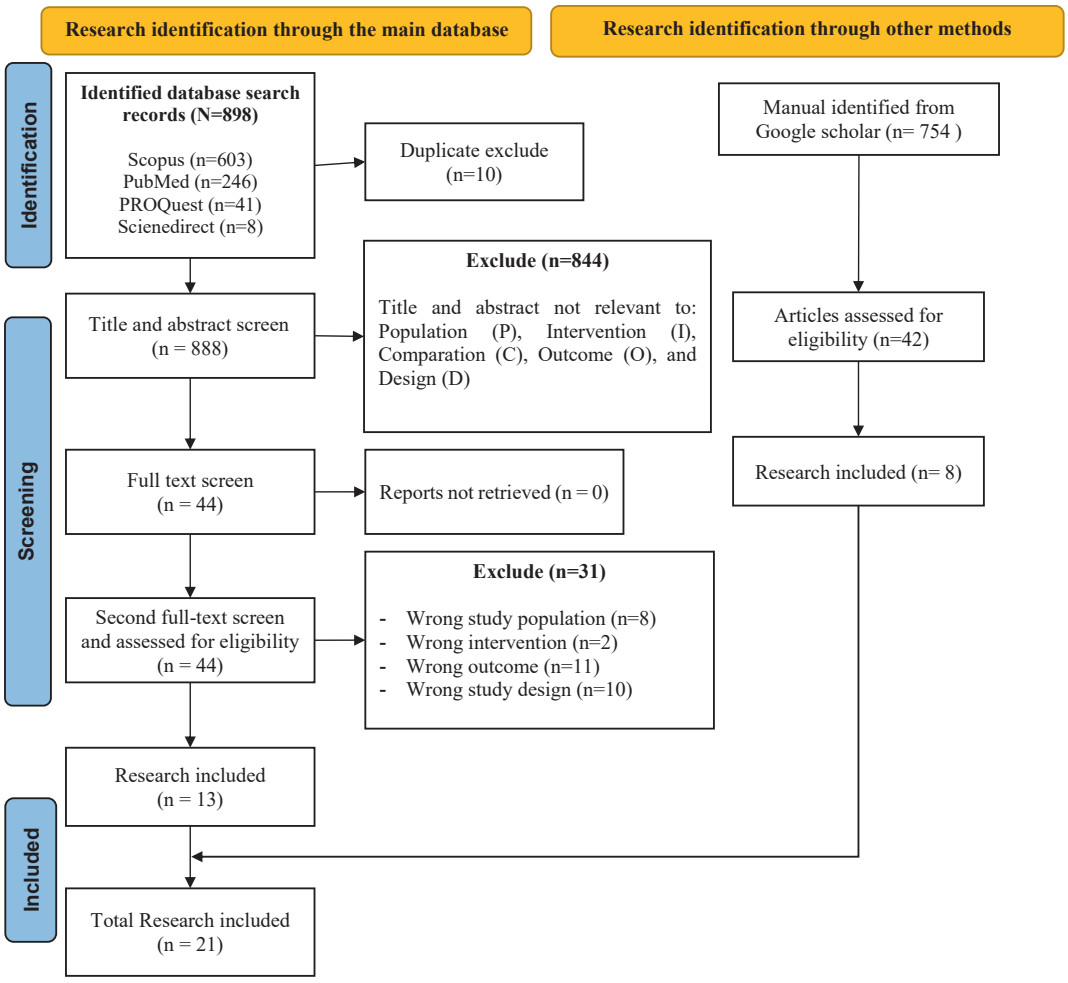

Figure 1. Flowchart Used in Selecting Studies Using PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) [32].

Model development

This study offers a new integrative model that shows the interaction between several factors affecting stress levels, which can be observed through neuroendocrine and immune mechanisms. Meanwhile, this integrative model also demonstrates how psychological interventions can modulate the effects of these various factors on neuroendocrine and immune mechanisms, ultimately influencing health outcomes. The conceptual framework of this new integrative model was created based on the conceptual framework of the biopsychosocial model [36] integrated with the field of PNI [19] and the results of this systematic review (Figure 2).

The biopsychosocial model is structured by several domains, including psychosocial, biological, and health behaviors, stress, psychological interventions, neuroendocrine and immune system mechanisms, and health outcomes. The biopsychosocial model describes the interaction among the factors that influence the stress of a person's life. Those factors encompass psychosocial, biological, and health behaviors that lead to susceptibility (or resistance) to disease, onset, disease symptoms, disease development, exacerbation, recovery, and quality of life through the process of involving neuroendocrine and immune mechanisms. Meanwhile, health psychological interventions are regarded to modulate the effects of these various factors on neuroendocrine and immune mechanisms, which in turn will influence health outcomes. The indicators for each domain refer to the results of a literature search and this systematic review's results.

The new integrative model shows the integration between the biopsychosocial model in the domain of neuroendocrine mechanisms and the immune system and psychoneuroimmunology (PNI). PNI is a field of medical science that examines the relationship between psychological stress and physiological processes in the body. The mind, nervous, endocrine and immune systems have a reciprocal relationship anatomically and biochemically [19]. PNI in the new integrative model is organized into four domains: psychology, physiology, neuroendocrinology, and immune systems. The indicators for these four domains are compiled based on our results in this systematic review.

In the psychological intervention domain, the authors arrange the types of psychological interventions in the new integrative model according to the results of the author's synthesis in this systematic review. Based on the biopsychosocial model, the domain of psychological intervention consists of cognitive behavioral stress management (CBSM), relaxation, hypnosis, meditation, emotional disclosure, adherence-based interventions, sleep hygiene, exercise, social support groups, psychotherapy, imagery, distraction, behavioral pain management, yoga, massage, biofeedback, drug/alcohol prevention/rehabilitation, psychotherapy, and behavioral conditioning. All of these interventions can be used in any type of disease or condition. However, the types of psychological interventions set in the integrative model framework are the psychological interventions that can be used in children with cancer, considering that this systematic review was carried out on the population of children with cancer.

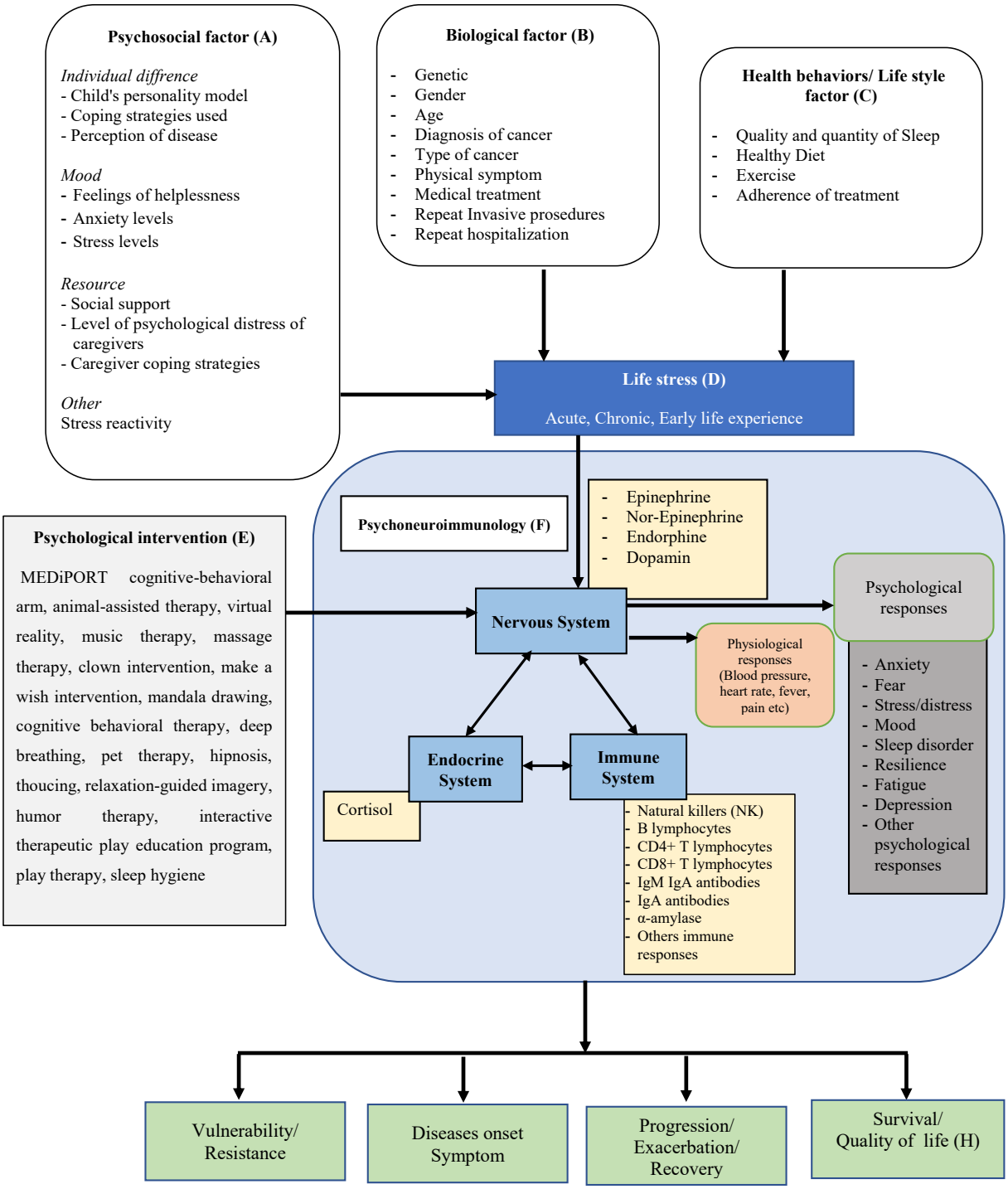

Figure 2. Illustration of the New Integrative Model [19,36].

Results

Study characteristic

The author obtained 1653 articles through all the specified databases. Studies that met the inclusion criteria in this systematic review were 21 articles. A description of the percentage of study characteristics obtained is shown in Table 1.

Based on the table above shows that most of the designs used were randomized controlled trials 12 (57.1%). At the same time, the types of psychological interventions used vary widely. The most common type of psychological intervention was massage therapy 3 (14.2%). Almost half of the studies measured psychological responses 8 (38.0%), and psycho-physiological responses 9 (42.9%), and only a small proportion assessed the effectiveness of psychological interventions on neuroimmunological markers in pediatric cancer.

Table 1 *Description of Study Characteristics (n = 21).*

Component	Characteristic	(n = 21)	Percentage (%)
Study design	Randomized controlled trial	12	57.1
	Nonrandomized controlled trial	9	42.9
Intervention type	Psychosocial intervention	1	4.8
	Mediport cognitive-behavioural arm	1	4.8
	Animal-assisted interventions	2	9.5
	Virtual reality	1	4.8
	Music therapy	1	4.8
	Massage therapy	3	14.2
	Clown intervention	1	4.8
	Make a wish intervention	1	4.8
	Mandala drawing	1	4.8
	The home-based multimodal symptom-management program	1	4.8
	Integrated experiential training program with coaching	1	4.8
	Adventure-based training	1	4.8
	Cognitive behavioral therapy	1	4.8
	Psychological intervention base psychoneuroimmunology	1	4.8
	Therapeutic play	1	4.8
	Mindfulness-based stress reduction	1	4.8
	Art therapy (drawing, painting and ceramic art)	1	4.8
	Drawing and writing technique	1	4.8
Outcome	Psychological responses	8	38.0
	Neuroimmunological markers	1	4.8
	Psychological and physiological responses	9	42.9
	Psychological responses and neuroimmunological markers	1	4.8
	Physiological responses and neuroimmunological markers	1	4,8
	Psycho-physio-neuroimmunological marker	1	4.8

Risk of bias and study quality

Almost all studies included in this systematic review (n = 18) have a study quality category as “Good” with a score above 75.0% using the Joanna Briggs Institute (JBI) critical appraisal so that all studies can be carried out synthesis analysis (see Table 2).

Impact of psychological intervention

From searching several scientific-based data, 21 studies illustrated that psychological interventions positively impacted psychoneuroimmunological responses in children with cancer. Based on this review, the author divides the impact of psychological intervention into two themes, including: (1) psychological responses (e.g., pain, anxiety, stress/distress, mood, fear, fatigue, depression, sleep quality, quality of life, and other psychological responses) and physiological responses (e.g., fever, pain, nausea, vomiting, blood pressure, heart rate, and other physiological responses); (2) psycho-physio and neuroimmunological marker (e.g., cortisol, NK cell, B lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, IgM antibodies, IgA antibodies, α-amylase, and another neuroimmunological marker).

1. Impact of psychological interventions on psychological and physiological responses.

Almost all of the research in this systematic review assesses the effectiveness of psychological interventions on psychological responses (stress/distress, fear, anxiety, fatigue, depression, decreased sleep quality, and quality of life) and physiological responses (blood pressure, heart rate, pain, nausea, vomiting, and fever). Nine studies assessed the effectiveness of interventions on psycho-physiological responses [37–45] and eight studies only assessed psychological responses but did not assess children's physiological responses [46–52].

Based on these studies, some studies show insignificant results. The psychological intervention in the form of MEDiPORT was reported to have no significant effect on the level of pain felt by children with cancer who underwent needle insertion. MEDiPORT is a 3-foot-tall humanoid robot (NAO hardware produced by Softbank Robotics and MEDi software produced by RxRobots. The robot is self-standing, able to walk, has hands that can self-adapt and grip, has eyes with light emission diodes, and has two speakers and four microphones to detect and project sounds. The robot can be programmed using a proprietary software development kit [37]. In addition, other studies have reported that massage therapy in adolescents with cancer undergoing hospitalization shows no significant changes in anxiety, mood, or fatigue from before to after the intervention [49]. This review shows that all studies that measure psychological responses use questionnaires. The questionnaires used varied, but most of the psychological problems assessed were the child's level of anxiety, mood, fear, and distress/stress level. At the same time, the physiological response is assessed through symptoms such as pain, nausea, vomiting, fever, and changes in vital signs such as blood pressure and heart rate. Measurement of pain level and assessment of symptoms such as nausea and vomiting in all studies used a questionnaire. Meanwhile, measuring vital signs such as blood pressure and heart rate uses standard tools. Diastolic and systolic blood pressure and heart rate in this study were used to measure children's physiological stress. Research has found that measuring physiological responses is always accompanied by assessing psychological responses using a questionnaire.

2. Impact of psychological intervention on the psycho-physio-neuroimmunological marker.

Based on this review, we found that there was one article that only assessed the effectiveness of psychological interventions on neuroimmunological markers [53], one article assessing psycho-neuroimmunological markers [54], one article assessing physio-neuroimmunological markers [24], and one article assessing psycho-physio-neuroimmunological markers [55].

Based on this review, music therapy is one of the psychological interventions used to manage neuroimmunological responses. Music therapy does not statistically affect cortisol levels but

Table 2 *Checklist For Randomized Control Trial (RCT) And Non Randomized Control Trial (Non RCT) From The Joanna Briggs Institute (JBI).*

Studies Included Randomised Control Trial (RCT) (13 Item Question)																
No	Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total score	Category
1	(Jibb et al., 2018)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/13	100.0% (Good)
2	(McCullough et al., 2018)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/13	100.0% (Good)
3	(Gerçeker et al., 2021)	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	11/13	84.6% (Good)
4	(Shoshani et al., 2016)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	10/13	76.9% (Good)
5	(Gürcan and Atay Turan, 2021)	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	10/13	76.9% (Good)
6	(Lam et al., 2018)	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	11/13	84.6% (Good)
7	(Jacobs et al., 2016)	N	N	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	9/13	69.0% (Fair)
8	(Li et al., 2018)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/13	100.0% (Good)
9	(Zhang et al., 2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	13/13	100.0% (Good)
10	(Hsiao et al., 2019)	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	Y	Y	9/13	69.0% (Fair)
11	(Cheng and Tan, 2021)	Y	Y	N	N	N	N	Y	Y	Y	Y	Y	N	N	7/13	53.8% (Fair)
12	(Liu et al., 2019)	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	10/13	76.9% (Good)
Studies Included Non-Randomized Control Trial (Non RCT) (9 Item Question)																
No	Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9					Total score	Category
13	(Hasanah et al., 2020)	Y	Y	Y	N	Y	N	Y	Y	Y	-	-	-	-	7/9	77.0% (Good)
14	(Genik et al., 2020)	Y	Y	Y	Y	Y	N	Y	Y	Y	-	-	-	-	8/9	88.8% (Good)
15	(Lopes-Junior et al., 2020)	Y	Y	Y	N	Y	N	Y	Y	Y	-	-	-	-	7/9	77.0% (Good)
16	(Cheng and Tan, 2021)	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-	-	9/9	100.0% (Good)
17	(Çelebioğlu et al., 2015)	Y	Y	Y	Y	Y	N	Y	Y	Y	-	-	-	-	8/9	88.8% (Good)
18	(Altay et al., 2017)	Y	Y	Y	N	Y	N	Y	Y	Y	-	-	-	-	7/9	77.0% (Good)
19	(Patil et al., 2021)	Y	Y	Y	Y	Y	N	Y	Y	Y	-	-	-	-	8/9	88.8% (Good)
20	(Silva and Osó Rio, 2018)	Y	Y	Y	N	Y	N	Y	Y	Y	-	-	-	-	7/9	77.0% (Good)
21	(Chacin-Fernández et al., 2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	-	-	-	-	9/9	100.0% (Good)

Note: Y: Present; NA: Not Applicable; N: Not Present; RCT: Randomized Control Trial; Non RCT: Non Randomized Control Trial; JBI: The Joanna Briggs Institute.

clinically shows a positive effect in reducing cortisol levels. The study suggested that the results that were not statistically significant could be caused by several things, including the small sample size, the range of results for measuring cortisol levels that were too far apart, the homogeneity of clinical conditions and levels of stress exposure, environmental factors, and the time and duration of therapy music that is too long [53]. Meanwhile, a study by Lopes Junior et al. (2020) reported that the clown intervention positively impacted cortisol levels but did not impact α-amylase levels in children with cancer. Future research should focus on a specific tumor type, have homogeneous samples, and use a more detailed investigation with robust statistical analyses. Future studies could also identify pediatric cancer inpatient profiles most likely to benefit from this type of intervention regarding age, gender, frequency of clown visits, and follow-up period [54]. In addition, a related study was also conducted in the UK and found that pediatric patients with leukemia who underwent PNI-based psychological interventions had a strong correlation between improvements in several key immune markers and a more satisfactory evolution of various clinical aspects of the disease, symptomatic treatment, and quality of life [24]. Quasi-experimental research conducted in Taiwan also identified the effectiveness of therapeutic play on changes in psychological, physiological, and neuroendocrine aspects. This study reports that therapeutic play interventions can reduce anxiety, heart rate (HR), and cortisol scores before External beam radiotherapy (EBRT) in children with brain tumors [55]. A summary of the studies can be seen in Table 3.

Development of a new integrative model

The following illustrates a new integrative model that explains the relationship between the biopsychosocial model, PNI, and psychological intervention in children with cancer. Based on the results of a systematic review and the incorporation of several theoretical concepts, the development of this new integrative model is divided into four domains, including.

1. Factors that affect stress (Box A-C)

Based on the biopsychosocial model, the factors influencing a person's stress condition include psychosocial, biological, and health behavior. Psychosocial processes (Box A) are factors that influence a person's interpretation and response to stressors which include individual differences (e.g., the child's personality model, coping strategies used, and perceptions of illness); mood (e.g., feeling of helplessness, anxiety levels, and stress levels); resources (e.g., social support, care-giver's coping strategies, care-giver's degree of psychological distress); other (stress reactivity). Biological factors (Box B) are factors that influence a person's response to a stressor, including genetics, gender, age, diagnosis of cancer, type of cancer, physical symptoms, medical treatment, repeat invasive procedures, and repeat hospitalization. Health behaviors/lifestyle factors (Box C) are factors that influence a person's response to a stressor, e.g., quality and quantity of sleep, healthy diet, exercise, and treatment adherence. The indicators for each psychosocial, biological, and health behavior domain refer to previous literature, which discusses the factors that influence stress regulation in children with cancer [23].

2. Stress

Stress is a person's inability to cope with perceived threats to one's mental, physical, emotional, and spiritual well-being, resulting in physiological responses and adaptations [56]. All cancer patients experience distress due to the diagnosis, effects of the disease, or treatment being undertaken [57]. Life stress (Box D) can be acute or chronic. Acute stress lasts minutes to hours, and chronic stress lasts months to years [19]. Acute and chronic stress will affect

Table 3 *Summary of Study Description (n = 21).*

No	Author, year	Country	Design	Sample Size (N) Age Mean ± SD/Median (Mean-Max)		Participant and setting	Type of intervention		Instrument	Outcome		Result
				Intervention group age	Control group age		Intervention group	Control group		Psychological and physiological responses	Psychoneuro immunological markers	
1	(Hsiao et al., 2019)	Taiwan	Quasi-Experimental	n = 7 Age: 0–18 years mean ± SD 0.65 ± 0.27	n = 6 Age: 0–18 years mean ± SD 4.81 ± 2.75	Patients with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) aged <18 years who underwent BMP and lumbar puncture (n = 13)	Psycho-social interventions consisting of preparation and cognitive behavioral interventions	Without psychosocial interventions	Observational Scale of Behavioral Distress (OSBD-R)	Distress level	–	The mean age at diagnosis of leukemic was 6.6 years (range: 3–11 years). Fifteen patients were diagnosed with acute lymphoblastic leukemic, and 3 were diagnosed with acute myeloid leukemic. The mean OSBD-R total score in the 7 patients with psychosocial intervention was significantly lower than the mean score in the 6 patients without intervention (0.65 vs 4.81, pZ0.002). Pre- and post-psychosocial interventions for BMA and LP behavioral disorders were evaluated for the remaining 5 patients. Consistently, there was a significant decrease in the OSBD-R score after the intervention (3.04 vs. 7.81, pZ0.025)
2	(Jibb et al., 2018)	Canada	Randomized controlled trial	n = 19 Age: 4–9 years mean ± SD 2.6 ± 3.5	n = 21 Age: 4–9 years mean ± SD 3.5 ± 3.9	Pediatric patients aged 4 to 9 years with cancer who underwent needle insertion (n = 40)	MEDiPORT cognitive-behavioral arm (robot using evidence-based cognitive-behavioural interventions) or active distraction arm (robot dancing and singing)	No control group	1. Face Pain Scale— Revised (FPS-R) 2. The Children's Fear Scale (CFS) 3. Behavioral Approach-Avoidance Scale (BAADS)	1. Pain level 2. Degree of fear 3. Distress level	–	Overall, MEDiPORT and this study were acceptable to the participants. There was no significant difference in pain intensity between arms (P = .68), but there was less pressure during the procedure on the distracted arm. No differences between groups were observed for the fear and distress subscale (P = .012).
3	(McCullough et al., 2018)	USA	Randomized controlled trial	n = 60 Age: 3–17 years mean ± SD 8.9 ± 4.5	n = 46 Age: 3–17 years mean ± SD 8.1 ± 4.6	Newly diagnosed cancer patients, aged 3 to 17 years (n = 106)	Animal-assisted interventions	standard care	1. The State-Trait Anxiety Inventory™ 2. Pediatrica Quality of Life Inventory 3. Child blood pressure and heart rate	1. Anxiety level 2. Blood pressure and heart rate	–	Children in both groups experienced a significant decrease in anxiety (P < .001). However, there were no significant differences between groups over time at any of the observed measures.
4	(Gerçeker et al., 2021)	Turkey	Randomized controlled trial	n = 21 Age: 6–17 years mean ± SD 2.4 ± 1.8	n = 21 Age: 6–17 years mean ± SD 5.3 ± 1.8	Hematology-oncology pediatric patients undergoing port with Huber needle aged >6 to <17 years (n = 42)	Virtual reality	standard care (without VR)	1. Wong-Baker Faces Pain Rating Scale 2. Children's Anxiety Meter 3. Child Fear Scale	1. Pain level 2. Level of anxiety 3. Degree of fear	–	Patient self-reported pain scores in the VR and control groups were 2.4 ± 1.8 and 5.3 ± 1.8, respectively. This study found statistically significant differences between groups in pain scores

												(p < .001). Statistically significant differences were found between groups according to self-reported and parental fear and anxiety scores after the procedure. Self-reported fear scores in VR and control groups were 0.8 ± 0.9, 2.0 ± 1.0, self-reported anxiety scores were 2.9 ± 2.0, 5.4 ± 2, respectively 0 (p < .001).
5	(Hasanah et al., 2020)	Indonesia	Pre-experimental study	n = 30 Age: 6–18 years median (min-max) Children: 0.00 (9.35 −3.18) Adolescent: 0.54 (2.47 −3.95)	None	Pediatric patients with leukemia aged 6–18 years who undergoing IV line insertion (n = 30)	Music therapy	no control group	ELISA	–	Cortisol levels	Cortisol levels before and after music therapy each had a median (min–max) of 4.14 (0.25–9.89) and 3.47 (0.16 −15.31). The median difference in cortisol levels was 0.67 ng/ml. This ≥0.05 ng/ml change indicates the clinical effect of music therapy on cortisol levels. Although music therapy did not significantly affect salivary cortisol levels (p = .99), this study revealed a clinical effect of music therapy in reducing cortisol levels.
6	(Genik et al., 2020)	Canada	Pre-post single group pilot study	n = 8 Age: 8–18 years mean ± SD 14.57 ± 2.51	None	Pediatric patients aged 8–18 years with cancer (n = 8)	Massage therapy	no control group	1. PainSquad App 2. Faces Pain Scale-Revised (FPS-R) 3. Children's Fear Scale (CFS).	1. Pain level 2. Degree of fear 3. Quality of life	–	All participants rated the MT intervention as acceptable and agreed that the intervention helped muscle pain (Mean = 4.80; Median = 5.00/5; range: 4–5; SD = 0.45), reduced anxiety/stress (Mean = 4.40; Median = 4, 00/5; range: 4–5; SD = 0.55), helped relax (Mean = 5.00; Median = 5.00/5; range: 5; SD = 0.00), and significantly increased their QOL overall (Mean = 4.60; Median = 5.00/5; range: 4–5; SD = 0.55).
7	(Lopes-Junior et al., 2020)	Brazil	Quasi Experimental	n = 16 Age: 6–14 years mean ± SD 11.4 ± 3.44	none	Pediatric patients with cancer undergoing chemotherapy aged 6–14 years (n = 16)	Clown intervention	no control group	1. High sensitivity enzyme-linked immunosorbent assay kit 2. Child Stress Scale-ESI 3. PedsQL Multidi mensional Fatigue Scale.	1. Stress level 2. Quality of life	Levels of salivary cortisol and α-amylase	Compared to baseline measurements, total psychological stress and fatigue levels improved after the clown intervention at the +4 h collection time point (P = .003 and P = .04, respectively). Salivary cortisol showed a significant decrease after the clown intervention at +1, +9, and +13 h collection time points (P < .05); however, α-amylase levels remained unchanged

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Table 3 (*continued*)

No	Author, year	Country	Design	Sample Size (N) Age Mean ± SD/Median (Mean-Max)		Participant and setting	Type of intervention		Instrument	Outcome		Result
				Intervention group age	Control group age		Intervention group	Control group		Psychological and physiological responses	Psychoneuro immunological markers	
8	(Shoshani et al., 2016)	Israel	Randomized controlled trial	n = 32 Age: 5–12 years mean ± SD 10.13 ± 3.51	n = 31 Age: 5-12 years mean ± SD 10.67 ± 4.71	Pediatric patients aged 5–12 with early diagnosis of cancer (n = 63)	Make a wish intervention	waiting list control group without make a wish intervention	1. The Brief Symptom Inventory-18 (BSI) 2. The Global Severity Index (GSI) 3. PedsQL 4. The Positive and Negative Affect Schedule for Children (PANAS-C) 5. Herth Hope Index (HHI) 6. The Life Orientation Test-Revised (LOT-R)	1. Level of distress 2. Depression 3. Level of anxiety 4. Quality of life	–	Children in the intervention group showed significant reductions in general distress (d = 0.54), depression (d = 0.70), and anxiety symptoms (d = 0.41), improvement in health-related quality of life (d = 0 .59), expectation (d = 0.71), and positive affect (d = 0.80) and there was no significant change in other measures in the control group.
9	(Gürcan and Atay Turan, 2021)	Turkey	Randomized controlled trial	n = 30 Age: 12–17 years mean ± SD 14.26 ± 1.79	n = 30 Age: 12–17 years mean ± SD 13.56 ± 1.67	Adolescent patients with cancer aged 12 –17 years who are hospitalized (n = 60)	Mandala drawing	routine care only	Anxiety and Depression Scale dan Memorial Symptom Assessment Scale	1. Levels of anxiety and depression 2. Psychological symptoms	–	Anxiety and depression scores decreased significantly in the intervention group, compared to the control group, after 5 days of intervention, $F(1.57) = 28.9$, $p < .01$, $\eta 2 = 0.337$. Similarly, psychological symptom scores decreased significantly in the intervention group, compared to the control group, $F(1.57) = 69.7$, $p < .001$, $\eta 2 = 0.550$).
10	(Cheng and Tan, 2021)	Singapore	Randomized controlled trial	n = 25 Age: 10–18 years mean ± SD 13.9 ± 2.4	n = 25 Age: 10–18 years mean ± SD 13.4 ± 2.6	Pediatric patients with cancer aged 10–18 who are undergoing chemotherapy (n = 50).	The home-based multimodal symptom-management program	usual care	Memorial Symptom Assessment Scale 10 –18 and the State Anxiety Scale for Children.	1. Symptoms 2. Anxiety	–	Between-group comparisons showed that the intervention group had significantly reduced fatigue over time ($P < .05$). However, no differences were found with respect to nausea and vomiting, pain, mucositis, and anxiety between groups. Both children and parents reported positive experiences with symptom management programs.
11	(Çelebioğlu et al., 2015)	Turkey	Quasy experimental	n = 12 Age: 4–15 years mean ± SD 7.66 ± 3.86	n = 13 mean ± SD 8.00 ± 3.31	Pediatric patients aged 4–15 years in children with cancer (n = 25)	massage therapy	standard treatment (without massage therapy)	Analog visual scale	Pain and anxiety levels	–	When the pain and anxiety levels of the pre-test and post-test groups were compared, no statistically significant difference was found ($P > .05$). It was determined that the pain and anxiety levels in the

											experimental group decreased significantly. This study provides preliminary evidence for the effectiveness of massage in children in reducing pain and anxiety arising from intrathecal therapy or bone marrow aspiration.
12	(Lam et al., 2018)	China	Randomized controlled trial	n = 37 Age: 9–18 years mean ± SD 12.8 ± 2.5	n = 33 Age: 9–18 years mean ± SD 12.5 ± 2.5	Pediatric patients with cancer aged 9–18 years (n = 70)	Integrated experiential training program with coaching	placebo interventions	1. The Chinese version of the Fatigue Scale (Cancer-related fatigue) 2. The Chinese University of Hong Kong Physical Activity Rating for Children and Youth 3. Paediatric Quality of Life Inventory cancer module v. 3.0 (Quality of life)	1. Fatigue level 2. Physical activity 3. Quality of life	–	The experimental group reported significantly lower levels of cancer-related fatigue, higher levels of physical activity and physical activity self-efficacy, greater right and left grip strength, and better quality of life than the control group at 9 months.
13	(Jacobs et al., 2016)	Washington DC	Randomized controlled trial	n = 18 Age: 12–21 years mean ± SD 15.5 ± 2.6	n = 16 Age: 12–21 years mean ± SD 16.0 ± 2.5	Adolescent patients aged 12–21 with cancer who are hospitalized for at least 4 consecutive days.	Massage therapy	waitlist control (without massage)	1. Sleep was measured with actigraphy 2. Fatigue Scale Adolescent 3. The State Trait Anxiety Scale, State Portion 4. Behavioral, Affective and Somatic Experiences Scale Revised, Parent-Report and Child-Report (BASES)	1. Sleep quality 2. Fatigue level 3. Level of anxiety 4. Moods	–	The results showed that there was no significant change in anxiety, mood or fatigue from pre to post intervention. However, there was a trend toward increased night time and overall sleep in the intervention group compared to standard care, but no between-group differences on patient-reported outcome measures (2.3, P = .049).
14	(Li et al., 2018)	Hongkong	Randomized controlled trial	n = 117 Age: 9–16 years mean ± SD 12.8 ± 1.9	n = 105 Age: 9–16 years mean ± SD 12.5 ± 2.6	Pediatric patients with cancer aged 9–16 years (n = 222)	Adventure-based training	placebo interventions	Fatigue Scale–Child (FS–C)	fatigue level	–	The experimental group showed statistically significantly lower levels of cancer–related fatigue (P < .001), higher levels of self-efficacy (P < .001) and physical activity (P < .001), and better quality of life (P < .01) than the control group at 12 months.
15	(Zhang et al., 2019)	China	Randomized controlled trial	53 cases were from the children aged from 8 to 12 years old and 46 cases from 13 to 18 years old. mean ± SD Not mentioned	53 cases were from the children aged from 8 to 12 years old and 46 cases from 13 to 18 years old. mean ± SD Not mentioned	Pediatric cancer patients receiving chemotherapy aged 8–18 years (n = 106)	Cognitive behavioral therapy	routine psychological care	The Conner–Davidson Resilience Scale (CD-RISC) and depression anxiety stress scale (DASS)	Resilience, stress and anxiety levels	–	Before the intervention, there was no significant difference in the psychological adjustment abilities between the 2 groups (P > 0.05 for all). After the intervention, the total CD-RISC score was significantly higher (56.09 ± 7.29 vs 44.75 ± 5.40),

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Table 3 (*continued*)

No	Author, year	Country	Design	Sample Size (N) Age Mean ± SD/Median (Mean-Max)		Participant and setting	Type of intervention		Instrument	Outcome		Result
				Intervention group age	Control group age		Intervention group	Control group		Psychological and physiological responses	Psychoneuro immunological markers	
												while the depression score (4.57 ± 2.94 vs 7.25 ± 4.25), anxiety (5.83 ± 3.07 vs 8.66 ± 4.92), stress (7.51 ± 4.33 vs 11.17 ± 4.25) were clearly lower in the CBT group than in the control group ($P < 0.05$ for all). Additionally, the reduction in negative mood scores in children with a yolk sac tumor was most pronounced in the CBT group.
16	(Chacin-Fernández et al., 2019)	UK	Non-randomized, open-label clinical trial	n = 16 Age: 5–15 years mean ± SD 10.1 ± 0.9	n = 10 Age: 5–15 years mean ± SD 9.8 ± 1.2	Pediatric patients with leukemia undergoing chemotherapy (n = 26)	Psychoneuro immunology-based psychological interventions.	psychoeducation in relation to their treatment and disease,	1. Immunological evaluation using flow cytometry and immunotur bidimetry 2. Quality of Life was assessed using the QoL Questionnaire in Pediatric Oncology.	1. Duration of signs and symptoms (Fever and Pain) 2. Duration of administration of pain therapy, antibiotics and antipyretics	Immune markers - Natural killers (NK) - B lymphocytes - CD4+ T lymphocytes - CD8+ T lymphocytes - IgM IgA antibodies - IgA antibodies	Psychoneuro immunology-based interventions improve immune markers (CD8+ T, B, and natural killer cells, serum immuno globulin A, and immuno globulin M) and quality of life, while shortening the duration of fever and the use of antipyretics, antibiotics, analgesics, and respiratory therapy. Immunity markers correlate with clinical conditions. Thus, psychoneuroimmunology-based interventions can reduce hospital costs and improve patient well-being
17	(Altay et al., 2017)	Turkey	Quasi-experimental design	n = 30 Age: 9–16 years mean ± SD 2.56 ± 267	Without control group	Pediatric patients with cancer who are undergoing treatment aged 9 –16 years (n = 30)	Drawing and writing technique	no control group	The State Anxiety Inventory	anxiety level	–	A lower State Anxiety Inventory score indicates lower anxiety after the intervention (36.86 ± 4.12 compared to before (40.46 ± 4.51) ($p < .05$).
18	(Patil et al., 2021)		Quasi-experimental design	n = 15 Age: 7–12 years Not mentioned mean ± SD	n = 15 Age: 7–12 years Not mentioned mean ± SD	Pediatric patients with cancer aged 7 –12 years (n = 30)	art therapy (drawing, painting and ceramic art)	routine therapy	Perceived stress scale dan Hamilton anxiety rating scale (HAM-A)	Stress and anxiety	–	The effect of art therapy in the experimental group showed a significant difference in mean post-test stress and anxiety scores ($p = .00069$ and $p = 0.000642$) compared to controls. Comparison of anxiety scores with all types of cancer showed a significance of $p = .010$ in the experimental group compared to the controls in the post-test

19	(Liu et al., 2019)	China	Randomized controlled trial	n = 46 Age: 10–21 years mean ± SD 15.9 ± 5.2	n = 45 Age: 10–21 years mean ± SD 16.2 ± 4.9	Pediatric patients with osteosarcoma aged 10–21 years (n = 91)	Mindfulness-based stress reduction	routine therapy (no psychological intervention)	1. Wong-Baker Faces Pain Rating Scale (WBRS) 2. The Hamilton Anxiety Rating Scale (HAM-A) 3. The Pittsburgh Sleep Quality Index (PSQI)	1. Pain level 2. Anxiety level 3. Sleep quality	–	There were no significant differences in sociodemographic and clinical parameters between the intervention and control groups. The intervention program significantly alleviated the psychological and physiological complications in patients with osteosarcoma. Specifically, this study revealed that 8 weeks of the combined MBSR/MT intervention effectively reduced pain and anxiety scores and improved sleep quality in patients.
20	(Tsai et al., 2013)	Taiwan	Quasi-experimental design	9 patients aged 3 –12 years (median = 8.12 years)	10 patients aged 3 –14 years (median = 8.9 years)	Brain tumor patients, aged 3 –15 years (n = 19)	Therapeutic play	general medical procedures	The Beck Youth Anxiety Inventory dan Faces Anxiety Scale	1. Anxiety level 2. Heart rate	Salivary cortisol concentration	The study group had significantly lower anxiety, HR and cortisol scores and expressed fewer negative emotions than the control group before External beam radiotherapy (EBRT).
21	(Silva and Osó Rio, 2018)	Italy	Quasi-experimental design	n = 24 Age: 6–12 years mean ± SD 8.58 ± 1.98	none	Pediatric patients with a diagnosis of solid tumor aged 6 to 12 years (n = 24)	Animal assisted therapy	no control group	1. Child Stress Symptoms Inventory 2. Quality of Life Evaluation Scale 3. Child Depression Inventory 4. Adapted Brunel Mood Scale: Faces Pain Scale 5. AAT Assessment Questionnaire	1. Stress 2. Pain 3. Mood 4. Anxiety, depression 5. Quality of life 6. Heart rate, and blood pressure.	-	This study reported reductions in pain (p = .046, d = −0.894), irritation (p = 0.041, d = −0.917), stress (p = .005; d = −1.404) and a trend toward improvement in depressive symptoms (p = .069; d = −0.801).

Note: AAT: Animal Assisted Therapy; ALL: Acute Lymphoblastic Leukemia; AML: Acute Myeloid Leukemia; BAADS: behavioral Approach-Avoidance Scale; BASES: behavioral, Affective And Somatic Experiences Scale; BMP: Bone Marrow Puncture; BMA: Bone Marrow Aspiration; CD4+: Cluster Of Differentiation 4; CFS: Children's Fear Scale; CBT: Cognitive behavioral Therapy; EBRT: External Beam Radiotherapy; DASS: Depression Anxiety Stress Scale; FPS-R: Faces Pain Scale-Revised; FS-C: Fatigue Scale–Child; HR: Heart Rate; HHI: Herth Hope Index; IgM: Immunoglobulin M; IgA: Immunoglobulin A; LP: Lumbar Puncture; MBSR/MT: Mindfulness-Based Stress Reduction; MT: Massage Therapy; NK: Natural Killers; OSBD-R: Observational Scale Of behavioral Distress; PedsQL: Pediatrics Quality Of Life; QoL: Quality Of Life; SD: Standard Deviation; BSI: The Brief Symptom Inventory-18; GSI: Global Severity Index; PANAS-C: The Positive And Negative Affect Schedule For Children; LOT-R: The Life Orientation Test-Revised; HAM-A: The Hamilton Anxiety Rating Scale; PSQI: The Pittsburgh Sleep Quality Index; CD-RISC: The Conner-Davidson Resilience Scale; VR: Virtual Reality; WBRS: Wong-Baker Faces Pain Rating Scale.

the stress response through psychoneuroimmunological markers (psychological responses, neuroendocrine and immune markers) (Box E).

3. Psychological interventions

Psychological interventions (Box F) are designed to modulate the stress response and promote health behaviors by teaching individuals more adaptive methods of dealing with perceived stress. Psychosocial interventions are useful for treating stress-related disorders and can influence the course of chronic disease [58]. Based on the results of this review, we identified 18 types of psychological interventions used to manage psychoneuroimmunological markers in children with chronic illness, including MEDiPORT cognitive-behavioral arm, animal-assisted therapy, virtual reality, music therapy, massage therapy, clown intervention, make-a-wish intervention, mandala drawing, cognitive behavioral therapy, deep breathing, pet therapy, hypnosis, touching, relaxation-guided imagery, humor therapy, interactive therapeutic play education program, play therapy, and sleep hygiene.

4. Neuroendocrine and immune mechanisms

Neuroendocrine and immune system mechanisms in the biopsychosocial model suggest integration from the field of psychoneuroimmunology (PNI). Box F shows the bidirectional communication of PNI, which is the mechanism that occurs in a two-way interaction between the neuroendocrine and immune axes that mediates the relationship between biobehavioral factors (Box A–D). PNI is divided into four domains: psychology, physiology, neuroendocrinology, and immunology. The indicators for all domains are compiled based on the results of this systematic review. Based on the results of our systematic review, the psychological system domain is assessed through several indicators such as anxiety, fear, stress/distress, mood, sleep disorder, resilience, fatigue, and depression. The physiology domain is evaluated through indicators such as blood pressure, heart rate, fever, and pain. The authors found no studies in this systematic review that assessed the neurological system through neurological markers such as dopamine, epinephrine, norepinephrine, β-endorphins, or other markers. Meanwhile, in the endocrine system domain, the indicators assessed were cortisol, and the immune system indicators assessed included: Natural killers (NK), B lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, IgM IgA antibodies, IgA antibodies, and α-amylase).

Table 3 provides a brief description of the new integrative model.

Discussion

Effectiveness of psychological interventions on the psychological and physiological responses in children with cancer

The utilization of psychological interventions in the management of mental health among pediatric oncology patients holds promise for enhancing both psychological and physical health outcomes. A total of nine studies were conducted to evaluate the efficacy of various interventions, including animal-assisted intervention, cognitive behavioral therapy, virtual reality, massage therapy, mandala drawing, the home-based multimodal symptom-management program, and mindfulness-based stress reduction, in terms of their impact on psychological and physical responses [37–45]. Three out of nine studies indicated that psychological interventions did not yield statistically significant outcomes in terms of the psychological and physiological responses observed in children diagnosed with cancer. The statistical analysis conducted in a study indicates that there is no significant evidence to support the effectiveness of massage therapy in managing the physiological and psychological responses of children diagnosed with cancer [43]. Moreover, the utilization of the MEDiPORT humanoid robot for the purpose of mitigating procedural pain and distress in pediatric cancer patients yielded comparable outcomes in both the control and intervention groups [37]. The study found that the home-based multimodal symptom-management program was effective in reducing fatigue among participants. However, there was no significant difference observed between groups in terms of reducing nausea and vomiting, pain, mucositis, and anxiety [42].

Out of the nine studies examined, six of them indicated that various psychological interventions, including animal-assisted intervention, cognitive behavioral therapy (CBT), virtual reality, mandala drawing, and mindfulness-based stress reduction (MBSR), have been found to be effective in managing the psychological and physiological responses experienced by children diagnosed with cancer. This aligns with a prior systematic review conducted in the United Kingdom in 2017. The review indicated that a total of nine studies demonstrated statistically significant enhancements in psychological outcomes. The aforementioned findings suggest that psychological interventions have demonstrated efficacy in diminishing anxiety, physical symptoms, depressive symptoms, and enhancing overall quality of life [59].

Several other studies have documented the efficacy of psychological interventions, particularly those that employ more targeted and specific approaches. Animal-assisted therapy has been successfully utilized across different age groups and for various disease diagnoses. For instance, it has been employed in the context of pediatric surgery for children [60]; as well as for children diagnosed with Post-Traumatic Stress Disorder (PTSD) [61]; and those receiving treatment in acute care pediatric settings [62]. Contrary to the aforementioned viewpoint, Feng et al. [63] conducted a systematic review that found no significant impact of animal-assisted therapy on anxiety, depression, stress, and heart rate among hosptialized children and adolescents. In the field of psychology, CBT has emerged as a prevalent intervention technique. This approach has been modified to cater to various age groups, including children, adolescents, adults, couples, and families. The cognitive aspect of CBT focuses on mitigating exaggerated and negative thoughts related to pain, while the behavioral component involves implementing relaxation techniques and activating coping behaviors [64,65] Psychological intervention has been found to have an impact on brain mechanisms, leading to a decrease in both pain and anxiety experienced by individuals. According to existing scholarly works, various aspects of successful psychological intervention may be corroborated by alterations in neural circuitry. These alterations are typically characterized by decreased activation and/or diminished hyperconnectivity in brain regions associated with pain processing, emotion, and cognitive control [64].

According to the review, a total of eight studies exclusively evaluate the efficacy of psychological interventions in managing the psychological reactions exhibited by children diagnosed with cancer [46–52,66]. Seven out of the eight studies presented in this analysis have indicated that psychological interventions possess considerable potential in effectively managing psychological responses among children. Additional empirical evidence has also documented the positive impact of psychological interventions on the psychological responses of children with various conditions. For instance, studies have shown the effectiveness of music therapy in children undergoing surgery and those with asthma [67,68]; virtual reality (VR) therapy in children with sickle cell disease and those undergoing surgery [69,70]; pet therapy for children undergoing hospitalization [71]; hypnosis in children with cancer, in children

with burns, and children with Crohn's disease [72–76]; parental touch followed by music therapy in critically ill children [77]; relaxation-guided imagery in children undergoing surgery [78]; humor therapy in children with atopic dermatitis [79]; interactive therapeutic play education program for children undergoing surgery [80]; and play therapy in children undergoing elective surgery and in children undergoing liver transplantation [81–84]. Certain studies have the potential to be grounded in empirical evidence, as they demonstrate that psychological interventions have a notable impact on the management of psychological reactions, thereby enhancing the overall quality of child healthcare [46]. The implementation of psychological interventions presents cancer patients with a comprehensive approach to healthcare, potentially safeguarding the overall physical and psychological welfare of individuals diagnosed with cancer [85].

According to a study conducted on children with cancer, approximately one out of every eight studies revealed no statistically significant alterations in anxiety, mood, or fatigue levels following the implementation of psychological intervention through massage therapy [49]. Nevertheless, this finding contradicts the conclusions drawn from previous systematic reviews, which demonstrated the efficacy of massage therapy in effectively mitigating stress levels among children receiving palliative care in hospital settings [86,87]. Massage therapy has been found to have beneficial effects on various pediatric conditions. The aforementioned factors encompass a range of issues affecting preterm infant growth, psychological well-being, gastrointestinal functioning, painful conditions such as burns and sickle cell disease, muscle tone disorders like cerebral palsy and Down syndrome, as well as chronic illnesses including diabetes, asthma, cancer, and HIV [88].

Effectiveness of psychological interventions on the psycho-physio-neuroimmunological markers in children with cancer

The current body of research examining the efficacy of psychological interventions on psycho-physio-neuroimmunological markers in pediatric populations, particularly those diagnosed with cancer, remains relatively scarce. Based on the findings of this comprehensive systematic review, it was determined that a mere four out of the total of 21 studies examined in this analysis focused on the evaluation of psycho-physio-neuroimmunological markers. In this investigation, the efficacy of psychological interventions on neuroimmunological markers was examined in one study [53]. Additionally, another study focused on psychoneuroimmunological markers [54], while a separate study explored physio-neuroimmunological markers [24]. Furthermore, a study was conducted to investigate the impact of psychological, physiological, and neuroimmunological factors on markers [55].

A single study was identified that exclusively evaluated the neuroimmunological response. According to the study, music therapy has a statistically significant impact on neuroimmunological markers, specifically salivary cortisol levels. This study elucidated the clinical impact of music therapy on the reduction of cortisol levels [53]. This finding aligns with the findings of Finn & Fancourt [89] who conducted a review and observed that 13 out of the 33 biomarkers tested exhibited changes following exposure to music. One of the biomarkers that has been extensively examined is cortisol, a stress hormone. Approximately half of the clinical studies conducted have indicated that listening to music has a stress-reducing impact. Several other biomarkers that have been examined are also components of biological stress pathways, suggesting that the primary mechanism by which music impacts us biologically is through the modulation of the stress response.

The previous literature has provided a description of the mechanism by which music therapy regulates cortisol levels. The auditory perception of music elicits neural responses in the hypothalamus, subsequently triggering the release of endorphins through the activation of the pituitary gland [56,90]. Endorphins, which are endogenous opiates similar to morphine, serve as the body's innate analgesics and possess the ability to mitigate the impact of stressful conditions by modulating cortisol levels [56,90]. According to previous studies, psychological interventions, including animal-assisted activities, have not shown statistically significant effects on salivary cortisol levels and C-reactive protein (CRP) in children who are hosptialized [91]. An additional discovery pertains to the impact of psychological interventions on the levels of noradrenaline and cortisol, while the levels of adrenaline remain unaffected. The intervention had a discernible impact on adrenaline levels exclusively within a time frame of 6-8 days following surgery in patients undergoing Coronary Artery Bypass Graft (CABG) procedures [92].

Three studies were identified that aimed to evaluate the neuroimmunological markers as well as the physical and psychological responses in pediatric patients diagnosed with cancer. The aforementioned studies have documented that various psychological interventions, such as clown intervention, therapeutic play, and psychoeducational intervention, yielded favorable outcomes in terms of physical, psychological, and neuroimmunological indicators in pediatric cancer patients. These indicators include cortisol levels, α-amylase levels, CD8+ T cells, B cells, natural killer (NK) cells, serum immunoglobulin A (IgA), and immunoglobulin M (IgM) [24,54,55]. The implementation of clown intervention has demonstrated efficacy in the management of psycho-physio-neuroimmunological markers among pediatric cancer patients. Nevertheless, the findings of this review exhibit notable disparities when compared to previous research. According to a previous conducted by Ding et al., it was found that clown intervention has a positive impact on distress levels, duration of crying following a medical procedure, and length of hospital stay. Nevertheless, the study findings did not reveal any statistically significant disparity in cortisol levels [93,94]. In contrast, there has been limited research conducted on the efficacy of therapeutic play. No comparable studies evaluating the efficacy of therapeutic play on psycho-physio-neuroimmunological markers were identified by researchers. Nevertheless, according to William et al. [95] it was found that children who underwent therapeutic play intervention exhibited reduced levels of state anxiety scores during both the pre-operative and post-operative periods. In addition, psychoeducation interventions have been implemented in patients undergoing multidrug therapy (MDT) treatment. The research findings indicated that psychoeducation was successful in enhancing spiritual response, perception, stigma, and anxiety, while also reducing cortisol levels [95].

Various psychological interventions have been documented for the management of psycho-physio-neuroimmunological markers. The study conducted by Chang et al. examines the efficacy of psychological interventions, specifically the Laughing Qigong program (LQP), in adolescent patients who are undergoing hospitalization. LQP is an integrative approach that combines the practices of qigong and laughter techniques, emphasizing the interplay between the mind and body. This study examined both neuroimmunological responses, specifically cortisol levels, as well as their impact on physical responses, including heart rate and heart rate variability, and psychological responses, such as mood states, self-esteem, self-efficacy, and depression [96]. In 2021, a study conducted in Peru yielded similar findings, indicating the positive impact of providing augmented reality books on the management of psychological and neuroimmunological responses. The evaluation of emotional stress and neuroimmunological markers in hosptialized children involved the utilization of the Weisz visual

analogue scale to assess psychological responses, alongside the measurement of cortisol levels. This study was unable to provide evidence supporting the hypothesis that reading augmented reality books resulted in a greater reduction of salivary cortisol levels compared to reading a standard book among children who were hosptialized. In addition, it has been found that augmented reality (AR) books have a positive impact on reducing emotional stress, as measured by the Weisz visual analogue scale [97].

Additional psychological interventions encompass the utilization of storytelling, which has been observed to exert an influence on both physiological responses and neuroimmunological markers. Specifically, this intervention has been found to elevate oxytocin levels while concurrently reducing cortisol and pain levels in children undergoing treatment in intensive care units (ICU) [98]. In the realm of psychological interventions, it has been observed that mindfulness-based stress reduction (MBSR) techniques have proven to be advantageous, resulting in notable enhancements in both psychological and biological aspects, including endocrine and immunological markers [99,100]. The existing body of literature pertaining to the neural underpinnings of psychological interventions in cancer patients is currently insufficient, necessitating additional investigation. A study conducted in the Netherlands in 2022 elucidates the mechanisms underlying psychological intervention in the regulation of psychoneuroimmunological responses. According to the study, psychological interventions administered to individuals with cancer have the potential to influence cortical and subcortical brain activity. These changes align with the brain regions associated with distress responses [85].

A new integrative model

Within the specific context of individuals diagnosed with cancer, the prevalence rate of psychological distress is observed to be four times greater compared to the general population. This heightened prevalence of psychological distress is frequently associated with inferior outcomes. Furthermore, a number of cellular and molecular studies have provided evidence supporting the intricate signaling networks influenced by chronic stress-induced psychological distress in the context of cancer development [101]. The experience of receiving a diagnosis, the effects of the disease, and the treatment process can elicit distress among individuals diagnosed with cancer [57]. The correlation between the specific cancer diagnosis of patients and the levels of physical distress, emotional distress, and depressive symptoms has been found to be statistically significant [102]. Furthermore, it should be noted that the administration of the treatment may lead to an exacerbation of the symptoms associated with heightened distress, as indicated by previous research [5]. Cancer survivors are at the greatest risk of developing endocrine disorders over time when they undergo cancer treatments involving radiation in major endocrine organs, including the hypothalamus, pituitary, thyroid, and gonads [13]. The immune system of an individual can be impacted by disorders within the endocrine system [18,56].

In addition to the diagnostic process, the presence of illness, or the administration of treatment, which are known stressors for pediatric cancer patients, a study conducted in Ohio, United States, elucidates that children with cancer experience stress in various domains. These domains include (a) disruptions in daily functioning and roles, such as missing school or falling behind in academic work, being unable to engage in previously enjoyed activities, frequent visits to hospitals or clinics, and concerns about the well-being of family and friends; (b) physical manifestations resulting from treatment, such as feelings of sickness or nausea, anxieties regarding changes in appearance, and discomfort or pain arising from medical procedures; and (c) uncertainties surrounding the nature of cancer, including difficulties comprehending medical explanations, confusion regarding the concept of cancer, and apprehensions about future outcomes [103].

The regulation of the neuroendocrine and immune systems can be influenced by a range of stressors, leading to potential impacts on the health outcomes of children. The impact of stress on immune function is exacerbated, while on the other hand, psychological interventions have the potential to regulate neuroendocrine activity and improve immune system functioning. However, there is limited knowledge regarding the extent to which children with cancer can achieve immunological recovery. The intricate nature of stress-induced factors in pediatric cancer patients and the limited amount of scholarly research examining potential mediating mechanisms, such as the impact of stress and psychological interventions on the immune system. Therefore, future research can employ this novel integrative model framework to manipulate the variables of psychological interventions, thereby facilitating the examination of direct effects on the immune response. The investigation of interventions that are most well-received by pediatric cancer patients is a fundamental aspect of immune effect preservation, thus necessitating additional scholarly inquiry in this domain.

There exist certain limitations to this review. Due to the diversity observed in the psychological interventions employed, the age range of the children included, the study design implemented, and the instruments utilized for outcome assessment, the feasibility of conducting a meta-analysis was precluded. Moreover, while the utilization of the JBI for evaluating bias in this review is comprehensive and adheres to explicit criteria, the individual assessment of studies by each author remains subjective. In order to enhance the comprehensiveness and validity of future research, it is recommended that subsequent investigations incorporate post-intervention evaluations to elucidate the enduring ramifications of the intervention. Additionally, it is crucial to account for the homogeneity of various indicators, including but not limited to gender, type of psychological intervention, type of cancer treatment, stage of cancer, type of instrument employed, methodologically appropriate sample size, and objective tools to assess bias. By considering these factors, researchers can obtain results that are more robust and reliable. Further research is required to comprehensively evaluate the effectiveness of psychological interventions in terms of their impact on neurobiological processes and clinical outcomes. The examination of the associations between observed neurobiological alterations and clinical outcomes is crucial in order to comprehend the potential neural activity changes that may be responsible for the clinical impact of an intervention [85]. The lack of clarity surrounding the terminology used in psychological interventions poses a potential limitation in this review, as it may hinder the identification of additional pertinent studies. When conducting further research, it is imperative to carefully select keywords that are more specific in order to avoid overlooking relevant studies.

Despite the presence of certain limitations, this review possesses several notable strengths. First, it stands as one of the pioneering evidence-based interventions that evaluates the efficacy of psychological interventions on psychoneuroimmunological markers in pediatric cancer patients. Second, it introduces a novel integrative model that can aid healthcare professionals in making informed clinical decisions. This model offers a comprehensive and holistic depiction of the various factors that impact stressful conditions in children with cancer. Furthermore, it provides insights into the mechanisms through which psychological interventions influence physical, psychological, and neuroimmunological markers in this population. It is imperative for future researchers to

thoroughly investigate the various integrative models, encompassing psychosocial factors, biological factors, health behaviors, neuroendocrine and immune system mechanisms, and disease outcomes. This examination should be conducted using a longitudinal design to comprehensively address the intricate interplay among these components and to gain a comprehensive understanding of their significance in relation to health outcomes. Psychological intervention is a viable evidence-based treatment option that can be employed by healthcare professionals in the field of nursing, particularly in the context of pediatric patients diagnosed with cancer. This intervention encompasses educational initiatives, counseling sessions, and training programs, all aimed at enhancing the overall well-being of children grappling with cancer. The findings of the study also emphasize the importance of nurses being aware that psychological intervention is a crucial aspect of providing comprehensive and high-quality nursing care for children with cancer. Consequently, the outcomes of this review may serve as valuable input for relevant stakeholders to incorporate psychological interventions into the nursing curriculum, thereby facilitating the enhancement of nursing students' skills during their collegiate education.

Conclusion

This review shows that many studies have identified the effectiveness of psychological interventions on psychological and physiological responses. However, research assessing the impact of psychological interventions on neuroimmunological markers is still very limited. This systematic review shows that psychological interventions positively impact psychoneuroimmunological markers in children with cancer. So, we recommend the use of psychological interventions as an additional intervention in pediatric cancer. This study offers a new integrative model demonstrating the interaction between several factors that influence stress in children with cancer through neuroendocrine and immune mechanisms. Meanwhile, this integrative model also shows how psychological interventions can modulate the effects of these various factors on neuroendocrine and immune mechanisms, ultimately affecting health outcomes. In addition, little literature evaluates possible mediation pathways, such as the effect of psychological interventions on the neuroendocrine system and the immune system, so this new integrative model framework can be utilized. Future researchers need to test all of these new integrative models, including factors that influence stress in children with cancer, modify psychological interventions, and evaluate their mechanisms on the neuroendocrine and immune systems. This will reveal the complex interactions among these components and understand their relevance to health outcomes.

Authors Contribution

IH: Do Conceptualization, Methodology, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing. NN: Supervision, Methodology, Investigation, Validation; IK: Do Supervision, Validation, Investigation, Data Curation; WFR: Validation, Formal analysis, Investigation, Data Curation, Writing - Original Draft; ZH: Project administration, Supervision; TR: Project administration, Data Curation.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

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Conflict of interest

The authors declare no conflicts of interest concerning the publication of this paper.

Ethical approval

This research is not research involving humans or animals, so the authors do not require ethical approval.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anr.2023.07.001.

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