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REVIEW ARTICLE

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A systematic review to explore the effectiveness of physical health and psychosocial interventions on anxiety, depression and quality of life in people living with blood cancer

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ABSTRACT

Problem identification: Anxiety and depression are more prevalent in hematological cancer patients who experience unpredictable illness trajectories and aggressive treatments compared to solid tumor patients. Efficacy of psychosocial interventions targeted at blood cancer patients is relatively unknown. This systematic review examined trials of physical health and psychosocial interventions intending to improve levels of anxiety, depression, and/or quality of life in adults with hematological cancers.

Literature search: PubMed and CINAHL databases were used to perform a systematic review of literature using PRISMA guidelines.

Data evaluation/synthesis: Twenty-nine randomized controlled trials of 3232 participants were included. Thirteen studies were physical therapy, nine psychological, five complementary, one nutritional and one spiritual therapy interventions. Improvements were found in all therapy types except nutritional therapy.

Conclusions: Interventions that included personal contact with clinicians were more likely to be effective in improving mental health than those without.

Implications for psychosocial oncology: Various psychosocial interventions can be offered but interactive components appear crucial for generating long-standing improvements in quality of life, anxiety and depression.

KEYWORDS

anxiety; depression; hematological cancer; psychosocial; quality of life

Background

In the United Kingdom 40,000 people are diagnosed with blood cancer each year and 250,000 are currently living with blood cancer. Promisingly,

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the survival rates for many types of blood cancer have increased substantially over the past decade: leukemia and myeloma five-year survival rates are over 50%, Non-Hodgkin's lymphoma is 65.9% and Hodgkin's lymphoma is 82.3%.[39] However, despite these increases in survival, the blood cancer patient pathway is frequently challenging, with treatment regimens for hematological malignancies often lengthy, aggressive, and an unpredictable illness trajectory compared to solid tumors,[2] with related widespread physical and psychological repercussions for patients.[53]

The psychological and social burden of a cancer diagnosis is considerable and can lead to patients experiencing higher levels of anxiety and depression than the general population.[31] Occasionally, emotional and psychological distress following a cancer diagnosis can lead to outcomes such as suicide or cardiovascular fatalities[25] and the presence of depression and anxiety can adversely affect cancer treatment, recovery and survival outcomes.[56] A number of studies have reported the prevalence of anxiety and depression of blood cancer patients as being higher than in patients with other forms of cancer.[1,18,28,35] Depression and anxiety may be greater in blood cancer patients due to the uncertainty they face from living with a non-solid tumor.[53] It may also be due to the significant impact on their quality of life. A systematic review of the impact of hematological malignancies on quality of life, identified deterioration in many areas of patients' lives including physical, psychological, social and even cognitive functioning.[5]

Hematological cancer patients often undergo chemotherapy treatment, which requires patient to isolate. Not only are physical and mental wellbeing impacted by chemotherapy itself, but the experience of isolation also negatively impacts the quality of life, with patients often feeling lonely.[54] Yet, a recent study identified considerable variation in the psychosocial support that patients receive and less than half of professionals agreed that their patients' psychosocial wellbeing were well supported.[13] Moreover, 85% of doctors and 40% of nurses stated they had no received training in the assessment and management of psychological needs of blood cancer patients.[13]

Multiple meta-analyses and literature reviews have focused on the effectiveness of psychosocial interventions in reducing anxiety and depression and increasing quality of life in cancer patients. Barsevick et al.[9] systematically reviewed 36 studies and concluded that psychoeducational interventions, including behavioral therapy, reduced depression in cancer patients. Similarly, a meta-analysis of 37 published controlled outcome studies conducted by Rehse and Pukrop[43] found that psychosocial interventions of at least 12 wk in length improved the quality of life of cancer patients. However, these studies included in these reviews either solely focused on patients with solid tumors or the majority of the study sample population were patients with solid tumors. Bryant et al.[15] conducted a review on the psychosocial outcomes of individuals with hematological

cancers, aiming to understand the proportion of measurement, descriptive and intervention study designs conducted in this area, as well as their efficacy in improving anxiety and depression. Few studies found improvements in psychosocial outcomes in blood cancer patients, with only five of the included studies being classed as randomized controlled trials (RCTs) and the methodological quality of these studies was described as variable.[15]

Thus, despite widespread evidence of the positive benefits of psychosocial interventions in enhancing mental health and health-related quality of life in cancer patients with solid tumors, there remains a paucity of evidence relating to the effectiveness of these psychosocial interventions targeted specifically at blood cancer patients. From the differences in prognosis and treatment for hematological malignancies compared to solid tumors, it is logical to expect that the psychosocial impact will also vary, and therefore it is important to ascertain which interventions improve the well-being of blood cancer patients.

This systematic review aims to build upon previous reviews on this topic, with an updated literature search for RCTs. It also has a broader scope as the definition of psychological outcomes has been extended to include measures of health-related quality of life. Thus, the aim of this paper is to report on a systematic review of RCTs of physical health and psychosocial interventions that aimed to improve levels of anxiety, depression, and health-related quality of life in adults with blood cancer.

Methods

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[37] The protocol for this systematic review was registered on PROSPERO, the international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=209492) in November 2020.

Procedure

The search strategy was limited to human studies published in peer reviewed journals between the years 2000 – 2021 that were written in the English Language. Systematic searches of PubMed and CINAHL were undertaken between June 2020 and December 2021. The keywords and index terms in Table 1 were used to search for relevant studies. The reference lists of all studies included in the review were also checked for relevant studies, as well as any related systematic reviews and literature reviews in this area. Grey literature was included in the search strategy but did not yield any results.

Table 1. Keywords and index terms used in systematic search of literature.

Condition	haematological cancer" OR "haematological oncology" OR "haematological neoplasm*" OR "blood cancer" OR leukemia OR leukemia OR lymphoma OR myeloma OR "Hodgkin's disease" OR "non-Hodgkin's lymphoma" OR "Myeloproliferative neoplasms" OR [leukemia[MeSH Terms]))
Intervention	(interven* OR counsel* OR support OR exercis* OR "physical activit*" OR "cognitive behavioral therapy" OR "cognitive behavioral therapy" OR CBT OR mindful* OR meditat* OR telehealth OR nutrition OR diet* OR yoga OR singing OR (psychological intervention[MeSH Terms]))
Outcome measure	psycho* OR distress OR depress* OR anxiety OR "post- traumatic stress" OR "quality of life" OR "mental wellbeing" OR "mental health" OR emotion OR wellbeing OR stress)

Eligibility

To be eligible for inclusion in the review, specific criteria were outlined. Studies needed to have utilized an RCT design. To be eligible for inclusion in the review, specific criteria were outlined. Studies needed to have utilized an RCT design. This review chose to only include RCT studies because this study design is the gold standard for testing the efficacy of interventions, as it reduces the bias inherently present in other study designs. This was a key consideration when designing this systematic review, as a previous review by Bryant et al.[15] included a variety of study designs and thus the papers included varied in quality and limited the conclusions that could be drawn. Study primary and/or secondary outcome measures included anxiety, depression or health related quality of life (HRQoL). Participants were aged 18 years or over and studies were only included if the majority of the study population sampled (>66%) had a diagnosis of blood cancer. Additionally, all included RCTs tested the effectiveness of a psychosocial intervention for blood cancer patients implemented in any setting. In accordance with previous reviews[15,50] a psychosocial intervention was considered an intervention that was designed to lead to psychological change or behavioral change. Studies that combined any psychosocial intervention with pharmacological or physical treatments were included. There were no restrictions on blood cancer stage or type of treatment undertaken.

Study selection

Once the database searches were completed, duplicates were removed. Titles and abstracts of identified citations were screened for eligibility according to the predefined Patient, Intervention, Comparison, Context, Outcome (PICCO) criteria listed below (Table 2). The remaining full text papers were collated and screened for inclusion. Three reviewers undertook the screening process to ensure that a rigorous and comprehensive process was adhered to. Any discrepancies relating to whether a paper should be included in the review were discussed by the reviewers (VA, AF, MA, PD,

Table 2. PICCO Criteria for included studies.

Population	Adults aged 18 years or over who have been diagnosed with hematological cancer. Anyone pre, post or currently receiving treatment.
Intervention	Any psychosocial intervention with the aim of improving anxiety, depression, or quality of life. Studies that evaluate psychosocial interventions combined with pharmacological or physical treatments.
Comparison	Care as usual Non-psychosocial intervention
Context	Any setting including inpatient, outpatient, community and home
Outcome	Measures of depression, anxiety and quality of life including: • GAD-7 • Beck Depression Inventory • MANSA • MADRAS • HRQOL (Health related quality of life) • EQ-5D-5L

FW). If no agreement could be achieved, then this was discussed at team meetings by the entire team until consensus was reached.

Data extraction

Data were independently extracted from each included paper by two authors (VA, AF, JB, MA and FW), utilizing a data extraction form developed from a Cochrane Collaboration template.[34] Any discrepancies in the data extraction process were resolved by a third researcher. The following information was systematically extracted from all the included articles: study authors, date of publication, study population and participant characteristics (sample size, age, gender, country of origin, type of cancer, study methodology, setting and duration), method of outcome measurement, study outcomes and results. Where possible, data on experimental conditions, including the number of study arms, name and description of intervention(s) and comparator(s) groups were also extracted.

Quality appraisal

The quality of the included studies and the risk of bias were independently assessed by at least two authors, using the Critical Appraisal Skills Programme checklist for Randomized Controlled Trials.[21]

Data analysis

Due to heterogeneity of the studies included in the review, meta-analysis was not conducted. However, all data were analyzed thematically to generate a descriptive and narrative synthesis.[41] For the purposes of the analysis, the included studies' data was split into primary and secondary

outcome measures and then further funneled into categories by intervention type: physical therapy interventions (e.g. Endurance training), complementary therapy interventions (e.g. Art Therapy, Hypnotherapy), psychological therapy interventions (e.g. Cognitive Behavioral Therapy), nutritional therapy interventions (e.g. Personalized nutrition programme) and spiritual therapy interventions (e.g. Spiritual Care).

Results

Included studies

The database searches returned 7522 articles to be assessed for eligibility. A total of 249 duplicates were removed, leaving 7273 for inclusion. After screening the titles and abstracts of these studies, 7070 were deemed to not meet the eligibility criteria for the review, leaving 203 abstracts remaining. On further inspection of the abstracts, an additional 157 were excluded. 46 of these remaining papers were reviewed by two authors. Upon examination, 17 studies were deemed to not meet the inclusion criteria. The main reasons for papers being excluded at the full text screening stage were as follows: wrong study design ($n = 10$); using the same study data as other included papers ($n = 3$); over one third of participants not being blood cancer patients ($n = 1$); not having access to the full text paper ($n = 2$); and not being explicit about the outcome measures used ($n = 1$). Therefore, twenty-nine studies were included in this review (Figure 1).

Study characteristics

All included papers were published between 2000 and 2021. 44% of the studies identified were physical therapy interventions designed to reduce anxiety, depression and/or HRQoL. Furthermore, 17% of included studies were complementary therapy interventions, 31% psychological therapy interventions, 4% nutritional therapy interventions and 4% spiritual therapy interventions. A total of 10 studies investigated the efficacy of psychosocial interventions on supporting individuals manage various aspects of undergoing or recovering from receiving hematopoietic stem cell transplants. In total, 3232 participants were recruited to the studies, with a wide range of blood cancers, including multiple myeloma, B-cell lymphoma, T-cell lymphoma, acute myeloid leukemia, acute lymphoblastic leukemia, Hodgkin lymphoma and non-Hodgkin lymphoma. Participants' ages ranged from 18 to 74 years, with a mean age of 50.5 years and 43.8% were women. Studies were conducted in many continents including Europe, Australasia, North America and Asia. Table 3 provides an overview of the characteristics of included studies.

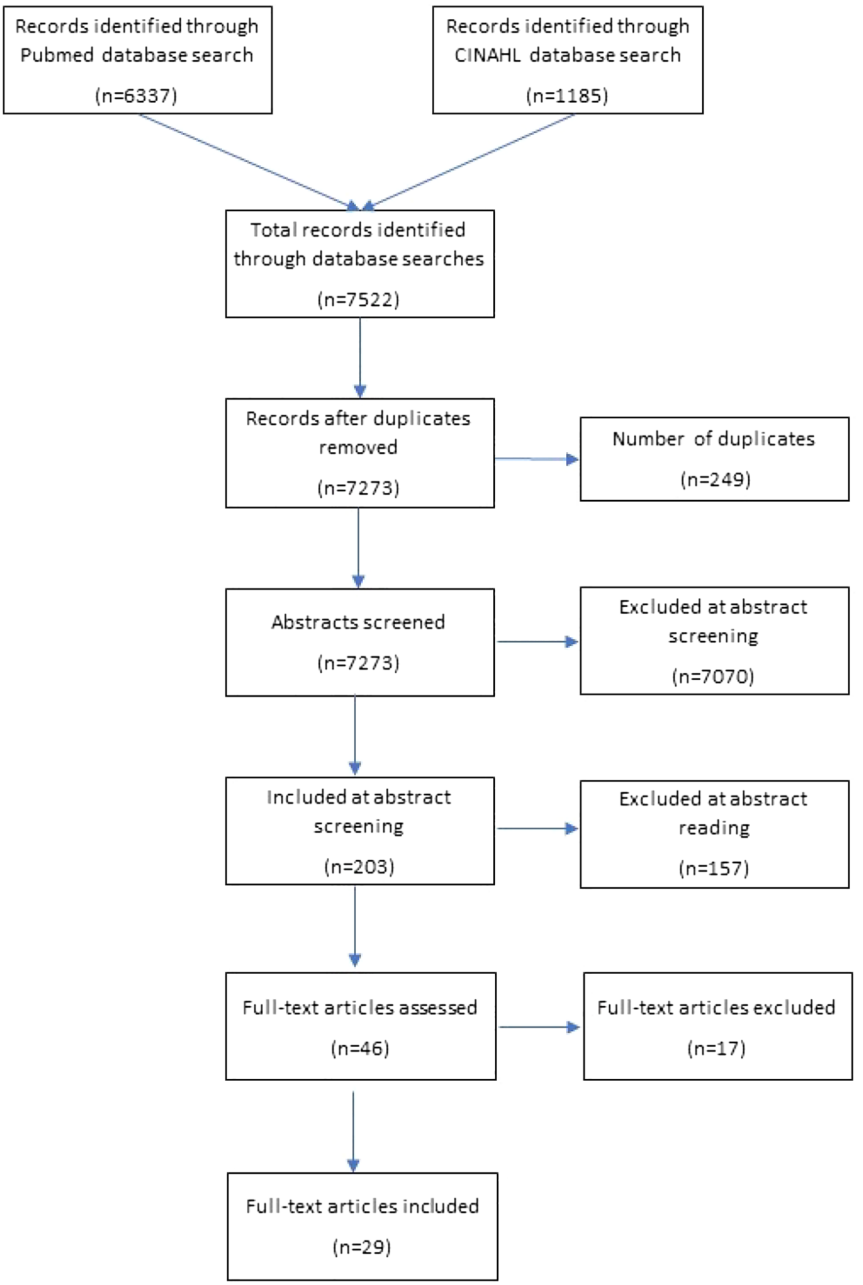

Figure 1. PRISMA flowchart.

Quality of included studies

All included studies were RCTs and were deemed to be of adequate to good quality according to the Critical Appraisal Skills Programme Checklist.[21] The risk of bias of studies included in the review is summarized in Table 4. The nature of the interventions included meant that

Table 3. Characteristics of randomized control trials included in the systematic review.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
10	Physical activity for patients undergoing an allogenic hematopoietic stem cell transplantation: benefits of a moderate exercise intervention	Europe	3 years.	Hematopoietic stem cell transplant patients, of who had: Acute myeloid leukemia, chronic lymphocytic leukemia, or chronic myelogenous leukemia. 33 42.1 55	Exercise: Strength and endurance training twice a day 20 – 30 min in total supervised	EORTC QLQ-C30	No significant differences in quality of life between the intervention and controls groups ($p>.05$).
26	A randomized controlled trial comparing the effects of a 12-week supervised exercise versus usual care on outcomes in hematological cancer patients	Australia	18 months.	Non-Hodgkin lymphoma, Hodgkin lymphoma and Multiple myeloma. 37 48.9 Not reported	Exercise: 12-week supervised tailored exercise intervention including an individualized programme, diary, gym access and a patient information pack.	Functional Assessment of Cancer Therapy—General (FACT-G) The Hospital Anxiety and Depression Scale (HADS)	Statistically significant improvements in quality of life assessed by the FACT-G for the intervention group compared to the control from baseline to week 12 ($p=0.005$) and between weeks 12 – 24 ($p=.020$). No statistically significant differences for depression or anxiety on the HADS between groups from baseline to week 12 ($p=.23$, $p=.88$ respectively), but significant reduction in anxiety in the intervention group compared to controls was seen from week 12-24 ($p=.028$).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
20	Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients	North America	3 years	Non-Hodgkin's Lymphoma indolent, Non-Hodgkin's Lymphoma aggressive or Hodgkin's lymphoma 122 53.2 41	Exercise: supervised program by exercise physiologists designed to maximize cardiovascular fitness completed on an upright or recumbent cycle ergometer (Life Fitness, Schiller Park, IL) three times per week for 12 wk.	The Trial Outcome Index-Anemia (TOI-An) from the Functional Assessment of Cancer Therapy-Anemia (FACTAn) scale The Happiness scale The short-form (SF) Center for Epidemiological Studies-Depression scale The SF Spielberger State Anxiety Inventory	Post intervention, exercise group superior to control for overall QoL (p=.021), happiness (p=.004), and depression (p=.005). At 6-months, a borderline significant change was observed in exercise group for overall QoL (p=.054), and significant differences for happiness (p=.034) and depression (p=.009)
30	Relaxation versus exercise for improved quality of life in lymphoma survivors-a randomized controlled trial	Europe	2 years and 3 months	Lymphoma 46 61 63	Exercise: The exercise intervention comprised a programme of aerobic, upper and lower limb resistance exercise, core stability and stretches to be performed independently at home.	The EORTC QLQ-C30 summary score	Intervention group demonstrated significantly higher scores on QoL compared to controls at 12 wk (p = 0.029).
15	The Effects of Exercise on Patient-Reported Outcomes and Performance-Based Physical Function in Adults With Acute Leukemia Undergoing Induction Therapy: Exercise and Quality of Life in Acute Leukemia (EQUAL)	North America	13 months	Acute myeloid leukemia or acute lymphocytic leukemia 17 Unclear 29.4	Exercise: individualized mixed-modality program supervised by exercise sport science specialists.	The PROMIS short form measures of fatigue (8 items), anxiety (6 items), depression (6 items), and sleep disturbance (8 items).	Overall, no statistically significant differences in change scores from pre intervention to post intervention were seen (Fatigue p=.11; Anxiety p=.44; Depression p=.35; Sleep disturbance p=.38).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
4	A pilot phase II RCT of a home-based exercise intervention for survivors of AML	North America	2 years	Acute myeloid leukemia 40 56.1 55.3	Exercise: individualized exercise program designed by a certified exercise physiologist (CEP).	QLQ-C30 The Hospital Anxiety and Depression Scale (HADS)	No significant differences between the intervention and control groups global QoL scores (p=.15), HADS Anxiety (p=.57) and depression scores (p=.92).
17	A nurse facilitated mind-body interactive exercise (Chan-Chuang qigong) improves the health status of non-Hodgkin lymphoma patients receiving chemotherapy: Randomized controlled trial	Asia	1 year	Non-Hodgkin Lymphoma 96 60.2 42.7	Exercise: Chan-Chuang qigong programme	Chinese version of the EORTC QLQ-C30	The subscales of Emotional Function, Social Function, Global Health, Fatigue, Pain, Cognitive Function, and Physical Function on the EORTC QLQ-30 significantly improved in the intervention group compared to controls post-intervention (All p's <.001).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
52	Effects of a partly self-administered exercise program before, during, and after allogeneic stem cell transplantation	Europe	21 months	Hematopoietic stem cell transplant patients, of who had: Acute myeloid leukemia, acute lymphoblastic leukemia, secondary acute myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, medulloblastoma, myelodysplastic syndrome, or chronic myelogenous leukemia. 105 48.8 34	Exercise: The outpatient intervention was conducted self-directed at home. The intervention took place 5 x weekly 20–40 min. Inpatient period was partly supervised for 2 times per week and adapted to the conditions of an isolation unit.	EORTC QLQ-C30 The Hospital Anxiety and Depression Scale NCCN distress thermometer	No significant group differences post-intervention for EORTC total QoL scores (p=.30), though the pain score significantly reduced over time for the intervention group compared to controls (p=.04). Significant group differences for HADS "anxiety" (p = .01) post- Intervention, where "anxiety" higher in exercise group. No significant difference between groups on depression scores (p=.07). No significant reduction in global distress between groups post hospital discharge (p = .14).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
48	Exercise program improves therapy-related side-effects and quality of life in lymphoma patients undergoing therapy.	Europe	3 years 2 months	Hodgkin's disease, B-Cell Non-Hodgkin Lymphoma, T-Cell Non-Hodgkin Lymphoma, Multiple myeloma, or N ID*/ relapse/PD 61 46 25	Exercise: Supervised sessions of aerobic endurance training, Sensorimotor training and strength training. Training took place twice per week for 36 wk.	EORTC QLQ-C30	The intervention group significantly improved in QOL scores within the first 12 wk compared to the control group ($p = 0.03$). There was also a significant improvement in emotional functioning between 12 and 24 wk for the intervention group compared to controls ($p = .007$)
33	Internet-Assisted Cognitive Behavioral Intervention for Targeted Therapy–Related Fatigue in Chronic Myeloid Leukemia: Results From a Pilot Randomized Trial	North America	2 years	Chronic myelogenous leukemia 44 55 48	Psychosocial: one to one CBT therapy delivered by FaceTime, with the initial session face-to-face. The majority of participants received at least 10 sessions scheduled between 1–2 wk apart over 18 wk.	Functional Assessment of Cancer Therapy -General (FACT-G)	CBT intervention group demonstrated significant improvements in their quality-of-life total score at follow up compared to controls ($p < .005$).

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Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
22	Internet-based program for coping with cancer: a randomized controlled trial with hematologic cancer patients	Europe	17 months	Acute myeloid leukemia, chronic lymphocytic leukemia, or chronic myelogenous leukemia 186 47.3 60	Psychosocial: Online guide CBT-based techniques. A 4-week intervention consisting of 4 modules of psychoeducation, CBT techniques and exercises. Patients communicated with psychologists *via* email about program content. No supplementary counseling provided.	Mental Adjustment to Cancer (MAC) scale Psychological distress evaluated using the Brief Symptom Inventory (BSI).	The Internet-based program only had a significantly improved patients' "fighting spirit" in the intervention group compared to controls after 4 wk (p=.003).
44	Emotion And Symptom-focused Engagement (EASE): A randomized phase II trial of an integrated psychological and palliative care intervention for patients with acute leukemia	North America	20 months	Acute myeloid leukemia or acute lymphocytic leukemia. 124 52.9 38.1	Psychosocial: EASE intervention integrates supportive psychotherapy with trauma-focused CBT. Patients received between 8–12 psychotherapeutic sessions of 30–60 min each, over 8 wk.	Quality of life (QOL) measured with Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (FACIT-Sp), Beck Depression Inventory-II (BDI-II). Traumatic Stress (SASRQ).	No significant differences in depression and QoL scores between intervention and control groups at any time point (p's .121–881). The intervention group showed significantly lower traumatic stress scores at 4 and 12 wk compared to the control group (p=.048 and p=.033 respectively).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
14	Effects of live music during chemotherapy in lymphoma patients a randomized, controlled, multi-center trial	Europe	3 years, 10 months	Hodgkin and Non-Hodgkin lymphoma. 143 60 44	Complementary Therapy – Music: Patients either listened to live, prerecorded or no music whilst receiving chemotherapy for 30 min.	Anxiety STAI-Y1 QoL EORTC-QOL-30	The reduction in patients' anxiety in live music group compared to standard care was borderline statistically significant ($p = 0.05$). No significant differences in anxiety between and prerecorded and standard care groups ($p = 0.18$). There was no significant difference in EORTC-QOL scores between the live and standard care groups ($p = .56$), and prerecorded and standard care groups ($p = .65$).
55	Effects of mindfulness-based psychological care on mood and sleep of leukemia patients in chemotherapy	Asia	Not reported	Acute lymphocytic leukemia, acute, myeloid leukemia, chronic lymphocytic leukemia or chronic myeloid leukemia. 65 39 48.7	Complementary Therapy – Mindfulness: Structured group program consisted of daily therapeutic sessions for five weeks. Caregivers guided the participants individually. Participants then practised independently, and caregivers provided help when required.	Self-Rating Anxiety Scale (SAS) The Self-Rating Depression Scale (SDS) Pittsburgh Sleep Quality Index (PSQI)	The intervention group showed significant improvements in quality of sleep ($p = .001$), anxiety ($p < .001$) and depression ($p < .001$) compared to controls.

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
19	Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma	North America	Duration of study unclear.	Patients with lymphoma. 39 51 30.8	Complementary Therapy -Tibetan Yoga: Patients received seven weekly yoga sessions. This yoga program consisted of controlled breathing and visualization, mindfulness, and postures. Participants also received printed and audio materials to guide them through the techniques they had learned in these sessions.	Depression (Center for Epidemiologic Studies-Depression; CES-D) Psychological adjustment was assessed across several domains, including distress (Impact of Events Scale; IES), anxiety (Speilberger State Anxiety Inventory; STATE) Sleep disturbances (Pittsburgh Sleep Quality Index; PSQI).	There were no significant differences between groups on scores of State Anxiety (p=.90), depression (p=.93) and Impact of Events (p=.92) at follow up. The intervention group showed significantly lower PSQI total score ($p = 0.004$) at follow up. Similarly, they also showed significantly higher score on Sleep Quality ($p = 0.02$), Sleep Latency ($p = 0.01$), Sleep Duration ($p = 0.03$), and lower use of Sleep Medications ($p = 0.02$ compared to controls at follow up.
46	A Randomized Trial of Hypnosis for Relief of Pain and Anxiety in Adult Cancer Patients Undergoing Bone Marrow Procedures	North America	Duration of study unclear.	Patients undergoing bone marrow aspirates and biopsies with diagnoses of: Leukemia, Lymphoma, Plasma cell dyscrasias, Myelodysplastic syndrome, Myeloproliferative disorder, and Aplastic anemia. 80 59.5 47.5	Complementary Therapy - Brief hypnosis: Intervention conducted approximately 15 min prior to bone marrow procedure.	Visual Analogue Scales to measure of pain and anxiety.	Significant reduction in anxiety in the intervention group compared to the control group (p=.026). No significant differences between intervention and control groups for pain scores (p=.92).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
36	Open Window: a randomized trial of the effect of new media art using a virtual window on quality of life in patients' experiencing stem cell transplantation	Europe	4 years and 2 months.	Hematopoietic stem cell transplant patients. 199 Unclear 40.7	Complementary Therapy - Art therapy: Open Window is a digital technology in the patients' hospital rooms that creates a virtual window. This is controlled by the patient, allowing them to choose a range of art and media experiences. Patient in the intervention group accessed this technology throughout their hospital stay.	The Hospital Anxiety and Depression Scale (HADS) and the Distress Thermometer (DT).	Intervention group had significantly lower levels of anxiety than control only at T2 ($p = 0.001$), T3 ($p = 0.041$) and T5 ($p = 0.035$). Depression scores were significantly reduced in the intervention group compared to the control group at T2 only ($p = 0.022$). No significant differences in levels of distress between groups at any time point ($p = 0.37$).
	Does a spiritual care program affect levels of depression in patients with Leukemia? A randomized clinical trial	Asia	Unclear	Leukemia 64 41.6 39	Complementary Therapy - Spiritual Therapy: Planned spiritual care program including two major components of supportive presence and support for religious rituals.	The depression subscale from the 42-item depression, anxiety and stress scale (DASS-42) The Depression Inventory (DBI) The profile of mood states (POMS)	Depression scores significantly reduced in the intervention group compared to the control group ($p < 0.001$).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
3	A phase II exercise randomized controlled trial for patients with acute myeloid leukemia undergoing induction chemotherapy	North America	1 year, 8 months.	Acute Myeloid Leukemia. 81 57 45.7	Exercise: Supervised intervention delivered 4-5days per week during admission, 30–60 min, consisting of aerobic (treadmill, hall walking, stationary bike), resistance training (BW, band, free weights), and static stretching.	Global Quality of life (EORTC QLQ-C30) Fatigue (FACT-F) Anxiety/depression (HADS)	No significant difference between control and intervention groups for QoL (p=.062), Fatigue (p=.23), Emotional functioning (p=.64), HADS anxiety (p=.20) and depression scores (p=.50).
6	A randomized controlled trial of problem-solving training (PST) for hematopoietic stem cell transplant (HSCT) patients: Effects on anxiety, depression, distress, coping and pain.	Europe	Not reported	Hematopoietic stem cell transplant patients, of who had: Acute myeloid leukemia, acute lymphoblastic leukemia, secondary acute myeloid leukemia, chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, medulloblastoma, myelodysplastic syndrome, non-Hodgkin lymphoma or chronic myelogenous leukemia. 95 52.6 37.9	Psychosocial: Intervention spread over 5 sessions and completed on day 1, +2, +4, +7, and +9 before or after the HSCT Intervention group: 5-steps, 1) problem orientation, 2) problem definition, 3) generation of alternatives, 4) decision making, 5) implementation of solution and verification.	Anxiety / depression (HADS) Overall Distress (SCL-K-9) Extent of existing distress (Distress Thermometer) Ability to cope (Brief COPE)	Anxiety scores were significantly lower for the intervention group compared to the controls over time (t2 p=.003; t3 p=.04) whereas depression scores did not significantly differ (t2 p=.24; t3 p=.87). At t2 and t3, the mean distress of the intervention group was significantly lower than the control group (t2 p=.0001; t3: p = 002). Active Coping scores were significantly greater for the intervention group compared to controls (t2 p=.01; t3 p=.01).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
7	Intensive patient's care program reduces anxiety and depression as well as improves overall survival in de novo acute myelocytic leukemia patients who underwent chemotherapy: a randomized, controlled study	Asia	3 years	De novo acute myeloid leukemia patients. 220 43.9 49.1	Psychosocial: 3 part intervention delivered by trained nurses AML health education Manual given first week post-enrolment (6 parts). Hospital based education sessions each week for 60 min in first 3 months Psychological guidance, 60 min, every 2 wk for 6 months Telephone counseling, 25–30 min, every 2 wk, 3 months after finishing month psychological counseling.	Anxiety / depression (HADS) Zung Self-Rating Anxiety Scale (SAS) Zung Self-Rating Depression Scale (SDS)	Only at 12 months the intervention group showed significantly lower scores on the HADS anxiety and depression scale (both $p<.05$). SAS score was significantly lower in the intervention group at month 6 ($p<.05$), 9 ($p<.01$), and 12 ($p<.001$). SDS score was significantly lower in the intervention group at month 12 ($p<.05$).
8	Inspiratory muscle training in allogeneic hematopoietic stem cell transplantation recipients: a randomized controlled trial	Asia	Not reported	Allo- HSCT recipients. 38 36.6 36.8	Exercise: 30 min per day, 7 days per week for 6 wk at 40% of baseline maximal inspiratory pressure (MIP), 25–30 breaths.	Fatigue (FIS) Depression (MADRS) Quality of life (EORTC QLQ C30)	No significant differences in fatigue, QoL and depression scores between the intervention and control groups (p's>.05).

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Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
24	Effect of Inpatient Palliative Care on Quality-of-Life 2Weeks After Hematopoietic Stem Cell Transplantation: A Randomized Clinical Trial	North America	1 year, 10 months.	Patients hospitalized for Hematopoietic stem cell transplant. 160 60 56.9	Psychosocial: patients seen by palliative care clinicians twice per week during HSCT hospitalization, focused on management of physical /psychological symptoms.	Quality of life (FACT-BMT) Fatigue (FACT-F) Anxiety/Depression (HADS) Symptom burden (ESAS) Patients' posttraumatic stress disorder (PTSD) symptoms	The intervention group had a higher quality of life score than controls at week 2 (p=.02). They also showed significantly lower scores than controls on symptom burden (p=.02), HADS depression (p=.008) and anxiety (p<.001). At 3 months, the intervention group had a higher quality of life score than controls (p=.048) and lower scores on the HADS depression scale (p=.002) and PTSD scores (p=.002). No significant differences between intervention and control groups on symptom burden (p=.21) and HADS anxiety scores (p=.13).

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Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
32	A randomized trial on the effect of a multimodal intervention on physical capacity, functional performance and quality of life in adult patients undergoing allogeneic SCT	Europe	2 years, 7 months.	Hematopoietic stem cell transplant patients, of who had: Acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, paroxysmal nocturnal hemoglobinuria, Waldenstorm's macroglobulinemia, Aplastic Anemia, myelofibrosis or chronic myelogenous leukemia. 95 39.1 38.1	Exercise: Intervention delivered from admission until discharge Intervention: aerobic exercise (stationary cycling, 15–30 min, 5 times per week, 50–75% HRR, RPE 10–13) stretching (15–20 min, 5 times per week, 1–2 sets, 10–12 reps, 15–30 sec hold) resistance exercise (15–20 min, 3 times per week, 1–2 sets, 10–12 reps, RPE 10–13) relaxation (20 min, twice per week, muscle tensing/relaxation, RPE 6–9), psychoeducation (5 times per week, based on behavioral and cognitive therapy techniques).	Quality of life (EORTC QLQ C30) Fatigue (FACT-An) Anxiety / distress (HADS)	No significant differences in QoL, fatigue, HADS anxiety and depression (all p's>.05).

(*Continued*)

Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
45	Effects of individualized nutrition after allogeneic hematopoietic stem cell transplantation following myeloablative conditioning; a randomized controlled trial	Europe	5 years, 6 months.	Allo- Hematopoietic stem cell transplant patients of who had: Acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome or chronic myelogenous leukemia. 117 Unclear 38.5	Complementary Therapy – Nutritional therapy: Intervention started when conditioning was initiated and continued until hospital discharge minimum daily energy intake of 126 kJ (30 kcal)/kg body weight and protein intake of 1.5–2.0 g protein/kg body weight during admission for HSCT. Enteral feeding used between days +3 and +5.	Quality of life (EORTC QLQ C30)	No difference in QoL scores between the intervention and control (p=.49).
47	A multi-center randomized controlled trial to reduce unmet needs, depression, and anxiety among hematological cancer patients and their support persons	Australia	Not reported.	Acute myeloid leukemia, acute lymphoblastic leukemia, Burkitt Lymphoma or Lymphoblastic. 60 50 31.7	Psychosocial: Web tool, tailored info for diagnosis, self-guided, available from diagnosis through treatment, Nurse delivered phone support, intended to supplement web tool.	Depression/anxiety (HADS) DASS-21	The control group only had significantly higher anxiety scores at week 2 compared to the intervention group (p=.016). No differences in depression scores between the groups were observed (p>.05).

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Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
51	Endurance and resistance training in patients with acute leukemia undergoing induction chemotherapy—a randomized pilot study	Europe	2 years, 8 months.	Acute myeloid leukemia, acute lymphoblastic leukemia, secondary acute myeloid leukemia and treatment-related acute myeloid leukemia. 29 48.6 41	Exercise: Intervention delivered throughout hospitalization, 3 times per week for 30–45 min, supervised by sports therapist. Aerobic exercise (stationary bike) 30 min at 60–70% HRmax, RPE 12–14 Resistance exercise (dumbbells, resistance bands) 4–6 exercises, RPE 12–14.	QOL (EORTC QLQ C30)	No significant differences in QoL post intervention (p=.76).
49	An Online Randomized Controlled Trial, with or without Problem Solving Treatment, for Long-Term Cancer Survivors after Hematopoietic Cell Transplantation	North America	Not reported	Hematopoietic cell transplantation survivors who had: Acute leukemia, Chronic myelogenous leukemia, Non-Hodgkin lymphoma, Myelodysplasias, Multiple Myeloma or Hodgkin lymphoma. 755 52 55.1	Psychosocial: The Problem-Solving intervention focused on identifying problems and solutions through goal setting. The initial session was 1 h with subsequent sessions lasting up to 30 min. Participants had between 3 and 7 sessions dependent on their needs, with each session scheduled every 2 wk. A subgroup of those receiving the Problem-Solving Intervention also had access to the Internet-based Survivorship Program with Information and Resources (INSPIRE). A further subgroup only had access to the INSPIRE program.	Cancer and Treatment Distress (CTXD) Symptom Checklist-90-R depression scale (SCL-90-R) Short Form 36 Health Survey (SF-36) Fatigue Symptom Inventory (FSI)	At follow up the INSPIRE + PST group's distress scores had reduced compared to controls, (p=.032). The INSPIRE only group showed a trend toward reduced scores (p=.075). No differences between any groups in the rate of change in physical functioning, fatigue and depressive symptoms (p>.05).

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Table 3. Continued.

Authors	Study	Continent	Study duration	Participants recruited Participants recruited (n) Mean age *(years) M* Gender (%female)	Description of intervention	Outcome measures	Key findings
23	Randomized Clinical Trial of Telephone-Administered Cognitive-Behavioral Therapy to Reduce Post-Traumatic Stress Disorder and Distress Symptoms After Hematopoietic Stem-Cell Transplantation	North America	Not reported	Hematopoietic stem-cell transplantation recipients. 81 50.8 52.6	Psychosocial: 10-sessions of T-CBT with the first session being approximately 90 min, and the remainder of sessions were approximately 60 min in duration. Sessions included education on illness-related PTSD symptoms and CBT, monitoring and altering maladaptive beliefs guided exposure to sensations associated with PTSD symptoms, communication skills and relaxation training.	PCL-C BSI Clinician Administered PTSD Scale for DSM-IV	Intervention group reported a reduction in general distress and fewer depressive symptoms ($p<.05$) compared to the control group. The intervention group had fewer illness-related PTSD symptoms, includingless avoidance ($p< .001$) and fewer intrusive thoughts ($p <.05$) at follow up.

Table 4. Risk of bias for studies included in this systematic review.

Study	Random sequence selection	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Total risk of bias within study
10	Low Risk	Low Risk	High Risk	High Risk	High Risk	Unclear	High Risk of Statistical Contamination Error	High risk of Bias for more than one key domains
26	Low Risk	Unclear	High Risk	High Risk	Low Risk	Low Risk	Low Risk	High risk of bias for more than one key domains
20	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
30	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk	High risk of bias for more than one key domains
15	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
4	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk	High risk of Bias for more than one key domains
17	Low Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk	High risk of bias for more than one key domains
48	Low Risk	Unclear	High Risk	Unclear	High Risk	Unclear	Unclear	High risk of bias for more than one key domains
52	Low Risk	Unclear	Unclear	Unclear	Low Risk	Low Risk	Unclear	Unclear Risk of bias for more than one key domains
	Low Risk	Low Risk	Low Risk	Low Risk	High Risk	Unclear	High Risk	High risk of bias for more than one key domains
33	Low Risk	High Risk	High Risk	High Risk	Low Risk	High Risk	Low Risk	High risk of bias for more than one key domains
22	Unclear	Unclear	High Risk	High Risk	High Risk	Unclear	Low Risk	High risk of bias for more than one key domains
44	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Unclear	Low Risk	Low Risk
14	Low Risk	Unclear	High Risk	High Risk	Unclear	Unclear	Low Risk	High risk of bias for more than one key domains
55	Low Risk	Low Risk	High Risk	High Risk	Unclear	Unclear	Low Risk	High risk of bias for more than one key domains
19	Low Risk	Low Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk	High risk of bias for more than one key domains
46	Unclear	Unclear	High Risk	High Risk	Low Risk	High Risk	Low Risk	High risk of bias for more than one key domains
36	Low Risk	High Risk	High Risk	High Risk	Low Risk	Unclear	Low Risk	High risk of bias for more than one key domains
3	Low Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	Low Risk	High risk of bias for more than one key domains

(*Continued*)

Table 4. Continued.

Study	Random sequence selection	Allocation concealment	Blinding of participants & personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Total risk of bias within study
6	Low Risk	Unclear	High Risk	Unclear	High Risk	Low Risk	Unclear	High risk of bias for more than one key domains
7	Low Risk	Unclear	High Risk	Unclear	High Risk	Low Risk	Low Risk	High risk of bias for more than one key domains
8	Low Risk	Low Risk	Low Risk	Unclear	High Risk	Low Risk	Low Risk	Low Risk
24	Low Risk	Unclear	High Risk	Unclear	Low Risk	Low Risk	High Risk. Attention-control placebo group not used.	High risk of bias for more than one key domains
32	Low Risk	High Risk	High Risk	High Risk	Low Risk	Low Risk	High Risk. Did not control for demographic differences.	High risk of bias for more than one key domains
45	Low Risk	Unclear	High Risk	Unclear	High Risk	Low Risk	Unclear	High risk of bias for more than one key domains
47	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	High Risk	High Risk. Unclear how much information patients received from clinicians as well as the intervention.	High risk of bias for more than one key domains
51	Low Risk	High Risk	High Risk	High Risk	High Risk	High Risk	High Risk. Variation in number of participants who completed each assessment due to organizational conflicts.	High risk of bias for more than one key domains
49	Low Risk	Unclear	High Risk	Unclear	Low Risk	Low Risk	Low Risk	Unclear Risk of bias for more than one key domains
23	Low Risk	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

participants could not be blinded to experimental or control arms meaning performance bias was unavoidable. Similarly, participant attrition was prominent in many studies; it is unclear whether this was directly related to the interventions under study or other confounders. Although selection bias was not evident, some studies included more male participants. Reporting bias appeared low.

Review findings

The identified RCT studies were grouped into the following categories based on the content of the intervention: physical therapy ($n = 13$), psychological therapy ($n = 9$), complementary therapies ($n = 5$), nutritional therapy ($n = 1$) and spiritual therapy ($n = 1$). Types of physical therapy intervention ranged from endurance training to mixed modality exercise programs, with some programs implemented independently at home whilst others were supervised by healthcare professionals, and one used a combination of supervised and unsupervised training. The length of the physical therapy interventions studied ranged from one day to 36 wk. Studies were categorized as psychological interventions if they included known psychological therapies such as Cognitive Behavioral Therapy (CBT), or core components of psychological therapies such as psychoeducation about anxiety and depression, developing problem-solving skills to help individuals cope with symptoms and the challenges they experience. Counseling or peer support programs that were designed to reduce anxiety, depression, distress and improve HRQoL were also included in this category. These therapies varied in format, including face-to-face and/or virtual sessions, and duration the varied from weeks to months. The RCT studies identified as complementary therapy interventions included art therapy ($n = 1$), hypnosis ($n = 1$), music ($n = 1$), mindfulness ($n = 1$) as well as Tibetan yoga, which incorporated mindfulness ($n = 1$). Only one RCT investigated nutritional therapy. This study compared the effect of individualized nutritional support to usual diet on the HRQoL of patients undergoing allogeneic hematopoietic stem cell transplantation.[45] Similarly, this review identified one RCT study of an intervention consisting of a planned spiritual care program designed to improve depression, anxiety and stress scores in blood cancer patients.[38]

Description of study outcomes

Health-related quality of life outcomes

Of the twenty-nine studies included in this review, twenty-six included a HRQoL measure.[3,4,6,8,10,14,15,17,19,20,22,23,24,26,30,32,33,36,44,45,46,48,49,51,52,55] The outcome measures of HRQoL varied from direct measures, with the EORTC

QLQ-C30 the most commonly used,[3,4,8,10,17,24,30,32,33,44,45,48,51,52] to other measures indicating of HRQoL improvements, such as coping with pain, fatigue, quality of sleep and psychological adjustment.[6,15,19,20,22,23,36,46,49,55] Many of the HRQoL measures were specifically developed for assessing these outcomes in cancer patients, for example the EORTC QLQ-C30 and the Functional Assessment of Cancer Therapy, and were therefore considered to be psychometrically strong.

Fifteen studies found significant improvements in HRQoL post-intervention. Of these studies, six were exercise interventions.[17,20,26,30,48,52] These exercise interventions varied in formats with two studies, with two studies[17,30] examining physical therapy programs implemented independently at home, whereas the other four assessed the efficacy of supervised training.[20,26,48,52] Seven studies that found significant HRQoL improvements were psychological therapy interventions.[6,22,23,24,33,44,49] The psychological therapies also differed in structure and content. One RCT investigated a face-to-face palliative care intervention focusing on the management of physical and psychological symptoms,[24] whereas another two RCTs focused on the efficacy of problem-solving training to improve psychosocial outcomes.[6,49] Three RCTs investigated CBT interventions, delivered by a therapist either *via* telephone[23] or in a virtual setting,[33] or as a self-directed internet-based program.[22] A fourth RCT investigated the efficacy of a novel program combining trauma-focused CBT and psychotherapy, delivered face-to-face.[44] The two complementary therapies were similar, with one RCT studying the efficacy of a mindfulness intervention to improve psychosocial outcomes[55] and the other of a Tibetan yoga intervention, which also incorporated mindfulness.[19]

Anxiety and depression outcomes

Twenty-two studies measured changes in patients' anxiety and/or depression scores.[3,4,6–8,14,15,19,20,22,23,24,26,32,36,38,44,46,47,49,52,55] These studies also varied in the tools used to measure anxiety and depression, including the Hospital Anxiety and Depression Scale,[4,7,26,32,52] the Visual Analogue Scales,[46] the Montgomery-Âsberg Depression Rating Scale (MADRS),[8] the short-form (SF) Center for Epidemiological Studies-Depression scale, the SF Spielberger State Anxiety Inventory[20] and the PROMIS short form measures of anxiety and depression.[15] The measures used to assess changes in individuals' anxiety and depression were considered to be psychometrically adequate, though it is acknowledged that there is a lack of literature specifically assessing these outcome measures in blood cancer patients.[57]

Twelve studies found significant improvements in anxiety and/or depression post-intervention. Three were physical exercise interventions and all were supervised.[20,26,52] Four psychological therapies were found to

significantly improve anxiety and/or depression.[6,7,23,24] Similar to the psychological therapies that were shown to improve HRQoL[6,7,22,23,24,44,49] also utilized telephone counseling as well as health education and psychological guidance as part of their intervention designed to improve psychosocial outcomes in acute myeloid leukemia patients. Four complementary therapies were found to improve anxiety and depression: a study examining the effect of hypnosis on anxiety and pain relief prior to bone marrow biopsy,[46] an RCT examining the effect of listening to live or prerecorded music on anxiety levels in patients undergoing chemotherapy,[14] an RCT assessing the effect of the art therapy on anxiety, depression, and distress in patients undergoing stem cell transplantation[36] and a mindfulness intervention.[55] Additionally, one spiritual care intervention, which included two major components of supportive presence and support for religious rituals, was also found to be effective in reducing anxiety and depression.[38]

Discussion

To our knowledge, this is the first systematic review of RCTs assessing the effectiveness of physical health and psychosocial interventions on anxiety, depression and quality of life in patients with blood cancer. Nineteen RCTs investigating a range of interventions utilized primary outcomes measures of anxiety, depression or HRQoL. A further 10 RCTs, of which all were physical interventions, investigated these as secondary outcomes.

Six studies that examined supervised or home-based exercise interventions[17,20,26,30,48,52] yielded statistically significant results regarding quality of life, depression and/or anxiety. A common factor between these studies was that participants had contact with hospital or research staff during the study duration.[17,20,26,48,52] While Hathiramani et al.[30] explored the effects of a home-based exercise intervention, participants had personal interaction with research staff at baseline for advice, instruction, demonstration, and practice. This pattern of personal contact suggests that this element of the intervention is an important factor in their success. A previous review of exercise adherence in cancer patients also found support from coaches was an important predictor of patients' adherence to exercise interventions.[40] Although those interventions aimed to improve physical health through increased engagement, similar findings in the current review potentially suggests that support from professionals is also important for the improvement of blood cancer patients' mental health.

The findings relating to the effectiveness of complementary therapies in reducing depression and anxiety in blood cancer patients indicate that more research in this area is required. The included studies encompassed complementary therapies including art therapy, yoga, mindfulness, music and hypnosis. Most of these studies reported a significant reduction in

anxiety and/or depression when comparing the intervention to usual care. Though different measurement scales were used across studies to measure levels of depression and anxiety, making cross study comparisons difficult, the findings do indicate that a variety of complementary therapies can be offered to blood cancer patients to provide them with psychological support throughout their cancer journey. Similarly, the significant improvements in depression scores in blood cancer patients who received a spiritual care program[38] highlights the important role of spiritual therapy in supporting blood cancer patients, something which is identified by other research in this area.[11,16,42] However, more studies are needed to investigate the effects of spiritual care interventions on a variety of cultures and populations to make generalizable conclusions regarding their effectiveness.

Of the four studies that investigated the use of CBT in improving blood cancer patients HRQoL and/or anxiety/depression[22,23,33,44] two utilized a virtual setting.[22,33] David et al.[22] did not find significant changes in anxiety or depression, only an increase in patients "fighting spirit", whereas Jim et al.[33] found significant improvements in HRQoL more broadly. Another study that utilized a survivorship program in a virtual environment also did not find any significant improvement on measures of depression, and only found a reduction in distress in participants who also engaged in additional problem-solving sessions *via* telephone.[49] Online interventions have many advantages, including convenience and ease of access, and their potential has been realized more fully during the recent COVID-19 pandemic. However, participants who took part in the modular format CBT sessions[22] reported limited benefits to the programme and that they would have appreciated the opportunity to share their experiences with other participants. This may suggest that although online and virtual sessions have benefits in terms of accessibility, flexibility, cost-effectiveness and inclusivity, the added value of interacting with others may have more widespread benefits than can be achieved through the sharing of information alone. This corroborates a recent systematic of the use of digital technologies in mental health.[12]

Despite differences between the interventions included in this systematic review, common themes were identified across all studies. Many psychosocial interventions reported statistically significant improvements in the mean scores of depression, anxiety and health-related quality of life of blood cancer patients when the delivery of these included some form of face-to-face interaction between those delivering the intervention and the participants. This finding was consistent across four of the five psychosocial intervention types, suggesting that the development of an interactive relationship between session facilitators and patients may be an important factor in improving symptom management and HRQoL in blood cancer patients. However, considerations need to be given regarding the cost and

feasibility of implementing interactive psychosocial interventions outside of research settings, and further research on the outcomes of interactive relationships in interventions is required.

Clinical implications

This systematic review demonstrates that the majority of studies and types of intervention were found to be effective in reducing anxiety, depression and/or health related QoL. This therefore suggests that hematological cancer patients could have a choice in the type of intervention that they engage in to reduce the psychological burden of their condition. The evidence-based intervention(s) that a patient chooses may depend on their preference and/or their stage of treatment, but with many options available this could make psychosocial support more accessible to this population. Findings from a recent study[27] suggested that people living with blood cancer were at increased risk of depression during COVID-19, due to an increasing sense of isolation. What is more, Harada, Masumoto and Kondo[29] examined the relationship between exercising alone, exercising with others, and mental health among middle-aged and older adults and discovered that exercising with others had a positive influence on participants' mental well-being compared to exercising alone. Many psychosocial interventions are currently hosted online, as a way of minimizing unnecessary face-to-face contact during COVID-19. This may result in fewer face-to-face interventions being delivered in the longer term, due to the benefits outlined above, which potentially has implications for blood cancer patients. This review suggests there may be advantages of blood cancer patients maintaining some human interaction with others, as the benefits of the psychosocial interventions may not be purely due to the content delivered within them. Though our findings potentially indicate that the relational aspects of face-to-face interventions are beneficial, many blood cancer patients may not be able to finance or access face-to-face supervised training sessions due to a lack of resource. Therefore, further work is needed to fully understand if and what the benefits of face-to-face interventions are, and how these elements can be incorporated into future online interventions.

Strengths and limitations

To date little systematic evidence has focused on the impact of psychosocial interventions in improving quality of life, anxiety and depression in blood cancer patients. The clearly defined eligibility criteria, search terms and selection strategy in this review yielded a large number of RCTs across many continents, though only two carefully selected databases were searched, which was a study limitation Most studies were of adequate to

good quality, adding confidence in the reliability of the findings. However, the heterogeneity amongst the different psychosocial interventions, as well as the time between participants' cancer diagnoses and their study participation, means that any findings should be interpreted with caution. There were noticeable differences in the intensity, duration and frequency of some of the psychosocial interventions, as well as the way they were delivered, making it difficult to draw true comparisons across studies. Across the included studies, participants received a wide range of treatments and their time since diagnosis was variable, making comparisons across studies limited. A range of scales were also used to measure anxiety, depression, and quality of life across the studies, increasing the heterogeneity of the findings. Greater consensus and consistency on scales used to measure these outcomes in future studies would improve understanding of intervention efficacy.

Conclusions

This systematic review has examined the effectiveness of RCT interventions aimed at improving HRQoL, depression and anxiety for people living with blood cancer. Most studies identified were physical therapy interventions, with some psychological, complementary, nutritional and spiritual therapy interventions. Four of the five intervention types demonstrated improvements in HRQoL, depression and/or anxiety. Future research is required to build on the review findings; however, policy makers and clinicians should consider these findings when deciding which types of psychosocial interventions to recommend to blood cancer patients. Whilst a variety of psychosocial interventions can be recommended to patients depending on their needs, preferences and beliefs an interactive component appears crucial for generating long standing improvements in the HRQoL, anxiety and depression of blood cancer patients.

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