



What information can we gain from the quality appraisal of guidelines with physical activity recommendations for cancer patients? A systematic review using the AGREE II and AGREE-REX tools

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Abstract

Purpose There has been growing amount of evidence supporting the benefits of physical activity (PA) on oncological patients' cancer-related health outcomes. Although guidelines on cancer rehabilitation are widely available, the varying quality and practical applicability limited the clinical application of PA recommendations. To assist the future development of guidelines, in this systematic review, we evaluated the quality and applicability of current cancer rehabilitation guidelines with PA recommendations and synthesized PA recommendations for the oncological population.

Methods A systematic search was conducted in PubMed, CINAHL, PEDro, EMBASE, and guideline repositories to identify guidelines with PA recommendations for cancer patients from 1 May 2016 to 1 June 2022. The quality of included guidelines was appraised using the tools "Appraisal of Guidelines for Research and Evaluation II" (AGREE II) and AGREE-REX (Recommendation Excellence). PA recommendations were synthesized from the guidelines.

Results Sixteen guidelines were extracted. The AGREE II domain "clarity of presentation" obtained the highest score, while "applicability" received the lowest, ranging from 33.33% to 98.58%. The AGREE-REX domains "values and preferences" and "implementability" generally scored lower and ranged from 45.83% to 74.17% and 55% to 88.33%, respectively. Eight high-quality guidelines were identified, and the included PA recommendations were extracted.

Conclusion There were some disparities in the quality of the included guidelines. Methodological weaknesses were commonly observed in domains "applicability," "values and preferences," and "implementability"; particular attention should be given to these domains when developing future guidelines. Furthermore, this analysis indicated that more rigorous, high-quality studies are needed to generate evidence for supporting PA recommendations and provide guidance on research gaps in the field of cancer rehabilitation.

Keywords Cancer · Physical activity · AGREE II · AGREE-REX · Practice guideline · Rehabilitation

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Introduction

Cancer is a major global health issue and one of the leading causes of death in the world, placing a substantial economic burden on both the societal and individual levels [1, 2]. In 2020, an estimated 19.3 million new cancer cases and 10.0 million cancer-related deaths occurred worldwide [1]. With advancements in cancer diagnosis, prognosis, and treatment options, the cancer mortality rates in America have declined significantly between 1991 and 2019 by a total of 32% [3], and the number of cancer survivors has increased. The 2006 Institute of Medicine landmark report “From cancer patient to cancer survivor: Lost in transition [4]” highlighted the unique issues in survivorship care faced by all cancer survivors. The report presented the potential physical and psychosocial challenges caused by cancer and/or cancer treatment (including surgery, chemotherapy, radiation therapy, hormonal therapy, immunotherapy, or a combination of the above treatment options). Cancer-related impairments include but are not limited to cardiotoxicity [5], sarcopenia [6], cancer-related fatigue [7], lymphedema [8], pain, osteoporosis, and chemotherapy-induced peripheral neuropathy [9, 10]. They can occur during active cancer treatment (acute response) and persist after treatment (long-term effects) or appear months or years after treatment ends (latent effects) [11].

The positive role of PA has been profoundly researched in cancer-related impairments and survivorship. Physical activity refers to any bodily movement produced by skeletal muscles or requires muscular contraction and results in energy expenditure [12]. As early as 1938, animal experiments have demonstrated PA as an inhibitory factor to tumor growth. Nowadays, there has been large research effort devoted to investigating the role of PA in cancer survivors; many positive impacts have been shown including lowered cancer mortality risks and improved cancer-related health outcomes [13]. According to a systematic review [14], a combined resistance training with aerobic exercise program can reduce cancer-related fatigue and improve patients’ quality of life. A clinical trial suggested that active exercises prevented lymphedema in female breast cancer patients [15]. A high-quality controlled trial demonstrated that home-based aerobic exercise combined with supervised resistance training significantly reduced arthralgia associated with aromatase inhibitor therapy in breast cancer patients [16]. Emerging evidence suggests that exercise can harness the immune system to improve colorectal cancer survival rate [17, 18]. Given the promising effects of PA intervention in this patient population, an increasing number of initiatives for the integration of PA into cancer care continuum have been put forward [19].

Clinical practice guidelines (CPGs) are protocols developed based on systematic reviews of the current available

evidence and the analyses of the benefits and harms. CPGs can assist clinicians with clinical decision-making and help identify gaps that may require further research [20]. Implementing good clinical practice guidelines could optimize clinical care quality while decreasing medical expenses and minimizing potential harm due to ineffective or unsafe interventions. Many guidelines and recommendations have supported PA intervention for cancer patients, but the wide variation in the quality of these guidelines may influence clinicians providing the optimal treatment for patients. At present, many quality assessment tools are frequently used to evaluate the guidelines [21]. As one of the most widely used instruments, the “Appraisal of Guidelines for Research and Evaluation (AGREE) II” was also recommended by WHO [22]. Numerous CPGs with PA recommendations for cancer patients have been appraised by this instrument and have met rigorous methodological quality criteria [23, 24]. However, previous studies [25] suggested that there may be a conflict between guideline methodologic quality and recommendation validity. Having high AGREE II scores does not guarantee that CPG recommendations are optimal, trustworthy, credible, or practical to implement, since some CPGs may have omitted common clinical situations or recommendations of uncertain clinical validity, which may affect the clinical application of recommendations [25, 26]. As a complementary tool to AGREE II, the Appraisal of Guidelines Research and Evaluation–Recommendations Excellence (AGREE-REX) was specifically developed to evaluate the clinical credibility and implementability of recommendations [26]. Therefore, the purpose of this review was to understand and appraise the quality of current CPGs with PA recommendations for cancer survivors and the clinical application of their recommendations using the AGREE II and AGREE-REX tools. In addition, we also wanted to identify research gaps through the synthesis of PA recommendations.

Materials and methods

Study design

We conducted a methodological appraisal of CPGs using the AGREE II and AGREE-REX instruments and reported our results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021265329.

Search strategy

We conducted a systematic search for guidelines and employed three approaches to identify guidelines with PA recommendations for cancer survivors.

We searched electronic databases including PubMed, CINAHL, PEDro, and EMBASE. In addition, we supplemented database searches by a hand-search of guideline repositories. We also conducted a supplementary search by scanning the reference lists of review articles and relevant conference abstracts to identify eligible CPGs. A publication date limitation from 1 May 2016 to 1 June 2022 was set for all searches.

We adopted a combination of Medical Subject Headings (MeSH), free text terms, including “neoplasms, cancer, tumor, exercise, physical activity, rehabilitation, guideline, practice guideline, recommendation” as database search strategy. The detailed search strategies were provided in the Supplementary Table S1.

Selection criteria

The eligibility of CPGs was identified according to the following criteria.

Inclusion criteria were as follows: ① CPGs published in English; ② recently published or updated from 1 May 2016 to 1 June 2022; ③ published in peer-reviewed scientific journals; ④ exclusive to adult (aged ≥ 18 years) cancer population; ⑤ provided specific PA intervention recommendations on at least one PA parameter (frequency, intensity, duration and/or type); and ⑥ provided recommendations and explicit methodology.

Exclusion criteria were as follows: ① did not include PA as part of intervention strategy; ② published or updated prior to 1 May 2016; ③ CPGs for pharmacological or rehabilitation interventions without PA recommendations; ④ received commercial funding; ⑤ provided recommendations for PA referrals; and ⑥ focused on cancer prevention other than cancer or cancer-related symptoms and impairments management.

Study selection

We first imported all results into Endnote (version X9, Clarivate Analytics) reference manager program, and eliminated duplicates using the software and manually. Two independent reviewers (X. Zhou, C.H. Li) scanned the remaining records against the titles and abstracts. For records that were considered potentially relevant, we retrieved the full-text guidelines following the inclusion and exclusion criteria. If any disagreement arose, a

decision was made by discussion with a third reviewer (X.G. Lai).

Data extraction and summary

Data screening and extraction were performed by two authors (X. Zhou, C.H. Li). One author performed data extraction which was confirmed for consistency by a second author. A third independent author (X.G. Lai) adjudicated unresolved discrepancies. We extracted and summarized the relevant information on the CPGs and recommendations on specific PA interventions. Main characteristics of the CPGs were collected, including title, organization/author, country of origin, publication year, methodological approach, and its scope.

Quality appraisal of the CPGs

The quality of each included guideline was appraised using the evaluation tools AGREE II and AGREE-REX by trained reviewers. All the reviewers received the online AGREE II training and evaluated CPGs on melanoma from published review [27] using the AGREE-REX tool to familiarize themselves with the instrument and compare their scores.

Both tools were rated on a 7-point scale ranging from 1 (strongly disagree) to 7 (strongly agree). Disagreement among reviewers of > 2 points for each item was discussed and resolved by consensus. Domain scores were calculated by adding scores of the individual items in a domain and standardizing the sum as a percentage of the maximum possible score for that domain, i.e., $(\text{obtained score} - \text{minimum possible score}) / (\text{maximum possible score} - \text{minimum possible score})$.

Two trained reviewers (C.H. Li, W.Q. Hou) independently appraised the methodological quality of each guideline by the AGREE II instrument. The instrument comprised 23 items within 6 domains: scope and purpose (items 1–3), stakeholder involvement (items 4–6), rigor of development (items 7–14), clarity of presentation (items 15–17), applicability (items 18–21), and editorial independence (items 22–23).

The Consortium of AGREE II does not set minimum domain scores or patterns of scores across domains to differentiate between high quality and low quality [28]. In this study, based on cut-off scores reported in previous guideline appraisals [23, 27, 29], we chose a cut-off “score of at least 60% for rigor of development (domain 3) as well as 60% in at least two other domains as a quality threshold. Guidelines meeting the cut-off scores were then evaluated by AGREE-REX.

Complementary to AGREE II, AGREE-REX is an instrument used for evaluating the clinical credibility and implementability of the recommendations. AGREE-REX consists

of 3 domains, including “clinical applicability (Domain 1), values and preferences (Domain 2) and implementability (Domain 3)” composed of 9 items that must be considered to ensure that guideline recommendations were of high quality. This instrument was used by five independent reviewers (X. Zhou, C.H. Li, W.Q. Hou, X.G. Lai, and L.W. Zhai).

Similar to AGREE II, AGREE-REX does not provide a standard threshold to differentiate between high quality and poor quality. In this study, we set the threshold to be 60% and identified high-quality guidelines when all domain scores were above the threshold.

Statistical analysis

All domain scores were calculated by adding the item scores in each domain and converting the number into a standardized percentage of the maximum score for that domain. We also listed mean (\pm standard deviation, SD) for analysis of the descriptive statistics. We used the intraclass correlation coefficient (ICC) with a two-way random effects model [30] to test the inter-rater agreement (measure agreement among reviewers). The degree of agreement (ICC) was classified according to Cicchetti (1994): poor (<0.40), fair ($0.40\text{--}0.59$), good ($0.60\text{--}0.74$), or excellent ($0.75\text{--}1.00$) [31]. $P < 0.05$ was considered statistically significant. Statistical

analyses were conducted using SPSS (version 24, IBM Corporation, Armonk, NY, USA).

Results

CPGs characteristics

The literature search of the databases and supplementary sources identified 5108 records. We reviewed 182 full-text articles for eligibility after removing the duplicates and screening the titles and abstracts and 16 CPGs that met selection criteria were included in this systematic review (Fig. 1). Reasons for exclusion ($n = 166$) are provided in Fig. 1. The fourteen CPGs included four for breast cancer [32–35], one for head and neck cancer [36], one for multiple myeloma [37], one for cancer survivorship [38], three for nutrition management and/or physical activity in cancer patients [39–41], and six for symptom or condition management [42–47]. Twelve CPGs were published in the USA, of which four CPGs were developed by the American Society of Clinical Oncology (ASCO) and four from National Comprehensive Cancer Network (NCCN). The remaining were published in the UK ($n = 1$), in Europe ($n = 1$), in Canada ($n = 1$), and in Germany ($n = 1$). The basic characteristics of the sixteen CPGs are shown in Table 1.

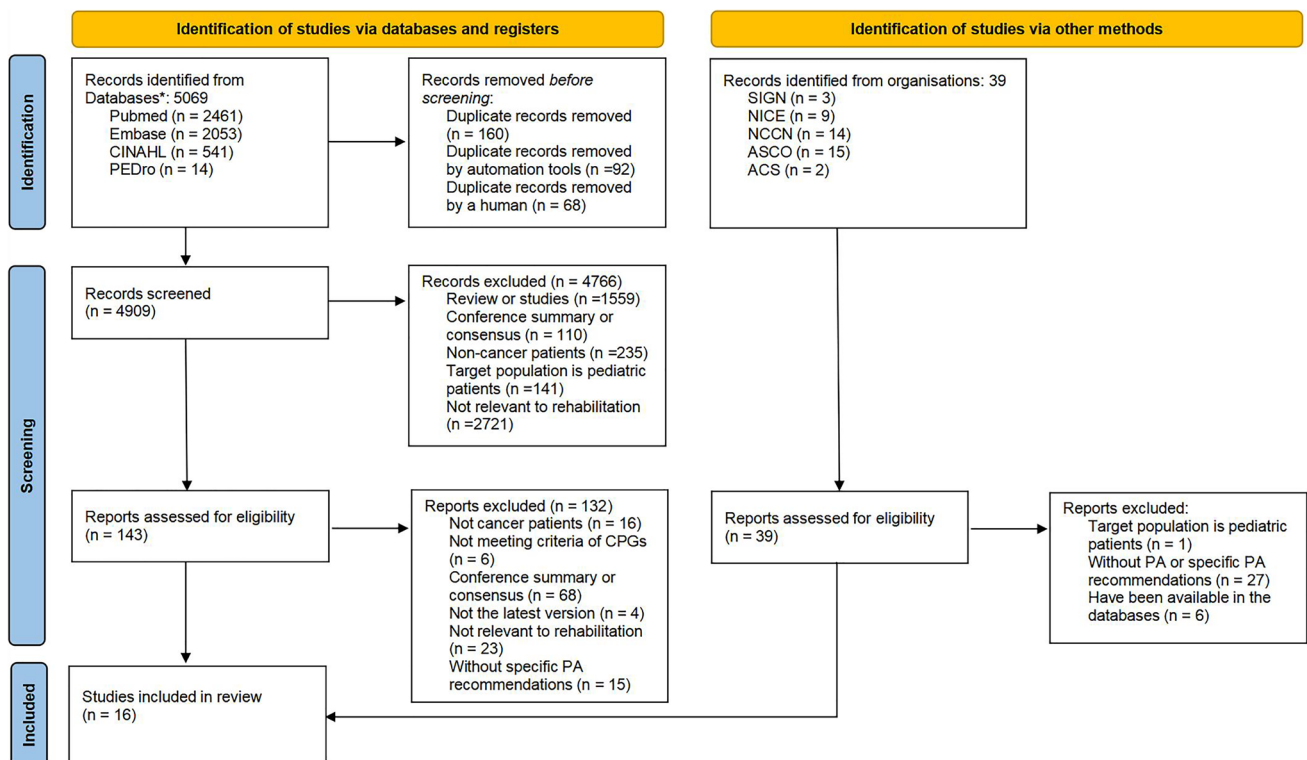


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart

Table 1 Characteristics of included CPGs with PA recommendations for cancer patients

Title	Year	Country	Organization/author	Topic
American Cancer Society Head and Neck Cancer Survivorship Care Guideline [36]	2016	USA	ACS (Cohen, et al. 2016)	Head and neck cancer
Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline [42]	2016	USA	ASCO (Paice et al. 2016)	Chronic pain
Management of Osteoporosis in Survivors of Adult Cancers With Nonmetastatic Disease: ASCO Clinical Practice Guideline [43]	2019	USA	ASCO (Shapiro et al. 2019)	Osteoporosis
Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Chemotherapy: ASCO Guideline for Geriatric Oncology [44]	2018	USA	ASCO (Mohile et al. 2018)	Vulnerabilities
Clinical practice guidelines on the evidence-based use of integrative therapies during and after breast cancer treatment [32]	2017	USA	SIO (Greenlee et al. 2017)	Breast cancer
Early and locally advanced breast cancer: diagnosis and management (NG101) [33]	2018	UK	NICE (NG101)	Breast cancer
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Adult Cancer Pain [45]	2021	USA	NCCN (Swarm et al. 2022)	Adult cancer pain
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Antiemesis [46]	2021	USA	NCCN (Berger et al. 2022)	Antiemesis
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Cancer-Related Fatigue [47]	2021	USA	NCCN (Jankowski et al. 2022)	Cancer-related fatigue
NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Survivorship [38]	2022	USA	NCCN (Sanft et al. 2022)	Survivorship
ESPEN guidelines on nutrition in cancer patients [39]	2017	Europe	ESPEN (Arends et al. 2017)	Nutrition
Interventions for Breast Cancer–Related Lymphedema: Clinical Practice Guideline From the Academy of Oncologic Physical Therapy of APTA [34]	2020	USA	APTA (Davies et al. 2020)	Breast cancer–related lymphedema
AGO Recommendations for the Diagnosis and Treatment of Patients with Locally Advanced and Metastatic Breast Cancer: Update 2020 [37]	2020	Germany	AGO (Ditsch et al. 2020)	Breast cancer
Mobilization and Exercise Intervention for Patients With Multiple Myeloma: Clinical Practice Guidelines Endorsed by the Canadian Physiotherapy Association [37]	2021	Canada	CPA (Jeevanantham et al. 2021)	Multiple myeloma
Exercise, Diet, and Weight Management During Cancer Treatment: ASCO Guideline [41]	2022	USA	ASCO (Ligibel et al. 2022)	Exercise, diet, and weight management
American Cancer Society nutrition and physical activity guideline for cancer survivors [40]	2022	USA	ACS (Rock et al. 2022)	Nutrition and physical activity

ACS, American Cancer Society; ASCO, American Society of Clinical Oncology; SIO, Society for Integrative Oncology; NICE, National Institute for Health and Care Excellence; NCCN, National Comprehensive Cancer Network; ESPEN, European Society for Clinical Nutrition and Metabolism; APTA, American Physical Therapy Association; AGO, German Gynecological Oncology Group; CPA, Canadian Physiotherapy Association

AGREE II

Scope and purpose

This domain assesses whether the guideline clearly described the main objectives, clinical questions, and target population. The guideline by Mohile et al. [44] scored the highest and fulfilled 100% of the criteria whereas

the guideline [35] from Germany achieved only 41.67% (Fig. 2).

Stakeholder involvement

This domain evaluates whether the guideline was developed by appropriate stakeholders and represents the views of its intended users. Furthermore, it covers whether the guideline

Supportive Care in Cancer

Domain Guideline	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence
ACS 2016	94.44	94.44	81.25	100	72.92	95.83
ASCO 2016	97.22	94.44	93.75	91.67	50	87.5
ASCO 2019	97.22	100	92.71	94.44	98.58	83.33
ASCO 2018	100	100	97.92	100	72.92	95.83
SIO 2017	94.44	69.44	89.58	88.89	54.17	79.17
NICE(NG101)	94.44	88.89	97.92	94.44	75	58.33
NCCN Adult Cancer Pain	86.11	86.11	95.83	94.44	87.5	100
NCCN Antiemesis	86.11	86.11	94.79	97.22	79.17	100
NCCN Cancer-Related Fatigue	88.89	72.22	90.63	91.67	79.17	100
NCCN Survivorship	88.89	97.22	95.83	94.44	93.75	100
APTA 2020	69.44	75	79.17	97.22	56.25	83.33
CPA 2021	94.44	94.44	94.79	94.44	75	100
AGO 2020	41.67	13.89	34.38	75	33.33	75
ESPEN 2017	91.67	88.89	98.96	83.33	87.5	100
ASCO 2022	100	94.44	89.58	88.89	64.58	87.5
ACS 2022	88.89	61.11	62.5	88.89	64.58	87.5
Mean score±sd	6.30±1.07	5.94±1.47	6.21±1.49	6.52±0.78	5.26±1.66	6.37±1.03

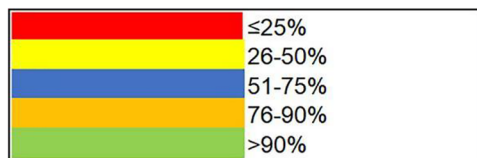


Fig. 2 Heat-map showing an overview of the final AGREE II scores on guidelines with physical activity recommendations for cancer patients

clearly defined its target users. Two ASCO guidelines [43, 44] achieved the highest score fulfilling 100% of the criteria, while the guideline [35] from Germany showed no consideration of the views of the other stakeholders such as patients, the public, payers, and policy-makers and therefore received a low score of 13.89%.

Rigor of development

This domain assesses the systematic methods used for gathering and synthesizing evidence, formulating recommendations, the expert external peer review process, and the procedure for updating the guideline. The mean score was 6.21 (± 1.49), with individual scores ranging from 34.38% to 98.96% (Supplementary Table S2). Most guidelines provided search strategies and clearly described the selection criteria except for the guideline from Germany [35]. Three guidelines [34, 35, 37] did not describe clear procedures for updates.

Clarity of presentation

This domain is related to whether the guidelines provided clear recommendations and whether important recommendations were easily identifiable. This domain achieved the highest mean score (6.52 ± 0.78), and the individual scores

ranged from 75% [35] to 100% [44]. This suggested all the included guidelines performed well in the presentation and clarity of the recommendations.

Applicability

This domain considers facilitators and barriers to guideline implementation, including potential cost implications, and presents key monitoring criteria for adherence to the guideline. Across the guidelines, AGREE II scores were lowest in this domain, with a mean score of 5.26 (± 1.66). The guideline by Shapiro et al. [43] achieved the best score of 98.58%, while the guideline from Germany [35] and the ASCO guideline [42] paid limited attention to the applicability, scoring only 33.33% and 50%, respectively.

Editorial independence

This domain focuses on whether guidelines are developed independently or have any existing conflicts of interest. The mean score was 6.37 (± 1.03). All of the guidelines fulfilled the criteria and scored above 75% except for the guideline from the UK.

AGREE-REX

Clinical applicability

This domain evaluates whether the guideline is evidence-based and the extent to which the recommendations apply to the guideline's target users in terms of the practice context and patient population. Among all the included guidelines, the AGREE-REX domain clinical applicability scored the highest with a mean score of 6.10 (± 0.82) (Supplementary Table S3), individual scores ranging from 68.89% [40] to 93.33% [33] (Fig. 3).

Values and preferences

This domain assesses whether the values and preferences of target users, patients, policy decision-makers, and guideline developers had been explored and considered in the development of the recommendations. This domain scored the lowest with individual scores ranging from 45.83% [34] to 74.14% [33] and seven guidelines scoring below 60%. Of the four items, the values and preferences of policy decision-makers and guideline developers had been omitted completely in several guidelines.

Implementability

This domain assesses the "purpose" and "local application and adoption" of the items. The mean score was 5.28 (± 1.11), with individual scores ranging from 55.00% to 88.33%. The NCCN guideline by Sanft et al. [38] scored the highest, at 88.33%. The NICE guideline [33] and the NCCN guideline by Swarm et al. [45] achieved 83.34%. Most guidelines paid limited attention to local application and adoption.

Among all, eight guidelines met the cut-off scores, achieving above 60% of all domains, and the NICE guideline earned the best scores in the three AGREE-REX domains, ranging from 74.17% to 93.33%.

Summary of recommendations and levels of evidence

Fifteen of the sixteen guidelines met the cut-off scores of AGREE II, six of which provided PA intervention recommendations within a disease-specific context, and the remaining guidelines provided management recommendations for symptoms or functional impairments. Notably, two of the fourteen guidelines were published by specialized rehabilitation organizations, and one guideline endorsed by the Canadian Physiotherapy Association provided information specifically for physical therapists on the management of patients with multiple myeloma. PA recommendations, the level of evidence, and the strength of recommendation are outlined in Table 2. Method to collect the evidence, formulate recommendations, and articles type/number are outlined in Table 3.

Discussion

This study presents the first systematic review using AGREE II and AGREE-REX to appraise the quality of CPGs with physical activity recommendations for cancer patients. Sixteen guidelines were evaluated and eight guidelines published by ASCO, NCCN, NICE, and ESPN obtained high quality. This is likely due to the strict framework provided by these organizations, and the guideline makers had strictly adhered to the CPGs development process. For example,

Guideline	Domain	Clinical applicability	Values and preferences	Implementability
ACS 2016		90	59.17	73.33
ASCO 2016		86.67	63.34	73.33
ASCO 2019		91.11	61.67	61.67
ASCO 2018		86.67	50	61.67
SIO 2017		81.11	47.5	63.33
NICE(NG101)		93.33	74.17	83.34
NCCN Adult Cancer Pain		80	60	83.34
NCCN Antiemesis		82.22	59.17	78.33
NCCN Cancer-Related Fatigue		82.22	55.83	70
NCCN Survivorship		84.44	67.5	88.33
APTA 2020		84.44	45.83	55
CPA 2021		81.11	47.5	56.67
ESPEN 2017		90	64.17	73.33
ASCO 2022		93.33	61.67	75
ACS 2022		68.89	60	73.33
Mean score \pm sd		6.10 \pm 0.82	4.51 \pm 0.94	5.28 \pm 1.11

Fig. 3 Heat-map showing an overview of the final AGREE-REX scores on guidelines with physical activity recommendations for cancer patients

Table 2 Summary of recommendations and levels of evidence

CPGs	Level of evidence	Strength of recommendation	PA recommendation
ACS 2016 [36]	LoE (IA-c, IIA-c, III, 0, 2a)	LoE (IA-c, IIA-c, III, 0, 2a)	Regular physical activity: (a) should avoid inactivity and return to normal daily activities as soon as possible after diagnosis (LOE = III); (b) should aim for at least 150 min of moderate or 75 min of vigorous aerobic exercise per week (LOE = I, IA); (c) should include strength training exercises at least 2 d/wk (LOE = IA)
ASCO 2016 [42]	Grade (high, moderate, low, very low)	Strength of recommendation (strong, moderate, weak)	Physical medicine and rehabilitation: Clinicians may prescribe directly or refer patients to other professionals to provide the interventions (physical therapy, occupational therapy, recreational therapy, individualized exercise program, orthotics, ultrasound, and heat/cold) to mitigate chronic pain or improve pain-related outcomes in cancer survivors. These interventions must take into consideration pre-existing diagnoses and comorbidities (type, evidence-based; benefits outweigh harms; evidence quality, intermediate; strength of recommendation, moderate)
ASCO 2019 [43]	Grade (high, moderate, low, very low)	Strength of recommendation (strong, moderate, weak)	Clinicians should actively encourage patients to engage in a combination of exercise types, including balance training, flexibility or stretching exercises, endurance exercise, and resistance and/or progressive strengthening exercises, to reduce the risk of fractures caused by falls. Whenever possible, exercise should be tailored according to the needs and abilities of the individual patient. Patients with an impairment hindering their gait or balance should be offered medical rehabilitation (type, evidence-based; benefits outweigh harms; evidence quality, low; strength of recommendation, moderate)
ASCO 2018 [44]	Grade (high, moderate, low, very low)	Strength of recommendation (strong, moderate, weak)	IADL deficits or falls: PT and/or OT should prescribe strength and balance training, assistive device evaluation, home exercise program, and safety evaluation (type, informal consensus; evidence quality, moderate; strength of recommendation, moderate)
SIO 2017 [32]	USPSTF (I, II-1, II-2, II-3, III)	USPSTF (grades A–D, H, and I)	Anxiety: Yoga is recommended for reducing anxiety (grade B) Depression/mood disturbance: Yoga is recommended for improving mood and depressive symptoms (grade B) Fatigue: Yoga can be considered for improving fatigue post treatment (grade C) Quality of life: Yoga is recommended for improving quality of life (grade B); Qigong can be considered for improving quality of life (grade C)
NICE (NG101) [33]	Grade (high, moderate, low, very low)	NA	Arm mobility: Give instructions on functional exercises, which should start the day after surgery, to all breast cancer patients undergoing axillary surgery. This should include relevant written information from a member of the breast or physiotherapy team

Table 2 (continued)

CPGs	Level of evidence	Strength of recommendation	PA recommendation
NCCN Adult Cancer Pain [45]	NA	NCCN (categories 1, 2A, 2B, 3)	Pain likely to be relieved or function improved with physical modalities, including supportive devices; positioning instruction; instruction in therapeutic and conditioning exercise; energy conservation and pacing of activities; massage; heat and/or ice; transcutaneous electrical nerve stimulation (TENS); acupuncture or acupressure; ultrasonic stimulation (category 2A)
NCCN Antiemesis [46]	NA	NCCN (categories 1, 2A, 2B, 3)	Anticipatory nausea and vomiting prevention/treatment: relaxation exercises (guided imagery; progressive muscle relaxation; biofeedback; music therapy); yoga, if approved by physician (category 2A)
NCCN Cancer-Related Fatigue [47]	NA	NCCN (categories 1, 2A, 2B, 3)	Interventions for patients on active treatment/post-treatment: yoga (category 1)
NCCN Survivorship [38]	NA	NCCN (categories 1, 2A, 2B, 3)	Physical activity for cancer survivors: Survivors should strive for at least 150 min of weekly activity with an ultimate goal of 300 min or more of moderate-intensity activity or 75 min of vigorous-intensity activity or equivalent combination spread out over the course of the week; two to three sessions per week of strength/resistance training that include major muscle groups; stretch major muscle groups at least 2 days per week on days that other exercises are performed (category 2A) Cancer-associated cognitive dysfunction interventions: Recommend routine physical activity (see physical activity for cancer survivors); consider meditation, yoga, mindfulness-based stress reduction, and cognitive training (category 2A) Fatigue: recommendations to maintain adequate level of physical activity (category 1) (see physical activity for cancer survivors) Lymphedema: compression garments; progressive resistance training under supervision; manual lymphatic drainage; range of motion exercises (category 2A) Pain syndromes: ① for post-radical neck dissection pain (stretching, range of motion, soft tissue massage, myofascial release, trigger point injections, botulinum toxin injections); ② myalgia, arthralgia pain (physical activity (category 1 for AI-induced arthralgia), heat, cold pack, aquatic therapy, massage, acupuncture, yoga); ③ skeletal or vertebral compression pain (bracing, mobility, weight bearing exercise when pain improves, thoracic and lumbar stabilization exercise); ④ myofascial pain syndrome (physical activity, range of motion exercises, strength exercises, soft tissue myofascial release, ultrasonic stimulation, acupuncture); ⑤ pelvic pain syndrome (pelvic floor exercises) (category 2A) Hormone-related symptoms: physical activity/exercise, Integrative therapies including yoga and cognitive behavior therapies (category 2A) Obstructive sleep apnea: physical activity (category 2A)

Table 2 (continued)

CPGs	Level of evidence	Strength of recommendation	PA recommendation
ESPEN 2017 [39]	LoE (high, moderate, low, very low)	Strength of recommendation (strong, weak)	Maintenance or an increased level of physical activity in cancer patients to support muscle mass, physical function, and metabolic pattern (strong, high) Individualized resistance exercise in addition to aerobic exercise to maintain muscle strength and muscle mass (weak, low) We recommend that cancer survivors engage in regular physical activity (strong, low)
APTA 2020 [34]	LoE (I–III)	APTA (A–C, best practice)	Postoperative exercise and resumption of activity should be coordinated with the interprofessional team, and an individualized exercise program should be gradually increased while monitoring for adverse events (best practice) Progressive resistance training is safe when an individualized program is supervised beginning at least 1 month postsurgery (grade A) Individualized aerobic exercise programs should be provided (grade A) Individualized programs of aerobic and resistance exercise should be provided for those who have BCRL (stages 0–III) (grade A) Yoga may be a safe form of exercise but does not show evidence of effectiveness for lymphedema volume reduction (grade C)
AGO 2020 [35]	Oxford (1a-c, 2a-c, 3a-b, 4, 5)	AGO (+++, ++, +/-, -, --)	Physical exercise (endurance training 3 times a week in combination with workout exercises 2 times a week) on quality of life, cardiorespiratory fitness, physical performance, sleep, pain, depression, lymphedema, and fatigue (LoE 1a/A/ AGO ++)
CPA 2021 [37]	BRIDGE-Wiz (I–V)	BRIDGE-Wiz (A–D, P, R)	Clinicians may offer home-based/unsupervised aerobic exercise to patients with MM to increase cardiorespiratory fitness and physical activity levels during the ambulatory period before autologous high-dose stem cell transplant (HSCT) (evidence quality, III; recommendation strength, C) Clinicians may offer supervised mixed aerobic/strength training exercise in the inpatient or outpatient setting to patients with MM while undergoing chemotherapy/HSCT (evidence quality, III; recommendation strength, C) Clinicians may offer home-based (unsupervised) mixed aerobic/strength training to patients with MM undergoing chemotherapy/HSCT (evidence quality, I; recommendation strength, B) Clinicians may offer supervised and/or unsupervised individualized strength and aerobic or strength training alone in the outpatient and/or home-based setting to multiple myeloma patients when they are medically stable after chemotherapy/HSCT (evidence quality, II; recommendation strength, B)

Table 2 (continued)

CPGs	Level of evidence	Strength of recommendation	PA recommendation
ASCO 2022 [41]	Grade (high, moderate, low, very low)	Strength of recommendation (strong, moderate, weak)	Oncology providers should recommend aerobic and resistance exercise during active treatment with curative intent to mitigate side effects of cancer treatment (type, evidence-based; benefits outweigh harms; evidence quality, moderate to low; strength of recommendation, strong)
ACS 2022 [40]	NA	NA	To improve long-term health and increase the likelihood of survival: Engage in regular physical activity, with consideration of type of cancer, patient health, treatment modalities, and symptoms and side effects. To reduce risk of a new cancer: Engage in 150–300 min of moderate-intensity physical activity per week (or 75–150 min of vigorous-intensity physical activity); striving to meet or exceed the upper limit of 300 min is ideal

ACS, American Cancer Society; ASCO, American Society of Clinical Oncology; SIO, Society for Integrative Oncology; NICE, National Institute for Health and Care Excellence; NCCN, National Comprehensive Cancer Network; ESPEN, European Society for Clinical Nutrition and Metabolism; APTA, American Physical Therapy Association; AGO, German Gynecological Oncology Group; CPA, Canadian Physiotherapy Association; NA, not applied; USPSTF, United States Preventive Services Taskforce; BRIDGE-Wiz, Building Recommendations in a Developer’s Guideline Editor

there is a representative from the ASCO Practice Guidelines Implementation Network (PGIN) and at least one patient representative in each expert panel of ASCO guidelines. Additionally, ASCO produces clinical tools and resources to assist with disseminating the recommendations contained in the guidelines. Based on the available clinical treatment resources, NCCN provides NCCN Framework, NCCN Harmonized Guidelines, and International Adaptations/Translations to extend the utility of the NCCN Guidelines. NICE incorporates economic evaluation in the development of guideline recommendations.

How might our findings impact CPGs development and future research?

Recommendations for guideline development

The potential benefits of clinical practice guidelines depend on the quality of the CPGs [28]. Ideally, guideline makers should strictly follow rigorous processes when developing CPGs. This review identified 16 relevant CPGs that showed acceptable quality in most AGREE II and AGREE-REX domains. Remarkably, some weaknesses have been revealed in AGREE II domain “applicability” and AGREE-REX domains of “values and preferences” and “implementability,” especially the items “values and preferences of policy/decision-makers” as well as “local application and adoption.” The lowest mean score (5.26 ± 1.66) was observed for the AGREE II domain “applicability,” and the evaluators gave low ratings (< 60%) to 4 out of 16 guidelines. Applicability refers to whether facilitators, barriers, and additional resources of the guideline application were presented and if monitoring or auditing criteria of the recommendations was provided. These parameters especially monitoring or auditing criteria were not clearly provided in most guidelines, which may explain the low values of this domain. However, ESPEN guideline did well in this domain, sufficiently providing all parameters [39]. The AGREE-REX domain “values and preferences” assesses whether the values and preferences of target users, patients, guideline developers, and policy decision-makers had been considered and how it influenced the recommendation formulation. Sackett [48] indicated that evidence-based medicine should be equally based on service users’ values and expectations, individual clinical expertise, and the best available clinical evidence. Previous studies [49, 50] suggested that CPGs were more implementable when they considered patients’ and stakeholders’ values and preferences and provided information to support patient involvement in decision-making. However, most CPGs [32, 34, 37, 44] included in this study achieved low scores (< 50%) because there were missing information on the values and preferences of users, patients, guideline developers, and policy/decision-makers’ influenced on the

Table 3 Method to collect the evidence and formulate recommendations and articles type/number

CPGs	Method to collect the evidence/article type/number	Article type/number related to PA	Method to formulate recommendation
ACS 2016 [36]	Systematic literature searches of PubMed for 2004 through April 2015. 184 articles were included as the evidence base. Level I, < 2%; level IA, < 4%; level IC, < 1%; level IIA, < 3%; level III, 28%; level 0, 64%	NA	Based on current evidence and expert consensus
ASCO 2016 [42]	Systematic literature searches from 1996 to 2015. 35 systematic reviews, 9 RCTs, and 19 comparative studies were included as the evidence base	Two systematic reviews, three RCTs	Based on current evidence and expert consensus
ASCO 2019 [43]	The USPSTF 2018 systematic review and a supplemental systematic review from 2000 to 2018. 229 studies were included as the evidence base	Four systematic reviews, two RCTs	Based on current evidence and expert consensus
ASCO 2018 [44]	Systematic literature searches of PubMed. Sixty-eight articles were included as the evidence base. Thirty prospective cohort studies, 19 RCTs, 9 systematic reviews, 10 comparative studies	NA	Based on current evidence and expert consensus
SIO 2017 [32]	Systematic literature searches of 9 electronic databases from 1990 through 2015. Only RCTs as the evidence base	Twenty-six RCTs (A and B grade)	Based on current evidence and expert consensus
NICE(NG101) [33]	Systematic literature searches of 6 electronic databases. A total of 127 articles were included as the evidence base (RCTs, cohort studies, systematic review)	Two cohort studies, eight RCTs	Based on current evidence and expert consensus
NCCN Adult Cancer Pain [45]	NA	NA	Based on current evidence and expert consensus
NCCN Antiemesis [46]	NA	NA	Based on current evidence and expert consensus
NCCN Cancer-Related Fatigue [47]	NA	NA	Based on current evidence and expert consensus
NCCN Survivorship [38]	NA	NA	Based on current evidence and expert consensus
ESPEN 2017[39]	Systematic literature searches of 2 electronic databases from January 1, 2006, to June 30, 2013	NA	Based on current evidence and expert consensus
APTA 2020 [34]	Systematic literature searches of 9 electronic databases from January 2000 to March 2019. A total of 209 articles were included as the evidence base. Level I, 6; level II, 25; level III, 147; unacceptable, 31	Level I, 5; level II, 10; level III, 44; unacceptable, 66	Based on current evidence and expert consensus
AGO 2020 [35]	NA	NA	Based on current evidence and expert consensus
CPA 2021 [37]	Systematic literature searches of 8 electronic databases published until 2018. 17 studies were included as the evidence base. Six RCTs, 11 comparative studies	NA	Based on current evidence and expert consensus
ASCO 2022 [41]	Systematic review of evidence identified through online searches of PubMed and the Cochrane Library from January 1, 2000, through May 17, 2021	Forty-two systematic reviews, thirteen exercise RCTs	Based on current evidence and expert consensus

Table 3 (continued)

CPGs	Method to collect the evidence/article type/number	Article type/number related to PA	Method to formulate recommendation
ACS 2022 [40]	Systematic literature searches of 5 electronic databases. Forty-five articles were included as the evidence base (systematic reviews, meta-analyses, pooled analyses of cohort studies, and large RCTs). Fifteen articles for anthropometrics, 9 articles for physical activity, 16 for diet, 5 for alcohol	Nine articles	Based on current evidence and expert consensus

ASC, American Cancer Society; ASCO, American Society of Clinical Oncology; SIO, Society for Integrative Oncology; NICE, National Institute for Health and Care Excellence; NCCN, National Comprehensive Cancer Network; ESPEN, European Society for Clinical Nutrition and Metabolism; APTA, American Physical Therapy Association; AGO, German Gynecological Oncology Group; CPA, Canadian Physiotherapy Association; NA, not applied; USPSTF, United States Preventive Services Taskforce; RCTs, randomized controlled trials

recommendation formulation, which may ultimately influence the acceptability and adoption into clinical practice of PA recommendations. The findings are consistent with the previous studies [51–53]; many factors such as physical activity preferences (type, place, time), convenience (e.g., there is no travel to and from a hospital), cost, knowledge of physical activity guidelines, and accessibility to the program had led to a low level of PA adherence among cancer patients. For the AGREE-REX domain “implementability,” low values were consistently rated on item 9 “local application and adoption” in most included guidelines. This item assesses the suitability of the guideline recommendations for the setting, patient population, and/or the healthcare system in which they are being implemented. Professor Robbie Foy suggested that successful implementation of a guideline depends on both the national and local resources/action [54]. Most of the included guidelines did not consider resources at the local setting or adjust recommendations to tailor local adaptations when developing CPGs. This may further influence applicability to implement across the different local practice settings. Importantly, this consequence can be found in a systematic review involving ninety-eight studies and reported that barriers to cancer patients’ PA engagement included competencies of healthcare professional guidance, social support, and inaccessibility to fitness facilities [53]. However, NCCN guidelines are the notable exception. They provided NCCN Framework for Resource Stratification, NCCN Harmonized Guidelines targeting the regional resources, and International Adaptations/Translations to extend the utility of the NCCN Guideline internationally.

In conclusion, this analysis shows there is substantial room for improvement in the following domains “applicability,” “values and preferences,” and “implementability” to facilitate the guideline implementation. It is essential to comprehensively consider the values and preferences of users, patients, policymakers, and guideline makers and provide advice or tools and resources to facilitate the implementation of the recommendations. In addition, providing a “Guideline Implementation Survey” and a clear “monitoring and auditing criteria” may facilitate application of guidelines. Furthermore, the transparency of the guideline development process should also be addressed.

Suggestions on study design

This study identified eight high-quality CPGs; notwithstanding, many studies that formed the exercise evidence base contained flaws in the study design. We reviewed the quality of studies included in 16 guidelines and summarized the main problems in their design as follows: ① small sample sizes, ② low adherence and high attrition rates, ③ short intervention durations, ④ observational studies or feasibility studies, and ⑤ serious inconsistency owing to various

interventions and outcomes. For example, the trials in the ASCO guideline [42] “Management of chronic pain in survivors of adult cancers” presented with some limitations, such as pain as the secondary outcome, a small sample size, and different measurement tools. Some studies included in the CPA guideline [37] were retrospective design, and we also found that most of the latest research for patients with multiple myeloma are feasibility studies [55]. Future research must be conducted using large sample sizes, randomized design, and rigorous method to decrease the risk of bias. Community or home-based exercise mode combined with a web-based guidance is also needed so as to enhance exercise compliance in patients.

Opportunities for future research

Findings of a bibliometric analysis suggested that the overall trend of cancer rehabilitation publications is optimistic [56]. However, this literature study revealed the presenting research deficits in some areas of physical activity interventions: ① Researches were mostly performed on the breast cancer, prostate cancer, colorectal cancer, and lung cancer populations. Of the 16 included guidelines, up to 25% CPGs were tailored to breast cancer survivors; ② previous studies on cancer rehabilitation emphasized on the cognitive, behavioral, and psychological therapies, whereas research on the health effects of PA in cancer rehabilitation is lacking; ③ there is still minimal research exploring the safety, feasibility, and potential benefits of exercise in patients with advanced cancer and cachexia [57].

Therefore, future study efforts should be devoted to ① the effectiveness of PA interventions on a wider range of cancer population other than breast, lung, prostate, and colorectal cancer; ② the immediate and long-term benefits of different modalities of PA on the physical and mental fitness of cancer survivors; and ③ the optimal PA prescription (frequency, intensity, duration, or type) for different symptoms or functioning impairments management. The previous studies [58] suggest that the optimal effects of PA are dependent on the dose appropriate to the individual level of physical fitness and health status. The PA prescription should follow FITT principles: frequency, intensity, time, and type [59]. Some guidelines included in this review are lacking specific PA prescriptions; therefore, for further in-depth exploration of the benefits of PA for cancer patients, future research should continue to explore specific FITT principles tailored towards cancer patients; ④ future research must focus on the effect of exercise on clinical symptoms in patients with advanced cancer and cachexia, especially for sarcopenia and pain.

Recent studies [60, 61] have demonstrated that telehealth-based exercise prescription is both feasible and effective for cancer survivors during the COVID-19 pandemic. Multiple novel web-based exercise systems are emerging as an

excellent option to provide individualized PA interventions for cancer survivors, such as breast cancer and prostate cancer [62, 63]. In addition, other factors such as cost-effectiveness, less expenditure on travel time, patients’ preference to home-based exercise, and less absence from work may be considered in favor of the patient [64]. Therefore, efforts should be performed to continue evaluating the value of web-based rehabilitation mode across the continuum of cancer care and survivorship.

Additionally, we also noted that some available evidence included in the CPGs suggested a potential benefit from exercise for some physical impairments or symptoms, yet latest evidence remain insufficient for a clear direction on recommendations. For example, exercise for chemotherapy-induced peripheral neuropathy in adult cancers with insufficient evidence to formulate a recommendation [65, 66]; Tai-Chi for depression with shallow evidence to support a recommendation [67, 68]; and yoga for chemotherapy-induced nausea and vomiting with insufficient data to support specific recommendations [69]. Therefore, future well-designed clinical trials are needed to confirm the effectiveness and safety of the PA interventions for treatment-related issues, especially chemotherapy-induced peripheral neuropathy, nausea, and cachexia.

What challenges are faced when integrating physical activity into oncology care?

There are numerous challenges in applying PA into routine oncology care practice. One solution to overcome the challenges is implementing practice guidelines. The potential benefits of guidelines depend on the quality [28]. In this review, we found some common issues in the content of selected guidelines not relating to methodological flaws. First, much of the guidelines covered information on medical management, while less information was relevant to non-pharmaceutical management. Professional guidance should be provided by experts in different disciplines; however, most expert panels which developed the selected guidelines [32, 33, 35, 39] did not consist of a rehabilitation specialist or exercise physiologist required during the development of PA recommendations. These existing problems may affect the process of integrating physical activity into routine oncology care practice. Hence, there is a compelling need to promote more collaboration between oncologists and rehabilitation specialists, establish multidisciplinary expert panels, improve the referral system, and eventually gain the recognition and promotion of PA intervention in oncology clinical setting. Besides, we also observed that most included CPGs did not provide relevant factors and resources to promote its successful dissemination, which may lower knowledge about PA guidelines in daily life. Previous studies demonstrated that most cancer patients did not know the PA guidelines, and providing more detailed knowledge

regarding PA guidelines in the oncological setting was an important facilitator to motivate their PA participation [51, 70, 71]. This phenomenon was also reported among healthcare professionals [72]. It's important to improve knowledge of PA guidelines in for narrowing the knowledge-to-practice gap. According to the AGREE-REX tool and relevant guidelines implementation projects [73, 74], we suggest that the PA guidelines promoting-strategies include the following: (1) Present information from the PA guidelines in an easy-to-understand format, such as developing PA guidelines for patients; (2) The PA guidelines for cancer patients should be sent to hospital decision-makers, managers, practitioners, and explained to them by the researchers; (3) provide routine training sessions and manual for healthcare professionals, education, and handbook for patients and their caregivers of PA guidelines; and (4) disseminate PA guidelines by holding public outreach events (public forums, reports, conferences, etc.).

Strengths and limitations

As with all systematic reviews, our review has several strengths. It is the first review of guidelines with PA recommendations for cancer patients using AGREE II and AGREE-REX instruments. We evaluated the quality and applicability of included CPGs, synthesized PA recommendations, which could guide future research. In this review, the study selection and data extraction were performed by two independent reviewers, and all included guidelines were assessed by five independent evaluators. Before this article, reviewers were trained to ensure the validity and reliability of the guideline evaluation. Our review team also consists of an expert who has experience in guidelines development.

There are some limitations in our review. First, albeit a comprehensive literature search strategy and covering grey literature, some CPGs may still be missed. Second, given that CPGs only published in English were included, there may be selection bias in our study. Finally, the methodological quality appraisal of guidelines may be somewhat subjective; AGREE II and AGREE-REX did not set defined thresholds to differentiate between high quality and low quality guidelines, we adopted cut-off scores based on previous studies in our review [27]. Other evaluators may interpret AGREE domains scores differently, so the results of AGREE II and AGREE-REX appraisal should be interpreted with discretion. The AGREE II and AGREE-REX only focus on the methodological quality and applicability of guidelines.

Conclusions

This review revealed several deficiencies in domains including “applicability,” “values and preferences” and “implementability,” so this study can serve as a baseline from

which to benchmark future development and improvement of cancer rehabilitation guidelines. Furthermore, this analysis indicated that more rigorous, high-quality studies are needed to generate trial-based evidence for supporting PA recommendations and provide guidance on research gaps in the field of cancer rehabilitation.

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Declarations

Ethics approval The study is a systematic review of published material; therefore, ethics approval was not required.

Conflict of interest The authors declare no competing interests.

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