

STATE-OF-THE-ART REVIEW

Role of Physical Activity and Cardiac Rehabilitation in Patients Undergoing Hematopoietic Stem Cell Transplantation



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ABSTRACT

Hematopoietic stem cell transplantation (HSCT) is a standard treatment for several malignancies, and >50,000 HSCT are performed annually worldwide. As survival after HSCT improves, cardiovascular disease and associated risk factors have gained importance as a significant cause of morbidity and mortality in this cohort. In this article, we detail the risk factors for cardiovascular disease and their impact in patients undergoing HSCT. Additionally, we critically review the data on the impact of physical exercise in patients undergoing HSCT. Although limited by significant heterogeneity in methodologies, small sample sizes, attrition, and lack of long-term cardiovascular follow-up, most of these studies reinforce the beneficial effects of physical activity and exercise in this patient population. Cardiac rehabilitation (CR) is a structured exercise and lifestyle modification program that is typically instituted in patients who experience acute cardiovascular events. We review the data on CR in the oncologic and nononcologic populations with an aim of building a framework for use of CR in HSCT patients. (J Am Coll Cardiol CardioOnc 2021;3:17-34) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Hematopoietic stem cell transplantation (HSCT) is a curative treatment option for several hematologic conditions, both malignant and nonmalignant. Worldwide, more than 50,000 HSCTs are performed annually (1), and according to the Center for International Blood and Marrow Transplant Research, a total of 23,706 HSCTs were performed in the United States in 2018 (2). With advances in transplant strategies, the life expectancy of HSCT survivors continues to improve, such that

by the year 2030, there are projected to be 502,000 HSCT survivors (3-5). However, the noted improvement in survival after HSCT has been associated with a resultant increased risk of non-disease-specific long-term complications. Specifically, the burden of cardiovascular disease (CVD) and associated risk factors have a significant adverse impact on long-term morbidity and mortality after HSCT (6).

The Centers for Disease Control and Prevention regards physical activity as an effective form of

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ABBREVIATIONS AND ACRONYMS

ACSM = American College of Sports Medicine

AHA = American Heart Association

CR = cardiac rehabilitation

CVD = cardiovascular disease

GVHD = graft-versus-host disease

HSCT = hematopoietic stem cell transplantation

MFI = Multidimensional Fatigue Inventory

MI = myocardial infarction

PCI = percutaneous coronary interventions

V_{o2max} = maximal oxygen consumption

treatment for and prevention of chronic diseases including CVD, metabolic syndrome, and certain cancers in the general population (7). These data suggest that physical activity leads to improvements not only from a physiological perspective but also from an overall health-related quality of life perspective (8). Cardiac rehabilitation (CR) is a structured comprehensive exercise and lifestyle modification program that is extensively used in cardiovascular practice after myocardial infarction (MI) as well as in patients with stable angina or heart failure and after percutaneous coronary interventions (PCI) and cardiac surgery.

In this review, we comprehensively evaluate published reports on the feasibility, implementation, and outcomes of exercise therapy and cardiac rehabilitation, and we

propose a framework to implement these strategies in the growing HSCT population.

THE BURDEN OF CVD AND RISK FACTORS AFFECTING OUTCOMES IN HSCT

Although HSCT has significantly enhanced the potential for cure and survival in patients with hematologic malignancies, long-term survival after HSCT is dependent on several factors including patient characteristics, prior cancer treatment, disease risk stratification, and transplant-related outcomes. In a large cohort of patients who were alive and disease free after 2 years of allogeneic HSCT, the 10-year probability of survival was 85% (3). Similarly, the 20-year survival was 80% in patients who were relapse free for ≥ 5 years after autologous HSCT (9). However, long-term CVD and CVD risk factors are a major cause of morbidity and mortality among these survivors, often relating to prior cancer treatment in addition to cardiovascular issues associated with HSCT. HSCT recipients are at increased risk of developing CVD risk factors, with reported incidence rates for hypertension of 28% to 74%; diabetes, 10% to 41%; dyslipidemia, 33% to 58%; and obesity, 20% to 44%. This translates into a 7- to 16-fold higher incidence of CVD risk factors in HSCT survivors compared to the general population (10-12).

Similarly, HSCT survivors have an increased risk of overt CVD with a reported incidence of MI, heart failure, and arrhythmias of 1% to 6%, 1% to 9%, and 2% to 13%, respectively (11-16), with a median age for overt CVD lower in HSCT survivors compared to the general population (age 54 years vs. 67 years,

HIGHLIGHTS

- Patients surviving HSCT have a higher incidence of cardiovascular risk factors and cardiovascular disease than the general population.
- Physical activity can improve cardiovascular fitness, strength, and quality of life and decrease fatigue in HSCT patients and survivors.
- In addition to physical exercise, cardiac rehabilitation also involves dietary and smoking cessation counseling, medication management, and psychosocial support, and it may therefore offer a unique framework to mitigate cardiovascular risk in HSCT.
- Early referral, cardiovascular risk stratification, monitoring for complications, and multimodal lifestyle interventions should form the backbone of cardiac rehabilitation in this population.
- Outcome data on quality of life indices and survival as potential benefits of cardiac rehabilitation in HSCT are needed.

respectively) (11,17,18). Furthermore, there is a 2- to 4-fold increased risk of CVD mortality in HSCT survivors compared with the general population (15,19). Although advanced age is a well-established independent risk factor for CVD (20), improvements in HSCT techniques have made it possible to offer HSCT to the geriatric population. To this end, in 2018, 39% of allogeneic HSCT and 55% of autologous HSCT recipients were in patients ages 60 years and older (2).

The increased burden of CVD and its risk factors in HSCT recipients is likely a consequence of direct organ damage from therapeutic exposure to chemotherapy and/or radiation, as well as indirect injury from graft-versus-host disease (GVHD), pre-existing CVD risk factors, and functional disability (16). Heart failure has been associated with chemotherapeutic agents such as anthracyclines (3% to 26%) and high-dose cyclophosphamide (28%) used as part of primary treatment or preparative regimens (20-23). Compared to autologous HSCT, higher incidence of cardiovascular risk factors like hypertension, diabetes, and dyslipidemia has been reported in allogeneic HSCT survivors (10). These risk factors are particularly more prevalent in patients who develop GVHD, and it has been hypothesized that the allogeneic reaction may cause an

accelerated atherosclerotic process (10). Moreover, in an analysis of 123 HSCT survivors, of whom 95.9% underwent allogeneic transplantation and all were treated with total-body irradiation, the 10-year cumulative incidences of elevated blood pressure, elevated glucose, low high-density lipoprotein cholesterol, hypertriglyceridemia, and obesity were 8.8%, 33.1%, 52.0%, 65.0%, and 18.6%, respectively (24).

Furthermore, HSCT recipients require an average of 4 or more weeks of inpatient hospital stay. During this prolonged stay, patients are often critically ill, lose muscle mass, and may develop decreased exercise capacity (16). Although there is a paucity of data on the effects of prolonged inpatient stay on CVD sequelae in HSCT patients, the impact may be extrapolated from studies in nononcologic patients. One such study reported that a 3-week bed rest may lead to similar deterioration in cardiopulmonary fitness as a 40-year-period aging process (25,26). The impact of prolonged bed rest on cardiopulmonary fitness in HSCT recipients is likely to be more pronounced, given associated higher CVD risks, than in otherwise healthy individuals.

PHYSICAL EXERCISE AS AN INTERVENTION IN THE HSCT POPULATION

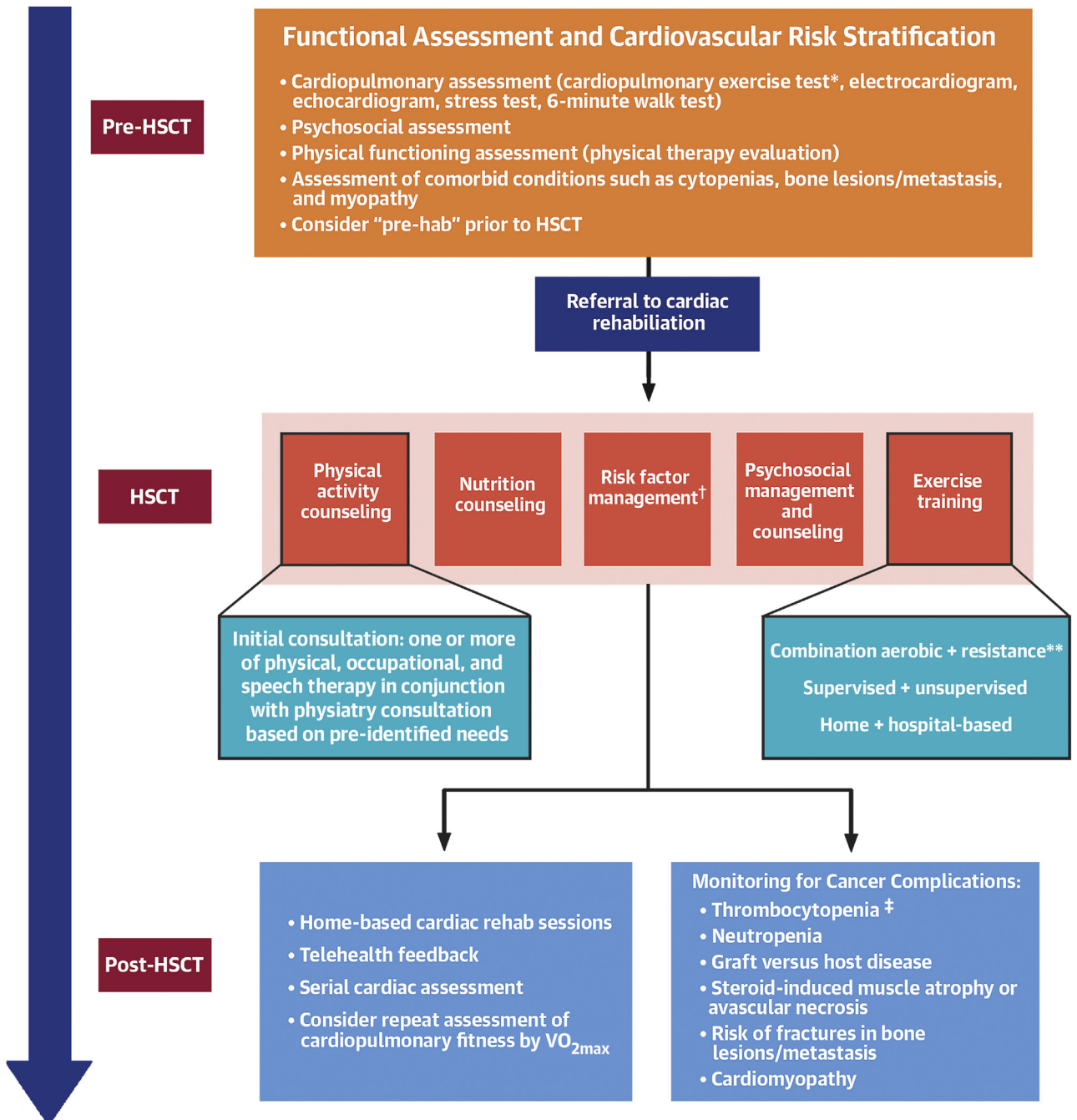
The physical activity guidelines by a federal advisory committee and the U.S. Department of Health and Human Services recommend for Americans that adults engage in at least 150 to 300 min of moderate-intensity or 75 to 150 min of vigorous-intensity aerobic physical activity per week, as well as muscle-strengthening activities 2 or more days a week (27). The American College of Sports Medicine (ACSM) suggests that an effective exercise prescription that most consistently addresses health-related outcomes in patients with cancer should include moderate-intensity aerobic training (at least 3 times/week, for at least 30 min, for at least 8 to 12 weeks) along with resistance training (at least 2 times/week, using at least 2 sets of 8 to 15 repetitions of at least 60% of 1 repetition maximum) (28,29). However, patients with HSCT require special considerations given their propensity toward deconditioning due to a unique set of challenges including, but not limited to, thrombocytopenia, infections, complications from chronic steroid use (avascular necrosis, steroid myopathy), GVHD, and consequent prolonged hospital stay/bed rest (30). For patients undergoing HSCT, the ACSM (using guidelines from the National Comprehensive Cancer Network) encourages home-based exercise regimens, a full recovery of the immune system

before return to gym facilities, initial lighter-intensity exercise, and individualized exercise prescription (28). The first step toward developing an exercise program is baseline assessment for the feasibility and safety of physical activity (Central Illustration).

EXAMINATION OF PUBLISHED REPORTS ON THE ROLE OF EXERCISE IN HSCT PATIENTS. The first study that examined the feasibility of exercise as an intervention in the HSCT population dates back to 1986, when Cunningham et al. (31) studied 30 patients with acute leukemia between the ages of 14 and 44 years undergoing allogeneic HSCT. They randomized patients to 3 groups: no physical therapy and physical therapy 3 or 5 times a week. The results suggested a sparing effect of exercise on skeletal muscle protein status during hospitalization (31). However, this study was limited by its small sample size and lack of clinical or functional outcomes. Since then, a number of randomized studies (31-49) (Table 1), non-randomized studies (50-64), and meta-analyses (65-67) have evaluated the different effects of physical therapy in adult patients undergoing HSCT.

Most studies that have examined the role of exercise in HSCT patients revealed either an improvement in endurance and strength or a signal toward improvement in these parameters. However, there is significant variability in these studies regarding the type, duration, and timing of exercise intervention, as well as significant variability in the exclusion criteria (Table 1). In particular, the exclusion of patients with CVD is of special concern because these patients may benefit most from physical activity. Another limitation of these studies is that they do not specifically evaluate the association of physical activity with cardiovascular outcomes. Although one may postulate that improvement in strength and endurance would translate into long-term cardiovascular benefit, the paucity of cardiovascular data highlighting the benefits of exercise in this population with a higher risk of CVD should incentivize further research.

In a study by Dimeo et al. (53) evaluating patients with solid tumor and non-Hodgkin lymphoma undergoing HSCT, walking on a treadmill for 6 weeks improved performance measured as metabolic equivalents (53). A randomized trial of patients with multiple myeloma undergoing HSCT studied a combination of walking, stretching, and strength training as an intervention and showed an improvement in 6-minute walk distance, but the study was limited by lack of statistical testing (32). Another randomized study of 18 patients undergoing allogeneic HSCT evaluated the use of active range of motion exercises,

CENTRAL ILLUSTRATION Cardiac Rehabilitation in Hematopoietic Stem Cell Transplantation Patients:
Our Proposed Model

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*Conditions specific to the HSCT population that may limit use of VO_{2max} include neutropenia; isolation during hospitalization; and presence of mucositis, which prevents patients from holding a mouthpiece. [†]Weight, blood pressure, lipid, diabetes, and tobacco cessation management. ^{**}Per the American College of Sports Medicine, 3 times/week for 30 min per session of moderate aerobic exercise, plus 2 times/week of resistance training for 2 sets of 8 to 15 repetitions for major muscle groups. Exercise prescription should be individualized based on exercise testing and comorbidities. [‡]Maintain platelet count of $>50,000/\mu\text{l}$. HSCT = hematopoietic stem cell transplantation.

TABLE 1 Description of Randomized Trials on Physical Exercise in the Stem Cell Transplant Population

First Author (Year) (Ref. #)	N	Type of Graft	Intervention	Control	Supervision	Duration of Intervention	Maximum Follow-Up	Main Results
Cunningham et al. (1986) (31)	30	Allogeneic	Physical therapy 3 or 5 times a week Resistive exercise, each session lasted 15 min	Usual care	N/A	Hospitalization until 35 days afterward	5 weeks*	No difference in median BW, arm muscle area, or arm fat between groups. Results favored a muscle protein-sparing effect of exercise. No additional benefit of 5 times/week regimen.
Coleman et al. (2003) (34)	24	Autologous	Individualized aerobic and strength resistance training	Encouragement to remain active and walk 20 min at least 3 times/week	Self-directed	3 months before transplant to approximately 3 months after	Approximately 3 months from transplant	Exercise group maintained LBW, whereas the usual care group lost LBW. Muscle strength, time on treadmill, fatigue, mood disturbance, and sleep were comparable between groups.
Mello et al. (2003) (38)	18	Allogeneic	Active range of motion exercises, stretching, and a modified treadmill walking program; 40-min sessions daily over weekdays	Usual care	Combined supervised and self-directed	This exercise program was initiated during the inpatient period and was concluded in the outpatient facility. Total duration was 6 weeks.	6 weeks†	At 6 weeks from discharge, the intervention arm had higher values for strength in all muscle groups but reached statistical significance only for the hip flexors. Compared to pre-transplant values, there was no change in strength for 16 of 18 muscle groups in the intervention group (indicative of normalization), whereas 11 of 18 muscle groups showed decreased strength in the control group.
DeFor et al. (2007) (35)	100	Allogeneic	Walking on a treadmill for at least 15 mins twice a day After discharge, patients asked to walk once a day for at least 30 min	Not asked to perform any formal exercise, and not provided with a treadmill unless requested by the patient/staff	Self-directed	Start of hospitalization to 100 days later	100 days*	Similar decline in Karnofsky performance score. In a subset of older and less fit patients receiving nonmyeloablative pre-transplant conditioning, the decline was lower in the exercise group. At 100 days, no difference in the scores for physical and emotional well-being. Among the non-myeloablative patients, scores for physical well-being were higher in the exercise arm. Comparable length of hospitalization and survival between the groups.

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TABLE 1 Continued

First Author (Year) (Ref. #)	N	Type of Graft	Intervention	Control	Supervision	Duration of Intervention	Maximum Follow-Up	Main Results
Coleman <i>et al.</i> (2008) (32)	120 (of which only 69 participated in the long term group)	Autologous	Individualized exercise prescription provided Daily stretching, walking, and strength training every alternate day	Asked to follow written exercise recommendations provided by their physician Advised to walk 20 min/day	Self-directed	Started before stem cell collection until 30 weeks after	30 weeks from stem cell collection	Fewer attempts at harvesting stem cells, lesser requirement for RBC transfusion, and greater distance walked at 6 min (no statistical testing) in the exercise group.
Jarden <i>et al.</i> (2009) (36)	42	Allogeneic	4-min warm-up followed by stationary cycling for a period of 15 to 30 min daily Daily dynamic exercises and stretching exercises Resistance training performed 3 times weekly Progressive relaxation training recommended twice weekly for 20 min	Physiotherapy offered following HSCT up to 1.5 h weekly	Supervised	Day of admission to day of discharge	6 months*	Exercise group had significantly higher Vo_2 max and muscle strength on day of discharge. No difference in QoL metrics, psychological metrics, and survival between the groups. Exercise group required lesser duration of TPN. At 6 months, no difference in reported physical activity, depression, or anxiety.
Shelton <i>et al.</i> (2009) (37)	61	Allogeneic	Individualized exercise program: aerobic and strengthening exercises, 3 times per week for 4 weeks	Instructions from a physical therapist for a home exercise program Variable-intensity resistive exercises and walking regimen Instructed to progressively increase walking time to 30 consecutive minutes, 3 times/week	N/A	4 weeks	4 weeks*	Supervised group increased their 6MW distance and 50-foot walk time significantly, whereas the self-directed group increased only their 6MW distance. Score for the worst fatigue decreased in both groups, but pre- and post-intervention values failed to achieve statistical significance. No difference between supervised and unsupervised groups for any of the performance outcomes at 4 weeks
Bauman <i>et al.</i> (2010) (39)	64	Both	Pre-transplant: aerobic endurance training for 10 to 20 min twice a day on a bicycle ergometer and ADL training During chemotherapy and after engraftment: daily 20 min of walking, stepping and stretching	Passive and active mobilization with a low intensity, 5 days a week	Supervised	From 6 days before transplant to 1 day before discharge	At time of discharge	Endurance, endurance time, strength, global QoL, and physical functioning were significantly better in the intervention group at time of discharge.

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TABLE 1 Continued

First Author (Year) (Ref. #)	N	Type of Graft	Intervention	Control	Supervision	Duration of Intervention	Maximum Follow-Up	Main Results
Bird et al. (2010) (40)	58	Both	Exercise, relaxation, and information for 10 weeks Circuit training in the gym under the supervision	Information leaflets from the discussion component of intervention program and a home-based exercise program ≥ 3 times a week for a minimum of 10 weeks	N/A	Eligible 6 to 8 weeks post-transplant Total exercise duration was 10 weeks	6 months*	No difference in physical functioning (measured by SF-36), Global Health Questionnaire, QoL, and shuttle walk test between the 2 groups.
Knols et al. (2011) (41)	131	Both	Twice-weekly endurance and resistive strength training Aim to maintain aerobic performance for at least 20 min at pre-specified heart rate	No supervised exercise or encouragement to exercise	Supervised	3 weeks to 6 months after transplant, for a total duration of 12 weeks	3 months*	At end of intervention, knee extension strength, walking speed, and functional exercise capacity were improved in the intervention arm. At 3 months after completion of the program, intervention group was superior in knee extension strength but not in the other measures. No difference in body composition, measures of health-related QoL, or fatigue. Diarrhea and emotional functioning were improved in the intervention arm at program completion but not at 3 months.
Hacker et al. (2011) (42)	19	Both	Progressive resistance training during hospitalization for HSCT and moderate-intensity training immediately following discharge from the hospital Supervised exercise 1 to 2 times per week and unsupervised 2 more times per week (total: 3 times per week)	Given recommendations regarding rest, physical activity, and exercise	Combined	Hospitalization to a total of 6 weeks thereafter	6 weeks†	No difference in physical activity, muscle strength, health status perceptions, and QoL assessment at follow-up; fatigue significantly improved in the intervention group. Significant time effects noted with anticipated declines in physical activity, muscle strength, fatigue, and health status perceptions immediately after HSCT and subsequent improvements 6 weeks following hospital discharge.

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stretching exercises, and a modified treadmill walking program for 6 weeks and revealed that the intervention arm had higher values for strength in all muscle groups but reached statistical significance

only in the hip flexors. The investigators also found that although strength in the intervention arm normalized at 6 weeks (compared with pre-transplant values), the control group continued to have

TABLE 1 Continued

First Author (Year) (Ref. #)	N	Type of Graft	Intervention	Control	Supervision	Duration of Intervention	Maximum Follow-Up	Main Results
Wiskemann et al. (2011) (45)	105	Allogeneic	3 endurance (up to 5 during hospitalization) and 2 resistance training sessions per week Endurance included walking, bicycle, and treadmill walking	Moderate physical activity recommended	Combined	Began on an outpatient basis before HSCT (1 to 4 weeks before admission to the hospital) and continued until 6 to 8 weeks after discharge	6 to 8 weeks†	Intervention group had significantly reduced fatigue, higher physical functioning and anxiety level and higher 6MW distance compared to control group. Comparing pre/post group mean differences, significant improvements were shown for the exercise group in anger/hostility and pain.
Coleman et al. (2012) (33)	187	Autologous	Daily stretching, strength and resistance training, and aerobic walking	Walk 20 min 3 times/week	Self-directed	15 weeks	15 weeks*	No difference between groups for fatigue, sleep, or performance.
Hung et al. (2014) (43)	37	Autologous	Home-based nutrition and exercise program Encouraged to begin aerobic exercise daily (walking or cycling) for ≥10 to 30 min and simple resistance exercise for 3 to 7 days a week After discharge, patients were called fortnightly to evaluate progress	Usual care	Self-directed	From day of discharge to 100 days post-transplantation	100 days post-transplantation	Between hospital discharge and 100 days post-HSCT, both groups improved in nutritional outcomes. Majority of patients were classified as well nourished, with no difference between the groups. Less fat loss and similar LBM loss in the intervention group No difference in QoL
Jacobsen et al. (2014) (44)	711	Both	4 groups: self-directed exercise program, self-administered stress management program, both, or neither Exercise goal was walking 3 to 5 times a week for at least 20 to 30 min	45-min DVD presenting general information about HSCT (keeping active and minimizing stress during transplantation)	Self-directed	From 30 to 60 days after discharge to 100 days afterward.	180 days after HSCT	No difference in Physical Component summary scale, Mental Component summary scale, distress, sleep quality, nausea, and pain between the exercise groups and usual care at 180 days post-transplant No difference in number of days alive and out of the hospital at 100 days post-transplant

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significantly decreased strength in a majority of the muscle groups (38). In a trial evaluating the impact of strength training as an intervention in patients undergoing HSCT, Hacker et al. (42) found that physical activity (as measured by a wrist-worn accelerometer) decreased during hospitalization, followed by a significant increase at 6 weeks post-hospitalization.

However, the increase was comparable between the groups and likely represented the natural course of physical fitness after transplantation. The researchers noted that this was a pilot study not powered to detect statistically significant differences (42). In a follow-up single-blinded, randomized trial enrolling 67 patients, Hacker et al. (47) evaluated the efficacy of

TABLE 1 Continued

First Author (Year) (Ref. #)	N	Type of Graft	Intervention	Control	Supervision	Duration of Intervention	Maximum Follow-Up	Main Results
Oechste et al. (2014) (46)	58	Autologous	Endurance training for at least 10 and up to 20 min and 3 resistance exercises for 20 min: 5 times per week	Given recommendations regarding rest, physical activity, and exercise	Supervised	During hospitalization Median: 21 days Range 16 to 33 days	12 months*	At the end of hospitalization, there was a significant increase in physical performance and muscle strength in the intervention group. Intervention group had higher levels of physical functioning but similar levels of emotional, cognitive, and social functioning. Analysis of fatigue using the Modified Fatigue Impact Scale revealed a significantly worse cognition and psychosocial function after the completion of chemotherapy for patients in the control group (compared to the intervention group), whereas the Physical subscale revealed no difference. No difference in length of stay, duration of aplasia, RBC, and platelet transfusions between the groups. At 12 months, no difference in survival, overall good condition, percentage of patients with normal physical activity, and integration into normal life between the groups.

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strength training as compared to usual health education and found that the intervention group was significantly more active than the control group by objective measures and was able to perform better on some measures of functional capacity, such as the timed up-and-go test and the 15-foot walk-time test, but not in other measures, such as the 30-s sit-to-stand or timed stair climb. Measures of strength showed improvement in some parameters, and others were comparable between the groups (47). In a meta-analysis of 8 studies evaluating the role of exercise in patients undergoing HSCT for hematologic

malignancies, Persoon et al. (65) showed a positive effect of exercise on lower and upper extremity strength and a moderately positive effect on cardiorespiratory fitness. An updated meta-analysis of 10 studies revealed no benefit of exercise on cardiorespiratory fitness (66). However, these meta-analyses are limited by significant heterogeneity in study methodologies.

TIMING OF PHYSICAL ACTIVITY/EXERCISE IN THE HSCT POPULATION. The timing of exercise in patients undergoing HSCT appears to affect the benefits of exercise in this population. Studies show that

TABLE 1 Continued

First Author (Year) (Ref. #)	N	Type of Graft	Intervention	Control	Supervision	Duration of Intervention	Maximum Follow-Up	Main Results
Hacker <i>et al.</i> (2017) (47)	67	Both	Progressive resistance training during hospitalization for HSCT and moderate-intensity training immediately following discharge from the hospital Supervised exercise 1 to 2 times per week and unsupervised 2 more times per week (total: 3 times per week)	Given recommendations regarding rest, physical activity, and exercise	Combined	Hospitalization to a total of 6 weeks thereafter	6 weeks†	Intervention group was significantly more active than control group when objective measures were used but not when self-reported activity was analyzed. Control group had increasing overall fatigue with time, whereas intervention group did not. However, the differences between the 2 groups were not significant. Intervention group was able to perform more arm curls, but hand grip strength and rectus femoris cross-sectional area were comparable between the 2 groups. Some tests of functional capacity (timed up-and-go test, 15-foot walk time) revealed a benefit of the intervention, whereas others were comparable (30-second sit-to-stand and timed stair climb). There were no differences in QoL measures.
Persoon <i>et al.</i> (2017) (49)	109	Autologous	18-week high-intensity resistance exercise and interval training program: twice a week in the first 12 weeks and once a week from week 13 onward 5 counseling sessions aiming to improve compliance	Usual care	Supervised	18 weeks	18 weeks*	In both groups, cardiorespiratory fitness and strength improved and fatigue declined over time. No significant favorable effects of a supervised high-intensity exercise program on physical fitness, fatigue, body composition, QoL, distress, or physical activity compared to usual care.

*After enrollment. †After discharge.

6MW = 6-min walk; ADL = activities of daily living; BW = body weight; HSCT = hematopoietic stem cell transplant; LBW = lean body weight; N/A = not applicable; QoL = quality of life; RBC = red blood cell; SF-36 = Short Form-36; TPN = total parenteral nutrition.

exercise therapy can be safely initiated during and even before hospitalization for transplantation (the concept of “pre-hab”) (32,36,45). Liang et al. (66), in their meta-analysis, reported that exercise had a significant positive impact on upper and lower extremity strength when initiated before HSCT but not when initiated after transplant. Wood et al. (68) demonstrated that patient-reported baseline physical functioning (as determined by the Medical Outcomes Study Short Form-36 Health Survey’s Physical Component summary scale) is associated with overall mortality post-HSCT; however, another analysis of the same trial by the same researchers showed that self-reported pre-HSCT exercise was not associated with survival (59,68). Both of these studies had significant limitations, and the results indicate that patient-reported assessment of physical function may not correlate with level of exercise. Other studies suggest that patient-reported physical functioning pre-HSCT does predict survival (69,70). Although there have been increasing data on evaluating pre-transplant frailty or physical function (“pre-hab”) for transplant patients, there are significant challenges to this concept in a high-risk malignancy population. HSCT survivors of all ages are at risk for developing frailty, with use of high-intensity chemotherapy and GVHD being risk factors for this (71-73). Nevertheless, this concept of pre-hab is important and worth considering as part of the exercise rehabilitation process in HSCT recipients. Of note, various frailty assessment tools have been validated for the general population, and these could potentially be used to improve existing pre-HSCT assessments and to identify individuals at highest risk for adverse outcomes (72).

ADDITIONAL BENEFITS OF PHYSICAL ACTIVITY/EXERCISE IN THE HSCT POPULATION. Physical therapy has been associated with higher rates of achieving engraftment and shorter duration of total parenteral nutrition (36,56). Exercise may also decrease the need for blood transfusions and decrease the number of attempts needed to harvest stem cells in patients undergoing autologous HSCT (32,56).

Physical therapy and exercise also have an impact on fatigue and mood in patients undergoing HSCT. Several scales have been used in studies to evaluate fatigue in this population, including the Multidimensional Fatigue Inventory (MFI), the functional assessment of cancer therapy anemia scale, and the Fatigue subset of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30. HSCT meta-analyses have found a significant positive effect of exercise on fatigue (65,66). In a randomized trial enrolling 105

patients, exercise was initiated 1 to 4 weeks before hospitalization for allogeneic HSCT and continued 6 to 8 weeks after discharge (45). Compared to baseline, the study revealed worsening of general fatigue as measured by the MFI at the time of discharge in both groups, with the exercise group improving to pre-transplant MFI values at 6 to 8 weeks after discharge and the control group continuing to have increased fatigue. The researchers also found that the exercise group reported decreased anger/hostility but not mental fatigue. Interestingly, contrary to previous data, the investigators found an increase in anxiety levels in the exercise group (45,52). They postulated that this may be due to anxiety related to decreased care by study personnel at the end of the exercise intervention (45). Although there was no clear evidence of improvement in reported quality of life measures with exercise in individual randomized trials, meta-analyses of study-level data report a significant improvement in quality of life (65,66). Finally, short-term exercise therapy does not seem to offer a survival benefit (66).

MAXIMAL OXYGEN CONSUMPTION IN THE ASSESSMENT OF CARDIORESPIRATORY FITNESS AMONG HSCT PATIENTS. Individual studies use different measures of cardiorespiratory fitness, including 6-min walk test, modified Balke protocol, vital capacity, and maximal oxygen consumption (VO_{2max}) (66). VO_{2max} refers to the greatest amount of oxygen that can be taken in during physical activity. For a constant pulmonary function and ambient oxygen level, VO_{2max} provides an accurate measure of maximal cardiovascular function (74). VO_{2max} testing is the gold standard for assessment of cardiorespiratory fitness. However, this requires specialized equipment and trained personnel, which limits its use. Other conditions specific to the HSCT population that may limit the use of VO_{2max} as an outcome measure are neutropenia, isolation during hospitalization, and presence of mucositis that prevents patients from holding a mouthpiece (53,75). Only 2 randomized trials used VO_{2max} for assessment of cardiorespiratory function (36,49). Of these, the study by Jarden et al. (36) is one of the most comprehensive assessments of multimodality intervention in patients with HSCT. The intervention in that trial included stationary cycling, daily dynamic exercises, and stretching, along with resistance training 3 times weekly. The researchers reported that patients in the intervention group had higher VO_{2max} and muscle strength on the day of discharge. Although there are no studies comparing aerobic and resistive training, a combination of both is likely to maximize benefit to these patients.

SUPERVISED VERSUS UNSUPERVISED EXERCISE PROGRAMS IN HSCT.

Although supervised exercise allows high-quality interventions by professional health care workers, self-directed exercise has the benefit of allowing immunocompromised individuals to exercise at home with minimal equipment. In an interesting randomized study, Hung *et al.* (43) evaluated the use of telephone-delivered nutritional and exercise counseling in patients undergoing HSCT compared to usual care. The patients were encouraged to begin daily aerobic exercise and simple resistance exercises for 3 to 7 days a week. After discharge from the hospital, the patients received telephone calls fortnightly to evaluate their progress (43). At 100 days post-transplantation, those in both the intervention and control arms improved in nutritional outcomes, and there was no difference in physical activity time and loss of lean body mass between the groups. However, the intervention group had decreased loss of fat mass. Of note, adherence was poor for this intervention, and <50% of patients received ≥ 3 phone calls for both exercise and nutritional advice. The results of this trial indicate that purely home-based therapy may not be as effective in the HSCT population (43).

Furthermore, Shelton *et al.* (37) conducted a study of 61 patients randomized to a supervised versus self-directed physical therapy intervention during hospitalization and up to 4 weeks after allogeneic HSCT. They reported that patients in the supervised group increased their 6-minute walk distance and 50-foot walk time, whereas the self-directed group increased only their 6-minute walk distance (37). At the same time, supervised interventions that may be effective during hospitalization may not show continued benefit at long-term follow-up (36). A Cochrane review for the general population suggested that a mixture of professional guidance and self-direction plus ongoing professional support leads to more consistent effects (76). A unique approach to this combined intervention was undertaken by Hacker *et al.* (47) In that study, patients underwent supervised exercise once or twice a week during their regularly scheduled clinic visits. Patients were encouraged to exercise on their own 2 more times per week for a total of 3 times per week. They postulated that this approach would reduce the risk of exposure to pathogens in places such as gyms and make effective use of clinic waiting times (47). They reported a fairly good compliance of 83% and significantly improved physical activity (as measured by a wrist-worn accelerometer) with the exercise intervention compared with usual care (47). Another study evaluating the role of self-directed exercise as well as stress management in patients undergoing

HSCT enrolled 711 patients, randomizing them into 4 groups: usual care, stress management intervention, exercise intervention, and a combined stress management and exercise intervention (44). The investigators noted no differences in the Physical and Mental Component summary scales 100 days after transplantation. They did note that at 180 days after transplantation, the exercise group was more physically active. They postulated that lack of sufficient exercise intensity as well as overwhelming stress and physical deconditioning at the time of transplantation, regardless of exercise, may have explained the lack of difference. Noting the higher achievement of physical activity in the exercise group, we postulate that the lack of long-term follow-up could also have influenced the study findings, which highlights one of the limitations of a number of physical activity studies in this population. Although there are many published studies on physical therapy as an intervention in HSCT, the heterogeneity in design, measurement parameters, small sample size, poor adherence, and high attrition result in challenges in data harmonization and cohesive guideline recommendations.

DESCRIPTION OF CR

CR is a structured exercise and lifestyle modification program that is typically instituted in patients who experience acute cardiovascular events. The incorporation of CR services in the health care of patients with coronary heart disease, especially following an acute MI, has become recognized as a Class I recommendation from several societies, including the American Heart Association (AHA) and the American College of Cardiology (77). Multiple meta-analyses and systematic reviews have analyzed the benefits of CR in this population (Supplemental Table 1), with a large proportion of studies demonstrating significant reductions in all-cause mortality, cardiovascular mortality, MI, and hospital readmissions. Historically, CR was offered to patients only after MI or after coronary artery bypass grafting. However, over time, the spectrum has broadened to include patients with chronic stable heart failure, peripheral arterial disease, post-PCI, post-heart transplantation, and post-valvular surgery (78).

The core of the program is supervised exercise, but most programs incorporate work with registered dietitians, smoking cessation counseling, medication management, and occasionally psychosocial support (79). CR is composed of primary prevention and secondary prevention programs. Primary prevention includes risk factor modification and education in the absence of a prior cardiac event and is typically

completed in the outpatient setting, whereas secondary prevention typically occurs after a cardiac event or disease has occurred and typically involves exercise and risk factor modifications.

The CR program typically begins with an initial assessment during hospitalization, followed by program initiation 1 to 2 weeks after discharge (80). At the initial assessment, patients are risk stratified based on their degree of medical illness to help determine the necessary level of supervision and program intensity. The duration and frequency of programs vary but typically involve 3 sessions per week for 12 weeks (79). These variables can be generally tailored to patient preference with equal efficacy (81). The intention is that once the program is completed, the patient will be able to continue self-motivated exercise and risk factor modification. There are exercise-only programs and programs with and without psychosocial support; some of the programs are unsupervised, or “home CR.”

Contraindications to the exercise component of CR include unstable angina, decompensated heart failure, ventricular arrhythmias, severe pulmonary hypertension, intracavitary thrombus, or severe valve disease (82). Patients at high risk for complications (AHA class C) are advised to undergo exercise in a supervised environment with electrocardiogram monitoring at a facility able to provide advanced life support. Once the initial program is completed, a recommendation is then provided for continued unsupervised exercise based on the patient’s performance (83). For patients at lower risk, however, unsupervised exercise provides an attractive flexible option. Ideally, the first few weeks are completed with supervision to evaluate for complications, and afterward, patients are provided specific instructions for activity and heart rate monitoring.

HOME-BASED CR AND TELEMEDICINE. Home-based CR has been demonstrated to be similar to group-based CR in terms of outcomes, safety, and cost, with superior adherence (84), and has gained even more importance during the coronavirus disease-2019 pandemic, with a global transition toward virtual care and telemedicine. Nonetheless, it is essential to recognize that although patients at high cardiovascular risk are also at high risk for coronavirus infection, exercise in these higher-risk patients without direct supervision is a daunting prospect, with few data to guide this approach (85). Several strategies could be used to aid with success in home-based CR, including wearable heart monitors, smartphone applications, and video observation by a CR therapist with coaching (86). In a study on HSCT patients at intermediate to

high risk of CVD, Chang *et al.* (87) piloted a 4-week remote monitoring program using blood pressure monitoring, pulse oximetry, and glucometer. There was $\geq 80\%$ compliance in this study, with at least two thirds of patients successfully performing ≥ 3 readings per week, thereby demonstrating the feasibility of a home monitoring program (87). However, data are insufficient to support improvement in short- or long-term outcomes for these patients using telemedicine. Additionally, it is important to recognize that the availability and usability of these technologies may be limited in the highest-risk population, that is, those from poor socioeconomic strata, in older age groups, and with physical impairments or lack of adequate social and family support.

THE POTENTIAL FOR CR IN THE HSCT POPULATION

Historically, CR has been indicated only for patients with recent acute coronary syndrome/MI, chronic stable angina, post-PCI, heart failure, post-coronary artery bypass grafting, post-valve surgery, or heart transplant (80). However, the fundamental benefits of CR may confer benefit to other at-risk patient populations as well. HSCT patients can be considered one of these populations because although they may not have established coronary disease, they generally experience significant deconditioning and loss of muscle mass post-transplant. CR may provide a well-established framework for physical, emotional, and nutritional rehabilitation in the HSCT population. In 2019, the AHA published a statement recommending cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors (88). They proposed the development of a comprehensive model (i.e., cardio-oncology rehabilitation) to identify oncology patients at high risk of CVD, including cardiotoxicity related to cancer therapies, and using the multimodality approach of CR (e.g., exercise plus nutritional counseling and cardiovascular risk factor assessment) to prevent or mitigate cardiovascular events (88). One of the advantages of exercise in a medically supervised setting, and particularly in cancer patients with the possibility of metastatic disease and/or physical limitations such as bone lesions in multiple myeloma, is the ability to recognize any physical impairment that, if unrecognized and/or untreated, can become barriers to recovery of function. Furthermore, patients with cancer usually have other impairments affecting nearly every organ system in the body. Therefore, cardio-oncology rehabilitation services that include physical, occupational, and speech therapy in conjunction with

physiatry consultation should always be included in the rehabilitation of oncology patients (89). Current recommendations call for at least an annual routine clinical assessment and cardiovascular risk factor evaluation for all HSCT recipients (90). More frequent and extended cardiac evaluations (for example, electrocardiogram and echocardiogram) may be undertaken in patients at higher risk for cardiovascular complications such as those with multiple cardiovascular risk factors or post-mediastinal radiation therapy, as clinically appropriate. All HSCT recipients should be educated and counseled on a heart-healthy lifestyle (regular exercise, maintaining a healthy weight, smoking cessation, and dietary counseling). All cardiovascular risk factors such as diabetes, hypertension, and dyslipidemia should be managed, and follow-up assessments should be performed based on published guidelines (90).

Despite a paucity of published reports exploring the impact of CR post-HSCT, its potential benefit is increasingly recognized. Rothe *et al.* (91) explored a proof-of-concept study in 30 patients post-autologous HSCT who completed an 8-week CR program. Multiple markers of activity tolerance such as grip strength, 6-min walk distance, and gait speed were used, and measurements taken pre-transplant, post-transplant, and post-CR. The study demonstrated that CR was feasible in patients with severe physical deconditioning and resulted in significant improvement in activity tolerance without any documented deaths or cardiovascular complications (91).

CHALLENGES AND FUTURE DIRECTIONS FOR CR IN THE HSCT POPULATION

CHALLENGES IN THE IMPLEMENTATION OF CR IN THE HSCT POPULATION. Potential factors that may diminish the positive impact of CR in the HSCT population include the expected time to initiation of exercise. Adherence to an exercise regimen requires high patient motivation and the establishment of a relationship with the CR team, which can be impaired by long temporal distance between the initiation of CR and the indicating event. Thus, patients who enter the CR program >30 days after their initial assessment have less beneficial outcomes compared to those who entered earlier (92). Furthermore, the nonexercise components of CR will need to be adapted to fit a different archetype. For example, the incidence of current cigarette smoking in HSCT patients is around 7% to 17% compared to 37% in patients presenting with MI (93). Similarly, nutritional advice will also need to be tailored carefully to each patient, because many HSCT patients may be

underweight post-transplant as opposed to overweight, with significant nutritional deficiencies (94).

Other factors that may complicate recovery and initiation or continuation of CR in the HSCT population include GVHD and musculoskeletal pathology such as bone lesions in multiple myeloma. Along with an increase in morbidity and mortality, patients with GVHD have significantly lower quality of life scores and functional capacity compared to patients without (95). Consequently, patients with GVHD may not be able to tolerate an exercise regimen (95). There are very few studies investigating the impact of exercise in patients with GVHD. Tran *et al.* (96) examined the effects of pulmonary rehabilitation on 11 patients with bronchiolitis obliterans due to severe GVHD. Of the 11 patients, 10 were able to complete rehabilitation, and the researchers reported an improvement in 6-minute walk distance as well as subjective physical functioning in these patients (96). A comprehensive review of the topic performed by Fiuza-Luces *et al.* (97) notes the lack of studies in the GVHD population and calls for further research into the effects of exercise based on the beneficial impact of exercise in other patient populations (97).

Patients undergoing HSCT for multiple myeloma represent a unique challenge represented by their predilection for bone lesions, which, if present in the vertebral column, can lead to pathological fractures and potential spinal instability. It is critical that each patient with spinal involvement be evaluated before initiation of CR, with an exercise prescription tailored as such in a monitored setting. Patients with high-risk lesions may not be appropriate for exercise therapy but could be after treatment (98). Scoring systems could be used to help predict which patients may be at highest risk, taking into account location, pain, imaging characteristics, and spinal alignment. Physical therapists could also design exercise that minimizes spinal load to reduce risk (99). Although data are limited, the available published reports suggest that exercise is feasible and safe in patients with multiple myeloma (100). In a small randomized controlled trial of 30 patients with multiple myeloma, patients were randomized to usual care versus an exercise routine. Two-thirds (67%) of these patients had bone disease, and some had their exercise routine modified to account for it. None of the patients in either arm experienced any adverse events attributed to physical activity (101).

There are also potential setbacks with treatment. Patients may suffer relapses that could preclude them from continuing CR. Complications could also arise with immunosuppressive therapy. Steroid use could lead to avascular necrosis or steroid myopathy, which

could subsequently limit functional capabilities. All of these functional and anatomic limitations should be accounted for in prescribing/tailoring exercise prescriptions in this challenging population.

Overall, perhaps the most potent limiting factor to adoption of CR for HSCT patients is insurance coverage. Currently, CR is not covered by Medicare in the oncology population who have not yet experienced a cardiovascular event or surgery. As data accumulate on the benefits of physical activity in patients undergoing HSCT, we are hopeful that insurance reimbursement will follow (102).

PROPOSED MODEL FOR CR IN HSCT. Although a number of studies have evaluated the role of exercise therapy in HSCT, there are very few published reports to guide the development of a CR model for HSCT. However, based on data on CR and exercise in the non-HSCT and HSCT populations, we propose a framework (**Central Illustration**). Although we acknowledge that this has not yet been tested, we propose this as a model to promote the consideration of CR at all stages of a patient's diagnosis. Early pre-transplantation referrals should be encouraged to incorporate the concept of "pre-hab" before HSCT. The referral process should be simplified and made easily available to cardiologists, oncologists, and primary care physicians. On referral, patients should undergo cardiovascular risk stratification and, if needed, stress testing. The CR program, at its core, should include an exercise regimen inclusive of both aerobic and strength training. The intensity and duration of exercise should be guided by updated recommendations from the ACSM (28). In addition, cardiopulmonary exercise testing can help guide recommendations for moderate intensity (88). CR should also include dietary advice, weight management, blood pressure management, diabetic management, smoking cessation, and psychosocial counseling. Attention must be paid to HSCT-specific side effects and complications such as neutropenia, immunodeficiency, thrombocytopenia, GVHD, avascular necrosis, and so forth. There are multiple potential advantages of CR over a simple exercise prescription in HSCT patients. The integration of lifestyle modification into the program likely provides a distinct benefit when compared to supervised exercise alone. Furthermore, CR programs incorporate stress management training/psychosocial support, which addresses a critically important and often overlooked element of rehabilitation. It stands to reason that any intervention designed to improve mental health will have a positive impact in the HSCT

population. This preliminary framework needs to evolve as further research into best practices pertaining to CR in HSCT becomes available.

We propose the following research agenda for future studies. First, the subset of HSCT patients who would most likely benefit from CR need to be identified. Although we may assume that patients referred for HSCT are likely to be a population with pre-existing CVD and/or risk factors for CVD, development of prognostic risk scores would be incremental. Second, the feasibility of pre-hab in future HSCT recipients needs to be established. It would be important to determine whether the severity of the underlying malignancy and urgency of HSCT allows for such an intervention. Third, we need to establish the efficacy and safety of supervised as well as home-based CR in HSCT recipients. This will not only help quantify the challenges but also help advance insurance and physician interest in prescribing CR as an intervention. Fourth, future studies would benefit from using standardized measures of cardiovascular fitness such as Vo_{2max} . However, given challenges to its use, other validated markers such as the 6-minute walk test may be utilized. Also, measuring functional status with measures such as grip strength, gait speed, and timed get-up-and-go test may be valuable. Finally, correlation of a multimodality CR program with quality of life indices and survival would be the ultimate test of efficacy.

CONCLUSIONS

Patients who have undergone HSCT for hematologic malignancies experience severe deconditioning associated with their treatment and are at elevated long-term risk for cardiovascular complications. Exercise therapy is being increasingly recognized as a safe and vital component of the recovery process post-transplant. Therefore, despite the limitations of available published reports, there is a good degree of randomized and nonrandomized evidence supporting the use of exercise as an intervention to improve cardiorespiratory fitness and strength in patients undergoing HSCT. Furthermore, although all the mentioned components (physical and occupation therapy, dietitian, psychosocial oncology) of rounded care are present as post-transplant care for HSCT patients, having a tailored and well-structured program such as CR could result in better adherence to the programs and, ultimately, clinical outcomes. It is important to integrate the cancer-specific teams into CR for continuity and compliance. In so doing, CR that is structured and specifically tailored to HSCT patients is likely to provide a well-established

framework for physical, emotional, and nutritional rehabilitation for this population.

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- KEY WORDS** cardiac rehabilitation, hematopoietic stem cell transplantation
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- APPENDIX** For a supplemental table, please see the online version of this paper.