Should Healthcare Organisations Offer Ongoing Rehabilitation Services for Patients Undergoing Haematopoietic Cell Transplant? A Narrative Review

ABSTRACT

Background and objective

Hematopoietic Cell Transplant (HCT) patients can suffer from long-term transplant-related complications that affect their quality of life and daily activities. This narrative review aims to report the impact of HCT complications, the benefits of rehabilitation intervention, the need for long-term care, and highlight the research gap in clinical trials involving rehabilitation.

Methods

A comprehensive search strategy was performed on several databases to look for relevant articles published from 1998 to 2018. Articles published in English with the following terms were used: Hematopoietic Stem Cell Transplant; Chronic graft versus host disease; Rehabilitation; Exercise; Physical Therapy; Occupational Therapy. A PICO framework (patient/population, intervention, comparison, and outcomes) was employed to ensure that the search strategies were structured and precise. Study year, design, outcome, intervention, sample demographics, setting, and study results were extracted.

Results

Of the 1411 records identified, 51 studies underwent title/abstract screening for appropriateness, 30 were reviewed in full, and 19 studies were included in the review. The review found that, for the majority of patients who underwent HCT and developed treatment-related complications, rehabilitation exercises had a positive impact on their overall quality of life. However, exercise prescription in this patient group has not always reflected the scientific approach; there is a lack of high-quality clinical trials in general. The review also highlights the need to educate healthcare policy makers and insurance companies responsible for rationing services to recognise the importance of offering long-term follow up care for this patient group, including rehabilitation services.

Conclusion

A large number of HCT patients require long-term follow-up from a multidisciplinary team, including rehabilitation specialists. It is important for healthcare policymakers and insurance companies to recognise this need and take the necessary steps to ensure that HSCT patients receive adequate long-term care. This paper also highlights the urgent need for high-quality rehabilitation trials to demonstrate the feasibility and importance of rehabilitation teams.

Keywords: Exercise, Hematopoietic Cell Transplant, Allogeneic, Physiotherapy, Healthcare policy, Occupational therapy

Word Count: 223

INTRODUCTION

Haematopoietic Stem Cell Transplants (HSCT) have gained popularity as a treatment of choice in managing both malignant and non-malignant conditions (Copelan, 2006). With the maturity of transplant technology and the growing body of research, overall survival among transplant patients has risen significantly over recent decades (Wingard et al., 2011). However, increased survivorship has also shifted the burden of suffering from disease-associated to treatment-related, resulting in long-term morbidity and a reduced quality of life (QoL) (Sun et al., 2010). Many patients develop complications and musculoskeletal deficiencies, including graft versus host disease (GVHD), with devastating consequences on patient's QoL.

While there may exist an overlap in pathogenesis, clinical symptoms developed within 100 days post-HSCT (though this time frame is not a simple classifier) are classified as acute GVHD and can include signs of dermatitis (skin rash), cutaneous blisters, crampy abdominal pain with or without diarrhoea, persistent nausea and vomiting, and hepatitis (Jacobsohn and Vogelsang, 2007). On the other hand, cGVHD typically occurs 100 days after transplant, and the disease itself is not believed to be a continuation of acute GVHD. The condition is mainly an inflammatory and fibrotic process affecting the skin, fascia, muscles, bones, and joints, as well as other organs (Lee, 2005; Perez-Simon et al., 2006). However, to date, there does not exist a standard safe regimen for cGVHD treatment, and the majority of the drugs result in side effects with negative implications for patients' QoL (Perez-Simon et al., 2006). The National Health Service (NHS) in the UK has found that there is sufficient evidence to support a proposal for the routine commissioning of Extracorporeal photopheresis (ECP) for acute GVHD, and a combination of ECP, pentostatin, rituximab, and imatinib for cGVHD (National Health Service, 2017). However, these treatments can also have adverse effects, and some require extensive logistic support.

Rehabilitation interventions are increasingly being seen as a major player in managing the musculoskeletal aspects of cGVHD due to the involvement of fascia, muscles, and bones, causing functional incapacity in patients (Hashmi et al., 2015; Dignan et al., 2013). A number of studies have demonstrated that rehabilitation interventions may be useful in reducing post-HSCT musculoskeletal manifestations (Rosenthal et al., 2019; Chatterjee and De, 2017; Fiuza-Luces et al., 2016; Wiskemann et al., 2015; Braveman et al., 2017), However, anecdotal reports have suggested that these patients, in many cases, are only receiving rehabilitation services as a reactive approach to disease progression (Gajewski et al., 2009). Furthermore, the majority of patients do not accept long-term follow up from the rehabilitation team. The current paper not only outlines the various complications faced by this patient group from a QoL perspective, but also analyses the decisive role of rehabilitation and its importance as a long-term team factor in treatment.

Impact of cGVHD on patients' QoL

cGVHD occurs in up to 77% of patients' post allotransplant condition in the long term (Gale et al., 1987; Lee et al., 2003) and can affect several organs in the body, including the liver, gut, eyes, mouth, oesophagus, skin, fascia, lungs, and musculoskeletal system (Higman and Vogelsang, 2004; Baird and Pavletic, 2006). Furthermore, cGVHD is often coupled with comorbidities that require ongoing drug and other therapies, leading to further damage to the musculoskeletal system and resulting in a major impact on patients' QoL (Smith et al., 2015; Gielissen et al., 2007). Avascular necrosis of the bones, steroid myopathy, fatigue, fasciitis, scleroderma, neuropathy, joint destruction, cardiovascular compromise, osteopenia and osteoporosis, reduced lung capacity, reduced sexual capacity, vaginal or genital GVHD, and poor pelvic floor muscles may be part of the impact of cGVHD and related drug treatments in patients (Smith et al., 2015; Lee et al., 2006; Pereira and de Carvalho, 2011; Kovalszki et al., 2008). Many of these complications can develop gradually over time and last for as long as two years of transplant, such is the case for avascular necrosis of the femoral head (Atkinson et al., 1987). Functional incapacity in this patient group can be long-lasting and range from five to 20 years, having a considerable impact on a patient's daily activities, psychological well-being, and social life (Syrjala et al., 2011; Arora et al., 2016). This long-term instability in health also means that many patients are unable to return to work, resulting in a loss of income and subsequent financial hardship (Hamilton et al., 2018). Furthermore, the impact of cGVHD has been reported on multiple domains of QoL, including physical function, body pain, social function, emotional, mental health, sexual health, and psychological wellbeing (Pidala et al., 2011; Amonoo et al., 2019).

One of the major challenges faced by cGVHD patients is that expected positive outcomes of pharmacological intervention have, so far, been limited, offer with little or no benefit (Linhares et al., 2013). Therefore, non-pharmacological methods of improving QoL in these patients are being explored because physical exercises are beneficial not only post-HSCT, but also before the transplant (Liang et al., 2018). Therefore, the role of rehabilitation in managing cGVHD involves exercise intervention to improve functioning in daily living activities (ADL). However, there is a growing concern that the expertise of the allied healthcare team is not fully exploited by healthcare organisations (Bakhsh et al., 2018).

Although a number of studies have looked at the benefits of rehabilitation in HSCT and cGVHD, none have looked at justifying the need for long-term, ongoing rehabilitation for this patient group from a policymaker point of view; policymakers are responsible for providing or prioritising services based on dialogue and evidence (Elliott and Popay, 2000). Therefore, this review has two objectives. The first of these objectives is to inform healthcare policymakers and insurance companies of the importance of providing ongoing access to rehabilitation services for patients undergoing HSCT. The second objective is to analyse the current evidence of rehabilitation intervention in HSCT and cGVHD and highlight the need for further research.

METHODS

Study team

To attain findings that are clinically robust and relevant, the team for this study encompassed individuals with expertise in evidence synthesis, quantitative research methodology, occupational therapy, physiotherapy, and haematology and transplantation. A systematic literature research was employed to answer the research question: should healthcare organisations offer ongoing rehabilitation services for patients undergoing haematopoietic cell transplant? And in order to answer this question, a narrative review was conducted. The results were summarized narratively due to the range of studies included in the review.

Search strategy and data sources

A systematic search was completed in compliance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guideline (Moher et al., 2009). The Population Intervention Comparison Outcome (PICO) framework (**Table 1)** was used to ensure that the search strategies were structured and of high precision.

A systematic literature search was performed using the following databases: Health Research Premium Collection; SciTech Premium Collection; Biological Science Database; Natural Science Collection; ProQuest Central (new); ProQuest Hospital Collection; ProQuest Health & Medical Complete; Medical Database; MEDLINE/PubMed (NLM); ProQuest Pharma Collection; OneFile (GALE); ProQuest Environmental Science Collection; Health Reference Centre Academic (Gale); and ProQuest Central Essentials from 1998 to 2018 to ensure that the review would cover a number of articles and because only a small number of clinical trials on physiotherapy have been undertaken over the past two decades. The review also involved manually searching the reference lists of all related articles and Google Scholar to determine relevant references. Boolean logic was used with the following terms, text word, and thesaurus to minimize chances of missing related articles: Hematopoietic Stem Cell Transplant; Chronic graft versus host disease; Rehabilitation; Exercise; Physical therapy; and Occupational therapy.

Study selection and eligibility criteria

The selection of included studies was completed over two stages. Initially, identified studies were independently screened for eligibility based on title and abstract by two independent reviewers (JM and RS); accordingly, results were compared for consistency. Secondly, the full texts of eligible studies were screened with the inclusion/exclusion criteria listed in **Table 2** by the same independent reviewers. A third independent reviewer (HB) resolved disagreements.

→ Insert Figure 1 here ←

→ Insert Table 1 here ←

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Data Extraction, synthesis, and analysis

The characteristics of the included studies are presented in **Table 3**. Studies were categorised by in-patient or out-patient, interventions, and qualitative or quantitative outcomes. The studies included in this narrative review were both quantitative and qualitative research studies. Therefore, a meta-analysis was not pursued due to the variations across studies, such as the statistical heterogeneity being too high, different interventions, different study designs and outcomes, and a lack of statistical findings.

→ Insert Table 3 here ←

Quality assessment

The Modified Jadad Quality scoring method was chosen to assess the quality of randomised control trial for the current narrative review **(Table 4)** (Jadad et al., 1996). **The** Jadad Quality scoring system demands randomization, masking, and accountability for all patients, including withdrawals against which the studies are scored. There are five questions which are answered as "yes" or "no". Each "yes" gives one point and each "no" means that a point is subtracted, as described by Schäfer *et al*. (Schäfer et al., 2016).

→ Insert Table 4 here ←

Study limitations

The search was primarily limited to RCTs to capture and analyse high-quality trials in order to examine existing evidence informing on intervention and outcomes published in English. Therefore, the conclusions of this research are a reflection of a limited number of articles that were available in this language. Systematic reviews, meta-analysis and review papers were used for supporting the literature.

Of the 19 included studies, only one was primarily pre-transplant intervention (Jacobsen et al., 2014), one was out-patient only (Persoon et al., 2017), nine were in-patient based, and nine were both in- and out-patient based. None of the studies considered continual rehabilitation exercise interventions to cover pre-transplant, in-patient, and out-patient treatment. Moreover, in the absence of the pre-transplant functional assessment by physical or occupational therapists, it is difficult to analyse the real outcomes of rehabilitation intervention programmes and whether patients were able to return to normal (pre-transplant functional capacity). Additionally, the included studies combined both adult and paediatric populations, with the majority of the studies having a small, heterogeneous sample, which may make it difficult to make strong recommendations. Finally, the lack of a specific grading system for RCTs in physical and occupational therapy is needed as most of the studies scored, which makes it apparent that the interventions as not as effective as is being described.

However, the findings of this review demonstrate that exercise intervention is safe for patients with malignancies pre-, during, and post-HSCT. Despite the variations in the exercise intervention, both strength and endurance exercises are well tolerated by patients and safe for patients undergoing an HSCT. Furthermore, the current review highlights not only the need for rehabilitation specific RCTs scoring system, but also the importance of future researchers investing in patient-specific exercise prescription that covers the entire duration of the transplant starting from pre-, during, and post-HSCT.

RESULTS

Identification of studies

A PRISMA flowchart of the study identification process is presented in **Figure 1**. After removing duplicates, 1411 studies were identified as potential records, 51 studies underwent title/abstract screening for their appropriateness to the current review, 30 were reviewed in full, and 19 studies were ultimately included in the review. The current review focuses on analysing exercise interventions and reported outcomes during and post-HSCT, including patients with cGVHD, on various health-related parameters, as presented in **Table 5.**

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Data extraction, synthesis, and analysis

Out of the 19 studies included in this review, nine are in-patient based, eight are in outpatient-based, one pre-transplant and one outpatient specific. The included studies covered approximately 1,776 patients, aged between 5 and 73 years, both male and female from various ethnic backgrounds and from nine countries. The outcomes studied included not only strength and QoL, but also other parameters such as muscle endurance, fatigue, physical fitness, functional capacity, cardiorespiratory fitness, muscle mass, cytopenia, physiological function, psychological wellbeing, diarrhoea, immune cell recovery, psychosocial, anxiety, depression, and haemoglobin.

Although the majority of the studies (n=16) have reported the positive impact of exercise interventions (84%), three studies reported little or no benefit on patient's physical fitness, strength, endurance, and fatigue, including one pre-transplant study, one in-patient, and one out-patient study (16%). In the trials reviewed, the following themes were identified:

Exercise prescription

The science of exercise prescription is being underutilised in the majority of the studies, out of the 19 studies included in this review only three studies mentioned prescribing exercises as per individual patient capacity (Shelton et al., 2009; Yildiz Kabak et al., 2016; Persoon et al., 2017).

Specialists involved in designing exercise protocols

Interestingly the exercise prescription for the patients was not limited to the exercise physiologists or an experienced physical therapist but, other healthcare professionals also appeared to be designing exercises. We found nurse specialist, professors, doctors, registered nurse practitioners, and rheumatologists providing exercise prescriptions for the studies. Futhermore, several studies mentioned and discussued exercise physiologist being involved in exercise prescription (Persoon et al., 2017; Shelton et al., 2009; Baumann et al., 2011; Yildiz Kabak et al., 2016; Jarden et al., 2009; Schumacher et al., 2018; Morishita et al., 2013a; Takekiyo et al., 2015; Wood et al., 2016; Wiskemann et al., 2011).

The rationale behind the chosen exercises

Shelton *et al.*, Kabak *et al.,* and Persoon *et al.* were the only studies that described the rationale for choosing the set of exercises concerning outcome measures (Shelton et al., 2009; Yildiz Kabak et al., 2016; Persoon et al., 2017).

No standardised exercise protocols

Significant variation was found in the clinical trials in terms of the design of exercises in trails such as Jacobsen et al. (Jacobsen et al., 2014), who used only walking three to five times a week for at least 20 to 30 minutes at 50% to 75% estimated heart rate reserve as their intervention. On the other hand, Jarden et al. (Jarden et al., 2009) implemented a diverse exercise programme, which included cardiovascular training, core exercises, strength and endurance for upper and lower limbs. Each study followed a specific design in terms of the number of repetitions, sets, frequency, and intensity and was influenced by a set of cautions and contraindications but did not always include a scientific methodology aimed at achieving optimal muscle performance, tissue endurance, cardiovascular fitness, and functional capacity.

Trial quality

Of the 19 studies included in this review, only 10 (53%) achieved a 2/5 score with randomisation in trials and outlined the dropout rates; three studies achieved 1/5 (16%) with randomisation in the trial but failed to mention dropouts from the trials, and six studies scored -1/5 (32%) as they did not mention randomisation or dropouts. Furthermore, none of the trials followed double-blinded approach due to the nature of the intervention.

DISCUSSION

The majority of patients develop some level of musculoskeletal and cardiovascular complications post-HCT (Armenian et al., 2017; Majhail et al., 2012; Mohammed et al., 2018a; Bar et al., 2020). Some patients may suffer from these complications for several decades, meaning that they have a significant impact on their health-related QoL. The current paper reiterates and highlights challenges faced by HSCT patients, ranging from functional incapacity to financial loss and psychological (Bieri et al., 2008; Morishita et al., 2013b; Bona et al., 2015), allowing informed decisions to be made by various stakeholders and policymakers responsible for rationing services for patients (Iacobucci, 2017).

Over the past several decades, rehabilitation intervention has been increasingly used, and recommended as beneficial in patients before, during, and after HSCT. The majority of the trials included in this review demonstrated the benefit of exercise interventions on various parameters, including strength, QoL, muscle endurance, fatigue, physical fitness, daily living activities, functional capacity, cardiorespiratory fitness, muscle mass, cytopenia, physiological function, psychological wellbeing, diarrhoea, immune cell recovery, psychosocial, anxiety, depression, and haemoglobin.

The need for more effective exercise prescription practice

Rehabilitation specialists should take into account the complex medical background of individual patients and treatment-related complications. The current review also highlighted the lack of standardisation in exercise prescription for rehabilitation trials in HSCT. Exercise prescription aimed at achieving optimal outcomes considers individual patient characteristics i.e. age, type of disease, previous and present treatments and their side effects, presence of specific symptoms such as GVHD, drug intake, and other physiological parameters (Hayes et al., 2009). HSCT patients are known to suffer from a diverse number of medical and musculoskeletal manifestations due to the nature of their disease and HSCT-related complications (Savani et al., 2011). These conditions can present a challenge if individual circumstances are not considered when designing an exercise plan.

Furthermore, exercises design follows a specific plan that is precise and aimed at positively influencing one's physiological/biological parameters (McDonnell et al., 2005; Lephart et al., 2007; Roach et al., 2011). For example, the Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE) studied the effects of exercise training regimens differing in dose (kcal.wk-1) and/or intensity (relative to peak VO2) and found that the amount and intensity of exercise are key in achieving both general and specific health benefits (Kraus et al., 2001). Therefore, HSCT rehabilitation specialists had to develop future trials using models implementing the science of exercise prescription and individualised program to study the optimal benefits of exercise as an intervention.

The need for high-quality hybrid trials

Although a number of studies have supported physical exercises and rehabilitation interventions for HSCT patients, the benefits seem to have been overshadowed by the level of the overall quality of trials. The issue surrounding the quality of trials is not new, with over 40% of rehabilitation trials being scored as poor (Armijo-Olivo et al., 2015). A significant emphasis on double-blinding by a majority of these scales has been attributed as one of the reasons for which rehabilitation trials score low in terms of quality (Armijo-Olivo et al., 2017). Unlike other areas of medical science research, double-blinding is almost impossible to achieve for the majority of rehabilitation interventions due to the nature of the treatment (Opara et al., 2013; Olivo et al., 2008). Therefore, "the lack of statistical significance between blinding and effect sizes should not be interpreted as meaning that an impact of blinding on effect size is not present in physical therapy" (Opara et al., 2013). Moreover, due to the diversity involved in the rehabilitation intervention and outcomes that are measured, other scales such as Cochrane scale have found to not be accurate in assessing the risk of bias as some trials have shown to have achieved different quality scores with the two different scales (Armijo-Olivo et al., 2015), highlighting the need for a more specific/hybrid grading system (Olivo et al., 2008; Armijo-Olivo et al., 2017)

The need for innovation

Electrotherapy modalities are widely used by rehabilitation specialists to enhance tissue healing and patients' overall recovery (Watson, 2000; Shah and Farrow, 2012). However, this literature review identified a significant gap in application and practice of electrotherapy modalities in managing a number of the common musculoskeletal manifestations related to post-HSCT, which may have otherwise been treated by electrotherapy as a standalone or as part of an exercise programme (Mohammed et al., 2018b). For example, osteonecrosis of the bones has been identified as a common complication in this patient group that results in reduced QoL and requires surgery in many cases (Atkinson et al., 1987). Extracorporeal shock wave therapy (ESWT) is a modality reported as beneficial for improving functional capacity, pain, or even slowing down or blocking the progression of disease, thereby reducing the need for surgery (Zhang et al., 2017). However, few high-quality trials involving these modalities exist in the literature, meaning that it may be too early to recommend or standardise this procedure. Similarly, other modalities such as vibration training and electrical nerve stimulation for neuropathic pain, as well as muscle stimulation for muscle atrophy, may have been reported as beneficial, though their use in HSCT patients remains widely unexplored (Streckmann et al., 2019; Mokhtari et al., 2020; Gobbo et al., 2019).

No adverse effects of exercise therapy

Despite discrepancies in the quality of the trials, type of intervention, and methodology, none of the studies included in this review mentioned an adverse event as a direct result of rehabilitation exercise intervention. This finding is in line with other studies, where the children with severe thrombocytopenia undergoing HSCT were found to have only minor and relatively rare bleeding complications due to physical and occupational therapy interventions (Ibanez et al., 2018). Furthermore, the majority of the previous systematic reviews, despite eluding to the need for more robust clinical trials, have agreed that exercise is safe and has a positive impact on patients' physical function, HRQoL, and fatigue (Persoon et al., 2013; Van Haren et al., 2013; Kruijsen-Jaarsma et al., 2013; Oberoi et al., 2018).

CONCLUSION

Based on the existing literature, it is evident that a large number of HCT patients develop transplant-related complications and require long-term follow-up from a multidisciplinary team that includes rehabilitation specialists. There is strong evidence base that long-term rehabilitation can help HCT patients gain their functional capacity, improve quality of life and help patients intergrate back to their social and work life. Furthermore, lack of long-term support can be detremental to HCT patients resulting in various complications and associated economic burden for managing them. The healthcare policy makers/managers need to rcognise this need and make special considerations when rationing services for HCT patients. Although rehabilitation interventions have been reported as having positive impact on the patients overall quality of life, high quality trials are urgently needed to better this claim. Furthermore, there appears to be a gap in the research in terms of the use of various electrotherapy modalities as standalone therapies or in combination with exercises for MSK-related complications post-HCT. Therefore, high-quality trials are needed using innovate treatment ideas in this patient group.

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Fig.1 **PRISMA Schematic presentation**

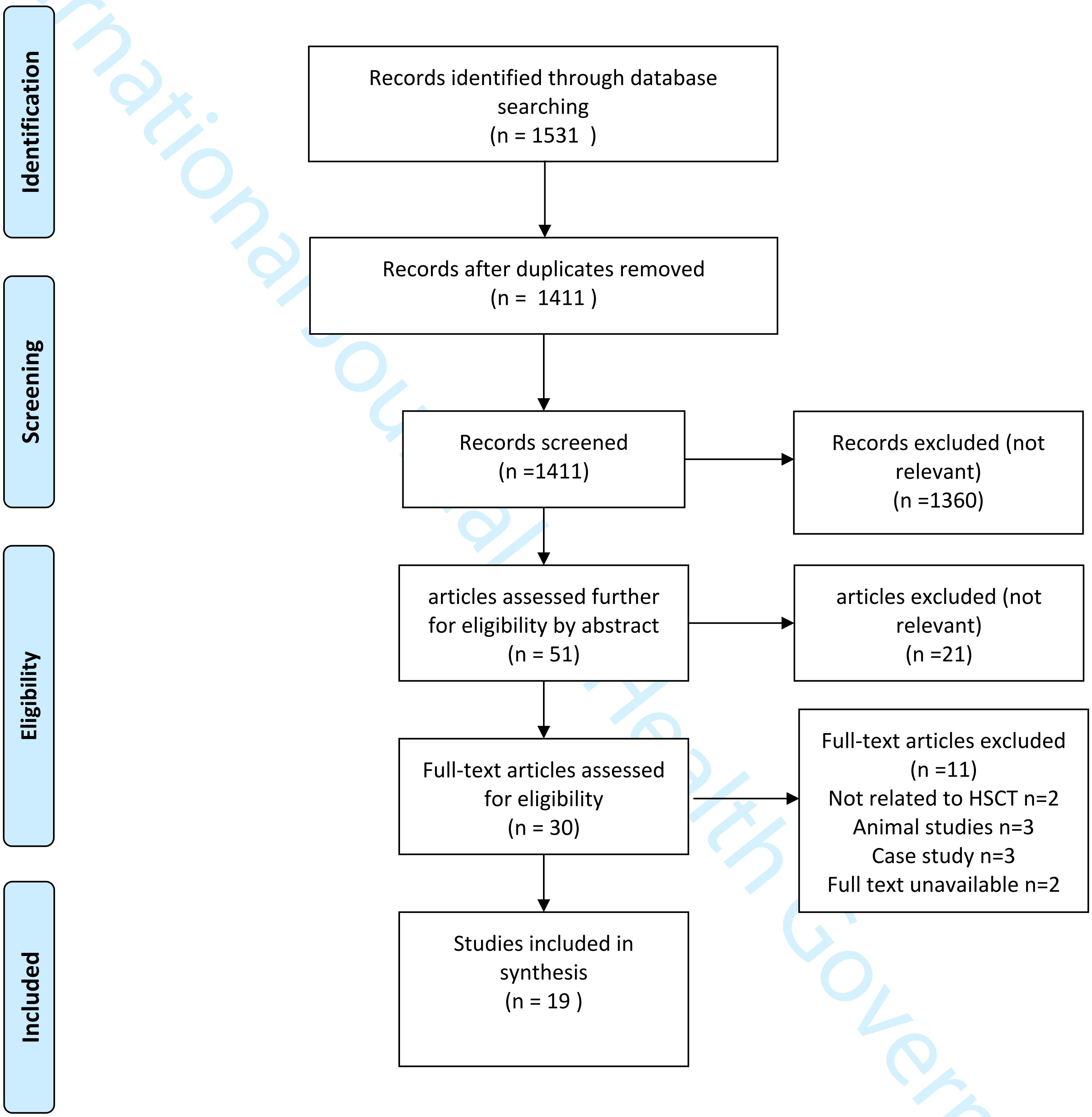

Table.1 PICO: Rehabilitation intervention in cGVHD and its outcome

Parameter	Evaluation	Explanation
Population	Male and female patients pre and post Hematopoietic "Stem Cell Transplant" OR "Bone Marrow Transplant" OR "hematopoietic cell transplant" with or without GVHD.	Both autologous and allogeneic transplant patients will be included.
Intervention	Rehabilitation exercises, cardiovascular and muscle training intervention and any other physical or occupational treatment are being evaluated. Clinical trials, case reports, observational studies (includes all types of retrospective studies), case-control studies,	Systematic reviews, review articles and meta-analyses will be excluded from the final data collection. Preclinical studies will be excluded.
Comparison	Comparison of various rehabilitation treatments and their outcomes	E.g. exercises specifically designed as per individual patient capability and medical condition versus generalized exercises.
Outcomes	1) Physical function 2) ADL 3) Muscle Strength 4) Cardiovascular fitness	And others which will be found via search

Table.2 Inclusion and exclusion criteria

	Inclusion	Exclusion
Type of study	All studies in English language only. Randomised control trials with randomisation either at the individual or cluster level Quasi-randomised design Duration: 1998 - 2018 Retrospective	Case reports (will be excluded for data synthesis) Systematic reviews Meta-analysis Preclinical studies Studies reported as only abstracts
Population	All HSCT patients and chronic GVHD patients.	Auto-transplant patients
Intervention	Exercise Electrotherapy Physiotherapy	
Outcome	Activities of daily life Muscle power and endurance	Return to work

Table. 3 Type of study, intervention used, Outcome measures and if the treatment was in or outpatient

Author & Country	Year	Type of Study	Participants demographics	Intervention	Objective outcome measure	Subjective outcome measure	Setting
Mello, Tanaka and Dulley Brazil	2003	Prospective cohort study	C = 9 (M:3, Avg y: 30.2) I = 9 (M:5, Avg y: 27.9) ID = 6 weeks	active exercises, muscle stretching and a walking-based program on a treadmill	Maximal isometric voluntary strength tests (MIVS) from four muscle groups of the upper limbs and five muscle groups of the lower limbs were collected to assess the subject's muscle strength	NIL	In-Patient and Out-Patient
Kim & Kim South Korea	2005	RCT	C = 17 (M:9, Avg y: 34.3) I = 18 (M:8, Avg y: 32.9) ID = 6 weeks	Relaxation Breathing Exercise	leukocyte count	Beck Depression Inventory (BDI)	In-Patient
Coleman *et al* USA	2008	RCT	C = 62 (M: 35, Avg y: 55) I = 58 (M: 35, Avg y: 55) ID = 15 weeks	individualized exercise prescription	six-minute walk test	Borg Scale	In-Patient
Jarden *et al* Denmark	2009	RCT	C = 21 (M:13, Avg y: 37.4) I = 21 (M:31, Avg y: 40.9) ID =Not clear	Dynamic and stretching exercises Resistance training Progressive relaxation	Aastrand-Rhyming cycle ergometer test, 1RM tests, maximal isometric strength, 2-min stair climb test,	EORTC QLQ-C30, FACT-An, Hospital Anxiety and Depression Scale (HADS)	In-Patient
Shelton *et al* USA	2009	RCT	C = 27 (M:16, Avg y: 48.9) I = 26 (M:17, Avg y: 43.6) ID = 4 weeks	Aerobic and strength exercises	50-foot fast walk, 6-min walk, forward reach, repeated sit-to-stand, uniped stance)	Brief Fatigue Inventory (BFI)	In-Patient
Chamorro-vin *et al* Spain	2010	a controlled trial using a ‘‘historical’’ control group	C = 13 (B: 9, Avg y: 7.30) I = 7 (B: 5, Avg y: 8.14) ID = 3 weeks	individually supervised exercise program including strength and cardiovascular training	Anthropometric variables, white blood cell population counts	None	In-Patient
Baumann *et al* Germany	2011	RCT	C = 16 (M: 5, Avg y: 42.81) I = 17 (M: 11, Avg y: 41.41) ID = Not clear	aerobic endurance training and ‘ADL-training’, gymnastics, massages	WHO-endurance test cycle ergometer, Lung function vital capacity, forced vital capacity, Strength Digimax2000 – load cell	EORTC QLQ-C30	In-Patient
Wiskemann *et al* Germany	2011	RCT	C = 40 (M: 39, Avg y: 50) I = 40 (M:32, Avg y: 47.6) ID = 6 to 8 weeks	Aerobic and strength training	6MWT, maximum of voluntary strength,	Multidimensional Fatigue Inventory (MFI), EORTC QLQ-C30, Borg Scale, National Comprehensive Cancer Network Distress-Thermometer	In-Patient and Out-Patient
Knols *et al* Germany	2011	RCT	C = 64 (M:39, Avg y: 46.6) I = 67 (M:38, Avg y: 46.7) ID = 3 months	Supervised personal exercise program including strength and cardiovascular	Maximum voluntary peak force in Nm, JAMAR dynamometer, 50-foot walk test, 6 min walk test, body composition	Health-Related Quality of Life (HRQOL), FACT An, EORTC QLQ-C30	Out-Patient

Tran *et al* USA	2012	Retrospective study	C = 0 I = 11 (M: 8, Avg y: 48) ID = 8 weeks	nutrition, medication and oxygen safety, pursed-lip breathing and other breathing techniques, use and care of metered dose inhaler. Upper and lower body strength training and cardiovascular exercise	spirometry/pulmonary function tests, 6-minute walk tests.	SF-36	In-Patient and Out-Patient
Morishita *et al* Japan	2013	Observational, longitudinal study	C = 51 (M:47, Avg y: 41.6) I = 51 (M:137, Avg y: 45.2) ID = 4 weeks	stretching exercises, resistance training and endurance training	BMI, Hand Grip Measure, Handheld dynamometer for Lower limb, 6min walk test	SF 36	In-Patient
Wiskemann *et al* Germany	2014	RCT	C = 53 (M:39, Avg y: 50) I = 52 (M:32, Avg y: 47.2) ID = 8 weeks	endurance and resistance exercises using stretch bands	6-min walk test,	BORG Scale	In-Patient and Out-Patient
Jacobsen *et al* USA	2014	RCT (phase III multicentre)	Usual care = 175 (M:93, Avg y: 55) Exercise = 180 (M:112, Avg y: 58) Stress management= 178 (M:100, Avg y: 58) Combination of exercise/stress management= 178 (M:100, Avg y: 57) ID = 180 days	walking 3 to 5 times a week for at least 20 to 30 minutes at 50% to 75% of estimated heart rate reserve	NIL	SF-36, Cancer and Treatment Distress (CTXD), Pittsburgh Sleep Quality Index (PSQI), Leisure Score Index (LSI) of the Godin Leisure-Time Exercise Questionnaire	Pre-Transplant
Takekiyo *et al* Japan	2015	Prospective cohort study	C = 18 (M:11, Avg y: 54) I = 17 (M:12, Avg y: 55) ID = 6 weeks	high- and low-frequency exercise	Body composition, 6-min walk test (6MWT) scores, and handgrip strength	None	In-Patient and Out-Patient
Kabak *et al** Turkey	2016	prospective cohort study	C = 11 (Avg y: 6.72) I = 11 (Avg y: 9.3) ID = 5 to 6 weeks	strengthening, endurance, stretching, and relaxation exercises	6-min walk test (6MWT), Handgrip strength, 30-sec chair-stand test, Time needed to stand up from bed rest exam, Time up and go (TUG) test of 3 m, Timed up and down stairs (TUDS) test	Functional independent measure for children (WeeFIM). WeeFIM	In-Patient and Out-Patient
Wood *et al* USA	2016	prospective cohort study	C = 0 I =A 20 (M: 14, Avg y: 60.5) B 20 (M: 12, Avg y: 52.5) ID = 6 weeks	Interval exercise training	maximal cardiopulmonary exercise testing with cycle ergometry (VO2peak), 6-minute walk distance,	None	In-Patient and Out-Patient
Hacker *et al* USA	2017	Single blind RCT	C = 34 (M: 21, Avg y: 54.6) I = 33 (M: 20, Avg y: 51.9) ID = 6 weeks	progressive resistance to strengthen the upper body, lower body, and abdominal muscles using elastic resistance bands	Accelerometer, 6-minute walk test, ultrasonic measurement of the cross-sectional area of the rectus femoris, hand grip strength, and arm curl test. timed stair climb, the timed up and go test, 15-foot walk time, and 30-second chair-stand test.	Godin leisure-time exercise questionnaire, Chalder fatigue scale, EORTC QLQ-C30,	In-Patient and Out-Patient

Persoon, *et al* Netherlands	2017	single-blind RCT	C = 55 (M:37, Avg y: 56) I = 54 (M:32, Avg y: 53.5) ID = 18 weeks	high-intensity resistance exercise and interval training program, counselling service for motivation	cardiopulmonary exercise test, performed on a cycle ergometer, Grip strength, BMI, accelerometers	Multidimensional Fatigue Inventory (MFI), ORTC-QLQ-C30, HADS	Out-Patient
Schumacher *et al* Germany	2018	RCT	C = 23 (M:9, Avg y: 56.5) I = 19 (M:16, Avg y: 56) ID = not clear	Stretching, strength training, endurance and exercising on the Nintendo Wii	2 min walking distance test (2MWT), isometric grip strength,	FACT-BMT, SF-36, HADS-D, distress thermometer	In-Patient

Abbreviations C= in control group; I=intervention group; ID=Intervention duration; M=Male; B=Boy; Avg y= Average age; RCT= Randomized Control Trial

***Participants demographics not reported**

Table 4. JADAD scoring of selected studies.

Author	Year	Was the study described as Yes randomized?	Was the randomization scheme described and appropriate?	Was the study described as double blinding?	Was the method of blinding appropriate?	Was there a description of dropouts and withdrawals	JADAD Score
Mello, Tanaka and Dulley	2003	+1	+1	0	-1	-1	1
Kim & Kim	2005	+1	+1	0	-1	-1	1
Coleman *et al*	2008	+1	+1	0	-1	+1	2
Jarden *et al*	2009	+1	+1	0	-1	+1	2
Shelton *et al*	2009	+1	+1	0	-1	1+	2
Chamorro-vin *et al*	2010	+1	+1	0	-1	+1	2
Baumann *et al*	2011	+1	+1	0	-1	+1	2
Knols *et al*	2011	-1	-1	0	-1	+1	-1
Wiskemann *et al*	2011	+1	+1	0	-1	+1	2
Tran *et al*	2012	-1	-1	0	-1	+1	-1
Morishita *et al*	2013	-1	-1	0	-1	+1	-1
Jacobsen *et al*	2014	+1	+1	0	-1	+1	2
Wiskmann *et al*	2014	+1	+1	0	-1	+1	2
Takekiyo *et al*	2015	-1	-1	0	-1	+1	-1
Kabak *et al*	2016	-1	-1	0	-1	+1	-1
Wood *et al*	2016	-1	-1	0	-1	+1	-1
Hacker *et al*	2017	+1	+1	0	-1	+1	2
Persoon,*et al*	2017	+1	+1	0	-1	+1	2
Schumacher *et al*	2018	+1	+1	0	-1	+1	2

Table 5. Various reported outcomes from the exercise interventions

Author & year of study	Main Parameter	Outcome
Mello, Tanaka and Dulley (2003)	Muscle strength	Exercises are efficient in promoting an increase in muscle strength
Kim & Kim (2005)	Anxiety and Depression	Relaxation breathing exercise can improve anxiety and depression levels
Coleman *et al* (2003)	Hgb	Exercise can help decrease the need for transfusions.
Jarden *et al* (2009)	Diarrhoea, QOL, Fatigue & Psychological wellbeing	Exercise can help decreased intensity of diarrhoea and days receiving TPN while undergoing allo-HSCT, improve QOL, fatigue and psychological well-being up to 6 months after allo-HSCT.
Shelton *et al* (2009)	Functional capacity	Short-term exercise training regardless of how the training program is supervised can help improve patient functional capacity.
Chamorro-vin *et al* (2010)	Immune cell recovery & BMI	Moderate-intensity exercise training does not negatively affect immune cell recovery in children with high-risk cancer while contributing to increasing body mass and BMI.
Baumann *et al* (2011)	physiological, psychological, and psychosocial	Physical exercise was found to be feasible and safe with positive impact on patient's physiological, psychological, and psychosocial constitution.
Wiskemann *et al* (2011)	Strength and functional capacity	Exercises had no major benefit on strength and functional capacity
Knols *et al* (2011)	Health-related quality of life and fatigue	Physical exercise has a positive impact on the health-related quality of life and fatigue.
Tran *et al* (2012)	Respiratory	Pulmonary rehabilitation appears to improve 6-minute walk distance, subjective symptoms of dyspnoea and exercise tolerance in patients with Bronchiolitis obliterans syndrome
Morishita *et al* (2013)	Cytopenia Quality of Life Physiological function	Physical therapt was found to be safe and beneficial in cytopenic patients and can help improve physiological function and QOL.
Wiskemann *et al* (2014)	Physical fitness and fatigue.	No significant beneficial effects of the supervised high-intensity exercise program on physical fitness and fatigue.
Jacobsen *et al* (2014)	Muscle mass	Exercise therapy can help to maintain lower extremity muscle mass.
Takekiyo *et al* (2015)	Muscle Strength, Fatigue, Functional capacity	Strength training intervention can enhance early recovery after HCT; reduce fatigue while maintaining and/or improving muscle strength and functional ability.
Hacker *et al* (2016)	Quality of Life and Fatigue	Structured physical activity program has positive effects on QOL and fatigue scores
Kabak *et al* (2016)	Cardiorespiratory fitness	Home-based, personalized intensive exercise programs have the potential to improve cardiorespiratory fitness.
Wood *et al* (2016)	Fatigue, Physical performance and functional capacity.	Physical exercise is beneficial for patients before, during, and after allo-HSCT, can significantly alter cancer-related fatigue in the context of allo-HSCT, improve physical performance and functioning.
Persoon, *et al* (2017)	Strength, endurance, quality of life and fatigue	No significant difference between supervised and unsupervised exercise group
Schumacher *et al* (2018)	Endurance Strength Quality of life	Exercise had favourable effect on physical fitness, fatigue, and QoL and exergaming is capable of eliciting physical activity intensity similar to that of moderate exercise