REVIEW

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Pulmonary Rehabilitation for Patients Undergoing Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis

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Abstract

Objective: Patients undergoing hematopoietic stem cell transfer experience various infectious and non-infectious complications, and pulmonary problems continue to be a leading cause of death and morbidity. This systematic review and meta-analysis aims to evaluate the effectiveness of pulmonary rehabilitation interventions on various pulmonary function parameters. **Methods:** We systematically searched for studies in PubMed, CINAHL, Embase, Cochrane, Scopus, Web of Science, ClinicalKey, and ProQuest for articles published in English from 2000 to 2024. Two reviewers independently identified the articles using key thesaurus terms and free-text terms based on the inclusion criteria. The review was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement. Meta-analysis was performed using RevMan 5.3 software. **Results:** The systematic review included 18 trials, with a total of 1,052 participants, of whom 621 were from randomized controlled trials (RCTs) and the remaining 431 were from quasi-experimental studies. Pooled data from randomized controlled trials showed that pulmonary rehabilitation programs were effective in improving forced vital capacity ($P < 0.001$), FEV1/FVC ($P = 0.004$), maximal inspiratory pressure ($P < 0.001$), and dyspnoea ($P = 0.03$) at a statistically significant level. **Conclusion:** The evidence from the review suggests that pulmonary rehabilitation programmes are effective in improving certain parameters of pulmonary function. This systematic review and meta-analysis protocol was registered in PROSPERO with the registration number (CRD42024522354).

Keywords: Hematopoietic stem cell transplantation- Rehabilitation- Lung- Physiology- Health and well-being

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Introduction

Hematopoietic stem cell transplantation (HSCT) is an important and increasingly available treatment for a number of cancerous and non-cancerous diseases throughout the world [1–3]. There is a consistent improvement in the survival of HSCT recipients due to advancements in supportive measures, conditioning regimens and management of complications [3–5]. However, HSCT recipients continue to experience range of issues and side effects related to conditioning regimens, graft versus host disease (GVHD), infectious and non infectious complications affecting almost every organ [3, 6], and associated with short and long term comorbidities [7]. Pulmonary problems continue to be the leading cause of death and morbidity in this population, despite previous improvements in HSCT results [8, 9]. The significance of non-infectious pulmonary complications was highlighted by recent developments in the treatment of infectious complications and prophylaxis [9, 10].

The non-infectious pulmonary complications include diffuse alveolar haemorrhage, bronchiolitis obliterans, fibroelastosis, interstitial lung disease, idiopathic pneumonia syndrome and pulmonary hypertension [3, 8, 11, 12]. While bronchitis obliterans syndrome is the most difficult chronic pulmonary complication for patients after HSCT, idiopathic pneumonia syndrome associated with acute lung injury is the primary acute lung complication with highest death and morbidity rates [10]. While bronchitis obliterans syndrome is the most difficult chronic pulmonary complication for patients after HSCT, idiopathic pneumonia syndrome associated with acute lung injury is the primary acute lung complication with highest death and morbidity rates [6]. Because there is little data on a number of HSCT-related disorders [12], the pulmonary care of patients after HSCT is a poorly understood subject and presents considerable difficulties [6]. Collaboration between pulmonologists and other

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experts is essential for the effective management of pulmonary problems [9], as is the requirement for an activity-focused, individualized supportive care plan [7].

There are several pathogenic mechanisms leading to chronic pulmonary conditions in HSCT patients. Leukemic pulmonary infiltration can cause lung disease with diffuse or focal involvement of the parenchyma, alveoli, bronchi, and pulmonary vessels. Alveolar amyloidosis and proteinosis may develop with few hematologic malignancies. Immune defects related to disease or treatment increases susceptibility to typical and opportunistic pulmonary infections, which may lead to respiratory failure, acute morbidity or mortality leading to long-term structural lung damage such as bronchiectasis, cavitation, and pleural adhesions. Post-infective structural lung changes can promote chronic bacterial colonization or recurrent infections or after HSCT that increases the exposure to pathogen-associated molecular patterns [6].

Thus, prior to receiving HSCT, a considerable percentage of patients have compromised respiratory and physical functions [3]. Reduced diaphragmatic excursion, respiratory muscle strength, and pulmonary volume are the effects of HSCT patients' sedentary lifestyles brought on by chemotherapy and radiation therapy even prior to transplantation [13, 14]. Lung function, functional capacity, and muscle strength is reduced among patients undergoing HSCT during hospitalization [15]. Moreover, sarcopenia and reduced respiratory function prior to HSCT in these patients also affect morbidity, mortality, and pulmonary concerns [3]. Additionally, a decrease in maximum inspiratory pressure (MIP) raises the likelihood mortality [15]. Early on following HSCT, physical and respiratory performance will deteriorate. This decrease is linked to factors that prevent activity, such as heightened weariness and impaired muscle oxygen metabolism [3].

Minimizing the functional decline throughout rehabilitation is crucial, considering the previously mentioned factors. Exercise has been shown to assist HSCT patients in a number of ways HSCT [3]. The purpose of chest physical therapy is to improve lung function, decrease pulmonary infections, and remove secretions [1, 16]. Pulmonary rehabilitation has been proven beneficial in improving respiratory muscle strength, lung capacity, exercise capacity [17] and improves the subjective symptoms of dyspnoea and exercise tolerance among HSCT patients [17, 18]. In order to prevent HSCT patients' respiratory function from declining, respiratory rehabilitation programs that incorporate respiratory muscle training and physical exercises are crucial [3]. However, these are not systematically explored, mapped and synthesised, necessitating the conduct of this systematic review. Pulmonary rehabilitation is a "comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours" [19]. Hence, in this review pulmonary rehabilitation interventions were primarily focused on strengthening the muscles of the upper body such as aerobic exercises, stretching and relaxation, endurance exercises and walking, strengthening the respiratory muscles such as inspiratory muscle training, breathing exercises and chest physiotherapy. The primary objective was to evaluate the effectiveness of pulmonary rehabilitation interventions on various parameters of pulmonary function.

Materials and Methods

Design

The review protocol was registered and can be accessed on the PROSPERO (CRD42024522354). This systematic review followed Cochrane Collaboration guidelines and the findings are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement [20].

Search strategy and study selection

The search strategy was iterative and was developed by the first two authors and validated with an academic librarian. Literature search was conducted across electronic databases such as PubMed, CINAHL, Embase, Cochrane, Scopus, Web of Science, Clinicalkey and ProQuest using a strategy tailored for each database. The primary author and the corresponding author independently searched the databases based on the search strategy to ensure the rigor. The search strategy employed a combination of MeSH terms and keywords. The free-text phrases and thesaurus terms were combined using appropriate Boolean operators, with filters applied to the title and abstract. The search strategy is described in the Supplementary File 1. Reference lists of included articles were reviewed for additional relevant studies, and the search history was documented. A search in Google and Google scholar was also completed to expand the literature search. The final database search was conducted between 6th June 2024 and 20th July 2024.

Eligibility criteria

This systematic review focused on evaluating the effectiveness of pulmonary rehabilitation for patients undergoing HSCT. The literature search included primarily sourced RCTs, quasi-experimental studies conducted using human participants published in English from 2000 to 2024, with no geographical restrictions. Studies that provided pulmonary rehabilitation programs either before or shortly after HSCT were considered. The only studies that were included were those that evaluated pulmonary function using a variety of respiratory metrics, including forced vital capacity, forced expiratory volume and ratios, vital capacity, maximal inspiratory pressure, respiratory rate, dyspnoea, six-minute walk, etc., and that were published as full-text articles. The conference abstracts, proceedings, and letters to the editor, as well as studies comparing two different types of exercises and those randomly assessing respiratory outcomes only once using the six-minute walk test, were also excluded.

Search outcome

Rayyan software [21], was used to process the search results, first removing duplicates and then screening the title, abstract, and full text. Each title and abstract were screened by the first reviewer (SGN) and second reviewer (AI) independently and any disputes resolved through discussion with the third reviewer (JG). All eligible full text articles were screened independently by the first reviewer (SGN) and second reviewer (AI).

Quality appraisal

The Cochrane risk of bias tool-2 (RoB-2) [22] was employed for evaluating the quality of the included RCTs (Figure 1), while the ROBINS-1 tool [23] was utilized to assess the quality of quasi-experimental studies. Two reviewers (SGN & AI) independently assessed the studies for risk of bias.

Data extraction

Data extraction template was developed by the first reviewer (SGN) and was validated with the subject experts. The data extraction template was piloted for three studies by the two reviewers (AI and JG) and then both checked it together for accuracy and completeness. The items of data extraction form included the key details of each study, including the title, authors, publication year, country, study objectives, design, participant information, sample size, data collection and analysis methods, and main findings (Supplementary File 2; Table 1). The data extraction was performed separately by two reviewers (SGN and AI), with any disagreements settled by a third reviewer (JG).

Data analysis

Meta- analysis of only RCTs with similar outcome variables was conducted and the findings from selected studies are presented descriptively. The variability among the studies was evaluated using the I^2 test. Heterogeneity was classified based on I^2 values as follows: low for values under 25%, moderate for values between 25% and 75%, and high for values exceeding 75%. The effect of the pulmonary rehabilitation intervention was evaluated using a random-effects model for the I^2 greater than 50% and fixed effects model for I^2 lesser than 50% to compute the weighted mean differences and standardized mean differences between the intervention and control groups. The data were analysed and pooled using the Rev Man v5.3 software.

Results

Of the 942 records identified, 18 met the inclusion criteria and were included in the final analysis. Figure 2 presents a detailed flowchart outlining the study selection process.

The review summarized findings from 18 research publications out of which 13 were RCTs in which four were pilot RCTs [24–27] and another five were quasi-experimental researches conducted in ten different countries; four each from Germany [24, 28–30] and Brazil [27, 31–33], three from Japan [34–36], another two from Turkey [37, 38], one each from Egypt [1], United kingdom [25], United States [26], Demark [39] and Slovenia [40]. The review included 1,052 participants, with 621 from RCTs and the remaining 431 from quasi-experimental studies, with sample sizes ranging from 18 to 321 participants in each study. Half of the researches were conducted among the patients undergoing allogenic HCT

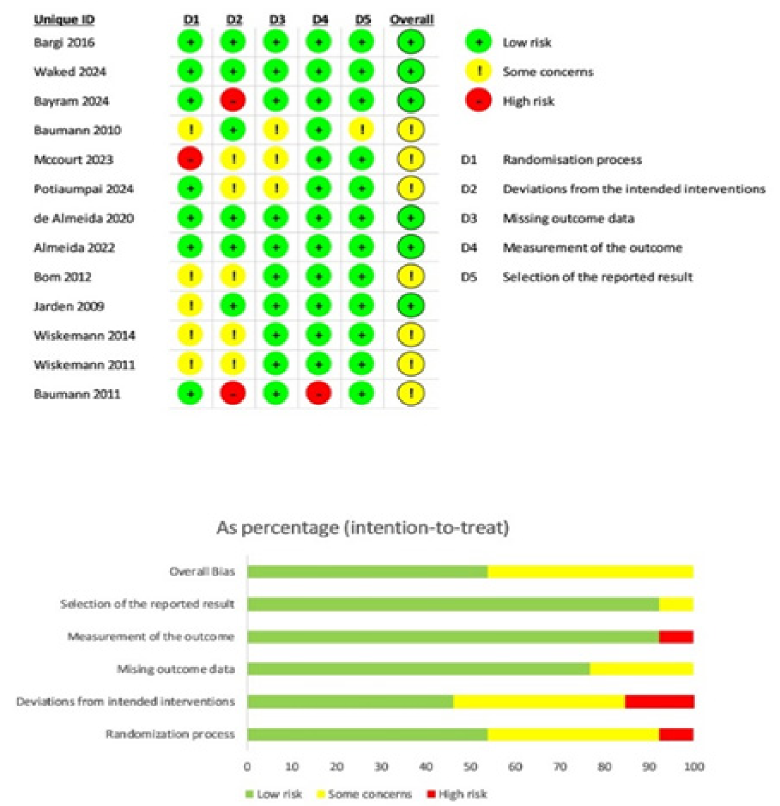

Figure 1. Risk of Bias Graph

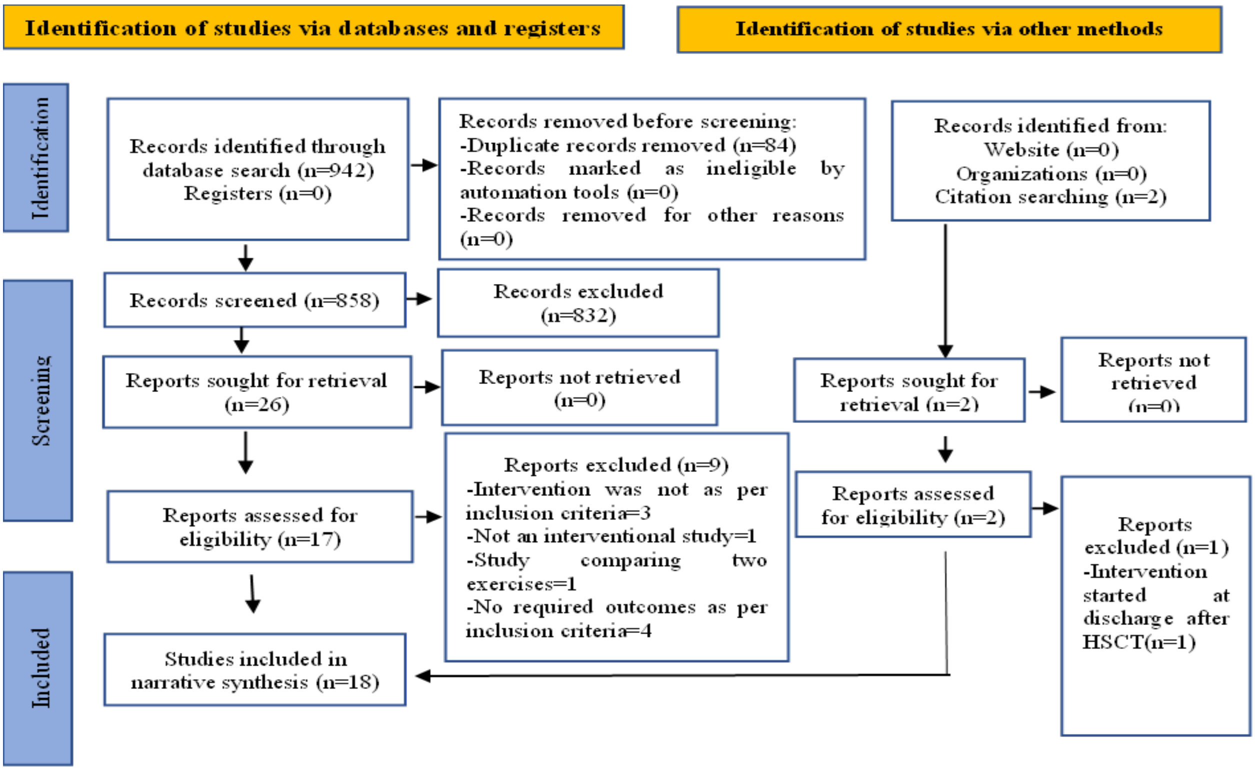

Figure 2. PRISMA Flow Diagram of the Study Selection

[1, 28–30, 34–37, 39] one study focused on autologous HCT [25] while the reaming studies included a mixed group of both allogenic and autologous HCT [24, 26, 27, 31–33, 38,40]. One study focused exclusively on multiple myeloma patients [25], while the other studies included a mixed sample of oncological conditions, predominantly haematological malignancies (Supplementary File 2; Table 1).

The exercises included in the pulmonary rehabilitation programs varied widely in terms of type, duration, frequency, and timing in relation to HSCT (Supplementary File 2; Table 2). The exercises varied widely across the studies, with all research reporting a combination of exercises targeting different muscle groups. Jarden et al. reported a multimodal intervention that included progressive relaxation, psychoeducation, and exercise (39), while Rupnik et al. incorporated nutritional support alongside exercise training as part of their intervention [40]. Three studies [1, 27, 37] reported the use of breathing exercises combined with inspiratory muscle training, while four other studies [31–33, 38] included inspiratory muscle training alongside various other exercises. Pulmonary rehabilitation intervention by Waked et.al., consisted of postural drainage, diaphragmatic breathing, forced expiration and mobilizing techniques [1]. The exercises were stretching, resistance or endurance in nature among twelve studies [24, 25, 36, 40, 28–35].

Pulmonary rehabilitation exercises were started before HSCT in eleven studies [1, 24, 40, 25, 26, 28–30, 34–36] ranging from one to four-weeks prior to HSCT and seven studies [24, 25, 28–30, 34, 35] reported that the exercises were conducted till discharge/entire clinical period. Another two studies [38, 39] reported that the exercises were started from the first day after HSCT and till discharge, whereas one each performed it during immediate post-transplant period [27] and during the intermediate/late post-transplant phase [37]. The exercises included in the pulmonary rehabilitation were performed at the hospital or institutions in 13 studies [1, 24, 36, 38, 39, 25, 27, 28, 31–35] and were carried under supervision. Another four studies [29, 30, 37, 40] reported the exercises were performed both at healthcare setting and home, with supervised at healthcare setting whereas either partially supervised or not supervised at home setting.

The outcomes measured related to pulmonary function were widely varied across the studies (Supplementary File 2; Table 1) and most common measure was six-minute walk test [25, 26, 30, 32, 34, 36, 37, 40], respiratory muscle strength [1, 31, 32, 38], spirometry measures and lung functions [1, 24, 28, 37, 38], respiratory vital signs, and symptoms related to the respiratory system [31], tidal volume, minute volume, oxygen saturation, heart rate, Maximal Inspiratory Pressure (MIP) and Maximum Expiratory Pressure (MEP) [27], physical capacity measured in estimated VO2 Max [39], aerobic capacity [33] and skeletal muscle oxygenation parameter in the tibialis anterior [35].

Findings showed mixed results on the effectiveness of pulmonary rehabilitation on various outcome parameters measured. Bom et.al., reported a statistically significant difference between the groups for TV (p-value = 0.004), MIP (p-value = 0.03) and MEP (p-value = 0.03) indicating that the pulmonary rehabilitation was effective [27]. Similarly, the study by Jarden et al. demonstrated a significant effect in favour of the intervention group at post-testing for VO2 max ($P < 0.001$) [39]. Waked et.al.,

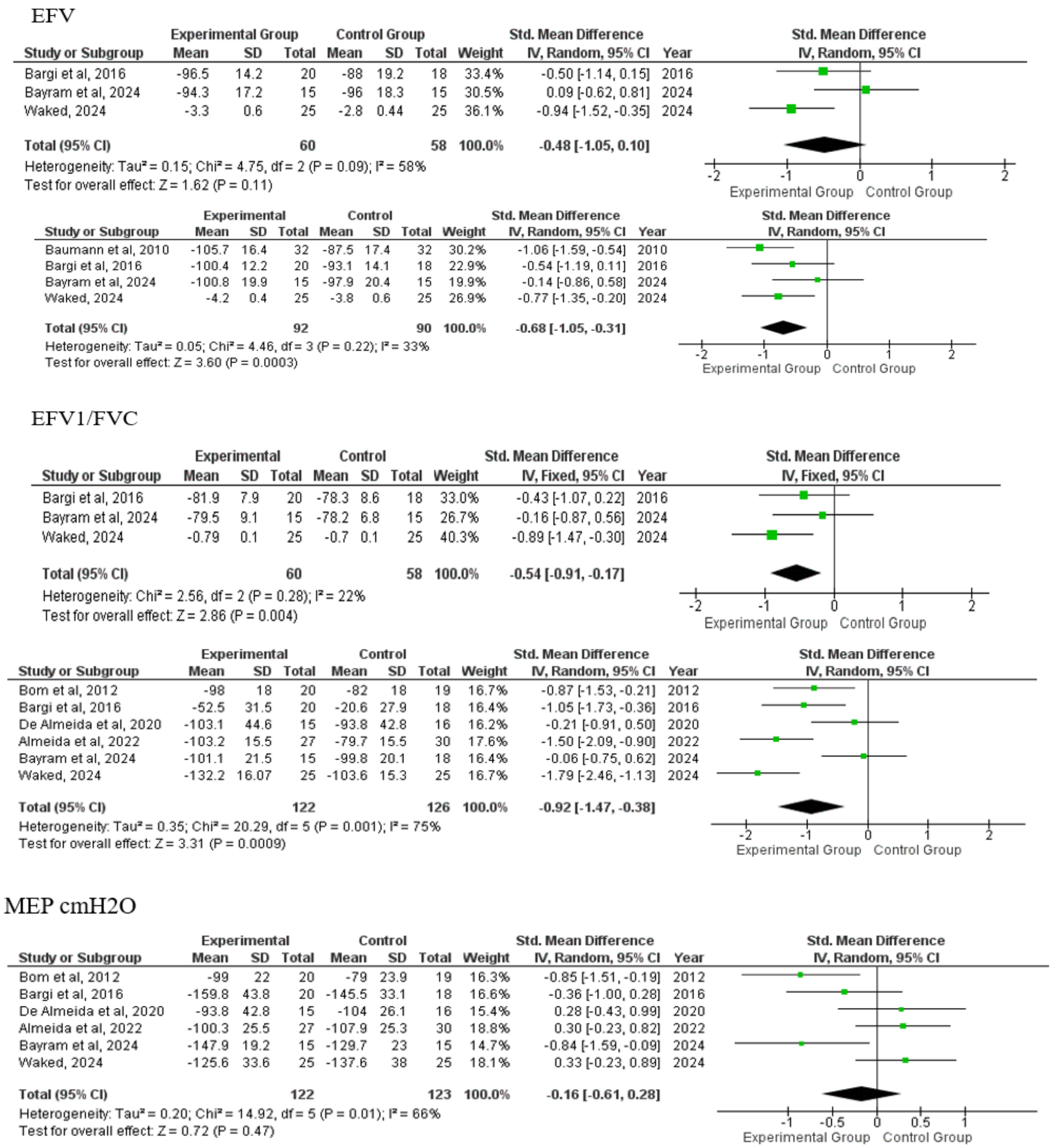

Figure 3. Effectiveness of Pulmonary Rehabilitation Interventions on EFV, FVC, FEV1/FVC, MIP, and MEP

reported significant improvement in mean spirometry values of FEV1, FVC, and FEV1/FVC in intervention group [1]. A significant group ($P < 0.01$) and group × time interaction effect in MIP ($P < 0.01$; $\eta 2 = 0.37$) where intervention improved (17%) in the IG compared with control where MIP reduced (10%) between admission and discharge [32]. Results also showed significant improvement with in the intervention group for the outcome parameters such as six minute walk test [25, 26, 29], FVC% (38), MIP and MEP [1]. Findings of quasi-experimental studies also showed similar results on six-minute walk test [33, 36, 40]. There was no significant difference between the groups in FEV1%, PEF%, and FEF25– 75% (37,38), FVC% and FEV1/FVC [37]. There were also no significant differences in MEP [31,38], MIP, MIP%, and MEP% between the groups [38]. There was no significant difference between the groups observed for respiratory signs and symptoms [31]. Baumann et.al., also reported that the intragroup changes in lung function values during hospitalization was not significant [24] and changes in also did not differ between the groups [28]. There was no significant difference between the groups for six minute step test [32]. (Supplementary File 2; Table 1).

Meta analysis of RCTs was conducted and forest plots containing summaries to evaluate the effectiveness of pulmonary rehabilitation among HSCT patients were employed. The pulmonary rehabilitation programmes were effective in FVC (MD: -0.68; 95% CI: -1.05, -0.31; P<0.001; I^2=33%), FEV1/FVC (MD: -0.54; 95% CI: -0.91, -0.17; P=0.004; I^2=22%), and MIP (MD: -0.92; 95% CI:

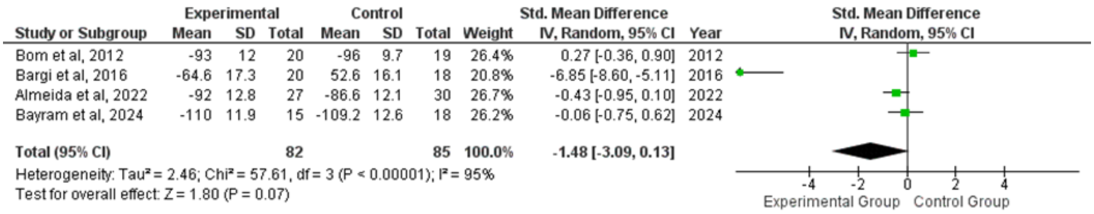

Figure 4. Effectiveness of Pulmonary Rehabilitation Interventions on Heartbeat

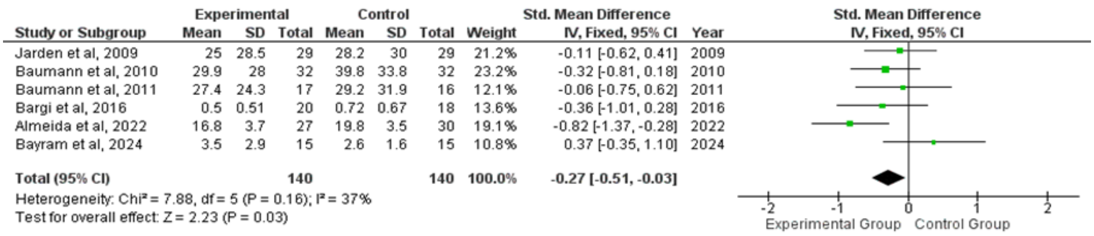

Figure 5. Effectiveness of Pulmonary Rehabilitation Interventions on Dyspnoea

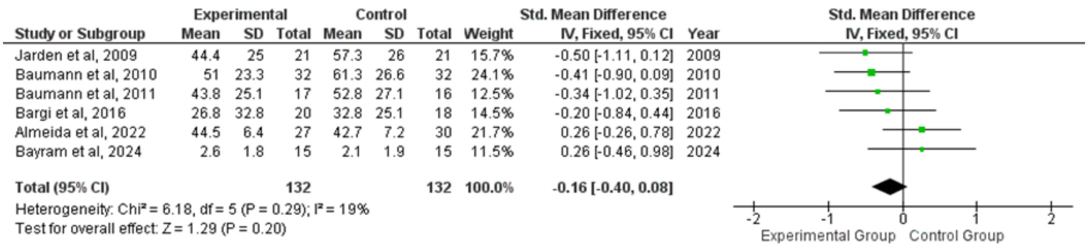

Figure 6. Effectiveness of Pulmonary Rehabilitation Interventions on Fatigue

-1.47, -0.38; P<0.001; I^2=75%) at statistically significant level. However, there was no statistically significant improvement in improving expiratory flow volume (EFV) (MD: -0.48; 95% CI: -1.05, 0.10; P=0.11; I^2=58%) and MEP (MD: -0.16; 95% CI: -0.61, 0.28; P=0.47; I^2=66%) (Figure 3). Similarly, it also did not show statistically significant difference in heartbeat (MD: -1.48; 95% CI: -3.09, 0.13; P=0.07; I^2=95%) (Figure 4) and fatigue (MD: -0.16; 95% CI: -0.40, 0.08; P=0.20; I^2=19%) (Figure 5). There was statistically significant difference noted in dyspnoea (MD: -0.27; 95% CI: -0.51, -0.03; P=0.03; I^2=37%) (Figure 6). There was a statistically significant difference noted in functional outcomes (MD: -0.29; 95% CI: -0.53, -0.04; P=0.02; I^2=17%) (Figure 7) and global health status (MD: -0.29; 95% CI: -0.55, -0.03; P=0.03; I^2=28%) (Figure 8).

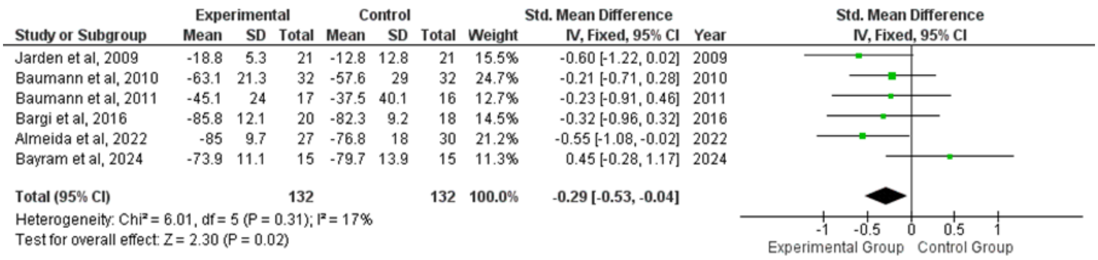

Figure 7. Effectiveness of Pulmonary Rehabilitation Interventions on Functional Outcomes

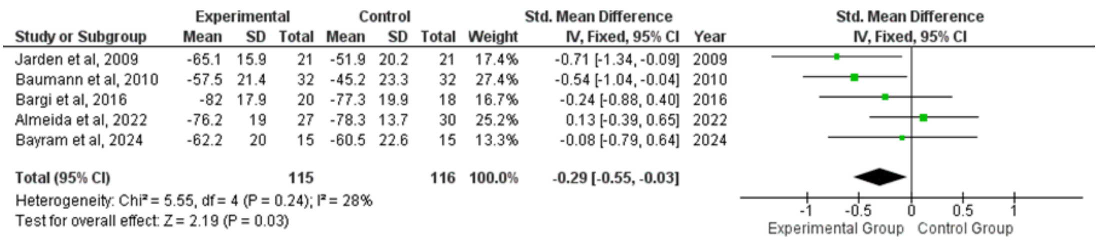

Figure 8. Effectiveness of Pulmonary Rehabilitation Interventions on Global Health Status

Discussion

This systematic review conducted an extensive search of RCTs and quasi-experimental studies evaluating various pulmonary rehabilitation interventions for patients undergoing HSCT, ultimately including 18 studies with 1,052 HSCT patients that met the inclusion criteria. The results showed mixed findings among the measured respiratory outcome parameters especially FVC%, FEV1/FVC, MIP and dyspnoea. These mixed results imply that although PR improves symptom management and functional capacities, it might not directly address underlying respiratory mechanics. PR is beneficial to patients with chronic lung diseases [41]. Pulmonary rehabilitation started prior to HSCT or immediately post HSCT was one of the inclusion criteria for this review. However, among HSCT patients the pulmonary complications may arise at any time during post HSCT and pre- engraftment period (within the first 30 days after HSCT) being the most common [8]. The complications are both infectious such as fungal or bacterial pneumonia, respiratory viral infections, acute respiratory distress syndrome or septic shock and non-infectious such as pulmonary haemorrhage, pulmonary oedema, engraftment syndrome, pleural effusion, chemotherapy and radiation induced lung injury, diffuse alveolar haemorrhage [8], which may restrict compliance to the activities of pulmonary rehabilitation programmes. Hence, the patient selection should be based on functional limitations and symptoms [41].

Maintaining adherence to pulmonary rehabilitation during post-HSCT is a considerable challenge, as retaining patient involvement and commitment frequently proves arduous, hence constraining the realisation of its therapeutic effects. Exercise capacity of post HSCT patients also affected by side effects of the treatment [42]. The studies included in this review also reported that the factors such as fever, nausea, vomiting, diarrhoea [34, 38], thrombocytopenia [31, 38], mucositis, fatigue [38], difficulties in studying, satisfaction with current activity level [43] limited the compliance to pulmonary rehabilitation activities. Rupnik et.al., reported one third of the patients having poor performance status due to worsening of pain, peripheral neuropathy, viral diarrhoea, upper respiratory tract infection [40]. In previous studies, exercises were started before HSCT and was not recommended while cytopenia was present [36]. Haemoglobin <8 g/dL and platelets <10 000/mL [24, 28], haemoglobin <5 g/dL and platelet <20000/mL [39] were the contraindication for exercises. However, exercise performed safely among cytopenia followed by intensive chemotherapy among leukaemia patients with haemoglobin at a minimum of 7.7 g/dL and platelets as low as 8000/mL, and no patients experience tachycardia or bleeding [44]. However, the studies included in this review also reported that the interventions implemented were feasible and safe [28, 31, 36].

Pulmonary rehabilitation is based on exercise training that emphasises strength, flexibility, and endurance [41]. The methods and length of pulmonary rehabilitation differed greatly among the research that were included in the current review. Exercise is only one aspect of pulmonary rehabilitation. Achieving patient well-being requires education, psychosocial support, and proper nourishment [41]. Majority of the studies included in this review had exercise techniques, which also necessitates for a comprehensive programme including the other components of rehabilitation such as nutrition, psychosocial support and education [41].

The review's findings should be evaluated considering both strengths and limitations. The effectiveness of pulmonary rehabilitation for HSCT patients, whether it be before or just after HSCT, is the particular emphasis of this review. The methods used in pulmonary rehabilitation during the post-HSCT phase, however, differed greatly between the included research studies. The information pertaining to traits associated with the condition is also diverse. Additionally, treatment-related data, including chemotherapy conditioning regimens, are not retrieved and analysed independently. Moreover, stratified analyses by key clinical modifiers (GVHD status, timing of infection, supervision of interventions, and exercise adherence) were not feasible due to inconsistent reporting and lack of extractable data across studies, which may limit generalizability as this could significantly affect recovery, exercise capacity, and health outcomes.

In conclusion, pulmonary rehabilitation has shown promising results for the patients undergoing HSCT. however, a tailored programme involving multidisciplinary team approach focusing on exercise training, education and psychosocial support is essential as underlying illness process and the side effects of therapies in HSCT patients may naturally influence the results.

Author Contribution Statement

SGN: Writing - review & editing, Writing -original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. AI: Writing - review & editing, Writing -original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. PM: Writing - review & editing, Formal analysis, Conceptualization. JG: Writing - review & editing, Formal analysis, Conceptualization, supervision

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None.

Data availability statement

Data sharing is not applicable to this article as no new data were created, and all the studies are available in the databases or with the request to corresponding authors

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