



Effects of Exercise Interventions on Immune Function in Children and Adolescents With Cancer and HSCT Recipients - A Systematic Review

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Background: Pediatric cancer patients are at high risk for life-threatening infections, therapy associated complications and cancer-related side effects. Exercise is a promising tool to support the immune system and reduce inflammation. The primary objective of this systematic review was to evaluate the effects of exercise interventions in pediatric cancer patients and survivors on the immune system.

Methods: For this systematic review (PROSPERO ID: CRD42021194282) we searched four databases (MEDLINE, Cochrane Library, ClinicalTrials.gov, SPORTDiscus) in June 2021. Studies with pediatric patients with oncological disease were included as main criterion. Two authors independently performed data extraction, risk of bias assessment, descriptive analysis and a direction ratio was calculated for all immune cell parameters.

Findings: Of the 1448 detected articles, eight studies with overall n = 400 children and adolescents with cancer and n = 17 healthy children as controls aged 4-19 years met the inclusion criteria. Three randomized, four non-randomized controlled trials and one case series were analyzed descriptively. The exercise interventions had no negative adverse effects on the immune system. Statistically significant results indicated enhanced cytotoxicity through exercise, while changes in immune cell numbers did not differ significantly. Interventions further reduced days of in-hospitalization and reduced the risk of infections. Several beneficial direction ratios in immune parameters were identified favoring the intervention group.

Interpretation: Exercise interventions for pediatric cancer patients and survivors had no negative but promising beneficial effects on the immune system, especially regarding cytotoxicity, but data is very limited. Further research should be conducted on the immunological effects of different training modalities and intensities, during various treatment phases, and for different pediatric cancer types. The direction ratio parameters given here may provide useful guidance for future clinical trials.

Systemic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021194282, Prospero ID: CRD42021194282.

Keywords: pediatric oncology, childhood cancer, exercise intervention, immune system, inflammation, natural killer cells, physical performance, physical activity

INTRODUCTION

Children and adolescents with cancer are at high risk for life-threatening infections and therapy associated complications. They further have a risk for disease recurrence or development of secondary malignancies (1, 2). Thus, interventions are needed to decrease the probability of cancer-related side effects and increase the patients' quality of life. Studies suggest that enhanced immunosurveillance by cytotoxic natural killer (NK) cells and T-cells after moderate exercise might be beneficial for anti-cancer surveillance, as both are highly activated during acute aerobic exercise (3–6). Especially exercise-induced NK cells were recognized to have an anti-tumor effect (7). Furthermore, phagocytosis and oxidative burst in granulocytes are also increased by exercise (8) suggesting that regular exercise strengthens the immune system. Exercise induced effects, like increased NK cell cytotoxicity, lymphocyte proliferation and increased frequencies of granulocytes, have been reported in adult cancer patients (9, 10). Thus, performing moderate exercise interventions regularly might result in fewer infections and better clinical outcome in cancer patients. Growing evidence summarized in systematic reviews suggests positive effects of exercise therapy in pediatric oncology on cardiopulmonary capacity, functional mobility, muscle strength, quality of life and fatigue (11–13). Even though research is still limited, the current studies underline that exercise programs are safe and feasible in children with oncological diseases, while not increasing the risk of mortality, cancer recurrence or side effects (14). Moreover, an in-hospital exercise program seems to reduce days of hospitalization and treatment costs (15). Of note, evidence from experimental murine studies have shown beneficial effects of exercise intervention on graft versus host disease (GvHD) after hematopoietic stem cell transplantation (HSCT) (16, 17).

Studies in adult cancer patients already suggest beneficial effects of exercise on the immune system (9, 10). However, as the immune system undergoes systematic changes from pre- to post-birth (18, 19) and during aging (20, 21), the knowledge taken from the immune response of adult cancer patients after exercise may not be directly transferable to pediatric cancer patients. The type, frequency, duration, and intensity of exercise could also affect the immune system in different ways (22). Therefore, research studies focusing on how exercise affects the pediatric immune system of cancer patients is a relevant research question. The most recent systematic review focusing on general exercise and the immune system including studies with children and adults with cancer has been published in 2013 (10). Thus, this

systematic review aims at analyzing the current knowledge on this topic. The primary objective of the review is to determine the effects of exercise interventions in pediatric oncology on the immune system. As secondary objectives the effects on physical and functional performance, body composition, and hematopoietic stem cell transplantation (HSCT) outcome will be discussed.

METHODS

Search Strategy and Selection Criteria

This systematic review was conducted according to the PRISMA recommendations (23). A comprehensive search by two authors (RB, MG) of four databases (MEDLINE, Cochrane Library, ClinicalTrials.gov, SPORTDiscus) was conducted in June 2021. Search terms were based on PICO (24) for children or adolescents with cancer and/or recipients of stem cell transplantation during and after acute cancer therapy (Patient Population), exercise (Intervention), usual care/healthy control group (Comparator group), and immune function (Outcome). A combination of MeSH terms and search terms in title/abstract and relevant headings, keywords and synonyms for the search focuses was used. There were no restrictions in terms of publication date. The exact search terms are listed in **Supplement 1** and inclusion and exclusion criteria are shown in **Supplement 2**. The protocol of this review was registered in PROSPERO https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021194282.

After removing duplicates, two authors (RB, SBB) independently reviewed all identified studies by reviewing titles and abstracts. Remaining studies were checked accordingly for eligibility in full text (**Supplement 5**). Disagreements between the reviewers were discussed between the two researchers. If no consensus was reached, a third researcher (MG) was contacted. Eligible studies as well as identified systematic reviews were further screened for potentially missed relevant studies (**Figure 1**).

Data Analyses

Two authors (RB, SBB) assessed the risk of bias of included studies according to the PEDro scale (26). The PEDro scale is based on the Delphi list and was made for assessment of internal validity and sufficient statistical information (27). This tool is applicable for randomized clinic trials like randomized controlled trials (RCTs) and controlled clinical trial (CCT). The risk of bias was rated on a scale of 0-10 points (**Supplement 3**) and any disagreements were resolved by consensus. Two authors (RB, SBB) independently reviewed all identified studies and extracted relevant information for each study into standardized tables (see **Supplement 4** for details on data extraction and **Table 1** for results). A third researcher (MG) collected this information for each study.

For clarity only p-values for significant values are shown in **Table 1**. Due to the limited numbers of studies, different study designs and heterogeneous immunological parameters analyzed, no meta-analysis was conducted. We calculated a direction ratio for each immunological parameter analyzed within the different studies between the start and end point: Direction arrows were given if the ratio of an immunological parameters within the

Abbreviations: A, Adherence; ALC, Absolute lymphocyte count; ALL, Acute lymphoblastic leukemia; ANC, Absolute neutrophil count; CCT, Controlled clinical trial; CG, Control group; D, Duration; DC, Dendritic cell; EM, Effector memory; F, Frequency; GvHD, Graft-versus-host disease; GvL, Graft-versus-leukemia; HSCT, Hematopoietic stem cell transplantation; I, Intensity; KIR, Killer-cell immunoglobulin-like receptors; IG, Intervention group; MVPA, Moderate-vigorous physical activity; NCT, Non-randomized controlled trials; NK cells, Natural killer cells; NKCC, Natural killer cytotoxicity; NKT, Natural killer T cell; OD, Other designs; RCT, Randomized controlled trials; T, Time; WBC, Whole blood cell.

intervention group (IG) differs more than 30% (value $IG > 30\%$ control group (CG)/healthy controls) compared to the CG or healthy controls. Calculation and results are shown in **Supplement 4** and **Table 1**.

RESULTS

In total, 1448 articles were identified in the systematic search, where eight studies were included within this review (**Figure 1**,

exclusion criteria listed in **Supplement 2**). Of those, three studies were RCTs (29, 31, 32), four were NCTs (15, 28, 30, 34) and one case series (33). Seven of these studies focused on chronic effects (15, 28–33) of regular exercise and one of them on acute effects after exercise (34). Immune parameters were primary outcomes in five studies (28, 29, 32–34) and secondary outcomes in three studies (15, 30, 31). A total of 400 children within an age range of four to 19 years with different cancer types, such as solid tumor, leukemia, and neoplasms, and 17 children as healthy controls participated in the included studies. 246 boys and 154 girls took

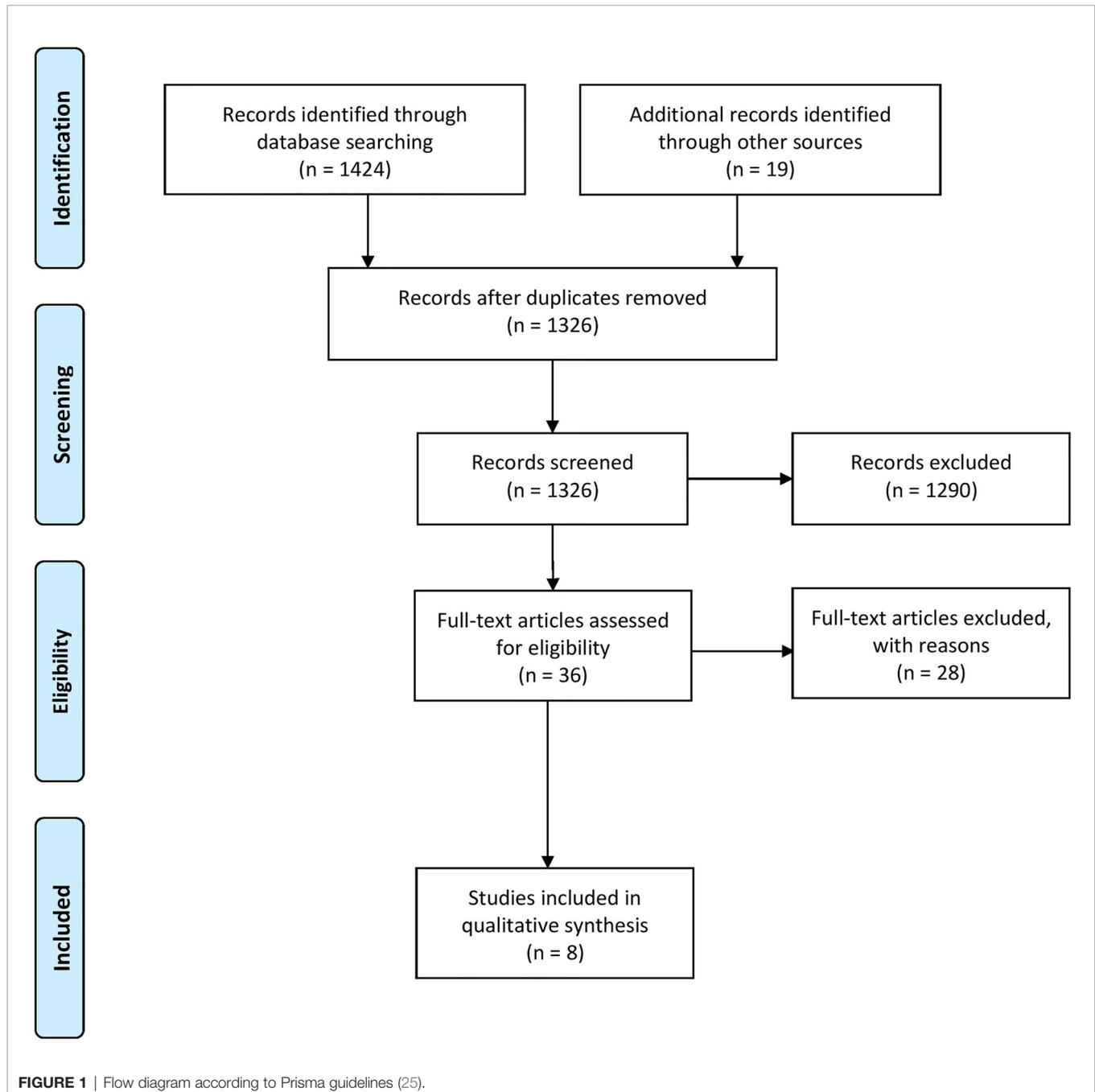


TABLE 1 | Characteristics and Results of Included Studies.

Reference number, Registration number and name of register	Study design	Participant characterization	N (IG/CG/HC)	Intervention Description	Frequency (F)/Intensity(I)/Time (T)/Duration (D)/Adherence (A)	Outcome Between-Group Differences (Group)	Outcome Within-Group Differences (Time)	Outcome interaction (group x time)	Direction ratio [Intervention (IG) vs. Control (CG) group or healthy control group (HC)]
Effects of exercise intervention in context of HSCT on immune parameter									
28	Historically controlled study – NCT	Age IG: 8 ± 4 yr (5-16 yr); CG: 7 ± 3 yr (4-13 yr) Cancer entities Mixed high-risk cancer needing allo-HSCT	20 (7/13/0)	IG: Supervised in-hospital strength & aerobic exercises CG: Usual care (no training)	F: 5x/wk (3 x aerobic, 2 x aerobic & strength) I: 50 % - 70 % of age predicted max. HR, hypertrophy training	No significant differences	Not significant after multiple correction: T-lymphocytes (p = .040); CD4 ⁺ (p = .032); DC's (p = .001)	Not significant after multiple correction: DC's (p = .045)	30d vs 15d post-HSCT: Leukocytes IG: 4.1 vs. ↑ CG: 2.5 Lymphocytes IG: 2.5 vs. ↓ CG: 5.1 Monocytes IG: 1.4 vs. → CG: 1.4 T-cells IG: 3.3 vs. ↓ CG: 5.2 NKs IG: 1.7 vs. ↓ CG: 3.5 NKT IG: 1.9 vs. ↓ CG: 4.1 CD4 ⁺ IG: 1.9 vs. ↓ CG: 3.8 CD8 ⁺ IG: 3.2 vs. ↓ CG: 7.4 DC's IG: 1.3 vs. → CG: 1.2
29	RCT	Age IG: 12.7 ± 4.0 yr (9-17 yr); CG: 13.3 ± 5.5 yr (8-19 yr)	6 (3/3/0)	IG: Supervised in-hospital & home-based strength & aerobic exercises CG: Usual care (no training)	F: 3x/wk (1x supervised, 2x home-based) N/A I: N/A T: 60 min D: 10 wks A: 80.3 ± 1.4%	N/A	N/A	Not significant after multiple correction: : Mean ratio CD56 ^{dim} (p = .03) Ratio: NKCC (p <.05)	Pre vs. post exercise program NKs: IG: 2.2 vs. → CG: 2.7 % NKs IG: 5.1 vs. ↑ CG: 2.1 CD56 ^{dim} IG: 1.3 vs. → CG: 1.0 CD56 ^{bright} IG: 0.5 vs. ↓ CG: 1.0 NKCC IG: 1.0 vs. → CG: 0.9 NK _p 30 IG: 1.2 vs. ↑ CG: 0.5 NK _c 44 IG: 0.4 vs. ↓ CG: 2.0 pg/ml: IL-2 IG: 2.0 vs. ↑ CG: 1.0 IL-4 IG: 2.6 vs. ↑ CG: 0.8 IL-6 IG: 3.5 vs. ↑ CG: 2.3 IL-8 IG: 4.8 vs. → CG: 4.1 IL-10 IG: 2.2 vs. ↑ CG: 1.1 IFN γ IG: 2.8 vs. ↑ CG: 0.8 TNF α IG: 2.5 vs. ↑ CG: 0.9 GM-CSF IG: 1.8 vs. ↑ CG: 0.5
30	NCT	Age IG: 11 ± 5 yr (5-18 yr);	118 (66/54/0)	IG: Supervised in-hospital strength & aerobic exercises	F: 5x/wk I: 65-80% of age predicted max. HR	Not significant after multiple corrections:	Not significant after multiple corrections:	Not significant after multiple corrections:	30d vs 15d post-HSCT allo-HSCT :

(Continued)

TABLE 1 | Continued

Reference number, Registration number and name of register	Study design	Participant characterization	N (IG/CG/HC)	Intervention Description	Frequency (F)/Intensity(I)/Time (T)/Duration (D)/Adherence (A)	Outcome Between-Group Differences (Group)	Outcome Within-Group Differences (Time)	Outcome interaction (group x time)	Direction ratio [Intervention (IG) vs. Control (CG) group or healthy control group (HC)]
		CG: 10 ± 4 yr (4-18yr)			T: ~60 min	allo- HSCT	allo- HSCT	allo- HSCT	Neutrophils IG: 8.6 vs. CG: 8.6 →
			allo-HSCT		D: ~3 wks	#:	#:	#:	Lymphocytes IG: 1.9 vs. CG: 2.4 →
						Lymphocytes		EM CD4 ⁺ (p = .005)	Monocytes IG: 0.9 vs. CG: 1.6 ↓
			IG: n = 47	CG:	A: 80.3 ± 1.4%	(p = .045)	Leukocytes (p <.001)	Naïve CD4 ⁺ (p = .005)	T-cells IG: 5.6 vs. CG: 2.8 ↑
						T-cells (p = .006)	Neutrophils (p <.001)	Treg (p = .003)	actCD4 ⁺ IG: 1.3 vs. CG: 2.8 ↓
						actCD4 ⁺ (p = .004)	Lymphocytes	CD56 ^{bright} (p = .003)	CM CD4 ⁺ IG: 1.3 vs. CG: 1.7 →
		Cancer entities		Usual care (no training)		CM CD4 ⁺ (p = .011)			EM CD4 ⁺ IG: 1.6 vs. CG: 2.0 →
			CG: n= 39			CD56 ^{bright} (p = .011)	T-cells (p <.001)		naïve CD4 ⁺ IG: 1.5 vs. CG: 2.6 ↓
		Mixed high risk cancer types needing allo- or auto-HSCT				CD8 ⁺ (p = .024)	actCD4 ⁺ (p <.001)		Treg IG: 1.0 vs. CG: 1.1 →
							CM CD4 ⁺ (p = .007)	auto-HSCT:	CM CD8 ⁺ IG: 1.7 vs. CG: 1.8 →
							EM CD4 ⁺ (p <.001)		EM CD8 ⁺ IG: 11.6 vs. CG: 26.3 ↓
							Naïve CD4 ⁺ (p <.001)		Naïve CD8 ⁺ IG: 4.0 vs. CG: 1.7 ↑
			auto-HSCT						NKs IG: 3.3 vs. CG: 2.4 ↑
							Treg (p <.001)		CD56 ^{bright} IG: 4.0 vs. CG: 2.0 ↑
						Leukocytes (p = .001)	Naïve CD8 ⁺ (p <.001)	Naïve CD4 ⁺ (p = .001)	CD56 ^{dim} IG: 3.0 vs. CG: 3.0 →
						Neutrophils (p = .048)	NKs (p = .001)	CD4 ⁺ (p = .048)	mB-cells IG: 2.3 vs. CG: 0.4 ↑
			IG: n = 18			Monocytes (p = .005)	CD56 ^{bright} (p <.001)	CD8 ⁺ (p = .041)	CD4 ⁺ IG: 1.4 vs. CG: 2.0 ↓
						T-cells (p = .037)	CD56 ^{dim} (p <.001)		CD8 ⁺ IG: 4.2 vs. CG: 3.9 →
		Treatment-phase				Naïve CD4 ⁺ (p <.001)	mB-cells (p <.001)		DCs IG: 0.8 vs. CG: 1.2 ↓
			CG: n = 14			CD4 ⁺ (p = .008)	DCs (p = .034)		
						DCs (p = .019)			
		On-treatment during allo- or auto-HSCT					Auto-HSCT:		auto-HSCT :
							Lymphocytes		Leukocytes IG: 1.0 vs. CG: 1.5 →
									Neutrophils IG: 1.2 vs. CG: 1.7 →
							CM CD4 ⁺ (p = .040)		Lymphocytes IG: 0.9 vs. CG: 1.5 ↓
							EM CD4 ⁺ (p <.001)		Monocytes IG: 1.7 vs. CG: 1.4 →
							Naïve CD4 ⁺ (p <.001)		T-cells IG: 1.3 vs. CG: 1.8 →
							Treg (p = .027)		actCD4 ⁺ IG: 1.0 vs. CG: 1.6 ↓
							CD4 ⁺ (p = .019)		CM CD4 ⁺ IG: 0.8 vs. CG: 1.5 ↓
							CD8 ⁺ (p = .008)		EM CD4 ⁺ IG: 1.3 vs. CG: 0.9 ↑
									naïve CD4 ⁺ IG: 1.6 vs. CG: 0.9 ↑
									Treg ↓

(Continued)

TABLE 1 | Continued

Reference number, Registration number and name of register	Study design	Participant characterization	N (IG/CG/HC)	Intervention Description	Frequency (F)/Intensity(I)/Time (T)/Duration (D)/Adherence (A)	Outcome Between-Group Differences (Group)	Outcome Within-Group Differences (Time)	Outcome interaction (group x time)	Direction ratio [Intervention (IG) vs. Control (CG) group or healthy control group (HC)]		
31; ClinicalTrials.gov ID: NCT01575704	RCT	Age	57 (28/29/0)	IG: Supervised in-hospital strength & aerobic exercises	F: 5x/wk I: IG: moderate training targeted with RPE (12–14) T: 30-60 min D: -6 wks (until discharge)	No significant differences	No significant differences	No significant differences	IG: 1.3 vs. CG: 2.2 CM CD8 ⁺ IG: 1.3 vs. CG: 0.4 EM CD8 ⁺ IG: 1.3 vs. CG: 2.7 Naive CD8 ⁺ IG: 2.1 vs. CG: 1.5 NKs IG: 1.3 vs. CG: 1.8 CD56 ^{bright} IG: 2.6 vs. CG: 2.0 CD56 ^{dim} IG: 0.9 vs. CG: 1.6 mB-cells IG: 0.8 vs. CG: 0.8 CD4 ⁺ IG: 1.2 vs. CG: 1.4 CD8 ⁺ IG: 1.5 vs. CG: 1.2 DCs IG: 0.9 vs. CG: 0.8		
		Cancer entities	CG: n = 30	Mental & relaxation training (no training)	A: IG: 94.4 (63.3-100) %, CG: 68.2 (5.8-100) %						
		Mixed high risk cancer needing allo- or auto-HSCT	IG: n = 4								
		Treatment-phase	CG: n = 5								
		On-treatment during allo- or auto-HSCT									
		Effects of regular exercise intervention in context of chemotherapy on immune parameter									
		32;	RCT	Age	20	IG: Supervised in-hospital (patient's room or hospital gym) strength & aerobic exercises	F: 3x/wk I: 60%–70% of measured max HR, 8-15 rep (hypertrophy training)	Not significant after multiple corrections:	%: NKT* (p <.001)	Not significant after multiple corrections:	Pre vs. Post exercise program
		ClinicalTrials.gov ID: NCT01645436	RCT	IG: 11 ± 4 yr	(9/11/0)			%:	Not significant after multiple corrections:	%:	#: Leukocytes IG: 0.7 vs. CG: 0.7 T-cells IG: 0.6 vs. CG: 0.7 B-cells IG: 0.8 vs. CG: 0.3 NKs IG: 2.2 vs. CG: 1.0 NKT IG: 1.5 vs. CG: 1.3
				CG: 12 ± 4 yr				NK 69 (p = .013) NKp44 (p = .021)		KIR2DS4 (p = .028) NKp46 (p = .037)	
				Cancer entities				T: 60-70 min D: 17 wks ± 5	NKCC (ratio): Ratio 8:1 (p=.038)	CD56 ^{bright} (p = .017) NKp44 (p=.004)	pg/ml: PDGF (p = .023)
Solid tumors (sarcoma, lymphoma, blastoma)						A: 70%				KIR3DL1 ↑	

(Continued)

TABLE 1 | Continued

Reference number, Registration number and name of register	Study design	Participant characterization	N (IG/CG/HC)	Intervention Description	Frequency (F)/Intensity(I)/Time (T)/Duration (D)/Adherence (A)	Outcome Between-Group Differences (Group)	Outcome Within-Group Differences (Time)	Outcome interaction (group x time)	Direction ratio [Intervention (IG) vs. Control (CG) group or healthy control group (HC)]
									IG: 0.5 vs. CG: 0.3
				CG:					NK 25 IG: 2.0 vs. CG: 2.0 →
									NK 69 IG: 2.0 vs. CG: 1.5 ↑
									KIR2DS4 IG: 1.7 vs. CG: 1.3 ↑
									NKG2D IG: 1.6 vs. CG: 1.0 ↑
				Usual care (no training)					NKp44 IG: 2.0 vs. CG: 1.0 ↑
									NKp46 IG: 1.5 vs. CG: 1.0 ↑
	Treatment-phase								NKp30 IG: 1.7 vs. CG: 1.0 ↑
	On-treatment during neoadjuvant therapy								DNAM IG: 2.3 vs. CG: 1.3 ↑
									NKG2A IG: 2.0 vs. CG: 1.2 ↑
									CXCR6 IG: 0.3 vs. CG: 1.0 ↓
									%:
									T-cells IG: 0.8 vs. CG: 1.1 →
									B-cells IG: 0.5 vs. CG: 0.3 ↑
									NKs IG: 2.4 vs. CG: 1.3 ↑
									NKT IG: 1.0 vs. CG: 1.7 ↓
									CD56 ^{dim} IG: 0.9 vs. CG: 1.1 →
									CD56 ^{bright} IG: 2.5 vs. CG: 1.8 ↑
									KIR2DL1 IG: 0.4 vs. CG: 0.6 ↓
									KIR2DL2/3 IG: 0.8 vs. CG: 1.2 ↓
									KIR3DL1 IG: 0.3 vs. CG: 0.4 →
									NK 25 IG: 1.1 vs. CG: 1.8 ↓
									NK 69 IG: 1.3 vs. CG: 1.1 →
									KIR2DS4 IG: 1.0 vs. CG: 1.8 ↓
									NKG2D IG: 1.0 vs. CG: 1.2 →
									NKp44 IG: 1.0 vs. CG: 1.7 ↓
									NKp46 IG: 1.2 vs. CG: 2.9 ↓
									NKp30 IG: 1.1 vs. CG: 1.3 →
									DNAM IG: 0.9 vs. CG: 1.5 ↓
									NKG2A IG: 1.0 vs. CG: 1.3 →
									CXCR6 IG: 1.0 vs. CG: 1.8 ↓
									NKCC (ratio):

(Continued)

TABLE 1 | Continued

Reference number, Registration number and name of register	Study design	Participant characterization	N (IG/CG/HC)	Intervention Description	Frequency (F)/Intensity(I)/Time (T)/Duration (D)/Adherence (A)	Outcome Between-Group Differences (Group)	Outcome Within-Group Differences (Time)	Outcome interaction (group x time)	Direction ratio [Intervention (IG) vs. Control (CG) group or healthy control group (HC)]
									4:1 IG: 0.8 vs. → CG: 0.7
									8:1 IG: 0.8 vs. ↑ CG: 0.7
									2:1 IG: 0.8 vs. → CG: 0.5
									1:1 IG: 0.7 vs. ↓ CG: 1.0
									pg/ml: CTACK IG: 1.1 vs. → CG: 0.9
									Eotaxin IG: 1.0 vs. ↓ CG: 1.5
									FGF IG: 1.1 vs. → CG: 1.3
									GSCF IG: 1.1 vs. ↑ CG: 0.7
									GRO- α IG: 1.4 vs. ↑ CG: 0.7
									HGF IG: 1.4 vs. ↑ CG: 1.0
									ICAM IG: 1.0 vs. → CG: 0.9
									IFN γ IG: 1.1 vs. → CG: 1.0
									IL-1 α IG: 0.9 vs. → CG: 0.9
									IL-2 IG: 1.1 vs. → CG: 1.1
									IL-3 IG: 0.7 vs. ↓ CG: 2.0
									IL-4 IG: 0.9 vs. → CG: 1.0
									IL-6 IG: 1.0 vs. → CG: 0.8
									IL-7 IG: 1.3 vs. ↑ CG: 0.5
									IL-8 IG: 0.5 vs. ↓ CG: 0.8
									IL-9 IG: 1.0 vs. → CG: 1.1
									IL-10 IG: 0.5 vs. → CG: 0.6
									IL-16 IG: 0.9 vs. ↑ CG: 0.6
									IL-18 IG: 1.3 vs. ↑ CG: 0.9
									IP10/ CXCL10 IG: 1.9 vs. ↑ CG: 0.6
									MCP1/CCL2 IG: 1.4 vs. ↑ CG: 1.0
									MCP3/CCL7 IG: 3.6 vs. ↑ CG: 0.5
									MIG/CXCL9 IG: 1.6 vs. ↑ CG: 0.9
									MIF IG: 1.4 vs. ↑ CG: 0.5
									MIP-1 α / CCL3 IG: 0.6 vs. ↓ CG: 0.9
									MSCF IG: 0.8 vs. ↓ CG: 1.5
									PDGF IG: 1.4 vs. ↑ CG: 0.8
									TNF- β IG: 0.6 vs. → CG: 0.8

(Continued)

TABLE 1 | Continued

Reference number, Registration number and name of register	Study design	Participant characterization	N (IG/CG/HC)	Intervention Description	Frequency (F)/Intensity(I)/Time (T)/Duration (D)/Adherence (A)	Outcome Between-Group Differences (Group)	Outcome Within-Group Differences (Time)	Outcome interaction (group x time)	Direction ratio [Intervention (IG) vs. Control (CG) group or healthy control group (HC)]
15	NCT	Age	169 (68/101/0)	IG: Supervised in-hospital strength & aerobic exercises	F: 2-3x/wk I: 65-80% of age predicted max. HR	No significant differences	# Leukocytes* (p <.0001)	No significant differences	TRAIL IG: 1.2 vs. CG: 0.8 ↑
		CG: 11 ± 4 yr (4-18yr) Cancer entities Solid tumor & leukemia		T: -60-70 min D: -22 wks A: N/A	VCAM1 IG: 1.1 vs. CG: 1.2 → VEGF IG: 0.7 vs. CG: 0.8 →				
33	CS	Age	17 (3/3/ 11)	IG & HC: Supervised of fitness instructor or parents aerobic exercise	F: 3x/wk I: 70%–85% of measured max HR,	Initial resting immune function (IG vs. HC):	No significant differences in IG	N/A	Pre vs. Post exercise program Leukocytes IG: 0.6 vs. CG: 0.8 ↓
		CG: Usual care (no training)		T: 30 min	Significant changes in HC: Leukocytes*				
		IG: 14 ± 0.6 yr; CG: 13.0 ± 3.1 yr; HC: N/A		Usual care (no training)	D: 12 wks A: N/A	Leukocytes*	CD3*	CD25*	Leukocytes IG: 0.9 vs. HC: 0.8 →
		Cancer entities				Lymphocytes*	CD3*	CD25*	Lymphocytes IG: 0.6 vs. HC: 1.3 →
		IG & CG: ALL & neoplasms				CD3*	CD25*		Monocytes IG: 0.7 vs. HC: 1.3 ↓
		HC: healthy controls				CD4*			Granulocytes IG: 0.6 vs. HC: 0.8 →
		Treatment-phase				CD8*			T-cells IG: 0.6 vs. HC: 0.8 →
		On Treatment after induction therapy				CD19*			CD4* IG: 0.4 vs. HC: 1.1 ↓
						CD25*			CD8* IG: 0.7 vs. HC: 0.9 →
						PHA-induced lymphocyte proliferation*			B-cells IG: 7.0 vs. HC: 1.1 ↑
									NKs IG: 0.8 vs. HC: 0.9 →
									CD25* IG: 0.3 vs. HC: 0.6 ↓
									CD122* IG: 1.3 vs. HC: 0.8 ↑
									Ratio: CD4*/CD8* IG: 0.8 vs. HC: 1.1 →
									Cytolytic activity: Spontaneous IG: 2.3 vs. HC: 0.6 ↑
									IL-2-induced IG: 1.3 vs. HC: 0.7 ↑
									Proliferation: PHA-induced IG: 0.5 vs. HC: 1.1 ↓
									PWM-induced IG: 0.6 vs. HC: 1.0 ↓
Effects of acute exercise intervention on immune parameter									
34	NCT	Age	10 (4/0/6)	IG & HC: Supervised in-hospital moderate to vigorous intermittent aerobic exercise	F: N/A I: 70-85% of measured VO2 peak	#: ALC* (p = .000) Eosinophils* (p = .006)	#: WBC* (p = .023) ALC* (p = .008) Monocytes	Ratio of active neutrophils compared to unstimulated neutrophils at time 0:	Pre vs. Post exercise intervention : WBC IG: 1.3 vs. HC: 1.4 → ALC IG: 1.5 vs. HC: 1.3 → Monocytes →

(Continued)

TABLE 1 | Continued

Reference number, Registration number and name of register	Study design	Participant characterization	N (IG/CG/HC)	Intervention Description	Frequency (F)/Intensity(I)/Time (T)/Duration (D)/Adherence (A)	Outcome Between-Group Differences (Group)	Outcome Within-Group Differences (Time)	Outcome interaction (group x time)	Direction ratio [Intervention (IG) vs. Control (CG) group or healthy control group (HC)]
					T: 30 min (10 min walk, 10 min run, 10 min walk)		(p = .059)	Ratio time15* (p = .006)	IG: 1.5 vs. HC: 1.5
		Cancer entities				Eosinophils*			IG: 1.0 vs. HC: 1.1 →
		IG: Pre B-ALL			D: N/A → acute effects	Ratio of active neutrophils compared to unstimulated neutrophils at time 0:	(p = .042)		Basophils IG: 1.6 vs. HC: 1.9 →
					A: N/A	Ratio time5*			Ratio of active neutrophils compared to unstimulated neutrophils at time 0 (Post vs. Pre exercise):
		HC: healthy controls				(p = .048)			
							pre-post exercise		Ratio time5 IG: 0.8 vs. HC: 0.7 →
						Ratio time10 [‡]			Ratio time10 IG: 0.6 vs. HC: 0.4 →
		Treatment-phase				(p = .074)	(p = .011)		Ratio time15 IG: 0.8 vs. HC: 0.6 →
						Ratio time15* [‡]	post to 1-h post exercise (p = .045)		Pre- vs. 2-h post exercise intervention
						(p = .050)	1-h to 2-h post exercise		:
									WBC IG: 1.1 vs. HC: 1.2 →
									ALC IG: 1.1 vs. HC: 1.1 →
		On maintenance treatment				Neutrophil oxidative burst:	(p = .052)		Monocytes IG: 1.3 vs. HC: 1.2 →
									Eosinophils IG: 0.7 vs. HC: 0.9 →
						time 0	(p = .029)		Basophils IG: 1.0 vs. HC: 1.6 ↓
									Ratio of active neutrophils compared to unstimulated neutrophils at time 0 (2-h post vs. Pre exercise):
									Ratio time 5 min IG: 0.6 vs. HC: 1.2 ↓
									Ratio time 10 min IG: 0.4 vs. HC: 1.2 ↓
									Ratio time 15 min IG: 0.5 vs. HC: 1.7 ↓

Characteristics, exercise descriptions and results from the included studies are summarized. P-values are shown within the columns: Outcome Between-Group Differences (Group), Outcome Within-Group Differences (Time), and Outcome interaction (group x time). A trend ratio was calculated by dividing values 30d post-HSCT by 15d post-HSCT (28, 30), post-HSCT by pre-HSCT (29), posttreatment by baseline (15, 32), final by initial (33), and post-exercise or 2-h post exercise by pre-exercise (34). *, significant (p-values are shown if reported), †, significant with p < .1 due to the small sample size of the study; ‡, no calculation of change possible, because only data for one time point is available even after further inquiry; #, cell count, %, percent, ↓↑→, Direction of trend or difference if the ratio of the intervention group differs >30% compared to the ratio of the control/healthy group, ALC, absolute lymphocyte count; ANC, absolute neutrophil count, B, B cells; CD, cluster of differentiation; CG, Control group; CS, case series; DC, dendritic cells; ex., exercise; HC, Healthy controls; HSCT, Hematopoietic stem cell transplantation; IG, Intervention group; IL, Interleukin; KIR, killer cell immunoglobulin-like receptors; min, minute(s); N/A, data not available; NCT, Non-randomized controlled trial; NK, natural killer cells; NK T, natural killer T cells; RCT, Randomized controlled trial; T, T cells; WBC, whole blood cells; wks, weeks; yr, years; h, hour(s); actCD4⁺, activated CD4⁺ T cells; CM CD4⁺, central memory CD4⁺ T cells; EM CD4⁺, effector memory CD4⁺ T cells; Treg, regulatory CD4⁺ T cell; mB-cells, mature B-cells.

part in the included studies, whereas sex is not mentioned in one study ($n = 17$) (33). Treatment phases and cancer treatment differed within the studies. Detailed study characterizations are available in **Table 1**. Risk of bias assessment could be performed for the three RCTs and studies scored with 4 out of 10 (32), 6 out of 10 (29), and 5 out of 10 (31) possible points (see **Supplement 3**).

Most studies focused on mixed interventions with strength and aerobic exercises. In the study of Chamorro-Vina et al. (28), Morales et al. (30) and Senn-Malashonak et al. (31) participants attended a supervised in-hospital exercise program five times per week for about three weeks until discharge during HSCT. In Chamorro-Vina et al. (29) children performed three times per week a supervised in-hospital & home-based training after discharge of HSCT for ten weeks. In Fiuza-Luces et al. (32) children participated at the supervised in-hospital exercise program three times per week for about 17 weeks on-treatment during neoadjuvant therapy. In Morales et al. (15) participants trained supervised in-hospital two to three times per week for about 22 weeks.

Only in two studies (33, 34) exercise programs consisted of aerobic exercises alone. In Shore and Shepard (33) children participated three times per week for 12 weeks in a supervised aerobic exercise training. In Ladha et al. (34) children attended a supervised in-hospital moderate to vigorous intermittent aerobic exercise test for 30 minutes. Detailed exercise modalities are described in **Table 1**.

Effects of Regular Exercise Intervention in the Context of HSCT on Immune Parameters

Four studies focused on the immunological changes in the context of HSCT (28–31). Significant effects of the intervention (group \times time) were seen for DC counts ($p = .045$) (28) and following T cell subset counts: effector memory (EM) $CD4^+$ ($p = .005$), regulatory $CD4^+$ T cells (Tregs, $p = .003$), and naïve $CD4^+$ T cells ($p = .005$) during allo-HSCT as well as $CD8^+$ T cells ($p = .041$), naïve $CD4^+$ T cells ($p = .048$), and total $CD4^+$ T cell counts ($p = .048$) during auto-HSCT (30). A significant intervention induced effect (group \times time) was noticed for $CD56^{\text{bright}}$ NK cell counts in patients receiving allo-HSCT and $CD56^{\text{dim}}$ NK cells (mean ratio) showing a significant increase in the IG compared to the CG ($p = .003$; $p = .03$) (29, 30). Detected time (within-group) effects within various immune cell subset counts were dominantly seen in patient receiving allo-HSCT, whereas patients receiving auto-HSCT showed more differences in immune cell counts between IG and CG (between-group) (30). All reported significances became non-significant after adjustment for multiple comparison (**Supplement 4**). No further significant intervention induced effect has been noticed for NK cell specific cell surface receptors, such as NKG2D, NKp30, and NKp44.

The NK cells were analyzed for their cytotoxic potential against the target cell line K562 from both groups. A ratio of observed natural killer cytotoxicity (NKCC) pre-training and post-training for groups was calculated. The NKCC was significantly higher in the IG compared to the CG (8 times higher, $p < .05$) (29). In line with slightly higher cytotoxic NK cell potential, a decreased risk of infections was reported within the IG (30).

Serum cytokines levels were measured for eight different cytokines (**Table 1**). No significant intervention effect was found between the two groups. However, a slight increase of IL-2, IL-4, IFN γ , TNF α , and GM-CSF was observed within the IG, while no change was seen within the CG for the first four cytokines, but a decrease for GM-CSF (29).

Effects of Regular Exercise Intervention in Context of Chemotherapy on Immune Parameters

Three studies examined changes within the immune system in patients with solid tumors and leukemia receiving chemotherapy (15, 32, 33). No significant interaction (group \times time) effect for leukocytes or lymphocyte subset counts was reported. Different dynamics in leukocyte counts were seen for IG and CG during follow-ups unto 5-years after posttreatment (15). From posttreatment and within the 1-year follow-up both groups showed significant decreased leukocyte counts compared to baseline (within-group, all p -values $< .001$). Within the 2-year follow-up, leukocyte counts in IG differed non-significantly compared to baseline ($p = .192$), while leukocyte counts remained significantly decreased in CG ($p = .011$). A slight decrease was also seen within the 3-year follow up in CG ($p = .061$), but not seen within the 4- and 5-year follow-up (15). The study further reported significantly decreased days of in-hospitalization for the IG compared to CG ($p = .031$) resulting in reduced treatment costs.

When analyzing various NK cell receptors needed for recognition of HLA-class I molecules and other important NK cell receptors, most receptors showed no intervention effect (group \times time), but a trend towards an interaction effect was seen for the KIR2DS4 which remained stable in the IG but increased in the CG ($p = .028$).

In two studies the cytotoxic potential of the cells were analyzed either by the spontaneous or IL-2-induced cytolytic activity of all mononuclear cells (33) or target-induced NKCC (32), however no significant intervention effect (group \times time) was reported. Shore and Shepard (33) showed higher baseline levels of spontaneous as well as IL-2-induced cytolytic activity in the healthy controls compared to the IG (pediatric cancer patients). After exercise, a decrease of spontaneous as well as IL-2-induced cytolytic activity was observed within the healthy controls, while both activities increased in the IG to comparable levels as the healthy controls (33). Fiuza-Luces et al. (2017) reported (32) higher baseline levels of NKCC for all four dilutions in the IG (8:1 – 1:1), which was stable for the next two time points after intervention as well. No significant intervention effect (group \times time) was reported for NKCC (32). No significant intervention effect (group \times time) was seen for the 31 analyzed inflammatory cytokines after testing for multiple corrections ($p = .0016$) (32).

Effects of Acute Exercise Intervention on Immune Parameters

One study focused on the effects on neutrophil count and function after an acute 30-minute exercise intervention (34). IG values were compared to age- and sex-matched healthy controls. Both groups received an acute bout of aerobic exercise and neutrophil counts and

function were analyzed pre-exercise, post-exercise, 1h, and 2h post-exercise. Neutrophil oxidative burst was monitored at 0min, 5min, 10min, and 15min (34). The authors observed a significant increase in whole blood cell (WBC, $p = .002$), absolute neutrophil count (ANC, $p = .006$), and absolute lymphocyte count (ALC, $p = .003$) as well as a significant decrease in eosinophils ($p = .003$) in both groups from pre-exercise to post-exercise. The effects on absolute lymphocyte counts and eosinophils were also significant within the group analyses (ALC, $p = .000$, eosinophils $p = .003$). When comparing the oxidative burst capacity of the neutrophils between IG and healthy controls, the study showed a significant higher capacity at 0min within the healthy controls compared to IG (main effect for group, $p = .029$). After 5min, 10min, and 15min the IG showed a significant higher oxidative burst compared to the healthy controls ($p = .048, .078, .050$, the study set the significant p -value to $p < .1$ due to low number of participants).

Direction Ratios of the Immunological Changes

Direction ratios in the context of HSCT with regular exercise intervention showed different immune cell reconstitution dynamics between allo-HSCT and auto-HSCT. In IG compared to CG 30d post-HSCT to 15d post-HSCT either no change or an increase in leukocytes counts were observed. An increase in mature immune cell subsets regarding total NK cell, CD56^{bright} NK cell, total T cell, effector memory (EM) CD8⁺ T cell, and memory B cell counts in patients receiving allo-HSCT was detected, compared to patients with auto-HSCT. Patients with auto-HSCT showed an increase in naïve CD4⁺ and EM CD4⁺ T cells. Both patients' cohorts showed increased naïve CD8⁺ T cell counts (Table 1).

NK cell and NKp30⁺ NK cell frequencies as well as serum cytokine levels of IL-2, IL-4, IL-6, IFN γ , IL-10, TNF α , and GM-CSF were higher in the IG compared to the CG post-exercise intervention compared to pre-exercise intervention after discharge of HSCT.

Total cell counts of NK cells and expression of certain NK cell specific molecules (3DL1, CD69, 2DS4, NKG2A, NKG2D, NKp44, NKp46, NKp30, DNAM) were increased in the IG receiving neoadjuvant therapy compared to the CG after usual care. This was also seen for NK cell frequencies, due to CD56^{bright} NK cells, but not for frequencies of NK-specific molecules which decreased. Furthermore, 13 out of 30 inflammatory serum cytokines levels were increased and five out of 30 decreased (Table 1). Two studies showed a direction ratio increase of the IG compared to CG or healthy controls in B cell counts and cytotoxicity (8:1 NKCC or spontaneous cytolytic activity). Besides increase in total lymphocyte counts, monocytes, CD4⁺ T cells, CD25⁺, and CD122⁺ cell counts as well as PHA- and PWM-induced proliferation were decreased between the IG and healthy controls.

For acute exercise intervention effects, a decrease in basophil counts as well as in neutrophil activity ratio time 5, 10, and 15 minutes was detected 2-h post exercise compared to pre-exercise within the IG compared to healthy controls.

Secondary Outcomes

In children undergoing a HSCT no significant differences in transplantation outcomes such as duration of myelosuppression,

neutropenic phase or duration of hospitalization were found between IG and CG (28). In Morales et al., 2020b (30) a trend towards between-group differences in the duration of hospitalization was noted ($p = .052$) with less days for IG. Same result was reported for children during neoadjuvant or intense chemotherapy treatment period in IG according to Morales et al., 2020a ($p = .031$) (15). Morales et al., 2020b (30) showed a lower number of infections after allo-HSCT in the exercise group ($p = .023$ and $p = .083$ for total and viral infections). Senn-Malashonak et al. (31) and Morales et al., 2020b (30) reported no differences in transplantation outcomes such as complications or GvHD for children undergoing HSCT. The effects on physical and/or functional performance as well as body composition have been reviewed in other studies in depth (13, 14, 35). Hence, this study focused on effects directly related to the immune system.

DISCUSSION

This systemic review included eight studies evaluating the changes in immune cell parameters after acute and chronic exercise in pediatric cancer patients, survivors, and HSCT recipients. In summary, no negative effects of exercise on the immune system, but positive effects on immune cell functionality, especially cytotoxicity, were noted, whereas immune cell counts, and inflammatory serum cytokine levels showed no significant intervention effect. Notably, some studies reported an exercise induced effect on slightly decreased infection rates and significant decreased days of in-hospitalization resulting in decreased treatment costs.

After acute aerobic exercise, patients with acute lymphoblastic leukemia showed a significant higher oxidative burst in neutrophils compared to healthy controls. This is of particular interest, as neutrophils belong to the innate immune system and are therefore responsible for the first line of defense. Neutrophils are able to migrate into tissues in order to eliminate invading pathogens by reactive oxygen species production, cytokine secretion, and phagocytosis (36). Thus, abnormal low frequencies of neutrophils, called neutropenia, can increase the chance of life-threatening infections and is a common side effect during cancer therapy (37–39). This finding by Ladha et al. (34) is in line with published data from adult cancer patients, where an increase in neutrophil function was observed after acute exercise (40). Studies in adult cancer patients and experimental mouse models further suggest that regular exercise intervention sustains enhanced neutrophil function and migratory capacity (40, 41). Furthermore, exercise can reduce chemotherapy related neutropenia in cancer patients (40) which might decrease the risk of infections in cancer patients. This is in line to a lower number of total and viral infections that could be observed (15).

Regular exercise interventions, comprising of combined aerobic and strength training, in pediatric patients post-HSCT led to significant higher mean ratio of CD56^{dim} NK cells and in patients receiving allo-HSCT also increased T cell, B cell, and NK cell counts. This is in line with current literature, as NK cells are one of the first immune cell subsets to reconstitute after HSCT

(42, 43). Besides cytotoxic CD8⁺ T cells, CD56^{dim} NK cells are the only other immune cell subset having cytotoxic potential. Indeed, NKCC was significantly higher (8-fold) within the IG compared to the CG suggesting that exercise increases the functionality of NK cells in pediatric cancer patients, which is comparable with literature in healthy adults (44–46) and adults with cancer (47). This is of major importance post-HSCT, as the reconstituted NK cells have been described to promote a graft-versus-leukemia effect, where the donor derived NK cells prevent a potential relapse (48). High NK cell counts (above a median of 120 per μ l blood) at day 32 post-HSCT have been described to predict a higher cumulative event-free survival rate, reduced transplant-related mortality and reduced cumulative relapse incidence (49). Hence, regular exercise in pediatric patients may increase NK cell functionality providing a natural defense against life threatening infections. Of note, within the study by Shore and Shepard (33) which focused on aerobic exercises IG showed a similar cytolytic activity compared to healthy children after exercise, although their initial levels of cytolytic activity were lower. Thus, this exercise induced effect of enhanced cytotoxicity is not only seen in patients receiving HSCT, but also in pediatric cancer patients without HSCT. It has to be mentioned that the type of exercise and exercise intensity also seems to influence NKCC (47). No study conducted in pediatric cancer patients so far focused on NK cell phenotyping and function after acute exercise.

Unfortunately, there is still too little data in pediatric cancer patients to define what exercise type and intensity is most beneficial for this population. Especially as most studies used a combination of aerobic and strength exercise programs. Of note, in healthy adults a recent systematic review highlights that aerobic/endurance training has a greater influence on NK cell cytotoxicity compared to strength training (45). Nevertheless, exercise programs during cancer therapy seem to be a useful and safe tool for children to keep their level of physical or functional performance or to improve muscle strength, physical fitness, body composition and functionality (12, 13, 35, 50). In this regard, guidelines regarding physical activity of pediatric cancer patients have recently been published (51) or are currently under development (52).

In summary, this systematic review suggests that no adverse effects on immunological parameters occurred during or after exercise intervention with pediatric cancer patients. Most studies reported an enhanced functional immune cell capacity after exercise indicating that exercise induces a boost to the immune system within pediatric cancer patients. This is in line with the reported reduced risks of infections and reduced days of in-hospitalization in the IG, which in turn decreases treatment costs. Interestingly, within an up to 5-year follow up, the IG was able to regain a comparable leukocyte count compared to baseline one year earlier compared to the CG, suggesting that exercise induced effects might have long lasting effects. Overall, both acute and chronic exercise interventions seem to enhance immune cell functionality in pediatric cancer patients, however data is limited to one immune cell subset in acute exercise intervention.

Some limitations of this review should be acknowledged. All studies included very limited or very heterogeneous populations.

Furthermore, varying exercise interventions, differently composed control groups, and a broad variety of immune parameters made accurate comparison of the studies difficult. Therefore, meta-analyses were not possible and descriptive analyses were used instead. We addressed this issue by including a direction ratio. Finally, assessment of quality was only possible for three RCTs, which have a middle and low-quality rating. This is mainly due to lack of participant blinding, missing intention-to-treat analysis and inadequate follow up. However, most of these difficulties are common in exercise intervention studies. Despite these limitations, the strengths of this review are the systematic and thorough search of several databases and the independent quality assessment by two reviewers. This review provides initial information for the planning and implementation of exercise interventions from an immunological point of view in pediatric oncology, as the included studies indicate that exercise is beneficial for the patients. It further highlights the need of further studies to evaluate and understand the mechanistic effects of different exercise modalities on the immune system in pediatric cancer patients and survivors, especially in the context of allo- and auto-HSCT.

DATA AVAILABILITY STATEMENT

All data collected for this article, including data extraction tables and the statistical analysis, will be made available. Requests to access these data should be made to the corresponding author.

AUTHOR CONTRIBUTIONS

RB: study design, search of four data bases, review of studies, risk of bias assessment, data extraction, data analyses, writing the manuscript. SB: review of studies, risk of bias assessment, data extraction, data analyses, writing the manuscript. MG: study design, search of four data bases, final decision on study inclusion, data collection, writing the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fimmu.2021.746171/full#supplementary-material>

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