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„*Using eHealth to support exercise and physical activity in patients with hematological malignancies – a systematic review* "

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"*Cancer is an expansionist disease; it invades through tissues, sets up colonies in hostile landscapes, seeking "sanctuary" in one organ and then immigrating to another. It lives desperately, inventively, fiercely, territorially, cannily, and defensively — at times, as if teaching us how to survive. To confront cancer is to encounter a parallel species, one perhaps more adapted to survival than even we are."*

— Siddhartha Mukherjee

The Emperor of All Maladies

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Abstract

Hintergrund Erkrankungen der blutbildenden und lymphatischen Systeme stellen eine ausgesprochen heterogene Gruppe mit differenzierten Prognosen dar. Diese beschränken sich selten auf einzelne Organsysteme und benötigen folglich intensive, systemische Therapien. Neben der durch den Krebs verursachten Symptomatik beeinträchtigen Nebenwirkungen der Behandlung die Lebensqualität maßgeblich. Entgegen der Vielzahl an Untersuchungen zur Durchführbarkeit und Vorzügen einer aktiven Gestaltung des PatientInnenalltags, ist die Datenlage zur unterstützenden Verwendung von elektronischen Devices und Applikationen überschaubar. **Ziel** Mit dieser Studie versuchten wir Wissenslücken in der Implementierung von modernen elektronischen Devices und Applikationen in der Trainingstherapie von malignen hämatologischen Erkrankungen zu schließen. **Methoden** Im Rahmen dieses systematischen Reviews wurde eine Literatursuche auf Pub Med mit Hilfe zweier vorgefertigter Suchtermini durchgeführt. Arbeiten ab Mai 2010 bis Mai 2020 wurden in die Auswahl gezogen und durchliefen drei konsekutive Auswahlverfahren. **Ergebnisse** Schlussendlich wurden siebenundzwanzig Arbeiten eingeschlossen, welche die Thematik Bewegung und Leukämien (n=8), Lymphome (n=7), Multiples Myelom (n=6) und Devices (n=6) behandelten. **Diskussion** Zukünftige elektronische Vorrichtungen und mobile Applikation besitzen enormes Potential zur Unterstützung der medizinischen Trainingstherapie. Technischer Fortschritt machen diese erschwinglicher und praktikabler in deren Anwendung. Dennoch ist deren Verwendung in der Hämatologie stark unterrepräsentiert und menschliche Interaktion weiterhin unabdingbar.

Background Hematological malignancies are considered highly heterogenous, ranging from potentially curable to being associated with devastating prognosis. Affecting several blood cell lines they require intense systemic chemotherapy, radiation and/or stem cell transplantation. Patients not only suffer mentally from prolonged hospitalization and cancers symptoms, but also from intense medication and side effects. Several articles have been published proofing feasibility and benefit of exercise interventions in this population. However, up to date, there is no such data on modern therapeutic approach of using mobile applications or electronic devices in exercise of patients with hematological malignancies. **Aims** We aimed to tackle current lack of evidence in electronic device or application-assisted exercise while treatment or at follow-up of patients with hematological malignancies. **Method** To address the research issue, a systematical review using literature search on Pub

Med was conducted. By two defined search terms relevant articles published from May 2010 to May 2020 were selected. Papers which passed through three consecutive selection steps (ST) were included and compared. **Results** After several selection steps twenty-seven articles were involved, consisting of exercise interventions in leukemic malignancies (n=8), lymphoma (n=7), multiple myeloma (n=6) and use of electronic devices in malignancies in general (n=6). **Discussion** Future holds great options for supportive use of electronic devices and applications, since they are getting more economical and practicable. However, as data on promoting exercise in hematological malignancies is still rare and each patient is individual, human therapists' expertise is still indispensable.

1 Introduction

As Charles Darwin already stated in 1859 it is not the most intellectual, nor the strongest species that survives – it's the one that adapts and adjusts in the best possible way to changing environment (Bouman, 1995). Still today these abilities of alignment are crucial in coping with unexpected developments. Dealing with the current pandemic of Covid-19, humans all around the globe experience far-reaching and profound changes in their daily routines and habits. Many of used-to activities were prohibited and yet they are strictly limited to avoid local transmission and spreading of SARS-CoV2. Even if not in a biological way, these new circumstances underline that still in 21st century adaption of behavior is necessary for human persistence (Romanov, 2020).

By reducing travel, staying at home and avoiding any non-essential contacts various governments, health authorities and experts have cut down most outdoor activities of numerous citizens and their possibilities to exercise regularly (Bundesministerium für Soziales Gesundheit Pflege und Konsumentenschutz, 2020; Centers for Disease Control and Prevention (CDCP), 2020; Romanov, 2020). Though the rate of published scientific papers is sky rocking, little is done to investigate possible ways to maintain physical activity levels in population (P. Chen et al., 2020). Distinctively this was done despite beneficial effects of exercise have been proven in healthy individuals (Piercy et al., 2018) as well as sickened (Luan et al., 2019). By the cease of engaging in physical activity and sports regularly, chronic diseases may worsen, possibly followed by sever and long-lasting consequences (Owen, Sparling, Healy, Dunstan, & Matthews, 2010). In consideration of progressing number of chronic diseases (Australian Institute of Health and Welfare, 2014; Brundtland, 2002) increasingly putting pressure on health care's finances and personal staff (Pollard, Zinder, Hoffman, & Nikodejevic, 1976), these developments have to be looked at closely.

Especially individuals with immunosuppressed status such as cancer patients belong to high-risk population for infection and serious courses of infectious diseases (Liang et al., 2020). By avoiding potential sources of contamination during pandemic they possess limited access to health care providers, unable to gain proper and necessary medical support (Wang & Zhang, 2020). Hospital and medical care centers are highly risky places for virus transmission, hence if possible, outpatient treatment instead of hospital setting is strongly recommended (Al-Quteimat & Amer, 2020). Following COVID-19 guidelines by reducing social contacts, supervised exercise seems almost not feasible.

Although these challenging times of social distancing confront medical trainings therapists and other health care providers with new unexpected barriers, modern devices and electronic applications may present sufficient opportunities to implement and maintain important exercise schedules in daily life of vulnerable cancer patients.

1.1 Hematological Malignancies

As life expectancy increases worldwide (Kontis et al., 2017) diseases of elderly become more frequently, financially impacting health systems, as well as rate of morbidities and causes of death. With more than 350.000 diagnosed patients and an incidence of more than 40.000 sickened (in 2017), cancer belongs to the most common diseases in Austria, causing about one quarter of all deaths nationwide. Still to date prostate cancer in male (n=5.697, 25%) and breast cancer in female (n=5.417, 28%) are considered as neoplasms with the highest incidences, closely followed by neoplasms of bronchial system (n=2.739, 22% in male and n=1.937, 24% in female) (Hackl, Hanika, & Klotz, 2018; Hackl, Hanika, Klotz, Leitner, & Zielonke, 2015; Statistik Austria, 2019). Incidences of patient with systemic cancer diseases such as neoplasm of hematopoietic and lymphoid tissue are less frequent. Only 7% of all newly diagnosed cancer types between 2015 and 2017 belong to hematological malignancies (Statistik Austria, 2019).

Not just limiting on a single organ system and affecting several crucial body parts, these cancer types may cause unspecific but sever symptoms. Treatment modalities and illness manifestations impair patient's quality of life severely. As simple surgery is not an option to cure these diseases, these urge for intense chemotherapy, radiation therapy and/or stem cell transplantations. First line medication often implicates antineoplastic agents, which impair physical performance as well as neurological and mental functioning. (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie, Österreichische Gesellschaft für Hämatologie & Medizinische Onkologie, & Schweizerische Gesellschaft für Medizinische Onkologie, 2018a, 2018b, 2018c, 2018d, 2018e; Fuchs, Greil, Lohri, & Engert, 2013). To cope with these side effects a combination of psychological and physiological support intervention is strongly recommended.

The most common entities of hematological malignancies shall be discussed below, focusing on their pathological characterization, prognosis, clinical presentation and issues impacting physical functioning and quality of life (QoL).

1.2 Leukemia

In 2017 about 10.000 persons were newly diagnosed with leukemia in Austria, corresponding to a stake of almost 3% of all cancer incidences within this country (Statistik Austria, 2019). There are several types and entities of blood cancer, which combine even more subtypes according to cell of origin, molecular and histoimmunological character. Yet there are hundreds of different kinds of leukemic neoplasms, some important and distinguishable macro-families shall be named to address the following topic:

Lymphatic neoplasms derive from lymphoid progenitor cells in the affected bone marrow, extramedullary site or patients' blood. According to the course of the disease, chronic lymphatic leukemia (CLL) and acute lymphatic leukemia (ALL) can be differentiated (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018c, 2018a).

In adults, acute lymphoblastic leukemia is considered the second most common acute leukemia. However, 80% of all incidences of ALL occur in childhood, peaking a second time around the age of 50 years (Paul, Kantarjian, & Jabbour, 2016). Importantly prognosis of these two populations differ widely. Many pediatric patients achieve long-term remission due to novel high-dose antineoplastic agents, whereas elderly patients face miserable prognosis (E. Jabbour, O'Brien, Konopleva, & Kantarjian, 2015). Even by application of those successfully in ALL children used regimes only up to 40% of adult patients achieve long-lasting survival (E. Jabbour et al., 2015), compared to 90% remission quotes in peds (Terwilliger & Abdul-Hay, 2017). With advancing age prognosis worsens even more (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018a).

ALL is caused by an abnormal, uncontrolled proliferation and development of lymphoid cells which are characterized by an inhibited differentiation process (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018a). Originating from a single sickened cell, a clonal population evolves, driving out healthy blood cells. In adult patients, pathologically proliferating B-cells cause 75% of all ALL cases, while T-cell ALL is responsible for the remaining (Terwilliger & Abdul-Hay, 2017). Particularly in pediatric patients these acute forms of leukemia are strongly associated with several far-reaching chromosomal abnormalities, genetic alterations and syndromes (Bielorai et al., 2013; Chessells et al., 2001; German, 1993; Ankit Shah, John, & Sondhi, 2013). Other triggering factors include virus diseases such as HIV or EBV, ionizing radiation or pesticides (Gérinière et al., 1994; Sehgal, Mujtaba, Gupta, Aggarwal, & Marwaha, 2010). Acute

leukemia is often described as a secondary neoplasm, if following radiotherapy or use of antineoplastic agents (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018a). However, pathogenetic reasons for ALL development is far from being fully understood (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018a).

Clinical presentation of affected patients is caused by accumulating clone cells. These malignant and poorly differentiated progenitor cells adversely affect the bone marrow function, decreasing the number of normal blood cells and consequently leading to leukopenia, thrombocytopenia and anemia. Ultimately, increased bleeding tendencies, cancer-related fatigue, dyspnea and deficient immune defense are resulting, as well as common B symptoms (Alvarnas et al., 2015; E. J. Jabbour, Faderl, & Kantarjian, 2005). Moreover, these cell clones are able to immigrate into lymphatic tissue such as spleen or lymph nodes, as well as non-lymphatic organs like liver, CNS, skin or testicles (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018a).

Diagnostic methods involve drawing blood samples and bone marrow biopsy. By presence of 20% or more lymphoblasts in sample, diagnosis is confirmed (Alvarnas et al., 2015). Beside diagnosis, these samples were used to determinate therapeutic protocols, matching to each specific genetic marker, mutation and cancer subtype (Arber et al., 2016). Treatment options also include Allo-SCT for high-risk and relapsing patients (Dombret et al., 2002; Jamieson, Amylon, Wong, & Blume, 2003; Thomas et al., 2004).

Though chronic lymphatic leukemia has a very similar pathogenesis to ALL, CLLs incidence peaks around 70 years. It is considered as the most common leukemic malignancy in western world, making up approximately 1,1% of all invasive cancer types (Robert-Koch-Institut, 2016). Key role of disease development are malfunctions in apoptosis mechanisms and dysregulation of proliferation. As in most hematological malignancies, several genetic abbreviations and defects in cellular pathways can be found in CLL (Döhner et al., 2000). Risk factors involve exogenic sources such as organic solvents and hereditary, yet not fully elucidated genetic predispositions (Cerhan & Slager, 2015).

CLL is a widely varying malignancy, differing profoundly in biological and clinical presentation. While most patient are asymptomatic at diagnosis, progression of disease may be associated with enlargement of lymph knots, spleen or liver, bone marrow failure or B symptoms (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al.,

2018c). Chronic lymphatic leukemia is confirmed by blood samples and histological evaluation of blood smear (Hallek et al., 2018). According to current stand of knowledge CLL is neither curable with conventional treatment agents such as chemotherapeutic agents, antibody therapy, nor specific immunological inhibitor drugs. The only potentially curable treatment option is allogeneic stem cell transplantation. Importantly, treatment is only advised if patient is symptomatic (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018c).

Similarly, AML covers several clinically as well as biologically heterogeneous malignancies. In 2016 a novel update (Arber et al., 2016) of WHO's classification (Vardiman et al., 2009) include six major disease entities. In contrast to CLL and ALL, myeloid leukemias arise from abnormal proliferation and differentiation of myeloid stem cell clones, often caused by de novo mutations in cellular maturation process pathways. Considerably almost 97% of all AML cases possess genetic malfunctions, chromosomal rearrangements and molecular changes (Patel et al., 2012).

As most hematological malignancies AML's clinical presentation is due to increasingly growing tumor mass infiltrating bone marrow. Hence, the decrease of physiologically functioning cell lines leading to fatigue, anemia, neutropenia and frequent infections, bleedings, petechia is associated with acute myeloid leukemia. Extramedullary manifestations such as gingival hyperplasia, cutaneous infiltration or infiltration of spleen and liver were also described (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018b).

Acute myeloid leukemia is the most common acute leukemia in adults, making up just about 80% of all cases of this population (Yamamoto & Goodman, 2008) (cf. CLL being the most common general leukemia in adults (Robert-Koch-Institut, 2016)). Incidences peak at the age of 72 (Juliusson et al., 2009). Despite vast advances in cancer knowledge and optimizing treatment through molecular differentiating in specific subtypes overall long-term survival and long-term remission still remains unlikely. If untreated AML is lethal within a few months (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018b). Particularly commonly affected elderly patients present adverse cytogenetic-risk profiles and optimal approach of this population has not yet been established (Anjali Shah, Andersson, Rachet, Björkholm, & Lambert, 2013). Notably, aged high-risk patients display lower response rates under chemotherapy while suffering more from treatment-related toxicities.

About 70% of all diagnosed patients aged 65 years or older will die within one year after diagnosis (Meyers, Yu, Kaye, & Davis, 2013). However, antineoplastic agents in induction therapy followed by consolidation therapy to eradicate any remaining cancer cells is recommended (Estey & Döhner, 2006).

Ultimately, chronic myeloid leukemia as model disease for molecular diagnostic and tailored therapy regime is worth mentioning. CML is defined by occurrence of so-called Philadelphia (Ph) chromosome, a translocation of specific chromosomal parts of chromosome 9 and 22. This t(9;22) causes a fusion of Abelson (ABL) tyrosine-protein kinase and break-point-cluster region (BCR) gene, consequently leading to a constitutionally active proliferation protein (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018d). Targeting this protein achieved significant increase of prognosis, enabling patients a normal life expectancy (Hehlmann, Hochhaus, & Baccarani, 2007). Though incidences occur in all ages, peaking between 55 and 60 years, the number of yearly newly diagnosed patients in Austria do not exceed more than 120 (Hehlmann et al., 2007; Rohrbacher & Hasford, 2009).

1.3 Lymphoma

By comparison with other solid cancer diseases Hodgkin-Lymphoma´s (HL) may seem to be rare. Though with little more than 180 newly diagnosed patients in 2017 in Austria (Statistik Austria, 2019) it is considered as the most common neoplasm in young patients (Robert-Koch-Institut, 2016). Average age at time of diagnosis is 32 years (Fuchs et al., 2013). Incidence is characterized by two peaks: First one, between the age of 20 and 30 years and second at advanced age after 65 (Rancea, 2013) or 55 (Bröckelmann et al., 2018).

HL belongs to the group of hematological malignancies, affecting the lymphatic system. It is characterized by pathological growth of B lymphocytes, with small amount of detectable malignant Hodgkins-Reed-Sternberg (H-RS) cells (Kanzler, Küppers, Hansmann, & Rajewsky, 1996; Marafioti et al., 2000). Within HL there are two distinctive disease entities which differ in affected age group, pathohistology and prognosis: More common classical HL and its subgroups, and rare nodular lymphocyte predominant HL (S.H. Swerdlow et al., 2017). Yet today underlying mechanism of cancer development are not fully understood and risk factors are not clearly defined (Glaser & Jarrett, 1996). Family factors may suggest a genetic association (Grufferman, Cole, Smith, & Lukes, 1977; Horwitz & Wiernik, 1999; Lynch, Marcus, & Lynch, 1992; Mack et al., 1995), as well as study assuming any connections between infection, immune deficiencies and HL incidences and prognosis

(Alexander et al., 2000; Andrieu et al., 1993; Franceschi, Dal Maso, & La Vecchia, 1999; Tirelli et al., 1995; Weiss, Strickler, Warnke, Purtilo, & Sklar, 1987).

Patients with HL often present with mild clinical symptoms such as painless enlargement of peripheral lymph nodes, regularly situated supradiaphragmatic. Unspecific B symptoms involve night sweat, fever with more than 38°C and involuntary weight loss of more than 10% of total body weight within 6 months or less. Other manifestation of HL may involve alcohol-induced pain (5%) (Fuchs et al., 2013) or chronic itching (Bröckelmann et al., 2018). Changes in blood count are unspecific and may show increased inflammation marker, leukocytosis, eosinophilia or lymphopenia. There is no such unique laboratory parameter for secure diagnosis of HL (Fuchs et al., 2013).

Diagnostic steps need to be approached if lymphadenopathy of unknown cause persists or progresses for more than four weeks. To confirm HL an excisional biopsy of an entire affected lymph node is needed. After sample collection histopathological examination is needed to properly confirm diagnosis. Furthermore, radiological imaging such as PET/CT and chest x-ray are strongly recommended to evaluate the extend of HL as well as testing of remaining functions of the affected organ systems. Invasive interventions of bone marrow puncture must not be performed if there is profound evidence by PET/CT (Bröckelmann et al., 2018).

Achieving more than 80% long term remissions it is associated with one of the best prognosis in adult malignancies (Fuchs et al., 2013). Treatment of HL is chosen by stage of disease. Beside Ann Arbor Staging Classification for Hodgkin Lymphoma, differentiating in 4 stages, presence or absence of additional specific clinical aspects are decisive. To those belong extra nodal involvement, involved lymph node areas, diameter of mediastinal tumor and elevated erythrocyte sedimentation rate (ESR). Implicating various risk factors therapy program and dosing regime is depending on classification of early, intermediate or advanced stage. Each of them involves chemotherapy and radiation. In young patients with desire to have children actions to preserve fertility within the first 4 weeks after diagnosis should be taken (Bröckelmann et al., 2018).

Guideline insists on strict controls and a precise follow-up for at least 5 years, as 90% of all recurrences happen in that range of time (Rancea, 2013). Regular check-ups every 3 months in the first year after finishing treatment, every 6 months in the second year and annually for the following years is strongly recommended, including drawing blood samples, taking

patient history and proper physical examination. Radiological image should only be intended if there are reasonable concerns about possible recurrence, followed by an additional biopsy (Bröckelmann et al., 2018).

As most patients receive chemotherapy and radiation as first line therapy, secondary cancer diseases occur more often than in general population (Schaapveld et al., 2015). Hence follow-up is advised not only surveilling HL recurrence, but also late side effects of intensive therapy (Bröckelmann et al., 2018). Depending on chosen therapeutic drug and location of radiation, check-up of distinctive body regions and organ systems were required. Young women who underwent axillary and/or thoracic radiotherapy are advised to get ultrasonography, palpation and MRI examinations done on regular basis. Patients who received chemo with anthracycline and/or radiation of thoracic trunk may perform electrocardiography, echocardiography and physical examination, due to cardiotoxic effects of these agents, ruling out coronary heart disease (A. J. Swerdlow et al., 2007). Thyroid dysfunction is often described in patients who underwent radiation of neck region, necessitating measuring thyroid-stimulating hormone (TSH) (Hancock, Cox, & Mcdougall, 1991). Pulmonary and gonadal damages may occur under and after chemotherapy as well, therefore pulmonary function testing including measurements of diffusion capacity and consultation of specialists is needed. Cessation of nicotine intake is proposed. (Fuchs et al., 2013) To tackle fatigue and psychological issues during and after treatment rehabilitation is strongly recommended in these patients (Bröckelmann et al., 2018).

Every malignancy of lymphatic system not classified as HL is called non-Hodgkin lymphoma (NHL). Diffuse large B cell lymphoma (DLBCL) belongs to this heterogenous group of cancer entities, by making up to 30-40% of all NHL in Western Countries being the most common subtype. In contrast to HL peaking in young patients around their third decade of life (Fuchs et al., 2013), DLBCL is more prevalent in elderly patients with its median around 70 years (Perry et al., 2016; Statistik Austria, 2019; Teras et al., 2016). Tough median age at first diagnosis of diffuse large B cell lymphoma occurs within more advanced age, some kinds of NHL such as Burkitt´s or primary mediastinal lymphoma may also affect children and younger adults (Armitage, 1997).

Its name is self-explanatory. According to WHO (S.H. Swerdlow et al., 2017; Steven H. Swerdlow et al., 2016) DLBCL is defined as a neoplasm of large sized B-cells arranged in a diffuse pattern and displacing physiological nodal or extra nodal architecture with rapidly

high proliferation rate (Korkolopoulou, Vassilakopoulos, Milionis, & Ioannou, 2016; S.H. Swerdlow et al., 2017). Another morphologically characterization of lymphoma tumor cells is being larger than the nuclei of benign histiocytes in the same tissue section (S.H. Swerdlow et al., 2017). Due to cell-of-origin classification, CD5 expression, immunohistochemistry or other prognostic factors affecting clinical course DLBCL itself is a highly heterogenous group of neoplasm with numerous subclassification (Steven H. Swerdlow et al., 2016). Despite vast number of subtypes and intensive research cause of most DLBCLs still remains unknown. Some may arise de novo (also called primary lymphoma), whilst others were documented to progress from less malign types of blood cancer (Morton et al., 2006). However, there is evidence that chemical substances, medical drugs and radiation of bone marrow or spleen can potentially cause lymphomas (Weisenburger, 1985). Moreover, immunological disorders (S.H. Swerdlow et al., 2017; Vianna, 1977) and diseases such as HIV (S.H. Swerdlow et al., 2017), EBV (Gibson et al., 2011; Hoeller, Tzankov, Pileri, Went, & Dirnhofer, 2010; Oyama et al., 2003), HHV8 (S.H. Swerdlow et al., 2017) or HCV (Ascoli et al., 1998; De Vita et al., 1997) can contribute to lymphomas development and progression.

Patients with DLBCL often present with rapidly but asymptomatic growing tumor cell mass in one or more lymph nodes or extra nodal localization (Martelli et al., 2013; S.H. Swerdlow et al., 2017). With approximately 40% of sickened patients showing extra nodal on-set literally any body tissue can be affected by this type of lymphoma. Still gastrointestinal tract is proven to be the most common site. By taking patient history about one third describes B symptomatic (fever, unintended weight loss and night sweat) or organ related symptoms (Brudno et al., 2016; Yao et al., 2018). To make an accurate diagnosis and right choice of treatment a complete and extensive medical work-up is required, including morphological and molecular diagnostic assessments, immunophenotypic and cytogenetic analysis (Li, Young, & Medeiros, 2018). This makes excisional lymph node biopsy and bilateral bone marrow biopsy mandatory, while core needle biopsy should be avoided (Andersson, Lindgren, & Elvin, 1992). Physical examination, carefully taking patients history as well as evaluating complete blood count are also strongly recommended (Lister et al., 1989; Martelli et al., 2013). Lactic dehydrogenase (LDH) is deemed to be an important indicator for tumor activity and part of the International Prognostic Index (IPI), decisively affecting chosen treatment protocol (Atkins, Moore, Shipp, & Harrington, 1994).

Current gold-standard therapy for DLBCL involves antineoplastic agents basing on so-called R-CHOP or R-EPOCH regimen. Exact explanation of this program and each drug is beyond

the scope of this review. However, DLBCLs are highly aggressive but potentially curable diseases and by using this combination of chemo drugs in approximately 60-70% of diagnosed patients remission is achievable. 5-year progression free survival (PFS) ranges from 80% to 85% (Martelli et al., 2013). Of those patients with poor treatment response or recurrence different treatment options such as autologous stem cell transplantation for younger afflicted is recommended (Epperla & Hamadani, 2017).

Similar to HS, patients diagnosed and after treatment of NHL such as DLBCL urge careful follow-up to establish re-employment, achieve reintegration in family and daily life. By regular check-ups potential recurrence of lymphoma is tried to be discovered as early as possible (Lister et al., 1989). Due to aggressive and intense treatment and side effects of administered chemo infertility (Elis et al., 2006; Pryzant, Meistrich, Wilson, Brown, & McLaughlin, 1993), secondary malignancies (Moser, Noordijk, Van Leeuwen, Baars, et al., 2006) and heart failure (Moser, Noordijk, Van Leeuwen, Le Cessie, et al., 2006) are described in literature. To prevent these affecting co-risk factors such as hypertension, diabetes, overweight or increased levels of blood fat need to be tackled (Ng, LaCasce, & Travis, 2011).

1.4 Multiple Myeloma

Multiple myeloma (MM) and plasmacytoma are rare malignancies with not much more than 500 newly diagnosed Austrian patients in 2017 all together (1% of all Austrian cancer incidences) (Hackl et al., 2015) and about 6.500 MM patients in Germany (Robert-Koch-Institut, 2016). Though much effort is put into defeating this heterogenic cancer type relative rate of 5-year overall survival does not exceed more than 50% as well as in men as in women, still considered incurable. Peaking at the age of 70 years, in all age groups sickened men are superior in numbers (Hackl et al., 2015; Robert-Koch-Institut, 2016).

Featuring numerous heterogenic subtypes of cancer, the term MM combines several biologically, genetically and clinically different diseases (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018e). Many aberrations can be found in patients with multiple myeloma, effecting therapy and prognosis. Still their origin remains unclear (American Cancer Society, 2017; Bergsagel et al., 2005) as well as there is no such effective measure to successfully prevent the development of MM (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018e). While this disease includes various, slightly differential entities WHO does separate some of them. Hence solitary

plasmacytoma or the preliminary stage of monoclonal gammopathy of undetermined significance (MGUS) are distinguished from MM (S.H. Swerdlow et al., 2017).

Common character of uncontrolled growth of monoclonal plasmatic cells within the patient's bone marrow is followed by massive production unfunctional immunoglobulins and IG chains. Accumulation of antibodies harms afflicted by harming crucial renal structures resulting in renal failure. Other cell lines are displaced by cancerous cells leading to bone lesion or fractures, hypercalcemia, pain, weight loss, suppressed production of erythrocytes and leucocytes, causing anemia, fatigue and increased risk of infections (Dimopoulos, Kastritis, Rosinol, Bladé, & Ludwig, 2008; Gerecke et al., 2016; Kyle et al., 2003; Yong et al., 2016). Consequently, symptoms are greatly unspecific leading to a long time of uncertainty about underlying cause. As one quarter of patients are asymptomatic at the time of first diagnosis, detecting and identifying multiple myeloma is difficult and needs profound medical knowledge and experience (Friese et al., 2009; Kariyawasan, Hughes, Jayatillake, & Mehta, 2007; Kyle et al., 2003).

As for several hematological malignancies final diagnosis of MM insists on a wide range of blood samples and tests, urine tests, bone marrow biopsy and various radiological imaging, such a x-ray, CT or FDG-PET/PET-CT (Kumar et al., 2017; Rajkumar et al., 2014; San-Miguel, Paiva, & Gutiérrez, 2013). Interestingly, therapy is just administered if one of the so-called SLiM-CRAB criteria is fulfilled. CRAB is a mnemonic, standing for hypercalcemia (C), renal insufficiency (R), anemia (A) and bone involvement (B). It is extended by SLiM, also a mnemonic which stands for monoclonal plasma cells making up sixty percent of bone marrow (S), predefined ratio or concentration of free light chain within patients' blood (Li) and focal lesions in MRI (M). Therapy is also started if patient suffers from burdens such as cancer associated pain, hyperviscosity syndrome, B-symptomatic, any symptoms which can be improved by treatment or can worsen under non-treatment, as well as recurrent infections. If none of the named above criteria is met, watch-and-wait strategy combined with close control is preferable (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018e; Rajkumar et al., 2014).

If initiation of therapy is advised, remission as well as rapid symptom control is considered as the primary goal (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018e). By choosing therapeutic goals each patient should be looked at differently by evaluating their desires, age, level of fitness, organic function and comorbidities (Merz et

al., 2016; Straka et al., 2016). Broadly speaking, therapy implicates preparation and induction of stem cell transplantation in suitable patients and several complex patterns of chemo- and immunotherapy, which shall not be discussed in this place (Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie et al., 2018e). The particularly important aspect of this issue is that patients of MM may have several symptoms of different intensity, as well as serve drug therapy and side effects, impacting quality of life (QoL).

1.5 Physical activity and exercise in cancer patients

Mentioning quality of life in cancer patients, exercise interventions has exceedingly been studied within the last decades. Though vast majority of conducted researches did address breast cancer, feasibility and benefits of physical activity has been scientifically proven in several entities (Christensen, Simonsen, & Hojman, 2018). As externally related factors such as lifestyle, fitness or diet were established to play crucial rolls in development and prognosis of this diseases (Brown et al., 2018), beside development of new antineoplastic agents, these became a novel opportunity to be approached by health workers (Christensen et al., 2018). Remarkably, most studies have focused on specific cancer types and a single cancer-related factor (e.g. muscle weakness or fatigue) or impairment tackled by a wide range of different exercise intervention, varying in period of time, trainings duration, frequency and intensity, exercise mode/method or timing (Smith, Devane, Begley, & Clarke, 2011; Stout, Baima, Swisher, Winters-Stone, & Welsh, 2017).

Hence, most of the current national guidelines approve and advise patients to get involved in sport, exercise prescription in these population shall be optimally tailored to this person's needs (Demark-Wahnefried et al., 2015; Wolin, Schwartz, Matthews, Courneya, & Schmitz, 2012). Importantly therapeutic use of exercise does not limit to the period while receiving treatment, but may also be used to tackle functional impairment and disabilities in a rehabilitation setting (Silver, Baima, & Mayer, 2013). Furthermore, it is essential that experts of all interacting disciplines and in the field of oncology, nutrition, exercise, rehabilitation, psychological, psychosocial and other supporting services muss pull on the same string to find a consensual way to implement physical activity on a long-term (Stout et al., 2017).

Already more than two decades ago some scientific study documented an impact on health, well-being and a connection between physical activity and risk of mortality in cancer patients (Adams et al., 2017). Since then literature on exercise and any kind of cancer related aspects grew rapidly, health care providers were confronted with vast amounts of information. These

continuously growing and complex data of entities, subtypes, molecular profiles, clinical representation and history, over-all health status or functional impairments challenges medical staff to give proper individual exercise recommendations (Wolin et al., 2012). Despite of being scientifically proven to be beneficial numerous times, exercise prescription and recommendation in determined treatment plan were overlooked frequently (MacAuley, Bauman, & Frémont, 2016; Smaradottir, Smith, Borgert, & Oettel, 2017). This could occur from the lack of necessary information and regular utilization (Cheville et al., 2017) or by absence of supporting infrastructure for planning and implementing exercise in cancer population (Stout et al., 2017). To overcome remaining supply gaps, supporting providers need clear and precise recommendation to easy integrate activity into therapy plan (Stout et al., 2016).

The majority of studies done on positive effects of leisure-time exercise in people diagnosed with neoplasms were epidemiological studies, relying on questionnaires. Though these self-reported measuring methods might be biased and not fully accurate, there are wide ranges of data available on significant value of physical movement (Agudelo et al., 2014; S. M.H. Alibhai et al., 2015). A recent and extensive epidemiological study did find clear and significant association between exercise and lower risk of almost all cancer entities (Moore et al., 2016). Incidences of solid tumor types of esophagus, kidney, lung, liver, colon, breast, as well as hematological neoplasm, such as MM and leukemia decreased by leisure-time physical activity. Interestingly, the rate of melanoma and low-grade prostate cancer raised with increased exercise, which could be linked to more frequent exposition to the sun concerning skin cancer and higher health awareness in active young men.

Hence the superiority of publication focused on the most common cancer types, data on seldomly diagnosed entities is lacking, and there is no data on optimal choice of exercise method or optimal scope of training. Beyond that, the underlying biological mechanisms of positive influence on cancers risk or prognosis is far from being fully understood (Idorn & thor Straten, 2017).

Exercise leads to a vast amount of changes in human body, affecting a range of physiological organ systems. Thus, cardiac performance capability increases to cope with elevated peripheral oxygen demands, resulting in an increased cardiac output and blood flow. To saturate strained body’s demand for energy, metabolism adjusts by raising blood glucose levels. Hormonal and endocrinological adaptions are made by release of catecholamines,

including epinephrine (adrenalin) and norepinephrine (noradrenalin) from adrenal gland. Even after cessation of physical exertion period, these increased levels can be detected within blood. Consequently, exercise triggers series of modifications in organism, affecting cardiovascular, hormonal, metabolic system and importantly the body's immune function (Walsh et al., 2011).

Interactions between immune system and cancer cells, as well as potential therapeutic treatment options are highly topical in science community. Speaking of exercise-induced anti-cancer effects, several investigations have shown an involvement of immunological mechanism. In animal studies, exercising mice with transplanted melanoma showed significantly increased expression of immunological pathway proteins and up-regulated immune function. By using PCR, flow cytometry and other new technical equipment, physically active murine models showed elevated density of T cells, B cells, DCs and NK cells. By intentionally targeting each of these immunological cell line and observing following effects, NK cells turned out to play the key role in exercise-induced anti-tumor response. While mouse models without B or T cells did show beneficial effects in tumor size through physical activity, these events vanished in absence of NK cells (Pedersen et al., 2016). NK cells have been attributed previously to potentially kill cancer cells (Kärre, Ljunggren, Piontek, & Kiessling, 1986). These cells are not only capable of increasing their blood count by acute exercise within a few minutes (Shephard & Shek, 1999; Walsh et al., 2011), but also already reach maximum after 30 minutes (Shephard & Shek, 1999). Though on-going activity does not increase maximum blood count, it can be maintained up to 3 hours by continuing exercise (Timmons & Cieslak, 2008).

Since the discovery of NK cells anti-cancer effects and their increased occurrence trough exercise, some studies have been made to investigate underlying molecular interaction. By stimulating ß-adrenergic receptors on the NK cells, catecholamines were assumed to constitute the missing link between training and increased activity of immune cells. These receptors are present in a very high number on NK cells surface proved to be activated by norepinephrine and epinephrine (Dimitrov, Lange, & Born, 2010). Similar but limited effects on exercise can be imitated by intentionally administering epinephrine (Schedlowski et al., 1996) or be blocked by administration of ß-adrenergic receptor inhibitor propranolol (Pedersen et al., 2016). Hence catecholamine levels are increased in exercising organism leading to NK cell mobilization, immigration of immune cells, and impacting tumor cells these hormones may be considered as crucial link between physical activity and anti-

neoplastic effects (Bigley et al., 2014; Cerwenka & Lanier, 2016; Idorn & thor Straten, 2017).

Since epinephrine only has limited effect by partially mimicking exercise, further contributing molecules and pathways were investigated. Interleukin-6 may play a crucial role in this phenomenon as well, being released from contracting muscles (Steensberg et al., 2002). Belonging to so-called group of myokines, it is controversially discussed to have pro-inflammatory effects on chronic inflammations and bacterial infection, as well as anti-inflammatory impact by activating immune suppressive Interleukine-10 and inhibiting TNF-α and IL-1 (Cullen, Thomas, Webb, & Hughes, 2016). Yet NK cells possess IL-6 receptor subtypes, recombinant monoclonal antibodies binding on this target could not imitate these effects assuming some complex interaction between these molecules (Idorn & thor Straten, 2017). Several other serum biomarkers being impacted by exercise intervention can be found in cancer patients' blood. These molecules involve IGF-I (Fong et al., 2012; Speck, Courneya, Mâsse, Duval, & Schmitz, 2010; Steel et al., 2014; Zhu et al., 2016), IGF-II (Cheema, Gaul, Lane, & Fiatarone Singh, 2008; Fong et al., 2012; Guinan, Connolly, & Hussey, 2013) being increased by physical activity, improved CD-4 cells (Cheema et al., 2008) or other decreased inflammatory molecules (Meneses-Echavez et al., 2016). Results of changes in insulin levels (De Backer, Schep, Backx, Vreugdenhil, & Kuipers, 2009; Zhu et al., 2016) or insulin-link markers (Guinan et al., 2013; Löf, Bergström, & Weiderpass, 2012; Spence, Heesch, & Brown, 2010) were inconclusive, as well as PSA or testosterone remarkably not being modulated by active sport (Hackshaw-McGeagh et al., 2015).

It should be noted that NK cells seem to have greater impact on very early phases of tumor development and be less important on already established cancer tissue (Fridman et al., 2014; Guillerey & Smyth, 2016). These suggestions go along with data supporting NK cells mainly affecting rapid growing tumor models (Pedersen et al., 2016), infiltration being barely present to completely absent in "cold tumors" 23. Consequently, exercise might play a more crucial role in prevention and early tumor stage than in therapy. Nevertheless, recent treatment methods use body's own immune system to target cancer cells. To do so, infiltration of anti-neoplastic NK cells, B cells, T cells and dendritic cells is urged. Therefore these "cold tumors" have to be turned into active "hot tumors", achieved either by radiation (Bockel, Durand, & Deutsch, 2018) or possibly by exercise. Logically, leisure-time physical activity does not only represent a preventive measure for cancer diseases, but may constitute

a tool to condition patients as a potential supportive therapeutic method combined with immune therapy (Idorn & thor Straten, 2017).

Literature addressing quality of life (QoL) in patients with hematological malignancies is extensive and has been studied exceedingly, whereas studies focusing on exercise interventions of these diseases are still limited. Especially if it comes down to articles about electronic devices and their use at physical activity in blood cancer, knowledge is rare.

1.6 Aim

Aiming for a better understanding of device-assisted physical exercise and modern treatment methods in patients with hematological malignancies, we reviewed current scientific data. Separated by individual diseases, this work shall provide an overview of possible use and serve as basis for further research.

2 Material and methods

2.1 Article selection

To gain information on the topic a search on Pubmed was conducted on 7th of May 2020 inclosing papers until 7th of May 2010. Addressing aspects of exercise in different entities of hematological malignancies we focused on science-based recommendations, feasibility studies of chosen hematological diseases, several therapy stages, aims and methods, age classes, as well as ethnic groups. We considered all types of leukemia, lymphoma and multiple myeloma, excluding diseases of pediatric population. Synonyms of physical exercise were used combined with these terms of diseases to cover all possible articles of this topic.

To include relevant studies, we included British and American English spellings. The following search request was used ("leukemia" OR "leukaemia" OR "lymphoma" OR "multiple myeloma" OR "hematological malignanc*" OR "haematological malignanc*" OR “blood cancer”) AND ("exercise" OR "training" OR "physical activity" OR "sport" OR “fitness” OR “fit”) NOT ("pediatr*" OR "cutaneous" OR "children"). It was defined as “search term 1”.

About the topic of feasibility and beneficial effects of using modern electronic health devices in implying and maintaining physical exercise in patients with hematological malignancies we conducted a separated search on Pub Med. As data of device-assisted exercise

intervention in patients with blood cancer is rare we added the term of cancer in general to include all different types of neoplasm. Excluding term of “NOT” was removed for this search, including devices used by young patients and children. Therefore, we used the term ("leukemia" OR "cancer" "leukaemia" OR "lymphoma" OR "multiple myeloma" OR "blood cancer" OR "hematological malignanc*" OR "haematological malignanc*") AND ("exercise" OR "training" OR "physical activity" OR "fitness" OR "sport*" OR "rehab*" OR "quality") AND ("ehealth" OR "mhealth" OR "device" OR "application" OR "app" OR "digital" OR "home" OR "home based" OR "smartphone" OR "tele*" OR "track*" OR "support*"). It was defined “search term 2”.

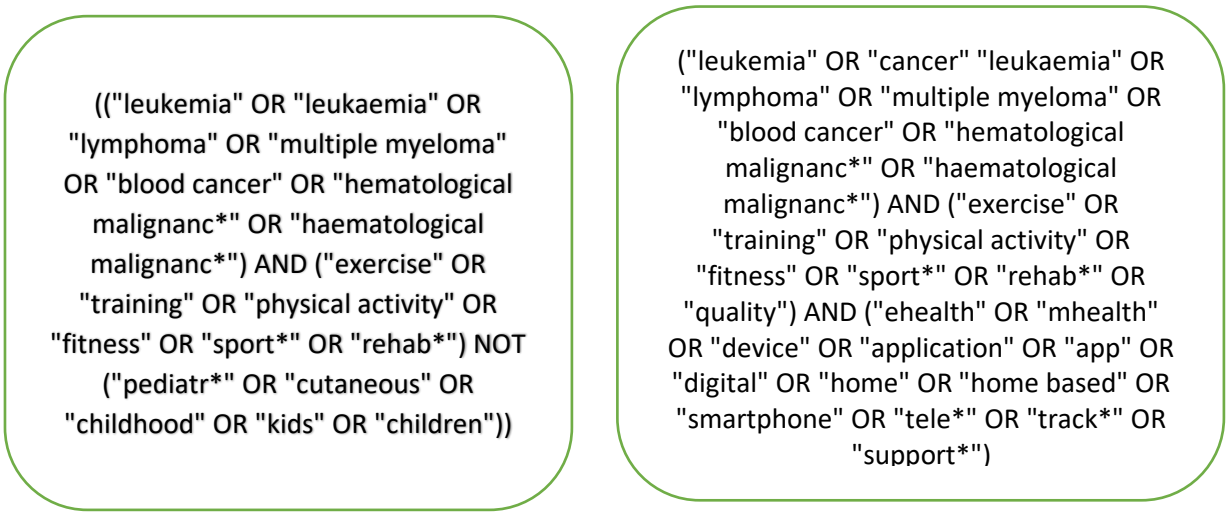

Figure 1. Search term 1 (left side) and search term 2 (right side used on PUB MED.

Addressing chosen diseases, intervention, support such as electronic application or devices we combined several possible combinations, as well as using synonymous terms using function “AND”. Selected species human was used for narrowing down the number of shown results. Publication dates within the last 10 years were selected to focus on more recent papers. Due to different spellings we used the American and British English forms of spellings, using function of “OR” for both of these variations. Function “NOT” was used to exclude results with pediatric or other common unmeant topics.

First all matches were screened for fitting titles. Articles not matching with our requirements were excluded. After this step abstracts of title-matching papers were read to select appropriate studies. Finally, all remaining papers were fully read to distinguish relevant data and to apply for certain subtypes of cancer and interventions. Crossmatched and cited articles

which match criteria and are considered as relevant were included as well. Table 1 displays stepwise elimination of unfitting articles.

2.2 Data collection

After shortlistening due to title and abstract, all remaining articles were fully read under standardized circumstances by the same person. Final selection of the included papers is made by working through all given information, thus providing necessary insight in discussed issues, collecting data about study design, statistical measures, population (gender, age, disease), intervention (type, duration) and results.

Findings of specific hematological malignancy were summed up in each section. These contain current exercise recommendation, as well as data on feasibility and benefits within different stages of disease and therapy. Interacting disease-pattern and their impact on daily life and physical activity, barriers, implication problems and other relevant results or specificity were also stated. If described in the articles, chosen exercises, intensity and repetitions were mentioned.

Device-supported findings, no matter what sort of, are mentioned in the section eHealth (electronic Health) and physical exercise. Characteristics, field of application such as cancer subpopulation or environment, price-performance ratio, barriers or benefits were covered in this chapter. As state of knowledge on use of device-assisted exercise intervention in adult hematological malignancies is especially rare, we included findings of other diseases.

2.3 Data synthesis

Essential data of several included studies are obtained in Table 2. It contains study design, location of execution, diagnosis, period of time and patients age, recruitment methods and case numbers as well as intervention, technical support and outcome. Findings about the selected types of diseases, their recommendations and results were addressed in the text. Chosen results and considerable figures were displayed as figures in the following chapter. Studies which go along with each other and those contrasting findings will appear in this roundup, giving different perspectives on the concerned subject.

3 Results

3.1 General findings

By using search-term 1 we received 2245 matches, 3465 by applying search term 2. Species "Humans" and Publication dates within the last 10 years were chosen, narrowing the search result down to 1092 matches in regard of cancer and exercise and 1830 of possible chosen articles inquiring cancer and device-assisted support of exercise. By excluding unfitting articles by title, we limited the range of possible studies to 158 for term 1 and 140 for search term 2. Overlapping articles were merged (n=125).

After several steps 153 articles were chosen for final quick scope reading. Cross referenced or cited articles were included if fitting to research question. Finally, 26 articles were included in this review. A single referring article was additionally chosen. Fig 2 demonstrates each step of selection (=ST).

After all, studies addressing electronic devices in supporting exercise interventions (n=6), multiple myeloma (n= 6), leukemic (n=8) and lymphoid malignancies (n=7) were included. In detail they investigated subpopulations of HL (n=6), NHL (n=6), AML (n=8), ALL (n=7), CML (n=1), MM (n=6), lymphoma (n=1) and lymphoid neoplasm in general (n=1), myelodysplastic syndrome (n=1), leukemia in general (n=1) and breast and colon cancer combined (n=1). None of these addressed CLL. Systematic search included randomized, controlled trials (n=7), descriptive studies (n=4), single (n=1) and consecutive case presentations (n=1), follow-up studies (n=3), quantitative cross-sectional (n=1), qualitative (n=1), retrospective explorative feasibility or pilot study (n=1), matched control study (n=2) and single arm interventions (n=4).

The majority investigated inpatient interventions (n=14), followed by outpatient (n=7), cancer survivors (n=5) and one with status not named. Intervention duration ranged from single measurement (n=5) to 6 months (n=1). Three papers did not mention period of intervention, a single trial was closed prematurely, and two lasted till drop out or end of admission, without stating average time of participation. Except one single-case study, the number of eligible participants ranged from 3 to 465 patients (mean n=85). Most of those studies were conducted in United States of America (n=8), followed by Canada (n=6), Australia (n=4), Germany (n=2), Great Britain (n=2), Iran, Belgium, Japan and Norway (each n=1). Particular and detailed interventions are displayed in Tab.2 and Tab.3.

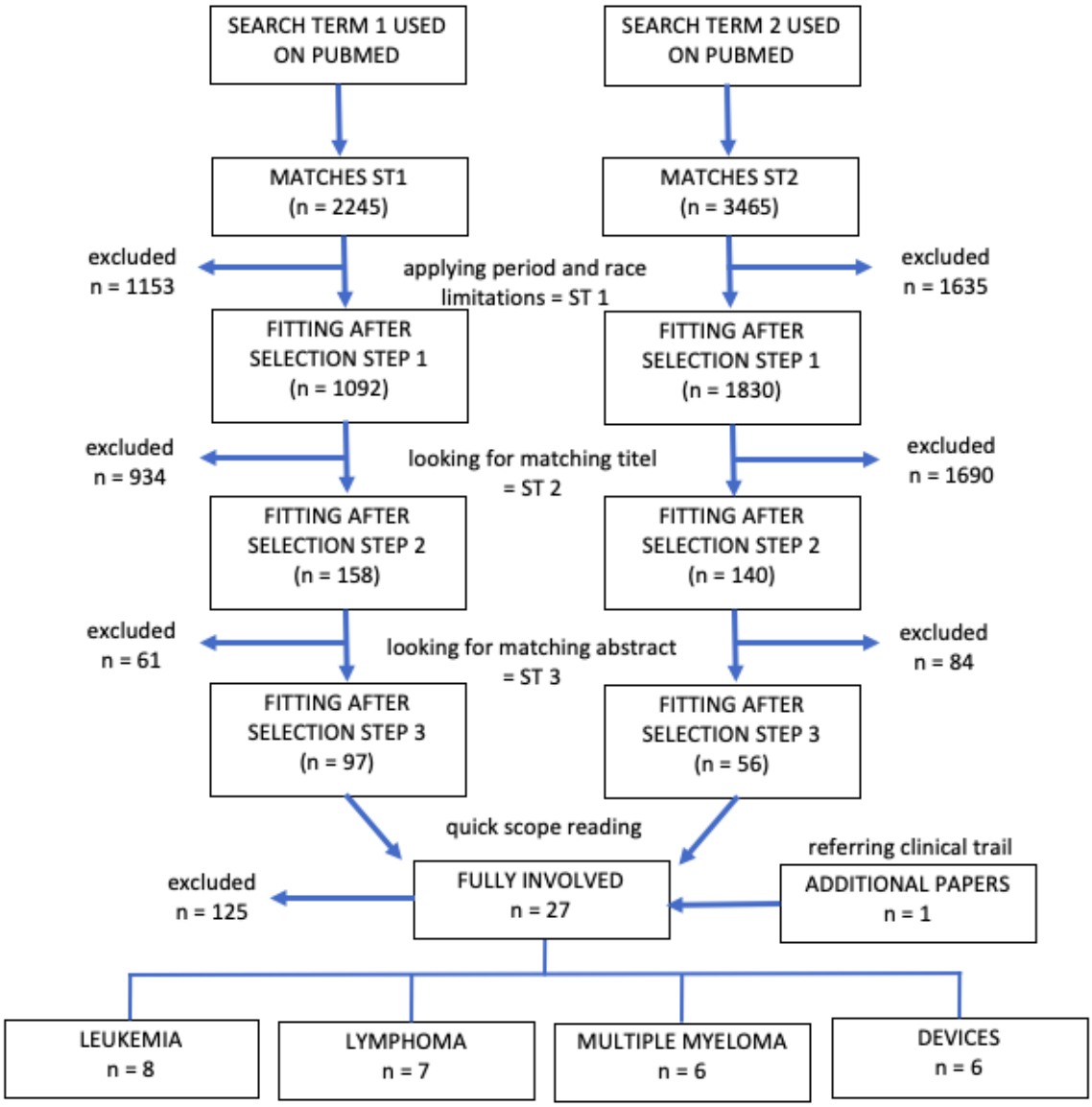

Figure 2. Stepwise process of paper selection.

Author year	Study design	Period	Place of study	Age (years)	Case recruitment	Intervention	Therapy setting	Treatment phase	Intervention duration	Diagnosis	Number of cases
Alibhai et al. (2015)	Randomized controlled trail, phase II	2011-2013	Canada (Toronto)	23-80	Princess Margaret Cancer Centre	individualized supervised mixed-modality programm	Inpatient	Induction chemotherapy	during admission period	AML	83
Bryant et al. (2017)	Descriptive exploratory study	2014-2015	USA (North Carolina)	35-67	EQUAL	semi-structured interview	Inpatient	Received treatment	Single measurement	ALL + AML	6
Bryant et al. (2018)	Randomized longitudinal pilot trial	2014-2015	USA (North Carolina)	28-69	EQUAL	supervised exercise program	Inpatient	Induction chemotherapy	4 weeks	ALL + AML	17
Cheng et al. (2011)	Consecutive case presentation	nn	USA (New York)	45-79	New York Presbyterian Hospital	Acute rehab	Inpatient	Received treatment	7-25 days	MM	8
Coleman et al. (2011)	Baseline measure	nn	USA (Little Rock)	nn	previous exercise intervention trail	nn	Inpatient	Newly diagnosed	nn	MM	187
Courneya et al. (2009)	Single-center two-armed RCT	2005-2008	Canada (Edmonton)	18-80	Cross Cancer Institute	supervised exercise program	Inpatient	Ongoing treatment	12 weeks	HL + NHL	122
Courneya et al. (2010)	Descriptive exploratory study	2005-2008	Canada (Edmonton)	18-80	HELP	supervised exercise program	Inpatient	Ongoing treatment	12 weeks	HL + NHL	60
Courneya et al. (2015)	Exploratory follow-up study	2005-2008	Canada (Edmonton)	≥18	HELP	supervised exercise program	Inpatient	Ongoing treatment	12 weeks	HL + NHL	110
Craike et al. (2013)	Quantitative cross-sectional study	2011-2012	Australia (Victoria)	nn	Australian Myeloma Impact Survey	no intervention	nn	Received treatment at least once	Single measurement	MM	229
Craike et al. (2013)	Qualitative study	2011-2012	Australia (Victoria)	48-78	Leukemia Foundation of Australia	semi-structured interview by phone call	Outpatient	Completed treatment	Single measurement	MM	24
Gheyasi et al. (2019)	Quasi-experimental study	2016-2017	Iran (Ahvaz)	≥18	Ahvaz Jundishapur University of Medical Sciences	Walking exercise programm	Inpatient	Ongoing treatment	10 days	AML	50
Groarke et al. (2015)	Matched control study	2003-2013	USA (Boston)	nn	Birmingham & Women's Hospital	Cycle Ergo	Survivor	Remission	Single measurement	HL	263
Groeneveldt et al. (2013)	Single arm phase II study	2006-2007	UK (London)	46-74	nn	aerobic and resistance	Outpatient	Remission, Rehabilitation	6 months	MM	37
Hathiramani et al. (2019)	Exploratory follow-up study	2014-2017	UK (London)	≥18	REIL	no intervention	Survivor	Remission	12 weeks	LY	35
Hooke et al. (2016)	Prospective, singel-arm, feasibility study	nn	USA (Minnesota, Minneapolis)	6-15	during clinic visit	fitness tracker	Outpatient	Maintanence therapy	2 weeks	ALL	17

Tab. 1: Selected studies. AACT .. Active After Cancer Trial, ALL .. acute lymphoid leukemia, AML .. acute myeloid leukemia, BC .. breast cancer, CALGB .. Cancer and Leukemia Group B, CC .. colon cancer, CML .. chronic myeloid leukemia, EQUAL .. Exercise and Quality of Life in Leukemia Adults, HDT-ASCT .. high-dose therapy and autologous stem cell transplantation, HELP .. Healthy Exercise for Lymphoma Patients, HL .. Hodgkins lymphoma, LK .. leukemia, LN .. lymphatic neoplasm, LY .. lymphoma, MM .. multiple myeloma, NHL .. non-Hodgkins lymphoma, nn .. not named, PNS .. peripheral nervous system, REIL .. Relaxation and Exercise In Lymphoma, RCT .. randomized, controlled trial.

Author year	Study design	Period	Place of study	Age (years)	Case recruitment	Intervention	Therapy setting	Treatment phase	Intervention duration	Diagnosis	Number of cases
Ligibel et al. (2012)	Randomized clinical trail	2007-2009	USA (San Diego)	mean 54	CALGB & AACT	telephone calls & pedometer	Outpatient	Remission	16 weeks	BC + CC	121
Russell et al. (2019)	Randomized controlled pilot trial	2018-2019	Australia	nn	Australian Multi Center	daily text messages	Outpatient	Ongoing treatment	closed prematurely	CML	3
Schuler et al. (2016)	Prospective non-randomized feasibility trial	2012-2014	Germany (Dresden)	29-87	University Hospital Dresden	home-based exercise intervention	Outpatient	Received treatment	12 weeks	MDS	21
Serpell et al. (2020)	Longitudinal, repeated measure case report	nn	Australia (Canberra)	30	nn	altitude training	Survior	Remission	5 weeks	AML	1
Shallwani et al. (2015)	Retrospective study	2011-2013	Canada (Montreal)	≥18	Jewish General Hospital Segal Cancer Center	no intervention	Inpatient	Ongoing treatment	nn	MM	41
Stenehjem et al. (2016)	Exploratory follow-up study	2012-2014	Norway (Oslo)	≥18	nn	no intervention	Survivor	Received HDT-ASCT treatment	10 weeks	HL + NHL	194
Story et al. (2016)	Randomized clinical trail	2016	USA (North Carolina)	28-69	EQUAL	Cycle Ergo	Inpatient	Before Induction Therapy	Single measurement	ALL + AML	14
Tsuda et al. (2016)	Prospective, singel-arm, feasibility study	2009-2013	Japan (Chiba, Ibaraki)	60-76	nn	virtual reality exercise	Inpatient	Ongoing treatment	till dropout	NHL + ALL + AML	16
Vallerand et al. (2018)	Randomized controlled trail, phase II	nn	Canada (Alberta)	18-80	post, email, telephone	telefone counseling exercise	Outpatient	Remission	12 weeks	NHL + HL + LK	51
Varedi et al. (2018)	Matched control study	nn	USA (New York)	≥18	St Jude Lifetime study	PNS function and balance measurement	Survivor	Remission	Single measurement	ALL	465
Vermaete et al. (2014)	Observational longitudinal single-center study	2010-2012	Belgium (Leuven)	18-80	University Hospital Leuven	no intervention	Inpatient	Ongoing treatment	nn	LN	29
Wehrle et al. (2019)	Randomized 3-armed pilot study	2010-2013	Germany (Freiburg)	21-63	University of Freiburg	endurance & strength training	Inpatient	Induction chemotherapy	31-52 days	AML + ALL	29

Tab. 2: Selected studies. AACT .. Active After Cancer Trial, ALL .. acute lymphoid leukemia, AML .. acute myeloid leukemia, BC .. breast cancer, CALGB .. Cancer and Leukemia Group B, CC .. colon cancer, CML .. chronic myeloid leukemia, EQUAL .. Exercise and Quality of Life in Leukemia Adults, HDT-ASCT .. high-dose therapy and autologous stem cell transplantation, HELP .. Healthy Exercise for Lymphoma Patients, HL .. Hodgkins lymphoma, LK .. leukemia, LN .. lymphatic neoplasm, L> .. lymphoma, MM .. multiple myeloma, NHL .. non-Hodgkins lymphoma, nn .. not named, PNS .. peripheral nervous system, REIL .. Relaxation and Exercise In Lymphoma, RCT .. randomized, controlled trial.

3.2 Disease-specific aspects

3.2.1 Leukemia

Since cancer-related fatigue (CRF) is noticeably common in patients undergoing chemotherapy for AML (Miladinia, Baraz, Ramezani, & Malehi, 2018; et al., 2012), it has been widely used as an outcome measure of success in oncological exercise interventions. The Brief Fatigue Inventory (BFI) (Mendoza et al., 1999) is frequently used to asses CRF, containing nine questions addressing impact on daily life, mood, relationship to others and CRF itself. Gheyasi et al. (2019) recently used the BFI to investigated perceived fatigue of 50 AML patients under induction therapy, before and after walking exercise. Each session lasted for 30 minutes, including 5 minutes of warm-up, 10 minutes walking at fast pace (40-60% of HRmax), 5 minutes active cool-down and 10 minutes of relaxation and rest. These were performed in two 5-day non-stop periods. BFI showed that a reduction of CRF could be achieved already after five consecutive days of mild exercise. Unfortunately, it was designed as single-armed trail, therefore control group was not given, and results have to be interpreted cautiously.

Statistically more validate data were from Alibhai et al. (2015), conducting a phase II exercise RCT for patients with newly diagnosed or relapsing AML undergoing induction chemotherapy (IC). Within the 4 to 6 weeks of admission intervention group participants (n=83) performed an individually adapted, supervised, mixed-modality training program, 4 to 5 days a week. Each session lasted for 30-60 minutes of light to moderate intensity exercise. Aerobic training involved treadmill, hall walking, or stationary cycling monitored by Borg scale (Heyward, 1992), aiming for 50-75% of HRR (Schmitz et al., 2010). Resistance exercise targeted major muscle groups by using free weights, resistance bands or body weight. Additionally, static stretching exercises were performed in each session. Post-interventional results of exercise group showed significant improvements in 6MWT, self-reported emotional and cognitive functioning, global fatigue and anxiety. Secondary physical fitness measures like timed chair stand or grip strength did not increase in intervention group, however, declined in control group, suggesting preventive effects on these parameters. VO2 increased significantly in exercise group, whereas adjusted between-group differences in global QoL did not differ significantly.

By a pilot, randomized, longitudinal, but not controlled study, Bryant et al. (2018) achieved similar results. To examine possible changes in adult AL patients (n=17) due to a 4-week

mixed-modality supervised exercise intervention, they focused on Patient-Reported Outcomes Measurement Information Systems (PROMIS), a tool to evaluate fatigue (Cella et al., 2010). Here, exercise program incorporated sessions twice a day and 4 days a week, involving resistance training with resistance bands, using different strengths and aerobic endurance training. Contrarily to expectations they could not find any significant changes preinterventional to postinterventional in scores concerning QoL. However, fatigue decreased in intervention and increased in control group, and so did perceived sleep disturbance score. Physical health did improve according to 6MWT and TUG test, yet not significantly.

Despite feasibility and safety of exercise during intensive induction therapy in patient with leukemia being proofed multiple times, knowledge about effects of diverse exercise programs still remains small. Therefore, Wehrle et al. (2019) conducted a randomized pilot study, including 29 adult acute leukemia patients (AML as well as ALL) into endurance (EG), resistance (RG) or control (CG) group, to investigate differences, specific impact on quality of life and physical capacity. During induction therapy three exercise sessions per week, each lasting for 30-45 minutes were performed. For aerobic endurance training included patients could choose treadmill or upright stationary bicycle, performing continuous or interval method. Intensity of 60-70% of heart rate maximum was aimed for, combined with rated perceived exertion (RPE) scale (12-14 score on 6-20 rating scale) (Borg, 1954). Resistance exercise was individually tailored to train major muscle groups with bodyweight or devices. If possible, especially fit patients were allowed to use resistance machines. RG performed 4-6 varying exercises, using RPE (Borg, 1954) and aiming for 12-14 repetitions. Comparatively, CG were limited to low-level mobilization and stretching exercise. All groups were supervised by certified sports therapists in inpatient setting. Each items and parameters were measured at baseline and after intervention. Ultimately, no adverse event took place and compliance rates were higher in intervention groups than in CG proofing feasibility, safety and interest in movement. Results on QoL changes revealed no significant improvements in all three exercise groups. Endurance capacity did not improve either. Nevertheless, resistance group increased their strength values while EG and CG perceived significant decreases in strength. These results may show that resistance training is superior to endurance training in AL patients undergoing induction therapy.

Tailored aerobic endurance exercise in acute leukemia patients displays another important disadvantage. To achieve optimally adapted trainings intensity individual cardiopulmonary

exercise testing (CPET) is crucial to determine VO_2 levels as well as each specific threshold. By an exploratory study Story et al. (2016) figured out huge discrepancies between calculated and commonly used Karvonen formula (HRR), percent of 220-age equation and gold-standard CPET in several intensity levels. Moreover, each method did not achieve consistent results even within same participants, questioning use of these measurements in hospital settings. As AL patient undergo daily changes in perceived feeling of disease, changes in treatment, side-effects or fluid shifts, blind faith in HR-based determination of exercise intensity in this population does not seem appropriate.

Although Wehrle et al. (2019) did not find any significant chances in endurance performance within 6 weeks of inpatient intervention, Schuler et al. (2016) achieved an improvement after 12 weeks. Therefore, patients were encouraged to engage in combined endurance and resistance exercise in a home-based setting, exercising 6 days a week. Duration of aerobic endurance training sessions amounts 15 to 30 minutes each and was individually adapted to 75% of HR_{max} (Dickhuth et al., 1999). Additionally, Borg scale was used by aiming for 12-14 scale points (Borg, 1970; Dimeo, Fetscher, Lange, Mertelsmann, & Keul, 1997). Strength exercise consisted of one to three sets of up to twenty repetitions, using elastic bands and body weight and focusing on muscle groups necessary for safely walking. QoL, symptoms, functional scales and general fatigue did not change through intervention, but physical capacity did: Covered distance at 6MWT, trunk flexion and extension increased significantly, while heart rate at anerobic threshold declined. However these results and its compare with studies earlier mentioned must be interpreted with caution, as Schuler et al. (2016) enrolled patients with myelodysplastic syndrome (MDS), a precursor of AML.

Not only population undergoing antineoplastic treatment faces sever burden, but also cancer survivors in long-term remission. Many regimes used in ALL treatment involve neurotoxic drugs (eg. vincristine) associated with peripheral neuropathy (PN) (Dougherty, Cata, Burton, Vu, & Weng, 2007; Harila-Saari, Vainionpää, Kovala, Tolonen, & Lanning, 1998; Vainionpää, Kovala, Tolonen, & Lanning, 1995), in a long term leading to a decline of muscle strength, particularly in lower extremities (Ness, Armenian, Kadan-Lottick, & Gurney, 2011; Ness et al., 2015, 2012). Varedi et al. (2018) conducted a match-controlled survey to evaluate impact of these side-effects on QoL, mobility, walking endurance and static balance in survivors of childhood ALL. 365 survivors more than 10 years after primary cancer diagnosis were enrolled. To measure the parameters of interest, computerized dynamic posturography (Nashner & Peters, 1990; Pedalini, Cruz, Bittar, Lorenzi, & Grasel,

2009), Timed Up and Go test (TUG) (Bohannon, 2006; Richardson, 1991), 6-minute walk test (6MWT) (Butland, Pang, Gross, Woodcock, & Geddes, 1982; Enrichi & Sherrill, 1998), modified Total Neuropathy Score (mTNS) (Wampler et al., 2006) and Medical Outcomes Study 36-Item Short Form Survey (Ware, 2000) were performed. Compared to individuals without history of childhood cancer, ALL survivors demonstrated higher rates of PN, poorer QoL, walking endurance and mobility, yet they did not display worse static balance.

To asses perceived barriers and benefits in physical activity while inpatient induction therapy Bryant et al. (Bunney, Zink, Holm, Billington, & Kotz, 2017) used semi-structured interviews in a descriptive, exploratory study. Six patients treated for acute leukemia were asked about their exercise experiences with participating in a previous intervention trial (Bryant et al., 2018). Even though most of the included patients did not meet exercise recommendations (Bergenthal et al., 2014; Jones, Eves, Haykowsky, Joy, & Douglas, 2008), nor half of them did engage in any kind of physical activity six months prior to diagnosis they experienced positive results. Among those who exercised low-to-moderate intensity sports like hiking, walking or playing tennis were preferred. However, all enrolled patients reported physical and psychological benefits, which decreased pain, fatigue, anxiety and aches. Furthermore, they mentioned that regular exercise routine and social contact kept them motivated throughout hospitalization. Common barriers to decrease adherence rates were closely connected to physical and psychological symptoms, or tightly organized treatment plans. Interestingly, two suggestion brought forward to improve exercise program were long-termed support of the same therapist for the whole stay as well as implying wearable devices or the use of electronic application to track activity.

3.2.2 Lymphoma

As fatigue accompanies all kind of hematological malignancies and their treatments, it consequently harms NHL and HL patients as well. To assess its prevalence before, during and after lymphoma management Vermaete et al. (Vermaete, Wolter, Verhoef, & Gosselink, 2014) designed an observational longitudinal single-center study, enrolling twenty-nine patients (NHL n=17 & HL n=12), going through chemotherapy. They hypothesized that fatigue is closely interrelated with inactivity and decrease of physical performance. Therefore, they performed basic laboratory investigations, cardiopulmonary function was assessed by body plethysmography, exercise capacity by cycle ergometer test, for functional exercise capacity 6MWT was used, acceleration sensors to measure physical activity and daily METs. Furthermore, they addressed quality of life by using the EORTY QLQ-C30

questionnaire (Aaronson et al., 1993), dynamometer for hand grip strength and instruments to collect data about isometric quadriceps strength. Results analyzation showed significant declines in muscle force which was suggested to be caused by administered antineoplastic agents rather than inactivity. Symptoms of fatigue did increase in the course of treatment, as well as hemoglobin and quality of life. These findings supported their idea of hypothesized vicious circle between physical inactivity, fatigue and deconditioning trough cancer treatment.

First large exercise RCT in lymphoma was conducted by Courneya et al. (Courneya et al., 2009) back in 2009. Within the so-called Healthy Exercise for Lymphoma Patients (HELP) trail, Canadian group of scientists hypothesized that patient-related outcome, cardiovascular fitness and body composition would be superior with additional aerobic exercise, compared to control patients receiving usual care. Each intervention group participant had to complete 3 weekly training sessions over the period of twelve weeks. Exercise sessions consisted of supervised cycling on an upright or recumbent exercise bike. Duration and intensity were progressed over time. To increase adherence rates sessions were scheduled flexible, telephone follow-up after missed sessions, positive reinforcement of the staff, exercise variation and paid parking were guaranteed. At postintervention exercise group (n=60) was superior to control group (n=62) regarding overall QoL (p=0,021), happiness (p=0,004), depression (p=0,005), fatigue (p=0,013), patients-related physical functioning (p=0,012), cardiovascular fitness (p<0,001) and lean body mass (p=0,008). At 6-months follow-up there were no statistically significant differences in terms of patient-related physical functioning (p=0,121). Ultimately, 6,4% (4/60) of intervention group patients experiences recurrence or progression, compared to 11,3% (7/62) of control group (p=0,37).

Mean adherence rate of intervention arm was 77,8% but variated significantly (SD=30%). Adherence in patients who received treatment during trail (44%) was slightly lower with 71%., whereas in off-treatment patients it was 83%. Beside active treatment phase, BMI, motivation scores and past exercise correlated with exercise adherence (Courneya et al., 2010). However, after a median follow-up of 61 months (interquartile range 36-67) there was no difference in 5-years progression-free survival between exercise and control group (64,8% vs. 65,0%), yet control group received one month of supervised exercise program after completion of HELP trial and therefore results may be affected. Secondary analyses comparing patients who completed supervised exercise and those who did not suggested

some associations between PFS and adherence, which did not reach statistical significance (68,5% vs. 59,0%, p=0,31) (Courneya et al., 2015).

Following the twelve-week home-based Relaxation and Exercise In Lymphoma (REIL) study (S. Hathiramani, Pettengell, Moir, & Younis, 2018) Hathiramani et al. (Suchita Hathiramani, Pettengell, Moir, & Younis, 2019) interviewed thirty-five included post-chemotherapy lymphoma survivors. To evaluate intervention and experiences, identify preferences and perceived barriers, all enrolled participants were asked to complete the End of Study (EOS) questionnaire, answering six open-ended questions (O'Brien, Harris, Beckman, Reed, & Cook, 2014). The majority (n=30/35, 85,7%) considered intervention as a positive experience which supported their recovery. Particularly they reported to have enjoyed structured daily routine, regular contact with researcher and fitness testing. They also pointed out that follow-up after trial is necessary, as much of them felt left alone, reverting into old inactive habits. Responders also called for important dietary advices during transition phase.

Even several years after end of treatment in long-term remission lymphoma survivors (LS) suffer from impairments of physical capacity. A group of scientists lead by Stenehjem et al. (Stenehjem et al., 2016) investigated cardiorespiratory fitness in follow-up of LS (n=194) treated with high-dose chemotherapy and autologous stem cell transplantation (HDT-ASCT). Compared to healthy sedentary subject, former cancer patients VO_{2peak} was on average 4,5% lower for women and 7,7% for men. Cardiopulmonary function was even more impaired in smoking patient or population of decreased diffusion capacity. Contrarily highly active LS could prevent adverse effects of HDT-ASCT and achieve VO_{2peak} of healthy sedentary control group. However, these findings were particularly impressive as average follow-up of this cohort was 10,2 (range 3-25) years after HDT-ASCT!

Beside long-lasting side-effects of antineoplastic agents in lymphoma survivor, thoracic radiation therapy (RT) may have adverse impact on these patients exercise tolerance as well. Survey of 263 HL survivors after RT (on average 19 years after radiation) assessed cardiorespiratory functioning by measuring resting heart rate and heart rate recovery under standardized exercise treadmill testing (Groarke et al., 2015). Compared with matched control group and by excluding any covariables LS demonstrated elevated resting heart rates and abnormal heart rate recovery. Suggesting an autonomic dysregulation caused by intense radiotherapy these effects amplifies with increasing dose of RT. Underlying mechanism may

lead back to a radiation-related injury of vagal nerve and carotid sinus. All named results increase with time interval from RT to exercise testing.

3.2.3 Multiple Myeloma

Comparing to several types of leukemia or lymphoma there have been even fewer studies on exercise in MM patients. Hitherto multiple myelomas symptoms such as risk of fractures or bone deformities, chronic pain and muscle weakness detain these patients from engaging in physical activity. For given reasons physicians not always advise their patients to move. Yet, there is evidence that tailored and individually prescribed exercise interventions in MM proved feasible and safe (Groeneveldt et al., 2013). Since remission rates and progression-free survival (PFS) increased (Kumar et al., 2008), additional non-drug therapy modalities are urged to optimized remaining quality of life and wellbeing. Adequate movement improves bone health and density as shown in osteoporotic women (Zehnacker & Bemis-Dougherty, 2007). Resistance training increases muscle strength and balance, preventing falls and consequently dreaded bone fractures (Hourigan et al., 2008). This is particularly important as the common MM patient in high age may not be suitable for moderate aerobic exercise (Groeneveldt et al., 2013).

Groeneveldt and colleagues (Groeneveldt et al., 2013) conducted a single arm pilot study including MM patients for a 6 month-long mixed exercise intervention. All eligible participants (n=45) undertook 3 weekly training. Within the first 3 months one session was a supervised group intervention, while the other two were performed in home setting, easing the transition between supervised inpatient intervention to non-supervised home-based exercise. Last ones were supported by regular phone calls by physiotherapist assessing logbooks and any health or exercise related issues. Interventions included stretching and mobility exercises, resistance training as well as 15 minutes of aerobic training for cardiovascular fitness. Endurance training initially started with an intensity of 50% of heart rate reserve (HRR) added Borg Scale (M. J. Chen, Fan, & Moe, 2002). Strength training focused on major muscle groups of both, upper and lower body parts. 3 sets of 10 to 15 repetitions were performed with body weight, weight-lifting equipment or elastic exercise bands. Howsoever, adherence rate reached 87% in the first 3 months and astonishing 100% attendance in the following 3 months. In conclusion, these interventions achieved to improve strength, QoL and fatigue in MM patients without any adverse events!

Effects on perceived side-effects seem to be interrelated, with cancer-related fatigue (CRF), pain, sleep, mood and functional performance impacting each other. High percentage of newly diagnosed patients are anemic, additionally contributing fatigue, decreasing quality of life. Furthermore, sleep disturbances are adversely affecting QoL including frequent awakenings at night and an increase of day sleep time of almost 20 % of total sleep capacity occurring during day. Inversely, expansion of sleep time positively influences functional performance (as indicated by extended distance traveled within 6MWT), mood, perceived pain, CRF and consequently QoL. Each of these interacting factors needs to be looked at closely (Coleman et al., 2011).

Particularly in regards to post-diagnostic decline of exercise participation qualitative studies assessed perceived barriers of MM patients in actively engaging in physical exercise (Craike, Hose, Courneya, Harrison, & Livingston, 2017; Craike, Hose, & Livingston, 2013). Comparing with pre-diagnostic levels all physical activity intensities (mild, moderate and strenuous) almost halved (n=89, 28,9% vs n=46, 20,1%; p<.001). Accordingly, only one out of five multiple myeloma patient meets physical activity guideline for health. Commonest difficulties were seen in battling with fatigue (37,8%), injuries (34,2%), pain (28,1%) and any other unfavorable health conditions (21,1%), followed by lack of knowledge about exercise being safe (19,7%) and lack of confidence (17,1%). Financial aspects, nausea or lack of company and time were described as secondary (Craike et al., 2013).

Gender differences regarding exercise preferences could be found. Generally speaking, female patients tend to a broader spectrum of physical activity like participating in yoga, pilates, gym work, aquatics, whereas most male report of preferring golf, gardening or biking. Almost all respondents considered exercise as beneficial, achieving faster recovery and better coping with physical and psychological symptoms (Craike et al., 2017).

These finding are consistent with results of Shallwani et al. (Shallwani, Dalzell, Sateren, & O'Brien, 2015) identifying walking as preferred exercise modality. In their retrospective study they emphasized on special precaution including positioning, external stabilization (e.g. wall support) or loading weight progressively during interventions. Usually reported barriers such as fatigue (n=7/12) or pain (n=6/12) were more frequent in non-compliant participants with history of pathological bone fractures, spinal cord compression or radiation. This group of patient may need greater supervision and specific exercise modalities (Shallwani et al., 2015).

However, 94 participants (41,1%) reported they were in favor of attending exercise program designed for MM patients, while 94 (41,1%) refused any engagement. Comparing with other cancer types MM patients' lower preferences is presumably due to higher median age at first diagnosis (70 years) and prolonged and high-dosed chemotherapy. Regarding demographic aspects the only significant factor influencing post-diagnostic exercise engagement was previous levels of physical activity. Therefore, patients who have not been physically active prior to diagnosis should receive additional attention. Moreover, providing crucial information about feasibility and beneficial exercises may tackle knowledge gaps, misinformation and discouragement (Craike et al., 2013).

As majority of MM patients suffer from several side effects of therapy as well as at disease itself, admission to inpatient floor of rehabilitation units in acute care hospitals may be necessary and perhaps the best. These include functional deficit after bone fracture, medical complexity urging for round-the-clock supervision, the ability of performing three hours of rehabilitation training daily, specific and precise discharge plans, social support as well as adequate length of stay. Often needed interdisciplinary support of experts is more likely to be available in inpatient settings (Cheng & O'Dell, 2011).

3.3 Use of supporting devices and applications

As displayed before, exercise does have a profound effect on prognosis and quality of life in cancer patients, demonstrating a cost-effective additional way of treatment. Tough conventional physical therapy in acute phase and rehabilitation for patients diagnosed with cancer is widely acknowledge, achieving adherence rates of 60-85% in sickened with solid tumors (Adamsen et al., 2009; Courneya et al., 2007, 2004), e.g. only 22,5-45,8% of AML patients participate in exercise program (Shabbir M.H. Alibhai et al., 2012; Klepin et al., 2011). Treatment of hematological malignancies often involve intensive high-dose chemotherapy, being accompanied with strong side effects. These may complicate traditional forms of training therapy and therefore require new feasible methods of interventions (Tsuda et al., 2016).

Considered one of the simplest electronic devices, easiest to handle and an effective method in encouraging patients exercise behavior without any physical contact is the pedometer. It has been used in children with ALL previously (Hooke, Gilchrist, Tanner, Hart, & Withycombe, 2016). Review of literature in children suggested 60 minutes of moderate to vigorous levels of physical activity (MVPA), corresponding to 11000-12000 daily steps in

school-age females and 13000-15000 steps per day in male. Adolescents need 11000 to 11700 daily steps to achieve 60 minutes of MVPA (Tudor-Locke et al., 2011). However, by utilizing these objects and using real time Internet tracking Hooke et al. (Hooke et al., 2016) proofed pedometer-assisted exercise intervention in childhood leukemia patients during maintenance therapy feasible. Moreover, daily counted steps in the study cohort did not only increase, but also approach recommended levels for healthy peers. Even tough recruitment rate was low, and participation being often refused by parents, adult cancer patients may show stronger willingness to actively engage in these forms of interventions. More importantly perceived level of fatigue decreased improving quality of life after all. Consequently, fitness tracker such as pedometer support patients with hematological malignancies during treatment.

Back in 2012, as number of randomized trials confirming associations between physical activity and malignant diseases was still small, Ligibel et al. (Ligibel et al., 2012) introduced the Active After Cancer Trial (AACT) to evaluate feasibility of telephone-based exercise interventions in randomized, 1:1 matched group settings. Patients diagnosed with invasive breast, colon and rectal cancer after completion of therapy (surgery, chemotherapy and/or radiation) were included. Over the period of 16 weeks 10-11 semi-structured phone calls, each lasting for 30-45min, were conducted to motivate participants to increase their physical activity level. In early intervention period these goals were focused on goal settings intending to build up self-efficacy and to optimize and encourage exercise behavior. Weekly leisure time of 180 minutes of moderate-intensity exercise was defined as target value. These phone calls included additional safety instructions and information about importance of physical movement. Furthermore, these calls guaranteed a regular check-up on weekly exercise time by providing tracking journals. There were no recommendations concerning form of sport as long as it involved moderate to intense level of activity. Each participant was equipped with a pedometer and advised to record the number of steps and active minutes. Hence exercise form and method were freely chosen by patient, measurement of physical functioning were considered secondary. 61 cancer patients were randomized into exercise group, with 41 participants completing 8 weeks of intervention. Tough physical activity increased by 54 min/week in the intervention group compared to 14 min per week in the control group these did not achieve statistical significance. However, self-reported physical functioning and distance on 6MWT increased significantly within the exercise

group, proving telephone-based exercise interventions feasible and providing improvement in fitness and physical functioning.

Vallerand et al. (Vallerand, Rhodes, Walker, & Courneya, 2018) recently used telephone counseling exercise (TCE) interventions in population of hematological cancer survivors (HCS). Due to findings suggesting low changes in much-needed exercise behavior through one-way communication e.g. automated messages or print media, bi-directional TCE is chosen more frequently (Bossen, Veenhof, Dekker, & De Bakker, 2014; Kuijpers, Groen, Aaronson, & Van Harten, 2013; O'Brien et al., 2015; Posadzki et al., 2016; Rose et al., 2017), providing more dynamic interaction (Eakin, Lawler, Vandelanotte, & Owen, 2007; Goode, Lawler, Brakenridge, Reeves, & Eakin, 2015; Goode, Reeves, & Eakin, 2012). Vallerand et al. (Vallerand et al., 2018) pointed out that interventions often miss intention-behavior gap (I-B gap) which reduce effectiveness of behavioral changes (Rhodes, Janssen, Bredin, Warburton, & Bauman, 2017). In contrast multi-process action control (M-PAC) framework targets this gap, initiating an ongoing motivational process, achieving higher adherence rates and consequently better study results (Rhodes, 2017). To compare TCE exercise intervention based on the M-PAC model with self-directed exercise (SDE) group Vallerand et al. (Vallerand et al., 2018) conducted a two-armed randomized controlled trial. Main goal of this survey was to proof feasibility and superiority of TCE by increased aerobic exercise adherence in HCS. Eligible participants were randomized in a 1:1 ratio to either TCE (n=26) or RDE-control group (n=25). Within the 12 weeks of exercise the intervention group received weekly phone calls addressing motivational processes, behavioral regulations, reflexive processing, brainstorming possible supporting locations or circumstances such as accompanying friends. With high compliance HCS in TCE-arm increased weekly aerobic exercise by 218 minutes compared to 93 minutes in SDE-arm. Although not being statistically significant secondary clinically meaningful differences regarding mental health QoL scores between the groups favored TCE group. However, telephone counseling exercise interventions based on a M-PAC model may provide a promising approach in patients with hematological malignancies.

Similar approach was launched by an Australian group of Russel et al. (Russell et al., 2019) to use mobile phone-based health (m-health) interventions in CML patients. Proper treatment of this subpopulation requires ensured, often life-long drug intake (Baccarani et al., 2009; Welch & Kaled, 2013). By tele-coaching in self-management of medications side-effects, self-care advises and regular telephone consultation it was tried to increase drug

adherence. Personal phone alerts asked for performed drug intake. Due to inadequate infrastructure, frequently missed eligibility criteria and inadequate number of participants with specific cancer type the trail was closed prematurely, pointing out difficulties in conducting supportive care trials.

Usefulness of virtual reality (VR) as an exercise support has already been demonstrated two decades ago (Broeren, Rydmark, & Sunnerhagen, 2004; You et al., 2005). Since then these modern techniques have become more economical, making them affordable for wide ranges of income groups (Kim, Son, Ko, & Yoon, 2013). Tough providing high potential and numerous possibilities in use scientific evidence in VR-supported training is rare, especially if it comes down to malignant diseases (Tsuda et al., 2016). Tsuda et al. (Tsuda et al., 2016) addressed this knowledge gap by implementing supervised VR exercise during chemotherapy in inpatients diagnosed with hematological malignancies such as NHL, HL or acute leukemia. The intervention in this single-armed study included exercises with the Wii Fit Balance Board (Nintendo, Kyoto, Japan) for approximately twenty minutes, five times a week. Hula Hoop (4 METs) and Basic Step (3 METs) were training modes freely selectable by the patients. 16 elderly patients were enrolled, achieving more than 66% adherence rate throughout their hospital admission. Therefore, use of virtual reality devices may represent a recent development of safe and fast recovery trough treatment and rehabilitation of patients with hematological malignancies (Tsuda et al., 2016).

Altitude-simulating devices may be considered as less practicable, but possibly used as an add-on for former professional athletes. Serpell et al. (Serpell et al., 2019) used this method combined with sport-specific conditioning program in a single-case study of a male rugby player after sibling allogeneic hematopoietic stem cell transplantation. These interventions were done approximately 16 months after achieving remission. Even if intermittent altitude exposure did not have any effect on performance it may seemed like it positively affected mobilization of available iron to incorporate into hemoglobin.

4 Discussion

The purpose of this systematic review was to explore and illustrate exercise interventions, as well as use of supporting electronic devices and applications in population of patients diagnosed with hematological malignancies. As displayed in the sections previously, exercise interventions in patients of different treatment phases with hematological malignancies is feasible, safe and beneficial. Considering the supportive use of electronic

devices, unfortunately data on implementing and maintaining exercise in these populations is limited. There are several reasons for this. First, there are some contraindications for physical activity in general, such as cytopenia (Elter et al., 2009). Yet, cytopenia is a complication often accompanying neoplasm of hematopoietic and lymphoid tissue, withholding patients from continuous movement therapy. Second, treatment of these disease requires intensive high-dose cytostatic regimens which adversely affect performance status. Thus, only a small percentage of patients undergoing chemotherapy meet level of recommended physical activity guidelines (Shabbir M.H. Alibhai et al., 2012; Schmitz et al., 2010).

Repeated clinical trials are crucial to enable evidence-based medicine and handle complex and prolonged diseases such as cancer in future. Despite increasingly fast developing, technology provides options for economical and fast supportive care programs specific training of conducting staff is hardly investigated. Still today some interventions fail due to poor documentation, cooperation and inexperience of medical staff or lack of proper information or communication (Russell et al., 2019). To target these frequent problems there were several suggested solutions: Using additional portable and versatile devices exclusively for scientific purposes may prevent shortage of crucial computers on training site. Specific enrollment and repeated training of clinical trial staff, collaborations with other supportive departments such as psychiatry or other hospitals could contribute necessary staff expertise. Overestimated prevalence and low participation rates call for expanding of patient eligibility criteria and adding multi-centered recruitment sites. As data collection on multiple separated online platforms complicates management combining these into a single software application may simplify handling (Russell et al., 2019). However, each respective intervention urges for tailored and individually adapted solutions to implement exercise training.

Results showed that physical activity declines from prediagnostic levels to levels during and after treatment of MM. Since movement before diagnosis is often associated with higher adherence rates and exercise levels, intervention prior to diseases onset possesses therapeutic, as well as preventive potential. Common barriers like fatigue or pain must be focused on to prevent early dropouts. Therefore, patients experiencing CRF and pain, who have not been physically active before should receive particular attention. Provision of knowledge about safety and information about reduction of fatigue trough exercise, not its increase, is crucial (Craike et al., 2013). Unfortunately, few physicians actively advise

patients to exercise (Groeneveldt et al., 2013). To do so, electronic information systems are economical ways to reach out to vast amounts of sickened. Furthermore, incentives such as encouraging text-messages or follow-up telephone calls from training therapists may be beneficial, as demonstrated in childhood ALL patients previously (Hooke et al., 2016). Particular courses for cancer-specialized health care staff like nurses should be considered as well to improve patients quality of life (Gheyasi et al., 2019).

Some electronic may be used to indirectly target or measure exercise interventions in cancer patients. As physical strain and sleeping behavior interact, devices to track sleep pattern may provide important information for successful interventions (Groeneveldt et al., 2013). Even after diagnosis preventive actions shall be taken to improve patient's quality of life and physical functioning. Applications of any kind to help cessation of smoking and encourage patients to stay smoke-free may be beneficial, as tobacco extensively impairs diffusion capacity and decreases VO_{2peak} levels in lymphoma survivors after stem cell transplantation (Stenehjem et al., 2016). Similarly, interacting and often underestimated mental issues like depression should be taken seriously and requires professional treatment (Courneya et al., 2010).

6-minute walk test is commonly used to efficiently measure someone's functional endurance (Alibhai et al., 2015; Bryant et al., 2018; Schuler et al., 2016). Devices or applications using exact GPS tracking may allow patient to check their progress by themselves more regularly (Bryant et al., 2017). Generally, regular self-checkups on exercise processes, whether regarding advances in physical functioning like strength or endurance, or mental changes measure by standardized questionnaires potentially encourage patients in exercise. Electronic logbooks or routine telephone calls by trained therapists should be considered (Ligibel et al., 2012; Vallerand et al., 2018).

In MM patients there are some gender specific differences regarding movement preferences. While moderate intensity exercise like walking or gardening are popular in both sex, women tend to gym works, pilates or aquatics (Craike et al., 2013). Consequently, female patients may be more suitable for video-based, distance exercise sessions to engage in home-based training since virtual reality exercise has already been proved feasible and increasingly cheaper (Tsuda et al., 2016). Considering common high age of patients with hematological malignancies handling of each supporting device needs to be as simple as possible.

However, after shattering diagnosis and burdensome treatment, patients frequently seek for consistent interaction, whether it is with, family members, exercise trainers or trainings partners who experience similar situation (Bryant et al., 2018). Ripped off from their familiar daily life, facing live-threatening disease, suffering from sickness and side-effects they strive for regaining control of a structured daily routine (Suchita Hathiramani et al., 2019). Despite future options for use of modern electronic devices and application in exercising patients with hematological malignancies is vast, they may not fully replace humans. With cancer diseases being as individual as affected patients, so is their needed exercise program.

5 Implication for further research

To our knowledge this systematical review is the first of its kind addressing modern electronic support devices and application to assist adult patients with neoplasm of hematopoietic and lymphoid tissue in taking up exercise and maintaining physical activity through every stage of treatment. To date there is strong evidence of feasibility and beneficial value of exercise in prevention, therapy and rehabilitation of cancer diseases, though most study understandably focusing on more common entities. To assess feasibility of device-assisted exercise intervention in larger population, additional prospective trials on specific malignancy, treatment phase and intervention method is warranted.

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Tab. 2: Selected studies. AACT .. Active After Cancer Trial, ALL .. acute lymphoid leukemia, AML .. acute myeloid leukemia, BC .. breast cancer, CALGB .. Cancer and Leukemia Group B, CC .. colon cancer, CML .. chronic myeloid leukemia, EQUAL .. Exercise and Quality of Life in Leukemia Adults, HDT-ASCT .. high-dose therapy and autologous stem cell transplantation, HELP .. Healthy Exercise for Lymphoma Patients, HL .. Hodgkins lymphoma, LK .. leukemia, LN .. lymphatic neoplasm, L> .. lymphoma, MM .. multiple myeloma, NHL .. non-Hodgkins lymphoma, nn .. not named, PNS .. peripheral nervous system, REIL .. Relaxation and Exercise In Lymphoma, RCT .. randomized, controlled trial.

Abbreviations and glossary

6MWT .. 6 minutes walking test

AACT .. Active After Cancer Trial

ABL1 .. Abelton tyrosine-protein kinase (formerly ABL)

ALL .. acute lymphatic leukemia

AlloSCT .. allogenic stem cell transplantation

AML .. acute myeloid leukemia

BCR .. break-point-cluster region gene

BFI .. Brief Fatigue Inventory

CD .. cluster of differentiation, cell surface molecule

CLL .. chronic lymphatic leukemia

CML .. chronic myeloid leukemia

CHT .. chemotherapy

CRAB .. diagnostic criteria of MM

CRAB SLiM .. advanced diagnostic criteria of MM

CRF .. cancer-related fatigue

CT .. computer tomography

DC .. dentritic cells

DLBCL .. diffuse large B cell lymphoma

EBV .. Epstein-Barr virus

ECOG .. eastern cooperative oncology group, performance score

ESR .. erythrocyte sedimentation rate

FDG-PET .. fluorodeoxyglucose-18 positron emission tomography

HCS .. heamatological cancer survivors

HCV .. hepatitis-C virus

HHV8 .. human herpes virus 8

HIV .. human immunodeficiency virus

HL .. Hodgkin lymphoma

HRR .. heart rate reserve

H-RS .. Hodgkins-Reed-Sternberg cells

I-B gap .. intention-behavior gap

IC .. induction chemotherapy

IGF .. isulin-like growth factor

IL .. interleukin

IPI .. International Prognostic Index

LDH .. lactic dehydrogenase

MDS .. myelodysplastic syndrome

MET .. metabolic equivalents of task

MGUS .. monoclonal gammopathy of undetermined significance

MM .. multiple myeloma

M-PAC .. multi-process action control

MRI .. magnetic resonance imaging

MVPA .. moderate to vigorous levels of physical activity

NHL .. non-Hodgkin lymphoma

NK cells .. natural killer cells

PCR .. polymerase chain reaction

PET .. positron emission tomography, also PET scan

PET/CT .. diagnostic method by combining PET and CT

PFS .. progression free survival

Ph+ .. Philadelphia chromosome positive (fusion of ABL1 and BCR)

PN .. peripheral neuropathy

PROMIS .. Patient-Reported Outcomes Measurement Information Systems

PSA .. prostate specific antigen

QoL .. quality of live

R-CHOP .. chemo regime, involving rituximab, cyclophosphamide, hydroxydaunorubicine (=doxorubicin), oncovine (=vincristine), prednisone

RCT .. randomized controlled trial

R-EPOCH .. chemo regime, involving rituximab, etoposide, hydroxydaunorubicine (=doxorubicin), cyclophosphamide, oncovine (=vincristine), prednisone

RT .. radiotherapy

t(9;22) .. reciprocal translocation of genetic material between chromosome 9 and chromosome 22, leading to BCR-ABL1 fusion gene

TCE .. telephone counseling exercise

TNF-α .. tumor necrosis factor α

TSH .. thyroid stimulating hormone

TUG .. Timed Up and Go

VR .. virtual reality

WHO .. World Health Organization

“I declare that this thesis has been composed solely by myself and that it has not been submitted, in whole or in part, in any previous application for a degree. Except where states otherwise by reference or acknowledgment, the work presented is entirely my own.”

Vienna, on 3rd of August 2020 Kleinberger Markus