Assessing Fatigue in Adult Blood Cancer Patients: A 24-Hour Repeated Cardiopulmonary Exercise Test in New Zealand (A pilot study)

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Abstract

Purpose: Cancer-related fatigue is a persistent issue in long-term survival for cancer patients in remission. This study assessed the effects of cancer-related fatigue/post-exertional malaise in adult blood cancer patients aged 20-35 years of age. **Methods:** Five adult blood cancer (ABC) patients in remission and five healthy controls (HC) were recruited. Each participant completed a maximal incremental cycle exercise test on day one and again 24 hr later. Heart rate (HR), blood pressure (BP), rating of perceived exertion (RPE), oxygen consumption (VO 2), carbon dioxide production (VCO 2) and workload (WL) were recorded during the 24-hour repeated CPET. Data analysis investigated these responses at anaerobic threshold (AT) and peak work rate (PWR). **Results:** On day one, VO 2 at PWR were similar between both groups (ABC 38.62 +/- 16.21 ml.kg.min -1, HC 38.91 +/- 14.14 ml.kg.min -1), despite a difference in WL (ABC: 186 +/- 44.49 Watts; HC: 222 +/- 35.81 Watts). On day two, ABC saw a decrease in WL (165 +/- 45 Watts) alongside VO 2 (35.34 +/- 16.67 ml.kg.min-1) at PWR, despite no change in WL (D2: 222 +/- 38.83 Watts) and a slight increase in peak VO 2 for HC (40.19 +/- 14.61 ml.kg.min-1) at PWR. Across the two-day comparison, there was a significant decrease in VCO 2 (P=0.32), Time to completion of the test (P=0.17), WL (P=0.05), and HR (P=0.02) at PWR in ABL compared to no significant changes in HC. No significant changes were seen at AT in either group. On the second day, ABC could only increase HR to 87% +/- 6.84% of Max HR, compared to achieving 95.09% +/- 4.69% of Max HR on day one. **Conclusion:** These results highlight significant cancer-related fatigue/post-exertional malaise in adult blood cancer patients in remission. This fatigue will affect participants' emotional, social, and physical well-being and reduce their ability to lead everyday lives. This study forms an important stepping stone for how fatigue is assessed and exercise prescribed in cancer survivors.

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Abbreviations

A

ADL - Activities of Daily Living

ALL - Acute Lymphoblastic Leukaemia

AML - Acute Myeloid Leukaemia

APMHR - Age Predicted Max Heart Rate

AT - Anaerobic Threshold

AYA - Adolescents and Young Adults

B

BC- Blood Cancers

C

CLL - Chronic Lymphocytic Leukaemia

CPET - Cardiopulmonary Exercise Test

CRF - Cancer-Related Fatigue

F

FAS- Fatigue Assessment Scale

H

HC - Healthy Control

HL - Hodgkin Lymphoma

HR - Heart Rate

M

ME/CFS - Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

MM - Multiple Myeloma

N

N/A - Not Applicable

NHL - Non-Hodgkin Lymphoma

NZREPs- New Zealand Register of Exercise Professionals

O

O_2 Sat - Oxygen Saturation

P

PEM - Post Exertional Malaise

R

RPE – Rating of Perceived Exertion

S

SD - Standard Deviation

SF-36 - Short Form 36 Questionnaire

Q

QOL - Quality of Life

V

VCO_2 - Carbon Dioxide production

VE - Pulmonary Ventilation

VO_2 Peak - Maximal oxygen consumption

W

WL – Workload

WR – Work Rate

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1. Introduction

Cancer is becoming increasingly widespread across all ages and genders within our communities, families and friends. The World Health Organisation reports that cancer is now the leading cause of death worldwide, accounting for nearly one in six deaths. In New Zealand, approximately 25,000 people are diagnosed with cancer annually (Cancer Society of New Zealand, 2023). That is 71 people every single day, and it is now the leading cause of death in New Zealand (Te Whatu Ora – Health New Zealand, n.d.). The continuous increase of cancer worldwide and in New Zealand is leading to an overburdened healthcare systems, increased healthcare costs, family strain and an increased dependency on social welfare and support programmes on top of the deaths and the significant struggle patients face. In addition to this, more and more people are being diagnosed with blood cancer (BC), which is the most complex cancer to treat and cure, requiring varied intensive treatment modalities and intensive regimes, most being incurable with unpredictable leading to more frequent relapses and are challenging diagnosis, leading to a poor prognosis (Howell et al., 2022).

Blood Cancer originates and metastasises in the bone marrow, soft tissues, and lymph nodes. BC typically transpires when cells produced in the bone marrow develop or in cells of the immune system and replicate uncontrolled and abnormally. (Cancer Council, 2017; National Cancer Institute, n.d.)

Every three minutes, a patient in the USA is diagnosed with blood cancer (leukaemia, lymphoma, or multiple myeloma) (American Cancer Society, 2023; Yabroff et al., 2021). As of 2023, leukaemia is the fifth most common cancer diagnosed in New Zealand and is the leading cancer among children. In adolescents aged 15 to 24, lymphoma represents many cancer diagnoses (Te Whatu Ora, n.d.; National Child Cancer Network, 2022). These statistics underscore the increasing incidence and prevalence of blood cancers worldwide.

Furthermore, Figure 1.1 by Zhang et al., 2023, provides further evidence of the rising global incidence and deaths from haematological malignancies, which have increased significantly over the past 30 years despite the advancements in treatment, technology, awareness and screening.

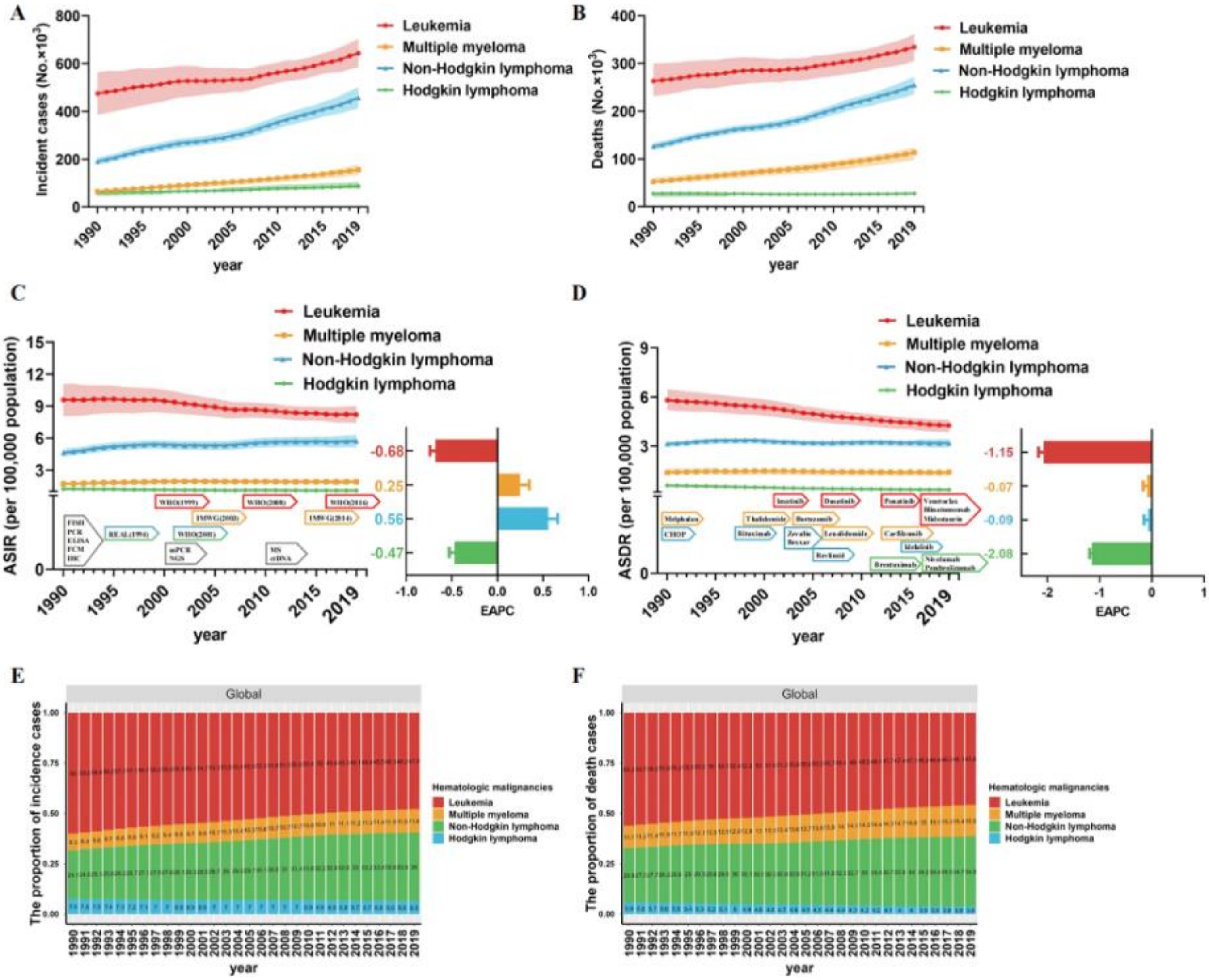


Figure 1.1 Global Incidence and Deaths of Leukaemia, MM and NHL

Figures 1.2, 1.3 and 1.4 from Zhang et al.'s 2023 study on the global burden of haematological malignancies demonstrate that MM, non-Hodgkin Lymphoma, and Leukaemia have the highest incidence and mortality rates in Australia, New Zealand, North America, and some parts of Europe compared to the rest of the world.

The global trends of leukemia by countries and territories.

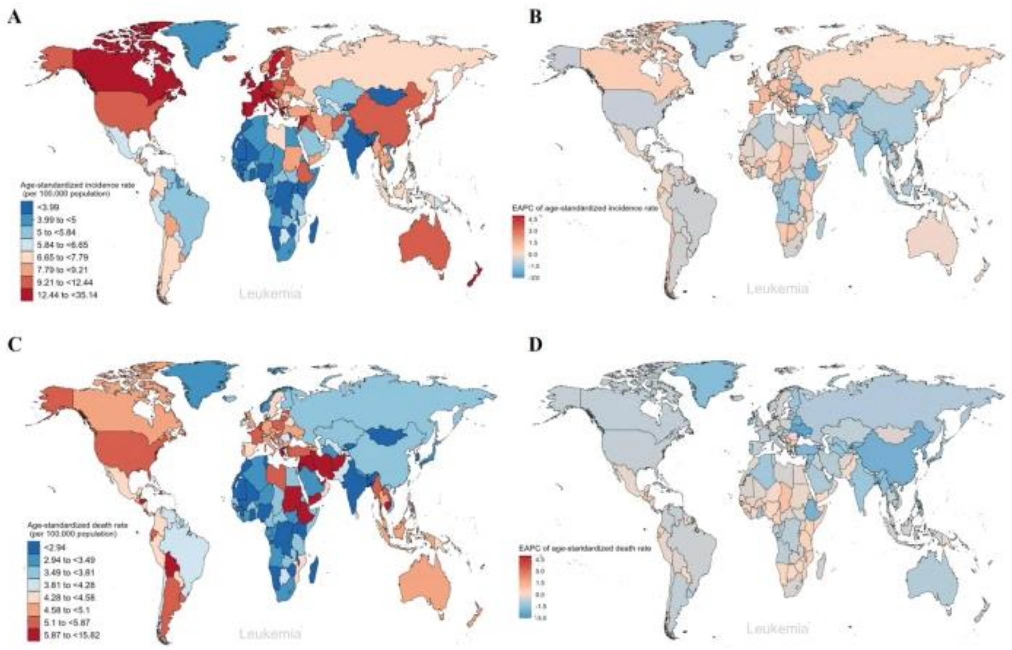


Figure 1.2 The Global Trends of Leukaemia by Countries and Territories

The global trends of multiple myeloma by countries and territories.

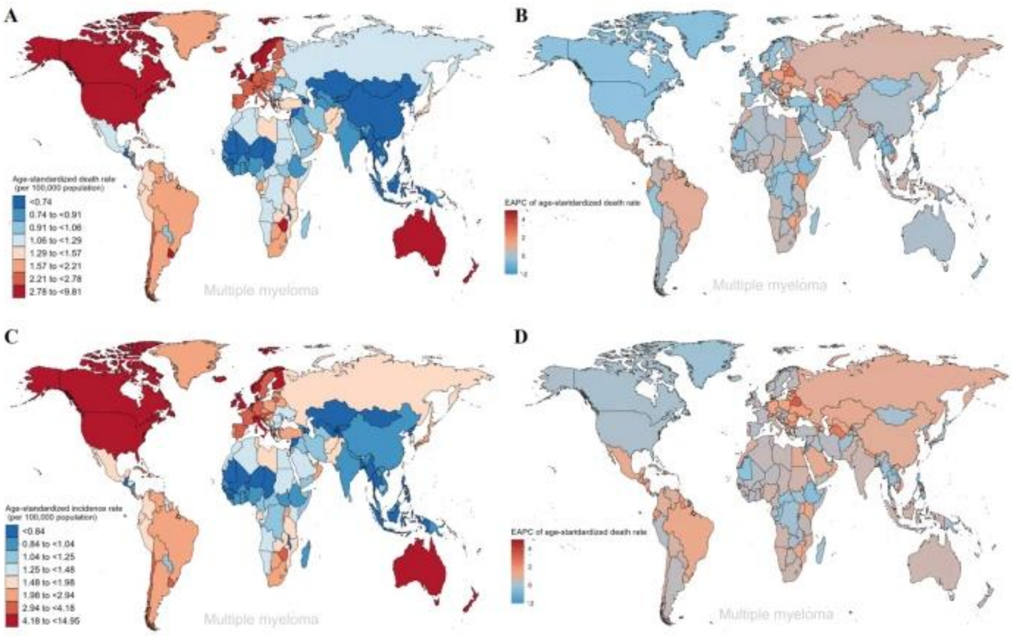


Figure 1.3 The Global Trends of MM by Countries and Territories

The global trends of Non-Hodgkin lymphoma by countries and territories.

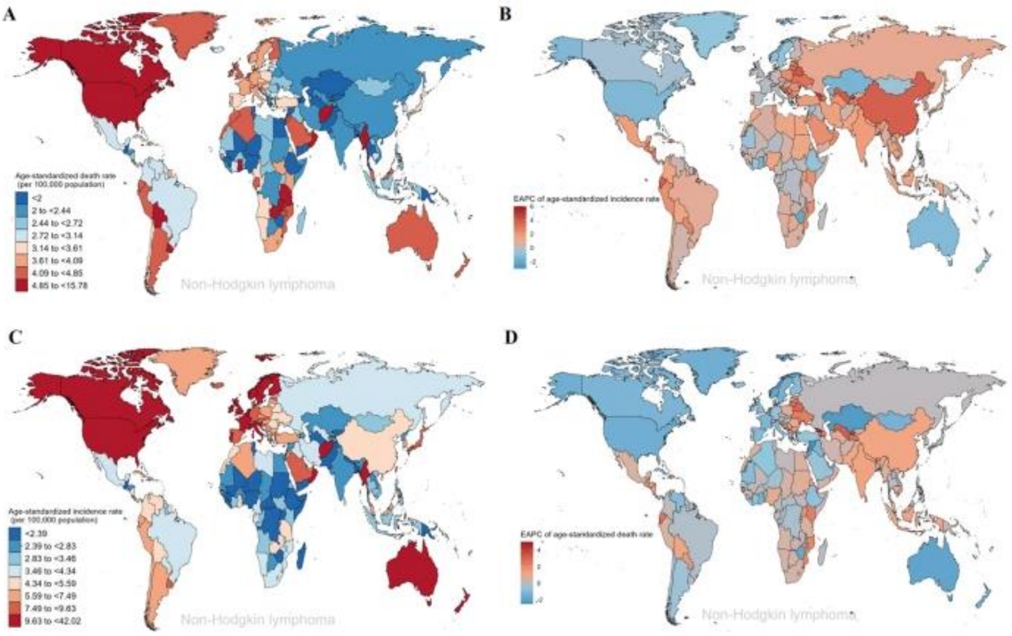


Figure 1.4 The Global Trends of NHL by Countries and Territories

Standard procedures for treating haematological malignancies (blood cancers) now include immunotherapy, immune checkpoint inhibitors and autologous or allogeneic bone marrow transplantation (Battaglini et al., 2010). This new and innovative treatment has improved overall survival and remission rates, with an estimated 85% of childhood cancer patients now living for five years or more after their diagnosis when it was typically months or weeks (Robison & Hudson, 2014). Unfortunately, the adverse side effects and reductions in QOL patients' experience from this new treatment may be worse now than in any other generations that have received cancer treatment (Mols et al., 2006; Eikeland et al., 2023). These adverse side effects from treatment Hogarty et al., 1998 Dennett et al., 2016 and Miladinia et al., 2017 uncover that childhood/AYA cancer survivors often experience significant detrimental and debilitating side effects from cancer and its necessary treatment (typically due to the abnormal and impaired functioning of organ and energy systems) late into their lives despite reaching and remaining in remission for many years (Liu et al., 2009). These side effects can be severe and include chronic health conditions (heart/vascular problems, hypothyroidism, a heightened risk of strokes, infertility, gastrointestinal issues, lung disease, memory issues and other related conditions), relapse of primary and secondary malignancies, increased hospitalisations, frailty and cancer (Tsuda et al., 2023 & Phillips et al., 2015).

Further consequences of cancer and its treatment, which are typically more common, include reduced cardiac output, thrombocytopenia, neuropathy, anaemia, diminished immunity and skeletal muscle mass, reduced cardiorespiratory fitness and muscle strength, and chronic fatigue/post-exertional malaise, which is deemed cancer-related fatigue (CRF) in this population (Allart-Vorelli et al., 2015; Tofthagen, 2010; Mavrogenis et al., 2010).

CRF's exact root cause and pathophysiology can be attributed to various metabolic abnormalities and mechanisms affecting the skeletal muscles, gastrointestinal, immune, energy, neuroendocrine, and central nervous systems. Cancer and its treatments damage the central nervous system, disrupt muscle energy metabolism, and cause sleep disturbances and state maintenance (ability to maintain both the sleep and waking states), leading to physical fatigue, mood changes, cognitive impairment, loss of autonomy and insomnia (Gutstein, 2001 & Parker et al. 2008) which all worsen CRF/PEM symptoms.

The physical deterioration of cancer patients receiving treatment is well known (Gulbrandsen et al., 2004; Holzner et al., 2004 & Smith et al., 2009), though fatigue and a lack of vitality tend to be the most dominant symptoms experienced by haematological patients with little action taken (Courneya et al., 2009; Else et al., 2008 & Sherman et al., 2003). The omnipresence of CRF in cancer patients who have reached remission varies in contemporary research (likely due to the different types of cancer and chemotherapy, treatment modalities, lifestyle changes, and diet patients maintain). Still, the consensus appears that between 70% and 90% of patients who receive chemotherapy alone or with radiotherapy will experience CRF (Hofman et al., 2007; Smets et al., 1993; Roila et al., 2019; Henry et al., 2008; and the National Comprehensive Cancer Network NCCN, 2015). These numbers are like those reported by caregivers of cancer patients, who reported CRF/PEM in 86% of the patients (Vogelzang et al., 1997).

Remarkably, a study conducted via surveys by Curt et al. (2000) discovered that out of the 379 patients who underwent chemotherapy alone or alongside radiotherapy, 91% reported that it impacted their ability to live normally, while 88% felt that their fatigue had altered their daily routine. However, despite these findings, there is a notable lack of research exploring the long-term prevalence and consequences of CRF/PEM in patients who have achieved remission. Hofman et al. (2007) also highlighted the significant and widespread effect CRF/PEM has on a patient's physical functioning and their ability to perform daily activities (ADL). Studies focusing exclusively on AYA BC survivors (the demographic targeted in this study) conducted by Bohn et al. (2019), Curt et al. (2000), Smeland et al. (2019), and Leblanc et al. (2022) have found that 25-30% of these patients experience CRF/PEM even 5-15 years post-treatment. Bøhn et al. (2019) even reported that clinically significant and impactful fatigue from treatment and the disease can persist for 5-30 years following diagnosis, with 34.4% of patients indicating that their fatigue had worsened over time. Flechtner et al. (1998) also discovered in BC patients that despite having completed treatment seven years prior, BC survivors remained in the midrange of physical and cognitive functioning but never fully returned to their pre-treatment energy levels. Variability in symptoms, duration, and experiences of PEM complicates the predictability and management of this condition.

The symptoms of CRF/PEM can vary from patient to patient but is often described as a whole-body and mind hardship that is usually vastly disproportionate to the catalyst with symptoms brought on by physical, cognitive, or emotional exertion (Mohandas et al., 2017; Feng et al., 2019; Hofman et al., 2007; Yoshiuchi et al., 2007; Chu et al., 2018). The main symptoms of CRF/PEM have a delayed onset following the original exertion and are often more harmful 24-48 hours after the initial event (Morrow et al. 2002 and Chiang et al. 2009). The effects participants suffering from CRF/PEM experience include a distressing sense of weariness, slurred speech, brain fog, getting easily lost or confused, flu-like feelings, joint pain, headache, sore throat and/or tender lymph nodes, and impaired memory and cognitive functions. These side effects can lead to a lack of concentration, ability to learn, decision-making skills, exhaustion, muscular weakness, orthostatic intolerance, and the inability to recover as expected from physical, mental, and emotional exertions (Deumer et al., 2021; Bazelmans et al., 2005; National Comprehensive Cancer Network 2015). These symptoms are typically not relieved by rest or sleep, with many symptoms lasting between two and seven days (Chu, Valencia, Garvert, & Montoya, 2018), leading to a reduced ability to perform ADL (basic activities such as getting dressed, preparing food, cleaning the house, light lifting >5kg and social interactions). Only one study was found in the literature review that contrasts these findings in which haematological patients were able to manage ADL without support after relevant treatment (Heinonen et al., 2001). This research used self-reported questionnaires, which have notable limitations.

The effects of CRF/PEM can even hamper the patient's desire to continue treatment, compliance, and worsening treatment outcomes (Winningham et al., 1994; Atabayeva et al., 2023). The severity of CRF/PEM varies from patient to patient and, as highlighted above, can be an insidious and incapacitating chronic disease with little treatment, awareness or help available. CRF/PEM presents additional long-term health complications if left unchecked, such as muscular atrophy, impaired physical capacity, reduced motivation to exercise, and a decreased cardiac output, as Patenaude & Kupst (2005) found in their study on childhood leukaemia survivors.

Victorson et al. (2024), Dadhania et al. (2023), Adams-Campbell et al. (2023), and Jereczek-Fossa et al. (2002) have all identified fatigue as the most significant factor limiting the QOL in cancer patients. The cancer patients rated CRF/PEM as more detrimental than all of the other commonly acknowledged treatment and disease side effects, such as pain, sexual dysfunction, and gastrointestinal issues. Research has also shown that CRF/PEM negatively impacts all domains of QOL (physical health, psychological health, social relationships, and environmental health), emphasising the severe impact CRF/PEM has on cancer patients' overall well-being years after treatment. (Bower, 2014; Muthanna et al., 2023; Hofman et al., 2007; Thong et al., 2020)

In contrast, one study investigated the QOL of 1482 patients with Chronic Lymphoblastic Leukaemia (CLL), and its results showed a similar or better level of QOL in the physical, social, family, and functional assessments to those of the comparison healthy population (Shanafelt et al., 2007). However, their study showed a marked decrease in the emotional well-being of CLL patients and concluded that CLL has a profound impact on the QOL of patients at all disease stages. Merli et al. (2004) found an improvement in the pain, appetite, sleep, and overall QOL of NHL patients after treatment. However, their results did not compare the cancer subjects' scores to the general population to gauge whether the QOL returned to normal or standardised levels post-treatment.

In addition to the apparent physiological and psychological effects of CRF/PEM, patients must also have a reduced employment rate and ability to work and hold down full-time employment (Duijits et al., 2014; Ekenga et al., 2018), leading to significant financial stress for themselves and their families. The financial strain can lead to additional stress on the broader support network of cancer patients as family members may have to take time off work or work extra hours to support these patients during treatment, with many cancer survivors never able to return to full-time work or self-fulfilling careers (Behringer et al., 2016 Eikeland et al., 2023 & Hofman et al., 2007)

The severe side effects and long-term sequelae of cancer treatment and fatigue should be of significant concern for patients and clinicians, as despite the advances in efficacy and treatment outcomes from modern medicine, current pharmaceutical approaches to circumvent the adverse effects of chemotherapy on patients' QOL are often wholly ineffective (Nurgali et al., 2018).

Doctors and healthcare providers/supporters should be highly concerned about the lack of current approaches to managing the adverse effects of fatigue, significant decreases in body mass and lack of physical activity in cancer survivors (Jang et al., 2020) as Miyamoto et al. (2015) and Nichols et al. (2019) demonstrate a muscle mass loss greater than 5% of participants' weight and a reduced aerobic capacity are associated with a twofold increase in cancer mortality rate. Additionally, Luthy et al. (2011) highlight how the patient's preference for rest rather than activity may be related to their high level of fatigue, leading them to disregard or not start physical exercise, worsening their health outcomes. Various chemotherapies (doxorubicin, cisplatin, and many others), mediastinal radiation and a lack of physical activity are the major factors affecting participant survival rates and cardiopulmonary health (Elbl et al., 2006; Stenehjem et al., 2016; Herradon et al., 2017). Impaired VO_2 peak (the peak oxygen consumption during exercise testing) was observed in 22% of haematological malignancy survivors and was associated with an increased risk of cardiovascular events (Rizwan et al., 2021; Stenehjem et al., 2016). Rizwan et al. (2021) also demonstrated that peak oxygen consumption (VO_2 peak) declines over time in patients in remission, with a 7.5% point decrease every ten years after radiation therapy, significantly limiting their exercise and work capacity.

A call to action to quantify and demonstrate the effects of CRF/PEM is desperately needed, as Vogelzang et al. (1997) and Passik et al. (2002) found that 27 - 40% of cancer patients experiencing CRF/PEM raise it with their physician and believe it to be an unavoidable and irremediable side effect and fear that reporting it may incite a change towards less aggressive cancer treatment and in turn less successful treatment outcomes. Of these cases where CRF/PEM was discussed between patients and their doctor, no intervention for fatigue was proposed, despite CRF/PEM being the most frequently reported side effect of treatment and its significant harmful impact on patient QOL (Morrow et al., 2002 and Vogelzang et al., 1997). Similar findings were found in research by Stone et al. (2000), which found that only 14% of the 576 patients received treatment or help to manage their CRF/PEM when discussed with their healthcare providers despite patients reporting CRF/PEM to be the most harmful side effect from treatment.

Mohandas et al. (2017) and Luthy et al. 2011 found that general practitioners and specialist doctors often omit CRF/PEM and overlook its significance on patients' QOL in remission. Some oncologists (61% v 37%) from the study by Vogelzang et al. (1997) believed pain adversely affected their patients more than fatigue. In near complete contrast, the patients of the same study were interviewed and reported that fatigue adversely affected their daily lives more than pain (61% vs 19%). In disparity, further on in the study, it was found that the majority of oncologists (80%) believed fatigue was overlooked and undertreated in cancer survivors, underscoring the necessity of this research.

Campos et al. (2011) and Mock et al. (2000) further stress that CRF/PEM remains underreported and untreated, worsening patient outcomes and QOL. These studies demonstrate the urgent need for research targeting CRF/PEM in patients who have reached remission to help improve their QOL and capacity for ADL and justify various non-pharmaceutical interventions. Given the growing recognition of CRF/PEM as a critical point lacking in cancer survivorship and patient QOL, this research is timely and necessary. This project will add to the relatively few research projects worldwide and be the first in New Zealand to investigate the physiological effects and prevalence of CRF/PEM in adult BC patients in remission.

The thesis begins with an overview of the current state of knowledge, including a literature review on exercise testing in cancer patients (Chapter 2). It discusses the prevalence of Cancer-Related Fatigue (CRF) and Post Exertional-Malaise (PEM) and its impacts on patients' lives. Chapter 3 outlines the project's hypothesis and objectives, followed by the methodology in Chapter 4. The results are presented in Chapter 5, followed by the discussion in Chapter 6, where future research recommendations are provided. Finally, Chapter 7 summarises the significant findings of the thesis.

2. Literature review

2.1 Literature Review Methodology

A literature review was conducted prior to the start of research and recruitment to examine the current state of knowledge on fatigue in blood cancer patients. This review aimed to identify critical practices and results to record from previous studies with similar methods (SF-36, FAS, CPET, and 24-hour repeated CPET) with the same population (blood cancer patients in remission aged 20-35 years old). This would ensure that we could adapt our research to fill a necessary gap in understanding and enhance the design and rigour of this research project.

Research published before the year 2000 was excluded from the literature review to ensure that only recent research incorporating modern cancer treatments with similar testing methodologies was included. Studies on non-haematological malignancies, non-blood cancer patients or those that did not explicitly state cancer subtypes were excluded as these were not relevant to the targeted demographic for this study. Non-English publications were also disregarded due to language barriers. Studies included in the literature review using the CPET procedure had to use an exercise protocol similar to the RAMP methodology employed in this research. This criterion ensured that findings would be compatible with our study, allowing for meaningful comparisons and potential data integration.

2.2 Search Strategy and Study Identification

From this, the following search strategy was developed: ("Blood cancer" OR Lymphoma OR Leukaemia OR Myeloma) AND (Fatigue OR "Chronic fatigue") AND ("Cardiopulmonary Exercise Testing" OR CPET) AND (Adults OR Patients) was input into peer-reviewed health databases, including Google Scholar, PubMed/Medline, Massey's Discover, CINAHL, PsycINFO, and the Cochrane Library.

A broad range of study designs were reviewed, including experimental, quasi-experimental, analytical, descriptive observational studies, qualitative research, and systematic reviews. This inclusive approach ensures that all relevant perspectives and methodologies are considered, providing a comprehensive overview of the topic and state of knowledge.

Extra consideration and exclusion criteria had to be applied to the Google Scholar results because of the large number of articles retrieved (1,380). The substantial number of articles retrieved from Google Scholar is due to many being irrelevant to this literature review, such as grey literature (e.g., dissertations and reports), which do not meet the inclusion criteria for a scholarly literature review. The search was stopped when the results became less relevant to this research project/literature review (this was noted after 60 articles). The Massey Discover database included articles from various databases, which explains the high number of duplicates in the literature review.

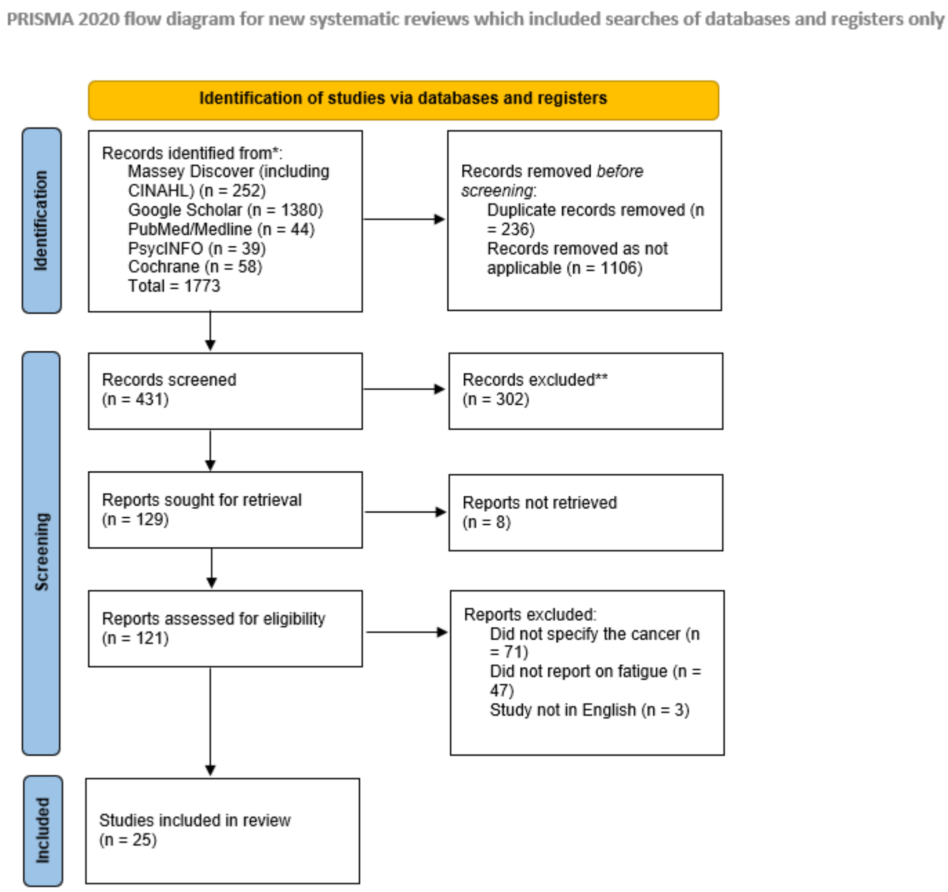


Figure 2.1 PRISMA Flow Diagram

Table retrieved from PRISMA. (2020). PRISMA 2020 flow diagram. PRISMA Statement. https://www.prisma-statement.org/prisma-2020-flow-diagram

The identified studies were systematically collected and organised using Zotero (version 6.0.23) to remove duplicates. Subsequently, titles, abstracts, populations, and methods were compared to the inclusion criteria; those that met the requirements were then fully retrieved and transferred into the JBI System for the Unified Management, Assessment, and Review of Information table (JBI SUMARI) (Zachary et al., 2019) attached in the appendices. This systematic approach extracted relevant and essential information such as implications, methods, and findings pertinent to this research hypothesis in an accessible format.

2.3 Overview of the Literature

Twenty-five studies were identified, and relevant data were extracted using the JBI Data Extraction Table (see Appendix A). A substantial number of studies were excluded because they did not provide detailed information regarding the specific cancer diagnoses and treatments received by the participants. Although the inclusion criteria stipulated that studies must have been published after the year 2000, most of the included studies were published after 2019. As detailed below, a significant gap in the literature was found, underscoring the limited research on this topic. Furthermore, existing studies consistently emphasised the need to raise awareness and provide enhanced support for individuals experiencing CRF/PEM, alongside advocating for further investigation in this domain.

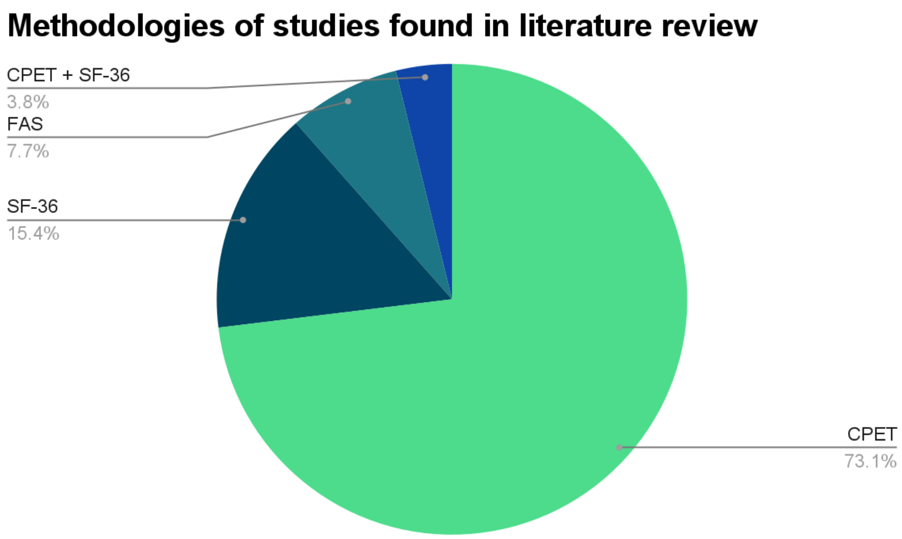


Figure 2.2 Methodologies of Studies Included in the Literature Review

Of the 20 studies that used CPET testing, two used the treadmill rather than the exercycle. This slight change in methodology is relevant to note as the peak VO_2 is typically higher on the treadmill tests than on the exercycle (Albouaini et al., 2007).

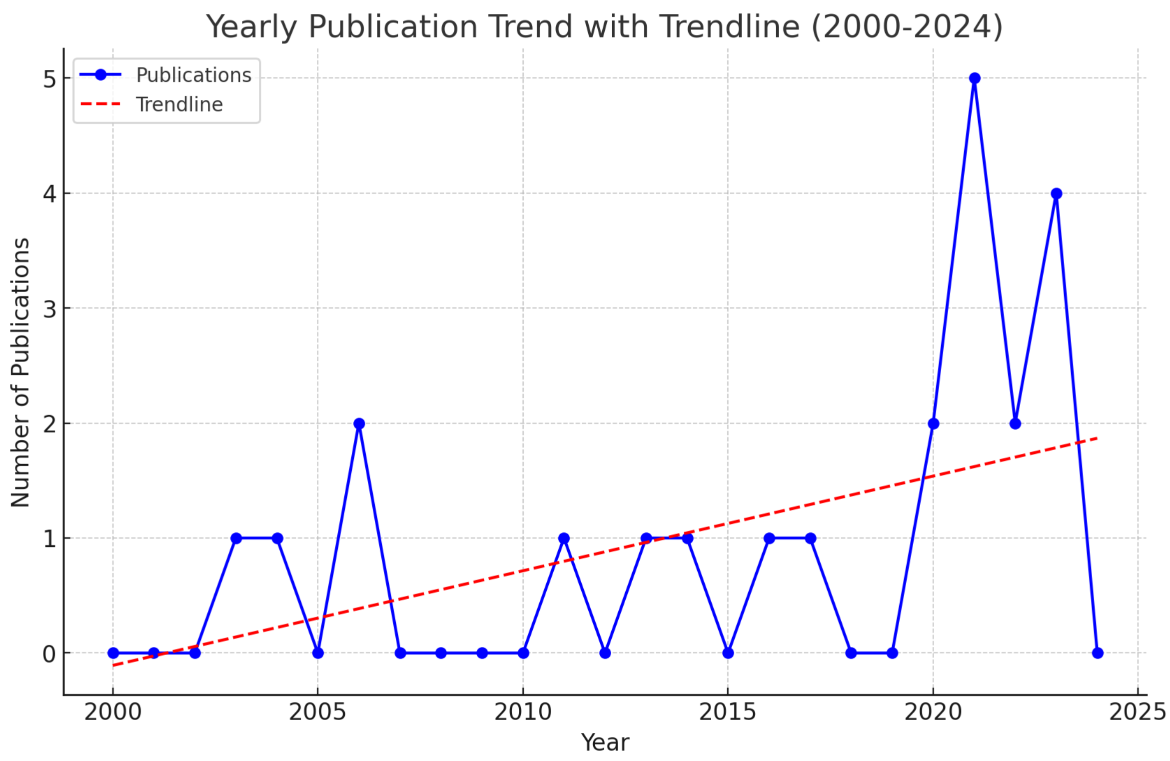


Figure 2.3 Yearly Publication Trendline of Studies Retrieved in the Literature Review

Research on the effects of CRF/PEM is a growing area of contemporary study. The yearly publication trendline graph above (Figure 2.3) indicates an increasing amount of literature published yearly.

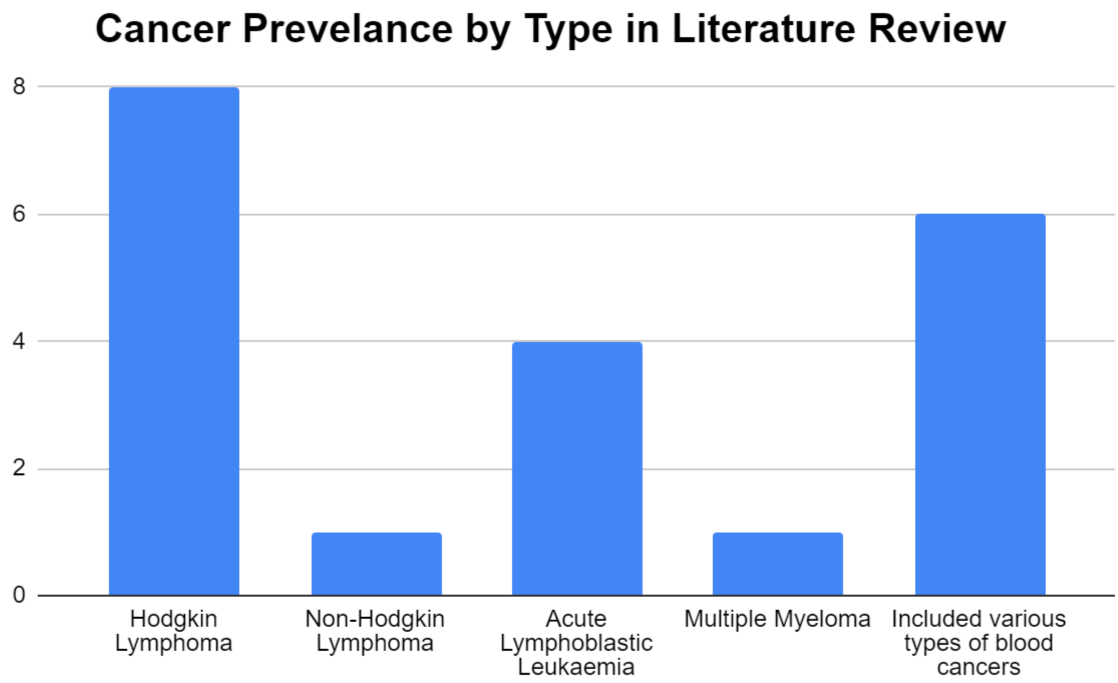


Figure *2.4 Cancer Subgroups in the Literature Review*

Lymphoma proved to be the most prevalent cancer in the literature review, although there was a high number of studies that had mixed blood cancer types, which could sway the results. This high number of studies with lymphoma participants could be due to the average age of diagnosis for lymphoma patients being in the 20s (Mayo Clinic 2024), which is part of the group that makes up the biggest group of participants in contemporary research (>18 years of 20%, 18-64-year-olds 58% 65 years old <19% National Institutes of Health. (2022, April 11).

This high incidence of participants with lymphoma is also in line with data from the Global Cancer Observatory (2021), which found Lymphoma to be the most prevalent in Asia (42.5%), Europe (23.4%), and Northern America (15.8%). Oceania only made up 1.4% of global Lymphoma cases, potentially explaining why no studies from Oceania were retrieved and that most studies were from Northern America and Europe.

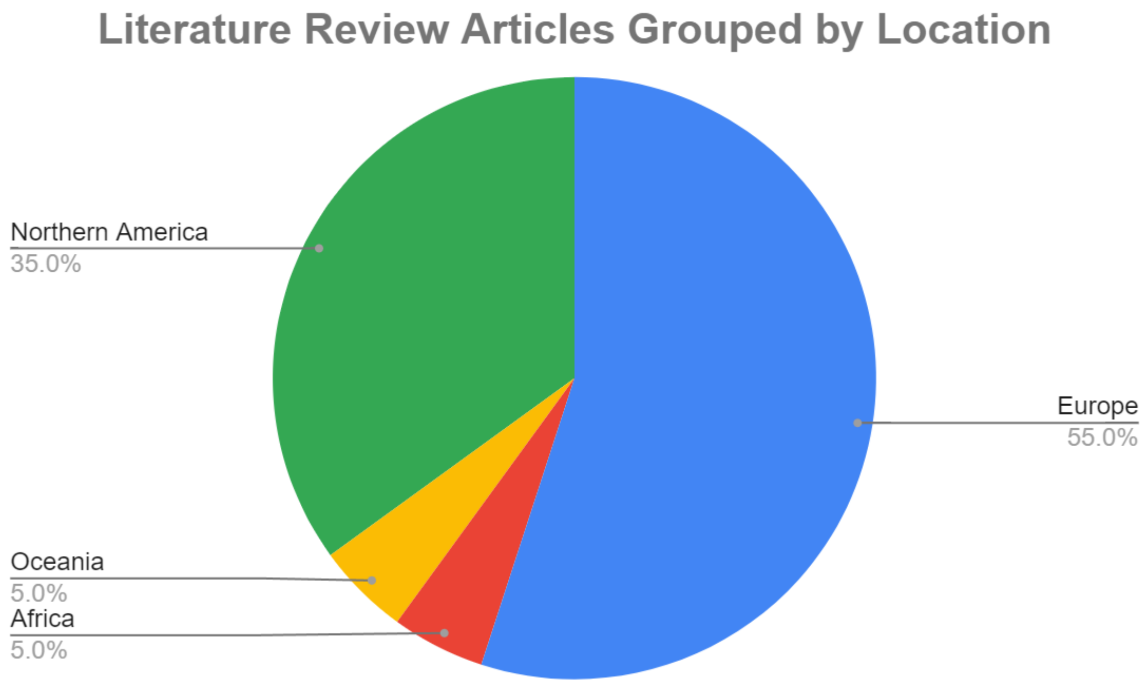


Figure ***2.5 Location-Based Analysis of Studies Retrieved in the Literature Review***

The locations of studies retrieved in this literature review were mainly from Europe and Northern America, aligning with other contemporary research by Zhang et al. (2023), which found that blood cancers are more common and have a rising age-standardised incidence rate in Europe, East Asia, and the Caribbean.

2.4 Literature Review CPET Data

The subsequent table has been employed to extract data from the pertinent literature in the literature review of studies that utilised the CPET examination. This data is categorised into baseline statistics for cancer patients and healthy controls, facilitating a comparative analysis between the findings of this study and those of the general public.

Authors	Elbl et al. (2006).	Oldervoll et al. (2003)	De Caro et al. (2006)	Elnaggar et al. (2021).	Atkinson et al. (2021).	MJ Adams et al (2004).	Caru et al. (2021).	Goodenough et al. (2022).	Persoon et al (2017).	Tsuda et al. (2023).
VO2 peak (ml/kg/min)	28.4 (7.8)	32.7	38.1 (8.4)	30.4	26.5 (7.2)	25.8 (7.2)	32.5	M 28.8 F 22.5	21.7 (5.5)	M 35.8 F 30.2
VE max (L/min)			78.2 (23)	83.5	94.25		86.55			M 79.7 F 60.75
RER/RQ max			1.1 (0.1)	1.17	1.33		1.3		1.28	M 1.24 F 1.24
Time to vo2 max (Seconds)							588			
Workload max (Watts)					162.69		176.15			M 137 F103.5
HR max (Bpm)	192	184	191	198			179.2			M188.5 F 188
Percent of max HR achieved (%)									96%	
O_2 Sat at max (%)										
RPE max										
Max blood pressure (mmHg)	132/82						170.55 / 75			M147.5 F 150
VO2 at AT (ml/kg/min)			24.9 (6.6)							
VE at threshold (L/min)										M23.85 F 24.85
Workload at AT (Watts)										
BMI (Kg/m²)	M 27 (4.7) F17.3 (41)	25.2		22.76	25 (6)		M 23.7 F 24.9	26.5	25.4	M21.55 F22.15
Time since treatment (Years)	1.17		6.4 (3.4)	3.37		14.3	15.3 (5.2)			7.8
Age (Years)	40 (15)	41 (11.3)	<21	13.31 (2.6)	21 (6)	16.5	22 (6.5)	36.6	55 (33)	14.68 (2.83)

Table 2.1 ***Cancer Patient Baseline and CPET Statistics from Literature Review.***

Authors	Bertrand et al. (2021).	Long et al. (2020).	Stenehjem et al. (2016).	Rizwan et al. (2021).	Canada et al (2023).	Klika et al. (2011).	Ruf et al. (2021).	Van Brussel et al. (2006).	Koutoukidis et al. (2020).
VO2 peak (ml/kg/min)	32.3 (8.4)	36.78 (11.49)	M 29.7 F 23.5	26		M 45 (10.5) F 34.8 (10.3)	39.1 (7.9)	36.64 (18.3)	18.1 (6.9)
VE max (L/min)		70.04 (17.12)	Male 107.8 F 71.4					64.69 (36.1)	
RER/RQ max	1.3	1.09 (0.11)	M 1.17 F 1.19	1.16	1.22		1.12 (0.16)		
Time to vo2 max (Seconds)					526.2				
Workload max (watts)			M 196 F 126		127	M 258 (46) F 172 (38)		155 (82.41)	
HR max (Bpm)	187.5 (11.3)	175 (18)			143	157 (20)	186 (10)		
Percent of max HR achieved (%)	97.3 (5.6)				87				
O_2 Sat at max (%)				92			98 (1.5)		
RPE max		17	17		16				
Max blood pressure (mmHg)						182/83.5			
VO2 at AT (ml/kg/min)									
VE at threshold (L/min)									
Workload at AT (Watts)						M 169 F 122			
BMI (Kg/m²)		25.2 (5.1)	Male 26.6 Female 25.8	25.6	26.2	M 26 (2.7) F24.2 (5.9)	20.78	20.75 (3.8)	
Time since treatment (Years)	15.3 (5.2)	12 (4)	12.9 (6.6)	23				5.16	1
Age (Years)	22 (6.4)	19 (3)	42 (13)	51	57	53.8 (11)	15.7 (6.7)	15.5 (5.8)	64

Table 2.1 ***Cancer Patient Baseline and CPET Statistics from Literature Review.***

VO_2 peak, the highest oxygen consumption rate measured during exercise, is a crucial indicator of cardiorespiratory fitness and aerobic capacity. In this literature review, VO_2 peak values shed light on the functional capacity of individuals with cancer compared to normative data from the general population. For females, the average VO_2 peak fell within the mid-range of the "fair" category (24–30 ml/kg/min), based on reference values established by Jay Hoffman (2006). In contrast, the average VO_2 peak for males aligned with the "average" category for healthy adults (34–42 ml/kg/min). As expected, males exhibited slightly higher VO_2 peak values than females, consistent with well-documented sex differences in aerobic capacity. These results highlight no significant abnormalities. Notably, Klika et al. (2010) contributed to the high standard deviation in this group, with their study reporting an average VO_2 max of 45 ml/kg/min for males and 34.8 ml/kg/min for females, significantly higher than the averages in this population observed in other studies (with an average of 35.8 ml/kg/min for male cancer patients ranging from 21.7 to 38.1 ml/kg/min, excluding Klika et al., 2010), suggesting that the average VO_2 peak may be even lower. This reduced cardiovascular capacity across studies compared to healthy controls underscores the long-term effects of cancer treatment, which can diminish cardiovascular and muscular efficiency (Foulkes et al., 2019; Sinclar et al., 2015; Jones et al., 2011), despite participants having an average of nearly 10 years since treatment among cancer survivors.

Oldervoll et al.'s (2003) findings contrasted the decreases in VO_2 seen above. They found no significant differences in cardiac capacity (VO_2) in cancer patients compared to the general population in their study. They concluded that aerobic capacity does not play an essential role in the pathophysiology of CRF/PEM, speculating that subjects in their research already use physical exercise to reduce the effects of CRF/PEM and improve their cardiovascular health.

Ventilation (VE) reflects the volume of air breathed per minute and is a key indicator of ventilatory efficiency. It provides insight into pulmonary function, gas exchange, and the respiratory response to exercise. VE is influenced by metabolic demand, lung function, and cardiovascular fitness, making it a crucial parameter in assessing exercise capacity and limitations.The VE and workload results from the literature reviewed were consistently higher in males than in females, but the overall averages remained below those of healthy individuals (Habedank et al., 1998). A reduced VE reflects a reduced cardiovascular efficiency, likely stemming from the treatment's harmful effects on pulmonary, muscular, and respiratory health. Klika et al. (2010) may skew the workload max values, with results for males (258 watts) and females (172 watts) significantly higher than those in other studies, which could again raise the mean well above what should be expected of blood cancer survivors.

Age-predicted maximal heart rate (APMHR) is an estimated upper limit of heart rate during maximal exertion. It is widely used in CPET to assess cardiovascular response, determine exercise intensity, and establish safe training zones. APMHR is particularly useful for cancer patients in evaluating cardiovascular fitness and monitoring potential cardiac limitations caused by cancer treatments such as chemotherapy or radiation. Since cancer therapies can impact heart function, using APMHR in exercise testing helps guide appropriate exercise prescriptions. Participants achieved over 90% of the age-predicted max HR (or close to their predicted maximal values; Gappmaier, 2002; Glaab & Taube, 2022), indicating adequate maximal exertion was exhibited during testing. The cancer patient's cardiopulmonary systems showed no obvious impairment or residual fatigue, allowing maximal effort on the first exercise test. Oxygen saturation was well maintained in the cancer patients throughout the exercise tests, demonstrating adequate oxygen transportation from the pulmonary system.

2.5 ME/CFS Participant 24-Hour Repeated CPET Data

Many of the studies reviewed in the literature and contemporary research have utilised a single CPET session, which significantly limits the ability to assess whether AYA blood cancer survivors experience cancer-CRF/PEM and their clinical significance. An additional literature review was completed to address this gap, focusing on studies involving patients with ME/CFS who underwent a 24-hour CPET protocol. This testing method is more commonly employed within the ME/CFS population and provides a robust framework for assessing PEM. Although CRF is not typically associated with PEM or the diagnostic criteria of ME/CFS, the symptomatology of ME/CFS—characterised by restlessness, sleep disturbances, and cognitive impairments—is strikingly similar to the fatigue reported by patients treated for haematological malignancies (Park et al., 2019; Ryan et al., 2007). Therefore, a comparative analysis of the results gained from this study with findings from the ME/CFS literature is warranted. This technique aims to determine whether cancer survivors exhibit a similar decline in peak and threshold variables to those observed in ME/CFS patients.

Table 2.2 ***ME/CFS Patients Reductions in Performance in the 24-Hour Repeated CPET***

	Number of participants	VO_2 peak	VO_2 at AT	Workload Peak	Workload at AT	HR peak	O2 pulse at AT
(VanNess et al., 2007)	6	-22%	-26%	/	/	/	/
(Vermeulen et al., 2010)	15	-6.3%	-7.0%	-5.3%	-7.0%	-1.9%	-8.8%
(Snell et al., 2013)	51	-5%	-10.8%	-7.2%	-55.2%	/	/
(Keller et al., 2014)	22	-13.8%	-15.8%	-12.5%	-21.3%	-5.9%	-12.6%
(Hodges et al., 2018)	10	+5.3%	+6.1%	-6.7%	-11.4%	-0.6%	+7%
(Nelson et al., 2019)	16	+0.4%	-3.1%	-1.2%	-17.4%	-0.5%	+2%
(Van Campen et al., 2020)	107	-9.6%	-20.6%	-13.8%	-30%	-5.3%	/
(Davenport, 2020)	51	-5%	-10%	-9%	-11%	-3%	-7%
(Van Campen, 2021)	76	-11%	-25%	-10.5%	-28.5%	-5.5%	-15%
(Keller, 2024)	84	-5.3%	-6.8%	-5.5%	-9.4%	/	/
Mean (SD)	43.80 (33.76)	-7.81% (6.29)	-12.52% (8.54)	-7.97% (3.70)	-21.24% (14.31)	-3.24% (2.16)	-7.25% (5.70)

As seen in Table 2.2, all the physiological and mechanical results declined in the second exercise test. There were two outliers: Hodges et al. (2018) and Nelson et al. (2019). Despite a significant reduction in workload at the ventilatory threshold (AT) of -11.4%, participants achieved higher values for VO_2 peak and O_2 saturation during the second day of testing in their research. This was despite a reduced maximal workload in the second test in the ME/CFS patients. The increased VO_2 max could be attributed to participants' increased familiarity with the exercise testing protocol yet still demonstrating the negatively affected exercise capacity through the reduced workload peak.

2.6 SF-36

The SF-36 (Short Form-36 Health Survey) is a widely used questionnaire designed to assess health-related quality of life (HRQoL) across eight domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional health, and mental health. It provides two summaries to evaluate overall well-being: the physical component summary (PCS) and the mental component summary (MCS). The SF-36 is commonly utilised in clinical research, including studies focused on cancer patients, to measure the impact of disease and treatment on daily functioning and QOL.

The second version of the SF-36 utilised in this study has received significant updates over the first generation. The response scales have been modified to broaden the range of responses allowed, enhancing the scores' precision (Ware Jr, 2000). Furthermore, changes to the content, including questions, structure, layout, and readability, have reduced the average completion time to 5-10 minutes, reducing the burden. These changes have also made the questionnaire more straightforward for participants to comprehend and have significantly improved its acceptability and data quality (Ware et al., 1992 & Farzanegan et al., 2011).

The SF-36 questionnaire (Appendix I) was selected because it has been certified as a valid method for assessing disease burden on participants' fatigue, QOL, ADL and pain (Stansfeld & Foot, 1997). It has already been used in many studies investigating QOL in cancer patients (Mosconi et al., 2002; Yoshimura et al., 2005; Rogers et al., 1998; Saegrov S, 2005; Pinar, 2005; Yang, 2013). Bech et al. (2003) compared the SF-36 to the WHO-FIVE among 9,542 Danish people in the general population. They found the SF-36 to be a just as reliable measure to capture insights into physical well-being and able to provide valuable data on mental health and fatigue subscale. Furthermore, the SF-36 meets and exceeds the rigorous psychometric standards required for group comparisons, allowing this study's findings to be compared with those of control groups and other research. (Ware et al., 1996; Sampogna et al., 2006; LeBlanc et al., 2022). The SF-36 also allows for a breakdown of results between the physical and mental health domains, allowing for an in-depth measure of health status and, thus, the effects of CRF/PEM in this study (Wada et al., 2017).

Studies retrieved in the literature review employing the SF-36 reported that the most frequently and significantly affected domains of QOL for blood cancer patients to score lowest were energy/fatigue, general health, and role limitation due to physical health domains. The use of the SF-36 in this study will help critique and explore the psychological effects of CRF/PEM, its relationship to QOL, and its other effects on the differing domains in the SF-36.

Table *2.3 SF-36 Cancer Patient and Healthy Controls Mean Results*

Health Domain	Cancer patient	Control
	Mean (SD)	Mean (SD)
Physical functioning	84.93 (4.71)	91.53 (2.45)
Role limitations due to physical health	68.53 (4.59)	83.60 (3.75)
Role limitations due to emotional problems	80.67 (2.47)	89.27 (1.16)
Energy/fatigue	54.67 (6.91)	60.60 (0.36)
Emotional well-being	77.00 (3.75)	80.40 (1.31)
Social functioning	81.90 (2.94)	89.37 (0.52)
Pain	70.30 (1.79)	74.90 (4.46)
General Health	63.27 (1.62)	76.03 (2.88)

As reported in Table 2.3, blood cancer patients scored lower in every SF-36 domain than the respective healthy controls in their studies. The high degree of variability and standard deviation from those studies utilising the SF-36 (Kanellopoulos et al., 2013; Eikeland et al., 2023; Kiserud et al.; LeBlanc et al., 2022) indicates a more pronounced effect on QOL in some cancer patients than others. This highlights that CRF/PEM should be treated uniquely and individually, as its adverse effects can differ in severity and domain from patient to patient.

An additional Literature review was done to investigate the baseline SF-36 for the New Zealand General public and compare it to a broader demographic representative of healthy controls in New Zealand. A study by Scott et al., 1999, included over 7,500 participants, and the following results were extracted into Table 2.4

Table 2.4 ***New Zealand General Population SF-36 scores***

	Physical functioning	Role Physical	Bodily pain	General Health	Energy/ Fatigue	Social Functioning	Role Emotional	Emotional well being
Male (15-44)	91.9	86.6	80.8	76	68.2	89	87.4	78.7
Female (15-44)	90.5	84.2	78.3	73.4	62	83.8	81.3	73.9
Combined Averages	91.2	85.4	79.6	74.7	65.1	86.4	84.4	76.3

Although the results in Table 2.4 are similar to those observed in overseas research by Ware, Kosinski, and Keller (1996), the New Zealand general population scored slightly higher across both genders when compared to the initial literature retrieved, which included healthy controls. This could be due to the more active lifestyle contributing to a higher QOL in New Zealand. These differences in general populations emphasise the importance of comparing data from similar populations when drawing initial conclusions.

2.7 FAS

The Fatigue Assessment Scale (FAS) is a self-reported questionnaire designed to measure the severity of fatigue in both clinical and non-clinical populations. The total score indicates overall fatigue levels, with higher scores reflecting greater severity. The FAS is widely used in research and clinical settings, including studies on cancer-related fatigue, to evaluate the impact of chronic conditions on daily functioning and quality of life. Its simplicity and reliability make it a valuable tool for tracking fatigue over time and assessing the effectiveness of interventions. In the literature reviewed (Daniëls et al., 2014; Schoormans et al., 2020), the average FAS score was 21.45 for cancer patients, considerably higher than the mean score of 18.4 observed in their healthy controls and existing baseline data. According to Drent et al. 2012, Kleijn et al. 2011, and De Vries et al. 2004, a participant scoring between 22 and 34 on the FAS can be classified as experiencing chronic fatigue. Substantial fatigue is noted if the participant scores 35 or above. Michelson et al. (2003) had three hundred fifty-one participants who worked part-time and took part in their study to create a baseline dataset. They found the mean score for this population was 19.26, with a standard deviation of 6.52, against which our results will also be compared.

The significant standard deviation in scores (7.6) suggests a high level of variability among patients, indicating that some may not experience CRF/PEM and that lower individual scores could lower the mean, potentially misrepresenting those with severe fatigue. Therefore, presenting individual results is essential to accurately describe the fatigue levels of participants.

2.8 Impact of CRF/PEM

All of the studies included in the literature review that exclusively implemented the FAS (Schoormans et al., 2020 and Daniëls et al., 2014) and the SF-36 (Adams et al., 2004; Kiserud et al., 2023; Le Blanc et al., 2022; Eikeland et al., 2023; Kanellopoulos et al., 2013) found that long-term cancer survivors experienced significantly worse QOL and higher fatigue levels than healthy controls from the general population. On top of this, all but three of the studies that used the CPET reported significant reductions in workload max and workload at AT, HR peak, and VO_2 peak among blood cancer survivors, justifying further research to understand and reduce the effects of CRF/PEM.

However, three studies that utilised a singular CPET (Oldervolle et al., 2003; Tsuda et al., 2023; and Klika et al., 2010) contradict the above findings, as they found no significant difference in VO_2 max between the healthy controls and patients in remission. Klika et al. (2010) acknowledged that it could be an anomaly, as the sample included individuals from high-altitude and activity-oriented regions who typically maintain a healthier lifestyle than the average population to which their findings, along with many others, are compared. Tsuda et al. (2023) emphasise that factors such as physical conditioning, level of puberty, ethnic background, and other external variables may influence their results, and it is vital to consider this when testing and comparing outcomes.

Le Blanc et al. (2022). Eikeland et al. (2023). Elbl et al. (2006) and Kiserud et al. (2023) found that CRF/PEM was a significant issue for 30-60% of cancer patients and persisted for up to 10 years after their last treatment. Interestingly, Kiserud et al. (2023) found that fatigue was more severe in Lymphoma survivors than in those with other blood cancers. This could explain why most of the literature focused on Lymphoma survivors.

2.9 Additional Findings and Considerations

The role of repeated exercise testing in assessing fatigue Was established as early as 1956 in Dr Melvin Ramsay's book *Encephalomyelitis Simulating Poliomyelitis* and the Royal & Free Hospital 1957 identified that patients with ME/CFS exhibit normal muscle strength in maximal exertion when compared to the general population, but after much research and testing, they found that "muscle power tests should be repeated after exercise and that repeated testing following exercise is needed to uncover the signs of exercise intolerance". The underlying message requiring repeated exercise tests remains true today, with Snell et al. (2013) and Clayton 2015 underscoring that a single exercise test cannot reliably demonstrate functional cardiopulmonary or muscular impairment in subjects with chronic fatigue and that a repeated exercise test must be used to assess the severity of PEM due to the onset of symptoms which can arise anywhere from 12-48 hours after the original stressor. Advancements in exercise testing have led to the use of the 24-hour repeated CPET for assessing ME/CFS's (CRF/PEM) effects on patient's functional capacity while identifying impairments in the cardiopulmonary and muscular systems not obtained in other singular physiological tests (Stickland et al., 2012). The 24-hour repeated CPET has been found to be the gold standard for diagnosing and assessing ME/CFS (CRF/PEM) while being highly reliable and reproducible (Lim et al., 2020; Davenport et al., 2020).

Elbl et al. (2006) and Stenehjem et al. (2016) demonstrate that chemotherapy and radiation compromise cancer survivors' cardiopulmonary function, as seen in the reduced VO_2 max/threshold ventilation data and impaired heart response to exercise. This signifies that treatment modalities may be an essential factor in the severity of fatigue experienced by participants after treatment. Research from Oldervoll et al. (2003) and Tsuda et al. (2023) suggests that while regular exercise can improve QOL and cardiopulmonary levels, it is hard for survivors to manage exercise regularly as if they over-exert themselves or exercise when fatigued, they can be out of action for 24 - 48 hours following the exertion/event which can get in the way of work and other life events.

Additionally, Schoomans et al. (2020) found that patients with a poorer understanding of their illness experienced far higher fatigue levels and reduced functioning than those more aware of their condition and health levels. Daniëls et al. (2014), Kiserud et al. (2023), Heinrich et al. (2016), and Schoormans et al. (2020) highlight the positive correlation between patients with CRF/PEM and those who suffer from depression and anxiety. This combination of mental health struggles and fatigue further decreases patients' QOL and physical functioning, which also negatively affects nutritional status, reducing motivation to exercise, diminishes ADL capacity, and inhibits recovery and sleep quality (Craft & Perna, 2004; Stults-Kolehmainen & Sinha, 2015; Gariballa & Alessa, 2017). On top of this, Eikeland et al. (2023) also found that these blood cancer patients who have reached remission are socioeconomically disadvantaged and struggle to balance their work-life balance due to the impact of CRF/PEM.

Several studies, such as those by Bisschop et al., 2012 Jones et al., 2007 Coleman et al., 2008 Kim et al., 2017 and Klika et al., 2011 have consistently shown the feasibility and safety (adverse effects occurring in less than 1% of all participants) of CPET testing in cancer patients. However, as detailed in Table 4.3, the cycle ergometer is a more practical tool for this population.

Table *2.5 Comparison of Cycle Ergometer vs Treadmill for CPET Examinations*

Variable	Cycle Ergometer	Treadmill
Peak Oxygen Consumption	Lower	Higher
Ability to Measure External Work Rate	Yes	No
Ease of Blood Gas Collection	Easier	More Difficult
Stress and Cognitive Load	Less	More Stress
Safety	Safer	Less Safe/Higher Risk
Weight Bearing	Less	More
Degree of Leg Muscle Training	Less	More
More Appropriate for:	Patients	Active Healthy Subjects

Note. This table has been adapted from Albouaini et al. 2007

The cycle ergometer has been selected for this study because it is more accessible and safer for more vulnerable populations (Albouaini et al., 2007; Stevens et al., 2018). Its stable seated position reduces the risk of falls or injury, which is particularly important for demographics such as blood cancer survivors with compromised balance or muscular weakness. Additionally, the cycle ergometer is strongly recommended for populations with compromised exercise tolerance or limited familiarity with exercise testing, as it helps avoid overwhelming participants (Stevens et al., 2018). Other benefits of using a cycle ergometer include having more control over the workload and cadence, which allows a precise and gradual increase in resistance throughout the test. The cycle ergometer also facilitates a more convenient and efficient collection of physiological measures (heart rate, blood pressure, oxygen uptake VO_2, and carbon dioxide production) than the treadmill (Albouaini et al., 2007). Although VO_2 peak can be 10–15% lower in healthy individuals when measured using a cycle ergometer compared to a treadmill, the benefits of safety and security on the cycle ergometer for CRF/PEM patients outweigh the risks associated with treadmill exercise for this population (Porszasz et al., 2007).

The ceiling effect is often seen in certain domains when interpreting the SF-36 results. This effect occurs when a significant proportion of participants achieve the highest possible score in a study or questionnaire, limiting the ability to differentiate between higher levels of function and reducing the data's interpretive value (Reulen et al., 2006).

Oldervoll et al. (2003) and De Caro et al. (2006) suggest that reduced aerobic capacity alone may not fully explain the pathophysiology of CRF/PEM. Future research should explore a holistic approach, including patient-supportive interventions, such as psychological aid, self-management education, and lifestyle modifications, in combination with or as alternatives to traditional exercise interventions like tailored strength and aerobic programs.

2.10 Literature Review Conclusion

After completing the literature review, it is clear that CRF/PEM is a complex, debilitating condition influenced by a range of physiological and psychological factors. It has a more significant impact on QOL than any of the other side effects of the treatment. Despite the proven safety, accuracy, and validity of the 24-hour repeated CPET, all studies included in the literature review used a singular CPET, which fails to capture the PEM effects of CRF. This underscores the importance and urgency of this research project to assess the delayed recovery and impairments blood cancer survivors experience in response to an exercise test. Such studies with repeated exercise testing are essential for capturing the PEM effects that cannot be captured in singular exercise tests and advancing understanding of CRF/PEM's full impact. Further, interpreting the results gained from the 24-hour CPET requires a critical, transparent, and thorough approach. Focusing solely on mechanical output or physiological data may overlook significant factors influencing performance and QOL. Research utilising the SF-36 and the FAS was more prevalent than those with an exercise test, likely due to the ease of implementation compared to exercise testing. The inclusion of repeated maximal exercise tests may also make subjects hesitant to participate due to the time and energy requirements. Incorporating the SF-36 and FAS questionnaires provides additional subjective information to comprehensively analyse the participant's well-being.

3. Research Aim and Hypothesis

This research project aims to raise awareness and provide valuable insights for patients and healthcare professionals by identifying and quantifying the physiological factors affected by CRF/PEM through a clinically approved exercise test (24-hour repeated CPET). Contemporary research lacks data on repeated CPET to capture the delayed effects of exercise and exertion in this population, overlooking the impact on physiological and psychological health. This project seeks to fill this void by utilising a 24-hour repeated CPET protocol, allowing us to quantify and evaluate the effects of PEM on participants' cardiopulmonary and physiological responses post-exercise. It will be the first study to apply this methodology with this population and include healthy controls, generating innovative insights that will complement data from Europe and America and deepen the field's research base. This study also seeks to evaluate CRF/PEM's impact on a patient's QOL and ability to achieve ADL via the SF-36 and FAS questionnaires. Potential correlations with lower QOL scores and physiological markers such as VO_2 peak, HR, VCO_2, ventilation (VE), time to fatigue, and workload max will be explored and reported if there are any consistent correlations. With more research and information on the physiological effects of CRF/PEM, new, innovative treatment and maintenance strategies to alleviate CRF/PEM could be developed. These strategies could improve QOL and help patients engage more in activities they enjoy.

It is anticipated that AYA blood cancer patients who have undergone treatment for their haematological malignancies and have achieved remission will show a significant reduction in their physiological functioning during the 24-hour repeated CPET on the second exercise test due to the impacts of CRF/PEM. We expect substantial declines in key metrics, including peak workload, maximal heart rate, VO_2 peak, and time to fatigue. In this study, the FAS and SF-36 scores are predicted to be considerably worse (higher in the FAS) for cancer survivors compared to healthy controls and reference values. The subsequent hypothesis is that the energy and fatigue score will be lowest in the SF-36 for cancer patients, followed by general health.

These reductions are anticipated to impair participants' ability to perform ADL (personal transportation, shopping, meal preparation, house cleaning, social interactions, among others) and reduce their QOL (due to impairments in physical functioning, emotional well-being, heightened energy costs, and cognitive focus in partaking in social interactions).

4. Methods

4.1 Study Design

This observational cohort study examined blood cancer patients' CRF/PEM, cardiopulmonary capacity, and exercise response through a 24-hour repeated CPET protocol. This approach provides real-world insights into the effects of CRF/PEM without any intervention that could alter the responses. Supplementary questionnaires (SF-36 and FAS) evaluated participants' quality of life and its impact on their mental and physical well-being, as well as effects on their everyday activities and social lives. Including healthy controls enabled a detailed cross-examination of fatigue levels, cardiopulmonary function, and physiological responses to exercise between cancer participants and controls, while strengthening the validity of the findings.

4.2 Study Materials

Figure 4.1 ***24-Hour Repeated CPET Equipment***

This study used a LODE Excalibur cycle ergometer along with a Polar heart rate chest strap and monitor to record each participant's heart rate (HR) and workload (WL) during the exercise testing. Additionally, participants were connected to an ECG monitor via a Bluetooth 12-lead ECG device. The software (COSMED) and equipment were calibrated before data collection, and the same devices were used consistently throughout the study.

4.3 Participant Recruitment Overview

The study gained ethical approval from the Massey Human Ethics Committee Ohu Matatika 1 on 09/07/2024 (application ID OM1 24/09). Additionally, collaboration with A/Prof. Bevan Erueti to ensure that ethical and cultural principles were upheld. This ensured that the study met all ethical and safety standards set by Massey University.

After gaining ethical approval, recruitment began immediately. Recruitment was achieved with the help of patient support organisations, such as Leukaemia and Blood Cancer New Zealand and Myeloma NZ. These organisations agreed to advertise information online and at events, contacting potential participants, which helped spread awareness of this research project. Additionally, the study was promoted by attending events, posting social media advertisements, and handing out physical flyers. This multifaceted approach ensured a diverse range of participants was reached during recruitment. Following identification, potential participants were encouraged to contact the researchers via the advertised email address if they wished to participate in this project. Participants had the option of an in-person or online meeting to discuss the study, its risks and benefits, how the data would be used and stored, and what would be required of them.

All participants were provided with an informed consent form (Appendix D) outlining the purpose of the study, the procedures involved, potential risks and benefits, and their right to withdraw at any time without consequence. Consent was obtained before participation or any data collection. Participants were made aware that if they changed their minds, their data could be excluded from the project for up to two weeks after the second of their exercise tests. Unique pseudonyms were assigned to each participant to ensure anonymity and privacy. Only the researchers had access to the identifiable information, and all data was secured in a password-protected document on the Massey database. Physical copies of forms were scanned, uploaded, and then destroyed. No sensitive information was stored on hard drives or easily lost devices.

Each participant received Koha as a token of appreciation for their time and energy partaking in this study.

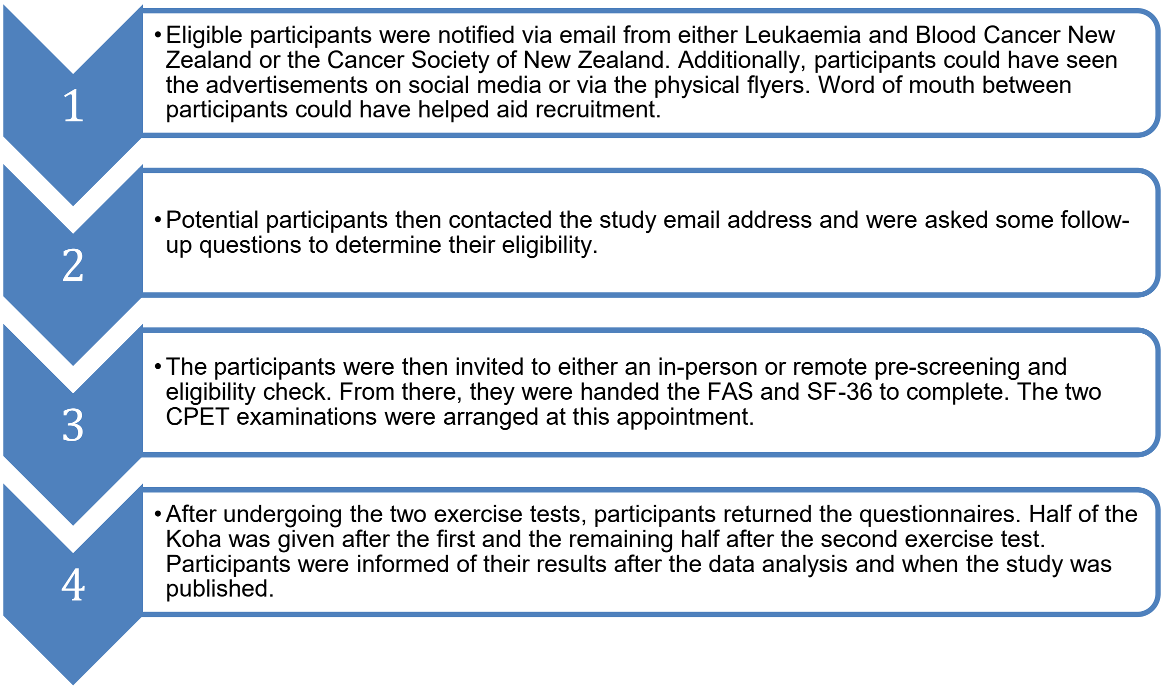


Figure *4.2 Research Procedure Framework*

4.4 Participant Eligibility Criteria

The eligibility criteria included:

- Participant to be in remission from a haematological malignancy
- Have must have received chemotherapy, radiotherapy or a stem cell transplant.
- Participants must be aged 20-35 years old
- Participants must be in the low-risk criteria of the NZREPs pre-screening form (details found in Appendix E)

The healthy controls must be between 20 and 35 years old and have no cardiovascular or other health conditions. Participants received an information sheet, an informed consent form, and the NZREPs pre-screening form, which they had to complete and sign before any testing commenced.

The NZREP pre-screening form (Appendix E) was selected for this study due to its comprehensive, multifaceted approach based on internationally accepted pre-screening risk assessment standards. Pre-screening exercise forms such as the NZREPS have been validated as practical and valuable tools for identifying health risks before exercise testing and training. For example, Kenjale et al. (2014) found that using a basic pre-screening questionnaire similar to the NZREPs in 413 cancer patients undergoing CPET was more practical and yielded just as valuable results as clinician-provided pre-exercise clearance.

The NZREPS form assigns risk factor points to currently diagnosed conditions (diabetes, heart disease, high blood pressure, among others) and subsequent information gained during the interview. These risk factor points were used to define a risk level for each participant (Low, moderate, or high) and determine whether it was safe to proceed with the exercise test or if the patient should be referred to a doctor. There are also red flag scenarios whereby a known cardiovascular, pulmonary and metabolic disease (or signs and symptoms of these diseases) would automatically trigger a need for clearance from a medical professional before the participant could take any part. Only participants considered low risk were allowed to participate in the 24-hour repeated CPET due to it being classified as a vigorous exercise test. It is important to note that the NZREPS pre-exercise screening form is not designed to diagnose any health conditions but rather to help identify conditions that could be aggravated by exercise.

The consort flow diagram (Fig 4.3) depicts the recruitment process and the number of potential participants who reached out. Due to the required equipment, the 24-hour Repeated CPET testing had to be conducted in Palmerston North, which restricted participation because most potential participants were based in Wellington. This is likely because more people are registered with the Leukaemia and Blood Cancer Society there. Fortunately, five out of five participants completed the exercise testing.

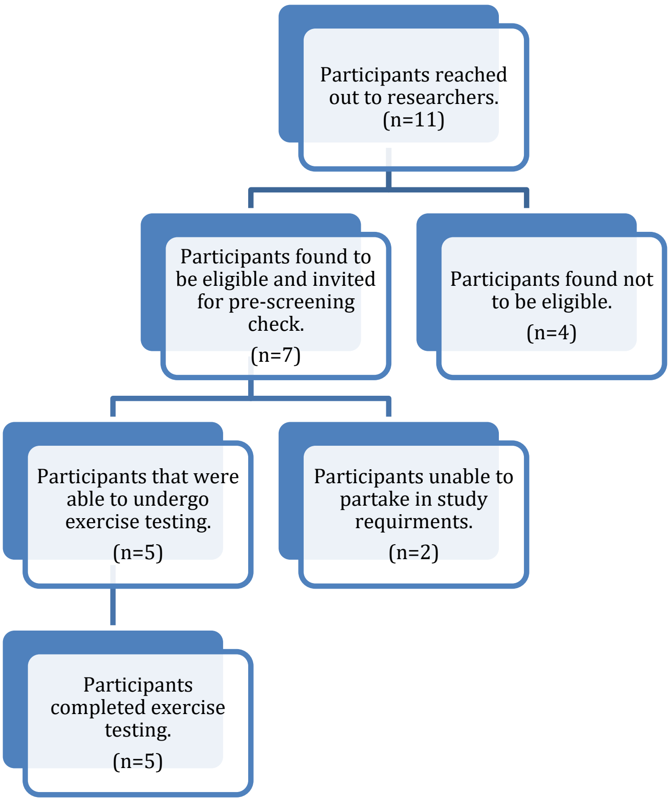


Figure *4.3 Consort Flow Diagram*

A total of ten participants, including five AYA cancer survivors and five healthy controls, seven females (70%) and three males (30%), were recruited for the study. Healthy controls were within three years of either side of their age-matched AYA blood cancer survivors. The average age and BMI of the cancer patients and healthy controls nearly had a perfect overlap, ensuring that an accurate comparison between the two groups was possible. The complete outline of the baseline participant characteristics can be seen in Table 4.1 and Table 4.2.

Table ***4.1 Baseline Cancer Patient Characteristics***

Cancer patients n=5	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Mean	SD
Age (years)	26	26	23	25	22	24.4	1.81
Gender	Male	Female	Female	Female	Female	NA	NA
Time Since last Treatment (years)	4	15	6	9	7	8.2	3.76
Type of Cancer	MM	Leukaemia	Leukaemia	Leukaemia	Leukaemia	NA	NA
Activity Levels	Very active	Moderately active	Moderately active	Moderately active	Moderately active	NA	NA
BMI (kg/m_2)	18.9	22.3	34	24.9	26.8	25.38	5.66
Resting HR (BPM)	78	77	74	53	70	70.4	9.13
Resting BP (mmHg)	119/90	131/63	132/83	114/80	118/90	122.8/81.2	7.3/9.91

Table ***4.2 Baseline Healthy Control Baseline Characteristics***

Healthy Controls n = 5	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Mean	SD
Age (years)	24	28	22	24	25	24.6	2.19
Gender	Male	Male	Female	Female	Female	NA	NA
Activity Levels	Very Active	Active	Very Active	Active	Active	NA	NA
BMI (kg/m_2)	19.6	24.2	19.9	35.6	35.4	26.94	8.02
Resting HR (BPM)	62	70	58	88	82	72	11.45
Resting BP (mmHg)	126/74	124/84	124/62	140/87	144/77	131.6/76.8	8.62/8.75

4.5 24-hour repeated CPET Methodology

The study will follow the RAMP (Raise, Activate, Mobilise, and Potentiate) protocol, which allows for a gradual increase in exercise resistance and intensity. This approach provides a proper warm-up period and keeps test durations brief. All participants completed tests lasting 8 to 12 minutes, minimising unnecessary strain on the patients (Chambers & Wisely, 2019). Participants were equipped with face masks for gas collection, a 12-lead ECG, and Polar heart rate chest straps to gather additional data. All data collected will be processed through the COSMED online metabolic system.

Participants were instructed to avoid food or smoking <2 h, caffeine <4 h and strenuous exercise 24h before participating in the study. The ventilatory or anaerobic threshold was identified from expired gases using the v-slope method (Schneider, Phillips, & Stoffolano, 1993). The laboratory environment remained at 17–18 degrees Celsius during all testing procedures. Blood pressure and heart rate were monitored during recovery until the participant was within 20 bpm and 10 mmHg of resting measures.

Table 4.3 24-Hour Repeated CPET Methodology

Start	● Before exercising, the seat height and handlebar position were set so the participants were comfortable and efficient and did not overextend their arms or legs. ● Participants were fitted with a Polar heart rate strap and 12-lead ECG for continuous data throughout the exercise test. ● Before the RAMP test, one minute of resting data was collected, including heart rate, blood pressure, oxygen saturation, and VO_2.
Exercise Protocol	● Participants maintained a cadence between 60-80 RPM. ● All participants had an increase of 15 Watts per minute, with more active participants starting at a higher wattage (45 to 60 Watts) than the untrained population (15 to 30 Watts)
During Exercise	● Blood pressure and O_2 saturation were recorded every 3 minutes. ● HR and RPE were recorded every minute. ● VO_2, VCO_2, and other physiological data were continuously monitored via the COSMED software from the seated rest at the start of the exercise until the testing terminated.
Peak Exercise	● RPE, HR, O_2, and blood pressure were taken at peak or as close to the exercise termination as possible.
Post-Exercise	● Blood pressure and O_2 saturation were recorded 1, 3, and 5 minutes after maximal exertion. ● HR and RPE were collected every minute. ● The resistance was significantly reduced so participants could gently spin their legs.
Confirm	● The reason for test termination was confirmed with the participant, and a few brief questions were recorded for further data analysis.

The exercise test finished when the participant could not maintain 60-80 RPM; their blood pressure exceeded 220/110 mmHg, the participant requested to stop, the participant experienced light-headedness, chest pain or if an abnormal heart rhythm was detected. Upon termination of the exercise test, the participant completed a 5-minute recovery protocol, where the power output was reduced (Generally 30-50w), and the participant was encouraged to keep pedalling. Data was still being collected throughout the recovery protocol to ensure participants warm down and provide further data for analysis. Participants returned 24 hours later, where the same test was repeated.

The participants' RER, HR, and RPE will be used to assess whether they have reached maximal effort during the exercise test and to evaluate the balance between internal and external effort. RER measures whether the participant has achieved maximal effort through energy metabolism, confirmed if the participant's RER equals or exceeds 1.10 (Lindheimer et al., 2020; Glaab & Taube, 2022). In addition to using RER as an indicator of maximal exertion, the percentage of participants' age-predicted maximal heart rate (APMHR) was calculated using the 220 minus age formula. A maximal response is recorded if the participant reaches 90% of their APMHR. Although slightly underestimated in older adults, it is a commonly used criterion for determining maximal exertion in exercise tests (Tanaka, Monahan, & Seaks, 2001). Furthermore, the Borg RPE scale will be used to assess the participant's subjective rating of perceived exertion. The Borg RPE scale is an accurate and straightforward questionnaire that quantifies participants' feelings of exertion and complements the physiological data (HR and RER) collected (Wilson & Jones, 1989). A score of 17-20 on the Borg RPE scale indicates the participant has reached their limit (Williams, 2017).

Participants completed exercise recovery questions immediately after the first and second exercise tests and the following day. Six questions (Appendix H) were designed to assess and gather subjective feedback on how participants felt right after the test, how long it took them to feel normal again, and the symptoms they experienced during the recovery period. The results section will briefly summarise the most common responses from participants.

4.6 Short Form 36 (SF-36) Methodology

The SF-36 was handed to participants at the pre-screening health check before the exercise testing. This gave the participants two days to complete the questionnaire and return it. The SF-36 provided helpful data as it encompasses eight different areas of functioning that make up an individual's health: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (Energy and Fatigue), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH). Figures 4.4 and 4.5 below show the various factors and how they relate to the mental and physical components of QOL.

The results were entered into (https://www.physiotutors.com/questionnaires/sf-36-rand-36-mos/) to generate scores out of 100 for each domain of QOL. This provided an overview of which areas of a patient's QOL are most impacted by CRF/PEM.

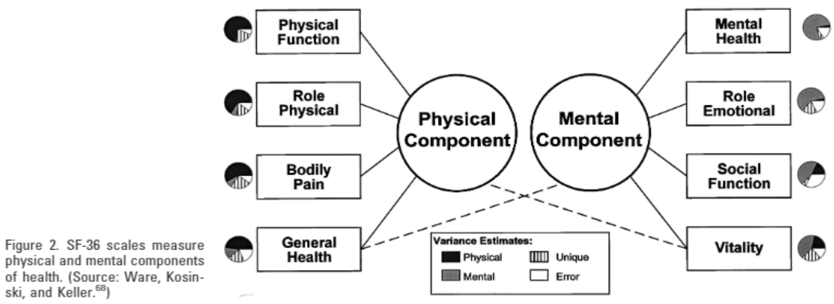
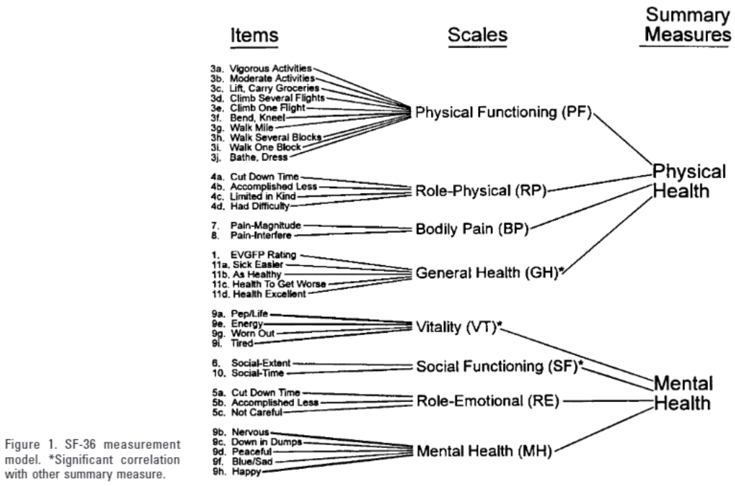


Figure *4.4 The Eight Domains of QOL Scored in the SF-36*

Ware 2000

Note. This graph depicts the eight domains of QOL scored in the SF-36 and how they relate to an individual's health's physical or mental component.



Ware 2000

Figure 4.5 ***Domains of QOL and Their Contributions to Mental/Physical Health in the SF-36***

Ware 2000

4.7 Fatigue Assessment Scale (FAS)

The FAS is one of the tools used in contemporary research investigating fatigue in subjects with chronic illnesses (including cancer). Despite only consisting of 10 questions, the FAS has consistently yielded statistically significant data and insights into the effects of chronic fatigue. (Poopady et al., 2022; Michielsen et al., 2003; Al Maqbali et al., 2019). These ten questions include five assessing physical and five assessing mental fatigue, totalling a score from 10 to 50. Responses are scored from 1 (never) to 5 (always), with higher scores indicating more severe fatigue. The first five questions are worded positively, while the last five are phrased negatively (e.g., "I feel tired when..."). This structure helps to avoid acquiescence bias and holds cognitive engagement, which adds to the accuracy and reliability of the FAS.

Healthcare professionals from multiple countries have consistently employed the FAS in clinical research and patient management and support the use of the questionnaire in clinical research on fatigue management, follow-up, and assessments of clinical care programs, underscoring its practical application (Kølner-Augustson et al., 2021; Bråndal et al., 2016; Esteban-Burgos et al., 2022 Hendriks et al. 2018). Additionally, De Vries et al. (2010) identified that the FAS scores can also help measure and monitor other conditions such as depression, anxiety, and neuroticism, affirming that its use in this research project will help gather significant and valid psychometric results alongside cardiopulmonary data.

5. Results

Data was analysed using the Statistical Package for the Social Sciences (SPSS), version 28. Independent t-tests were conducted to compare differences between AYA blood cancer survivors and healthy controls. Paired t-tests were used to evaluate variable changes measured repeatedly over 24 hours within each group. Additionally, paired comparisons between the two groups assessed individual responses (e.g., differences between day 1 and day 2 results). This analytical approach aligns with established methodologies for comparing group and repeated measures data (Kim, 2015). The t-statistic refers to the ratio of the difference between the consecutive days of testing. A larger t-statistic demonstrates a more significant difference in the means relative to the data's variability. The p-value was also calculated as it is commonly used to predict if the value change happened by accident, error or random chance. It appears in nearly all medical research papers and has been used for almost a century (Fisher, 1950). It is critical to the credibility of the results. If the p-value is <0.05, it can be concluded that those findings are statistically significant. If the p-value is ≥ 0.05, the results are not considered statistically significant and may be due to random variation rather than an observed effect/correlation. An effect size from 0.0 to 0.2 is considered small, 0.4 to 0.7 medium, and large from 0.8 to 1.1 (Becker, 2000).

All results, except for time to fatigue and maximum workload, were taken as an average of the last-minute data from peak exertion. Variables such as RER peak and AT and O2 saturation peak and AT showed nearly perfect overlap with a minimal percentage difference between D1 and D2, demonstrating consistent efforts from both populations.

The mean body mass index (BMI) for healthy controls was 26.94 (± 8.02), while the mean BMI for cancer patients was 25.38 (± 5.66). Overall, the average BMI of the combined population was 26.2, categorising them as overweight. Baseline measurements, including blood pressure and resting heart rate (HR), showed no abnormalities in either group, with an average blood pressure of 127/79 mmHg and a resting HR of 71 bpm, both falling within the normal range for healthy adults (American College of Sports Medicine, 2014). The average age of participants ranged from 22 to 28 years, with a mean age of 25. An independent samples t-test showed no statistically significant differences in resting data between the two groups (Table 4.1 and 4.2).

The initial exercise test revealed no statistically significant differences between the two groups across various variables (VO_2 peak, VCO_2 peak, RER peak, RPE peak, O_2 Sat peak), indicating substantial similarities (Table 5.1). Cancer patients exhibited a shorter time to fatigue and a lower peak workload during the initial exercise test compared to the healthy controls; however, these results were not statistically significant. Cancer patients showed a higher average peak heart rate and a greater percentage of their age-predicted maximal heart rate (APMHR) during the first exercise test than the healthy controls. All participants reached the threshold for maximal effort, suggesting a solid baseline fitness level in the initial exercise test (Jay Hoffman, 2006; Lindheimer et al., 2020; Glaab & Taube, 2022).

Table 5.1 ***Day 1 CPET Data Cancer Patients vs Healthy Controls***

Day 1 CPET Results	**Cancer Patients**	**Healthy Controls**
Variables	**Day 1 Mean (SD)**	**Day 1 Mean (SD)**
VO_2 peak (ml/kg/min)	38.62 (± 16.21)	38.91 (± 14.14)
VCO_2 peak (ml/min)	3195.59 (± 1291.03)	3273.71 (± 590.79)
VE peak (L/min)	82.64 (± 32.91)	91.88 (± 23.44)
RER peak	1.21 (± 0.98)	1.20 (± 0.08)
Time to fatigue (seconds)	664.20 (± 112.96)	776.00 (± 208.99)
Workload peak (Watts)	186 (± 44.49)	222 (± 35.81)
HR peak (bpm)	185 (± 8.87)	178 (± 14.46)
Per cent of MHR achieved (%)	95.09 (± 4.69)	91.16 (± 6.89)
O_2 Sat peak (%)	95 (± 5.08)	94 (± 2.17)
RPE peak (6-20)	18 (± 1.41)	18 (± 1.64)
SBP peak (mm Hg)	142.8 (± 10.35)	150.0 (± 16.91)
DBP peak (mm Hg)	85.2 (± 10.06)	91.2 (± 6.57)

AT VO_2 (ml/kg/min)	17.64 (± 3.38)	23.11 (± 8.96)
AT VCO_2 (ml/min)	1143.96 (± 377.84)	1588.46 (± 288.11)
AT VE (L/min)	31.55 (± 9.49)	39.78 (± 6.94)
AT RER	1.01 (± 0.04)	0.98 (± 0.04)
HR AT (bpm)	132.4 (± 12.4)	121 (± 20.38)
AT O_2 sat (%)	89 (± 8.14)	94 (± 3.21)
AT Workload (Watts)	75 (± 31.82)	108 (± 24.65)

The second day of testing revealed many significant declines in the cancer patients' peak variables (VO_2 peak, VCO_2 peak, time to fatigue, Workload peak, HR peak, per cent of MHR achieved). At the same time, the healthy controls had relatively little change or even saw slight improvements in peak physiological variables (VO_2 peak, VCO_2 peak, Workload peak).

The anaerobic threshold data contrasted the two groups, with the cancer patients having a much more significant increase of VO_2 and VCO_2 at AT than the healthy controls.

Table 5.2 ***Day 2 CPET Data Cancer Patients vs Healthy Controls***

Day 2 CPET Results	Cancer Patients	Healthy Controls
Variables	Day 2 Mean (SD)	Day 2 Mean (SD)
VO_2 peak (ml/kg/min)	35.34 (± 16.67)	40.19 (± 14.61)
VCO_2 peak (ml/min)	2604.27 (± 928.01)	3313.29 (± 793.39)
VE peak (L/min)	72.91 (± 25.89)	90.95 (± 23.14)
RER peak	1.14 (± 0.65)	1.16 (± 0.07)
Time to fatigue (seconds)	528.60 (± 70.59)	738.20 (± 202.55)
Workload peak (Watts)	165 (± 45.00)	222 (± 38.83)
HR peak (bpm)	170 (± 13.16)	176 (± 19.73)
Per cent of MHR achieved (%)	87.11 (± 6.84)	89.51 (± 10.04)
O_2 Sat peak (%)	94 (± 5.36)	94 (± 3.05)

RPE peak (6-20)	18 (± 1.30)	18 (± 1.92)
SBP peak (mmHg)	162.4 (± 39.25)	149.4 (± 8.47)
DBP peak (mmHg)	85.8 (± 10.40)	91.2 (± 3.89)
AT VO_2 (ml/kg/min)	18.80 (± 5.13)	24.10 (± 10.12)
AT VCO_2 (ml/min)	1286.33 (± 207.15)	1642.39 (± 306.87)
AT VE (L/min)	36.05 (± 5.93)	42.54 (± 7.83)
AT RER	1.02 (± 0.05)	0.98 (± 0.03)
HR AT (bpm)	124 (± 9.85)	120 (± 12.62)
AT O_2 sat (%)	89 (± 9.36)	96 (± 2.05)
AT Workload (Watts)	78 (± 28.85)	108 (± 19.56)

Table 5.3 displays the mean percentage change in variables monitored during the 24-hour repeated CPET. Significant results are highlighted in red and discussed below.

Table 5.3 ***Per Cent Change in CPET Physiological Variables of Cancer Patients and Healthy Controls***

	Cancer Patients	Cancer Patients	Healthy Controls	Healthy Controls
	% Difference D1 vs D2 results	T value (Two-sided p-value)	% Difference D1 vs D2 results	T value (Two-sided p-value)
VO_2 peak (ml/kg/min)	-8.93%	1.774 (0.151)	3.24%	0.155 (0.310)
VCO_2 peak (ml/min)	-18.50%	3.216 (0.032)	1.20%	0.409 (0.819)
VE peak (L/min)	-11.77%	1.641 (0.176)	-1.02%	0.389 (0.777)
RER peak	-5.79%	1.166 (0.309)	-3.39%	0.127 (0.254)
Time to fatigue (seconds)	-20.42%	3.950 (0.017)	-4.99%	0.167 (0335)
Workload peak (Watts)	-12.59%	5.715 (0.005)	0.00%	0.500 (1.000)
HR peak (bpm)	-8.60%	6.935 (0.002)	-1.24%	0.330 (0.660)

Per cent of MHR achieved (%)	-8.39%	6.915 (0.002)	-1.83%	0.244 (0.487)
O_2 sat peak (%)	-0.84%	0.259 (0.808)	-0.64%	0.383 (0.766)
RPE peak	1.11%	-0.535 (0.621)	-2.22%	0.187 (0.374)
SBP peak (mm Hg)	13.73%	-0.962 (0.390)	-0.40%	0.474 (0.948)
DBP peak (mm Hg)	0.70%	-0.318 (0.766)	0.00%	0.500 (1.000)
AT VO_2 (ml/kg/min)	6.46%	-0.888 (0.425)	4.19%	0.180 (0.359)
AT VCO_2 (ml/min)	12.45%	-0.820 (0.458)	3.34%	0.259 (0.518)
AT VE (L/min)	14.26%	-0.887 (0.425)	6.71%	0.033 (0.066)
AT RER	0.99%	-1.291 (0.266)	0.00%	0.500 (1.000)
HR AT (bpm)	-6.88%	(0.253)	-0.99%	
AT O_2 sat (%)	-0.32%	0.125 (0.906)	1.47%	0.192 (0.385)
AT Workload (Watts)	6.67%	0.302 (0.778)	0.00%	0.500 (1.000)

5.1 24-hour repeated CPET Results

On the second day of testing, the cancer patients' time to fatigue decreased significantly (p 0.017) by 20.42% (over 2 minutes on average). In contrast, the reduction in the healthy controls was roughly four times less, declining by 4.99% (Figure 5.2). In addition, every cancer patient's test duration decreased, whereas only ⅗ of healthy controls had a reduction (Figure 5.1). There was an immense t value (3.95)

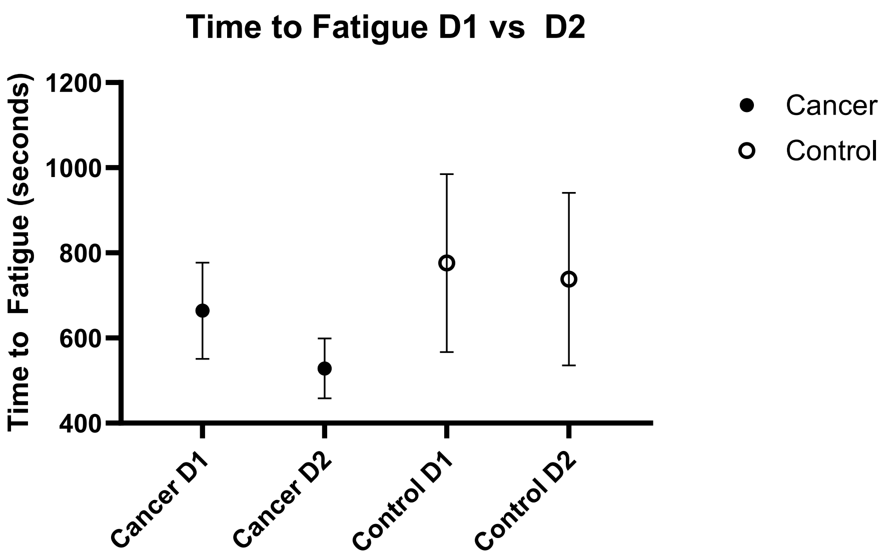


Figure 5.1 ***24-Hour Repeated CPET Results Time to Fatigue***

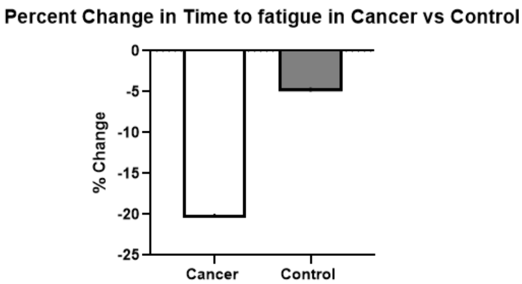


Figure 5.2 ***Percent Change in Time to Fatigue Cancer vs Control***

Cancer patients exhibited significant reductions in HR peak, with an average decrease of 8.40% (Figure 5.3 & 5.4) in HR peak and 8.39% in the percentage of age-predicated maximal heart rate (APMHR) achieved. In contrast, healthy controls showed much smaller reductions of 1.24% in HR peak (Figure 5.4) and 1.83% in the percentage of APMHR achieved. The differences were supported by large t-values in this study for HR max achieved (6.935), with statistically significant p-values (p = 0.002). On the first day of exercise testing, all bar one cancer patients scored over 90% of their APMHR, with the other scoring 89.69%. In complete comparison, only one cancer patient exceeded 90% of their APMHR on the second day.

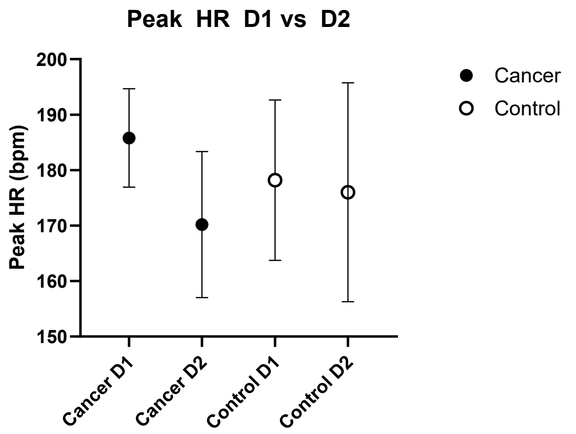


Figure 5.3 ***HR Peak Cancer vs Control***

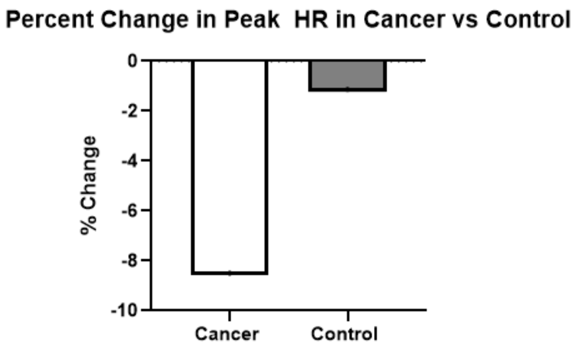


Figure 5.4 ***Percent Change in Peak HR Cancer vs Control***

Every cancer patient had a reduced workload peak in the second exercise test (Figure 5.5). The most minor difference was 5.88% (Interestingly, this participant happened to have the shortest time since the last treatment for their cancer, 4 years), and the most significant decrease was 16.67% (conversely, they had the second longest time since treatment, 9 years). The average decrease for the cancer patients was 12.59%. Interestingly, the healthy controls workload max (and workload at threshold) did not change between days, signifying no reductions in exercise capacity in this population. The fact that the healthy controls had no reduction, and such a massive change was recorded in the cancer patients, highlights that there is a profound effect limiting the exercise capacity in cancer patients despite the average test duration being around 10 minutes on both days for the cancer patients. The t-value was significantly high at 5.715, and the two-sided p-value was below the 0.05 threshold (p = 0.005).

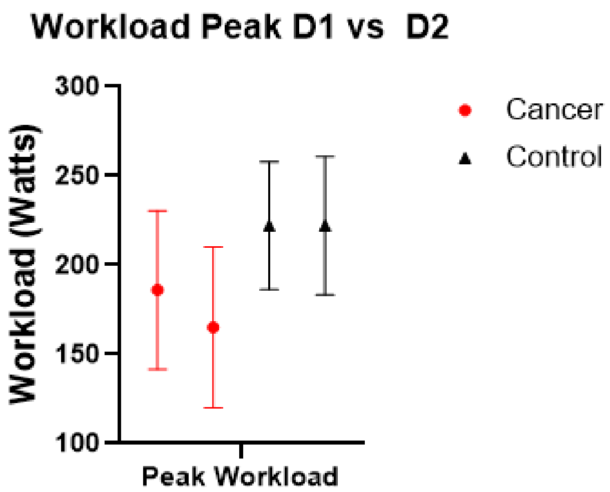


Figure 5.5 ***Workload Peak Cancer vs Control***

Every cancer patient's VCO_2 peak decreased significantly (18.50% on average), while the VCO_2 of healthy controls increased on average on the second exercise test (1.20%). Despite the lower VCO_2 peak in the cancer patients, their VCO_2 at AT was 12.45% higher on the second exercise test, whereas the healthy controls' VCO_2 at AT only increased by an average of 3.34%.

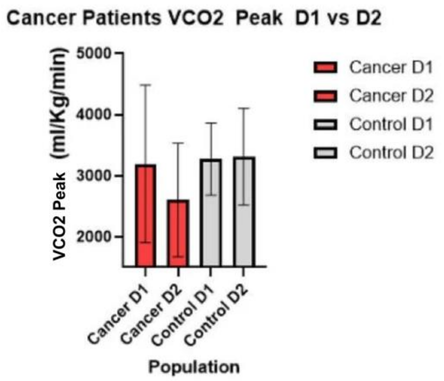


Figure 5.6 ***VCO2 Peak Cancer vs Control***

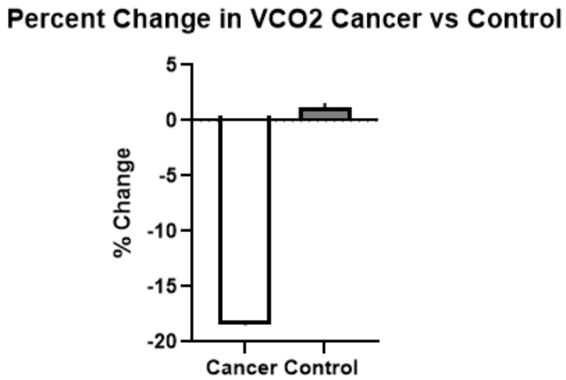


Figure 5.7 ***Percent Change in VCO2 Peak Cancer vs Control***

Cancer patients' peak ventilatory equivalent (VE peak) decreased by 11.77%, whereas healthy controls experienced only a 1.02% decline. This substantial reduction in VE peak among cancer patients suggests impaired respiratory and muscular efficiency, likely driven by systemic inflammation. The between-group comparison yielded a large t-value of -2.506, highlighting a that there is a key between cancer patients and healthy controls. Within the cancer group, the t-value was -0.887, indicating a less pronounced but a notable decline.

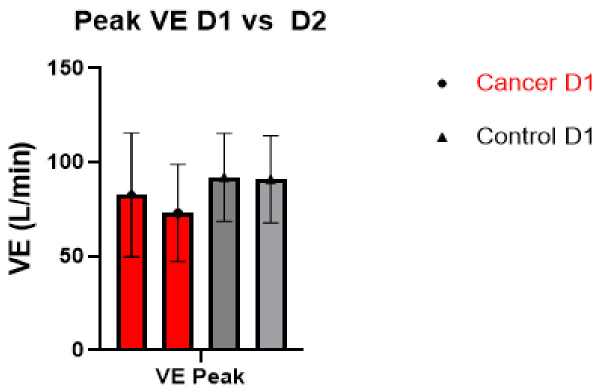


Figure 5.8 ***Peak VE Cancer vs Control***

All cancer patients experienced a decline in VO_2 peak on the second day of exercise testing. The magnitude of the decrease varied, with Participant #1 showing the smallest reduction of VO_2 peak, declining by only 1.03% (Day 1: 61.83 ml/kg/min; Day 2: 61.2 ml/kg/min). Notably, this participant had a VO_2 peak considerably higher than the other cancer participants and the general population, potentially limiting their representativeness of blood cancer patients. The largest decline in cancer patients was observed in Participant #3, with a 25.59% reduction in their VO_2 peak. Cancer patients exhibited an average 8.49% decrease ($p = 0.151$). In contrast, healthy controls showed an average increase of 3.24% ($p = 0.310$) on the second exercise test. Statistical analyses revealed a trend toward significance in the cancer group ($t = 1.774$) but not in the control group ($t = -1.161$).

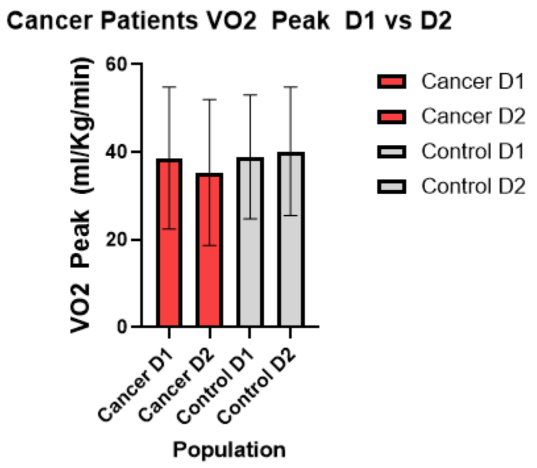


Figure 5.9 ***Peak VO_2 Cancer vs Control***

Cancer patients reported similar or higher RPE scores during the second day of exercise testing despite significant reductions in the internal (HRmax and % of APMHR achieved) and external measures (peak workload and time to fatigue) during the second test, indicating a physiological limit but unchanged self-perceived exertion.

Results were mixed for the VO_2 at the threshold for both groups. Three participants in the cancer patients had an increased VO_2 at AT, while two in the healthy controls had an increased VO_2 at AT. Overall, the cancer patients had an increase in the total mean VO_2 at AT of 6.58%, and the healthy controls increased by 4.19%.

All participants met the threshold (1.10) for maximal exertion as seen through their RER results (AYA blood cancer patients D1 1.21, D2 1.14; HC D1 1.20, D2 1.16). There was a similar decrease in RER in test two, but this was non-significant and still reached the threshold, which indicates maximal exertion from participants.

All cancer patients' HR was higher in the first minute of the 5-minute recovery protocol on the first exercise test than in the second (Table 5.4). Interestingly, when comparing the two groups' recovery data, the total decrease in HR (difference in HR at minute 5 vs minute 1) was lower in the cancer patients (dropping from 32.6 on day 1 to 24.6 on day 2). At the same time, the healthy controls had an increase in the HR difference at the start of the recovery protocol compared to day 1 (D1 25.4 - D2 33.4), showing a reduced recovery efficiency, fatigue accumulation or impaired autonomic recovery in the cancer patients. These results clearly contrast the two populations, but neither was statistically significant.

Table 5.4 ***Reductions in HR throughout the Recovery Protocol Cancer Patients vs Healthy Controls***

	Cancer Patient Mean Day 1	Cancer Patient Mean Day 2	Healthy Control Mean Day 1	Healthy Control Mean Day 2
Patient	Reductions in HR (Bpm) during recovery protocol after CPET			
#1	49	50	27	48
#2	31	32	24	13
#3	26	13	21	48
#4	35	22	32	39
#5	22	6	23	19
Mean (SD)	32.6 (4.16)	24.6 (6.89)	25.4 (1.71)	33.4 (6.58)
T-test	1.43		-0.83	
P value	0.21		0.43	

The additional questionnaires and the CPET data provided additional supporting information; only the responses to the first question had a similar undertone. Both groups reported a feeling of fatigue expected from an exercise test and that their legs felt "heavy" (Table 5.5 and 5.6). The responses noticeably differed when asked, "*How they felt the day after the first exercise test"* (question 2). Many of the cancer patients reported symptoms of fatigue, yet none of the healthy controls reported any residual fatigue. Following the second exercise test (question 3), two cancer patients reported brain fog and a higher level of fatigue than the first exercise test. Again, the healthy controls did not report any significant fatigue and found the test and feeling after exercising similar to that from the first day of testing. The day following the second exercise test, the results differed significantly. Nearly all (4) cancer patients reported that the fatigue affected their ability to function normally: "I struggled to get through work the following day after the exercise test", whereas the healthy controls reported little change or effects ("I felt normal"). When asked how long it took the participants to review following the second exercise test, cancer patients reported feeling ill effects from testing 24-48 hours after exercising. In contrast, the healthy controls felt fine the following day. The symptoms reported by cancer patients after the exercise test, such as brain fog, impaired memory, and light-headedness, were not reported by the healthy controls.

Table 5.5 Cancer *Participants Most Common Comments Following the 24-Hour Repeated CPET*

1.) How did you feel following the first exercise test?	*"It felt like my legs gave out first."* *"I had cramps in my quads."* *"I felt breathless."* *"I feel tired, but nothing out of the ordinary"*
2.) Describe how you felt the day after the first exercise test.	*"I felt like I had not gotten much sleep; this made me easily agitated, lots of bodily fatigued and had a lot of brain fog."* *"I did not feel too bad; I did not feel any obvious signs of fatigue."*
3.) How did you feel following the second exercise test?	*"I had bad brain fog again."* *"My legs feel very heavy and numb."* *"I feel less out of breath than the first exercise test but found breathing harder during the testing."*
4.) Describe how you felt the day after the second exercise test.	*"I felt a lot of brain fog and lethargic."* *"I struggled to get through work the following day."* *"I had a lot of mental fatigue in the afternoon and more fatigue than usual in the evenings."*
5. How long did it take you to recover from the second exercise test? For example, how long did it take to feel normal again?	*"I felt the effects of the exercise test two days after."* *"The fatigue was worse for me the day after the second exercise test."*
6.) Describe symptoms, if any, experienced after the exercise tests.	*"My muscles felt tight, and I felt a little lightheaded."* *"Brain fog impaired my memory and ability to concentrate."*

Table 5.6 ***Healthy Controls Most Common Comments Following the 24-Hour Repeated CPET***

1.) How did you feel following the first exercise test?	*"I felt a bit tired immediately after the test, but it was normal after exercise."* *"My legs feel almost numb"*
2.) Describe how you felt the day after the first exercise test.	*"I felt completely normal. No soreness, no remaining weariness."* *"I felt fine within a couple of hours and did not notice any fatigue during my everyday tasks."* *"I don't think it affected my ability to exercise on the second exercise test."*
3.) How did you feel following the second exercise test?	*"Similar to the first test—I was a little fatigued straight after, but nothing unusual."* *"I recovered pretty quickly and felt fine within a few hours."*
4.) Describe how you felt the day after the second exercise test.	*"I felt normal; there was no muscle soreness or fatigue, and I could exercise normally."*
5. How long did it take you to recover from the second exercise test? For example, how long did it take to feel normal again?	*"Within a few hours after finishing, I felt normal."*
6.) Describe symptoms, if any, experienced after the exercise tests.	*"I did not really experience any symptoms. Just the usual temporary tiredness after exercise, but no soreness, headaches, or anything unusual."*

5.2 SF-36 results

The findings from the SF-36 dimensions indicated significant differences in health-related quality of life between cancer patients and healthy controls across various areas. Cancer patients reported notably lower scores in role limitations due to emotional problems, energy levels, and fatigue, with large effect sizes of 3.13 and 2.99, respectively. This suggests a substantial impact on their emotional functioning and feelings of fatigue.

Furthermore, cancer patients experienced significantly lower emotional well-being, with an impressive effect size of 5.56. This emphasises the emotional challenges faced by cancer survivors. General health was also reported to be significantly poorer among cancer patients, showing a statistical difference ($p = 0.0255$) and a large effect size of 2.99.

While differences in physical functioning, role limitations due to physical health, social functioning, and pain were noted, these did not reach statistical significance. However, the effect sizes in these areas ranged from moderate to large, indicating potential clinical relevance.

Overall, cancer patients reported a lower health-related quality of life, particularly in emotional and fatigue-related domains. This underscores the lasting impact of cancer and its treatment on both physical and emotional well-being.

Cancer patients and healthy controls completed the SF-36 questionnaire. Paired t-tests revealed significant differences in role limitations due to emotional issues, energy and fatigue, emotional well-being, and general health (see Table 5.7).

Table 5.7 ***Cancer Patient and Healthy Controls SF-36 Results***

SF-36 Dimensions	**Cancer Patients n = 5 Mean (SD)**	**Control n = 5 Mean (SD)**	**P value**	**Effect Size**
Physical Functioning	95.00 (±5.00)	98.57 (±2.44)	0.1959	1.4766
Role limitations due to Physical Health	85.00 (±22.36)	92.86 (±12.20)	0.5036	0.7135
Role Limitations Due to Emotional Problems	66.80 (±23.69)	100 (±0.00)	0.0351	3.1337
Energy and Fatigue	55.00 (±16.96)	80.71 (±10.58)	0.0230	2.9997
Emotional Well-Being	58.40 (±7.27)	80.43 (±6.00)	0.0006	5.5602
Social Functioning	72.60 (±22.45)	86.57 (±16.71)	0.2770	1.1780
Pain	83.60 (±9.74)	92.57 (±9.98)	0.1542	1.5572
General Health	50.00 (±20.31)	80.00 (±11.18)	0.0255	2.9947

The mean scores of the cancer patients are lower in every dimension of the SF-36 compared to the healthy controls. The cancer patients scored lowest in the general health category (37.5/100), energy and fatigue (52.5/100), and emotional well-being (54/100).

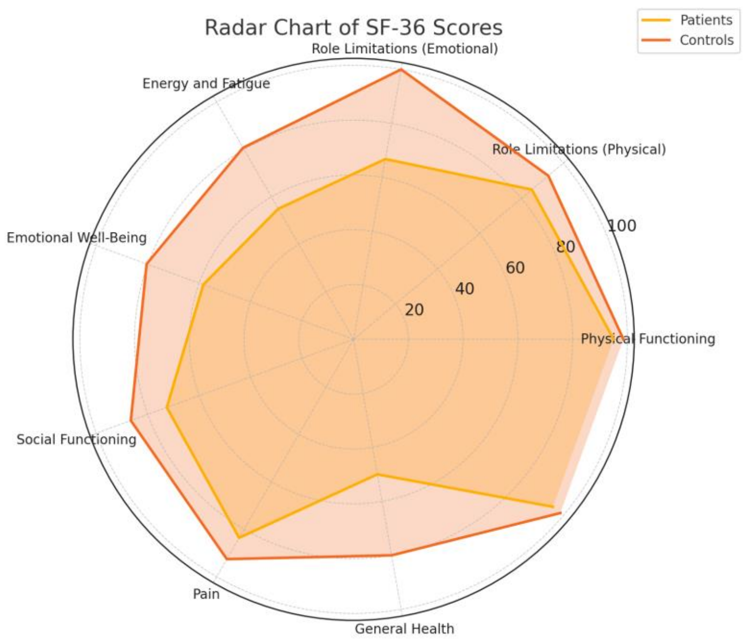


Figure 5.11 ***Radar Chart of the Healthy Controls vs Cancer Patients Scores***

Role limitations stemming from emotional issues were significantly lower in cancer patients (66.80 vs. 100.00, $p = 0.0351$, effect size = 3.1337). Additionally, cancer patients exhibited notably reduced energy levels and increased fatigue compared to healthy controls (55.00 vs. 80.71, $p = 0.0230$, effect size = 2.9997). The large effect size underscores the significant impact of fatigue in cancer patients, aligning with reports that identify cancer-related fatigue as a considerable burden. Furthermore, cancer patients' emotional well-being was significantly diminished (58.40 vs. 80.43, $p = 0.0006$, effect size = 5.5602). This substantial difference indicates that cancer patients experience poorer mental health and emotional stability relative to healthy controls. Cancer patients also reported significantly worse perceptions of their general health (50.00 vs. 80.00, $p = 0.0255$, effect size = 2.9947), suggesting they regard their health as substantially poorer than that of healthy individuals of similar age, which may reflect both subjective experiences and genuine health limitations.

The SF-36 results show that the cancer patients had slightly lower physical functioning scores (95.00 vs. 98.57, $p = 0.1959$), role limitations due to physical health (85.00 vs. 92.86, $p = 0.5036$), social functioning (72.60 vs. 86.57, $p = 0.2770$) and higher pain levels (83.60 vs. 92.57, $p = 0.1542$) compared to healthy controls. However, these differences were not statistically significant. They had a limited effect size, although social functioning had an effect size of 1.1780, which suggests a moderate impact, implying that social engagement might be affected by CRF/PEM.

FAS Results 5.3

The Fatigue Assessment Scale (FAS) has been used to assess the impact of chronic conditions on fatigue levels experienced by different populations. Its efficient completion time, coupled with the substantial data it provides, has led to its use in various research studies (Poopady et al., 2022; Michielsen et al., 2003; Al Maqbali et al., 2019). Scoring out of a maximum of 30 shows that higher scores correlate with increased fatigue levels.

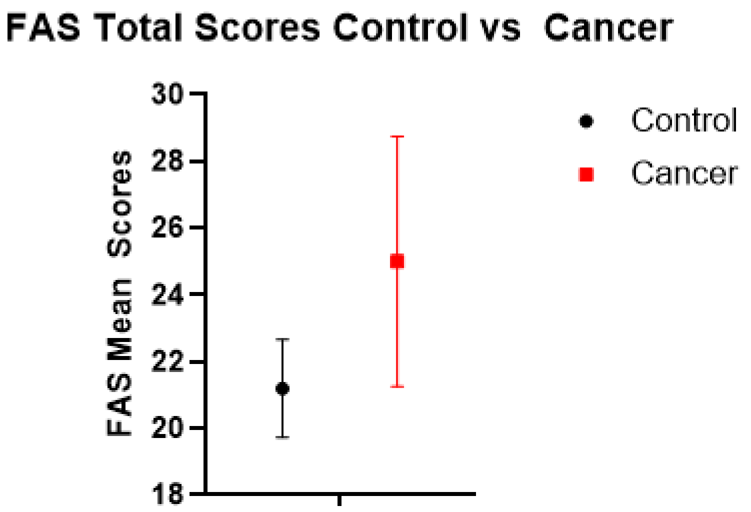


Figure 5.12 ***FAS Mean Scores***

The FAS measures fatigue with total scores ranging from 10 to 50. A score below 22 indicates no fatigue, while a score between 22 and 34 suggests mild to moderate fatigue, and a score of 35 or above indicates severe fatigue. The mean total score for the healthy controls shows no significant fatigue, with a score of 21.1 (Table 5.9), whereas cancer patients exhibit mild to moderate fatigue with an average score of 25. Although a significant difference was observed, the p-value exceeded the traditional threshold of <0.005. The repeated CPET test further demonstrated this, as the cancer patient group could not recover within the 24 hours between tests. In contrast, the healthy controls replicated the data from the first day of exercise testing. Additionally, the healthy controls reported no effects of fatigue in the supplementary fatigue group, compared to cancer patients who experienced various side effects from exercising, such as brain fog and fatigue, despite having comparable fitness levels (VO_2 peak).

Table 5.9 ***FAS Data Analysis***

FAS Data Analysis	Total Score (SD)	Cohen's d	P-value
Healthy control	21.1 (±1.09)	1.2	0.095
Cancer Patient	25 (±3.74)		

6. Discussion

Until recently, CPET exercise testing was primarily conducted as a pre-surgical assessment for cancer patients and not for any other purpose (Jones et al., 2008). However, more recently, it has been employed to evaluate cardiorespiratory fitness both before and after treatment as well as screening patients before they can participate in clinical trials (Stenehjem et al., 2016; Armand et al., 2023 and Weinkauf et al., 2024) yet this study demonstrates it has further value in assessing CRF in cancer survivors. This study aimed to assess a gap in the literature by examining changes in physiological responses associated with CRF and the impact on exercise capacity parameters in adult blood cancer survivors and healthy controls over a 24-hour repeated exercise protocol (the first study to directly compare adult blood cancer survivors' repeated exercise responses to healthy controls). This study assessed various physiological variables at VO_2 peak and the anaerobic threshold to better characterise, define and understand fatigue in adult blood cancer survivors. We hypothesised that patients receiving treatment for haematological malignancies who have achieved remission would exhibit a significant decline in their physiological exercise capacity during the second day of testing in a 24-hour repeated CPET as seen through a considerable reduction in their VO_2 peak, workload peak and time to fatigue on the second exercise test. Notable decreases in key metrics were anticipated, including peak workload, maximal heart rate, VCO_2 peak, VO_2 peak, and time to fatigue. As hypothesised, significant declines in all of these variables were observed; however, there was only a slight decrease in the VO_2 peak among cancer patients. Furthermore, it was anticipated that the FAS and the SF-36 scores of cancer survivors would be significantly lower than those of healthy controls, with FAS scores being notably higher. Additionally, it was hypothesised that cancer patients would score the lowest in the energy and fatigue domain, followed closely by their general health. This hypothesis was confirmed; however, the most pronounced decline and notable difference compared to healthy controls and existing literature was observed in the emotional well-being section of the SF-36 among AYA blood cancer survivors.

This study has shown that performing a single maximal exercise test cannot accurately observe differences between healthy controls and adult blood cancer survivors as both AYA blood cancer survivors and healthy controls were of similar cardiorespiratory fitness (38.62 and 38.91 $ml.kg.min^{-1}$, respectively) on the first day of testing, contrary to that which was recently reported in a systematic meta-analysis by Weinkauf et a. 2024, where a marked reduction in childhood cancer survivors was seen when compared with age-matched controls (7.1 $ml.kg.min^{-1}$). However, several other studies have reported similar fitness levels between childhood cancer survivors and age-matched controls (Armand et al., 2023; Lanfranconi et al., 2014; Hasuer et al., 2001) similar to that found in this study (on the first day of exercise testing) and similar to adult lymphoma survivors (42.2 +/- 9.8) (Armand et al, 2023) as well as healthy active college athletes (Srivastava et al., 2024; Fitzgerald et al., 1997) Akin to the research from Weinkauf et al. 2024. No differences were found in any of the traditional measures, such as peak heart rate, systolic blood pressure, diastolic blood pressure, rating of perceived exertion, carbon dioxide production, or ventilation in the first exercise test, suggesting that there is no indication of cardiac dysfunction or increased cardiovascular risk within this group solely from the first day of exercise testing.

Repeated exercise protocols were used in this study to elicit a CRF response in cancer patients, as it was distinguished that functional differences in individuals with symptoms of PEM did not become evident until day two of the protocol in individuals with ME/CFS (Hodges et al., 2018). Furthermore, the current study provides new reasoning and backing for a repeated exercise testing protocol in adult blood cancer survivors, identifying those differences between AYA blood cancer survivors and healthy control responses, which only became evident after a second maximal exercise test. Thus, a repeated exercise protocol is required to distinguish the effects of exercise on AYA blood cancer survivors compared to comparable healthy populations and further discover the effects of CRF, which appears to have a similar presentation to those with ME/CFS.

The study's findings support the hypothesis and align with existing literature on post-exertional malaise (PEM) in individuals with ME/CFS. Specifically, those affected by PEM who cannot maintain the same exercise workload between consecutive days (Snell et al., 2013; Hodges et al., 2018). In this study, a significant reduction in peak workload on day 2 among AYA blood cancer survivors, with a decrease of -21 W compared to healthy controls, who exhibited no change was observed. This is consistent with recent research on ME/CFS, which reported substantial decreases of -12 W (Hodges et al., 2018) and -27.31 W (Snell et al., 2013) within the ME/CFS population. Therefore, we can conclude that a 24-hour repeated cardiopulmonary exercise test (CPET) is a valid method for assessing PEM, or, in this instance, CRF among cancer survivors.

A notable difference between this study and those PEM studies was that four out of five AYA blood cancer participants experienced a reduction in VO_2 peak between repeated tests. The VO_2 peak reflects the highest VO_2 uptake achieved by participants during the exercise test. This variable is determined by the combined functions of the cardiovascular, pulmonary, and skeletal muscle systems, making it a robust indicator of overall cardiorespiratory fitness. VO_2 peak is widely recognised as a critical marker of disease severity in conditions such as heart failure (HF), hypertrophic cardiomyopathy (HCM), pulmonary arterial hypertension (PAH), and chronic obstructive pulmonary disease (COPD) and serves as a valuable prognostic tool for many patients (Swank et al., 2012; Guazzi et al., 2012). Although this was a non-significant finding, this was a pilot study, and if participant numbers increased, this could become significant and worthy of future research and attention. This finding aligns with the prevalence of CRF and its associated impacts on QOL due to impaired cardiorespiratory performance and an increased risk of pulmonary complications. The diminished VO_2 peak in these participants highlights the physiological challenges posed by CRF/PEM, suggesting an impaired ability to sustain high-intensity exercise and recover adequately between sessions. Armand et al. 2023, demonstrated that adult survivors of childhood lymphoma survivors had lower muscular efficiency, causing greater fatiguability in response to exercise, possibly related to chemotherapy and other cancer treatments (radiation therapy and stem cell transplants).

As there were little physiological variables differed at the anaerobic threshold, unlike those in the ME/CFS group (Hodges et al., 2018). Therefore, this is further evidence that cancer survivors with CRF must undertake repeated maximal cardiorespiratory fitness tests to comprehend and assess the physiological limitations that may be contributing to their fatigue symptoms.

The VO_2 at the ventilatory threshold (AT) indicates the point at which the energy demands on the muscles and cardiovascular system become disproportionately high in relation to oxygen consumption. An elevated VO_2 at AT suggests less efficient oxygen utilisation and an increased energy cost to achieve the same power output. This inefficiency, observed in four out of five cancer patients, highlights the effect of CRF on oxygen utilisation and delivery during exercise in cancer patients in remission. These findings are the opposite of those in Table 6.1, whereby ME/CFS patient's VO_2 at the threshold decreased significantly on the second exercise test (-12.52%). The increase of VO_2 at the threshold in cancer patients implies dysregulation and impaired blood flow and oxygen delivery (common characteristics of CRF) in this demographic, exacerbating metabolic impairment and diminishing exercise performance and recovery (Keller et al., 2024). The rise in VO_2 at AT underscores the heightened physiological strain experienced by cancer patients during submaximal exercise, contributing to a greater cardiovascular strain despite a constant workload. This reflects a compensatory response to compromised oxidative metabolism. Such inefficiency may lead to fatigue, reduced endurance, and a decreased capacity for physical activity in individuals affected by CRF. There was little change in other physiological variables at the anaerobic threshold in the 24-hour repeated CPET, unlike those in the ME/CFS group (Hodges et al., 2018). Therefore, this is further evidence that cancer survivors with CRF must undertake repeated maximal cardiorespiratory fitness tests to comprehend and assess the physiological limitations that may be contributing to their fatigue symptoms.

VCO_2 represents the body's carbon dioxide production, which is influenced by various physiological factors, including cardiac output, the blood's capacity to carry CO_2, and gas exchange efficiency at the tissue level. Oxygen consumption and carbon dioxide production are closely matched during shorter, less intense exercise bouts where glycogen is the primary energy source. Notably, fat metabolism produces less CO_2 per unit of O_2 consumed than carbohydrate metabolism, resulting in relatively lower VCO_2 during fat utilisation. However, during prolonged or maximal exercise (particularly evident in the later stages of the CPET exercise test), VCO_2 production increases significantly, reflecting the metabolic shift in the body as it transitions from carbohydrates to fat utilisation, which usually occurs due to glycogen depletion or fatigue. At greater exercise intensities, the slope of the VCO_2 vs. VO_2 relationship (analysed using the V-slope method) steepens sharply as bicarbonate buffering of lactic acid is the primary driver of this neutralising lactic acid. As bicarbonate neutralises hydrogen ions, it results in an elevated output of CO_2. This study found a statistically significant decrease in the VCO_2 peak among all cancer participants (mean difference = -559.21, 95%

CI = [-956.85, -161.58]). This decreased VCO_2 peak on the second exercise test highlights the reduced capacity for the cancer patients to sustain exercise due to the reduced ability of the cardiorespiratory and metabolic systems to fail to meet the demands of the exercise test due to the effects of CRF/PEM. It is unknown if these findings are shared with other demographics and research on CRF/PEM or ME/CFS, as VCO_2 is not commonly reported in the literature.

Pulmonary ventilation (VE) represents the total volume of air passing through the lungs, which increases proportionally with metabolic demand during exercise to maintain arterial blood gas levels, acid-base balance, and pH (Phillips et al., 2020). VE is a crucial indicator of ventilatory efficiency and cardiovascular health and is widely used as a marker of disease severity and prognosis in people with cancer and heart failure (Guazzi et al., 2012; Yang et al., 2011). The average reduction of 11.77% in cancer patients when the healthy controls only had a decrease of 1.02% suggests that there are altered VE patterns in the cancer patients that signify an impaired ventilatory uptake, which will contribute to decreased exercise tolerance.

Oxygen saturation (O_2 Sat) measures the percentage of haemoglobin in the blood bound to oxygen molecules and is often considered a fifth vital sign in the medical field. O_2 sat is frequently used to interpret, identify and monitor lung function, blood flow, and tissue metabolic activity (Sharma, 2018). The normal range in adults is 95–100. In this study, O_2 Sat remained stable in blood cancer participants at the ventilatory threshold (AT) and during maximal exertion. Similarly, healthy controls demonstrated a slight decrease in O_2 Sat at maximal exertion (-0.64%) and a minor increase at AT (1.47%). O_2 Sat in both groups remained above the clinical threshold of 95% throughout the exercise protocols. These findings indicate that oxygen transport and utilisation were preserved during exercise, suggesting that CRF/PEM did not significantly impact this parameter.

The cancer patient (#1) with the shortest time since treatment had the most minor decrease in workload peak, and the cancer patient (#4) who had been in remission for the second longest time (9 years) had the most significant decrease in workload peak. This suggests that the time since the cancer patient's last treatment may be indicative of the severity of CRF/PEM they experience. These two patients do have different cancers and could have received differing treatments, highlighting the question of whether other types of cancers and treatments will have a more profound effect on cancer patients' CRF/PEM.

This study also observed significant decreases in peak heart rate and percent of APMHR from day one to day two, underscoring the profound impact of CRF on the autonomic nervous system. This condition impairs cardiovascular responsiveness and reduces exercise capacity. The lower maximal heart rate recorded in the second test likely indicates compromised autonomic regulation, delayed recovery, and cardiovascular fatigue—hallmarks of CRF. This reduced physiological exercise reserve limits participants' ability to achieve their maximum heart rate, constraining their exercise capacity and ability to perform ADL.

The participant HR data throughout the recovery protocol revealed some noteworthy distinctions. Cancer patients experienced a more minor reduction (minute 5 compared to minute 1) in HR than the first day, whereby the healthy controls had an increase in the amount of bpm reduced during the recovery protocol on the second exercise test. Since both groups were determined to be of comparable fitness levels (as indicated by D1 VO_2 peak and baseline characteristics), the differences in heart rate data underscore the negative impact of CRF on the cardiovascular system's ability to recover from exercise. The reduced bpm during the cancer patients' recovery protocol in the second exercise test suggests impaired recovery efficiency over multiple days, likely attributed to chemotherapy, radiation, or other treatments that may affect autonomic function and heart rate recovery (Javorka et al., 2002). The high standard deviation in cancer patients indicates variability in their recovery patterns. This inconsistency may stem from individual differences in factors such as autonomic function, fatigue levels, treatment effects, and variations like differing fitness levels, treatment histories, or diagnoses. While current evidence from this study is insufficient to definitively state that cancer patients exhibit significantly different heart rate reduction responses compared to healthy individuals, this limitation may be attributed to the small sample size. The restricted dataset impacts statistical power, potentially accounting for the lack of notable differences observed.

The data comparison of the first exercise test in this study and those studies from the literature review, which included a CPET examination (Table 6), shows that study participants outperform the literature averages in peak performance metrics, such as VO_2 peak and maximal workload, but underperform in submaximal measures like VO_2 and workload at the ventilatory threshold. The results (VE max, Time to Fatigue, Workload Max, O_2 sat and BMI) are surprisingly similar to those of the literature review, in which papers focus on singular CPET examinations.

When comparing the results from the initial test of the cancer patients to those found in the literature review, it is evident that the cancer patients in this study perform better at peak levels (VO_2 peak, peak workload, time to fatigue). However, they significantly underperform at the threshold level (VO_2, workload, VE). This discrepancy may be attributed to the younger average age and the shorter duration since the last cancer treatment among the participants in this study. However, the reduced efficiency—likely due to CRF/ PEM—emphasises the need for targeted interventions to improve submaximal endurance. Some physiological parameters remained relatively consistent between the two groups; for instance, measures such as RER peak, O_2 saturation, and BMI indicated similar body compositions across both cohorts.

Table 6.1 ***Literature Review Cancer Patients Data vs Included Cancer Patients Data***

Variables	Literature Review Cancer Patients Singular CPET Data	Cancer Patients included in This Study Data results from the first CPET	Percent (%) Difference of Lit Review VS this Study Results
VO_2 peak (ml/kg/min)	30.98	38.62	21.95%
VE peak (L/min)	80.42	82.64	2.72%
RER peak	1.21	1.19	-1.67%
Time to VO_2 max (seconds)	566	664.4	15.99%
Workload peak (watts)	162	186	13.79%
HR max (bpm)	185	186	0.54%
% of max HR achieved	93.43	95.09	1.76%
O_2 Sat at max (%)	95	96	1.05%
RPE max	17	18	5.71%
Blood pressure max (mmHg)	162/ 80	143/85	-12.46% / 6.06%
VO_2 at AT (ml/kg/min)	24.9	17.64	-34.13%
VE at AT (L/min)	24.35	31.55	25.76%
Workload at AT (watts)	146	75	-64.25%
BMI kg/m²	24.06	25.38	5.34%
Time since treatment	9.81	8.2	17.88%

Variables	Literature Review Cancer Patients Singular CPET Data	Cancer Patients included in This Study Data results from the first CPET	Percent (%) Difference of Lit Review VS this Study Results
VO_2 peak (ml/kg/min)	30.98	38.62	21.95%
VE peak (L/min)	80.42	82.64	2.72%
RER peak	1.21	1.19	-1.67%
Time to VO_2 max (seconds)	566	664.4	15.99%
(years)			
Average Age (years)	33.33	24.4	30.94%

It is well-documented that healthy individuals achieve a consistent maximum heart rate across both tests in the 24-hour repeated CPET (Becker et al., 2000; Riley et al., 1990; Montague et al., 1989). However, patients with ME/CFS exhibit a higher resting heart rate but a significantly lower maximum heart rate at exhaustion on the second test than the healthy controls in the reviewed studies. Similarly, in this study, cancer patients demonstrated a significant decline in maximal heart rate on the second test. In contrast, the healthy controls maintained a relatively stable HR peak across both tests. This decline in cancer patients likely reflects impaired autonomic regulation and delayed recovery, which can compromise cardiovascular response and exercise capacity. Consequently, these impairments may lead to fatigue, dizziness, irregular heartbeats, and heightened parasympathetic activity. As a result, cancer patients may struggle to maintain physical activity, limiting their ability to perform daily tasks and reducing overall functional independence. The similarities between patients with ME/CFS and those with CRF may provide a helpful comparison, while evidence, understanding and literature on this topic are limited. These parallels may also offer valuable insights into the potential mechanisms and clinical implications for cancer survivors.

Table 6.2 ***Cancer Patients vs ME/CFS Patients Percent Change in D1 vs D2 Variables in the 24-Hour Repeated CPET***

	AYA Blood Cancer Patients	ME/CFS Patients (literature review)
	Mean (SD)	
VO2 peak	-8.93 (±9.07)	-7.81 (±6.29)
VO2 at AT	6.46 (±10.82)	-12.52 (±8.54)
Workload Peak	-12.59 (±4.05)	-7.97 (±3.7)
Workload at AT	6.67 (±20.68)	-21.24 (±14.31)
HR peak	-8.6 (±2.7)	-3.24 (±2.16)
O_2 pulse at AT	-0.32 (±3.73)	-7.25 (±5.7)

Table 6.3 ***SF-36 Scores From the Literature Review Cancer Patients vs AYA Blood Cancer Patients Included in This Study***

Cancer patients	Literature Review Blood Cancer Patients Mean Scores	AYA Blood Cancer Patients in This Study Mean Scores
Physical functioning	84.93	95
Role limitations due to physical health	68.53	85
Role limitations due to emotional problems	80.67	66.8
Energy/fatigue	54.67	55
Emotional well-being	77.00	58.4
Social functioning	81.90	72.6
Pain	70.30	83.6
General Health	63.27	50

The AYA blood cancer patients included in this study displayed levels of physical functioning comparable to those of the healthy control group, as supported by the baseline fitness (VO_2 peak) and outcomes in this area. This aligns with the baseline results of Scott et al. (1999) and findings from literature reviews that include healthy controls and cancer patients. A similar observation can be made regarding the relationship between physical functioning and bodily pain, which are critical components of overall physical well-being measured by the SF-36 instrument.

There is a notable similarity among the three groups from New Zealand concerning physical functioning, role-physical, and bodily pain domains, suggesting minimal impact from CRF/PEM in this area. The consistency of results in these sections underscores the reliability of this study's methodology and the accuracy of group comparisons.

The results in the energy and fatigue domain align with the predicted hypothesis that cancer patients will score lower than healthy controls. Moreover, these scores are significantly lower than those reported in the literature and baseline values from Scott et al. (1999). Notably, the results are closely aligned with findings from other blood cancer patients in the literature (54.67 vs. 55), highlighting the substantial challenges these individuals face in this area. The pronounced lack of energy and high fatigue levels adversely affect emotional well-being and overall health. The inability to recover from previous tasks, along with low energy and the struggle to complete even basic activities, severely hampers daily functioning and QOL.

The role emotional domain of the SF-36 revealed unexpected and significant findings among the cancer patients in this study. They scored lower than every control and comparison group. They scored markedly worse than the other blood cancer patients from the literature review, who exhibited minimal effects and maintained a relatively high score in this domain (80.67). In contrast, the blood cancer patients in this study scored substantially lower (66.8), indicating significant difficulties in concentration and task completion due to emotional distress. This sharp decline suggests a reduced QOL linked to depression or anxiety associated with PEM, which will further impair their ability to carry out ADLs. The persistence of negative emotions may also severely impact overall well-being and daily functioning.

The emotional well-being scores were again lower than those of the healthy controls and data from the literature review. However, these results were not statistically different. This can indicate that participants do not struggle with social interactions throughout the day. However, the scores in the energy and fatigue domain may indicate that they may suffer from this after the interactions are over.

The most pronounced differences in scores were observed in the general health domain. Notably, blood cancer patients in this study scored a mere 50, a strikingly lower result than all comparison data and blood cancer patients from the literature. This domain reflects participants' perceptions of their overall health and expectations for future well-being.

The exceptionally low scores highlight a severe lack of confidence in their health, indicating a significant disease burden and long-term health concerns despite finishing their treatment. These findings may also signal the lasting detrimental effects of treatment, further impacting their QOL.

The findings indicate that cancer patients experience significant impacts on the emotional and fatigue-related dimensions of QOL as well as the physical. This underscores the importance of interventions aimed at mental health support, fatigue management, and emotional well-being, which could greatly enhance overall QOL. The results were consistent across some domains when comparing the general public, healthy controls, and other blood cancer patient's data from the literature review; however, notable differences emerged between emotional well-being, general health, and role emotional well-being. Remarkably, cancer patients in this study scored lower than healthy controls across all domains of the SF-36, with the most significant deficits observed in general health, energy and fatigue, and emotional well-being. These findings suggest that, although some physical aspects (e.g., role physical) are affected and the more obvious symptoms, the mental health challenges and emotional strain associated with CRF/PEM are a major concern, even for those in remission. Additionally, the results highlight the harmful effects of CRF and PEM on emotional regulation and social engagement. Consistent with the findings by Reulen et al. (2006), a ceiling effect was noted in the role limitation domain of the SF-36, which may restrict the generalisability of findings in this area. Ultimately, these results accentuate the necessity for future research into the cognitive and emotional consequences of CRF and PEM, particularly their effects on mental health and emotional well-being. Practical support strategies may include psychological counselling, social support services, and community-based interventions to enhance the quality of life for affected individuals.

Table 6.4 ***SF-36 scores From the Literature Review, New Zealand General Population and Healthy Controls Included in This Study***

Healthy controls/baseline	Literature Review Healthy Control Mean Scores	Baseline Values for the NZ General Population (Scott et al., 1999)	Healthy Controls in This Study
Physical functioning	91.53	91.20	98.57
Role limitations due to physical health	83.60	85.40	92.86
Role limitations due to emotional problems	89.27	84.40	100.00
Energy/fatigue	60.60	65.10	80.71
Emotional well-being	80.40	76.30	80.43
Social functioning	89.37	86.40	86.57
Pain	74.90	79.60	92.57
General Health	76.03	74.70	80.00

Note. The literature review includes the studies published by Kiserud et al., 2023, Eikeland et al.,2023 and Kanellopoulos et al., 2013.

The findings of this study highlight the burden of fatigue experienced by cancer patients, reinforcing existing literature that identifies fatigue as a pervasive and debilitating symptom in this population. Compared to healthy controls (21.1) and general population norms from the literature review (18.4), blood cancer patients in this study reported markedly higher fatigue levels. The consistency of fatigue scores among healthy controls with previous studies supports the reliability of the questionnaire used, further validating its use in assessing cancer-related fatigue. Interestingly, the cancer patients in this study (25) reported even higher fatigue levels than those documented in previous research on individuals with blood cancers (21.45). This suggests that the specific characteristics of this study cohort, such as treatment status, disease severity, or other contributing factors, may have amplified fatigue symptoms. Cancer patients consistently reported higher scores on the first two questions: "I am bothered by fatigue" and "I get tired quickly." Conversely, they provided lower scores on the fourth question: "I have enough energy for everyday life." This clearly illustrates the profound impact of fatigue as seen in the SF-36 and 24-hour repeated CPET. These scores signify a reduced overall quality of life in the cancer patient group, limiting engagement in their daily routines and lives. Although statistical significance was not observed, the effect size suggests that these findings remain meaningful, particularly given the well-established challenges associated with fatigue in cancer populations.

The consistently worse QOL and higher levels of fatigue perceived by the blood cancer patients highlight the need for targeted interventions to manage fatigue more effectively, including structured exercise programs, psychological support, and tailored lifestyle modifications. Given the far-reaching consequences of fatigue on both physical and emotional well-being, addressing this symptom should remain a priority in cancer care and survivorship planning.

6.1 Strengths, Limitations and Recommendations

A key strength of this study lies in its use of standardised and transparent methods for data collection and presentation, which ensure the repeatability and validity of the results. This standardised approach, along with a clear outline of the methods and materials, promotes collaboration and fosters the hope of advancing knowledge and sharing data with researchers globally.

Another vital strength of this study was the similarity in age and BMI between cancer patients and healthy controls. The average age was almost identical for both groups (AYA blood cancer survivors at 24.4 kg/m^2 and healthy controls at 24.6 kg/m^2). The BMI of AYA blood cancer survivors averaged 25.38, while that of healthy controls averaged 26.94. This ensured an accurate comparison between the two nearly identical populations, given their comparable levels of cardiovascular fitness (as observed in the first exercise test).

The innovative use of the 24-hour repeated CPET provided valuable insights not seen in other studies into this population's cardiovascular and physiological responses to maximal exercise testing. This approach gathers data that is scarce globally and cannot be obtained through a single CPET examination. The repeated exercise test revealed significant findings that could be missed with other methodologies. Additionally, the implementation of self-reported and subjective questionnaires aided in creating a more comprehensive understanding of CRF/PEM effects on patients' QOL experiences instead of relying solely on a single data collection method.

Limitations of this study included that this testing was conducted in a teaching university, so the heart rate monitors had slight variations despite being of the same make and model. Due to equipment failures, we were required to use two alternatives (Apple Watch and the SPo2 sensor) to measure the heart rates of two participants on the second day of exercise testing.

Additionally, selection bias cannot be ruled as a limitation in this study. Selection bias may have arisen as physically active participants are more likely to participate in a study with exercise requirements than sedentary participants. Consequently, this could lead to an overestimation of health-related physical fitness and exercise capacity compared to more sedentary eligible participants, who may be more representative of patients suffering from CRF/PEM, which this study aims to assess.

This study has a small sample size due to the difficulty of recruiting eligible participants and the short timeframe typical of research utilising the 24-hour repeated CPET. The small sample size limits the findings' generalisability, reliability, and weight. However, results can still be used in conjunction with other research. In addition to the small sample size, there is high variability in the modality and time since participants last received treatment, restricting the ability to generalise the information found in this study.

Self-reported questionnaires will always have limitations when included in research projects despite the potential for reliable and valid information; they remain subjective and can be influenced by many external factors, such as motivation, mood, sleep quality/duration, and hunger, as well as additional factors that can vary daily and affect results.

While a 2-day CPET protocol is critical for assessing PEM and chronic fatigue symptoms, it has several limitations. One notable drawback already discussed is the typically small sample sizes observed in studies utilising the 24-hour repeated CPET, primarily due to the significant time commitment required from participants and researchers. Additionally, there is a risk of relapse and episodes for individuals with conditions ME/CFS and CRF/PEM, which complicates the challenge of balancing comprehensive data collection with patient safety. The protocol is also costly, necessitating specialised equipment and trained personnel, which adds to the financial burden of such studies.

6.2 Implications for Future Research

Further research is needed into non-pharmacologic interventions such as low to moderate-intensity exercise programs, weight training, nutritional and sleep interventions, and restorative therapies. An exercise program has been proven feasible, as studies involving a training program with cancer patients have reported participation rates comparable to or exceeding those in studies with the general population (Oldervoll et al., 2003; Tsuda et al., 2023). This research project had a similar outcome, with 100% of cancer patients completing the exercise tests and expressing interest in how they could manage and possibly improve their CRF/PEM. These potential exercise interventions, as highlighted by Schoormans et al., 2020, Yeh et al., 2011, and Mock et al., 2000, alleviate cognitive dysfunction, enhance mood states, and reduce CRF/PEM, all while being low-cost to implement. Furthermore, Hilfiker et al. (2018) found that some non-pharmacological interventions could be more effective than prescribed medications at reducing the adverse effects of CRF/PEM, while also decreasing hospitalisation time and the burden on patients and hospitals.

Lucia et al. (2003) found that, given the current state of knowledge, cancer patients are advised to rest, reduce their physical activity levels, and manage their stress to avoid CRF/PEM. However, such recommendations can paradoxically worsen fatigue symptoms, as sedentary habits lead to muscular atrophy (and a loss of muscle greater than 5% of body weight, along with reduced cardiac output associated with sedentary behaviour, which doubles the mortality risk in cancer patients, according to Nichols et al., 2019) and diminish the body's ability to tolerate light exercise and cope with stressors. This sedentary behaviour can also adversely affect pain and stiffness, leading to a further decline in functional capacity.

Given the limited availability of comparative data, this study provides a crucial foundation and justification for future research to enhance the understanding of CRF/PEM. This could be done by comparing the modalities and larger sample sizes and examining different intervals and stimuli between repeated CPETs, various treatments that blood cancer patients receive, the resulting CRF/PEM, and its effects on other aspects of QOL. For instance, a study by Navidi et al. (2018) found that neoadjuvant chemotherapy had the most significant impact on patients' peak oxygen uptake (VO_2 peak, which was not seen in this study) and anaerobic threshold compared to other chemotherapy types. Future research would provide deeper insights into how various treatments influence recovery and CRF/PEM for cancer survivors.

Future studies should follow the same cancer survivors over several years with repeated appointments using a form of repeated CPET, measures of self-reported fatigue and standardised psychometric assessments (such as the FAS and SF-36) to garner data on the long-term effects of various interventions and monitor the progress of CRF/PEM and QOL. The benefits of these results gained from long-term interventions and studies could include faster recovery for patients from treatment, reduced hospital stays, and number of appointments required (Colemen et al. 2008 found that exercise can reduce the number of RBC transfusions in patients receiving therapy for MM) Additionally, this long-term research approach could overcome the typically low participant numbers seen with exercise testing due to the more generous timeframes. Collaboration with specialists (oncologists, haematologists, physiologists, and other healthcare providers) could also develop an integrative approach to maintaining, understanding, and treating CRF/PEM.

6.3 Recommendations

Specific endurance-based strength exercises are intriguing and could reduce the effects of CRF/PEM due to their known capability to improve the body's capacity to resist fatigue (Chovanec & Gropel, 2020). Exercise training could be trialled in the rehabilitation phase following treatment with cancer patients due to the implementation of strength-based training programmes, which is most pronounced in early childhood and adolescence (Zimmer-Gembeck & Skinner, 2010). As such, resistance and exercise rehabilitation programmes should be implemented as soon as possible after chemotherapy in AYA patients to mitigate the development and management of CRF/PEM.

The positive effects of strength training in reducing stress—while also improving the body's ability to regulate stress—include enhancing heart rate recovery and variability, boosting oxidative buffering capacity, increasing capillarisation and mitochondrial density, and improving metabolic enzyme activity in the muscles (Tripllet & Haff, 2015). All these factors can increase stress tolerance and lessen the impact of external demands such as social interactions, physical stress, loneliness, and brain fog (Gerber, M., & Pühse, U. 2009).

The effectiveness and optimal training intensity of strength-based programs for people with CRF/PEM are still under evaluation. Nevertheless, intensity constitutes the most significant factor impacting cardiovascular stress during strength training (Moreira et al., 2017). High-intensity exercise limits the oxygen supply to muscle fibres post-exercise (Greater exercise intensity requires a more significant change in blood oxygen levels, lowering them in inactive muscles and increasing them in active muscles Mulliri et al., 2022), causing an increase in metabolites and the accumulation of waste products within the muscles. (MacDougall et al. 1985). The accumulation of waste products and metabolites alters blood pH, triggering chemoreceptors that stimulate tachycardia and other changes in the cardiorespiratory response, ultimately limiting exercise capacity (Wicher & Marion-Poll, 2018). Additional factors such as muscle compression, muscle action, and the cross-sectional area of muscle fibres influence the magnitude of the response. In individuals with impaired recovery, these mechanisms may lead to chronic fatigue and PEM.

Given the information on exercise intensity and its compounding effect on CRF/PEM, the most beneficial approach may be to engage in workouts with a higher volume and lower intensity. Patients may find it advantageous to adopt a training regimen focused on endurance through strength and resistance training (The typical guidelines for muscular endurance exercises are 12-20 reps of a weight 60% of their one rep max with a rest of 30 seconds to a minute between sets Shoenfeld et al., 2021) and to avoid intense training sessions the following day or exercise following particularly taxing days or events. High-intensity training sessions that place excessive stress on the body and cardiovascular system and are scheduled inappropriately for patients with CRF/PEM or ME/CFS can result in prolonged and severe fatigue. This fatigue can negatively impact patients for 48 hours after exercise (Pinot & Polito, 2016).

When working with individuals experiencing chronic fatigue symptoms, the choice of exercises prescribed by healthcare professionals is crucial and should be tailored to each person's needs. Exercises that target the upper limbs impose a greater cardiovascular load and stress on the body than those that engage the lower extremities due to the limited capabilities of the vascular network in the upper limbs compared to the lower ones (Moreira et al., 2017). This can exacerbate the fatigue these individuals are striving to reduce.

VO_2 and workload at AT are important measures to record and track for participants. It has been demonstrated to be a valuable predictor of an individual's ability to perform ADL, and positivity corresponds with their QOL (Knaggs et al., 2011). AT represents the maximum level of exercise at which the cardiorespiratory system can supply the necessary oxygen for aerobic metabolism in active skeletal muscles without supplementation from the anaerobic energy systems (Jennings & Esler, 1990). Participants in this study and others experiencing CRF/PEM have significantly lower AT than comparatively healthy populations. This reduced AT or work capacity below AT will negatively affect CRF/PEM patients' ability to achieve activities of daily living without exceeding their AT. Cancer patients and sufferers of PEM who have to work beyond their AT regularly will experience chronic stress and inflammation as they struggle to recover from repeated exertions while trying to manage basic ADL. This can lead to overexertion and an accumulation of chronic fatigue, exacerbating their CRF/PEM symptoms and increasing their need for rest. Implementing tailored programs focused on enhancing AT may help reduce the impact of CRF/PEM on patients' lives.

After discussing this study with all the cancer patients, we found that every patient wanted advice on exercise and improving their results. This desire from cancer patients to improve their health was seen in many other studies, such as Groeneveldt et al. (2013), who found that 80% of eligible cancer patients wished to participate in their exercise intervention study. Furthermore, the average attendance and adherence to exercise interventions in studies with cancer patients ranged from 86 - 97% (Hacker et al. 2017 & Persoon et al. 2017). The high participation, adherence, and willingness highlight the determination of these patients to exercise and take charge of their health. However, many cancer patients still face barriers that hold them back. Lecat et al. (2021) and Oldervoll et al. (2003) found that the most significant barrier to entry is the participant's current state of weakness, fatigue and lack of confidence in their ability to exercise safely. Overcoming this hurdle to exercise is crucial. Oldervoll et al. (2003) found that cancer patients wished to exercise more frequently and specifically to improve their fatigue. They wanted to receive advice on how to exercise safely but often did not start due to their fears of injury or relapse. The development and implementation of exercise programmes and education in this population will drastically help improve their QOL and reduce the symptoms of CRF/PEM.

All cancer participants in this study exhibited good cardiovascular fitness (VO_2 and peak workload). However, their cancer treatment had altered their capacity to perform repeated exercises, thereby affecting their ability to achieve ADL due to an inability to recover normally from exercise and experiencing longer-lasting and more severe fatigue. Numerous studies have indicated that cancer patients may be unfit and undertrained; however, this study highlights the impact of cancer-related fatigue rather than a lack of fitness within this population.

7. Conclusion

At the time of writing this thesis, no published studies have employed 24-hour repeated CPET in this population to evaluate CRF/PEM, despite its severe impact on patients QOL many years into their remission (Stone et al., 2000). This study reveals the many detrimental effects of CRF/PEM on participants' QOL and exercise capacity. The primary aim of this study was to investigate the prevalence and severity of delayed recovery and fatigue in blood cancer survivors. It was hypothesised that AYA blood cancer patients in remission would exhibit significant reductions in exercise capacity (e.g., peak workload, VO_2 max, and time to fatigue) during the 24-hour repeated CPET. Furthermore, we predicted that when compared to healthy controls and standardised data (healthy controls included in the study and from other standardised data collected in New Zealand), there will be a diminished QOL and fatigue affecting cancer patient's daily lives, as indicated by reduced SF-36 and FAS results.

The findings support the hypothesis, revealing that blood cancer survivors experience significantly impaired recovery post-exercise and CRF/PEM despite the average time since treatment being 8.2 years (SD 3.76 years). These reductions and CRF/PEM symptoms are demonstrated by notable reductions in VCO_2 and workload peak, time to fatigue, maximum heart rate, and the per cent of APMHR achieved on the second day of testing. Participants with more pronounced performance declines in the 24-hour repeated CPET reported lower SF-36 scores in general health, energy, and emotional role domains and lower FAS scores. These findings highlight the broad impact CRF/PEM has on patient QOL, exercise capacity, and ability to achieve ADL and emphasise the interconnected nature of physical and emotional health in this population.

The findings of this study emphasise the necessity of incorporating regular assessments and non-pharmaceutical interventions for CRF/PEM into standard clinical practice. This aligns with Mock et al. (2000) and the NCNN 2015, which suggest that healthcare professionals should establish regular assessments to review patients' medications, perform nutritional and metabolic assessments, and evaluate physical activity levels and exercise capacity. The SF-36 and FAS questionnaires can be readily implemented during patient appointments to identify at-risk patients, monitor symptoms, and facilitate timely interventions. This would ensure clinicians are aware of the lasting impact of CRF/PEM and the domains it most affects. It would also allow for better follow-up and longitudinal care for blood cancer patients (and others suffering from CRF/PEM) to avoid the insidious effects of a sedentary lifestyle.

This study proves that the 24-hour repeated CPET is critical and a safe method for accurately assessing CRF/PEM in blood cancer survivors. This methodology highlights impairments in exercise recovery that may not be evident in single-session cardiopulmonary exercise testing (CPET), presenting a promising opportunity to develop personalised rehabilitation programmes. Currently, there is a significant gap in contemporary research regarding cancer patients experiencing CRF/PEM and effective management strategies. As a result, many patients and healthcare providers find themselves uncertain about the safety of exercise and the appropriate measures to alleviate fatigue. Moreover, utilising 24-hour repeated CPET as a diagnostic tool could assist healthcare providers in identifying impairments in exercise recovery and capacity.

This approach would enable the establishment of a standardised database for comparative analysis and development of effective rehabilitation and maintenance programmes. In the long term, these modifications can enhance patient health outcomes, further understanding of the mechanisms behind CRF/PEM, and refine interventions for cancer survivors, thereby improving their QOL and physical functioning while simultaneously reducing healthcare costs, hospital stays, and health complications. By addressing this critical research gap, it is possible to offer patients and healthcare providers invaluable insights into improving health outcomes for all cancer survivors while also empowering these patients to take action and enable them to do more things they enjoy and live fuller lives.

Conflict of interest

The authors declare that the research was conducted without commercial or financial relationships that could create a conflict of interest.

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Appendices

Appendix A: Literature Review Data Extraction Table

The data extraction form for scoping reviews required one necessary modification, as seen in the paper by Danielle et al. (2021). These modified the form to combine the article title, authors, journal, and publication date into one APA reference section.

Author/ Date	Research Question(s)/ Hypotheses + Theory	Methodology	Analysis & Results	Conclusions	Implications for Future research	Limitations and comments
Elbl, L., Vasova, I., Tomaskova, I., Jedlicka, F., Kral, Z., Navratil, M., ... & Vorlicek, J. (2006). Cardiopulmonary exercise testing evaluates functional capacity after treatment of lymphomas in adults. *Leukemia & lymphoma*, *47*(5), 843-851.	This study aimed to identify functional capacity after treatment in adults with lymphomas and assess the influence of cancer treatment on cardiopulmonary performance status.	One hundred six patients aged 40 ± 15 years were examined 1-2 years after treatment. Rest and dynamic stress echocardiography and cardiopulmonary test. EF, Doppler parameters, VO_2 peak	60% of patients experienced fatigue after treatment. 32% demonstrated impaired diastolic function.	There is a significant relationship between the VO_2 peak and diastolic filling parameters, age, and CD of DOX. Diastolic dysfunction was the most affected parameter of cardiopulmonary function in cancer survivors.	Cancer treatment negatively influences cardiopulmonary performance. Elbl et al. (2006) support the introduction of regular aerobic exercise for cancer survivors. Hypothetically, aerobic training will improve diastolic function.	A singular CPET test Only a relatively small number of patients show a depressed pVO_2

Oldervoll, L. M., Kaasa, S., Knobel, H., & Loge, J. H. (2003). Exercise reduces fatigue in chronically fatigued Hodgkin's disease survivors—results from a pilot study. *European Journal of Cancer*, *39*(1), 57-63.	Does exercise reduce fatigue in chronic fatigue HDS survivors? It aimed to assess the effects of an aerobic training program on fatigue and evaluate its feasibility.	33 participants Survey, Exercise testing and medical examination Intervention study	VO_2 max did not differ between chronically fatigued HDS patients and HDS without chronic fatigue.	Aerobic capacity does not play an essential role in the pathophysiology of chronic fatigue. However, the reduction of fatigue after 20 weeks of aerobic exercise may suggest its use as an alternative treatment for HDS.	Feasibility and adherence rates compare well to similar exercise interventions of the general population.	A singular CPET test. 12 of the 18 chronic fatigue patients completed the study, No reduction in VO_2 when compared to the general population
LeBlanc, M. R., Zimmerman, S., LeBlanc, T. W., Bryant, A. L., Hudson, K. E., & Smith, S. K. (2022). Persistent fatigue among long-term non-Hodgkin lymphoma survivors. *Leukemia & lymphoma*, *63*(2), 344-352.	This study assessed the Prevalence of fatigue in long-term non-Hodgkin survivors. Identify factors associated with the prevalence of fatigue at baseline and persistence across time points.	Mailed survey (SF-36) 555 responders	27.7% reported clinically meaningful Fatigue at baseline, and 18.7% reported persistent fatigue at five years. 34.4% reported clinically meaningful worsening of fatigue over time	Suggests that one in three NHL survivors experience clinically meaningful fatigue long after their diagnosis and treatment.	Many people experience worsening or persisting fatigue, highlighting the need for vigilance in assessing and treating fatigue in this population.	Utilise scientific fatigue testing compared to questionnaires to further support findings. This study used the SF-36.
De Caro, E., Fioredda, F., Calevo, M. G., Smeraldi, A., Saitta, M., Hanau, G., ... & Haupt, R. (2006). Exercise capacity in apparently healthy survivors of cancer. *Archives of disease in childhood*, *91*(1), 47-51.	To evaluate the exercise capacity and cardiopulmonary exercise tolerance in a large cohort of apparently healthy paediatric cancer survivors.	84 paediatric cancer survivors (<21 years old) and 79 controls underwent a CPET The mean interval since finishing anticancer treatment was 6.4 years.	There is no difference in exercise responses between patients and controls. Mean v02 max was slightly but clinically significantly	The reduced VO_2 max directly results from decreased physical fitness, as all the other exercise parameters due to treatment.	CPET is helpful for the functional evaluation of paediatric cancer survivors	Utilised the treadmill for a singular CPET This paper is the most extensive study at the time using CPET testing for paediatric cancer survivors.

			lower than in controls			
Elnaggar, R. K. (2021). Within 5-year off-chemotherapy: How the cardio-respiratory response to exercise is related to energy expenditure, fatigue, and adiposity in children with acute lymphoblastic leukaemia. *European Journal of Cancer Care*, *30*(4), e13418.	To assess whether cardio-respiratory fitness in survivors of ALL is remarkably lower compared with healthy controls	70 participants aged 13.31 ±2.6 years old and 34 control from siblings 12.71 ± 2.36 years old were assessed for submaximal and maximal exercise capacity, body composition EE and fatigue	All cancer survivors had significantly lower VO_2 peak and VO_2max aerobic capacity than the controls. HR was significantly higher in submaximal exercise compared to the controls	Children survivors of ALL experience low cardio-respiratory fitness compared to that of expected norms within 5-year off-chemotherapy.	Associations exist between measures of cardio-respiratory fitness, EE, fatigue and adiposity. However, whether these are cause or effect has yet to be proven.	This study utilised the treadmill for maximal and submaximal testing via a singular CPET test.

Kiserud, C. E., Lockmer, S., Baerug, I., Dahl, A. A., Kimby, E., & Østenstad, B. (2023). Health-related quality of life and chronic fatigue in long-term survivors of indolent lymphoma–a comparison with normative data. *Leukemia & Lymphoma*, *64*(2), 349-355.	Cancer survivors may have ongoing health problems affecting their HRQoL long after their treatment has been completed. This study aims to describe health-related quality of life (HRQoL, SF-36) and fatigue in long-term indolent lymphoma survivors,	A follow-up study of two clinical trials with chemo-free first-line therapy included 136 participants, with a median follow-up after first-line treatment of 9.8 years. The present survey included questionnaire-based data.	The non-Hodgkin lymphoma survivors reported statistically significantly lower levels in 4 of the 8 SF-36 dimensions (physical function, role physical, general health, and role emotional) compared to the normative group, with clinically significant effect sizes.	Findings highlight the importance of awareness of HRQoL and fatigue on long-term follow-up of survivors of indolent lymphoma, in particular among those with comorbidities and psychological late effects such as anxiety and depressive symptoms.	As overall survival in lymphoma patients continues to improve, related long-lasting clinical needs will become even more critical.	The most significant difference in results in the SF-36 was in physical function and general health.

Eikeland, S. A., Smeland, K. B., Simensen, V. C., Fagerli, U. M., Bersvendsen, H. S., Kiserud, C. E., & Fosså, A. (2023). Chronic fatigue in long-term survivors of Hodgkin's lymphoma after contemporary risk-adapted treatment. *Acta Oncological*, *62*(1), 80-88.	Chronic fatigue (CF), substantial fatigue for ≥ six months, can manifest as a late effect (LE) after cancer treatment and may affect several aspects of life. This study set out to quantify the prevalence of CF, factors associated with CF, and possible implications of CF on work ability (WA) and socioeconomic status (SES).	HL survivors treated between 1997 and 2006 and aged 8–49 at diagnosis were invited to participate in a Norwegian population-based cross-sectional study on LEs. The Cancer Registry of Norway identified survivors. Of 518 invited HLS, 304 consented and returned the questionnaire, with 298 responding fully to the FQ, yielding a response rate of 58%. Scores were Norwegian general population mean scores equal to 50	Using FQ, 42% of the responders were classified as having CF. CF is associated with lower HRQoL in all individual subdomains of SF-36, as well as in the MCS and PCS, and all with significant ES. Similarly, higher levels of depressive symptoms and pain were seen in HLS with CF, with large and small ES, respectively.	Analysis reveals a high prevalence of CF in HLS after contemporary risk-adapted therapy, possibly higher than seen in HLS treated in previous eras. No association with disease stage or cancer treatment was found. In sub-group analysis, they found that HLS with CF were socioeconomically disadvantaged and less integrated in work life.	With CF's high prevalence and unknown etiology, emphasis should be put on studying its etiopathological factors. Preventing and alleviating CF would probably immensely benefit HLS′ health, HRQoL, workability, and the societal cost of survivorship.	CF was found to be associated with depression, lower education, higher BMI, and an increasing number of comorbid conditions at the time of the survey. Utilised the SF-36.

Author/ Date	Theoretical/ Conceptual Framework	Methodology	Analysis & Results	Conclusions	Implications for Future research	Limitations and comments
Schoormans, D., Jansen, M., Mols, F., & Oerlemans, S. (2020). Negative illness perceptions are related to more fatigue among haematological cancer survivors: a PROFILES study. *Acta oncological*, *59*(8), 959-966.	Negative illness perceptions are related to more fatigue among haematological cancer survivors. This study examined the associations between modifiable illness perceptions and substantial fatigue while controlling for sociodemographic, clinical, and psychological factors (symptoms of depression and anxiety) among haematological cancer survivors.	This paper included survivors diagnosed between 1999 and 2013 with Hodgkin lymphoma (N = 164), non-Hodgkin lymphoma (N = 655) and chronic lymphocytic leukaemia (N = 174) Survivors completed the Fatigue Assessment Scale (FAS); substantial fatigue was diagnosed if the participant scored >21 on the FAS.	Haematological cancer survivors with worse illness perceptions based on the symptoms of their illness and a poorer illness understanding were more often substantially fatigued.	Those who experience more consequences of their disease, attribute more symptoms to their illness and have a poorer illness understanding have a higher risk of experiencing substantial levels of fatigue even years after diagnosis.	Psychological interventions changing these illness perceptions may be beneficial in reducing fatigue among haematological cancer survivors.	Utilised the FAS, It could be insightful to gather specific information on illness perceptions regarding their fatigue and the experienced fatigue

Atkinson, M., Murnane, A., Goddard, T., Pendergrast, C., Rogers, P., Manudhane, R., & Osborn, M. (2021). A randomized controlled trial of a structured exercise intervention after the completion of acute cancer treatment in adolescents and young adults. *Paediatric Blood & Cancer*, *68*(1), e28751.	Cancer treatment is frequently associated with impaired physical fitness, QOL and fatigue persisting into survivorship. Whether a structured 10-week exercise intervention was associated with improved cardiorespiratory fitness, fatigue and QOL in AYA	Forty-three participants aged 21 ± 6 years old with a haematological malignancy or solid tumour. 21 in control, 22 in the 10-week exercise intervention	The mean VO_2 peak at baseline was 26.5 ± 7.2, substantially lower than population norms.	Cancer treatment is associated with reduced VO_2 peak in AYA.	Considering low patient numbers and attrition, alternative approaches may be worth using for AYA participants who cannot participate in conventional exercise programs.	This was an Intervention study, but it still provides valid preliminary data. The participants' exercise equipment was determined based on their preference (bicycle, arm ergometer, or treadmill) via a single-CPET test.

Adams, M. J., Lipsitz, S. R., Colan, S. D., Tarbell, N. J., Treves, S. T., Diller, L., ... & Lipshultz, S. E. (2004). Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *Journal of clinical oncology*, *22*(15), 3139-3148.	This study hypothesised that there may be an increased risk for cardiovascular abnormalities after diagnosis and treatment in long-term survivors of Hodkin's disease.	48 HD survivors with a median age of 14.3 years old (5.9 – 27.5) underwent SF-36, echocardiography, exercise stress testing and resting/24-hour ECG	Reduced average left ventricular (LV) dimension suggested restrictive cardiomyopathy. 42% had significant valvular defects, and 75% had conduction defects.	Peak oxygen uptake during exercise, a predictor of mortality in heart failure, was significantly reduced in 30% of survivors. VO_2 max correlated with increasing fatigue, shortness of breath, and decreasing physical component score on the SF-36	A variety of unsuspected, clinically significant cardiovascular abnormalities are common in long-term survivors of HD who are treated at a young age with mediastinal irradiation. We recommend serial, comprehensive cardiac screening of HD survivors who fit this profile.	Utilised a slightly different cardio test on the bike (Bruce protocol) but still a maximal CPET protocol. Utilised the SF-36.

Daniëls, L. A., Oerlemans, S., Krol, A. D. G., Creutzberg, C. L., & Van De Poll-Franse, L. V. (2014). Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *British journal of cancer*, *110*(4), 868-874.	Fatigue is a frequent and persistent problem among Hodgkin lymphoma (HL) survivors. They Investigated the prevalence of clinically relevant fatigue in HL survivors and the relation between fatigue anxiety and depression.	Fatigue was measured through the generic European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and Fatigue Assessment Scale (FAS) The response rate was 68% (median age 46 years, mean time since diagnosis 4.6 years). 267 HL survivors.	The prevalence of fatigue and fatigue levels were significantly higher among HL survivors than in the normal population (FAS 41% vs 23%, QLQ-C30 43% vs 28%). There was a significant association between fatigue, anxiety, and depression. Of the HL survivors with high symptom levels of depression, 97% also reported fatigue.	Prevalence rates of fatigue are significantly higher in HL survivors than in the general population, and differences are clinically relevant. Depression and anxiety were strongly associated with high levels of fatigue.	These results have implications for diagnosing and treating fatigue in the clinical setting.	Utilising the FAS scale. Psychosocial therapies have proven effective in reducing anxiety and depression and could, therefore, be beneficial in reducing fatigue levels as well. This should be further examined in future trials

Kanellopoulos, A., Hamre, H. M., Dahl, A. A., Fosså, S. D., & Ruud, E. (2013). Factors associated with poor quality of life in survivors of childhood acute lymphoblastic leukaemia and lymphoma. *Paediatric blood & cancer*, *60*(5), 849-855.	This study aimed to assess the prevalence of poor QoL in adult LTSs of childhood ALL and LYM compared with age-matched controls from the general population and investigate factors associated with poor QoL in LTSs that could be amenable to targeted interventions.	All participants had ALL or Lymphoma as identified by the cancer registry of Norway; 430 were contacted; of these, 285 patients were included in the study that consisted of an extensive questionnaire (including the SF-36) and an outpatient clinical examination, performed between September 2007 and June 2009. Median age of 30	The LTSs showed statistically significantly poorer QoL life scores on all SF-36 dimensions except Role Emotions. They reached clinical significance (ES ≥ 0.40) for the Role Physical, General Health, Vitality, and PCS-36 subscales.	This long-term follow-up study demonstrates that 7–40 years after curative treatment for ALL and lymphoma in childhood, 32% of the LTSs have poor QoL compared to 19% among NORMs. The mean scores on seven out of eight QoL dimensions were significantly lower among LTSs than NORMs.	These factors are amenable to interventions; they should be looked for, particularly at follow-up examinations.	Utilised the SF-36 questionnaire Higher fatigue was directly related to lower QOL scores and perceptions. ALL and LYM experienced significantly poorer QoL than age-matched controls from the general population.

Caru, M., Laverdière, C., Lemay, V., Drouin, S., Bertout, L., Krajinovic, M., ... & Curnier, D. (2021). Maximal cardiopulmonary exercise testing in childhood acute lymphoblastic leukaemia survivors exposed to chemotherapy. *Supportive Care in Cancer*, *29*, 987-996**.**	Childhood acute lymphoblastic leukaemia (ALL) survivors have a substantially lower cardiorespiratory fitness level compared with healthy populations. The purpose of this study was to demonstrate if childhood acute lymphoblastic leukaemia (ALL) survivors exposed to chemotherapy (i.e., doxorubicin) can achieve a safe maximal cardiopulmonary exercise test (CPET)	250 childhood ALL survivors were eligible to undergo a CPET on a cycle ergometer. Analyses were performed on 216 survivors and stratified according to their prognostic risk groups: 99 survivors (55 males and 44 females) at standard risk and 117 survivors (56 males and 61 females) at high risk	100% (n = 216) completed a maximal CPET confirmed by Linear regression analysis, which showed a significant association between the survivors' cumulative dose of doxorubicin and their VO_2 peak measured. Two non-fatal adverse events were observed and reported at the end of the maximal CPET.	They achieved a maximal exercise test without being limited by symptoms, potential overprotection, or musculoskeletal issues.	In childhood, ALL survivors with exposure to chemotherapy can achieve a safe maximal CPET. This study provides important information regarding the maximal physiological parameters that ALL childhood survivors can reach. It has important clinical implications in the exercise and oncology field for this population of survivors.	Singular CPET Strongly advocates for the use of maximal CPET to observe significant differences between survivors at standard vs high-risk prognostics vs cardiorespiratory health. Further replication studies are needed in childhood cancer survivors since their findings can only be generalised to the childhood ALL survivor population.

Goodenough, C. G., Wogksch, M. D., Kundu, M., Lear, M., Thomas, P. G., Srivastava, D. K., ... & Ness, K. K. (2022). Associations between exercise capacity, p16INK4a expression and inflammation among adult survivors of childhood cancer. *Frontiers in Oncology*, *12*, 1014661.	Over 50% of childhood cancer survivors are exercise intolerant, with maximal aerobic capacities comparable to individual's decades older, suggesting early physiological ageing. This study evaluated associations between a cellular senescence biomarker, inflammation, and exercise capacity among adult childhood cancer survivors.	Maximal oxygen uptake (VO_2, ml/kg/min) was obtained *via* cardiopulmonary exercise testing using a modified Bruce protocol. Participants included 185 five-year childhood cancer survivors (mean age 36.6 [range 20.1 - 55.7] years, 44% male, 77% non-Hispanic white, 53% leukaemia/lymphoma).	Compared to males, females had lower peak VO_2 (mean ± SD, 22.5 ± 8.2 vs. 28.8 ± 7.7 ml/kg/min, $p<0.01$),	Inflammation and $p16^{INK4a}$ expression, a biomarker of cellular senescence, is associated with lower exercise capacity in childhood cancer survivors,	In our study, cellular senescence and inflammation biomarkers were associated with lower exercise capacity, further mediated by body fat in female survivors.	Again, there is a slight difference in the CPET. This study utilised the Bruce protocol. Accelerated ageing among childhood cancer survivors. Interventions designed to improve exercise capacity have the potential to remediate the accelerating ageing
Persoon, S., Kersten, M. J., Buffart, L. M., Vander Slagmolen, G., Baars, J. W., Visser, O., ... & Chinapaw, M. J. (2017). Health-related physical fitness in patients with multiple myeloma or lymphoma recently treated with autologous stem cell transplantation. *Journal of Science and Medicine in Sport*, *20*(2), 116-122.	The physical fitness of patients with blood cancer contributes to impaired mobility and, thereby, to a decrease in physical fitness. This study examined health-related physical fitness and its demographic and clinical correlates in patients recently treated with autologous stem cell transplantation.	One hundred nine patients, 58 with myeloma and 51 with lymphoma. Median age of 55 (19-67). Maximal exercise testing was conducted to assess cardiorespiratory fitness (VO_2).	The average VO_2 peak was 21.7 (5.5) mL/min/kg, 26% below the reference values.	Blood cancer patients' cardiorespiratory and muscular fitness and body composition were significantly compromised. Compared to the given values, both myeloma and lymphoma patients have a lower cardiovascular capacity	Further research is needed to confirm our findings, examine the relation between health-related physical fitness and survival after Auto-SCT, give insight into the evolution of physical fitness during and after treatment, and elucidate the optimal intervention for physical fitness deficiencies.	This study utilised a singular ramp CPET examination on the bike. Twenty-three patients had missing values due to technical problems.

Tsuda, T., Davidow, K., D'Aloisio, G., & Quillen, J. (2023). Surveillance cardiopulmonary exercise testing can risk-stratify childhood cancer survivors: underlying pathophysiology of poor exercise performance and possible room for improvement. *Cardio-Oncology*, *9*(1), 42.	Surveillance cardiopulmonary exercise testing can risk-stratify childhood cancer survivors: underlying pathophysiology of poor exercise performance and possible room for improvement. Tsuda et al., 2023, used a novel CPET approach combining peak and submaximal parameters to delineate possible underlying mechanisms of poor exercise performance in CCS.	From 2018 to 2021, the Nemours Institutional Review Board approved a retrospective chart review of CPET data from the database of the Exercise Laboratory, Nemours Cardiac Centre, at Nemours Children's Health in Wilmington, DE. 38 participants aged 7.1 ± 4.4 at diagnoses ± 6.8 3.8 years after diagnosis and The participants were 4 ± 2.9 years old and 10.3 ± 3.7 years after diagnosis.	Peak heart rate (HR) and RER were comparable in all four groups. Peak work rate, peak oxygen consumption, peak oxygen pulse, and ventilatory anaerobic threshold were significantly lower in the childhood cancer survivors, who had decreased skeletal muscle mass and reduced stroke volume reserve.	The relationship between VAT and pVO_2 was almost identical between the two groups in both sexes.	Decreased skeletal muscle mass, reduced stroke volume reserve, and a slightly decreased ventilatory efficiency were seen in CCS of both sexes. This unique combined CPET analysis provides useful clinical biomarkers to screen subclinical cardiovascular abnormality in CCS and identifies an area for improvement.	32/38 were blood cancers (Leukaemia, ALL, AML, post-HSCT, Lymphoma Hodgkin + non-Hodgkin), with 5 "others." A singular Ramp test was used for the CPET on a cycle ergometer. Variable physical conditioning, body habitus, level of puberty, and ethnic background all affect exercise performance assessed by CPET

Bertrand, É., Caru, M., Lemay, V., Andelfinger, G., Laverdiere, C., Krajinovic, M., ... & Curnier, D. (2021). Heart rate response and chronotropic incompetence during cardiopulmonary exercise testing in childhood acute lymphoblastic leukaemia survivors. *Paediatric Haematology and Oncology*, *38*(6), 564-580.	Childhood cancer survivors are 7x more likely to die from cardiovascular complications and sudden death compared to healthy individuals. Moreover, childhood cancer survivors are more at risk of developing heart failure earlier than non-cancer populations. The first aim of this study was to examine survivors' HR responses during a maximal CPET.	A total of 250 childhood ALL survivors underwent a CPET on a cycle ergometer to assess their HR response. A multiparametric structure of three methods to determine survivors' CI, as follows: 1) age-predicted HR_{max} (APMHR): failure to achieve 85% of the APMHR at the peak of CPET; 2) HR reserve (HRR): failure to achieve 80% of the HRR at the peak of CPET; and 3) metabolic chronotropic relationship (MCR): failure to reach an MCR slope ratio >0.8 at each stage of the CPET.	They observed that 73 males and 74 females did not achieve their predicted HR max. Six survivors did not reach 85% of their APMHR (80.9 ± 3.9%) and had an MCR below 80% (53.9 ± 13.8%). In addition, 16 survivors did not achieve 80% of their HRR (71.0 ± 7.4%), and 15 survivors had an MCR below 80% (61.0 ± 12.1%).	Survivors with CI had significantly lower cardiorespiratory fitness than those without CI. One hundred thirty-two survivors did not achieve their HRmax, which is like those observed in heart failure patients.	This study shows that survivors are at risk of developing altered HR responses and CI many years after the end of their cancer treatments. These findings highlight the importance of early detection of cardiac damage due to cancer treatments.	Singular CPET examination A maximal CPET is required to unmask potential CI in childhood ALL survivors.

Long, T. M., Lee, F., Lam, K., Wallman, K. E., Walwyn, T. S., Choong, C. S., & Naylor, L. H. (2020). Cardiovascular Testing Detects Underlying Dysfunction in Childhood Leukemia Survivors. *Medicine and science in sports and exercise*, *52*(3), 525-534.	Childhood leukaemia survivors commonly develop late-onset cardiovascular disease after treatment with anthracyclines. Resting echocardiograms are the standard procedure for monitoring cardiac health, but this method may not be sensitive enough to detect subclinical injury. Exercise echocardiography may provide a viable alternative.	Nineteen (9 males; age 19 ± 3 yr) anthracycline-treated survivors of childhood leukaemia and 17 healthy individuals of similar age (22 ± 2 yr) were recruited. Cardiorespiratory fitness (VO_2 peak) was assessed by a CPET test.	Mitral valve peak flow velocity in late diastole increased from rest in survivors and controls immediately post-exercise but did not recover again in the survivors after the recovery phase. Consequently , The E/A ratio was lower in the survivors. Compared to controls, survivors had reduced FMD and recovery HR minute ventilation and VO_2 peak.	Exercise echocardiography unmasked subclinical diastolic dysfunction that may indicate late anthracycline toxicity in apparently healthy survivors of childhood leukaemia. This toxicity leads to a reduced capacity for daily activities and exercise.	The presence of secondary risk factors indicates an increased predisposition to comorbidities and highlights the importance of assessing cardiovascular health during follow-up care of childhood leukaemia survivors.	Singular CPET Small sample size

Stenehjem, J. S., Smeland, K. B., Murbraech, K., Holte, H., Kvaløy, S., Thorsen, L., ... & Kiserud, C. E. (2016). Cardiorespiratory fitness in long-term lymphoma survivors after high-dose chemotherapy with autologous stem cell transplantation. *British journal of cancer*, *115*(2), 178-187.	To investigate whether cardiorespiratory fitness, measured by peak oxygen consumption (VO_2 peak), strongly predicts longevity and may be compromised by anticancer therapy, inactivity, and smoking.	Three hundred thirty lymphoma survivors aged 18 and over were tested. CPET was used to assess VO_2 peak. Treatment, physical activity, and smoking data were collected from hospital records and questionnaires. VO_2 peak was compared with age–sex predicted reference data. Linear regression was used to associate clinical factors with $VO_2$2 peak cross-sectionally.	Mean VO_2 peak was 4.5% and 7.7% below norms in females and males, respectively. Twenty-two percent had impaired (<80% predicted) VO_2 peak	The decreased VO_2 peak was associated with impaired diffusion capacity and current smoking, while physical activity level and VO_2 peak were positively associated.	We suggest increased attention towards physical activity counselling and smoking cessation advice to preserve cardiorespiratory fitness in LSs after HDT-ASCT. Patients with impaired diffusion capacity may benefit from subsequent monitoring to detect pulmonary vascular diseases.	A high physical activity level mitigates the inverse association between doxorubicin and VO_2 peak. Singular CPET examination
Rizwan, R., Gauvreau, K., Vinograd, C., Yamada, J. M., Mangano, C., Ng, A. K., ... & Chen, M. H. (2021). VO2peak in adult survivors of Hodgkin lymphoma: rate of decline, sex differences, and cardiovascular events. *Cardio Oncology*, *3*(2), 263-273.	To assess if adult survivors of Hodgkin lymphoma (HL) are at increased risk of cardiovascular (CV) events secondary to mediastinal radiation therapy (RT).	Sixty-four survivors of HL who were >10 years post-treatment underwent 1 CPET.	VO_2 peak in survivors declined by 7.5 percentage points every 10 years after RT, compared with age—and sex-based norms. Both male and female patients had a similar rate of VO_2 peak decline.	Vo $_2$ peak in long-term survivors of HL who were treated with chest RT progressively declined as compared with population- and sex-based norms. Notably, women developed abnormal pp VO_2 peaks more than 2 decades earlier than male survivors.	Abnormal VO_2 peak was associated with an increased risk of CV events in this group of patients.	Higher maximal exercise capacity consistently predicts a lower risk of adverse cardiac events at all ages. Singular CPET examination.

Canada, J. M., McCarty, J., Jordan, J. H., Trankle, C. R., DeCamp, K., West, J. D., ... & Hundley, W. G. (2023). Simultaneous exercise stress cardiac magnetic resonance and cardiopulmonary exercise testing to elucidate the Fick components of aerobic exercise capacity: a feasibility and reproducibility study and pilot study in hematologic cancer survivors. *Cardio-Oncology*, *9*(1), 31.	Patients treated for hematologic malignancy often experience reduced exercise capacity and increased fatigue. This reduction in exercise capacity may be related to cardiac dysfunction, impairment of skeletal muscle, or oxygen extraction during activity.	Sixteen haematologic cancer survivors were recruited to determine exercise cardiac reserve with simultaneous measures of VO_2. Repeatability inf was assessed in seven healthy controls. Finally, we measured the Fick determinants of peak VO_2 in hematologic cancer survivors with fatigue (n = 6) and compared them to age/gender-matched healthy controls (n = 6)	All subjects completed Study procedures without adverse events (N = 16, 100%). The protocol demonstrated excellent test-retest reproducibility for peak VO_2	Non-invasive measurement of peak VO_2 Fick determinants is feasible and reliable with an ExeCMR + CPET protocol in patients treated for hematologic malignancy. It may offer insight into the mechanisms of exercise intolerance in fatigued patients.	Hematologic cancer survivors with fatigue demonstrated a significantly lower peak VO_2	Singular CPET on cycle ergometer The current feasibility study was designed to assess the reproducibility of this procedure. Therefore, it was not powered to detect group differences. Results should not be viewed as conclusive due to the low number of subjects
Klika, R. J., Golik, K. S., Drum, S. N., Callahan, K. E., & Thorland, W. G. (2011). Comparison of physiological response to cardiopulmonary exercise testing among cancer survivors and healthy controls. *European journal of applied physiology*, *111*, 1167-1176.	Klika et al. aimed to see if exercise intensity based on lactate threshold determination may be helpful in exercise prescription for CS (cancer survivors).	During cycle ergometry, CS's physiological responses (heart rate, blood pressure, O_2 saturation, RPE, lactate, VO_2 Peak, and peak power) were compared to healthy controls.	This sample did not confirm the hypothesis. Virtually all subjects in this study showed a precise, definable breakpoint associated with lactate accumulation during increasing intensity on a cycle ergometer, confirming a curvilinear response.	CS who continued to engage in physical activity before their diagnosis and those continuing to remain active through treatment appeared to maintain 'normal' physiological response to CPET (independent of ECG abnormalities)	it appeared that individuals self-selecting to live in a rural, activity-oriented region would naturally choose to live a healthier lifestyle than the average person.	This study adds to the evidence that CPET is a safe and effective method for evaluating functional capacity in CS.

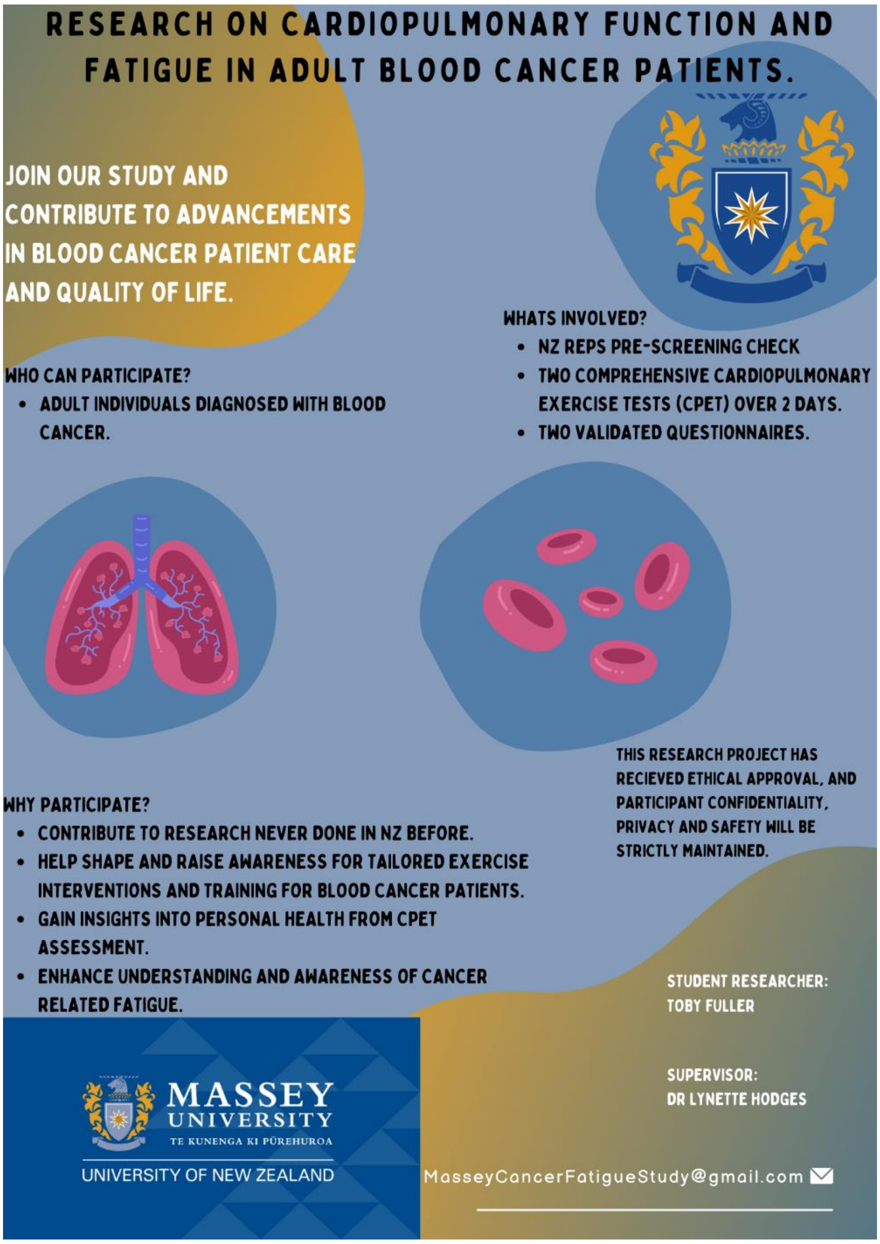
Ruf, K., Badran, A., Siauw, C., Haubitz, I., Schlegel, P. G., Hebestreit, H., ... & Wiegering, V. (2021). Does allogeneic stem cell transplantation in survivors of paediatric leukaemia impact regular physical activity, pulmonary function, and exercise capacity? *Molecular and Cellular Pediatrics*, *8*, 1-10.	This study aimed to determine exercise capacity, physical activity, cardiac and pulmonary function, and quality of life in survivors of leukaemia undergoing allo-HSCT in childhood or adolescence.	A sample of 17 patients (Survivors of paediatric leukaemia) after allo-HSCT (HSCT—12 male, page 15.7±6.7 years, time after HSCT 5.3±2.8 years) underwent pulmonary function testing, echocardiography, and an incremental exercise test on a bike.	These cancer survivors have normal cardiac function but decreased diffusion capacity.	Patients who had received treatment for leukaemia had a reduced exercise capacity compared to healthy controls. Pulmonary impairment is present and contributes to impaired exercise capacity.	Further studies are needed to analyse the complex interaction between cancer therapy and the mode of conditioning on the one hand and pulmonary and cardiac impairment and its impact on exercise capacity and regular physical activity on the other hand.	Singular CPET examination. Small sample size
van Brussel, M., Takken, T., Net, J. V. D., Engelbert, R. H., Bierings, M., Schoenmakers, M. A., & Helders, P. J. (2006). Physical function and fitness in long-term survivors of childhood leukaemia. *Paediatric rehabilitation*, *9*(3), 267-274.	To evaluate the physical function and fitness in survivors of childhood leukaemia 5–6 years after cessation of chemotherapy.	Thirteen children (six boys and seven girls; mean age 15.5 years) who were treated for leukaemia were studied 5–6 years after cessation of therapy were recruited for this study. A CPET test determines physical function and fitness.	Compared to reference values, aerobic and anaerobic capacity in childhood cancer survivors were significantly lower.	Even 5–6 years after cessation of childhood leukaemia treatment, there are still clear late effects on motor performance and physical fitness. Chemotherapy-induced neuropathy and muscle atrophy are the prominent causes of these reduced test results.	Physical training might benefit leukaemia survivors by improving fitness levels and muscle strength.	Singular CPET Test Slightly younger population

Koutoukidis, D. A., Land, J., Hackshaw, A., Heinrich, M., McCourt, O., Beeken, R. J., ... & Yong, K. L. (2020). Fatigue, quality of life and physical fitness following an exercise intervention in multiple myeloma survivors (MASCOT): an exploratory randomised Phase 2 trial utilising a modified Zelen design. *British Journal of Cancer*, *123*(2), 187-195.	The MASCOT survivorship study aims to explore the main determinants of fatigue and QoL in patients who have completed chemotherapy, with particular emphasis on bone pain, physical fitness and strength.	Eighty patients aged 36-78 years (male, n=46) were studied at a median of 13.5 months (range 2-161) since the last treatment. Cardiovascular fitness was assessed using the VO_2 peak (CPET on a cycle ergometer)	We observed that pain was associated with more fatigue. Higher-than-expected levels of fatigue in this population were found, and worse depression even when adjusting for sex, age, time since treatment and physical health and fitness. Depression was found to be a predictor of QOL, with higher depression scores associated with greater fatigue levels.	Findings confirm the significant contribution of physical fitness to fatigue and QoL in these patients. Regardless of physical fitness status, however, the presence of pain and impaired psychological health remain independent drivers of fatigue and diminished QOL.	Research involving exercise programmes designed to improve physical strength and fitness combined with effective pain management and psychological support is needed to provide the evidence base for much-needed rehabilitative interventions.	Singular CPET Examination Age was slightly higher than in this study targeted population.

Literature review CPET data										
	ELBL	Oldervoll	De Caro	Elnaggar	Atkinson	MJ Adams	Caru	Goodenough	Persoon	Tsuda
VO2 max (ml/min)	28.4 (7.8)	32.7	38.1 (8.4)	30.4	26.5 (7.2)	25.8 (7.2)	32.5	M 28.8 F 22.5	21.7 (5.5)	M 35.8 F 30.2
VE max (L/min)			78.2 (23)	83.5	94.25		86.55			M 79.7 F 60.75
RER/RQ max			1.1 (0.1)	1.17	1.33		1.3		1.28	M 1.24 F 1.24
Time to vo2 max (mm:ss)							9.8			
Workload max (watts)					162.69		176.15			M 137 F 103.5
HR max (bpm)	192	184	191	198			179.2			M 188.5 F 188
% of max HR achieved									96%	
O2 Sat at max (%)										
RPE max										
blood pressure max (mmHg)	132/82						170.55 / 75			M 147.5 F 150
VO2 at VT (ml/min)			24.9 (6.6)							
VE at threshold (L/min)										M 23.85 F 24.85
Workload at VT (watts)										
BMI kg/m²	M 27 (4.7) F17.3 (41)	25.2		22.76	25 (6)		M 23.7 F 24.9	26.5	25.4	Male 21.55 Female 22.15
Time since treatment (years)	1.17		6.4 (3.4)	3.37		14.3	15.3 (5.2)			7.8
Age	40 (15)	41 (11.3)	<21	13.31 (2.6)	21 (6)	16.5	22 (6.5)	36.6	55 (33)	14.68 (2.83)

	Bertrand	Long	Stenehjem	Rizwan	Canada	Klika	Ruf	Van Brussel	Koutoukidis
VO2 max (ml/min)	32.3 (8.4)	36.78 (11.49)	M 29.7 F 23.5	26		M 45 (10.5)F 34.8 (10.3)	39.1 (7.9)	36.64 (18.3)	18.1 (6.9)
VE max (L/min)		70.04 (17.12)	Male 107.8 F 71.4					64.69 (36.1)	
RER/RQ max	1.3	1.09 (0.11)	M 1.17 F 1.19	1.16	1.22		1.12 (0.16)		
Time to vo2 max (mm:ss)					8.77				
Workload max (watts)			M 196 F 126		127	M 258 (46) F 172 (38)		155 (82.41)	
HR max (bpm)	187.5 (11.3)	175 (18)			143	157 (20)	186 (10)		
% of max HR achieved	97.3 (5.6)				87				
O2 Sat at max (%)				92			98 (1.5)		
RPE max		17	17		16				
blood pressure max (mmHg)						182 / 83.5			
VO2 at VT (ml/min)									
VE at threshold (L/min)									
Workload at VT (watts)						M 169 F 122			
BMI kg/m²		25.2 (5.1)	Male 26.6 Female 25.8	25.6	26.2	M 26 (2.7) F24.2 (5.9)	20.78	20.75 (3.8)	
Time since treatment (years)	15.3 (5.2)	12 (4)	12.9 (6.6)	23				5.16	1
Age	22 (6.4)	19 (3)	42 (13)	51	57	53.8 (11)	15.7 (6.7)	15.5 (5.8)	64

Appendix C: Research Flyer



Appendix D: Informed Consent and Information Sheet

Assessing Fatigue in Adult Blood Cancer Patients: A 24-Hour Repeated Cardiopulmonary Exercise Test (CPET) Study in New Zealand (A pilot study)

Informed Consent Form

Primary Researcher:	Toby Fuller
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Location:	Wellington
Email:	MasseyCancerFatigueStudy@gmail.com
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Supervisor:	Dr Lynette Hodges
Department:	School of Sport, Exercise and Nutrition
Location:	Palmerston North
Email:	MasseyCancerFatigueStudy@gmail.com

Aims

This study aims to enhance the understanding of fatigue in adult blood cancer patients by identifying factors contributing to fatigue. It seeks to improve symptom management and overall quality of life during and after cancer treatment. Additionally, it aims to provide valuable data for further oncology and exercise science research into cancer-related fatigue. This topic has yet to be researched in New Zealand and, overall, a lesser explored area of research. Participating will help raise awareness, and participants will gain insights into their personal cardiopulmonary health.

Procedures

Participants will be asked to:

- Complete two questionnaires. The Fatigue Assessment Scale (FAS) and the V2 Short Form (SF-36) questionnaire. These questionnaires are an accurate self-reported measure of health, quality of life and fatigue.
- Participants will be needed to complete the New Zealand Register of Exercise Professionals (REPS) pre-screening exercise form and a blood pressure assessment as part of participant safety measures.
- Undergo two Cardiopulmonary Exercise Tests (CPET) repeated 24 hours (+/- 2 hours) apart. These will be completed to standardise guidelines following the Rise in Metabolic Rate Protocol (RAMP) approach on an exercise cycle. This process involves a 3-minute warm-up followed by incremental increases in resistance until participant exhaustion. This should take between 15-30 minutes to complete.

This study will take three visits, including one initial appointment to hand out questionnaires, discuss the study and sign the informed consent form. Each CPET assessment is expected to take 15-25 minutes of cycling.

Risks

During the Cardiopulmonary Exercise Tests (CPET), you may experience physical discomfort and fatigue. CPET involves incremental increases in exercise intensity until exhaustion, leading to temporary sensations of breathlessness, muscle fatigue, perspiration and increased heart rate. Participants may also experience mild dizziness or light-headedness during or after the tests.

It is important to note that these sensations are temporary and are a normal part of the CPET procedure. The exercise resistance and duration will be adjusted based on fitness level.

You have the right to stop the CPET at any point if you feel unable to continue or if you experience any undue discomfort. The right to withdraw additionally applies for up to 2 weeks after data collection if you wish your information to be excluded from the study. We are committed to ensuring your safety and well-being during the study. If you have any concerns about the potential risks associated with CPET, please feel free to discuss them with me or my supervisor at any time.

Benefits

- Personal insights into your cardiopulmonary health and physiological function from the CPET assessment.
- Contribute to research yet to be done in New Zealand and raise awareness of the effects of Cancer Related Fatigue (CRF)
- Koha, in the form of vouchers, will be provided as gratitude for the time and energy participation in this study requires.

Confidentiality

Your privacy and confidentiality are of utmost importance. All information collected during the study will be anonymised and kept confidential. This data will then be stored securely and safeguarded by myself, and my supervisor is the only other person who may have access to this data.

Voluntary participation

Participation in this study is voluntary, and there is no pressure to participate. Your involvement is entirely your decision, and you are free to withdraw at any time without consequence. Your comfort and autonomy are of utmost importance to us, and we respect your right to choose whether or not to participate.

Contact information

Student Researcher: Toby Fuller
Mobile: [redacted]
Email: MasseyCancerFatigueStudy@gmail.com

Supervisor: Dr Lynette Hodges
Email: L.D.Hodges@massey.ac.nz

Approval

This study has been approved by the Massey University Ethics Committee - 400002832

Cancer information

Please circle or place a tick next to the relevant options

Cancer type:

- Leukaemia
- Lymphoma
- Myeloma
- Other (please specify)

How long since you finished treatment?

- Undergoing active treatment
- <1 year
- 2-5 years
- >5 years

Treatment history

- Chemotherapy
- Radiation therapy
- Stem cell transplant
- Immunotherapy
- Surgery
- Other (please specify)

Consent

By signing your details below, you indicate that you have read and understood the information about the study and voluntarily agree to participate in this research project.

Full Name:

Signature:

Email:

Mobile:

Date:

Appendix E: NZREPS Pre-Exercise Screening Form

Pre-Exercise Screening Form

REPs NZ Register of Exercise Professionals

APPROVED AND RECOMMENDED BY THE NZ REGISTER OF EXERCISE PROFESSIONALS (REPs). To be used in conjunction with the REPs New Zealand Pre-Screening Guide and associated risk stratification best practice. For use exclusively for REPs Registered Exercise Professionals only.

Name:	Age:
Medical Provider(s) Name and Contact:	

SECTION 1 : IMPORTANT MEDICAL INFORMATION

	YES	NO
CARDIOVASCULAR AND PULMONARY CONDITIONS*: Diagnosed heart condition or stroke, or unreasonable leg or chest pain during exercise? Blood pressure over 200/110mm/Hg (measured at time of this pre-screen)? Diagnosed pulmonary disease? (Exercise Professional - see note 1 below) IF YOU TICK YES TO THIS QUESTION PROCEED ONLY UNDER MEDICAL GUIDANCE		

IF YOU TICK YES TO 2 OR MORE OF THE FOLLOWING QUESTIONS, THEN PROCEED WITH CAUTION UNDER GUIDANCE

		YES	NO
	FAMILY HISTORY: Father or brother under 55 years with a history of heart disease or stroke? Mother or sister under 65 years with a history of heart disease or stroke?		
	AGE: Male over 45 years? Female over 55 years?		
	BLOOD PRESSURE: Over 140mm/Hg systolic or 90mm/Hg diastolic. Or, on blood pressure medication?		
	ASTHMA: Attack that required medical attention last 12 months?		
	SMOKING: Currently or quit within previous 6 months?		
	GENERAL ACTIVITY LEVEL: Currently sedentary?		
	BODY COMPOSITION (INDICATIVE): BMI ≥ 30 kg/m2 or Waist (cm) ÷ Height (cm) ratio above 0.6?		
	BONE AND JOINT: Known bone of joint problem that could be aggravated by exercise?		
	OTHER: Any other condition that may increase risk of adverse reaction to exercise?		
OPTIONAL	**LIPIDS:** Identified blood lipids outside recommended range (Exercise professional see note 2 below):		
OPTIONAL	**GLYCEMIC CONTROL:** Diagnosed Type 1 or 2 diabetes (Exercise Professional - see note 3 below)		

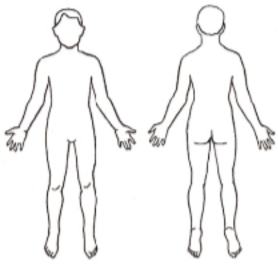
NOTES FOR EXERCISE PROFESSIONAL

1) Cardiovascular / pulmonary disorder
Angina
Shortness of breath with mild exertion or during sleep (Dyspnea)
Dizziness during exercise (Syncope)
Ankle swelling (Edema)
Heart murmur
Unpleasant, rapid beating of heart (Palpitations / Tachycardia)
Intermittent claudication (Cramping/pain in legs unexplained)
Pulmonary disorder such as COPD, cystic fibrosis, emphysema, other

2)) Dyslipidemia. Known result or measured at time of pre-screen:
LDL ≥ 3.37 mmol/L
Total ≥ 5.18 mmol/L
HDL < 1.04 mmol/L
Triglycerides (TG) ≥ 1.7 mmol/L
TG/HDL ratio ≥ 4.0

3) Glycemic control. Known result or measured at time of pre-screen:
Glucose ≥ 5.5 mmol/L over several readings
HbA1c ≥ 40 mmol/mol

SECTION 2 : OTHER IMPORTANT CONDITIONS

MUSCULOSKELETAL Any pain or major injury to: *(Please tick any which apply)* ○ Feet / Ankles ○ Calf / Shin ○ Knees ○ Hamstrings ○ Hips / Groin ○ Lower Back / Abs ○ Upper back / Ribs ○ Neck / Shoulders ○ Arm / Elbow ○ Wrists / Hands	Please circle any area that may be adversely affected by exercise: 
○ **PREGNANT** now or in last 12 months	
○ **EPILEPSY**	
○ **ARTHRITIS**	
MEDICATIONS: ○ Beta blockers ○ ACE inhibitors ○ Diuretic ○ Statin ○ Oral hypoglycemic ○ Other	

NOTES: ____

____

____

Thank you for taking the time to answer the questions above. Your answers will help your REPs Registered Exercise Professional determine the best approach to help you reach your exercise goals.

Informed Consent

I acknowledge that that information provided above regarding my health and personal information is, to the best of my knowledge, correct. I will inform my exercise professional immediately if there are any changes in my health status.

I understand that participating in physical activity and exercise can carry a risk, and I accept all responsibility for that risk.

I understand that due care will be undertaken by my REPs Registered Exercise Professional at all times.

NAME: ____

SIGNATURE: ____

DATE: ________ / ________ / ________

Appendix F: Recovery Data from 24-Hour Repeated CPET

5-minute recovery data for cancer patients post CPET						
Participant	Metric	Minute 1	Minute 2	Minute 3	Minute 4	Minute 5
Cancer patient #1 Day 1	HR (bpm)	190	168	151	144	141
	RPE (6-20)	19	11	9	7	7
	O_2 Sat			93		95
Cancer patient #1 Day 2	HR (bpm)	181	160	143	135	131
	RPE (6-20)	19	15	11	9	7
	O_2 Sat			96		98
Cancer patient #2 Day 1	HR (bpm)	173	160	149	144	142
	RPE (6-20)	11	9	8	7	7
	O_2 Sat			93		99
Cancer patient #2 Day 2	HR (bpm)	154	139	129	121	122
	RPE (6-20)	12	11	9	9	7
	O_2 Sat					
Cancer patient #3 Day 1	HR (bpm)	158	146	141	135	132
	RPE (6-20)	13	12	11	9	7
	O_2 Sat			94		98
Cancer patient #3 Day 2	HR (bpm)	132	123	121	118	119
	RPE (6-20)	10	7	6	6	6
	O_2 Sat			99		98
Cancer patient #4 Day 1	HR (bpm)	158	154	135	124	123
	RPE (6-20)		13	7	6	6
	O_2 Sat			99		97
Cancer patient #4 Day 2	HR (bpm)	130	114	105	104	108
	RPE (6-20)	12	7	6	6	6
	O_2 Sat			96		99
Cancer patient #5	HR (bpm)	156	148	143	144	134
	RPE (6-20)	8	6	6	6	6

Day 1	O_2 Sat			98		96
Cancer patient #5 Day 2	HR (bpm)	144	135	135	132	138
	RPE (6-20)	9	7	7	6	6
	O_2 Sat			98		98

5-minute recovery data for healthy controls post CPET						
Participant	Metric	Minute 1	Minute 2	Minute 3	Minute 4	Minute 5
Control #1 Day 1	HR (bpm)	159	149	139	135	132
	RPE (6-20)	13	10	9	8	7
	O_2 Sat			88		99
Control #1 Day 2	HR (bpm)	178	157	144	133	130
	RPE (6-20)	19	15	12	10	9
	O_2 Sat			97		94
Control #2 Day 1	HR (bpm)	142	130	124	118	118
	RPE (6-20)	16	13	11	10	9
	O_2 Sat			99		99
Control #2 Day 2	HR (bpm)	126	117	114	112	113
	RPE (6-20)	14	11	10	9	8
	O_2 Sat			99		93
S Control #3 Day 1	HR (bpm)	127	116	107	108	106
	RPE (6-20)	12	11	9	8	7
	O_2 Sat			97		97
Control #3 Day 2	HR (bpm)	142	99	101	93	94
	RPE (6-20)	13	9	7	7	7
	O_2 Sat			97		96
Control M #4 Day 1	HR (bpm)	164	150	142	144	132
	RPE (6-20)	11	9	9	9	7

	O_2 Sat			93		96
M Control #4 Day 2	HR (bpm)	184	161	159	146	145
	RPE (6-20)	14	11	9	9	9
	O_2 Sat			97		94
J Control #5	HR (bpm)	142	128	125	125	119
	RPE (6-20)	11	9	9	7	7
	O_2 Sat			95		98
J Control #5	HR (bpm)	131	116	118	104	112
	RPE (6-20)	13	10	8	6	6
	O_2 Sat			98		93

Appendix G: Borg RPE Scale

Borg RPE Scale®

Use this scale to tell how strenuous and tiring the work feels to you. The exertion is mainly felt as fatigue in your muscles and as breathlessness or possibly aches. When the exercise is hard it also becomes difficult to talk. It is your own feeling of exertion that is important. Don't underestimate it, but don't overestimate it either. For common exercise, such as cycling, running or walking, 11-15 is a good level. For strength and high-intensity interval training (HIIT), 15-19 is good. If you are sick follow your doctor's advice. Look at the scale and the descriptions and then choose a number. Use whatever numbers you want, even numbers between the descriptions.

6	**No exertion at all**	No muscle fatigue, breathlessness or difficulty in breathing.
7	**Extremely light**	Very, very light.
8		
9	**Very light**	Like walking slowly for a short while. Very easy to talk.
10		
11	**Light**	Like a light exercise at your own pace.
12	**Moderate**	
13	**Somewhat hard**	Fairly strenuous and breathless. Not so easy to talk.
14		
15	**Hard**	Heavy and strenuous. An upper limit for fitness training, as when running or walking fast.
16		
17	**Very hard**	Very strenuous. You are very tired and breathless. Very difficult to talk.
18		
19	**Extremely hard**	The most strenuous effort you have ever experienced.
20	**Maximal exertion**	Maximal heaviness.

Borg RPE Scale®
Ratings (R) of Perceived (P) Exertion (E).

English

Appendix H: Supplementary 24-Hour Repeated CPET Questions

1.) How did you feel following the first exercise test?	*"It felt like my legs gave out first."* *"I had cramps in my quads."* *"I felt breathless."* *"I feel tired, but nothing out of the ordinary"*
2.) Describe how you felt the day after the first exercise test.	*"I felt like I had not gotten much sleep; this made me easily agitated, lots of bodily fatigued and had a lot of brain fog."* *"I did not feel too bad; I did not feel any obvious signs of fatigue."*
3.) How did you feel following the second exercise test?	*"I had bad brain fog again."* *"My legs feel very heavy and numb."* *"I feel less out of breath than the first exercise test but found breathing harder during the testing."*
4.) Describe how you felt the day after the second exercise test.	*"I felt a lot of brain fog and lethargic."* *"I struggled to get through work the following day."* *"I had a lot of mental fatigue in the afternoon and more fatigue than usual in the evenings."*
5. How long did it take you to recover from the second exercise test? For example, how long did it take to feel normal again?	*"I felt the effects of the exercise test two days after."* *"The fatigue was worse for me the day after the second exercise test."*
6.) Describe symptoms, if any, experienced after the exercise tests.	*"My muscles felt tight, and I felt a little lightheaded."* *"Brain fog impaired my memory and ability to concentrate."*

Appendix I: SF-36 Questionnaire

SF-36 QUESTIONNAIRE

Name:____________________ **Ref. Dr:**__________________ **Date:** _______

ID#: ______________ **Age:** _______ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

Compared to one year ago, how would you rate your health in general now?

○ Much better now than one year ago
○ Somewhat better now than one year ago
○ About the same
○ Somewhat worse now than one year ago
○ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

○ Yes, Limited a lot ○ Yes, Limited a Little ○ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Lifting or carrying groceries

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing several flights of stairs

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing one flight of stairs

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bending, kneeling, or stooping

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking more than a mile

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking several blocks

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking one block

○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bathing or dressing yourself
◯Yes, Limited a Lot ◯Yes, Limited a Little ◯No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
◯Yes ◯No

Accomplished less than you would like
◯Yes ◯No

Were limited in the kind of work or other activities
◯Yes ◯No

Had difficulty performing the work or other activities (for example, it took extra effort)
◯Yes ◯No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
◯Yes ◯No

Accomplished less than you would like
◯Yes ◯No

Didn't do work or other activities as carefully as usual
◯Yes ◯No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

◯Not at all ◯Slightly ◯Moderately ◯Severe ◯Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

◯None ◯Very Mild ◯Mild ◯Moderate ◯Severe ◯Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

◯Not at all ◯A little bit ◯Moderately ◯Quite a bit ◯Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
Definitely true Mostly true Don't know Mostly false Definitely false

I am as healthy as anybody I know
Definitely true Mostly true Don't know Mostly false Definitely false

I expect my health to get worse
Definitely true Mostly true Don't know Mostly false Definitely false

My health is excellent
Definitely true Mostly true Don't know Mostly false Definitely false

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

Appendix J: FAS Questionnaire

Fatigue Assessment Scale (FAS)

The following ten statements refer to how you usually feel. Per statement you can choose one out of five answer categories, varying from Never to Always.
Please circle the answer to each question that is applicable to you. Please give an answer to each question, even if you do not have any complaints at the moment.

1. **Never**
2. **Sometimes** (about monthly or less)
3. **Regularly** (about a few times a month)
4. **Often** (about weekly)
5. **Always** (about every day)

		Never	Sometimes	Regularly	Often	Always
1.	I am bothered by fatigue	○	○	○	○	○
2.	I get tired very quickly	○	○	○	○	○
3.	I don't do much during the day	○	○	○	○	○
4.	I have enough energy for everyday life	○	○	○	○	○
5.	Physically, I feel exhausted	○	○	○	○	○
6.	I have problems to start things	○	○	○	○	○
7.	I have problems to think clearly	○	○	○	○	○
8.	I feel no desire to do anything	○	○	○	○	○
9.	Mentally, I feel exhausted	○	○	○	○	○
10.	When I am doing something, I can concentrate quite well	○	○	○	○	○

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