Universidade de Évora - Escola de Saúde e Desenvolvimento Humano

Mestrado em Exercício e Saúde

Dissertação

Multidisciplinary prehabilitation for improving physical fitness in patients with colon cancer before the surgery: the ONCOFIT randomized controlled trial

Sofia Carrilho da Graça Estêvão Candeias

Orientador(es) | Armando Manuel Raimundo

Francisco J. Amaro Gahete

Évora 2023

Esta dissertação não inclui as críticas e as sugestões feitas pelo júri.

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JURY CONSTITUTION

President of the Jury- José Alberto Frade Martins Parraça

Vogals- Armando Manuel Mendonça Raimundo **(Supervisor)**

Jorge Duarte dos Santos Bravo **(Arguer)**

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ABSTRACT

INTRODUCTION: Colon cancer is currently ranked as the 5th most prevalent cancer worldwide. Surgical resection represents an elective therapy for treating patients with colon cancer. In patients with colon cancer, poor functional capacity is highly related to increased postoperative complications and higher morbidities risk. Therefore, a multidisciplinary prehabilitation program seems to be appropriate for maintaining and/or improving functional capacity before a colon cancer' surgical procedure. **OBJECTIVE:** To evaluate the effects of a 4-week multidisciplinary prehabilitation program on physical fitness in patients undergoing colon cancer resection. **METHODS:** This study is based on a preliminary ONCOFIT randomized controlled trial analysis. Twenty-nine participants were included in the present analysis (n=16 intervention and n=13 usual care). The multidisciplinary prehabilitation intervention included (i) supervised exercise training, (ii) dietary behavior changes and (iii) psychological support. Cardiorespiratory fitness, gait speed, upper and lower limb muscle strength and subjective physical fitness were assessed. **RESULTS:** The intervention significantly increased gait speed (Hedges´g = 0.84). A moderate effect was reported in the lower limb muscle power (Hedges´g = 0.54) and in the cardiorespiratory fitness (Hedges´g = 0.51), a small effect was noted in the lower limb muscle strength (Hedges´g =0.22) and the upper muscle strength [Handgrip Left (Hedges´g = 0.26), Handgrip Right (Hedges´g = 0.23)] and no effects on subjective physical fitness (Hedges´g = 0.19). **CONCLUSIONS:** A 4-week multidisciplinary prehabilitation program was effective at improving functional capacity.

KEYWORDS: Functional Capacity; Colon Cancer; Multidisciplinary Program, Prehabilitation; Exercise

PRÉ-HABILITAÇÃO MULTIDISCIPLINAR PARA MELHORAR A APTIDÃO FÍSICA EM DOENTES COM CANCRO DO CÓLON ANTES DA CIRURGIA: ENSAIO CONTROLADO E ALEATÓRIO ONCOFIT

RESUMO

INTRODUÇÃO: O cancro do cólon é o 5º cancro mais prevalente em todo o mundo. A ressecção cirúrgica representa uma terapia eletiva para o tratamento de doentes com cancro do cólon. A baixa capacidade funcional nestes doentes está altamente relacionada com o aumento das complicações pós-operatórias e com um maior risco de morbilidade. Por conseguinte, um programa de pré-habilitação multidisciplinar parece ser adequado para manter e/ou melhorar a capacidade funcional antes de um procedimento cirúrgico de cancro do cólon. **OBJETIVO**: Avaliar os efeitos de um programa de pré-habilitação multidisciplinar de 4 semanas na aptidão física de doentes submetidos a ressecção de cancro do cólon. **MÉTODOS:** Este estudo baseia-se numa análise preliminar do ensaio aleatório controlado ONCOFIT. Vinte e nove participantes foram incluídos na presente análise (n=16 intervenção e n=13 cuidados habituais). A intervenção multidisciplinar de pré-habilitação incluiu (i) treino de exercício supervisionado, (ii) alterações do comportamento alimentar e (iii) apoio psicológico. Avaliou-se a aptidão cardiorrespiratória, a velocidade de marcha, a força muscular dos membros superiores e inferiores e, a aptidão física subjetiva. **RESULTADOS:** A intervenção aumentou significativamente a velocidade da marcha (Hedges'g = 0.84). Observou-se nos membros inferiores (Hedges'g = 0.54) e na aptidão cardiorrespiratória (Hedges'g = 0.51), um pequeno efeito na potência muscular dos membros inferiores (Hedges'g = 0.22) e na força muscular dos membros superiores [Handgrip esquerdo (Hedges'g = 0.26), Handgrip direito (Hedges'g = 0.23)] e, nenhum efeito na aptidão física subjectiva (Hedges'g = 0.19). **CONCLUSÃO:** Um programa de pré-habilitação multidisciplinar de 4 semanas foi eficaz na melhoria da capacidade funcional.

PALAVRAS-CHAVE: Capacidade Funcional; Cancro do Cólon; Programa Multidisciplinar de Pré-Habilitação; Exercício

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ABBREVIATIONS

PP- Prehabilitation Program

BMI- Body Mass Index

CIMP-CpG Island methylation Phenotype

Cm- Centimeters

CT- Computed Tomographic

CTC- Computed Tomographic Colonography

ERAS- Enhanced Recovery After Surgery

FBOT- Stool Blood Test

FIT- Fecal Immunochemical Test

FSIG- Flexible Sigmoidoscopy

gFOBT- Fecal Occult-blood Test

Handgrip L- Handgrip Left

Handgrip R- Handgrip Right

HDI-High Development Index

HDL- High-density protein

HIIT- High-intensity Interval Training

IFIS- International Fitness Scale

IGF1- Insuline-growth factor 1

FAP- Famial Adenomatous Polyposis

Kg- Kilograms

Kg/m^2 - kilogram per square meter

LPL- Lipoprotein Lipase

M- Metastases

m-meters

MMR-Mismatch Repair Complex

MSI- Microsatelite Instability

mt-sDNA-Multi-target Stool DNA

N- Nodules

n- sample

n^o-score

NIC- Chromosonal Instability

pHR-Peak Heart Rate

RPE- Rate of Perceived Exertion

Rep- Repetitions

s- second

SAT- Subcutaneous Adiposr Tissue

T- Tumor

Tis- Melona in situ

VAT- Visceral Adipose Tissue

30s STS- 30-s Sit-to-Stand Muscle Power Test

4 week-Prehab – 4-week multidisciplinary (supervised concurrent exercise training, dietary behavior changes and psychological support) prehabilitation group

5STS- 5-Times Sit-to-Stand Test

6MWT – 6 Min Walking Test

CHAPTER I. INTRODUCTION

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1.1. CONTEXTUALIZATION

Colon cancer is the fifth most common neoplasia in the world, with ~1.1 million patients diagnosed each year, and is responsible for more than 500,000 deaths (Sung et al., 2021). In addition, it can be considered a marker of socioeconomic development since there is a positive relationship between the Human Development Index (HDI) and its incidence (Sung et al., 2021). As a result, countries such as Southern Europe, Northern Europe, and Australia/New Zealand have higher incidence rates (Rawla et al., 2019).

Nowadays, surgery is considered the elective and curative treatment (Ahmed, 2020; Labianca et al., 2010). However, a surgical procedure is a stressful process that can lead to many immunological, hematological, and endocrinological complications (Desborough, 2000). The average age at diagnosis is ~70 years old (Sung et al., 2021). Given their age, it is relatively common for these patients to have various comorbidities and disorders. For this reason, there is an increased incidence of postoperative complications observed in more than 50 % of patients (Fagard et al., 2016). These post-operative complications are associated with inadequate lifestyle behaviors, including unhealthy eating habits, alcohol intake, smoking, and decreased physical and physical fitness (Loogman et al., 2021).

Functional capacity has also emerged as another important factor that modulates postoperative complications and prolonged hospital stays (Ezzatvar et al., 2021; Sánchez-Jiménez et al., 2015). Functional capacity encompasses the individual's ability to perform daily-living activities in general and also extends to particular domains of functioning, such as physical, mental, emotional, and social (Mera-Mamián et al., 2021). Physical fitness comprises cardiorespiratory, motor, and musculoskeletal fitness (Bizzozero-Peroni et al., 2022). As we older there is a decline in physiological reserves, loss of mass, difficulty walking at an average pace, altered muscle function, and loss of mobility, all of which are increased by factors associated with cancer (Beaudart et al., 2019; Ezzatvar et al., 2021; Pal & Hurria, 2010).

The presence of postoperative complications is strongly associated with a reduction of long-term overall survival in patients with colon cancer (Breugom et al., 2016; Warps et al., 2022). It is, therefore, essential to change lifestyle habits before surgery to improve these patient's functional capacity and prognosis (Molenaar et al., 2023).

Exercise can be considered both a preventive tool and an effective way of improving physical fitness, relieving depression, reducing fatigue, controlling body fat, and improving sleep quality (B. Singh et al., 2020). The loss of muscle mass and altered muscle function are key factors frequently present in patients who undergo a surgical procedure or who suffer cancer. The combination of aerobic and resistance training has been suggested as an effective method for the enhancement of the individual's functional capacity (Molenaar et al., 2023; Reis et al., 2018). These improvements seem to be mediated by adaptations at the muscular level, namely an increase in oxidative capacity, power, and strength to the detriment of endurance (Bishop-Bailey, 2013).

Moreover, dietary habits are crucial for individuals with cancer, as it is associated with reductions in nutritional reserves that can lead to malnutrition (Lewandowska, Rudzki et al., 2022; Vitaloni et al., 2022), an status that can increase the rate of post-operative complications and mortality (D. U. Lee et al., 2021). In addition, malnutrition can lead to cachexia. Cachexia is characterized by loss of weight, muscle mass, impaired immune, mental and physical function and lean body mass (Vitaloni et al., 2022). Another condition that is associated with this factor is sarcopenia, which has a negative impact on functional capacity due to the loss of muscle mass (Hu, 2015; D. U. Lee et al., 2021; Maia et al., 2020; Vitaloni et al., 2022). The Mediterranean diet has been proposed as a dietary pattern that provide important health-related benefits (Itsiopoulos et al., 2022; Monllor-Tormos et al., 2023). Indeed, it has been demonstrated that a proper adherence to the Mediterranean adherence helps to prevent malnutrition, ensures protein and energy intake, and reduces the symptoms of negative nutritional impact (Vitaloni et al., 2022).

Finally, another crucial factor in the patient's prognosis is their psychological statues since patients are exposed to an additional stress (Ghoneim & O'Hara, 2016; Pitman et al., 2018; Smith, 2015). Anxiety and depression – the most frequent disorders in this context - are associated with the individual's lack of enthusiasm for social and functional activities, which altogether leads to decreased functional capacity and increased fatigue perception (Ghoneim & O'Hara, 2016; Pitman et al., 2018; Stark & House, 2000).

Previous studies show that a prehabilitation program helps to improve not only postoperative recovery (K. C. H. Fearon et al., 2005), as well as functional capacity in some of its parameters, namely cardiorespiratory fitness, muscle strength and walking speed (Bruns et al., 2019; Minnella et al., 2017, 2020; Molenaar et al., 2023; F. Singh et

al., 2018; Suen et al., 2022). Molenaar et al. 2023, implemented a personalized and supervised preoperative program in hospital, lasting 4 weeks, including combined high-intensity interval training (HIIT), nutritional and psychological support. Although this study shows that this type of program is effective on cardiorespiratory capacity and reduces operative complications, it has some limitations that may affect the validity and generalizability of the results, namely the impact of the pandemic. While there are studies that show a positive effect of exercise programs or the combination of exercise and nutrition on muscle strength and walking speed (Bruns et al., 2019; F. Singh et al., 2018; Suen et al., 2022). However, there is no evidence to show the effect of a multidisciplinary prehabilitation program (exercise, nutrition, and psychology) encompassing several domains on cardiorespiratory fitness, gait speed, muscular strength, and subjective physical fitness in patients undergoing colon cancer resection. Therefore, this study aimed at investigating the effects of a 4-week multidisciplinary prehabilitation program on cardiorespiratory fitness, gait speed, muscular strength, and subjective physical fitness in patients undergoing colon cancer resection.

1.2. DISSERTATION STRUCTURE

The dissertation consists of seven chapters. The first chapter is a brief introduction to the chosen topic, in which its contextualization, the relevance of the topic, and its justification are discussed.

In the second chapter, a literature review is carried out, in which a theoretical framework of the study is performed, mentioning the most critical colon cancer' points of interest: (i) epidemiology, (ii) the pathophysiology of colon cancer, (iii) the different diagnostic methods, (iv) how to classify the stage of each patient, (v) risk factors and, (vi) its treatment. In addition, the functional capacity and the three dimensions of the multidisciplinary program - exercise, nutrition, and psychology - are addressed. The same chapter presents the relevance of the study and both the general and specific objectives.

The third chapter is the study methodology, which describes the study design, the sample, the selection criteria, the procedures for the usual care group and the intervention group, the instruments and materials used, and how the statistical analysis was carried out. The fourth chapter presents the results of the study.

The fifth chapter discusses the findings of the study. The sixth chapter presents the main conclusions of the study and, finally, the last chapter presents future perspectives on the topic and the main limitations.

CHAPTER II. LITERATURE REVIEW

CHAPTER II. LITERATURE REVIEW

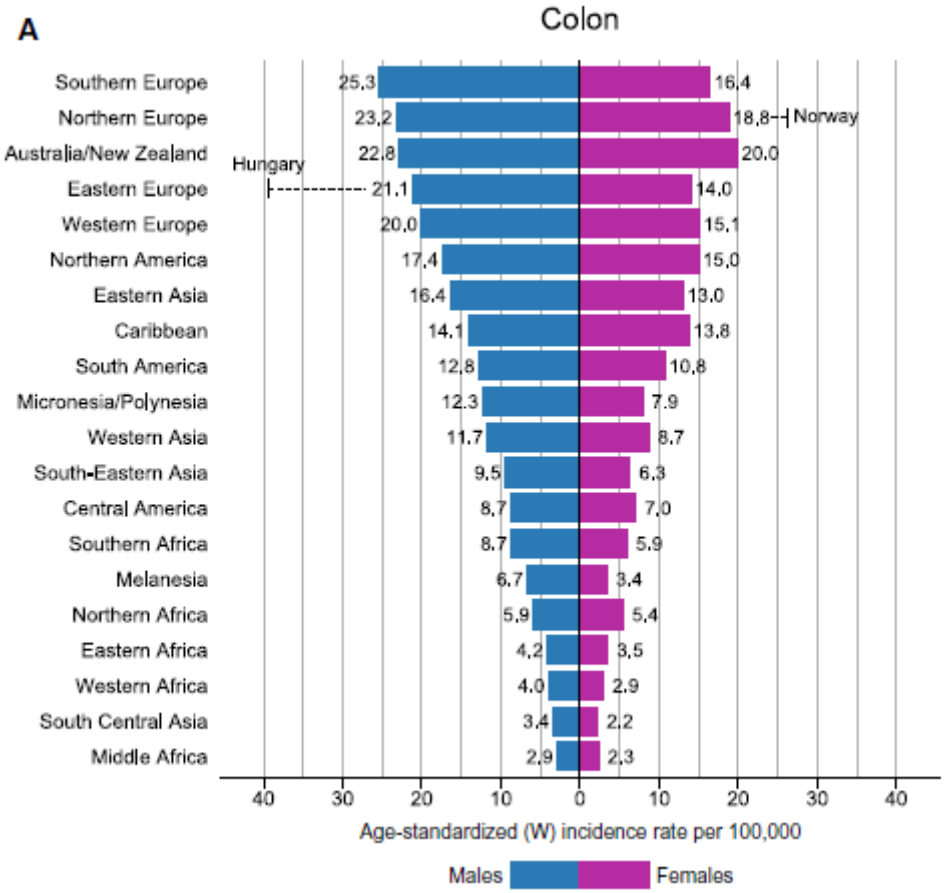
2.1. COLON CANCER

2.1.1 EPIDEMIOLOGY

Cancer is one of the leading global causes of mortality, resulting in an estimated 9.3 million deaths annually (World Health Organization, 2023). The incidence rate of cancer varies according to the Human Development Index. It should be emphasized that, in developing countries, the incidence rates are lower vs. those observed in developed countries for both genders (Sung et al., 2021). This is due to industrialization and economic growth, which in turn lead to a sedentary lifestyle, a Western dietary pattern (i.e., high in fat, low in fruit, high consumption of red or processed meats), and an increase in obesity prevalence (Keum & Giovannucci, 2019; Sung et al., 2021). In 2020, Europe (9.7% of the world's population) accounted for 22.8% of global cases and 19.6% of cancer deaths (Sung et al., 2021).

Colon cancer is the 5th most common cancer type worldwide (Sung et al., 2021), with around 1.1 million individuals diagnosed yearly and responsible for more than 500,000 deaths (Sung et al., 2021). Colon cancer incidence rates are higher in men (600,896 cases per year), with an age-standardized incidence rate (worldwide) of 13.1/100,000 (Sung et al., 2021). Conversely, women have 547,619 cases per year, and the age-standardized incidence rate (worldwide) per 100,000 is 10.0 (Sung et al., 2021). Colon cancer can be considered a marker of economic development, with incidence rates tending to rise evenly as HDI increases. Figure 1, shows that Europe, Australia/New Zealand, and South America are the most affected regions, with a higher incidence among men in Southern Europe and women in Australia/New Zealand (Rawla et al., 2019; Sung et al., 2021).

Figure 1. Region-Specific Incidence Age-Standardized Rates by Sex for Cancers of the Colon (Sung et al., 2021).



2.1.2 PHYSIOPATHOLOGY

The colon comprises several distinct segments, including the cecum, appendix, ascending colon, transverse colon, descending colon, and sigmoid colon (Carmichael & Mills, 2016). This anatomical structure comprises muscle and connective tissue, measuring approximately 150 cm in length (Carmichael & Mills, 2016). When observing the interior of the lumen from an external perspective, the following layers become evident: (i) serosa layer, (ii) muscular layer, (iii) submucous layer, and (iv) mucous layer (Bleier & Wilkins, 2016). The serosa contains the external layer and is enveloped by the visceral peritoneum (Bleier & Wilkins, 2016). The muscle layer includes an inner circular muscle layer and an outer longitudinal muscle layer with three thickened bands called taenia coli (Bleier & Wilkins, 2016). The submucosal layer is denser and contains blood vessels, lymphatic vessels, and nerves (Bleier & Wilkins, 2016). Finally, the innermost layer, the mucosa, is lined by the epithelium (Bleier & Wilkins, 2016).

The colon's primary function is the absorption of water, electrolytes, and unabsorbed nutrients, as well as the creation of solid stool (Bleier & Wilkins, 2016).

These mechanisms depend on the intestinal flora's metabolic activity, the colon's motility, and the mucosa's capacity to absorb water and secrete potassium, chlorine, hydrogen, and bicarbonate ions (Bleier & Wilkins, 2016). Thus, the epithelium comprises crypts containing cells that facilitate the absorption of minerals and are continually regenerating (Bleier & Wilkins, 2016). As the cells transform into specialized epithelial cells, they move to the upper part of the crypt, where they undergo the process of apoptosis and are later expelled through the feces (Bleier & Wilkins, 2016).

Colon cancer is a malignant neoplasm that results from the complex interaction between environmental and genetic factors, disenrolling from adenomas (Kuipers et al., 2015). Adenomas are epithelial polyps resulting from abnormal proliferation of the cells that comprise the mucous layer (Keum & Giovannucci, 2019; Testa et al., 2018). These benign precursors can develop into a malignant disease depending on their type. Adenomatous polyps and serrated polyps are two specific types that serve as direct precursors to the development of most cases (Keum & Giovannucci, 2019). Adenomatous polyps are considered the classic precursor of colon cancer (Keum & Giovannucci, 2019). Serrated polyps can be divided into (i) hyperplastic polyps, (ii) traditional serrated adenoma, (iii) sessile serrated adenoma, and (iv) mixed polyps, with hyperplastic polyps being the most prevalent (Keum & Giovannucci, 2019).

The development from the beginning precursor stage of adenoma to carcinoma includes several stages (Keum & Giovannucci, 2019). During the initial phase, genetic and /or epigenetic modifications manifest within the cells located in the mucosal layer. Subsequently, there is an increase in the abnormal growth of mutated cells (neoplasms) and the proliferation of first tumor cells (Keum & Giovannucci, 2019; Testa et al., 2018). When the first tumor cells appear, the progression phase initiates. At this phase, pre-cancerous cells (benign tumor cells) multiply rapidly, acquiring characteristics that make them more invasive and have metastatic potential (Keum & Giovannucci, 2019; Testa et al., 2018).

Colon carcinogenesis includes three genetic and epigenetic aberrations: Microsatellite instability (MSI), chromosomal instability (NIC), and CpG island methylation phenotype (CIMP) (Malki et al., 2020; Rawla et al., 2019). MSI is related to alterations in DNA sequences called microsatellites, which consist of short nucleotide repeats. Thus, MSI occurs due to alterations in the mismatch repair complex (MMR) gene, which causes modifications in DNA repair (Malki et al., 2020). When it has two or

more repeat patterns, MSI is referred to as high microsatellite instability. Otherwise, low microsatellite instability (Malki et al., 2020). This type of aberration occurs in >95% of cases of Lynch Syndrome, also called HNPCC (Malki et al., 2020). NIC is the most common instability in around 85 % of adenocarcinoma transitions (Malki et al., 2020). This is characterized by changes in the number and structure of the chromosomes of cancer cells, which leads to deregulation of cell function, affecting essential genes in the control of cell growth (Malki et al., 2020; Rawla et al., 2019). CIMP is characterized by the aberrant methylation of several CpG islands, which are regions of DNA rich in cytosine-guanine and are located close to gene promoters. This methylation of CpG islands can lead to the inactivation of tumor suppressor genes that are responsible for preventing tumor development and controlling cell growth (Malki et al., 2020).

2.1.3 DIAGNOSTIC AND SCREENING

Colon cancer can be diagnosed through either the manifestation of symptoms or by screening programs. The diagnosis based on symptoms manifestations typically occurs at a more advanced stage, resulting in a poorer prognosis (Cappell, 2005; Labianca et al., 2010).

Rectal bleeding, involuntary weight loss, altered bowel habits, and abdominal pain are the most common symptoms of colon cancer (Cappell, 2005; Labianca et al., 2010). On the other hand, malaise, vomiting, abdominal distension, nausea, and anorexia are the less common symptoms (Cappell, 2005; Labianca et al., 2010). The symptomatology depends on the size of the cancer, its location, and the presence of metastases (Cappell, 2005). However, screening tests such as Colonoscopy, Computed Tomographic Colonography, Flexible Sigmoidoscopy, Fecal Test, and Multi-targeted Stool DNA Test are performed for an earlier and more accurate diagnosis.

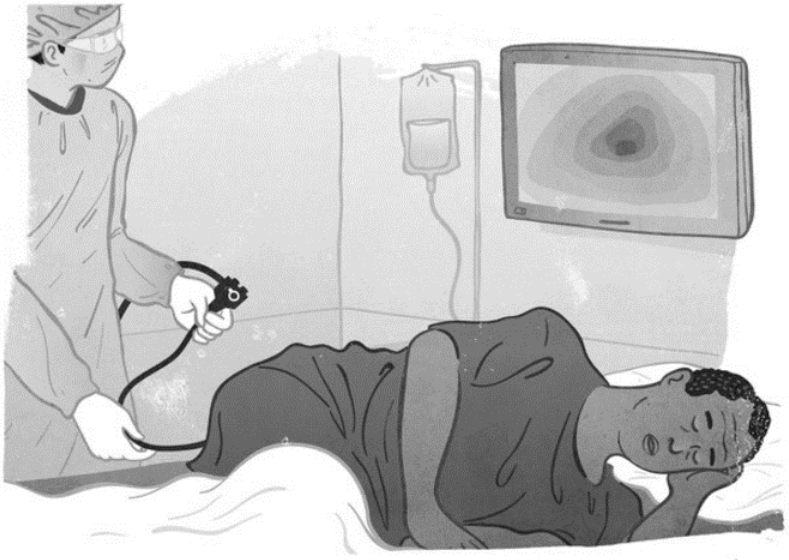
2.1.3.1 Colonoscopy

A colonoscopy is a diagnostic procedure based on visually examining the large intestine's internal lining through a flexible tube. (Couric, 2006; Gupta, 2022). During this examination, potentially malignant polyps can be detected, and samples can be taken to diagnose colon cancer (Moore & Aulet, 2017; Thanikachalam & Khan, 2019). Polyps are characterized according to their color, size, location, number, and appearance, with a detection error rate of 6% for large polyps (>1 cm) and 27% for small polyps (Cappell, 2005).

For the most effective colonoscopy, it is necessary to have a good bowel preparation 24 hours before the procedure, ensuring that it does not cause dehydration or alterations to the mucous membrane or electrolyte (Cappell, 2005; Moore & Aulet, 2017). The primary aim of this preparation is to increase the evacuation of the intestinal contents to allow a clear and unobstructed view of the colon (Couric, 2006).

Although it is highly accurate and safe, colonoscopy has some risk factors as it is an invasive exam. The patient may experience discomfort during the examination, and occasionally, there is a potential risk of bowel perforation(Cappell, 2005; Couric, 2006). Furthermore, its realization requires many resources and conscious sedation can cause low blood pressure, low oxygen saturation in the blood, and low respiratory rate (Cappell, 2005; Couric, 2006).

Figure 2. Colonoscopy (Thakkar,B., 2019)



2.1.3.2 Computed Tomographic Colonography (CTC)

CTC, commonly known as virtual colonoscopy, is a non-invasive medical imaging technique that is based on computed tomography (CT) images (Labianca et al., 2010). This method allows the entire large intestine to be scanned with X-ray images of a specific anatomical area. The computer reconstructs These images into two and three-dimensional formats so they can be studied (Florie et al., 2005; Couric, 2006; Labianca et al., 2010).

To conduct this examination, an intestinal preparation is initially carried out to remove most of the feces (Robbins & Kim, 2013). Subsequently, gaseous distension of the colonic lumen is performed, enabling the detection of polyps (Robbins & Kim, 2013). This distension is achieved through the automatic insufflation of carbon dioxide with

limited pressure (Robbins & Kim, 2013). Finally, after the colon is distended, images are taken in a supine and prone position, as there may be some collapsed bowel segments in either position (Florie et al., 2005; Robbins & Kim, 2013).

Despite the advantages associated with CTC, including its non-invasive nature, lack of sedation requirement, and the ability to revisit the examination, it is not considered to be the gold standard method for screening of colon cancer, as colonoscopy has more advantages than CTC (Gupta, 2022; Hultcrantz, 2021). Thus, this is performed when the colonoscopy cannot be executed or if the individual refuses to undergo the examination as a colonoscopy (Florie et al., 2005; Hultcrantz, 2021).

Figure 3. Computed Tomographic Colonography (Phoenix Hospital Group, 2023)

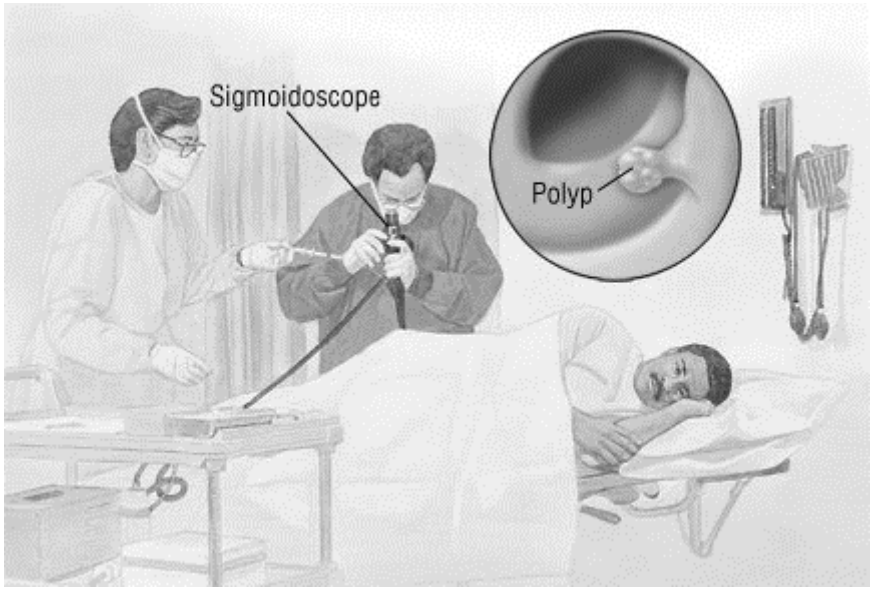
2.1.3.3 Flexible Sigmoidoscopy (FSIG)

FSIG is a diagnostic method that examines the sigmoid colon and rectum (Gupta, 2022; Moore & Aulet, 2017). Before the examination is performed, the distal colon is cleaned by administering enemas or laxatives without requiring oral preparation (Hultcrantz, 2021; Moore & Aulet, 2017; Robertson et al., 2017). Subsequently, a 60 cm flexible endoscope is inserted through the anus and distal colon to directly visualize the mucosa (Moore & Aulet, 2017). During the examination, the patient is in a lateral reclining or pronating position (Gupta, 2022; Moore & Aulet, 2017).

This diagnostic procedure has several advantages: (i) it does not require a complete bowel preparation, (ii) it is usually not performed with sedation, (iii) its duration is shorter than a colonoscopy, and (iv) if abnormalities are found, they can be removed or biopsied (Gupta, 2022; Moore & Aulet, 2017; Robertson et al., 2017). However, this technique exhibits limitations as only the distal colon is analyzed. Therefore, there is a

strong likelihood that one-third of adenomas and cancers will not be detected (Cappell, 2005; Moore & Aulet, 2017)

Figure 4. Flexible Sigmoidoscopy (Drug.com, 2000)



2.1.3.4 Stool Blood Test (FBOT)

FBOT is one of the most widely used non-invasive methods for screening colon cancer or larger polyps. To optimize efficacy, it is necessary to carry out the test annually as small polyps do not tend to exhibit bleeding, and bleeding from cancerous or large polyps may be intermittent or undetectable within a single stool sample (Levin et al., 2008). FOBT includes the guaiac Fecal Occult-Blood Test (gFOBT), Fecal Immunochemical Test (FIT), and multitarget stool DNA (mt-sDNA).

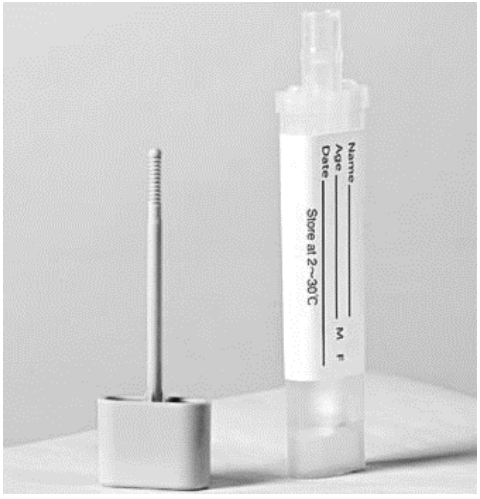
gFOBT detects the presence of blood in feces using a chemical reaction involving peroxidase activity on the heme subunit of hemoglobin (Binefa, 2014; Cappell, 2005; Levin et al., 2008). This is considered a qualitative test, as the results are obtained through a reagent that causes a change in the color of the stool, thus depending on a subjective assessment (Binefa, 2014). The gFOBT protocol takes two samples from each of three consecutive home evacuation results (Binefa, 2014; Levin et al., 2008; Moore & Aulet, 2017). Therefore, before it is performed, the patient should avoid taking anti-inflammatory drugs, vitamin C, red meat, poultry, fish, and some raw vegetables (Levin et al., 2008). These recommendations stem from the test identifying peroxidase activity in human blood and dietary components, potentially leading to an elevated risk of false-positive or false-negative results (Binefa, 2014; Levin et al., 2008). Following this

procedure, if the test is positive, the patient has to undergo a colonoscopy to ensure the result (Moore & Aulet, 2017).

FIT is an immunochemical method for the detection of occult blood in feces. Compared to gFOBT, this is a more specific test, as it detects human globin, a protein that constitutes human hemoglobin and hem (Binefa, 2014; Levin et al., 2008). Moreover, this test offers certain advantages as it does not react to dietary components, eliminating the necessity for dietary restriction (Levin et al., 2008). In addition, sample collection is less demanding than gFOBT, as fewer samples are needed, and less direct handling of the stool is required (Levin et al., 2008). Nevertheless, it is essential to note that both gFOBT and FIT are recommended to be performed annually, and if the test yields a positive result, patients are referred for colonoscopy.

Finally, mt-sDNA is an automated test based on two highly discriminating methylated genes (BMP3 and NDRG4), KRAS point mutations, a DNA marker (β-actin), and an immunochemical sample of human hemoglobin (Ahlquist, 2015; Sweetser & Ahlquist, 2016). It does not require dietary restriction, medication, or bowel preparation and can be conducted at home (Ahlquist, 2015). After the test has been carried out, it is subjected to software analysis utilizing logistic regression, and based on an established cut-off score, the test outcome is evaluated to determine whether it yields a positive or negative result (Ahlquist, 2015; Sweetser & Ahlquist, 2016). This analysis is more sensitive for larger precancerous polyps than fecal blood analysis tests. Additionally, it has a point sensitivity similar to colonoscopy (Sweetser & Ahlquist, 2016).

Figure 5. Recipient for Stool Blood Test (Mayo Clinic, 2022)



2.1.4. STAGE

Using staging as a standardized classification system allows healthcare practitioners to accurately and precisely characterize specific cancers using the universally recognized (Couric, 2006). Consequently, the primary objective of staging is to facilitate treatment decision-making by furnishing prognostic information, enhancing therapy efficacy assessment, and streamlining information exchange among different treatment centers (Couric, 2006).

In 1932, Dukes introduced an initial iteration of a tripartite classification system, referred to in Table 1 for staging colorectal cancer, which incorporated the assessment of tumor dissemination and the presence of lymph node involvement (Banias et al., 2022). Stage A encompassed tumors confined to the rectal wall, stage B included tumors extending beyond the wall but lacking lymph node metastases, and stage C denoted tumors with confirmed lymph node involvement (Banias et al., 2022). Over the years, this classification has suffered numerous changes, with the Astler and Coller Modified (MAC) classification system being the most widely recognized and prominent one (Couric, 2006). In this, sub-classifications were introduced, along with a supplementary modification of Dukes' classification, which encompassed the categories from A-D (Couric, 2006).

Table 1. Comparison of colon staging systems (adapted from Couric, 2006)

DUKES (1932)	DUKES (1935)	MAC
A		A
		B1
B		B2
		B3
C	C1	C1
	C2	C2
		C3
		D

In addition to these two types of classification, the TNM classification can be found, which is considered a dual system in which it presents a clinical system and a pathological system (Labianca et al., 2010). The clinical system employs physical examination and imaging findings, while the pathologic system integrates clinical data with information obtained from surgical interventions (Barriera-Silvestrini et al., 2021).

This classification provides information on the size and the extension of the tumor, the involvement of lymph nodes, and the presence or absence of metastases based on three components: T (Tumor), N (Nodules), and M (Metastases) (Cappell, 2008). The T component describes the size and extent of the primary tumor (Table 2). This ranges from T0, which indicates no evidence of a primary tumor, and T4, a large and invasive tumor that has spread to nearly tissues or organs (table 2) (Couric, 2006; Cappell, 2008). The N component refers to the development of regional lymph nodes, ranging from N0, which indicates the absence of lymph node involvement, to N3, which suggests the presence of lymph nodes (table 2). Finally, the M component describes the presence or absence of distant metastases, where M0 corresponds to the absence of metastases. At the same time, M1 represents the presence of cancer metastases that have spread to distant organs or tissues (table 2). However, if the minimum requirements of the assessment are not met, the symbols Tx, Nx, and Mx are used (Couric, 2006; Cappell, 2008).

Table 2. TNM Classification (adapted from Couric, 2006)

Tx	No description of the tumor´s extent is possible because of incomplete information
T0	No evidence of a primary tumor
Tis	The cancer is in the earliest stage. It´s has not grown beyond the mucosa (inner layer) of the colon or rectum. This stage is also known as carcinoma in situ or intramucosal carcinoma
T1	The cancer has grown through the mucosa an extends into the submucosa
T2	The cancer has grown through the mucosa and the submucosa and extends into the thick muscle layer
T3	The cancer has grown through the mucosa, the submucosa, and completely through the thick muscle layer. It has spread to the subserosa but not to any nearby organs or tissues
T4	The cancer has spread completely through the wall of the colon or rectum into nearby tissues or organs
Nx	No description of lymph node involvement is possible because of incomplete information
N0	No lymph node involvement
N1	Cancer cells found in one to three regional lymph nodes
N2	Cancer cells found in four or more regional lymph nodes
Mx	No description of distant spread is possible because of incomplete information
M0	No distant spread
M1	Distant spread is present

Based on the TNM components, the cancer is assigned a stage and can be classified into five stages (Table 3). Stage 0 corresponds to melanoma in situ (Tis). Stage I denotes localized tumors without evidence of spreading beyond the primary tumor, which can be further divided into IA and IB subgroups. The subgroup includes melanomas less than 1mm thick with and without ulceration and tumors up to 2mm wide without ulceration. Stage II represents localized tumors with a higher risk of recurrence due to the depth and presence of ulceration. It is divided into three subgroups: IIa, IIb, and IIc. These cover tumors more than 1 mm thick with ulceration and more than 2 mm thick with or without ulceration (Barriera-Silvestrini et al., 2021). Stage III, known as the regional stage, pertains to tumors that have spread to both the primary tumor and the regional lymph nodes but are not too distant sites. This is subclassified as IIIa, IIIb, IIIc, and IIId, depending on the extent of lymphatic disease. Lastly, stage IV is classified when tumors have metastasized to regional lymph nodes and distant sites (Barriera-Silvestrini et al., 2021).

Table 3. Stage groupings (adapted from Couric, 2006)

STAGE	T	N	M	DEFINITION
0	Tis	0	0	Carcinoma in situ: cancer in its earliest stages that has not progressed beyond the inner surface of the colon
I	1 or 2	0	0	Cancer has grown in to the wall of the colon, but it has not spread outside of the colon wall
IIa	3	0	0	Cancer has grown through the wall of the colon but it has not spread in the lymph nodes or to distance sites
IIb	4a	0	0	Cancer has spread through the wall of the colon into nearby tissues but it has not spread in the lymph nodes or to distance sites
IIc	4b	0	0	The cancer has grown through the wall of the colon and is attached to or has grown into other nearby tissues or organs. It has not yet spread to nearby lymph nodes or to distant sites
IIIa	1 or 2	1	0	The primary cancer is confined to the bowel wall but it has spread to 1 to 3 regional lymph nodes. There is no distant spread
IIIb	3 or 4	1	0	The primary cancer has spread through the bowel wall and may have spread into nearby tissues; 1 to 3 regional lymph nodes are involved but there is no distant spread
IIIc	Any	2	0	The cancer has metastasized to 4 or more regional lymph nodes but there is no distant spread
IV	Any	Any	1	Cancer has spread to other parts of the body(usually to the liver or lungs and rarely to bone, peritoneum, brain, adrenal glands, or kidney

2.1.5. RISK FACTORS

In the context of the pathology, multiple risk factors have been identified that contribute to the onset of colorectal cancer. These risk factors encompass a range of factors, including genetic predisposition, environmental factors, dietary habits, lifestyle choices, and the presence of coexisting pathological conditions. Remarkably, scientific evidence unequivocally asserts that a marginal 5% of colon cancer cases can be attributed to hereditary factors (Labianca et al., 2010).

2.1.5.1. Age

Within both genders, the risk of developing colon cancer increases significantly between the ages of 40 and 50 (Keum & Giovannucci, 2019; Lewandowska, Rudzki, et al., 2022). It is known that 90% of colon cancer cases and associated mortalities occur after this age bracket (Keum & Giovannucci, 2019; Lewandowska, Rudzki, et al., 2022).

According to Sung et al. (2021), the average age of colon cancer diagnosis is ~70 years old

The relationship between cancer and aging is weel-established because the aging process is associated with decreased physiological reserves (Pal & Hurria, 2010). In addition, other factors contribute to this phenomenon. These include changes in DNA that occur throughout an individual's lifetime, thus facilitating increased mutations (Pal & Hurria, 2010). Prolonged exposure to carcinogens, telomere shortening, increased vulnerability to oxidative stress, and immune dysregulation are potential mechanisms involved (Pal & Hurria, 2010).

2.1.5.2. Diet Patterns

Diet is considered one of the most important exogenous factors in the development of colon cancer, as it can play both a protective and detrimental role (Labianca et al., 2010; Rawla et al., 2019). It has been found that there are two types of dietary patterns: "unhealthy" patterns and "healthy" patterns (Keum & Giovannucci, 2019).

The "unhealthy" pattern is characterized by a high intake of red and processed meats, simple sugars, refined cereals, and desserts, resembling the dietary composition observed in the Western diet (Keum & Giovannucci, 2019). Due to the high consumption of red and processed meats, this pattern is associated with a 12% increase in colon cancer (Keum & Giovannucci, 2019), a factor that is partially explained by important quantities of red and processed meat being high in fat and containing carcinogenic substances (Keum & Giovannucci, 2019; Rasool et al., 2013; Rawla et al., 2019). Heme iron in red meat and exogenous nitrous compounds are highlighted among these substances. Moreover, heterocyclic amines and polycyclic hydrocarbons are generated when meat is cooked at high temperatures (Keum & Giovannucci, 2019).

On the other hand, the "Healthy" dietary pattern, such as the Mediterranean diet, contains a high intake of fruit, vegetables, fish, low-fat dairy products, and dried fruit, among others (Keum & Giovannucci, 2019). Unlike the 'unhealthy' dietary pattern, many of these foods have dietary fiber, which helps reduce the risk of colon cancer development (Rasool et al., 2013).

2.1.5.3. Sedentarism

Sedentary behavior is a factor that increases the risk of developing colon cancer (Park et al., 2020; Schmid & Leitzmann, 2014). The Sedentary Behavior Research

Network defined any behavior characterized by ≤ 1.5 metabolic equivalent energy expenditure in a sitting, reclining, or lying position as sedentary behavior. (Tremblay, 2017). These behaviors are associated with metabolic dysfunctions such as an increase in triglycerides and a decrease in high-density lipoprotein (HDL) cholesterol due to the low concentration of lipoprotein lipase (LPL) (Park et al., 2020). It is also linked to increased peripheral insulin resistance and chronic systemic inflammation (Hermelink et al., 2022). A meta-analysis suggested that the risk of colon cancer increases by 30 % in sedentary individuals (Cong et al., 2014). In addition, another meta-analysis showed that for every 2-hour increase in sitting time per day, there is an 8 %increase in the risk of colon cancer (Schmid & Leitzmann, 2014).

2.1.5.4. Obesity

Abdominal obesity is a key factor associated with an increased colon cancer risk, regardless of physical activity (Rawla et al., 2019). Previous studies have shown that the risk of getting cancer in overweight women increases by 20% while 50% in men (Rawla et al., 2019). Within abdominal fat are two adipose tissue types: visceral (VAT) and subcutaneous (SAT). VAT has been linked to heightened insulin resistance and systemic inflammation, attributed to its reduced secretion of insulin-sensitizing hormones (such as adiponectin) and elevation of pro-inflammatory response (Keum & Giovannucci, 2019). The consequently generated insulin resistance and hyperinsulinemia are known to elevate the levels of insulin-growth factor 1, which is closely related to the process of carcinogenesis (Keum & Giovannucci, 2019).

2.1.5.5. Genetic

Individuals with hereditary cancer syndromes or a family history of cancer are known to have a greater risk of developing colon cancer (Keum & Giovannucci, 2019; Rawla et al., 2019; Spaander et al., 2023). Among the various hereditary cancer syndromes, the most common are (i) Lynch syndrome and (ii) familial adenomatous polyposis. Lynch syndrome, also called po HNPCC, is associated with mutated genes that impair the DNA repair system (Labianca et al., 2010). This syndrome increases the chance of cancer development by about 20% in individuals under the age of 50 and by 50% in individuals aged 50 to 70, with women having a lower risk than men (Rawla et al., 2019). On the other hand, in familial adenomatous polyposis (FAP), individuals present several precancerous polyps at around 10-12 years old. As polyps develop, the likelihood of carcinogenesis increases, and these individuals may have a nearly 100% risk of developing colon cancer (Rawla et al., 2019).

Significantly, when it comes to family history, the risk of this disease increases according to the degree of kinship and the number of relatives (Keum & Giovannucci, 2019). Thus, it was found that the presence of cancer in the first degree of kinship significantly increases the risk of developing the disease (Keum & Giovannucci, 2019). If there is only one relative with this disease, the risk increases by 2.24 times, while in other cases, the risk increases by 3.97 times (Keum & Giovannucci, 2019).

2.1.5.6. Tobacco and Alcohol

Smoking is considered one of the main risk factors for at least 12 different cancers, including colon cancer (American Cancer Society, 2023). Several studies have shown that smokers or ex-smokers are more likely to develop colon cancer than non-smokers, as smokers are more likely to have altered DNA methylation patterns (Durko & Malecka-Panas, 2014; Keum & Giovannucci, 2019). The constituent chemicals found in tobacco, such as nitrosamines, aromatic animas, polycyclic aromatic hydrocarbons, and heterocyclic amines, are considered to be significant carcinogens due to their ability to damage cellular DNA and induce mutations that contribute to the development of this cancer (Durko & Malecka-Panas, 2014; Labianca et al., 2010).

In addition to smoking, alcohol intake also increases the development of colon cancer (Rawla et al., 2019). Alcohol is predominantly composed of ethanol, which in turn consists of principally metabolite acetaldehyde. This metabolite is classified as a carcinogen and can cause DNA damage or modifications (Durko & Malecka-Panas, 2014; Keum & Giovannucci, 2019). Studies have shown that moderate alcohol intake (2-3 alcoholic drinks per day) increases the risk of developing colon cancer by about 20%. Furthermore, excessive intake ($\geq$ 4 alcoholic drinks per day) increases the risk by 40% (Rawla et al., 2019). Commonly, this association is less strong in women than in men, which is mainly explained by the higher amount of alcohol ingested by men (Keum & Giovannucci, 2019; Rawla et al., 2019).

2.1.6. TREATMENT

When detected early, colon cancer is considered one of the most curable cancers (Ahmed, 2020). The selection of an appropriate treatment is contingent upon several key considerations, including the individual's characteristics, tumor stage, and location. Usually, most patients undergo surgical procedures (Ahmed, 2020; Labianca et al., 2010). Some high-risk stage II and stage III patients may be considered for chemotherapy after surgery (Costas-Chavarri et al., 2019).

The main types of surgery are open resection and laparoscopic resection. Surgery requires tumor resection and complete oncological lymphadenectomy (Costas-Chavarri et al., 2019; Morneau et al., 2013). The segment resected depends on lymphatic drainage at the tumor site, vascularization, and a minimum of 12 lymph nodes (Morneau et al., 2013). Initially, colon cancer resection was performed exclusively by open resection. However, with technological advances, laparoscopy has also become the surgery of choice for this type of cancer, as it has proved safe and effective (Morneau et al., 2013). Although laparoscopic resection is a non-invasive method with some advantages, such as reduced surgical mortality and decreased length of stay in the hospital, it cannot be performed in all cases (Costas-Chavarri et al., 2019). Contraindications are obesity, previous abdominal surgery, advanced-stage disease, if the procedure does not complete resection, and/or inability to tolerate pneumoperitoneum (Costas-Chavarri et al., 2019; Kuipers et al., 2015).

In non-obstructive stage I-IIC patients, when faced with basic and limited environments, open resection is performed, otherwise, non-invasive surgery is applied (Costas-Chavarri et al., 2019). In obstructive patients (T3N0 or T4N0), it involves performing emergency surgery to stabilize the patient (Costas-Chavarri et al., 2019).

A meta-analysis aimed at verifying the differences in the impact of laparoscopic surgery on quality of life compared to open surgery found no significant differences in the improvement of quality of life in the long term. However, it appears that laparoscopic surgery is superior to open surgery only in terms of functional capacity, as it allows shorter hospital stays, an attenuated inflammatory responses, and a better post-operative recovery (Cui & Liu, 2023).

2.2. FUNCTIONAL CAPACITY

Functional capacity refers to an individual's ability to carry out daily activities (Caspersen et al., 1985; Mera-Mamián et al., 2021). It covers different aspects of functioning: physical, mental, social, and emotional domains (Mera-Mamián et al., 2021).

Physical fitness is considered a measure that integrates the functions involved in exercise and daily physical activities, such as skeletal, cardiorespiratory, haematocirculatory, endocrine-metabolic, and psychoneurological. This is made up of (i) muscular endurance, (ii) cardiorespiratory fitness, (iii) muscular strength, and (iv) body composition (Bizzozero-Peroni et al., 2022; Caspersen et al., 1985). Muscular endurance

is characterized as the component of physical fitness that relates to the ability of muscle groups to exert external force over a long period (over many repetitions or successive exercises) (Caspersen et al., 1985). Cardiorespiratory fitness is the ability to exercise for long periods without generating fatigue (Caspersen et al., 1985). Muscular strength is characterized as the ability of a muscle or group of muscles to generate force against an external resistance (Caspersen et al., 1985). Finally, body composition is one of the components related to health. It concerns the constitution of muscle, bone, and other fundamental parts (Caspersen et al., 1985).

The loss of speed, endurance, strength, and coordination characterizes the decline of functional capacity (Hollmann & King, 2007). Cancer and aging are two factors that adversely affect the musculoskeletal and cardiovascular systems, specifically a decrease in physiological reserves and muscle alteration and loss (Beaudart et al., 2019; Ezzatvar et al., 2021; Hollmann & King, 2007; Pal & Hurria, 2010). Sarcopenia is a geriatric syndrome characterized by decreased muscle mass, loss of performance levels, and muscle function. This is associated with a poor prognosis and increased postoperative complications with cancer (Anjanappa et al., 2020; Cruz-Jentoft et al., 2010). A previous study showed how low preoperative functional capacity can lead to increased postoperative complications and even mortality rates (Sánchez-Torralvo et al., 2022). Therefore, assessing and improving functional capacity in the preoperative phase is crucial. This approach helps to mitigate the adverse effects of the disease as well as the stress of the surgical procedure (Mayo et al., 2011; Molenaar et al., 2023; Reis et al., 2018; Van Rooijen et al., 2019).

2.3. EXERCISE

Physical activity is any bodily movement that results in energy expenditure (Caspersen et al., 1985). According to the American Cancer Society, adults should complete at least 150 minutes of moderate or 75 minutes of vigorous physical activity per week (Patel et al., 2019). Being physically inactive increases the prevalence of major non-communicable diseases, such as type 2 diabetes and cancer (Lee et al., 2012).

Nowadays, exercise is a versatile strategy to prevent impact injuries (Hossain et al., 2022; Keum & Giovannucci, 2019). However, it also improves physical fitness, fatigue, depression, body fat, and sleep quality. (B. Singh et al., 2020). Exercise is a physical activity that is planned, structured, repetitive, and voluntary. Its main aim is to

improve the individual's physical fitness and other health-related conditions (Patel et al., 2019). There are two types of exercise: resistance and aerobic training. Resistance training is carried out under anaerobic conditions and is characterized by short periods of maximum or high-intensity activity involving overload or weights (Chen et al., 2022), while aerobic training is carried out under aerobic conditions since glucose metabolism depends on oxygen (Chen et al., 2022).

The combination of these two types of training has been considered a more effective strategy for improving functional capacity in individuals with cancer (Molenaar et al., 2023; B. Singh et al., 2020). These improvements can be explained by several mechanisms (Amirsasan et al., 2022). Exercise induces phenotypic and metabolic changes in skeletal muscle, which depend on the type of training performed. Aerobic training stimulates and increases type I and IIa muscle fibers (Bishop-Bailey, 2013). These fibers have a high oxidative capacity, are rich in mitochondria, and are more vascularized (Bishop-Bailey, 2013). On the other hand, resistance training favors hypertrophy and the growth of type IIb muscle fibers, which provide power and strength to the detriment of endurance and boost anaerobic metabolism (Bishop-Bailey, 2013). In addition, exercise affects the endogenous system by influencing the growth processes of neoplasms and cellular processes (Amirsasan et al., 2022; Patel et al., 2019). Various factors such as insulin, the function of the immune system, sex hormones, oxidative stress, genomic instability, and inflammation are considered to be responsible for regulating these physiological processes (Patel et al., 2019).

Previous studies have proposed that an intervention including a supervised simultaneous exercise program is essential to improve functional capacity, reduce fatigue, and decrease the production of inflammatory markers (Molenaar et al., 2023; Reis et al., 2018). In addition, it has been suggested that high-intensity interval training (HIIT) is more effective at achieving the beneficial effects induced by exercise than other methods (Herranz-Gómez et al., 2022).

2.4. NUTRITION

Nutritional status is an essential factor affecting each individual's clinical evolution. Cancer is associated with a reduction/depletion of protein reserves, vitamins, and minerals (Lewandowska, Religioni et al., 2022; Vitaloni et al., 2022). In addition, additional problems such as (i) a decreased ability to digest, (ii) a lowered ability to

synthesize food, (iii) an inadequate food intake, and (iv) altered homeostasis are also frequent (Lewandowska, Religioni et al., 2022; Vitaloni et al., 2022). Malnutrition is one of the most prominent problems in colon cancer, which in turn, is associated with (i) increased mortality, (ii) higher rates of post-operative complications, and (iii) poor functional performance in patients with cancer (Hu, 2015; D. U. Lee et al., 2021; Maia et al., 2020).

The Mediterranean diet has been proposed as a dietary pattern that provides essential health benefits. This is characterized by a healthy eating pattern with olive oil as the primary source of fat, a high consumption of fruit, vegetables, and unrefined cereals. On the other hand, it has a low consumption of processed foods, red meat, and sweets (Bizzozero-Peroni et al., 2022; Finicelli et al., 2022; Itsiopoulos et al., 2022). In addition, the Mediterranean diet encompasses cultural and lifestyle elements, such as regular physical activity and adequate resting patterns (Bizzozero-Peroni et al., 2022).

High adherence to this dietary pattern reduces the risk of cardiovascular disease, some types of cancer (such as colon cancer), type 2 diabetes, neurodegenerative diseases, and a reduction in all-cause mortality. (Itsiopoulos et al., 2022; Monllor-Tormos et al., 2023). In addition, Bizzozero-Peroni et al. (2022) have shown that Mediterranean countries have a higher functional capacity than non-Mediterranean countries. These beneficial outcomes are due to the presence of polyphenols (bioactive found in plant-derived foods), hydroxytyrosol, tyrosol, resveratrol, and oleocanthal, which contain anti-inflammatory, antioxidant, chemopreventive, and pro-apoptotic properties (Finicelli et al., 2022; Itsiopoulos et al., 2022). Therefore, individuals diagnosed with colon cancer must receive a proper nutritional intervention, as it can prevent malnutrition, improve energy and protein intake, maintain a healthy weight, and reduce symptoms of negative nutritional impact (Vitaloni et al., 2022). Since personalized nutritional monitoring can be expensive, behavior change approaches are presented as an effective and viable alternative to achieve the desired results (Gans et al., 2015).

2.5. PSYCHOLOGY

A cancer diagnosis can substantially impact mental health (Pitman et al., 2018; Smith, 2015). Approximately 40% of colorectal cancer patients develop some psychological disorder (Dunn et al., 2013). They are exposed to prolonged periods of psychological stress that can lead to depression and anxiety due to the losses inherent in

the treatment, the expectations of survival, and the effects of the disease on their personal and professional lives (Pitman et al., 2018). Anxiety can disrupt the individual' quality of life, including impaired social functioning, reduced physical capacity, and fatigue (Stark & House, 2000).

Levels of anxiety and depression vary depending on various factors, such as gender and age (Linden et al., 2012; Pitman et al., 2018). A previous study reported that women have a higher prevalence rate of depression and anxiety than men. This fact can be observed since there is a gender difference when reporting feelings of distress (Linden et al., 2012). On the other hand, this study also shows that, contrary to popular belief, there is an inverse relationship between age and emotional distress. Thus, there is a higher prevalence of anxiety and depression in the younger age group (Linden et al., 2012). According to Linden et al. (2012), this is due to more substantial perturbation in the daily lives of younger patients. Meanwhile , older patients, owing to potential impairments in cognitive and physical faculties associated with their age, may exhibit greater emotional preparedness in facing their medical conditions.

Since psychological disorders can influence motivation to carry out functional and social activities, it is necessary to implement well-designed psychological programs in the preoperative phase to help deal with the stress of surgery and the disease itself (Ghoneim & O'Hara, 2016; Stonerock & Blumenthal, 2017).

2.6. FRAMING THE THEME AND JUSTIFICATION OF CHOICE

The relevance of this study lies in the need of increasing functional capacity in the preoperative phase through a multidisciplinary program of patients undergoing colon cancer surgery. As the literature reflects, surgery is a stressful process that can lead to several postoperative complications. In addition, cancer is associated with a loss of functional capacity, a factor that decreases the patient's prognosis. It is, therefore essential to improve functional capacity in order to reduce inherent complications and increase quality of life.

2.7. OBJECTIVE OF THE STUDY

2.7.1. General Objective

This study aimed at investigating the effect of a multidisciplinary prehabilitation program on physical fitness in patients undergoing colon cancer resection.

2.7.2. Specific objective

To evaluate the effects of a 4-week multidisciplinary prehabilitation program on cardiorespiratory fitness, gait speed, muscular strength and subjective physical fitness in patients undergoing colon cancer resection.

CHAPTER III. METHODOLOGY

CHAPTER III. METHODOLOGY

3.1. STUDY DESIGN

This preliminary analysis was performed under the framework of the ONCOFIT study, which is still ongoing (ClinicalTrials.gov ID: NCT05379205 (Amaro-Gahete et al., 2022). The ONCOFIT study is a randomized controlled trial where patients were randomly allocated to a usual care group (control group) or Prehabilitation Program group (PP), which will be further explained in the following sub-chapter 3. The study was designed following the Ethical Principles for Medical Research Involving Human Subjects contained in the Declaration of Helsinki (last revised version, 2013) and has been approved by The Human Research Ethics Committee of the "Junta de Andalucía" (2019529142937) (Annex 2). Information regarding patients' participation in the project and other information, such as the location of where the evaluations were performed, the project protocol, the feces collection protocol, and the preconditions for evaluations, was provided through information leaflets created by the doctors of the general surgery unit and orally. Then, before enrolment, they were instructed to sign an informed consent (Annex 1). Only individuals in the "San Cecilio University Hospital" (Granada, Spain) diagnosed with colon cancer who met the criteria were recruited.

3.2. PARTICIPANTS AND SELECTION CRITERIA

The study sample consisted of 29 adults aged between 40 and 85 diagnosed with colon cancer. Before their inclusion, potential participants underwent a comprehensive medical history assessment and physical examination to ensure their suitability for the intervention and assessment protocols. The primary objective of these evaluations was to identify any pre-existing conditions or potential harm-related concerns. The participants' eligibility was also determined based on the predefined inclusion and exclusion criteria. A detailed compilation of these criteria can be found in table 4.

Table 4. Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
Patients older than 40 years	Medical contraindication for being engaged in an exercise or dietary program.
Diagnostic of nonmetastatic colon cancer (i.e., including right, transverse, left, sigmoid, subtotal, total, and hemicolectomy)	Additional surgery planned within the 3-month intervention
Not participating in a nutritional/dietary intervention	History of another primary invasive cancer
Being physical inactive (i.e., not to be participating in any physical exercise program in the last 3 months, or performing less than 600 metabolic equivalents (METS)/week of moderate-vigorous physical activity).	Planning to receive adjuvant chemotherapy
To be capable and willing to provide informed consent	To be pregnant
Not to suffer from any specific condition that may impede testing of the study hypothesis or make it unsafe to engage in the multidisciplinary intervention (i.e., determined by the research staff)	To present any of the following cardiac conditions: (i) myocardial infarction or coronary revascularization procedure within prior 3 months, (ii) uncontrolled hypertension (i.e., systolic ≥180 mmHg or diastolic ≥100 mmHg), (iii) uncontrolled arrhythmias (iv) valvular disease clinically significant, (v) decompensated heart failure or (vi) to suffer from known aortic aneurysm

3.3. USUAL CARE/ CONTROL GROUP

All enrolled individuals in this research were adhered to the standard institutional pre-surgical procedures by the well-established Enhanced Recovery After Surgery (ERAS) guidelines (Gustafsson et al., 2019). These guidelines involve various aspects, including medication management, assessment of surgery-related risks, and measures to promote smoking cessation and peri-operative blood management. Furthermore, a qualified nutritionist evaluated the nutritional status of all patients and provided oral protein/vitamin supplementation when needed (Weimann et al., 2017). The usage of vitamin/protein supplementation was appropriately registered and recorded.

Patients allocated to the control group received essential expert recommendations regarding the adoption of a healthier lifestyle to maintain their overall well-being.

Specifically, they were informed about the positive effects of physical exercise, healthy dietary practices, avoidance of tobacco and alcohol, and the importance of psychological health. In addition, they were offered the opportunity to receive the ONCOFIT intervention after the 1- year follow up assessment.

3.4. INTERVENTION DESCRIPTION

Four weeks before the surgery, the intervention was developed in Laboratory of Exercise Physiology, Sport and Health University Research Institute (iMUDS), Granada, Spain. The patients performed 12 training sessions, 4 nutritional sessions, and 2 psychology sessions during the intervention.

3.4.1. Attendance Control

During the intervention, the attendance of the individuals was controlled using a previously prepared Excel sheet (Appendix 1). Attendance was recorded after each session, from the first day of the intervention to the session before the surgery**.** This table consisted of each participant's ID on the vertical column, while in the horizontal column, the different weeks that compound the preoperative period are shown. The sessions of each week, in particular, the three training sessions (TS), the nutrition session (NS), and the psychology session (PS), are presented following each participant´ ID. Participants were scored according to their attendance, with a 1 if they attended the session provided, a 2 if they did not attend but the session was provided, and a 0 if there was no possibility of the session taking place.

3.4.2. Exercise Intervention

As previously mentioned, several recent studies emphasize that exercise is an effective, safe, and viable treatment method for colorectal cancer patients. Recent studies have demonstrated the benefits of a training-based preoperative exercise intervention in patients undergoing colon cancer resection (Berkel et al., 2022; Molenaar et al., 2023).

The present exercise intervention consisted of a concurrent program (aerobic + resistance training). This was done three times/week (Monday, Wednesday, and Friday), so all participants had at least 48 hours of rest between sessions. The training session duration was 60 minutes, starting with aerobic training and then resistance training (table 5). HIIT modality was proposed in both aerobic and resistance training parts, which is a safe and effective method in the oncological population (Herranz-Gómez et al., 2022).

Aerobic HIIT training consisted of an uphill treadmill walking with personalized slopes. Strength HIIT training was organized in a circuit form. It comprised a combined selection of upper and lower body exercises (i.e., basic movement patterns) using elastic bands and the patient's body weight. Each exercise had three levels of difficulty based on the resistance band and the increasing complexity of the basic movement pattern task.

The first week of the interventions was designed as a familiarization period in which the patients learn the structure and organization of training sessions. The training session constituted an initial phase aerobic training followed by resistance training. The training sessions began with a 4-minutes warm-up walking on a treadmill at 50–60% of the peak heart rate (pHR) and was followed by three 4-minutes intervals at 80–85% of pHR interposed by three 4-minute of active recovery at 60–65% of pHR. After finishing the aerobic part, we implemented the strength HIIT as follows: two circuit training sets (8 min × 2 = 16 min) of eight exercises (20 s work/40 s rest) at 7–8 RPE, on the Borg scale of 0-10, with an active between-set rest of 4 min performed at 50–60% of pHR. A cool-down protocol (i.e., active global stretching) of 4 min was performed at the end of the session. The total exercise session duration was, therefore, 60 min.

We had a similar structure and organization with some particularities in the following three weeks. The aerobic HIIT total volume was 32 minutes organized as follows: a 4-minutes warm-up at 50–60% pHR followed by four intervals of 4-minute at 85–95% pHR interposed by 4 intervals of 3-minute of active recovery at 65–75% of pHR. Strength HIIT total volume was 20 min organized as follow: two circuit training set (8 min × 2 = 16 min) of eight exercises (30 s work/30 s rest) at 8–9 RPE, with an active between-set rest of 4 min performed at 50–60% of pHR. The same cool-down protocol of 4 min was also conducted. The total exercise session duration was, therefore, 60 minutes.

Table 5. Exercise Intervention

	WARM UP	AEROBIC HIIT		STRENGTH HIIT	ACTIVE RECOVERY	STRENGTH HIIT	COOL DOWN
							
		High-intensity interval	Active recovery interval				
Familiarization week	**Volume:** 4 min **Intensity:** 50–60% pHR	**Volume:** 4 min **Intensity:** 80–85% pHR **Intensity:** 3	**Volume:** 4 min **Intensity:** 60–65% pHR **Intensity:** 3	**20 sec work/ 40 sec rest** **Intensity:** 7–8 RPE **Total volume:** 16 min	**Volume:** 4 min	**20 sec work/ 40 sec rest** **Intensity:** 7–8 RPE **Total volume:** 16 min	**Volume:** 4 min
The others weeks	**Volume:** 4 min **Intensity:** 50–60% pHR	**Volume:** 4 min **Intensity:** 85–95% pHR **Intensity:** 4	**Volume:** 4 min **Intensity:** 65–75% pHR **Intensity:** 4	**30 sec work/ 30 sec rest** **Intensity:** 8–9 RPE **Total volume:** 16 min	**Volume:** 4 min	**30 sec work/ 30 sec rest** **Intensity:** 8–9 RPE **Total volume:** 16 min	**Volume:** 4 min

3.4.2.1. Intensity Control

The intensity monitoring of the training sessions was performed through the Polar Ignite 2 watch (Polar Electro Oy, Kempele, Finland) and three previously prepared worksheets. The heart rate monitors were placed in the participants' right hand before starting the session to control the intervals established for the training sessions. The first worksheet (Appendix 2) was prepared to calculate the percentages of the target heart rate, and the metric used was HRmax=208 – (0.7 * age) (Tanaka et al., 2001) . The second and third worksheet (Appendix 3) was prepared to obtain information about the participant and whether the programmed intensity was achieved during the training session. Therefore, the worksheet was divided into four main parts: (i) before the session information, (ii) during the session characteristics, (iii) after the session details, and (iv) information that the trainer had to fill in. The first part, 'before the session', consisted of ID, date, time of the session, number of heart rate monitors used, type of heart rate monitors exercise, means of transport of the participant, RPE before the session, and feeling scale before the session. Then, the worksheet section of 'during the session', was subdivided into two parts of the training session: aerobic HIIT and strength HIIT. The aerobic HIIT consisted of four intervals, each containing the type of exercise (treadmill, bike, or elliptical), the speed, the incline, the final HR, the RPE of each interval, and the

RPE in general. The strength HIIT part consisted of two sets, and in each set, the parameters were the type of exercise, the RPE of each set, and the overall RPE. The fill-in part after the session consisted of the participant's means of transport to and from the session, the RPE of the entire session, and the feeling scale after finishing the session. Finally, the section to be completed by the trainer was composed of the trainer's name, the week in which the patient was, the session number, the initial and final temperature, the initial and final humidity percentage, and the incidents. The third worksheet was created and printed to be used during the session and later passed these data to the second worksheet, it consisted of a Borg scale, items to put the RPE and feeling scale before the session, the RPE and HR of each interval and total RPE of the aerobic HIIT, the RPE of each exercise and general RPE of the strength HIIT part, total RPE of the session and feeling scale after the training session.

3.4.3. Dietary Behavior Change

The nutritional intervention in the present study was based on nutritional advisory talks conducted by a certified nutritionist dietitian in a face-to-face way using audiovisual support. They were conducted on Mondays before the training sessions, with a duration of 15 minutes each.

The 1st (Title:" Mediterranean diet") and 3rd (Title: "Dietary fats, sugar and alcohol") sessions, were focused on general and specific recommendations concerning a healthy and balanced diet, emphasizing the Mediterranean diet pattern. A significant emphasis has been placed on the Mediterranean diet due to its relationship with functional capacity, with high adherence associated with high levels of physical fitness (Bizzozero-Peroni et al., 2022).

The 2nd session, entitled "Healthy changes," aimed to facilitate the adoption of healthy dietary practices by guiding the organization of diverse and nutritious meals, as well as the acquisition of essential culinary skills (Metcalfe & Leonard, 2018).

The last session was entitled ("Preparation for the surgery") and was focused on facing the surgery in an appropriate nutritional status. The information established was based on: (i) the importance of appropriate protein intake (Gillis et al., 2016), (ii) the consumption of biocomponents with beneficial effects on the immune system and inflammation process (Moya et al., 2016), (iii) the management of fluid, and carbohydrate

consumption immediately before surgery (Miller et al., 2015), and (iv) the importance of reaching the operating room in a correct hydration status (Miller et al., 2015).

Figure 6. Behavior dietary change sessions

3.4.4. Psychology Sessions

The psychology sessions were conducted in an individual format and were led by clinical psychologists. Two sessions were held before the surgery to reduce anxiety levels, depression, feelings of helplessness, and despair; and to increase and promote the perception of control, social support, and adequate interpersonal communication. Additionally, one of the main objectives of this part of the intervention was focused on improving adherence to the other intervention components (medical, nutritional, and physical exercise).

Figure 7. Psychology sessions

3.5. INSTRUMENTS AND ASSESSMENTS

The instruments used were selected to objectively and quantifiably assess functional capacity, and are described in Table 6.

Table 6. Variables assessed, tests and instruments used.

	OUTCOME	INSTRUMENT
BODY COMPOSITION	Height	SECA model 799, Electronic Column Scale, Hamburg, Germany
	Weight	SECA model 799, Electronic Column Scale, Hamburg, Germany
	Body Mass Index (BMI)	(World Health Organization, 2000)
	OUTCOME	**ASSESSMENT**
FUNCTIONAL CAPACITY	Cardiorespiratory fitness	6 min walking test (6MWT) (American Thoracic Society, 2002)
	Gait speed	4 min usual walking speed test (Patrizio et al., 2020)
	Muscular strength	Handgrip strength (Patrizio et al., 2020) 5-Times sit-to-stand test (Cruz-Jentoft et al., 2019) The 30s sit-to-stand muscle power (Alcazar et al., 2020)
	Subjective physical fitness	Internacional fitness scale (Sánchez-Jiménez et al., 2015)

3.5.1 BODY COMPOSITION

3.5.1.1. Height

The height measurement was determined by a SECA model 799 stadiometer, an Electronic Column Scale, manufactured in Hamburg, Germany, and expressed in centimeters (cm). The participant' height was assessed in a standing position, with bare feet positioned together. The stadiometer was positioned to ensure contact with the posterior region of the heel, pelvic waist, and scapular waist. The participant' head was aligned by the Frankfort plane, which encompasses the lower edge of the eye socket and the edge of the external auditory meatus. The participant's arms were extended alongside the body, with the palms of the hands facing the thighs. The examiner, situated beside the subject, performed the height measurement by gently pressing the cursor against the participant's head, ensuring minimal interference with the individual's hair. Two measurements were obtained, and between each one, the participant was instructed to temporarily vacate and then return to the original position. The recorded height measurements were subsequently documented on the RedCap platform.

3.5.1.2. Weight

Body mass was assessed using a SECA model 799, Electronic Column Scale, Hamburg, Germany. Before measurement, participants were instructed to remove their shoes and to wear minimal clothing. The patient was instructed to lie on their back and face upward while stepping onto the scale. The assessor, positioned to the side, ensured clear visibility of the displayed value. Two measurements were obtained, with the recorded values expressed in kilograms (kg). After each measurement, participants were instructed to disembark from the scale and resume their initial position. The collected information was subsequently recorded on the RedCap platform.

3.5.1.3. Body Mass Index (BMI)

The Body Mass Index (BMI) is a statistical index which uses an individual' weight and height to provide an estimate of body fat (World Health Organization, 2000). This is calculated using the following equation: $BMI = \frac{WEIGHT}{HEIGHT^2}$. Weight and height were measured using appropriate and properly calibrated equipment.

The reference values for BMI may vary depending on your context or region. However, this study followed the guidelines established by the World Health Organization (WHO) for its classification (Table 7).

Table 7. BMI (Adapted from (Couric, 2006))

BMI (Kg/m²)	Classification
< 18,5	Low Weight
18.5 – 24.9	Normal Weight
25.0 – 29.9	Overweight
30.0 – 34.9	Obesity I
35.0 – 39.9	Obesity II
≥ 40	Obesity III

3.5.2. FUNCTIONAL CAPACITY

3.5.2.1. 6 min walking test

The 6MWT is a submaximal assessment method employed to quantify the distance covered by an individual within a duration of 6 minutes on level ground. Consequently, this test generally facilitates the evaluation of the physiological requirements associated with moderate physical exertion, while also serving as an indicator of performance in routine activities of daily living (American Thoracic Society, 2002)

This assessment was conducted following the established guidelines set forth by the American Thoracic Society (American Thoracic Society, 2002). Participants were provided with instructions to engage in forward and backward walking for six minutes, aiming for a moderate level of intensity while covering a distance of thirty meters. The aim was to induce fatigue by the end of the test. Before starting the activity, participants were equipped with a Polar Ignite 2 watch (Polar Electro Oy, Kempele, Finland), a cardio frequency monitor to measure parameters including resting heart rate, heart rate during the test, and heart rate after one minute of recovery. Furthermore, the number of laps completed, the total distance covered, and the RPE after the test were recorded. Previous investigations have demonstrated that the 6MWT serves as a reliable indicator for

postoperative recovery, with a clinical significance threshold of >20 meters considered a meaningful improvement (Moriello et al., 2008; Pecorelli et al., 2016).

3.4.2.2. 4-meter usual walking speed test

Gait speed predicts adverse outcomes related to various health complications, such as cognitive decline, disability, falls, sarcopenia, and mortality (Pamoukdjian et al., 2015; Peters et al., 2013; Santos et al., 2022). Furthermore, it is widely used in studies as it is considered an easy-to-perform, risk-free, and highly reliable test for various populations and is known to predict sarcopenia (Bruyère et al., 2016; Cruz-Jentoft et al., 2010; Kim et al., 2016). Sarcopenia is defined by muscle mass and strength loss and is considered the key component of physical frailty (Knoedler et al., 2023). The 4-meter usual walking speed test is extensively employed as a primary assessment tool, and by the recommendations of the European Working Group on Sarcopenia in Older Persons 2 (EWGSOP2), it has been established that a singular threshold value of ≤0.8 m/s is indicative of the presence of severe sarcopenia (Cruz-Jentoft et al., 2010).

The 4-meter usual walking speed test is a measurement that evaluates the duration taken to traverse a distance of 4 meters while walking at a customary pace (Studenski, 2011). The administration of the 4-meter usual walking speed test involved the establishment of a marked distance spanning 5 meters, using three different markers with the aim of the patient not stopping before the 4-meter line.

Participants were provided with clear instructions to position themselves behind the starting line and walk upon receiving a signal from the evaluator. They maintained a normal and comfortable pace until they concluded the designated course. Timing of the test commenced as soon as the participant crossed the 0-meter line and completed once one foot passed the 4-meter line, denoting the completion of the trial. The test procedure was conducted twice, and the recorded times were documented within the RedCap platform. Subsequently, the speed of each individual was calculated, accounting for the best attempt made by the participant during the assessment.

3.5.2.3. Handgrip Strength

Isometric handgrip strength is correlated with upper limb muscle power (Cruz-Jentoft et al., 2010). Furthermore, handgrip strength is inversely associated with the risk of colon cancer incidence and mortality (Celis-Morales et al., 2018).

This assessment was performed with a hand dynamometer (TKK 5401 Grip-D; Takei, Tokyo, Japan), expressed in total kg. The participants were instructed to perform two separate attempts for each hand, with a resting period of 1 minute between each attempt. During each trial, the assessor encouraged the subjects to exert maximum force while gripping the dynamometer. In the case of male participants, the grip strength of the dynamometer was set at 5.5 cm. For female participants, the optimal grip span was determined using the previously validated equation: $Optimal\ grnumerator$. The total handgrip strength was calculated by summing the best attempts for both the left hand and the right hand, respectively.

3.5.2.4. 5-times sit-to-stand test

The 5-Times sit-to-stand test is a valuable assessment tool used to evaluate lower limb strength and endurance (Cruz-Jentoft et al., 2019). It is recognized for its efficiency and simplicity in administration. During the test, participants were instructed to rise from a seated position five times consecutively as swiftly as possible, refraining from utilizing their arms for assistance, followed by returning to a seated position. Upon the patient' readiness, the assessor provided the command to commence, simultaneously initiating the timing process, which concluded when the patient completed the fifth repetition and attained a fully upright position. The test was conducted twice, considering the best recorded time achieved by the participant.

3.5.2.5. 30-s sit-to-stand muscle power test

The 30-second sit-to-stand test serves as a reliable means to assess an individual's physical performance and offers a valid measure of bilateral lower limb power (Alcazar et al., 2020). Participants were given explicit instructions to rise fully, achieve complete extension, and sit back down repeatedly within a 30-second. The starting position required the participant to be seated with their feet at shoulder width and arms crossed. Throughout the designated duration, the evaluator assiduously tallied the number of successful transitions made by the participants as they stood up and sat down.

3.5.2.6. International fitness scale

IFIS is designed to evaluate overall physical fitness and its associated components, including muscle strength, cardiorespiratory fitness, speed, agility, and flexibility (Pereira et al., 2020). The assessment instrument employed in this study comprised five questions, each rated on a 5-point Likert scale, offering response options ranging from "very bad"

to "very good" (Sánchez-Jiménez et al., 2015). Participants were asked to provide their perception-based answers to these questions. It is important to note that higher scores on the scale indicate better performance in the assessed areas.

3.6. STATISTICAL ANALYSIS

As this master's thesis includes preliminary data from the ONCOFIT randomized control trial, no specific sample size calculations were made. A descriptive statistical analysis was carried out, using the mean ± standard deviation, for the whole sample and stratified by group (control vs. 4-week-prehab).

Statistical comparison techniques were used to study the effects of the program intervention. Firstly, the distribution of the variables under study was analyzed, verifying their normality. The Shapiro-Wilk test, visual histograms, and Q-Q graphs were used for this purpose. Once the distribution of the variables was expected, the parametric inferential statistical analysis of repeated measures (ANOVA) was applied, using the T-test for unpaired samples.

Hedges' g size and the associated 95% confidence interval were calculated and interpreted as previous guidelines indicate: g< 0.2 " No effect size", 0.2< g <0.5 " Small effect size," 0.5< g < 0.8 " Medium effect size," 0.8 < g "Large effect size" (Zach, 2021).

The Statistical Package for the Social Sciences (SPSS) v.25.0 (IBM Corporation, Chicago, IL, USA) was used for all analyses. GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) produced the graphs. Significance was set at $p < 0.05$.

CHAPTER IV. RESULTS

CHAPTER IV. RESULTS

4.1. RESULTS

Figure 8 shows the registration and analysis flowchart. Of the 179 potential participants, 116 were excluded because they did not fulfill the inclusion criteria and 29 did not agree to take part in the study. Thus, 34 participants were randomized to the 4-week program or usual care. A total of 29 participants completed the study (n=16 in the 4-week prehabilitation group; n=13 in the control group). The descriptive characteristics of the study participants are shown in Table 8. No significant differences between groups were noted at baseline.

Figure 8. Enrolment and analysis flow-chart

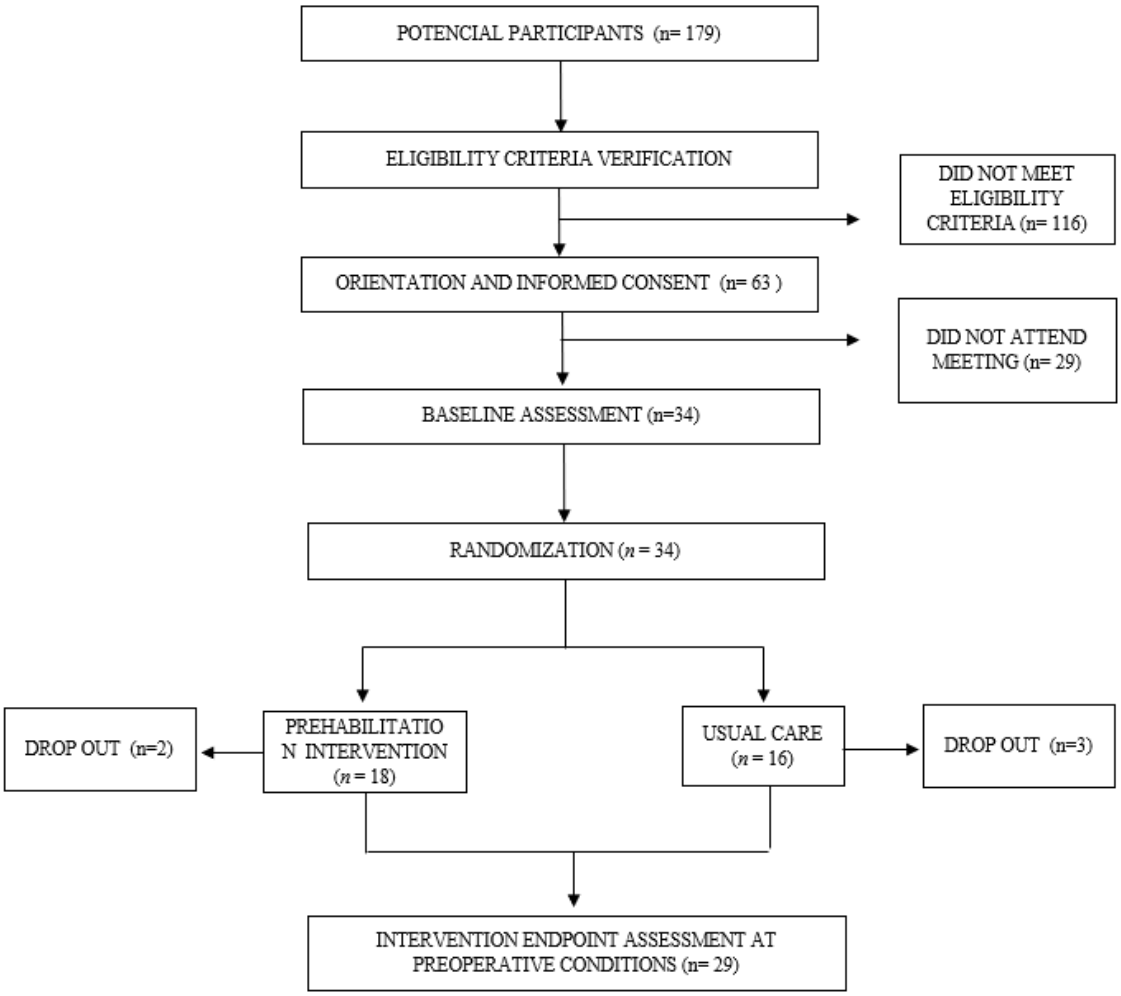


Table 8. Baseline descriptive characteristics of the study subjects including in per-protocol analysis

	All (n= 29)	**4-week-Prehab (n=16)**	**Usual Care (n= 13)**	***p-value***
Age (y)	64.6 (11.7)	63.6 (13.2)	65.7 (10.1)	0.646
Sex (%)				
Men	19 (65.5)	11 (68.8)	8 (61.5)	
Women	10 (34.5)	5 (38.5)	5 (38.5)	
Anthropometry				
Weight (Kg)	73.5 (10.6)	72.7 (12.1)	74.4 (9.0)	0.673
Height (cm)	163.4 (9.7)	164.9 (10.1)	161.5 (9.3)	0.365
Body Mass Index (Kg/m^2)	27.5 (3.3)	26.7 (3.0)	28.6 (3.5)	0.117
Functional Capacity				
6 min walking test (m)	547.6 (136.7)	570.8 (105.6)	519.1 (167.6)	0.345
4 min usual walking speed test (m/s)	1.3 (0.3)	1.3 (0.3)	1.3 (0.4)	0.554
Handgrip strength (Kg)				
Right hand	30.0 (9.7)	31.6 (9.3)	27.9 (10.1)	0.307
Left hand	29.3 (9.2)	31.2 (9.4)	27.1 (8.6)	0.235
5-Times sit-to-stand test (s)	9.3 (3.8)	9.2 (3.1)	9.5 (4.7)	0.804
30 sit-to-stand muscle power (rep.)	16.2 (5.0)	16.4 (4.0)	15.8 (6.1)	0.757
International fitness scale (nº)	14.9 (3.7)	14.3 (3.8)	15.6 (3.5)	0.355

Data are shown as means (standard derivation). **Abbreviations:** n- sample, 4-week-Prehab – 4-week multidisciplinary (supervised concurrent exercise training, dietary behavior changes, and psychological support) prehabilitation group, kg- kilogram, cm-centimeters, Kg/m^2 - kilogram per square meter, rep.- repetitions, m-meters, s- seconds, nº- score ; Significant *p-value*<0.05

Figure 9. Changes in functional capacity after the prehabilitation in our study's patients. Hedges´ g is calculated as a measure of the effect size. Data are shown as mean (standard deviation). **Abbreviations:** 4 week-Prehab – 4-week multidisciplinary (supervised concurrent exercise training, dietary behavior changes and psychological support) prehabilitation group; 6MWT – 6 Min Walking Test; 5STS- 5-Times Sit-to-Stand Test; 30s STS- 30-s Sit-to-Stand Muscle Power Test.

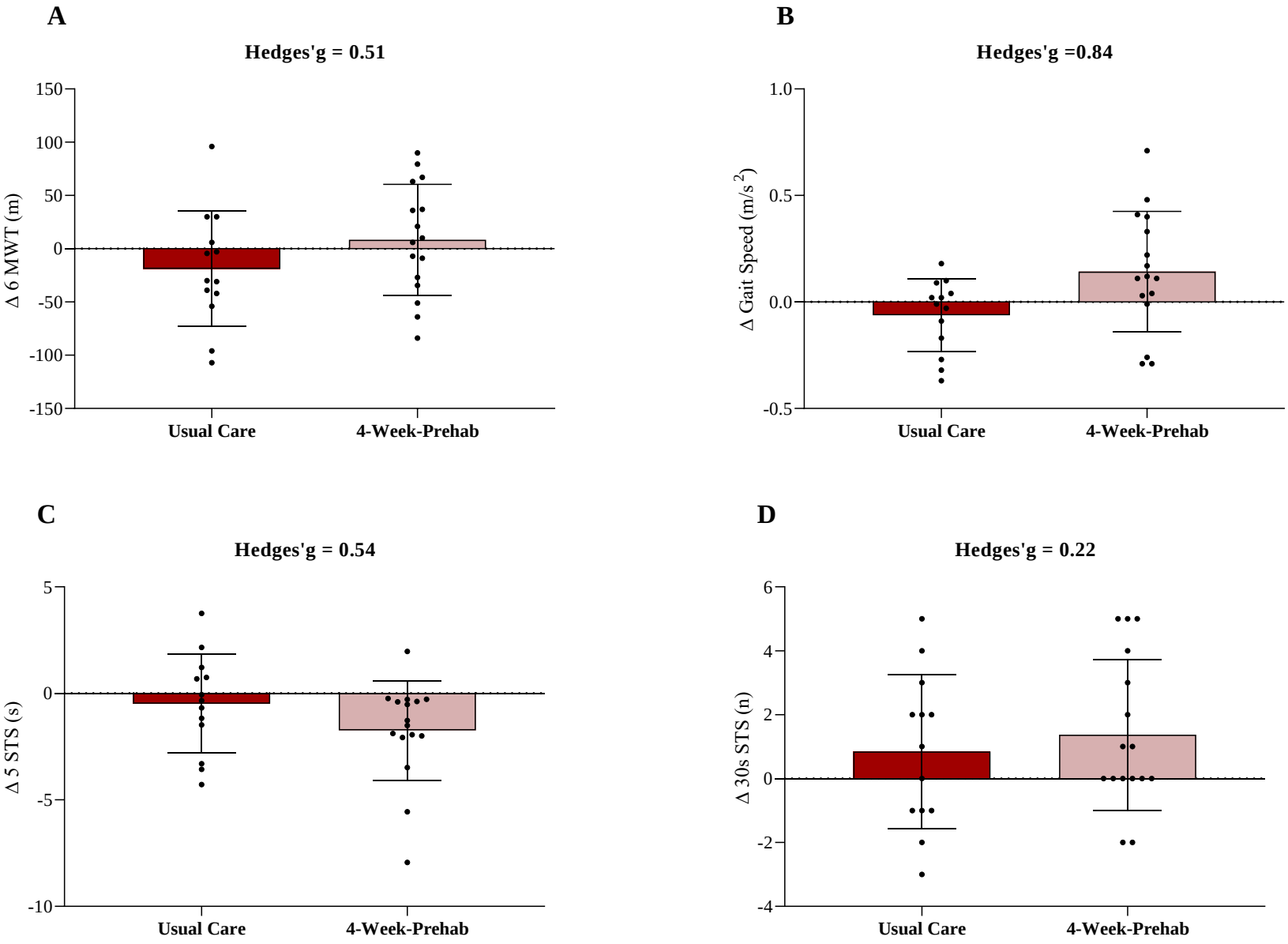


Figure 10. Changes in functional capacity after the prehabilitation in our study's patients. Hedges´ g is calculated as a measure of the effect size. Data are shown as mean (standard deviation). **Abbreviations:** 4 week-Prehab – 4-week multidisciplinary (supervised concurrent exercise training, dietary behavior changes and psychological support) prehabilitation group; Handgrip L- Handgrip Left; Handgrip R- Handgrip Right; IFIS- International Fitness Scale.

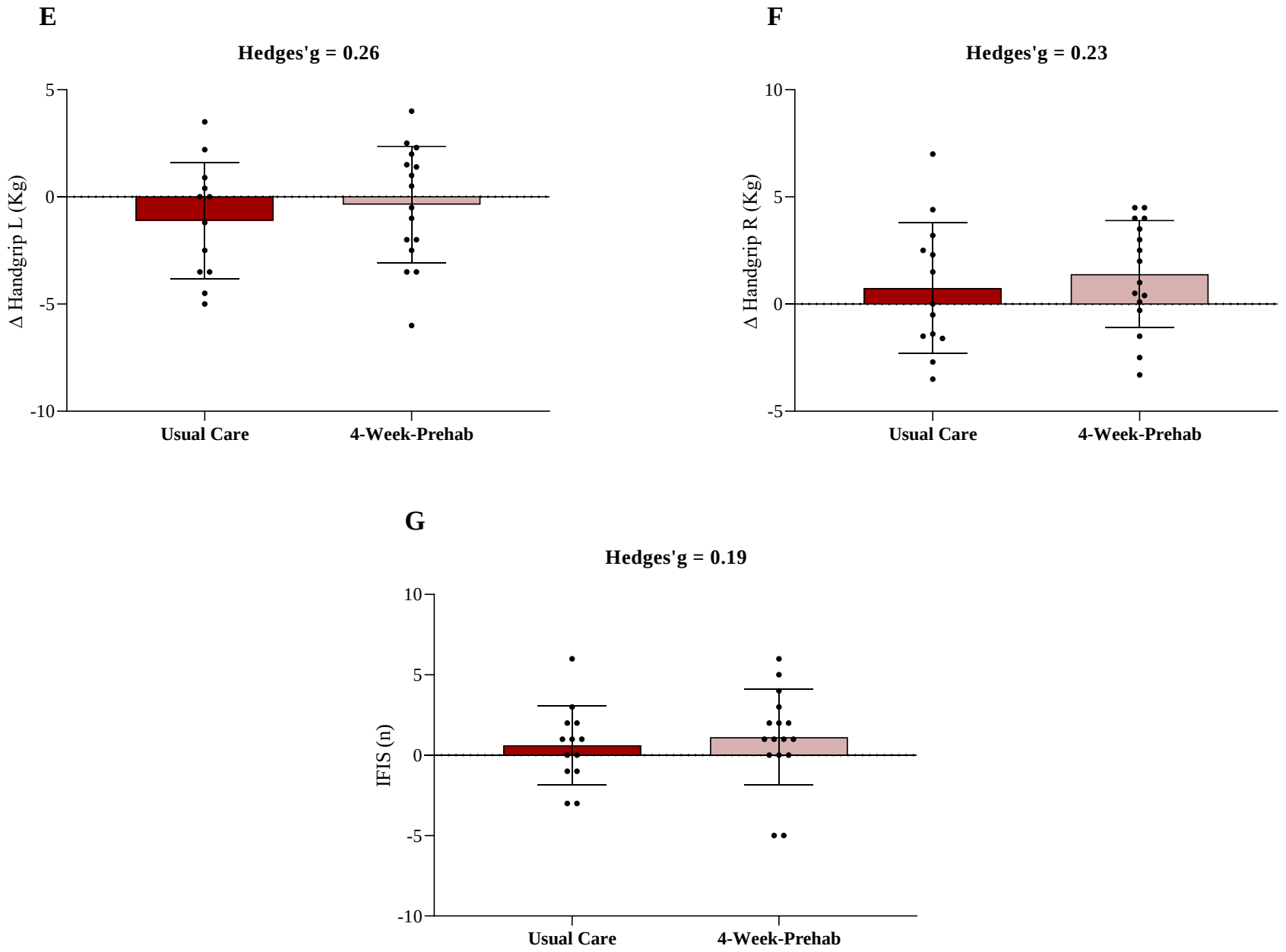


Figure 11- Changes in functional capacity after prehabilitation for each patient in our study. **Abbreviations:** 4 week-Prehab – 4-week multidisciplinary (supervised concurrent exercise training, dietary behavior changes and psychological support) prehabilitation group; m/s- meters per second.

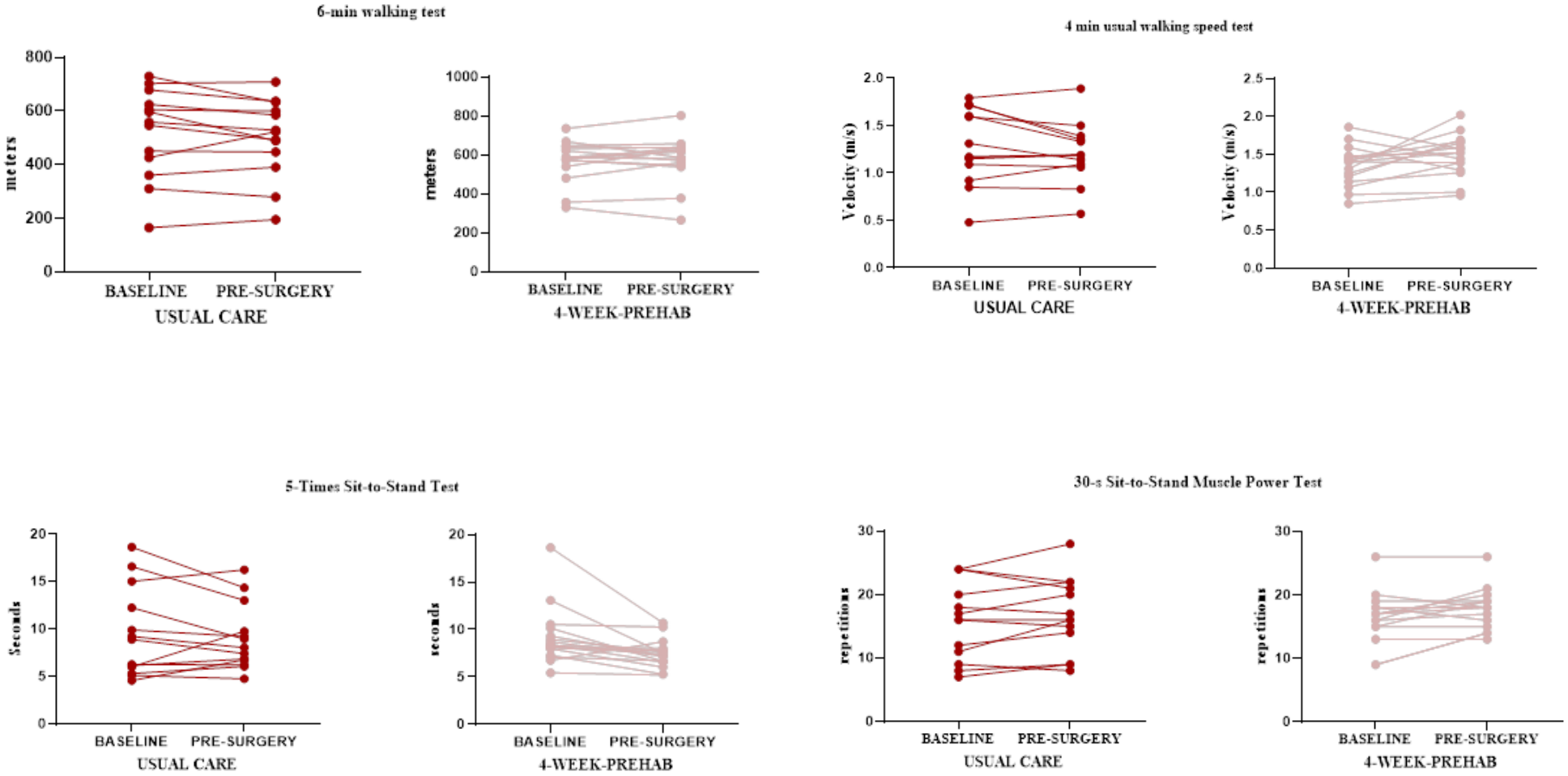
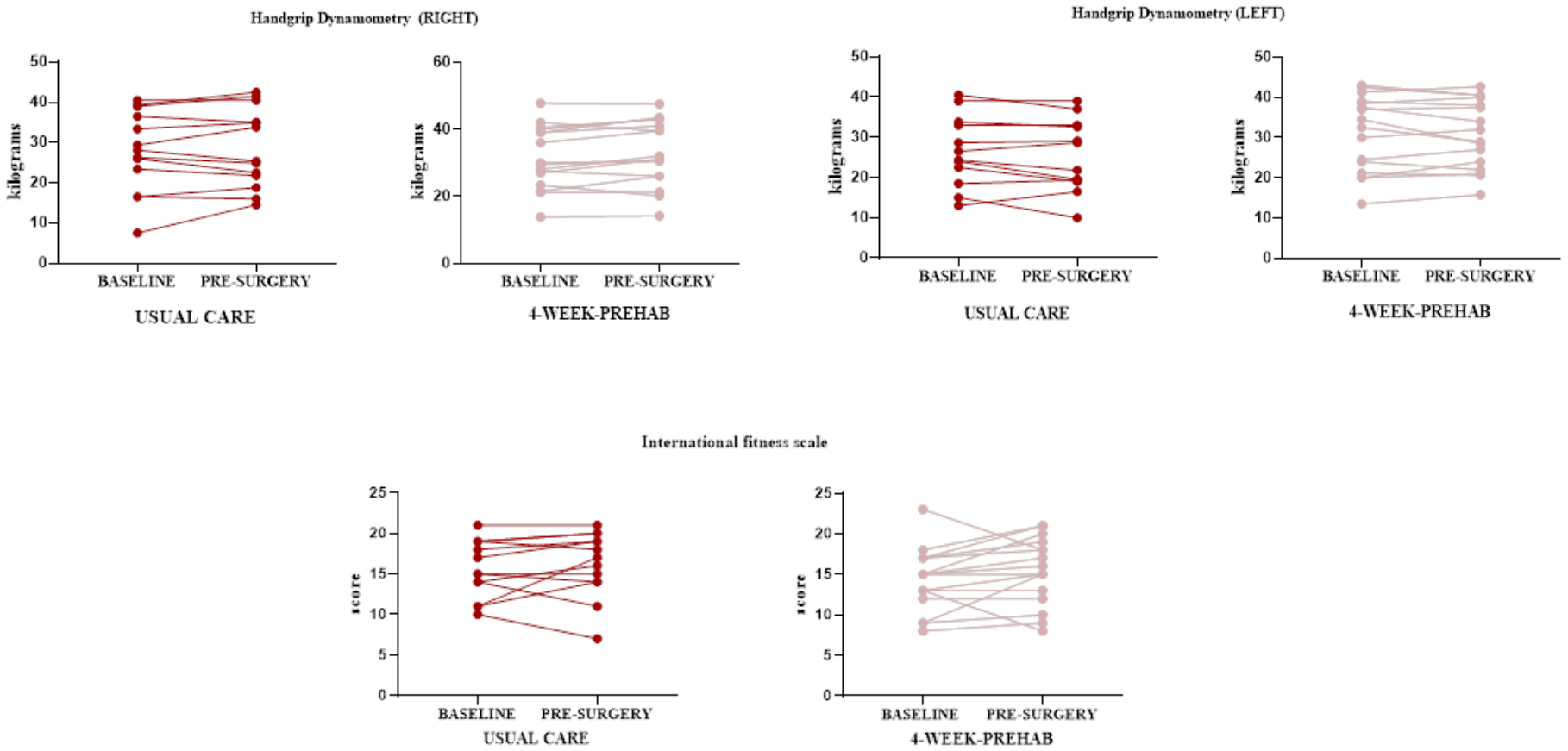


Figure 12- Changes in functional capacity after prehabilitation for each patient in our study. **Abbreviations:** 4 week-Prehab – 4-week multidisciplinary (supervised concurrent exercise training, dietary behavior changes and psychological support) prehabilitation group.



Figures 9 and 10 shows the changes in functional capacity after the intervention. Compared to the control group, the 4-week-Prehab significantly increases the gait speed test (0.14 ± 0.17 vs. -0.06 ± 0.17 , p = 0.030, Hedges'g = 0.84, Figure 9B). Although the other variables had no significant differences between groups, a small effect was reported in the 30-s sit-to-stand muscle power test (1.38 ± 2.36 vs 0.85 ± 2.41, p = 0.557, Hedges'g = 0.22, Figure 9D) and the manual pressure test (Handgrip L (-0.36 ± 2.72 vs -1.10 ± 2.71, p = 0.483, Hedges'g = 0.26, Figure 10E); Handgrip R (1.4 ± 2.50 vs 0.75 ± 3.05, p = 0.531, Hedges'g = 0.23, Figure 10F), a moderate effect on the 5-times sit-to-stand test (-1.74 ± 2.34 vs -0.49 ± 2.31, p = 0.162, Hedges'g = 0.54, Figure 9C) and on the 6-min walking test (8.31 ± 52.16 vs. -18.81± 54.17 ; p = 0.182, Hedges'g = 0.51, Figure 9A). There are no effects on the IFIS (1.13 ± 2.96 vs. 0.62 ± 2.43; = 0.063, Hedges's = 0.19, Figure 10G). Figures 11 and 12 illustrate the individual changes in capacity function after the intervention.

Table 9. Changes in anthropometric variables and functional capacity

Outcome	n	4-week-Prehab	n	Usual care	Mean differences	p-value
Anthropometry						
Weight (Kg)	16	0.6 (-0.2 to 1.5)	13	0.4 (-0.2 to 1.0)	-0.2 (-1.3 to 0.9)	0.671
Body Mass Index (Kg/m^2)	16	0.1 (-0.2 to 0.5)	13	0.1 (-0.1 to 0.4)	-0.0 (-0.5 to 0.5)	0.951
Functional Capacity						
6 min walking test (m)	16	8.3 (-19.5 to 36.1)	13	-18.8 (-51.5 to 13.9)	-27.1 (-67.8 to 13.5)	0.182
4 min usual walking speed test (m/s)	16	0.1 (-0.0 to 0.3)	13	-0.1 (-0.1 to 0.0)	-0.2 (-0.4 to -0.0)	**0.030**
Handgrip strength (Kg)						
Right hand	16	1.4 (0.1 to 2.7)	13	0.7 (-1.1 to 2.6)	-0.7 (-2.8 to 1.5)	0.531
Left hand	16	-0.4 (-1.8 to 1.1)	12	-1.1 (-2.8 to 0.6)	-0.7 (-2.9 to 1.4)	0.483
5-Times sit-to-stand test (s)	16	-1.7 (-3.0 to -0.5)	13	-0.5 (-1.9 to 0.9)	1.3 (-0.5 to 3.0)	0.162
30 sit-to-stand muscle power (Rep.)	16	1.3 (0.1 to 2.6)	13	0.8 (-0.6 to 2.3)	-0.5 (-2.4 to 1.3)	0.557
International fitness scale (nº)	16	1.1 (-0.5 to 2.7)	13	0.6 (-0.9 to 2.1)	-0.5 (-2.6 to 1.6)	0.623

Data are shown as means (95% interval confidence). **Abbreviations:** n-sample, 4 week-Prehab – 4-week multidisciplinary (supervised concurrent exercise training, dietary behavior changes and psychological support) prehabilitation group, kg-kilogram, cm-centimeters, Kg/m^2 - kilogram per square meter, rep.- repetitions, m-meters, s-seconds, nº- score; Significant *p-value* < 0.05

CHAPTER V. DISCUSSION

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The present randomized controlled trial aimed at investigating the effects of a 4-week multidisciplinary prehabilitation program on functional capacity in patients undergoing resection of colon cancer. The main results of this study showed an improvement of cardiorespiratory fitness, gait speed and muscular strength in response to the implemented intervention based on concomitant supervised exercise training, changes in dietary habits and psychological support. These results have significant clinical implications, since improving pre-surgical functional capacity seems crucial in reducing potential postoperative complications and improving patients' prognosis (Molenaar et al., 2023).

5.1. Impact of a 4-week multidisciplinary prehabilitation intervention on cardiorespiratory fitness

Surgical intervention requires high metabolic demands on the human body, making essential an elevate oxygen supply to effectively address the physiological stress induced by this procedure (Rose et al., 2022). The surgery supposes an increase in oxygen demands, a fact that may imply changes in the patient' energy metabolism that can lead to mitochondrial dysfunction, leukocyte activation, concomitant depletion of antioxidants and ischemia-reperfusion in the postoperative period (Rose et al., 2022). In that sense, low cardiorespiratory fitness is known to be a highly predictor of postoperative complications and all-cause mortality risk (Schmid & Leitzmann, 2015). Therefore, to elevate oxygen uptake and cardiorespiratory fitness in the preoperative period may be a key strategy for improving the patient' prognosis (Schmid & Leitzmann, 2015).

This study observed a moderate effect of the 4-week multidisciplinary prehabilitation program at increasing cardiorespiratory capacity. Although there were no significant differences, it should be noted that the average distance traveled in the 6 MWT test was increased by 8.3 m in the intervention group while decreased by 18.8 m in the usual care group. According to the literature, both unimodal (nutrition or exercise) and multidisciplinary (i.e. exercise, nutrition and psychological support) prehabilitation programs are effective at improving cardiorespiratory fitness, a result that is in concordance with the present findings (Bousquet-Dion et al., 2018; Falz et al., 2022; Gillis et al., 2016; Li et al., 2013; Minnella et al., 2017; Molenaar et al., 2023; Northgraves et al., 2020). Although the previous preoperative programs were effective at improving cardiorespiratory fitness, it seems that multidisciplinary interventions reached even better adaptation in this physical fitness dimension (Bausys et al., 2022; Bousquet-Dion et al.,

2018; Li et al., 2013; Minnella et al., 2017; Molenaar et al., 2023). This can be explained by the synergistic effect of exercise interventions when combined with nutrition and/or psychological support. Eating a proper diet is essential as it can improve performance during exercise, providing the necessary energy and aiding recovery. On the other hand, psychological support is also crucial since anxiety is prevalent in this type of population (Dunn et al., 2013). As mentioned earlier, anxiety can lead to increased fatigue, which in turn influences motivation to carry out activities (Ghoneim & O'Hara, 2016; Stonerock & Blumenthal, 2017). Thus, including psychological support can also be a key factor in these improvements as it can help to increase and decrease anxiety levels and in turn help to maintain motivation to exercise and adhere to changes in their diet. The findings of the present manuscript contribute to the body of knowledge regarding the greater improvements generated by a well-designed multidisciplinary program. Furthermore, it was suggested that exercise constitutes a fundamental component of these interventions as, from a mechanistic perspective, the body's cells need more oxygen to produce energy efficiently (Rose et al., 2022). Thus, over time and in response to exercise, the body will undergo adaptations to increase oxygen capacity (Rose et al., 2022). In this sense, Minnella et al. demonstrated that both moderate-intensity continuous aerobic training and HIIT combined with psychological and nutritional support significantly improved cardiorespiratory capacity in patients diagnosed with colon cancer. Interestingly, the HIIT program demonstrated even more efficient improvements in peak VO2 (Minnella et al., 2020). Therefore, as the period between diagnosis and surgery is usually short (~ 4 weeks), it appears essential to implement multidisciplinary programs with supervised exercise training at high intensity to provide additional benefits on cardiorespiratory fitness.

5.2. Impact of a 4-week multidisciplinary prehabilitation intervention on gait speed

The gait requires a complex interaction between the nervous, cardiorespiratory and musculoskeletal systems (Pirker & Katzenschlager, 2017). Gait speed is a robust predictor of medical complications related to frailty, disability, falls, hospitalization and early death (Pamoukdjian et al., 2015). Indeed, previous studies have pointed out that a low walking speed in cancer patients increases both the risk of adverse side effects from treatment and mortality rates (Dociak-Salazar et al., 2022). Hence, it is imperative to improve the gait speed to decrease postoperative complications and increase survival (Bruns et al., 2019; Koh et al., 2022; F. Singh et al., 2018).

This study demonstrated a robust positive effect of the implemented 4-week multidisciplinary prehabilitation program at improving gait speed. Concretely, the walking speed was increased by 0.1 m/s in the intervention group, while an important decrement (0.1 m/s) was registered in the usual care group. Previous studies have shown that the application of exercise-based programs in colorectal cancer patients before surgery increases walking speed (Bruns et al., 2019; Koh et al., 2022; F. Singh et al., 2018). Concretely, while Bruns et al. implemented a 7-minute unsupervised daily strength training focused on basic movements, Koh et al. carried out a supervised strength training program using resistance bands. Both studies also included a nutritional intervention based on protein and micronutrients supplementation. Although both intervention found significant improvements on gait speed, the main reason why Koh et al. obtained even better results in this outcome may be mainly explained by the supervised nature of the exercise intervention. In a resistance training intervention which is supervised by sport scientific expert, the gait speed increments may be related to a subsequent increases in muscle mass, metabolic rates, and movement control, among other health-related factors (Westcott, 2012).

Singh et al. suggested that combining aerobic and resistance training would be more effective than carrying out an exercise training program with only aerobic or resistance training alone. This combination offers a wide range of benefits, both in terms of the cardiovascular component and muscular strength. Aerobic training predominantly increases VO_2max and anaerobic capacity, which is associated with increased mitochondrial biogenesis (Rose et al., 2022). Mitochondria are highly dynamic organelles that play an essential role in supplying ATP to the contractile filaments within the muscle to facilitate contraction (Hood et al., 2019). Considering the above-mentioned positive adaptations related to resistance exercise, the combination of these two types of training may result in the best exercise approach for improving colon cancer patient' prognosis.

It should also be emphasized that nutritional supplementation is a crucial factor in this context. According to the Bruns et al. study, the ingestion of an appropriate quantity of proteins in the preoperative phase appears to be fundamental since an inadequate balance may cause a disturbance on protein homeostasis, a process which can negatively contribute with the physiological adaptations to exercise (e.g., decreased muscle mass and function explained by an increased amino acids catabolic status (Carbone & Pasiakos, 2019).

5.3. Impact of a 4-week multidisciplinary prehabilitation intervention on muscular strength

Sarcopenia is a muscle disease characterized by low muscle mass and strength (Cruz-Jentoft et al., 2010). This is strongly related to the aging process, but other factors such as malnutrition, hospitalization, or cancer help accelerate this process (Cruz-Jentoft et al., 2010). The onset and progression of sarcopenia involve molecular and physiological mechanisms related to protein synthesis, muscle fat content, proteolysis and neuromuscular integrity, which are associated with an increased risk of physical disability, falls, fractures, and mortality (Cruz-Jentoft et al., 2010, 2019). Cachexia is a multifactorial syndrome characterized by sarcopenia with or without changes in fat mass (Cruz-Jentoft et al., 2010; K. Fearon et al., 2011). This pathology is recognized as an adverse effect of cancer and is related to increased muscle catabolism, insulin resistance, inflammatory processes and anorexia (Cruz-Jentoft et al., 2010; K. Fearon et al., 2011).

The present investigation showed clinically relevant improvements in both upper and lower limb muscle strength. In terms of the upper limbs, our findings contrast with the prevailing scientific literature since to the best of our knowledge, only two previous studies evaluated the effects of prehabilitation programs on upper limb strength in patients with colorectal cancer obtaining no positive effect in this dimension (Northgraves et al., 2020; Suen et al., 2022). The lack of positive results can be explained by the design of these exercise interventions, which may not be conducive to enhancing the strength of the upper limb. On the other hand, improvements in the lower limb strength were found in both these and other studies (Northgraves et al., 2020; Suen et al., 2022). Suen et al. implemented a multidisciplinary preoperative intervention (i.e., Exercise, nurse-led phone support and Information on General Nutritional Guidelines), while Northgraves et al. designed an exercise-based prehabilitation program. Regarding the exercise intervention programs, there exist important disparities between these studies and our intervention. Concretely, Suen et al. 2022 prescribed two supervised 60-minute concurrent training sessions, focusing on moderate-intensity for aerobic exercise and no specifying intensity for resistance exercise. On the other hand, Northgraves et al. 2020 intervention had a similar structure differing only in the training frequency (3 days/week). It has been reported the importance of achieving high intensity loads for obtaining an optimal improvement in strength (Lacio et al., 2004; Lopez et al., 2021) . In our study, the target intensity for resistance exercise was set at an intensity level >8 RPE. In contrast, the studies performed by Suen et al. and Northgraves et al. did not provide explicit

guidance regarding the prescribed intensity for resistance training, potentially resulting in suboptimal intensity levels. Consequently, it appears that the application of high load for resistance exercise seems to be essential for augmenting muscle strength, particularly considering the limited timeframe. This can be also seen in the study by Karlsson et al. which implemented a supervised training program including inspiratory muscle training, resistance training at an intensity >7 RPE of 10, and aerobic training between 7-8 RPE of 10. One factor that may substantiate these observations is the occurrence of heightened adaptations at the neuronal and skeletal muscle levels, when subjected to high-intensity resistance training programs (Jenkins et al., 2017).

It is also crucial to mention the potential role of the nutritional intervention in this context. Northgraves et al. did not incorporate any nutritional intervention, while Suen et al. only offered basic dietary recommendations at the baseline. This is noteworthy because healthy dietary patterns have demonstrated effectiveness in the preservation and enhancement of muscle quality and strength (Bloom et al., 2018; Burd et al., 2013). Furthermore, nutritional interventions are known to have a synergistic effect when combined with resistance or concurrent training (Gielen et al., 2021). This can primarily be attributed to an adequate protein intake, which is known to promote muscle protein synthesis and anabolic procedures . Moreover, the inclusion of adequate levels of vitamin D, antioxidant nutrients and polyunsaturated fatty acids in the diet also positively contributes with higher muscle quality (Robinson et al., 2018).

The reasons behind the discrepancies obtained in the studies mentioned above remain unclear. Future studies investigating in an appropriate manner the dietary quality score, protein intake or the exercise training load components are required.

CHAPTER VI. CONCLUSIONS

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The findings of the present study pointed out that a 4-week multidisciplinary program that includes supervised exercise training, modifications to eating behavior and psychological support improves functional capacity in patients undergoing colon cancer resection. The program demonstrated effectiveness in improving gait speed, cardiorespiratory fitness, and muscular strength. However, there was no effects on subjective physical fitness. These results have significant scientific and clinical relevance since improving functional capacity before surgical procedures can enhance energy metabolism and help to mitigate the loss of muscle and bone mineral mass, thus improving the prognosis of patients undergoing colon cancer surgery and reducing potential complications that may arise in the future.

CHAPTER VII. LIMITATIONS AND FUTURE STUDIES

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The main limitation of this study was the small sample size since it is a preliminary study. However, it should be noted that no scientific evidence is available regarding the effect of a 4-week multidisciplinary prehabilitation program that includes supervised combined exercise training, eating behaviors and psychological support on cardiorespiratory fitness, walking speed, muscle strength and subjective physical fitness in this population.

Another limitation of this study is the presence of two members of the scientific staff in the data collection (high inter-researcher variability), although appropriate protocols were implemented to minimize discrepancy between them. In addition, the inclusion of gold standard methods to determine functional capacity (e.g., cardiorespiratory fitness – maximal exercise test to obtain VO2max through indirect calorimetry) instead of field test for assessing physical fitness.

Future studies with a larger and more homogeneous sample size are needed to determine potential differences between groups and gender. Moreover, it would be interesting to check the effect of this intervention on functional capacity after surgery, in order to determine whether the individuals who underwent this program showed as a marked decrease in functional capacity as expected.

CHAPTER VIII. BIBLIOGRAPHY

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CHAPTER IX. ANNEX

Annex 1. Informed Consent

UNIVERSIDAD DE GRANADA

CONSENTIMIENTO INFORMADO

Este documento constituye su aceptación formal para colaborar voluntaria y libremente en este proyecto de investigación y firmarlo es requisito indispensable para que pueda participar en él.

Comprendiendo todo lo anterior:

D. _____, con DNI . _____, acepto participar en el estudio titulado "**Prehabilitación multidisciplinar y rehabilitación postoperatoria para evitar complicaciones en pacientes sometidos a resección de cáncer de colon: el estudio ONCOFIT** (*Multidisciplinary prehabilitation and postoperative rehabilitation for avoiding complications in patients undergoing resection of colon cancer: the ONCOFIT study*)" que se va a llevar a cabo en el Hospital Universitario Clínico San Ceclio y el Instituto Mixto Universitario Deporte y Salud de la Universidad de Granada.

Si decido participar en el estudio, comprendo que durante el proceso me comprometo a:

1. Indicar cualquier problema, síntoma o condición que sea relevante de mi estado de salud que pueda afectar directamente mi seguridad durante el entrenamiento, o durante las mediciones de las diferentes variables a analizar.
2. Permitir la utilización de mis datos para la elaboración de dicho proyecto.
3. Realizar el programa de intervención que, por azar, se me asigne.
4. Permitir la realización de cada una de las mediciones de las variables de estudio en los distintos momentos temporales indicados.

Certifico haber recibido información clara sobre la participación en este proyecto, pudiendo consultar y aclarar todas las dudas y preguntas que me han surgido o me surjan acerca del mismo. Doy mi consentimiento para que mis datos sean empleados para el desarrollo de este estudio, garantizandose en todo momento la confidencialidad de los mismos y no siendo empleados para otros fines.

Igualmente he sido informado, que de requerir algún tipo de aclaración o mayor información sobre los resultados u otras inquietudes, puedo ponerme en contacto con los profesionales responsables de este proyecto y que vienen expuestos en la página anterior.

Por último soy consciente de que la participación es totalmente voluntaria y que podré dejar de participar en el estudio en cualquier momento.

Granada, a de del 202_

DATOS PERSONALES DEL PARTICIPANTE	**INVESTIGADOR RESPONSABLE**
Nombre _____	Nombre: Francisco J. Amaro Gahete
Teléfono _____	Teléfono: 697287022
Correo electrónico: _____	Correo electrónico: amarof@ugr.es
FIRMA:	FIRMA:

Annex 2. Ethics committee approval

JUNTA DE ANDALUCIA CONSEJERÍA DE SALUD Y FAMILIAS

DICTAMEN ÚNICO EN LA COMUNIDAD AUTÓNOMA DE ANDALUCÍA

D/Dª: CRISTINA LUCIA DAVILA FAJARDO como secretario/a del CEIM/CEI Provincial de Granada

CERTIFICA

Que este Comité ha evaluado la propuesta del promotor/investigador (No hay promotor/a asociado/a) para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Influencia de la actividad física, fuerza de presión manual, calidad del sueño y hábitos nutricionales sobre diversos marcadores de evolución postquirúrgica tras cirugía colorrectal
Protocolo, Versión:	v1
HIP, Versión:	v1
CI, Versión:	v1

Y que considera que:

Se cumplen los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio y se ajusta a los principios éticos aplicables a este tipo de estudios.

La capacidad del/de la investigador/a y los medios disponibles son apropiados para llevar a cabo el estudio.

Están justificados los riesgos y molestias previsibles para los participantes.

Que los aspectos económicos involucrados en el proyecto, no interfieren con respecto a los postulados éticos.

Y que este Comité considera, que dicho estudio puede ser realizado en los Centros de la Comunidad Autónoma de Andalucía que se relacionan, para lo cual corresponde a la Dirección del Centro correspondiente determinar si la capacidad y los medios disponibles son apropiados para llevar a cabo el estudio.

Lo que firmo en Granada a 29/05/2019

D/Dª. CRISTINA LUCIA DAVILA FAJARDO, como Secretario/a del CEIM/CEI Provincial de Granada

Código Seguro De Verificación:	c94175cbbe1300205550f4a55193f053c1ede831	Fecha	29/05/2019
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Cristina Lucia Davila Fajardo		
Url De Verificación	https://www.juntadeandalucia.es/salud/portaldeetica/xhtml/ayuda/verificarFirmaDocumento.iface/code/c94175cbbe1300205550f4a55193f053c1ede831	Página	1/2

CERTIFICA

Que este Comité ha ponderado y evaluado en sesión celebrada el 29/04/2019 y recogida en acta 5/19 la propuesta del/de la Promotor/a (No hay promotor/a asociado/a), para realizar el estudio de investigación titulado:

TÍTULO DEL ESTUDIO:	Influencia de la actividad física, fuerza de presión manual, calidad del sueño y hábitos nutricionales sobre diversos marcadores de evolución postquirúrgica tras cirugía colorrectal
Protocolo, Versión:	v1
HIP, Versión:	v1
CI, Versión:	v1

Que a dicha sesión asistieron los siguientes integrantes del Comité:

Presidente/a

D/Dª.

Vicepresidente/a

D/Dª. Francisco Manuel Luque Martínez

Secretario/a

D/Dª. CRISTINA LUCIA DAVILA FAJARDO

Vocales

D/Dª. Encarnación Martínez García
D/Dª. Juan Ramón Delgado Pérez
D/Dª. Berta Gorlat Sánchez
D/Dª. José Darío Sánchez López
D/Dª. Juana María de Haro Castellano
D/Dª. José Cabeza Barrera
D/Dª. Juan Mozas Moreno
D/Dª. José Uberos Fernández
D/Dª. MARIA ESPERANZA DEL POZO GAVILAN
D/Dª. MAXIMILIANO OCETE ESPINOLA
D/Dª. Joaquina Martínez Galán
D/Dª. AURORA BUENO CAVANILLAS
D/Dª. Paloma Muñoz de Rueda
D/Dª. Manuel Gálvez Ibáñez
D/Dª. Esther Espínola García
D/Dª. ANTONIO MORALES ROMERO
D/Dª. MIGUEL LÓPEZ GUADALUPE
D/Dª. JUAN ROMERO COTELO
D/Dª. JUAN DIAZ GARCIA
D/Dª. LUIS MIGUEL DOMENECH GIL
D/Dª. Luis Javier Martínez González
D/Dª. JESÚS CARDONA CONTRERAS
D/Dª. Pilar Guijosa Campos
D/Dª. José Luis Martín Ruiz

Que dicho Comité, está constituido y actua de acuerdo con la normativa vigente y las directrices de la Conferencia Internacional de Buena Práctica Clínica.

Lo que firmo en Granada a 29/05/2019

Código Seguro De Verificación:	c94175cbbe1300205550f4a55193f053c1ede831	**Fecha**	29/05/2019
Normativa	Este documento incorpora firma electrónica reconocida de acuerdo a la Ley 59/2003, de 19 de diciembre, de firma electrónica.		
Firmado Por	Cristina Lucia Davila Fajardo		
Url De Verificación	https://www.juntadeandalucia.es/salud/portaldeetica/xhtml/ayuda/verificarFirmaDocumento.iface/code/c94175cbbe1300205550f4a55193f053c1ede831	**Página**	2/2

CHAPTER X. APPENDICES

Appendix 1. Patient attendance excell sheet

ID	NOMBRE	PRE-QX (SEMANA 1)					PRE-QX (SEMANA 2)					PRE-QX (SEMANA 3)					PRE-QX (SEMANA 4)				
		TS	TS	TS	NS	PS	TS	TS	TS	NS	PS	TS	TS	TS	NS	PS	TS	TS	TS	NS	PS
OF001																					
OF002		1	1	1	1	1	1	1	1	1	1	1			1						
OF003		1	1	1	1	1	1	1	1	1		1			1						
OF004		1	1	1	1	1	1	1	1	1	1	1	1	1	1		1	1	1	1	
OF005		1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	
OF006		1	1	1	1	1	1	1	1	1		1	1		1	1	1			1	
OF007		1	1	1	1	1	1	1	1	1		1	1	1	1	1	1	1	1	1	
OF008																					
OF009																					
OF010																					
OF011		1	1	1	1	1	1		1	1		1	1	1	1	1	1	1	1	1	
OF012																					
OF013		1	1	1	1	1															
OF014																					
OF015		1	1		1	1		1				1			1	1					
OF016		1	1	1	1	1	1	1		1		1	1		1	1					
OF017																					
OF018		1	1	1	1	1	1	1		1											
OF019		1	1	1	1	1	1	1	1	1		1	1	1	1	1					
OF020		1			1																
OF021																					
OF022																					
OF023																					
OF024																					
OF025																					
OF026																					
OF027																					

Appendix 2. Spreadsheet used to define target heart rate percentages

	A	B	C	D	E	F	G	H	I	J	K	L
1	ID	Edad	FCMAX	Fcreposo	50	60	65	75	80	85	95	
2	OF001	68	160,4	106	80,2	96,24	104,26	120,3	128,32	136,34	152,38	
3	OF002	61	165,3	74	82,65	99,18	107,445	123,975	132,24	140,505	157,035	
4	OF003	49	173,7	64	86,85	104,22	112,905	130,275	138,96	147,645	165,015	
5	OF004	74	156,2	59	78,1	93,72	101,53	117,15	124,96	132,77	148,39	
6	OF005	55	169,5	83	84,75	101,7	110,175	127,125	135,6	144,075	161,025	
7	OF006	73	156,9	59	78,45	94,14	101,985	117,675	125,52	133,365	149,055	
8	OF007	55	169,5	58	84,75	101,7	110,175	127,125	135,6	144,075	161,025	
12	OF011	63	163,9	90	81,95	98,34	106,535	122,925	131,12	139,315	155,705	
14	OF013	76	154,8	67	77,4	92,88	100,62	116,1	123,84	131,58	147,06	
16	OF015	81	151,3	90	75,65	90,78	98,345	113,475	121,04	128,605	143,735	
17	OF016	75	155,5	67	77,75	93,3	101,075	116,625	124,4	132,175	147,725	
19	OF018	44	177,2	75	88,6	106,32	115,18	132,9	141,76	150,62	168,34	
20	OF019	84	149,2	92	74,6	89,52	96,98	111,9	119,36	126,82	141,74	
23	OF022	53	170,9	62	85,45	102,54	111,085	128,175	136,72	145,265	162,355	
25	OF024	51	172,3	70	86,15	103,38	111,995	129,225	137,84	146,455	163,685	
27	OF026	77	154,1	95	77,05	92,46	100,165	115,575	123,28	130,985	146,395	
30	OF029	46	175,8	77	87,9	105,48	114,27	131,85	140,64	149,43	167,01	
33	OF032	77	154,1	96	77,05	92,46	100,165	115,575	123,28	130,985	146,395	
34	OF033	63	163,9	123	81,95	98,34	106,535	122,925	131,12	139,315	155,705	

Appendix 3. Sheet to record information about the participant and the intensity during the training session.

ID:

¿Cómo se siente ANTES DE COMENZAR?

Muy mal		Mal		Ligeramente mal	Neutral	Ligeramente bien		Bien		Muy bien
-5	-4	-3	-2	-1	0	1	2	3	4	5

HIIT	Calent.	I1	RA1	I2	RA2	I3	RA3	I4	RA4	Total

			1		2		3		4		5		6		7		8		Tot
0	Reposo																		
1	Muy muy suave																		
2	Muy suave																		
3	Suave																		
4	Algo duro																		
5	Duro																		
6	Más duro																		
7	Muy duro																		
8	Muy muy duro																		
9	Máximo																		
10	Extremadamente máximo																		

¿Cómo se siente DESPUÉS DE REALIZAR LA SESIÓN DE ENTRENAMIENTO?

Muy mal		Mal		Ligeramente mal	Neutral	Ligeramente bien		Bien		Muy bien
-5	-4	-3	-2	-1	0	1	2	3	4	5

RPE TOTAL