PREHABILITATION AND POSTOPERATIVE BURDEN OF HIGH-RISK CANCER PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

PRÉ-HABILITAÇÃO E PROGNÓSTICO PÓS-OPERATÓRIO EM DOENTES ONCOLÓGICOS DE ALTO RISCO: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

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ABSTRACT

Introduction. Prehabilitation aims to optimize patients before surgical treatment in order to improve postsurgical recovery. While its efficacy to improve major postoperative clinical outcomes have been recognized for the broader low-risk surgical population, it remains unclear if the high-risk surgical population also benefits. This meta-analysis assessed the impact of prehabilitation on postoperative outcomes in high-risk surgical cancer patients **Methodology:** We searched for experimental (randomized and non-randomized) and observational studies investigating the impact of prehabilitation in the frequency and/or severity (e.g minor and major complications) of post-surgical complications (primary outcome), type of complications, functional capacity, hospital readmissions, length of hospital stay and 30 day post-surgical mortality (secondary outcomes). High-risk patients for adverse surgical events were defined as frail and / or age ≥70 years and / or with an ASA score of ≥III. **Results**: 136 articles were found, of which only 6 were eligible for qualitative and quantitative evaluation (3 randomized and 3 observational studies). The analysis resulted in a total of 674 participants, with an average age of 78 years, mostly male. Prehabilitation resulted in a lower risk of major complications (risk difference −0.09, 95% CI: −0.15, – 0.03, p = 0.005; i^2 = 27%, p = 0.24) and surgical complications (RR 0.62, 95% CI 0.43 to 0.89, p=0.01; I^2 = 33%, p = 0.22) in comparison to patients receiving standard care. Also, prehabilitation reduced the length of hospital stay (mean difference of – 2.7, 95% CI: −5.37 to −0.17, p = 0.04) and improved functional recovery as assessed by the distance covered in the 6 MWT (mean difference 29.06 meters, 95% CI 26.55 to 31.57, I^2 = 42%, p < 0.001). No differences were observed for the rate of overall complications, medical complications 30-day postoperative mortality or hospital readmission. **Conclusion**: Our work suggests that prehabilitation is effective in reducing postoperative burden in high-risk cancer patients. Future randomized controlled trials for the high-risk surgical patients, using well-established and clinically relevant outcome measures, and with appropriate sample size calculation are needed.

Key words: *High-risk; Cancer patients; Postoperative burden; Prehabiliation.*

RESUMO

Introdução: A pré-habilitação visa otimizar os doentes antes do tratamento cirúrgico, com o objetivo de melhorar a sua recuperação pós-cirúrgica. Embora a eficácia desta intervenção para melhorar os principais desfechos clínicos pós-operatórios tenha sido reconhecida para a população cirúrgica de baixo risco, ainda não está claro até que ponto estes benefícios serão extensíveis também para doentes considerados de alto risco. Esta meta-análise avaliou o impacto da pré-habilitação em desfechos pós-operatórios de

doentes oncológicos cirúrgicos de alto risco. **Metodologia:** Procuramos estudos experimentais (randomizados e não randomizados) e observacionais que avaliaram o impacto da pré-habilitação na frequência e / ou gravidade (major e minor) das complicações pós-cirúrgicas (desfecho primário), tipo de complicações, capacidade funcional, readmissões hospitalares, tempo de hospitalização e mortalidade pós-cirúrgica até 30 dias (desfechos secundários). Doentes de alto risco para eventos cirúrgicos adversos foram definidos como frágeis e / ou com idade ≥70 anos e / ou com score ASA> III. **Resultados:** foram encontrados 136 artigos, dos quais apenas 6 foram elegíveis para avaliação qualitativa e quantitativa (3 estudos randomizados e 3 estudos observacionais). A análise global incluiu um total de 674 participantes, com idade média de 78 anos, a maioria do sexo masculino. A pré-habilitação reduziu o risco de complicações major (diferença do risco −0,09, IC 95%: −0,15, − 0,03, p = 0,005; i^2 = 27%, p = 0,24) e de complicações cirúrgicas (RR 0,62, IC 95% 0,43 a 0,89, p = 0,01; I^2 = 33%, p = 0,22) em comparação com doentes que receberam o tratamento habitual. Além disso, a pré-habilitação reduziu o tempo de hospitalização (diferença média de − 2,7, IC 95%: −5,37 a −0,17, p = 0,04) e melhorou a recuperação funcional avaliada pela distância percorrida no teste de marcha de 6 minutos (diferença média de 29,06 metros, IC de 95% 26,55 a 31,57, I^2 = 42%, p <0,001). Não foram observadas diferenças para as complicações gerais, complicações médicas, mortalidade pós-operatória até 30 dias ou na readmissão hospitalar. **Conclusão:** O nosso trabalho sugere que a pré-habilitação é eficaz na melhoria do prognóstico pós-operatório de doentes oncológicos considerados de "alto risco" para complicações cirúrgicas. Ficou evidente a necessidade de desenvolver ensaios clínicos randomizados especialmente focados em doentes cirúrgicos de alto risco, usando medidas de desfecho bem estabelecidas e clinicamente relevantes, e com cálculo de tamanho amostral adequado.

Palavras-chave: *Alto risco; doentes oncológicos; prognóstico pós-operatório; pré-habilitação.*

INTRODUCTION

The ageing of population worldwide is leading to an unprecedented increase in cancer cases and casualties. By 2030, it was projected that 70% of all cancers will occur among adults ≥65 years old[1], which will also lead to an unparalleled rise in the number of surgeries[2]. Due to the heterogeneity within the elderly population, with its variation in physiological reserves, comorbidity and geriatric conditions like frailty and polypharmacy, a significant increase in postoperative complications can be anticipated. Postoperative complications can impose a significant burden by increasing morbidity and mortality, in-hospital length of stay and need for a greater level of care at discharge[3-5]. Moreover, postoperative complications are associated with delays in chemotherapy that lead to worse disease-free and overall survival[6]. Presumed fear of greater postoperative morbidity and mortality in these high-risk patients often results in sub-optimal delivery of cancer surgery, which is the most efficient curative approach for solid tumors.

The preoperative period offers a window of opportunity to help these high-risk patients by intervening with factors known to contribute to postoperative outcomes[7]. The process of enhancing the functional capacity in order to improve tolerance to treatment and optimize postsurgical recovery has been termed prehabilitation[8]. The potential benefits of prehabiliation are becoming widely appreciated for surgical patients. Meta-analysis supports the safety and efficacy of prehabilitation programs to reduce postoperative complications and improve recovery in the broader surgical populatio[9-12]. However, it remains unclear if such benefits can be extended to cancer patients[13-16], particularly to the older and/or frail. These vulnerable patients are usually underrepresented in prehabilitation studies but are the ones who could gain the most from prehabilitation[16.17]. Small studies have confirmed patient satisfaction, safety and feasibility of these interventions, but clinical outcomes are lacking or provide inconsistent results[18-20]. Therefore, the present work aims to review the existing information on the effect of prehabilitation on older and/or frail cancer patients submitted to surgery. We assessed the impact of this intervention on the incidence and/or severity of postoperative complications (primary outcome), type of postoperative complications,

functional capacity, length of hospital stay, hospital readmissions and post-surgical mortality (secondary outcomes).

METHODS

To carry out this work, we performed a systematic literature search in accordance with PRISMA recommendations[21]. The protocol of this work has not been published in advance.

Eligibility criteria

A study was considered eligible if it included the following criteria:

Participants: cancer patients (both genders) at high-risk for adverse postoperative events, submitted to elective surgery (with or without neoadjuvant therapy), without any restrictions regarding race / ethnicity or sociodemographic characteristics. High-risk patient was defined as frail and / or age ≥70 years and / or with an ASA score of ≥III).

Intervention: assessed the efficacy of unimodal (intervention with physical exercise) or multimodal (intervention with physical exercise and psychological and / or nutritional intervention) prehabilitation program. All studies of prehabilitation programs in patients undergoing surgery for other reason that not cancer were excluded.

Comparison: compared the efficacy of prehabilitation with a control group receiving usual care. This could include control of risk factors, optimal medical therapy, education and advice about diet and exercise, psychosocial support but with no formal exercise intervention. It could also include exercise as rehabilitation.

Outcome: measured frequency and/or severity (e.g minor and major complications) of post-surgical complications (primary outcome). If available, we also included articles reporting the type of complications (e.g. surgical and medical), functional capacity (e.g assessed by the cardiopulmonary test or 6-minute walking test), hospital readmissions (number of hospitalizations after hospital discharge), length of hospital stay (days of hospitalization after surgery) and 30 day post-surgical mortality (secondary outcomes).

Study design: randomized and non-randomized controlled clinical trials, pilot studies (if randomized) and observational studies.

Sources of information

The search was conducted by two independent researchers (F.O. and G.S.) on PubMed, EBSCO and Web of Science database for papers published from database inception to 15-07-2020. Search terms included: old, age, high-risk, frail, frailty, ASA III, prehabilitation, physical exercise, before surgery, preoperative, cancer, neoplasm. The search in the PubMed database was conducted by inserting the following sequence: (old OR age OR "high-risk" OR frail OR frailty OR ASA III [All Fields]) AND (prehabilitation OR "physical exercise" [All Fields]) AND ("before surgery" OR preoperative [All Fields]) AND (cancer OR neoplasm [All Fields]). A manual search was also carried out by checking the references of primary articles and systematic reviews. All retrieved articles were download for a reference manager software (EndNote).

Data extraction and management

The selection of studies was carried out by two researchers (F.T.O. and G.S.), independently. The first stage of screening included reading the title and abstract, followed by reading the full articles to verify eligibility. In case of disagreement, the arguments were discussed, and, in the absence of consensus, a third reviewer was recruited (D.M.G). Studies not meeting the eligibility criteria were excluded and the reason was registered.

For each eligible study, we collected general information (title, authors, place and date of publication), characteristics of the study (study

design, sample size, age, gender, surgical approach, type of cancer and risk definition), intervention (duration, components of intervention, place of intervention and adherence) and outcome measures (primary and secondary). Whenever necessary, data was transformed to allow further use in quantitative analysis using mathematical formulas previously described[22,23]. In case of need for additional or missing information, the authors of the studies were contacted. In case of no response, the study in was removed from the analysis.

Risk bias

For the analysis of the risk of bias, the selected articles were independently assessed by two researchers (F.T.O. and G.S.) and a third evaluator (D.M.G) was requested in situations where consensus was not reached. For this assessment we used the Downs and Black checklist[24]. The checklist contains of 27 items that address the following methodological components: reporting, external validity, internal validity (bias and confounding) and power. Twenty-six items were rated either as yes (=1) or no/unable to determine (=0), and 1 item was rated on a 3-point scale (yes=2, partial=1, and no=0). Scores ranged from 0 to 28, with higher scores indicating a better methodological quality. The following cut-points were used to categorize the quality of studies: excellent[26-28], good[20-25], fair[15-19] and poor (⩽14).

Data analysis

We processed data in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[22]. Dichotomous variables are expressed as relative risks (RR) and 95% confidence intervals for each outcome. For continuous variables, we calculated the mean differences and 95% confidence intervals for each outcome.

Heterogeneity was tested statistically using the χ^2 test of heterogeneity and I^2 statistic. Values of 0% to 25% were considered low heterogeneity, 26% to 50% moderate heterogeneity, 51% to 75% high heterogeneity and> 75% very high heterogeneity. In addition, I^2 was considered statistically significant if the p value <0.10[42]. Date from each study were pooled using the random model when heterogeneity ≥ 50% or by the fixed model when the heterogeneity was <50%[42].

We completed data synthesis and analyses using the Review Manager 5.2 software (RevMan 2016) for all outcome measures that were reported in at least 2 articles.

RESULTS

Description of studies

The study selection process is summarized in the PRISMA flow diagram shown in Figure 1. The search resulted in a total of 138 articles. After screening the title and abstract, 25 articles were selected for full

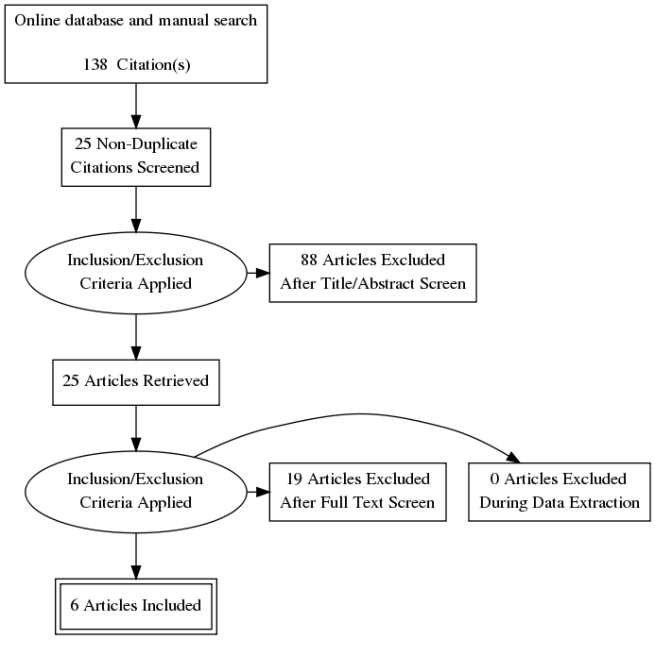


Figure 1 – **PRISMA flow chart.**

reading, of which 19 were subsequently excluded for not meeting the eligibility criteria, making a total of 6 articles selected for qualitative and quantitative analysis. Excluded studies and reasons for exclusion are shown in supplementary Table 1.

Overall characteristics of the identified studies are disclosed in Table 1 and the characteristics of the intervention in Table 3. Three studies were randomized controlled trials[18-20] and 3 were observational, using historical controls[25-27]. The selected studies

Table 1 – **Overall characteristics of the studies**

STUDY	PLACE	STUDY DESIGN	SAMPLE SIZE	GENDER	AGE	TYPE OF CANCER	SURGICAL APPROACH	DEFINITION OF RISK
Barbean, B, et, al. 2018[19]	Clinical hospital of Barcelona Spain	Randomized Controlled Trial	**Intervention group**: 62 participants **Control group:** 63 Participants	**Intervention group**: Male:43 (68%) Female:19 (32%) **Control group:** Male:51 (80%) Female:12 (20%)	**Intervention group**: Mean (DP)= 71 (14) **Control group:** Mean (DP)= 71 (10)	Upper and lower gastrointestinal cancer	**Laparoscopy** 89% in control group 79% in intervention group	Age >70 years or ASA III, IV
Karlsson, E., et al 2019[18]	South general hospital of Stockholm, Sweden	Randomized feasibility study	**Intervention group:** 10 participants **Control group:** 11 participants	**Intervention group:** Male:4 (40%) Female: 6 (60%) **Control group:** Male: 4 (36%) Female: 7 (64%)	**Intervention group:** Median (IQR)= 83.5 (76-85) **Control group:** Median (IQR)= 74.0 (73-76)	Colorectal cancer	**Laparoscopy** 73% in control group 70% in intervention group	Age ≥70 years
Carli, F, et al. 2020[20]	Montreal General Hospital, McGill University Health Center, Canada	Randomized Controlled Trial	**Intervention group:** 55 participants **Control group:** 55 participants	**Intervention group:** Male: 29 (53%) Female: 26 (47%) **Control group:** Male: 23 (42%) Female: 32 (58%)	**Intervention group:** Median (IQR)= 78 (72-82) **Control group:** Median (IQR)= 82 (75-84)	Colorectal cancer	**Laparoscopy** 81.2% in control group 76.4% in intervention group	Fried Frailty
Souwer, E. T. D, et al. 2018[27]	Reinier de Graaf Hospita, Netherlands	Observational	**Intervention group**: 86 participants **Historical control group:** 138 participants (sum of two cohorts)	**Intervention group:** Male: 42 (49%) Female: 44 (51%) **Historical control group:** Cohort 2010/2011: Male: 33 (52%) Female 30 (48%) Cohort 2012/2013 Male: 38 (51%) Female 37 (49%)	**Intervention group:** Median (IQR)= 80.6 (6.2) **Historical control group:** Cohort 2010/2011: Median (IQR)= 81.4 (7.3) Cohort 2012/2013 Median (IQR)= 79.7 (5.0)	Colorectal cancer	**Laparoscopy** 70% and 84% in the first and second cohort, respectively, in control group 83% in intervention group	Age ≥75 years
M.Mazzola et al. 2017[26]	ASST Grande Ospedale Metropolitano Niguarda, Italy	Observational	**Intervention group:** 41 participants **Historical control group:** 35 participants	**Intervention group**: Male: 27 (66%) Female:14 (34%) **Control group:** Male: 23 (66%) Female: 12 (34%)	**Intervention group:** Mean (DP)= 75 (44-90) **Control group:** Mean (DP)75 (59-91)	Upper gastrointestinal cancer	**Laparoscopy** % NA	Edmonton Frail Scale
Chia, C. L. K. et al 2015[25]	Hospital Khoo Teck Puat, Singapore	Observational	**Intervention group**: 57 participants **Historical control group:** 60 participants	NA	**Intervention group:** Median (range)= 79.0 (65-93) **Control group:** Median (range)= 80.5 (75-97)	Colorectal cancer	**Laparoscopy** 16.7% in control group 24.6% in intervention group	Fried Frailty

Supplementary Table 1 – **Articles that were excluded and the underlying reason**

STUDY	REASON FOR EXCLUSION
Alejo, L. B., et al. (2019). "Exercise prehabilitation program for patients under neoadjuvant treatment for rectal cancer: A pilot study."	No control group; Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III No surgical patients;
Blackwell, J. E. M., et al. (2020). "High-intensity interval training produces a significant improvement in fitness in less than 31 days before surgery for urological cancer: a randomised control trial."	Did not assessed postoperative complications ;
"Fit4SurgeryTV At-home Prehabilitation for Frail Older Patients Planned for Colorectal Cancer Surgery: A Pilot Study."	No control group; Did not assessed postoperative complications;
Gravier, F. E., et al. (2019) "Effect of prehabilitation on ventilatory efficiency in non-small cell lung cancer patients: A cohort study."	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; No surgical patients; Did not assessed postoperative complications;
Gillis, C., et al. (2019). "Trimodal prehabilitation for colorectal surgery attenuates post-surgical losses in lean body mass: A pooled analysis of randomized controlled trials."	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; Did not assessed postoperative complications;
Heldens, 2016 "Feasibility and preliminary effectiveness of a physical exercise training program during neoadjuvant chemoradiotherapy in individual patients with rectal cancer prior to major elective surgery."	No control group; Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; No surgical patients; Did not assessed postoperative complications;
Li, C., et al. (2013). "Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study."	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III;
Hillen, B., et al. (2019). "Use of a Perioperative Web-Based Exercise Program for a Patient with Barrett's Carcinoma Scheduled for Esophagectomy." Case Reports in Oncology	Study-case; Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III;
Minnella, E. M., et al. (2018). "Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial."	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III;
Parker, N. H., et al. (2019). "Physical activity and exercise during preoperative pancreatic cancer treatment."	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; Did not assessed postoperative complications;
Moug, S. J., et al. (2019). "Prehabilitation is feasible in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and may minimize physical deterioration: results from the REx trial."	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; No surgical patients; Did not assessed postoperative complications;
Ngo-Huang, A., et al. (2019). "Home-Based Exercise Prehabilitation During Preoperative Treatment for Pancreatic Cancer Is Associated With Improvement in Physical Function and Quality of Life.	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; Did not assessed postoperative complications;
Handoo, A., et al. (2018). "Gait speed predicts post-operative medical complications in elderly gastric cancer patients undergoing gastrectomy.	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; Did not assessed the role of prehabilitation;
Inoue, T., et al. (2016). "Changes in exercise capacity, muscle strength, and health-related quality of life in esophageal cancer patients undergoing esophagectomy."	Did not include high-risk patients as defined by frailty, age $\geq$ 70 years old and/or ASA score > III; Did not assessed the role of prehabilitation; Did not assessed postoperative complications;
Dunne, D. F. J., et al. (2016). "Randomized clinical trial of prehabilitation before planned liver resection." British Journal of Surgery	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; Did not assessed postoperative complications;
West, M. A., et al. (2015). "Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study."	Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; No surgical patients; Did not assessed postoperative complications;
Valkenet, K., et al. (2016). "Feasibility of Exercise Training in Cancer Patients Scheduled for Elective Gastrointestinal Surgery."	No control group; Did not include high-risk patients as defined by frailty, age > 70 years old and/or ASA score > III; No surgical patients; Did not assessed postoperative complications;
Janssen, T. L., et al. (2019). "Multimodal prehabilitation to reduce the incidence of delirium and other adverse events in elderly patients undergoing elective major abdominal surgery: An uncontrolled before-and-after study."	No control group;
Looijaard, S., et al. (2018). "Physical and Nutritional Prehabilitation in Older Patients With Colorectal Carcinoma: A Systematic Review."	Systematic review

Table 2 – **Prehabilitation Characteristics and outcomes**

STUDY	DURATION	INTERVENTION AND COMPONENTS	LOCATION	ADHERANCE	OUTCOMES
Barbean, B, et, al. 2018[19]	Mean of 6 weeks	Prehabilitation - Exercise	Supervised and home-based	87%	**Primary Outcome** - Postoperative complications **Secondary Outcomes** - Number and severity of postoperative complications - Hospital and intensive care unit (ICU) days of stay - Endurance time - Distance covered in the 6-minute walking Test - Physical activity level - Self-perceived health status - Psychological status
Karlsson, E., et al 2019[18]	2–3 weeks or until surgery	Prehabilitation - Exercise	Supervised	97%	**Primary outcome** - Feasibility **Secondary outcome** - Adverse events - Patient-reported recovery - 30-day postoperative complications - Length of hospital stay
Carli, F, et al. 2020[20]	4 weeks	Prehabilitation - Exercise - Nutrition - Psychological	Supervised and home-based	**Supervised sessions** 68% Prehab 14% Rehab **Overall program** 80% Prehab 30% Rehab	**Primary Outcome** - 30-day postoperative complications **Secondary Outcome** - Primary and total LOS, readmissions, and emergency department visits within 30 days after surgery - Functional walking capacity - Patient-reported outcome measures (generic health status, anxiety and depression and self-reported energy expenditure
Souwer, E. T. D, et al. 2018[27]	4-6 weeks	Prehabilitation + Rehabilitation - Exercise - Nutrition - Psychological	Supervised and home-based	NA	**Primary Outcome** - 1-year overall mortality **Secondary Outcome** - Postoperative complication rates readmission rates - 30-day mortality
M.Mazzola et al. 2017[26]	5-14 days	Prehabilitation - Exercise - Nutrition - Psychological	NA	NA	- 30-days and 3-months mortality - Overall and severe complication rates - Length of stay, referral to post-discharge institutionalization and hospital re-admission
Chia, C. L. K. et al 2015[25]	2 weeks	- Exercise - Nutrition - Psychological	Rehabilitation center or home-based	NA	- Length of acute hospital stay - Severity of postoperative complication - 30-day mortality - Recovery of functional status

were carried out between 2007 and 2019, 1 study in Spain (19), 1 in Sweden[18], 1 in the Netherlands[27], 1 in Singapore[25], 1 in Canada[20] and 1 in Italy[26].

A total sample of 674 participants was obtained, with an average age of 78 years, 47% male, 36% female and 17% mixed (one study did not mentioned the sex of participants[25]). Four studies included participants with colorectal cancer[18,20,25,27], 1 study with upper and lower gastrointestinal cancer[19] and 1 study with upper gastrointestinal cance[26]. In 1 study, 25% of the surgical population included non-oncologic patients[19]. Laparoscopy was the main surgical approach in 5 studies[18-20,26,27]. High risk for postoperative complications was defined by frailty status in 3 studies[20,25,26] and age ≥70 years and or ASA III-IV in the remainder[18,19,27]. The Clavien-Dindo system was used to classify the severity of postoperative complications in 5 studies[18-20,25,26]. A score ≥ III was used to define severe complication 4 studies[18-20,25] and ≥ II in 1 study[26]. Finally, 1 study defined severe complications as complications leading to ICU admission (longer than 2 days), to a reintervention, to a prolonged hospital stay of more than 14 days, or to postoperative mortality[27].

The prehabilitation programs lasted from 2 to 6 weeks, with home and hospital-based programs, mostly supervised. Prehabilitation was unimodal (physical exercise) in 2 studies[18,19] and multimodal in the remaining studies (exercise, nutritional and psychosocial intervention). The programs varied between 2 or 3 sessions per week, lasting between 30 and 60 minutes per session. The exercise programs consisted of increasing physical activity levels and/or formal exercise prescription with aerobic exercise or functional exercises or muscle strength exercises. In 1 study, exercise rehabilitation was offered after surgery to the control group[20] and to both groups in another[25].

Risk of bias

The overall assessment of the articles suggests good quality [average of 22.7 points], suggesting low risk of methodological bias (Table 3). Two observational studies[25,26] presented fair quality, 1 presented good quality[27] and the 3 RCT's presented excellent quality[18-20].

Effect of the intervention on primary outcomes

Post-surgical complications

Five studies[18-20,26,27] assessed the effect of prehabilitation on overall complications, expressed

Table 3 – **Qualitative assessment of studies**

AUTHOR (YEAR)	REPORTING (max score=11)	EXTERNAL VALIDITY (max score=3)	BIAS (max score=7)	CONFOUNDING (max score=6	POWER (max score=1)	TOTAL OF POINTS
Barbean, B., et al. 2018[19]	11	3	7	6	1	28
Sower, E. T. D., et al. 2018[27]	9	3	4	3	1	20
karlsson, E., et al. 2019[18]	11	3	6	6	1	27
Carli, F., et al. 2020[20]	10	3	6	6	1	27
Mazzola M., et al. 2017[26]	7	3	4	3	1	18
Chia, C. L. K., et al. 2015[25]	8	2	4	3	1	18
Total of points (mean)	**9,3**	**2,8**	**5,1**	**4,5**	**1**	**22,7**

as number of patients experiencing at least 1 complication (Figure 2-A). Individually, only 2 studies[19,26] found a reduction in the risk of general complications in the group undergoing prehabilitation compared to standard treatment. However, the cumulative effect did not show differences between groups (RR 0.79, 95% CI: 0.53-1.16, p = 0.23; I^2 = 70% and p = 0.23).

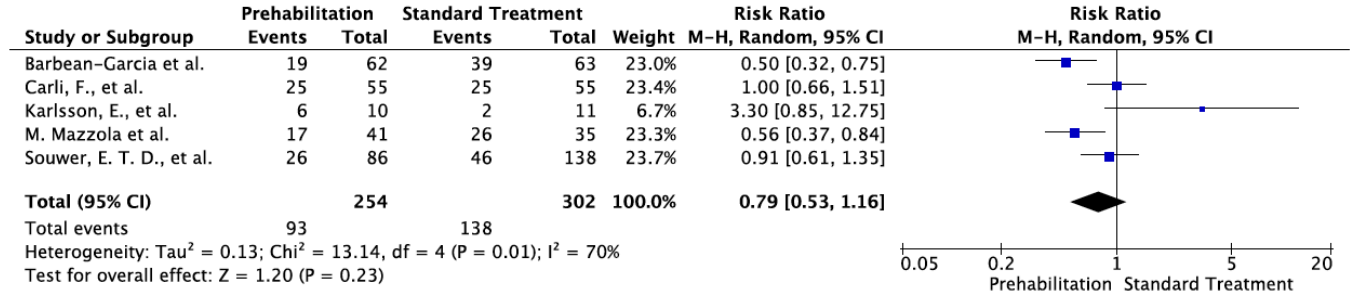
Major complications were reported as the number of adverse events and one patient could have more than one. The impact of prehabilitation on this outcome is shown in Figure 2-B and was assessed in 5 studies[18,20,25-27]. Only 1 study[26] showed a reduction in the risk of major complications in the group submitted to prehabilitation when compared to the standard treatment. The pooled analysis supports that prehabilitation promotes a significant reduction in major complications (risk difference –0.09, 95% CI: –0.15, – 0.03, p = 0.005) with low heterogeneity (i^2 = 27%, p = 0.24).

Effect of the intervention on secondary outcomes

Type of postoperative complications

We were able to obtain data about the total number of surgical complications in 4[19,20,26,27] and medical complication in 3 studies[19,20,27]. Each patient could have more than 1 adverse event. Surgical complications were reduced by prehabilitation in two studies[19,26], while medical complications were reduced in one study[19]. When assessing the cumulative effect, we found that the prehabilitation group presented a significant reduction in the risk for surgical complications (RR 0.62, 95% CI 0.43 to 0.89, p=0.01; I^2 = 33%, p = 0.22) (Figure 3-A), but no differences were noted for the risk of medical complications (RR 0.68, 95% CI 0.31 to 1.848, p=0.33; I^2 = 91%, p < 0.001) (Figure 3-B). Because some studies reported

A



B

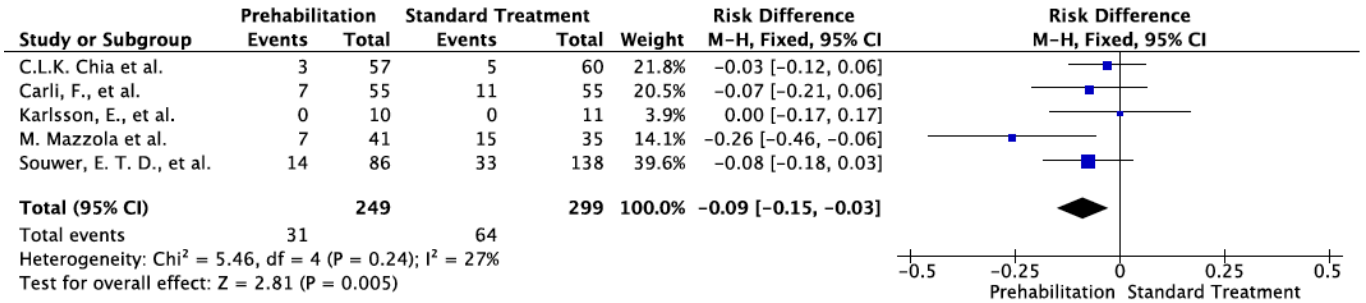


FIGURE 2 – **Forest plot evaluating the effect of prehabilitation on overall (A) and major postoperative complications (B).**

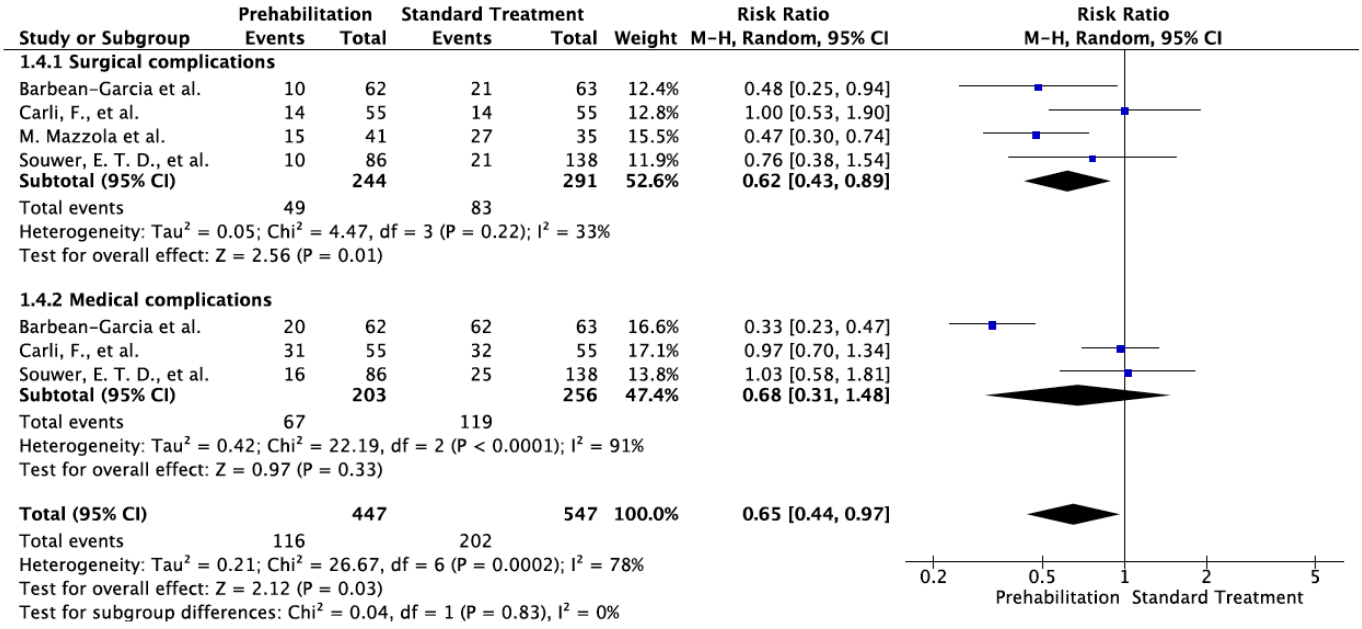


FIGURE 3 – **Forest plot evaluating the effect of prehabilitation on the type of postoperative complications: surgical complications (A) and medical complications (B).**

the type of medical complications, we were able to perform subgroup analysis and further explore the role of prehabilitation on cardiac, pulmonary and infectious complications (Figure 4-A, B and C). Polled analysis showed no effect of prehabilitation in any of these medical complications, but a trend to lower risk of cardiac complications was observed (RR 0.34, 95% CI 0.10 to 1.19, p=0.09; I^2 = 53%, p = 0.09).

Postoperative mortality

Four studies (19, 25-27) assessed the impact of prehabilitation on 30-day postoperative mortality (Figure 5) and none reported a significant reduction in the group undergoing prehabilitation. The cumulative assessment showed a reduction in the risk of postoperative mortality in the prehabilitation group but without statistical significance (RR 0.44, 95% CI: 0.16-1.25; p = 0.12; I^2 = 0 % and p = 0.43).

Length of hospital stay

The impact of prehabilitation on length of stay (Figure 6) was assessed in four studies, with two of the studies[25,26] showing a significant reduction in those patients submitted to the intervention. The cumulative assessment corroborates the beneficial effect of prehabilitation in the length of hospital stay, with patients from the prehabilitation group remaining at the hospital, on average, 3 days less than patients from the control group (mean difference of – 2.7, 95% CI: –5.37 to –0.17, p = 0.04), but the heterogeneity was found to be elevated and significant (I^2 = 77% and p = 0.002).

Hospital readmission

Regarding hospital readmission (Figure 7), it was reported in three studies (20, 26, 27). We did not find significant differences between groups (RR 0.73, 95% CI: 0.39 to –1.36, p = 0.32; I^2 = 38% and p = 0.20).

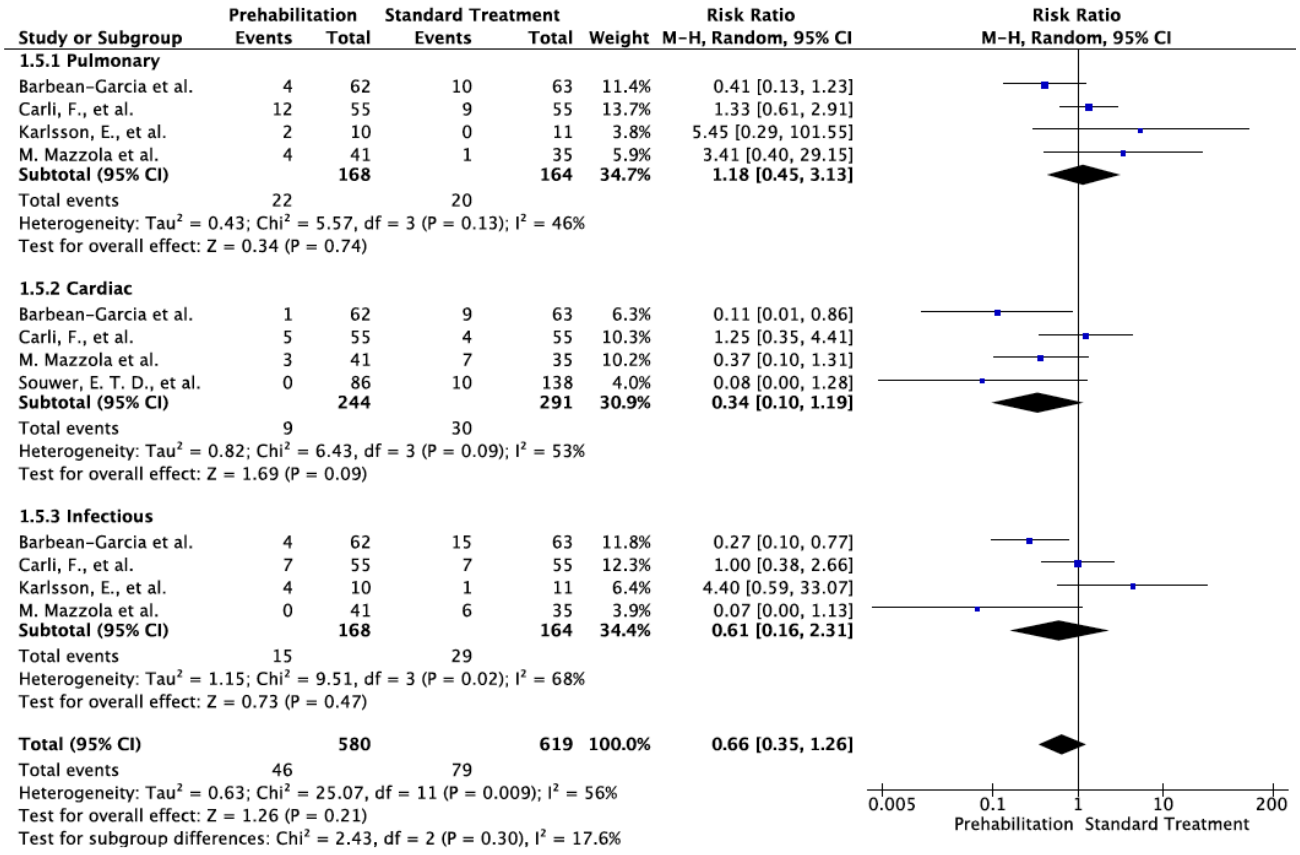


FIGURE 4 – Forest plot of subgroup analysis for the effect of prehabilitation in the type of postoperative medical complications: cardiac (A), pulmonary (B) and infectious (C).

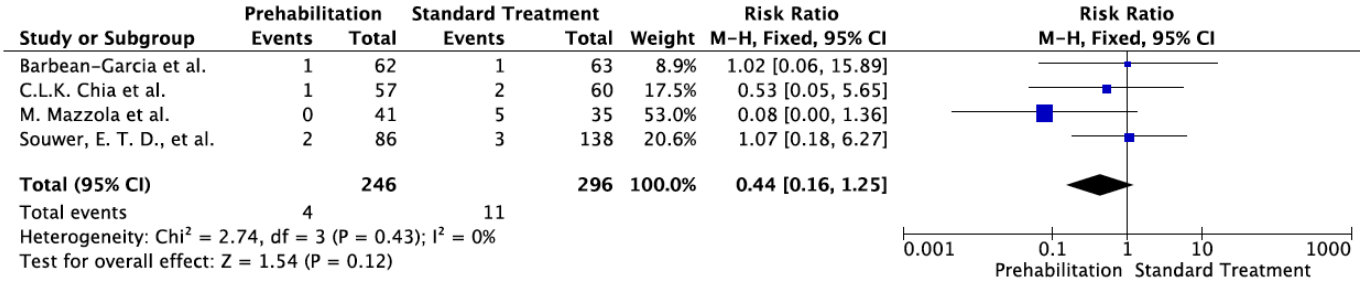


FIGURE 5 – Forest plot evaluating the effect of prehabilitation on 30-day postoperative mortality.

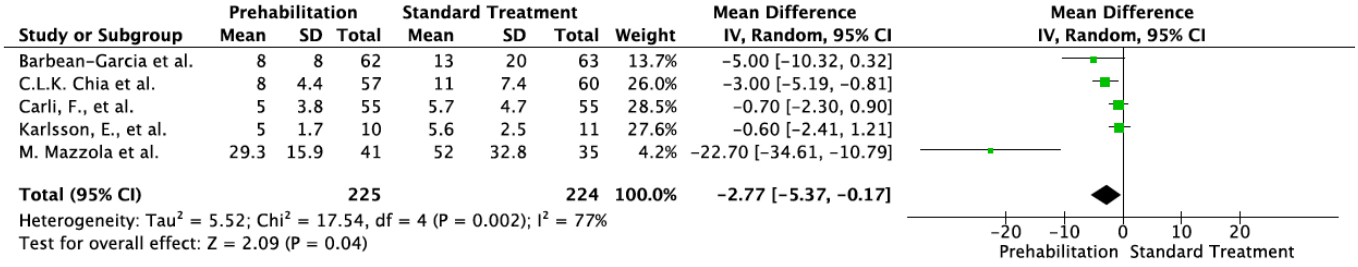


FIGURE 6 – Forest plot evaluating the effect of prehabilitation on length of hospital stay.

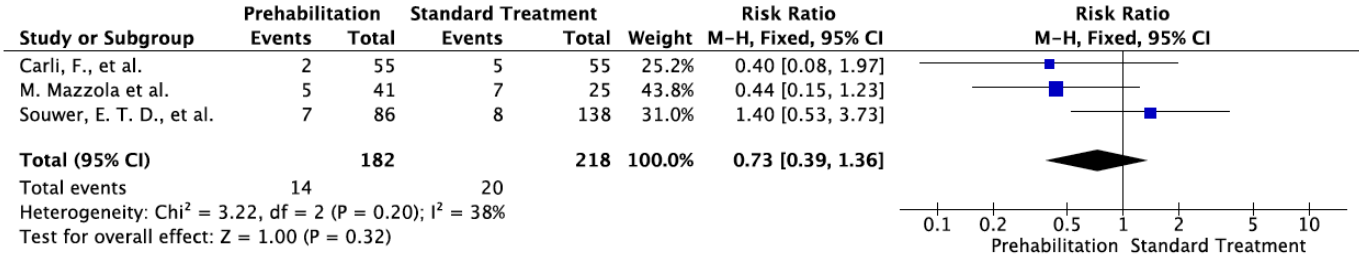


Figure 7 – **Forest plot evaluating the effect of prehabilitation on hospital readmission.**

Functional capacity

Postoperative functional capacity (Figure 8) was evaluated by the 6 min walk test was in two studies[18,20] and both reported a significant increase in the distance covered in the prehabilitation group in comparison to standard treatment group. Pooled analysis reflects that prehabilitation improved functional capacity in prehab patients, who performed on average more 29.06 meters than those submitted to the usual treatment (95% CI 26.55 to 31.57, $I^2 = 42\%$, $p < 0.001$).

DISCUSSION

The objective of this systematic review and meta-analysis was to evaluate the effectiveness of prehabilitation program with exercise (unimodal or multimodal) in reducing postoperative complications in cancer patients considered to be at high-risk for postoperative outcomes. Our results suggest that prehabilitation reduces i) major complications, ii) surgical complications, iii) length of hospital stay and iv) improves post-surgical functional capacity.

Meta-analysis supports the safety and efficacy of prehabilitation programs to improve exercise capacity both before and after surgery in cancer patients[14,15]. However, because of several methodological constraints presented by most studies (e.g. differences in the design of prehabilitation programmes, type/stage of cancer, risk profile of patients, adherence rates, assessment and reporting of outcome measures) a definite conclusion about the impact of this intervention on major clinical outcomes remains to be shown[13-16]. In order to overcome one of these constraints (diverse risk profile), we assessed the impact of prehabiliation specifically in those with higher risk for poor outcomes: the older/frail segment of surgical cancer patients[16,17]. Previous systematic reviews

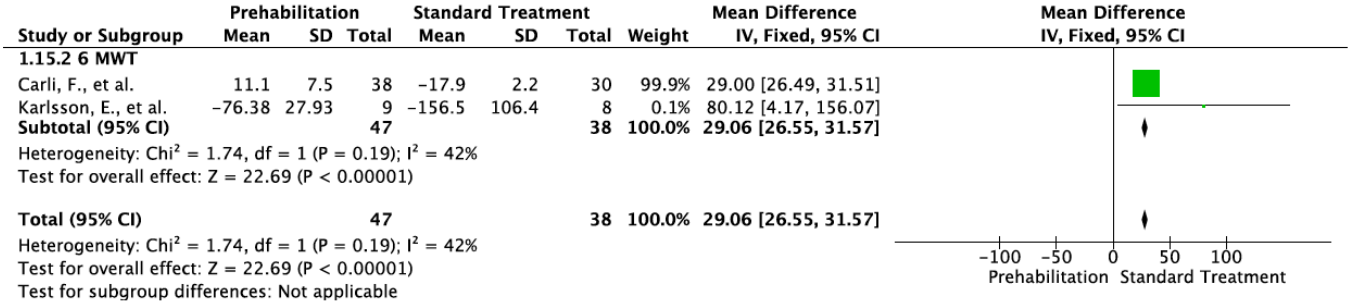


Figure 8 – **Forest plot evaluating the effect of prehabilitation on functional capacity.**

tried to address this issue by capturing a mixture of prehabilitation studies with frail patients from different surgical fields (e.g. cancer, orthopedics and cardiology) but, due to the heterogeneity that characterizes the surgical approaches, the clinical population and outcomes assessment, meta-analysis was not performed[17,28]. In the recent years, some additional studies have been published on high-risk cancer patients, which allowed us to perform our systematic review and proceed to meta-analysis.

According to our data, prehabilitation was not able to reduce the incidence of overall complications but it significantly reduced major complications, as previously shown for the broader surgical population after major abdominal and cardiothoracic surgery[9-12]. The observation that prehabilitation significantly reduced the risk of major postoperative complications is extremely relevant because these are associated with poorer quality of life[29], greater functional dependence, delay or interruption in subsequent treatments[30] and lower short- and long-term survival[4,5]. In fact, we found that participants undergoing prehabilitation had a tendency for a lower risk of 30-day postoperative mortality. A previous systematic review that assessed the role of prehabilitation in the overall surgical frail patients also pointed in the same direction[17]. Future randomized clinical trials should definitely address this issue.

In addition to its degree of severity, postoperative complications should be interpreted according to their type (e.g. surgical vs. non-surgical). Surgical complications are related to surgical procedures or techniques (e.g. bleeding, leaks, sepsis due to leaks, etc.) while non-surgical complications are more dependent to the patient's physiological health or comorbidities (e.g., acute kidney injury, acute respiratory failure, etc.)[31]. Thus, in theory, medical complications would be more preventable with prehabilitation than surgical complications. However, our data suggest that prehabilitation reduced surgical complications but had no effect on medical complications in these high-risk patients. We believe that this could be related to bias due to the poor reporting of the type of medical complications. When medical complications were categorized as pulmonary, cardiac and infectious, we noted a tendency for a reduction in cardiac complications. Future studies should report the type of medical complications in a detailed and standardized manner in order to allow comparisons and reduce the bias on the interpretation.

The impact of prehabilition in the length of hospital stay has been assessed in previous meta-analysis for the general surgical population, with inconsistent findings[10-12], which might be in part attributed to the heterogeneous features of the general surgical population. By focusing only in high-risk cancer patients, our data suggests that prehabilitation is capable to promote a faster recovery, translating into decreased length of hospital stay. This might result in important reductions in the economic burden for hospitals providing surgical care by saving health resources[32]. As for the risk of readmission, the present meta-analysis does not show a significant reduction, which in our understanding is due to the small number of primary studies evaluating this outcome in high-risk patients.

Regarding functional capacity, it has been shown that even in the absence of complications, major surgery is associated with a 20-40% reduction in functional capacity, which may take several months to recover to near baseline values, with obvious implications for carrying out the patient's daily tasks[33,34]. In our meta-analysis, prehabilitation attenuated the loss of functional capacity assessed by the 6-minute walk test. By mitigating functional impairment, prehabilitation can thus accelerate recovery and provide patients a faster return to their normal daily activities. Since a greater preoperative functional capacity is associated with better tolerance to cancer treatments, it might be the case that a greater postoperative functional capacity will also provide support to better tolerate subsequent treatments (e.g. adjuvant chemotherapy)[35].

Limitations

Our data should be interpreted with caution by several reasons. First, there is currently no single standard measure to identify a "high-risk" patient to postoperative death and/or severe complications, so it cannot be discharged that using other definitions would lead to different results. While we believe that the definition we used reasonably identifies those patients with the lowest preoperative physiological reserve (which is the ultimate risk factor for morbidity and mortality), it cannot be assumed that the risk profile of a frail patient is similar to a patient with ≥70 years or an ASA score of ≥III. Even frailty was assessed using different tools, which can be a source of bias as it has been shown that different tools have poor agreement in identifying the same person as frail[36]. Second, we were only able to include studies that recruited gastrointestinal cancer patients (mainly colorectal), so it will be important to address the impact of prehabilitation in high-risk patients with other types of cancer. Third, we observed the use of different measures for the same outcome (e.g. definition of severe complications, mortality), which might be a source of bias. Fourth, due to the small number of studies on the topic, we did not limit our research strategy to randomized clinical studies and included 3 observational studies that used historical control groups, which can also increase bias in the interpretation of our data. Finally, only two studies had postoperative complications as their primary outcome and did the appropriate sample size calculations. Future studies should definitely address these major clinical outcomes with the appropriate sample size calculation.

CONCLUSION

The current data supports the use of prehabilitation as part of the preoperative optimization plan of high-risk cancer patients, despite the small number of studies on the topic. While standardization of prehabilitation programs or a single definition of "high-risk" patient will be very difficult to accomplish, we believe that important advances could be obtained by running randomized controlled trials, using well-established and clinically relevant outcome measures, and with appropriate sample size calculation.

Financial support

CIAFEL is funded by the European Regional Development Fund (ERDF) through the Operational Programme for Competitiveness and Internationalization (COMPETE) and by Fundação para a Ciência e a Tecnologia (FCT) grant (UIDB/00617/2020). This work was supported by FCT (grant PTDC/SAU-DES/7945/2020).

Author contributions

D.M.G and F.T.O: study conception and design. F.T.O and G.S.: data collection and analysis, tables and figures preparation. D.M.G, F.T.O, G.S., F.S. and P.C.M., data interpretation, manuscript writing and revision. All authors have given approval to the final manuscript for submission.

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Data de recepção do artigo:
03/02/2021

Data de aceitação do artigo:
06/04/2021