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Enhanced recovery after surgery programmes in older patients undergoing hepatopancreatobiliary surgery: what benefits might prehabilitation have?

Bart C. Bongers [a, b, *], Cornelis H.C. Dejong [c, d], Marcel den Dulk [c, d]

[a] Department of Nutrition and Movement Sciences, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University, Maastricht, the Netherlands
[b] Department of Epidemiology, Care and Public Health Research Institute (CAPHRI), Maastricht University, Maastricht, the Netherlands
[c] Department of Surgery, Maastricht University Medical Centre, Maastricht, the Netherlands
[d] Department of Surgery, Uniklinikum RWTH-Aachen, Aachen, Germany

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A B S T R A C T

Due to an aging population and the related growing number of less physically fit patients with multiple comorbidities, adequate perioperative care is a new and rapidly developing clinical science that is becoming increasingly important. This narrative review focuses on enhanced recovery after surgery (ERAS®) programmes and the growing interest in prehabilitation programmes to improve patient- and treatment-related outcomes in older patients undergoing hepatopancreatobiliary (HPB) surgery. Future steps required in the further development of optimal perioperative care in HPB surgery are also discussed. Multidisciplinary preoperative risk assessment in multiple domains should be performed to identify, discuss, and reduce risks for optimal outcomes, or to consider alternative treatment options. Prehabilitation should focus on high-risk patients based on evidence-based cut-off values and should aim for (partly) supervised multimodal prehabilitation tailored to the individual patient's risk factors. The program should be executed in the living context of these high-risk patients to improve the participation rate and adherence, as well as to involve the patient's informal support system. Developing tailored (multimodal) prehabilitation programmes for the right patients, in the right context, and using the right outcome measures is important to demonstrate its potential to further improve patient- and treatment-related outcomes following HPB surgery.

Introduction

Perioperative medicine encompasses the integrated, multidisciplinary care for patients from decision-making for surgery and preparation for surgery to full recovery postoperatively, including the phase of recovery at home after discharge from the hospital. Due to an aging population and the related growing number of less physically fit patients with multiple comorbidities, adequate perioperative care is a new and rapidly developing clinical science that is becoming increasingly important. The patient should not only be approached from a traditional anaesthesiologic and surgical viewpoint during the perioperative period. Pre- and postoperative lifestyle interventions (*e.g.*, physical exercise training, nutritional support, psychological support, smoking and/or alcohol cessation), pain management, and comorbidity management (*e.g.*, treatment of (the cause of) anaemia) are important as well for optimal patient- and treatment-related outcomes. The aim of this article is to review the background and content of the current focus on improving perioperative pathways in hepatopancreatobiliary (HPB) surgery. The emphasis is on enhanced recovery after surgery programmes and the growing interest in prehabilitation programmes, as well as on future steps required in the further development of optimal perioperative care in elderly patients undergoing HPB surgery.

* Corresponding author. Department of Nutrition and Movement Sciences, Maastricht University, UNS50 room G2.224, P.O. Box 616, 6200, MD, Maastricht, the Netherlands.

E-mail addresses: bart.bongers@maastrichtuniversity.nl, bart.bongers@maastrichtuniversity.nl (B.C. Bongers), chc.dejong@mumc.nl (C.H.C. Dejong), marcel.den.dulk@mumc.nl (M. den Dulk).

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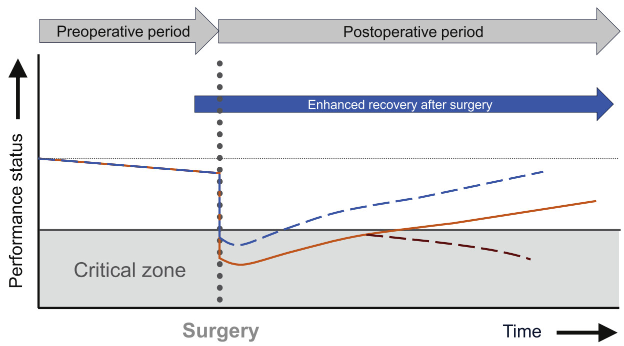

Fig. 1. Surgery in unfit and/or older patients can cause their physical performance status to drop below a dependency threshold (critical zone) as a consequence of the surgical stress response and hospitalization. This increases the risk of complications and recovery of physical performance status may take time. The ERAS® programme (blue, dashed line) aims to attenuate the stress response to surgery by optimal control of pain and by early oral diet and mobilization, thereby reducing the risk of complications, facilitating rapid recovery of physical performance status, and decreasing length of hospital stay.

Improving perioperative care: enhanced recovery after surgery

At the end of the last millennium, a group of surgeons from Northern Europe formed the enhanced recovery after surgery (ERAS®) research group to optimise and standardise the ultimate care pathway for patients undergoing colonic resections [1], in order to enable rapid recovery of physical performance status by attenuating the stress response to surgery, by optimal control of pain, and by early oral diet and early mobilization (see Fig. 1) [2,3]. This might be particularly of importance for older and/or less physically fit patients. In several trials it was shown that the protocol could be implemented in a structured way, leading to a decreased length of hospital stay [2,4,5]. This formed the basis of the creation of the ERAS® Society, which was officially registered in Sweden in 2010 (www.erassociety.org) [1]. Although the group primarily focussed on colorectal surgery, the ERAS® principals were then applied in other major surgical procedures, including the field of HPB surgery, upper gastrointestinal surgery, urology, and gynaecology.

Enhanced recovery after surgery in hepatopancreatobiliary surgery

Surgery, with or without (neo)adjuvant chemotherapy, is currently the only treatment that can potentially offer cure for pancreatic cancer, cholangiocarcinoma, vast majorities of colorectal cancer metastatic to the liver, and most cases of hepatocellular carcinoma. However, HPB surgery is an invasive treatment and perioperative morbidity is high, especially for large and complex pancreatic and hepatic procedures. A recent study in patients registered in the obligatory national Dutch audit reported that 43% of the patients had a complicated postoperative course after major liver resection (≥3 segments) and 26% after minor liver resection (<3 segments) performed for colorectal liver metastasis [6]. Additionally, the Dutch Institute for Clinical Auditing (DICA) reported that between 2014 and 2018, 29% of the patients who underwent a pancreatoduodenectomy in the Netherlands developed a major complication (Clavien-Dindo grade ≥3) [7].

Several studies showed that enhanced recovery projects are also feasible for both pancreatic and liver resections [8–10]. In 2012, the ERAS® Society guideline for enhanced recovery after pancreatoduodenectomy was published, in which recommendations for optimal perioperative care after pancreatoduodenectomy were provided [3]. Several studies have shown that this protocol was feasible and safe [11,12]. This guideline was recently revised and it was found that an ERAS protocol for pancreatic surgery was associated with a reduction in postoperative complications and length of hospital stay (to be published by the ERAS® Society). The highest level of evidence was available for several items including avoiding hypothermia and the use of wound catheters as an alternative to epidural analgesia. Also for liver surgery, a separate ERAS® programme was developed and published in 2016, as liver surgery differs from colorectal surgery in terms of underlying disease (such as cirrhosis), comorbidities, and (organ specific) complications [13].

Although ERAS® programmes have been developed for both pancreatic and liver resections, a Cochrane review published in 2016 concluded that although these programs may reduce length of hospital stay and costs, the quality of the studies published on this topic was low and new randomized controlled studies with low risk of bias are necessary to provide evidence for the effectiveness of ERAS® in pancreatic and liver surgery [14].

Major surgery in older patients

Life expectancy continues to increase, and the proportion of elderly in the population expands rapidly. Where increased age itself in the past used to be a drawback for major surgical procedures, the number of surgical procedures performed in older patients increases nowadays. In several studies it has been shown that pancreatic and liver resections can be safely performed in selected elderly [15,16]. At present, age as such is therefore not considered as a selection criterion to undergo major surgery, but comorbidity status and preoperative physical performance status are. Compared with younger patients, older patients have a higher risk of morbidity and mortality after HPB surgery [16–18]. This is related to the age-dependent decrease in physiological reserves in combination with a more frequent occurrence of comorbidity (*e.g.*, decreased kidney and liver functioning, diabetes, cardiorespiratory disease, dementia) [16–18] and polypharmacy. Risks further increase when a patient suffers from sarcopenia or cancer cachexia. Most patients will probably benefit from ERAS® programmes; however, unfit and/or older patients will benefit even more from a thorough preparation prior to major surgery. In many of the abovementioned programs, the main focus for intervention was postoperatively. It is however essential to understand the physiological aspects (stress response) coinciding with major surgery to fully optimise the treatment for unfit elderly HPB surgical patients preoperatively as well.

Surgical stress response

Surgical trauma causes physiological changes at all levels of metabolism. These include hormonal, haematological, metabolic, and immunological changes. The magnitude of this metabolic activation is in theory proportional to the extent of the surgical procedure. This also depends on the patient's ability to adapt to these changes in order to cope with the surgical stress response while maintaining homeostasis. It is important to recognize that the metabolic response after a surgical trauma, and after any other trauma, is necessary to successfully overcome this trauma. The surgical stress response clinically manifests itself by salt and water retention to maintain plasma volume [19,20], an increase in cardiac output and oxygen delivery [21–23] to guarantee the systemic supply of nutrient-rich and oxygen-rich blood to meet the increased metabolic demand, mobilization of energy reserves from glycogen, adipocytes, and lean body mass for adequate continuous resynthesis of adenosine triphosphate, tissue repair, and the synthesis of proteins involved in the immune response [19,20].

Briefly, the activation of the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary axis rises circulating glucocorticoids, glucagon, and catecholamines [23]. Stimulation of the adrenal gland induces the release of cortisol, a glucocorticoid that has complex metabolic effects on proteins, carbohydrates, and lipids [24]. Increased cortisol and cytokine concentrations lead to protein catabolism in order to release essential amino acids for the synthesis of acute phase reactants and gluconeogenesis in the liver [23]. This elevation in protein turnover (protein degradation and protein synthesis) results in a loss of lean body mass up to 0.5 kg/day, depending on the invasiveness and extent of the surgical procedure and preoperative nutritional status of the patient [25]. In addition, cortisol also stimulates lipolysis, promotes glycogenolysis in the liver, and inhibits the use of glucose by cells [26]. This mobilization of energy reserves, in combination with a reduced insulin secretion, increased insulin resistance, and a brief increase in glucagon levels, leads to an increase in blood glucose levels that induces hyperglycaemia.

To successfully overcome the surgical stress response, a patient needs to be physically fit for surgery. Adequate preoperative aerobic fitness is required to guarantee oxygen delivery and oxygen utilization to cope with the increased metabolic demand. Moreover, adequate preoperative energy reserves (*e.g.*, muscle mass) are required to support the mobilization of reserves induced by the surgical stress. Hence, (elderly) patients with a low aerobic fitness and/or with low energy reserves, including malnourished, sarcopenic, and/or cachectic patients, are vulnerable because of a reduced capacity to meet the increased demands following major surgery. Nonetheless, an unfit older patient can theoretically be prepared for major elective surgery by preoperatively optimizing the patient's performance status in order to increase the adaptive capacity to the surgical stress response.

A variable fraction of older patients shows a decline in performance status preoperatively [27,28], which might be related to the underlying pathophysiology and a general "*sit, wait, and see*" approach of the patients themselves, their informal support system, and healthcare professionals [29]. In addition to aerobic fitness, it is important to preoperatively gain insight into the general muscle strength of a patient as an indicator of lean body mass (muscle mass), as well as into the functional mobility of a patient. An adequate preoperative lean body mass is important in order to have sufficient spare capacity for the protein catabolism induced by the surgical stress response. A significant proportion of patients who have undergone major surgery have not returned to preoperative muscle strength and ability to perform activities in daily life six months postoperatively [30]. To stimulate the postoperative recovery of physical performance status, as well as to prevent the loss of muscle mass and muscle strength, a patient needs to mobilize sufficiently postoperatively, practice daily transfers, and be physically active. For this, a patient must also have sufficient functional mobility (*e.g.*, muscle strength, balance, and coordination) prior to surgery. Additionally, preoperative data on muscle strength and functional mobility offer reference points for monitoring recovery of physical performance status postoperatively.

Increased metabolic demands: a rational for exercise prehabilitation

The clinical consequence of the surgical stress response that is relevant in relation to a patient's aerobic fitness is the significantly increased metabolic demand (energy expenditure) postoperatively compared to preoperative values. By determining arterial and mixed venous blood gases, Older and Smith [31] reported that oxygen consumption rose from a mean of 121 mL/min/m^2 preoperatively to 174 mL/min/m^2 postoperatively, an average increase of 44%. To meet the increased oxygen demand, oxygen transport capacity (*e.g.*, depending on ventilation-perfusion matching, haemoglobin content, cardiac output) and oxygen utilization capacity of tissues (*e.g.*, depending on myoglobin content, mitochondrial function, oxidative enzyme activity) are essential. Oxygen transport and utilization capacity is also referred to as aerobic fitness. There is an age-related decline in aerobic fitness, in which the longitudinal rate of decline in aerobic fitness in healthy adults seems not constant across the age span in healthy persons, but accelerates markedly with each successive age decade, especially in men, regardless of physical activity habits [32–34]. More specifically, the rate of decline in aerobic fitness seems to accelerate from 3% to 6% per decade in adults between 20 and 40 years to >20% per decade in adults >70 years [33].

Patients with a low preoperative aerobic fitness, often elderly and comorbid patients, are vulnerable due to a reduced ability to meet the increased oxygen demand during and after surgery. Obviously, the extent of the increase in metabolic requirement depends on the extent of the surgical trauma, and a complication itself also causes a further increase in the metabolic demands of the body. This underlines the importance for patients of being as physically fit as possible, so that they can meet the increased metabolic requirements. Several studies have demonstrated that preoperative aerobic fitness in patients undergoing HPB surgery is an independent predictor of the risk of postoperative complications, time to recovery of physical performance status, length of hospital stay, and mortality; the more aerobically fit for surgery, the lower the risks [35–42]. Furthermore, aerobic fitness might be reduced postoperatively due to a reduced intravascular circulating volume and anaesthesiologic interventions. Next to blood loss, extracellular fluid evaporates from the wound area, and some intravascular fluid shifts to the extravascular space due to the surgical trauma [43,44]. With extensive trauma, this leads to a decrease in circulating intravascular volume, which decreases stroke volume by a reduced venous return and preload. The body responds to this situation by reducing renal excretion of water and salt due to an increased secretion of aldosterone and vasopressin [26], as well as by tachycardia as an indicator of hypovolemia. Besides, general anaesthesia during surgery affects respiratory function (*e.g.*, gas exchange impairment, deteriorated cilia and cough reflex) [45]. Postoperative medication and sedatives might cause respiratory depression, whereas postoperative pain might cause hypoventilation (rapid shallow breathing pattern) [45]. These factors might contribute to a decreased aerobic fitness postoperatively. Patients with a low preoperative aerobic fitness might therefore have insufficient aerobic reserve capacity postoperatively, which puts them at risk of tissue hypoxia and complications, thereby putting further demands on the body (see Fig. 2). This underlines the importance of formal preoperative risk stratification for adverse postoperative outcomes in individual patients (*e.g.*, complications, delayed recovery or permanent loss of physical performance) by assessing their preoperative aerobic fitness. Unfit (older) patients will benefit the most from exercise prehabilitation [46].

Preoperative risk assessment: determining aerobic fitness

The gold standard for the objective measurement of aerobic fitness is the cardiopulmonary exercise test (CPET), in which the exercise intensity, and therefore the metabolic demand, progressively increases until the patient can no longer maintain the required exercise intensity. During the CPET, continuous respiratory gas analysis measurements are performed to measure the body's oxygen uptake and carbon dioxide production, as well as heart rate and rhythm using an electrocardiogram, blood pressure, and peripherally measured oxygen saturation. For adequate preoperative risk stratification, the CPET is a suitable test for which consistent evidence-based cut-off points for preoperative aerobic fitness are available in the literature [41,42].

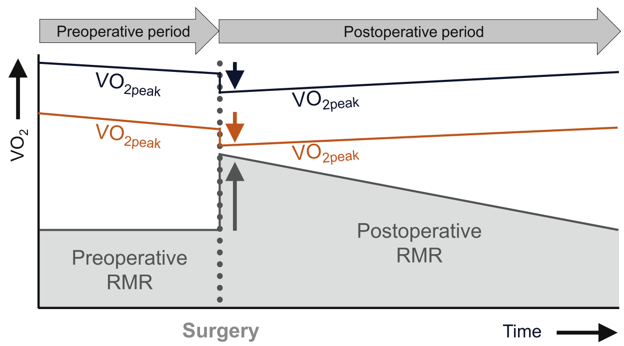

Fig. 2. Hypothesis of a rational for exercise prehabilitation. The surgical stress response, which is dependent on the extent of the surgical procedure, induces a significantly increased metabolic demand (RMR, expressed as VO_2) postoperatively, while aerobic fitness (expressed as VO_{2peak}) might be reduced due to a reduced intravascular circulating volume and by anaesthesiologic causes. Patients with a low preoperative aerobic fitness (orange line) might have insufficient aerobic reserve capacity puting them at risk of tissue hypoxia and complications. Abbreviations: RMR = resting metabolic rate; VO_2 = oxygen uptake; VO_{2peak} = peak oxygen uptake (aerobic fitness).

The CPET is the gold standard test to determine a patient's aerobic fitness by measuring the body's oxygen uptake (VO_2) at peak exercise during a valid maximal effort (VO_{2peak}), whereas the VO_2 at the ventilatory anaerobic threshold and oxygen uptake efficiency slope serve as submaximal indicators of aerobic fitness [42,47,48]. When a patient is unable or unwilling to perform a valid maximal effort, these submaximal measures of aerobic fitness are valuable for preoperative risk assessment. The VO_2 at the ventilatory anaerobic threshold represents the submaximal point at which the energy needed for the required exercise intensity can no longer be entirely provided by the aerobic metabolism. It indicates a shift to anaerobic glycolysis as additional source of energy production in order to meet the metabolic demand. In general, patients undergoing major abdominal surgery with a VO_2 at the ventilatory anaerobic threshold $\leq$11 mL/kg/min or a $VO_{2peak} \leq$ 18 mL/kg/min are considered as patients with an increased risk of postoperative complications [41,42]. In these high-risk patients, preoperative optimisation of aerobic fitness by a prehabilitation programme is recommended. The preoperative CPET also provides valuable information to determine physical exercise training safety (*e.g.*, contraindications), by assessing the body's integrated physiological response to progressive metabolic demands, and to optimise and personalize training intensity.

When performing a preoperative CPET is not possible, more practical performance-based field tests to estimate a patient's preoperative aerobic fitness might be useful for risk assessment. Better performance at the steep ramp test, a short time maximal exercise test on a cycle ergometer, has been found to be associated with more favourable postoperative outcomes and may be valuable in outcome prediction in patients undergoing HPB surgery [49,50]. Moreover, an increased distance walked at the 6-min walk test was related to a reduced risk of major postoperative complications in surgery for HPB malignancies; patients that walked <400 m had a considerably higher Clavien-Dindo grade than patients who walked $\geq$400 m [51]. Although maximal field tests (*e.g.*, steep ramp test, incremental shuttle walk test) appear to be prognostically superior to submaximal field tests in patients undergoing major abdominal surgery (*e.g.*, 6-min walk test, stair-climb test), further validation is required [52]. Moreover, optimal field test-specific cut-off values to discriminate between patients with and without adverse postoperative outcomes (*e.g.*, complications, prolonged time to recovery of physical performance status and length of hospital stay, mortality) should be developed.

Multidisciplinary preoperative risk assessment in older patients undergoing hepatopancreatobiliary surgery

The main goal of prehabilitation is to preoperatively improve the physical, nutritional, and psychological aspects of a patient's health, which requires a multidisciplinary team that is able to interact together to personalize prehabilitation [53]. When a patient, well informed by the multidisciplinary team, decides to opt for surgery, a preoperative risk assessment in multiple domains should therefore be performed as early as possible to reflect on its prognostic implications in the decision for surgery. Hereby, sufficient time remains to identify, discuss, and reduce risks for optimal patient- and treatment-related outcomes, or to consider alternative treatment options. Besides evaluating physical fitness (*e.g.*, aerobic fitness, muscle strength, and functional mobility), also other potential patient-related risk factors should consequently be assessed (see Fig. 3).

Aging is characterized by the progressive loss of skeletal muscle mass and strength, a phenomenon called sarcopenia [54]. Unfit, sarcopenic, and/or malnourished surgical patients have a diminished capacity to cope with the surgical stress response, which increases the risk of postoperative complications and mortality [55,56]. Additionally, patients undergoing HPB surgery are at a particular risk of cancer cachexia, since most major surgical procedures are performed for malignancies. Cancer cachexia is a multifactorial syndrome characterised by persistent skeletal muscle atrophy (with or without atrophy of adipose tissue) that cannot be fully reversed by conventional nutritional support [57]. Besides loss of body mass, sarcopenia, and a low body mass index, the syndrome of cancer cachexia can include many more pathophysiological drivers (*e.g.*, inflammation, altered protein metabolism, anorexia, malabsorption) [57,58]. It is well accepted that cachexia is indirectly responsible for the death of over 20% of all patients with cancer [59]. In patients with gastric or pancreatic cancer, the incidence of cachexia is more than 80% [60]. Body composition assessment, measured using routinely performed abdominal computed tomography (CT scan), demonstrated that both sarcopenia [61–63] and myosteatosis [64] contribute to poor postoperative outcomes following major abdominal surgery. As a recent study found that myosteatosis, and not sarcopenia, was associated with reduced aerobic fitness, combining preoperative body composition and aerobic fitness variables may provide additive risk assessment accuracy and guide interventions during the perioperative period in patients undergoing HPB surgery [65].

Malnutrition has been reported to be associated with an increased risk of postoperative complications, prolonged hospitalization, readmissions, delayed recovery of physical performance status, and poorer quality of life [66]. Preoperative nutritional assessment should therefore be performed, for example by using the patient-generated subjective global assessment that includes the evaluation of (short-term) weight loss, dietary intake change, gastrointestinal symptoms persisting for more than two weeks, and changes in functional capacity, as well as a physical examination (*e.g.*, loss of subcutaneous fat, muscle wasting) [67]. Outcomes of a nutritional assessment deliver input for personalised nutritional prehabilitation to provide an adequate reserve capacity to compensate for protein catabolism related to surgical stress.

Haemoglobin level is a primary determinant of oxygen transport capacity, which might consequently influence aerobic fitness (*e.g.*, VO_{2peak}, VO_2 at the ventilatory anaerobic threshold, oxygen uptake efficiency slope) and thus surgical outcomes. Although haemoglobin level was found to explain only a small proportion of variation in aerobic fitness in major non-cardiac surgery, both preoperative anaemia and a low aerobic fitness are reported to be associated with postoperative complications, and may therefore be modifiable

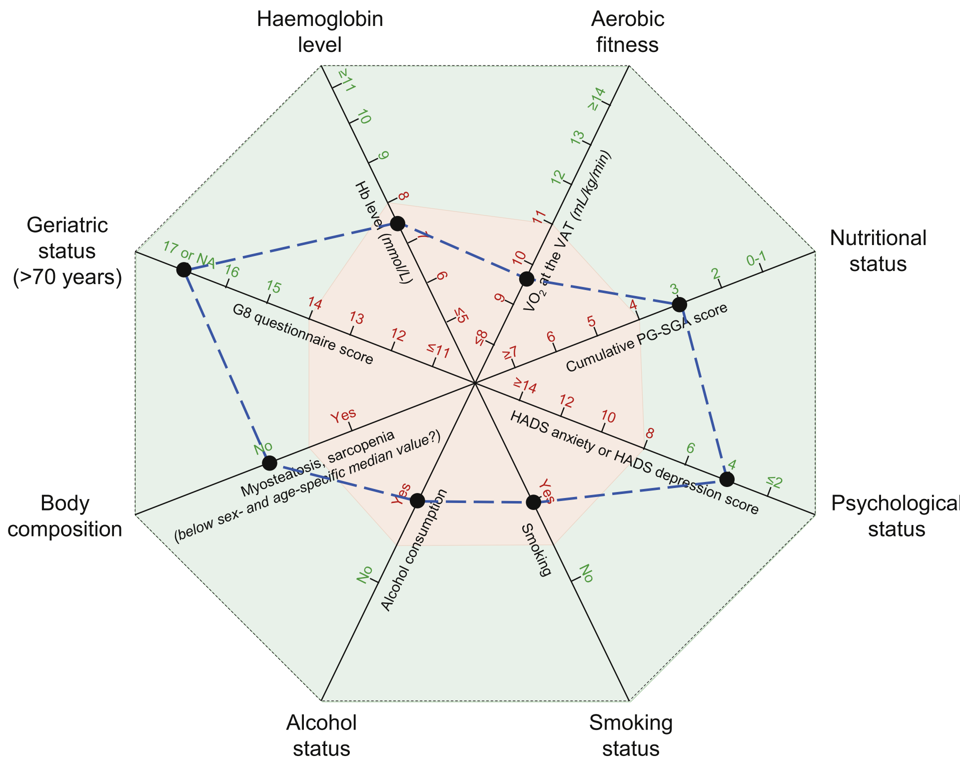

Fig. 3. An example of a comprehensive multidisciplinary preoperative risk assessment, of which the outcomes can subsequently be used to personalize prehabilitation. Abbreviations: G8 = geriatric 8; HADS = hospital anxiety and depression scale; Hb = haemoglobin; PG-SGA = patient-generated subjective global assessment; VAT = ventilatory anaerobic threshold; VO_2 = oxygen uptake.

targets for preoperative optimisation [68]. Furthermore, preoperative smoking cessation interventions, providing behavioural support and offering nicotine replacement therapy, may reduce postoperative complications [69]. Intensive preoperative alcohol cessation interventions, including pharmacological strategies for relapse prophylaxis and withdrawal symptoms, may significantly reduce postoperative complications as well [70]. Next to preparing physiologically for surgery, patients also need to be mentally fit. Preoperative anxiety, depression, and low self-efficacy are consistently associated with worse surgical outcomes and quality of life [71]. However, there is currently insufficient evidence to be sure that preoperative psychological interventions are of benefit, or which interventions are most effective [72].

Prehabilitation in hepatopancreatobiliary surgery: current evidence base

As ERAS® programmes aim to shorten the length of hospital stay next to reducing risks of postoperative complications, it is important that patients are able to function well physically, and be relatively self-sufficient, once discharged [66]. Postoperative complications are a main determinant of the time needed to return physical performance status to preoperative levels, as these have a significant impact on the patient's postoperative physical performance status, thereby also prolonging length of hospital stay and increasing readmissions. Prehabilitation aims to preoperatively improve the physical, nutritional, and psychological aspects of a patient's health in order to reduce the risk of postoperative complications and, consequently, to facilitate a swift recovery of physical performance status (see Fig. 4).

Currently available evidence consistently reports that exercise prehabilitation improves physical fitness before HPB surgery; however, there seems to be inconclusive and opposing evidence

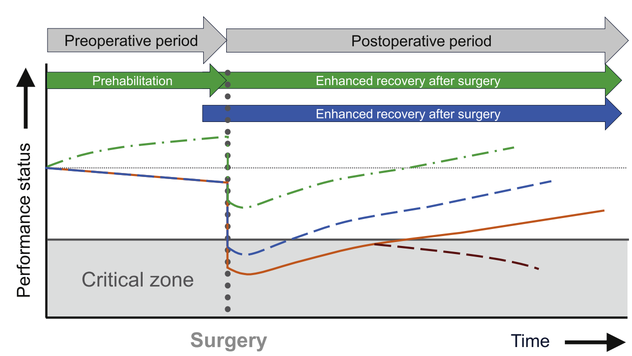

Fig. 4. Prehabilitation in unfit and/or older patients (green, dashed line) aims to preoperatively increase a patient's physical performance status, thereby increasing adaptive capacity to cope with the surgical stress response and reduce the risk of complications. Along with the ERAS® programme (blue, dashed line) that aims to minimize the surgical stress response, prehabilitation further improves short-term outcomes and facilitates a swift recovery of physical performance status.

concerning its effect on postoperative outcomes. A randomized controlled trial in patients undergoing hepatectomy for hepatocellular carcinoma demonstrated that four weeks of home-based prehabilitation, consisting of unsupervised aerobic and stretching exercises combined with nutritional support, did not lead to differences in any postoperative outcomes between the prehabilitation and usual care group [73]. Postoperative complications (9% versus 13%, respectively; $P = 0.671$) and length of hospital stay (mean ± SD of 13.7 ± 4.0 versus 17.5 ± 11.3 days, respectively; $P = 0.120$) did not differ statistically significant between the prehabilitation and usual care group [73]. The randomized controlled trial of Dunne et al. [28] showed that a four-week supervised hospital-based exercise prehabilitation programme (high-intensity interval training) improved aerobic fitness before liver resection in the prehabilitation group, while these values did not improve in the usual care group. However, there were no statistically significant differences between the prehabilitation and usual care group in postoperative complications (42% versus 47%, respectively) and length of hospital stay (median of 5 versus 5 days, respectively) [28]. Nakajima et al. [74] demonstrated that unsupervised home-based prehabilitation, consisting of aerobic and resistance exercises in combination with protein supplementation, was associated with improved functional exercise capacity and preservation of nutritional status prior to HPB surgery for malignancy. Overall postoperative complication rate did not differ between the prehabilitation and retrospectively matched usual care group, whereas postoperative length of hospital stay was shorter in the prehabilitation group (median value of 23 versus 30 days; $P = 0.045$) [74]. In a randomized controlled trial, Ausania et al. [75] investigated whether a prehabilitation strategy (median duration of 13 days) of physical and respiratory exercise training, nutritional support, and control of diabetes and exocrine pancreatic insufficiency could reduce postoperative complications compared to usual care following pancreaticoduodenectomy in patients with pancreatic or periampullary tumours. Physical and respiratory exercise training consisted of a five-day supervised high-intensity interval training programme at the hospital, where after patients performed unsupervised functional and breathing exercises at home. Although physical fitness improved in the prehabilitation group, overall postoperative complication rate (33.3% versus 54.5%, respectively; $P = 0.180$) and length of hospital stay (median of 13.2 versus 11.4 days, respectively; $P = 0.449$) did not significantly differ between the prehabilitation and usual care group [75].

While the abovementioned studies provide inconclusive evidence for its postoperative effectiveness, it seems that prehabilitation does improve postoperative outcomes when specifically focused at patients with an increased risk of adverse postoperative outcomes. In a randomized controlled trial in high-risk patients undergoing elective major abdominal surgery, a combination of home-based (unsupervised functional exercise training) and hospital-based (supervised high-intensity interval training) prehabilitation with a mean duration of 6 weeks was found to improve preoperative aerobic fitness, as well as to be a protective factor of postoperative complications, with a 51% reduction in the number of patients with postoperative complications (31% versus 62%; $P = 0.001$) [76]. Postoperative length of hospital stay tended to be shorter in the prehabilitation group compared to the usual care group (mean $\pm$ SD of 8 ± 8 versus 13 ± 20 days; $P = 0.078$) [76]. Likewise, the case study of van Beijsterveld et al. [77] reported that four weeks of supervised community-based prehabilitation (aerobic, resistance, and functional exercises) in a high-risk 75-year-old patient opting for pylorus-preserving pancreaticoduodenectomy improved preoperative physical fitness and resulted in an uncomplicated postoperative course. The preoperative period thus provides a window of opportunity for older patients undergoing elective HPB surgery, especially for those classified as high-risk patients, to decrease the risk of adverse postoperative outcomes by optimizing reserve capacity before surgery.

Lessons learned: future challenges for further optimizing perioperative care

A decade after the establishment of the ERAS® Society, there is an increasing interest in multidisciplinary preoperative risk mitigation, to which relatively little attention has been paid in traditional ERAS® guidelines. The increasing life expectancy, together with anaesthesiologic and surgical improvements, requires proactive, preventive perioperative innovations to support shared decision-making and to ensure best perioperative care for optimal patient- and treatment-related outcomes. Physical exercise training is a fundamental part of prehabilitation, as a low preoperative physical fitness, specifically a low aerobic fitness, has consistently been reported to be independently associated with a higher risk of adverse postoperative outcomes following HPB surgery [35–42]. Although there is accumulating evidence about the effectiveness of exercise prehabilitation to improve preoperative physical fitness [78–80], there seems to be inadequate and opposing evidence concerning its effect on postoperative outcomes.

Most published studies evaluating the effectiveness of prehabilitation in major abdominal surgery included a high proportion of relatively fit, low risk patients [79]. Comprehensive multidisciplinary preoperative risk assessment is important to identify patients with a higher risk of postoperative complications, prolonged time to recovery of physical performance status and length of hospital stay, and mortality. Hence, it may identify patient needs in terms of counselling, physical exercise training, nutritional support, psychological support, and smoking cessation, with tailored prehabilitation and personalised and patient-centred care as a result [81]. Indeed, multimodal preoperative interventions should be tailored to these high-risk patients, as they will benefit the most from prehabilitation [46,79,82]. Importantly, high-risk patients should be persuaded to participate in preoperative preventive interventions by ensuring that preoperative risk assessment is used for shared decision-making, which, together with prehabilitation, is highly recommended to be integrated in usual perioperative care. When the surgeon, anaesthesiologist, and other involved healthcare professionals consistently suggest participation in the program, a patient might be more motivated to comply [83], thereby increasing the participation rate.

To further maximize participation rate, adherence, and effectiveness in high-risk patients, a prehabilitation programme must be performed in the patient's pre-existent living context in which the patient's informal support system should be involved [29]. The most reported barrier to participate in a prehabilitation programme was related to transportation (*e.g.*, paying for parking, arranging transportation), besides finding the time [84]. In major abdominal surgery, high-risk patients, who are often older and frailer, are less likely to participate in a hospital-based physical exercise program, than in a home-based physical exercise programme [46,84–86]. Though, there are only a few studies available that included home-based prehabilitation prior to HPB surgery [73–75]. These currently described home-based prehabilitation programs were not supervised and not specifically targeted at high-risk patients, probably limiting therapy adherence and effectiveness respectively. Community-based perioperative care networks should be established, in which trained and competent therapists, along with the patient and the patient's informal support system, aim to make a patient fit for surgery. When patients participate in lifestyle interventions in their own environment, a setting to which they return after hospital discharge, it makes it more likely that patients will continue these interventions soon after surgery.

For the physical exercise training component of prehabilitation, high-intensity interval training seems an effective method to preoperatively improve aerobic fitness [28,87], as the period before HPB surgery is often short. Sufficient progress in aerobic fitness should be the main outcome parameter. Frequent objective monitoring of training progress is therefore important, but this has not been reported in currently published studies that evaluated the effects of preoperative physical exercise training [79]. Monitoring of training progress is important to motivate responders, to timely identify non-responders, and to subsequently make necessary programme adjustments concerning training frequency, intensity, and duration.

Most studies in major abdominal surgery used the incidence of postoperative complications as primary outcome for the effectiveness of prehabilitation, without taking the variability in a patient's ability to cope with these postoperative complications into account [79]. Being fit for surgery might not always prevent postoperative complications; however, the impact of any given postoperative complication may be reduced in patients with a higher preoperative physical fitness. A small study in patients undergoing pancreatic resection demonstrated that those who were younger and those with a higher preoperative physical fitness were more likely to better cope with a major postoperative complication [49]. Investing in adequate prehabilitation programs therefore seems an effective way to improve surgical outcomes by reducing preoperative risks and, consequently, both the incidence and the impact of postoperative complications. Finally, future studies evaluating the effectiveness of prehabilitation should include (long-term) patient-centred outcome measures, such as time to recovery of physical performance status and return to normal activities and participation.

Conclusion

Next to continuing improvements in surgery and anaesthesiology, ERAS® programmes seem to improve outcomes in HPB surgery. Due to an ageing surgical population and the associated perioperative risks however, there is an increasing interest in prehabilitation programmes, consisting of additional preoperative interventions, to further reduce the risk of postoperative complications, to facilitate a swift postoperative recovery of physical performance status, and to ensure return to normal activities and participation. Hereto, multidisciplinary preoperative risk assessment in multiple domains should be performed to identify, discuss, and reduce risks for optimal outcomes, or to consider alternative treatment options. Based on current knowledge, prehabilitation should focus on including high-risk patients based on evidence-based cut-off values and should aim for (partly) supervised prehabilitation tailored to the individual patient's risk factors. The program should be executed in the living context of these high-risk patients to improve the participation rate and adherence, as well as to involve the patient's informal support system. Developing tailored (multimodal) prehabilitation programmes for the right patients, in the right context, and using the right outcome measures is important to demonstrate its potential to further improve patient- and treatment-related outcomes.

Declaration of competing interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Bart C. Bongers: Conceptualization, Visualization, Writing - original draft, Writing - review & editing. **Cornelis H.C. Dejong:** Writing - review & editing, Supervision. **Marcel den Dulk:** Conceptualization, Writing - original draft, Writing - review & editing.

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