Prehabilitation programs in liver resection: a narrative review

En Qi Toh[1]^, Hoi Pong Nicholas Wong[1]^, Jia Dong James Wang[1], Matthias Yi Quan Liau[1]^, Yi Fang Tan[2], Vishalkumar Girishchandra Shelat[3,4]^

[1]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; [2]Department of Physiotherapy, Tan Tock Seng Hospital, Singapore, Singapore; [3]Department of General Surgery, Tan Tock Seng Hospital, Singapore, Singapore; [4]Surgical Science Training Centre, Tan Tock Seng Hospital, Singapore, Singapore

Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Vishalkumar Girishchandra Shelat, MBBS, MS, DNB, MMed, FRCSEd, FAMS, MRCPS, FICS, FAIS, MNAMS, FIMSA, MCI, Hesperis diploma in Organ Transplantation (ECOT). Department of General Surgery, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore; Surgical Science Training Centre, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore, Singapore. Email: vgshelat@gmail.com.

Background and Objective: Liver resection (LR) is a commonly performed surgical procedure for the management of hepatocellular carcinoma and other liver conditions. Despite its benefits in providing patients a potential cure, it is also associated with significant postoperative complications and prolonged recovery periods. In recent years, pre-operative rehabilitation (prehabilitation) has emerged as an up-and-coming strategy to optimize patients' physical, psychological and functional status before LR, leading to improved surgical and patient postoperative outcomes. Hence, our review aims to explore and synthesize the existing literature on prehabilitation in LR to provide an overview of the current evidence to help guide physicians in managing their patients.

Methods: A comprehensive literature search was conducted in multiple electronic databases from inception to July 2023. The search strategy was tailored to capture studies investigating the role of prehabilitation in LR, and the factors that contribute to beneficial outcomes in the postoperative period.

Key Content and Findings: Prehabilitation programs encompass a multifaceted approach to enhance surgical outcomes and patient well-being. This considers the specific needs of the varying patient populations, such as the elderly, or the cancer ridden. Improving physical fitness, nutritional supplementation and psychological support are the common tenets of prehabilitation. In physical prehabilitation, patients are engaged in intensive physical exercise often by means of a cycle ergometer. Addressing nutritional deficiencies through supplements and dietary interventions is also vital. Psychosocial assessments, advance care planning, music therapy, and progressive relaxation exercises are shown to enhance patient resilience and well-being. In addition, innovative approaches such as optimizing fluid balance, avoiding epidural analgesia, perioperative steroid administration, phosphate correction and branched-chain amino acid supplementation are being explored.

Conclusions: Prehabilitation is important in optimizing patients before LR and is key in improving postoperative outcomes. Several prehabilitation strategies exist, but no formal consensus exists on patient selection and an ideal program.

Keywords: Prehabilitation; liver resection (LR); physical exercise; nutritional supplementation; psychological support

^ ORCID: En Qi Toh, 0000-0002-8469-936X; Hoi Pong Nicholas Wong, 0000-0003-1815-1352; Matthias Yi Quan Liau, 0009-0007-0623-2477; Vishalkumar Girishchandra Shelat, 0000-0003-3988-8142.

Submitted Sep 16, 2023. Accepted for publication Jan 12, 2024. Published online Feb 01, 2024.
doi: 10.21037/cco-23-102
View this article at: https://dx.doi.org/10.21037/cco-23-102

Introduction

Liver resection (LR) is the treatment of choice for patients with resectable hepatocellular carcinoma (HCC), owing to a shortage of livers for transplantation (1). With improvements in perioperative medicine, critical care, and technological innovation, LR is becoming a safe procedure with lower mortality risk, albeit with a high morbidity rate. A study of 245 patients who underwent LR reported 38.3% morbidity and 3.7% 90-day mortality. The high postoperative morbidity can result in prolonged hospitalization, high readmission rates, and increased cost of care, negatively impacting physical function and quality of life (QoL) (2). Therefore, interventions are needed to improve the postoperative outcomes of LR further. Prehabilitation has become prominent in recent years, involving multidisciplinary collaboration to preoperatively optimize a patient's physical, nutritional, and psychological aspects (3). This has been shown to bring significant benefits to postoperative outcomes, including reduced postoperative morbidity, better QoL, shorter length of stay (LOS), and reduced healthcare costs (2,4). As such, this review aims to explore and synthesize existing literature on prehabilitation in LR and its impact on post-operative outcomes. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-102/rc).

Methods

A comprehensive literature search was done on PubMed, Scopus, Web of Science, Embase, and CENTRAL from inception to July 2023 using the following keywords: "liver resection", "hepatectomy", "liver surgery", "prehabilitation", "preoperative exercise", "preoperative conditioning", "preoperative rehabilitation", "nutrition", "diet", "relaxation" and "psychotherapy". Information from relevant articles on the indications for LR, enhanced recovery after surgery (ERAS) guidelines, components of prehabilitation programs (PPs), and patient factors are extracted, with the aim to synthesize existing literature on prehabilitation in LR, focusing on the factors that affect postoperative outcomes and how the components of PPs can aid in improving morbidity and mortality. We also present novel components of PPs such as branched-chain amino acids (BCAA) supplementation and intraoperative blood cell salvage and autotransfusion (IBSA) that are currently being trialed. *Table 1* summarizes the search strategy used in this review.

Indications for LR

Hepatic resections are performed for myriad indications, including benign liver diseases, primary liver malignancies, and liver metastases (5). HCC is a common indication of LR, and the incidence of HCC is expected to increase with diabetes, obesity, and aging. Further, with hepatitis B screening initiatives and imaging advances, early diagnosis is possible with a corresponding increase in patients amenable to LR (4). The use of systemic therapy also improves the resectability of initially unresectable tumors (6). Without sufficient donor livers for a liver transplant, LR remains the first-line curative option (7). Donor hepatectomy is a common undertaking and donor patients are healthy individuals with normal nutritional status (8).

Factors contributing to postoperative morbidity

Treatment factors

LR is more complex than other abdominal operations, with inherent intraoperative risks of bleeding and intraoperative fluid shifts. Postoperative complications include pleuro-pulmonary complications, biliary leak, post hepatectomy liver failure (PHLF), acute renal failure (ARF), and death (9). Low central venous pressure and hepatic inflow occlusions (Pringle's maneuver) can induce an inflammatory response with cytokine and free radical release that causes ischemia-reperfusion injury and contributes to higher perioperative morbidity (10).

Disease factors

The most common indications for hepatic resection are HCC and liver metastases, commonly on a background of chronic liver disease, including cirrhosis. These patients are more prone to cachexia, frailty, malnutrition, reduced effort tolerance, and sarcopenia (11,12). These deficits contribute

Table 1 Summary of search strategy

Items	Specification
Date of search	31 July 2023
Databases and other sources searched	PubMed, Scopus, Web of Science, Embase and CENTRAL
Search terms used	"liver resection"; "hepatectomy"; "liver surgery"; "prehabilitation"; "preoperative exercise"; "preoperative conditioning"; "preoperative rehabilitation"; "nutrition"; "diet"; "relaxation"; "psychotherapy"
Timeframe	Inception of database to July 2023
Inclusion criteria	All article types relevant to prehabilitation programs in liver resection were included
Selection process	The search and selection of articles were conducted by primary authors E.Q.T., H.P.N.W., J.D.J.W. and M.Y.Q.L. These were then reviewed by senior authors Y.F.T. and V.G.S.

to postoperative morbidity, mortality, and impact long-term survival outcomes. Taura *et al.* reported a post-LR 5-year survival rate of 81%, 54%, and 28% in non-cirrhotic, Child-Pugh Class A and Child-Pugh Class B cirrhotics, respectively (11). In addition to above factors, recurrence or metachronous HCC also contributes to a lower long-term survival rate (13).

In malignant conditions, macrovascular invasion (5) is associated with a 5-fold risk for 1-year mortality due to a high recurrence rate. In the same study, 85% of patients who developed ARF passed on, prompting exploration of earlier renal interventions for higher-risk patients (13). The predictive factors for 90-day mortality post-LR include Child-Pugh Class B or C, volume of intraoperative blood loss, PHLF according to the 50–50 criteria, and peak serum bilirubin of more than 119 μmol/L (14). Independent of LR, factors related to the underlying disease are also associated with 1-year mortality in HCC patients undergoing curative LR. These are Child-Pugh Class B or C, multinodularity, macrovascular invasion, ARF, and International Study Group of Liver Surgery PHLF criteria (13). Prehabilitation may thus improve the outlook for these patients.

Furthermore, excess intra-hepatic fat (IHF), termed hepatic steatosis (HS), occurs in up to 40% of LR patients. Etiologies include non-alcoholic fatty liver disease (NAFLD), competing causes of HS such as chemotherapy, and other causes of chronic liver disease. Raised IHF is linked to a higher frequency of more severe postoperative complications, including organ failure and sepsis. IHF above 10% is associated with significantly longer intensive care unit and hospital stays (15). Patients with multiple co-morbidities and poor functional reserves cannot withstand the surgical stress response (16), causing higher postoperative morbidity.

Existing measures to improve postoperative mortality and morbidity

There are various measures in place to improve post-operative outcomes. These encompass standardization of care provision to reduce variation, centralization of services to ensure sufficient case volume of individual units, and cautious adoption of technological advances with opportunities to improve technical skills by peer mentoring. Proper case selection, multidisciplinary team-led decision-making, benchmarking of outcomes with centers of excellence, and regular audits focusing on improved key performance indicators are integral pillars of care provision that assure good clinical outcomes. This section will discuss the core issues of ERAS and prehabilitation initiatives.

ERAS

ERAS is a multimodal, evidence-based program of care employing a multidisciplinary approach to minimize the response to surgical stress. It has been implemented in major surgery domains, including colorectal, pancreatic, and liver surgery, and is associated with improved postoperative outcomes and shorter LOS (4,17). Key principles of ERAS include preoperative counselling, preoperative nutrition, avoidance of perioperative fasting and carbohydrate loading up to 2 hours preoperatively, standardized anesthetic and analgesic regiments, and early mobilization (18). Improved rates of postoperative mobilization in elective major hepatopancreatobiliary (HPB) surgery have been shown to improve clinical outcomes with potential economic gains (19).

In general, prehabilitation complements the preoperative aspect of ERAS. ERAS programs emphasize intraoperative and postoperative care standardization with minimal guidance on the preoperative phase. Therefore, prehabilitation provides a more comprehensive preoperative strategy (4).

Prehabilitation

With aging populations, technological advances, and improved critical care strategies, more high-risk patients are eligible for surgical therapy. The increasing number of older adults undergoing surgery poses great healthcare challenges as they have multiple co-morbidities and greater functional decline. Thus, initiating rehabilitation pre-operatively to optimize their functional reserves is vital.

The socio-cultural shift of recovering at home rather than in the hospital has fueled the concept of prehabilitation, where patients are made stronger before surgery to withstand surgical stress better. "Prehabilitation" is an intervention administered before an operation, designed to prepare the patient for the cardiovascular, pulmonary, and metabolic demands of undergoing major abdominal surgery and to minimize impairment from underlying comorbidities (3). It aims to optimize a patient's health and fitness to facilitate faster postoperative recovery. Most studies over the past decade have focused on exercise and physical conditioning. Recently, there has been increasing interest in comprehensive "trimodal" prehabilitation, which involves physical fitness, nutrition, and emotional readiness. Other multimodal regimens may include medical risk factor optimization or geriatric assessment and intervention (3).

The success of PPs is multifaceted, with outcomes involving mortality, morbidity, resources, and efficacy (4). In a study by Strijker *et al.*, postoperative complication rates were significantly lower in patients who underwent prehabilitation at 37.5% than the control group at 70.2% (20). However, the specific benefits of prehabilitation vary between patients due to inter-individual variation. Therefore, individualized PPs are also of growing interest (3).

PPs now involve multidisciplinary teams, combining nutritional, psychological, and behavioral interventions with exercise. In addition, PP models vary across places of practice (3), which also impacts the effectiveness of programs across studies.

Patient factors

Geriatric population

Geriatric patients undergoing LR are more susceptible to postoperative complications and mortality. A study by Hao *et al.* on patients 55–73 years old reported complications and mortality of 23.9% and 4.8%, respectively, even with minor LR (3). This is due to the association of increasing age with higher rates of comorbidities, including cardiovascular, respiratory and endocrine diseases, making elderly patients poor surgical candidates (3). Older adults with frailty are also more vulnerable to cognitive, physical, and psychosocial problems, and thus postoperative complications and reduced survival (4). Even if they do not meet the frailty criteria, they can rapidly deteriorate after a major LR when dealing with stressors due to lower physiological reserve, depending on premorbid function. Further, the ability to rescue, defined as the ability of the provider to prevent mortality after the development of morbidity, decreases by more than a third in older patients (3), making any complication more dangerous.

An older patient requiring LR is more likely to have complications related to the primary disease due to a longer duration for disease development. Primary HCC often arises on a background of cirrhosis, which increases mortality and morbidity of a surgery, depending on the extent of cirrhosis (11). The clinical success of a major LR relies on the ability of the remnant liver to hypertrophy, which is also limited greatly by the degree of HS and cirrhosis. Malnutrition and protein depletion often coincide with cirrhosis, and both predict PHLF, which has mortality rates above 90% even with the best possible care. Additionally, liver disease has implications of coagulopathy, poor nutritional status, adaptive immune dysfunction, cirrhotic cardiomyopathy, and renal and pulmonary dysfunction (21). Together with other multi-organ effects of cirrhosis, these contribute to higher rates of postoperative morbidity and mortality. Besides, patients with metastases to the liver may have gone through the debilitating effects and liver-specific toxicity of systemic chemotherapy before LR. The resulting sarcopenia is associated with a poor prognosis postoperatively with decreased recurrence-free survival (RFS) (3). Therefore, the underlying disease also puts elderly patients at higher risk post-LR.

These risks impact the postoperative outcomes of geriatric patients, including postoperative functional status. This includes the need for permanent or temporary devices such as drains or stomas and the ability to return home versus the need for rehabilitative or skilled nursing stay (3). PPs may thus improve their postoperative outcomes. Firstly, PPs may improve the surgical candidacy of older patients, allowing more to undergo curative LR. Secondly, PPs can reduce the incidence of postoperative complications.

Finally, PPs can enable older patients to return to a desired QoL (3).

Oncologic population

Oncologic patients with HCC or secondary metastases may have HS secondary to obesity, metabolic syndrome, or insulin resistance independent of treatment, or chemotherapy-associated steatosis (CAS) or chemotherapy-associated steatohepatitis (CASH). The systemic treatment with neoadjuvant chemotherapy spreads beyond the target lesions. Some regimens cause changes in the remaining healthy liver parenchyma, resulting in steatosis or the progression of HS or CAS to CASH (15).

After chemotherapy, it is accepted practice that a period of 4–6 weeks (6–8 weeks in patients receiving bevacizumab) should precede LR to allow some resolution of chemotherapy-induced liver injury to lower the risk of postoperative complications. This "washout" period is perfect for PPs to optimize the patient's physiology. this modifiable risk factor without much delay in the surgery. Indocyanine green (ICG) clearance reduces after chemotherapy, suggesting some functional liver impairment. This can lead to higher morbidity and PHLF (15). ICG retention above 15% after 15 minutes is a contraindication for major LR due to the risk of PHLF (22) with 10% being a safe cut-off (22). This thus further pushes for enrolling oncologic patients into PPs.

Another benefit of reducing IHF is that interventions, including dietary modifications and weight loss help optimize any underlying metabolic syndrome. This can improve postoperative outcomes, as metabolic syndrome puts patients at higher risk of surgical site infection, re-intubation, longer ventilation requirements, and overall cardiorespiratory complications. In some patient cohorts, metabolic syndrome may be a confounding variable inseparable from IHF (15).

Preoperative assessment

Assessing whether a patient is a good surgical candidate and predicting postoperative morbidity risk can help modify the care delivery to improve postoperative outcomes. Several established generalized risk stratification tools include the American Society of Anesthesiology Physical Status and Physiological and Operative Severity Score in the enUmeration of Mortality and Morbidity (POSSUM). However, they have limited validation in major HPB surgery and are cumbersome for routine clinical use (23). Therefore, other assessment methods are used instead.

Physical fitness

An objective evaluation of physical fitness before surgery is crucial due to its impact on postoperative recovery. Cardiopulmonary exercise testing (CPET) is the gold standard to determine aerobic fitness. It is a maximal exercise stress test that measures variables including VO_{2max} and anaerobic threshold (AT). VO_{2max} is one's maximum capacity to use oxygen during incremental exercise, reflecting physical fitness. AT refers to the level of oxygen consumption beyond which aerobic energy production is supplemented by anaerobic mechanisms, causing sustained increase in lactate and metabolic acidosis (24). A low AT below 11 mL/min/kg is associated with elevated risk of cardiopulmonary complications (25), making LR contraindicated. However, CPET is not routinely used in clinical practice as it requires high expertise and extensive equipment.

The six-minute walk test (6MWT) is a submaximal test commonly used in older adults to estimate VO_{2max} (3). The 6MWT is a simple, safe and inexpensive test that can be used even in patients with cardiopulmonary diseases (26). Patients walk a predetermined course at their own pace for 6 min, and the distance is measured (27). Major postoperative complications after HPB surgeries can be predicted by low preoperative 6MWT. In patients who walked less than 400 m, the incidence rate of Clavien-Dindo grade ≥3 complications is significantly higher at 81% than those with 6MWT of at least 400 m, at 34% (27).

Handgrip strength (HGS) assessed using a handheld dynamometer is a surrogate marker of overall muscular strength. It is a low-cost, quick, and non-invasive method in determining the maximal voluntary force of the hand. HGS may be a viable alternative to CPET in immobile patients (28). It reflects the patient's muscle strength and lean body mass, and can indicate frailty, malnutrition and cardiopulmonary or metabolic diseases (28). However, HGS has a limited and inconsistent role in major elective hepatobiliary surgery. A trial by Chan *et al.* did not find a statistically significant difference in postoperative morbidity in patients with poor preoperative HGS, although LOS was more than 21 days (23). Many contributing factors can affect LOS; long LOS is not necessarily attributed to poor HGS alone. These factors include poor nutritional and functional status, cognitive impairment, comorbidities, and

Table 2 European Society for Clinical Nutrition and Metabolism malnutrition criteria

Body mass index <18.5 kg/m^2
Unintentional weight loss >5% over the past 3–6 months combined with body mass index <20 kg/m^2 if age <70 years or <22.0 kg/m^2 if age ≥70 years
Unintentional weight loss combined with fat-free mass index <15.0 kg/m^2 for women or <17.0 kg/m^2 for men

Patients who satisfy ≥1 criteria are malnourished.

admission diagnosis (23).

Nutritional status

Nutritional risk screening plays a vital role in preoperative optimization before liver surgery. It helps identify patients at risk of malnutrition and guides nutritional interventions to optimize their nutritional status before surgery. Besides body mass index and weight, a wide range of nutritional screening tools have been validated, including prognostic nutritional index (PNI) (29), controlling nutritional status (CONUT) score (30), European Society for Clinical Nutrition and Metabolism (ESPEN) malnutrition criteria (31) and Malnutrition Universal Screening Tool (MUST) (3). Poor nutritional status determined by these scores correlate with postoperative complications, decreased survival and shorter RFS.

After screening, proper nutritional assessment provides valuable information about patients' dietary intake, nutritional deficiencies, and overall health, allowing healthcare professionals to develop individualized nutrition plans (32). Traditionally, serum albumin level alone was used as a surrogate marker for preoperative nutritional assessment. However, it is confounded by active inflammation and comorbidities such as liver or renal disease. Like HGS, lower serum albumin levels are associated with LOS longer than 21 days but do not result in statistically significantly higher postoperative morbidity (23). Henceforth, Mini Nutritional Assessment, a comprehensive nutritional assessment is available as an alternative. Physical fitness tests and anthropometric measurements of muscle mass and body composition may also be surrogate markers (3) to guide preoperative nutritional interventions.

PNI

PNI, first developed by Buzby *et al.*, is based on serum albumin and circulating peripheral blood lymphocyte count (33). According to Pinato *et al.*, PNI is a reliable predictor of prognosis for HCC patients after curative hepatectomy (34). In addition, a retrospective cohort study and meta-analysis by Fan *et al.* demonstrated that preoperative PNI is an independent prognostic factor for overall survival and RFS in HCC patients receiving hepatectomy (29), showing the role of PNI in LR patients.

CONUT score

CONUT score is a nutritional screening tool created by Ignacio de Ulíbarri *et al.* (35). The score was derived using serum albumin concentrations, peripheral lymphocyte counts, and total cholesterol concentrations (35). It is an independent prognostic factor in patients with chronic or malignant disorders such as end-stage liver disease (30,36). It is also associated with postoperative major complications and hepatic functional reserve in patients undergoing hepatectomy for HCC (30), and can be used for assessing nutritional status.

ESPEN malnutrition criteria

Malnutrition can be diagnosed based on the 2015 ESPEN criteria (31), if patients satisfy at least one of the following criteria (*Table 2*). Fukami *et al.* investigated the utility of the ESPEN malnutrition criteria in LR patients and found that it is independently associated with major postoperative complications (37).

Psychosocial needs

Assessing a patient's psychosocial needs before an intervention enhances discharge readiness by promoting mental readiness and setting postoperative expectations. This may also identify the patient's socioeconomic needs, which can affect the LOS, discharge destination and readmission rates. Assessment for any anxiety, depression and sense of self-efficacy (3) has benefits too. Metrics include the Hospital Anxiety and Depression Scale score, where a score of more than 15 puts patients at risk (20).

Geriatric needs

Frailty is correlated with worse overall survival and RFS (3).

Therefore, identifying frailty may be a key for LR patients, as multimodal prehabilitation may be able to reverse the frailty phenotype (3), especially among geriatric patients. The Fried frailty phenotype criteria (38) or Clinical Frailty Scale (39) can predict death, disability and longer LOS in older patients undergoing non-cardiac surgery. The Clinical Frailty Scale is a judgement-based frailty tool evaluating specific domains including comorbidity, function, and cognition to generate a score ranging from 1 (very fit) to 9 (terminally ill) (39).

Disease status

For a patient undergoing LR, an assessment of the severity of the underlying liver disease helps reduce the risk of PHLF. Investigation modalities include laboratory evaluation and cross-sectional imaging. Laboratory values can help calculate the Child-Turcotte-Pugh and Model for End-Stage Liver Disease scores, which have predictive value, informing the required size of liver remnant and acting as a surrogate measure of residual liver function. Imaging can be repeated in 2–8 weeks to assess the rate of hypertrophy and the volume of functional liver (3) to predict patient outcomes.

To quantify IHF, preoperative histological assessment involves a liver biopsy. However, this is associated with morbidity and inaccuracy secondary to heterogenous fat deposition. Advances in magnetic resonance (MR) imaging techniques have allowed MR spectroscopy (MRS) and chemical shift MR (CS-MR) to be used to quantify hepatic fat. MRS is the gold standard for radiological assessment of IHF but is largely limited to the research arena. CS-MR, however, can be used clinically to assess IHF reliably. Since patients routinely have preoperative MR scans to measure tumor size and number, an additional CS-MR sequence is feasible and does not add much burden to the patient (15).

After LR, synthetic liver function is a key determinant of postoperative outcomes. Some modes of assessment include ICG to detect functional changes with CAS or CASH and to assess improvement after cessation of chemotherapy. The LiMAX (maximum liver function capacity) test which measures the breakdown of ^{13}C-methacin, can also track changes in function post-chemotherapy. ICG clearance testing and LiMAX are simple, safe, and can be performed in the clinic or at the bedside. Limitations of ICG clearance testing include dependence on adequate hepatic perfusion, reduced accuracy in hyperbilirubinemia and greater ability to detect mild chemotherapy-induced injuries. Some of these can be overcome by LiMAX, causing it to be regarded as a superior mode of assessment, but its use is not widespread yet. Contrast Enhanced MR (CE-MR) using gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid (Gd-EOB-DPTA) is another way to assess regional and global liver function as its uptake is greatly affected by liver function (15).

Prognostic scoring systems

Risk prediction models and scoring systems for morbidity rates following LR are useful for the overall screening of a patient for surgical candidacy. Based on the predicted outcomes, targeted interventions such as prehabilitation can be conducted to improve LR outcomes.

The POSSUM score is an 18-variable system to predict mortality and morbidity in general surgery. Based on numerous factors, it generates a physiology score, operative severity score, predicting the morbidity and mortality percentage scores. Another model is the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP) risk calculator, a 21-variable system estimating percentage risk of 30-day postoperative outcomes, and the chance of each complication happening. Madhavan *et al.* found that ACS-NSQIP has better discriminatory power, calibration and performance than POSSUM (40).

A systemic inflammatory response is associated with poor survival in oncologic patients. Therefore, preoperative inflammation-based scores can be used to predict post-LR outcomes. These include Glasgow Prognostic Score (GPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) (41) and PNI (42). Specifically, an elevated preoperative combined NLR-PLR score predicts overall and recurrence-free survival following curative LR for HCC. Further, these are easy to calculate from routine biochemical tests and are inexpensive (1), making them convenient for clinical practice.

Components of PPs

Physical exercise

Physically fitter patients have lower mortality, morbidity and shortened LOS post major surgeries (43,44), highlighting the importance of physical exercise. Physical prehabilitation has been shown to enhance cell energy supply for improved function and increased potency of liver regeneration (2,45). Conversely, patients with poor aerobic fitness preoperatively have increased risk of adverse outcomes in HPB surgery (27,43). In this section, we present literature to assess the effects of physical prehabilitation on patients undergoing LR.

Dunne *et al.* studied intensive physical exercise in one month preoperatively, including 30 minutes to an hour of interval training between moderate and vigorous intensity at above 60% VO_2 max at peak exercise on a cycle ergometer. With a cohort of 38 patients randomized into 2 separate prehabilitation arms, the exercise prehabilitation arm saw improved peak VO_2, heart rate reserve and oxygen pulse. There was also an increased score in health-related patient reported outcomes, such as QoL as measured by the Short Form Health Survey 36. Notably, a handful of patients initially deemed high-risk preoperatively due to limited cardiovascular reserves were eventually modulated to non-high risk after prehabilitation (46). This supports the view that physical prehabilitation not only improves the objective chances of a successful postoperative period, but it can also improve patients' subjective satisfaction.

Wang *et al.* also studied PPs in patients undergoing elective LR. This program involved a physiotherapist review that educated patients on deep breathing exercises with an incentive spirometer 4 times a day, an emphasis on postoperative early mobilization and individualized exercise program consisting of lower limb strengthening exercises and a walking program lasting 30 minutes per session, 5 times per week. This is alongside dietitian advice and frequent review on social setups, caregiver concerns and mental readiness by a dedicated case manager. Of the 104 patients enrolled and analyzed, there was a significantly lower incidence of complications (30% versus 52.9%, P=0.02) and reduced severity of postoperative complications. Fewer patients in the prehabilitation arm faced postoperative social issues that may prolong stay and delay discharge, including functional independence for daily living activities. Although not statistically significant, LOS was also shorter in the prehabilitation group (6 versus 8.5 days). Overall QoL also improved, and there was a net numerical decrease in cost to the patients of up to 16.5% (2). Though not randomized and only included a small sample, it sets a strong precedent for future studies that aim to prove positive outcomes from prehabilitation.

Kaibori *et al.* (47) studied solely the outcomes of diet therapy with or without exercise therapy in HCC patients undergoing hepatectomy. With a bicycle ergometer, an individualized exercise program was tailored for each patient consisting of three 60-min exercise sessions per week a month before the operation. In the 51 patients analyzed, lower whole-body and fat mass were reduced 6 months postoperatively. Fasting serum insulin was significantly lower in high-frequency exercise subgroups, indicating reduced insulin resistance. Physical exercise in prehabilitation thus has encouraging results with benefits in various areas such as cardiovascular and metabolic health.

Nutritional supplementation

After nutritional assessments are performed, a plan to optimize the nutritional status of patients is formulated. Firstly, any nutritional deficiency is replaced with nutritional supplements or feeding. Secondly, dieticians work with patients to establish daily nutritional goals through patient education and nutritional counselling. Additional resources are provided for patients to read at the end of each session. Furthermore, where patients cannot meet their nutritional needs through regular food intake alone, dieticians can also prescribe oral nutritional supplements, which help bridge nutrient gaps and improve overall nutritional status (2). It is also important to identify and correct barriers to adequate food intake in patients identified as malnourished from screening. These patients may benefit from individualized dietary plans, including fortified food, high protein foods and parenteral nutrition (48).

LR itself may lead to metabolic disturbances such as in glucose homeostasis, leading to the development of insulin resistance postoperatively (49). This is associated with increased postoperative complications, such as infections, renal failure, and mortality (50). Blixt *et al.* found optimal glucose during surgery can reduce postoperative insulin resistance (51). Hence, maintaining optimal glycemic control preoperatively through a balanced diet and medications (if required), and regular monitoring is crucial for patients with diabetes or impaired glucose tolerance.

Certain specialized enteral formulas enriched with specific nutrients have been linked with better surgical outcomes. These nutrients, such as arginine, omega-3 fatty acids and others, modulate the immune and metabolic response to stress and reduce postoperative complications (52). A meta-analysis by Wong *et al.* showed that immunonutrition administration significantly reduces postoperative wound infection and LOS (53). Therefore, incorporating immunonutrition into PPs may provide additional benefits.

Psychological support

Psychological interventions in prehabilitation for LR should be used as an adjunct to other strategies. Specific strategies include psychosocial assessments and medical social workers' advance care planning (54). It has been shown that when psychosocial assessments and advance care planning are used in combination with exercise and diet-based approaches, there is an improvement in frailty. These psychosocial assessments use a combination of Montreal Cognitive Assessments, Charlson comorbidity index, Patient Health Questionnaire-2 and 9 which measures depressed mood and anhedonia, and CAGE questionnaire for substance abuse (54). This is based on Fried's frailty index (P<0.0001) which could have long term prognostic value on eventual patient clinical outcomes. Other strategies like music therapy (55) or progressive relaxation exercises may have a role (56). Music therapy can be further split into two approaches, emotional versus active, based on coping methods. The emotional approach is less proven, with the main effects only in improving positive affects while the active approach has been proven to reduce pain, stress, and anxiety (55). Progressive relaxation exercises of at least 25 min can also reduce fatigue severity scores, respiratory rates, blood pressure and pulse rates and improve oxygen saturation levels (all indices P<0.001). These can improve preoperative physical status, potentially improving surgical outcomes (56). PP may confer psychological benefits which can improve psychological, emotional and social functioning and overall QoL in cancer patients (20).

Newer components

Newer "atypical" measures are currently being trialed. These include improving fluid balance, avoidance of epidural analgesia, phosphate correction, perioperative steroid use, elastomeric pump delivered continuous infusion of local anesthetics agents in intermuscular plane, IBSA, BCAA supplementation, and acute normovolemic dilution (57).

Fluid balance

Optimizing the fluid balance can improve surgical outcomes by improving end organ perfusion. Fluid overload is associated with ileus and delayed recovery of gastrointestinal function, whereas fluid underload can trigger acute kidney injury. Thus, fluid stewardship initiatives are integral to postoperative care of LR patients. Active attention to perioperative fluids has been shown to reduce mortality to 3.8%, blood loss to a median number of blood transfusions of two or less, and preserves renal function with only 3% showing a significant increase in creatinine values (58).

Elastomeric pump for delivering anesthetics

Epidural analgesia may increase the risk of blood transfusion due to excessive fluid infusion secondary to hypotension from peripheral vasodilation. In a review of 367 patients, there was an odds ratio of 3.67 for increased risk of blood transfusions (P<0.001) (57). In TTSH, "triple therapy" analgesia is used—intravenous paracetamol, patient-controlled analgesia with either morphine or fentanyl bolus, and continuous infusion of anaesthetic agents, such as bupivacaine or ropivacaine with the elastomeric pump via the catheters placed intraoperatively in abdominal muscle layers (19). In patients with major LR and postoperative liver dysfunction, paracetamol is omitted or dose-adjusted.

Intraoperative salvage and autotransfusion and acute normovolemic dilution

LR and liver transplantation procedures are associated with high blood loss intraoperatively. Although lifesaving, allogeneic blood transfusions are linked to significant morbidity, with increased rates of complications. As such, IBSA can potentially reduce overall blood loss, while avoiding the adverse effects of allogeneic blood transfusion (59). Acute normovolemic dilution. involves hemodilution of the anticipated blood loss before the operation. This leads to lower red blood cells lost per blood volume during the surgery and has been associated with lower intraoperative transfusions (1.6% *vs.* 10.4%) (60). However, the utility of this approach is limited unless it hits a sizable amount of blood loss and is not commonly used in hepatic surgery.

Perioperative steroid administration

Given the potentially detrimental effects of the inflammatory response post-LR, perioperative steroid administration has gained interest. This may promote recovery of liver function and inhibit the inflammatory response without increasing complications. However, current study findings are inconsistent regarding whether this reduces morbidity. A caveat to this is that IL-6 response is pivotal in postoperative hepatic regeneration, and attenuation of the IL-6 response with perioperative steroids may be harmful instead (10). More evidence is necessary before strong recommendations can be made.

Phosphate correction

Post-hepatectomy hypophosphatemia (PHH) has an incidence of 55.5% to 100%. The pathophysiology of this is due to the rapid uptake of phosphate for liver regeneration with concurrent increased urinary excretion of phosphorus (61). A retrospective cohort study by Squires *et al.* found that higher serum phosphate levels post-hepatectomy from postoperative day 2 onwards were associated with hepatic insufficiency, mortality, and major complications. Hence, PHH suggests hepatic regeneration and is a predictor of good outcomes in hepatectomy (62). Conversely, if left untreated, PHH may also result in other postoperative complications like altered mental status, seizures, heart failure, muscle pain and weakness (63). George *et al.* showed that severe PHH was associated with cardiorespiratory and infection complications, and early replacement of the phosphate imbalance can minimize these complications (64). Despite the consequences of PHH, there is no standardized phosphate replacement regime. PHH should be corrected based on the extent of the hypophosphatemia, as overzealous replacement may result in hyperphosphatemia (61).

BCAA supplementation

BCAA administration influences cellular glucose metabolism, amino acid transport, protein turnover, gene expression and mitochondrial biogenesis. BCAA is also one of the markers of protein synthesis in liver disease, and plasma BCAA levels are reduced post LR. As such, preoperative BCAA supplementation can prevent ascites and pleural effusion by maintaining osmotic pressure and improving albumin metabolism, reducing the risk of complications and LOS (65). It is a possible area for exploration in PPs.

Overall benefits of PPs

A prospective study in a single hospital comparing patients who underwent PP versus the standard care plan reported an overall improvement in QoL in the PP group. PP reduced the LOS, morbidity, hospitalization bills, social issues, and improved social well-being. A multidisciplinary PP was useful in identifying problems and intervening promptly before the surgery. There was also increased postoperative positive behavior, with patients being more cooperative and proactive in early mobilization and breathing exercises. Notably, PP also changed the traditional belief regarding needing prolonged bed rest after a major surgery (2).

Many PPs now employ a multi-pronged approach to prepare patients for LR, usually comprising of a combination of one or more components including physical exercise, nutritional supplementation, psychological support as well as more novel techniques that are being explored as described above. These measures aim to optimize LR patients for better postoperative outcomes. The various components of PPs are summarized in *Figure 1*.

Recovery of Surgery in Elderly (ROSE) program at Tan Tock Seng Hospital (TTSH)

The ROSE program was initiated in 2018, to intensively prepare frail older adults above 65 years old before major colorectal and HPB surgeries. It is a multi-disciplinary approach, involving physiotherapists for exercise, Geriatric Surgical Service for medical optimization and dietician review for nutritional intervention. The PP can be done either as an outpatient or inpatient. Outpatient prehabilitation is done for patients planned for elective LR with at least 2 weeks of buffer time. On the other hand, inpatient prehabilitation is reserved for patients newly diagnosed with HCC on hospital admission and pending medical investigations, who cannot otherwise do their prehabilitation as outpatients.

The TTSH Nutrition Screening Tool was developed locally and validated against subjective global assessment. It accurately predicts the risk of malnutrition, which predicts 6-month mortality and LOS (66). Patients are selected based on risk prediction models, maximizing resources. These patients are seen by a multidisciplinary team of health professionals, including a dietician, physiotherapist, nurse, geriatric surgery service, financial counselor, anesthesiologist, and case manager (4).

Challenges of PPs

The three main hurdles to successfully implementing PPs are delaying surgery, patient compliance, and resource constraints. Delaying surgery to complete a PP may not be optimal for cancer patients as disease may progress (27). Some patients deemed poor surgical candidates are scheduled to be re-evaluated for candidacy after prehabilitation. Patients may perceive this as a delay in treatment, resulting in anxiety (3). In-hospital supervised PP ensures compliance but is resource intensive, and patients may not want to spend time away from family members. Home-based PP may mitigate the drawback of

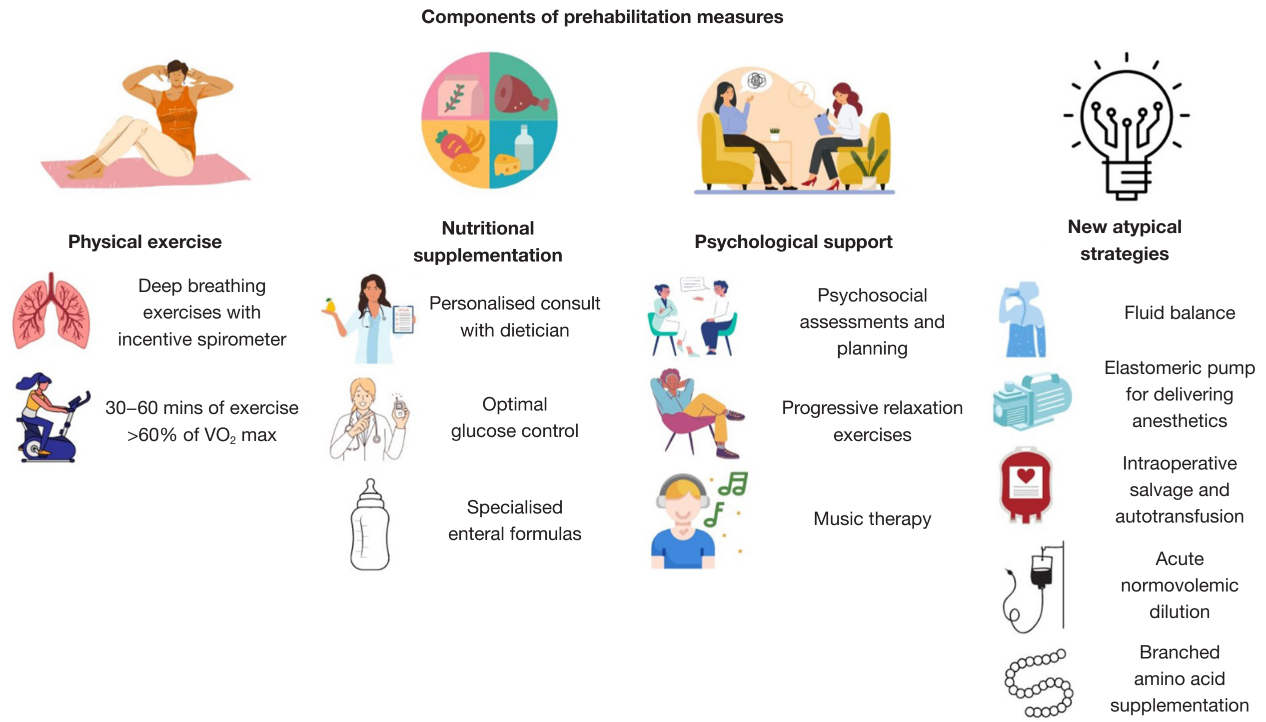

Figure 1 Summary of the components of prehabilitation programs. Physical exercise, nutritional supplementation and psychological support are the mainstay of most prehabilitation regimes. New atypical prehabilitation strategies such as achieving fluid balance, using elastomeric pumps for delivering anesthetics, intraoperative salvage and autotransfusion, acute normovolemic dilution and branched amino acid supplementation, have shown promise in improving postoperative outcomes in liver resection patients.

supervised in-hospital PP to some extent (67). However, a home-based PP may lack compliance and thus reduce the beneficial effect. Compliance may be improved with close follow-up such as frequent phone calls and a diary requirement (3). PPs are resource- and system-dependent. For instance, geriatric assessments require the time for specialist evaluation and necessary resources (3). Resources are finite, and expending resources on one initiative leaves a lacuna somewhere else (19). PPs may also incur indirect patient costs, such as traveling to and from hospitals (68).

Future directions

Future research should focus on further elucidating specific nutritional requirements, exploring novel interventions such as personalized diets and nutrigenomics, and evaluating the impact of PP on postoperative QoL and socio-economic outcomes (19). Fluid management is not a prominent feature of PP. Excessive fluid intake before LR may increase blood loss. Point-of-care ultrasonography (POCUS) can be used in selected patients to evaluate fluid status and any cardiovascular complications (69). This provides some insight into the underlying liver disease severity, and the suitability of the patient for LR, allowing tailored fluid management. More evidence is needed. Translating clinical innovations into practice takes 17 to 20 years, with less than half making it into widespread use (70). Therefore, understanding of implementation science may be crucial to increase the uptake of PPs.

Conclusions

Prehabilitation is important in optimizing patients before LR and is key in improving postoperative outcomes. Several prehabilitation strategies exist, but no formal consensus exists on patient selection and an ideal program.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-102/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-102/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-102/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Kabir T, Ye M, Mohd Noor NA, et al. Preoperative Neutrophil-to-Lymphocyte Ratio Plus Platelet-to-Lymphocyte Ratio Predicts the Outcomes after Curative Resection for Hepatocellular Carcinoma. Int J Hepatol 2019;2019:4239463.
2. Wang B, Shelat VG, Chow JJL, et al. Prehabilitation Program Improves Outcomes of Patients Undergoing Elective Liver Resection. J Surg Res 2020;251:119-25.
3. Hao S, Reis HL, Quinn AW, et al. Prehabilitation for Older Adults Undergoing Liver Resection: Getting Patients and Surgeons Up to Speed. J Am Med Dir Assoc 2022;23:547-54.
4. Mohan R, Huey CWT, Junnarkar S, et al. Prehabilitation in elderly patients scheduled for liver resection and protocol for Recovery Of Surgery in Elderly. Hepatoma Res 2020;6:13.
5. Kar I, Qayum K, Sofi J. Indications and Complications of Hepatic Resection Patients at Sher-I-Kashmir Institute of Medical Sciences: An Observational Study. Cureus 2021;13:e19713.
6. Kumari S, Semira C, Lee M, et al. Resection of colorectal cancer liver metastases in older patients. ANZ J Surg 2020;90:796-801.
7. Janicko M, Drazilova S, Jarcuska P. R0 Liver Resection should be a First-line Treatment for Selected Patients with Intermediate Hepatocellular Cancer. J Clin Transl Hepatol 2023;11:757-60.
8. Walcott-Sapp S, Billingsley KG. Preoperative optimization for major hepatic resection. Langenbecks Arch Surg 2018;403:23-35.
9. Agarwal V, Divatia JV. Enhanced recovery after surgery in liver resection: current concepts and controversies. Korean J Anesthesiol 2019;72:119-29.
10. Hai HH, Aw P, Teng TZJ, et al. Perioperative steroid administration reduces overall complications in patients undergoing liver resection: A meta-analysis. World J Gastrointest Surg 2021;13:1079-94.
11. Taura K, Ikai I, Hatano E, et al. Influence of coexisting cirrhosis on outcomes after partial hepatic resection for hepatocellular carcinoma fulfilling the Milan criteria: an analysis of 293 patients. Surgery 2007;142:685-94.
12. Ruiz-Margáin A, Román-Calleja BM, Moreno-Guillén P, et al. Nutritional therapy for hepatocellular carcinoma. World J Gastrointest Oncol 2021;13:1440-52.
13. Sheriff S, Madhavan S, Lei GY, et al. Predictors of mortality within the first year post-hepatectomy for hepatocellular carcinoma. J Egypt Natl Canc Inst 2022;34:14.
14. Lei GY, Shen L, Junnarkar SP, et al. Predictors of 90-Day Mortality following Hepatic Resection for Hepatocellular Carcinoma. Visc Med 2021;37:102-9.
15. Doherty DT, Coe PO, Rimmer L, et al. Hepatic steatosis in patients undergoing resection of colorectal liver metastases: A target for prehabilitation? A narrative review. Surg Oncol 2019;30:147-58.
16. Russell MC. Complications following hepatectomy. Surg Oncol Clin N Am 2015;24:73-96.
17. Brustia R, Monsel A, Skurzak S, et al. Guidelines for Perioperative Care for Liver Transplantation: Enhanced Recovery After Surgery (ERAS) Recommendations. Transplantation 2022;106:552-61.
18. Melnyk M, Casey RG, Black P, et al. Enhanced recovery after surgery (ERAS) protocols: Time to change practice? Can Urol Assoc J 2011;5:342-8.
19. Tang JH, Wang B, Chow JLJ, et al. Improving postoperative mobilisation rates in patients undergoing

elective major hepatopancreatobiliary surgery. Postgrad Med J 2021;97:239-47.
20. Strijker D, Meijerink WJHJ, van Heusden-Schotalbers LAG, et al. Multimodal Prehabilitation in Patients Undergoing Complex Colorectal Surgery, Liver Resection, and Hyperthermic Intraperitoneal Chemotherapy (HIPEC): A Pilot Study on Feasibility and Potential Efficacy. Cancers (Basel) 2023;15:1870.
21. Lopez-Delgado JC, Ballus J, Esteve F, et al. Outcomes of abdominal surgery in patients with liver cirrhosis. World J Gastroenterol 2016;22:2657-67.
22. Kobayashi K, Uldry E, Kokudo T, et al. Correlation Between Portal Pressure and Indocyanine Green Retention Rate is Unaffected by the Cause of Cirrhosis: A Prospective Study. World J Surg 2021;45:2546-55.
23. Chan KS, Chia CLK, Ng FKL, et al. Impaired Handgrip Strength Does Not Predict Postoperative Morbidity in Major Hepatobiliary Surgery. J Surg Res 2020;256:549-56.
24. Wasserman K. The anaerobic threshold: definition, physiological significance and identification. Adv Cardiol 1986;35:1-23.
25. Yanni F, Moyes LH, McCaffer CJ, et al. Cardiopulmonary exercise testing as a predictor of complications. Ann R Coll Surg Engl 2014;96:86.
26. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919-23.
27. Hayashi K, Yokoyama Y, Nakajima H, et al. Preoperative 6-minute walk distance accurately predicts postoperative complications after operations for hepato-pancreato-biliary cancer. Surgery 2017;161:525-32.
28. Garg K, Mohan B, Luthra N, et al. Role of handgrip strength testing in pre-anaesthetic check-up: A prospective cross-sectional study. J Anaesthesiol Clin Pharmacol 2022;38:440-4.
29. Fan X, Chen G, Li Y, et al. The Preoperative Prognostic Nutritional Index in Hepatocellular Carcinoma After Curative Hepatectomy: A Retrospective Cohort Study and Meta-Analysis. J Invest Surg 2021;34:826-33.
30. Takagi K, Domagala P, Polak WG, et al. Prognostic significance of the controlling nutritional status (CONUT) score in patients undergoing hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis. BMC Gastroenterol 2019;19:211.
31. Cederholm T, Bosaeus I, Barazzoni R, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr 2015;34:335-40.
32. Evans DC, Martindale RG, Kiraly LN, et al. Nutrition optimization prior to surgery. Nutr Clin Pract 2014;29:10-21.
33. Buzby GP, Mullen JL, Matthews DC, et al. Prognostic nutritional index in gastrointestinal surgery. Am J Surg 1980;139:160-7.
34. Pinato DJ, North BV, Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: the prognostic nutritional index (PNI). Br J Cancer 2012;106:1439-45.
35. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 2005;20:38-45.
36. Dalmiglio C, Brilli L, Campanile M, et al. CONUT Score: A New Tool for Predicting Prognosis in Patients with Advanced Thyroid Cancer Treated with TKI. Cancers (Basel) 2022;14:724.
37. Fukami Y, Saito T, Arikawa T, et al. European Society for Clinical Nutrition and Metabolism (ESPEN) Malnutrition Criteria for Predicting Major Complications After Hepatectomy and Pancreatectomy. World J Surg 2021;45:243-51.
38. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146-56.
39. Church S, Rogers E, Rockwood K, et al. A scoping review of the Clinical Frailty Scale. BMC Geriatr 2020;20:393.
40. Madhavan S, Shelat VG, Soong SL, et al. Predicting morbidity of liver resection. Langenbecks Arch Surg 2018;403:359-69.
41. Chan KS, Shelat VG. The role of platelet-lymphocyte ratio in hepatocellular carcinoma: a valuable prognostic marker. Transl Cancer Res 2022;11:4231-4.
42. Shelat VG. Role of inflammatory indices in management of hepatocellular carcinoma-neutrophil to lymphocyte ratio. Ann Transl Med 2020;8:912.
43. Junejo MA, Mason JM, Sheen AJ, et al. Cardiopulmonary exercise testing for preoperative risk assessment before hepatic resection. Br J Surg 2012;99:1097-104.
44. Snowden CP, Prentis J, Jacques B, et al. Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people. Ann Surg 2013;257:999-1004.
45. Daradics N, Levay K, Horvath I, et al. Physical prehabilitation improves the postoperative outcome of associating liver partition and portal vein ligation for staged hepatectomy in experimental model. Sci Rep

2022;12:19441.
46. Dunne DF, Jack S, Jones RP, et al. Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg 2016;103:504-12.
47. Kaibori M, Ishizaki M, Matsui K, et al. Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy. Am J Surg 2013;206:202-9.
48. Gillis C, Wischmeyer PE. Pre-operative nutrition and the elective surgical patient: why, how and what? Anaesthesia 2019;74 Suppl 1:27-35.
49. Durczynski A, Strzelczyk J, Wojciechowska-Durczynska K, et al. Major liver resection results in early exacerbation of insulin resistance, and may be a risk factor of developing overt diabetes in the future. Surg Today 2013;43:534-8.
50. Blixt C, Ahlstedt C, Ljungqvist O, et al. The effect of perioperative glucose control on postoperative insulin resistance. Clin Nutr 2012;31:676-81.
51. Blixt C, Larsson M, Isaksson B, et al. The effect of glucose control in liver surgery on glucose kinetics and insulin resistance. Clin Nutr 2021;40:4526-34.
52. Xu J, Yunshi Z, Li R. Immunonutrition in surgical patients. Curr Drug Targets 2009;10:771-7.
53. Wong CS, Praseedom R, Liau SS. Perioperative immunonutrition in hepatectomy: A systematic review and meta-analysis. Ann Hepatobiliary Pancreat Surg 2020;24:396-414.
54. Baimas-George M, Watson M, Thompson K, et al. Prehabilitation for Hepatopancreatobiliary Surgical Patients: Interim Analysis Demonstrates a Protective Effect From Neoadjuvant Chemotherapy and Improvement in the Frailty Phenotype. Am Surg 2021;87:714-24.
55. Ghetti CM. Active music engagement with emotional-approach coping to improve well-being in liver and kidney transplant recipients. J Music Ther 2011;48:463-85.
56. Kömürkara S, Cengiz Z. Effects of Progressive Relaxation Exercises on Vital Signs and Fatigue in Liver Transplant Patients: A Randomized Controlled Trial. Clin Nurs Res 2022;31:497-508.
57. Page AJ, Kooby DA. Perioperative management of hepatic resection. J Gastrointest Oncol 2012;3:19-27.
58. Melendez JA, Arslan V, Fischer ME, et al. Perioperative outcomes of major hepatic resections under low central venous pressure anesthesia: blood loss, blood transfusion, and the risk of postoperative renal dysfunction. J Am Coll Surg 1998;187:620-5.
59. Rajendran L, Lenet T, Shorr R, et al. Should Cell Salvage Be Used in Liver Resection and Transplantation? A Systematic Review and Meta-analysis. Ann Surg 2023;277:456-68.
60. Jarnagin WR, Gonen M, Maithel SK, et al. A prospective randomized trial of acute normovolemic hemodilution compared to standard intraoperative management in patients undergoing major hepatic resection. Ann Surg 2008;248:360-9.
61. Chan KS, Mohan S, Shelat VG. Outcomes of patients with post-hepatectomy hypophosphatemia: A narrative review. World J Hepatol 2022;14:1550-61.
62. Squires MH 3rd, Dann GC, Lad NL, et al. Hypophosphataemia after major hepatectomy and the risk of post-operative hepatic insufficiency and mortality: an analysis of 719 patients. HPB (Oxford) 2014;16:884-91.
63. Sharma S, Hashmi MF, Castro D. Hypophosphatemia. Treasure Island (FL): StatPearls Publishing; 2023. [cited 2023 Aug 7].
64. George R, Shiu MH. Hypophosphatemia after major hepatic resection. Surgery 1992;111:281-6.
65. Hachiya H, Aoki T, Iso Y, et al. Effects of branched-chain amino acids on postoperative tumor recurrence in patients undergoing curative resection for hepatocellular carcinoma: A randomized clinical trial. J Hepatobiliary Pancreat Sci 2020;27:819-29.
66. Shelat VG, Pandya GJ. Nutritional Support in Dysphagia. In: Seminars in Dysphagia. InTech; 2015.
67. Chan KS, Junnarkar SP, Wang B, et al. Outcomes of an outpatient home-based prehabilitation program before pancreaticoduodenectomy: A retrospective cohort study. Ann Hepatobiliary Pancreat Surg 2022;26:375-85.
68. Heil TC, Driessen EJM, Argillander TE, et al. Implementation of prehabilitation in colorectal cancer surgery: qualitative research on how to strengthen facilitators and overcome barriers. Support Care Cancer 2022;30:7373-86.
69. Kajal K, Premkumar M, Chaluvashetty SB, et al. Point-of-Care Thoracic Ultrasonography in Patients With Cirrhosis and Liver Failure. Cureus 2021;13:e15559.
70. Bauer MS, Kirchner J. Implementation science: What is it and why should I care? Psychiatry Res 2020;283:112376.

Cite this article as: Toh EQ, Wong HPN, Wang JDJ, Liau MYQ, Tan YF, Shelat VG. Prehabilitation programs in liver resection: a narrative review. Chin Clin Oncol 2024;13(1):9. doi: 10.21037/cco-23-102

