Best Practice & Research Clinical Anaesthesiology 34 (2020) 199–212

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

6

Preoperative frailty assessment combined with prehabilitation and nutrition strategies: Emerging concepts and clinical outcomes

Karina Gritsenko, M.D., Associate Professor of Anesthesiology [a], Erik Helander, MBBS, Assistant Professor [b], Michael P.K. Webb, MSc., MBChB, Anaesthetic Fellow [c], Chikezie N. Okeagu, MD, Resident Physician [b], Farees Hyatali, M.D., Resident Physician [d], Jordan S. Renschler, BS, Medical Student [e], Fallon Anzalone, Medical Student [f], Elyse M. Cornett, PhD, Assistant Professor [d, *], Richard D. Urman, MD, MBA, Associate Professor [g], Alan D. Kaye, MD, PhD, Professor, Provost, Chief Academic Officer, and Vice Chancellor of Academic Affairs [h]

[a] *Family & Social Medicine, and Physical Medicine & Rehabilitation. Program Director, Regional Anesthesia and Acute Pain Medicine Fellowship, Montefiore Medical Center, Montefiore Multidisciplinary Pain Program. Department of Anesthesiology. 1250 Waters Place, Tower II, 8th Floor, Bronx, NY 10461, USA*
[b] *Department of Anesthesiology, LSU Health Sciences Center, 1542 Tulane Avenue, New Orleans, LA 70112, USA*
[c] *Department of Anaesthesia and Pain Medicine, Counties Manukau Health, Hospital Road, Otahuhu, Auckland 1640, New Zealand*
[d] *Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, Shreveport LA 71103, USA*
[e] *Louisiana State University Health Sciences Center, New Orleans, LA 70112, USA*
[f] *LSUHSC New Orleans, New Orleans, LA, USA*
[g] *Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115, USA*
[h] *Departments of Anesthesiology and Pharmacology, Toxicology, and Neurosciences; Provost, Chief Academic Officer, and Vice Chancellor of Academic Affairs, LSU Health Shreveport, 1501 Kings Highway, Shreveport LA 71103, USA*

* Corresponding author.
E-mail addresses: kgritsen@montefiore.org (K. Gritsenko), ehelan@lsuhsc.edu (E. Helander), mpkwebb@hotmail.com (M.P.K. Webb), cokeag@lsuhsc.edu (C.N. Okeagu), fhyata@lsuhsc.edu (F. Hyatali), jrensc@lsuhsc.edu (J.S. Renschler), fanzal@lsuhsc.edu (F. Anzalone), ecorne@lsuhsc.edu (E.M. Cornett), rurman@bwh.harvard.edu (R.D. Urman), akaye@lsuhsc.edu (A.D. Kaye).

https://doi.org/10.1016/j.bpa.2020.04.008
1521-6896/Published by Elsevier Ltd.

Keywords:
preoperative frailty
nutrition
total parenteral nutrition
adverse outcomes
geriatric

Important elements of the preoperative assessment that should be addressed for the older adult population include frailty, comorbidities, nutritional status, cognition, and medications. Frailty has emerged as a plausible predictor of adverse outcomes after surgery. It is present in older patients and is characterized by multisystem physiologic decline, increased vulnerability to stressors, and adverse clinical outcomes. Preoperative preparation may include a prehabilitation program, which aims to address nutritional insufficiencies, modify chronic polypharmacy, and enhance physical and respiratory conditions prior to hospital admission. Special considerations are taken for particularly high-risk patients, where the approach to prehabilitation can address specific, individual risk factors. Identifying patients who are nutritionally deficient allows practitioners to intervene preoperatively to optimize their nutritional status, and different strategies are available, such as immunonutrition. Previous studies have shown an association between increased frailty and the risk of postoperative complications, morbidity, hospital length of stay, and 30-day and long-term mortality following general surgical procedures. Evidence from numerous studies suggests a potential benefit of including a standard assessment of frailty as part of the preoperative workup of older adult patients. Studies addressing validated frailty assessments and the quantification of their predictive capabilities in various surgeries are warranted.

Published by Elsevier Ltd.

Introduction

The proportion of older adult individuals in the US population continues to rise annually. By the year 2030, the percentage of individuals greater than 65 years of age is expected to increase from 12.4% to 19.6% of the population [1]. While the percentage of older adult individuals in the overall population has increased steadily, the rising rate of the older adult surgical population has continued to grow disproportionately faster [2]. The growing rate of the older adult population has become an emerging concern for anesthesiologists and the entire perioperative healthcare team. Older adult individuals have a higher prevalence of pre-existing comorbidities and risk factors that put them at higher risk for adverse sequalae compared to younger individuals. The primary goal for every perioperative healthcare team is to improve postoperative outcomes and long-term health for patients. Preserving quality of life, independence, and personal capability is especially important in this growing and vulnerable population [3].

Despite continued efforts to improve perioperative care for the elderly population, both major and minor complications occurring after general surgery are still a significant cause of morbidity and mortality. These complications are well documented causes of increased healthcare costs and duration of hospital stay [4,5]. Improving postoperative care in the older adult population begins with identifying and addressing pertinent risk factors for major and minor complications.

Risk Factors for complications:

- Medical comorbidities including cerebrovascular disease, cardiovascular disease, pulmonary disease, renal disease, osteoporosis, and cognitive impairment
- Increased fall risk
- Poor nutritional status
- Polypharmacy

- Anticoagulation use

Performing risk-assessments with the patient prior to surgical procedures is recommended. A thorough perioperative work-up on each patient allows for accurate identification of various perioperative risk factors, so healthcare providers and patients can weigh the risks and benefits of performing various surgical and non-surgical procedures. Accurate detection of risk factors also allows for the opportunity to mitigate some of these risks. For example, it is recommended that the PRICUS list, which contains a reference of potentially inappropriate medications, is utilized in the preoperative phase to help reduce the risk of perioperative complications caused by polypharmacy [3]. Verified risk-assessment tools can be especially helpful in the older adult population, since risk factors associated with increased age vary vastly compared to those of younger patients [2]. The focus of risk-stratification has centered on gaining accurate measurement of preoperative frailty, which includes information on age and pre-existing comorbidities. It has been demonstrated that the identification of frailty status provides a means to identify perioperative risk factors, and therefore improves healthcare costs and health outcomes in older adult patients [5].

Frailty is considered a geriatric syndrome that is quantified by a constellation of age-related impairments in health status and functional autonomy. All of these impairments increase a patient's risk of complications and cause a decline in health outcomes during the post-operative period [3]. Pre-existing frailty is an important prognostic factor of adverse sequelae following surgery [6–9]. Previous studies have shown that risk of postoperative complications, morbidity, hospital length of stay, and 30-day and long-term mortality after general surgical procedures in older adults is increased relative to an increase in baseline frailty [4]. The magnitude of preoperative frailty has been further demonstrated to be predictive of mortality risk after major cardiac surgical procedures postoperatively at 6 months or later. Preoperative frailty also predicts decline in functional status after minor cardiac surgical procedures [10]. The evidence from these studies indicates the potential benefit of including a standard assessment of frailty as part of the preoperative workup of older adult patients [6]. The healthcare system has yet to establish one specific assessment as the gold standard protocol, although the Edmonton frail scale is one of the more prominent and useful preoperative frailty assessment tools [2].

Studies demonstrating the potential benefit of preoperative frailty assessment as a risk stratification tool are limited by the large variety of frailty assessments in existence, surgical procedure types, and heterogeneity of individual primary postoperative outcomes that must be anticipated. Despite limitations, the further development of frailty assessments as a risk-stratification tool for adults undergoing general surgery is supported by evidence. Moving forward, studies addressing the focuses of validated frailty assessments and the quantification of their predictive capabilities in various surgeries are needed. It has been suggested that evaluation of these frailty assessment includes practicality in a clinical setting [4]. A previous survey showed that insufficient knowledge concerning frailty issues impeded the use of frailty assessments as a practical tool in the clinical setting [6]. Despite current limitations, evidence has indicated that preoperative frailty assessments are a valuable tool in modern perioperative medicine [2].

The care of older adult patients in the perioperative period may also experience improvement due to an emerging holistic healthcare approach, known as enhanced recovery after surgery, or ERAS [11–14]. ERAS, previously acknowledged as fast track programs, aims to enhance patient recovery after major surgery and anesthesia by implementing various interventions in the perioperative period [15]. Interventions aim to minimize the physical and emotional stress of surgical procedures and to encourage patient participation in their perioperative care, especially during the time immediately following surgical procedures. Preoperative preparation includes "prehabilitation," which aims to address nutritional insufficiencies, modify chronic polypharmacy, and enhance physical and respiratory conditions prior to hospital admission [3]. Special considerations are taken for particularly high-risk patients, where the approach to prehabilitation can address specific, individual risk factors. Successful prehabilitation and implementation of ERAS has the potential to offer an individualized plan for optimizing postoperative and long-term health for each patient. Three aspects of focus in prehabilitation in this review are nutrition, physical activity, and psychological support.

Malnutrition is prevalent in 45%–55% of the older adult population and is associated with poor prognosis during the perioperative course, increased rate of health complications, and increased rate of other pre-existing comorbidities [3]. These include osteoporosis, postoperative fall complications, overall frailty, and anemia due to vitamin deficiencies. Malnutrition is also associated with an increased incidence of post-operative delirium (POD) [16,17]. POD is a frequently occurring, serious postoperative complication that has major implications effecting the long-term health of the individuals. Such consequences include loss of independent functional status, heightened mortality and morbidity, and increase risk of other complications in the postoperative period. Previous studies have demonstrated that early interventions, including addressing inadequate nutritional status, decreases the rate of developing POD by 30–50% [3]. As a result of the well demonstrated benefits associated with addressing malnutrition in the older adult population, it is recommended that older adult patients be examined for malnutrition early in the perioperative care process [18,19].

Further, another major component of prehabilitation in older adult patients involves evaluation and improvement of physical fitness. Prior evidence indicates that level of physical fitness has a significant, positive relationship with health outcomes in the postoperative period [3,15,20,21]. For example, reduced mobility and muscle strength increases fall risk, thus heightening the potential for poor long-term health outcomes [3]. Studies have demonstrated promising results regarding physical exercise training programs carried out within the older adult population. Participation in these programs has shown improvement in clinical outcomes, especially in high-risk older adult patients with pre-existing comorbidities [15].

Preoperative assessment

Thorough preoperative assessment is vital to ensuring that patients are given the best chance at favorable surgical outcomes. This is particularly relevant in the older adult. This population largely has an increased burden of medical morbidity, reduced physiological reserve, and polypharmacy relative to younger cohorts. Primary care physicians (PCPs) can play an invaluable role in optimizing patients prior to surgery. Although several objective tools exist to aid in the assessment of frailty, the complex, multidimensional, and dynamic nature of the syndrome means that the importance of clinical gestalt cannot be discounted [22]. Since PCPs have a longitudinal relationship with their patients, they are uniquely positioned to assess multiple elements that determine frailty, and implement any necessary interventions [22,23]. This relationship also makes PCPs ideal for initiating goals and ceiling of care discussions and identifying those patients who may be better suited for foregoing certain elective surgeries [9].

Elements of the preoperative assessment that should be addressed for the geriatric population include frailty, comorbidities, nutritional status, cognition, and medications. As patients age, they are more likely to be more comorbid and have a higher burden of illness. Frailty directly affects perioperative and longitudinal mortality rates and is also associated with higher rates of postoperative long term care [24]. There are many tools to assess and to manage frailty. The Comprehensive geriatric assessment (GCA) is considered the gold standard in caring for frail patients and allows for assessment, diagnosis, and institution of individualized therapies [25]. Sensory input such as hearing and vision, psychology, medications, comorbidities, nutritional status, social circumstance, and functional capabilities are areas targeted for optimization with CGA. Application of CGA preoperatively was associated with shorter hospital stays, fewer complications, and lesser dependency [25,26]. Frailty assessments are often poorly implemented, resulting in many patients undergoing surgical procedures with standard care and without proper attention given to preoperative frailty optimization [24].

Malnutrition is a significant risk factor for perioperative morbidity, mortality, hospital readmission, and increased length of stays [27]. Despite this, only around 20% of hospitals have a nutritional screening program and only about 20% of patients receive nutritional support. Malnourished patients undergoing gastrointestinal surgery were shown to be three times more likely to encounter a complication and five times more likely to die [27]. Patients that are suspected to be at high risk for malnutrition should have a comprehensive nutritional assessment performed by a registered dietician [27,28].

Pre-existing or even mild cognitive impairment has been associated with worse perioperative outcomes [8,29–32]. Impairment of cognition in the postoperative period can result from delirium or postoperative cognitive dysfunction. Risk factors that are associated with postoperative delirium in the geriatric population include frailty, pre-existing cognitive impairment, sensory impairment, central nervous system medications, metabolic derangements, malnutrition, underlying comorbidities, and exacerbation/presentation of mental health disease [33]. Postoperative cognitive dysfunction is associated with increased social dependency, inability to work, and increased mortality. Advanced age, low educational level, history of stroke, depression, and pre-existing cognitive impairment have been cited as associated risk factors [27]. The Mini-Cog, Mini-Mental Status Examination (MMSE), and Montreal Cognitive Assessment (MoCA) are screening tools that have been validated in the literature and are used in a wide variety of clinical settings [29]. Due to the impact that cognitive impairment can have on perioperative outcomes, both the American Geriatrics Society and the American College of Surgeons recommend preoperative cognitive screening exams for older adult patients undergoing surgery [29].

Geriatric patients are at high risk for polypharmacy and, when compared to younger adults, commonly have relatively decreased renal function, which makes dosage adjustment imperative for the prevention of unwanted side effects. Risk of medication side effects also increases with increasing numbers of medication and prescribers [34]. Best practice guidelines from the American College of Surgeons and American Geriatric Society recommend discontinuation of nonessential medications prior to surgery [35].

Assessment and treatment of pain in the perioperative period can be difficult and is often under treated in the geriatric population. Cognitive impairment can make assessment of pain severity and efficacy of treatments more difficult. Validated pain scores may be difficult to use or unhelpful in those with altered sensorium or cognitive deficits. Older adult populations are also more susceptible to the respiratory depressive effects of opioids [34,36]. Early use of regional anesthesia has been shown to be effective in hip fractures [37,38]. In one study, continuous femoral nerve block reduced postoperative cognitive dysfunction in high risk patients with femoral neck fractures [39]. Nonsteroidal anti-inflammatory drugs can be useful but should be used with caution and in reduced doses due to potential for kidney injury. Acetaminophen is generally safe for use in older adult populations [34].

After appropriate preoperative screening for the presence and degree of frailty, many measures can be taken to ensure that any modifiable risk factors for poor postoperative outcomes are mitigated ahead of the impending surgical insult. In addition to the traditional course of medication adjustments, biochemical assessment, and imaging, a relatively new concept of enhancing patient fitness prior to surgery has emerged. This process is commonly termed “prehabilitation” and refers to improving functional capacity to allow patients to withstand and recover from the stress of surgery [9,40]. Preoperative functional status has been shown to predict postoperative length of stay (LOS), need for postacute placement, and mortality [9,41,42]. Prehabilitation programs generally encompass three domains: exercise, nutrition, and psychological support. Previous studies have shown that targeting each of these areas individually can confer health benefits [19].

With regular exercise, the body becomes more efficient at adapting to states of physiological stress [43]. Thus, it is reasonable to infer that conditioning patients prior to surgery would lead to similar adaptions, allowing them to better tolerate the challenge of surgery. The exercise component of prehabilitation typically consists of aerobic, resistance, and range of motion (ROM) exercises. There is evidence that such interventions may improve early postoperative pain and function in patients undergoing hip and knee arthroplasty, however, the clinical significance of these findings is questionable [44,45]. Similar moderate benefits have been observed in surgical oncology, colorectal, intraabdominal, and thoracic surgery patients [9].

Patients with poor preoperative nutritional status are at increased risk for postoperative morbidity and mortality [9,43,46]. Identifiable postoperative complications associated with poor nutrition range from issues with wound healing to impairment in immune and cognitive function [47,48]. The surgery-induced catabolic state which causes metabolism of structural proteins, primarily from muscle, is thought to be a major contributor to many of the unfavorable outcomes seen postoperatively [9,43,46]. As such, the nutritional component of prehabilitation programs aims to minimize negative protein

balance. Generally, a protein goal of 1.2–1.5 g/kg/day is targeted. Enteral nutrition is preferred, but parenteral supplementation may be necessary if a patient is unable to obtain adequate nutrition through the enteral route. Assessment of nutritional status with appropriate supplementation must be continued throughout the perioperative period [9,40,43,48].

The psychological interventions of prehabilitation programs are typically aimed at reducing depression and anxiety related to illness and surgery and increasing motivation to actively participate in the treatment regimen [9,40,41,43]. Anxiety and depression have been shown to correlate with adverse postoperative outcomes including pain, infection, poor wound healing, longer LOS, and reduced postoperative functional capacity [41,43,49,50]. Of the prehabilitation domains, psychological interventions are the least standardized. Commonly employed techniques include non-pharmacological strategies such as counseling, deep breathing, meditation, and music therapy [9,40,41]. A Cochrane review conducted in 2016 suggested such interventions may be beneficial, however, the results were tepid [51].

Despite the promise that has been seen in optimizing each of these independent domains in different patient populations, a clear benefit with regards to postoperative outcomes from prehabilitation programs has not yet been demonstrated in frail patients [9,40]. Given the variability in type of surgery and the vast heterogeneity of patients' health, even within frail populations, further work needs to be done to refine prehabilitation programs. Multiple ongoing trials seek to further elucidate the best regimens for each individual for a particular type of surgery [52,53]. See Fig. 1.

Intraoperative care

Total Parenteral Nutrition

Total Parenteral Nutrition (TPN) is defined as the administration of nutrients via central venous catheterization (CVC) in patients who are unable to receive nutrient supplementation via enteral nutrition (EN). In general, EN is preferred as administration of nutrition via the gastrointestinal tract helps to preserve the integrity of the intestinal mucosa [54]. See Tables 1 and 2.

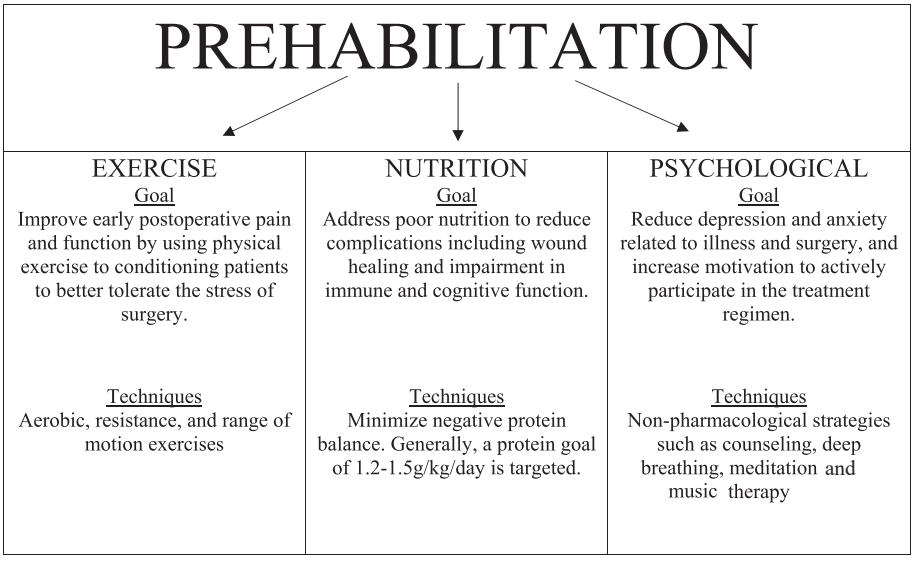

Fig. 1. Flow chart of prehabilitation for preoperative frailty condition.

Table 1
Table illustrating daily requirements of macronutrients for adult patients on TPN.

	Standard Range	Maximum
Calories (kcal/day)	28–30	40
Protein (g/kg/day)	0.8–1.0	2.0
Dextrose rate	4–5 mg/kg/min	7 mg/kg/min
Fat	15–30% kcal	60% kcal

Table 2
Table illustrating daily electrolytes and micronutrient requirements of adult patients. TPN formulations are made taking into account these daily requirements.

Component	Range
Sodium	60-200 mEq
Potassium	60-200 mEq
Magnesium	8-40 mEq
Calcium	10-30 mEq
Phosphorus	10-40 mMol
Chloride	As needed to maintain acid base balance
Acetate	As needed to maintain acid base balance
Copper	300-500 mcg
Manganese	60-100 mcg
Zinc	2.5–5 mg
Chromium	10-15 mcg
Selenium	60 mcg
Molybdenum	As needed
Iodine	As needed
Iron	As needed

Preoperative fasting

Abrupt discontinuation of TPN is not recommended as it can lead to severe hypoglycemia. In many cases, on the night prior to surgery, the rate of the TPN infusion is decreased and substituted with a 5–10% dextrose solution, as the hyperosmolar TPN solution can lead to fluid overload [1]. It is imperative to replace all serum potassium, phosphorus, and glucose prior to surgery [54]. During the surgical procedure, the TPN is continued with strict aseptic technique maintained to reduce the risk of infection. In patients who are receiving EN, a rapid sequence induction is indicated as these patients are considered to have a full stomach [54,56].

Hyperglycemia and insulin resistance

Peripheral insulin resistance during stress and illness is common and is associated with down-regulation of intracellular signalling through the insulin receptor. Bed rest by itself has been demonstrated to diminish glucose uptake and insulin signalling by insulin-dependent tissues. Additionally, due to the increased hepatic glucose production secondary to the increased stress of hospitalization, hyperglycemia can occur [3].

Hyperglycemia is a frequent complication of TPN and is reported to be an estimated incidence of up to 50% of patients receiving TPN [4]. Patients on TPN or EN are closely monitored and subsequently treated for hyperglycemia as it is associated with increased mortality (approximately 33%) risk of cardiac complications, infections (such as pneumonia), systemic sepsis, acute renal failure, and surgical site infection rates. The normal blood glucose in patients who receive TPN ranges between 140 and 180 mg/dl, with hyperglycemia defined as a blood glucose>180 mg/dl [57].

In patients who develop hyperglycemia (glucose >180 mg/dl), an insulin infusion is recommended for optimal glucose control in the perioperative period with postoperative admission to the intensive care for strict blood glucose monitoring. Furthermore, a previous randomized controlled study showed

that parenteral nutrition consisting of 25 kcal/kg and 1.5 g/kg provided no increased risk of hyperglycemia and infectious complications [4].

Immunonutrition

Immunonutrition is based on the concept that malnutrition impairs immune function, and supranormal quantities of nutrients are thus supplied to achieve pharmacological effects via the enteral or parenteral route. Immunonutrition involves the addition of supplements such as arginine, omega-3 fatty acids, and glutamine to enteral and parenteral feeds to upregulate the immune response, to control the inflammatory response, and to improve gut function after surgery. Glutamine is essential for lymphocyte proliferation and cytokine production, macrophage phagocytic and secretory activities, and neutrophil bacterial killing [5]. Arginine supplementation can stimulate T cell and natural killer cell activity and promotes t pro-inflammatory cytokine production [6]. The anti-inflammatory properties of omega-3 fatty acids on macrophages reduces the secretion of proinflammatory cytokines, modulates neutrophil function, and modulates the production of reactive oxygen species and cytokines [7].

Previous studies have shown that perioperative immunonutrition improved short-term outcomes in patients who underwent elective major gastrointestinal (GI) surgery. In addition, immunonutrition in patients receiving TPN for acute pancreatitis reduces length of stay, infectious complications, and mortality. Reduction of surgical site infection in gynecologic oncology patients receiving immune modulating dietary supplements has also been documented as a benefit of this type of nutrition [8].

Drug administration

In patients receiving concomitant drug administration in addition to TPN, the use of a multi-lumen central venous catheter is recommended, with a designated port for TPN. In some intensive care units, drugs may be added to the TPN mixture [56,58]. Adding the drug into the parenteral nutrition bag is a frequently encountered practice due to its various advantages, including lack of a need for additional fluids in patients with fluid restriction, low venous catheter requirement, and reduced time of administration [56,58]. However, the risks of stability and incompatibility problems are very high due to the presence of several nutrients in parenteral nutrition admixtures (lipid emulsion, amino acids, glucose, trace elements, vitamins, electrolytes). Consequently, addition of most drugs into parenteral nutrition solutions is not recommended [56,58].

The two drugs which are commonly added to the TPN solution, are ranitidine and famotidine, as these drugs are given to reduce the pH of the stomach and are compatible additions to the TPN mixture. Adding insulin infusions are clinically safe with TPN, however caution needs to be taken as case reports of hypoglycemia have been described. Other drugs should not be added to the TPN mixture [9].

Additionally, liver damage secondary to TPN administration can lead to reduction of the CYP-450 enzymes and can have an effect on drug metabolism. Furthermore, TPN mixtures are hyperosmolar solutions which can affect total volume and extracellular fluid volume in the body. As a result of an increased extracellular fluid volume, drugs that are specially distributed into extracellular fluids (aminoglycoside, beta-lactam antibiotics, etc.) may be affected and changes in their pharmacological effects can be observed [4].

Antibiotic prophylaxis

The routine use of antibiotic prophylaxis via either systemic or local antibiotic administration is not routinely recommended in patients with CVC for TPN as it does not reduce the risk of catheter related bacterial infections [10]. The European Society on Parenteral Nutrition (ESPEN) guidelines recommend using tunnelled and implanted catheters (value only confirmed in long-term use), antimicrobial coated catheters (value only shown in short-term use), single-lumen catheters,

peripheral access (PICC) when possible, appropriate choice of the insertion site (preference of internal jugular and subclavian compared to femoral sites), ultrasound-guided venepuncture, use of maximal barrier precautions during insertion, proper education and specific training of the staff, an adequate policy of hand washing, use of 2% chlorhexidine as skin antiseptic, appropriate dressing of the exit site, disinfection of hubs, stopcocks, and needle-free connectors, and regular change of administration sets. These have been well-documented ways to reduce the risk of CVC related infections [10].

Postoperative care

Delirium screening

Delirium is an acute neuropsychiatric syndrome involving global cognitive dysfunction and inattention caused by reversible neuronal disruption [65]. Delirium is a clinically based diagnosis and may involve alterations in level of consciousness throughout the day, disorganized thinking, and hallucinations. Delirium is further specified by the underlying etiology which includes: substance withdrawal, substance intoxication, delirium due to comorbidities, and delirium resulting from multiple etiologies [66]. Postoperative delirium is recognized from within 10 min after emergence from anesthesia to as late as 7 days after the operation [67]. Delirium may affect patients of all ages, but is more prevalent in older individuals, especially those with cognitive impairment at baseline [68]. See Table 3.

Preoperative screening for delirium should include assessment of vision and hearing as declines in sensory input exacerbate delirium. Encouraging patients to bring glasses and hearing aids will help to improve sensory input postoperatively [68]. Validated delirium screening instruments should be administered in the postoperative period for early detection [18]. In high risk individuals, use of daily assessments for delirium may be considered up until the fifth postoperative day [69]. Detection of postoperative delirium should prompt evaluation of triggers for inciting delirium which include poorly managed pain, infection, hypoxia, electrolyte derangements, urinary retention, fecal impaction, hypoglycemia, and medications [70]. Methods to prevent postoperative delirium include cognitive stimulation, early mobilization, avoiding medications known to induce delirium (including benzodiazepines), and adequate fluid and nutrition. Following the appropriate pain management, nutrition, bowel, and monitoring protocols is essential in combating delirium in older adult individuals.

Age-appropriate care in inpatient routine

Proper preventative measures in the nursing care of older adult individuals can reduce the risk of delirium by as much as 30–50% [3]. Care for these patients should include prevention of falls, dietary and fluid logs, and sufficient pain management. Non-pharmacologic care includes:

- Early mobilization
- Frequent orientation

Table 3
Risk Factors for Delirium.

• Preexisting cognitive impairment
• Age >65 y
• Hearing or vision impairment
• Inadequately controlled pain
• Sleep deprivation or disturbance
• Poor nutrition/hydration
• Polypharmacy
• Functional status determined by Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs)
• Abnormal Lab Values
• Depression
• Comorbidities—Including Alcohol Misuse

- Stimulation and communication
- Regulation of the sleep-wake rhythm
- Involvement of contacts close to the individual

Care for older adult individuals includes reducing use of potentially harmful and unnecessary interventions. This includes documenting indications for Foley catheter indication, as retention of catheters increases risk for urinary tract infections. Furthermore, implementing Beers' criteria can avoid use of inappropriate medications. Additionally, for individuals who cannot mobilize early, frequent reposition should be considered to prevent pressure ulcers.

Postoperative resumption of normal diet

Early resumption of a normal diet reduces the risk of infection and reduces the length of hospital stay. Early encouragement of food and fluid intake is especially important in older adult individuals as they typically have a reduced sense of hunger and thirst [3]. As the risk of dysphagia is increased in the postoperative period, all older adult patients should have the head of their bed elevated during eating and for 1 h after eating [70]. Monitoring of urine and stool output helps to ensure adequate hydration and nutritional status. In patients with a body mass index of <22 kg/m^2, enteral supplements combined with parenteral supplements should be given if oral food intake is inadequate [19].

Exercise programs

Immobilization after surgery results in early and rapid muscle loss. In older adult patients with lower physiologic reserve, further muscle wasting may have profound effects on function [71]. Therapeutic exercise in the perioperative period improves functional status, thereby reducing the risk of delirium [72]. In elective procedures, exercise programs should be initiated preoperatively to improve cardiorespiratory function [20]. Preoperative physical therapy has been demonstrated to reduce postoperative pulmonary complications, including pneumonia and atelectasis, that are associated with cardiovascular surgery [73]. Postoperative exercise and mobilization should begin as soon as possible following surgery, as prolonged immobilization is associated with complications and worsened functional outcomes [74]. The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Best Practices Guideline suggests focus on balance, gait, and positioning assistance [70]. Postoperative exercise therapy should be aimed at the retraining of functional abilities and can be initiated as early as 4 h after surgery [75]. Preliminary reconditioning programs have been demonstrated to be safe and feasible in the inpatient setting after surgery [71].

6-Minute walk test

The 6-minute walk test (6MWT) is a simple and well tolerated method of assessing patients' functional exercise capacity. It measures the distance that an individual can quickly walk on a flat surface in 6 min. A 6MWT allows for concurrent evaluation of multiple organ systems including cardiovascular, pulmonary, musculoskeletal, peripheral circulation, and neuromuscular units, as all of these must be functioning to tolerate a brisk 6-minute walk. Unlike other methods of testing functional exercise capacity, it requires no equipment and allows for breaks as needed throughout the exercise. While it does not assess maximal levels of exertion, it may better reflect functional exercise levels important for ADLs, as these tasks are performed at submaximal exertion [76]. 6MWT is well tolerated by most patients and has few contraindications as listed below.

Absolute Contraindications:

- Unstable angina within one month prior
- Myocardial infarction within one month prior

Relative Contraindications:

- Resting heart rate >120
- Systolic blood pressure >180 mmHg
- Diastolic blood pressure >100 mm Hg

6MWTs are typically done before and after therapeutic interventions to evaluate for clinical improvements or to predict risk of complications prior to surgery. Multiple studies have demonstrated the utility of the 6MWT in predicting cardiopulmonary complications after surgeries requiring general anesthesia [21,77–79].

Future directions in preoperative frailty assessment

As discussed herein, it is well established that preoperative frailty is associated with poorer outcomes after surgeries. Frailty is associated with increased length of stay in hospitals, higher rates of complications, and overall mortality. What remains unanswered is how to best assess preoperative frailty and how to efficiently address preoperative frailty to improve outcomes. As different surgeries trigger stress reactions of varying degrees, depending on the invasiveness, duration of surgery, and other factors, studying the effects of preoperative frailty in different types of surgery is important moving forward [4]. As standardized methods of preoperative frailty assessment come into practice, the detection of frailty should prompt initiation of interventions that aim to reduce adverse sequelae. These may include the initiation of Enhanced Recovery After Surgery protocols which have been demonstrated to improve outcomes in older adult patients undergoing colorectal surgery [80,81]. Prehabilitation aimed at improving functional status, as discussed earlier, should be implemented upon detecting frailty prior to elective surgeries.

Summary

Addressing frailty and mitigating its consequences should ideally be done well before surgery; however, there is data to support a beneficial role preoperatively. Validated assessments of functional status and potential risks of surgery allows for the perioperative team to adequately address issues to improve clinical outcomes. By addressing factors that influence frailty, the healthcare team has the potential to improve clinical outcomes of the most vulnerable patient population. Targeted approaches to address frailty in the preoperative, intraoperative, and postoperative periods can help to reduce postoperative morbidity and mortality.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Practice points

- The growing rate of the older adult population has become an emerging concern for anesthesiologists and the entire perioperative healthcare team.
- Older adult individuals have a higher prevalence of pre-existing comorbidities and risk factors that put them at higher risk for adverse sequalae compared to younger individuals.
- Improving postoperative care in the older adult population begins with identifying and addressing pertinent risk factors for major and minor complications.

Research agenda

- Previous studies have shown that risk of postoperative complications, morbidity, hospital length of stay, and 30-day and long-term mortality after general surgical procedures in older adults is increased related to an increase in baseline frailty.
- Evidence from these studies indicates the potential benefit of including a standard assessment of frailty as part of the preoperative workup of older adult patients.
- Moving forward, studies addressing the focuses of validated frailty assessments and the quantification of their predictive capabilities in various surgeries are needed.

Declaration of Competing Interest

None.

References

[1] Control C for D. Public health and aging: trends in aging — United States and worldwide. MMWR Wkly 2003;101–6. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5206a2.htm.
[2] Bissot M, Henin PY, Aunac S, et al. Preoperative frailty assessment: a review. Acta Anaesthesiol Belg 2016;67:157–73.
*[3] Olotu C, Weimann A, Bahrs C, et al. The perioperative care of older patients-time for a new, interdisciplinary approach. Dtsch Arztebl Int 2019;116:63. https://doi.org/10.3238/arztebl.2019.0063.
*[4] Ko FC. Preoperative frailty evaluation: a promising risk-stratification tool in older adults undergoing general surgery. Clin Therapeut 2019;41:387–99. https://doi.org/10.1016/j.clinthera.2019.01.014.
*[5] Eamer GJ, Clement F, Holroyd-Leduc J, et al. Frailty predicts increased costs in emergent general surgery patients: a prospective cohort cost analysis. Surg (United States) 2019;166:82–7. https://doi.org/10.1016/j.surg.2019.01.033.
[6] Eamer G, Gibson JA, Gillis C, et al. Is current preoperative frailty assessment adequate? Can J Surg 2017;60:367–8. https://doi.org/10.1503/cjs.001417.
*[7] Acosta A, Garzon MP, Urman RD. Screening and diagnosing frailty in the cardiac and noncardiac surgical patient to improve safety and outcomes. Int Anesthesiol Clin 2019;57:111–22. https://doi.org/10.1097/AIA.0000000000000239.
*[8] Jablonski SG, Urman RD. The growing challenge of the older surgical population. Anesthesiol Clin 2019;37:401–9. https://doi.org/10.1016/j.anclin.2019.04.001.
[9] Alvarez-Nebreda ML, Bentov N, Urman RD, et al. Recommendations for preoperative management of frailty from the society for perioperative assessment and quality improvement (SPAQI). J Clin Anesth 2018;47:33–42. https://doi.org/10.1016/j.jclinane.2018.02.011.
[10] Kim DH, Kim CA, Placide S, et al. Preoperative frailty assessment and outcomes at 6 months or later in older adults undergoing cardiac surgical procedures: a systematic review. Ann Intern Med 2016;165:650–60. https://doi.org/10.7326/M16-0652.
*[11] Elhassan A, Elhassan I, Elhassan A, et al. Perioperative surgical home models and enhanced recovery after surgery. J Anaesthesiol Clin Pharmacol 2019;35:46–50. https://doi.org/10.4103/joacp.JOACP_47_18.
*[12] Kaye A, Urman R, Cornett E, et al. Enhanced recovery pathways in orthopedic surgery. J Anaesthesiol Clin Pharmacol 2019;35:35–9. https://doi.org/10.4103/joacp.JOACP_35_18.
*[13] Kendrick J, Kaye A, Tong Y, et al. Goal-directed fluid therapy in the perioperative setting. J Anaesthesiol Clin Pharmacol 2019;35:29–34. https://doi.org/10.4103/joacp.JOACP_26_18.
*[14] Elias KM, Stone AB, McGinigle K, et al. The reporting on ERAS compliance, outcomes, and elements research (RECOvER) checklist: a joint statement by the ERAS® and ERAS® USA societies. World J Surg 2019;43:1–8. https://doi.org/10.1007/s00268-018-4753-0.
[15] Gupta R, Gan TJ. Preoperative nutrition and prehabilitation. Anesthesiol Clin 2016;34:143–53. https://doi.org/10.1016/j.anclin.2015.10.012.
[16] Mazzola P, Ward L, Zazzetta S, et al. Association between preoperative malnutrition and postoperative delirium after hip fracture surgery in older adults. J Am Geriatr Soc 2017;65:1222–8. https://doi.org/10.1111/jgs.14764.
[17] Ringaitiene D, Gineityte D, Vicka V, et al. Impact of malnutrition on postoperative delirium development after on pump coronary artery bypass grafting. J Cardiothorac Surg 2015;10:74. https://doi.org/10.1186/s13019-015-0278-x.
[18] Inouye SK, Robinson T, Blaum C, et al. Postoperative delirium in older adults: best practice statement from the American geriatrics society. J Am Coll Surg 2015;220:136–148.e1. https://doi.org/10.1016/j.jamcollsurg.2014.10.019.
[19] Volkert D, Beck AM, Cederholm T, et al. ESPEN guideline on clinical nutrition and hydration in geriatrics. Clin Nutr 2019;38:10–47. https://doi.org/10.1016/j.clnu.2018.05.024.
[20] Lemanu DP, Singh PP, MacCormick AD, et al. Effect of preoperative exercise on cardiorespiratory function and recovery after surgery: a systematic review. World J Surg 2013;37:711–20. https://doi.org/10.1007/s00268-012-1886-4.
*[21] Shulman MA, Cuthbertson BH, Wijeysundera DN, et al. Using the 6-minute walk test to predict disability-free survival after major surgery. Br J Anaesth 2019;122:111–9. https://doi.org/10.1016/j.bja.2018.08.016.
[22] Korenvain C, Famiyeh IM, Dunn S, et al. Identifying frailty in primary care: a qualitative description of family physicians' gestalt impressions of their older adult patients. BMC Fam Pract 2018. https://doi.org/10.1186/s12875-018-0743-4.

[23] Chen CY, Gan P, How CH. Approach to frailty in the elderly in primary care and the community. Singapore Med J 2018. https://doi.org/10.11622/smedj.2018052.
[24] Birkelbach O, Mörgeli R, Spies C, et al. Routine frailty assessment predicts postoperative complications in elderly patients across surgical disciplines - a retrospective observational study. BMC Anesthesiol 2019. https://doi.org/10.1186/s12871-019-0880-x.
[25] Subramaniam A, Tiruvoipati R, Lodge M, et al. Frailty in the older person undergoing elective surgery: a trigger for enhanced multidisciplinary management – a narrative review. ANZ J Surg 2020. https://doi.org/10.1111/ans.15633.
[26] Palmer K, Onder G. Comprehensive geriatric assessment: benefits and limitations. Eur J Intern Med 2018. https://doi.org/10.1016/j.ejim.2018.02.016.
[27] Chan SP, Ip KY, Irwin MG. Peri-operative optimisation of elderly and frail patients: a narrative review. Anaesthesia 2019. https://doi.org/10.1111/anae.14512.
[28] Wischmeyer PE, Carli F, Evans DC, et al. American Society for Enhanced recovery and perioperative quality initiative joint consensus statement on nutrition screening and therapy within a surgical enhanced recovery pathway. Anesth Analg 2018. https://doi.org/10.1213/ANE.0000000000002743.
[29] Stoicea N, Koehler KN, Scharre DW, et al. Cognitive self-assessment scales in surgical settings: acceptability and feasibility. Best Pract Res Clin Anaesthesiol 2018;32(3-4):303–9. https://doi.org/10.1016/j.bpa.2018.08.001.
[30] Arias F, Wiggins M, Urman RD, et al. Rapid in-person cognitive screening in the preoperative setting: test considerations and recommendations from the society for perioperative assessment and quality improvement (SPAQI). J Clin Anesth 2020;62:109724. https://doi.org/10.1016/j.jclinane.2020.109724.
[31] Viramontes O, Luan Erfe BM, Erfe JM, et al. Cognitive impairment and postoperative outcomes in patients undergoing primary total hip arthroplasty: a systematic review. J Clin Anesth 2019;56:65–76. https://doi.org/10.1016/j.jclinane.2019.01.024.
[32] Sherman JB, Chatterjee A, Urman RD, et al. Implementation of routine cognitive screening in the preoperative assessment clinic. A&A Pract 2019;12:125–7. https://doi.org/10.1213/XAA.0000000000000891.
[33] Buettner S, Wagner D, Kim Y, et al. Inclusion of sarcopenia outperforms the modified frailty index in predicting 1-year mortality among 1,326 patients undergoing gastrointestinal surgery for a malignant indication. J Am Coll Surg 2016. https://doi.org/10.1016/j.jamcollsurg.2015.12.020.
[34] Lim B-G, Lee I-O. Anesthetic management of geriatric patients. Korean J Anesthesiol 2020;73:8–29.
[35] Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American college of surgeons national surgical quality improvement program and the American geriatrics society. J Am Coll Surg 2012;215:453–66. https://doi.org/10.1016/j.jamcollsurg.2012.06.017.
[36] Cepeda MS, Farrar JT, Baumgarten M, et al. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther 2003. https://doi.org/10.1016/S0009-9236(03)00152-8.
[37] Uysal Aİ, Altıparmak B, Yaar E, et al. The effects of early femoral nerve block intervention on preoperative pain management and incidence of postoperative delirium geriatric patients undergoing trochanteric femur fracture surgery: a randomized controlled trial. Ulus Travma ve Acil Cerrahi Derg 2020. https://doi.org/10.14744/tjtes.2019.78002.
[38] Garlich JM, Pujari A, Debbi EM, et al. Time to block. J Bone Jt Surg 2020. https://doi.org/10.2106/jbjs.19.01148.
[39] Wu Y, Han R. Perioperative continuous femoral nerve block reduces postoperative cognitive dysfunction of high-risk patients with femoral neck fracture: evidence from a retrospective propensity-matched study. Med Sci Monit 2020. https://doi.org/10.12659/MSM.919708.
[40] Carli F, Bousquet-Dion G, Awasthi R, et al. Effect of multimodal prehabilitation vs postoperative rehabilitation on 30-day postoperative complications for frail patients undergoing resection of colorectal cancer: a randomized clinical trial. JAMA Surg 2020. https://doi.org/10.1001/jamasurg.2019.5474.
[41] Le Roy B, Selvy M, Slim K. The concept of prehabilitation: what the surgeon needs to know? J Visc Surg 2016. https://doi.org/10.1016/j.jviscsurg.2016.01.001.
[42] Santa Mina D, Clarke H, Ritvo P, et al. Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. United Kingdom: Physiother; 2014. https://doi.org/10.1016/j.physio.2013.08.008.
[43] Carli F, Scheede-Bergdahl C. Prehabilitation to enhance perioperative care. Anesthesiol Clin 2015. https://doi.org/10.1016/j.anclin.2014.11.002.
[44] Jahic D, Omerovic D, Tanovic AT, et al. The effect of prehabilitation on postoperative outcome in patients following primary total knee arthroplasty. Med Arch 2018. https://doi.org/10.5455/medarh.2018.72.439-443.
[45] Wang L, Lee M, Zhang Z, et al. Does preoperative rehabilitation for patients planning to undergo joint replacement surgery improve outcomes? A systematic review and meta-analysis of randomised controlled trials. BMJ Open 2016. https://doi.org/10.1136/bmjopen-2015-009857.
[46] Schwegler I, Von Holzen A, Gutzwiller JP, et al. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. Br J Surg 2010. https://doi.org/10.1002/bjs.6805.
[47] Evans DC, Martindale RG, Kiraly LN, et al. Nutrition optimization prior to surgery. Nutr Clin Pract 2014. https://doi.org/10.1177/0884533613517006.
[48] Braga M, Ljungqvist O, Soeters P, et al. ESPEN guidelines on parenteral nutrition: surgery. Clin Nutr 2009. https://doi.org/10.1016/j.clnu.2009.04.002.
[49] Gouin JP, Kiecolt-Glaser JK. The impact of psychological stress on wound healing: methods and mechanisms. Immunol Allergy Clin North Am 2011. https://doi.org/10.1016/j.iac.2010.09.010.
[50] Munafò MR, Stevenson J. Anxiety and surgical recovery: reinterpreting the literature. J Psychosom Res 2001. https://doi.org/10.1016/S0022-3999(01)00258-6.
[51] Powell R, Scott NW, Manyande A, et al. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database Syst Rev 2016. https://doi.org/10.1002/14651858.CD008646.pub2.
[52] Allen S, Brown V, Prabhu P, et al. A randomised controlled trial to assess whether prehabilitation improves fitness in patients undergoing neoadjuvant treatment prior to oesophagogastric cancer surgery: study protocol. BMJ Open 2018. https://doi.org/10.1136/bmjopen-2018-023190.

[53] Van Rooijen S, Carli F, Dalton S, et al. Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications: the first international randomized controlled trial for multimodal prehabilitation. BMC Canc 2019. https://doi.org/10.1186/s12885-018-5232-6.
[54] Abunnaja S, Cuviello A, Sanchez JA. Enteral and parenteral nutrition in the perioperative period: state of the art. Nutrients 2013;5:608–23. https://doi.org/10.3390/nu5020608.
[56] Ekincioğlu AB, Demirkan K. Clinical nutrition and drug interactions. Ulus Cerrahi Derg 2013;29:177–86. https://doi.org/10.5152/UCD.2013.112013.
[57] Pasquel FJ, Spiegelman R, McCauley M, et al. Hyperglycemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. Diabetes Care 2010;33:739–41. https://doi.org/10.2337/dc09-1748.
[58] Gosmanov AR, Umpierrez GE. Management of hyperglycemia during enteral and parenteral nutrition therapy. Curr Diab Rep 2013;13:155–62. https://doi.org/10.1007/s11892-012-0335-y.
[65] Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nat Rev Neurol 2009;5:210–20. https://doi.org/10.1038/nrneurol.2009.24.
[66] Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-20181. J Alzheimers Dis 2018;66:1–10. https://doi.org/10.3233/JAD-189004.
[67] Oh ST, Park JY. Postoperative delirium. Korean J Anesthesiol 2019;72:4–12. https://doi.org/10.4097/kja.d.18.00073.1.
[68] Rudolph JL, Marcantonio ER. Postoperative Delirium: acute change with long-term implications. Anesth Analg 2011;112:1202–11. https://doi.org/10.1213/ANE.0b013e3182147f6d.
[69] Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol 2017;34:192–214. https://doi.org/10.1097/EJA.0000000000000594.
[70] Mohanty S, Rosenthal RA, Russell MM, et al. Optimal perioperative management of the geriatric patient: a best practices guideline from the American college of surgeons NSQIP and the American geriatrics society. J Am Coll Surg 2016;222:930–47. https://doi.org/10.1016/j.jamcollsurg.2015.12.026.
[71] McComb A, Warkentin LM, McNeely ML, et al. Development of a reconditioning program for elderly abdominal surgery patients: the Elder-friendly Approaches to the Surgical Environment-BEdside reconditioning for Functional ImprovemenTs (EASE-BE FIT) pilot study. World J Emerg Surg 2018;13:21. https://doi.org/10.1186/s13017-018-0180-7.
[72] Hoogeboom TJ, Dronkers JJ, Hulzebos EHJ, et al. Merits of exercise therapy before and after major surgery. Curr Opin Anaesthesiol 2014;27:161–6. https://doi.org/10.1097/ACO.0000000000000062.
[73] Hulzebos EH, Smit Y, Helders PP, et al. Preoperative physical therapy for elective cardiac surgery patients. Cochrane Database Syst. Rev.. John Wiley & Sons, Ltd; 2012. https://doi.org/10.1002/14651858.cd010118.pub2.
[74] Patel BK, Hall JB. Perioperative physiotherapy. Curr Opin Anaesthesiol 2013;26:152–6. https://doi.org/10.1097/ACO.0b013e32835e8b34.
[75] Ibrahim MS, Khan MA, Nizam I, et al. Peri-operative interventions producing better functional outcomes and enhanced recovery following total hip and knee arthroplasty: an evidence-based review. BMC Med 2013;11:37. https://doi.org/10.1186/1741-7015-11-37.
[76] Crapo RO, Casaburi R, Coates AL, et al. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7. https://doi.org/10.1164/ajrccm.166.1.at1102.
[77] Km H, Ja T, Burrell M, et al. Venous thrombotic, thromboembolic, and mechanical complication safterretrievable inferior vena cava filters for major trauma. Br J Anaesth 2015;99:6–9. https://doi.org/10.1093/bja.
[78] Miccichè V, Esposito C, Santaniello W, et al. Six-minute walk test in pre-operative evaluation of patients for upper abdominal surgery. Eur J Anaesthesiol 2019;36:164–6. https://doi.org/10.1097/EJA.0000000000000904.
[79] Keeratichananont W, Thanadetsuntorn C, Keeratichananont S. Value of preoperative 6-minute walk test for predicting postoperative pulmonary complications. Ther Adv Respir Dis 2016;10:18–25. https://doi.org/10.1177/1753465815615509.
[80] Braga M, Pecorelli N, Scatizzi M, et al. Enhanced recovery program in high-risk patients undergoing colorectal surgery: results from the PeriOperative Italian society registry. World J Surg 2017;41:860–7. https://doi.org/10.1007/s00268-016-3766-9.
[81] Ljungqvist O, Hubner M. Enhanced recovery after surgery—ERAS—principles, practice and feasibility in the elderly. Aging Clin Exp Res 2018;30:249–52. https://doi.org/10.1007/s40520-018-0905-1.