

REVIEW

Unmet needs in surgical prehabilitation: a narrative review

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Abstract

To date, surgery remains the only curative treatment for many pathological conditions, and the number of surgical procedures is expected to increase in the coming years. Continuous advances in medical care now allow invasive procedures to be planned even for elderly and frail patients who were previously considered unsuitable for surgery. Combined with the general aging of the population, this has resulted in an increase in the number of frail patients undergoing surgery, who are more prone to postoperative complications and significant functional decline. It is, therefore, crucial to utilize the entire preoperative period not only to stratify preoperative risk but, shifting from a reactive to a proactive approach, also to optimize patients' functional capacity through multimodal prehabilitation programs. After an initial assessment, surgical patients should receive a personalized, multidisciplinary optimization program aimed at improving their physical, nutritional, and psychological status. Clinical and scientific interest in prehabilitation has grown substantially in recent years. However, several unmet needs about prehabilitation still remain. In this narrative review we examine and discuss the current state of the art in prehabilitation, focusing specifically on unanswered questions and possible future developments.

Keywords

Prehabilitation; Anesthesia; Surgery; Cancer; Preoperative care

1. Introduction

Every year, more than 200 million people worldwide undergo major surgery [1]. Recent data report that more than 49 million patients experience at least one postoperative complication and that more than 3 million die within 30 days after surgery [2]. Therefore, careful planning of all phases of the perioperative period is essential to reduce postoperative morbidity and mortality.

Advances in intraoperative management and in postoperative monitoring are critical to improving patient outcomes, however, prevention of postoperative complications should begin in the preoperative period. A modern preoperative evaluation should provide not only a specific risk assessment, appropriate anesthetic planning, comprehensive patient education through shared decision-making, and interdisciplinary communication between healthcare professionals, but also optimization of functional capacity, including physical, nutritional, and psychological status [3]. Traditional preoperative risk scores may, therefore, no longer be sufficient on their own to accurately estimate the risk of postoperative complications [4], but must be combined with a comprehensive assessment of functional capacity. In a large randomized clinical trial (RCT), Wijeyesundera *et al.* [5] demonstrated that higher preoperative

functional capacity, assessed using the Duke Activity Status Index (DASI) questionnaire, is associated with a reduced postoperative morbidity and mortality after major surgery. In a prospective observational study of 38,293 patients, functional capacity classified by metabolic equivalent of tasks (MET) was associated with long and short-term morbidity and mortality in a dose-response-like manner [6]. Therefore, effective clinical strategies aimed at improving preoperative functional capacity, such as prehabilitation, could have a significant beneficial impact on clinical outcomes.

According to the most recent definition "Prehabilitation is a process from diagnosis to surgery, consisting of one or more preoperative interventions of exercise, nutrition, psychological strategies, and respiratory training, that aims to enhance functional capacity and physiological reserve to allow patients to withstand surgical stressors, improve postoperative outcomes, and facilitate recovery" [7]. By focusing on functional capacity and physiological reserve, prehabilitation is closely linked to the patient's frailty as it reflects reduced physiological reserve and increased vulnerability to surgical stress, and has been associated with worse postoperative outcomes [8]. From this perspective, frailty assessment may help identify patients who are most likely to benefit from prehabilitation programs, while

prehabilitation may target potentially modifiable frailty-related domains, including physical performance, nutritional status, respiratory function, and psychological resilience [9, 10]. In addition to patient-related factors, the type and magnitude of surgery and the complexity of anesthetic management should also be considered, as perioperative risk is influenced by multiple clinical and procedure-related factors [11], several of which may be addressed through perioperative optimization and prehabilitation strategies.

The continuing scientific interest in this topic is confirmed by the publication of over 3000 scientific articles on prehabilitation on PubMed in the last five years (>1000 in the year 2025). However, several clinical and scientific aspects of prehabilitation are not yet fully clarified. In 2023 a consensus of international experts identified the main research priorities in prehabilitation, including the need to define the optimal composition of prehabilitation programs, their impact on relevant clinical outcomes, and their optimal mode of delivery and duration [12].

To the best of our knowledge, this is the first narrative review specifically aimed at summarizing and discussing the most important scientific evidence on prehabilitation, focusing on possible unmet needs, emerging trends and future developments (Fig. 1). By integrating the available literature from this perspective, this review seeks to provide an updated overview of the field and to identify key priorities for future research and clinical implementation.

2. Search strategy

We identified key areas of research on surgical prehabilitation that still lack solid scientific support, including the optimal composition of prehabilitation programs, the impact of prehabilitation on relevant clinical outcomes, the optimal delivery

modality and duration of prehabilitation, cost-effectiveness analyses, the role of potential biomarkers as indicators of prehabilitation effectiveness, and possible future directions in this field.

Four authors independently searched PubMed, Scopus, and Google Scholar to identify relevant studies, from their inception to June 2026, that evaluated the selected topics related to surgical prehabilitation. Two additional authors independently determined study eligibility. Any discrepancies were solved by a third senior investigator. No specific exclusion criteria were used. Based on the authors' assessment, the most recent and scientifically relevant studies evaluating the role of selected items in surgical prehabilitation were included in the final analysis.

3. Unmet needs in prehabilitation

3.1 Optimal composition of prehabilitation program

Prehabilitation programs are typically based on a multimodal, multidisciplinary approach and involve various healthcare professionals aimed at improving perioperative functional capacity and physiological reserve, including nutritionists, physiotherapists, and psychologists (Table 1). However, in some cases, unimodal treatments are described, focusing exclusively on nutritional or physical optimization.

In 2022, McIsaac presented an umbrella review of 55 meta-analyses on surgical prehabilitation, highlighting the high heterogeneity observed in prehabilitation treatments. Indeed, the included reviews presented prehabilitation programs focused on both unimodal and multimodal treatments. Furthermore, high variability was also observed in adopted nutritional and exercise programs. The most common types of physical exercises were strength and aerobic training, followed by res-

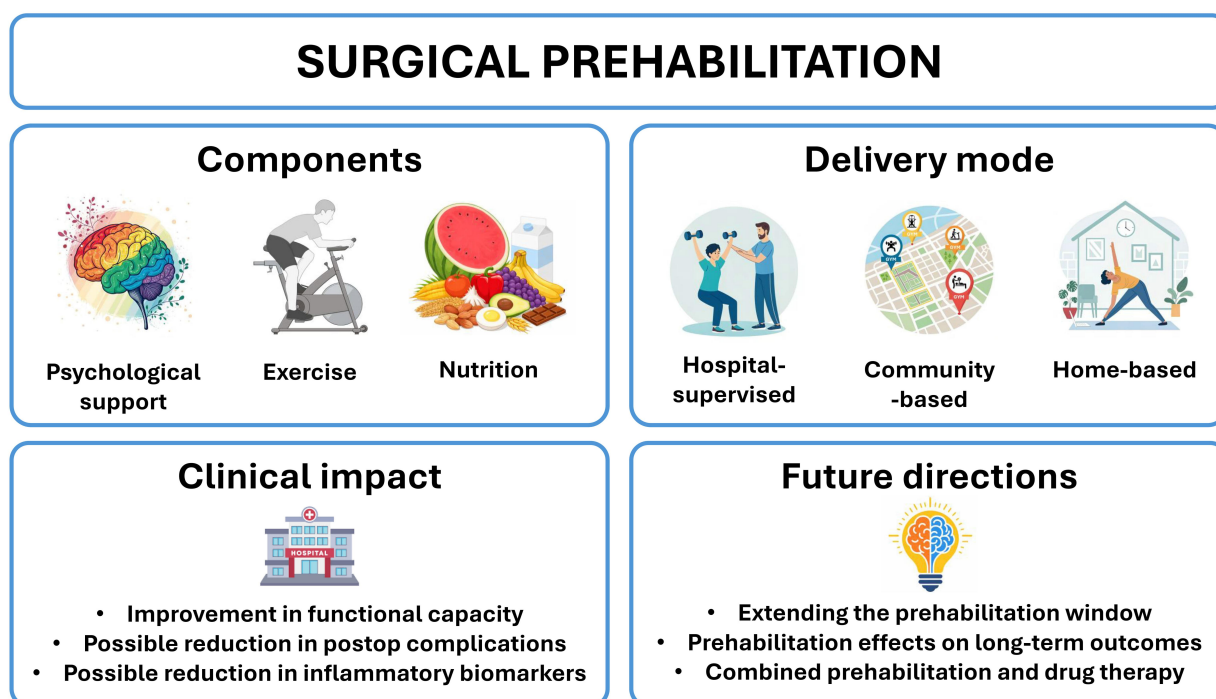


FIGURE 1. Visual abstract.

TABLE 1. Multimodal prehabilitation.

Multimodal prehabilitation	Physical	Nutritional	Psychological
Baseline assessment	-6-minute walking test -Gait Speed test -Handgrip strength test -Time Up and Go test	-Body Mass Index -Bioimpedance analysis -Patient-Generated Subjective Global Assessment	-Hospital Anxiety and Depression Scale -EuroQol-5D
Intervention	-Endurance exercise (HIIT or MICT) -Resistance exercise	-Comprehensive tailored diet management program	-Relaxation techniques -Cognitive interventions

HIIT, high-intensity interval training; MICT, moderate intensity continuous training.

piratory and stretching exercises; while nutritional programs included nutritional counselling, dietary supplementation or both [13].

In addition to exercise and nutrition, psychological support is increasingly recognized as an important component of multimodal prehabilitation. Psychological factors may influence perioperative recovery and programs often include psychological evaluation and targeted interventions, such as cognitive-behavioral therapy, mindfulness, relaxation techniques, stress management, and patient education [14, 15]. Recent evidence suggests that multimodal prehabilitation programs incorporating psychological components may reduce anxiety, improve recovery, and potentially reduce postoperative complications [15, 16].

Notably, a meta-analysis of studies enrolling patients undergoing surgery for esophagogastric cancer found that multimodal prehabilitation was associated with a reduction in overall complication rate, while unimodal treatment was not [17]. On the contrary, a different meta-analysis of 25 studies evaluating surgical prehabilitation showed no difference between unimodal and multimodal prehabilitation on relevant clinical outcomes [18].

The latest Enhanced Recovery After Surgery (ERAS) guidelines on colorectal surgery do not recommend a specific prehabilitation regimen, due to inconsistent program definitions across studies (in the context of colorectal surgery for cancer, 15 studies focused on multimodal interventions and 5 on physical exercise alone) [19].

In 2025, McIsaac *et al.* [20] analyzed 186 randomized trials including 15,684 patients and found that exercise-based, nutritional, and exercise-containing multicomponent prehabilitation were the strategies most consistently associated with improved postoperative outcomes, including complications, length of hospital stay (LOS), quality of life, and physical recovery. In the component analysis, exercise and nutrition emerged as the individual components most likely to improve critical outcomes. However, the certainty of evidence was generally low to very low, mainly because of trial-level risk of bias.

In conclusion, although recent evidence suggests that exercise and nutrition are the most promising core components of prehabilitation, there is no strong consensus on the optimal composition of a prehabilitation program (multimodal or unimodal) or on the specific elements of each module (type of nutrition, physical activity, psychological support), partly due to the need to tailor each treatment to the patient's characteristics,

the surgical context, and available local resources.

3.2 Impact of prehabilitation on relevant clinical outcomes

Several studies showed that prehabilitation, compared with standard care, is associated with improved functional capacity [21, 22]. It remains unclear whether these positive changes in physical and nutritional status are also associated with improved clinical outcomes, such as reduced postoperative complications, shorter LOS, and lower mortality [20].

The latest ERAS guidelines on colorectal surgery indicate a possible beneficial effect of prehabilitation in this surgical setting, with a moderate level of evidence for improving functional capacity and a low level of evidence for reducing LOS and postoperative complications [19]. Indeed, most studies analyzing prehabilitation, due to small sample sizes and a single-center design, were not sufficiently powered to establish the impact of prehabilitation on relevant clinical outcomes. In 2024, the PREHAB RCT randomized 251 patients scheduled for colorectal cancer surgery to receive either a 4-weeks hospital-supervised prehabilitation or standard treatment. Prehabilitation was shown to be effective in reducing postoperative complications compared with standard treatment. Notably, this difference was statistically significant for severe complications, according to the Comprehensive Complication Index (CCI), and for medical complications (Table 2). However, among the study's limitations, it is important to highlight the inability to reach the planned sample size (714 patients) due to the COVID-19 pandemic [23].

Furthermore, while it is reasonable to expect a greater effect of prehabilitation in patients with lower baseline functional capacity, it is unclear whether specific patient subgroups may benefit more from prehabilitation in terms of clinical outcomes. Accordingly, prehabilitation should not be regarded as a universal standard intervention for all frail patients, but as a targeted and individualized strategy, particularly for those with modifiable impairments and sufficient time for preoperative optimization. Recent evidence in frail surgical populations suggests potential reductions in overall postoperative complications, but also highlights heterogeneous effects and uncertain benefits on major postoperative outcomes [24, 25].

The single-center PREHEP study evaluated the effect of 6-week prehabilitation in 60 sarcopenic patients undergoing major oncological liver surgery. The authors found that, in this population, prehabilitation was associated with a significant reduction in overall and major morbidity compared with

TABLE 2. Assessment of the severity of post-operative complications.

Clavien-Dindo Classification*
Grade I—Any deviation from the ordinary post-operative course without giving pharmacological and surgical/endoscopic interventions
Grade II—Complication requires pharmacological treatment
Grade IIIa—Complication requires surgical intervention not under general anesthesia
Grade IIIb—Complication requires surgical intervention under general anesthesia
Grade IV—Life-threatening complication that requires intensive care unit management
Grade IVa—Single-organ dysfunction
Grade IVb—Multi-organ dysfunction
Grade V—Death

*Modified from Bolliger M, Kroehnert JA, Molineus F, Kandioler D, Schindl M, Riss P. Experiences with the standardized classification of surgical complications (Clavien-Dindo) in general surgery patients. *European Surgery*. 2018; 50: 256–261. The Clavien-Dindo classification captures only the highest grade of complication, which can underestimate the impact of multiple minor complications. The Comprehensive Complication Index (CCI) is a sum of all complications tabulated according to the Clavien-Dindo classification and weighted for their severity.

standard care [26].

3.3 Mode of delivery, adherence, and compliance

After baseline assessment phase, patients undergoing prehabilitation are required to complete the assigned program. Prehabilitation can be completed at home (home-based prehabilitation) or through periodic sessions held in hospital (hospital-supervised prehabilitation). Depending on the local organization, a special form of supervised prehabilitation may be performed at the community level [27].

No large-scale studies compared home-based prehabilitation with hospital-supervised prehabilitation. The potential benefits of supervised programs include professional monitoring of exercise quality and quantity, as well as individualized progression, useful to improve adherence, and strong motivation. Conversely, high costs, high resource requirements (space, equipment, personnel), limited accessibility, and poor scheduling flexibility can be considered as possible limitations. On the other hand, high accessibility and convenience, flexible schedule, low costs and resource requirements are the strengths of home-based programs. The effectiveness of home-based approach may be weakened by limited supervision and monitoring, the risk of low adherence and motivation, the difficulty of objectively monitoring progress, and the need for digital literacy when using mobile or web applications.

In 2022, an RCT on 204 frail patients undergoing elective cancer surgery showed no effect of home-based prehabilitation compared with standard care on functional capacity or postoperative complication rates. However, patients who completed more than 80% of the prescribed prehabilitation protocol presented significant improvements in six-minute walk test performance and a reduction in postoperative complications [28]. In 2025, D'Amico *et al.* [29] analyzed 29 RCTs including 3508 patients, comparing home-based prehabilitation programs with standard care. Home-based prehabilitation was associated with a reduction in postoperative complication rate, levels of anxiety and depression, LOS, and an improvement in

functional capacity, as measured by the six-minute walk test. The median proportion of patients who were adherent to the program was 82%.

The recent PREPARE study enrolled 834 frail patients, defined as those aged 65 years and older with a Clinical Frailty Scale score of 4 or higher, to receive either home-based prehabilitation or standard of care, representing the largest RCT of its kind. Home-based prehabilitation was not associated with an improvement in the 30-day disability score, as measured by the World Health Organization Disability Assessment Schedule (WHODAS), and in the rate of postoperative complications. Adherent patients, defined as those who completed more than 75% of the program for at least 3 weeks, were included in the per-protocol analysis, in which the comparison between prehabilitation and standard care showed an improvement in the 30-day disability score [25]. A subsequent RCT evaluating home-based prehabilitation in 347 frail patients undergoing gastrectomy for cancer demonstrated that this preoperative multimodal treatment was effective in reducing minor and medical complications, as well as in improving postoperative recovery [30].

Therefore, home-based prehabilitation appears to be potentially useful for improving functional capacity and postoperative outcomes. However, although its effectiveness requires strict adherence to the prescribed program, there is no single, clear definition of adherence in prehabilitation, as studies have used different methods and metrics to assess it, primarily based on varying thresholds for program duration and the number of training sessions completed [31]. Given this, it is crucial for home-based programs to identify simple and effective methods to measure and verify adequate patient adherence. Furthermore, frail patients, who could benefit most from prehabilitation, may not be suitable for home-based prehabilitation due to potential poor adherence to prescribed treatment in the absence of adequate supervision. Direct comparisons between studies are also difficult due to the different criteria used to identify frail patients.

A meta-analysis of 23 studies (13 RCTs and 10 observational

studies, including 1849 patients), reported a good level of adherence (>75%) over different models, settings, and durations of prehabilitation [32]. Among factors that may negatively influence adherence to prehabilitation, the authors identified patients' desire for expedited surgery, self-assessment of physical fitness, personal and professional obligations, health problems, holidays, and advancement of surgery. Preliminary evidence suggests the potential effectiveness of online platforms and web applications in increasing patient adherence to prehabilitation [33, 34]. Future studies should aim to better personalize these digital strategies by focusing on reducing potential difficulties in use related to poor digital health literacy [35].

3.4 Optimal duration of prehabilitation programs

There is no strong consensus on the optimal duration of surgical prehabilitation, given the need to strike a balance between surgical planning and allowing sufficient preparation time to achieve significant improvements in functional capacity. Previous reviews and large RCTs have generally reported a mean prehabilitation duration of 4–6 weeks [13, 23].

Notably, recent studies have reported positive results from prehabilitation even when the prehabilitation duration was reduced to three [36] or two weeks [30].

3.5 Optimal outcome measures and patient assessment

Recent evidence shows significant heterogeneity in outcome measures and patient assessment across prehabilitation RCTs, with up to 50 different outcomes and 184 assessment instruments reported, highlighting the need for standardization [37]. Common domains include postoperative complications, LOS, functional recovery, quality of life, psychological outcomes, and biomarkers [37]. This variability is also evident in cancer prehabilitation services, where similar domains are often assessed using different tools and at different time points limiting comparisons across studies and services [38]. Although cardiopulmonary exercise test is considered the gold standard for the objective assessment of exercise capacity, risk stratification, and exercise prescription, it may not be feasible in all settings. Therefore, pragmatic alternatives such as the 6-minute walk test, sit-to-stand tests, and handgrip strength are also important [37, 38]. Assessment should be multidimensional, including frailty, nutritional status, sarcopenia, comorbidities, psychological status, patient-reported outcomes and barriers to adherence [12, 38]. International consensus on a multidisciplinary patient-centered core outcome set is needed to harmonize research, support service evaluation, and guide implementation in routine surgical pathways [12, 37, 38].

3.6 Effects of prehabilitation on biomarkers

A recent scientific report indicated that excessive fat mass may be associated with a proinflammatory state, potentially related to worsening postoperative outcomes, also suggesting that a multimodal prehabilitation treatment may play a beneficial role in patients with excess fat mass [39]. In a prospective

cohort study, Sun *et al.* [40] reported that prehabilitation, compared with standard care, reduced proinflammatory (*e.g.*, Interleukin6 (IL-6) and Tumor Necrosis Factor (TNF)- α) and oxidative stress markers in 110 gastric cancer patients. In addition, Cambriel *et al.* [41] demonstrated that a two-week personalized multimodal prehabilitation program, compared with a standardized optimization protocol, improved functional capacity, immune and cognitive function, and reduced postoperative complications, with significant changes in specific immune biomarkers. These findings suggest that inflammatory and immune-related biomarkers may have translational relevance in prehabilitation, supporting patient selection, perioperative risk stratification, and monitoring of biological response to treatment [41, 42]. In this perspective, biomarkers including C-reactive protein (CRP), IL-6, TNF- α , and white blood cell count may help move prehabilitation toward a more personalized strategy and serve as complementary endpoints alongside functional measures [41–43].

Beyond inflammatory and immune biomarkers, heart rate variability (HRV) is emerging as a non-invasive marker of autonomic nervous system activity and physiological reserve [44]. This may be particularly relevant in prehabilitation, as autonomic dysfunction has been associated with frailty, impaired stress response, inflammation, and worse clinical outcomes, while exercise training may modulate autonomic balance [44]. In line with this perspective, recent perioperative study protocols are exploring the potential role of HRV as a tool for perioperative risk stratification and assessment of functional reserve [45], while two ongoing RCTs (NCT06398301, NCT06744413) are evaluating the potential effect of prehabilitation on HRV and its association with postoperative outcomes [46, 47].

3.7 Cost-effectiveness analysis

The development and implementation of prehabilitation programs are associated with high costs, both in terms of personnel and facilities. Given the presence of several variables, which can affect the entire perioperative period, conducting a cost-effectiveness analysis in this context is particularly challenging. Furthermore, economic evaluations that are valid in a specific clinical context may not be generalizable to others. Rombey *et al.* [48] conducted a systematic review of 45 studies (25 completed and 20 ongoing) comparing prehabilitation with standard care and presenting an economic evaluation. The authors found some evidence suggesting that prehabilitation may be more cost-effective compared with standard care. However, they also highlighted a high risk of bias, low methodological quality of the available data, and substantial heterogeneity in the study populations, thus indicating the need for more rigorous, high-quality research. A recent review identified potential barriers to implementing prehabilitation programs, in addition to cost-effectiveness, including staff shortage and a lack of national policies [49]. These challenges may be even greater in low-income countries, such as Sub-Saharan Africa, due to limited infrastructure, socioeconomic constraints and patient malnutrition, and late diagnosis [50].

4. Future directions

4.1 Extending the prehabilitation window

Neoadjuvant therapy refers to any cancer treatment administered before primary treatment (surgery), with the aim of increasing the chance of success, and includes chemotherapy, radiotherapy, or both. Although it is associated with increased survival rates, neoadjuvant therapy can negatively affect cardiorespiratory capacity and muscle strength, thereby worsening patient quality of life. Preliminary studies evaluated the possibility of extending prehabilitation to the neoadjuvant period, aiming to balance costs, patient adherence, and clinical benefits.

A meta-analysis of 30 studies comparing prehabilitation with standard care during neoadjuvant therapy demonstrated, with a low-to-moderate level of evidence, that prehabilitation in this setting may be feasible and effective in preserving functional capacity and muscle mass, as well as increasing the likelihood of completing neoadjuvant treatment [51]. However, prehabilitation showed no beneficial effects on postoperative complication rate, LOS, and health-related quality of life (Table 3).

4.2 Impact of prehabilitation on long-term outcomes

Current scientific literature has primarily focused on evaluating the effects of surgical prehabilitation on the immediate postoperative period, in terms of clinical outcomes, functional capacity, and quality of life. Given the relatively recent introduction of prehabilitation into clinical practice, high-quality data on its potential effects on long-term survival are lacking.

In a preliminary study, van der Hulst *et al.* [52] analyzed data from 137 patients undergoing elective surgery for colorectal cancer, managed either with standard care or with prehabilitation. In a six-year follow-up, survival rate was similar between the two groups. Interestingly, patients who underwent prehabilitation had fewer hospital admissions during the follow-up period than those managed with standard care.

4.3 Prehabilitation and pharmacological therapy

Obesity is a complex, chronic, and multifactorial disease. Numerous pathological conditions, such as cardiovascular diseases, type 2 diabetes, cancer, osteoarthritis, and obstructive sleep apnea, are caused or exacerbated by obesity. According to reports from American College of Surgeons, obesity is associated with higher rates of postoperative infections, thromboembolism, and renal failure [53].

Over the past decade, the US Food and Drug Administration (FDA) has approved medications for the treatment of obesity, and multiple large RCTs have demonstrated their efficacy in weight reduction. However, no studies have evaluated the role of these pharmacological therapies in the preoperative period and their potential synergism when combined with multimodal prehabilitation programs.

5. Limitations

This review has some limitations. Although a structured literature search was performed by independent authors, the narrative design did not include a formal systematic review methodology or quantitative synthesis. As a result, study selection was partly based on the authors' assessment of scientific relevance and may be subject to selection bias. Nevertheless, this approach allowed us to provide a broad overview of current evidence, unmet needs, and future research priorities in surgical prehabilitation. Moreover, because the aim of this review was to identify gaps and unmet needs in prehabilitation research, the findings should be interpreted as a critical synthesis rather than as a quantitative assessment of effectiveness.

6. Conclusions

Prehabilitation is an effective strategy for improving functional capacity in patients undergoing surgery, shifting perioperative management from a reactive to a proactive approach. By addressing modifiable physical, nutritional, and psychological factors before surgery, prehabilitation has the potential to enhance surgical resilience and improve postoperative recovery.

TABLE 3. PROS and CONS—future developments.

Future Developments	PROS-CONS
Extension of prehabilitation during neoadjuvant treatment	PROS: Reduction in loss of functional capacity related to neoadjuvant therapy CONS: High costs, risk of low feasibility and adherence during the long-term program
Long term outcomes	PROS: Potential reduction in postoperative complications could be beneficial for long-term outcomes and quality of life CONS: Limited available data—Presence of multiple confounding factors
Association with drugs	PROS: Possible synergic effect of prehabilitation with weight-loss drugs, by preserving muscular mass CONS: Costs and potential side effects, need for careful selection and monitoring of patients—to add sarcopenia without prehab

PROS: Favorable points, advantages; CONS: Unfavorable points, disadvantages.

Future large-scale, high-quality RCTs and international expert consensus should focus on defining the optimal composition, duration, and delivery mode of prehabilitation programs, as well as identifying patients most likely to benefit. In this context, personalized prehabilitation programs should be developed according to baseline functional capacity, comorbidities, nutritional status, psychological vulnerability, and surgical risk.

Emerging digital tools, including online platforms, web applications, wearable devices, and remote monitoring systems, may further support patient adherence and individualized intervention adjustment. However, their implementation should carefully consider usability, accessibility, and digital health literacy to avoid disparities in patient's care. In addition, artificial intelligence-assisted perioperative optimization may help integrate clinical, functional, biomarker, and patient-reported data to improve risk stratification, personalize interventions, and support multidisciplinary decision-making.

7. Key points

- (1) Optimal composition
 - No clear consensus
 - Should be individualized
 - Multimodal approaches preferred
- (2) Clinical impact
 - Limited evidence on outcomes
 - Need to identify patients who benefit most
- (3) Delivery mode
 - Home-based programs improve access and reduce costs
 - Adherence monitoring is essential
- (4) Duration
 - Typically 4 weeks
 - Shorter (2–3 weeks) may also be effective
- (5) Effectiveness markers
 - Inflammatory markers may help assess response
 - HRV under investigation
- (6) Cost-effectiveness
 - Limited data
 - Poor generalizability

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

FMO, FDA and ST—contributed to the study conception or design, assessed and verified the data reported in the manuscript, and wrote the original draft. NDP, LN, MV, LF, MG, BC and CN—contributed to the review and editing of the manuscript. RL, DP, FM, SF and FP—contributed to the review and creation and refinement of the tables and figures in the text. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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