World J Surg (2019) 43:1661–1668
https://doi.org/10.1007/s00268-019-04950-y

SCIENTIFIC REVIEW

Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis

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Published online: 20 February 2019

Abstract

Introduction Prehabilitation prior to major surgery has increased in popularity over recent years and aims to improve pre-operative conditioning of patients to improve post-operative outcomes. The beneficial effect of such protocols is not well established with conflicting results reported. This review aimed to assess the effect of prehabilitation on post-operative outcome after major abdominal surgery.

Methods EMBASE, Medline, PubMed and the Cochrane database were searched in August 2018 for trials comparing outcomes of patients undergoing prehabilitation involving prescribed respiratory and exercise interventions prior to abdominal surgery. Study characteristics, overall and pulmonary morbidity, length of stay (LOS), maximum inspiratory pressure and change in six-minute walking test (6MWT) distance were obtained. The primary outcome was post-operative overall morbidity within 30 days. Dichotomous data were analysed by fixed or random effects odds ratio. Continuous data were analysed with weighted mean difference.

Results Fifteen RCTs were included in the analysis with 457 prehabilitation patients and 450 control group patients. A significant reduction in overall (OR 0.63 95% CI 0.46–0.87 I^2 34%, $p = 0.005$) and pulmonary morbidity (OR 0.4 95% CI 0.23–0.68, $I^2 = 0\%$, $p = 0.0007$) was observed in the prehabilitation group. No significant difference in LOS (WMD −2.39 95% CI −4.86 to 0.08 $I^2 = 0\%$, $p = 0.06$) or change in 6MWT distance (WMD 9.06 95% CI −35.68, 53.81 $I^2 = 88\%$, $p = 0.69$) was observed.

Conclusions Prehabilitation can reduce overall and pulmonary morbidity following surgery and could be utilised routinely. The precise protocol of prehabilitation has not been completely established. Further work is required to tailor optimal prehabilitation protocols for specific operative procedures.

Introduction

Despite many recent improvements in peri-operative care, major abdominal surgery continues to be associated with significant post-operative morbidity. Complication rates of between 30 and 40% are reported routinely after major abdominal surgery [1, 2], which contribute significantly to the length of post-operative hospital stay and increased hospital costs [3].

Optimisation of peri-operative care has focused on attenuation of the surgical stress response and improved post-operative mobility and nutrition under the umbrella of Enhanced Recovery After Surgery (ERAS) care [4]. More recently, this concept has been extended to the pre-operative period, with the aim being of optimising or improving patients' functional (and nutritional) status in the weeks leading up to surgery. This pre-operative optimisation has been termed "prehabilitation", and a key component

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includes prescribed exercise interventions to improve overall conditioning of patients, in an attempt to further reduce post-operative complications [5]. Although a precise definition of prehabilitation is not consistently employed, techniques commonly used to improve conditioning prior to surgery include aerobic exercises, e.g. cycling and walking, resistance training and specific deep breathing training and exercises. Improvements in these parameters are often objectively assessed by measuring markers of respiratory muscle strength (e.g. maximum inspiratory pressure) and distance walked over a specific time period (e.g. the six-minute walk test). This concept has been developed predominantly in orthopaedic procedures although, more recently, other operations in other branches of surgery have been investigated.

Recently, the efficacy of prehabilitation with regards to outcomes following major abdominal surgery has become a focus of investigation. Published trials have included a variety of different prehabilitation protocols and outcome measures. The benefit of such interventions on post-operative outcomes is not clear [6, 7] with new evidence emerging.

This systematic review aims to assess the current literature to determine whether prehabilitation involving pre-operative exercise interventions can improve post-operative outcomes following major abdominal surgery.

Methods

This study was conducted according to the PRISMA guidelines for meta-analysis [8]. A literature search was performed independently by two researchers of EMBASE, Medline, PubMed and the Cochrane databases in August 2018.

The databases were searched for clinical trials from 1966 to August 2017 with the following key terms: “prehabilitation or (pre-operative exercise) or (peri-operative exercise) or (pre-operative inspiratory training) or (peri-operative exercise training)”.

All abstracts were reviewed for relevance. Relevant full-text articles were subsequently reviewed. All trials assessing prehabilitation prior to abdominal surgery were included. Exclusion criteria included: paediatric studies, cardiac/thoracic only surgery, pharmaceutical interventions, nutritional interventions alone and non-randomised controlled trials. Trials that performed abdominal surgery but assessed only pre-operative training of localised muscle groups (e.g. pelvic floor training) were also excluded. Two independent reviewers assessed all studies included in the final analysis. Study quality and bias were assessed independently using the Jadad score [9]. Data were extracted directly from the papers. If medians and ranges only were reported, these were converted to mean/standard deviation using methods described by Hozo et al. [10].

The primary outcome measure was the occurrence of any complication within 30 days post-operatively. The following were assessed as secondary outcomes: post-operative pulmonary morbidity—defined as a composite measure of all reported pulmonary morbidities; post-operative length of stay (LOS); pre-operative, post-intervention maximal inspiratory pressure (MIP); and post-intervention change in six-minute walking test (6MWT).

The meta-analysis was performed using review manager (RevMan ver 5.2, The Nordic Cochrane Centre, Copenhagen). Dichotomous data were analysed by fixed effects odds ratio. Continuous data were analysed with weighted mean difference (WMD). Heterogeneity was assessed by using I^2 and X^2 and adjudged to be significant if $I^2 > 50\%$ and/or $p < 0.05$. Statistical significance was set at $p < 0.05$. Where continuous quantitative data were not distributed normally, meta-analysis was not performed and a qualitative assessment was utilised.

Results

Fifteen RCTs were identified [11–25] with 457 prehabilitation patients and 450 control group patients included. The PRISMA diagram is shown in Fig. 1. The trial details and prehabilitation protocols are illustrated in Tables 1 and 2. All studies included open abdominal surgery except Llorens et al. [19] who reported laparoscopic bariatric surgery. Five of the trials did not include patients undergoing operations for cancer [11, 13, 19, 24, 25]. All RCTs incorporated prehabilitation protocols for the intervention group that included pre-operative exercise training and/or inspiratory muscle training.

The overall quality of the included studies was moderate (Table 1). Only RCTs were included, and the overall randomisation was appropriate in all of the included studies. Blinding of participants in the treatment groups undergoing prescribed exercise/training was not possible, and so only single blinding was performed at best with some studies being completely unblinded.

There was heterogeneity observed in the protocols performed. The length of pre-operative programme was between 2 and 4 weeks in length but varied in how many sessions per week were incorporated and the length of each session (Table 2). Supervision and direction were mostly by way of departmental physiotherapy teams. Two trials incorporated the prehabilitation programme as part of a peri-operative ERAS pathway [18, 20]. Compliance was not specifically reported, but the majority of trials incorporated supervision and adherence measures to aid completion of the prescribed programmes. The level of

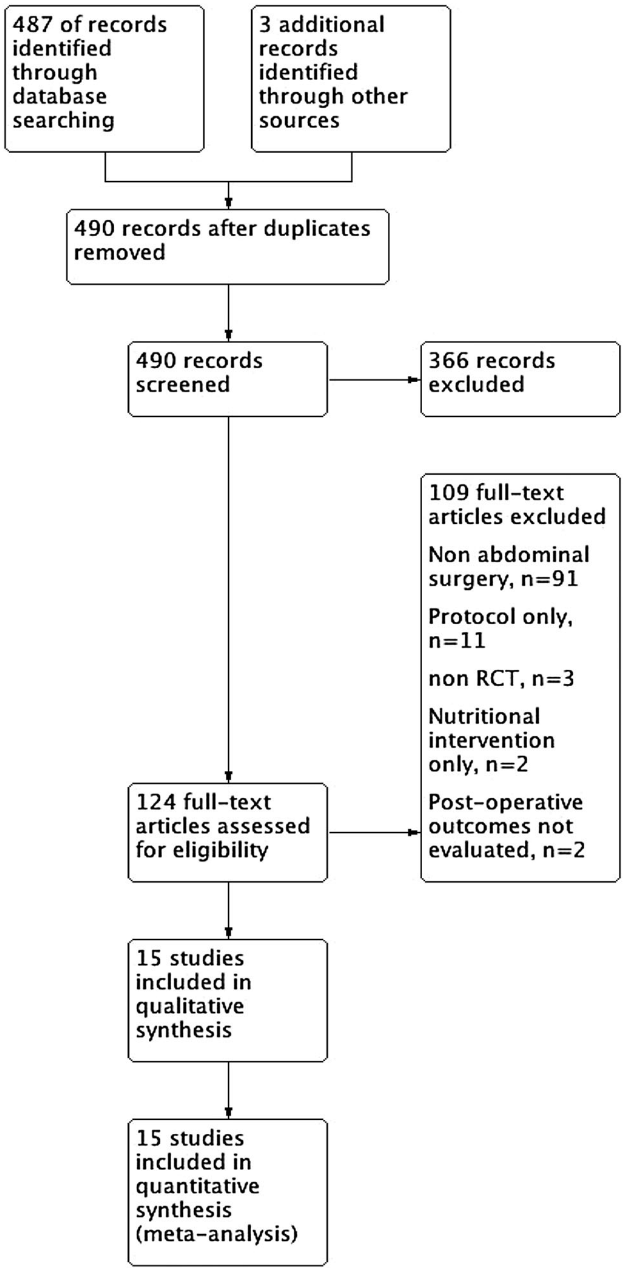


Fig. 1 PRISMA diagram

intensity of the activity was also monitored. The most frequently cited techniques were for a targeted percentage of MIP for inspiratory muscle training and the Borg scale of subjective exertion for aerobic activities (Table 2).

Carli et al. [12], Dronkers et al. 2010 [14], Kaibori et al. [15] and Barberan-Garcia et al. [23] incorporated elements of prehabilitation in the control groups, albeit either less intensive, less supervised or reduced sessions. Control participants in the remainder of the trials had standard pre-operative care where no required elements of prehabilitation were included in the patient care pathway (Table 2).

Effect of prehabilitation on post-operative morbidity

Nine trials [12–15, 18–20, 23, 25] assessed overall morbidity and were included in the meta-analysis with 354 patients undertaking a prehabilitation regimen prior to surgery versus 354 control patients. A significant reduction in overall morbidity was observed in the prehabilitation group (OR 0.63 95% CI 0.46–0.87 I^2 34%, $p = 0.005$; Fig. 2). Pulmonary morbidity was also assessed by nine trials [11, 13, 14, 16–18, 21, 23, 25]: 261 patients underwent prehabilitation versus 261 controls. The majority of studies utilised a composite group of pulmonary morbidities defined by atelectasis determined by radiological evidence; lower respiratory tract infection defined according to positive microbiology and/or radiological evidence and respiratory failure requiring additional oxygenation and/or ventilation [13, 14, 16, 21, 25]. Two studies did not specifically define pulmonary complications [17, 23], one study included pulmonary oedema only [18] and one study included atelectasis only—as defined from radiological evidence [11].

Prehabilitation was associated with a significant reduction in composite pulmonary morbidity compared with controls (OR 0.40 95% CI 0.23–0.68, $I^2 = 0\%$, $p = 0.0007$; Fig. 3).

Length of stay

Eight studies assessed LOS [11, 12, 14, 15, 17, 18, 20, 23]. Of these eight studies, none showed a significant reduction in LOS in the intervention group. Six studies [11, 12, 14, 15, 20, 23] were included in the meta-analysis, and no significant difference was observed between prehabilitation groups compared with controls (WMD −2.39 95% CI −4.86 to 0.08 $I^2 = 0\%$, $p = 0.06$).

Maximum inspiratory pressure (MIP)

Five studies [11, 13, 14, 16, 19] assessed maximum inspiratory pressure after the prehabilitation course had been completed but before surgery. It was not possible to perform a quantitative analysis of the difference between baseline and pre-operative MIP, and so this was reviewed qualitatively. Three trials [11, 16, 19] showed a significant improvement in MIP over the training period in the prehabilitation groups. These trials all incorporated inspiratory muscle training sessions as part of their prehabilitation protocols and compared this to standard care alone. The trials that did not show improvement in MIP [13, 14] included a pilot study with only ten participants in each

Table 1 Study details

	N (Ex/C)	Procedure	Cancer operation	Neoadjuvant therapy Ex versus C	Jadad score
Barakat et al. 2016 [25]	62/62	AAA surgery	N	n/a	3
Barbalho Moulim et al. 2011 [11]	15/17	Open bariatric surgery	N	n/a	3
Barberan-Garcia et al. 2018 [23]	62/63	Abdominal surgery	Y	NR	3
Carli et al. 2010 [12]	58/54	Colorectal resection	Y	NR	3
Dronkers et al. 2008 [13]	10/10	Aortic Surgery	N	n/a	3
Dronkers et al. 2010 [14]	22/20	Elective colon surgery	Y	NR	3
Dunne et al. 2016 [17]	20/17	Liver resection	Y	11/20 versus 7/17	3
Gillis et al. 2014 [18]	38/39	Colorectal resection	Y	10/38 versus 8/39	3
Jensen et al. 2015 [20]	47/53	Radical cystectomy	Y	NR	2
Kaibori et al. 2013 [15]	25/26	Liver resection for HCC with cirrhosis	Y	NR	2
Kim et al. 2009 [22]	14/7	Colorectal resection	Y	NR	2
Kulkarni et al. 2010 [16]	18/19	Major abdominal surgery	Y	NR	3
Llorens et al. 2015 [19]	23/21	Laparoscopic bariatric surgery	N	n/a	3
Soares et al. 2013 [21]	16/16	Upper abdominal surgery	Y	NR	3
Tew et al. 2017 [24]	27/26	AAA surgery	N	n/a	3

NR not reported, *N/A* not applicable, *Ex* experimental, *C* control

group and control group containing exercise activities. Meta-analysis of the absolute difference in MIP between intervention and control groups recorded at the end of the training period was performed. No significant difference was observed in the MIP recorded at the pre-operative stage after the prehabilitation process had been completed (WMD 11.46 95% CI −2.09 to 25.0, $I^2 = 77\%$, $p = 0.10$).

Six-minute walking test (6MWT)

Change in 6MWT was reported by three trials [12, 18, 22]. Only one trial, Gillis et al. 2014 [18], reported a significant improvement in 6MWT distance at the end of the prehabilitation period. These three trials were included in the meta-analysis, and no significant difference in 6MWT was observed between those who had undergone the prehabilitation protocol ($n = 110$) versus the control groups ($n = 100$) (WMD 9.06 [95% CI −35.68, 53.81] $p = 0.69$, $I^2 = 88\%$). Significant heterogeneity was observed in this analysis, and a random effects model was used.

Discussion

Prehabilitation is associated with an improvement in overall and pulmonary-specific morbidity following major abdominal surgery. Prehabilitation has become increasingly employed and investigated in recent years [26]. Two previous meta-analyses of prehabilitation have been performed [27, 28]. The study by Mans et al. [28] differed in design to the current review in that non-abdominal surgery, namely cardiac and thoracic surgery, made up the majority of included trials. Overall morbidity was not assessed either. Pulmonary morbidity was the primary outcome and was significantly reduced in the prehabilitation group, similar to our own findings. The second meta-analysis by Moran et al. 2016 [27] included nine RCTs and reported significant improvement in both overall morbidity and pulmonary morbidity rates in prehabilitated patients undergoing abdominal surgery. In our study, only four of the nine trials used in the primary outcome analysis by Moran et al. [27] were included in our primary outcome analysis of overall morbidity. This is because Moran et al. chose to include trials in which the only reported post-operative morbidity rates were *pulmonary* in their meta-analysis of *overall* morbidity rates. We, however, elected to include such pulmonary-specific studies [13, 16, 21] in our secondary meta-analysis of pulmonary morbidity rates, and reserve our primary meta-analysis of overall morbidity rates for those trials that specifically reported this outcome measure. Furthermore, since publication of the previous meta-analysis several new RCTs [23–25] have become available, having a marked contribution to the overall meta-analyses. Taken together, the results of this meta-analysis confirm the potential post-operative benefits that can be achieved when prehabilitation programmes are

Table 2 Prehabilitation protocols

	Sessions	Session length (min)	IMT	Aerobic exercise	Resistance training	NS	Control group	Length (weeks)	Supervision/monitoring	Intensity target
Barakat [25]	3/week	60		X	X		Standard care	6	Instructions given and timetable	NR
Barbalho-Moulim [11]	6/week	15	X				Standard care	2–4	Twice weekly supervised sessions	%MIP
Barberan-Garcia [23]	1–3/week	47		X			Non-supervised activity promotion	4	Supervised sessions	NR
Carli [12]	7/week	20–45		X	X		30 min walk per day, deep breathing exercises 5 min/day	4	One home visit plus follow-up phone calls	Repetitions recorded and cycling timed
Dronkers 2008 [13]	6/week	15	X				Standard care	2	One session per week Daily diary kept	%MIP and Borg scale
Dronkers 2010 [14]	7/week	30–60	X	X	X		Home-based exercise advice + instruction on breathing exercises	2	Twice weekly supervised sessions, unsupervised, directed sessions	Max HR % and Borg scale
Dunne [17]	3/week	30		X			Standard care	4	NR	Timed sessions
Gillis [18]	3/week	50		X		X	Same intervention commenced post-operatively	4	Instructional booklet and activity diary, weekly phone calls Heart monitor to assess intensity of exercise	Borg scale
Jensen [20]	Twice daily	15		X			Standard fast-track protocol	2	Written exercise programme, personal diary, step trainer	NR
Kaibori [15]	3/week	60		X		X	Diet supplement	From diagnosis to 4 weeks pre-op	Activity monitored and confirmed 2 × per month	Anaerobic threshold
Kim [22]	7/week	20–30		X			Standard care	3	Written exercise programme, exercise diary (duration and HR intensity), home visits	%HR and Borg scale
Kulkarni [16]	Twice daily	15	X				Standard care	2	Instructions Self-assessment	%MIP
Llorens [19]	Once daily	20	X				Standard care	30 days	Weekly evaluation of adherence	%MIP and Borg scale
Soares [21]	6/week	25–50	X	X			Standard care	2–3	Two supervised 50-min sessions per week, patient reported adherence	%MIP and Borg scale
Tew [24]	3/week	47		X			Standard care	4	Direct supervision by nurse and physiotherapist	Patient ratings of perceived exertion 5–7

NR not reported, *X* included in protocol, *MIP* maximum inspiratory pressure, *HR* heart rate, *NS* nutritional supplements, *IMT* inspiratory muscle training

Fig. 2 Overall morbidity

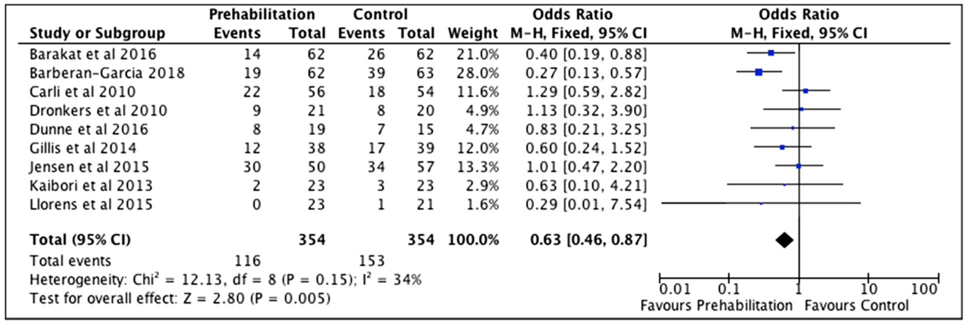
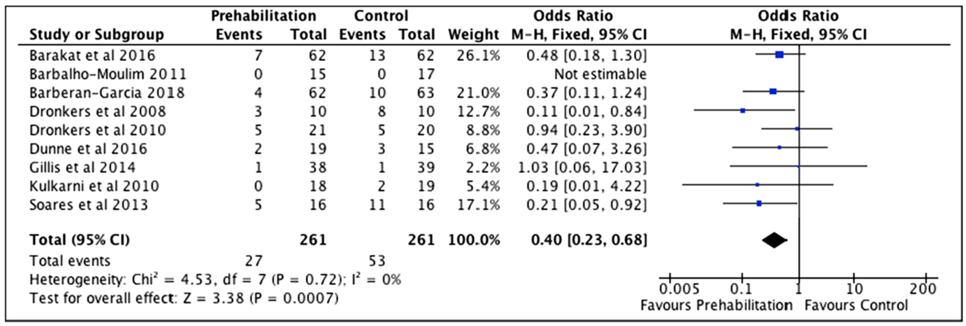


Fig. 3 Pulmonary morbidity



implemented appropriately. Such observed improvements in outcome suggest routine implementation of prehabilitation could be indicated.

A reduction in pulmonary complications following prehabilitation is perhaps predictable when considering the form of prehabilitation regimens employed, chiefly inspiratory muscle training, deep breathing exercises and aerobic conditioning. Trials that compared prehabilitation and standard care showed greater magnitude of difference in pulmonary morbidity rates [13, 21] compared with those trials in which the control groups received prehabilitation but at reduced supervision or intensity [14, 18]. Prehabilitation may, therefore, be particularly beneficial when utilised in surgical procedures associated with high pulmonary morbidity rates. Cardiac and thoracic surgery exponents have embraced this concept, and the current review would recommend respiratory prehabilitation for abdominal surgery, and particularly procedures which involve both an abdominal and thoracic component, e.g. oesophagogastric resectional surgery.

Length of stay was not significantly different between the intervention and control groups. Similar findings have been reported by previous meta-analyses investigating prehabilitation in abdominal [27] and chest [28] surgeries. Yet, two further meta-analyses involving a mixture of cardiac and abdominal procedures [29] or cardiothoracic, abdominal and orthopaedic procedures [30] found a reduction in LOS in association with prehabilitation. The reason for these conflicting results is unclear but potentially highlights the heterogeneity of operative procedures included in the analyses, and variations in post-operative care protocols. In the current meta-analysis, included trials made minimal references to fast-track/ERAS care pathways. Thus, in the future, procedure-specific analyses of standardised care pathways will be required in order to clearly establish effect of prehabilitation programmes on outcome and, specifically, length of stay.

The final analyses performed assessed the objective effect of the prehabilitation interventions on physical function and respiratory function, namely the 6MWT and MIP. The improvements observed in MIP in the intervention groups suggest there is evidence for the beneficial effect of prehabilitation on objective respiratory function, and such a conclusion would be consistent with the observed improvement in pulmonary morbidity rates.

Change in 6MWT over the prehabilitation period, after meta-analysis, showed no significant difference. However, significant heterogeneity was observed between studies. Interestingly, the most successful included trial, in which a significant improvement in 6MWT was identified, incorporated dietary supplementation in the prehabilitation regimen as well as aerobic exercise [18]. This observation is consistent with the hypothesis that skeletal muscle mass and function require anabolic stimulation through both exercise and nutrition. Determination of protocol compliance is also a key factor. Lack of improvement in 6MWT may have resulted from lack of adherence to the prescribed exercises. There was variation in the level of supervision of exercise programmes, and factors were introduced to assist with protocol adherence, namely activity diaries, but compliance levels were not specifically reported. This may be of benefit in future studies assessing prehabilitation protocol success.

The main limitation of this meta-analysis is the heterogeneity of the included trials. Despite a focus on abdominal surgery, the trials were still heterogenous regarding their peri-operative care pathways, the prehabilitation regimens employed and the types, units and timeframes of outcome measures. The optimum prehabilitation regimen components are yet to be established or defined, but the benefits seen in terms of overall and pulmonary morbidity suggest a continued focus on inspiratory muscle training and aerobic exercises may be a useful approach. An alternative approach, not mentioned in the included trials, is also to address lifestyle issues such as pre-operative smoking cessation, diabetic and co-morbidity optimisation. The search criteria of the current meta-analysis may have excluded such interventions, focusing in physical prehabilitation and conditioning. The focus on respiratory exercises and aerobic training of the included studies may have played a part in optimising respiratory co-morbidity, and it is this that had an influence on post-operative pulmonary morbidity. One of the main aims of future trials, however, should be to establish the optimum schedule, intensity and degree of supervision of such exercises as well as incorporating optimisation of co-morbidities and lifestyle issues.

The main target population for prehabilitation regimens has also not yet been established. However, prehabilitation may be particularly beneficial for cancer patients who have experienced muscle loss as a key component of cachexia, or neoadjuvant therapy [31, 32]. A randomised controlled trial by West et al. [33] showed that physical fitness declined in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy and that this was negated in the treatment group enrolled in a prehabilitation programme.

In summary, this meta-analysis has shown that prehabilitation results in improved morbidity rates after abdominal surgery and could be implemented routinely. Future research should be aimed at ascertaining the exact components and timing of the prehabilitation regimen (including nutritional supplementation) and the ideal target patients and operative procedures in order to maximise implementation.

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