Response to the Comments of Onerup et al and Lu and Song on: "Effects of Community-based Exercise Prehabilitation for Patients Scheduled for Colorectal Surgery With High Risk for Postoperative Complications: Results of a Randomized Clinical Trial"

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Response to the Comments of Onerup et al. and Lu & Song on: "Effects of community-based exercise prehabilitation for patients scheduled for colorectal surgery with high risk for postoperative complications: results of a randomized clinical trial"

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To the Editor, with interest we read the recently published comments of Onerup et al.[1] and Lu & Song[2] on our randomized controlled trial (RCT).[3] We thank the authors for their valuable comments. Prehabilitation programs have been shown to improve physical fitness before hospitalization and surgery. However, evidence that this consequently also reduces postoperative complications still seems inconclusive and opposing.[4] The systematic review of Thomas and colleagues[4] states that prehabilitation of patients before hospitalization and surgery for major intra-abdominal cancer seems to improve postoperative outcomes when specifically focused on adequately identified high-risk surgical patients. Onerup and colleagues[5] recently performed an RCT with 761 patients to evaluate the effect of a short-term, unsupervised home-based physical exercise intervention before and after colorectal cancer surgery on self-assessed physical recovery. All eligible patients ≥20 years of age planned for elective colorectal cancer surgery were included. No effect from their perioperative physical exercise intervention on short-term self-reported physical recovery was found. Carli and colleagues[6] demonstrated that prehabilitation by (pre)frail patients, selected with help of the Fried frailty index that combines two short performance items with three self-reported items, preparing for resection of colorectal cancer did not reduce the incidence of postoperative complications. Although they intended to include less physically fit (prefrail and frail) patients undergoing colorectal cancer resection, an alternative strategy might be more appropriate to select those patients that truly require prehabilitation. Patients with a low preoperative aerobic fitness would be expected to benefit the most from prehabilitation. Therefore, identification and – in the context of clinical a trial – selection of high-risk patients based on cardiopulmonary exercise testing (CPET) might be the risk assessment strategy of choice. When performing CPET is not possible, more practical performance-based field tests might be useful for preoperative risk assessment. The steep ramp test (SRT), a short-time maximal test on a cycle ergometer, might be a suitable alternative as SRT performance is strongly related to aerobic fitness. Moreover, lower SRT performance is associated with postoperative morbidity in colorectal cancer surgery.[7] As Lu & Song[2] suggested, the 6-minute walk test (6MWT), though being a submaximal field test and therefore less correlated with aerobic fitness, might be an alternative strategy. Nevertheless, further validation is required for both the SRT and 6MWT.[8]

Onerup et al.[1] stated that our supervised community-based physical exercise intervention could only be performed by <5% of the total population with colorectal cancer screened and assessed during our study period, which limits the generalizability of the results. We think this statement is not correct, since we specifically aimed at identifying and including patients at high risk for postoperative complications, based on a predefined CPET-criterion, and to evaluate the effectiveness of an exercise prehabilitation program in this specific group, and not

in the total population of patients with colorectal cancer. Consequently, in line with what Onerup et al.[1] stated we focused statements concerning generalizability purely on this specific subpopulation, while the moderate participation rate of 56% among high-risk patients who were eligible should be kept in mind. When preoperative screening for potential modifiable risk factors is incorporated in the perioperative care pathway as part of usual care, Van Wijk et al.[9] recently showed in their study that all of the 100 screened patients with hepatobiliary and pancreatic cancer participated in preoperative risk assessment.

One of our inclusion criteria was the willingness to perform community-based prehabilitation at a physical therapy practice in the catchment area of both hospitals. Onerup et al.[1] stated that this information should have led to several participants suspecting the nature of the intervention and included a selection of study participants. However, since we informed patients in the prehabilitation group and the usual care group differently, patients in the usual care group did not receive information about the possible effects of prehabilitation. These patients received a patient information letter about the registration of perioperative data and the hypothesized relation of aerobic fitness with postoperative complications after colorectal resection. Therefore, the aforementioned inclusion criteria (willingness to perform community-based prehabilitation) only applied to patients randomized to the prehabilitation group. Moreover, patients in the usual care group were planned for surgery at the earliest convenience. This resulted in a mean (SD) time between inclusion and surgery of 34.6 (28.8) days in the prehabilitation group versus 19.0 (10.2) days in the usual care group (p<0.001).

As Onerup et al.[1] and Lu & Song[2] properly declare, there is a small, non-significant, difference in the number of smoking patients in the prehabilitation group (n=1, 4%) and usual care group (n=6, 21%, p=0.112) and in the number of patients with an age-adjusted Charlson comorbidity index of 6+ in the prehabilitation group (n=4, 14%) and usual care group (n=7, 24%, p=0.416). Smoking was not associated with postoperative complications, as there were 3 smoking patients without complications and 4 smoking patients with complications (p=1.00). Onerup et al.[1] questioned whether there could have been any bias in the final allocation of the participants with participants with unhealthy lifestyle habits and comorbidity dropping out between randomization and the final intention to treat population. Of the 39 patients allocated to the prehabilitation group, 11 patients were excluded from the final intention-to-treat analyses. Of these 11 patients, only one patient with an unhealthy lifestyle was excluded because he withdrew from surgery. The remaining 10 patients were excluded for other reasons, not related to unhealthy lifestyle habits (e.g., adequate preoperative aerobic fitness, complete remission after neoadjuvant therapy). Based on these figures, we are convinced that the small

differences in smoking and age-adjusted Charlson comorbidity index between the groups not affected the allocation and drop out.

Our study was specifically and exclusively powered to detect a statistically significant difference in the number of patients with one or more postoperative complications between the prehabilitation group and usual care group.[3] We agree with Onerup et al.[1] that especially the prevention of severe complications would be of great relevance to the patients, caregivers, the need of health care resources, and, consequently, costs. However, costs associated with the prevention of (the impact of) complications would probably outweigh costs of the care for the postoperative complications, and preventing complications (also minor complications) would considerably reduce the patient's physical, mental, and social burden. In the Netherlands, it was shown that the average total hospital costs (primary admission and after discharge up to 90 days) for a patient without complications is ~€9,000, versus ~€11,500 and ~€27,000 for a patient with minor and severe complications, respectively.[10] The estimated costs of a *multi*modal prehabilitation program are €969 per patient (containing twelve supervised physical therapy sessions, protein supplements, project management, and data collection).[11] Moreover, the results of our study showed that the total hospital costs of patients in the prehabilitation group were €1,300 lower than of patients in the usual care group (to be published). We therefore expect prehabilitation to be a cost-effective ingredient of the care of high-risk patients undergoing colorectal surgery and suggest implementing the interventions according to what was shown to be successful in our paper. On top of that, we recommend, while implementing, to evaluate the cost-effectiveness in the context of each unique hospital and its catchment area.

In future research, multidisciplinary preoperative risk assessment in multiple domains should be performed to identify patients at higher risk of an impaired postoperative outcome.[12] Preferably, the identified modifiable risk factors should be optimized before surgery. Future prehabilitation trials should focus on the adequate selection of high-risk surgical patients (i.e., patients with a low preoperative aerobic fitness based on evidence-based cutoff values of field tests), and should provide personalized, multimodal, and (partly) supervised high-intensity prehabilitation programs at home or in a community-based setting with objectively monitoring a patient's progression.[3] To support patient adherence to the program and empowerment for self-management, remote monitoring (i.e. physical activity, physiological signs, and patient-reported outcomes and experience measures) might be useful, as Lu & Song[2] suggested, but needs to be proven in proper experimental trials. Moreover, to reach all patients, we would advise to have prehabilitation considered in every hospital and/or clinical guideline as usual care in high-risk patients scheduled for elective colorectal surgery.

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