

Peer Review File

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Reviewer A

Thank you for this pragmatic study. That whet curiosity.

Comment 1

- it is interesting to see that in the end, only 18% of patients with an indication for an anatomical resection will/can have a pre-habilitation program. So what can we do to improve this percentage for future studies? Indeed, as noted, it is the fittest patients who will want to benefit from this program. You should analyze the characteristics and outcomes of the patients who were not included and see if there is a difference with the patients included.

Reply Comment 1: We would like to thank the reviewers for their comments. We agree in stating that the percentage of participating patients is low. Most common reasons for not participating were study-related (other trials, other hospitals, no NSCLC, COVID stop). Furthermore, 19 patients could not participate because the pre-operative work-up was not straightforward. Only 15 patients could not participate because of patient characteristics. Since the completion of this study, prehabilitation is standard of care in our hospitals and the participation rate is now in the range of 70-80%. To ensure this rate we recommend a structured care pathway with a coordinator to oversee the whole process and cooperation with physiotherapy practices in the neighborhood of other hospitals to offer prehabilitation to patients from other hospitals. We agree with the reviewer that analyzing the characteristics of the patients not participating in the study is interesting. However, only 3 patients gave informed consent and therefore analyzing these 3 patients will not lead to enhanced insights in gaining knowledge of not participating.

Change in text:

L243-247: Most common reasons that patients did not meet the inclusion criteria were study-related (other trials, other hospitals, no NSCLC, COVID stop, inability to give informed consent). Furthermore, 19 patients could not participate because the pre-operative work-up was not straightforward. Only 15 patients could not participate because of patient characteristics.

L357-361 Possible solutions for offering prehabilitation to more patients could be offering training in physiotherapy practices in the neighbourhood and appointing a coordinator to optimise the preoperative care pathway, including prehabilitation. Future studies should focus on offering prehabilitation to every patient planned for lung cancer surgery to increase participation rate, so the value of prehabilitation in lung surgery can be determined.

Comment 2

- the question of post-operative complications will be important but also in the long term. Do you think that post-operative rehabilitation is also necessary or even more adequate for your further trial?

Reply Comment 2: We agree with the reviewer that ensuring functional capacity of patients is not just limited to a preoperative intervention. Prehabilitation will not lead to a complication reduction of 100% and therefore postoperative complications will still occur. We hypothesize that patients will recover faster of these complications after prehabilitation, but unfortunately we could not test this hypothesis in this study. Prehabilitation will never replace post-operative rehabilitation and we see added value in both offering prehabilitation and rehabilitation to patients with lung surgery. However, we hope that in the future with more knowledge on prehabilitation we can have more insights in defining patients that will have benefit from prehabilitation and post-operative rehabilitation. This will lead to enhanced perioperative care in lung surgery while also looking at the most efficient way of spending hospital finances.

Changes in text:

L329-332 A sufficient functional capacity is of utmost importance in the postoperative period and patients with low postoperative functional capacity should be assessed for rehabilitation. In order to definitely assess the beneficial effect of prehabilitation on functional capacity, both preoperative and postoperatively, large cohort studies are necessary.

Comment 3

- I think there is an error in the percentage of re-intervention, table 3.

Reply Comment 3: The reviewer is correct. We mistakenly gave the percentage of total re-interventions, we adjusted the percentages in Table 3

Changes in text: Table 3

Re-intervention	4 (<u>26.7</u>)	1 (<u>7.125</u>)	3 (<u>30.75</u>)
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Comment 4

- How many patients underwent VATS procedure? can you please better detail the surgery in the methodology?

Reply comment 4: All patients included in this study had VATS procedure, since we did not specify this outcome, we added this in the Results section.

Changes in text:

L246-247: All included patients had video assisted thoracoscopic surgery (VATS).

Table 2: AJCC staging of NSCLC is added as replacement of pTNM staging.

Comment 5

- How do you explain the significant differences of postoperative outcomes between centers?

Reply Comment 5: The difference between postoperative outcome could be influenced by the number of included patients. This study was not powered on defining surgical outcome and therefore these results should be interpreted with caution. Nevertheless, there are some differences in perioperative care between the two centers. ASz has implemented ERATS, while MMC is currently in the process of implementation of ERATS. This could have had an influence on postoperative outcome, but for truly defining the effect of prehabilitation on postoperative outcome, large cohort studies are necessary.

Comment 6

- were there differences between centers regarding change in functional capacity?

Reply Comment 6: to evaluate the change in functional capacity we chose to analyze the data with a linear mixed models analysis. Due to the limited number of included patients we chose to take age, gender and center site into account for correlation, since these could influence the results. Center site was a significant factor for the 1RM tests, whereas MMC had overall higher scores, but this could be mere coincidence. Since protocol was identical in both hospitals we chose to show the combined results.

Reviewer B

Thank you for letting me read this interesting manuscript “Multimodal prehabilitation in patients with non-small cell lung cancer: a feasibility study”. This is an area where the potential for creating beneficial outcome for patients with lung cancer is high.

I have some major concerns and some minor concerns.

Major Concerns:

Comment 7

You state that: “The interventions “HIIT training, strength training and protein supplementation” were the most important interventions of our prehabilitation program to improve functional capacity” What is the rationale for choosing the other interventions? And how can you rule out the effect comes only from these interventions?

Reply Comment 7: We would like to thank the reviewer for the compliment and hope that our revisions meet your expectations. We have to conclude that we have given the wrong impression in stating that HIIT training, strength training and protein supplementation are the most important interventions of the program. Prehabilitation has proven to be successful in colorectal surgery due to its multimodal aspect. Stating that one of the interventions is more important than the other is therefore wrong. We strongly believe in the synergistic effect of all interventions combined. This is also why we chose to grade all the interventions evenly. We simply cannot simplify the effect of prehabilitation without taking all interventions into account.

Additionally to the protocol for colorectal surgery we chose to offer respiratory optimization due to the fact that lung tissue will be removed and to lower the risk of postoperative pneumonia. We found that 70.8% of patients had more than 80% of training sessions, but only 54.2% of patients had sufficient protein supplementation. The relatively low protein supplementation rate can be explained due to that patients did not completely fill in their daily dairy and true protein supplementation rate could therefore be higher. Additionally, it was challenging to plan sufficient amount of training sessions in 2-3 weeks. Therefore, we strongly advocate the importance of a prehabilitation coordinator to monitor all the interventions of the program.

Since this program is multimodal, we graded all interventions evenly and found a feasibility rate of 95.8%. However, monitoring training adherence and protein supplementation in the near future is of importance for improving this program.

Changes in text:

L177: Feasibility was scored on a total of eighteen interventions in six pillars which all were graded equally due to its synergistic effect.

L177-182: A successful programme would be if a patient had $\geq 80\%$ out of eighteen interventions achieved. Different interventions and goals per intervention are shown in Table 1.

The number of supervised training sessions differed depending on the time available between T0 and surgery. Table 1 presents the number of sessions that could be planned for these interventions in case of an “optimal window of opportunity (i.e. with T0 performed the day after MDT and surgery performed three weeks after MDT)

L312-318: However, completion rates in protein supplementation and training were relatively low compared to the other interventions. Reasons for the low completion rate included: no filled in dairies on protein- and vitamin supplementation but also in problems of planning the training sessions within the timeframe. Due to the multimodal aspect of this intervention program, which is conducted in a short time period, we strongly advise reserving time slots for prehabilitation patients and preferably appointing a prehabilitation coordinator in hospitals implementing prehabilitation.

Comment 8

As a feasibility study the difference between screened patients and included patients seems rather high (131 patients screened and 89 excluded). According to the protocol exclusions criteria's some of the reasons for exclusions in figure 1 is not mentioned in the protocol. Could you explain why some of the patients are excluded without reaching the exclusions criteria.

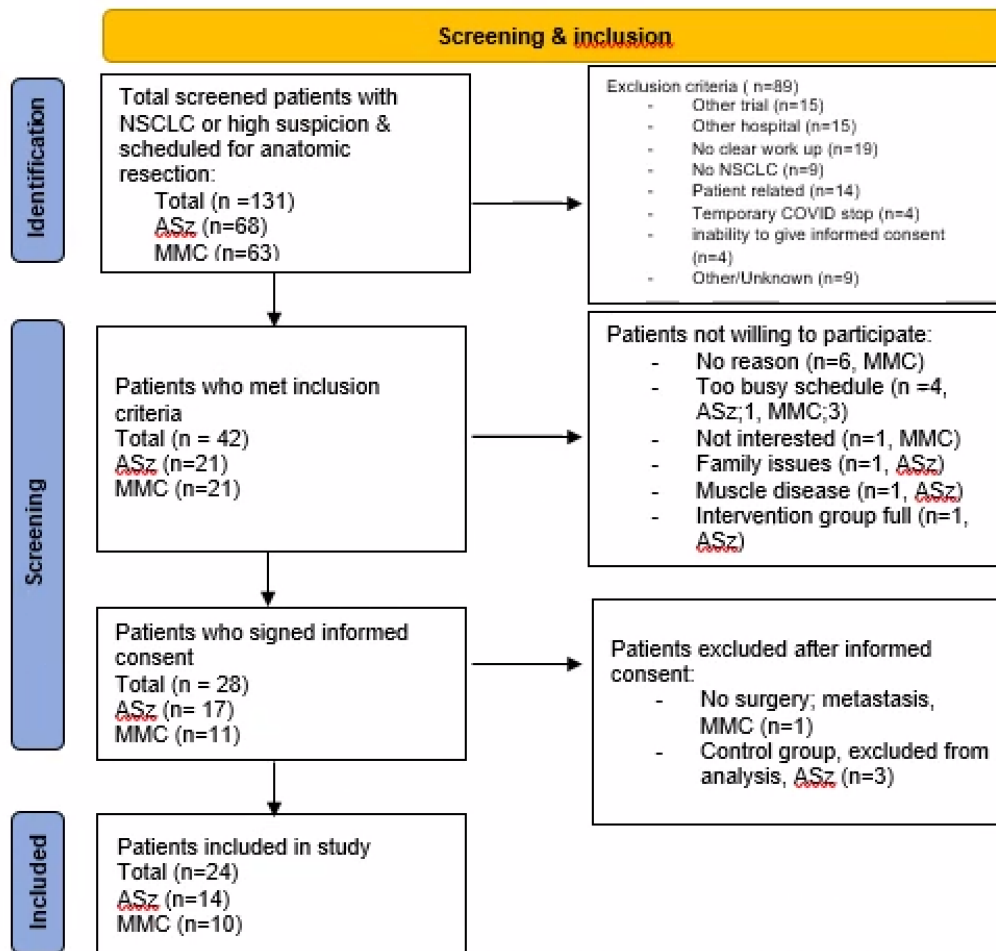
Reply Comment 8: We agree with the reviewers comment that the participation rate in this study is relatively low. However in only 14 patients the reason for not participating was patient related and only 4 patients were not able to provide informed consent due to a language barrier. In all other patients the reason for not participating was study-related (participation in other trials, treatment in other hospitals and no NSCLC) are all reasons that can be resolved by offering prehabilitation to every patient with elective lung surgery.

We agree in the reviewer that the exclusion criteria in Figure 1 is not completely according to the protocol and we changed the exclusion criteria reasons accordingly. Six patients could not be included due to holidays of the study team. We chose to depict these patients as hospital related, since they differ from a clear work up. To maintain consistency throughout the article we have now shown all patients in the predefined exclusion reasons. Temporary stop due to COVID virus was something we had not foreseen and was therefore added as a reason for exclusion.

“Other/unknown” reasons for exclusion included: operation plan was changed to open resection and in the remaining patients the study was mistakenly not discussed and therefore it is unknown if patients were willing to participate.

Changes in text:

Figure 1



Minor concerns:

Comment 9

“All patients received a protein powder supplement of 30 grams (Refit®-TMP-90-Shake, Friesland Campina Domo, Amersfoort, the Netherlands) for daily use, and twice a day on supervised training days. Additionally, vitamin D (dosage based on the guideline of the Health

Council of the Netherlands) and multivitamin supplements were provided for daily use”. How was it supervised that they took the tailored dietary advice, including energy and protein requirements? And how did you record the daily dietary intake?

Reply Comment 9: Dietary advice was not supervised, patients were asked to provide insights in their supplementation with the use of a daily diary. This could have had an influence on the relative low rate of protein supplementation since not all the diaries were filled in.

Changes in text:

L161-163: A handbook containing information on interventions of the programme and a logbook was provided to register all study related activities and to register LIT and daily protein and vitamin supplementation.

Comment 10

The clinical psychologist determined whether follow-up sessions were needed during the perioperative phase and/or referral to a psychiatrist was indicated. How many follow-up sessions were needed and what was the criteria for follow-up

Reply Comment 10: All but one patient had consultation with the clinical psychologist. In none of the patients follow up sessions were deemed necessary. No criteria were set for defining the necessity of follow up sessions. The expert opinion of the clinical psychologist was followed.

Changes in Text:

L258: Completion rate of psychological support was 95.8% (n=23), whereas one patient refused consultation. No follow-up sessions were deemed necessary.

Comment 11

“Although we designed our study including a control group to test for functional capacity without multimodal prehabilitation, only three patients were willing to join the control group.” How many patients were asked to be control?

Reply Comment 11: If patients were deemed eligible for inclusion they were asked for participation in the intervention group. A total of 14 patients (figure 1) were not willing to participate in the study, after which they were asked to participate in the control group, which they also declined. In total 17 patients were asked to be in the control group, of which 3 signed informed consent.

Comment 12

The complications rate is rather high for this group what type of operation was performed?

Reply Comment 12: We agree that the complication rate is relatively high in this study. However if we look at the type of complications, they are predominantly minor complications (CCI 4.3). Additionally, our patients had a relatively high amount of comorbidities and ASA 3-4. Nevertheless, this study was not powered on postoperative complications and to assess the benefits of prehabilitation on postoperative outcome, large cohort studies are necessary.

All included patients had video assisted thoroscopic surgery and we have added a sentence in the results section.

Changes in text: L247-248: All included patients had video assisted thoroscopic surgery (VATS)

Reviewer C

In this manuscript entitled “Multimodal prehabilitation in patients with non-small cell lung cancer: a feasibility study”, the authors assessed the feasibility of the prehabilitation program in NSCLC patients. This topic is significant because it is one of the major problems for some operable lung cancer patients in that their ADLs or pulmonary functions decrease after the surgery.

However, there are several concerns regarding this study. I feel that a substantial revision would be required before publication.

Reply: We would like to thank the reviewer for this compliment and hope that our revisions meet your expectations.

Major comments

Comment 13

The feasibility of prehabilitation depends on the patient’s condition. For patients with pulmonary disease, the respiratory condition is also important to evaluate the feasibility of this program. Please show me the detailed respiratory functions such as FVC and FEV1.

Reply Comment 13:

We agree with the reviewer in the added value of showing FVC and FEV1. We have added this in the Methods and in Table 2.

Changes in Text:

L223-225: Baseline characteristics such as gender, age, BMI, American Society of Anaesthesiologists score(ASA), respiratory function such as forced vital capacity (FVC), forced expiratory volume in first second (FEV1) and the percentage of predicted FEV1, chronic obstructive pulmonary disease (COPD), tumour, node, metastasis (TNM) stage, operation type and operation time were collected.

Table 2

Respiratory function			
FVC (SD)	3.5 (3.3)	3.5 (1.1)	3.6 (0.9)
FEV1 (SD)	2.6 (0.9)	2.4 (1.0)	2.7 (0.7)
FEV1 (%predicted, SD)	89.6 (20.1)	86.1 (20.8)	94.4 (19.2)

Comment 14

2. The completion rates of some programs, such as HIIT, strength training, and protein supplementation were relatively low. However, as you mentioned, these programs seem more important than other programs to maintain patients' conditions or ADLs. Please explain in the Discussion part why the completion rates of these programs were not sufficient and you can say these programs were feasible despite these results.

Reply Comment 14: We agree with both Reviewer B and C that we have given the wrong impression in stating that HIIT training, strength training and protein supplementation are the most important interventions of the program. Prehabilitation has proven to be successful in colorectal surgery due to its multimodal aspect. Stating that one of the interventions is more important than the other is therefore wrong. We strongly believe in the synergistic effect of all interventions combined. This is also why we chose to grade all the interventions evenly.

We found that 70.8% of patients had more than 80% of training sessions, but only 54.2% of patients had sufficient protein supplementation. The relatively low protein supplementation rate can be explained due to that patients did not completely fill in their daily dairy and true protein supplementation rate could therefore be higher. Additionally, it was challenging to plan sufficient amount of training sessions in 2-3 weeks. Therefore, we strongly advocate the importance of a prehabilitation coordinator to monitor all the interventions of the program.

Since this program is multimodal, we graded all interventions evenly and found a feasibility rate of 95.8%. However, monitoring training adherence and protein supplementation in the near future, while also reserving time slots for training sessions is of importance for improving this program.

Changes in text:

L177: Feasibility was scored on a total of eighteen interventions in six pillars which all were graded equally due to its synergistic effect.

L177-182: A successful programme would be if a patient had $\geq 80\%$ out of eighteen interventions achieved. Different interventions and goals per intervention are shown in Table 1.

The number of supervised training sessions differed depending on the time available between T0 and surgery. Table 1 presents the number of sessions that could be planned for these interventions in case of an "optimal window of opportunity (i.e. with T0 performed the day after MDT and surgery performed three weeks after MDT)

L312-318: However, completion rates in protein supplementation and training were relatively low compared to the other interventions. Reasons for the low completion rate included: no filled in dairies on protein- and vitamin supplementation but also in problems of planning the training sessions within the timeframe. Due to the multimodal aspect of this intervention program, which is conducted in a short time period, we strongly advise reserving time slots for prehabilitation patients and preferably appointing a prehabilitation coordinator in hospitals implementing prehabilitation.

Minor comments

Comment 15

In Table 1, the completion rate of IMT was 95.8%(23/24). However, in the manuscript, the completion rate of IMT was 62.4%(n=15). Which is correct?

Reply Comment 15: We would like to thank the reviewer for pointing out this contradictory sentence in the manuscript. The correct completion rate is 95.8% (23/24) and is changed in the text.

Changes in text: L267 Completion rate of IMT was 95.8% (n=23).

Comment 16

In Table 2, the ratio of COPD with GoldIorII. However, the ratio of whole COPD patients should also be shown. Please show me the ratio of COPD patients.

Reply Comment 16: The total of 7 patients with COPD is added in Table 2

Changes in text: Table 2 addition of COPD total group 7 (29.2)

COPD Gold (%)	7 (29.2)		
I	6 (85.7)	4 (80)	2 (100)
II	1 (14.3)	1 (20)	-

Comment 17

Table 2 shows detailed patient characteristics, however, this table is a bit busy. For example, comorbidities such as solid tumors in the past or leukemia don't seem to correlate with the feasibility. In addition, when you describe the tumor condition, staging of the NSLCL would be enough. Please remake the Table more simply.

Reply Comment 17: We agree in the reviewers comment in stating that Table 2 seems busy. We have removed the tumor condition and changed it with AJCC NSCLC staging. However, we think showing the comorbidities of these patients is of added value since it can be an explanation for the relative high amount of postoperative complications that occurred.

Changes in text: Table 2

AJCC staging (%)			
IAI	1 (4.2)	1 (7.1)	-
IAII	6 (25.0)	4 (28.6)	2 (20.0)
IAIII	2 (8.3)	-	2 (20.0)
IB	6 (25.0)	5 (35.7)	1 (10.0)
IIA	4 (16.7)	1 (7.1)	3 (30.0)
IIB	2 (8.3)	1 (7.1)	1 (10.0)
IIIA	2 (8.3)	1 (7.1)	1 (10.0)
IIIB	1 (4.2)	1 (7.1)	-