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Barriers To The Completion Of A Home-Based Rehabilitation Program For Patients Awaiting Surgery For Lung Cancer

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Abstract:

Objectives: Home-based rehabilitation programs (H-RP) could facilitate the implementation of pulmonary rehabilitation prior to resection for non-small cell lung cancer (NSCLC), but their feasibility has not been evaluated. The aim of this study was to identify determinants of non-completion of an H-RP and the factors associated with medical events occurring 30-days after hospital discharge.

Design: A prospective observational study.

Intervention: All patients with confirmed or suspected NSCLC were enrolled in a four-component H-RP prior to surgery: (i) smoking cessation, (ii) nutritional support, (iii) physiotherapy (at least one session/week) and (iv) home cycle-ergometry (at least 3 times/week).

Outcomes: The H-RP was defined as "completed" if the four components were performed before surgery.

Results: Out of 50 patients included, 42 underwent surgery (80% men; median age: 69 (IQR 25%-75% 60-74) years; 64% COPD; 29% type-2 diabetes). Twenty patients (48%) completed 100% of the program. Univariate analyses showed a BMI>26.5 kg/m2, diabetes, polypharmacy (≥5 drugs), living alone and a long delay between inclusion and starting the H-RP were associated with a risk of non-completion. Multivariate analysis showed polypharmacy OR=12.2 (95% CI: 2.0; 74.2), living alone (single vs couple) OR=21.5 (95% CI: 1.4; >100) and a long delay before starting the H-RP OR=6.24 (95% CI 1.1; 36.6) were independently associated with a risk of non-completion. Factors associated with medical events at 30-days were H-RP non-completion, diabetes, polypharmacy, social precariousness, and female sex.

Conclusion: Facing multiple comorbidities and living alone increase the risk of not completing preoperative H-RP.

Trial registration : NCT03530059

Keywords: lung cancer, thoracic surgery, rehabilitation, home-based, pulmonary rehabilitation.

Strengths and limitations of this study

- This is the first study to explore barriers to the completion of a home-based rehabilitation program for patients awaiting lung resection surgery for lung cancer.
- This study provide important information to identify patients who are at risk of failure of a home-based program.
- The sample size was small, thus the power of this exploratory study may be limited
- Since there are no recommendations, the criterion on which completion of a rehabilitation program was defined was arbitrary.

Introduction:

Lung cancer is the leading cause of cancer related deaths worldwide.[1] Surgical resection for early stage non-small cell lung cancer (NSCLC) offers the best chance of cure, but is associated with a risk of postoperative complications and rehospitalisation.[2-4] Fragile patients are particularly at risk of such complications.[5 ,6] Guidelines from the European Respiratory Society and the European Society of Thoracic Surgery recommend early preoperative rehabilitation for patients with resectable lung cancer who have borderline lung function or poor exercise capacity.[7] It is well recognised that pulmonary rehabilitation programs effectively improve exercise capacity and help to maintain pulmonary function and quality of life following surgery; they also reduce the risk of developing postoperative pulmonary complications and shorten hospital stay.[8 ,9] Despite those recommendations, preoperative rehabilitation programs remain difficult to set up. The two main barriers are (i) the time available before surgery is often only a few weeks,[10 ,11] and (ii) the lack of standardized protocols.[8]

Pulmonary Rehabilitation is a comprehensive intervention that includes, but is not limited to, smoking cessation, nutritional support, cardiopulmonary training and physiotherapy.[12] This is standard care for patients with respiratory disability and rehabilitation programs can be conducted in both healthcare establishments and at home.[13-15] However, very few studies have assessed the feasibility and efficacy of pre-surgery, home-based rehabilitation programs. [16]

The aim of this clinical trial was to identify the barriers to the completion of a home-based pre-surgical, multimodal rehabilitation program.

Methods:

Study design

This prospective, observational study was conducted in four different medical facilities (one tertiary university hospital and three private hospitals). The study was approved by the ethics committee (CPP Ile de France XI, 2017-A02697-46) in accordance with current French legislation. It was registered on Clinical Trials.Gov (# NCT03530059).

Participants:

Participants were included if they 1) were at least 18 years old, 2) had proven or suspected operable non-small cell lung cancer (NSCLC) and scheduled lung surgery, 3) were referred for a home-based rehabilitation program and 4) required at least two out of the four components of the program (see details below). Written informed consent was obtained from all patients.

Patients involvement: patients were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Components of the rehabilitation program:

The H-RP was prescribed by a thoracic surgeon or a pulmonologist at the time the surgery date was scheduled. The minimum time before surgery should be 4 weeks.

The multimodal rehabilitation program targeted four aspects of care that are important for good post-surgical outcomes in patients with NSCLC: (1) support for smoking cessation for active smokers, (2) nutritional support, (3) physiotherapy and (4) a home-based training program.

(1) A tobacco consultation with a physician was proposed to active smokers, along with a prescription for nicotine patches.

(2) Nutritional support: a dietician carried out a nutritional assessment at home; in case of nutritional deficiency, defined as BMI<21, or unintentional body weight loss > 10 % in 6 months or >5 % in 1 month, food fortification advices were given and oral nutritional supplements were prescribed.

(3) Physiotherapy consisted of weekly sessions supervised by a physiotherapist. These consisted of strengthening exercises, stretching, respiratory muscle training (POWERbreathe® International Ltd, Southam, UK), advice and teaching regarding the importance of breathing and coughing techniques during the postoperative period. Participants were asked to attend at least one physiotherapy session per week.

(4) The training program consisted of exercise on a cycle-ergometer. Each patient was provided with a cycle-ergometer at inclusion until their date of surgery. Participants were asked to perform at least three 20-40-minute exercise sessions per week. The initial cycling intensity was fixed at 50% of peak work rate. The participants were instructed to reach at least 30 minutes at this intensity without excessive dyspnoea (<6 on a modified Borg Scale) and then to progressively increase the intensity by 10%Wmax increments whilst still being able to achieve 30 minutes of exercise.

Data collection

(i) Demographic data (age, sex, body mass index and medical history) were collected by the physician in charge in each center.

(ii) Preoperative respiratory function tests were performed according to the ATS/ERS standards. [17] A Symptom-limited Cardio-Pulmonary Exercise Test (CPET) was performed on an electronically braked cycle ergometer with breath-by-breath expired gas analysis, determined as the highest average values over 30 seconds, and peak Work Rate was identified.[18]

(iii) Quality of Life was assessed just before the beginning of the rehabilitation program by using three different standard questionnaires: the Hospital Anxiety and Depression scale (HADS), [19] the Pichot fatigue scale and the French EPICES questionnaire to assess social precariousness and health inequity.[20]

Post-operative medical events after hospital discharge were collected by telephone interviews with participants as well as by review of their medical charts at the end of the study (30 days after hospital discharge). Surgical complications such as pneumothorax, pleural effusion and nerve injuries, and medical complications such as infection, prolonged pain, or any other problem requiring medical attention were recorded.

Outcomes

Primary outcome:

The completion rate of the rehabilitation program was defined as the proportion of participants who completed 100% of the four components of the program defined as follows: 1) for current smokers - initiation and maintenance of smoking cessation; 2) for those with dietary requirements - initiation and maintenance of dietary changes; 3) participation in at least one supervised physiotherapy session per week (this component of physiotherapy was initially determined at 2 supervised sessions/week but was subsequently reconsidered because it was considered too difficult to achieve); 4) performance at least three home cycle-ergometry sessions per week.

Each component achieved was attributed a rating of 25%. The smoking cessation and diet components were automatically rated as 25% if they were unnecessary (i.e. former smoker at inclusion and no nutritional requirements)

Secondary outcome:

The secondary outcome was the rate of postoperative medical events assessed 30 days after hospital discharge.

Statistical analysis

Data were analyzed using Statistical Analysis System (SAS) software version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were expressed as medians (25^{th}-75^{th} percentiles) and categorical variables were reported as absolute numbers and percentages.

To assess the determinants of completion of a home-based rehabilitation program, univariate logistic regression models were used. Variables that were associated with the risk of non-completion of the program in the univariate analysis ($p < 0.05$) were used to determine the optimal multivariable regression model (lowest Akaike Information Criterion (AIC) to find the independent variables associated with the risk of non-completion of the program. Co-linearity between variables (defined as $r > 0.4$) was verified by Pearson's or Spearman's coefficient, or Cramer's V2. Variables associated with the risk of 30-day post-discharge events were also assessed by univariate and multivariate logistic regression models.

For all the tests, two-sided p values < 0.05 were considered significant.

Results:

Study Population:

Between February 2018 and July 2019, 50 patients scheduled for surgery were included and started the program. Eight participants were later excluded, 7 because the surgery was subsequently cancelled (small cell lung cancer (n=2), metastatic disease (n=2), frailty (n=2), misdiagnosis (n=1)), and one because he withdrew his consent (n=1)). The characteristics of the 42 participants who completed the study are reported in table 1. Most participants were male; there was a high rate of cardio-respiratory co-morbidities and exercise capacity was generally relatively low. Most participants (62%) were non-smokers at inclusion. Twenty-four participants (57%) required 3 components of the program and 15 (36%) required 4 components. The median delay between inclusion and the first day of rehabilitation was (median [25th-75th percentiles]) 8 [6; 13] days and the median delay between inclusion and surgery was 43.5 [31.0; 57.0] days.

Primary outcome:

The completion rate of each component of the program and the completion rate of the overall program is reported Table 2. Twenty participants (48%) completed the whole program.

Figure 1 shows the forest plots of factors related to non-completion of the rehabilitation program: BMI at inclusion over 26.5 kg/m2 (OR=6.43 95 CI (1.66; 24,86), p = 0.007), diabetes mellitus (OR=7.45 95 CI (1.39; 40.43), p = 0.019), polypharmacy (≥ 5 drugs) (OR=6.31 95 CI (1.63; 24.5), p = 0.008) and a short delay between program initiation and surgery (OR=4.67 95 CI (1.19; 18,35), p=0.028) were significantly associated with the risk of non-completion in the univariate analysis. [21] Living alone also tended to increase the risk of non-completion (OR=8.87 95CI (0.98; 80.18), p=0.052). The risk of non-completion was also associated with a long delay between inclusion and starting the program (OR=4.67 95 CI (1.19; 18.35),

p=0.028). In contrast, high scores on the fatigue scale, depression and anxiety scale and social status (EPICES score) were not associated with the risk of non-completion. Finally, living alone, polypharmacy and a long delay before starting the program were the three independent variables that best explained the risk of non-completion (Table 3).

Secondary outcomes:

Thirteen patients (31%) had at least one post-operative medical event within 30 days of hospital discharge (one recurrent nerve injury, one pneumothorax, two late postoperative episodes of severe pain and/or pain that was not alleviated by treatment, five infections, one pleural effusion, one transfusion for hemorrhage of a stomach ulcer, one hypertensive crisis and one post surgical anemia).

Figure 2 shows the forest-plots of factors related to the occurrence of at least one medical event after hospital discharge. Diabetes mellitus (p=0.020), polypharmacy (≥ 5 drugs) (p = 0,011), social precariousness (p=0.043) and female sex (p=0.043) were significantly associated with the occurrence of late complications in the univariate analysis. Non-completion of the program was also associated with the risk of late complications. It was not possible to build a multivariate model to determine independent variables due to the high co-linearity between the variables.

Discussion:

The aim of this prospective study was to identify barriers to the completion of a home-based rehabilitation program for patients awaiting lung resection surgery for lung cancer. Living alone, polypharmacy and a long delay before starting the rehabilitation program were the main factors associated with the risk of not completing the program. Furthermore, the results showed that polypharmacy, social precariousness and non-completion of the rehabilitation program were associated with a risk of late medical events.

Although the impact of the delay between the diagnosis of NSCLC and surgery on patient prognosis is still debated, [22] current guidelines recommend that this time should be minimised (~ 6 weeks). [23-25] Thus, any delay in the implementation of the rehabilitation program reduces the possibility of completing the program, especially if the date of surgery is already scheduled. In the present study, all patients were prescribed pre-surgical pulmonary rehabilitation by a lung cancer specialist as soon as surgery was scheduled. The initiation of the rehabilitation program could be delayed either by the time required to pass a cardio-respiratory test (cardiac clearance) or because of patient related constraints (difficulty in scheduling an appointment). Our results show that a period of at least six weeks is likely to be required to complete such a pre-surgical pulmonary rehabilitation program.

One of the main patient-related factor that prevented the completion of the home-based program was polypharmacy. Polypharmacy indicates the presence of multimorbidity, which can be burdensome for individuals to manage (drug management, self-monitoring, visits to the doctor, laboratory tests, etc.). In a very elegant modelling approach, Buffel du Vaure et al showed that people who have diabetes and hypertension could spent about 40 hours/month managing their pathologies. [26] It is therefore reasonable to expect that the diagnosis of cancer, along with the examinations and appointments involved, considerably increases this burden and limits engagement in a rehabilitation program. However, it was surprising that engagement did

not seem to be limited by mood in this study, since there was no relationship between non-completion of the program and anxiety-depression or fatigue scores. Furthermore, the results also showed that both patients with multi-morbidity and those in precarious social situations were also at risk of late post-surgical complications. In the light of these important results, we suggest that inpatient pre-surgical rehabilitation programs might be more appropriate for patients with multi-morbidity and those in precarious social situations than home-based programs to enhance post-surgical recovery. This issue should be the object of future research.

Several studies have shown that family support and encouragement enhance participation and adherence to pulmonary rehabilitation [27 ,28] particularly when the partner is able to participate in the patient's care.[29] In the present study, all but one of the participants who completed the full program lived with a partner, which explains why the upper limit of the confidence interval for this variable was very high (Table 3; OR). In contrast with recent results published on nonadherence to home-based pulmonary rehabilitation, neither depression nor anxiety scores were found to be associated with the risk of not completing the home rehabilitation program.[30]

This study has several limitations. First, from a methodological point of view, although the planned sample size was recruited, the sample was small and thus the power of this exploratory study was limited. Secondly, the criterion on which completion of a rehabilitation program was defined was arbitrary. However, no recommendations regarding this type of program have been published and most of the studies evaluating rehabilitation program adherence only considered the number of exercise sessions performed, but not others components of rehabilitation.[31] Thirdly, it could be argued that some of the participants could have been considered at a low risk of post-operative complications,[7] however our aim was not to estimate the effect of the program on post-operative risks but to assess the barriers to completion of the home-based program.

Finally, this study was not controlled and thus conclusions cannot be drawn as to the effectiveness of the home-based program regardless of whether it was completed or not by the patient.

Conclusion:

The presence of multiple comorbidities and living alone were found to be the main obstacles to the completion of a home rehabilitation program. These results provide important information for clinicians to identify patients who are at risk of failure of a home-based program and thus would benefit more from supervised pre-surgical rehabilitation programs.

Ethical approval and consent to participate: The study was approved by the ethics committee (CPP Ile de France XI, 2017-A02697-46). Written informed consent was obtained from all patients.

Funding support: This work was supported by AGIR à dom a non-profit home care provider

Conflict of interest: Jean Christian Borel and Sandy Gorain are salaried by AGIR à dom. Other authors have no conflict of interest regarding this study.

Data sharing statement: All of the anonymised individual participant data collected during the trial are available upon reasonable request (no end date). Requests should be directed to j.borel@agiradom.com

Contributorship statement: concept and design: JCB, SG, FA, CA; acquisition of data: HC, SG, FA; supervision of the study: JCB, FA; analysis and interpretation of data: HC, ACT, PYB, FA, JCB, drafting the article: HC; JCB; revising it critically for important intellectual content and final approval of the version to be published: all authors. JCB had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Subject characteristics (n=42)

	n (%) or median [25th _ 75th]
Age (years)	69 [60 -74]
Sex (% male)	34 (81)
BMI (kg/m^2)	26.5 [23.4 -30]
Living with a partner (yes)	34 (81)
Delay to start the program (days)	8 [6 -13]
Medical History	
Hypertension	20 (47.6)
Cardiac arrhythmias	3 (7.1)
Coronary artery disease	4 (9.5)
Chronic Obstructive Pulmonary Disease	27 (64.2)
Type 2 Diabetes	12 (28.6)
Current Smoker	16 (38.1)
Pulmonary function	
FEV1 (% predicted value)	72.5 [57 – 86]
FEV1/ FVC	64 [58 – 73]
Peak Work Rate (watt)	90 [70 – 110]
VO2 peak (mL/kg/min)	18 [15.5 – 20]
VO2 peak (% predicted value)	67 [58 – 85]
Health related quality of life	
HAD anxiety scale	7 [5 – 11]
HAD depression scale	5 [2 – 7]
EPICES >30, n (%)	19 (45.2)
Pichot Fatigue scale	7 [4 – 15]
Postoperative cancer stage	
Stages I-II, n (%)	26 (61.9)
Stages III, n (%)	11 (26.2)
Stages IV, n (%)	3 (7.1)
Stages other, n (%)	2 (4.8)

BMI: Body Mass Index ; FEV1: Forced expiratory volume in 1 s ; FVC: Forced vital capacity; HAD = Hospital Anxiety and Depression scale ; EPICES: Evaluation of Deprivation and Inequalities in Health Score

Table 2. Completion rate for each component of the program

	Number of patients concerned	Completion rate, n (%)
Smoking cessation	16	12 (75)
Nutritional support	38	30 (79)
Physiotherapy	42	31 (74)
Exercise training	42	33 (79)
Full program	42	20 (48)

Table 3. Factors associated with the risk of not completing the rehabilitation program in the multivariate analysis.

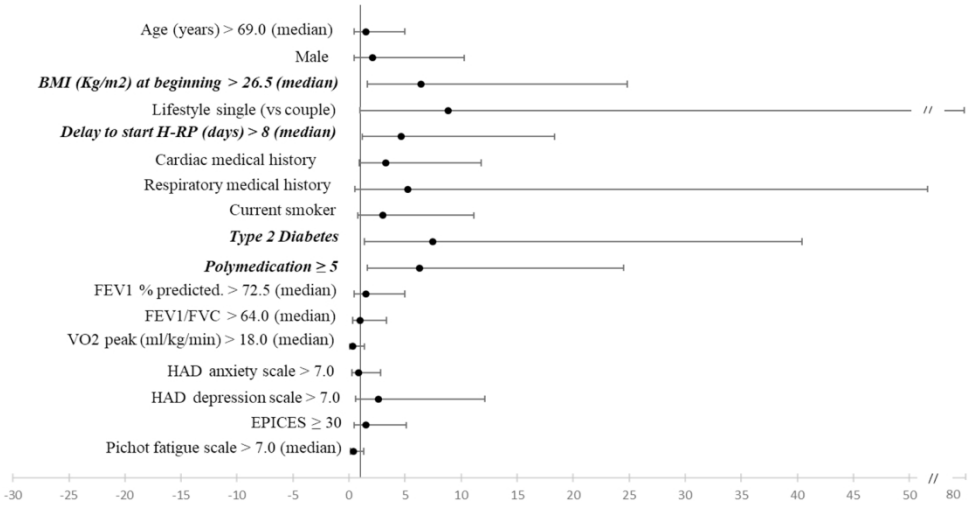
Variables	OR (CI 95%)	P-Value
Living alone	21.5 (1.4 ; >100)	0.0269
Polypharmacy ≥ 5	12.19 (2.01 ; 74.15)	0.0066
Delay in starting the program (from inclusion to the first day of the rehabilitation)	6.24 (1.07 ; 36.57)	0.0423

Result of Akaike information criterion *(AIC) = 47.4 (lower values indicate a better model), p-value global test = 0.0225, OR: odds ratio, CI: confidence interval*

Figure 1. Forests Plots: Odds ratios related to non-completion of the rehabilitation program

Figure 2. Forests plots: Odds ratios related to one adverse event or more

Figure 1.



Forests Plots: Odds ratios related to non-completion of the rehabilitation program

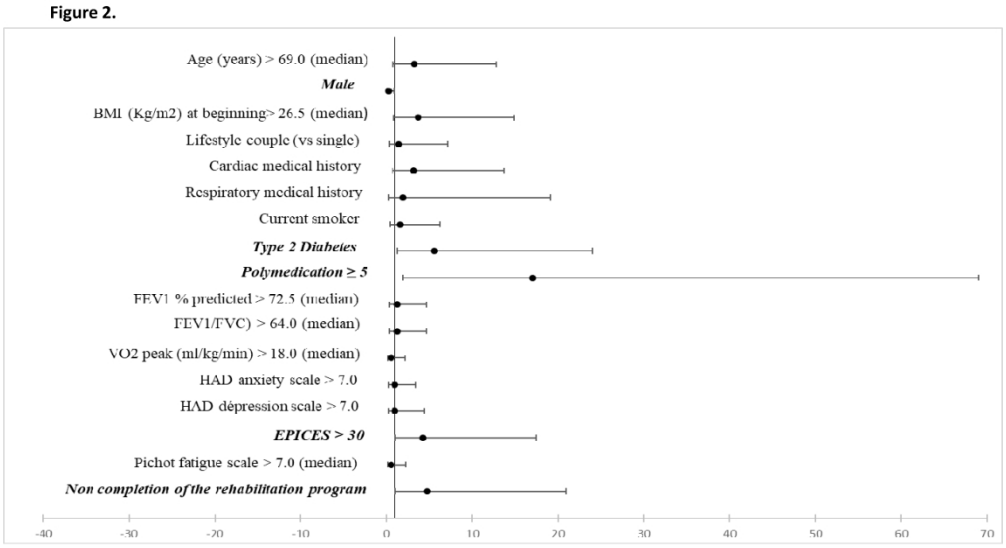


Figure 2. Forests plots: Odds ratios related to one adverse event or more (univariate analyses)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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What are the barriers to the completion of a home-based rehabilitation program for patients awaiting surgery for lung cancer: a prospective observational study.

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What are the barriers to the completion of a home-based rehabilitation program for patients awaiting surgery for lung cancer: a prospective observational study.

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Abstract:

Objectives: Home-based rehabilitation programs (H-RP) could facilitate the implementation of pulmonary rehabilitation prior to resection for non-small cell lung cancer (NSCLC), but their feasibility has not been evaluated. The aim of this study was to identify determinants of non-completion of an H-RP and the factors associated with medical events occurring 30-days after hospital discharge.

Design: A prospective observational study.

Intervention: All patients with confirmed or suspected NSCLC were enrolled in a four-component H-RP prior to surgery: (i) smoking cessation, (ii) nutritional support, (iii) physiotherapy (at least one session/week) and (iv) home cycle-ergometry (at least 3 times/week).

Outcomes: The H-RP was defined as "completed" if the four components were performed before surgery.

Results: Out of 50 patients included, 42 underwent surgery (80% men; median age: 69 (IQR 25%-75% 60-74) years; 64% COPD; 29% type-2 diabetes). Twenty patients (48%) completed 100% of the program. The median [IQR] duration of the H-RP was 32 [19 ; 46] days. Multivariate analysis showed polypharmacy (n=24) OR=12.2 (95% CI: 2.0; 74.2), living alone (n=8) (single vs couple) OR=21.5 (95% CI: 1.4; >100) and a long delay before starting the H-RP (n=18) OR=6.24 (95% CI 1.1; 36.6) were independently associated with a risk of non-completion. In univariate analyses, factors associated with medical events at 30-days were H-RP non-completion, diabetes, polypharmacy, social precariousness, and female sex.

Conclusion: Facing multiple comorbidities,living alone and a long delay before starting the rehabilitation increase the risk of not completing preoperative H-RP.

Trial registration : NCT03530059

Keywords: lung cancer, thoracic surgery, rehabilitation, home-based, pulmonary rehabilitation.

Strengths and limitations of this study

- This is the first study to explore barriers to the completion of a home-based rehabilitation program for patients awaiting lung resection surgery for lung cancer.
- This study provides important information to identify patients who are at risk of failure of a home-based program.
- The sample size was small, thus the power of this exploratory study may be limited.
- The lack of collection of information relating to participation refusals means the risk of selection bias cannot be determined.
- Since no recommendations exist, the criterion on which completion of a rehabilitation program was defined was arbitrary.

Introduction:

Lung cancer is the leading cause of cancer related deaths worldwide.[1] Surgical resection for early stage non-small cell lung cancer (NSCLC) offers the best chance of cure, but is associated with a risk of postoperative complications and rehospitalisation.[2-4] Fragile patients are particularly at risk of such complications.[5 ,6] The overall rate of hospital readmissions within 3 months after lobectomy for lung cancer can reach 18% ; in patients with comorbidities, each additional comorbidity was associated with a 2.0% increased probability of readmission. [7] Thomas et al. have shown that underweight patients had a higher surgical complication rate than normal-weight patients (23.2% vs 13.8% $p<0.001$ respectively). [5] Guidelines from the European Respiratory Society and the European Society of Thoracic Surgery recommend early preoperative rehabilitation for patients with resectable lung cancer who have borderline lung function or poor exercise capacity.[8] It is well recognised that pulmonary rehabilitation programs effectively improve exercise capacity and help to maintain pulmonary function and quality of life following surgery; they also reduce the risk of developing postoperative pulmonary complications and shorten hospital stay.[9 ,10] Despite those recommendations, preoperative rehabilitation programs remain difficult to set up. The two main barriers are (i) the time available before surgery is often only a few weeks,[11 ,12] and (ii) the lack of standardized protocols.[9]

Pulmonary Rehabilitation is a comprehensive intervention that includes, but is not limited to, smoking cessation, nutritional support, cardiopulmonary training and physiotherapy.[13] This is standard care for patients with respiratory disability and rehabilitation programs can be conducted in both healthcare establishments and at home.[14-16] However, very few studies have assessed the feasibility and efficacy of pre-surgery, home-based rehabilitation programs. [17]

The aim of this study was to identify the barriers to the completion of a home-based pre-surgical, multimodal rehabilitation program.

Methods:

Study design

This prospective, observational study was conducted in four different medical facilities (one tertiary university hospital and three private hospitals). The study was approved by the ethics committee (CPP Ile de France XI, 2017-A02697-46) in accordance with current French legislation. It was registered on Clinical Trials.Gov (# NCT03530059).

Participants:

Patients were included if they 1) were at least 18 years old, 2) had proven or suspected operable non-small cell lung cancer (NSCLC) and scheduled lung surgery, 3) were referred for a home-based rehabilitation program and 4) required at least two out of the four components of the program (see details below). All patients were asked to participate by their lung cancer specialist during the appointment when surgery was scheduled. Written informed consent was obtained from all participants.

Patients involvement: patients were not involved in the design, conduct, reporting or dissemination plans of our research

Components of the rehabilitation program:

The H-RP was prescribed by a thoracic surgeon or a pulmonologist at the time the surgery date was scheduled. The minimum time before surgery should be 4 weeks.

The multimodal rehabilitation program targeted four aspects of care that are important for good post-surgical outcomes in patients with NSCLC: (1) support for smoking cessation for active smokers, (2) nutritional support, (3) physiotherapy and (4) a home-based training program.

(1) A tobacco consultation with a physician was proposed to active smokers, along with a prescription for nicotine patches.

(2) Nutritional support: a dietician carried out a nutritional assessment at home; in case of nutritional deficiency, defined as BMI<21, or unintentional body weight loss > 10 % in 6 months or >5 % in 1 month, food fortification advice was provided and oral nutritional supplements were prescribed. The participant's nutritional requirements were assessed by calculating the number of calories received from the 24-h dietary recalls and compared to the required amount calculated through the Harris-Benedict equations. [18 ,19]

(3) Physiotherapy consisted of weekly sessions supervised by a physiotherapist located near the participant's home (out-patient clinic). These consisted of strengthening exercises, stretching, respiratory muscle training (POWERbreathe® International Ltd, Southam, UK), advice and teaching regarding the importance of breathing and coughing techniques during the postoperative period. Participants were asked to attend at least one physiotherapy session per week.

(4) The training program consisted of exercise on a cycle-ergometer. Each patient was provided with a cycle-ergometer at inclusion until their date of surgery. The cycle-ergometer was delivered to the patient's home by a homecare provider technician during a scheduled appointment. All patients had sufficient space within their homes for the device. Participants were asked to perform at least three ~~20-40-minute~~ exercise sessions per week. The initial cycling intensity was fixed at 50% of peak work rate. The participants were instructed to reach at least 30 minutes at this intensity without excessive dyspnoea (<6 on a modified Borg Scale) [20] and then to progressively increase the intensity by 10%Wmax increments whilst still being able to achieve 30 minutes of exercise. All patients were asked to complete a logbook to record the exercise sessions carried out.

Data collection

(i) Demographic data (age, sex, body mass index, medical history and living situation) were collected by the physician in charge in each center.

(ii) Preoperative respiratory function tests were performed according to the ATS/ERS standards. [21] A Symptom-limited Cardio-Pulmonary Exercise Test (CPET) was performed on an electronically braked cycle ergometer with breath-by-breath expired gas analysis, determined as the highest average values over 30 seconds, and peak Work Rate was identified.[22]

(iii) Patient-Reported Outcomes were assessed just before the beginning of the rehabilitation program by using three different standard questionnaires: the Hospital Anxiety and Depression scale (HADS), [23] the Pichot fatigue scale and the French EPICES questionnaire to assess social precariousness and health inequity.[24]

Post-operative medical events after hospital discharge were collected by telephone interviews with participants as well as by review of their medical charts at the end of the study (30 days after hospital discharge). Surgical complications such as pneumothorax, pleural effusion and nerve injuries, and medical complications such as infection, prolonged pain, or any other problem requiring medical attention were recorded.

Outcomes

Primary outcome:

The completion rate of the rehabilitation program was defined as the proportion of participants who completed 100% of the four components of the program defined as follows: 1) for current smokers - initiation and maintenance of smoking cessation; 2) for those with dietary requirements - initiation and maintenance of dietary changes; 3) participation in at least one

supervised physiotherapy session per week (this component of physiotherapy was initially determined at 2 supervised sessions/week but was subsequently reconsidered because it was considered too difficult to achieve); 4) performance at least three home cycle-ergometry sessions per week.

Each component achieved was attributed a rating of 25%. The smoking cessation and diet components were automatically rated as 25% if they were unnecessary (i.e. former smoker at inclusion and no nutritional requirements)

Example 1: If at inclusion a participant was 1) a non-smoker, 2) did not need nutritional intervention, and during the H-RP participated in at least one supervised physiotherapy session/week and performed at least three home cycle-ergometry sessions/week, completion was rated as 100%
Example 2: If at inclusion a participant was 1) non-smoker, 2) did not need nutritional intervention, and during the H-RP participated in at least one supervised physiotherapy session/week but performed only one cycle-ergometry session/week, completion was rated as 75%.

Secondary outcome:

The secondary outcome was the rate of postoperative medical events assessed 30 days after hospital discharge.

We also reported early post-surgical complications before hospital discharge.

Statistical analysis

Data were analyzed using Statistical Analysis System (SAS) software version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were expressed as medians (25^{th}-75^{th} percentiles) and categorical variables were reported as absolute numbers and percentages.

To assess the determinants of completion of a home-based rehabilitation program, univariate logistic regression models were used (all variables were categorized (> median versus ≤ median). Variables that were associated with the risk of non-completion of the program in the univariate analysis ($p < 0.05$) were used to determine the optimal multivariable regression model (procedure involving all subsets with optimization on lowest Akaike Information

Criterion (AIC)) to find the independent variables associated with the risk of non-completion of the program. Co-linearity between variables (defined as r>0.4) was verified by Pearson's or Spearman's coefficient, or Cramer's V2. Variables associated with the risk of 30-day post-discharge events were also assessed by univariate and multivariate logistic regression models.

For all the tests, two-sided p values < 0.05 were considered significant.

Results:

Study Population:

Between February 2018 and July 2019, 50 patients scheduled for surgery were included and started the program. Eight participants were later excluded, 7 because the surgery was subsequently cancelled (small cell lung cancer (n=2), metastatic disease (n=2), frailty (n=2), misdiagnosis (n=1)), and one because he withdrew his consent (n=1)). The characteristics of the 42 participants who completed the study are reported in table 1. Most participants were male; there was a high rate of cardio-respiratory co-morbidities and exercise capacity was generally relatively low. Most participants (62%) were non-smokers at inclusion. Twenty-four participants (57%) required 3 components of the program and 15 (36%) required 4 components. The median delay between inclusion and the first day of rehabilitation was (median [25th-75th percentiles]) 8 [6; 13] days and the median delay between inclusion and surgery was 43.5 [31.0; 57.0] days. The median [25th-75th] duration of the H-RP was 32 [19 ; 46] days.

Primary outcome:

The completion rate of each component of the program and the completion rate of the overall program is reported Table 2. Twenty participants (48%) completed the whole program.

Figure 1 shows the forest plots of factors related to non-completion of the rehabilitation program: BMI at inclusion over 26.5 kg/m2 (OR=6.43 95 CI (1.66; 24,86), p = 0.007), diabetes mellitus (OR=7.45 95 CI (1.39; 40.43), p = 0.019), polypharmacy (≥ 5 drugs) (OR=6.31 95 CI (1.63; 24.5), p = 0.008) and a short delay between program initiation and surgery (OR=4.67 95 CI (1.19; 18,35), p=0.028) were significantly associated with the risk of non-completion in the univariate analysis. [25] Living alone also tended to increase the risk of non-completion (OR=8.87 95CI (0.98; 80.18), p=0.052). The risk of non-completion was also associated with a long delay between inclusion and starting the program (OR=4.67 95 CI (1.19; 18.35),

p=0.028). In contrast, high scores on the fatigue scale, depression and anxiety scale and social status (EPICES score) were not associated with the risk of non-completion. Finally, living alone, polypharmacy and a long delay before starting the program were the three independent variables that best explained the risk of non-completion (Table 3).

Secondary outcomes:

Thirteen patients participants (31%) had at least one post-operative medical event within 30 days of hospital discharge (one recurrent nerve injury, one pneumothorax, two late postoperative episodes of severe pain and/or pain that was not alleviated by treatment, five infections, one pleural effusion, one transfusion for hemorrhage of a stomach ulcer, one hypertensive crisis and one post surgical anemia).

Figure 2 shows the forest-plots of factors related to the occurrence of at least one medical event after hospital discharge. Diabetes mellitus (p=0.020), polypharmacy (≥ 5 drugs) (p=0,011), social precariousness (p=0.043) and female sex (p=0.043) were significantly associated with the occurrence of late complications in the univariate analysis. Non-completion of the program was also associated with the risk of late complications. It was not possible to build a multivariate model to determine independent variables due to the high co-linearity between the variables.

Table 4 reports early post-surgical complications (before hospital discharge) and length of hospitalization: neither early post-surgical complications nor the duration of hospitalisation differed between participants who had completed the H-RP and those who had not.

Discussion:

The aim of this prospective study was to identify barriers to the completion of a home-based rehabilitation program for patients awaiting lung resection surgery for lung cancer. Living alone, polypharmacy and a long delay before starting the rehabilitation program were the main factors associated with the risk of not completing the program. Furthermore, the results showed that polypharmacy, social precariousness and non-completion of the rehabilitation program were associated with a risk of late medical events.

Although the impact of the delay between the diagnosis of NSCLC and surgery on patient prognosis is still debated, [26] current guidelines recommend that this time should be minimised (~ 6 weeks). [27-29] Thus, any delay in the implementation of the rehabilitation program reduces the possibility of completing the program, especially if the date of surgery is already scheduled. In the present study, all patients were prescribed pre-surgical pulmonary rehabilitation by a lung cancer specialist as soon as surgery was scheduled. The initiation of the rehabilitation program could be delayed either by the time required to pass a cardio-respiratory test (cardiac clearance) or because of patient related constraints (difficulty in scheduling an appointment). Our results show that a period of at least six weeks is likely to be required to complete such a pre-surgical pulmonary rehabilitation program.

One of the main patient-related factors that prevented the completion of the home-based program was polypharmacy. Polypharmacy indicates the presence of multimorbidity, which can be burdensome for individuals to manage (drug management, self-monitoring, visits to the doctor, laboratory tests, etc.). In a very elegant modelling approach, Buffel du Vaure et al showed that people who have diabetes and hypertension could spent about 40 hours/month managing their pathologies. [30] It is therefore reasonable to expect that the diagnosis of cancer, along with the examinations and appointments involved, considerably increases this burden and limits engagement in a rehabilitation program. However, it was surprising that engagement did

not seem to be limited by mood in this study, since there was no relationship between non-completion of the program and anxiety-depression or fatigue scores. Furthermore, the results also showed that both patients with multi-morbidity and those in precarious social situations were also at risk of late post-surgical complications. In the light of these important results, we suggest that inpatient pre-surgical rehabilitation programs might be more appropriate for patients with multi-morbidity and those in precarious social situations than home-based programs to enhance post-surgical recovery. This issue should be the object of future research.

Several studies have shown that family support and encouragement enhance participation and adherence to pulmonary rehabilitation [31 ,32] particularly when the partner is able to participate in the patient's care.[33] In the present study, all but one of the participants who completed the full program lived with a partner, which explains why the upper limit of the confidence interval for this variable was very high (Table 3; OR). In contrast with recent results published on nonadherence to home-based pulmonary rehabilitation, neither depression nor anxiety scores were found to be associated with the risk of not completing the home rehabilitation program.[34]

This study has several limitations. First, from a methodological point of view, although the planned sample size was recruited, the sample was small and thus the power of this exploratory study was limited. Secondly, the criterion on which completion of a rehabilitation program was defined was arbitrary and we did not collect information relating to the reasons for non-completion and at which point in the process non-completion occurred. However, no recommendations regarding this type of program have been published and most of the studies evaluating rehabilitation program adherence only considered the number of exercise sessions performed, but not others components of rehabilitation.[35] Thirdly, it could be argued that some of the participants could have been considered at a low risk of post-operative complications,[8] however our aim was not to estimate the effect of the program on post-operative risks but to assess the barriers to completion of the home-based program. Fourthly,

we did not collect information relating to the number and the reasons for refusal, therefore, we cannot we be sure there was no selection bias.

Finally, this study was not controlled and thus conclusions cannot be drawn as to the effectiveness of the home-based program regardless of whether it was completed by the patient or not.

Conclusion:

The presence of multiple comorbidities and living alone were found to be the main obstacles to the completion of a home rehabilitation program. Although other factors relating to non-completion may not have been identified, these results provide important information for clinicians to identify patients who are at risk of failure of a home-based program and thus would benefit more from supervised pre-surgical rehabilitation programs.

Ethical approval and consent to participate: The study was approved by the ethics committee (CPP Ile de France XI, 2017-A02697-46). Written informed consent was obtained from all participants.

Funding statement: no funding

Conflict of interest: Jean Christian Borel and Sandy Gorain are salaried by AGIR à dom. Other authors have no conflict of interest regarding this study.

Data sharing statement: All of the anonymised individual participant data collected during the trial are available upon reasonable request (no end date). Requests should be directed to j.borel@agiradom.com

Contributorship statement:

Planning of the study : JCB, SGo (S Gorain), FA, CA, BW

Conduct of the study : SGu (S Guiguard), FA, ACT, GF, TC, PYB, JFR, LS, DB

Reporting of the study: HC, JCB, FA, SG (S Gorain)

JCB had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1: Subject characteristics (n=42)

	n (%) or median [25th _ 75th]
Age (years)	69 [60 -74]
Sex (% male)	34 (81)
BMI (kg/m^2)	26.5 [23.4 -30]
Living with a partner (yes)	34 (81)
Delay to start the program (days)	8 [6 -13]
Medical History	
Hypertension	20 (47.6)
Cardiac arrhythmias	3 (7.1)
Coronary artery disease	4 (9.5)
Chronic Obstructive Pulmonary Disease	27 (64.2)
Type 2 Diabetes	12 (28.6)
Current Smoker	16 (38.1)
Pulmonary function	
FEV1 (% predicted value)	72.5 [57 – 86]
FEV1/ FVC	64 [58 – 73]
Peak Work Rate (watt)	90 [70 – 110]
VO2 peak (mL/kg/min)	18 [15.5 – 20]
VO2 peak (% predicted value)	67 [58 – 85]
Patient reported Outcomes	
HAD anxiety scale	7 [5 – 11]
HAD depression scale	5 [2 – 7]
EPICES >30, n (%)	19 (45.2)
Pichot Fatigue scale	7 [4 – 15]
Postoperative cancer stage	
Stages I-II, n (%)	26 (61.9)
Stages III, n (%)	11 (26.2)
Stages IV, n (%)	3 (7.1)
Stages other, n (%)	2 (4.8)

BMI: Body Mass Index; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; HAD = Hospital Anxiety and Depression scale; EPICES: Evaluation of Deprivation and Inequalities in Health Score

Table 2. Completion rate for each component of the program

	Number of patients concerned	Completion rate, n (%)
Smoking cessation	16	12 (75)
Nutritional support	38	30 (79)
Physiotherapy	42	31 (74)
Exercise training	42	33 (79)
Full program	42	20 (48)

Table 3. Factors associated with the risk of not completing the rehabilitation program in the multivariate analysis.

Variables	OR (CI 95%)	P-Value
Living alone	21.5 (1.4 ; >100)	0.0269
Polypharmacy ≥ 5	12.19 (2.01 ; 74.15)	0.0066
Delay in starting the program (from inclusion to the first day of the rehabilitation)	6.24 (1.07 ; 36.57)	0.0423

Result of Akaike information criterion *(AIC) = 47.4 (lower values indicate a better model), p-value global test = 0.0225, OR: odds ratio, CI: confidence interval*

Table 4. Early post-surgical complications (before discharge) and length of hospitalization in patients who completed the H-RP versus those who did not.

Variables	Patients who completed H-RP (n = 20)	Patients who did not complete H-RP (n = 22)	OR (95% CI)	p-value
Pleuro-pulmonary complications, n (%)	12 (60.0)	9 (40.9)	0.46 (0.13 ; 1.59)	0.22
Chest-wall complications, n (%)	1 (5.0)	2 (9.1)	1.90 (0.16 ; 22.71)	0.61
Cardiovascular complications, n (%)	3 (15.0)	3 (13.6)	0.90 (0.16 ; 5.04)	0.90
Neurologic complications, n (%)	1 (5.0)	1 (4.6)	0.91 (0.05 ; 15.49)	0.94
Lenght of postoperative hospitalisation, days (median, [25th-75th])	7.5 [6.0 ; 9.5]	7.0 [6.0 ; 12.0]	0.69 (0.20 ; 2.35)	0.56

Figure 1. Forests Plots: Odds ratios related to non-completion of the rehabilitation program (univariate analyses)

Figure 2. Forests plots: Odds ratios related to one adverse event or more (univariate analyses)

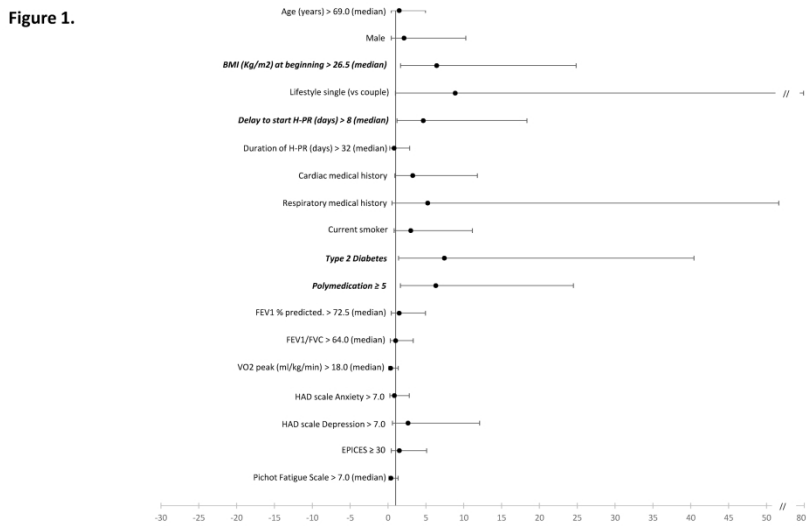

Figure 1. Forests Plots: Odds ratios related to non-completion of the rehabilitation program (univariate analyses)

297x209mm (300 x 300 DPI)

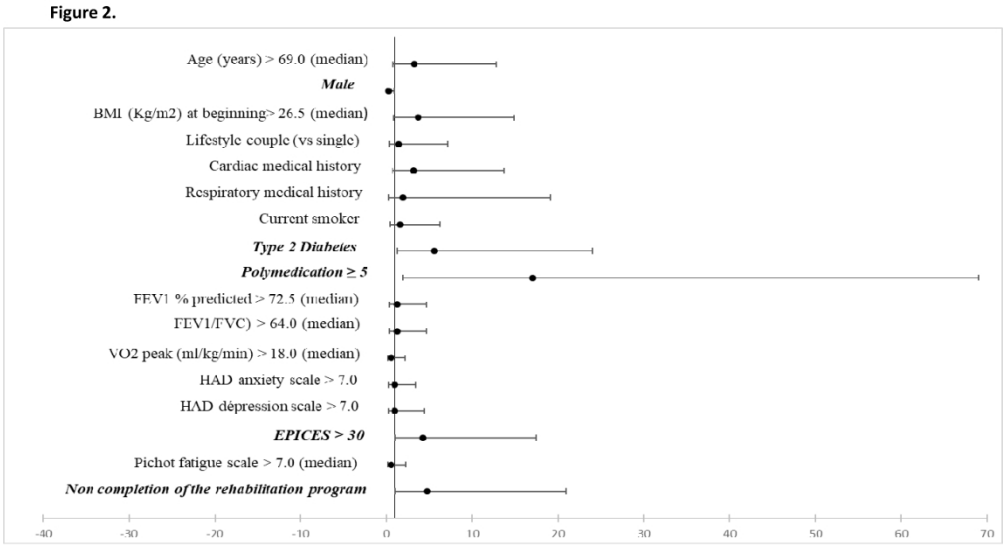

Figure 2. Forests plots: Odds ratios related to one adverse event or more (univariate analyses)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	12
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	Tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.