Tailored exercise is safe and beneficial for acutely hospitalised older adults with COPD

To the Editor:

COPD is predicted to affect approximately half of the older population in the next decade. The incidence of hospitalisations associated with this condition is also likely to rise, even surpassing those caused by major conditions (notably, ischaemic cardiomyopathy) [1]. In this context, the collateral effects of hospitalisation, even for a few days, must not be overlooked, especially in the oldest segment (>80 years). Nearly one third of older adults lose their ability to independently perform one or more activities of daily living from hospital admission to discharge even if successfully treated from the condition that caused hospitalisation, the so-called "hospital induced-disability". This condition has major short- and long-term consequences, notably an increased risk of re-admission and mortality. Moreover, hospitalised patients with COPD present with a proinflammatory profile (*i.e.* elevated serum C-reactive protein (CRP)) and high range of variation in red blood cell volume (*i.e.* elevated red blood cell distribution width (RDW)), both features associated with poorer outcomes [2].

The inverse relationship between physical activity levels and functional decline in hospitalised patients with COPD [3] and the benefits of exercise intervention on inflammation [4] and RDW [5] provide rationale to the hypothesis that in-hospital exercise might be beneficial for them. However, controversy exists as to the actual safety and effectiveness of this type of intervention [6]. Exercise rehabilitation programmes have proven to increase exercise capacity and quality of life (QoL) in hospitalised patients with COPD [7]. Yet, recent joint guidelines from the European Respiratory Society (ERS) and American Thoracic Society (ATS) discourage implementation of these programmes in hospitalised patients with COPD [8]. This recommendation was based, at least partly, on previous results showing an increased long-term mortality in patients with COPD (45–93 years) who had participated in an exercise programme [9].

We assessed the effects of an individualised exercise programme on the functional capacity of acutely hospitalised older adults with COPD. Depression and QoL indicators, as well as CRP and RDW were also determined.

The original trial is registered at ClinicalTrials.gov (identifier: NCT02300896) and its full details have been published [10]. Patients admitted to an Acute Care for Elders unit (between 1 February, 2015 and 30 August, 2017) who provided written informed consent were eligible for inclusion. Participants were randomised to receive usual care alone (controls); or combined with an in-hospital supervised exercise intervention lasting 5–7 days per week and including two sessions per day of 15–20 min duration where participants performed moderate-intensity resistance (uprising from a chair, leg press, knee extension/flexion, hip abduction, seated bench press (2–3 sets, 8–10 repetitions, 30–60% of one-repetition maximum (1RM))) and walking exercises [11]. Patients diagnosed with COPD in their primary care clinical record, and presenting with COPD-exacerbation related symptoms (increased dyspnoea or increased sputum volume/purulence) with a duration range from 24 h to 21 days were included in the present analysis.

The primary end-point was pre-/post-intervention change in functional ability (as assessed with Barthel index and physical performance (Short Physical Performance Battery (SPPB))). Secondary end-points included changes in CRP, RDW, 1RM leg strength, mood status (15-item Yesavage Geriatric Depression Scale; Spanish version), and visual analogue scale of the EuroQol-5 Dimension for QoL. Exercise-related side-effects and incidence of readmission and mortality at 3- and 12-month follow-up were also reported.

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TABLE 1 a) Baseline characteristics of study participants and b) results of primary and secondary end-points

a) Baseline characteristics

	Control (n=40)	Exercise intervention (n=46)
Age years	87±5	87±5
Women	18%	19%
Weight kg	69±11	68±17
BMI kg·m^{-2}	28±4	27±6
CIRS score	14±5	14±5
FEV_1 %	71±26	68±26
FVC %	76±21	74±20
FEV_1/FVC %	65±11	64±15

b) End-points

	Control		Exercise intervention		Between-group difference (95% CI)
	Pre-intervention	Post-intervention	Pre-intervention	Post-intervention	
Primary					
SPPB score[#]	4.7±2.7	4.7±2.9	4.7±2.2	6.8±3.0	−2.1 (−2.9 to −1.3)
Barthel index score[¶]	83.2±16.1	75.9±20.5	83.6±18.2	86.0±15.3	−9.3 (−14.2 to −4.5)
Secondary					
1RM leg press kg	59.8±26.8	57.8±27.5	59.1±24.7	76.1±32.7	−19.0 (−26.2 to −11.9)
GDS score[+]	4±3	5±3	4±2	2±2	2 (2 to 3)
EQ-5D score[§]	58±21	57±20	58±20	67±18	−11 (−21 to −1)
RDW %	15.0±2.5	15.2±2.6	13.8±1.6	14.1±1.9	0.1 (−0.3 to 0.4)
CRP mg·L^{-1}	95.1±27.0	93.8±47.6	78.5±37.7	72.7±55.3	−22.2 (−52.9 to 8.4)

Data are mean±SD, unless otherwise stated. Forced expiratory volume in 1s (FEV_1), forced vital capacity (FVC) and FEV_1/FVC are expressed as percentage of normal age-predicted values. BMI: body mass index; CIRS: Cumulative Illness Rating Scale-Geriatric; SPPB: short physical performance battery; 1RM: one-repetition maximum; GDS: Geriatric Depression Scale; EQ-5D: EuroQol-5 Dimensions questionnaire; RDW: red blood cell distribution width; CRP: C-reactive protein. [#]: SPPB ranges from 0 (worst) to 12 (best); [¶]: Barthel Index ranges from 0 (severe functional dependence) to 100 (functional independence); [+]: GDS ranges from 0 (best) to 15 (worst); [§]: EQ-5D ranges from 0 (worst health status) to 100 (best health status).

We used the intention-to-treat approach. Between-group comparisons of continuous variables were conducted using linear mixed models. Time was treated as a categorical variable.

Of the 370 patients initially included in the randomised controlled trial [11], 86 with COPD were identified (40 and 46 for the control and exercise intervention group, respectively; table 1a). The median length of stay was 8 days (interquartile range 4 days) for both groups. All patients in both groups were discharged home. The multicomponent physical exercise programme "Vivifrail" (www.vivifrail.com) [11] to prevent weakness and falls was recommended as post-hospitalisation care. The exercise intervention improved all functional and physical performance-related outcomes (Barthel index, SPPB, 1RM leg strength) as well as depression and QoL scores, but no significant changes were found for CRP or RDW (table 1b). No side-effects associated were noted with the exercise sessions. No between-group differences were found for the incidence of readmission at 3-month (25.0 *versus* 30.4% for the control and exercise intervention group, respectively; OR (95% CI): 1.313 (0.506–3.401)) or 12-month follow-up (52.5 *versus* 56.5%; OR (95% CI): 1.176 (0.502–2.756)); or for the incidence of mortality at 3-month (10.0 *versus* 17.4%; OR (95% CI): 1.895 (0.525–6.841)) or 12-month follow-up (37.5 *versus* 34.8%; OR (95% CI): 0.889 (0.368–2.147)).

The results of functional/physical performance and depression/QoL-related outcomes are in agreement with previous research. There is high-quality meta-analytical evidence supporting a beneficial effect of rehabilitation programmes on exercise capacity and QoL in patients with COPD after an exacerbation [8]. The ERS/ATS guidelines in fact state that rehabilitation programmes initiated during hospitalisation are effective for increasing exercise capacity in these patients [8]. Of note, is that even though the SPPB increased following intervention, the patients were still physically frail when they were discharged home. Accordingly, the multicomponent individualised physical exercise programme "Vivifrail" [11] was prescribed at post-hospitalisation. The lack of changes in blood biomarkers is also in line with previous findings in hospitalised patients with COPD [12].

There is, nevertheless, controversy as to whether individuals with COPD exacerbation should exercise during hospitalisation. A randomised controlled trial by Greening *et al.* [9] found a higher risk of mortality during a 12-month follow-up (OR 1.74 (95% CI 1.05–2.88)) in patients hospitalised due to COPD exacerbation who had been involved in an early rehabilitation intervention. Mostly based on this result, an ERS/ATS joint meta-analysis concluded that rehabilitation programmes initiated during hospitalisation increase exercise capacity, but they might also be associated with an increased risk of mortality [8]. As such, initiating rehabilitation during hospitalisation should be discouraged, even if the quality of the evidence for an actual risk was acknowledged to be "very low" [8]. It must noted, however, that in the Greening *et al.* [9] study no between-group differences were found when per-protocol, instead of intention-to-treat, analyses were conducted, suggesting that those who actually received the intervention did not have an increased mortality risk.

Finally, a considerable heterogeneity of response for muscle function, physical performance, cognitive function and QoL-related outcomes could be also detected after usual care or physical exercise. Thus, as previously reported [13], response rate for functional capacity could not predict similar changes in other clinical characteristics, such as muscle strength and cognition. These findings support the need for a individualised tailored exercise and cognitive training programme as a leading treatment strategy to prevent the functional and cognitive decline usually associated with prolonged bed-rest during hospitalisation in older populations with COPD.

In summary, our findings add to the existing limited literature supporting the benefits and safety of early rehabilitation programmes in acutely hospitalised, older patients with COPD. Of note, the fact that our results were found in very old people (87 years on average) strengthens the potential safety of this type of interventions. Further evidence is needed to confirm our findings.

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References

1 CDC. Data Access - Health Data Interactive - Homepage. www.cdc.gov/nchs/hdi/index.htm
2 Hurst JR, Donaldson GC, Perera WR, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 174: 867–874.
3 Pitta F, Troosters T, Probst VS, *et al.* Physical activity and hospitalization for exacerbation of COPD. *Chest* 2006; 129: 536–544.
4 Fedewa M V, Hathaway ED, Ward-Ritacco CL. Effect of exercise training on C reactive protein: a systematic review and meta-analysis of randomised and non-randomised controlled trials. *Br J Sports Med* 2017; 51: 670–676.
5 Nishiyama Y, Niiyama H, Harada H, *et al.* Effect of exercise training on red blood cell distribution width as a marker of impaired exercise tolerance in patients with coronary artery disease. *Int Heart J* 2016; 57: 553–557.
6 Spruit MA, Singh SJ, Rochester CL, *et al.* Pulmonary rehabilitation for patients with COPD during and after an exacerbation-related hospitalisation: Back to the future? *Eur Respir J* 2018; 51: 1701312.

7 Puhan MA, Gimeno-Santos E, Cates CJ, *et al.* Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2016; 12: CD005305.
8 Wedzicha JA, Miravitlles M, Hurst JR, *et al.* Management of COPD exacerbations: A European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017; 49: 1600791.
9 Greening NJ, Williams JEA, Hussain SF, *et al.* An early rehabilitation intervention to enhance recovery during hospital admission for an exacerbation of chronic respiratory disease: Randomised controlled trial. *BMJ* 2014; 349: g4315.
10 Martínez-Velilla N, Casas-Herrero A, Zambom-Ferraresi F, *et al.* Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med* 2019; 179: 28–36.
11 Izquierdo M, Casas-Herrero A, Zambom-Ferraresi F, *et al.* Multicomponent physical exercise program vivifrail. A practical guide for prescribing a Multicomponent Physical training program to prevent weakness and falls in people over 70. 2017. http://vivifrail.com/wp-content/uploads/2019/11/VIVIFRAIL-ENG-Interactivo.pdf
12 Troosters T, Probst VS, Crul T, *et al.* Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 181: 1072–1077.
13 Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, *et al.* Inter-individual variability in response to exercise intervention or usual care in hospitalized older adults. *J Cachexia Sarcopenia Muscle* 2019; 10: 1266–1275. .