RESEARCH

Early rehabilitation program and weaning outcomes in critically ill chronic obstructed airway disease patients: a randomized trial

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Abstract

Background: To compare the effectiveness of early rehabilitation program on mechanical ventilated COPD patient in RICU to those using current usual care regarding diaphragm function and weaning outcomes.

Methods: The study was a randomized controlled trial. It included 108 newly admitted COPD patients to RICU, Chest Department, Assiut University Hospital, Egypt, in the period from June 2018 to May 2020. They were divided into two groups: group **I** received the usual care plus pulmonary rehabilitation program, and group II received the usual care alone. The outcomes (MV duration, rates of successful weaning, diaphragm function, and lengths of hospital and ICU stay) were recorded and evaluated. The data was analyzed using Student t-test, Mann–Whitney U-test, Wilcoxon signed-rank test, chi-square (χ^2) test or Fisher Exact test, receiver operating characteristics (ROC) curve, and logistic regression analysis.

Results: One-hundred and eight COPD patients were included. Early rehabilitation program for COPD patients in the ICU shortened the duration of their MV, increases the rates of successful weaning and decreases 30-day mortality, and shortened the duration of their ICU and hospital stays, as compared to COPD patients who received usual care.

Conclusions: Management of COPD patients with early rehabilitation program is associated with better outcome with improvement of the quality of life of COPD patients.

Trial registration: Clinical trial.gov: NCT03253380

Keywords: Chronic obstructive pulmonary disease, Intensive care unit, Mechanical ventilation, Early rehabilitation program, Weaning, Mortality

Background

COPD has grown dramatically and accounting for the fourth leading cause of death worldwide. In the last years, according to the World Health Organization (WHO) report, COPD predicted to become the third leading cause of death by 2030 [1]. Also, it has a great effect on patients' well-being and mortality [2] with subsequent economic and social burden for both individuals and communities [3]. Patients with COPD commonly complicated with attacks of acute exacerbation mostly need mechanical ventilation (MV) in an intensive care unit (ICU). A non-pharmacological therapy that has been recently added to the conventional care for COPD patients was a pulmonary rehabilitation program (PRP) [4, 5] as several evidence document and support its effectiveness [6–8]. Many previous studies [4, 5, 7–10] have reported the role of PRP in reducing dyspnea, improved exercise capacity, with subsequent improvement in the quality of life (QoL). Another study reported that PRP also reduce the length of hospital stays, even for COPD patients with a recent exacerbation [6, 11–13]. All these

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studies have proved that PRP is an effective and safe intervention that reduces the need for hospital readmission. However, the role of early pulmonary rehabilitation for respiratory failure acute exacerbation COPD patients, which requires invasive MV, is rarely discussed before. Therefore, the aim of this study was to evaluate the effects of early rehabilitation program on the outcome of patients with COPD who required invasive or not invasive MV in the ICU. We collected data on MV duration, type and outcome of weaning, and duration of hospital and ICU stays among COPD patients.

Methods

It was a randomized controlled trial registered at ClinicalTrials.gov (NCT03253380). The study was conducted on 108 COPD patients newly admitted to respiratory intensive care unit (RICU), Chest Department, Assiut University Hospita, Egypt, from the 1st of June 2018 to the 1st of May 2020. The protocol of the study was approved by the Assiut University Medical Ethical Review Board.

Eligible participants

This study consecutively enrolled newly admitted adult COPD patients ($\geq$ 18 years old) according to GOLD guideline 2018 [14] who were presented with respiratory failure acute exacerbation of COPD and admitted to RICU, Chest Department, Assiut University Hospital, to receive mechanical ventilatory support either noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV) as line of management of acute exacerbation of COPD. The exclusion criteria were COPD patients with neuromuscular disease or overlap with obstructive sleep apnea (OSA) and patients who have major disorders with persistent neurological deficit, and patients who refused to participate in the study were also excluded.

Enrollment

Written consent was obtained from all eligible participants after explaining the nature of the study. Then, patients who met the entry criteria were subjected. Detailed history which included demographic data, full clinical examination, and comorbidities (including diabetes mellitus, hypertension, liver diseases, renal impairment, or cardiac disease) was recorded.

All patients underwent biochemical investigations including complete blood count (CBC), RDW, kidney function tests (serum urea, serum creatinine), liver function tests, c-reactive protein (CRP), serum troponin I, and serum creatine kinase (CK) enzyme which were measured within the first 24 h after RICU admission. Arterial blood gases (ABGs) were obtained before the start of MV and after weaning by arterial blood sampling

and analyzed using a blood gas analyzer. The diaphragmatic US was performed for assessment of diaphragmatic thickness and motion. This was done within 24 h after RICU admission and then at time of weaning whether the patient was on IMV or NIV, during spontaneous breathing trial (SBT), or if the patient was on IMV. All patients need ventilator support, either NIV OR IMV using Puritan Bennett ventilator (NPB 840, Puritan-Bennett/Covidien, Carlsbad, California, USA). Patients who were on NIV were using different interfaces according to their comfortability. Ventilator parameters were recorded during SBT on pressure support (PS) mode of MV: tracheal airway occlusion pressure (P0.1) and negative inspiratory force (NIF).

After that, the participants were randomly divided into two groups: group I received the usual care in combination to pulmonary rehabilitation program ($n = 53$). Group II received the usual care alone ($n = 55$).

The pulmonary rehabilitation program included peripheral muscle training using the following tools (passive upper and lower limb exercise during the period in which the patient is unconscious and active upper and lower limb exercise done by the patient) and electrical muscle stimulation (EMS) for quadriceps muscle by EMS device.

Respiratory muscle training by two exercise sessions were performed at 9 AM and 5 PM. Training will be based on decreasing the trigger sensitivity gradually in order to increase muscle endurance. The trigger sensitivity was adjusted to 20% of the first recorded NIF at the start of training (in the first session); inspiratory muscle training (IMT) was limited to 5 min, afterwards the duration was increased by 5 min at every session until it reached 30 min. If a patient tolerated 30 min of IMT, the next session would be performed with increasing trigger sensitivity by 10% of the initial MIP.

Patients who could not tolerate IMT with 20% of MIP for 5 min were trained with 10% of MIP [15].

IMT sessions stopped after 5 days, and the trial of weaning was done, and the mean of duration and percent for each patient was calculated.

The inspiratory muscle training session was stopped if the patients had any of the following signs: respiratory frequency of more than 38 breaths per minute, arterial oxygen saturation below 90%, tidal volume less than 4–6 ml/kg. systolic blood pressure above 180 mm Hg or below 90 mm Hg, paradoxical breathing, and heart rate more than 120/min [16] Fig. 1.

The study outcomes

Patient outcomes were considered within 30 days after extubation either by the need for MV within the first 48 h (primary weaning failure), the need for MV after 48 h

Fig. 1 Flow diagram of the study
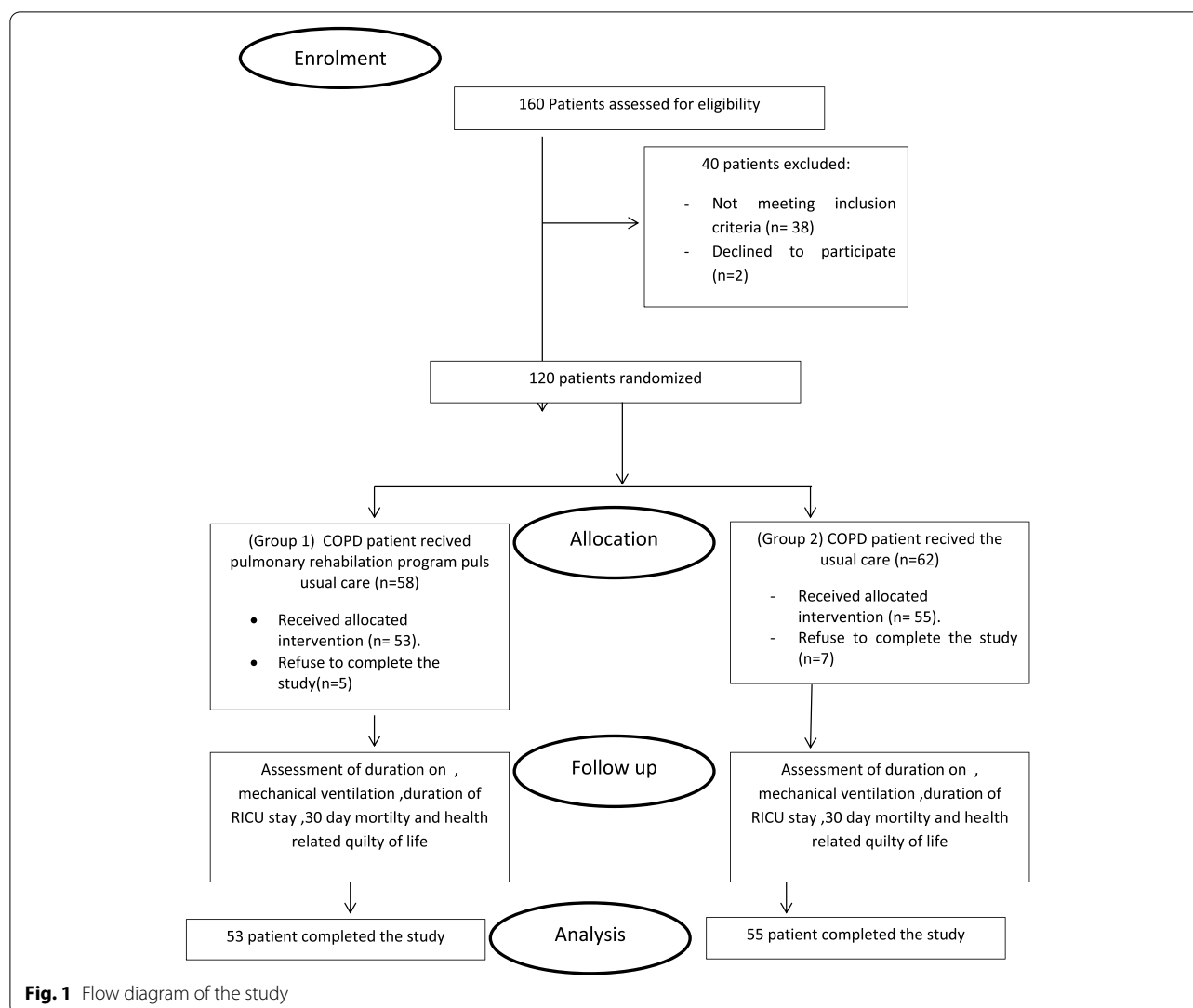
(secondary weaning failure), discharge from RICU, or death. Patients were considered to have survived if they were discharged from the hospital.

Sample size

This study enrolled 108 COPD patients with acute exacerbation and in need of either invasive or noninvasive mechanical ventilation.

Statistical analysis

The data was collected and entered into Microsoft Excel database to be analyzed using the Statistical Package for Social Science (SPSS Inc., Chicago, version 22). Data were statistically described in terms of mean ± standard deviation (± SD), or median and range when not normally distributed, and frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using *Student t-test* or *Mann-Whitney U-test* when the data were not normally distributed. Comparison of paired quantitative variables was done by *Wilcoxon signed-rank tes*t for non-normally distributed data. For comparing categorical data, *chi-square (χ^2) test or exact test* was used instead of *chi-square (χ^2)* test because when expected frequency is less than 5, the receiver operating characteristic curve (ROC) analysis was used to find out the cutoff values and to validate predicted probabilities of weaning. Odds ratio (OR) with 95% confidence interval (CI) and logistic regression was calculated to differentiate different predictors

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of weaning outcome. *P*-value is always 2-tailed set significant at 0.05 level.

Results

Demographic characteristics of patients

The baseline sociodemographic and clinical data were comparable in both studied groups with no significant differences in (age, sex, smoking status, addiction, the presence of other comorbidities, previous exacerbation, ICU admission, and previous MV need) among both studied groups (*P* > 0.05) (Table 1). Also, all their laboratory findings, arterial blood gases, and ICU scores (APACHE II score and SOFA score) were not significantly different (Table 2).

Diaphragmatic function assessment

No significant difference was found between both studied groups as regard all baseline diaphragmatic function, namely (respiratory thickness and excursion) (*P* > 0.05). Meanwhile after weaning, group 1 has statistically higher mean (mm) for all diaphragmatic function than group 2 (*P* = 0.046, 0.011, and 0.038), respectively (Table 3).

Outcome analyses

Outcome analyses showed that the early rehabilitation group either invasive or noninvasive MV had a shorter duration of MV and ICU stay (days), higher rate of simple successful weaning, less incidence of nosocomial pneumonia, and significantly lower PCO2 (mmHg) as compared to group 2 (63.07 ± 5.05 versus 65.97 ± 4.89

Table 2 Baseline laboratory data, arterial blood gases, and ICU scores among enrolled patients (*n* = 108)

Variable name	Group 1 (*n* = 53)	Group 2 (*n* = 55)	*p-value*
Laboratory data			
• WBCs (10^3/ul)	13.57 ± 4.19	12.78 ± 4.01	0.323
• Platelet (10^3/ul)	308.28 ± 27.04	313.22 ± 92.34	0.787
• Hemoglobin (gm/dl)	12.56 ± 1.83	12.56 ± 1.74	0.898
• Hematocrit (%)	43.13 ± 5.36	42.85 ± 5.46	0.791
• RDW (%)	17.19 ± 5.79	18.29 ± 6.29	0.346
• CRP (mg/dl)	53.45 ± 25.43	53.69 ± 26.01	0.962
• Creatine kinase (u/l)	53.79 ± 26.74	60.04 ± 31.37	0.345
• Creatine kinase-MB (u/l)	40.87 ± 21.39	45.06 ± 25.31	0.526
• Troponin (ng/ml)	0.04±0.06	0.05±0.06	0.640
Arterial blood gases at admission			
• PH$^+$	7.19 ± 0.08	7.19 ± 0.06	0.733
• PCO_2 (mmHg)	87.13 ± 10.92	89.98 ± 11.02	0.180
• PO_2 (mmHg)	39.62 ± 2.81	38.33 ± 2.90	0.063
ICU scores			
• APACHE-II score	10.42 ± 4.00	9.82 ± 4.23	0.322
• SOFA score	10.72 ± 3.49	10.44 ± 3.27	0.694

WBCs white blood cells, *RDW* red cell distribution width, *CRP* C-reactive protein, *PCO2* partial pressure of carbon dioxide, *PO2* partial pressure of oxygen, *ICU* intensive care unit, *APACHE-II* acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment. Data are presented in the form of mean ± SD. *Significance defined by *P* < 0.05

(mmHg); *P* = 0.023), respectively. And also, among invasive MV patients, group 1 had significantly higher NIF (−21.39 ± 3.96 versus −19.00 ± 4.78; *P* = 0.006) and

Table 1 Baseline data of enrolled patients (*n* = 108)

Variable name	Group 1 (*n* = 53)		Group 2 (*n* = 55)		*p-value*
Age (years), mean ± SD	66.30 ± 7.97		65.82 ± 9.31		0.773
Median (range)	67 (48–83)		67 (49–83)		
Sex, *n* (%)					0.920
• Male	39	(73.6)	40	(72.7)	
• Female	14	(26.4)	15	(27.3)	
Smoking status, *n* (%)					0.950
• Nonsmoker	4	(7.5)	4	(7.3)	
• smoker	36	(67.9)	36	(65.5)	
• Passive smoker	13	(24.5)	15	(27.3)	
Smoking index, mean ± SD	36	3.78 ± 119.31	37	6.58 ± 90.62	0.610
Drug addiction, *n* (%)	17	(32.1)	12	(21.8)	0.229
Diabetes mellitus, *n* (%)	16	(30.2)	16	(29.1)	0.901
Hypertension, *n* (%)	11	(20.8)	12	(21.8)	0.893
Chronic kidney disease, *n* (%)	4	(7.5)	3	(5.5)	0.713
Liver disease, *n* (%)	5	(9.4)	4	(7.3)	0.740
Cardiac disease, *n* (%)	8	(15.1)	7	(12.7)	0.722

Data are presented in the form of mean ± SD with median (range) or *n* (%). *Significance defined by *P* < 0.05. Group 1 (*n* = 53), patients. who had undergone early rehabilitation. Group 2 (*n* = 55), patients who had usual care

Table 3 Baseline and weaning diaphragmatic function assessment among enrolled patients ($n = 108$)

Variable name	Group 1 ($n = 53$)	Group 2 ($n = 55$)	p-value
Inspiratory thickness (mm)			
• Baseline	0.24 ± 0.04	0.23 ± 0.04	0.558
• Weaning	0.22 ± 0.04	0.21 ± 0.05	**0.046***
Expiratory thickness (mm)			
• Baseline	0.21 ± 0.03	0.19 ± 0.03	0.123
• Weaning	0.19 ± 0.03	0.17 ± 0.03	**0.011***
Excursion (mm)			
• Baseline	2.54 ± 0.41	2.63 ± 0.33	0.186
• Weaning	2.55 ± 0.39	2.33 ± 0.56	**0.038***

Data are presented in the form of mean ± SD. *Significance defined by $P < 0.05$

significantly lower airway occlusion pressure (4.79 ± 1.47 versus 6.65 ± 2.79; $P = 0.007$) as compared to group 2 (Table 4).

Regarding patients with invasive ventilator support, patients with simple weaning have significantly higher mean electrical stimulation of quadriceps muscle and higher mean duration as compared to difficult weaning patients (13.10 ± 4.21 versus 9.00 ± 4.09, $P = 0.011$ and 22.57 ± 6.42 versus 18.08 ± 4.89, $P = 0.040$). In contrast, trigger sensitivity (%) shows no significant difference with the type of weaning ($P > 0.05$).

Regarding patients with noninvasive ventilator support, no significant difference was observed between the type of weaning and the mean electrical stimulation of quadriceps muscle ($P = 0.203$), and also no significant difference was found between the outcome of weaning (success or failed) and rehabilitation components either among patients with *invasive or noninvasive ventilator support* ($P > 0.05$) (Table 5). The predictive ability of electrical stimulation (ms), trigger sensitivity (%), and diaphragmatic functions (at inspiration, at expiration, and at excursion) in COPD patients for prediction of simple weaning using the ROC curves shows that the areas under the ROC curves for them were 75.6%, 58.7%, 72.2%, 70.6%, and 68.0%, respectively. Electrical stimulation (ms) and weaning IT were observed to be significantly better predictors of simple weaning with higher AUC ($P = 0.016$ and 0.000) respectively (Table 6).

Univariate logistic regression analysis showed that the DT at inspiration, DT at excuration, APACH, SOFA

Table 4 Functional assessment and outcome among patients need invasive or non-invasive ventilatory support in both groups

Variable name	Invasive ventilatory support					Noninvasive ventilatory support					
	Group 1 ($n = 33$)		Group 2 ($n = 40$)		p-value[1]	Group 1 ($n = 20$)		Group 2 ($n = 15$)		p-value[2]
Duration of MV (day)	9.06 ± 5.90		12.10 ± 6.86		**0.039***	4.75 ± 1.45		7.73 ± 3.90		**0.021***
Median (range)	8 (3–29)		12 (3–35)		**0.039***	5 (3–8)		7 (3–15)		**0.021***
Type of weaning					**0.004***					**0.027***
• Simple	21	(63.6)	11	(29.7)		15	(83.3)	6	(42.9)	
• ifficult	12	(36.4)	26	(70.3)		3	(16.7)	8	(57.1)	
Outcome of weaning					**0.008***					**0.006***
• Successful	23	(69.7)	14	(37.8)		15	(83.3)	5	(35.7)	
• Failed	10	(30.3)	23	(62.2)		3	(16.7)	9	(64.3)	
Re-MV after weaning	6	(18.2)	14	(37.8)	0.069	4	(22.2)	3	(21.4)	1
Need tracheostomy	2	(6.1)	8	(20.0)	0.101	0	(0.0)	1	(6.7)	0.429
Nosocomial pneumonia					**0.049***					**0.036***
• No	20	(60.6)	15	(37.5)		15	(75.0)	6	(40.0)	
• VAP	13	(39.4)	25	(62.5)						
• HAP						5	(25.0)	9	(60.0)	
Negative inspiratory force	−21.39 ± 3.96		−19.00 ± 4.78		**0.006***					
Airway occlusion pressure	4.79 ± 1.47		6.65 ± 2.79		**0.007***					
Blood gases after weaning										
• PH[+]	7.40 ± 0.03		7.39 ± 0.04		0.753	7.41 ± 0.02		7.41 ± 0.03		0.765
• PCO2 (mmHg)	63.07 ± 5.05		65.97 ± 4.89		**0.023***	61.72 ± 2.95		66.00 ± 5.07		**0.026***
• PO2 (mmHg)	67.00 ± 2.84		67.57 ± 2.65		0.551	69.28 ± 3.27		66.00 ± 4.63		0.070
Duration of ICU stay (day)	10.94 ± 5.55		15.90 ± 6.43		**0.003***	9.65 ± 2.64		13.73 ± 3.56		**0.028***
Median (range)	10 (4–23)		15 (5–35)			11 (5–13)		13 (5–17)		

MV mechanical ventilation, *VAP* ventilator-associated pneumonia, *HAP* hospital-acquired pneumonia, *PCO2* partial pressure of carbon dioxide, *PO2* partial pressure of oxygen. Data are presented in the form of mean ± SD with median (range) or n (%). *Significance defined by $P < 0.05$

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Table 5 Rehabilitation parameters based on weaning outcome

	Type of weaning		
Variable name	Simple	Difficult	*p-value*
Electoral stimulation (for IMV)	13.10 ± 4.21	9.00 ± 4.09	**0.011***
Electoral stimulation (for NIMV)	9.40 ± 3.27	7.00 ± 2.65	0.203
Trigger sensitivity (%)	23.81 ± 5.89	21.67 ± 3.89	0.427
Mean duration	22.57 ± 6.42	18.08 ± 4.89	**0.040***
	Outcome of weaning		
	Successful	Failed	*p-value*
Electoral stimulation (for IMV)	12.61 ± 4.39	9.30 ± 4.29	0.054
Electoral stimulation (for NIMV)	9.40 ± 3.27	7.00 ± 2.65	0.203
Trigger sensitivity (%)	23.39 ± 5.83	21.00 ± 3.16	0.269
Mean duration	22.17 ± 6.29	18.10 ± 5.32	0.068

Data are presented in the form of mean ± SD. * Significance defined by $P < 0.05$

Table 6 The best cutoff, sensitivity, and specificity for simple weaning prediction by different rehabilitation program categories and at weaning diaphragmatic thickness

	Cutoff	95% CI	Sensitivity	Specificity	AUC	*p-value*
Electrical stimulation	10.5	0.577–0.935	66.7%	75.0%	0.756	**0.016**
Trigger sensitivity (%)	25.0	0.389–0.786	33.3%	83.3%	0.587	0.410
At weaning IT	0.21	0.619–0.825	75.0%	68.2%	0.722	**0.000**
At weaning ET	0.18	0.603–0.810	75.0%	59.1%	0.706	**0.000**
At weaning excursion	2.35	0.570–0.789	75.0%	56.8%	0.680	**0.002**

IT inspiratory thickness, *ET* expiratory thickness, *AUC* area under the curve, *CI* confidence interval. Significance defined by $P < 0.05$

scores and simple weaning are statistically significant predictors for successful weaning. In the multivariate analysis, we only included the highly significant predictors, namely DT at inspiration, excursion, and simple weaning due to small sample size. Multivariate analysis confirmed simple weaning to be associated with successful weaning ($OR = 0.134.2$, 95% CI: 10.07–1787.7, $P = 0.000$). Other variables have no role in detection of weaning outcome ($P > 0.05$) (Table 7).

Discussion
In this randomized controlled trial, we evaluate the effect of early rehabilitation program, namely (ES, TS (%), and mean duration) on acute exacerbation COPD patients who were treated in our RICU and need either invasive or noninvasive MV on their outcome of weaning. We found that the diaphragmatic thickness of both studied groups was decreased, but the degree of reduction in DT was lower in group 1 as compared to group 2, as we found that at the time of weaning, group 1 has significantly higher mean DT, namely (at inspiration, at expiration, and at excursion, $P = 0.046$, 0.011, and 0.038) respectively. COPD patients, with either invasive or noninvasive MV, treated with early rehabilitation program, show shorter duration of MV (days)

and higher rate of simple successful weaning in comparison with matched controls. Martin et al. (2002) [16] reported that a highly significant success rate was found in the inspiratory muscle training (IMT) group; Routsi et al. (2010) [17] found that the duration of mechanical ventilation was significantly shorter in EMS group as compared to the control group ($P = 0.003$), and also, both the short- and long-term weaning period was significantly shorter in EMS patients as compared with the control group (for both $P = 0.003$). Cader et al. (2010) [18] reported that IMT reduce the period of weaning. Also Martin et al. (2011) reported higher successful weaning among patients who received IMT ($P = 0.039$). Therefore, our findings are consistent with those previous studies [11, 14, 17–23]. However, our findings are different from the previous RCT of Greening et al. (2014) [24] who reported that early rehabilitation program for ARF during hospital admission did not reduce the risk of readmission or improve patients' recovery of physical function and Kurtoğlu et al. (2015) [25] who evaluated the effectiveness of NMES in patients with COPD treated in the ICU. As they found no significant differences in terms of weaning duration between NMES applied group and controls, the recent study of Leite et al. 2018 [26] reported that

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Table 7 Predictors of successful weaning in group 1 COPD patients by univariate and multivariate analyses using logistic regression

Variables	n	Univariate analysis			Multivariate analysis		
		OR	*p*-value	95% CI	OR	*p*-value	95% CI
Age (years)	51	0.911	0.051	0.830–1	Not included in the model		
Gender					Not included in the model		
· Female	13	Ref					
· Male	38	0.446	0.341	0.085–2.351			
At weaning IT							
· < 0.21	17	Ref			Ref		
· ≥ 0.21	34	8.437	**0.003***	2.055–34.649	7.817	0.099	0.682–89.662
At weaning ET					Not included in the model		
· < 0.18	12	Ref					
· ≥ 0.18	39	2.768	0.150	0.662–11.069			
At weaning excursion							
· < 2.4	15	Ref			Ref		
· ≥ 2.4	36	4.375	**0.031***	1.145–16.719	0.558	0.659	0.042–7.462
APTCHII	51	0.823	**0.027***	0.693–0.978	Not included in the model		
SOFA	51	0.762	**0.013***	0.614–0.944	Not included in the model		
Ventilator support							
· Noninvasive	18	Ref			Not included in the model		
· Invasive	33	0.460	0.292	0.108–1.951			
Type of weaning							
· Difficult	15	Ref			Ref		
· Simple	36	140.0	**0.000***	13.269–1477.2	134.0	**0.000***	10.072–1787.7
NIF	51	1.029	0.767	0.851–1.244	Not included in the model		
P0.1	51	1.960	0.249	0.624–6.159	Not included in the model		
PCO2 at weaning	51	0.937	0.461	0.788–1.114	Not included in the model		
ES (ms)	51	1.177	0.069	0.987–1.403	Not included in the model		
TS (%)	51	1.163	0.172	0.937–1.443	Not included in the model		

IT inspiratory thickness, *ET* expiratory thickness, *APACHE-II* acute physiology and chronic health evaluation, *SOFA* sequential organ failure assessment,*NIF* negative inspiratory force, *PO.l* airway occlusion pressure, *ES* electrical stimulation, *TS* trigger sensitivity, *CI* confidence interval, *OR* odds ratio, *P*-value is significant (s) 0.05

the duration of MV was significantly lower in the control group when compared with diaphragm group and quadriceps group ($P = 0.0001$). Differences between our study and those studied might be because of different sample size, methods, and outcome measurements. In the cited RCT [24], not all studied patients were COPD, the setting was not an ICU, and the outcomes of readmission and physical performance were measured, not the outcomes of early rehabilitation. In Kurtoğlu et al. (2015) [25] study, the authors use neuromuscular electrical stimulation on auxiliary respiratory muscles for 10 days rather that the quadriceps muscle as we use in our study. Finally, the last study Leite et al. 2018 evulate NMES in all critically ill patients not only COPD patient like our study this may explain different between results [26] states that not all studied patients were COPD, but the author evaluates the effects of neuromuscular electrical stimulation of quadriceps and diaphragm in all critically ill patients not only COPD

patients. Thus, our findings were different. The current study revealed that the rehabilitation group (either with invasive or noninvasive MV) has significantly lower incidence of nosocomial pneumonia. In line with our study, Elbouhy et al. (2014) [23] reported that the duration of hospital and ICU stay in IMT group was significantly shorter that the control group. This indicates that RP minimize the length of hospital and ICU stay and its subsequent complications.

Interestingly, we found a direct relationship between the effect of the estimated intensity of quadriceps muscle stimulation and the patient's outcome, as we found that among *patients with invasive ventilator support*, simple weaning patients have significantly higher mean electrical stimulation of quadriceps muscle and higher mean duration as compared to difficult weaning patients ($P = 0.011$ and 0.040). In contrast, trigger sensitivity (%) shows no significant difference with the type of weaning ($P > 0.05$). This effect was not found among *patients with*

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noninvasive ventilator support ($P > 0.05$). Also, we found that the mean electrical stimulation of quadriceps muscle and the mean duration were higher among patients with successful weaning but not reach statistically significant difference may be because of small sample size as we divided the studied cases into two subgroups according to the type of MV received by the studied participants. This could be explained by NMES training which was associated with gains in muscle strength and the ability to tolerate higher stimulation intensity. This is not surprising and confirms previous findings showing a direct relationship between training intensity and improvement of outcomes. Similarly, Vivodtzev et al. (2012) and Abu-Khaber et al. (2013) reported that NMES improved muscle CSA and associated with gains in muscle strength, reduced ventilation during walking, and minimized the degree of muscular weakness [21, 27].

A ROC curve was used in the current study to assess the accuracy of ES and TS (%) in predicting weaning outcome. A cutoff value of ES of > 10.5 ms was associated with simple extubation, with a sensitivity of 66.7% and a specificity of 75%. A cutoff value of TS (%) of > 25.0% failed to predicts simple extubation with a sensitivity of 33.3% and a specificity of 83.3%. Electrical stimulation (ms) of quadriceps muscle was a significantly better predictor of simple weaning with higher AUC than trigger sensitivity (%) ($P = 0.016$). No previous publications have addressed this issue to be compared with. Larger randomized well-controlled trials are recommended to confirm our finding. Also, the diaphragmatic function by ultrasound was assessed as predictors of successful extubation and to determine cutoff values for predicting success or failure of extubation. The diaphragmatic thickness at inspiration cutoff value predictive of weaning was 20.5 mm, with a specificity of 68.2% and a sensitivity of 75.0%, respectively, and the diaphragmatic thickness at expiration cutoff value predictive of weaning was 17.5 mm, with a specificity of 59.1% and a sensitivity of 75.0%, respectively, and the diaphragmatic thickness excursion cuoff value predictive of weaning was 2.35 mm, with a specificity of 56.8% and a sensitivity of 75.0%, respectively. At weaning, IT was observed to be a significantly better predictor of successful weaning with higher AUC than other used parameters ($P = 0.000$).

In contrast to our study, the systematic review of Llamas-Alvarez et al. (2017) [28] which compares different studies that assessed the contribution of DE and DTF in prediction of weaning outcome and compared the two parameters with each other, DTF was concluded to be superior over DE in prediction of weaning outcome. Meanwhile, Elshazly (2020) [29] found that DE showed superior sensitivity and specificity to those of DTF.

Univariate logistic regression analysis showed that DT at inspiration, diaphragmatic excuration, APCH, SOFA score and simple weaning better predictor for succus weaning as statistically significant variables for successful weaning prediction. In the multivariate analysis, we only included the highly significant predictors, namely (DT at inspiration, excursion, and simple weaning) due to small sample size. Multivariate analysis confirmed simple weaning to be associated with successful weaning ($OR = 0.134.2$, 95% *CI*: 10.07–1787.7, $P = 0.000$).

Many weaning parameters have been used to predict weaning failure. But no previous studies address the role of ES and TS (%). We suggested that we failed to find prognostic role of rehabilitation program mainly due to small sample size which could mask the role of RP in predicting weaning outcome as we found better outcome among patients who received RP. Larger randomized well controlled trials are recommended to assess the prognostic role of diaphragmatic function and early rehabilitation program on prediction weaning outcome.

Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Local Ethics Committee of the Assiut University Hospital and was conducted in accordance with the previsions of the Declaration of Helsinki. Written informed consent was obtained from all the participants before enrollment.

Consent for publication
All the authors approved the manuscript for publication. Identifying images or other personal or clinical details of participants is "not applicable." Consent for publication from the participants is "not applicable."

Competing interests
The authors declare that they have no competing interests.

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