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Original Article

Official Journal of Erciyes University Faculty of Medicine

DOI: 10.14744/cpr.2023.70299
J Clin Pract Res 2023;45(4):377–84

The Effects of a Pulmonary Rehabilitation Program in Severe and Critical COVID-19 Disease: A Prospective Observational Study

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ABSTRACT

Objective: The pulmonary rehabilitation program has beneficial effects on Coronavirus Disease 2019 (COVID-19). However, the response of each patient is not the same. The aim of this study is to compare the rehabilitation processes of severe and critical patients with COVID-19 infection and investigate the effects of sarcopenia and nutritional parameters on the rehabilitation course.

Materials and Methods: Patients with COVID-19 infection who continued to use oxygen were enrolled and classified into severe or critical disease groups. The modified Medical Research Council scale, Borg Rating of Perceived Exertion scale, and Barthel Index were evaluated. A 6-minute walking test, hand grip strength (HGS), and chair stand test were performed. The thickness of the quadriceps muscle was measured by ultrasound to diagnose sarcopenia. Nutrition risk screening and daily protein and calorie intake were computed.

Results: Twenty-two patients were included. The oxygen requirement at discharge was reduced compared to those admitted to the rehabilitation unit ($p<0.001$). Sarcopenia was present in 17 (77.3%) patients in all subjects, 12 (80%) patients in the severe disease group, and in 5 (71.4%) patients in the critical disease group. HGS and the Barthel Index were lower in the critical disease group ($p=0.044$ and $p=0.037$, respectively). The duration of rehabilitation was longer in the critical disease group ($p=0.044$). Daily protein and calorie consumption per kilogram were similar and low in both groups (both $p>0.05$).

Conclusion: Sarcopenia and malnutrition were common in severe and critical COVID-19 disease patients. HGS was lower in critical disease patients, while muscle measurements were similar in both groups.

Keywords: COVID-19, hand grip strength, malnutrition, rehabilitation, sarcopenia.

Cite this article as:
Ata AM, Alemdaroğlu E, Önal R, Kesikburun B, Borman P, Adigüzel E, Yaşar E. The Effects of a Pulmonary Rehabilitation Program in Severe and Critical COVID-19 Disease: A Prospective Observational Study. J Clin Pract Res 2023; 45(4): 377–84.

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Submitted: 25.02.2023
Revised: 09.05.2023
Accepted: 16.06.2023
Available Online: 10.07.2023

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), although a multi-organ infection, often manifests as a respiratory infection with a wide range of manifestations, including mild disease, pneumonia, severe pneumonia, Acute Respiratory Distress Syndrome (ARDS), sepsis, and septic shock.[1] Fever, frequent dry cough, sore throat, headache, fatigue, muscle soreness, and dyspnea are common clinical symptoms. The adverse consequences, such as fatigue, shortness of breath, and myalgia, have been observed to

persist after the patient is discharged from the hospital and have an impact on their functional levels and physical performance over time. It has been shown that approximately 23% of the patients discharged from the intensive care unit (ICU) received supplemental oxygen therapy.[2] Furthermore, the pulmonary rehabilitation program has been shown to have beneficial effects in patients who continue to require oxygen supplementation, have difficulty ambulating, complain of weakness, dyspnea, and experience difficulties during daily living activities.[3]

A multi-component pulmonary rehabilitation program in post-COVID rehabilitation is of utmost importance in minimizing disability and preventing complications after COVID-19 infection.[3] However, the response of each patient to the rehabilitation program is not the same. Sarcopenia has been found to be associated with the length of hospital stay, the rate of weaning from the ventilator, and even mortality in COVID-19 infection.[4,5] To our knowledge, there is only one study investigating the relationship between sarcopenia and rehabilitation outcomes in post-acute COVID-19 patients.[6]

The aim of this study is to compare the rehabilitation processes of severe and critical patients who have had COVID-19 infection and continue to have oxygen demand, and to investigate the effects of sarcopenia and nutritional parameters on the rehabilitation course.

MATERIALS AND METHODS

Participants

In this prospective observational study, hospitalized patients who had COVID-19 infection and continued to use nasal or mask oxygen, and were referred to the rehabilitation service, were recruited from December 2021 to June 2022. The study included patients aged 18 to 90 years. The following conditions had to be met for inclusion in the study: fraction of inspired oxygen (FiO_2) ≤0.6, blood oxygen saturation (SpO_2) ≥90% with oxygen support, respiratory rate ≥20 or ≤40 breaths/min, systolic blood pressure ≥90 mmHg or ≤180 mmHg, mean arterial pressure (MAP) ≥65 mmHg or ≤110 mmHg, heart rate ≥40 beats per minute (bpm) or ≤120 bpm, and Richmond Agitation-Sedation Scale (RASS) score: −2 to +2. Patients were excluded if they experienced any of the following: new arrhythmia or myocardial ischemia, shock with lactic acid level ≥4 mmol/L, ventilator resistance, airway issues, breathing difficulties, severe or productive coughing episodes, new unstable deep-vein thrombosis and pulmonary embolism, suspected aortic stenosis, loss of consciousness, agitation, active hemorrhage, and temperature ≥38.5°C. All participants were informed of the study's protocols and provided written consent before enrollment. This study was conducted in line with the principles of the Declaration of Helsinki. Approval was granted by Ankara Bilkent City Hospital's local ethics committee (E2-21-1005).

Clinical Parameters

Demographic data, smoking status, comorbidities, and length of hospital stay were recorded. Clinical and laboratory information of the patients during COVID-19 infection were documented, and disease severity was noted. The level of oxygen support the patients currently received was recorded. The Borg Rating of Perceived Exertion (RPE) for dyspnea during exertion and the modified Medical Research Council (mMRC) scale for dyspnea during everyday activities were utilized.[7] To evaluate functional exercise capacity, a 6-minute walking test was conducted, and for muscle strength and function evaluation, hand grip strength (HGS) and chair stand test were performed, respectively. The activities of daily living (ADLs) were assessed using the Barthel Index. Quadriceps muscle thickness measured by ultrasound was used to assess muscle mass, and the Sonographic Thigh Adjustment Ratio (STAR) value was calculated for the diagnosis of sarcopenia. Sarcopenia was diagnosed if a patient has both loss of muscle function (low HGS; <19 kg for females and <32 kg for males or prolonged Chair Stand Test (CST); ≥12 s) and low muscle mass (low STAR, <1.0 for females and <1.4 for males).[8] Nutritional status was evaluated with nutrition risk screening 2002 (NRS2002), and daily protein and calorie intake were calculated using a detailed daily food intake record. The length of hospital stays and the number of days patients attended rehabilitation were recorded. The patients were classified into severe or critical disease groups. Patients considered severe had a history of dyspnea, a respiration rate greater than 30/min, an oxygen saturation below 93%, or a Partial Pressure of Oxygen (PaO_2)/FiO_2 below 300 mm Hg. Patients in critical condition had a history of multiple organ failure, septic shock, or respiratory failure.[9]

Rehabilitation Program

All patients underwent training on positioning, pressure ulcer prevention, oral care, and nutrition after the initial evaluation. They were evaluated for medical complications. The rehabilitation program began with range of motion exercises, progressive resistance exercises, posture exercises, and gradual mobilization under the supervision of an individual physiotherapist. The pulmonary rehabilitation program included airway clearance, breathing control, breathing exercises, and aerobic exercises. Aerobic exercises using ergometric cycling were initiated once sitting balance was achieved and progressed while monitoring oxygen saturation, pulse, blood pressure, and symptoms (such as dyspnea and fatigue). Patients' rehabilitation programs were individually continued with multidisciplinary care plans.[3,10]

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) 20.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to examine the normal distribution. Descriptive analyses were conducted using medians and interquartile range (IQR) for non-normally distributed and ordinal variables. COVID-19 patients were divided into two groups, severe and critical, based on the severity of the disease. The Mann-Whitney U test was utilized to compare groups that did not follow a normal distribution. Chi-square or Fisher's exact tests were employed to compare categorical variables. The statistical significance level was set at $p<0.05$.

RESULTS

This study involved 22 patients, comprising 7 females and 15 males. The median age was 65.0 years (range: 35–84). Table 1 presents the demographic information and clinical outcomes of the patients. With the exception of four patients, all others had a history of ICU admission. During COVID-19 treatment, six patients were intubated, six received high-flow nasal cannula oxygen therapy, four received a non-rebreather oxygen mask, and six received nasal cannula oxygen therapy. Steroid treatment was administered to 77.3% of the patients. The median (IQR) length of hospital stay in rehabilitation unit was 43.5 days (29.8–57.5). Although 14 (63.6%) patients required long-term oxygen therapy (LTOT), the oxygen requirement at discharge was significantly reduced compared to admission to the rehabilitation unit [2 (1–4) vs. 1 (0–1.25), $p<0.001$]. The group requiring LTOT at discharge had a higher oxygen requirement before [2.5 (2–4) vs. 1.5 (0.5–2)] ($p=0.026$) and after [1 (0.8–2) vs. 0 (0–0)] ($p<0.001$) rehabilitation compared to those who did not. The comparison of clinical and laboratory findings according to disease severity is provided in Table 2 and Table 3, respectively. Median age was lower in the critical disease group ($p=0.024$). Daily protein and calorie consumption per kilogram were similar and low in both groups ($p=0.072$ and $p=0.053$, respectively). Eleven (50%) of the patients were taking an oral nutritional supplement to meet their daily protein/calorie requirements, with 6 (40%) in the severe disease group and 5 (71.4%) in the critical disease group, and there was no significant difference between the groups ($p=0.361$). HGS and Barthel Index were lower in the critical disease group ($p=0.044$ and $p=0.037$, respectively). The duration of rehabilitation was longer in the critical disease group ($p=0.044$). Sarcopenia was present in 17 (77.3%) of all subjects, 12 (80%) in the severe disease group, and 5 (71.4%) in the critical disease group. There was no significant difference between the groups in terms of the presence of sarcopenia ($p>0.05$). Only two patients were able to complete the CST and 6-minute walking test, and both had a prolonged CST (12.19 s and 20.11 s) and a short 6-minute walking distance (108 m and 57 m). C-reactive protein (CRP), interleukin-6 (IL-6), and pro-brain natriuretic peptide (NT-ProBNP) levels were higher in the critical disease group ($p=0.022$, $p=0.027$, and $p=0.039$, respectively).

DISCUSSION

The present study has shown that the prevalence of sarcopenia in all patients was 77.3%, and it was similar between the critical and severe disease groups. However, HGS was lower in the critical disease group. Daily protein and calorie consumption per kilogram were lower than the normal energy and protein needs in both groups. It is noteworthy that the oxygen needs of all patients decreased after rehabilitation treatment, and the duration of rehabilitation was longer in the critical disease group.

Sarcopenia can result from COVID-19 infection due to muscle wasting caused by systemic inflammation, decreased physical activity, and poor nutritional status. On the other hand, sarcopenia can lead to negative consequences for patients, such as extubation failure, increased in-hospital mortality, prolonged hospital and ICU length of stay, ICU admission, and disease severity.[5,11,12] A meta-analysis demonstrated that the prevalence of sarcopenia was highest (69.7%.) among those who were admitted to the ICU.[11] In our study, the prevalence of sarcopenia was found to be 77.3%. Except for four patients, all other patients had a history of ICU admission, and all patients had a history of severe or critical disease. To our knowledge, there is only one study investigating the effect of sarcopenia on post-COVID-19 rehabilitation programs so far.[6] Sarcopenia was measured in that study using bioelectrical impedance analysis, and the prevalence of sarcopenia was found to be lower than in the current study. This difference may be attributed to the inclusion of more severe patients in our study and the use of different evaluation methods for assessing sarcopenia. Notably, ultrasound (US) can evaluate regional sarcopenia and enable earlier diagnosis.[8] In that study, it was demonstrated that sarcopenic patients started rehabilitation in a worse condition but showed better responses.[6] In contrast, a study conducted in Chronic Obstructive Pulmonary Disease (COPD) patients, where muscle mass was evaluated with bioelectrical impedance analysis, found no difference in response to pulmonary rehabilitation between the groups with and without sarcopenia.[13] Since the number of non-sarcopenic patients was very small in our study, we could were unable to compare sarcopenic and non-sarcopenic patients. However, all patients benefited from the rehabilitation program, leading to a reduction in their their oxygen needs. Similar to our study, a study that recruited 72 elderly patients with COVID-19, 36 of whom underwent a six-week respiratory rehabilitation program, found that rehabilitation improved respiratory function, quality of life, and anxiety.[14]

Table 1. Clinical and functional parameters of the patients

P	G	A	Disease severity	Steroid use	Comorbidities	Smoking	Length of hospitalization (days)	LTOT	MRC	Borg dyspnea	FAC	HGS (kg)	Anterior thigh muscle thickness (cm)	STAR	Barthel Index
1	F	84	Severe	+	HT, hypothyroidism	–	20	+	1	2	0	16	1.29	0.32	10
2	M	55	Critical	+	–	–	32	+	5	5	0	15	2.12	0.87	60
3	F	60	Severe	+	HT, DM, AF, CKD, gout	–	27	-	5	5	1	17	1.73	0.37	45
4	F	63	Critical	+	DM	–	37	-	5	7	0	4	1.96	0.64	10
5	M	70	Critical	-	HT, CAD, COPD	+	30	+	5	7	0	26	2.24	1.25	10
6	M	81	Severe	+	HT, DM, CHF, CAD, AML	–	20	+	4	3	3	12	3.29	1.01	50
7	M	80	Severe	+	HT, CAD	Ex smoker	30	-	5	3	0	25	3.37	1.35	20
8	F	78	Severe	-	HT, DM, CKD	–	20	-	3	2	3	15	2.47	0.79	50
9	M	70	Severe	-	COPD	Ex smoker	55	+	4	3	1	26	2.59	1.84	55
10	M	79	Severe	+	COPD	Ex smoker	30	+	5	7	0	24	2.99	1.09	65
11	M	49	Critical	+	–	–	89	+	5	6	0	22	2.12	1.06	35
12	F	67	Severe	+	HT, DM	–	18	+	5	2	0	24	2.80	0.95	40
13	F	58	Severe	+	HT, membranous glomerulonephrithis	–	60	+	5	3	0	18	2.21	0.82	40
14	M	60	Critical	+	HT, CAD, COPD	Ex smoker	33	+	5	5	0	10	1.99	0.70	20
15	M	61	Severe	+	–	+	7	+	4	3	5	28	3.17	1.24	80
16	M	56	Severe	+	DM	–	17	-	5	5	0	25	1.87	0.93	40
17	F	35	Critical	+	Stroke	–	22	-	4	3	0	20	1.70	0.58	25
18	M	51	Severe	+	DM	Ex smoker	40	+	5	3	0	17	1.04	0.36	20
19	M	76	Severe	-	COPD	Ex smoker	36	+	4	3	4	35	3.54	1.61	65
20	M	61	Critical	+	HT, DM	–	20	+	4	2	1	8	2.97	1.57	35
21	M	76	Severe	-	HT, CAD	–	18	-	2	0.5	2	30	4.65	1.60	60
22	M	79	Severe	+	HT	Ex smoker	44	+	4	2	3	30	2.06	0.96	60

P: Patient; G: Gender; A: Age; AF: Atrial fibrillation; AML: Acute myeloid leukemia; CAD: Coronary artery disease; CKD: Chronic kidney disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; FAC: Functional ambulation category; HGS: Hand grip strength; HT: Hypertension; LTOT: Long term oxygen therapy; mMRC: Modified Medical Research Council; STAR: Sonographic thigh adjustment ratio.

Table 2. Comparison of disease groups in terms of clinical and functional parameters

	Severe disease	Critical disease	p
Age (years)	76.0 (60.0–79.0)	60.0 (49.0–63.0)	**0.024**
BMI (kg/m^2)	27.5 (22.0–29.4)	25.5 (18.9–29.4)	0.459
Pre-rehabilitation oxygen support (L/min)	2.0 (2.0–4.0)	1.0 (0.5–2.0)	0.069
Post-rehabilitation oxygen support (L/min)	1.0 (0.0–2.0)	0.25 (0.0–1.0)	0.306
Duration of rehabilitation (days)	30 (26–56)	55 (48–65)	**0.044**
mMRC	4 (4–5)	5 (4–5)	0.209
Borg	3 (2–3)	5 (3–7)	**0.041**
HGS (kg)	24.0 (17.0–28.0)	15.0 (8.0–22.0)	**0.044**
STAR	0.96 (0.81–1.34)	0.83 (0.64–1.24)	0.597
NRS2002	4 (3–4)	4 (4–5)	0.119
Protein (g/kg/day)	0.63 (0.44–0.94)	0.83 (0.78–1.01)	0.072
Energy (kcal/kg/day)	15.26 (12.80–19.69)	20.25 (16.60–21.60)	0.053
Barthel Index	50 (40–60)	25 (10–35)	**0.037**

BMI: Body mass index; HGS: Hand grip strength; mMRC: Modified Medical Research Council; NRS2002: Nutrition Risk Screening; STAR: Sonographic thigh adjustment ratio.

Table 3. Comparison of disease groups in terms of laboratory parameters*

	Severe disease	Critical disease	p
Lymphocytes (per/mcL)	210 (162.5–677.5)	260 (170–520)	0.832
CRP (mg/L)	114.2 (59.2–153.0)	201 (130–322)	**0.022**
Procalcitonin (mcg/L)	0.23 (0.08–0.44)	2.5 (0.2–5.7)	0.062
IL-6 (pg/mL)	45.3 (20.7–67.8)	147.2 (61.3–259.4)	**0.027**
Ferritin (mcg/L)	592.0 (339.7–1572.0)	580.2 (302.3–1507.9)	0.972
D-dimer (mg/L)	7.3 (4.0–35.2)	9.9 (5.0–34.4)	0.970
Fibrinogen (g/L)	6.0 (5.3–7.5)	7.3 (5.9–10.2)	0.067
NT-ProBNP (ng/L)	613 (324–2069.2)	3287.0 (1108.7–13916.0)	**0.039**
Troponin (ng/mL)	33.6 (13.0–93.5)	97.7 (78.1–1963.4)	0.086
LDH (U/L)	567 (461–658)	788 (470–969)	0.053
CK (U/L)	153.0 (96.7–410.0)	128 (71–361)	0.654
Vitamin D (nmol/L)	27.9 (21.7–38.9)	41.9 (24.5–78.1)	0.285

*: The highest laboratory values observed during the disease course; CK: Creatine kinase; CRP: C-reactive protein; IL-6: Interleukin-6; LDH: Lactate dehydrogenase; NT-ProBNP: N-terminal pro-brain natriuretic peptide.

It has been reported that muscle evaluation using US can be used to predict mortality in COVID-19 patients.[15] It is widely known that a low HGS value is independently associated with an unfavorable prognosis in many diseases. This relationship has also been demonstrated in COVID-19 disease. A cross-sectional study of 312 COVID-19 patients evaluated in the inpatient clinic found that low HGS was related to increased disease severity in COVID-19 patients.[16] Similarly, another study evaluating 3600 individuals, of whom 316 tested positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and 83 were hospitalized for COVID-19, showed that low HGS was independently associated with hospitalization and disease severity.[17] Furthermore, a meta-analysis emphasized that muscle function evaluation may be a more useful tool than muscle mass for the prognosis of COVID-19.[18] Likewise, although both HGS and muscle mass assessments were

low in both groups, we found that HGS was lower in the critical disease group than in the severe disease group. This is consistent with the observation that low handgrip strength is associated with many negative outcomes. Therefore, it can be considered an indispensable marker for disease severity, as suggested earlier.[19]

Malnutrition has been associated with ICU stay, multimorbidity, and older age, and it is a risk factor for increased morbidity and mortality in both chronic and acute diseases.[20] The prevalence of malnutrition in COVID-19 is high, estimated at approximately 50%.[20] The severity of COVID-19 infection has been shown to be associated with malnutrition.[21] Additionally, prolonged stay in the ICU may lead to malnutrition and sarcopenia, resulting in disability, poor quality of life, and increased morbidity and mortality.[20] Therefore, it has been suggested that the prevention, diagnosis, and treatment of malnutrition be routinely included in the management of COVID-19 patients.[22] In a study conducted in ICU patients, calorie intake was found to be lower in the critically ill group, while protein intake was similar.[23] Another study demonstrated that protein and energy supplementation were associated with lower mortality.[24] In our study, the NRS2002 score was found to be high and similar in both the severe and critical disease groups. Similarly, protein and energy intakes were below the daily requirement in both groups. Although the diet was prepared by calculating the daily calorie and protein needs of the patients, it was observed that the patients did not consume enough when evaluated using the daily food consumption record. In a study including 176 COVID-19 patients hospitalized in the ICU, which assessed nutrition and functional capacity, it was reported that 66.7% of the patients received oral nutritional support during their hospitalization, and it was prescribed for 36.8% of the patients at hospital discharge.[25] In our study, oral nutritional support was initiated in 50% of the patients.

Limitations in activities of daily living (ADL) develop due to malnutrition, sarcopenia, and symptoms of COVID-19 itself, such as dyspnea, weakness, myalgia, and several complications of the disease.[26] Various ADL assessments are used to define functional limitations and understand the prognosis of patients, especially in rehabilitation units. Among these, the most commonly used scale is the Barthel Index.[26] The functional status of patients has been shown to be associated with disease severity and mortality.[27] Consistent with the literature, we found that the Barthel Index was lower in the critical illness group in our study. Interestingly, the median age of the critical disease group is lower than that of the severe disease group, which is likely due to the small number of patients.

Studies have reported that serum levels of CRP, procalcitonin, and IL-6 are higher in patients with severe symptoms compared to those with mild symptoms. COVID-19 can lead to multi-organ dysfunction by increasing systemic blood inflammation factors. Increased IL-6 levels have been identified as a biomarker for early disease progression in patients with COVID-19 infection.[28] COVID-19 also affects the cardiovascular system, causing chronic myocardial injury and severe damage to the cardiovascular system. High levels of cardiac biomarkers (myoglobin, creatine kinase (CK) isoenzyme, amino-terminal pro-brain natriuretic peptide, and troponin I) have been associated with disease severity and mortality.[29] According to our results, inflammatory factors (CRP, IL-6), and cardiac biomarker (N-terminal pro-B-type natriuretic peptide (NT-ProBNP)) levels were found to be higher in the critical disease group.

The most significant limitation of this study is the small sample size. Since the study was conducted during the fourth wave and vaccination period, the disease severity was milder, and the hospitalization rate was lower.[30] Additionally, only the critical and severe disease groups were included, resulting in a majority of sarcopenic patients and no comparison with non-sarcopenic patients. Another limitation is that the muscle mass and function of the patients before discharge were not evaluated. Although the main outcome is to discontinue oxygen support, the final status of the patients in terms of sarcopenia and nutrition is unknown. It is important to note that several variables such as smoking, alcohol, physical activity, age, and gender may have an impact on the findings of this study, but we were unable to perform regression analysis due to the small number of patients.

CONCLUSION

In conclusion, sarcopenia and malnutrition are prevalent in patients with severe and critical COVID-19 disease who continue to require oxygen support. Both disease groups show benefits from a comprehensive rehabilitation program. Therefore, it is crucial to include these patients in rehabilitation programs as soon as they are medically stable, and healthcare providers should be mindful of sarcopenia and malnutrition. Patients should be closely monitored using simple methods such as hand grip strength assessment and food consumption records. Furthermore, this issue should also be considered in other respiratory-related diseases that cause systemic inflammation and in acute exacerbations of chronic diseases, not limited to COVID-19. Future studies with larger sample sizes are warranted to further investigate these factors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: The Ankara Bilkent City Hospital Clinical Research Ethics Committee granted approval for this study (date: 10.11.2021, number: E2-21-1005).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Author Contributions: Concept – AMA; Design – AMA, EA, EAd, EY, PB; Supervision – EA, EAd; EY, PB; Resource – EAd, EY, PB; Materials – AMA, EA, EAd, EY, PB, BK, RÖ; Data Collection and/or Processing – AMA, RÖ, BK; Analysis and/or Interpretation – AMA, BK, EA; Literature Search – AMA, BK, EA, RÖ; Writing – AMA; Critical Reviews – AMA, BK, EA, EY, EAd, PB, RÖ.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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