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# Weaning Outcomes and Clinical Characteristics of Severe Mechanically Ventilated COVID-19 Patients During the Three Waves of the COVID-19 Pandemic in Israel

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**Abstract:** Background: Most of severe COVID-19 patients who survive the intensive care remain mechanically ventilated and require weaning and further rehabilitation. Objectives: This study compares the characteristics and outcomes of severe mechanically ventilated COVID-19 patients admitted to a weaning facility. In addition, the study describes patterns of weaning experienced during the three waves of COVID-19 in Israel. Methods: Clinical, demographic and outcome data was gathered retrospectively for 70 severe mechanically ventilated patients. Univariate analysis was performed to explain the variability in outcome variables. Results: Weaning success was 94% with mean weaning duration of 13±17 days. None of the demographic and clinical variables examined influenced the weaning duration, however patients with morbid obesity and/or diabetes were found to have shorter total duration on mechanical ventilation, hereby suggesting the presence of an obesity paradox. Extra corporal membrane oxygenation (ECMO) was used in 29% of the patients, and didn't influence the weaning duration in spite being associated with higher rate of pleural complication. There were three main weaning patterns seen in different overlapping levels in the cohort patients: low capacity extra pulmonary pattern, fibrotic-bullosic pulmonary injury pattern and nonspecific interstitial pneumonitis pattern. Conclusions: The current study shows a high success rate of weaning, independent on comorbidities and previous ECMO use.

**Keywords:** COVID-19, Obesity Paradox, Weaning, Mechanical Ventilation

## 1. Introduction

Since its outbreak in December 2019, numerous cases of COVID-19 patients that deteriorated to severe respiratory and required mechanical ventilation have been described and characterized .With the progression to chronic critical illness, many patients remained dependent on mechanical ventilation and require weaning and rehabilitation. [1]. With each wave, severe mechanically ventilated patients have been admitted to The Department of Respiratory Care and Rehabilitation within the Sheba Medical Center which serves as a national ventilator weaning facility. The department provides a multi-professional, comprehensive bundle of care, which includes liberation from mechanical ventilation, respiratory and general rehabilitation for tracheostomy-ventilated patients.

Several studies have been published on the outcomes of tracheostomized patients [2]. This study compares the characteristics and outcomes of these patients, for better understanding the factors which influence the trajectory of weaning, de-cannulation and outcomes. Moreover, with the rising use of extra corporal membrane oxygenation (ECMO) in this patient population, detailed analysis of outcomes in required and lacking [3]. In addition, the study describes patterns of weaning experienced in a dedicated weaning facility during the three waves of COVID-19 in Israel.

## 2. Methods

This study is a retrospective cohort study of 70 patients infected with COVID-19 hospitalized in our department during the first (Jan-May 2020), second (May-July 2020) and third (December 2020 to April 2021) waves of the COVID-19 pandemic in Israel. Patients were admitted from ICUs of several hospitals in Israel. Patients were post COVID-19, with a positive or negative PCR for COVID-19, tracheostomized, and were not receiving intravenous vasopressors, intravenous sedation or paralyzing agents. By reviewing the electronic medical records, we collected demographic, clinical and outcome related data for all patients. Quantitative variables are summarized both as mean ± standard deviation (SD). Qualitative variables are presented as proportions. Statistical analyses were conducted with RStudio©. Using a Chi squared test for categorical variables and t-test for continuous variables. *P*-value was considered significant at below 0.05.

The study was approved by the Sheba institutional review and ethics committee. No patient consent was needed as the data used was retrospective. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors declare no conflicts of interest in preparing this article.

***Table 1.*** *Demographic and clinical characteristics of patients in the study cohort (N=70).*

| Parameter | Mean (SD) # (%) |
|---|---|
| Demographics | |
| Age | 58.8±13.1 |
| Gender (Male) | 56 (80%) |
| Weight (Kg) | 86.9±18.4 |
| Smoker* | 17 (24%) |
| Co-morbidities | |
| Over-weight† | 45 (64%) |
| Morbid obesity† | 20 (29%) |
| Hypertension | 35 (50%) |
| Hyperlipidaemia | 32 (46%) |
| CV co-morbidities†† | 12 (17%) |
| COPD/Asthma | 8 (11%) |
| DM | 26 (37%) |
| Past VTE | 5 (7%) |
| OSA | 16 (23%) |
| Neoplastic disease | 9 (13%) |
| Disease management and severity* | |
| ECMO | 20 (29%) |
| Days on ECMO | 28.6±18.1 |
| Remdesivir | 27 (39%) |
| Plasma | 16 (23%) |
| HIT | 7 (10%) |
| D-dimer (ng/dl) | 2288±1820 |
| Full anticoagulation | 46 (66%) |
| Delirium* | 36 (51%) |
| Pleural Complication | 15 (21%) |
| Outcomes | |
| Weaned | 66 (93%) |
| Died | 3 (9%) |
| Home discharge | 10 (14%) |
| Rehabilitation discharge | 56 (80%) |
| Oxygen on Discharge | 56 (86%) |

*Smoker includes past or present smokers; †Overweight: BMI>25; †Morbid Obesity: BMI>30; ††CV comorbidity includes: atrial fibrillation, ischemic heart disease, chronic heart failure; *Delirium was defined by Richmond Agitation-Sedation Scale (RASS) above +1; *Neoplastic disease – defined as any neoplastic disease within 5 years from positive COVID-19.

# 3. Results

Table 1 shows the demographic, clinical and outcome data for all 70 patients in the cohort. Patients were mostly overweight males, although 16 patients (22%) were without any co-morbidity. The cohort had two healthy women infected with COVID-19 while pregnant, needing urgent caesarean section. Twenty (30%) patients had required ECMO as part of the management in the ICU, of which 7 (35%) developed HIT. Fifteen patient had one or more pleural complication (empyema, pneumothorax or bronchoalveolar fistula). Most patients (80%) were discharged to another rehabilitation facility after being liberated from mechanical ventilation.

Sixty-six (94%) patients were weaned successfully and went through de-cannulation of the tracheostomy in a mean time of 13±17 and 25±25 days, respectively (Table 2). On average another week was needed to perform de-cannulation (as there were few patients that were outliers, the median time and range are also shown). None of the successfully weaned patients required non-invasive ventilation (NIV) upon discharge from the unit, apart from two patients who had premorbid need for NIV.

Table 3 shows a univariate analysis for the main outcome variables; Weaning duration was nondependent on any of the demographic and clinical variables examined. The number of days the patient was on ECMO was positively correlated with weaning duration (in the 20 patients that were on ECMO in the cohort). Total days on mechanical ventilation was negatively correlated on weight, being morbidly obese, being diabetic or with history of VTE. Pleural complication, HIT and ECMO were all positively correlated with duration of mechanical ventilation.

Oxygen need at discharge (rest and effort) from the weaning facility was examined in all patients weaned. Resting oxygen need was higher in smokers (present or past) and with patients with hyperlipidemia (34% of hyperlipdemic patients were smokers). Both weaning duration and total mechanical ventilation duration were positively correlated with resting and effort oxygen needs.

The weaning duration (from admission to weaning) was similar in the three waves (see appendix), however the total duration on mechanical ventilation and the time from positive PCR COVID-19 to tracheostomy was longer during the second and third waves. During the second and third waves, more patients required oxygen on discharge from the weaning facility, and although non-significant, there was a trend for higher oxygen demands in these patients.

ECMO was used in 29% of the cohort patients during their ICU stay, with a mean time of 28±18 days (range 8-79 days). All of these patients were weaned from mechanical ventilation (see table 4). In comparison to all other patients, the patients previously on ECMO were younger, thinner, had less cardiovascular comorbidities but more had pleural complications. D-dimer levels on admission were lower in the ECMO population. Weaning time was similar between both groups, however, the patient previously on ECMO had longer duration of total mechanical ventilation, and spent longer time in the ICU. A trend towards longer time to de-cannulation was seen, although non-statistically significant.

***Table 2.*** *Continuous outcome variables of the study cohort (N=70).*

| Parameter | Mean SD | Median IQR | Range |
|---|---|---|---|
| Durations (Days) | | | |
| Admission to Weaning | 13±17 | 9±8 | 0-112 |
| Admission to De-cannulation | 25±25 | 16±14 | 1-125 |
| Total Ventilated | 58±36 | 48±38 | 16-191 |
| Positive COVID-19 to tracheostomy | 22±17 | 20±18 | 0-111 |
| Positive COVID-19 to Intubation | 7±8 | 4±7 | 0-41 |
| Intubation to tracheostomy | 15±14 | 13±13 | 0-95 |
| Oxygen (L/min) | | | |
| Resting oxygen need | 0.82±0.65 | 1±0.87 | 0-3 |
| Effort* oxygen need | 1.78±1.68 | 1±0.23 | 0-8 |

*Oxygen saturation measured during the last few days of rehabilitation during walking 10m with or without walking aids.

***Table 3.*** *Univariate analysis - linear regression for outcome variables.*

| Parameter | Admission to Weaning [Days] | | Total Ventilated [Days] | | Resting Oxygen Need [L/min] | |
|---|---|---|---|---|---|---|
| | Beta [CI] | Pvalue | Beta [CI] | Pvalue | Beta [CI] | Pvalue |
| Demographics | | | | | | |
| Age | 0.2 [-0.13; 0.52] | 0.228 | 0.04 [-0.6; 0.7] | 0.906 | .006 [-.006; .01] | 0.327 |
| Gender (Male) | -4.5 [-15.5; 6.3] | 0.408 | 12.0 [-10; 34] | 0.286 | 0.07 [-0.3; 0.4] | 0.733 |
| Weight | -0.1 [-0.3; 0.08] | 0.211 | -0.6 [-1.1; -0.1] | 0.006 | .004 [-.005; .01] | 0.373 |
| Smoker | 2.0 [-8.4; 12.5] | 0.697 | 2.0 [-19; 23.0] | 0.845 | 0.4 [0.02; 0.7] | 0.039 |
| Co-morbidities | | | | | | |
| Over-weight | 1.0 [-8.1; 10.2] | 0.814 | -10 [-29; 7.9] | 0.256 | 0.3 [-0.03; 0.6] | 0.078 |
| Morbid obesity | -2.8 [-12.6; 6.9] | 0.565 | -18 [-37; -0.9] | 0.050 | 0.12 [-0.2; 0.4] | 0.497 |
| Hypertension | -5.6 [-31.2; 19] | 0.196 | -14 [-32; 2.5] | 0.090 | 0.18 [-0.1; 0.5] | 0.254 |
| Hyperlipidaemia | 3.1 [-5.7; 11.9] | 0.483 | -8.9 [-26; 8.9] | 0.322 | 0.3 [0.05; 0.68] | 0.022 |
| CV co-morbidities | -5.7 [-19.0; 7.6] | 0.397 | -7.0 [-34; 20] | 0.609 | 0.05 [-0.4; 0.5] | 0.824 |
| COPD/Asthma | 0.25 [-18.0; 18] | 0.978 | 16.8 [-20; 54] | 0.370 | -0.08 [-0.7; 0.6] | 0.815 |
| DM | -4.2 [-13.2; 4.8] | 0.356 | -20 [-38; -2.9] | 0.020 | -0.15 [-0.4; 0.1] | 0.372 |
| Past VTE | -12.9 [-48; 22] | 0.464 | -135 [-200; -69] | 0.001 | -0.1 [-1.5; 1.1] | 0.795 |
| OSA | -0.11 [-10; 10] | 0.984 | -11 [-32.9; 10.5] | 0.307 | 0.2 [-0.1; 0.6] | 0.268 |
| Neoplastic disease | -5.5 [-18; 7.8] | 0.409 | 3.2 [-24.2; 30.6] | 0.816 | -0.3 [-0.7; 0.19] | 0.231 |
| Disease management and severity | | | | | | |
| ECMO | 4.9 [-4.5; 14.4] | 0.302 | 36 [18.7; 53.3] | 0.001 | 0.1 [-0.2; 0.4] | 0.424 |
| Days on ECMO | 0.53 [0.2; 0.8] | 0.006 | 1.2 [0.16; 2.3] | 0.020 | -0.01 [-.03; .01] | 0.322 |
| Remdesivir | 6.7 [-2.1; 15.0] | 0.134 | 10.7 [-7.3; 28.8] | 0.241 | 0.19 [-0.1; 0.5] | 0.250 |
| Plasma | 0.4 [-9.9; 10.9] | 0.925 | 5.1 [-16; 26.4] | 0.633 | 0.1 [-0.2; 0.5] | 0.350 |
| HIT | 13 [-0.6; 27.1] | 0.06 | 43 [16.2; 70.2] | 0.002 | -0.04 [-0.5; 0.4] | 0.867 |
| D-dimer (ng/dl) | 0.002 [-0.1; 0.4] | 0.207 | -0.02 [-0.01; 0.1] | 0.383 | .0001 [-.001; .1] | 0.983 |
| Full anticoagulation | 5.6 [-3.3; 14.6] | 0.215 | -8.2 [-26; 10.2] | 0.377 | 0.05 [-0.2; 0.3] | 0.753 |
| Delirium | 2.5 [-6.2; 11.2] | 0.568 | -0.4 [-18; 17.4] | 0.96 | -0.01 [-0.3; 0.3] | 0.926 |
| Pleural Complication | 6.4 [-4.1; 17.0] | 0.232 | 51 [33.9; 69.3] | 0.005 | 0.2 [-0.1; 0.6] | 0.180 |
| Oxygen | | | | | | |
| Resting oxygen need | 3.7 [1.1; 6.4] | 0.005 | 6.3 [1; 11.7] | 0.02 | - | - |
| Effort oxygen need | 8.5 [2.1; 14.8] | 0.009 | 14.3 [1.1; 27.5] | 0.03 | - | - |

***Table 4.*** *ECMO vs Non-ECMO.*

| Parameter | ECMO | Non-ECMO | Pvalue |
|---|---|---|---|
| **N** | **20** | **50** | **-** |
| Demographic | | | |
| Age | 51.0±12.1 | 61.9±12.3 | <0.05 |
| Gender (Male) | 16 (80%) | 40 (80%) | 0.999 |
| Weight | 81.4±10.9 | 89.1±20.4 | <0.05 |
| Smoker | 4 (20%) | 13 (26%) | 0.826 |
| Co-morbidities | | | |
| Over weight | 13 (65%) | 32 (64%) | 0.900 |
| Morbid obesity | 5 (25%) | 15 (30%) | 0.999 |
| Hypertension | 5 (25%) | 30 (60%) | <0.05 |
| Hyperlipidaemia | 6 (30%) | 26 (52%) | 0.160 |
| CV co-morbidities | 0 (0%) | 12 (24%) | <0.05 |
| COPD/Asthma | 3 (15%) | 5 (10%) | 0.859 |
| DM | 5 (25%) | 21 (42%) | 0.291 |
| Past VTE | 0 (0%) | 5 (10%) | 0.340 |

| Parameter | ECMO | Non-ECMO | Pvalue |
|---|---|---|---|
| **N** | **20** | **50** | **-** |
| OSA | 2 (10%) | 14 (28%) | 0.192 |
| Neoplastic | 1 (5%) | 8 (16%) | 0.397 |
| Disease management and severity | | | |
| Remdesevir | 10 (50%) | 17 (34%) | 0.332 |
| Plasma | 6 (30%) | 10 (20%) | 0.559 |
| HIT | 7 (35%) | 0 (0%) | <0.05 |
| D-dimer (ng/dl) | 1597±908 | 2598+2040 | <0.05 |
| Anticoagulation | 14 (70%) | 32 (64%) | 0.842 |
| Delirium | 8 (40%) | 28 (56%) | 0.345 |
| Pleural complication | 8 (40%) | 7 (14%) | <0.05 |
| Outcomes | | | |
| Weaned | 20 (100%) | 45 (90%) | 0.340 |
| Died | 0 (0%) | 4 (8%) | 0.464 |
| Home | 2 (10%) | 8 (16%) | 0.787 |
| Rehabilitation | 18 (20%) | 38 (76%) | 0.321 |
| Oxygen on Discharge* | 16 (80%) | 40 (89%) | 0.570 |
| Time (days) | | | |
| Admission to Weaning | 16±16 | 11±18 | 0.284 |
| Admission to De-cannulation | 35±29 | 21±22 | 0.065 |
| Total Ventilated | 83±46 | 47±24 | <0.05 |
| Positive COVID-19 to tracheostomy | 24±16 | 21±17 | 0.511 |
| Positive COVID-19 to Intubation | 8±9 | 6±8 | 0.420 |
| Intubation to tracheostomy | 16±13 | 15±14 | 0.809 |
| Oxygen need on discharge [L/m] | | | |
| Oxygen Rest | 0.92±0.75 | 0.78±0.61 | 0.467 |
| Oxygen Effort | 1.85±1.63 | 1.75±1.7 | 0.828 |

*Smoker includes past or present smokers; †Overweight: BMI>25; †Morbid Obesity: BMI>30; ††CV comorbidity includes: atrial fibrillation, ischemic heart disease, chronic heart failure; *Delirium was defined by Richmond Agitation-Sedation Scale (RASS) above +1; *Neoplastic disease – defined as any neoplastic disease within 5 years from positive COVID-19.

# 4. Discussion

Herby, we describe a cohort of 70 mechanically ventilated post COVID-19 patients, hospitalized between March 2020 to April 2021 in a mechanical ventilation weaning facility. As in other parts of the world there was a learning curve for the weaning process that was optimized with experience. The cohort characteristics in terms of age, gender and physical characteristics was comparable to other studies in tracheotomised COVID-19 patients [1, 5-6].

Out of the 70 patients in the cohort, 66 were weaned completely from mechanical ventilation and went through de-cannulation of the tracheostomy. Comorbidities and physiological parameters didn't influence the ability to be weaned or had influence on the weaning duration, given the patient has survived the ICU. As expected, the total duration of mechanical ventilation was longer in patient that were on ECMO, but surprisingly was negatively correlated with weight, presence of hypertension and diabetes mellitus. Although obesity is a risk factor for COVID-19 severe disease, a paradox exists in which given severe COVID-19 these patient spend less time ventilated, and might even survive longer [7-8]. A multivariate analysis of the contribution of these three co-morbidities shows that the variability explained by weight is the highest.

## *4.1. Patients Previously on ECMO*

Due to it retrospective nature, it is hard to achieve definite conclusion about the contribution of ECMO use to COVID-19 patients; Patients who were not treated with ECMO were older, with more cardiovascular comorbidities. This might stem from a bias as older and more morbid patient might not have survived the ICU despite being on ECMO. Be that as it may, those who survived the ICU didn't differ in weaning time, the need for rehabilitation and the need for oxygen at discharge.

Patients requiring ECMO had a longer total ventilation time and required more oxygen on discharge from rehabilitation department. Pleural complications (e.g. empyema, pneumothorax) were seen more in ECMO patients in this cohort, and were a delaying factor for de-cannulation but not for weaning. The reason for the higher prevalence in ECMO patients is not fully understood, as one of the benefits of ECMO is the reduction of positive pressure ventilation complications. However, pleural complications might serve as a marker for the severity of the COVID-19 disease in these patients.

Seven of the 70 patients developed HIT during their ICU stay, all of them were on ECMO, which results in 35% chance to develop HIT during ECMO use. This risk might be higher than previously reported in non-COVID-19 patients [10], which might suggest synergistic influence of COVID-19 on the development of HIT [11]. However, given the complexity of diagnosis of HIT in these patients, and given patient arrived to our facility from different ICUs further research is required for definite conclusion.

## *4.2. Comparison of Patients Between Waves*

The patients during the first wave differ from the preceding waves in that they were weaned and went through de-cannulation faster, as comparable to other cohorts from the same time period [12]. As previously reported [13], these patients might not have been ventilated or tracheotomised in later periods of the epidemic when more knowledge was collected. In addition, the weaning process during the first wave was done while the patients were still positive for the virus, therefore the weaning process took place outside of the main rehabilitation department. This might explain the reasons for the higher mortality during the first wave. The patients in the second and third wave were mechanically ventilated longer, and more of them required ECMO use during their hospitalization in the ICU.

### *4.3. Weaning Patterns*

There were three main weaning patterns seen in different overlapping levels in the cohort patients; The first pattern was of patients with low capacities due to extra-pulmonary causes; although still hypoxemic, patient falling into this pattern had severe polyneuropathy [14-15] and delirium which influence the ability to overcome the respiratory load [16]. In addition infections (extra and intra pulmonary) also influenced the ability to recover and continue the weaning process.

The second pattern was of patients with a fibrotic-bullosic pulmonary injury pattern, with relativity small ground glass opacities in CT scans (see figure 1A), but with multiple pleural complications (mainly pneumothorax). In these patients there was often the challenge of managing the air leaks and removing the pleural drains as the challenge of diagnosing whether the air leak stems from Broncho-alveolar fistula (BAF) or trapped lung. In all 15 patient with pleural complications, only one patient required bronchoscopic intervention for BAF. In all other cases partial expansion of the lung took place after removal of the drainage.

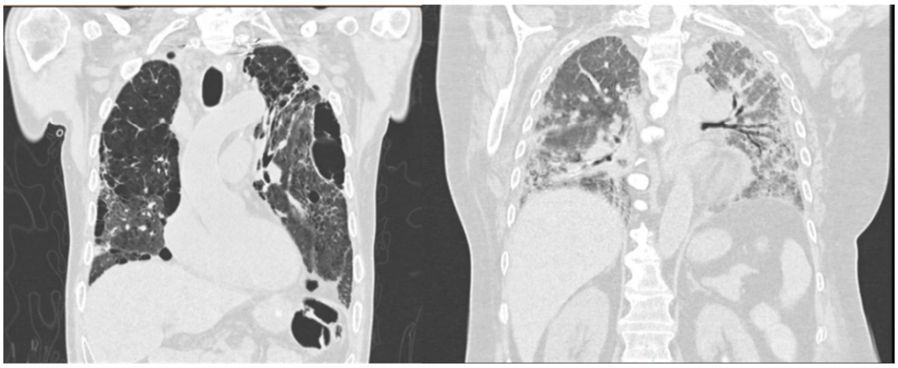

***Figure 1.*** *A) the second pattern characterized by large bullae, areas of traction bronchiectasis, relatively small areas of ground glass opacities; B) the third pattern characterized by diffuse ground glass opacities, traction bronchiectasis and the absence of bullae.*

The third pattern was of severely hypoxemic patients with a diffuse ground glass opacities with fibrotic areas but with no or very mild bullous disease. NSIP pattern after COVID-19 has already described [17]. Most of these patients required high percentage of oxygen, and clinically behaved with large shunt that worsened with cough and effort and were hypocarbic to mildly hypercarbic. Those patients went through a routine investigation of ruling out cardiac shunt, autoimmune disease [18] and required bronchoscopy to rule out infectious diseases with similar patterns (CMV, PCP). These patients received dosage of 1mg/kg prednisone (or equivalent), and all of them were eventually weaned, but all required between 2-3 liter of oxygen during rest. The benefit of giving high dose glucocorticoids in these patients is still in debate [19]. Although unproven, it is our opinion that the second and third patterns are different pulmonary insult patterns (that can coexist) and are not patterns in different points in the natural history of the disease.

As not all patient in our cohort required high resolution CT scan, a firm conclusion about the prevalence and overlap of the above patterns cannot be achieved, nor the long term consequences.

## 5. Limitations

Most study limitation arise from the population admitted to our facility; serving as a national weaning facility, survivors from all ICUs in Israel are transferred to our facility for weaning. As the mortality of ICU patients with COVID-19 is poor [20], a survival bias exists. In addition, there wasn't a rigid protocol for weaning. Slight changes in management of these patient exist, especially during the first wave when performed outside the main weaning centre. However, as most of the medical decisions are taken in joinet daily meetings, we believe that the variability explained by this is small.

## 6. Conclusion

The current article summarizes almost 2 years of experience of weaning severe COVID-19 patients at a leading weaning centre in Israel. First, it demonstrates a high success rate of weaning, independent from comorbidities and placement on ECMO. Second, it suggests that an obesity paradox exists in COVID-19 patients; while obesity has been demonstrated to be a severe COVID-19 risk factor, morbidly obese patients were on mechanical ventilation for shorter duration. Third, it shares the practice and knowledge of a dedicated and fully staffed national ventilator weaning process and weaning patterns.

# Authors' Contribution

Conception and design: DO; Analysis and interpretation: DO; Drafting the manuscript for important intellectual content: DO, KF; Critical review and editing: DO, KF; Data collection: DO, SA; All authors provided and cared for study patients.

# References


[1] Broderick D, Kyzas P, Baldwin AJ, et al. Surgical tracheostomies in COVID-19 patients: A multidisciplinary approach and lessons learned. *Oral Oncol*. 2020; 106: 104767. doi: 10.1016/j.oraloncology.2020.104767.

[2] Grabowski DC, Joynt Maddox KE. Postacute Care Preparedness for COVID-19: Thinking Ahead. *JAMA - J Am Med Assoc*. 2020. doi: 10.1001/jama.2020.4686.

[3] Benito DA, Bestourous DE, Tong JY, Pasick LJ, Sataloff RT. Tracheotomy in COVID-19 Patients: A Systematic Review and Meta-analysis of Weaning, Decannulation, and Survival. Otolaryngol Head Neck Surg. 2021 Sep; 165 (3): 398-405. doi: 10.1177/0194599820984780. Epub 2021 Jan 5. PMID: 33399526.

[4] Lorusso, R., Combes, A., Lo Coco, V. *et al.* ECMO for COVID-19 patients in Europe and Israel. *Intensive Care Med* 47, 344–348 (2021).

[5] Hamilton NJI, Jacob T, Schilder AGM, et al. COVIDTrach; the outcomes of mechanically ventilated COVID-19 patients undergoing tracheostomy in the UK: Interim Report. *Br J Surg*. 2020; 107 (12): e583-e584. doi: 10.1002/bjs.12020.

[6] Cardasis JJ, Rasamny JK, Berzofsky CE, Bello JA, Multz AS. Outcomes After Tracheostomy for Patients With Respiratory Failure due to COVID-19: *https://doi.org/101177/0145561321993567*. Published online February 11, 2021. doi: 10.1177/0145561321993567.

[7] Abumayyaleh M, Gil IJN, El-Battrawy I, et al. Does there exist an obesity paradox in COVID-19? Insights of the international HOPE-COVID-19-registry. *Obes Res Clin Pract*. 2021; 15 (3): 275. doi: 10.1016/J.ORCP.2021.02.008.

[8] Ni Y-N, Luo J, Yu H, et al. Can body mass index predict clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome? A meta-analysis. *Crit Care 2017 211*. 2017; 21 (1): 1-10. doi: 10.1186/S13054-017-1615-3.

[9] K J, BH J, MG K, et al. Impact of delirium on weaning from mechanical ventilation in medical patients. *Respirology*. 2016; 21 (2): 313-320. doi: 10.1111/RESP.12673.

[10] Choi JH, Luc JGY, Weber MP, et al. Heparin-induced thrombocytopenia during extracorporeal life support: incidence, management and outcomes. *Ann Cardiothorac Surg*. 2019; 8 (1): 19. doi: 10.21037/ACS.2018.12.02.

[11] Steinlechner B, Kargl G, Schlömmer C, et al. Can Heparin-Coated ECMO Cannulas Induce Thrombocytopenia in COVID-19 Patients? *Case Reports Immunol*. 2021; 2021: 1-5. doi: 10.1155/2021/6624682.

[12] Tornari C, Surda P, Takhar A, et al. Tracheostomy, ventilatory wean, and decannulation in COVID-19 patients. *Eur Arch Oto-Rhino-Laryngology*. 2021; 278 (5): 1595-1604. doi: 10.1007/s00405-020-06187-1.

[13] Ovadya D, Bachar K, Peled M, Skudowitz M, Wollner A. Weaning of severe COVID-19 mechanically ventilated patients: experience within a dedicated unit in Israel. *Isr Med Assoc J*. 2021; 22 (12): 733-735. Accessed June 27, 2021. https://europepmc.org/article/med/33381942.

[14] Estraneo A, Ciapetti M, Gaudiosi C, Grippo A. Not only pulmonary rehabilitation for critically ill patients with COVID-19. *J Neurol*. 2021; 268 (1): 1. doi: 10.1007/S00415-020-10077-1.

[15] Zhou C, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: A systematic review. *Neural Regen Res*. Published online 2014. doi: 10.4103/1673-5374.125337.

[16] Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological Features of Covid-19. *N Engl J Med*. 2020; 383 (10): 989-992. doi: 10.1056/NEJMc2019373.

[17] Salcedo RM, Flores RG, Medina CA, Mogollon RJ, Madariaga MG. Postinfectious Interstitial Pneumonia After COVID-19 Infection. *Infect Dis Clin Pract (Baltim Md)*. 2021; 29 (3): e193. doi: 10.1097/IPC.0000000000000985.

[18] Cauwelaert S Van, Stylemans D, D'Haenens A, Slabbynck H, Nieuwendijk R. Even if it looks like COVID-19, think again: the importance of differential diagnosis during a pandemic. *https://doi.org/101080/1784328620211872312*. Published online 2021. doi: 10.1080/17843286.2021.1872312.

[19] Tanni SE, Fabro AT, Albuquerque A de, et al. Pulmonary fibrosis secondary to COVID-19: a narrative review. *https://doi.org/101080/1747634820211916472*. Published online 2021. doi: 10.1080/17476348.2021.1916472.

[20] C M-V, C PM-R, M B-B, M B-S. Outcome of 1890 tracheostomies for critical COVID-19 patients: a national cohort study in Spain. *Eur Arch Otorhinolaryngol*. 2021; 278 (5). doi: 10.1007/S00405-020-06220-3.