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Original article

The effect of driving pressures in COVID-19 ARDS: Lower may still be better as in classic ARDS

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Abstract

Background: The respiratory dynamics of coronavirus disease 2019 (COVID-19) patients under invasive ventilation are still not well known. In this prospective cohort, we aimed to assess the characteristics of the respiratory system in COVID-19 patients under invasive mechanical ventilation and evaluate their relationship with mortality.

Methods: Fifty-eight COVID-19 patients who underwent invasive mechanical ventilation between March 11, 2020 and September 1, 2020 were enrolled for the present study. Demographics and laboratory values at baseline were recorded. Respiratory variables such as tidal volume, plateau pressure, positive end expiratory pressure, static compliance, and driving pressure were recorded daily under passive conditions. Further, the median values were analyzed.

Results: Median age of the patients was 64 years (58–72). Mortality was 60% on day 28. Plateau pressure, driving pressure, and static compliance significantly differ between the survivors and non-survivors. When patients were categorized into two groups based on the median driving pressure (Pdrive) of \( \leq 15 \text{ cmH}_2\text{O} \) or \( > 15 \text{ cmH}_2\text{O} \) during their invasive mechanical ventilation period, there was significantly better survival on day 28 in patients having a Pdrive \( \leq 15 \text{ cmH}_2\text{O} \) (28 days [95% CI = 19–28] vs 16 days [95% CI = 6–25], log-rank \( p = 0.026 \)).

Conclusion: COVID-19 related acute respiratory distress syndrome (ARDS) seemed to have similar characteristics as other forms of ARDS. Lung protective ventilation with low plateau and driving pressures might be related to lower mortality.

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1. Introduction

Over 25 million people worldwide were diagnosed with coronavirus disease 2019 (COVID-19) caused by the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 2 September 2, 2020 [1]. Rate of critical cases varied from 5% to 36% in different countries [2,3]. Hypoxemic respiratory failure due to COVID-19 is the main reason for intensive care unit (ICU) admission [3–5]. Patients receiving invasive mechanical ventilation (IMV) during their ICU stay included 29%–90% of the total COVID-19 infected patients [5–7].

COVID-19 patients primarily experience hypoxemic respiratory failure. It has been recommended that such patients should be treated like other cases of hypoxemic respiratory failure [8]. Lung protective ventilation has been advocated for these patients to minimize ventilator-induced lung injury (VILI) and maintain adequate oxygenation [9,10]. The case fatality rate is found to be 2.3% in all cases and 49% in critical cases [11]. The highest mortality rate is reported in patients who received IMV [7]. Advanced age, laboratory findings, such as lower lymphocyte count, higher IL-6 levels, higher D-dimer levels, and presence of comorbidities were also found to be associated with higher mortality [5,7,12].

Mortality is found to increase with IMV use; however, information about the effects of mechanical ventilatory parameters such as driving pressure (Pdrive) on mortality of COVID-19 patients is limited. Pdrive is one of the most important mortality predictors in acute respiratory distress syndrome (ARDS) and is defined by normalizing tidal volume (VT) to the static compliance (Crs) and reflects the functional size of the lung [13]. ARDS is the most common complication of COVID-19 [4,7]. Although COVID-19 pneumonia can fulfill the Berlin definition for ARDS, it may have different respiratory mechanics in ARDS [14]. Gattinoni and colleagues have suggested that COVID-19 patients have two phenotypes according to respiratory system compliance [15]. Different respiratory compliances may cause different responses to the lung-protective ventilation.

While studies have focused mostly on laboratory findings and comorbidities for mortality predictors, evidence for respiratory mechanics on mortality is scarce. Therefore, we designed this prospective cohort study to observe the characteristics of the respiratory system in COVID-19 patients who received IMV and evaluate their relationship with mortality.

2. Materials and methods

A single-center, prospective, observational study was conducted at the University of Health Sciences, Dr. Suat Seren Chest Disease and Thoracic Surgery Teaching and Research Hospital, Intensive Care Unit, Izmir, Turkey between March 11, 2020 and September 1, 2020. During this period, only confirmed or highly suspected COVID-19 cases were admitted to the ICU. This hospital is the biggest center in the western part of the country specialized in pulmonary diseases and has 23 ICU beds. The study was approved by the IRB 49109414-604.02 (22.07.2020). Written informed consent was obtained from all participants.

2.1. Patients

Patients who were intubated due to COVID-19 were included in the study. COVID-19 pneumonia was confirmed according to the World Health Organization (WHO) interim guidance [16]. According to the Turkish Ministry of Health COVID-19 Guidance [17] and intensivist opinion, patients were admitted to the ICU if one or more of the following conditions occurred: respiratory rate ≥ 35 breaths/min, partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) < 200-mmHg, need for mechanical ventilation (non-invasive or invasive), hemodynamic instability, loss of consciousness, respiratory or cardiac arrest, and progression in chest radiography and clinical deterioration despite optimal therapy.

2.2. Treatment

According to the Turkish Ministry of Health COVID-19 Guidance [17], antiviral treatment against SARS-CoV-2 was recommended. Hydroxychloroquine and favipiravir were the two main antiviral drugs prescribed during the study period. The other treatment options including tocilizumab, corticosteroids, and convalescent plasma were used on case to case basis. In case of any complications (secondary infection, arrhythmia, acute kidney injury, etc.), treatment according to the recommended guidelines was followed.

2.3. Management of acute respiratory failure

Management of acute respiratory failure included primarily, oxygen supplementation via a non-breathable oxygen mask to target an oxygen saturation level >90% and PaO2 ≥ 60 mmHg. Patients who failed to reach these targets or experienced dyspnea were allowed to lie in a prone position for spontaneous breathing. High flow nasal cannula or non-invasive ventilation was applied when oxygen supplementation was insufficient. Patients were intubated if there was no improvement of hypoxemia despite optimal non-invasive treatments.

After intubation, all patients received sedative, analgesic, and neuromuscular blocking agents for a short period (first 24–8 h). The continuation of sedation and neuromuscular blocking was decided on a case to case basis.

2.4. Ventilatory settings

Following intubation, all patients were administered volume control mode. The VT was limited to 4–8 mL/kg for predicted body weight (PBW) and end-inspiratory plateau pressure (Pplat) ≤ 30 cmH2O. The positive end-expiratory pressure (PEEP) and FiO2 were adjusted according to the best compliance and oxygen saturation of pulse oximeter above 90% and PaO2 ≥ 60 mmHg. Higher PEEP levels were preferred over lower
Patients' demographic features, comorbid diseases, smoking status, the time from the first symptom to the hospital admission, and the days before ICU admission were obtained from medical records.

The Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE-2), and Simplified Acute Physiology Score 2 (SAPS-2) were determined on the ICU admission day.

Ventilatory parameters such as VT, PEEP, Pplat, Pdrive, CRS, mean airway pressure (Pmean), peak airway pressure (Ppeak), FiO₂, and respiratory rates were recorded daily. All measurements were performed under static conditions when patients were receiving deep sedation and/or neuromuscular blockage without spontaneous respiratory effort. Pplat was measured after 0.5–1 s inspiratory hold during zero flow. Pdrive was calculated as Pplat minus PEEP. The other parameters were directly obtained from the digital readout of the ventilator. All variables were recorded daily until the patients were weaned off the ventilator or they died. Median values of the daily recordings were included in the analyses.

| Table 1 – Patient characteristics and laboratory findings at the time of ICU admission. |
|---------------------------------------------------------------|
| Variables | Survivors (n = 22) | Non-survivors (n = 36) | p value |
|—— | ———— | ———— | ——— |
| Age, years (range) | 62 (47–68) | 69 (63–75) | 0.02 |
| Gender, male (%) | 13 (59%) | 27 (75%) | 0.32 |
| Days from appearance of the first symptoms to hospitalization | 4 (3–6) | 5 (3–7) | 0.5 |
| Days after transfer to ICU | 3 (0–7) | 4 (2–8) | 0.1 |
| Days from first symptoms to intubation | 7 (5–13) | 8 (7–15) | 0.06 |
| Intubation in first 24 h following ICU admission (%) | 15 (68%) | 22 (61%) | 0.77 |
| History (%) | | | |
| COPD | 6 (27) | 19 (53) | 0.1 |
| Hypertension | 17 (77) | 21 (58) | 0.16 |
| DM | 10 (46) | 13 (36) | 0.58 |
| CHF | 3 (14) | 3 (8) | 0.41 |
| Coronary Artery Disease | 2 (10) | 8 (22) | 0.29 |
| Any Malignancy | 3 (14) | 10 (28) | 0.33 |
| Neurological Disease | 2 (10) | 3 (8) | 0.64 |
| Active smoker | 11 (50) | 23 (64) | 0.27 |
| Smoking (package/year) | 19 (15–30) | 35 (25–40) | 0.028 |
| APACHE-2 Score | 20 (12–26) | 25 (15–29) | 0.25 |
| SAPS-2 Score | 48 (39–57) | 51 (37–72) | 0.76 |
| SOFA Score | 6 (4–7) | 6 (4–9) | 0.89 |
| Respiratory Rate, breaths/min | 23 (22–26) | 22 (20–22) | 0.06 |
| Heart rate, beat/min | 100 (92–110) | 95 (86–112) | 0.57 |
| Mean Arterial Pressure, mmHg | 83 (65–100) | 77 (70–86) | 0.23 |
| PaO₂/FiO₂ | 136 (92–219) | 140 (96–190) | 0.85 |
| White Blood Cell × 10⁹/L | 11.6 (9.6–13.5) | 10.6 (6.9–17.8) | 0.56 |
| Neutrophil × 10⁹/L | 10.3 (7.7–10.9) | 8.5 (5.6–14) | 0.29 |
| Lymphocyte × 10⁹/L | 0.9 (0.6–1.2) | 0.7 (0.4–1.1) | 0.16 |
| Hemoglobin × 10⁹/L | 11.7 (10.4–12.7) | 11.7 (10.1–13) | 0.28 |
| Platelets × 10⁹/L | 258 (230–310) | 240 (198–320) | 0.64 |
| Creatinine, mg/dl | 0.87 (0.8–1.3) | 1.02 (0.76–1.42) | 0.93 |
| AST, UL | 33 (22–38) | 41 (22–63) | 0.33 |
| ALT, UL | 28 (18–38) | 28 (18–39) | 0.75 |
| CRP, mg/dL | 15.5 (9.1–23.4) | 17.5 (7.3–27.1) | 0.92 |
| Prolactin, ng/mL | 0.21 (0.11–0.45) | 0.25 (0.19–0.34) | 0.17 |
| Ferritin, ng/mL | 433 (275–1254) | 1112 (493–1723) | 0.6 |
| D-Dimer, ng/mL | 1799 (1251–4234) | 2082 (1275–6366) | 0.35 |

Data are shown as n (%) and median (25th – 75th percentiles). ALI = Alkaline transaminase, APACHE-2 = Acute Physiology and Chronic Health Evaluation-2, AST = Aspartate transaminase, CHF = Congestive heart failure, COPD = Chronic obstructive pulmonary disease, CRP = C-reactive protein, DM = Diabetes mellitus, ICU = intensive care unit, SAPS-2 = Simplified Acute Physiology Score-2, SOFA = Sequential Organ Failure Assessment, PaO₂ = partial pressure of oxygen, FiO₂ = fraction of inspired oxygen.

Statistically significant values are presented in bold characters.

2.6. Definitions

Septic shock was defined according to the guidance of the Survival Sepsis Campaign [10]. Myocardial injury was defined if the serum levels of the cardiac biomarkers (troponin I) were above the 99th percentile upper reference limit [18]. Acute kidney injury (AKI) was defined according to the guidelines of Kidney Disease: Improving Global Outcomes (KDIGO) [19]. Liver injury was diagnosed if serum level of alanine transaminase (ALT), aspartate transaminase (AST), or bilirubin were above the 99th percentile upper reference limit.
Common complications including septic shock, acute kidney injury (AKI), and myocardial damage were observed in 79%, 60%, and 55%, cases respectively. Among these complications, only septic shock was found to be associated with mortality ($p = 0.041$, Table 3).

When patients were categorized into two groups as having a median $P_{\text{drive}} \leq 15$ cmH$_2$O and $>15$ cmH$_2$O during their IMV period, a significantly better survival at day 28 in patients having a $P_{\text{drive}} \leq 15$ cmH$_2$O [28 days (95% CI = 19–28) vs. 16 days (95% CI = 6–25), log-rank $p = 0.026$, Fig. 2]. The presence of septic shock did not differ between these two groups (15/23 vs. 23/33, $p = 0.77$). Mortality at day 28 was 43% and 74% in patients with a $P_{\text{drive}} \leq 15$ cmH$_2$O and $>15$ cmH$_2$O, respectively ($p = 0.027$).

4. Discussion

The most important finding of this study was the lower median $P_{\text{drive}}$ during IMV in the survivors compared to the non-survivors. We found a mortality rate of 62% in patients who received IMV. Lower $P_{\text{drive}}$, $P_{\text{plat}}$, and higher $C_{\text{RS}}$ were associated with lower mortality. Patients having a $P_{\text{drive}} \leq 15$ cmH$_2$O, displayed a significantly better survival at day 28. Higher median $P_{\text{drive}}$ and $P_{\text{plat}}$ were associated with higher mortality in the current study. $P_{\text{drive}}$ is a well-known predictor of mortality in patients with ARDS. Amato et al. have demonstrated $P_{\text{drive}}$ as the best indicator during low VT ventilation [13]. Lower $P_{\text{drive}}$ on the first day of mechanical ventilation is associated with better survival in both ARDS and non-ARDS patients [20–23]. Ventilatory parameters such as the tidal volume, PEEP, $P_{\text{plat}}$, and $P_{\text{drive}}$ were similar to that at the early terms of intubation in our study. Only $C_{\text{RS}}$ was found to be better in the survivor group. Although these parameters were comparable in the first few days after intubation, they might have got worse over the period of mechanical

| Table 2 – Respiratory system mechanics. |
|----------------------------------------|
| Parameters                                     | Survivor | Non-survivor | $p$ value |
| VT, kg.mL/kg (first day of IMV)               | 8 (6–10) | 7 (7–7) | 0.29          |
| PEEP, cmH$_2$O (first day of IMV)             | 12 (10–14) | 12 (10–13) | 0.63          |
| $P_{\text{plat}}$, cmH$_2$O (first day of IMV) | 27 (23–31) | 28 (26–33) | 0.15          |
| $P_{\text{drive}}$, cmH$_2$O (first day of IMV) | 15 (13–17) | 18 (13–22) | 0.15          |
| $C_{\text{RS}}$, mL/cmH$_2$O (first day of IMV) | 36 (28–41) | 28 (21–36) | 0.01          |
| Median VT, kg, mL/kg (during IMV)            | 7 (6.2–8.5) | 7 (6.9–8.4) | 0.42          |
| Median PEEP, cmH$_2$O (during IMV)           | 10 (9–12) | 12 (8–14) | 0.53          |
| Median $P_{\text{plat}}$, cmH$_2$O (during IMV) | 27 (24–29) | 30 (28–33) | 0.007         |
| Median $P_{\text{drive}}$, cmH$_2$O (during IMV) | 15 (12–17) | 19 (14–22) | 0.011         |
| Median $C_{\text{RS}}$, mL/cmH$_2$O (during IMV) | 36 (30–49) | 29 (22–39) | 0.018         |

Data are shown as median (25th–75th percentiles). $VT =$ Tidal volume, $IMV =$ Invasive mechanical ventilation, $PEEP =$ Positive end expiratory pressure, $P_{\text{plat}} =$ Plateau pressure, $P_{\text{drive}} =$ Driving pressure, $C_{\text{RS}} =$ Static compliance of respiratory system. Statistically significant values are presented in bold characters.
Complications during invasive mechanical ventilation. Data are shown as n (%).

| Parameters              | Survivor (n = 22) | Non-survivor (n = 36) | Total (n = 58) | p value |
|-------------------------|-------------------|-----------------------|----------------|---------|
| Septic shock (%)        | 14 (63.6)         | 32 (88.8)             | 46 (79.3)      | 0.041   |
| Acute kidney injury (%) | 11 (50)           | 24 (66.6)             | 35 (60.3)      | 0.67    |
| Renal replacement therapy (%) | 5 (22.7) | 13 (36.1)             | 18 (31)        | 0.24    |
| Myocardial damage (%)   | 11 (50)           | 21 (58.3)             | 32 (55.1)      | 0.77    |
| Liver injury (%)        | 6 (27.3)          | 13 (36.1)             | 19 (32.7)      | 0.57    |

Statistically significant values are presented in bold characters.

ventilation in non-survivors. This could have led to the difference in terms of median Pdrive, Pplat, and CRS between the survivors and non-survivors.

Survival was better in cases where Pdrive was kept below 15 cmH2O. Lung protective ventilation has been recommended in patients receiving IMV to minimize VILI [24]. We preferred a lower VT of 6–8 ml/kg, Pplat of <30 cmH2O, and a relatively higher PEEP [8]. Low respiratory system compliance is a hallmark of ARDS. Compliance is the change in volume for the applied pressure. CRS is one of the determinants of Pdrive and it is inversely proportional to Pdrive. Therefore, it might be difficult to keep Pdrive lower in patients with low compliance. We found that lower CRS was associated with mortality at the beginning and was an ongoing process. CRS might be one of the most important respiratory system variables because it influences the other variables Pdrive, Pplat, etc.

High respiratory system compliance is expected in patients with chronic obstructive pulmonary disease (COPD) [25]. Although there were more COPD patients in the non-survivor group than the survivor group (53% vs. 27%), the lower respiratory system compliance in the non-survivor group might indicate higher disease severity.

Lower static compliance is one of the characteristic features of ARDS. Our results corroborated with previous studies [20–22]. Non-ARDS patients have slightly higher CRS than ARDS patients [26]. However, our results did not support the hypothesis of Gattinoni and colleagues [15]. They suggested that COVID-19 has a time-related disease spectrum within two primary phenotypes. In the beginning, patients with Type I had high compliance, with time they became Type H with lower compliance [15]. CRS on the first day of IMV and median CRS were lower and consistent with non-COVID-19 ARDS.

Prone ventilation was applied in this study as a rescue therapy in 26 (49%) patients. Prone position ventilation improves survival in patients with moderate to severe ARDS [27]. Despite the positive effect of prone position on survival, the use is generally low (7%–16%) in multicenter studies [28,29]. The prone position is not preferred due to lack of experienced staff, hemodynamic instability, and fear of complication (endotracheal tube dislodgement, pressure sores, etc.). With the COVID-19 outbreak, the prone position was increasingly used and the popularity of the prone position in the mainstream media got extended. Rate of prone position ventilation varies from 10% to 28% in COVID-19 patients [4,5,30,31]. In our ICU, we were well-adopted with prone position ventilation in patients with ARDS before the COVID-19 outbreak and the number of patients receiving prone ventilation was much higher. The prone position did not improve the patient survival in our study. The fact that hemodynamic instability was more common in COVID-19 patients might have reduced the positive effects of the prone position.

COVID-19 involves high mortality in critical cases, especially in patients receiving IMV. Reports of mortality rate in patients undergoing IMV in early publications were high: 92%–97% from Wuhan [7,32] and 47%–80% from the United States [3,6,30,33]. Pooled IMV mortality rate was reported to be 43% in a meta-analysis study [34]. Our study presented a IMV mortality rate of 62% which was lower than those reported in early publications. However, the mortality rate in COVID-19 patients who received IMV is much higher than in patients with ARDS caused due to other reasons. The mortality rate was 35% in invasively ventilated ARDS patients [28] and pooled mortality rate reported in a meta-analysis study was 43%–44% in Refs. [35,36]. ARDS has heterogeneous etiologies and the mortality rate may vary depending on underlying causes. ICU mortality in ARDS patients with viral etiology was 41% in H1N1 pneumonia cases and 54% in SARS cases [37,38]. In this study, septic shock was found to develop in 79% of patients but it did not differ with Pdrive value higher or lower than 15 cmH2O. COVID-19 patients are prone to develop septic shock. Vasopressor drugs are prescribed in 15%–94% of COVID-19 patients in ICU [4,7,33,39]. The development of septic shock is relatively lower in H1N1 pneumonia (58%) and SARS (34%) cases [37,38]. The high mortality rate in COVID-19 patients on mechanical ventilation might be due to their predisposition to septic shock.

To our knowledge, this is the first study to evaluate the relationship between respiratory system mechanics and mortality. Nevertheless, our study had some limitations. First, as a single-center study, the results could not be generalized to other centers. Secondly, due to the observational nature of the study, we could not randomize the patients to different ventilation procedures with different targets; hence, the results might have been influenced by other factors. Last, we could not measure the transpulmonary pressures, so the effect of Pdrive during spontaneous breathing periods remained unknown.

5. Conclusion

Although it is debated whether the pathophysiology of respiratory failure due to COVID-19 has the same characteristics as the typical ARDS, the higher Pdrive and Pplat in our ARDS patients with COVID-19 were found to be associated with higher mortality. Further randomized controlled trials are warranted to demonstrate the positive effect of lung-protective ventilation with low Pdrive on patients’ survival in COVID-19 related ARDS.

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Conflict of Interest

The authors have no conflicts of interest.

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REFERENCES

[1] WHO Coronavirus Disease (COVID-19) Dashboard | WHO [cited 2020]. Available from: https://covid19.who.int/ (accessed September 2, 2020).

[2] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708–20. https://doi.org/10.1056/NEJMoA2002032.

[3] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O’Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369. https://doi.org/10.1136/bmj.m1966.

[4] Yu Y, Xu D, Fu S, Zhang J, Yang X, Xu L, et al. Patients with COVID-19 in 19 ICUs in Wuhan, China: a cross-sectional study. Crit Care 2020;24:1–10. https://doi.org/10.1186/s13054-020-02939-x.

[5] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the lombardy region. Italy. JAMA - J Am Med Assoc 2020;323:2052. https://doi.org/10.1001/jama.2020.6775.

[6] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. J Am Med Assoc 2020;323:2052. https://doi.org/10.1001/jama.2020.6775.

[7] Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, et al. Clinical course and outcomes of 344 intensive care patients with COVID-19. Am J Respir Crit Care Med 2020;201:1430–4. https://doi.org/10.1164/rccm.202003-0736LE.

[8] Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020 Mar:1–34. https://doi.org/10.1007/s00134-020-06622-5.

[9] Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of intensive care medicine/society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63. https://doi.org/10.1164/rccm.201703-0548ST.

[10] Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer K, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock, vol. 45; 2016. https://doi.org/10.1097/CCM.0000000000002255.

[11] Wu Z, McGoohan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. JAMA, J Am Med Assoc 2020;323(13):1239–42. https://doi.org/10.1001/jama.2020.2648.

[12] Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- research that is available on the COVID-19 resource centre - including this for unrestricted research re-use a. 2020. p. 19–21.

[13] Amato MBP, Meade MO, Slutsky AS, Brochard L, Costa ELV, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2014;372:747–55. https://doi.org/10.1056/NEJMa1410639.

[14] Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020;24:154. https://doi.org/10.1186/s13054-020-02880-z.

[15] Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatment for different phenotypes? Intensive Care Med 2020;1–6. https://doi.org/10.1007/s00134-020-06622-5.

[16] Organization WH. Global surveillance for COVID-19 disease caused by human infection with novel coronavirus (COVID-19). interim guidance 27 February 2020:7–9.

[17] Türkiye Cumhuriyeti Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. COVID-19 rehberi. 2020. p. 25. https://doi.org/10.1017/CBO9781107415324.004.

[18] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical characteristics of patients with coronavirus disease 2019 in Wuhan, China. Lancet 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

[19] Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL, et al. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012:2:1–138. https://doi.org/10.1038/kisup.2012.1.

[20] Guérin C, Papazian L, Reignier J, Ayazc L, Loundou A, Forel JM. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. Crit Care 2016;20:384. https://doi.org/10.1186/s13054-016-1556-2.

[21] Villar J, Martin-Rodriguez C, Dominguez-Berrot AM, Fernández L, Ferrando C, Soler JA, et al. A quantile analysis of plateau and driving pressures: effects on mortality in patients with acute respiratory distress syndrome receiving lung-protective ventilation. Crit Care Med 2017;45:843–50. https://doi.org/10.1097/CCM.0000000000002330.

[22] Fuller BM, Page D, Stephens RJ, Roberts BW, Drewry AM, Wu HP, Hu HC, Chu CM, Kao KC. The association between higher driving pressure and higher mortality in patients with pneumonia without acute respiratory distress syndrome. J Formos Med Assoc 2020 Jan;120:204–11. https://doi.org/10.1016/j.jfma.2020.04.027.

[23] Weiss CH, McSparron JI, Chatterjee RS, Herman D, Fan E, Wilson KC, et al. Summary for clinicians: mechanical ventilation in adult patients with acute respiratory distress syndrome clinical practice guideline. Ann Am Thorac Soc 2017;14:1235–8. https://doi.org/10.1513/AnnalsATS.201704-332CEM.
[25] Papandrinopoulou D, Tzouda V, Tsoukalas G. Lung compliance and chronic obstructive pulmonary disease. Pulm Med 2012;2012(542769). https://doi.org/10.1155/2012/542769.

[26] Schmidt MFS, Amaral ACKB, Fan E, Rubenfeld GD. Driving pressure and hospital mortality in patients without ARDS: a cohort study. Chest 2018;153:46–54. https://doi.org/10.1016/j.chest.2017.10.004.

[27] Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulin T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68. https://doi.org/10.1056/NEJMoa1214103.

[28] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA, J Am Med Assoc 2016;315:788–800. https://doi.org/10.1001/jama.2016.0291.

[29] Moss M, Huang DT, Brower RG, Ferguson ND, Ginde AA, Gong MN, et al. Early neuromuscular blockade in the acute respiratory distress syndrome. N Engl J Med 2019;380:1997–2008. https://doi.org/10.1056/NEJMoa1901686.

[30] Rasmussen Sonja A. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-. MD, MS JCS Ann Oncol 2020;19:e21. https://doi.org/10.1007/s00013-020-05991-x.Bizzarro.

[31] Hua J, Qian C, Luo Z, Li Q, Wang F. Invasive mechanical ventilation in COVID-19 patient management: the experience with 469 patients in Wuhan. Crit Care 2020;24. https://doi.org/10.1186/s13054-020-05044-9.

[32] Argenzian MG, Bruc SL, Slate CL, Tia JR, Baldwi MR, Barr RG, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020;369. https://doi.org/10.1136/bmj.m1996.

[33] Chang R, Mossad Elhusseiny K, Yeh Y-C, Sun W-Z. Full Title: COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis Short Title: COVID-19 ICU and mechanical ventilation characteristics and outcomes. PLOS ONE 2021;16(2):e0246318. https://doi.org/10.1371/journal.pone.0246318.

[34] Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. Chest 2008;133:1120–7. https://doi.org/10.1378/chest.07-2134.

[35] Phua J, Badia JR, Adhikari NKJ, Friedrich JO, Fowler RA, Singh JM, et al. Has mortality from acute respiratory distress syndrome decreased over time?: a systematic review. Am J Respir Crit Care Med 2009;179:220–7. https://doi.org/10.1164/rccm.200805-722OC.

[36] Tai D, Lew T, Loo S, Earnest A, Chen M. Critically ill patients with severe acute respiratory syndrome (SARS) in a designated national SARS ICU: clinical features and predictors for mortality. Crit Care 2004;8:F38. https://doi.org/10.1186/cc2505.

[37] Dominguez-Cherit G, Lapinsky SE, Macias AE, Torre A de, Poblano-morales M, Baltazar-torres JA, et al. Influenza A (H1N1) in Mexico. J Am Med Assoc 2009;302:1880–7.

[38] Auld SC, Caridi-Scheible M, Blum JM, Robichaux C, Kraft C, Jacob JT, et al. ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. Crit Care Med 2020 Sep;48(9):e799–804. https://doi.org/10.1097/ccc.0000000000004457.