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Type-H, and Type-L COVID-19: are they different subtypes or the same?

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Abstract. – OBJECTIVE: SARS-CoV-2 infection, which causes severe pneumonia, caused an epidemic that started in Wuhan, China in December 2019 and spread to the whole world. COVID-19 mainly affects the respiratory system and causes the development of severe pneumonia and related acute respiratory distress syndrome (ARDS) in some patients. We aimed to investigate whether COVID-19 pneumonia cases can be evaluated in different categories in clinical and radiological terms.

PATIENTS AND METHODS: COVID-19 associated ARDS cases being treated with the diagnosis of severe pneumonia between March 21, 2020 and June 15, 2020 in Anesthesia Intensive Care Unit were examined and divided into 2 groups (type-L and type-H, total 29 cases) according to their clinical findings (according to whether they benefited from high PEEP and their lung compliance) and lung computed tomography findings (according to the severity of the ground glass appearance). The groups were compared with each other in terms of inflammatory markers [CRP (C reactive protein), ferritin, D Dimer, PCT (procalcitonin), white blood cell, lymphocyte count, arterial blood gas analysis] and imaging findings.

RESULTS: It was observed that the prone position was beneficial in improving oxygenation in both H-type and L-type patients. 7 of 22 L-type patients were intubated and 5 of these patients died. There was no statistical difference between the two groups in terms of intubation times, hospital stays, cytokine levels, prone position application responses and mortality rates.

CONCLUSIONS: Are there two separate forms of COVID-19 pneumonia, such as h-type and l-type, or are they intertwined and describe the early and late stages of the disease? This question needs to be discussed. In addition, we believe that subtyping COVID-19 pneumonia patients does not make a difference in the treatments to be applied.

Key Words:
COVID-19, Pneumonia, Intensive care, Type-h type-l.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes severe pneumonia. SARS-CoV-2 caused an epidemic that started in Wuhan, China, in December 2019 and spread to the whole world[1-3]. In March 2020, the World Health Organization (WHO) declared that coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, was a danger to all nations. COVID-19 mainly affects the respiratory system and causes the development of severe pneumonia and related acute respiratory distress syndrome (ARDS) in some patients; other organ systems are less affected[4,5].

The number of cases is increasing rapidly worldwide, and information about the clinical course and treatment of the disease has been shared with the scientific world by researchers. The fact that a large number of cases were seen at the same time in different countries and there were disparities between them caused disagreements among experts. Although some patients were severely hypoxemic, the relative improvement of their clinics and the difficulties experienced in the treatment of some patients led to the thought that COVID-19-related ARDS was different from other ARDS forms[6,7]. Some experts argued that patients had two different subtypes (type-H, type-L) and the pathophysiology of these groups was different, whereas others thought that type-L was the early stage of the disease[6,8,9]. Experts who argued that the disease had two phenotypes thought that the treatments should be administered differently according to these groups. By contrast, experts who thought that type-L was the early stage of type-H argued that classic ARDS treatment should be given in both patient groups[10,11].

In this retrospective cohort study, patients who developed ARDS due to severe pneumonia asso-

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ciated with COVID-19 were examined. After the patients were classified clinically and radiologically as type-H and type-L, the responses of these groups to hypoxemia, inflammatory cytokine levels, prone positioning, high positive end expiratory pressure (PEEP) treatments were compared. In this way, the prognostic value of typing and whether it guided treatment were investigated.

Patients and Methods

The study was approved by the Local Ethics Committee (Keçiören Training and Research Hospital Ethics Committee. Date 08.07.2020, Decision no_2143) and the Ministry of Health. Patients with diagnoses of COVID-19-associated ARDS being treated for severe pneumonia between March 21st, 2020, and June 15th, 2020, in the Anesthesia Intensive Care Unit (ICU), were examined and divided into two groups (type-L and type-H) according to their clinical findings, whether they benefited from high PEEP and their lung compliance, and lung computed tomography (CT) findings (according to the severity of the ground-glass appearance).

Among the patients treated in our ICU, more ground-glass opacities and less consolidated areas determined radiologically were considered as type-L (Figure 1). Patients with more radiologically consolidated areas and less ground-glass areas were determined as type-H (Figure 2).

The groups were compared with each other in terms of inflammatory markers [C reactive protein (CRP), ferritin, D-dimer, procalcitonin (PCT), white blood cells, lymphocyte count, arterial blood gas analyses] and imaging findings. It was evaluated whether there was a difference between the groups regarding the responses of the patients who required mechanical ventilation support and prone positioning. Demographic data of the patients were analyzed.

Inclusion Criteria for the Study

Patients who were diagnosed as having a COVID-19-related ARDS and severe pneumonia [partial pressure arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2)<300 mmHg, peripheral arterial oxygen saturation (sPO_2) < 90%)], who were treated in anesthesia ICU, requiring respiratory support (noninvasive mechanical ventilation, high-flow oxygen therapy, prone positioning, and PEEP) between March 21st, 2020, and June 15th, 2020, were included in the study. All patients had CT scan images and positive COVID-19 polymerase chain reaction (PCR) tests.

Exclusion Criteria

Patients who were treated in the anesthesia ICU with a diagnosis of severe pneumonia between March 21st, 2020, and June 15th, 2020, but whose PCR tests were negative, were excluded from the study to prevent mortality bias.

Statistical Analysis

Continuous variables are expressed as mean±-standard deviation, and categorical data as numbers and percentages. In the intergroup analysis of continuous variables, normality analyses were performed using the Kolmogorov-Smirnov goodness of fit test. Analyses between the two groups

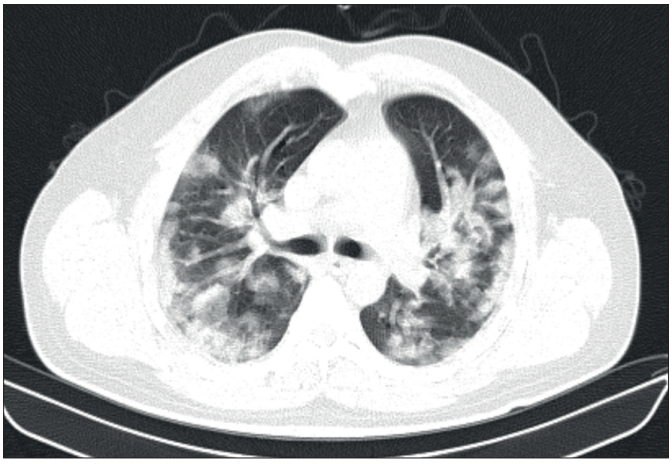

Figure 1. Type-L pneumonia.

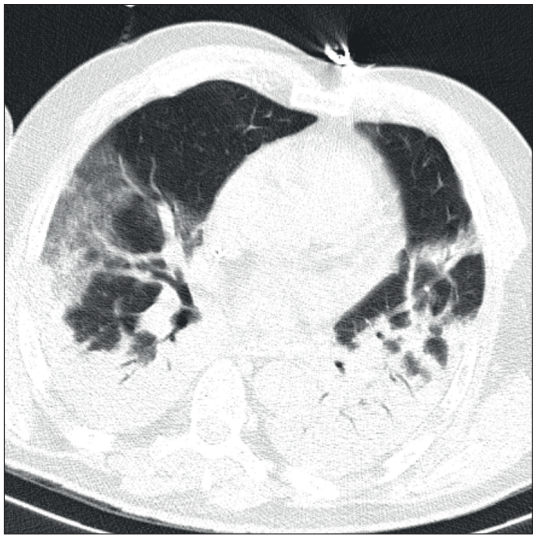

Figure 2. Type-H pneumonia.

were performed using the *t*-test when the data had normal distribution, and the Mann-Whitney U test when they did not. Comparisons of categorical data were made using the Chi-square test (Fisher's exact test when necessary). Analyses were performed using the IBM Statistics Package for the Social Sciences version 24.0 software (IBM Corporation, Armonk, NY, USA). The level of statistical significance was considered as $p<0.05$.

Results

The age, body mass index (BMI), and acute physiology, and chronic health evaluation (APACHE) II scores of patients with type-H lung structures (67.00±16.63, 33.70±6.07, and 20.71±15.31, respectively) were high compared with type-L structures (61.68±13, 29.17±4.24, and 15.14±7.27, respectively), the difference was significant only for BMI levels (p=0.036). NUTRIC scores 3 and 4 were found in 59.1% (n=13) of patients with type-L lung structures, and this rate was 85.8% (n=6) in patients with type-H structures (p=0.574). There was no significant difference between the groups in terms of sex, diabetes mellitus (DM), hypertension, coronary artery disease (CAD), chronic kidney disease (CKD), asthma, chronic obstructive pulmonary disease (COPD), and cerebrovascular accident (CVA) rates (Table I).

Although the length of stay in the ward was longer in patients with type-L lung structures [4 (0-12)] compared with type-H structures [0 (0-6)], the difference was not statistically significant (p=0.142). The length of stay in the ICU, the duration of noninvasive ventilation, and the number of days intubated were similar in patients with type-L and type-H lung structures (p=0.709 and, p=0.228, respectively). Although patients with type-H structures were intubated earlier than patients with type-L structures (0.5 days *vs.* 2.5 days, respectively), the difference was not statistically significant. The rates of entering cytokine storm (according to the trend of serially measured inflammatory parameters), prone positioning, receiving tocilizumab treatment, and administering immunoplasma, and performing plasmapheresis were similar in both groups (Table II). Although the mortality rates were higher in patients with type-H structures (57.1%) than in patients with type-L structures (22.7%), the difference was not statistically significant (p=0.158).

When the inflammatory parameters were examined, no difference was found between the two groups in terms of CRP, ferritin, and PCT values. Although the mean basal D-dimer levels in patients with type-H lung structures were higher than those of patients with type-L structures [(1598.33±1524.43) *vs.* (1161.50±1240.71), respectively], the difference was not significant (p=0.479). Again, during cytokine storm, the mean D-dimer levels in patients with type-H lung structures were higher than in those with type-L structures [(2760.00±181.83) *vs.* (2218.11±3204.85), respectively], but the difference was not significant (p=0.791).

Discussion

COVID-19 mainly affects the respiratory system. It causes ARDS with severe pneumonia in some patients; other organ systems are less involved[4,5]. Mortality is mostly associated with ARDS[12]. The risk of mortality is the highest in patients who develop severe ARDS, those who are hospitalized in ICUs, the elderly, and those with comorbidities. As the disease spread around the world and the number of patients increased, it was understood that the ARDS clinic in some patients with COVID-19 was different from that in other patients. Despite the severe hypoxemia of some patients, it was confusing that their clinics were relatively better. Some experts argued that COVID-19-associated ARDS was a different subgroup from the classic ARDS we knew, whereas others argued that it was not different from classic ARDS, only that the early stage of the disease was different. Although some studies[6,13-19] on the clinical appearance of COVID-19 have been published, our information remains limited.

In their article published in Critical Care, Li and Ma[6] suggested that not all respiratory failures associated with COVID-19 should be considered as ARDS, because there were many differences between COVID-19-related ARDS and other ARDS cases that met the Berlin. They stated that the onset time of the disease was longer (8-12 days) than in other ARDS, and lung compliance was relatively normal in some patients. Also, high-flow oxygen therapy was effective even in some moderate-severe ARDS cases, the time to start mechanical ventilation was very important, and the effect of corticosteroids was not fully known[6]. They stated that because the most common respiratory system symptom was dry cough (59.4-82%) and sputum production was less common, the alveolar epithelium was more affected in COVID-19-associated

Table I. Comparison of some socio-demographic and clinical features according to lung structure (Type-H, Type-L) of patients followed in the intensive care unit due to COVID-19.

	Type-H (n=7)	Type-L (n=22)	Total (n=29)	*p*
Age (years) (mean±SD)	67.00±16.63	61.68±13.20	63.80±14.47	0.390*
BMI (kg/m²) (mean±SD)	33.70±6.07	29.17±4.24	30.48±5.47	**0.036***
APACHE II score (mean±SD)	20.71±15,31	15.14±7,27	16.53±9,62	0.194*
NUTRIC score (n, %)				
0	1 (14.3%)	8 (36.4%)	9 (31.0%)	
1	0 (0.0%)	1 (4.5%)	1 (3.4%)	0.574**
3	3 (42.9%)	8 (36.4%)	11 (37.9%)	
4	3 (42.9%)	5 (22.7%)	8 (27.8%)	
Sex (n, %)				
Female	2 (28.6%)	7 (31.8%)	9 (31.0%)	1.000**[a]
Male	5 (71.4%)	15 (68.2%)	20 (69.0%)	
DM (n, %)	3 (42.9%)	6 (27.3%)	9 (31.0%)	0.642*[a]
HT (n, %)	3 (42.9%)	9 (40.9%)	12 (41.4%)	1.000*[a]
CAD (n, %)	2 (28.6%)	4 (18.2%)	6 (20.7%)	0.612*[a]
CKD (n, %)	0 (0.0%)	1 (4.5%)	1 (3.4%)	1.000*[a]
Asthma (n, %)	1 (14.3%)	4 (18.2%)	5 (17.2%)	1.000*[a]
COPD (n, %)	3 (42.9%)	2 (9.1%)	5 (17.2%)	0.075*[a]
CVA (n, %)	0 (0.0%)	1 (4.5%)	1 (3.4%)	1.000*[a]
Total	7 (100.0%)	22 (100.0%)	29 (100.0%)	

BMI: Body mass index, APACHE II Score: Acute physiology and chronic health evaluation II score (APACHE II), DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVA: Cerebro vascular accident

* *t*-test.

** Chi-square test ([a]Fisher's exact test).

ARDS, and endothelial cells were less affected. The reason for the lower incidence of other organ dysfunction might be less involvement of endothelial cells[6,13-16].

Gattinoni et al[7,11] published two similar articles. In the first article[7], they argued that COVID-19-associated ARDS was different from other ARDS, that even though ARDS met the Berlin criteria, COVID-19-associated pneumonia was a specific disease with specific phenotypes. In the first article, they divided the patients (n=16) into two groups as type-H and type-L based on their clinical findings, arterial blood gas analysis, and tomography images. In Gattinoni et al[7], type-L patients were those with isolated viral pneumonia with near-normal compliance. Although respiratory system compliance was high, they had severe hypoxemia, and it was stated that this hypoxemia was primarily due to ventilation/perfusion (VA/Q) mismatch. They stated that hypoxic pulmonary vasoconstriction disappeared, pulmonary blood flow regulation was impaired, lung gas volumes were high, and their recruitability was minimal. High PEEP and prone positioning in these patients did not open collapsed areas and improve oxygenation, but by rearranging the pulmonary perfusion distribution, they improved the ventilation-perfusion compatibility. They stated[7] that type-H patients were in the form of patients with classic ARDS, their compliance was low, their hypoxemia was more serious, and 20-30% of them were hospitalized in ICUs. They claimed that the low compliance (decreased gas volume, increase in recruitability) of these patients might be due to the natural course of the disease. Also, that the addition of continuous positive airway pressure (CPAP) or NIV support to these patients with high respiratory drives, strong inspiratory efforts, and high intrathoracic negative pressures might cause self-inflicted lung injury (P-SILI)[7].

In the second article[10], they suggested that most of the patients were admitted to the hospital with type-L, and some of them converted to type-H with worsening of COVID-19 pneumonia or with P-SILI. Therefore, they argued that patients with excessive inspiratory effort should be intubated early after being sedated and be ventilated with volumes higher than 6 mL/kg (predicted body weight) if the patients were hypercapnic. They claimed that these patients with good compliance could tolerate strain without the risk of ventilator-related lung injury (VILI)[10].

In this study, we examined patients who were treated in our ICU with the diagnosis of

Table II. Comparison of length of stay in the ward, and intensive care unit, the duration of noninvasive ventilation, day of intubation, the number of days in intubation, various treatment methods applied in patients, mortality rates.

	Type-H (n=7)	Type-L (n=22)	Total (n=29)	*p*
LOS of stay in ward (Pre- ICU) (day) [Median (min-max)]	0 (0-6)	4 (0-12)	1 (0-12)	0.142*
LOS of stay in the ICU (day) [Median (min-max)]	10 (1-66)	9,5 (1-84)	8,5 (1-84)	0.709*
NIV (day) [Median (min-max)]	2 (1-3)	3 (1-8)	3 (1-8)	0.250*
Day of intubation [Median (min-max)]	0.5 (0-2)	2.5 (0-4)	1 (0-4)	0.228*
Total intubation time (day) [Median (min-max)]	20.5 (1-66)	19.5 (1-114)	18 (1-114)	0.852*
PP (n, %)	3 (42.9%)	8 (36.4%)	11 (37.9%)	0.999*[a]
CS (n, %)	2 (33.7%)	7 (35.0%)	9 (34.5%)	0.999*[a]
IL 6 antagonist (n, %)	2 (28.6%)	7 (31.8%)	9 (31.0%)	0.999*[a]
Immunoplasma (n, %)	2 (28.6%)	6 (27.3%)	8 (27.6%)	0.999*[a]
Plasmapheresis (n, %)	3 (42.9%)	4 (%18.2)	7 (24.1%)	0.311*[a]
Exitus (n, %)	4 (57.1%)	5 (22.7%)	9 (31.0%)	0.158*[a]

LOS: Los of stay, NIV: Noninvasive ventilation, PP: Prone positioning, CS: Cytokine storm, IL 6: Interleukin 6
* Mann Whitney U test.
** Chi-square test ([a]Fisher's exact test).

COVID-19-related ARDS over a three-month period. Most of our patients were admitted to our unit with the type-L clinic as stated by Gattinoni et al[7,11] (type-L n=22, and type-H n=7). Seven of the type-L patients were intubated. The day they were intubated was later than in the type-H patients (3rd -4th day *vs.* 0-1st day). Five of the intubated patients (type-L) died.

Almost all patients with type-H were intubated (6/7). All these patients were intubated in the early period (0-1st days). Two of six patients were extubated. Noninvasive mechanical ventilation was applied to only one of the type-H patients without intubation and the patient recovered. Despite this difference in intubation rates, no statistically significant difference was found in mortality rates. A significant mortality difference may not have been detected due to the small number of patient outcomes.

As the 6-month period from the beginning of the pandemic passed and the observations of physicians on this issue increased, different articles were published on the pathophysiology and treatment of COVID-19. Jain and Doyle wrote a letter[8] to the editor to the Journal of Intensive Care Medicine in May 2020. In the letter, they claimed that the pathophysiology of COVID-19 should be carefully studied because Gattinoni et al[7] had failed to offer any logical mechanism while suggesting that pulmonary vasoplegia was key to the onset of severe hypoxemia, epithelial-endothelial events should be examined in detail to understand different stages of COVID-19 pneumonia, and P-SILI was not the only underlying reason for the transformation of COVID-19 pneumonia into severe ARDS. They continued saying that endothelial-epithelial interaction was the major factor in disease progression, SARS-CoV-2 entered the pulmonary capillaries and infected the pulmonary endothelial cells through the ACE-2 protein on the luminal surface with the deterioration of alveolocapillary membrane integrity, endothelial cells turned into a pro-inflammatory/procoagulant type, and this event accelerated alveolar and epithelial apoptosis, causing cytokine storm and enabled COVID-19 pneumonia to turn into ARDS[8,20].

In another article, Farkas et al[21] challenged Gattinoni et al's[10] view that the early stage of COVID-related ARDS was not recruitable. Farkas et al[21] presented a 7-step algorithm that examined the definition of ARDS from different perspectives, arguing that the prone position should be applied to patients according to the criteria in the PROSEVA study (patients with PaO_2/FiO_2<150 mmHg despite 12-24 hours ventilator optimization) instead of the Berlin criteria[21]. Farkas et al[21] emphasized that Gattinoni et al[10] found recruitability to be low in patients with COVID-19 because they performed the recruitment maneuver for a short time (a single breath). They did not have enough time to see how the patients would respond to higher mean airway pressures, and that this maneuver, while technically correct, ignored cascading recruitment that could occur over longer periods. Farkas claimed that if the definition of recrutability was made as in the PROSEVA study, it would be understood that early COVID-19 was actually recruitable because the increase in airway pressures could gradually improve oxygenation. Farkas stated that the implementation of CPAP with a helmet was generally considered

successful for COVID-19, and the working mechanism of CPAP was largely through recruitment, thus CPAP would not work if COVID-19 was not recruitable[21]. He stated that seeing COVID-19-associated ARDS as a different entity might lead to the need to abandon the current treatment and use a new approach, but without solid evidence, a new approach might be harmful. He recommended that patients with moderate-to-severe COVID-19-related ARDS be placed in the prone position, and that only patients with severe ARDS who were unresponsive to treatment should receive extracorporeal membrane oxygenation (ECMO) if they complied with the indications in international guidelines and if resources were available[21].

Limitations

The sample size of our study, which consisted of patients we treated in the 3 months after our COVID-19 ICU was opened, was small. This limitation may have prevented us from obtaining statistically significant results. Despite the limitation of our study, we believe that we do not have enough scientific evidence to evaluate COVID-19 pneumonia in different subtypes and determine treatment modalities according to these types. Larger, prospective studies with long-term results are needed on this subject.

Conclusions

In our study, we examined patients with COVID-19-related ARDS who we treated in our ICU during a three-month period. Our patients were divided into two groups as type-H and type-L according to their clinical findings and tomography imaging. Most of our patients were type-L when they were admitted to the unit. Although some of these patients showed clinical and radiologic progression to type-H, some remained at the same level. Among the intubated type-H and type-L patients, those conforming to the definition of PROSEVA were converted to the prone position. Type-L patients whose oxygenation deteriorated during NIV or high-flow oxygen therapy applications were also converted to the prone position. It was observed that the prone position was beneficial in improving oxygenation in both type-H and type-L patients. Seven of 22 type-L patients were intubated and five of these patients died. The lack of statistical difference between the two groups in terms of intubation times, hospital stays, cytokine levels, prone position application responses, and mortality rates may be due to the small number of patients. Significant results can be achieved with a larger number of patients.

Although initial reports reported that COVID-19-associated ARDS had features that distinguished it from classic ARDS, subsequent data showed that the respiratory mechanics of patients with ARDS were broadly similar with or without COVID-19. Therefore, mechanical ventilation based on evidence-based existing ARDS treatment, where adjustments are made according to patient-specific problems, may be more rational rather than typing and treating COVID-19-related ARDS. In this context, prone position applications that correct ventilation-perfusion mismatch in patients with moderate-to-severe ARDS may be beneficial in all patients with COVID-19. New studies conducted in different countries may guide the treatment of patients with COVID-19 in terms of prone position applications.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Informed Consent

The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

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