Original Article

COVID-19-Related Severe Heterogeneous Acute Respiratory Distress Syndrome: A Therapeutic Challenge

Hamidreza Jamaati[1], Lida Fadaizadeh[2], Batoul Khoundabi[3], Seyed Mohammad Reza Hashemian[1], Fatemeh Monjazabi[4], Alireza Jahangirifard[1], Mohammad Taghi Beigmohammadi[5], Behrooz Farzanegan[6], Seyedpouzhia Shojaei[7], Payam Tabarsi[8], Farzaneh Dastan[1,9], Seyed Ali Reza Nadji[10], Mihan Pourabdollah Toutkaboni[11], Majid Malekmohammad[6], Abdolreza Mohamadnia[1], Esmail Mortaz[12], Maryam Mirenayat[13], Fatemeh Yassari[14], Jalal Heshmatnia[14], Alireza Eslaminejad[1], Ali Akbar Velayati[15]

[1]Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2]Telemedicine Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3]Iran Helal Institute of Applied Science and Technology, Research Center for Health Mnagement in Mass Gathering, Red Crescent Society of the Islamic Republic of Iran, Tehran, Iran, [4]Department of Medical-Surgical Nursing, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [5]Anaesthesiology and Intensive Care Department, Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran, [6]Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [7]Department of Critical Care Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [8]Clinical Tuberculosis and Epidemiology Research Centre, National Research Institute for Tuberculosis and Lung Disease (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [9]Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [10]Virology Research Center, National Research Institute for Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [11]Pediatric Respiratory Diseases Research Center, National Research Institute for Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [12]Clinical Tuberculosis and Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [13]Lung Transplantation Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [14]Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [15]Mycobacteriology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Background: A heterogeneous pattern was detected in COVID-19 severe acute respiratory distress syndrome (ARDS) patients. The aim of this study was to define special features and individualized treatment modalities for this fatal infectious disease. **Methods:** Thirty-six patients diagnosed as COVID-19 severe ARDS were chosen. Lung mechanics (compliance), the extravascular lung water index (EVLWI) and pulmonary vascular permeability index (PVPI), and serum concentrations of immunology markers (interleukin [IL]-1β, IL-6, IL-8, ferritin, and C-reactive protein) were measured. Accordingly, individualized treatment consisting of Actemra, hemoperfusion (HP), continuous renal replacement therapy (CRRT), and extracorporeal membrane oxygenation (ECMO) was implemented for each patient. **Results:** Patients were categorized according to the lung compliance: 18 in "L type" with compliance >40 cc/cmH2O and 18 in "H type" with compliance ≤40 cc/cmH_2O. In 16 patients, standard mechanical ventilation management and antiviral therapy were unsuccessful; therefore, hemodynamic and immunity responses were evaluated. Results of transpulmonary thermodilution in L-type patients surprisingly showed EVLWI = 8.8 ± 1.3 (6.9–9.7) and PVPI = 2.4 ± 0.1 (2.2–2.6). In the H-type patients, five cases showed EVLWI = 8.7 ± 0.8 (7.5–9.8) and PVPI = 2.6 ± 0.3 (2.1–2.8) which were subclassified as "Ha type" and five cases with EVLWI = 17.5 ± 1.9 (15.7–20.6) and PVPI = 3.9 ± 0.4 (3.5–4.5) were named "Hb type". By measuring immunologic markers, these two groups were subdivided into high and low marker groups. Individualized treatment resulted in 2 survivals with Actemra, 1 with HP, 2 with HP + CRRT, and 1 with ECMO. **Conclusion:** According to the heterogeneity of COVID-19 severe ARDS presentation, which is due to various immunologic and hemodynamic responses, a systematic approach is an important and relatively successful strategy in choosing the appropriate treatment modality.

Keywords: COVID-19, heterogeneity, immunity, severe acute respiratory distress syndrome, thermodilution

Address for correspondence: Dr. Lida Fadaizadeh, Telemedicine Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail: lfadaizadeh@yahoo.com

ORCID: 0000-0002-0736-2130

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Introduction

Since the introduction of first cases of coronavirus-related acute respiratory distress syndrome (ARDS) in China,[1] various definitions, categorizations, and treatment modalities have been proposed by clinicians of affected countries.[2,3]

Clinicopathologically, ARDS is regarded as a severe inflammatory injury to the alveolar-capillary barrier, surfactant depletion, and loss of aerated lung tissue.[4,5] On the other hand, Berlin definition categorizes ARDS into mild, moderate, and severe considering its clinical course, deterioration of lung mechanics, and the PaO_2/FiO_2 ratio in mechanically ventilated patients which is considered the treatment guideline for these patients.[4,6]

Coronavirus-related ARDS seems not to be compliant with the previous definitions of this lung involvement. Interestingly, COVID-19 ARDS has demonstrated an atypical presentation during its clinical course. This special feature may be due to the fact that COVID-19 is a systemic disease which primarily affects the vascular endothelium and can eventually progress in a stepwise manner to multiorgan failure. The lungs can be affected similarly, starting from a more benign L-type ARDS with higher compliance on one side of the spectrum and deteriorating to a severe H type with low compliance and more typical of ARDS "baby lung" on the other side. However, with appropriate treatment, disease progression can be stopped at the L type or more intermediate stages.[7,8]

The mortality rate of COVID-19-related ARDS has been reported from 22% to 62% in the early Hubei province case series.[9] It seems that the current intensive care unit (ICU) management protocols implemented for ARDS patients are not effective for this type of disease. Therefore, using special treatment modalities tailored to vasoactive feature may reduce mortality.[4,8]

Targeting the immunologic system is one way of preventing disease progression in less severe cases. However, there is a very fine line between the rapidly evolving stages of the disease which requires special vigilance to keep pace with and thereafter change treatment method.

One novel method of ARDS patient evaluation available nowadays is transpulmonary thermodilution (TPTD) technique which measures the extravascular lung water (EVLW) and pulmonary vascular permeability index (PVPI), an indicator of vascular endothelium damage, and thus predicts the severity of disease. It has been proposed that this measurement will be regarded as one of the diagnostic and treatment criteria of ARDS in the near future.[10-12]

In this study, we described the clinical course of patients with COVID-19 severe ARDS admitted to multicenter ICUs. Furthermore, a systematic approach to treatment was defined considering the heterogeneous pattern in severe ARDS, the diagnostic criteria, individualized therapy protocols, and patient outcome. The main aim of this study was to define special features and new individualized treatment modalities for this fatal infectious disease.

Methods

Management strategies

This study was performed at ICUs of hospitals related to Shahid Beheshti University of Medical Sciences and was approved by the Research Ethics Committee of National Research Institute of Tuberculosis and Lung Diseases (IR.SBMU.NRITLD.REC.1399.034).

Eighty-nine mechanically ventilated patients from coronavirus ICUs of multiple centers during March through May 2020 were observed. According to Berlin criteria, all patients were considered as severe ARDS among which 36 were chosen for further evaluation according to the following inclusion criteria [Graph 1]:

1. Age older than 18 years
2. Intubated and under mechanical ventilation (MV)
3. No hemodynamic instability
4. PaO_2/FiO_2 ratio <100
5. Bilateral lung involvement
6. Polymerase chain reaction (PCR) test positive for coronavirus
7. Normal echocardiography
8. Blood culture and peripheral smear results negative for bacteria, PCR negative for influenza virus, and sputum smear negative for mycobacterium tuberculosis.

These patients underwent invasive protocols of MV with or without prone position. Medication protocol was basically similar in all patients consisting of hydroxychloroquine, azithromycin, lopinavir/ritonavir, and favipiravir or remdesivir. Furthermore, all patients were fully sedated with midazolam and fentanyl infusion and paralyzed with cisatracurium as neuromuscular blocker (NMB).

At this stage, lung compliance was evaluated for all patients, and accordingly, the cases were categorized into patients with high or low compliance. After an observation period of 3 ± 1 day, If there is no improvement, worsening of oxygenation indexes, or the need to increase plateau pressure for 48 hours, other diagnostic measures will be performed.

TPTD technique was used to evaluate extravascular lung water index (EVLWI) and PVPI. For this purpose, an arterial thermistor-tipped catheter was placed in the femoral artery and a central venous line in the superior vena cava region. EV1000®, Edwards Lifesciences, Irvine, CA, USA, was used for measurement.

Simultaneously, serum concentrations of inflammatory markers, C-reactive protein (CRP), ferritin, and interleukin (IL)-1β, IL-6, and IL-8 were measured by ELISA using Quantikine kits (R&D Systems). The operating procedure provided by the manufacturer was strictly followed.

Considering the results of initial lung compliance, EVLWI, PVPI, and inflammatory markers and cytokines, the patients were classified as L-type and H-type ARDS and further categorized

into subtypes Ha and Hb. Accordingly, individualized treatment consisting of anti-inflammatory therapy, extracorporeal membrane oxygenation (ECMO), hemoperfusion (HP), and continuous renal replacement therapy (CRRT) was utilized considering each patient's condition.

Medical anti-inflammatory therapy consisted of tocilizumab (Actemra) 8 mg/kg, at a maximum dose per infusion of 400 mg, with an intravenous drip time of 2 h was used to treat cytokine storm.

Considering the indication for CRRT in ARDS patients, it can remove the excess water accumulation in the lungs. But still, the rise of functional markers of kidneys (blood urea nitrogen [BUN] and creatinine) is the main purpose for this action.

Patients with kidney involvement combined with rise in cytokines were candidate for CRRT + HP. If normal or low levels of inflammatory markers or cytokines were combined with severe hypoxemia and lung tissue edema, CRRT + ECMO was chosen.

CRRT was performed with an ultrafiltration rate of 50–200 cc/h for 24 h every other day. PrismaFlex system and ST150, Baxter filter, were used. The blood flow rate was set at 50–250 mL/min, and the dialysis rate was set at 25–35 mL/kg/h.

In the combined group, patients underwent CRRT + HP cartridge using a HA380 membrane filter, which was changed routinely after 6 h over the course of 24 h.

During each blood purifying technique, continuous infusion of heparin (ranging from 5 to 20 units/kg/h) was used to keep blood from clotting, and to monitor the patient response to heparin infusion, an activated partial thromboplastin time ranging between 15 and 20 times, the normal was considered.

For patients undergoing venovenous ECMO, femoral or internal jugular cannulation was performed and Stöckert Centrifugal Pump Console (Sorin Group Deutschland GmbH Lindberghstraße, München, Germany) was used. The ECMO flow and sweep rate was adjusted to maintain peripheral capillary oxygen saturation >90%.

Statistical analysis

Data were analyzed using the statistical package IBM SPSS version 24.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) and also by GraphPad Prism 8 (GraphPad Software, San Diego, CA). The categorical variables were expressed as proportions and frequencies. Kolmogorov–Smirnov test (K–S test or KS test), as a nonparametric test, was used to test the normality assumption of continuous variable. The normal continuous variables were summarized as means and standard deviations while nonnormal continuous variables were displayed by median and interquartile range. *t*-test and Mann–Whitney *U*-test were used to compare mean/median between two groups. $P < 0.05$ was considered statistically significant.

Results

Of the total 89 patients with severe ARDS, 36 cases were selected according to the inclusion criteria of the study. The mean age of patients was 57.9 ± 16.8 (26–86) years, and 28 (77.8%) of the patients were male. Comorbidities of patients are mentioned in Table 1.

Mean values of MV, ICU managements performed, respiratory mechanics and its relation to survival status, and overall outcome of patients are mentioned in Table 1.

Table 1: Characteristics of mechanically ventilated patients and outcomes

Baseline characteristics of the patients	Patients (*n*=36)
Mean age (range)	57.9±16.8 (26-86)
Sex, *n* (%)	28 (77.8)
Male	8 (22.2)
Female	18.5±3.0 (9-27)
Mean APACHE II (range)	
Risk factors, *n* (%)	7 (19.4)
HTN	1 (2.8)
CLL	3 (8.4)
DM	2 (5.6)
DM + HTN	2 (5.6)
Lymphoma	1 (2.8)
COPD	1 (2.8)
Obesity	19 (52.8)
Without risk	Patients (*n*=36)
Mechanical ventilation characteristics	
Compliance (ml/cmH_2O), median (IQR)	40 (34-60)
PaO_2/FIO_2 (mmHg), mean (range)	64.7±23.9 (28-100)
ΔP (cmH_2O), mean (range)	11.7±3.5 (6-17)
P_{plat} (cmH_2O), mean (range)	22.8±4.9 (13-29)
Vt (ml), median (IQR)	500 (457-535)
Tracheostomy, *n* (%)	5 (13.9)
Outcomes	
Intubation time (days), median (IQR)	4 (3-8)
Length stay in ICU (days), mean (range)	7.9±3.0 (3-14)
Length stay in hospital (days), mean (range)	11.6±6.1 (3-24)
Survival status *n* (%)	
Survived	15 (41.7)
Died	21 (58.3)
ICU management	
Invasive mechanical ventilation	36 (100.0)
Prone position	15 (41.7)
Neuromuscular blockade	36 (100.0)
Echocardiogram	36 (100.0)
Actemra	2 (5.6)
Hemoperfusion	2 (5.6)
Extracorporeal membrane oxygenation	7 (19.4)
Hemoperfusion and continuous renal replacement therapy	3 (8.3)
Extracorporeal membrane oxygenation and continuous renal replacement therapy	2 (5.6)

Plus-minus values are means±SD (range). Vt: Tidal volume, CLL: Chronic lymphocytic leukemia, HTN: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, IQR: Interquartile range, SD: Standard deviation

Considering the lung compliance, patients were categorized into two groups: 18 in "L type" with compliance >40 cc/cmH2O and 18 in "H type" with compliance ≤40 cc/cmH_2O [Table 2].

For all patients in the L group, MV setup consisted of a tidal volume of 7–9 cc/kg and a low PEEP/FIO_2. All patients received NMB and five were prone positioned. Six patients died during the initial process. Nine patients were weaned from MV and again three patients did not survive for further evaluation. Six patients entered the next stage of evaluation after 3 ± 1 days of no progress [Graph 2].

For the H-type patients, MV setup was assist-control mode with 6–8 cc/kg tidal volume, high PEEP, and plateau pressure ≤30 mmHg. All patients received NMB and ten were put into prone position. Eight patients died before further evaluation and ten entered the next stage of evaluation consisting of TPTD, inflammatory marker, and cytokine measurement after 3 ± 1 days of no progress [Graph 2].

Results of TPTD in L-type patients surprisingly showed EVLWI = 8.8 ± 1.3 (6.9–9.7) and PVPI = 2.4 ± 0.1 (2.2–2.6), which means having dry lungs. In the H-type patients, five cases showed EVLWI = 8.7 ± 0.8 (7.5–9.8) and PVPI = 2.6 ± 0.3 (2.1–2.8), which were subclassified as "Ha type," and five cases with EVLWI = 17.5 ± 1.9 (15.7–20.6) and PVPI = 3.9 ± 0.4 (3.5–4.5), which were considered classic severe ARDS, were named "Hb type" with statistically significant differences of values according to Table 2.

The final therapeutic decision was premised on the aforementioned subtyping and the results of cytokine and inflammatory marker measurement [Graph 2]. Accordingly, two L-type patients with EVLWI <10 and PVPI <3 and high level of markers were given Actemra 400 mg/intravenous (IV) infusion over 2 h to suppress their inflammatory responses, who survived. Four patients of the same group with low level of markers underwent ECMO but unfortunately three patients died and one survived.

The five patients in Ha type was classified into two groups: two patients with increased markers who underwent HP and one of them survived and 3 patients with decreased markers who underwent ECMO but unfortunately died. Of the five patients with Hb type, three patients had increased markers along with BUN and creatinine [Graph 2] who underwent HP and CRRT among which two patients survived. Two patients had low markers and BUN and creatinine [Graph 2], and therefore, ECMO and CRRT were performed, but unfortunately, both of them died [Graph 2].

The serum levels of CRP, IL-1β, IL-6, IL-8, ferritin, and PaO_2/FiO_2 ratio, BUN, and creatinine before and after therapeutic modalities are demonstrated in Graph 2. Surprisingly cytokine and inflammatory agents and PaO2/FiO2 ratio showed dramatic improvement. The only exception was the significant rise in IL6 level in patients taking Actemra, which was due to its release in serum after drug-related receptor blockade.

Discussion and Conclusion

Management of coronavirus-induced ARDS has become challenging during the recent months, and none of the proposed medication protocols have been proven effective, therefore, the mortality of this disease still remains high.[13-17] Finding the best management protocol is still the main goal of most intensive care physicians. The aim of this study was to initially define the clinical situation of our patients, regarding pathophysiology, immunologic status, and extent of lung involvement, and accordingly implement the best therapeutic strategy among all available options.

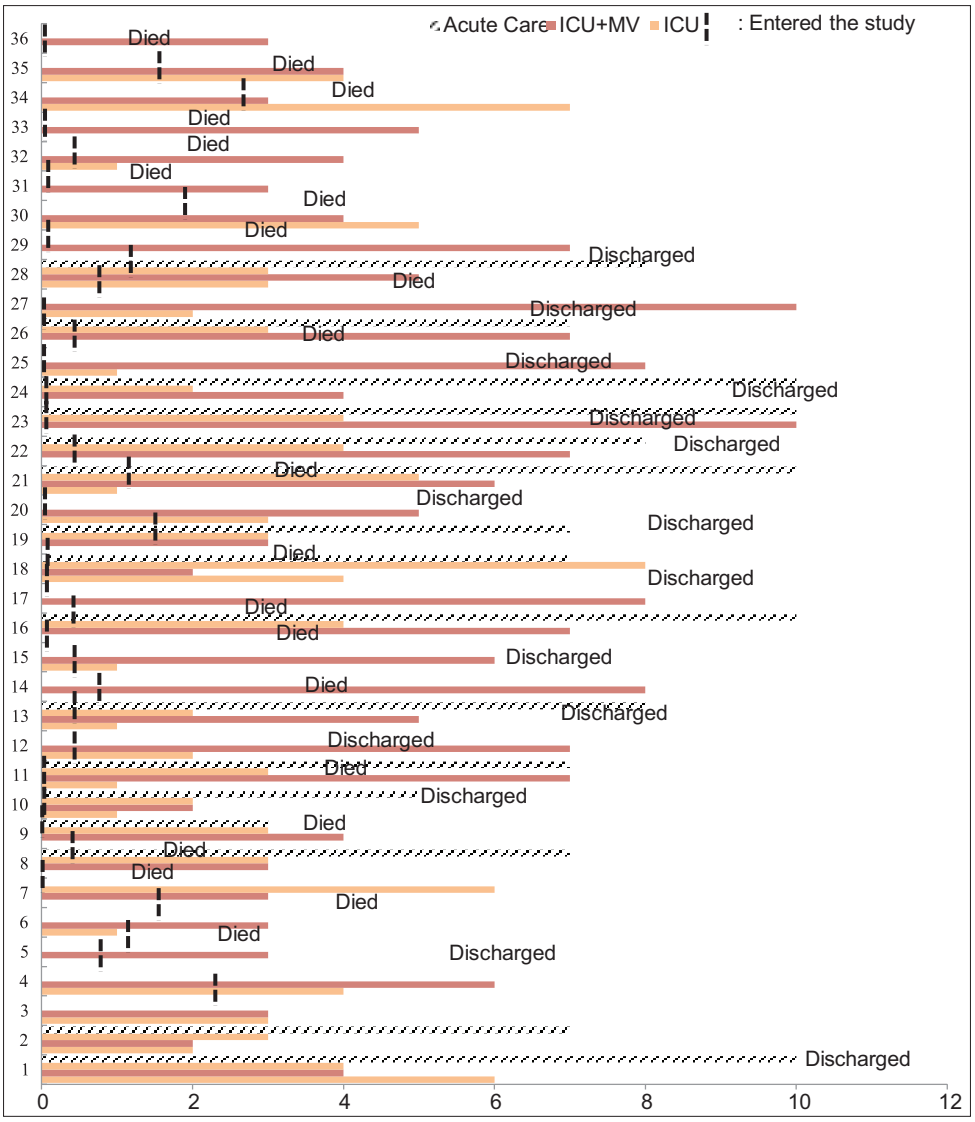
Recent studies have shown that lung involvement in COVID-19 patients, especially the ones progressing to severe ARDS, is not uniform and has a heterogeneous presentation.[8] Disrupted vasoregulation and endothelium result in a spectrum of lung involvement starting from high compliance lungs on one end to low compliance on the other end of the spectrum. Another related feature is a highly activated coagulation cascade which results in micro/macrothrombosis in lung and other organs.[8]

In our study, we categorized patients as severe cases with poor oxygenation, high compliance "L-type", and the rest with poor compliance as "H type." Measuring EVLWI and PVPI in patients with L-type ARDS, that is, patients with high compliance and

Table 2: Transpulmonary thermodilution technique results and mortality in patients requiring further assessment

Items	L Type (*n*=18)	H Type (*n*=18)		*P*
	Assessment required (*n*=6)	Assessment required (*n*=10)		
	EVLWI <10 and PVPI <3	Ha (*n*=5) EVLWI <10 and PVPI <3	Hb (*n*=5) EVLWI >10 and PVPI >3	
Mean EVLWI (ml/kg) (range)	8.8±1.3 (6.9-9.7)	8.7±0.8 (7.5-9.8)	17.5±1.9 (15.7-20.6)	<0.050*
Mean PVPI (range)	2.4±0.1 (2.2-2.6)	2.6±0.3 (2.1-2.8)	3.9±0.4 (3.5-4.5)	<0.050*
Mortality before assessment and intervention (3±1 days)	3 (16.7)	8 (44.4)		0.048$
Total mortality	6 (33.3)	15 (83.3)		0.002$

*Significant at level 0.05 for the comparison of three groups, $Significant at level 0.05 for two group high and low compliance. L Type: Compliance >40 and decrease in the elastance. H Type: Compliance <40 and increase in the elastance. EVLWI: Extravascular lung water index, PVPI: Pulmonary vascular permeability index



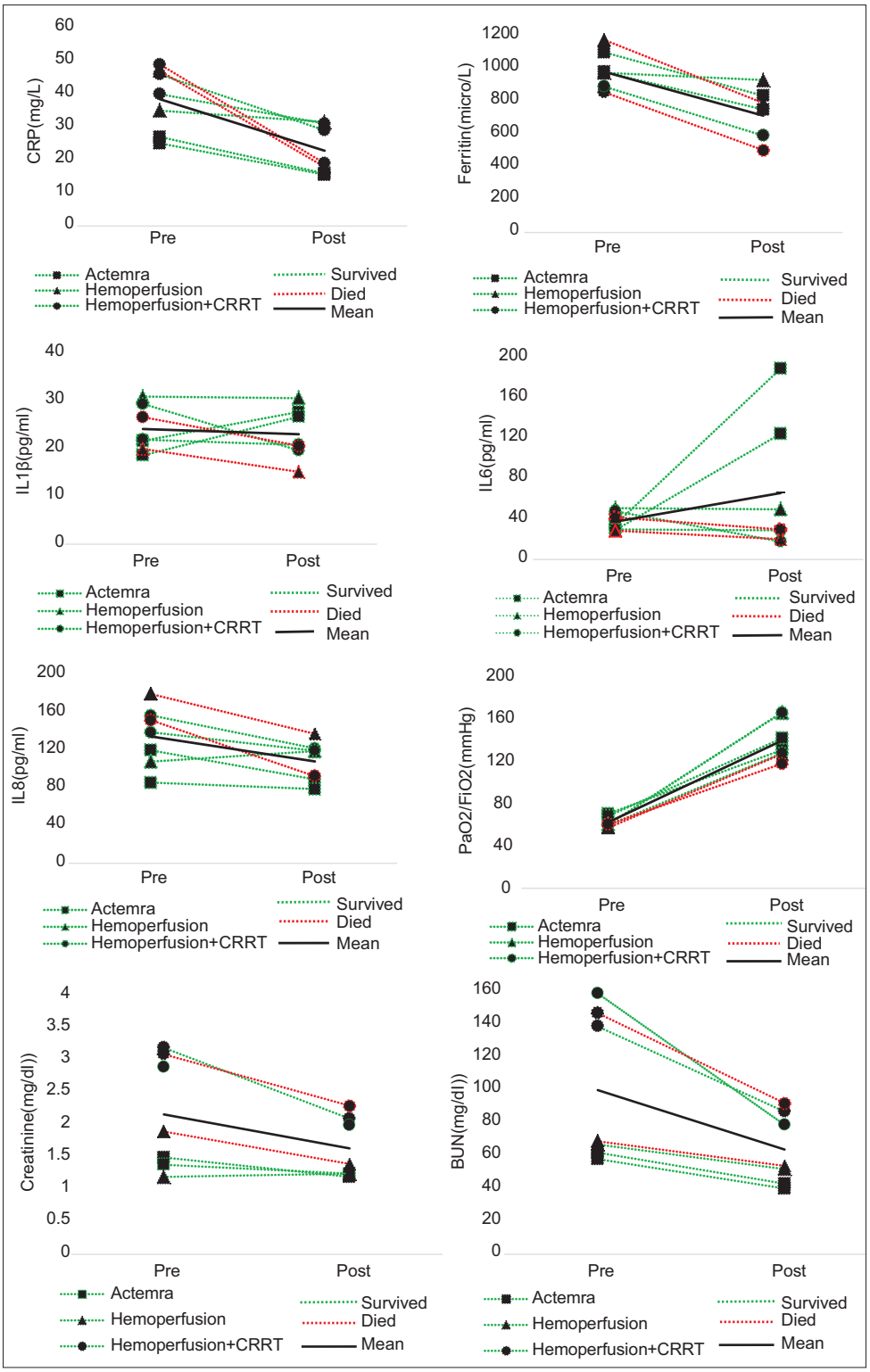
Graph 1: Outcome of individual patients included in the study

low elastance lung mechanics, revealed that these patients have low EVLWI and PVPI values and were, therefore, considered as "dry lung ARDS" cases. Similarly, the H-type patients with low compliance and high elastance lung tissue also underwent EVLWI and PVPI evaluation, and interestingly, these patients also showed diverse patterns: first – "Ha type" and second – "Hb type" with classic severe ARDS "wet lung" pattern.

According to Gattinoni, this atypical and heterogeneous pattern of severe ARDS may be progressing stages of one disease, and the illness evolves from L type to more severe H type.[7,8,18] Some of the factors responsible for this event may be host response, severity of infection, comorbidities, immunocompromise, and many others.[19] However, our results suggest that there may be another explanation for this condition and that each type and subtype of ARDS may be an independent illness in its own right, so it requires individual management. This may explain the unresponsiveness of some patients to the standard therapies that are implemented for all ARDS patients and on the contrary their positive response to some treatment modality individually selected for them.

Medically blocking of IL-related receptors, which is basically a method of choice for patients with rheumatologic diseases,[20,21] has been proposed as a treatment for COVID-19 ARDS patients.[22] It is presently unclear if elevated IL-6 level is detrimental or beneficial for disease control, but blocking its receptors has been considered effective in symptom control.[22,23] Accordingly, the use of IL-6 or IL-6-receptor-blocking antibodies such as tocilizumab (Actemra) has been encouraged.[24,25] In our study, two patients in the L type had increased levels of IL-6 and were given Actemra. After drug administration, the level of IL-6 showed a dramatic rise relating to receptor blockade and rise of free IL-6. Fortunately, these patients were weaned from MV and survived. Similarly, in another case study in France, Actemra showed promising results.[26]

Surprisingly, some patients with severe ARDS do not present with this typical immunologic profile, and cytokine levels are



Graph 2: Change of cytokines, inflammatory markers , PaO_2/FiO_2, BUN, and creatinine before and after treatment for 7 patients with abnormal values by survival status

not as prominent. Therefore, it is thought that these cases are immunologically exhausted or immunocompromised. One hypothesis is that in these patients, exhaustion may be related to T-cell function, which eventually ends in poor prognosis.[27-29]

In the L type, four cases had low cytokine levels and severe hypoxemia and had to undergo ECMO treatment, among which only one survived. Patients with more typical ARDS presentations, namely Ha type and Hb type in our study,

needed a totally different approach. Results showed that in both subtypes, we had patients with high and low levels of inflammatory agents and cytokines which directly influenced the severity and eventually choice of therapeutic modality.

According to experts, extracorporeal organ support is considered the mainstay of COVID-19 patient management in ICU.[30] CRRT is usually considered a renal replacing therapy, but this technique can eliminate the excess cytokines and inflammatory markers by filtering the blood and, therefore, reduce the detrimental action they have on end organs.[31-35] Furthermore, HP technique which is a blood purification treatment has been specified for patients with COVID-19, and it has been proposed that using this method should be goal oriented and in some cases combined with CRRT. Considering the use of this combination (HP + CRRT), we found no similar studies in literature, but our experience showed that two out of three patients survived, and therefore, it seems that this combined technique is beneficial for severe ARDS patients and improves their overall status and survival.

The last but not least method for increasing ARDS patient survival is ECMO which has been known as an oxygen replacement therapy for severely hypoxemic patients (PaO_2/FIO_2) and as a support for patients with cardiac-related hemodynamic instability. However, the effectivity of this method in COVID-19 patients needs to be worked on. As ESLO guideline indicates, this method should not be regarded as a universal treatment for all severe ARDS patients. Cases should be highly selected, and patients with end-organ damage and long period of MV are not considered good candidates.[36-38] Although not many studies have reported the outcome of ECMO in COVID-19 ARDS treatment, the available studies did not have favorable outcome and the mortality rate was 82.3%.[39] A report from Shanghai also showed not so promising results but has recommended ECMO as an integral care provided for these patients but with strict protocols.[40] Reports from other centers have also had similar results.[41] A recent Euro Extracorporeal Life Support Organization Adult ECMO-COVID-19 Patients Survey has been started regarding the use of ECMO for COVID-19 in Europe and data is being gathered to date.[42]

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Nil.

Conflicts of interest

There are no conflicts of interest.

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