Austin Journal of Infectious Diseases

Open Access

Austin Publishing Group

Research Article

Helmet Continuous Positive Airway Pressure in COVID-19 Related Acute Respiratory Distress Syndrome in Respiratory Intermediate Care Unit

Piluso M[1]*, Scarpazza P[1], Oggionni E[1], Celeste A[1], Bencini S[1], Bernareggi M[1], Bonacina C[1], Cattaneo R[1], Melacini C[1], Raschi S[1], Usai P[1], Sioli P[2], Bellini R[3], Salandini MC[3], Iozzia M[1], Di Franco G[1] and D'Arcangelo F[1]

[1]Division of Respiratory Diseases with Intermediate Respiratory Intensive Care Unit, Vimercate Hospital, Vimercate, Monza e Brianza, Italy

[2]Department of Cadiopulmonary and Neuromotor Rehabilitation, Seregno Hospital, Seregno, Monza e Brianza, Italy

[3]Department of Surgery, General Surgery Division, Vimercate Hospital, Vimercate, Monza e Brianza, Italy

***Corresponding author:** Piluso M, Respiratory Diseases and Respiratory Intermediate Care Unit, Vimercate Hospital, via SS. Cosma e Damiano 10, 20871 Vimercate (MB), Italy

Received: September 20, 2021; **Accepted:** October 27, 2021; **Published:** November 03, 2021

Abstract

Background: The SARS-CoV-2 outbreak spread in Lombardy Region (Italy) rapidly saturating intensive care unit beds, forcing the application of noninvasive respiratory support in RICU.

Objectives: We aimed to analyze the effects of helmet CPAP in COVID19-related ARDS in RICU. The primary outcome was CPAP failure, defined as the occurrence of either intubation or death due to any cause during RICU stay; the secondary one was the identification of factors related to patients' prognosis.

Methods: 150 consecutive patients with ARDS due to COVID-19 and referred to Vimercate Hospital (MB) between March and May 2020 were enrolled. All patients were treated with helmet CPAP. Demographics, clinical and laboratory tests and blood gas analysis were collected.

Results: Patients had a mean (SD) age of 62 (±11) years. The worst PaO_2/FiO_2 ratio during continuous positive airway pressure stratified the subjects in mild (26/150), moderate (39/150) and severe (85/150) ARDS. Most of patients were treated with systemic corticosteroids (79%). 93 patients (62%) were successfully treated while 57 (38%) failed; of the latter, 32 patients were transferred in the intensive care unit to receive invasive mechanical ventilation. Dimer test and ferritin at admission, use of steroids, P/F in oxygen at admission and age were independently associated with CPAP failure. The severity of ARDS and the use of steroids strongly correlate with clinical outcomes. Mortality rate in our cohort of patients was 28%.

Conclusions: The application of helmet CPAP in RICU and the administration of corticosteroids in COVID19-related ARDS are associated with satisfactory clinical outcomes.

Keywords: Helmet CPAP (Continuous Positive Airway Pressure); COVID-19; ARDS (Acute Distress Respiratory Syndrome); RICU (Respiratory Intermediate Care Unit); Corticosteroid

Abbreviations

CPAP: Continuous Positive Airway Pressure; COVID-19: Coronavirus Disease-19; ARDS: Acute Distress Respiratory Syndrome; RICU: Respiratory Intermediate Care Unit; P/F: PaO_2/FiO_2 ratio; PaO_2: Arterial Oxygen Tension; FiO_2: Inspiratory Oxygen Fraction; WHO: World Health Organization; ICU: Intensive Care Unit; NIV: Non-Invasive Ventilation; IMV: Invasive Mechanical Ventilation; HFNC: High Flow Nasal Cannula; PEEP: Positive End-Expiratory Pressure; BPM: Breaths Per Minute; DNI: Do-Not-Intubate; SD: Standard Deviations; IQR: Interquartile Ranges; CT: Computed Tomography; RCT: Randomized Controlled Trial; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; APACHE: Acute Physiology and Chronic Health Evaluation; IL: Interleukin; HR: Hazard Ratio; CI: Confidence Interval

Introduction

In December 2019, a novel coronavirus–related pneumonia has been firstly reported in the city of Wuhan, China [1]. The World Health Organization (WHO) declared the outbreak of a pandemic on 11th March 2020 [2].

Although in most cases it causes very mild symptoms, approximately 20% of patients develops significant respiratory disease, with bilateral interstitial pneumonia [3]. Acute Respiratory Distress Syndrome (ARDS) is a major complication of COVID-19 that occurs in 20-41% of patients with severe disease [4].

It is well known that, despite advances in supportive care, mortality rates of ARDS in Intensive Care Unit (ICU) are still high (35-40%) and increase with the severity of hypoxemia (27% in mild, 32% in moderate, 45% in severe ARDS as defined by the Berlin definition) [5].

The frequent lack of ICU beds has pushed the authorities to create respiratory intermediate care units (RICU), in order to face the increasing number of patients with ARDS needing respiratory support and monitoring [6].

Non-Invasive Ventilation (NIV) is a reasonable initial

Citation: Piluso M, Scarpazza P, Oggionni E, Celeste A, Bencini S, Bernareggi M, et al. Helmet Continuous Positive Airway Pressure in COVID-19 Related Acute Respiratory Distress Syndrome in Respiratory Intermediate Care Unit. Austin J Infect Dis. 2021; 8(4): 1061.

approach in less severely ill patients with ARDS [7]; the beneficial role of Continuous Positive Airway Pressure (CPAP) in acute, non-hypercapnic respiratory insufficiency is well known in terms of improvement in oxygenation and reduction in endotracheal intubation rate as compared to oxygen therapy, even if no difference in outcomes is demonstrated [8,9].

One of the main issues in CPAP treatment failure is the interface, as technical problems and compliance often represent a major concern; in this perspective, the helmet has been proposed, as an alternative to the facemask and evidence of its superiority is reported [10].

In ARDS due to COVID-19 infection treated with invasive mechanical ventilation (IMV) in ICU, prognosis seems to be even worse than non COVID-19 related ARDS, as reported in numerous recent published data: a 28-day mortality exceeding 60% emerges in Wuhan City Hospital [11], at least 50% in Seattle region [12] and, from the experience in New York, 76.4% in the 18-to-65 and 97.2% in older than 65 groups respectively [13].

In Lombardy, northern Italy, the COVID-19 pandemic has led to a substantial increase in the number of patients admitted to hospital with ARDS, causing a stressful burden on the healthcare system, particularly on ICUs, with almost 10% of the hospitalized COVID-19 patients needing invasive respiratory assistance, rapidly saturating resources and the availability of ICU beds [6].

To avoid aqueous droplets dispersion during active disease, the use of high flow nasal cannula (HFNC) oxygen therapy and NIV is generally not recommended [14]. Nevertheless, in a recent overview of the indications for the healthcare workers' protection from SARS-CoV-2 infection, Ferioli and co-workers showed how the helmet have negligible air dispersion with a tight air cushion around the neck-helmet interface [15].

The aims of our study were the evaluation of helmet CPAP efficacy in COVID19-related ARDS in our RICU and the identification of factors related to patients' prognosis.

Bed's quick filling and high mortality rate of these patients in ICU led to the need of treating this disease with a non-invasive ventilation approach in a proper specialized environment (RICU).

Materials and Methods

During COVID-19 pandemic, 230 patients were admitted in the Pulmonology Division at Vimercate Hospital, Lombardy, Italy, between March and May 2020 with a diagnosis of COVID-19 pneumonia, defined as the presence of interstitial pulmonary infiltrates and a positive SARS-CoV-2 nasal-pharyngeal swab. Of these, 150 were enrolled in our study, selected for having ARDS criteria satisfied during hospital-stay as defined by the Berlin definition (P/F ≤300 with PEEP ≥5cm H_2O); all of the 150 patients were treated with helmet CPAP in RICU; patients aged more than 80 and those who never developed ARDS were excluded.

In our Hospital the ad hoc RICU dedicated to patients with COVID-19-related severe respiratory failure (implemented with 50 beds) was characterized by negative pressure rooms, continuous multiparametric monitors, access to high flow oxygen and air source with blender systems to obtain adequate values of delivered FiO_2, on-site life support and intubation kit, a nurse: patient ratio between 1:6-1:10 and active full day shift run by pulmonologists.

This is a monocentric observational study. The primary outcome was CPAP failure, defined as the occurrence of either intubation or death due to any cause during RICU stay; the secondary one was the identification of factors related to patients' prognosis.

All patients included in the study were hemodynamically stable, had a normal Glasgow Coma Scale score, did not show multiorgan system failure, acidosis or hypercapnia [16], and were poor respondent to treatment with high flows oxygen therapy with Venturi mask or non-rebreathing oxygen mask (SpO_2 < 92%, respiratory rate > 24 Breaths Per Minute (BPM), $paCO_2$ <35mmHg, thoraco-abdominal dyssychrony).

Indications to intubation were a reduced level of consciousness, altered breathing mechanic, hypoxiemia and hemodynamic instability.

The Do-Not-Intubate (DNI) order was the decision to withhold intubation and to use CPAP as "ceiling" treatment considering patient's characteristics and the reduced availability of ICU beds. "DNI" criteria was considered only in the cases needing intubation by intensivists, not at the admission.

Helmet CPAP was delivered with pressure between 7.5-15 cm H_2O (mean pressure 13 ± 1.91) and FiO_2 variable between 50 and 99% (mean FiO_2 81% ± 12.37) with a target oxygen saturation of 92% or more. During helmet CPAP therapy patients were moved, when feasible, into prone position, which was maintained for a minimum duration of 2 hours. During each blood, gas control the PaO_2/FiO_2 ratio was re-calculated. The most critical patients were selected by pulmonologists and evaluated by intensivists to decide ICU transfer.

Qualitative and quantitative variables were summarized with frequencies (absolute and relative, percentage) and central tendency (means and medians) and variability (standard deviations, SD, and interquartile ranges, IQR) indicators, depending on their parametric distribution. A chi-squared or Fisher exact test was computed for qualitative variables; Student t test or Mann Whitney was used for quantitative variables with a parametric or non-parametric distribution, respectively. Survival analysis were performed with Kaplan – Meier method. A Cox proportional hazards regression analysis was carried out to assess the relationship between the composite primary outcome and independent variables. A two-tailed p-value less than 0.05 was considered statistically significant. Statistical computations were performed with R Studio.

Results

Demographics and patients' characteristics are summarized in Table 1.

At admission, most patients presented an ARDS pattern: ARDS was mild in 50 (33%), moderate in 60 (40%) and severe in 15 (10%). There is a small number of patients enrolled (25/150, 17%) who did not fulfill ARDS criteria at admission but, as shown in Figure 4, all of them developed ARDS during hospital stay (we define this initial condition as "pre-ARDS").

Table 1: Baseline characteristics, hospital treatment and outcomes of the study population according to CPAP failure or success.

	Total	Success	Failure	p-value
Number of patients	150	93 (62%)	57 (38%)	-
Demographics				
Meanage	62 ± 11	60 ± 11	65 ± 9	0.005**
Male sex	123 (82%)	75 (81%)	48 (84%)	0.739
Neversmokers	104 (69%)	69 (74%)	35 (61%)	0.143
BMI ≥ 24.5	48 (32%)	33 (35%)	15 (26%)	0.323
Comorbidities and prognostic score				
Hypertension	72 (48%)	43 (46%)	29 (51%)	0.701
Ischemic cardiac disease	15 (10%)	6 (6%)	9 (16%)	0.116
Cardiovascular diseases	21 (14%)	9 (10%)	12 (21%)	0.088
Hypercholesterolemia	28 (19%)	12 (13%)	16 (28%)	0.036*
Diabetes	11 (7%)	6 (6%)	5 (9%)	0.749
Tumors	6 (4%)	1 (1%)	5 (9%)	0.030*
COPD/asthma	14 (9%)	5 (5%)	9 (16%)	0.044*
Chronicrenalfailure	1 (0.7%)	0	1 (1.8%)	-
APACHE II score	8.6 (2.1)	8.3 (2.2)	9.1 (1.8)	0.015*
Pharmacological treatment duringhospitalization				
Antivirals	104 (69%)	61 (66%)	43 (75%)	0.277
Remdesivir	4 (2.7%)	2 (2.2%)	2 (3.5%)	0.635
Azytromicin	37 (25%)	26 (28%)	11 (19%)	0.318
Tocilizumab	11 (7%)	6 (6%)	5 (9%)	0.749
Hydroxychloroquine	145 (97%)	91 (98%)	54 (95%)	0.369
Steroids	118 (79%)	81 (87%)	37 (65%)	0.003**
Heparin	136 (91%)	87 (94%)	49 (86%)	0.151
Outcomes				
DNI order	22 (15%)	1 (1%)	21 (37%)	-
Intubation	32 (21%)	0 (0%)	32 (56%)	-
Survived	108 (72%)	93 (100%)	15 (26%)	-
Blood tests				
Dimer test (admission) (ng/mL)	4365 ± 9423	1617 ± 4685	7113 ± 13699	0.007**
Dimer test (worst) (ng/mL)	8258 ± 12382	3130 ± 6249	13386 ± 16848	-
Ferritin (admission) (ng/mL)	2193 ± 1943	1378 ± 984	3007 ± 2613	<0.001***
Ferritin (worst)(ng/mL)	2750 ± 3115	1772 ± 1810	4362 ± 4039	-
IL-6 (admission) (pg/mL)	67 ± 83	41 ± 55	93 ± 103	0.06
IL-6 (worst)(pg/mL)	362 950 ± 338.2	111 ± 196	613 ± 1366	-
CPAP treatment				
PEEP	13 ± 1.91	12 ± 1.90	14 ± 1.65	<0.001***
FiO_2	81 ± 12.37	77 ± 12.6	88 ± 8.66	<0.001***
Days of CPAP	8 ± 5.00	9 ± 5.1	6 ± 4.1	-
P/F (in oxygen)	132 ± 64.4	144 ± 68.2	114 ± 53.3	0.004**
First P/F (in CPAP)	218 ± 105.8	235 ± 109	189 ± 95	0.008**
Worst P/F (in CPAP)	123 ± 73.8	156 ± 74.9	68 ± 16.6	<0.001***
Number of pronedpts	73 (49%)	37 (40%)	36 (63%)	0.824
P/F post-pronation (in CPAP)	242 ± 119.6	271 ± 120	184 ± 96.8	<0.001***

Data are presented as n (%), mean ± standard deviation, unless otherwise stated. BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; APACHE: Acute Physiology and Chronic Health Evaluation; DNI: Do-Not-Intubate; IL: Interleukin; PEEP: Positive End-Expiratory Pressure; P/F: PaO_2/FiO_2 Ratio; PaO_2: Arterial Oxygen Tension; FiO_2: Inspiratory Oxygen Fraction; CPAP: Continuous Positive Airway Pressure. Besides; *: Statistically Significant p-Value < 0.05; **: Statistically Significant p-Value < 0.01; ***: Statistically Significant p-Value < 0.001.

Table 2: Multivariate analysis of factor associated with helmet CPAP failure.

Factor	p-Value	Statistically significant	HR=exp (coef)	95% CI
Dimer test (admission)	0.00230	**	1.000	1.000;1.000
Ferritin (admission)	0.03973	*	1.000	1.000;1.000
Steroids	0.00048	***	0.24	0.108;0.353
P/F in oxygen at admission	0.00393	**	0.99	0.984;0.997
Age	0.02558	*	1.04	1.005;1.083

HR: Hazard Ratio; HR = 1 no effect, HR <1 reduction of risk, HR>1 increase of risk, 95% CI = 95% Confidence Interval.

Most of the patients were treated with systemic corticosteroids (79%, receiving methylprednisolone at a dose of 1 mg/kg a day for 10 days than gradually reduced). Other drugs administered are summarised in Table 1.

Ninety-three patients (62%) were successfully discharged without need of invasive support, while in 57 subjects (38%) non-invasive treatment failed; of those, 25 died without intubation while 32 were transferred in ICU to receive IMV. Between the two groups (success vs failure), we found significant statistical difference in mean age (60 ± 11 *vs.* 65 ± 9 respectively, p-value 0.005).

Of the 26 patients who died in the RICU ward: 21 with a DNI order and 5 with sudden deaths (2 massive pulmonary thromboembolism, 1 sudden cardiac arrest, 1 acute cardiac ischemic attack, 1 cerebral stroke after ICU discharge).

Complications developed during RICU stay included: 4 supraventricular tachyarrhythmias, 5 Pulmonary Embolisms (PE) (2 fatal and 3 non-fatal), 5 thrombosis (1 fatal stroke, 1 cerebral transient ischemic attack, 1 popliteal thrombosis, 1 fatal cardiac ischemic attack, 1 thrombosis in descending aorta), 1 fatal diffuse intravascular coagulation, 1 acute renal failure, 2 bleedings treated with embolization, 2 pneumothoraxes (1 fatal and 1 non-fatal) and 2 episodes of pneumomediastinum (1 fatal and 1 non-fatal), 1 cardiac arrest with possible non demonstrated PE.

The PaO_2/FiO_2 ratio in CPAP at presentation is significantly different between the two groups, as lower P/F are associated with a worse prognosis (mean P/F 189 vs 235, p-value 0.008) and this is even more evident if we consider the worst P/F in CPAP during hospital staying (mean value of 68 vs 156, p-value < 0.001).

The severity of ARDS at admission strictly correlates with the clinical outcome (p-value 0.0047) (Figure 1).

The most important inflammatory biomarkers collected at admission were higher in those patients who failed CPAP. We have defined 4 levels for ferritin (1: ≤1000 ng/mL; 2: 1000-1500; 3: 1500-2000; 4: >2000) and 3 for dimer-test values (1: ≤ 500 ng/mL; 2: 500-1000; 3: >1000) considering the two biomarkers as qualitative variables (Figure 2). We found a statistically significant difference between the surviving curves in both cases as shown in Figure 2.

We finally searched for a correlation between the P/F ratio and the value of the two biomarkers recorded and we observed a prognostic relevance in dimer-test only: an increase in dimer-test class is associated to a lower P/F.

In our study 96 patients (almost 65%) were put in prone position

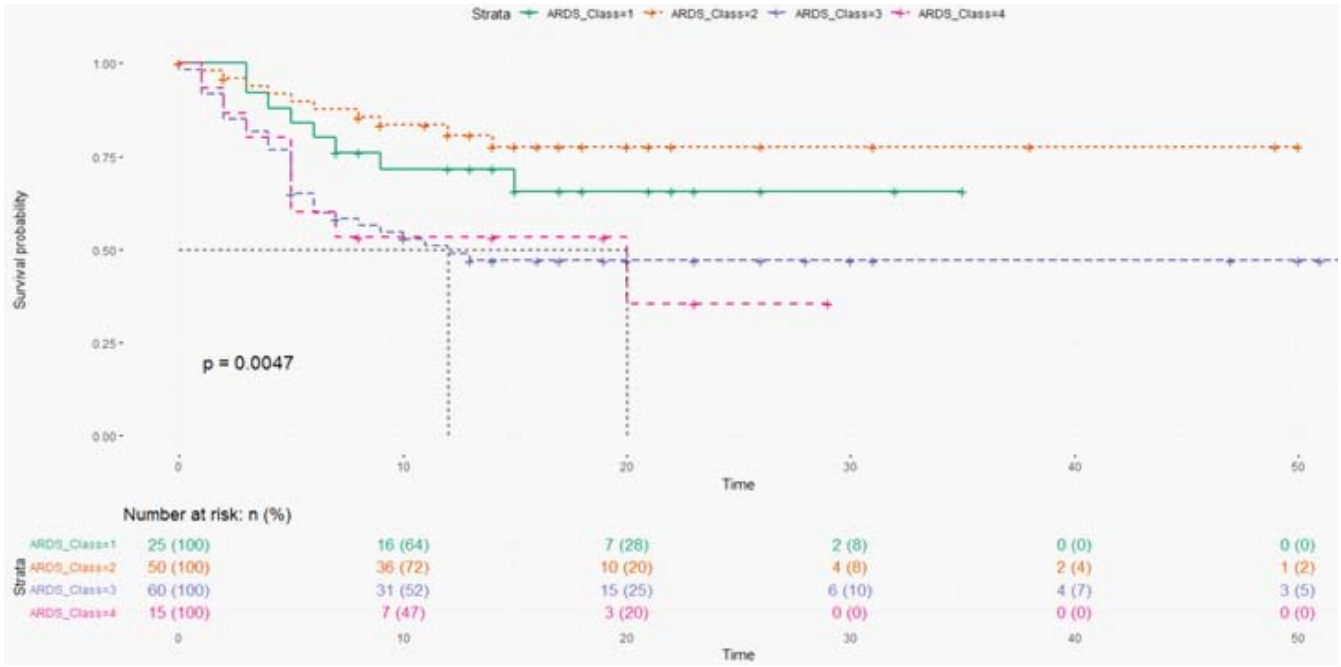

Figure 1: Survival analysis according to ARDS class.

during CPAP therapy (not applied only if not considered necessary; 58/96 patients were compliant to pronation). If we consider the P/F ratio after 1 hour of prone position, a positive prognostic role seems to emerge in treated patients (mean P/F 271 *vs.* 184) but this evidence is lacking in the multivariate analysis.

Another parameter analyzed was steroids use. Steroids were more frequently used in the "success" group (87% *vs.* 65%, p-value 0.003). The use of steroids strongly correlated with the clinical outcome ($p < 0.0001$) also stratifying for ARDS severity classes. The use of systemic steroids increased the probability of a positive outcome even compared to patients belonging to a better ARDS class but not receiving the drug (p-value: <0.0001) (Figure 3). According to the Cox model (Table 2), expressing the prognostic relevance of a number of variables in a multivariate analysis (Dimer test and ferritin at admission, use of steroids, P/F in oxygen at admission and age), a 0.24 coefficient emerges in the group treated with steroids, meaning that, maintaining consistent all other parameters, being treated with steroids reduces helmet CPAP failure risk of 76%. In addition, in patients failing the treatment, we observe an increase in the risk of failure of 4% for each additional year of age.

Discussion

The use of NIV in "*de novo*" ARDS has received a growing interest over the last decades in order to avoid complications related to IMV. Until the outbreak of COVID-19 pandemic, evidence suggested to limit this treatment to carefully selected patients with mild to moderate ARDS (failure in fact is higher than 50% in severe ARDS) and applied in experienced centers with close monitoring of blood gases and respiratory mechanics in order to avoid delayed intubation in case of failure [17,18].

It is well known that in ARDS the application of a positive end expiratory pressure (PEEP) recruits non aerated alveoli in dependent pulmonary regions, stabilizes the airways and reduces the inhomogeneity of lung volume distribution [16]. PEEP can be applied to spontaneous breathing patients in the form of CPAP [19] with an increase in functional residual capacity and improvement of oxygenation [8,20]. The benefits of prone position in non-COVID-19 related ARDS treated with IMV in terms of improved oxygenation and reduced mortality are well-know [21] and is due to improved ventilation–perfusion matching and recruitment of more gas-exchange-efficient dorsal regions [22,23].

A large number of COVID-19 patients in early phase of the disease present bilateral ground glass opacities at Computed Tomography (CT) [24], with an atypical, recently termed "L-type" ARDS, characterized by severe hypoxemia and a relatively high compliance [25,26]; the greater part of the lung is still not affected, which explains the low pulmonary elastance, but in affected areas the vessels are maximally dilated with a postulated loss of hypoxic vasoconstriction and a secondary increase in shunt volume; due to the preserved lung compliance, however, the patient is able to increase ventilation, often not perceiving dyspnoea despite hypocapnia and simultaneous significant hypoxemia [27]. In this scenario, most patients successfully proceed with helmet CPAP. Gattinoni and co-workers stress the idea that, in this first stage of disease, improvement in oxygenation by application of PEEP or pronation is mainly not due to the recruitment mentioned above, but to the redistribution of perfusion in the lungs [25,26].

In many cases this is followed by a progressive worsening of hypoxemia, which perhaps corresponds to the "cytokine storm" typical of COVID-19 infection and characterized by elevated concentration of ferritin, interleukin-6 and D-dimers: a severe primarily local inflammation that can lead to widespread damage to

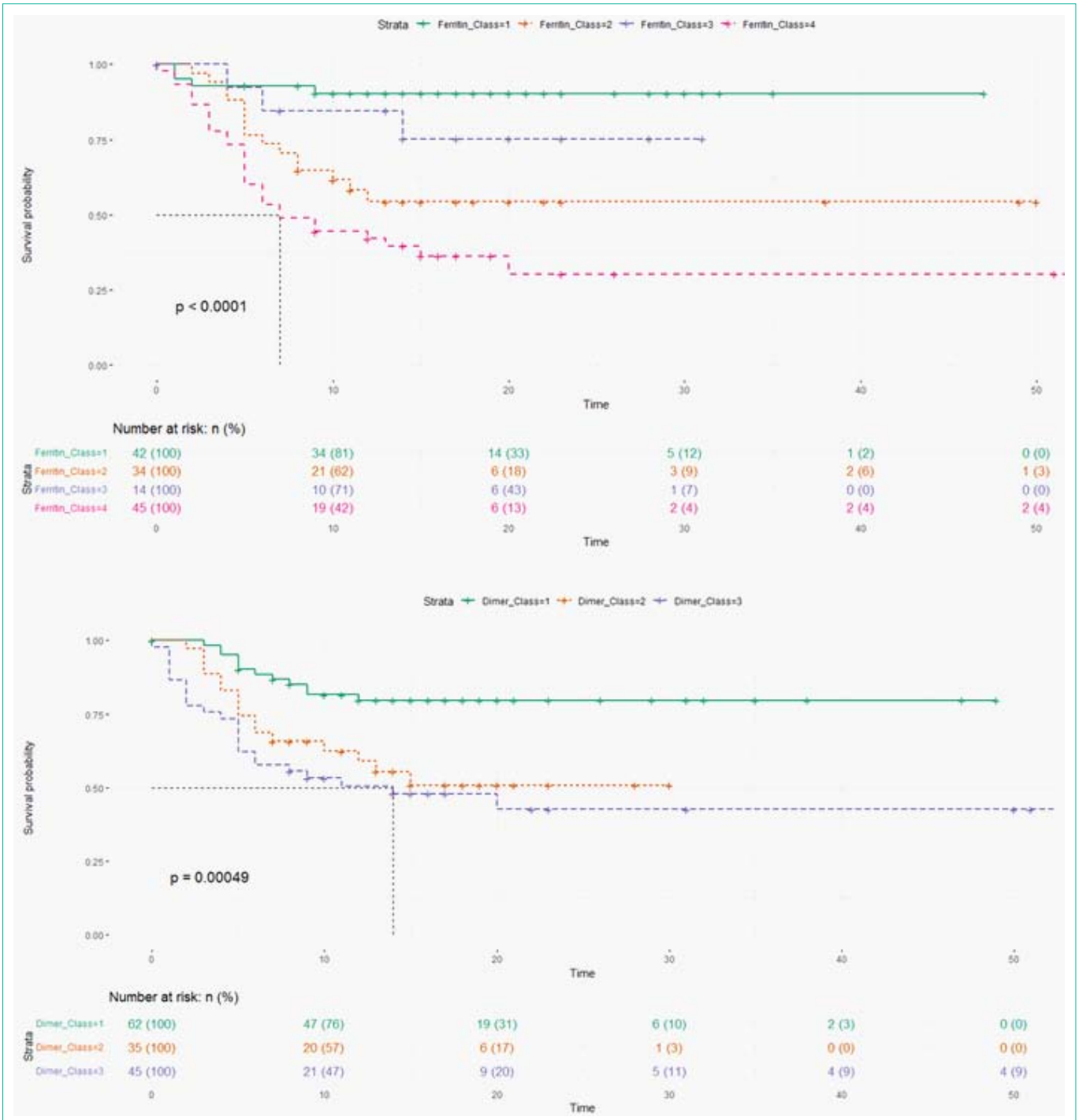

Figure 2: Survival analysis according to ferritin and dimer-test classes.

the lung parenchyma towards a so called "H type" ARDS [25,26] with low compliance as a result of increasing oedema and atelectasis with high right to left shunt, and associated to an extensive densification on the CT, similar to those seen in typical ARDS.

A hypercoagulability state, with consequent pulmonary microvascular coagulation [28], is also well-know.

The RECOVERY TRIAL [29], a large multicenter Randomized Controlled Trial (RCT), demonstrated that patients receiving Dexamethasone 6 mg for 10 days had a death rate reduced by up to one-third with more prominent effect in-patient on mechanical ventilation. These results suggest that corticosteroids, acting as inflammatory attenuators, could slow down the transition from L- to H-ARDS pattern in COVID-19 pneumonia.

Our study shows good clinical outcomes in patients affected by COVID19-related ARDS treated with helmet CPAP in RICU and

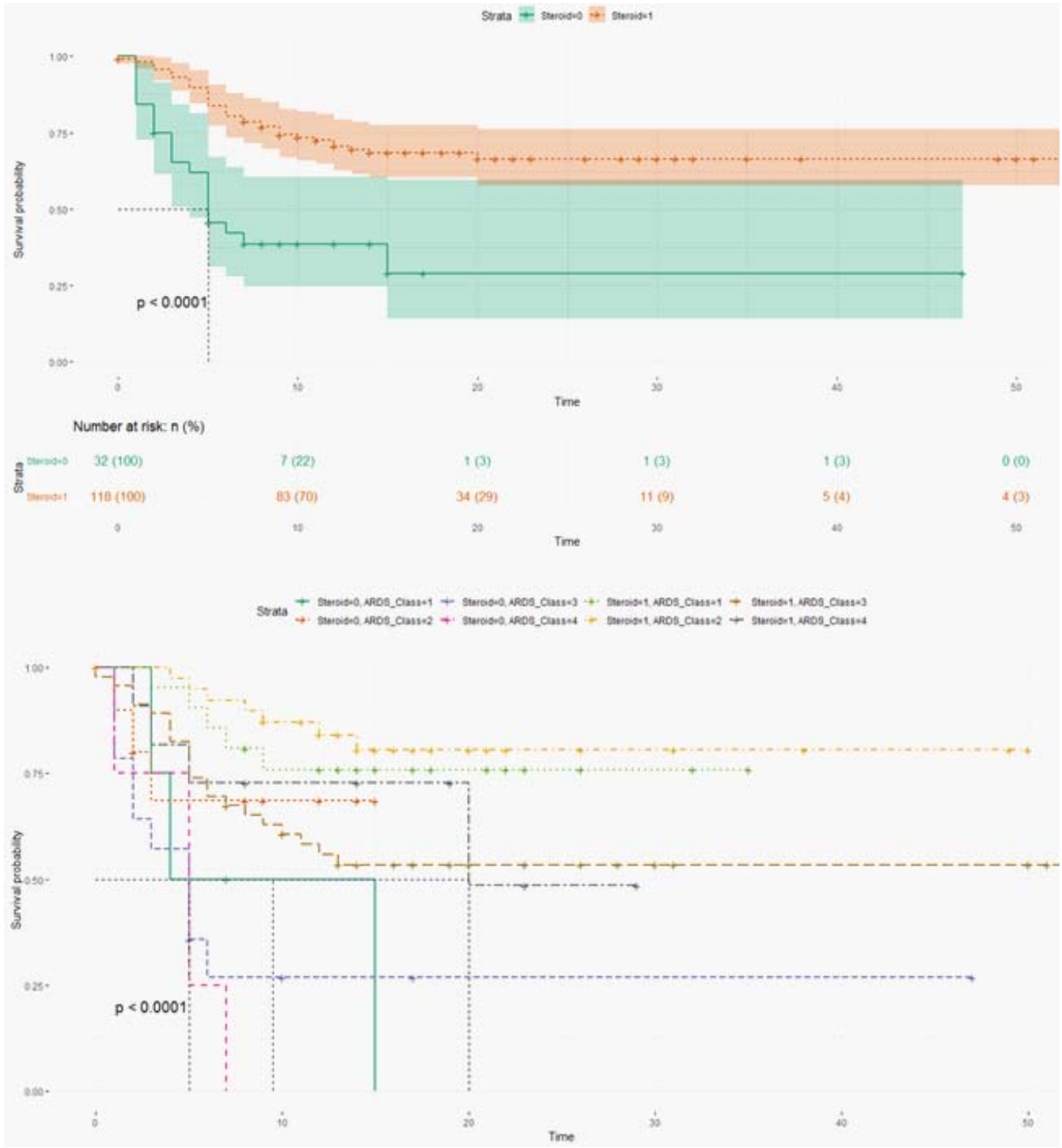

Figure 3: Survival analysis according to steroid therapy.

a significant improvement of prognosis in subjects who received corticosteroids. Dimer test and ferritin at admission, use of steroids, P/F in oxygen at admission and age all influence the overall outcome by expressing the entity of the cytokines storm on one side (the two biomarkers) and the severity of respiratory compromission on the other (P/F ratio). As previously mentioned, in patients failing the treatment, an increase in the risk of failure of 4% is observed for each additional year of age.

Many management models for non-invasive treatment of COVID-19 ARDS in RICU have been proposed in literature [14,33,34].

Aliberti and co-workers [30] have recently described, in a multicentric study, a group of patients with COVID-19 pneumonia

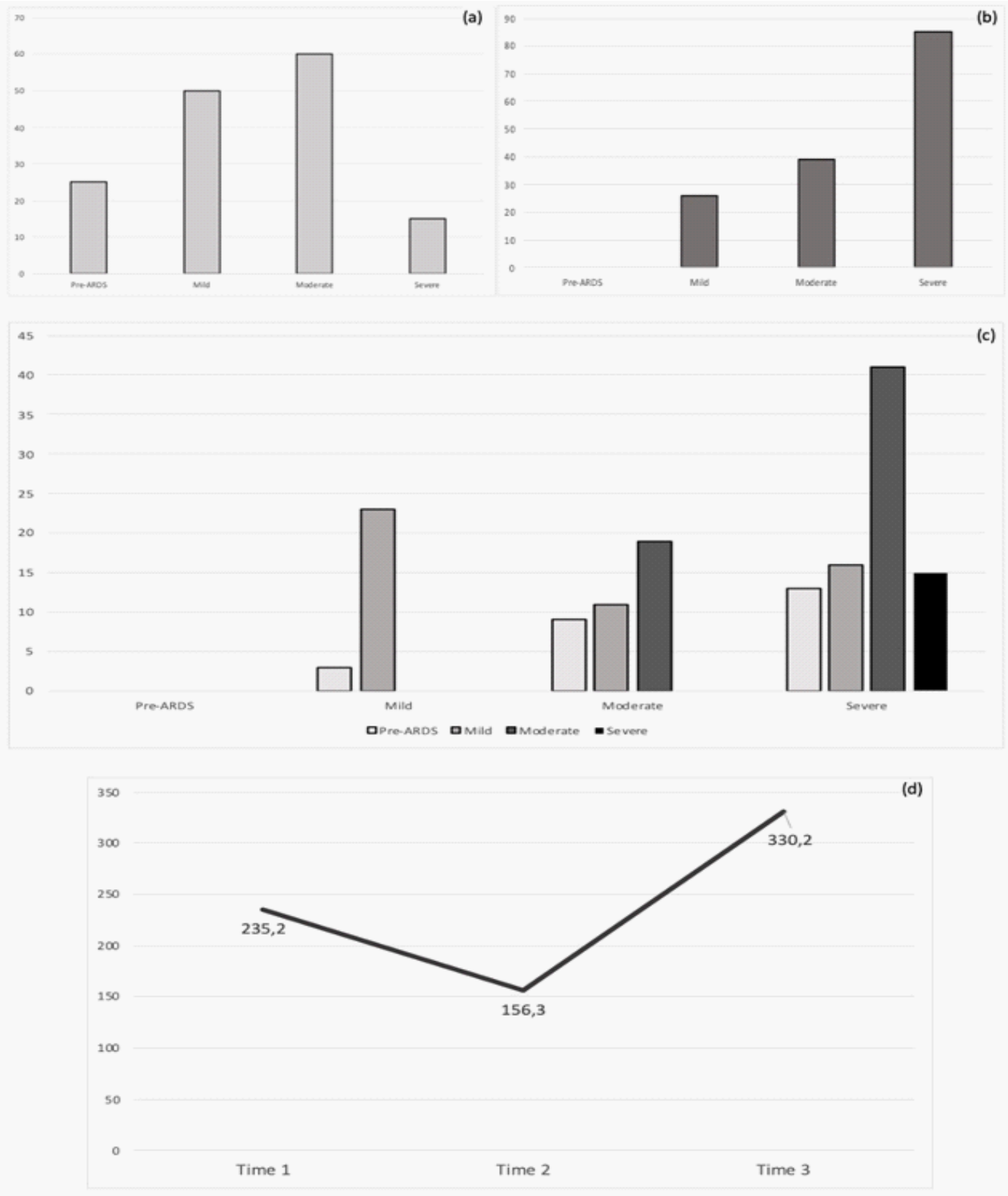

Figure 4: Distribution of the study population according to ARDS severity at admission (a) and during disease evolution (b) focusing on shifts in ARDS classes (c). Pre-ARDS: P/F ratio >300; Mild: 200 < P/F ratio ≤ 300; Moderate: 100 < P/F ratio ≤ 200, Severe: P/F ratio ≤ 100.(d) Trend of P/F ratio in the success group over time of the disease ("V-shaped" trend).

Note: Time 1: initial P/F ratio in CPAP; Time 2: worst P/F ratio in CPAP; Time 3: better P/F ratio in CPAP. P/F ratio was calculated as mean in success group. P/F: PaO_2/FiO_2Ratio; PaO_2: Arterial Oxygen Tension; FiO_2: Inspiratory Oxygen Fraction; CPAP: Continuous Positive Airway Pressure.

in RICU; despite a lower level of disease severity (ARDS criteria were not needed) the study shows worse outcomes; we bring forth the hypothesis that a more diffuse use of steroids in our center (79% versus 46% of patients treated) could play a role in this regard.

The other two trials conducted on the application of helmet CPAP in COVID19 hypoxic pneumonia were carried out in different specialistic units in a multicentric study [35] and in general wards [36].

In detail, a multicentric observational study published by Franco and co-workers [35] sustained the feasibility of non-invasive respiratory support including HFNC, CPAP and NIV outside the ICU, describing favorable outcomes in a cohort of 670 patients. Considering the CPAP group only (n=330), the failure rate (IMV/death) was 47.3% (*vs.* 38% in our study), although the percentage of patients treated with steroids was similar but mean age was higher (70.3 years).

Also in another, recent observational study conducted by Coppadoro and co-workers [36] in general ward, the risk of clinical failure (always defined as the occurrence of either intubation or death) in patients treated with helmet CPAP was 48%. Furthermore, 29% of patients had hypoxic pneumonia without ARDS.

We may therefore assume that the proper management in a specialistic intermediate care setting (RICU) affects the prognosis of patients with COVID-19 ARDS; a constant clinical and parametric monitoring during hospitalization by the pulmonologist in RICU is critical in promptly recognition and treatment of every possible worsening in clinical conditions, an event that can arise even later in the course of the disease (Figure 4d). In fact, the majority of patients move to a worse ARDS class during hospitalization ("V-shape" trend of hypoxemia in successful patients) (Fig. 4d). This explains why the APACHE II ("Acute Physiology and Chronic Health Evaluation II") score, by definition an admission score, is not predictive of mortality in these patients.

Prone position determined in all our patients a meaningful increase in P/F value, although this improvement does not represent a good prognostic factor in itself. As far as we have observed, this response provided a delay in the need of intubation and mechanical ventilation so giving the patient a chance to overcome the critical phase of ARDS.

We want to emphasize the fact that, despite the extremely low values of worst PaO2/FiO2 ratio recorded (26/150 mild ARDS; 39/150 moderate ARDS; 85/150 severe ARDS), 62% of our patients were finally discharged without need of IMV. If we divide the subjects in the different severity stages of ARDS we can appreciate that in mild patients we have a success of 100%, in moderate patients of 97% (only 1 patient failing, died in ICU with pneumomediastinum) and, in severe patients, of 34%. In addition, of the 56 patients in the "severe ARDS" group, 31 were transferred to ICU and, of these, 15 finally survived, with a mortality rate of 48%, in agreement with the mortality rate described for patients with severe ARDS in ICU (45%). We underline that, in our group of patients, mortality rates in mild and moderate ARDS are inferior to those reported in literature [5,17], considering the different features of patients admitted to ICUs (i.e. multiorgan failure).

Furthermore, our data seem to exclude a possible delay in intubation timing due to CPAP treatment and this is remarked by a mortality rate of almost 50% in patients finally admitted to ICU, substantially comparable with 55% of all Lombardy ICUs [31].

In addiction we must remember that, even if delayed intubation is associated with increased mortality in patients with acute respiratory failure [32], it is also true that premature intubation in patients in whom non-invasive respiratory support is adequate exposes patients to potentially unnecessary risks associated with IMV [10,37].

Our study has several limitations that can limit the generalizability of our results, among them the relatively small number of patients enrolled, the lack of control group and, at least, the peculiar setting of the study, characterized by an emergency pandemic situation with continuous changes in scientific evidence and ongoing shifts in clinical indications.

Conclusion

Our study suggests satisfactory clinical outcomes with helmet CPAP in COVID-19 ARDS in RICU. The proper management in a specialistic intermediate care setting (RICU) may affect the prognosis of these patients. We observed a significant improvement of prognosis in subjects who received corticosteroids. The severity of acute respiratory distress syndrome strongly correlates with clinical outcomes. Finally, dimer test and ferritin at admission and age all influence the overall outcome.

To our knowledge, till now this is the only study entirely carried out in RICU on patients with COVID-19 related ARDS treated with helmet CPAP.

Nevertheless, further multicentric and more numerous trials are needed in order to confirm these data.

References

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from Patients with Pneumonia in China. N Eng J Med. 2020; 382: 727-733.
2. WHO Directors-General's opening remarks as the media briefing on COVID-19. 2020.
3. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl). 2020; 133: 1015-1024.
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020; 323: 1061-1069.
5. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acuterespiratorydistresssyndrome: the Berlin Definition. JAMA. 2012; 307: 2526-2533.
6. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020; 323: 1574-1581.
7. Chiumello D, Brochard L, Marini JJ, Slutsky AS, Mancebo J, Ranieri VM, et al. Respiratory support in patients with acute respiratory distress syndrome: an expert opinion. Crit Care. 2017; 21: 240.
8. Delclaux C, L'Her E, Alberti C, Mancebo J, Abroug F, Conti G, et al. Treatment of acute hypoxemic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: A randomized controlled trial. JAMA. 2000; 284: 2352-2360.
9. Brambilla AM, Aliberti S, Prina E, Nicoli F, Del Forno M, Nava S, et al.

Helmet CPAP *vs.* oxygentherapy in severehypoxemicrespiratoryfailure due topneumonia. Intensive Care Med. 2014; 40: 942-949.

10. Patel BK, Wolfe KS, Pohlman AS, Hall JB, Kress JP. Effect of Noninvasive Ventilation Delivered by Helmet vs Face Mask on the Rate of Endotracheal Intubation in Patients with Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. JAMA. 2016; 315: 2435-2441.

11. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020; 8: 475-481.

12. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med. 2020; 382: 2012-2022.

13. 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. JAMA. 2020; 323: 2052-2059.

14. Radovanovic D, Rizzi M, Pini S, Saad M, Chiumello DA, Santus P. Helmet CPAP to Treat Acute Hypoxemic Respiratory Failure in Patients with COVID-19: A Management Strategy Proposal. J Clin Med. 2020; 9: 1191.

15. Ferioli M, Cisternino C, Leo V, Pisani L, Palange P, Nava S. Protecting healthcare workers from SARS-CoV-2 infection: practical indications. EurRespir Rev. 2020; 29: 200068.

16. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. Am J RespirCrit Care Med. 2003; 168: 1438 1444.

17. Grassi A, Foti G, Laffey JG, Bellani G. Noninvasive mechanical ventilation in early acute respiratory distress syndrome. Pol Arch Intern Med. 2017; 127: 614-620.

18. Demoule A, Hill N, Navalesi P. Can we prevent intubation in patients with ARDS? Intensive Care Med. 2016; 42: 768-771.

19. Chiumello D, Esquinas AM, Moerer O, Terzi N. A systematic technical review of the systemic for the continuous positive airway pressure. Minerva Anestesiol. 2012; 78: 1385-1393.

20. Cosentini R, Brambilla AM, Aliberti S, Bignamini A, Nava S, Maffei A, et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. Chest. 2010; 138:114-120.

21. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368: 2159-2168.

22. Mure M, Glenny R, Domino K, Hlastala M. Pulmonary gas exchange in pigs improves in the prone position with abdominal distension. Crit Care. 1998; 2: 122.

23. Albert RK, Hubmayr RD. The prone position eliminates compression of the lungs by the heart. Am J RespirCrit Care Med. 2000; 161: 1660-1665.

24. Han R, Huang L, Jiang H, Dong J, Peng H, Zhang D. Early Clinical and CT Manifestations of Coronavirus Disease 2019 (COVID-19) Pneumonia. AJR Am J Roentgenol. 2020; 215: 338-343.

25. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J RespirCrit Care Med. 2020; 201: 1299-1300.

26. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med. 2020; 46: 1099-1102.

27. Pfeifer M, Ewig S, Voshaar T, Randerath W, Bauer T, Geiseler J, et al. [Position Paper for the State of the Art Application of Respiratory Support in Patients with COVID-19 - German Respiratory Society]. Pneumologie. 2020; 74: 337-357.

28. Tan CW, Low JGH, Wong WH, Chua YY, Goh SL, Ng HJ. Critically ill COVID-19 infected patients exhibit increased clot waveform analysis parameters consistent with hypercoagulability. Am J Hematol. 2020; 95: E156-E158.

29. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in Hospitalized Patients with Covid-19-Preliminary Report. N Engl J Med. 2021; 384:693-704.

30. Aliberti S, Radovanovic D, Billi F, Sotgiu G, Costanzo M, Pilocane T, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study. EurRespir J. 2020; 56: 2001935.

31. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al; COVID-19 Lombardy ICU Network. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA Intern Med. 2020; 180: 1345-1355.

32. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J RespirCrit Care Med. 2017; 195: 438-442.

33. Editorial. Role of Helmet-Delivered Noninvasive Pressure Support Ventilation in COVID-19 Patients. J CardiothoracVascAnesth. 2020; 34: 2575-2579.

34. Longhini F, Bruni A, Garofalo E, Navalesi P, Grasselli G, Cosentini R, et al. Helmetcontinuous positive airwaypressureandpronepositioning: A proposalfor an earlymanagementof COVID-19 patients. Pulmonology. 2020; 26:186-191.

35. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibilityandclinicalimpactof out-of-ICU noninvasiverespiratorysupport in patientswith COVID-19-related pneumonia. EurRespir J. 2020; 56: 2002130.

36. Coppadoro A, Benini A, Fruscio R, Verga L, Mazzola P, Bellelli G, et al. Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. CRITICAL CARE. 2021; 25: 80.

37. Tobin MJ. Basing Respiratory Management of COVID-19 on Physiological Principles. Am J RespirCrit Care Med. 2020; 201: 1319-1320.