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Clinical Determinants of Outcome and Respiratory Management in COVID-19 Mechanically Ventilated Patients with Acute Respiratory Distress Syndrome: A 15-Month Prospective Observational Study in a Greek Intensive Care Unit

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COVID-19; Acute respiratory distress syndrome; Intensive care unit; Mechanical ventilation; Risk factors; Mortality

1. Abstract

1.1. Background: Covid-19 associated acute respiratory distress syndrome (CARDS) and prolonged mechanical ventilation imposes a major burden on affected critically ill individuals, in light of high mortality. We aimed to identify possible risk factors for mortality among the three categories of ARDS severity according to Berlin definition and to examine the effect of time on patients' oxygenation and respiratory mechanics.

1.2. Methods: We prospectively investigated the clinical characteristics and outcome of 196 consecutive mechanically ventilated patients with CARDS, along with oxygenation and respiratory mechanics, on ICU days 1, 3 and 7.

1.3. Results: ICU mortality accounted for 63.3%. Non-survivors were significantly older and presented higher disease severity on ICU admission and higher incidence of chronic obstructive pulmonary disease (COPD), neurologic disease and immunosuppression. PaO2/FiO2 was significantly higher in the survivors group at all time points, whereas significant increase over time (day 7 vs day 1) was observed only in survivors group. Static respiratory system compliance was higher and driving pressure was lower in survivors compared to non survivors, on days 3 and 7. Regarding the non-survivors group, oxygenation remained unchanged through different time points, while compliance reduced significantly and plateau and driving pressures increased through evolution of time. Mild, moderate and severe CARDS was reported in 16 (8.2%), 88 (44.9%) and 92 (46.9%) patients respectively. Incidence of obesity was higher in severe CARDS. PEEP levels and plateau pressures were higher in the severe CARDS, while respiratory system compliance and driving pressure did not differ among the CARDS categories.

1.4. Conclusions: In our case series, ICU mortality was high and increased accordingly to CARDS severity. Mortality risk factors included older age, COPD, neurological disorders and immunosuppression. Body mass index was significantly increased across CARDS severity. Trajectories of hypoxemia and respiratory mechanics were also associated with outcome.

2. Introduction

Infection with the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) was first reported in December 2019 in Wuhan, China. Three months later the World Health Organization (WHO) declares COVID-19 a pandemic. Since then, COVID-19 outbreak has posed a huge burden on the whole global health system, either by crippling health resources or afflicting health care delivery. Although most patients present with mild symptoms, 17-32% of patients presenting to hospital may require admission to the Intensive Care Unit (ICU) due to acute hypoxemic respiratory failure [1, 2].

Respiratory support is provided through high-dose oxygen therapy or non-invasive mechanical ventilation but, in the majority of ICU patients, intubation and mechanical ventilation is essential due to COVID-19 associated Acute Respiratory Distress Syndrome (CARDS) [3, 4]. Patients may present with profound hypoxemia accompanied by a wide range of respiratory compliance [5, 6]. Current intensive care treatment for CARDS is mostly supportive and in line with ARDS recommendations. ICU mortality of COVID-19 patients is striking high, ranging between 15-74% [7-9] and is associated not only with CARDS but also with additional organ dysfunctions, including cardiovascular [10], cerebrovascular [11] or renal dysfunction [12].

In the present observational prospective study, we describe the clinical characteristics, inpatient selected treatments and adverse events of 196 ICU patients with CARDS on mechanical ventilation. Moreover, we analyze the oxygenation and respiratory mechanics, along with mechanical ventilation settings over days 1, 3 and 7 from ICU admission. Our main objectives were to identify risk factors for mortality and to examine the effect of time on patients' oxygenation and respiratory mechanics. A secondary objective was to investigate for differences among the three categories of ARDS severity, according to Berlin definition [13].

3. Materials and Methods

3.1. Study Setting, Design and Population

This prospective observational study was conducted at the nine-bed general ICU of Konstantopouleio- Patision General Hospital (Athens, Greece), which is a 330-bed tertiary-care hospital. It enrolled 196 consecutive adult patients with confirmed COVID-19 admitted to the ICU between 25 February 2021–25 May 2022, who required mechanical invasive ventilation and met the criteria of ARDS, according to the three categories of the Berlin definition. All clinical decisions and management of the patients were performed by attending physicians, according to institutional protocols and regular practice. All patients were mechanically ventilated with volume-controlled ventilation. Neuromuscular blockade was administered when significant patient ventilator desynchrony was observed. All patients received remdesivir as antiviral medication and intravenous dexamethasone. Antibiotics were administered to patients with suspected bacterial co-infections.

3.2. Data Collection

We registered date of symptoms onset, hospital and ICU admission, demographic data, body mass index (BMI, kg/m2), obesity (BMI $\geq$ 30 kg/m2) and other co morbidities, Acute Physiology and Chronic Health Evaluation II (APACHE II) score on ICU admission day, usage of medications, vasopressors and renal replacement therapy, adverse events, ICU length of stay and outcome.

Physiological respiratory and mechanical ventilation variables were collected on days 1, 3 and 7. Static respiratory compliance was calculated by dividing the tidal volume (Vt) by the driving pressure (plateau pressure minus positive end-expiratory pressure, Pplat-PEEP). The study was reviewed and approved by the institutional Ethical Committee of our hospital (Act 29321/02-11-2021) and informed consent of the participants was waived due to the observational nature of the study.

3.3. Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) as appropriate and compared using Student's t-test and Mann –Whitney respectively. Categorical variables were presented as numbers (%) and compared using the chi-squared or Fisher's exact test, as appropriate. One way analysis of variance for repeated measures was used to examine the effect of time on PaO2/ FiO2 and respiratory mechanics. When analysis of variance revealed a significant difference, Holm-Sidak t-test was used to correct for multiple comparisons. A p value less than 0.05 was considered significant.

4. Results

4.1. Clinical Characteristics of Study Population

During the 15-month study period, a total of 196 CARDS patients were admitted to our ICU. The patients were predominantly males (61.2%) and had mean age of 67± 13 years and mean BMI of 32.2 ±7.8 kg/m2. Cardiovascular disease (59.2%), obesity (52.5%), diabetes (33.7%) and chronic obstructive pulmonary disease (COPD) (22.4%) were the most frequent comorbidities. The median time from infection onset to hospital admission was 6 (4-8) days, whilst to intubation and transfer to ICU was 11 (8-14) days (Table 1).Mortality for our cohort was 63.3%. Regarding patient- related risk factors for mortality, patients who finally died in ICU were significantly older (69 ±12 vs 64 ± 13 years, p=0.013) and presented higher disease severity on ICU admission, as measured by APACHE II (17.8 ± 6.4 vs 12.8 ± 6, p<0.001). Additionally, COPD (27.4% vs 13.9%, p=0.044), neurologic disease (10.5% vs 1.4%, p=0.036) and immunosuppression (13.7% vs 2.8%, p=0.025) were significantly more frequent in non-survivors.

4.2. Mechanical Ventilation Variables and Respiratory Parameters

On day 1 mean applied tidal volume (VT) was 7.8 ± 1.1 ml/kg ideal body weight (IBW) for the entire population and positive end - expiratory pressure (PEEP) level was 10.7 ± 3 cmH2O, while partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/ FiO2) levels were 121 ± 64 mmHg. In between-group analysis, PaO2/ FiO2 was significantly higher in the survivors group at all time points. Within each outcome group, PaO2/ FiO2 was significantly increased over time (day 7 vs day 1) only for survivors (Table 2). PEEP utilized values were significantly decreased over time in both outcome groups.

Static respiratory system compliance (Cst, rs) was higher and driv-

ing pressure was lower in survivors group, on days 3 and 7. Corresponding plateau pressures were lower on day 7, while on day 3 marginally did not reach statistical significance (p=0.065).

Regarding the non-survivors group, oxygenation remained unchanged through different time points, while Cst,rs reduced significantly and plateau and driving pressures increased through evolution of time.

Table 1: Demographic characteristics and co-morbidities of CARDS patients

	All patients (n=1 96)	Non survivors (n=124)	Survivors (n=72)	Significance
Demographics				
Age (years) (mean ± SD)	67 ± 13	69 ± 12	64 ± 13	**0.013**
Female sex, n (%)	76 (38.8)	46 (37.1)	30 (41.7)	0.632
BMI (kg/m^2) (mean ± SD)	32.2 ± 7.8	32.1 ± 7.7	32.5 ± 7.9	0.744
Days from symptom onset to hospital admission [median (IQR)]	6 (4-8)	6 (3.75-8)	7 (4-9)	0.061
Days from symptoms onset to intubation [median (IQR)]	11 (8-14)	11 (8-14)	11 (9-14.75)	0.701
APACHE II (mean ± SD)	15.9 ± 6.7	17.8 ± 6.4	12.8 ± 6	**<0.001**
Co-morbidities, n (%)				
Diabetes mellitus	66 (33.7)	44 (35.5)	22 (30.5)	0.584
Chronic Obstructive Pulmonary Disease	44 (22.4)	34 (27.4)	10 (13.9)	**0.044**
Cardiovascular Disease	116 (59.2)	80 (64.5)	36 (50)	0.065
Neurological disorders	14 (7.1)	13 (10.5)	1 (1.4)	**0.036**
Psychiatric disorders	10 (5.1)	7 (5.6)	3 (4.2)	0.907
Chronic renal failure	9 (4.6)	8 (6.4)	1 (1.4)	0.201
Neoplasia	10 (5.1)	9 (7.2)	1(1.4)	0.974
Immunosuppression	19 (9.7)	17 (13.7)	2 (2.8)	**0.025**
Obesity (BMI > 30 kg/m^2)	103 (52.5)	67 (54)	36 (50)	0.692

SD, standard deviation; IQR, interquartile range; BMI, Body Mass Index; APACHE, Acute Physiology and Chronic Health Evaluation;

Table 2: Respiratory parameters and mechanical ventilation variables over time according to patients' outcome

	All patients (n=196)	Non survivors (n=124)	Survivors (n=72)
Vt / IBW (ml /kg)	7.8 ± 1.1	7.8 ± 1.2	7.8 ± 0.9
PEEP(cmH_2O)			
Day 1	10.7 ± 3$^{\&}$	10.4 ± 2.9	11 ± 3.2
Day 3	10.1 ± 3.4	10.2 ± 3.3	10.2 ± 3.6$^{\#}$
Day 7	9 ± 3.3$^{\#\&}$	9.8 ± 3.2$^{\#}$	7.7 ± 3.1$^{*\#}$
PaO_2/FiO_2(mmHg)			
Day 1	121 ± 64	111 ± 57	139 ± 72*
Day 3	126 ± 51	112 ± 46	149 ± 50*
Day 7	130 ± 55	108 ± 52	164 ± 43$^{*\#}$
Respiratory system compliance (mL/cmH_2O)			
Day 1	35.1 ± 9.2	34.9 ± 9.5	35.5 ± 8.6
Day 3	34.5 ± 9.5	33.3 ± 9.8$^{\#}$	36.6 ± 8.8*
Day 7	33 ± 10.2$^{\#\&}$	31.8 ± 9.9$^{\#}$	36.1 ±10.3*
Plateau pressure(cmH_2O)			
Day 1	25.6 ± 4.6	26 ± 4.6	26 ± 4.5
Day 3	25.9 ± 4.3	26.3 ± 4.4	25 ± 4$^{\#}$
Day 7	26.3 ± 4.8	27.2 ± 4.6$^{\#}$	24 ± 4.5$^{*\#}$
Driving pressure(cmH_2O)			
Day 1	15 ± 4	15.2 ± 4	14.5 ± 4
Day 3	15.4 ± 3.8	16 ± 4.2$^{\#}$	14.2 ± 2.7*
Day 7	16.5 ± 3.8$^{\#\&}$	17.1 ± 4.1$^{\#}$	15.1 ± 2.8$^{*\#}$

Values are mean ± SD; Vt/IBW, tidal volume per kilogram of ideal body weight; PEEP, positive end-expiratory pressure; PaO2/ FiO2, partial pressure of arterial oxygen to fraction of inspired oxygen

In between-group (non-survivors and survivors) analysis, * corresponds to $p < 0.05$

For within-group comparisons (changes within each survival group over time), # corresponds to $p < 0.05$ vs day 1, &corresponds to $p < 0.05$ vs day 3

4.3. Treatments, ICU Resources and Adverse Events

All patients received a 5 days course of remdesivir, either before, or during ICU hospitalization. Dexamethasone was also administered in the whole study population for 12 (8-18) days. Tocilizumab was administered in 15.3% and anakinra in 15.8% of the patients (Table 3).

Concerning utilization of ICU resources, patients who died received more frequently renal replacement therapy (23.4% vs 2.8%, p<0.001) and supported with vasopressors for longer periods of time (median time: 9 vs 5 days, p<0.001). Conversely, duration of ICU stay was significantly shorter for this outcome group (median time: 12 vs 15 days, p<0.001).

Regarding the incidence of adverse events, barotraumas were reported in 11 (5.6%) and thrombotic events in 21 (10.7%) patients, which included pulmonary embolism (18), ischemic stroke (1), acute coronary infarction (1) and mesenteric thrombosis (1). Notably, all major hemorrhagic events (12; 6.1%) concerned non-survivors and included alveolar hemorrhage (8), retroperitoneal hematoma (1), adrenal gland hemorrhage (1), and hemorrhagic shock (2).

4.4. Comparison of Variables among the Three Categories of CARDS Severity

Mild, moderate and severe CARDS was reported in 16 (8.2%), 88 (44.9%) and 92 (46.9%) patients respectively. No differences regarding age, gender and comorbidities were identified, except from BMI and incidence of obesity which were significantly higher in the severe CARDS category (30.4 ± 4.8 vs 30.5 ± 6.7 vs 34.2 ±8.6 kg/m2, p=0.003; 37.5% vs 44.3% vs 63%, p=0.019, respectively).

The three categories were mechanically ventilated with similar Vt. However, PEEP levels and plateau pressures were higher in the severe CARDS compared to mild and moderate CARDS, at the three time points (Table 4). Respiratory system compliance and driving pressure did not differ among the CARDS categories. Analysis within each CARDS category over time revealed that driving pressure through day 7 was significantly increased in moderate CARDS patients, while on same day, Cst,rs was significantly decreased in severe CARDS patients. Survivors with severe CARDS revealed delayed extubation compared to the other two categories, although the difference marginally did not reach statistical significance (median time: 8 vs 10 vs 12 days, p=0.06).

Utilization of ICU resources and adverse events were similar among the CARDS categories. However, patients with moderate CARDS stayed for longer period in ICU compared to patients with severe CARDS (median time: 15 vs 12 days, p=0.024), while ICU mortality was significantly higher in severe CARDS patients compared to other two categories (43.75% vs 53.4% vs 76.1%, p = 0.002)

Table 3: Treatments, ICU resources and adverse events of CARDS patients

	All patients (n=196)	Non survivors (n=124)	Survivors (n=72)	Significance
Inpatient selected treatments				
Days on mechanical ventilation [median (IQR)]	11 (7-20)	12 (6-21)	10 (8-19)	0.596
Days on vasopressors [median (IQR)]	8 (3-14)	9 (5-17)	5 (2-9)	**< 0.001**
Corticosteroids (days) [median (IQR)]	12 (8-18)	12 (6-19)	12 (9-18)	0.196
Continuous renal replacement therapy, *n* (%)	31(15.8)	29 (23.4)	2 (2.8)	**< 0.001**
Anakinra, *n* (%)	31(15.8)	19 (15.3)	12 (16.7)	0.964
Tocilizumab, n (%)	30 (15.3)	19 (15.3)	11(15.3)	0.864
ICU LOS (days) [median (IQR)]	13 (8-23)	12 (6-21)	15 (11-27)	**0.001**
Adverse events, *n* (%)				
Barotrauma	11(5.6)	10 (8.1)	1(1.4)	0.102
Thrombotic events	21(10.7)	11 (8.9)	10 (13.9)	0.392
Major hemorrhagic events	12 (6.1)	12 (9.7)	0	**0.016**

IQR, interquartile range; ICU LOS, Intensive Care Unit length of stay

Table 4: Demographic characteristics and co-morbidities of patients according to CARDS severity

	Mild CARDS (n=16)	Moderate CARDS (n= 88)	Severe CARDS (n=92)
Demographics			
Age (years) (mean ± SD)	73 ± 13	67 ± 13	66 ± 12
Female sex, n (%)	9 (56.25)	34 (38.6)	33 (35.9)
BMI (kg/m^2) (mean ± SD)	30.4 ± 4.8	30.5 ± 6.7	34.2 ± 8.6$^{*,\$}$
Days from symptom onset to hospital admission [median (IQR)]	5 (3-8)	6 (4-8)	6 (4-8)
Days from symptoms onset to intubation [median (IQR)]	10 (6-14)	11 (8-15)	11 (8-14)
APACHE II (mean ± SD)	19.2 ± 8.2	14.6 ± 6.5*	16.6 ± 6.3
Co-morbidities, n (%)			
Diabetes mellitus	6 (37.5)	29 (32.9)	31(33.7)
Chronic Obstructive Pulmonary Disease	4 (25)	18 (20.4)	22 (23.9)
Cardiovascular Disease	11 (68.75)	49 (55.7)	56 (60.8)
Neurologic disease	1 (6.25)	5 (5.7)	8 (8.7)
Psychiatric disease	2 (12.5)	1 (1.1)	7 (7.6)
Chronic renal failure	1 (6.25)	4 (4.5)	4 (4.3)
Neoplasia	1 (6.25)	4 (4.5)	5 (5.4)
Immunosuppression	2 (12.5)	7 (7.9)	10 (10.8)
Obesity (BMI > 30 kg/m^2)	6 (37.5)	39 (44.3)	58 (63)$^{*,\$}$
Inpatient selected treatments			
Days on mechanical ventilation[median (IQR)]	13 (7-23)	11 (8-22)	11 (6-19)
Days on vasopressors[median (IQR)]	7 (3-15)	8 (3-16)	7 (3-12)
Corticosteroids (days) [median (IQR)]	10 (8-14)	13 (9-24)	12 (6-16)
Continuous renal replacement therapy, *n* (%)	1 (6.25)	16 (18.2)	14 (15.2)
Anakinra,*n*(%)	1 (6.25)	16 (18.2)	14 (15.2)
Tocilizumab, *n*(%)	1 (6.25)	16 (18.2)	15 (16.3)
Extubation day[a] [median (IQR)]	8 (5-11)	10 (7-13)	12 (10-18)
ICU LOS (days) [median (IQR)]	13 (10-28)	15 (9-28)	12 (6-20)$^{\$}$
Adverse events, *n*(%)			
Barotrauma	1 (6.25)	4 (4.5)	6 (6.5)
Thrombotic events	2 (12.5)	8 (9.1)	11 (11.9)
Major hemorrhagic events	1 (6.25)	2 (2.3)	9 (9.8)
Mortality, *n*(%)	7 (43.75)	47 (53.4)	70 (76.1)$^{*,\$}$

SD, standard deviation; IQR, interquartile range; BMI, Body Mass Index; APACHE, Acute Physiology and Chronic Health Evaluation; ICU LOS, Intensive Care Unit length of stay

a Among patients who survived

In between- CARDS group analysis, * corresponds to $p < 0.05$ vs mild CARDS, $ corresponds to $p < 0.05$ vs moderate CARDS

5. Discussion

The emergence and rapid spread of SARS-CoV-2 brought about an unprecedented burden on society and global health care systems. Covid-19 associated ARDS and prolonged mechanical ventilation imposes a major burden on affected critically ill individuals, in light of the high mortality [3]. In the present prospective observational study we documented the poor outcome associated with CARDS along with determinants of mortality. The overall mortality (63.3%) was higher compared to that in previous reports [14-16]. However, mortality rates of ICU patients varied substantially between different countries ranging up to 30-50% and may be attributed to variations in patients characteristics, along with ICU admission criteria or availability of ICU capacities [4, 14, 17]. Notably, in our case series, all patients admitted in ICU were intubated and suffered from moderate to severe CARDS, given the initial mean PaO2/FiO2 of 121 mmHg. Likewise most studies of CARDS, patients were old, predominantly male and exhibited cardiovascular disease and obesity as the most frequent co

morbidities, followed by diabetes and COPD. Prevalence of these comorbidities was different from the observed ones in non-COVID-19 ARDS patients, as reported in the largest study about ARDS (LUNG-SAFE) in which COPD, diabetes and immunosuppression predominated [38].

Regarding patient-related factors for mortality, non-survivors were older, suffered more frequently from COPD, neurological disorders and immunosuppression and presented with higher disease severity at the time of intubation and ICU admission. Advanced age has been uniformly reported as risk factor for severe disease [21,22], while COPD has been identified as risk factor for mortality [23]. Despite being among the most frequent comorbidities, obesity did not affect our patients' outcome. Nevertheless, BMI increased significantly across CARDS severity, resulting in an almost two-fold higher incidence of obesity in severe CARDS compared to mild CARDS. Previous workers have confirmed the association of obesity with severity of disease in COVID-19 [19, 24] Obese patients are prone to severe respiratory failure due to excessive load of respiratory muscles and tendency toward atelectasis. Moreover, obesity may affect the course of COVID-19 through other mechanisms, such as low grade chronic inflammatory state, coagulopathy and risk of diabetes and cardiovascular disease [25].

Notably, our patients with unfavorable outcome revealed a 10-fold higher incidence of neurological disorders. Accordingly, a recent systematic review concluded that overall preexisting mental and neurological disorders were related to higher incidence and worse prognosis of COVID-19 infection [26]. Specifically, dementia and Parkinson's disease have been related to higher susceptibility to COVID-19 [27]. These patients are usually old, have other comorbid medical conditions and may present with atypical symptoms of infection that impede early recognition of disease and thus increase mortality.

Almost half of our patients suffered from severe CARDS and this remained as such over the first week, despite a tendency toward improved oxygenation. As in the LUNG-SAFE study and previous reports about CARDS, mild, moderate and severe ARDS were associated with increasing mortality [19,20]. Regarding mechanical ventilation parameters, our patients were managed with low Vt (7.8 mk/kg PBW) and intermediate PEEP levels (11 cmH2O) and were in alignment with the standard recommendations for lung protective ventilation28 and other studies of CARDS,29 maintaining plateau pressure below 30 cmH2O, in the majority of patients. PEEP levels utilized in our study were comparable with those in LUNG-SAFE study and were significantly increased with hypoxemia severity at all time points (day 1, 3 and 7), whereas the applied Vt remained stable across severity categories. According to the increasing degree of pulmonary compromise from mild to severe CARDS, oxygenation and plateau pressures were progressively more affected at all time points, with values similar to other studies of CARDS [3,18]. Interestingly, respiratory system compliance was not affected according to the corresponding severity of CARDS. Timing of the initiation of the mechanical ventilation might affect respiratory compliance, given that in COVID-19 patients intubation time varies considerably, depending on the criteria set institutionally and the available resources [30]. In our study, patients were intubated after a median period of 5 days after hospital admission, indicating that many patients who met ARDS criteria based on hypoxemia and bilateral infiltrates did not receive mechanical ventilation until several days after admission, probably due to preservation of mental status despite profound hypoxemia.

Although applied Vt and PEEP were similar among survivors and non survivors, in between-group analysis revealed significant difference in oxygenation at all time points, and in respiratory system compliance and driving pressure after the day 3. Moreover, analysis within each survival group over time revealed significant improvement in PaO2/FiO2 values and reduction in plateau pressure on day 7 for the survivors. Previous researchers have also reported that progressive increases in PaO2/FiO2 values showed higher association with survival compared to a single value on intubation day [31]. Our non-survivors patients disclosed severe and refractory hypoxemia through day 7, which is in accordance with an observational study from United Kingdom that reported refractory hypoxemia as a major determinant of mortality in CARDS [32]. However, although non-survivors suffered from worse pulmonary function at ICU admission, the duration of mechanical ventilation was similar to survivors, which could be attributed to their shorter ICU length of stay.

Concerning management of CARDS after intubation and ICU admission, all our patients received a median 12-day course of corticosteroids. Although adopted in clinical practice, the definite benefits of corticosteroid treatment in severe CARDS along with the 'optimal' corticosteroid, timing and best route of administration are questions to be answered [33]. In addition to corticosteroids, a number of immunomodulating therapeutic approaches have been used in severe CARDS. However, results from randomized controlled studies did not reveal survival benefit either from tocilizumab, a blocker of IL-6 receptor or anakinra, an IL-1 receptor antagonist.34,35 In our study population, administration of anakinra (15.8%) or tocilizumab (15.3%) concerned mainly moderate and severe CARDS patients and did not affect their outcome.

Although survivors were hospitalized for longer period in the ICU, they had more vasopressor-free days and less usage of continuous renal replacement therapy (CRRT), indicating less severe course of COVID-19 disease. Indeed, acute kidney injury is a frequent organ manifestation of COVID-19 and RRT is often required [12]. Mortality of CARDS patients with acute kidney injury is increased, particularly if RRT is instituted [36]. On the other hand, usage of the aforementioned treatments did not differ between CARDS severity groups, likewise previous reports.19

Due to high number of thrombotic complications in CARDS pa-

tients [37], a subtherapeutic to therapeutic regime of low-molecular –weight heparin (LWMH) has been proposed [38]. Accordingly, our patients received prophylactic anticoagulation with LMWH, unless an absolute contraindication was present. However, 11% suffered from thrombotic events, mainly pulmonary embolism. Observational studies reported 3-31% incidence of thrombosis, despite administration of LWMH [37,39]. On the contrary, bleeding complications are considered rare in patients with severe COVID-19 [38]. Although a small percentage of our patients (6.1%) suffered from major hemorrhagic events, it is noteworthy that all bleeding cases concerned the non-survivors group.

Limitations of the present study are inherent to its single centre observational nature. We acknowledge our limitation to control for factors which affected decisions about management of respiratory failure and timing of intubation for COVID-19 patients, as all patients had been admitted to ICU already intubated. We studied patients on precise time points after initiation of mechanical ventilation, so there is a certain possibility that oxygenation and respiratory system mechanical characteristics might have varied over time. Moreover, ventilation management was not standardized.

Nevertheless, the present study has certain strengths, such as its adequate sample size, along with full representativeness of re- allife clinical practice, which cannot be depicted by a randomized controlled trial study. We recorded several demographic, respiratory and treatment characteristics of unselected patients that presented one similarity, the severe COVID-19 infection. Besides, observational studies are the first step to identifying findings that could trigger the design of larger randomized trials.

6. Conclusions

In our case series of critically ill patients with CARDS, ICU mortality was 63.3% and was increasing accordingly to CARDS severity. Risk factors for mortality included old age, disease severity, COPD, neurological disorders, immunosuppression and emergence of major hemorrhagic events. Body mass index increased significantly across CARDS severity. Patients who finally died received more frequently renal replacement therapy and supported with vasopressors for longer periods. Trajectories of hypoxemia and respiratory mechanics were associated with outcome, given that non-survivors presented refractory hypoxemia through day 7, along with decrease of static respiratory compliance. Clinicians could be aware that a single value of PaO2/FiO2 on intubation day may not be enough to determine patient's outcome.

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