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Intensive care for seriously ill patients affected by novel coronavirus sars - CoV – 2: Experience of the Crema Hospital, Italy

William Zuccon, MD [b,*], Paolo Comassi, MD [a,*], Luca Adriani, MD [a], Giulio Bergamaschini, MD [a], Elena Bertin, MD [b], Raffaella Borromeo, MD [a], Serena Corti, MD [b], Federica De Petri, MD [b], Francesco Dolci, MD [b], Attilio Galmozzi, MD [b], Alberto Gigliotti, MD [a], Livio Gualdoni, MD [a], Claudia Guerra, MD [b], Anna Khosthiova, MD [b], Giovanni Leati, MD [c], Giuseppe Lupi, MD [a], Paolo Moscato, MD [a], Vittorio Perotti, MD [a], Miriam Piantelli, MD [b], Alain Ruini, MD [b], Silvia Sportelli, MD [b], Micaela Susca, MD [b], Carmine Troiano, MD [a], Giampaolo Benelli, MD [c], Elisabetta Buscarini, MD [d], Ciro Canetta, MD [e], Guido Merli, MD [a], Alessandro Scartabellati, MD [f], Giovanni Melilli, B.S.C. [g], Roberto Sfogliarini, MD [h], Germano Pellegatta, MD [i], Giovanni Viganò, MD [b]

[a] Emergency Department, Intensive Care Unit, Major Hospital, Crema, Italy
[b] Emergency Department, Emergency Unit, Major Hospital, Crema, Italy
[c] Radiology Unit, Major Hospital Crema, Italy
[d] Gastroenterology Unit, Major Hospital Crema, Italy
[e] Emergency Medicine Unit, Major Hospital Crema, Italy
[f] Pneumology Unit, Major Hospital Crema, Italy
[g] Health Management, Major Hospital, Crema, Italy
[h] Health Director, Major Hospital Crema, Italy
[i] General Manager, Major Hospital Crema, Italy

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ABSTRACT

Aims: In this work, the survival and mortality data of 54 consecutive patients admitted to the Intensive Care Unit (ICU) and suffering from severe respiratory insufficiency imputable to viral SARS - CoV - 2 infection were analyzed and shared, after a critical review of the evidence in order to optimize the most dedicated clinical and treatment strategy, for a future 'targeted' management in the care of the possible return flu outbreak.
Methods: At our Emergency Department of the Crema Hospital, from the beginning of the pandemic until the end of June 2020, 54 consecutive patients admitted to ICU suffering from severe acute respiratory infection (SARI) and severe respiratory distress (ARDS) attributable to viral SARS - CoV - 2 infection were recruited. The recruitment criterion was based on refractory hypoxia, general condition and clinical impairment, comorbidities and CT images. The incoming parameters of the blood chemistry and radiology investigations and the timing of the gold - tracheal intubation were compared. Medical therapy was based on the application of shared protocols.
Results: The onset of symptoms was varyng, i.e. within the range of 1–14 days. The average time from the admission to the emergency room to the admission to intensive care was approximately 120 h. The average number of days of hospitalization in the ICU was 28 days. With a majority of male patients, the most significant age group was between 60 and 69 years. There were 21 deaths and, compared to the survivors, the deceased ones were older at an average age of about 67 years (vs an average age of the survivors of about 59 years). From the available data entering the ICU, the surviving patients presented average better values of oximetry and blood gas analysis, with a lower average dosage of D-Dimer than the deceased. Ones with a presence of bilateral pneumonia in all patients, the worsening of the ARDS occurred in 31 patients. 9 out of 25 patients early intubated died, while 12 out of 23 patients died when intubation was performed after 24 h of non-invasive ventilation. The presence of multiple comorbidities was shown in 17 of 28 patients and revealed an additional adverse prognostic factor. Also, more than one complication in the same patient were detected; after respiratory worsening, renal failure was more frequently found in 16 patients. Some particular complications such as lesions induced by ventilation with barotrauma mechanism (VILI), ischemic heart disease and the appearance of central and peripheral neurological events were detected too.

* Corresponding authors at: Major Hospital, Crema, Italy.
E-mail addresses: w.zuccon@asst-crema.it (W. Zuccon), p.comassi@hotmail.it, p.comassi@asst-crema.it (P. Comassi).

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Considerations: SARS - CoV - 2 disease is caused by a new coronavirus that has its main route of transmission through respiratory droplets and close contact, resulting in a sudden onset of the clinical syndrome with acute respiratory infection (SARI) and severe respiratory distress (ARDS). But it can also appear with other symptoms such as gastrointestinal or neurological events, as to be considered as a disease with multisystem phenotype. This pathology evolves towards a serious form of systemic disease from an acute lung damage to venous and arterial thromboembolic complications and multi-organ failure, mostly associated with high mortality. All patients received empirical or targeted antibiotic therapy for prevention and control of infections of potential pathogens, together with low molecular weight heparin therapy. The majority of patients was subjected to the off - label protocol with antivirals and hydroxychloroquine therapy, we used cortisone support therapy under surveillance and in 3 cases the protocol with anti - IL6 monoclonal antibody (Tolicizumab). In a simplified classification of the tomographic examination of the chest, mostly 3D and 2C lesions were found in the deceased patients with a prevalence of severe and moderate forms, whilst in the survivors the distribution appears with a prevalence of medium and moderate forms. Among the intubated patients, 21 patients, all suffering from worsening ARDS, died whilst there was no mortality in patients subjected to non-invasive ventilation it so. The heterogeneity of the respiratory syndromes and the presence of multiple comorbidities represent an unfortunate prognostic factor. Among the complications, besides the respiratory worsening, renal failure, liver failure and the state of sepsis were most frequently found; less frequent complications were lesions induced by ventilation with a barotrauma mechanism, ischemic heart disease, the appearance of central neurological events of sensory alterations, meningo - encephalitis and cerebral hemorrhage, and peripheral neurological events with polyneuro - myopathies. Mechanical ventilation can adversely affect the prognosis due to lung damage induced, protective ventilation remains the necessary treatment during severe hypoxia in patients with SARS - CoV - 2. The essential prerequisite remains the search for optimal 'customized' values since conditions can vary from patient to patient and, in the same patient, during different times of ventilation.
Conclusions: In these extraordinary circumstances, our reality was among the most affected and was able to hold the impact thanks to the immediate great response set in place by the operators, although it costed us an effort especially the one to try to guarantee a high quality level of assistance and care compared to the huge wave of patients in seriously bad conditions. Further research on this heterogeneous pathology and data sharing could help identify a more dedicated clinical decision-making and treatment pathway that, together with a resource planning, would allow us to better face any new disease outbreak.

1. Introduction

The new emerging infectious disease called SARS-CoV-2 generates a serious threat to public health. It spread rapidly also in Italy causing a wide morbidity and mortality, especially in Lombardy region. This new coronavirus can reveal itself with different symptoms and intensities, depending on the age group, the presence of pathologies, the timeliness of the diagnosis and other factors [1].

At our Emergency Department of the Crema Hospital, from the beginning of the pandemic until the end of June 2020 and from the analysis of the general chronology of the data collected so far and still under consideration for validation, access to the Emergency Department of cases attributable to SARS - CoV - 2 infection, confirmed and suspected (based on the symptoms, the lung CT picture and the nasopharyngeal swab), were 4343 equal to 4.6% of the cases of Lombardy Region; considering in our reality a catchment area of about 168,000 people, the prevalence was equal to about 25.8 cases for 1000 inhabitants.

Of these confirmed and suspected patients, 2590 patients (59.64%) were discharged and put in home isolation, 1369 patients (31.52%) were hospitalized, 274 patients (6.31%) were transferred to others hospitals, 110 patients (2.53%) died in emergency areas and 171 patients (12.4%) died in the ward; in this regard, the deceased patients were 190 males (67.62%) and 91 females (32.38%) of which 10 patients under 60 years (3.56%), 25 patients between 60 and 70 years (8,90%), 99 patients between 70 and 80 years (35.23%), 120 patients between 80 and 90 years (42.70%) and 27 patients over 90 years (9.61%).

In this work we took into consideration the clinical course and the outcomes of 54 consecutive patients (3.9%) admitted to Intensive Care Unit (ICU) and suffering from severe respiratory insufficiency attributable to viral SARS - CoV - 2 infection, with comparison of data between survivors and deceased. The main aim is to analyze and to share data at according to a critical review of the tests and in order to optimize the most dedicated clinical and treatment strategy for a future 'targeted' management if there will be an effective return of the outbreak.

2. Methods

At our Emergency Department of the Crema Hospital, from the start of the pandemic until the end of June 2020, 54 consecutive patients (3.9%) were admitted to the Intensive Care Unit (ICU) suffering from severe acute respiratory infection (SARI).) and severe respiratory distress (ARDS) attributable to viral SARS - CoV - 2 infection. Dyspnoic and hypoxic patients were hospitalized in whom the onset of symptoms varied between 1 and 14 days. The general reference parameters were SpO2 ≤ 92%, respiratory rate ≥ 28 acts per minute and a p/F ratio ≤ 300; further recruitment criteria were the general status (performance status) and clinical impairment, comorbidities and CT images. Of these patients 44 were male (81.5%) while 10 were female (18.5%), of which 1 patient (1 man) between 30 and 39 years (1.85%), 7 patients (6 men and 1 woman) between 40 and 49 years (13%), 11 patients (10 men and 1 woman) between 50 and 59 years (20.3%), 20 patients (14 men and 6 women) between 60 and 69 years (37, 1%), 14 patients (12 men and 2 women) between 70 and 79 years (25.9%) and 1 patient (1 man) between 80 and 89 years (1.85%).

All patients presented SARS CoV - 2 nasopharyngeal swab with Real Time PCR testing, complete blood chemistry, serial blood gas analysis, and chest CT scan. Gold tracheal intubation (IOT) was performed in 48 patients (88.8%) while 6 patients (11.2%) were treated only with non-invasive support ventilation (NIV); the IOT was sudden, or in any case performed within the 24 h from the access to the ICU, in 25 patients (4 women and 21 men) equal to 52%, while in the other 23 patients (6 women and 17 men) it was practiced after 24 h of non-invasive ventilation, equal to 48%; 3 patients underwent tracheostomy (6%).

All patients were given antibiotic, prophylactic or targeted therapy, and low molecular weight heparin therapy, 48 patients received support therapy with cortisone drugs, 50 patients were treated with the off-label compassionate therapy protocol with antivirals whilst 44 patients received hydroxychloroquine therapy, the protocol with tolicizumab was applied in 3 patients. The synergistic treatment of comorbidities present in 28 patients (51.8%) was not overlooked, the

hepato-renal, neurological and metabolic complications were extremely treated, and some cases of ventilation-induced lung complications were also managed (VILI).

3. Results

The ICU patient admission time interval was between 1 and 56 days, with an average of 28 days in hospital; with a prevalence of male patients, the most significant age group is between 60 and 69 years (37.1%). Of these ICU patients, there were 21 deaths (D) equal to about 38% and, compared to the survivors (S), the deceased ones were older with an average age of about 67 years (vs an average age of the survivors of about 59 years).

As from the data collected when patients entered the ICU, body temperature was in a range between 33,3 and 39 degrees Celsius for patients who then died and between 36 and 39.2 degrees Celsius for patients who then survived, the average PCR dosage (VN = 0–5) was 14,27 mg/dl for the former and 12,86 mg/dl for the latter, while the D-Dimer dosage (VN = 0,0–0,5 μg/ml) was elevated in 21 patients out of 25 available dosages, with an average concentration of 1,85 μg/ml in the patients died compared to an average concentration of 1,24 μg/ml in patients who later survived. The surviving patients presented on average better oximetry and blood gas values compared to the patients who died (S: SpO2 92% vs D: SpO2 86% - S: pO2 50.5 mmHg vs D: pO2 46.9 mmHg - S: p/F ratio 240 vs D: p/F ratio 223).

As from the CT scan of the chest, all patients had bilateral pulmonary impairment, the worsening of the ARDS occurred in 31 patients (57.4%). 8 patients were transferred to other hospitals, of which 2 patients underwent extracorporeal membrane oxygenation (ECMO) for hypoxemia refractory to invasive protective mechanical ventilation.

Among intubated patients 21 patients (including 3 women and 18 men) died at 56 days, all suffering from worsening ARDS. Among the deaths, 10 patients had an ICU stay of more than 10 days. 9 patients died out of 25 patients intubated early or in any case within 24 h of access to the ICU, while 12 patients died out of 23 patients where intubation was practiced after 24 h of ventilation. Non-invasive (NIV) which has become ineffective for the subsequent clinical worsening of the patient; of these two groups, the calculation of the average time from admission to the emergency room to admission to intensive care was approximately 120 h in both groups. There was no mortality in the 6 patients who underwent non-invasive ventilation alone.

The presence of multiple comorbidities was present on 17 deceased patients on 28 patients affected by these and represented an additional unfavorable prognostic factor; specifically for pre-existing diseases, 26 patients with 0 pathologies (4 D), 3 patients with 1 pathology (1 D), 11 patients with 2 pathologies (6 D), 13 patients with 3 pathologies (9 D) and 1 patient with 4 pathologies (1 D).

As regards complications, more than one complication occurred in the same patient during the ICU admission. After respiratory worsening, renal failure was more frequently found in 16 patients (29.6%) where there were 13 deaths; of the patients with renal insufficiency, including 2 patients undergoing peritoneal dialysis, 7 patients also had liver failure and 6 patients experienced an evolution of the clinical state in sepsis. Specific complications such as lesions induced by ventilation with a barotrauma mechanism (pneumothorax, pneumomediastinum, subcutaneous emphysema) were found in 6 complicated cases, ischemic heart disease in 3 complicated cases, the appearance of both central neurological events of sensory changes in 5 complicated cases, meningo - encephalitis in 2 complicated cases, cerebral hemorrhage in 1 complicated case, and peripheral neurological events with neuropathy in 2 complicated cases and with paresis in 3 complicated cases.

4. Notes of physiopathology

The respiratory system is the preferential pathway of the virus which, following the inhalation of droplets and the binding of the virus with the receptors type ACE2 of the broncho-alveolar mucosa, invades the bronchial epithelium, the alveolar epithelial cell and endothelial cells, resulting in a severe alteration of the capillary alveolus membrane; subsequently, it inhibits the immune response and continues systemic diffusion.

As can be seen from the literature data, the pulmonary pathological process corresponds to diffuse alveolar damage (where the ground glass density is its radiological representation), accompanied by thrombotic microangiopathy (microvascular pulmonary thrombosis) and associated foci of alveolar hemorrhage up to a more general organ failure, up to the proliferative phase of lung consolidation, interstitial and intralobular fibrosis. Although the reasons for these hemostatic changes are still under study, that is, if they are a consequence of a 'superinflammation' or are due to the mediated effect of the coronavirus, in patients with SARS - CoV - 2 the theory seems to be demonstrated where the pathological process lung starts with a high production of early response proinflammatory cytokines, type IL-1, IL-6, IL-7 and TNFα, which would thus confer a hyperinflammatory cascade state with damage to microvascularization and endothelial damage/dysfunction, haemostatic aggregation changes platelet and thrombus generation within pulmonary vascularization [2]. In fact, the patients in critical conditions affected by this disease are the ones to have a high risk of thromboembolism. Therefore a higher risk of death, in relation to immobility, the inflammatory state induced by viral infection, platelet activation, dysfunction endothelial with activation of plasminogen and blood flow stasis, develop coagulation anomalies and define a state of systemic coagulopathy [3]. This form of disseminated intravascular coagulation, as a basic hematological characteristic, seems to be confirmed by the combination of an increase in D-Dimer concentration, a reduction in the platelet count and an extension of the prothrombin time in patients severely affected by SARS - CoV - 2, values increasingly prevalent if the disease is in its evolutionary phase; other relevant laboratory anomalies are the increase in lactate dehydrogenase or LDH and ferritin. In these serious patients, if the concentration of D - Dimer greater than 1 mg/L seems to have entailed an 18 times greater risk of death, mild thrombocytopenia (70–95% of affected patients) does not currently seem to be a specific predictor of the disease progression [4,5].

5. Considerations

SARS - CoV - 2 disease is caused by a new coronavirus that has its main route of transmission through respiratory droplets and close contact, resulting in a sudden onset clinical syndrome of acute respiratory infection (SARI) with at least one fever symptom, dry cough or wheezing [6]; on the other hand, in relation to the different clinical symptoms with which it can occur, such as respiratory pneumonia of rapidly progressive pneumonia or with gastrointestinal or neurological prevalence, this disease can be considered a multisystem phenotype whose natural history we do not know well yet.

In this retrospective observational study, 54 consecutive patients admitted to Intensive Care Unit (ICU) suffering from severe acute respiratory infection (SARI) and severe respiratory distress (ARDS) were recruited in certain or suspected manner to be explicit SARS - CoV - 2 coronavirus.

Regarding the recruitment criterion, their access to the ICU was provided for dyspnoic patients with hypoxic respiratory insufficiency. The patients were assessed on the basis of different variables such as the status of the general conditions (performance status) and clinical impairment, comorbidities and Tac images, also considering general reference parameters such as a SpO2 ≤ 92% in ambient air, a tachypnea with respiratory rate ≥ 28 acts per minute and a ratio between partial pressure and inspiratory fraction of oxygen PaO2/FiO2 ≤ 300 mmHg (mild hypoxemia with value ≤300, moderate with value ≤200 and severe with value ≤100) [7]. As shown in the simplified comparison chart A, among all ICU candidate patients, those who survived presented, on an average, have better blood gas values than the patients who died; these reference values could guide the clinical outcome and prognosis.

Reference values blood gas analysis DEATHS	Reference values blood gas analysis SURVIVORS
SpO2: 86%	SpO2 92%
pO2: 46,9 mmHg	pO2 50,5 mmHg
p/F ratio: 223 mmHg	p/F ratio 240 mmHg
Lactates: 2,06 mmol/L	Lactates: 1,4 mmol/L
Respiratory and Metabolic Alkalosis	Respiratory and Metabolic Alkalosis
88.8% of patients	78.7% of patients

The simplified comparison chart A, for patients entering the ICU, shows the average reference values of the blood gas analysis between those who survived and died; in the latter the reference values are worse and hyperlactacidemia is present.
SpO2 (V.N.: 94–97%) - pO2 (V.N.: 83–108 mmHg) - p/F ratio (V.N. ≥ 350 mmHg) - Lactates (V.N.: 0.5–1.6 mmol/L).

All patients performed SARS CoV - 2 nasopharyngeal swab with Real Time PCR tests, blood chemistry, serial blood gas analysis, and chest CT scan. In this regard, as shown in a simplifying manner in classification B, as regards the first chest tomographic, in the later deceased patients, an extension of the 3D and 2C type lesions was found with a prevalence of severe and moderate forms, whilst in the surviving patients the extension appears to be prevalent for the medium and moderate forms. If, on the one hand, the type and extent of lung lesions were distributed variably in all patients entering the ICU, just as the radiological findings were variable in relation to the onset of symptoms, on the other, the subsequent mortality was greater not only in those patients with worse 3D radiological severity, but also in type 2C, or where the number of comorbidities present, on average equal to 2 pathologies for each group, was similar between these groups; in this regard, it appears likely to expect a negative prognostic evolution if the presence of multiple comorbidities, the clinical worsening of respiratory distress and systemic complications in the subsequent stages are associated.

Type and Extension of lung lesions (bilateral) ---------- Onset of symptoms and radiology ---------- DEATHS	Type and Extension of lung lesions (bilateral) ---------- Onset of symptoms and radiology ---------- SURVIVORS
Type 3D	Type 3D
from 3 to 15 days	from 3 to 9 days
(7 patients)	(4 patients)
Type 3C	Type 3C
from 4 to 7 days	from 3 to 10 days
(4 patients)	(6 patients)
Type 3B	Type 3B
from 3 to 14 days	from 4 to 6 days
(2 patients)	(3 patients)
**********	Type 2D
	from 1 to 12 days
	(6 patients)
Type 2C	Type 2C
from 3 to 7 days	from 1 to 14 days
(6 patients)	(6 patients)
Type 2B	Type 2B
from 3 to 10 days	from 3 to 9 days
(2 patients)	(7 patients)
	Type 2A
**********	to 5 days
	(1 patient)

Simplified classification B. The different types of lesions and the pulmonary compromise of patients undergoing pulmonary CT of the ICU patients are reported. Both the variability of the type and extent of lung lesions and the variability of radiological findings in relation to the onset of symptoms are shown.
Legend:
Pulmonary parenchyma involvement: bilateral.
Lung injury: 1. Absence of injury 2. Presence of ground glass lesions without consolidation areas 3. Presence of ground glass lesions with consolidation areas 4. Presence of consolidation areas.
(consolidation: parenchyma filled with inflammatory cell exudate in the pulmonary alveoli)
- Lung injury extension: A. Minimal (1–25%) B. Medium (26–50%) C. Moderate (51–75%) D. Severe (76–100%).

With a prevalence of male patients, the most represented age group in ICU was between 60 and 69 years, the worsening of the ARDS occurred in 31 patients, the average hospitalization time was 28 days and the calculation of the average time from the admission at the emergency room and the admission at intensive care was approximately 120 h. Tracheal gold intubation was practiced in most patients, whilst 6 patients were treated only with non-invasive support ventilation, i.e. in those patients who did not shown clinical deterioration; among intubated patients, 21 patients all with worsening ARDS died, whilst there was precisely no mortality in patients subjected to non-invasive ventilation alone.

All our patients have received empirical or targeted antibiotic therapy as needed, for the prevention and control of infections of potential pathogens responsible for severe respiratory failure, together with low molecular weight heparin therapy [8]. The majority of patients were also treated with the off - label compassionate therapy protocol with antivirals, such as the one for hydroxychloroquine therapy, while under cortisone therapy under surveillance, although under conditions of clinical deterioration and ARDS, its effectiveness may be controversial [9-12]. The anti-IL6 monoclonal antibody protocol (Tolicizumab) was applied in 3 patients with severe respiratory distress and instability. In fact, based on evidence, starting from the assumption that this multifunctional cytokine (acute phase protein) is the mediator of fever and systemic inflammatory response for severe forms, some research displayed the correlation between inflammation and lung damage induced by cytokine release with the clinical evolution of rapidly progressive pneumonia in critically ill patients; therefore, significant differences were found in the serum expression of IL-6 receptor levels in the different disease stages with levels of this cytokine significantly higher in patients with severe disease than in patients presenting mild symptoms [13].

As from the data collected on entry to the ICU, the average PCR dosage was 14.27 mg/dl for patients who died and 12.86 mg/dl for patients who survived, the dosage of D-Dimer was increased and had an average concentration of 1.85 μg/ml in patients who died compared to an average concentration of 1.24 μg/ml of patients who survived. Multiple comorbidities were present in 17 deceased patients out of 28 affected patients including cerebral vasculopathy, heart disease, diabetes mellitus, chronic bronchopathy, renal failure, high blood pressure, liver cirrhosis, obstructive apnea syndrome OSAS, obesity, immunodepression and neoplasms.

Some general considerations apply in this regard.

Although most SARS - CoV - 2 patients have predominantly a respiratory tract infection, in these cases a part of the patients evolve towards a serious form of systemic disease, i.e. from acute lung damage we move on to venous and arterial thromboembolic complications and multi-organ failure, mostly associated with high mortality; in particular, it is clear that pneumonia, respiratory failure and sepsis, including myocardiopathies and neuropathies, represent serious complications among patients hospitalized for this virus, therefore the possibility of developing systemic diseases and multi-organ failure is high [14]. Furthermore, starting from the assumption that the evaluation of comorbidities serves to adapt the treatment of the critically ill patient and therefore to allow to formulate a prognosis, the heterogeneity of the respiratory syndromes and the presence of multiple comorbidities represent an unfavorable prognostic factor. Furthermore, in patients with sudden respiratory deterioration, and high blood concentrations of D - Dimer, pulmonary embolism may be the cause. In fact, pending further studies, the recommendations are to monitor hemostatic markers (D - Dimer, Prothrombin Time and Platelet Count) in patients with SARS - CoV - 2, adopting in the prevention of coagulopathy, and therefore in term to reduce mortality, the systematic use of low molecular weight heparin (LMWH), with

the dual anticoagulant and anti-inflammatory effect, unless there are no contraindications (other anticoagulants, such as Antithrombin III or complement inhibitors, are still being tested).

As regards complications, more than one complication occurred in the same patient during the ICU admission. After the respiratory worsening, renal failure was more frequently found, then liver failure and sepsis. Some particular complications have been found such as lesions induced by ventilation with a barotrauma mechanism (pneumothorax, pneumomediastinum, subcutaneous emphysema), ischemic heart disease, the appearance of central neurological manifestations of sensory alterations, meningo - encephalitis and cerebral hemorrhage, and of peripheral neurological manifestations with polyneuro - myopathies (CRIMYNE or CRitical Illness MYopathy and NEuropathy), conditions often associated with multiorgan failure. In this regard, further preliminary research observations are starting to take shape in the meantime, such as the identification of the genetic mutations (genetic susceptibility) underlying the serious neurological complications caused by this virus, as they seem to make some people highly vulnerable to viral infections [15].

As regards lung complications, the ventilation-induced damage (VILI) with the barotrauma mechanism represented a side effect that affected 6 complicated cases. As reported in the literature, the iatrogenic effect of ventilation, which relaxes an already pathological lung, adversely affects through a mechanical stress mechanism with a high tidal volume, followed by a biological response with activation of inflammation mediators and subsequently the achievement of the rupture limit of alveolar walls and pulmonary capillaries [16]. The objective to be pursued in an emergency, also in order to limit VILI damage, should be to prefer the use of a contained tidal volume (6–8 ml/kg of ideal weight and depending on the degree of hypoxemia) and to contain the driving pressure (without exceeding 15 cmH2O), the latter regulating it with the application of a 'modulated' PEEP according to the case (allows a more uniform distribution of stress), that is, testing different plateau pressure values, a parameter mostly related to pressure transpulmonary, or pulmonary distension force, and not at tidal volume [16]. On one side it is to be provided that mechanical ventilation can adversely affect the prognosis due to lung damage induced, in a mortality rate that is already high in those patients who generally have ARDS, on the other side protective ventilation remains the necessary care during severe hypoxia in patients with SARS - CoV - 2. The essential prerequisite is to be the search for optimal 'personalized' values as conditions can vary from patient to patient and, in the same patient, during different times of ventilation. Furthermore, further studies are underway on the prevention of VILI such as the evaluation of the two phenotypes of patients with SARS - CoV - 2 pneumonia, type L (high compliance) and type H (severe ARDS) [17].

As from the reported data, it is therefore evident that mortality can be high in critically ill patients with SARS-CoV-2 pneumonia who access the ICU. In the reported series, patients with an average age of about 67 years (vs an average survivor age of about 59 years) and with multiple comorbidities were the subjects most at risk of death; the associated conditions of sepsis, cardiopathies and neuropathies, as well as the situation of VILI damage, have further complicated the intensive clinical management of patients already suffering from a pathological lung for ARDS.

We believe that further studies are needed for this heterogeneity of clinical pictures so that, targeted therapies can be obtained and therefore will meet the needs of individual patients.

6. Conclusions

The SARS - CoV - 2 outbreak put a strain on our emergency and intensive care units, exceptional measures to contain this disease, which led to an overcoming of the effective capacity of the hospital and of the places in ICU also for long hospital stays had to be activated. In these extraordinary circumstances, our reality was among the most affected but withstood the impact thanks to the great immediate response put in place by the operators, although it cost a lot of effort especially to try to guarantee a high quality level of assistance and care compared to the huge wave of number of serious patients.

At the beginning just, little was known about the natural history, virulence, infectivity and lethality of the disease but during this challenge many 'lessons' were learned on the management of this clinical spectrum. Let's not forget that this emergency triggered collaborative efforts and impressive therapeutic interventions, where it was necessary to quickly train a part of the healthcare personnel involved and teach them the multiple management procedures (airway, sedation and analgesia, treatment with oxygen therapy, ventilatory and hemodynamic support) in order to have an 'intensive' approach such as to give rapid and adequate diagnostic and therapeutic responses for the local emergency.

At the time of the pandemic, although a standardization of procedures and specific protocols was adopted, the lack of certain procedures and targeted therapies for this unknown pathology influenced some aspects of the clinical management of these patients by virtue of the critical and heterogeneous conditions and particular therapeutic needs they require. On the other hand, the treatment for SARS -CoV - 2 infection has taught us a lot, for example, on the need to exploit as much as possible the interventions with proven benefits, such as protective lung ventilation for severe acute respiratory distress, i.e. limit the use of particular interventions that could instead cause damage.

Further research on this pathology, such as data collection and sharing and a critical review of the evidence, or identifying patients at high risk of severe respiratory distress and the key elements of intensive treatment, will be useful in order to get a clinical decision-making process and care treatment more specified, where resource planning also becomes essential to deal with any new disease outbreak.

Declaration

The Authors transfer ownership of the copyright to the American Journal Emergency Medicine in the event that their work is published in the same Magazine. They declare that the article is original, has not been sent for publication to another magazine and has not already been published. They also state that the research reported in their work was performed in accordance with the Helsinky Declaration and the principles governing animal research.

Collaborators

Surgery Unit: Roberto Bassi, MD, Stefano Beltrami, MD, Filiberto Fayer, MD, Italo Galli, MD, Domenico Giuliani, MD, Gianattilio Puerari, MD, Edoardo Segalini, MD, Agostino Savoia, MD, and Marco Monti, MD.

Authors contribution

ZW: Conducted the study, did the literature search and prepared the manuscript.

PC: Conducted the study, did the literature search and prepared the manuscript.

FD: Literature review and prepared the manuscript.

GM: Statistical data analysis.

GM: Helped in contributed to preparation of manuscript.

GV: Revision of the manuscript for publication.

All Authors have seen the final manuscript and approve its publication.

Ethical considerations

Support for this study was provided exclusively from institutional and/or departmental sources.

The data of the participants will be provided after the approval of the corresponding author and of the Health Management of the Crema Hospital.

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Declaration of Competing Interest

This study does not have any financial support from manufacturer or other sources. None of the Authors has any conflict of interest to declare.

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