Clinical presentation and initial management critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Brescia, Italy

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ABSTRACT

Purpose: An ongoing pandemic of COVID-19 that started in Hubei, China has resulted in massive strain on the healthcare infrastructure in Lombardy, Italy. The management of these patients is still evolving.

Materials and methods: This is a single-center observational cohort study of critically ill patients infected with COVID-19. Bedside clinicians abstracted daily patient data on history, treatment, and short-term course. We describe management and a proposed severity scale for treatment used in this hospital.

Results: 44 patients were enrolled; with incomplete information on 11. Of the 33 studied patients, 91% were male, median age 64; 88% were overweight or obese. 45% were hypertensive, 12% had been taking an ACE-inhibitor. Noninvasive ventilation was performed on 39% of patients for part or all or their ICU stay with no provider infection. Most patients received antibiotics for pneumonia. Patients also received lopinivir/ritonavir (82%), hydroxychloroquine (79%), and tocilizumab (12%) according to this treatment algorithm. Nine of 10 patients survived their ICU course and were transferred to the floor, with one dying in the ICU.

Conclusions: ICU patients with COVID-19 frequently have hypertension. Many could be managed with non-invasive ventilation, despite the risk of aerosolization. The use of a severity scale augmented clinician management.

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Research in Context

In 2019, a novel coronavirus emerged from Wuhan, China. This virus, called SARS-CoV-2 and its disease, COVID-19, spread beyond China, causing a global pandemic. Italy has recently been devastated by the pandemic, resulting in emergency triage and massive strain on resources for critically ill patients.

Evidence before this study

The clinical presentation and transmission of COVID-19 have been described elsewhere. Other countries that have reported large infections have mitigated spread through massive testing, such as

South Korea, or complete lockdown and massive construction of hospitals and medical equipment, as in China. Italy's crisis appears to foreshadow the sort of crisis expected in the rest of Europe and the Americas. In the Lombardy region of Italy, there have been massive shortages in equipment and personnel, with non-intensivists managing critically ill patients.

Added value of this study

This is the first reported cohort of ICU patients with COVID-19 from the Lombardy region. In addition to describing the clinical management of such patients, this study details a proposed severity scale that was used to communicate with non-intensivists for management and triage, and for a step-up approach to drug therapy including antivirals, desamethasone and selective cytokine blockers.

Implications of all the available evidence

The COVID-19 global epidemic will require hospitals to prepare for resource shortages and utilization of non-intensivist physicians. Creation of a severity scale to assess patients with COVID is of value to hospitals and physicians facing such shortages.

1. Introduction

The pandemic spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its disease, COVID-19, has resulted in massive strain in healthcare systems in several countries. Recently, the Lombardy region of northern Italy has reported massive infection, overwhelming the region's capacity to care for such patients. At present, there are over 700 intensive care patients in Lombardy, and over 1400 deaths in Italy attributed to this infection. As this infection is novel, there is no proven treatment for patients presently. The global tracking of spread suggests other countries are likely to have similar strains on their infrastructure in caring for these patients. China, where the SARS-CoV-2 originated, has slowed the progression of the pandemic with strict social distancing, while South Korea has similarly impeded spread with widespread testing. Europe and the United States appear poised for similar pandemics as Italy in the absence of significant societal or governmental interventions.

The experience of Lombardy is interesting in that despite Italy having the third most number of ICU beds per capita, after the United States and Germany, physicians have had to limit resources due to shortages [1]. Practicing physicians have previously not experienced massive triage based on resource limitations prior to this pandemic. These resource limitations have resulted in the creation of ethical guidelines on conserving resources at the expense of many human lives [2]. Clinicians have been overwhelmed and working beyond capacity. Many non-intensivist physicians have had to manage critically ill patients with limited expertise or guidance. Additionally, in the absence of proven therapies and overwhelming disease, many physicians have been attempting novel therapies in the hopes of mitigating the disease. Part of the reason for attempting these novel therapies is the realization that rigorous study of therapies will likely be too late to be of benefit for many people who will otherwise die. In the absence of clinical trials, bedside clinicians need an instrument to assess disease progression or improvement in patients with COVID-19.

We report the experience of the Brescia Spedali Civili hospital, a large general regional university hospital serving an area of 1.2 million people in Lombardy Italy, in the hopes that this information might be informative for other hospitals in preparing for the pandemic.

2. Methods

This is a prospective, observational cohort of critically ill patients with confirmed SARS-CoV-2 infection admitted to the intensive care

units in Brescia, Italy between March 2 and March 13, 2020. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. This study was performed with waiver of informed consent by the Brescia Institutional Review Board and ethics board. Viral infection was confirmed at a World Health Organization (WHO) reference laboratory. Bedside clinicians recorded clinical data upon admission to the ICU and daily thereafter. Clinicians recorded medical history and outpatient medications and calculated the Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Assessment (SOFA) score upon admission. Clinicians also recorded daily clinical, ventilator, and laboratory data, diagnostic tests, and therapies administered. Clinical outcomes were recorded but are incomplete at the time of this manuscript. Data are reported using simple descriptive statistics. We report central tendencies of continuous variables as medians with interquartile ranges. All statistical analyses were performed using Stata, v16 (Statacorp, College Station,Texas, USA).

2.1. Creation and use of the Brescia Respiratory COVID Severity Scale (BRCSS)

During the management of these patients, intensivists had limited guidance on management. These intensivists created a management schema (Fig. 1) to describe the clinical improvement or worsening of disease and used this schema to try to create replicable treatments among patients in ICU and admitted to the ward. The aspiration of this schema was twofold: It allowed for consistent communication and decision-making among providers who were working beyond capacity, and it offered some bedside assessment of whether patients were clinically improving while receiving adjunctive therapies.

The BRCSS was created by sharing experience between physicians of different specialties. Since the onset of the Lombardy COVID-19 pandemic, a daily multidisciplinary meeting was held to coordinate patient care and transfer between units. Participants of these meetings included intensivists, infectious disease physicians, chest physicians, immunologists, rheumatologists, and internists. The scale (Fig. 1) was designed for rapid and common communication between clinicians, to achieve consistency on when to initiate therapies (antiretroviral therapy, corticosteroids, tocilizumab), and to help clinicians not familiar with ventilation to manage the outbreak.

The study hospital had two ten-bed general intensive care units (20 beds total), and one six-bed cardiac intensive care unit. At the time of drafting this paper, the hospital is actively managing 49 COVID-19 ICU beds and 14 general ICU beds, for a total of 63 ICU beds. Daily operating room surgical activity has ceased, and many COVID-19 patients are managed with NIV ventilation on the wards. Despite these efforts, the hospital is still unable to sufficiently staff patients in need. Non-intensivists staffing these beds relied on the BRCSS to communicate efficiently regarding the state of patients to other clinicians.

The BRCSS uses clinical criteria to rate the non-intubated patient, assigning a score of 0 to 3, relying on the four testing criteria: 1) dyspnea or staccato speech, defined as being unable to count rapidly up to 20 after a deep breath, at rest or during minimal activity, such as sitting up in bed, standing, talking, swallowing, coughing; 2) respiratory rate > 22 breaths/min; 3) PaO2 <65 mmHg or SpO2 < 90% with supplemental oxygen; 4) Significant worsening of chest radiograph. Among intubated patients, a threshold $PaO_2/FiO_2 < 150$ mmHg determined a score of 5 or higher, and adjunctive therapies including prone positioning and neuromuscular blockade agents increased the score higher.

3. Results

We studied 44 patients. At the time of this manuscript, data information concerning the outcome was incomplete on 11 patients, making a study population of 33 patients. Patient characteristics are detailed in
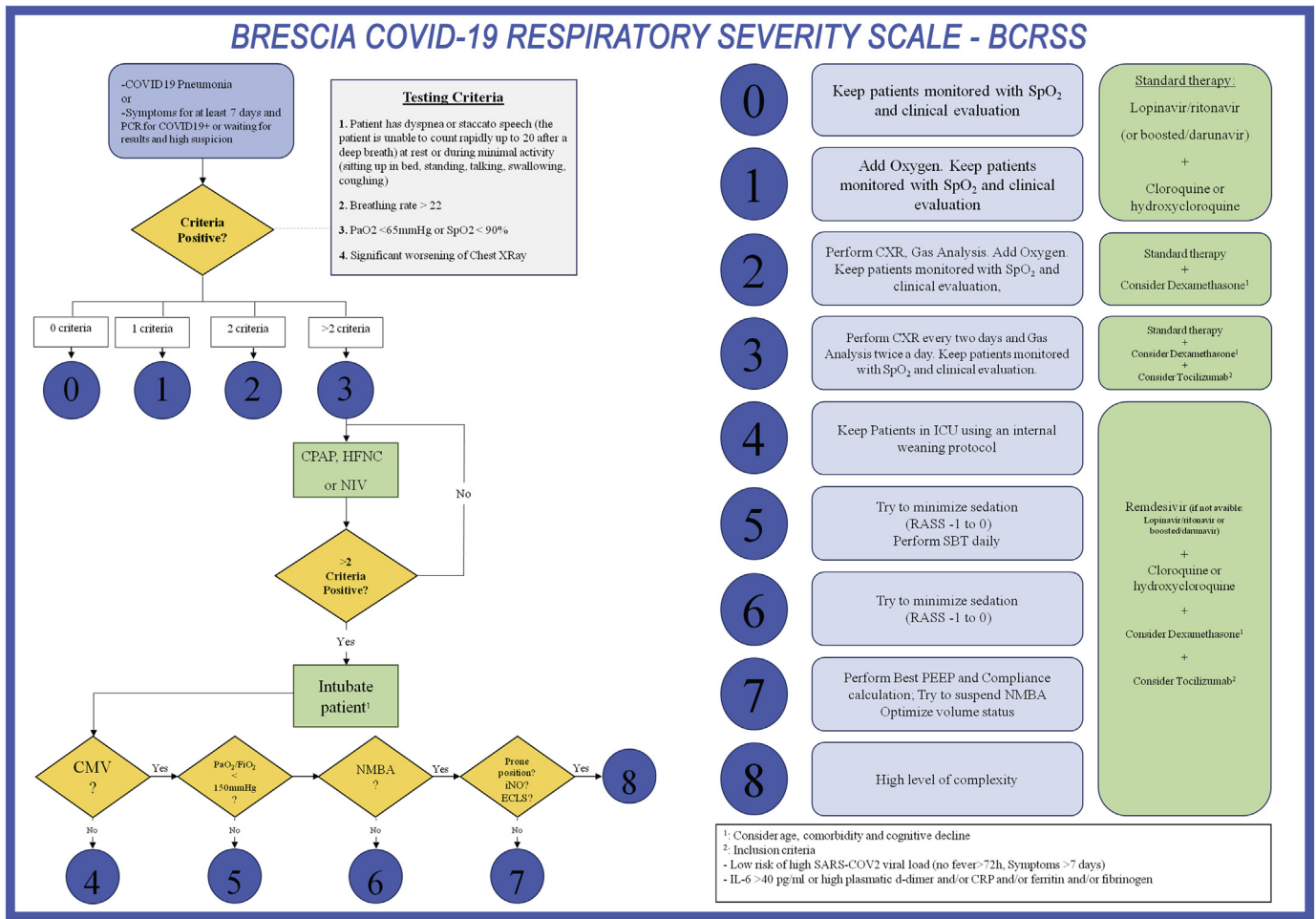
Fig. 1. The Brescia Respiratory COVID-19 Severity scale.

Table 1. The study population was 90.9% male, with a median age of 64 years (interquartile range 59–72). The youngest was 50 years old, and the oldest was 76 years old. Obesity was present in 31% of patients, with an additional 58% being overweight. Almost half (43%) the patients had heart disease, with hypertension being most common. Fifteen patients (45%) had hypertension, and four (12%) had been taking an angiotensin-converting enzyme (ACE) inhibitor. Most patients presented neurologically intact. Many patients were euthermic their first day in the ICU, with only one patient having fever >38.4 °C, and one patient hypothermic <35 °C. The majority of the patients who presented to the ICU had already been intubated prior to arrival or on the first day of ICU admission. All but one patient (97%) required FiO$_2$ ≥ 50% at admission to the ICU, with a median of 80%, although patients were able to oxygenate with adequate SaO$_2$ values. Severe ARDS, with paO$_2$/FiO$_2$ < 150 mmHg, was present in 64% of patients. Half the patients were receiving neuromuscular blockade agents on their first day of ICU care. Although one third of the patients required vasoactive medications to maintain blood pressure, there was generally no difficulty in maintaining adequate mean arterial pressures at admission. Initial laboratory data is also presented in Table 1. Of note, patients often presented with normal white blood count, with almost invariably reduces lymphocytes. Troponin often was mildly to moderately elevated. Procalcitonin was more often normal (median 0.35 ng/dL, IQR 0.15–23), while C-reactive protein was often extremely elevated (median 133.55 mg/L, IQR 89.7–167). One patient was found to have extended spectrum beta-lactamase E. coli in the blood. Otherwise, blood culture data revealed no other infections. Basic chemistry panels were often normal, as was arterial lactate.

3.1. ICU course and therapies received

During hospitalization, echocardiography was performed in 7 patients (21%), of which 4 (57%) were abnormal. Three patients (9%) developed pneumothorax during their ICU stay. Thirteen (39%) patients were managed with non-invasive positive pressure ventilation for part or all of their ICU stay. Patients who received invasive mechanical ventilation were ventilated with low tidal volume ventilation. The median tidal volume adjusted for predicted body weight, measured from mechanically ventilated patients over all ICU days, was 6.3 mL/kg (Interquartile range 5.7–6.9). Patients adhered to a high PEEP strategy. Median PEEP measured from mechanically ventilated patients over all ICU days, was 14 cm H$_2$O (IQR 12–15). Patients receiving noninvasive ventilation had lower EPAP values (11 cm H$_2$O, IQR 8–12)

Most patients received targeted therapies for COVID-19. These therapies were administered according to the BRCSS. As a patient had increasing disease severity, more adjunctive therapies were administered (Fig. 1). Patients received combination lopinivir/ritonavir (82%), hydroxychloroquine (79%), dexamethasone (85%) and tocilizumab (12%). The decision to administer therapies was based upon the BRSSNine of 10 patients survived their ICU course and were transferred to the floor, with one dying in the ICU. The remainder of the patients remain in the ICU at the time of drafting this manuscript.

4. Discussion

The SARS-CoV-2 pandemic is perhaps the most devastating global event in modern medicine. Physicians and scientists are struggling for

Table 1

Demographic characteristics, symptoms, evaluation, and clinical course of 33 case patients. All continuous data are presented as median and interquartile range. ACE: Angiotensin Converting Enzyme.

Characteristic	Value
Male sex – no./total (%)	30/33 (91)
Age, y ($n = 31$)	64 (59–72)
Weight, kg ($n = 26$)	85 (80–95)
Body Mass Index, kg/m^2	27.8 (27.0–32.1)
Medical history	
Heart disease	14/33 (43)
Obesity	6/33 (18)
Lung disease	4/33 (12)
Diabetes	2/33 (6)
Autoimmune disease or immunodeficiency	1/33 (3)
None of the above	8/33 (24)
Outpatient medications	
ACE inhibitor	4/33 (12)
Beta blockers	2/33 (6)
Immunosuppressive drugs	0/33 (0)
Aspirin	0/33 (0)
Non-steroidal anti-inflammatory drugs	0/33 (0)
Disease severity on day of ICU admission	
Simplified Acute Physiology score ($n = 22$)	32.5 (30–38)
Sequential Organ Failure Assessment score ($n = 22$)	3.5 (3–7)
Glasgow Coma Score ($n = 27$)	15 (3–15)
Lowest Mean Arterial Pressure, mm Hg ($n = 29$)	73 (70–86)
Lowest SaO$_2$,% ($n = 29$)	96 (92–97)
FiO$_2$, % ($n = 29$)	80 (60–80)
PaO$_2$/FiO$_2$, mmHg ($n = 28$)	132.5 (80–178.5)
Temperature, °C ($n = 29$)	36 (35.8–36.8)
Ventilatory status	
Mechanical Ventilation	20/29 (69)
Non-invasive positive pressure ventilation	4/29 (14)
Spontaneously breathing	5/29 (17)
Receipt of vasopressors	10/29 (34)
Renal Replacement Therapy	1/29 (3)
Prone position ventilation	0/29 (0)
Neuromuscular Blockade Agents	14/29 (48)
Laboratory data on admission	
White blood cell count/mm^3 ($n = 27$)	6.53 (3.87–8.93)
Hemoglobin, g/dL ($n = 27$)	13.1 (11.9–14)
Platelet count 1000/mm^3 ($n = 27$)	173 (137–229)
International normalized ratio ($n = 22$)	1.1 (1–1.2)
Partial Thromboplastin Time ($n = 25$)	31.2 (25.8–32.4)
Sodium, mEq/L ($n = 27$)	138 (135–141)
Potassium, mEq/L ($n = 27$)	3.7 (3.5–4.0)
Creatinine, mg/dL ($n = 27$)	1 (0.88–1.24)
Troponin T, ng/L ($n = 14$)	15 (11–35)
Procalcitonin, ng/mL ($n = 7$)	0.35 (0.15–23)
C-reactive protein, mg/L ($n = 22$)	133.55 (89.7–167)
Lactate, mmol/dL ($n = 27$)	1 (0.9–1.4)
PaO$_2$, mmHg ($n = 28$)	83.5 (64.5–108.5)
PCO$_2$, mmHg ($n = 28$)	38.5 (34.5–49)
Arterial pH ($n = 28$)	7.42 (7.32–7.49)
Therapies received during ICU hospitalization	
Carbapenem antibiotic	4/33 (12)
Cephalosporin antibiotic	7/33 (21)
Macrolide antibiotic	18/33 (55)
Penicillin antibiotic	23/33 (70)
Other antibiotic	2/33 (6)
Dexamethasone	28/33 (85)
Lopinivir/Ritonavir	27/33 (82)
Hydroxychloroquine	26/33 (79)
Tocilizumab	4/33 (12)
Parenteral nutrition	10/33 (30)
Vasopressors	18/33 (55)
Renal Replacement Therapy	2/33 (6)
Prone position ventilation	3/33 (10)
Neuromuscular Blockade Agents	18/33 (55)
Clinical outcome	
Discharged from ICU alive	9/33 (27)
Died in ICU	1/33 (3)
In ICU at time of manuscript	23/33 (70)

therapies to mitigate this disease. Lombardy has been affected heavily enough to require ethical triage that has not been seen in several generations. We report the clinical practice of intensive care physicians from one of the public hospitals in this region.

The physicians practicing in this hospital are currently overwhelmed with staffing and resource shortages. Many of the hospitals in the United States are currently drafting their own protocols. Many such protocols have avoided the use of non-invasive positive pressure ventilation due to its risk of further aerosolizing the COVID-19 virus. However, with the possibility of a crisis, such plans may need to be revised for the possibility of non-invasive ventilation. Brescia hospital has managed a sizable proportion of its patients with non-invasive ventilation, without evidence of transmission to hospital staff who use appropriate personal protective equipment.

The physicians at the study hospital have administered targeted therapies for COVID-19. SARS-CoV-19 is a betacoronavirus, as are SARS and Middle East respiratory syndrome (MERS) coronoviridae. Drugs such as lopinavir-ritonavir, interferon, chloroquine, and corticosteroids, have been used in patients with SARS or MERS, with controversial efficacy. The proteinase inhibitor lopinavir inhibits SARS coronavirus, and ritonavir inhibits metabolism of lopinavir, thus increasing its concentration [3]. The combination lopinavir/ritonavir is speculated as a possible therapy for COVID-19, as it has demonstrated some efficacy as a treatment for SARS. Chloroquine and hydroxychloroquine are anti-malarial drugs that have demonstrated in-vitro efficacy against COVID-19 by an as yet not fully understood mechanism [4,5]. Hydroxychloroquine might be preferred as it has fewer side effects than chloroquine, but have neither have yet demonstrated efficacy in infected patients. Similarly, remdesivir is a potent inhibitor of RNA-dependent RNA polymerase from MERS, and has also demonstrated in-vitro efficacy against COVID-19 [6,7]. Tocilizumab is an interleukin-6 inhibitor with a fairly good safety profile is being studied in China for treatment of COVID-19 [8]. At present, there are several trials underway in China to test these therapies [9], but the answers to such trials may be well after the SARS-CoV-2 virus has swept across the globe, killing millions.

These therapies are not supported in the current WHO's interim guidance on managing COVID-19 disease [10]. There is no clear benefit of these interventions, and recommendations are that investigational therapies should only be conducted in the setting of randomized trials or Monitored Emergency Use of Unregistered Interventions (MEURI). Our cohort is insufficiently powered to draw any useful inferences from these anti-COVID-19 drugs. We describe these interventions to offer insight of how physicians treated critically ill patients suffering from a disease with no proven therapies. However, the value of adhering to a severity scale was that interventions could be applied consistently between patients. We believe an instrument, even unvalidated, to guide adjunctive therapies is extremely import for future studies that will attempt to make inferences on those therapy. At present, the numbers are insufficient to make any inferences on the efficacy of therapy. However, as more data accrue, the adherence to a treatment algorithm will improve the quality of such inferences. The ventilator management in this cohort adhered to the WHO guidelines on low tidal volume ventilation and higher PEEP. However, the interim guideline advocates for prone positioning in patients with severe ARDS, and avoidance of routine neuromuscular blockade. Prone positioning was employed in only 10% of patients, and neuromuscular blockade was performed in over half. This practice is underscored by the proposed treatment schema from Brescia, which employed neuromuscular blockade prior to prone positioning.

Many of our patients received antibiotics, which is also in accordance with the WHO interim guidelines to treat for possible bacterial infection. Of note, despite the severity of disease in these patients with confirmed viral infection, procalcitonin was often normal, suggesting it was of low clinical utility in these patients.

The severity scale proposed by the authors has not been clinically validated, and likely will warrant further revision as this SARS-CoV-19 pandemic progresses. In future iterations, the authors would move prone positioning as a therapy earlier in the scale, and consider omitting corticosteroid therapies based on newer evidence and guideline recommendations from the WHO [10]. Other drug therapies, such as hydroxycholoroquine, may appear earlier in the treatment plan, as additional data develops. Additionally, the inclusion of non-invasive ventilation is a sub-optimal ventilation strategy for patients with COVID-19, but was chosen due to resource limitations [11]. Non-invasive ventilation may be obviated at other institutions with a surfeit of mechanical ventilators. However, clinicians believed this scale was useful for practicing clinicians to gauge clinical improvement or worsening of patients with SARS-CoV-19. Additionally, several patients in the study hospital were managed by non-intensivists out of necessity. These physicians needed guidance for management of patients and the creation of a scale allowed for consistent communication. We believe the value of the scale was to unify communication and management of such patients for intensivists working beyond their normal capacity. The scale also offered value in triage and assignment of resources, aspects of care that are foreign to most physicians. This scale may be of use in the United States, which appears to be on a trajectory for a comparable experience as Italy. While the United States has nearly three times the number of ICU beds per capita as Italy, the staffing limitations may require a two-tier model of physician management, as proposed by the Society of Critical Care Medicine [1]. In such a model, use of the BRCSS or a similar severity scale may augment communication between non-intensivist physicians and nurses. We would recommend intensivists in Europe and the Americas to consider creating or adapting a similar scale to address the anticipated need for simple and consistent communication with non-intensivist physicians and nurses.

Our study is quite limited by the nature of the pandemic crisis. However, the need to promulgate the clinical information and management in Lombardy required expediency over completion. Consequently, clinical outcome data are incomplete. Many of the treatments described in this manuscript are unproven. The BRCSS not been validated for clinical progression of COVID-19. Data collection was limited to ICU stay only and cannot inform on non-ICU patients or recovery course outside the ICU.

5. Conclusion

We describe the early ICU experience of patients with COVID-19 in the Lombardy region of Italy. Patients often received non-invasive ventilation as well as invasive, with several adjunctive therapies such as prone position ventilation and neuromuscular blockade. Patients also received unproven targeted COVID-19 therapies. The creation of a severity scale helped clinicians communicate and replicate their treatment plans.

Contributors

SP, NL conceived of and designed the study and data collection tools. SP, MF, FT, FR, SC, SDF, IN, SB, LF, RT, GE, EF, FC, NL collected data and created the Brescia COVID severity scale. ML analyzed the data. SP, ML drafted the manuscript. NL, SP, revised the manuscript for important intellectual contribution. All authors read the final manuscript and approved submissions.

Declaration of Competing Interests

No competing interests relevant to this study to disclose for all authors. Full forms submitted and on file for all authors.

Data sharing requests

In order to protect patient privacy and comply with relevant regulations, identified data are unavailable. Requests for de-identified data from qualified researchers with appropriate ethics board approvals and relevant data use agreements may contact comitato.etico@asst-spedalicivili.it

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