Respiratory Intensive Care Unit management and efficacy during the COVID-19 outbreak in Naples, Italy

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Abstract

The World Health Organization declared the Coronavirus Diseases 2019 (COVID-19) outbreak a global pandemic on March 11, 2020. COVID-19 had an impact on over 500 million people worldwide. According to the American Thoracic Society criteria, the respiratory spectrum of this disease ranges from mild illness to severe pneumonia, with the latter occurring in a not insignificant 15% of patients. A rapid increase in the incidence of COVID-19 pneumonia cases has been observed all over the world, resulting in a saturation of the Intensive Care Unit's capacity (ICUs). Because of this impressive outbreak, the ICU beds and invasive mechanical ventilators reached their capacity. Non-invasive supportive care has become an important option for keeping respiratory conditions under control. As a result, proper healthcare resource management was required to ensure adequate patient care. Respiratory Intensive Care Units (RICUs) have become a useful resource for managing complex patients due to a shortage of ICU capacity. This highlighted the importance of RICUs, where patients with moderate to severe respiratory failure can be treated with non-invasive respiratory support rather than being admitted to the ICU. The clinical outcomes and baseline characteristics of patients admitted to the RICU of Cotugno Hospital, a tertiary referral center in Naples (Italy), from January 2021 to October 2021 are described in this report.

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Introduction

Coronavirus diseases 2019 (COVID-19) shows different clinical manifestations, from asymptomatic infection and mild upper respiratory tract illness to severe viral pneumonia with acute hypoxemic respiratory failure (AHRF), often fulfilling the criteria for admission to the intensive care unit (ICU) [1].

In China, the epicenter of the initial wave of the pandemic, the first data from literature showed that 5% to 32% of patients admitted to the emergency department (ED) required admission to ICU [2]. Due to the sudden increase in admission of patients with AHRF, many countries experienced a capacity shortage in acute care beds, also in light of the prolonged length of ICU stay for patients requiring invasive mechanical ventilation [3-4]. From Wuhan, in China, alarmingly poor outcomes were reported among patients requiring invasive mechanical ventilation, with mortality rates ranging between 81 and 97% [5]. The sharp ICU saturation, which negatively affected patient survival, brought to the worldwide attention the problem of ICU beds availability. A potential solution was offered by the Respiratory Intensive Care Units (RICUs) when available in hospitals in order to avoid ICU saturation by reducing the need for endotracheal intubation (ETI) through non-invasive respiratory management.

In the available literature, most of the reports showed that only less than half of patients were treated in ICU with invasive mechanical ventilation (IMV) and the rest of them with non-invasive respiratory support. Grasselli *et al*. reported in a recent study that, in Chinese ICUs, IMV was performed only in less than half of patients while non-invasive ventilation (NIV) and high flow nasal cannula (HFNC) were used much more frequently than in other hospital wards [6-7].

In the context of COVID-19 respiratory failure, RICUs may be the ideal structure to evaluate patients' responsiveness to non-invasive respiratory support, such as HFNC and continuous positive airway pressure (CPAP), and to restrict ICU admission for those patients who fail to respond to non-invasive treatment. In addition, early discharge to the RICU of ICU patients still requires monitoring, a heavy burden of care, or specific procedures such as ventilation or tracheotomy weaning, which may contribute to preserving ICU capacity [8]. RICUs, especially where patient monitoring and/or non-invasive respiratory support are required, can represent an escalation and/or de-escalation management space. Multiple sources reported the efficacy of HFNC and NIV in adult respiratory distress syndrome (ARDS), even as therapies that could reduce mortality and/or intubation rate [9-10]. Moreover, some studies reported the use of awake prone position (PP) in COVID-19 AHRF in combination with Venturi oxygen mask, Helmet CPAP, HFNC. Prolonged active PP was well-tolerated, improved oxygenation, and reduced the treatment failure of HFNC [11-13].

Eventually, mortality rates of patients in critical care are high, ranging from 26 to 32% [14-16]. Due to the lack of data on COVID-19 patients admitted to an RICU, the mortality burden has not been widely studied in this specific setting.

In this study, we described baseline features and prognosis in terms of variables influencing unfavorable outcomes of adult patients with moderate to severe COVID-19 admitted to the RICU of the referral hospital for COVID-19 emergency in Naples.

Methods

Study design

An observational, retrospective study was carried out on consecutive patients admitted to the RICU of a tertiary referral center in Naples (Italy), the Cotugno Hospital, from January 2021 to October 2021. The final date of follow-up was October 31, 2021.

All adult patients (>18 years old) admitted to RICU during the aforementioned period, due to respiratory failure related to COVID-19 pneumonia, were included in the study. The admission to RICU was based on the value of the ratio between PaO_2 and FiO_2 (P/F ratio) lower than 200. The transfer in ICU was evaluated in patients with clinical deterioration, severe respiratory failure, or non-responders to non-invasive ventilation. The exclusion criterion was the need for invasive mechanical ventilation and the previous admission to Covid-ICU. Patients were diagnosed with a positive polymerase chain reaction for SARS-CoV-2 from nasopharyngeal swab and the presence of bilateral interstitial pneumonia on chest imaging, performed through high resolution computed tomography (HRTC).

Patients were admitted directly from the emergency department (ED) of the hospital or from general wards of the same institution when clinical worsening occurred; alternatively, patients were referred to the RICU of the Cotugno Hospital from other structures.

The Institutional Review Board of the hospital approved this study (number: AOC00200532020), and informed consent was obtained from all subjects involved in the study.

Data collection, procedures, and outcome

Demographic, clinical, radiological, and laboratory data were collected from electronic medical records for all patients. In particular, the following variables were of interest on admission: gender, age, comorbidities, Charlson comorbidity index (CCI), HRTC score according to Chung [17], Horowitz index (also called the P/F ratio), type of viral variant (Figure 1). During the RICU stay were collected the following variables: respiratory support, main pharmacological treatments (corticosteroids, antiviral, monoclonal antibodies, interleukin-6 blockers, immunoglobulin M-enriched immunoglobulins), complications (such as pneumothorax or pneumomediastinum, secondary bacterial/fungal infections, thromboembolic events, acute myocadiac injury), length of stay and mortality. All patients were instructed and assisted to lie in PP during oxygen supplementation. Patients with PaO_2/FiO_2 <150 and HRTC signs of basal and posterior consolidations were considered eligible. Exclusion criteria were destructive dystrophic diseases of the lung parenchyma, massive cough and pregnancy. Moreover, they were encouraged to hold the PP for as long as possible, with intervals for meals and personal care. Continuous pulse oximetry (SpO_2) and electrocardiogram monitoring were ensured during PP. The outcome of interest was a composite one, made of death during RICU stay or ICU transfer owing to one or more of the following reasons: cardiopulmonary arrest, sudden fall in consciousness level, invasive ventilation requirement, and shock requiring support with vasoactive drugs. At any rate, the ICU transfer was always established after a thorough assessment made by a multidisciplinary team, including pulmonologists and intensive care physicians, in accordance with local protocols.

Statistical analysis

Categorical variables were expressed as absolute numbers and their relative frequencies. Continuous variables were expressed as mean ± SD if normally distributed or as median and interquartile range (IQR) if not normally distributed. Normality was gauged by means of the Shapiro-Wilk test. To analyze risk factors for the composite outcome of in-hospital mortality and ICU admission, patients meeting and not meeting the primary outcome were compared. All the variables with a $p \leq 0.1$ at the univariate analysis were entered into a multivariate Cox backward regression model after assuming proportional hazards through Schoenfeld residual testing to evaluate the hazard ratio (HR) of each variable, with the relative 95% confidence interval (CI). The final model consisted only of predictors independently associated in a statistically significant way with the outcome. Time-to-event techniques were used to ana-

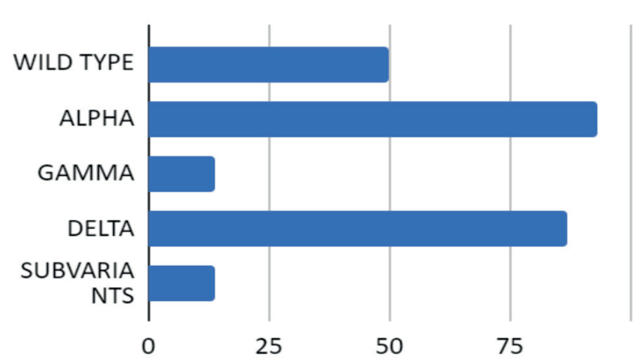

Figure 1. Different variants of SARS-CoV-2 on admission.

lyze survival from ward admission. Days from RICU admission to the composite outcome of interest (death or ICU admission) or October 15, 2021, represented the time of analysis. At the time of censoring, patients may be alive in the RICU, alive in other wards (not in ICU but in settings at lower intensity of care), or alive and discharged. Kaplan-Meier survival estimates were calculated, and the log-rank test was used to compare significant groups in terms of survival. More details about the specification of the Cox model as well as about sensitivity analysis based on multiple imputations of missing data are provided in *Supplementary Material*).

Statistical significance was considered for p<0.05. The software used for the analysis was R version 4.0.3 (R Project for Statistical Computing, Austria, Vienna) in RStudio statistical software version 1.3.1093, exploiting the following packages: 'finalfit', 'tableone', 'survminer', 'mice', 'naniar', 'coin'.

Results

Features of the population under investigation at baseline and during RICU stay are shown in Table 1, stratified according to clinical outcome. The study population included 292 hospitalized patients: 120 subjects (41%) met the primary endpoint, requiring ICU transfer or dying during RICU stay. Comparison of patients fulfilling the criteria for the main endpoint and not fulfilling them showed significant differences for age (median 68 *vs* 59 years, p<0.001), the Charlson comorbidity index (median 3 *vs* 2, p<0.001), the presence of cardiovascular disease as comorbidity (65.2% *vs* 46%, p=0.002), the HRTC score value on RICU admission (median 15 *vs* 14, p<0.001), the P/F ratio (median 79 *vs* 108, p<0.001), the type of ventilation (especially as for CPAP, 40.3% *vs* 74.1%, p 0.001), the development of pneumomediastinum as complication (21.8% *vs* 11% p=0.019), the length of stay (median 10 *vs* 22 days, p<0.001) (Table 1). At the time of data collection, full vaccination coverage required two drug administrations. In our population, 253 patients (87%) were unvaccinated, 25 (8.6%) received a single dose of the COVID-19 vaccine, and 14 (4.8%) completed full vaccination coverage with two doses of the COVID-19 vaccine for at least 14 days. In the study population, 272 patients were eligible, and well-tolerant to active PP:106 patients of 172 (62%) were in treatment with HFNC, 32 patients of 47 (68%) in CPAP, and 45 patients of 54 (83%) in BiPAP. Other patients did not match the eligibility criteria or did not tolerate the procedure. The multivariable Cox regression analysis showed that only age as a continuous predictor (HR 1.03, 95% CI 1.01-1.06), Charlson Comorbidity Index (HR 1.23, 95% CI 1.04-1.47), and P/F ratio <100 on RICU admission (HR 5.38, 95% CI 2.30-12.59) were independently associated with the primary outcome (Figure 2). In other words, there is a 10.3% increase in the expected hazard relative to a one-year increase in age (or the expected hazard is 1.03 times higher in a person who is one year older than another). Similarly, there is a 12.3% increase in the expected hazard relative to a one-point increase in the Charlson score. The expected hazard is eventually 5.23 times higher in subjects with P/F lower than 100 on RICU admission as compared to persons with higher values after accounting for age and comorbidity burden. The performance of the model was good, as showed by ROC curve analysis, with an area under the curve of 0.75 (c-statistic). Stratifying the model specifically for the P/F ratio, the benefit of a value over 100 was apparent (Figure 3). The sensitivity analysis confirmed the results: after multiple imputations of missing data (see supplementary for the details), the hazard associated with age and Charlson Comorbidity Index was overlapping, somewhat inferior to the P/F ratio under 100 (Table 2). Patients in our RICU during hospitalization underwent non-invasive respiratory support provided by CPAP (13,4%), BPAP (4,1%), and HFNC (73,8%); 8,7% of patients were treated with low flow oxygen therapy (Figure 4).

Discussion

To our knowledge, this is one of the few works describing experiences of patients with respiratory failure due to COVID-19 treated in a RICU during the first, second, and third pandemic wave.

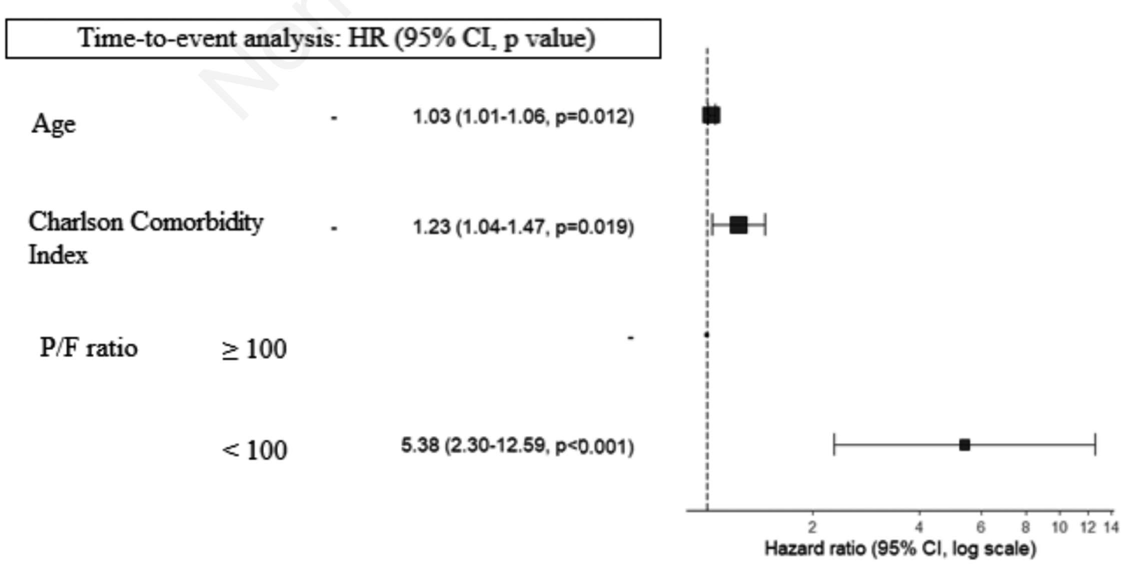

Figure 2. Graphical representation of independent predictors of death or ICU transfer (composite outcome) at multivariate Cox regression analysis.

Table 1. Baseline features of population and outcomes.

	Patients not fulfilling criteria for composite primary outcome (death or ICU transfer) n=172 (%)	Patients fulfilling criteria for composite primary outcome (death or ICU transfer) n=120 (%)	p-value
Demographic variables			
Male sex	122 (70.9)	77 (64.2)	0.274
Age (years) (median, IQR)	59 (47-66)	68 (59-76)	<0.001
Age as factor (years)			
<50	50 (29.1)	8 (67)	<0.001
50-59	41 (23.8)	23 (19.2)	
60-69	54 (31.4)	31 (25.8)	
70-79	23 (13.4)	42 (35)	
≥80	4 (2.3)	16 (13.3)	
Underlying conditions			
Charlson comorbidity Index (median, IQR)	2 (0-2)	3 (2-4)	<0.001
Cardiovascular disease	75 (46.0)	75 (65.2)	0.002
Diabetes mellitus	25 (15.3)	24 (20.9)	0.302
Kidney disease	8 (4.9)	5 (4.3)	1.000
Lung disease	159 (97.5)	109 (94.8)	0.871
Hematological disorder	4 (2.5)	6 (5.2)	0.373
Neoplasia	9 (5.5)	9 (7.8)	0.602
Obesity	65 (39.9)	41 (36.0)	0.594
Distinctive features of SARS-CoV-2 infection and related pneumonia			
Variants			
Alpha (B.1.1.7)	57 (36.8)	36 (35)	0.342
Delta (B.1.617.2)	54 (34.8)	33 (32)	
Gamma (B.1.1.28.1)	10 (6.5)	4 (3.9)	
Subvariants (ay4 / ay4.2 / ay5 / ay9 / ay9.1 / ay12 / ay24 / ay36 / ay43 / ay44 / ay46.6 / ay61 / ay68 / ay122)	5 (3.2)	9 (8.7)	
Wild type	29 (18.7)	21 (20.4)	
HRTC score on RICU admission (median, IQR)	14 (12-16)	15 (13-17)	<0.001
P/F ratio on RICU admission (median, IQR)	108 (88-143)	79 (69-95)	<0.001
P/F ratio on RICU admission as factor			
≥100	102 (60)	24 (20)	<0.001
<100	67 (39.6)	95 (79.8)	
Therapies			
Remdesivir	70 (43.2)	42 (37.5)	0.412
Steroids	160 (97.6)	115 (98.3)	1.000
IgM-enriched immunoglobulin	13 (8.0)	16 (14.0)	0.155
Antimicrobials other than antivirals	48 (63.2)	56 (84.8)	0.006
Type of ventilation on RICU admission			
HFNC	127 (73.8)	45 (37.5)	<0.001
CPAP	23 (13.4)	24 (20)	
BPAP	7 (4.1)	47 (39.2)	
Other	15 (8.7)	4 (3.3)	
Complications			
Bacterial and/or fungal super-infections	85 (50.3)	55 (49.5)	1.000
Pulmonary thromboembolism	18 (10.5)	13 (10.8)	1.000
Pneumothorax	5 (2.9)	7 (5.9)	0.340
Pneumomediastinum	19 (11.0)	26 (21.8)	0.019
Myocardial infarction	0 (0.0)	3 (2.5)	0.133
Length of RICU stay (days) (median, IQR)	22 (15-29)	10 (6- 13)	<0.001

ICU, intensive care unit; IQR, interquartile range; RICU, respiratory intensive care unit; HRTC, high resolution computed tomography; HFNC, high-flow nasal cannula; CPAP, continuous positive airway pressure; BPAP, bilevel positive airway pressure.

Since March 2020, the Cotugno Hospital has become one of Italy's main COVID-19 hospital with a dedicated RICU and ICU. In the RICU, patients were admitted from ED with acute respiratory failure due to COVID-19 as the first step of severe COVID-19 pneumonia not fulfilling strict criteria for ICU admission. After implementing a strategic emergency plan, RICU was allocated strategically near the ICU on the same floor across the corridor to facilitate and speed patients' rapid transit from one unit to the other.

Our patient model management includes daily assessment by respiratory medicine specialists, critical care, and infectious disease physicians.

The RICU allows a secure environment for providing non-invasive respiratory support and patient monitoring to improve healthcare resource management.

Furthermore, our study suggests that RICU management may prevent ICU admission and invasive mechanical ventilation in many patients with COVID-19-associated AHRF. This finding may be highly relevant in a respiratory pandemic where ICU capacity is a critical issue. However, our results must be interpreted with caution, given the observational design of our study and the absence of a control group. Various factors, including standardized admission criteria, self-proning, staff expertise, and non-invasive respiratory support, could contribute to the favorable outcome of the majority of RICU patients.

Our cohort includes patients with severe respiratory failure due to COVID-19 pneumonia, determined by a median SpO_2/FiO_2 ratio <100, and bilateral pneumonia quantified with median of 15 on total severity score index of HRTC. As reported in the literature, these patients should be admitted to ICU in hospitals without RICU, with a consequential progressive collapse owing to ICU's resources exhaustion. Our hospital, in this regard, rapidly increased the number of RICU beds due to the pandemic situation. In our cohort, only 28% of patients admitted to an RICU with severe respiratory failure due to COVID-19 required upscaling management to the ICU.

After almost two years of the COVID-19 outbreak, the role of non-invasive respiratory support for severe COVID-19 patients is currently under debate, and the role of RICU has not been clarified yet. Multiple European cohort studies demonstrated the role of RICU in the management of non-invasive respiratory support and favorable result on mortality [18,19]. We observed that mortality in RICU patients who did not require ICU admission was 18%, with a median length of stay of 22 days for patients not fulfilling the criteria for the composite primary outcome (death or ICU transfer). Considering the resource limitations imposed by the COVID-19 pandemic, it is important to determine whether selected patients might be treated outside ICU and which is the correct non-invasive respiratory support setting. The role of non-invasive ventilation in COVID-19 pneumonia has been debated in the literature from the beginning of the outbreak, as delaying intubation for patients requiring invasive mechanical ventilation has been reported to be associated with negative patient outcomes [20]. The use of NIV as initial ventilator support for respiratory failure in the presence of COVID-19 pneumonia appears to be a reasonable option, albeit under strict infection control measures [21].

From the beginning of the outbreak, our group shared multiple experiences on the treatment of COVID-19 patients treated with HFNC or NIV and even collected multiple data about the interface and consequential parenchymal complications [22-24]. Furthermore, COVID-19 patients with AHRF show good tolerance to high positive end-expiratory pressure (PEEP) normally obtainable with CPAP, related to atelectatic lung areas recruitment and reduced work-of-breathing. Benefits from the addition of inspiratory pressure support in BPAP NIV are less known. The network effect estimates suggested that helmet non-invasive ventilation might be the most effective option by allowing higher levels of positive end-expiratory pressure and reducing inspiratory

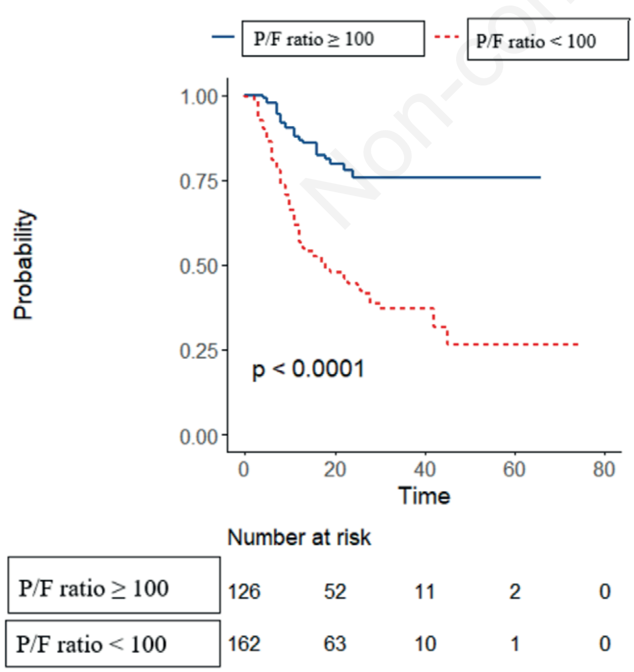

Figure 3. Cox regression analysis of primary outcome stratified for P/F ratio.

Table 2. Multivariate Cox regression analysis after multiple imputation of missing data.

Variable	Hazard ratio	95% Confidence interval
Age	1.03	1.02.1.05
Charlson comorbidity index	1.21	1.02-1.43
P/F ratio	3.40	2.15-5.37

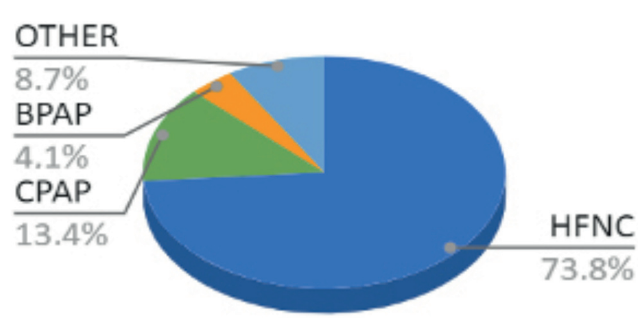

Figure 4. Non-invasive respiratory support on RICU admission.

efforts. Indeed, different phenotypes of acute lung injury have been reported among patients with COVID-19-associated AHRF, including near-preserved lung compliance and low ventilation-to-perfusion ratios [25]. However, the optimal mode of respiratory support in COVID-19 patients has not been clarified yet, but it is important to know which damage can be caused if inappropriate treatment is used [26]. We observed, on pulmonary parenchyma already compromitted from COVID-19 pneumonia, complication as pneumothorax (2.9%) and pneumomediastinum (11%). Finally, the role of RICU showed the possibility of avoiding invasive mechanical ventilation in the context of the COVID-19 pandemic and preserving ICU capacity. RICUs may also benefit patients by preventing invasive mechanical ventilation-related complications.

This study has several limitations as the retrospective design of the analysis, including a single center or the lack of a control group (non-RICU hospital) that does not allow to directly quantify the impact of RICU on COVID-19 mortality or healthcare burden. However, the number of participants is higher than in most previous studies, and our results agree with observations from different cohorts.

Conclusions

In this study, the endotracheal intubation rate in patients with severe respiratory failure from COVID-19 was 28%. Management of these patients with NIV in RICU could reduce complications and mortality due to endotracheal intubation.

The strategic allocation of our RICU on the same floor with the ICU and the multidisciplinary management with physicians might have played an important role in positively influencing the clinical outcomes of the observed population.

We suggest a correct choice of ventilatory support and interface. Early self-prone positioning, if possible, should be considered as part of the current respiratory therapeutic arsenal to reduce the need for endotracheal intubation.

This model of care may be beneficial to preserve ICU capacity and reduce the complications associated with invasive mechanical ventilation.

References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:72733.
2. Guan W, Ni Z, Hu Yu, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020;382:1708-20.
3. Emanuel EJ, Persad G, Upshur R, et al. Fair allocation of scarce medical resources in the time of Covid-19. N Engl J Med 2020; 382:2049–55.
4. Ramachandran P, Swamy L, Kaul V, Agrawal A. A national strategy for ventilator and ICU resource allocation during the COVID-19 pandemic. Chest 2020;158:887–9.
5. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395:1014–5.
6. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323:1574-81.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9.
8. Plate JDJ, Leenen LPH, Houwert M, Hietbrink F. Utilisation of intermediate care units: a systematic review. Crit Care Res Pract 2017;2017:8038460.
9. 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;315:2435–41.
10. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185–96.
11. Pierucci P, Ambrosino N, Di Lecce V, et al. Prolonged active prone positioning in spontaneously breathing non-intubated patients with COVID-19-associated hypoxemic Acute respiratory failure with PaO2/FiO2 >150. Front Med (Lausanne) 2021;8:626321.
12. Longhini F, Bruni A, Garofalo E, et al. Helmet continuous positive airway pressure and prone positioning: A proposal for an early management of COVID-19 patients. Pulmonology 2020;26:186-91.
13. Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. Lancet Respir Med 2021;9:1387-95.
14. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
15. Prin M, Wunsch H. The role of stepdown beds in hospital care. Am J Respir Crit Care Med 2014;190:1210–6.
16. Plate JDJ, Leenen LPH, Houwert M, Hietbrink F. Utilisation of intermediate care units: a systematic review. Crit Care Res Pract 2017;2017:8038460.
17. Capuzzo M, Volta CA, Tassinati T, et al. Hospital mortality of adults admitted to intensive care units in hospitals with and without intermediate care units: a multicentre European cohort study. Crit Care 2014;18:551.
18. Chung M, Bernheim A, Mei X, et al. CT imaging features of 2019 novel coronavirus (2019-nCoV). Radiology 2020;295:202-7.
19. Franco C, Facciolongo N, Tonelli R, Dongilli R, Vianello A, Pisani L, et al. Feasibility and clinical impact of out-of-ICU non-invasive respiratory support in patients with COVID-19 related pneumonia. Eur Respir J 2020;56:2002130.
20. Higgs A, McGrath BA, Goddard C, et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth 2018;120:323-52.
21. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 2007;35:18-25.
22. Polistina GE, Lanza M, Di Somma C, et al. A rare evolution to pneumopericardium in patient with COVID-19 pneumonia treated with high flow nasal cannula. Medicina (Kaunas) 2021;57:1122.
23. Simioli F, Annunziata A, Langella G, et al. Clinical outcomes of high-flow nasal cannula in COVID-19 associated postextubation respiratory failure. A single-centre case series. Anaesthesiol Intensive Ther 2020;52:373-6.
24. Imitazione P, Polistina GE, Annunziata A, et al. Acute respira-

tory failure in COVID-19 pneumoniae: The best interface for an optimal management. A South Italian experience. Turk Thorac J 2020;21:289-90.
25. Primmaz S, Le Terrier C, Suh N, et al. Preparedness and reorganization of care for coronavirus disease 2019 patients in a Swiss ICU: characteristics and outcomes of 129 patients. Crit Care Explor 2020;2:e0173.
26. McEnery T, Gough C, Costello RW. COVID-19: Respiratory support outside the intensive care unit. Lancet Respir Med 2020;8:538-9.

Online supplementary material:

Cox model

Table 1. Diagnostics for the Cox model.

Figure 1. Graph of the scaled Schoenfeld residuals against the transformed time as for P/F continuous variable.

Figure 2. Pattern of missingness.