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ORIGINAL RESEARCH

Bilevel and continuous positive airway pressure and factors linked to all-cause mortality in COVID-19 patients in an intermediate respiratory intensive care unit in Italy

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ABSTRACT

Objectives: In the present single-centered, retrospective, observational study, we reported findings from 78 consecutive laboratory-confirmed COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS) hospitalized in an intermediate Respiratory Intensive Care Unit, subdividing the patients into two groups according to their clinical outcome, dead patients and discharged patients.
Methods: We further subdivided patients depending on the noninvasive respiratory support used during hospitalization.
Results: In those patients who died, we found significant older age and higher multimorbidity and higher values of serum lactate dehydrogenase, C-reactive protein, and D-dimer. Among patients who were submitted to bilevel positive airway pressure (BPAP), those who died had a significant shorter number of days in overall length of stay and lower values of arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO2/FiO2 ratio) compared to those who survived. No difference in all-cause mortality was observed between the two different noninvasive respiratory support groups [48% for continuous positive airway pressure (CPAP) and 52% for BPAP].
Conclusion: In COVID-19 patients with moderate-to-severe ARDS using BPAP in an intermediate level of hospital care had more factors associated to all-cause mortality (shorter length of stay and lower baseline PaO2/FiO2 ratio) compared to those who underwent CPAP.

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Critical care; respiratory infection; viral infection; assisted ventilation; SARS-CoV-2; intermediate RICU

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing coronavirus

disease 2019 (COVID-19) pandemic, has a wide clinical spectrum, encompassing asymptomatic

infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure [1]. COVID-19 patients develop acute respiratory distress syndrome (ARDS), require respiratory support [2], and may require hospitalization in Intensive Care Unit (ICU). Defined as Type 1 respiratory failure, there is hypoxia (PaO2 < 8kPa), without hypercapnia (carbon dioxide retention or PaCO2) [3], with patients commonly presenting with hypoxia worsening, and additional signs such as tachypnea, increased use of accessory muscles, tachycardia, pale and cold peripheries, sweating, confusion, agitation or reduced level of consciousness and cyanosis [4].

The disease trajectory of COVID-19 is not yet fully understood, which has resulted in a rapidly changing and understanding of treatment options. In China, the percentage of COVID-19 patients who required ICU hospitalization varied from 5% to 32% [5]. The availability of ICU beds and the prevision of intensive care varies among countries and often ICU overbooking may negatively influence patients' survival. Preliminary findings from China and Italy suggest high mortality and stressed ICU capacity of care [6,7]. Although these studies focused on clinical management with noninvasive respiratory support of COVID-19 patients in ICU, there is no evidence coming from an intermediate Respiratory Intensive Care Unit (RICU) or noninvasive respiratory care unit [8], a model of care designed for monitoring and treating respiratory patients whose illness is at a level of severity that is intermediate between that which requires ICU facilities and that which can be managed on a conventional ward. An intermediate RICU is an area for monitoring and treating patients with acute or exacerbated respiratory failure caused by a disease that is primarily respiratory [8]. The essential aim is adequate and appropriate cardiorespiratory monitoring and/or treatment of insufficiency by noninvasive ventilation (NIV). A RICU also provides continuous monitoring of patients

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Article highlights

- Findings from 78 consecutive laboratory-confirmed COVID-19 patients with moderate-to-severe acute respiratory distress syndrome (ARDS) hospitalized in an intermediate Respiratory Intensive Care Unit (RICU) were reported subdividing the patients in two groups according to their clinical outcome, dead patients and discharged patients. We further subdivided patients depending on the non-invasive respiratory support used during hospitalization.
- In those patients who died, we found significantly older age and higher multimorbidity and higher values of serum lactate dehydrogenase, C-reactive protein, and D-dimer. However, in our study population, the median values of these laboratory parameters were not associated to a significant change of all-cause mortality rates because underpowered. Among patients who were submitted to bilevel positive airway pressure (BPAP), those who died had a shorter statistically significant number of days in overall length of stay as well as lower values of arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO2/FiO2 ratio) compared to those who survived. No difference in all-cause mortality was observed between the two different noninvasive respiratory support groups [48% for to continuous positive airway pressure (CPAP) and 52% for BPAP].
- In an Italian intermediate RICU, despite having more factors associated to negative outcomes, COVID-19 patients with moderate-to-severe ARDS who underwent BIPAP had similar all-cause mortality compared to those who underwent CPAP. We need further evidence on larger samples to evaluate the correct non-invasive respiratory modality in COVID-19 patients to reduce short-term all-cause mortality.

after thoracic surgery or of those undergoing invasive mechanical ventilation (IMV) through a tracheostomy and may treat critical patients whose weaning from IMV is difficult [8]. Recent evidence has shown NIV may have a more significant and positive role in COVID-19 patients than initially thought [4]. NIV may be an appropriate bridging adjunct in the early part of the disease progress and may prevent the need for intubation or IMV. Therefore, COVID-19 patients requiring NIV may be managed in settings outside of the ICUs. In the present single-centered, retrospective, observational study, we aimed to investigate clinical findings on laboratory-confirmed COVID-19 patients with moderate-to-severe ARDS hospitalized in an intermediate RICU according to their short-term survival and the noninvasive respiratory support used during hospitalization.

2. Materials and methods

In the present study, we reported findings from 78 consecutive laboratory-confirmed COVID-19 patients, all with moderate-to-severe ARDS, hospitalized in an intermediate RICU, Policlinico University Hospital, Bari, Italy and collected from March 11 to 27 April 2020 and subdivided in patients into two groups: dead patients and discharged patients. We further subdivided patients depending on the noninvasive respiratory support used during hospitalization. The present study adhered to the 'Standards for Reporting Diagnostic Accuracy Studies' (STARD) guidelines (http://www.stard-statement.org/), the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines (https://www.strobe-statement.org/), and was conducted in accordance with the Helsinki Declaration of 1975. The present study was approved by the Policlinico Hospital of University of Bari 'Aldo Moro' institutional review board and informed consent was obtained from all subjects involved in the present analyses.

Laboratory-confirmed COVID-19 patients were affected by ARDS defined according to the Berlin definition, so a respiratory failure characterized by arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO2/FiO2) < 300 mmHg despite PEEP> 5 cmH2O, associated to bilateral chest opacities (not fully explained by effusions, lobar/lung collapse or nodules) with an acute onset, within 1 week of a known clinical insult or new or worsening respiratory symptoms [9]. In these laboratory-confirmed COVID-19 patients, apart from moderate to severe hypercapnic patients, who clearly needed the bilevel positive airway pressure (BPAP) respiratory support rather than continuous positive airway pressure (CPAP) respiratory support, our choice was driven by patient's clinical evaluation. After a CPAP trial with a progressive pressure raising up to 12–15 cmH2O (when needed), if respiratory rate still >30 we decided to switch CPAP to BPAP. High respiratory rate in ARDS patients is an indicator of respiratory fatigue, and BPAP can reduce work of breathing giving relief in these patients [10]. Laboratory-confirmed COVID-19 patients affected by severe ARDS, non responding to NIV, in which intubation and ICU transfer would not modify their outcome according to resuscitator counseling, remained in our intermediate RICU. Therefore, all patients who did not respond to NIV were asked for resuscitator counseling, whose opinion determined the possibility of an ICU transfer or not. The Charlson comorbidity index (CCI), a weighted index that takes into account the number and the seriousness of comorbid disease, was calculated [11].

2.1. Statistical analysis

Sociodemographic and health characteristics were presented as numbers, mean and median values, interquartile ranges, standard deviations (SDs) values, and percentages. Differences in sociodemographic and health characteristics between who died and who survived were analyzed using t-test for differences in means for independent-sample, the Mann–Whitney U test for medians, and chi-square test for proportions. Length of stay or PaO2/FiO2 values by type of respiratory support and outcome were analyzed using analysis of variance (ANOVA) and the multiple comparisons were adjusted by Bonferroni inequality procedure. Multivariate Cox regression models were used to analyze the relation between median LDH, D-dimers, and PCR values on the rates of all-cause mortality.

3. Results

The study population included 78 patients (men 73% *vs.* women 27%). Median age was 69 years [interquartile range (IQR):58–80.25]. Mean CCI for all patients was 4.12 (±2.76), while median value was 4 (IQR:2–6). Mean PaO2/FiO2 was 186.36 (±80.39). Thirty-five patients (45%) died during hospitalization, 15 patients in intermediate RICU (43%) and 20 patients in ICU (57%), while discharged patients were 43 (55%). Twenty-four patients underwent intubation and subsequent IMV in ICU. For these patients, mean NIV days before

intubation was 2.96 (± 2.73). Sixteen patients underwent pronation during hospitalization in our intermediate RICU, however none of them during NIV, but during standard oxygen therapy. Twenty patients died after performing IMV, in fact, all patients transferred to ICU performed IMV, and no one performed IMV in our intermediate RICU. Among the above mentioned 20 patients, 2 underwent extracorporeal membrane oxygenation (ECMO). We did not know specific death causes of these patients and among these, two patients died in the days following the end of the study, and all of them within one month from the end of the study.

Comparison of values between the two groups are shown in Table 1. Sixty-four patients (82%) had additional therapy with enoxaparin, following the evidence of raising in D-dimer values or computed tomography findings of pulmonary perfusion defects. Sixty-three patients (81%) had antibiotic therapy, 52 of whom (67% of total patients) assumed azithromycin. Thirty-five patients (45%) had antiviral therapy with lopinavir-ritonavir, no one had remdesivir, unavailable at that time at our Hospital. Seventy-one patients (91%) had hydroxychloroquine, 4 patients (5%) had tocilizumab, and 8 patients (10%) had dexamethasone. The relatively low percentage of corticosteroid usage in our patients is explained by the therapy indications for COVID-19 of March and early April 2020, in which corticosteroid usage was not recommended.

Among patients who underwent to CPAP, no difference in overall length of stay in days (13.17 ± 5.53 who died *vs*. 10.25 ± 9.46 who survived; difference between means 2.92 ± 2.46, Bonferroni inequality adjustment = NS) as well as in PaO2/FiO2 (169.58 ± 52.43 *vs*. 226.75 ± 8.64, difference between means −57.17 ± 24.49, Bonferroni inequality adjustment = NS) between who died and who survived were observed. These CPAP patients were younger than those who were submitted to the BPAP respiratory support (64.08 ± 12.34 *vs*. 71.36 ± 13.15 years, respectively, $p < 0.05$), had a lower CCI score (3.36 ± 2.27 *vs*. 4.72 ± 2.85, respectively, $p < 0.05$), and a higher baseline PaO2/FiO2 (207.69 ± 77.40 *vs*.163.32 ± 73.47, respectively, $p < 0.05$). On the other hand, among patients who were submitted to BPAP, those who died had a shorter statistically significant number of days in overall length of stay (19.58 ± 8.34 who survived *vs*.12.54 ± 6.68 who died; difference between means −7.04 ± 2.78, Bonferroni inequality adjustment $p < 0.05$) as well as lower values of PaO2/FiO2 (210.83 ± 67.58 who survived *vs*. 118.46 ± 47.62 who died; difference between means −92.37 ± 27.71, Bonferroni inequality adjustment $p < 0.05$) compared to those who survived. No difference in all-cause mortality was observed between the two different noninvasive respiratory support groups (48% for CPAP and 52% for BPAP, $p < 0.15$). Regarding the laboratory findings, we found significantly higher values of serum lactate dehydrogenase (LDH), C-reactive protein (CRP), and D-dimer in those who died in comparison with those who survived (Table 1). The median values for LDH [coded 0 for LDH<319 units/L and coded 1 for LDH≥319 units/L, incidence rate ratios (IRR):1.154, 95% confidence interval (CI):0.485–2.873, $p = 0.737$], for D-dimer (coded 0 for D-dimer < 947 ng/ml and coded 1 for D-dimer ≥ 947 ng/ml, IRR:1.663, 95% CI:0.671–4.357, p = 0,238), and for CRP mg/L (coded 0 for PCR < 101 and coded 1 for PCR ≥101 mg/L, IRR: 2.030, 95% CI:0.830–5.396, $p = 0.091$) were not associated with a significant change in incidence rate ratios of all-cause mortality. However, the rates of all-cause mortality of these parameters were underpowered (statistical power <0.50 for a type I error set to 0.05).

4. Discussion

To the best of our knowledge, the present single-centered, retrospective, observational study is the first report of laboratory-confirmed COVID-19 patients with moderate-to-severe ARDS hospitalized in an intermediate RICU, and not in ICU facilities. Older age was associated to all-cause mortality, and men were more represented in both groups. Multimorbidity was significantly higher in the group of dead patients, confirming its role in increasing the risk of short term all-cause mortality in COVID-19 patients.

Table 1. Sociodemographic and clinical characteristics, therapeutic approaches, laboratory findings and clinical outcomes of COVID-19 patients hospitalized in an intermediate Respiratory Intensive Care Unit subdivided according to their short-term survival, i.e. patients who died and patients who have been discharged.

	Dead patients Mean (±DS) or count (%) or median (IQR)	Discharged patients Mean (±DS) or count (%) or median (IQR)	P </ =
N.	35 (45%)	43 (55%)	
Age (years)	75.17 (±12.71)	64.42 (±14.04)	<0.001[b]
Men	26 (74%)	31 (72%)	0.84[c]
CCI	5.31 (± 2.63)	3.14 (± 2.48)	<0.001[b]
Noninvasive respiratory support HFNC	2 (7.41%)	5 (12.20%)	0.28[c]
CPAP	12 (44.44%)	24 (58.54%)	
BPAP	13 (48.15%)	12 (29.27%)	
CPK (U/L)	251.81 (± 217.6)	175.54 (± 172.71)	0.12[b]
D-dimer (ng/mL)	2365 (IQR 717–4848)	786 (IQR 530–1982)	<0.05[a]
Absolute lymphocytes (x 10^9/L)	798 (± 375)	1006 (±704)	0.15[b]
LDH (mU/mL)	378.96 (± 135.45)	316.49 (± 89.79)	<0.05[b]
CRP (mg/L)	142.58 (±79.39)	100 (± 67)	<0.05[b]
PaO2/FIO2 ratio	137.49 (± 54.33)	226.14 (± 76.47)	<0.001[b]
Length of stay (days)	10.77 (±7.67)	13.77 (±7.63)	0.09[b]

IQR: interquartile range; CCI: Charlson Comorbidity Index; HFNC: high-flow nasal cannula; CPAP: continuous positive airway pressure; BPAP: bilevel positive airway pressure; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; CRP: C-reactive protein; PaO2/FIO2: arterial oxygen partial pressure to fractional inspired oxygen

[a]Two-sample Wilcoxon rank-sum (Mann-Whitney) test.

[b]Student T-test for independent samples.

[c]Pearson Chi-squared.

Regarding the laboratory findings, we found significantly higher values of serum lactate dehydrogenase (LDH), C-reactive protein (CRP), and D-dimer in the group of dead patients. This finding was not surprising. In fact, in other observational studies, LDH and CRP were higher in severe and extremely severe COVID-19 patients [12], while higher baseline D-dimer levels were a predictor of in-hospital mortality in COVID-19 patients [13]. However, in our study population, the median values of these laboratory parameters were not associated to a significant change of all-cause mortality rates because underpowered. Baseline PaO2/FiO2 ratio was considerably lower in our group of dead patients confirming findings from another Chinese study on 52 critically ill patients [5], suggesting this parameter as a good predictor of mortality. This finding confirms that patients with worse pulmonary condition, independently from the noninvasive respiratory support at admission, need to be considered early for IMV, but considering the resource limitations imposed by COVID-19 pandemic, it is crucial to determine whether selected patients can be treated outside ICU [14,15].

5. Expert opinion

Several studies consider NIV, but most of them were implemented in ICU as clinical setting. In a study on 138 patients hospitalized for respiratory failure with a PaO2/FiO2 ratio of 136 250 (IQR:105–234) only 36 patients (26%) were admitted to ICU, but of these only 19 underwent intubation and mechanical ventilation [1]. This increasing body of knowledge showed that many patients admitted to ICU did not undergo to IMV and that almost always NIV is used in ICU, requiring an unnecessary 255 high economic effort. However, the role of noninvasive©respiratory support and its correct modality for severe COVID-19 patients is currently a subject of major debate [15]. COVID-19 patients with acute respiratory failure show a good tolerance to high positive end-expiratory pressure normally obtainable with 260 CPAP, related to atelectasic lung areas recruitment and reduced work-of-breathing. We found that patients using BPAP had more factors associated to negative outcomes (shorter length of stay and lower baseline PaO2/FiO2 ratio) compared to those who underwent CPAP, but nonetheless we did not find a statistically 265 significant difference in all-cause mortality between these groups. Benefits of the addition of an inspiratory pressure support in BPAP NIV is less known, with a theoretical advantage due to further reducing inspiratory work-of-breathing [16] and improved mean airway pressure, which is known to improve 270 oxygenation. However, there is a lack of valid evidence of its role in real-life setting related to COVID-19 pandemic. It is fundamental to remark the need of avoiding delays in intubation and IMV start. At this regard, we decided to allocate our intermediate RICU strategically near ICU, in order to minimize intubation time 275 and to decide in short times pathways for patients who are suddenly worsening.

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6. Conclusions

In conclusion, we found that, despite having more factors associated to negative outcomes, laboratory-confirmed COVID-19 patients with moderate-to-severe ARDS who underwent BPAP had similar all-cause mortality compared to those who underwent CPAP. We need further evidence on larger samples to evaluate the correct noninvasive respiratory modality in COVID-19 patients to reduce short-term all-cause mortality.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contributions

Conceived and designed the study: GEC, VS, FP, and OR. Collected data: EB, GM, ER, VDL, and MLDC.

Analyzed the data: ER and VS. Wrote the manuscript: GEC, VS, FP, and OR.

Final supervision and guarantors of the paper: GM, SG, VP, FP, and OR.

Ethics statement

This study was compliant with Ethical Standards. Ethical approval and informed consent were obtained.

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