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Research Paper

Severity of respiratory failure and outcome of patients needing a ventilatory support in the Emergency Department during Italian novel coronavirus SARS-CoV2 outbreak: Preliminary data on the role of Helmet CPAP and Non-Invasive Positive Pressure Ventilation

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ABSTRACT

Background: Novel Coronavirus SARS-CoV-2 pandemic is spreading around the world. At the end of February, the outburst of the pandemic has hit hard on northern Italian's hospitals. As of today, no data have been published regarding the severity of respiratory failure of patients presenting to the Emergency Departments. Moreover, the outcome the patients forced to undergo Continuous Positive Airway Pressure (CPAP) or Non-Invasive Positive Pressure Ventilation (NIPPV) due to lack of Intensive Care resources is unknown. "Papa Giovanni XXIII" hospital (HPG23) of Bergamo is one of the largest hospitals in the Country, with an Emergency Department (ED) managing over 100,000 patients per year.

Methods: This is a retrospective observational study based on chart review of patients presenting to the Emergency Department of HPG23 from 29/02/2020 to 10/03/2020 with a clinical condition highly suspicious for COVID-19 infection. Registration of admission rates, severity of respiratory failure (ARDS classification), need of respiratory support, SARS-CoV-2 PCR test and outcome of patients treated with a ventilatory support were registered on 10th of May 2020.

Findings: From 29/02 to 10/03 611 patients with a suspected diagnosis of COVID-19 infection were evaluated in our ED; 320 (52%) met the criteria for hospital admission and 99 (31%) needed to be immediately started on ventilatory support (81% CPAP, 7% NIPPV, 12% Invasive Mechanical Ventilation). Eighty-five (86%) of the 99 patients needing a ventilatory support eventually had SARS-CoV-2 infection confirmed by PCR test on nasal-pharyngeal swab. Their median PO2/FiO2 ratio was 128 (IQR 85–168), with 23 patients (29.5%) classified as severe ARDS. Mortality rate as of 10th of May was 76.5%, ranging from 44.4% within patients <60 years old to 85% within those older than 60 years (p = 0.001). NIPPV/CPAP failure occurred in 91.5% of patients.

Interpretation: The population of patients suspected for COVID-19 infection presenting at our ED showed a very high rate of severe respiratory failure, with urgent need of a large amount of intensive care resources. Mortality rates of critically ill patients with confirmed COVID-19 (76.5%) are similar to previously reported studies with similar population. CPAP/NIPPV could be a valid strategy to treat severely hypoxic patients that cannot be intubated in the ED due to lack of intensive care resources.

Funding: No funds were received for this research project.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-

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Research in context

Evidence before this study

We searched PubMed on May 7, 2020, for articles that describe the epidemiological and clinical characteristics of the coronavirus disease 2019 (COVID-19), using the search terms "coronavirus", "COVID-19″, "intensive care unit", "pneumonia", "ventilation", "emergency department". Many articles describe clinical characteristics and mortality of patients admitted to regular wards and intensive care units but none describes the characteristics of the patients presenting to Emergency Departments (ED). Few data are available about the outcome of patients with severe acute respiratory syndrome treated with noninvasive ventilation.

Added value of this study

We describe the population of patients with severe respiratory failure due to COVID-19 infection needing a ventilatory support who presented to the Emergency Department of a big hospital in Bergamo at the start of the pandemic in Italy. Due to lack of Intensive Care resources most of the patients were treated with Non Invasive Ventilation; we registered the outcome after a 2 months period follow-up.

Implications of all the available evidence

The population of patients presenting EDs during COVID-19 pandemic shows a high rate of severe respiratory failure, with urgent need of a large amount of intensive care resources. CPAP/NIV could be a valid strategy to treat severely hypoxic patients that cannot be intubated in the ED due to lack of intensive care resources.

CoV-2). The World Health Organization (WHO) declared the outbreak a pandemic on 11 March [1].

The percentage of admitted patients experiencing severe acute respiratory failure is described between 6.1% and 41% of all admissions; among them the need for invasive ventilation ranged from 30% to 88%. Mortality rates within critically ill patients varies from 16% to 78% [2–15].

The characterization of patients needing a ventilatory support could help countries far from the outbreaks to prepare to face the emergency. The role of non-invasive ventilation (NIV) in this setting is not clear; some authors suggest the use of NIV only in selected patients, while others propose NIV or high flow nasal cannula (HFNC) as first line support in acute respiratory failure due to COVID-19 [18,19]. NIV/HFNC is reported to be used in 11–62% of all patients COVID-19 admitted to Intensive Care Units (ICU) [3–19].

Only scattered data are available on the mortality rates and NIV failure rates of patients started on NIV in the Emergency Department (ED) because of unavailability of ICU resources. The province of Bergamo (accounting for 1.1 million people) is one of the first area hit by the epidemic in Northern Italy, with Ospedale Papa Giovanni XXIII (HPG23) being the largest hospital in the area: it is a level 1 trauma center, with a busy ED seeing over 100,000 patients/year.

The objective of this study is to describe the severity of respiratory failure and the need of respiratory support of patients presenting to HPG23 during the study period and to evaluate the outcome of patients who were started on a ventilatory support.

2. Methods

This is a retrospective observational cohort study based on chart review of patients presenting to the Emergency Department of HPG23 with suspected COVID-19 infection during the initial massive surge of the Italian outbreak, from 29/02/2020 to 10/03/2020. IM, FZ, CP, AA, LDB and EG screened the charts of all the patients presenting to the ED during the study period and reviewed those of the patients coded as "suspected COVID-19 infection".

We recorded the number of patients presenting to the ED every day and their demographic features. All of the patients were tested for SARS-CoV-2 via a nasopharyngeal swab PCR test. Among patients admitted to the hospital who tested positive for COVID-19, we recorded the number undergoing mechanical ventilation in the ED (either invasive or non-invasive), their comorbidities, ARDS rates based on pO2/FiO2 ratio during ventilation[20] and the results of PCR for COVID-19 on nasopharyngeal swab test. We registered the rate of CPAP and Non-Invasive Positive Pressure Ventilation (NIPPV) failure and patient's outcome (death vs discharged from hospital) on May, 10th.

Based on our protocol, patients were coded as "suspected COVID-19 infection" in the triage area of the ED if they presented body temperature >37.5 °C and/or any respiratory symptom. Criteria for hospital admission were peripheral oxygen saturation (SpO2) < 94% while resting or SpO2 decrease of more than 5 percent points after walking for 30 m. The presence of isolated interstitial pneumonia was not considered an indication to admission. Non-Invasive Positive Pressure Ventilation or Helmet Continuous Positive Airway Pressure were considered in any patient with arterial oxygen pressure (PaO2) < 60 mmHg on arterial blood gas analysis (ABG) and/or respiratory rate (RR) >30/min after being on 15 L/min nonrebreather mask for 15 min. NIPPV (BiPAP mode) was considered over CPAP in patients who showed respiratory acidosis (pCo2 > 40 mmHg and pH <7.35) or exhaustion of respiratory muscles. Due to our limited intensive care resources, invasive mechanical ventilation was considered in the ED only if patients remained hypoxic (PaO2 < 60 mmHg) on CPAP/NIPPV with 100% FiO2. The decision on which patient to intubate first within those on CPAP/NIPPV was made evaluating age, comorbidities and respiratory failure severity, with criteria varying from time to time depending on the number of available ICU beds and ventilators.

The primary outcome of the study is to describe the severity of respiratory failure of the patients with COVID-19 infection presenting to the ED during the study period and the ventilatory support started to manage it.

The secondary outcome is to evaluate the outcome (death or intubation) of patients who needed a ventilatory support.

The statistical analysis was carried out with IBM SPSS. Continuous variables were expressed as median and interquartile range (IQR). Kruskal–Wallis test was used to compare continuous variables; χ^2, Pearson χ^2 or Fisher exact test was used for categorical variables as appropriate. All statistical test were 2-tailed; statistical significance was defined as $P < 0.05$.

Due to the retrospective design of the study we did not predetermined the sample size. The number of patients coded as "suspected COVID-19 infection" in the triage area of the ED in the study period determined the sample size.

2.1. Ethics committee approval

This retrospective study was approved by the Ethic Commission of our Bergamo which, due to the retrospective nature of the study, waived the need for informed consent from individual patients.

2.2. Role of funding

We received no funds for this research project

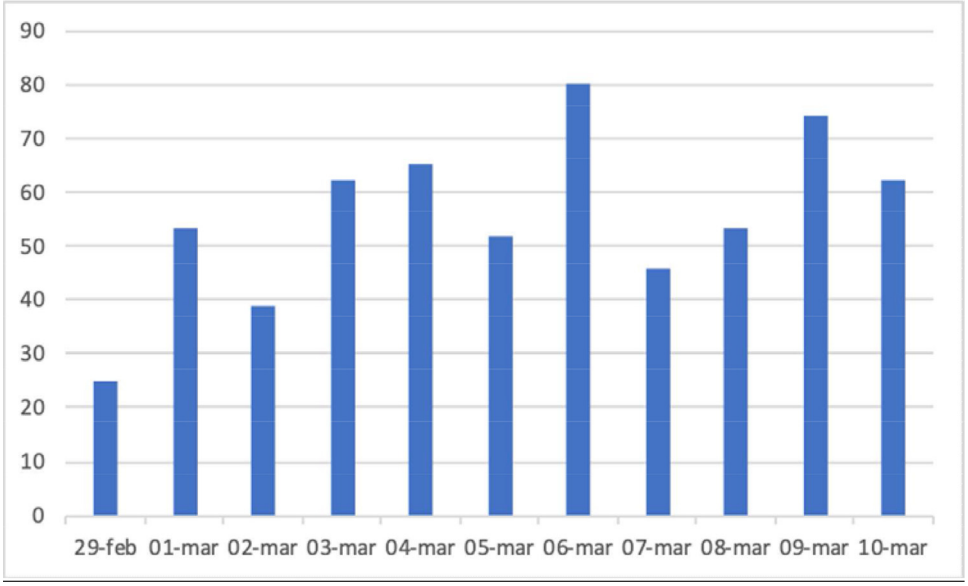

Fig. 1. Patients. presenting to ED with suspected COVID-19 infection. *X*-axis: observational period. *Y*-axis: daily number of patients presented at our ED.

3. Results

From 29/02 to 10/03, 611 patients suspected to be COVID-19 infection positive presented to our ED. The number of suspected COVID-19 patients attending our ED progressively increased from 25 patients/day to a maximum of 80 patients on the 6th of March (Fig. 1).

Among 611 patients presenting to the ED, 291 were eventually discharged home (48%). The hospital admission rate increased from 28% on the 29th of February to a maximum of 68% on the 9th of March 8 (Fig. 2).

The number of ICU beds available inside the hospital increased from 16 beds on the 29th of February to 68 beds on the 10th of March Figure 3.

Among the 320 admitted patients, 99 (31%) were hypoxic and/or dyspneic on 15 L/min nonrebreather mask and were started on Helmet CPAP (80 pts, 81%), non-invasive ventilation positive (7 pts, 7%) or invasive ventilation (12, 12%pts) in the ED.

85 (86%) of the patients started on a ventilatory support in the ED eventually showed a positive nasopharyngeal swab PCR test for SARS-CoV-2 and were included in this report (Fig. 4).

4. Clinical characteristics

Among 85 patients needing immediately ventilatory support 71 (83.5%) were started on Helmet CPAP, 7 (8.2%) on NIPPV and 7 (8.2%) were intubated and treated with IMV.

The demographic characteristics and comorbidities of COVID-19 patients treated with different ventilatory support modalities are listed in Table 1. Overall, 72 (84%) patients were male. The median age was 70 years (IQR 62−79).

Seventy-four percent of the patients had at least 1 comorbidity. Hypertension was the most common comorbidity, affecting 46 (54%) of the patients. The second most common comorbidity was Diabetes (19 patients, 22%), followed by Coronary Artery Disease and Congestive Heart Failure (14 patients 16.5% and 7 patients, 8.2%

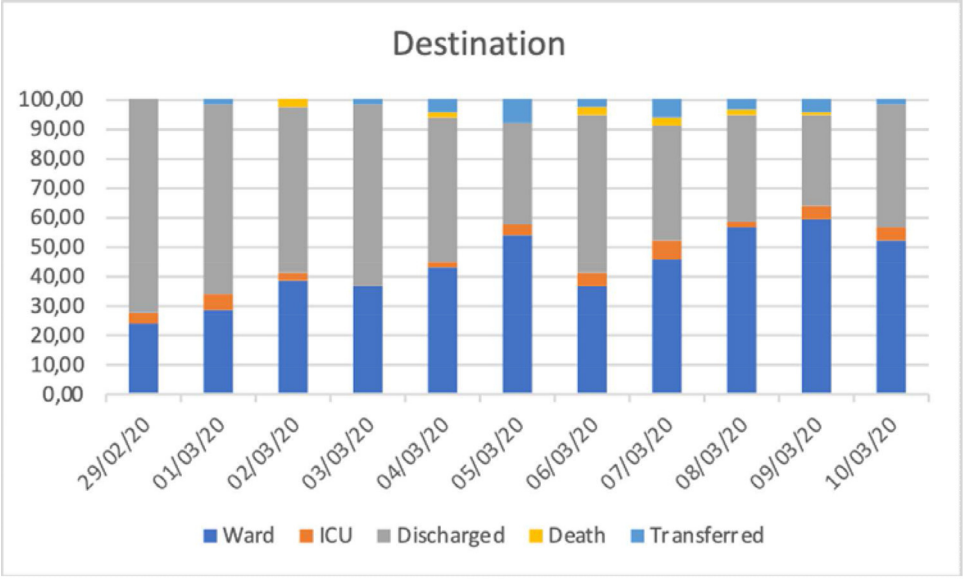

Fig. 2. Rates of disposition of patients with suspected COVID-19 infection. *X*-axis: observational period. *Y*-axis: percentages of patients presented at our ED.

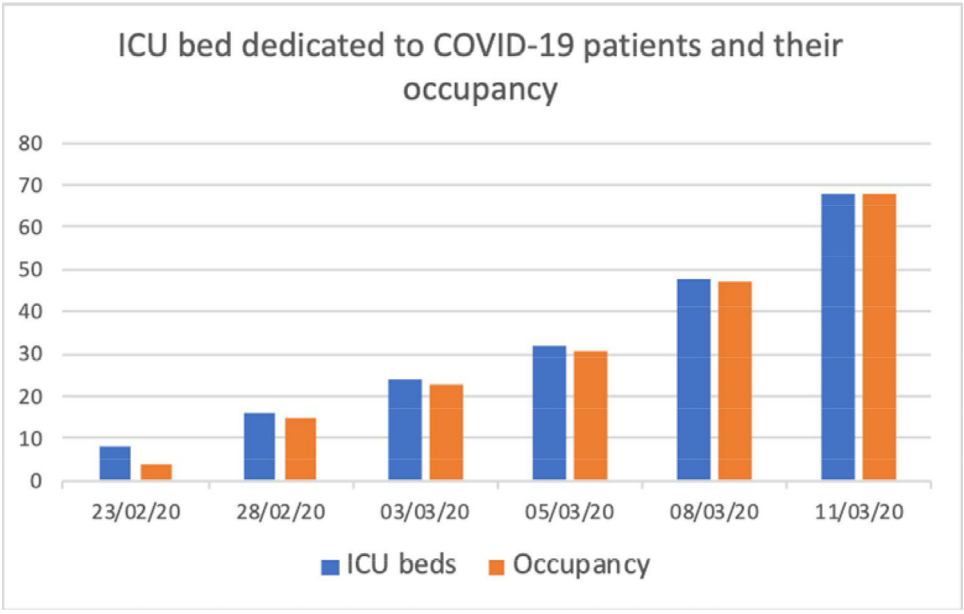

Fig. 3. Increase in the number of ICU beds dedicated to COVID-19 patients during epidemic and their occupancy. *X*-axis: observational period. *Y*-axis: number of ICU beds.

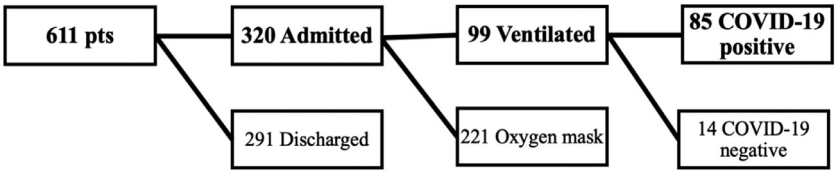

Fig. 4. Selection of the cohort of patients with confirmed COVID-19 presenting to the Emergency Department and being admitted on a ventilatory support.

Table 1
Number of patients treated with different ventilatory supports and their demographic characteristics and comorbidities.

	CPAP	NIPPV	IMV	Total	*p* Value	Test
N total	71	7	7	85		
Age, years median (IQR)	70 (62–79)	72(59–80)	64 (62–72)	70 (62–79)	0.35	KW
Sex *n*; M/F	61/10	5/2	6/1	72/13	0.595	Pearson χ^2
CAD *n* (%)	12 (16.9)	1(14,3)	1(14.3)	14(16.5)	0.971	Pearson χ^2
Hypertension *n* (%)	41(57.7)	3(42.9)	2(28.6)	46(54.1)	0.276	Pearson χ^2
COPD *n* (%)	4 (5.6)	2(28.6)	0(0)	6(7.1)	0.058	Pearson χ^2
CHF *n* (%)	6 (8.5)	1(14.3)	0(0)	7(8.2)	0.605	Pearson χ^2
Peripheral vascular disease *n* (%)	1 (1.4)	0(0)	0(0)	1(1.2)	0.905	Pearson χ^2
Stroke or TIA *n* (%)	5 (7)	0(0)	0(0)	5(5.9)	0.592	Pearson χ^2
Connective tissue disease *n* (%)	1(1.4)	0(0)	1(14.3)	2(2.4)	0.09	Pearson χ^2
Dementia *n* (%)	2(2.8)	0(0)	0(0)	2(2.4)	0.817	Pearson χ^2
Diabetes *n* (%)	16(22.5)	3(42.9)	0(0)	19(22.4)	0.156	Pearson χ^2
Peptic ulcer *n* (%)	1(1.4)	0(0)	0(0)	1(1.2)	0.905	Pearson χ^2
Liver failure *n* (%)	1(1.4)	0(0)	0(0)	1(1.2)	0.905	Pearson χ^2
CKF *n* (%)	1(1.4)	0(0)	0(0)	1(1.2)	0.905	Pearson χ^2
Hemiplegia *n* (%)	0 (0)	0(0)	0(0)	0(0)	nv	Pearson χ^2
AIDS *n* (%)	1(1.4)	0(0)	0(0)	1(1.2)	0.905	Pearson χ^2
Lymphoma *n* (%)	0(0)	0(0)	0(0)	0(0)	nv	Pearson χ^2
Neoplasia *n* (%)	5 (7)	0(0)	0(0)	5(5.9)	0.592	Pearson χ^2
Leukemia *n* (%)	0(0)	0(0)	0(0)	0(0)	nv	Pearson χ^2
CCI median (IQR)	3 (2–4)	4 (2–4)	2 (2–3)	3 (2–4)	0.271	KW

CPAP = continuous positive airway pressure; NIPPV = Non-Invasive Positive Pressure Ventilation; IMV = Invasive Mechanical Ventilation, CAD = coronary artery disease, COPD= chronic obstructive pulmonary disease, CHF= congestive heart failure, CKF= chronic kidney failure, AIDS= autoimmune deficiency syndrome, IQR= interquartile range, CCI = Age Adjusted Charlson Comorbidity Index.

respectively). The median Age Adjusted Charlson Comorbidity Index (CCI) was 3 (IQR 2–4).

The clinical characteristics of the patients are shown in Table 2. The median PO2/FiO2 ratio (measured after starting the ventilatory support) was 128 (IQR 85–168) ranging from 76 (60–177) within patients treated with IMV to 131 (97–190) within those treated with Helmet CPAP. The median pCO2 was lower in the CPAP group compared to NIPPV and IMV groups (34 mmHg, IQR 31–37 vs 38 mmHg, IQR 35–46 and 41 mmHg, IQR 35–45; $p = 0.013$).

Table 2
Clinical characteristics.

	CPAP	NIPPV	IMV	Total	*p* Value	Test
FiO2						
n with aivailable data	68	7	7	82		
%; median (IQR)	60 (60–80)	60 (50–100)	80(70–100)	60 (60–80)	0.079	KW
PEEP						
n with aivailable data	70	5	7	82		
CmH2O; median (IQR)	15 (12–18)	16 (12–20)	18(10–18)	15 (12–18)	0.468	KW
P/F						
n with aivailable data	64	7	6	78		
median (IQR)	131 (97–190)	87(53–120)	76 (60–177)	128 (85–168)	0.038	KW
PO2						
n with aivailable data	62	3	6	71		
mmHg; median (IQR)	85 (69–123)	58 (53)	62 (58–95)	81 (64–122)	0.173	KW
pCO2						
n with aivailable data	61	5	6	72		
mmHg, median (IQR)	34 (31–37)	38(35–46)	41 (35–45)	34 (31–38)	**0.013**	KW

CPAP = continuous positive airway pressure; NIPPV = Non-Invasive Positive PressureVentilation; IMV = Invasive Mechanical Ventilation; PEEP = Positive End Expiratory Pressure IQR= interquartile range. KW= Kruskall–Wallis.

Table 3
ARDS classification. CPAP = continuous positive airway pressure; NIPPV = Non-Invasive Positive PressureVentilation; IMV = Invasive Mechanical Ventilation.

	CPAP	NIPPV	IMV	Total	*p* Value	Test
n with aivailable data	66	6	6	78		
Mild ARDS *n* (%)	15 (22.7)	0(0)	1(16.7)	16(20.5)	0.354	Pearson χ^2
Moderate ARDS *n* (%)	35(53)	3(50)	1(16.7)	39(50)	0.205	Pearson χ^2
Severe ARDS *n* (%)	16(24.2)	3(50)	4(66.7)	23(29.5)	**0.048**	Pearson χ^2

Table 4
Outcome on 10th of May. NIV Failure = death or intubation. CPAP = continuous positive airway pressure; NIPPV = Non-Invasive Positive Pressure Ventilation; IMV = Invasive Mechanical Ventilation.

	CPAP	NIPPV	IMV	Total	*p* Value	Test
n	71	7	7	85		
Death *n* (%)	54(76.1)	4(57.1)	7(100)	65(76.5)	0.164	Pearson χ^2
Intubation *n* (%)	26(36.6)	0(0)	7(100)	33(38.8)		
Death before intubation *n* (%)	39(54.9)	4(57.1)	nv	43(55.1)		
NIV failure (death + intubation) *n* (%)	65(91.5)	4(57.1)	nv	69(88.5)		
Death after intubation						
n	26	0	7	33		
N (%)	15(57.7)	0(0)	7(100)	22(66.7)	0.067	Fisher's Exact test

Overall, 16 patients (20.5%) were classified as mild ARDS; 39 (50%) as moderate ARDS and 23 (29.5%) as severe ARDS (Table 3). The proportion of patient with severe ARDS was higher in the IMV group (4 patients, 66.7%) and in the NIPPV group (3 patients, 50%) compared to the CPAP group (16 patients, 24.2%); $p = 0.048$.

4.1. Outcome

The clinical outcome of the 85 patients with confirmed COVID-19 infection being admitted after starting a ventilatory support was registered on May 10th 2020 and is shown in Table 4 and Fig. 5. As of May 10th 65 patients died (76.5%), 18 were discharged from the hospital and 1 is still in hospital on IMV Fig. 5).

All patients who were directly started on IMV died. None of the patient on NIV were intubated and 4 (57.1%) died. 39 patients started on CPAP (54.9%) died before intubation; 26 (36.6%) were intubated and 15 of them (57.7%) died after intubation.

NIV failure, considered as death or intubation, occurred in 88.5% of patients.

Mortality was lower in younger patients (<60 years) compared to older patients (≥ 60 years) (44.4% vs 85%; $p = 0.001$ Fisher exact test) Table 5.

5. Discussion

To our knowledge, this is the first report describing the severity of respiratory failure of patients presenting to the ED during COVID-19 outbreak in Italy and their outcome after a 2 months period follow-up.

The rate of admission within patients presenting with suspected COVID-19 infection increased progressively with time. This is probably due to the fact that during the initial period of the outbreak most patients presented with isolated upper airway symptoms, while in the following days the proportion of patients with persistent fever and bilateral interstitial pneumonia increased. The triage done by the Emergency Medical System (EMS) on the territory could also have contributed to the high rates of admission: during the epidemic only the sickest patients, hypoxic on room air, were brought to the Hospital by the EMS due to hospital overcrowding.

The prevalence of critically ill patients needing a ventilatory support on first evaluation was very high (31% of all admissions in our cohort). Given the initially insufficient ICU resources at the onset of the outbreak (see Fig. 3), we adopted a protocol for starting Helmet CPAP or NIPPV on any patient who was still hypoxic (SpO2 <90%) or tachypneic (respiratory rate >30/min) on 15 L/min nonrebreather mask and admitting them to regular wards until an ICU bed was

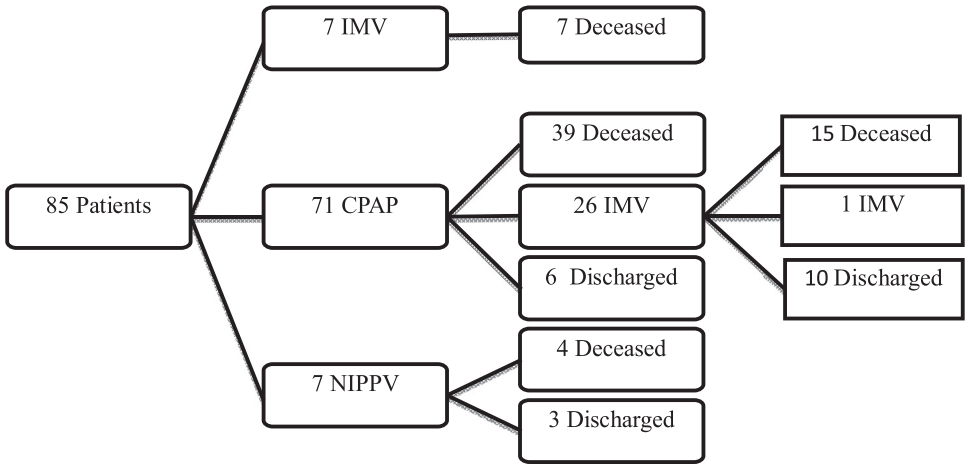

Fig. 5. Outcome registered on 10th of May 2020. CPAP = continuous positive airway pressure; NIPPV = Non-Invasive Positive Pressure Ventilation; IMV = Invasive Mechanical Ventilation.

Table 5
Mortality according to age.

Age (years)	N	Death n (%)
30–39	1	1 (100)
40–49	3	0(0)
50–59	14	7(50)
60–69	22	13(59.1)
70–79	29	28(96.6)
80–89	15	15(100)
90–99	1	1(100)

available. Only those patients who were still hypoxic on NIV underwent invasive mechanical ventilation in the ED. This is likely the reason why the number of patients undergoing invasive mechanical ventilation in the ED is quite low. The lower value of pCO2 in the Helmet CPAP group could be explained by the fact that NIPPV (BiPAP mode) was chosen as first line for patients who showed respiratory acidosis.

Interestingly, our population showed a lower median PO2/FiO2 ratio than the one reported from Grasselli et al. [14] (Median PO2/FiO2 ratio = 128 IQR 85–168 vs 160 IQR 114–220) even though our patients were admitted to regular wards and treated with NIV in a much higher proportion (91.7% vs 11%). Mortality rates are not comparable to their cohort due to the different length of the follow-up.

Mortality rates of patients needing a ventilatory support in our study (76.5%) are comparable to those previously reported in China related to critically ill patients with ARDS [2–17]. The high mortality rate could be explained by the fact that our cohort of patients was a very selected cohort of critically ill patients seen at our ED during the first surge of the outbreak, all hypoxic on maximal oxygen therapy and all needing a ventilatory support.

NIV failure rates are, as expected, very high (88.5%); however, in a limited resource setting without the possibility to intubate all patients with respiratory failure due to pneumonia, the policy of starting these patients on NIV seems the only available option to buy some time to free an ICU bed and, in our data as of 10th of May, this strategy may have contributed to save the life of 23.5% of the patients who were hypoxic on maximal oxygen therapy, had not the possibility to be intubated in the ED and would have probably died without any ventilatory support.

The limitations of our study are mostly related to its observational and retrospective design: the EMS triage on the territory could have made a pre-selection of the patients to be presented to the ED in favor of the most severely ill; some of the respiratory parameters were not registered in the chart by the attending physician and the different application of intubation criteria and ICU beds allocation, strongly depending on daily resources, has most likely affected overall mortality rates. Moreover, the absence of a control group does not allow us to compare NIV to oxygen alone.

The strength of this study lays in its description of a real-life situation where the resources resulted suddenly much lower than the demands of critically ill patients.

In conclusion, our data show that the patients presenting to the ED during the onset of COVID-19 pandemic in Northern Italy was a severely ill population, needing an unexpectedly high amount of intensive care resources and mandating a reorganization of Emergency Departments and hospitals who are in charge of facing this challenge, with the need to dedicate ICU beds to up to 30% of the admitted patients.

In case of disproportion between the number of critically ill patient and the ICU resources available, a strategy using NIV in the ED and in regular wards was feasible and, in our experience, did not lead to higher mortality rates compared to other studies on patients with similar clinical characteristics. Only a randomized controlled trial however could tell if this strategy is a valid alternative to early invasive mechanical ventilation in “usual” settings, helping to identify which patient will benefit from NIV alone without the need to be shifted to IMV afterwards.

Funding

No funds were received for this research project.

Declaration of Competing Interest

Roberto COSENTINI reports personal fees from Fisher & Paykel, outside the submitted work; none of the other authors have any interest to disclose.

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