Noninvasive Ventilatory Support of COVID-19 Patients Outside the Intensive Care Units (WARd-COVID)

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Abstract

Rationale: Treatment with non-invasive ventilation (NIV) in COVID-19 is frequent. Shortage of Intensive care unit (ICU) beds led clinicians to deliver NIV also outside intensive care units (ICUs). Data about the use of NIV in COVID-19 is limited.

Objective: To describe the prevalence and clinical characteristics of patients with COVID-19 treated with NIV outside the ICUs. To investigate the factors associated with NIV failure (need for intubation or death).

Methods: In this prospective single day observational study, we enrolled adult COVID-19 patients, treated with NIV outside the ICU from thirty-one hospitals in Lombardy, Italy.

Results: We collected data on demographic, clinical characteristics, ventilatory management and patients' outcome. Of 8753 COVID-19 patients present in the hospitals on the study day, 909 (10%) were receiving NIV outside the ICU. 778/909 (85%) patients were treated with Continuous Positive Airway Pressure (CPAP), delivered by helmet in 617 (68%). NIV failed in 300 patients (37.6%), while 498 (62.4%) were discharged alive without intubation. Overall mortality was 25%. NIV failure occurred in 152/284 (53%) patients with a PaO_2/FiO_2 ratio < 150 mmHg. Higher C-reactive protein, lower PaO_2/FiO_2, and platelet counts were independently associated with increased risk of NIV failure.

Conclusions: The use of NIV outside the ICUs, in COVID-19 was common, with a predominant use of helmet CPAP, with a rate of success greater than 60% and close to 75% in full treatment patients. C-reactive protein, PaO_2/FiO_2, platelet counts were independently associated with increased risk of NIV failure.

Clinical trial registered with ClinicalTrials.gov (NCT04382235)

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After report of the first cases, Coronavirus (SARS-CoV-2) rapidly spread worldwide, affecting millions of patients and killing several hundred thousand. Coronavirus disease 2019 (COVID-19) is well known to cause Severe Acute Respiratory Failure, with profound hypoxaemia, chest x-ray infiltrates and dyspnea, often requiring intubation and mechanical ventilation. Mortality of the disease is elevated, ranging from 16 to 78% overall and even higher for patients admitted to Intensive Care Units (ICUs). In this context, clinicians have attempted the application of non-invasive respiratory support (NIV), including continuous positive airway pressure (CPAP)[1] and non-invasive pressure support ventilation (NPPV). In this study, for reasons expressed below, high flow nasal oxygen (HFNC), frequently applied in COVID-19[2–4], is treated separately. On one hand, avoiding intubation might reduce complications associated with invasive ventilation and, ultimately, morbidity and possibly mortality. On the other hand, several concerns exist on the use of this strategy: similarly to ARDS[5,6], NIV might only delay (and not avoid) intubation, carrying additional risks primarily related to the lack of monitoring and control over both tidal volume and transpulmonary pressure, with risk of patient self-inflicted lung injury(PSILI)[5,7]. Moreover, deferring intubation to the point when it is performed in a condition of emergency may increase the likelihood of complications related to the procedure itself[8] . Additionally, the exhaled gas leaking from patient's interface (an inherent risk to the use of NIV), might contaminate the ambient air and cause infection of healthcare providers[9,10].

Published data on the use of NIV in COVID-19 patients with acute respiratory failure is very limited and indications are largely adapted from ARDS literature. The recent Surviving Sepsis Campaign COVID-19 guidelines[11] expressed a weak statement in favour of the use of HFNC over NIV, and did not make any recommendation on the use of helmets ("it is an option,

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but we are not certain about its safety or efficacy in COVID-19"). More recently, the Managing ICU surge during the COVID-19 crisis rapid guidelines expressed a weak recommendation for hospitals to "develop and implement (…) the use of high-flow nasal oxygen (HFNO) and noninvasive ventilation (NIV) in order to reduce the need for intubation"[12].

Another peculiar aspect of COVID-19 pandemic is the overwhelming number of patients needing respiratory assistance, causing a rapid shortage of ICU beds[13]. Hence, doctors, nurses and respiratory therapists have been forced to apply NIV not only in the "classical" environments, such as ICUs or high dependency units, but also in regular hospital wards[14]. This practice has been particularly frequent in Italy, where application of helmet CPAP in low-intensity floors has been rather common since several years. NIV is also often provided to those patients in whom a do-not-intubate decision has been taken. However, the high volume of patients, the lack of familiarity of nurses and clinicians with the device and the limited monitoring possibilities represent additional concerns in this practice[15].

The primary aim of this study was to describe the prevalence and clinical characteristics of patients with COVID-19 treated with NIV outside the ICUs on a single day. Patients receiving HFNC were excluded from main analysis, given the very limited number and the differences with classical positive pressure ventilation systems. Moreover, we investigated the factors associated with NIV failure in the entire population and, separately in patients with and without a Do-Not-Intubate (DNI) decision.

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Methods

This is a single day observational study. The institutional Ethics Board of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, and local Ethics Committees of participating centers (listed in online eAppendix #1, recruited in the COVID-19 Lombardy Network) approved the study. Informed consent from individual patients was waived in most cases. Investigators from each Center collected data on March 26th or 31st at their choice. In the selected day, all patients present in the hospital were screened for enrollment in the study. Inclusion Criteria were:

- Age> = 18 years
- Diagnosis of COVID-19 pneumonia
- Non-invasive respiratory support (HFNC, NPPV or CPAP), performed outside the ICU

The only exclusion criterion was the lack of informed consent, where required. All eligible patients were enrolled. The following variables were collected: age, sex, main comorbidities, smoking history, Clinical Frailty Score[16], type of respiratory support (NPPV, CPAP or HFNC), level of positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2). When available, arterial blood gas and peripheral oxygen saturation, hemodynamic parameters, main blood chemistry and number of quadrants involved on the chest x ray were also collected. If more than one value was available for the day, investigators were pragmatically asked to input the most "representative" value, at their clinical judgment. Patients were then followed-up, recording need for intubation, decision to limit the intensity of treatment and status at

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hospital discharge (alive, transferred to another hospital, dead). We defined NIV failure as intubation (independently following outcome) or death without intubation.

Statistics

Data collection was performed using an electronic Case-Report Form implemented in the platform RedCapCloud (powered by nPhase), in accordance with the European Statement 679/2016/UE, with online access available to the participating centers. The databases were compiled in compliance with the ICH Good Clinical Practice. Continuous data were described by mean and standard deviation or median and interquartile range, depending on the distributional shape. Comparison across groups was performed by T-test or Wilcoxon nonparametric test, depending on the distributional shape. Categorical data were described by absolute frequencies and percentages, comparison across groups was performed by the Chi-square test on association. Horizontal bar plot was used for graphical representation of categorical variables. Univariate and multivariable analysis relating binary outcome to explanatory variables were obtained by logistic regression. Significance level was set equal to 5%, tests were two sided. Given the purpose of the study, we did not pre-specify a sample size, but enrolled all patients fulfilling inclusion criteria on the study day.

A logistic regression of a binary response variable on a continuous, normally distributed variable X with a sample size of 800 observations achieves 90% power at a 5% significance level to detect a change in the probability of observing the endpoint from the percentage of 30% at the mean of X to 35% when X is increased to one standard deviation above the mean. This change corresponds to an odds ratio of 1.284. When the percentage at the mean of X is raised

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to 35%, 40%, 45%, the detectable change is 5.5%, 5.7%, and 5.7%. Stata version 16 software was used for data quality assessment, statistical analysis and graphics.

Results

Of thirty-seven centers initially expressing their interest in participating to the study, 31 enrolled patients. On average, the number of ICU beds dedicated to COVID patients was increased by 223 ± 86% as compared to the pre-COVID period, but 96 ± 8% of the beds were occupied, on the study date. Study flowchart is presented in eFigure 1. Overall, 8753 COVID-19 patients were present in these hospitals on the study day (accounting for 62 ± 25% of total hospital beds). Of these, 909 (10.4%) were receiving NIV outside the ICU, while 854 (9.7%) were being treated in the ICUs: of these only 53 (6.2%) was receiving NIV, in 40 cases after extubation, while the remaining were intubated. There was a weak negative correlation (r=-0.34, p=0.07) between the fraction of patients treated with NIV in the ICU (as percentage of total ICU beds) and those outside (as percentage of total non-intensive COVID beds). For the 909 patients treated with NIV outside the ICU, in the vast majority of cases 778/909 (85%) patients were treated with CPAP, NPPV was used in 90 (10%). In the majority of patients treated with NIV (617, corresponding to 68%), this was delivered by helmet, while face mask was used in 248 patients. HFNC was used only in 39 patients. Given the substantial difference between positive pressure devices and HNFC, we decided to remove from the subsequent analyses this small subset (described in the eTable 1) and also the 33 (3.7%) patients who received NIV after extubation (described in the eTable 2).

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At the moment of database freezing (i.e. after a follow-up of 60 days), outcome could be determined in 798 patients, while 37 were still in the hospital. Intubation occurred in 123 patients (15.4%), after 5 [3-9] days since initiation of NIV while 177 died without being intubated 8 [5- 13] days since initiation of NIV. In 138 (78%) of these patients a DNI decision had been taken. NIV failure, hence, occurred in 300 patients (37.6%) while 498 (62.4%) were discharged or transferred alive without intubation. Overall mortality of the cohort was 25%.

Table 1 summarizes main demographic variables and comorbidities of the patients. Patients failing NIV were older (72 [64-78] vs 64 [56-73]) and more fragile (eFigure 2) and had more frequently a history of ischemic heart disease, diabetes, malignancies, active or former smoke habit. No difference was observed regarding the presence of hypertension or the use of ACE-inhibitors or angiotensin-receptor blockers.

NIV was initiated shortly after hospital admission, with a median interval of 1 [0-4] days in the whole cohort with no difference between NIV failure vs success. No difference was also found in the time between symptom onset and hospital admission, which had a median of 7 [5-10] days. Overall, the population was moderately hypoxemic (PaO_2/FiO_2 172 ± 102 mmHg), and most patients were hypocapnic, since 430 (53.9%) patients had a $PaCO_2$ < 40 mmHg. PEEP levels averaged 10.8 ± 2.6 cmH_2O, (but the range was very high, from 2 to 20 cmH_2O), without any association with the severity of radiological impairment. As expected, patients who failed NIV had a significantly lower PaO_2/FiO_2, slightly lower $PaCO_2$ and presented more often dyspnea than those who succeeded. NIV failure occurred in 50/279 (18%) patients with a PaO_2/FiO_2 ratio > 150 mmHg and in 152/284 (53%) patients with a PaO_2/FiO_2 ratio < 150 mmHg (figure 1).

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As shown in table 1, patients failing NIV had also worse kidney function, higher white blood cell, lower platelet counts and higher C-reactive protein. With regards to hemodynamics, heart rate was higher, and so was systolic blood pressure, but the difference was clinically negligible. Only six patients (<1%) received vasopressors. When we analyzed separately the groups of patients with and without DNI decision, the same patterns described above were found in each of the two groups (Table E3).

Multivariate analysis (Table 2) showed that higher C-reactive protein, lower PaO_2/FiO_2, and platelet counts were independently associated with increased risk of NIV failure. Increasing age showed a trend towards higher risk of failure, but did not reach statistical significance (p = 0.052). When the presence of DNI care was introduced in the model, this was associated with an almost three-fold risk of NIV failure, but the same variables remained significant, with the exception of age (Table e4).

Discussion

Treatment of COVID-19 associated respiratory failure constituted, during the surge phase, an incredible challenge for clinicians and healthcare systems, due to the overwhelming number of patients requiring respiratory support[13]. Hence, the need to provide effective treatments must be balanced with the available resources. A large uncertainty exists over the risk-to-benefit ratio of noninvasive treatment of acute hypoxemic respiratory failure in COVID-19 patients[17], since the available literature data is rather scarce. To our knowledge, this is the report of the largest cohort of patients with COVID-19 (and one of the largest in acute respiratory failure

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from any cause) treated with NIV as first-line therapy. Our results show that, during the peak of COVID-19 pandemics, the prevalence of use of NIV outside ICU was high, involving about 12% of hospitalized COVID-19 patients. For each patient treated in the ICU with invasive mechanical ventilation, approximately another patient was assisted in other hospital environments with NIV. This is not surprising, since the peak of COVID patients led to devoting ICU beds almost entirely to the intubated ones.[18–20] This was the case also in our cohort, where ICUs were basically saturated with almost 95% of patients were invasively ventilated, mandating the seek for alternative solution, whenever possible. The incidence of NIV application in the examined setting was similar to previous reports from China[21], but ten-fold higher than that reported in the same period in New York City, where NIV was applied only in 1% of the hospitalized patients[18], clearly reflecting pre-existing clinical practices and attitudes as well as the number of available ICU beds.

Overall, about one third of the patients experienced NIV failure, while this strategy could be applied with success as the sole treatment in the remaining population. At variance with what recommended by the guidelines[11], NIV was predominantly used over HFNC. The most common form of respiratory support was helmet CPAP, applied in 76% of the patients. This might reflect the availability of the device, the familiarity of the operators and the efficacy of PEEP in improving gas exchange. A recent meta-analysis showed that helmets had the highest probability of reducing risk of endotracheal intubation and death, over face mask and high flow oxygen[22]. Helmet allows to deliver a constant and stable level of PEEP with free flow systems and a PEEP valve[23], without the need for a ventilator, making this choice particularly appealing for use in lower-intensity settings[24]. In addition, the use of helmets carries the additional

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advantage of a lower risk of environmental contamination and of nosocomial transmission of the infection, since this interface is characterized by reduced leaks compared with nasal high-flow and facemasks[25]. Finally, high-efficiency particulate air filters can be positioned on the exhalation port of the device, further reducing the risk of viral spread[26]. In this respect, we did not directly assess whether the use of either form of NIV was associated with increased (or decreased) transmission of virus to healthcare workers.

A crucial point in the decision to apply NIV as first-line strategy in patients with acute hypoxemic respiratory failure is the balance between the potential benefits of avoiding intubation and the risks deriving from self-inflicted lung injury. The proposed pathophysiological mechanisms of PSILI in hypoxemic patients with high respiratory drive include volutrauma due to the generation of high tidal volumes and excessive transpulmonary pressure swings, and capillary leak due to increased trans-vascular pressures. Due to the prevalent use of free flow CPAP with helmet, tidal volume (and hence minute ventilation) could not be monitored, but given the high incidence of hypocapnia we speculate that it might have been quite high, particularly in consideration of the high dead space that characterizes lung involvement in COVID-19. Indeed, patients who failed NIV had higher incidence of dyspnea and use of accessory muscles, as well as lower $PaCO_2$, levels, suggesting higher inspiratory efforts, respiratory drive and work of breathing. However, we cannot determine to what extent the higher work of breathing was a contributor to NIV failure or simply a marker of a more severe disease.

In this cohort of COVID-19 patients, some of the factors independently associated with of NIV failure were in line with those previously reported for other forms of acute hypoxemic

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respiratory failure [5,27], like age and PaO_2/FiO_2, while others appear more specific of COVID 19, like serum levels of C-reactive protein[28] or platelet counts[29], likely indicating an hyperinflammatory status or a progression towards multiple organ failure. Concerning the PaO_2/FiO_2 ratio, the threshold value of 150 mmHg was highly predictive of NIV outcome, and, albeit this is still a speculation, it could probably be used as a simple criterion to decide which patients should undergo early intubation. Careful continuous monitoring of hypoxemic patients treated with first-line NIV remains of cornerstone importance, to detect early signs of failure and avoid delay in tracheal intubation. Interestingly, the sensitivity analyses revealed that patients with or without a DNI decision do not present relevant differences regarding the factors associated with risk of NIV failure, albeit the patients with a DNI decision at greater risk, due to higher severity. While this sensitivity analysis is reassuring in regard to the robustness and generalizability of our findings, it must be interpreted cautiously given its post-hoc nature, the heterogeneity in groups size and possible differences among centers in DNI dispositions.

This study has several limitations. At first, this study is purely descriptive and all enrolled patients were being treated with NIV: hence it is not possible to draw and conclusion of superiority or inferiority of NIV to other forms of support (e.g. standard oxygen, invasive ventilation). The single-day approach was chosen to minimize the burden on the investigators but does not allow a longitudinal follow-up of patients (including the reason from NIV discontinuation, i.e. improvement vs intolerance), who are then captured at different stages of the disease. Moreover, this approach could underestimate the actual use of NIV, since patients treated with NIV for shorter periods of time (either because of failure or low severity) have less chances of being captured. We also had to keep within reasonable limit the number of

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variables, hence we did not collect data in regard to various drugs that were inconsistently administered during pandemics and that might have influenced outcomes. Sleep apnea is a frequent cause for CPAP application, but unfortunately, we did not capture this data in our database: hence it is possible that some of the patients (particularly those treated with face mask as an interface), presented this as the main indication for NIV. However, in a context where all patients had COVID-19 pneumonia and was hypoxemic in most cases, we believe that the incidence of this patients was minimal. We did not have access or possibility to monitor the source data, which was, however, quite straightforward to collect. The centers participating to the study are in a specific geographic region, in northern Italy, where the use of helmet CPAP outside the ICU was quite common even before COVID-19 and were resources were particularly strained during the surge: hence results might not be generalizable elsewhere.

In conclusion, this single day observational study shows that NIV outside the ICU is feasible, since about 10% of COVID-19 patients present in the hospital were treated with NIV outside the ICUs, with a predominant use of helmet CPAP. The overall rate of success was about 65%: being 73% in the full treatment patient was, while only one third of the DNI patients survived. C-reactive protein, PaO_2/FiO_2, platelet counts and probably age were independently associated with increased risk of NIV failure.

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Figure Legends:

Figure 1: Survival curves of COVID-19 patients treated with noninvasive ventilation (NIV) and stratified according to PaO_2/FiO_2 ratio on the date of data collection. Log-rank test $P<0.001$

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Figure 1

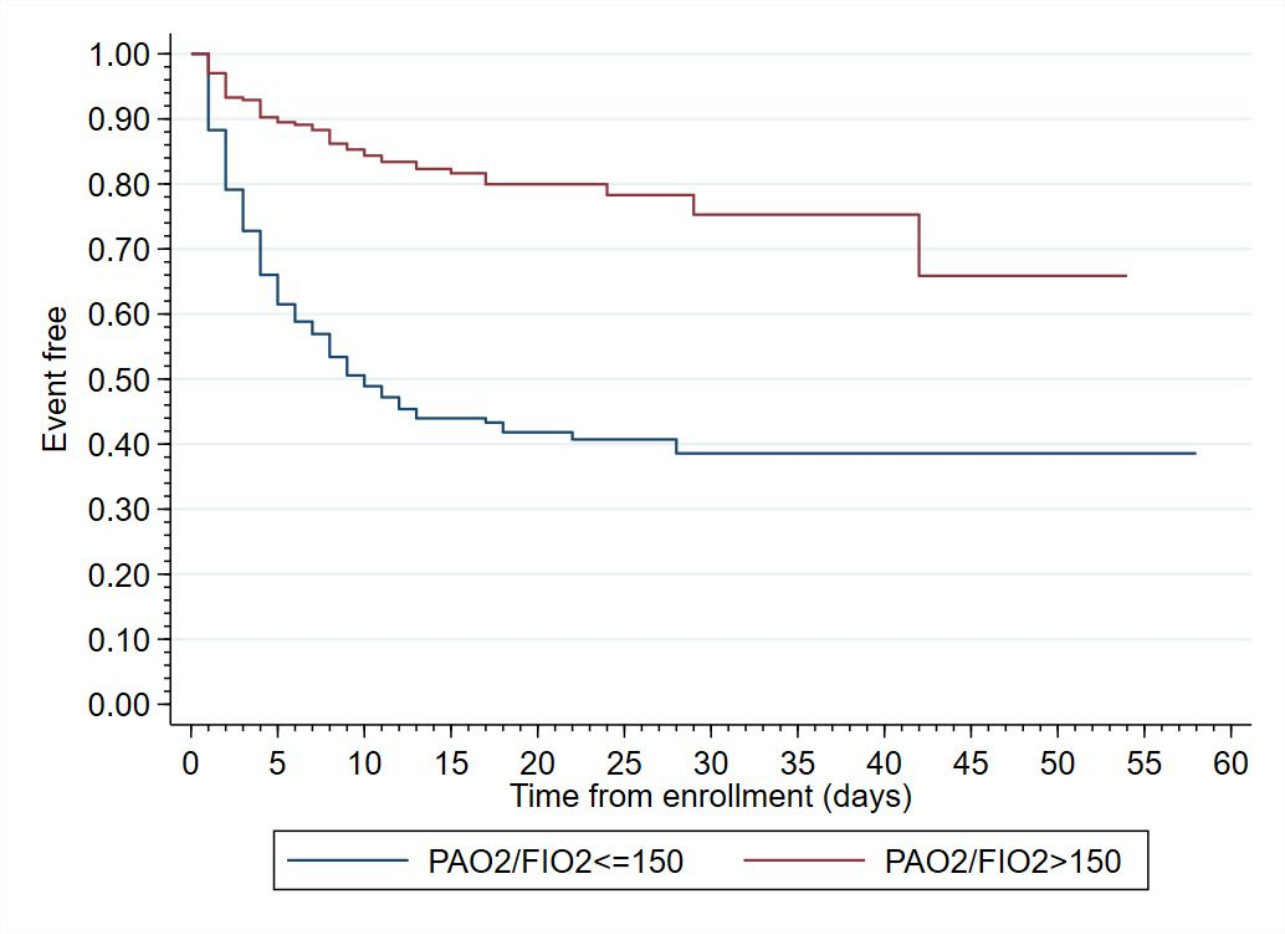

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Table 1: Main demographic variables and comorbidities of the enrolled patients.

	n	**All population (n=798)**	**Success (n= 498, 62.4%)**	**Failure (n=300, 37.6%)**
Male, No. (%)		595 (74,56)	367 (73,69)	228(76,0)
Age, Median [IQR], years	798	68 [59-75]	64 [56-72]	72 [64-78]*
Body Mass Index, Median [IQR], (kg/m^2)	539	27.2 [24.5-30.5]	27.3 [24.7-30.9]	27 [24.3-29.4]
Comorbidities				
Ischemic or congestive heart disease, No. (%)	798	119 (14.9)	57 (11.4)	62 (20.7)*
Hypertension, No. (%)	798	438 (54.9)	262 (52.6)	176 (58.7)
ACE-inhibitors, No. (%)	798	142 (17.8)	88 (17.8)	54 (18.0)
Angiotensin-receptor blockers, No. (%)	798	115 (14.4)	71 (14.3)	44 (14.7)
Vascular disease, No. (%)	798	81 (10.2)	36 (7.2)	45 (15)*
COPD, No. (%)	798	76 (9.6)	49 (9.8)	27 (9.0)
Autoimmune disease, No. (%)	798	33 (4.1)	20 (4.0)	13 (4.3)
Diabetes, No. (%)	798	160 (20.0)	90 (18.1)	70 (23.3)
Chronic Kidney Disease, No. (%)	798	32 (4.0)	15 (3.0)	17 (5.7)
Malignancy, No. (%)	798	34 (4.3)	15 (3.0)	19 (6.3)*
Smoking history	798			
Active smoker, No. (%)			19 (3.8)	17 (5.8)§
Former smoker, No. (%)			87 (17.6)	77 (26.5)§
Never smoked, No. (%)			221 (44.7)	102 (35.1)§
Not declared, No. (%)			167 (33.8)	95 (32.7)§
Time between hospital admission and data collection, Median [IQR], **days**	798	7 [4-10]	7 [5-11]	5 [3-8]*
Time between hospital admission and NIV initiation, Median [IQR]**, days**	763	1 [0-3]	1 [0-4]	1 [0-3]
Time between symptoms onset and hospital admission, Median [IQR], **days**	772	7 [5-10]	7 [5-10]	7 [4-10]
Received seasonal Flu Vaccine, No. (%)		92 (11.59)	28 (9.4)	64 (12.9)
DNI decision , No. (%)	727	215 (28.4)	70 (14.6)	145 (52.3)*
Respiratory parameters				
FiO_2, mean (SD), %	758	67.5 (20.5)	61.2 (18.6)	78.2 (19.1)*
PEEP, mean (SD), cmH2O	783	10.79 (2.5)	10.6 (2.6)	11.3 (2.5)*

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pH, mean (SD)	598	7.45 (0.05)	7.445 (0.04)	7.44 (0.06)*
PaO_2, mean (SD) (mmHg)	599	103 (52)	113 (56)	89 (43)*
PaO_2 /FiO_2, mean (SD) **(mmHg)**	592	168 (98)	198 (104)	122 (66)*
$PaCO_2$, mean (SD) **(mmHg)**	599	37.4 (6.9)	37.9 (6.6)	36.6 (7.2)*
$PaCO_2$ <40 mmHg, No. (%)	599	430 (53.9)	257 (51.6)	173 (57.7)
SaO_2 mean (SD), %	576	95.4 (4.6)	96.5 (3.4)	93.7 (5.6)*
SpO_2 mean (SD), %	164	94.6 (5.5)	96.5 (2.9)	90.8 (7.3)*
SpO_2 /FiO_2, mean (SD)	141	160.3 (51.9)	175.2 (49.7)	126.5 (40)*
Respiratory Rate	605	23.9 (6.6)	22.1 (5.4)	26.7 (7.4)*
Use of accessory respiratory muscles , No. (%)	631	183 (27.64)	59 (14.4)	124 (49.2)*
Dyspnoea, No. (%)	631	179 (27.2)	60 (14.5)	119 (48.8)*
Laboratory Values				
Creatinine, mean (SD) **(mg/dL)**	700	1.03 (0.8)	0.9 (0.6)	1.25 (1.0)*
Urea, mean (SD) **(mg/dL)**	493	56.8 (43.9)	47.3 (28.9)	71.7 (57.2)*
White blood cells , mean (SD) **(103/µL)**	708	10.2 (8.9)	9.4 (6.5)	11.6 (11.7)*
Platelets (103/µL) , mean (SD)	703	302 (130)	330 (131)	253 (114)
Haemoglobin, mean (SD) **(g/dL)** , mean (SD)	708	12.4 (1.7)	12.4 (1.5)	12.4 (1.8)
Bilirubin, mean (SD) **(mg/dL)**	485	0.82 (1.02)	0.77 (0.92)	0.89 (1.15)
C-reactive protein , mean (SD) **(mg/L)**	675	106 (89)	82 (77)	148 (95) *
Procalcitonin, Median [IQR] **(ng/DL)**	275	0.21 [0.1 - 0.63]	0.15 [0.08 - 0.37]	0.42 [0.2 - 1.3]*
Hemodynamic Parameters				
Systolic Blood pressure , mean (SD) **(mmHg)**	741	130 (18)	1290 (1)	132 (20)
Diastolic Blood pressure , mean (SD) **(mmHg)**	741	75 (11)	76 (11)	75 (12=
Heart Rate, mean (SD) **(1/min)**	734	81.2 (15.9)	78.4 (14.0)	86.0 (17.8) *
Temperature , mean (SD) **(°C)**	692	36.5 (0.7)	36.4(0.7)	36.8 (0.8) *

List of abbreviations: **COPD**: Chronic bronchopulmonary disease; **DNI:** Do-Not-Intubate. **FiO_2:** inspired oxygen fraction, **PEEP:** Positive End Expiratory Pressure; **PaO_2**, arterial partial pressure of oxygen; **$PaCO_2$**, arterial partial pressure of Carbon dioxide;

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Table 2: Multivariate analysis of factors independently associated with probability of NIV failure

	Odds Ratio	**Std. Err.**	**P>z**	**[95% Conf. Interval]**	
Age (per year increment)	1.04	0.02	0.052	1.00	1.08
Ischemic or congestive heart disease (ref. No)	1.84	0.87	0.2	0.73	
Vascular disease (ref. No)	0.94	0.60	0.92	0.27	3.30
Malignancy (ref. No)	2.73	3.66	0.46.	0.20	37.87
Former smoker (Ref. Active Smoker)	0.88	0.69	0.87	0.19	4.04
Never smoked. (Ref. Active Smoker)	0.52	0.38	0.37	0.12	2.21
Not declared. (Ref. Active Smoker)	0.96	0.74	0.96	0.21	4.38
PEEP. mean (SD). cmH_2O	0.95	0.07	0.52	0.83	1.10
pH. mean (SD)	0.01	0.04	0.22.	0.00	15.90
PaO_2 /FiO_2 (per mmHg increment)	0.99	0.003	<0.001	0.99	1.00
$PaCO_2$. (per mmHg increment)	0.97	0.02	0.23	0.92	1.02
Respiratory Rate (per 1/min increment)	1.04	0.03	0.15	0.99	1.10
Creatinine (per 1 mg/dL increment)	0.88	0.26	0.65	0.49	1.55
Urea (per 1 mg/dL increment)	1.01	0.01	0.21	1.00	1.02
White blood cells (per **10^3/µL** increment)	0.99	0.03	0.75	0.94	1.05
Platelets (per 10^3/µL increment)	**1.006**	**0.001**	**<0.01**	**0.99**	**1.00.**
Haemoglobin (per **g/dL** increment)	0.97	0.12.	0.79	0.76	1.23
C-reactive protein (per g/dL increment)	**1.01**	**0.003**	**<0.01**	**1.00**	**1.01**
Procalcitonin <0.5 (ref. Missing value)	1.10	0.44.	0.81	0.51	2.39
Procalcitonin >0.5 (ref. Missing value)	0.78	0.40.	0.63	0.29	2.12
Systolic Blood pressure (per mmHg increment)	1.01	0.01	0.41	0.99	1.03
Heart Rate (per 1/min increment)	1.02	0.01	0.10	1.00	1.05

List of abbreviations: **FiO_2:** inspired oxygen fraction, **PEEP:** Positive End Expiratory Pressure; **PaO_2**, arterial partial pressure of oxygen; **$PaCO_2$**, arterial partial pressure of Carbon dioxide

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Supplementary Online Content

Noninvasive ventilatory support of COVID-19 patients outside the Intensive Care Units (WARd-COVID)

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eAppendix 1:

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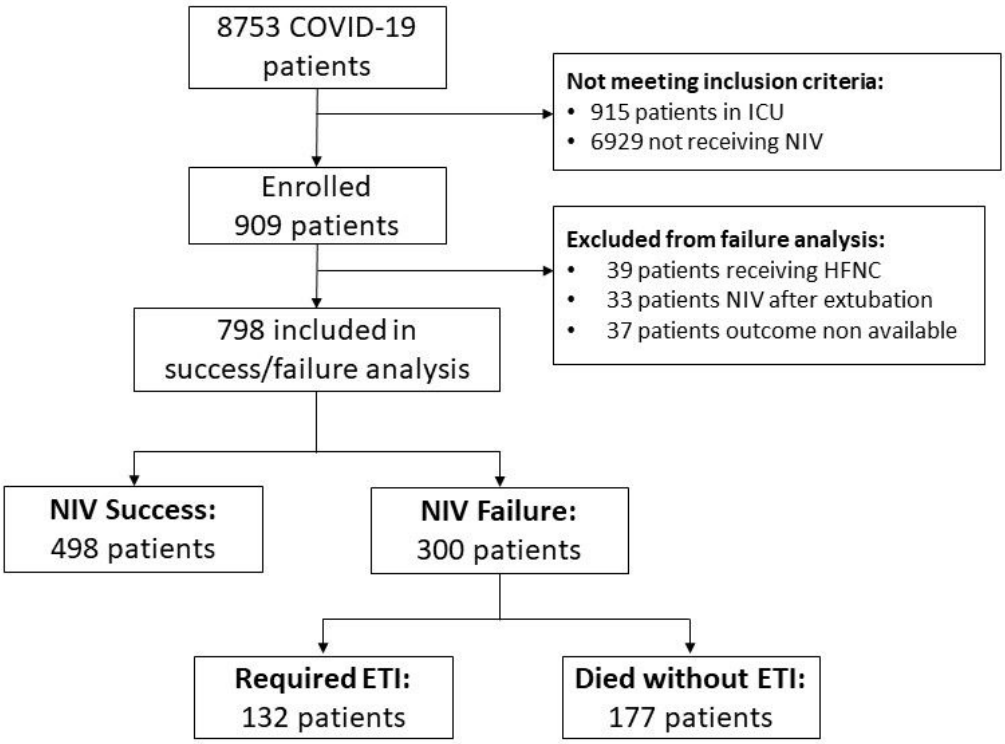
eFigure 1



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eTable 1

		Patients treated with HFNC
Age, Median [IQR], years	39	62 [51-71]
BMI (kg/m^2)	27	26.8 [24.7-29.4]
Limitation of Care	39	4 (14)
FiO_2, mean (SD), %	38	59.2 (18.5)
PEEP, mean (SD), cmH2O		
pH, mean (SD)	27	7.5 (0.0)
PaO_2, mean (SD) (mmHg)	27	91.2 (35.0)
PaO_2 /FiO_2, mean (SD) **(mmHg)**	27	166.8 (94.5)
$PaCO_2$, mean (SD) **(mmHg)**	27	36.8 (5.2)
$PaCO_2$ <40 mmHg, No. (%)	27	19 (48.72)
SaO_2 mean (SD), %	27	96.0 (2.5)
SpO_2 mean (SD), %	11	96.5 (2.8)
Respiratory Rate	32	20.7 2.8
Creatinine (mg/dL)	35	0.9 (0.5)
Urea (mg/dL)	19	58.1(44.7)
White blood cells (103/µL)	36	9.4 (4.0)
Platelets (103/µL)	36	339.2 (123.3)
Haemoglobin (g/dL)	36	11.8 (1.5)
Bilirubin (mg/dL)	32	0.8 (0.5)
C-reactive protein (mg/L)	36	59.7 (57.4)
Procalcitonin (ng/DL)	19	0.3 (0.4)
Systolic Blood pressure (mmHg)	37	123.9 (16.2)

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Diastolic Blood pressure (mmHg)	37	71.2 (10.1)
Heart Rate (1/min)	37	74.5 (12.1)
Temperature (°C)	35	36.3 (0.4)

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eTable2

		Patients treated with NIV after extubation
Male, No. (%)		
Age, Median [IQR], years	33	61 [54-66]
BMI (kg/m^2)	28	26.7 [25.6-31.9]
Limitation of Care	33	0 (0%)
FiO_2, mean (SD), %	32	60.5 (21.7)
PEEP, mean (SD), cmH2O	33	10.6 (2.6)
pH, mean (SD)	30	7.4 (0.1)
PaO_2, mean (SD) (mmHg)	30	110.7 (47.4)
PaO_2 /FiO_2, mean (SD) **(mmHg)**	30	202.0 107.2
$PaCO_2$, mean (SD) **(mmHg)**	30	40.0 (6.8)
$PaCO_2$ <40 mmHg, No. (%)	30	16 (48.48)
SaO_2 mean (SD), %	30	97.2 (2.2)
SpO_2 mean (SD), %	3	90.3 (6.0)
Respiratory Rate	28	22.8 6.2
Creatinine (mg/dL)	30	1.0 (0.8)
Urea (mg/dL)	23	66.5 (27.2)
White blood cells (103/µL)	31	12.2 (4.9)
Platelets (103/µL)	31	339.8 (119.1)
Haemoglobin (g/dL)	31	10.6 (2.0)
Bilirubin (mg/dL)	32	1.0 (0.6)
C-reactive protein (mg/L)	31	76.9 (79.3)
Procalcitonin (ng/DL)	19	8.2 (34.3)

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Systolic Blood pressure (mmHg)	33	136.4 (15.7)
Diastolic Blood pressure (mmHg)	33	78.2 (8.9)
Heart Rate (1/min)	33	82.6
Temperature (°C)	32	36.5

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eTable 3

	Patients with limitation of treatment (n= 215, 27 %)			**Patients without limitation of treatment (n=583, 73 %)**		
		Success (n= 70, 33%)	**Failure (n=145, 67%)**		**Success (n= 428, 73%)**	**Failure (n=155, 27 %)**
Male, No. (%)	143 (66.5)	43 (61)	100 (69)	452 (77.5)	324 (76)	228 (76)
Age, Median [IQR], years	76 [71- 80]	75 [69- 79]	76 [71- 80]	64 [56- 71]	63 [54- 70]	66 [60- 73]
Body Mass Index, Median [IQR], (kg/m^2)	26.57 [24.22- 29.41]	26.45 [24.22- 29.97]	26.87 [24.36- 29.41]	27.36 [24.64- 30.5]	27.51 [24.69- 30.97]	26.99 [24.3- 29.41]
Ischemic or congestive heart disease, No. (%)	59 (27.44)	16 (22.86)	43 (29.66)	60 (10.29)	41 (9.58)	19 (12.26)
Hypertension, No. (%)	149 (69.3)	47 (67.14)	102 (70.34)	289 (49.57)	215 (50.23)	74 (47.74)
ACE-inhibitors, No. (%)	41 (19.07)	11 (15.71)	30 (20.69)	101 (17.32)	77 (17.99)	24 (15.48)
Angiotensin-receptor blockers, No. (%)	38 (17.67)	13 (18.57)	25 (17.24)	77 (13.21)	58 (13.55)	19 (12.26)

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Vascular disease, No. (%)	48 (22.33)	13 (18.57)	35 (24.14)	33 (5.66)	23 (5.37)	10 (6.45)
COPD, No. (%)	35 (16.28)	17 (24.29)	18 (12.41) *	41 (7.03)	32 (7.48)	9 (5.81)
Autoimmune disease, No. (%)	7 (3.26)	3 (4.29)	4 (2.76)	26 (4.46)	17 (3.97)	9 (5.81)
Diabetes, No. (%)	55 (25.58)	16 (22.86)	39 (26.9)	105 (18.01)	74 (17.29)	31 (20)
CKD, No. (%)	17 (7.91)	5 (7.14)	12 (8.28)	15 (2.57)	10 (2.34)	5 (3.23)
Malignancy, No. (%)	17 (7.91)	5 (7.14)	12 (8.28)	17 (2.92)	10 (2.34)	7 (4.52)
Smoking history						
Active smoker, No. (%)	10 (4.74)	0 (0)	10 (7.04)	26 (4.53)	19 (4.47)	7 (4.7)
Former smoker, No. (%)	52 (24.64)	15 (21.74)	37 (26.06)	112 (19.51)	72 (16.94)	40 (26.85)
Never smoked, No. (%)	65 (30.81)	24 (34.78)	41 (28.87)	258 (44.95)	197 (46.35)	61 (40.94)
Not declared, No. (%)	84 (39.81)	30 (43.48)	54 (38.03)	178 (31.01)	137 (32.24)	41 (27.52)
Respiratory Parameters						
FiO_2, mean (SD), %	75.64 ± 20.44	66.17 ± 19.03	80.13 ± 19.6*	64.59 ± 19.71	60.36 ± 18.41	76.37 ± 18.42*
PEEP, mean (SD), cmH2O	10.85 ± 2.48	10.49 ± 2.6	11.02 ± 2.4	10.84 ± 2.63	10.57 ± 2.61	11.56 ± 2.59*
pH, mean (SD)	7.43 ± 0.06	7.43 ± 0.05	7.42 ± 0.07	7.45 ± 0.04	7.45 ± 0.04	7.44 ± 0.46

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PaO_2, mean (SD) (mmHg)	89.99 ± 39.21	99.25 ± 36.57	85.5 ± 39.83*	107.33 ± 55.49	113.89 ± 58.02	91.22 ± 45.02*
PaO_2 /FiO_2, mean (SD) **(mmHg)**	132 ± 75	168 ± 88	114 ± 61*	181 ± 102	202 ± 105	127 ± 69*
$PaCO_2$, mean (SD) **(mmHg)**	37.73 ± 9.13	40.1 ± 9.41	36.58 ± 8.8*	37.29 ± 5.96	37.58 ± 6.05	36.58 ± 5.7
$PaCO_2$ <40 mmHg, No. (%)	107 (69.93)	30 (60)	77 (74.76)	323 (72.42)	227 (71.61)	96 (74.42)
SaO_2 mean (SD), %	94.06 ± 5.4	96.02 ± 3.26	93.14 ± 5.95	95.82 ± 4.23	96.53 ± 3.48	94.09 ± 5.31
SpO_2 mean (SD), %	91.67 ± 6.81	94.59 ± 4.6	90.06 ± 7.35	95.86 ± 4.26	96.79 ± 2.36	91.91 ± 7.37
SpO_2 /FiO_2, mean (SD)	134 ± 40	148 ± 40	127 ± 39	171 ± 53	179 ± 50	126 ± 43*
Respiratory Rate	25.4 ± 7.3	22.9 ± 5.5	26.4 ± 7.7*	23.4 ± 6.3	22.0 ± 5.3	27.0 ± 7.2*
Use of accessory respiratory muscles , No. (%)	59 (14.39)	10 (18.52)	60 (50.85)*	124 (49.21)	49 (13.76)	64 (47.76)*
Dyspnoea, No. (%)	60 (14.49)	12 (22.64)	52 (46.43)*	119 (48.77)	48 (13.3)	67 (50.76)*
Laboratory Values						
Creatinine mean (SD), **(mg/dL)**	1.34 ± 1.12	1 ± 0.53	1.51 ± 1.29*	0.93 ± 0.57	0.88 ± 0.51	1.04 ± 0.7*
Urea mean (SD), **(mg/dL)**	78± 63	56 ± 37	88 ± 70*	49 ± 31	46 ± 27	57 ± 37*
White blood cells mean (SD), **(103/µL)**	10.8 ± 6.7	10.54 ± 8.4	11.0 ± 5.7	10.0 ± 9.5	9.2 ± 6.1	12.12 ± 15*

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Platelets mean (SD), **(103/µL)**	252 ± 114	296 ± 115	229 ± 106	319 ± 131	336 ± 132	274 ± 117
Haemoglobin mean (SD), **(g/dL)**	12.2 ± 1.9	12.1 ± 1.7	12.3 ± 2.0	12.6 ± 1.6	12.5 ± 1.5	12.6 ± 1.7
Bilirubin mean (SD), **(mg/dL)**	0.74 ± 0.51	0.7 ± 0.49	0.77 ± 0.52	0.84 ± 1.14	0.78 ± 0.98	0.99 ± 1.46
C-reactive protein mean (SD), **(mg/L)**	123 ± 89	90 ± 75	139 ± 92	100 ± 89	81 ± 77	153 ± 97
Procalcitonin Median [IQR], **(ng/DL)**	0.37 [0.15-1.23]	0.2 [0.1-0.56]	0.5 [0.18-1.65]	0.2 [0.9-0.5]	0.13 [0.7-0.31]	0.38 [0.2-1.23]
Hemodynamic Parameters						
Systolic Blood pressure mean (SD), **(mmHg)**	130 ± 19	131 ± 20	129 ± 19	130 ± 18	129 ± 17	134 ± 20
Diastolic Blood pressure mean (SD), **(mmHg)**	75 ± 12	75 ± 13	74 ± 12	76 ± 11	76 ± 10	76 ± 13
Heart Rate mean (SD), **(1/min)**	82.8 ± 17.3	78.9 ± 14.1	84.5 ± 18.3	80.6 ± 15.3	78.3 ± 13.9	87.2 ± 17.2
Temperature mean (SD), **(°C)**	36.6 ± 0.7	36.4 ± 0.6	36.7 ± 0.7*	36.6 ± 0.77	36.4 ± 0.7	36.9 ± 0.2*

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List of abbreviations: **COPD**: Chronic bronchopulmonary disease; **CKD**: Chronic Kidney Disease; **FiO_2:** inspired oxygen fraction, **PEEP:** Positive End Expiratory Pressure; **PaO_2**, arterial partial pressure of oxygen; **$PaCO_2$**, arterial partial pressure of Carbon dioxide; * $p<0.05$ vs Success, within the same group; § $p<0.05$ overall value for Chi-Square

Table e4

	Odds Ratio	**Std. Err.**	**P>z**	**[95% Conf. Interval]**	
Age (per year increment)	1.02	0.02	0.25	0.98	1.07
Ischemic or congestive heart disease (ref. No)	1.71	0.82	0.26	0.67	4.4
Vascular disease (ref. No)	0.68	0.46	0.57	0.18	2.55
Malignancy (ref. No)	1.75	2.44	0.69	0.11	26.97
Former smoker (Ref. Active Smoker)	0.84	0.66	0.82	0.18	3.92
Never smoked. (Ref. Active Smoker)	0.52	0.39	0.39	0.12	2.28
Not declared. (Ref. Active Smoker)	0.85	0.67	0.84	0.18	3.99
PEEP. (per cmH_2O increment)	0.97	0.07	0.64	0.84	1.12
pH.	0.97	0.04	0.41	0.9	1.05
PaO_2 /FiO_2 (per mmHg increment**)**	**0.99**	**0.002**	**<0.001**	**0.99**	**1**
$PaCO_2$. (per mmHg increment)	0.97	0.03	0.21	0.92	1.02

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Respiratory Rate (per 1/min increment)	1.04	0.03	0.17	0.98	1.1
Creatinine (per 1 mg/dL increment)	0.89	0.27	0.71	0.49	1.63
Urea (per 1 mg/dL increment)	1.01	0.01	0.28	0.99	1.02
White blood cells (per **10^3/µL** increment)	0.99	0.03	0.85	0.94	1.05
Platelets (per 10^3/µL increment)	**0.995**	**0.0017**	**<0.01**	**0.992**	**0.999**
Haemoglobin (per **g/dL** increment)	0.97	0.12	0.78	0.76	1.23
C-reactive protein (per g/dL increment)	**1.01**	**0**	**<0.01**	**1**	**1.01**
Procalcitonin <0.5 (ref. Missing value)	0.96	0.39	0.91	0.43	2.12
Procalcitonin >0.5 (ref. Missing value)	0.68	0.35	0.46	0.25	1.87
Systolic Blood pressure (per mmHg increment)	1.01	0.01	0.33	0.99	1.03
Heart Rate (per 1/min increment)	1.02	0.01	0.09	1	1.05
Do Not Intubate decision (ref. NO)	2.79	1.33	0.03	1.1	7.08

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eFigure2

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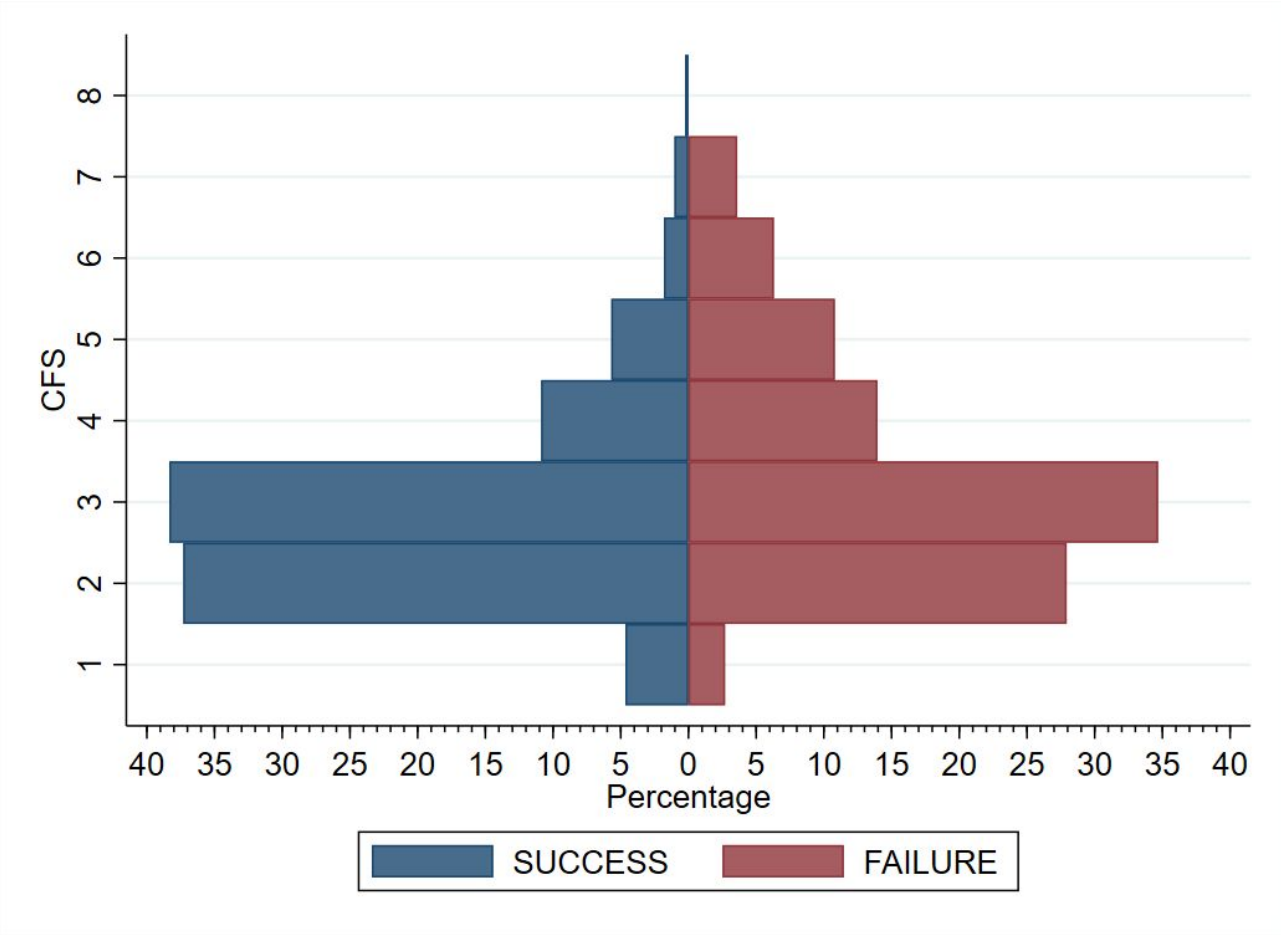

Patients who fail non invasive ventilation present with higher Clinical Frailty Scores (CFS). P<0.005

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