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Original Article

Effectiveness of Non-Invasive vs. Invasive Ventilation in Acute Hypoxic Respiratory Failure in COVID-19 Patients in Critical Care: A Retrospective Cohort in Rahim Yar Khan, Pakistan

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Abstract

Background: Acute hypoxic respiratory failure (AHRF) is the most common reason of ICU admissions. Invasive (IV) and non-invasive ventilation (NIV) methods are incorporated in ICUs as part of initial treatment.
Objective: To compare the outcomes of COVID-19 patients with acute hypoxic respiratory failure on non-invasive and invasive ventilation.
Study type, settings & duration: This retrospective cohort study was conducted at Intensive Care Unit, Sheikh Zayed Medical College/Hospital, Rahim Yar Khan from March to August 2020.
Methodology: The 72 COVID-19 positive patients, placed in two groups "IV" (invasive ventilation) and "NIV" (non-invasive ventilation) as per treatment they received in ICU. Outcome was defined in terms of patient's survival and number of complications associated with both modes of ventilation.
Results: More patients showed survival on NIV than on IV (36.6 % vs. 6.4% respectively) with a significant *p* =0.003. Number of complications was low in NIV group vs. IV group. Males were more affected than females (83.3% vs. 16.7%). Middle and old aged groups were more prone to develop severe hypoxia and required ICU admission as compared to young people (47.2% vs. 37.5% vs. 15.3%) respectively with p=0.017, reflecting better survival in younger people.
Conclusion: NIV should be prioritized in ICUs for early management of acute hypoxic respiratory failure associated with COVID-19 as NIV has negligible adverse affects and better outcome than IV.
Key words: Non-invasive ventilation, COVID-19, Critical care, Acute Hypoxic repiratory failure.

Introduction

In the global pandemic of COVID-19, it is quite challenging for anesthetists/intensivists to manage associated respiratory complications in limited critical care resources. Until today, August 2020, more than 292,765 cases of COVID-19 have been confirmed in Pakistan[1] and 23.1 million cases worldwide[2]. Globally its mortality is approx 803,000 and in Pakistan, it is around 6235+12 till date (23 august 2020).[1,2] It has shown a spectrum of complications like pneumonia, Adult respiratory distress syndrome (ARDS), thromboembolism, myocarditis, stroke, etc, leading to an increasing number of ICU admissions, necessitating ventilatory support.[3-9,10,11]

During the first month of this pandemic, early endotracheal intubation and initiating mechanical ventilation also known as invasive ventilation (IV) was a part of management of acute hypoxic respiratory failure (AHRF) in COVID-19 patients.[7-9] A clinical trial was done in Milan, Italy where researchers specifically presented data on patients with invasive ventilation due to acute

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Authors Contribution

SS & HDD conceptualized the project and did the statistical analysis. SS also did the data collection. Literature search, drafting, revision and writing of manuscript was done by SS, HDD & BB.

hypoxic respiratory failure (AHRF).[8] Later some concerns arose regarding the safety of endotracheal intubation and invasive ventilation because of the adverse effects on the frail lungs as well as on other body systems leading to an increase in morbidity and mortality rate.[4,10,11] To avoid unnecessary endotracheal intubations, we are left with some non-invasive ventilation (NIV) techniques to manage acute hypoxic respiratory failure, thus to establish proper oxygenation in COVID-19 patients. NIV techniques being used at some centers are High flow nasal cannula (HFNC) also known as high flow oxygen (HFO), Oxygen hoods, CPAP, and Bi-PAP with variable outcomes.[10,13-16] These non-invasive techniques have good physiological impacts like preservation of spontaneous respiration, hemodynamic stability, improvement of oxygenation, a decrease in work of breathing, and 50% reduction in the need for mechanical ventilation.[14]

There are few studies found which were published during the early phase of eruption of this pandemic in china, mostly comprising the characteristic features and pathological aspects of this novel disease.[3-9,10,11] Only a few retrospective cohorts were done until today, indicating the need for extensive research specifically on the management of acute hypoxic respiratory failure either with invasive ventilation or non-invasive ventilation techniques. The role of NIV is yet to be established and is under debate, due to aerosol generation, as reflected by some studies.[12,17] This has highlighted the need to establish, such a respiratory support strategy for the COVID-19 induced hypoxic respiratory failure, which may decrease the work of breathing, improve oxygenation & ventilation, and also having the least systemic adverse effects. The objective of the study was to compare the outcomes of non-invasive and invasive ventilation in the patients with acute hypoxic respiratory failure in COVID-19 ICU.

Methodology

The electronic data obtained from critical care patient's records, for our retrospective cohort study. In total, there were 573 confirmed COVID-19 patients admitted in COVID-19 isolation wards, who maintained their oxygen saturation above 90% on low flows of oxygen (4-5 Liters of O_2). Out of which, 72 COVID-19 positive patients were admitted to COVID-19 dedicated ICU for elaborated oxygen requirement from 27th March 2020 to 24th August 2020. The capacity of COVID-19 HDU/ICU was increased from 4 beds to 13 COVID-19 dedicated beds.

In our study, we included patients who were PCR positive for COVID-19 after a throat or nasal swab along with positive radiological findings, severely hypoxic as evident through SPO_2 (O_2 saturation <90%) and/or paO_2 (arterial O_2 < 60 mmHg), aged between 18 to 90 years of both genders. We defined age groups into three categories: young (18-39 years), middle-aged (40-59 years), and old age (60 and above). Patients who were received dead or in gasping condition were excluded from the study. We placed the patients into two groups "NIV" and "IV" according to the treatment they had received in COVID-19 ICU. Outcome variables were defined as survival of patients and number of complications associated with both of the ventilation modes. We labeled patients' outcome as "survivors" and "non-survivors".

In initial months, all admitting patients, coming with hypoxic respiratory failure were mechanically ventilated (IV) according to ARDS guidelines i.e. low volume lung protection ventilation plus high PEEP. In the month of June, the facility of non-invasive oxygen therapy (HFO, CPAP and Bi-PAP) became freely available at our center. Since then NIV was adapted as a part of oxygenation therapy to next admitting patients with acute hypoxic respiratory failure and an algorithm protocol was made to follow from then onward (Figure-1). A criterion was set that patients with hemodynamic instability and/or low GCS would not be a candidate for NIV.

The "high flow Oxygen machine" was capable of providing flows, as high as 60 liters/min. In the Drager ventilator, options for NIV such as HFO and CPAP are present, which are capable of providing oxygen as high as 50 liters/min, PEEP up to 10cm H_2O along with 20 cm H_2O of pressure support. This was facilitated with tight fitted CPAP or PEP mask, and high flow oxygen nasal cannula.

All patients received anticoagulants, antibiotics for superimposed bacterial infection, and high dose steroids (dexamethasone) as a main part of pharmacotherapy. While few patients also received antiviral (remdesivir) and anti-inflammatory (tocilizumab) as an adjunct in the later months of ICU stay.

Serial serum levels of lactate dehydrogenase (LDH), D-Dimers, ferretin, pro-BNP, and C-reactive protein (CRP) were done on every 3rd day while routine blood count, renal and liver markers, serum electrolytes, sugar levels, ABGs, and chest radiographs on daily basis.

We obtained all the data from the time of admission till the last day in ICU, like patients' vitals, ABGs, labs and chest radiographs. Information

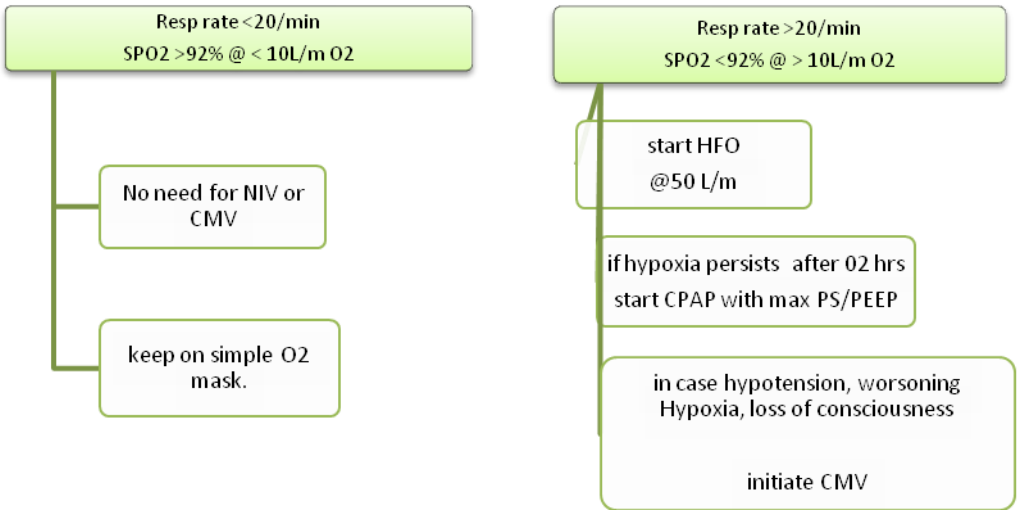

Figure 1: Algorithm for COVID19 AHRF.

regarding co-morbidities like Diabetes Mellitus (DM), hypertension (HTN), ischemic heart disease (IHD), chronic renal failure (CKD), hypothyroid, and stroke, the most probable cause of death, duration of ICU stay, patients' survival, discharge from ICU and total ICU deaths were also obtained. Daily progress of all patients were collected in the form of their labs e.g. ABGs (arterial blood gases), complete blood count (CBC), blood sugar, coagulation profile, renal and liver markers, inflammation markers like sr. ferritin, C-reactive protein (CRP), Lactate dehydrogenase (LDH), and D-Dimers.

Data was analyzed using SPSS version 23.0. String variables like gender, hypoxia, hypotension, septicemia, presence of co-morbid, and presence of chest infiltrates were presented as percentages and frequencies. The survival of patients on "IV" and "NIV" was compared using crosstabs and significance of differences was analyzed by chi-square test. The outcome was also compared in the two genders as well as in different age groups i.e. young age, middle age, and old age by using layered cross tabs and applying chi-square test. Survivors and non-survivors were compared with and without co-morbids. The duration of ICU stay and all lab data were presented as mean and median.

The ethical approval was obtained from ethical review committee of Sheikh Zayed Medical College/Hospital, Rahim Yar Khan.

Results

Mostly, patients arriving in ICU were having 45-88% SpO_2 (Mean=62%). Only 40% patients were cooperative enough to be agreed upon proning. While remaining 60% patients were apparently not comfortable with the proning position. It is evident from the results (Table-1) that males were more affected by this pandemic than females (83.3% vs. 16.7%) but their overall survival was not significantly different (p =0.901). Middle and old aged patients were more prone to develop severe hypoxia and required ICU admissions as compared to young age group (47.2% vs. 37.5% vs. 15.3%) respectively. The difference of outcome between these age groups was statistically significant (p =0.017) reflecting better survival in younger patients.

It was found that survival of the patients was better on NIV than IV mode (36.6% vs. 6.4% respectively). This difference was statistically significant (p =0.003).

In this study, we found 43% of patients with diabetes mellitus, 52.8% with hypertension, 26.4% with Ischemic heart disease, 12.5% with chronic kidney disease (CKD) and 39% patients having superimposed bacterial infection leading to septic shock. There was no significant difference found in the outcome of patients with and without co-morbidities. However, survival was poor in the patients with septicemia.

A number of complications were associated with the IV mode (Table-2) such as hypotension, hypercarbia and renal impairment developed in some patients who were on invasive ventilation according to ARDS guidelines with high levels of PEEP (positive end-expiratory pressure). While the patients, who were managed on NIV, showed a negligible number of complications. The exact cause of mortality among these patients is mentioned in Table-2**.**

Table 1: Summary of the demographic and clinical data of participants.

Clinical Data		*Total (%)*	*Survivors n (%)*	*Non-survivors n (%)*	*p value*
Gender	Male	60 (83.3)	14(23.3)	46(76.7)	0.901
	Female	12 (16.7)	3(25)	9(75)	
Age	Young	11(15.3)	6(54.5)	5(45.5)	0.017
	Middle aged	34 (47.2)	8(23.5)	26(76.5)	
	Old age	27(37.5)	3(11.1)	24(88.9)	
Mode of ventilation	IV	31 (43)	2(6.4)	29(93.5)	0.003
	NIV	41 (57)	15(36.6)	26(63.4)	
Over all Outcome	-	-	17/72 (23.6)	55/72 (76.4)	-
Presenting condition:	Hypoxia	72 (100)		-	
	Hypotension	16 (22.22)			
	Fever	28 (38.8)			-
	Chest infiltrates	72 (100)			
MEAN	IV	5.0		-	0.153
Length of ICU stay (days)	NIV	7.7			
Lab findings	*Mean±SD*	*Median (IQR)*			*Range (min-max)*
TLC (10^3/cmm)	18.6±7	17.8 (11)			8.7-32
paO2 (mmHg)	59	65			45-90
CRP (mg/L)	72±71	48 (112)			1.7-235
Sr. Ferretin (ng/ml)	1487±1590	1193 (1574)			98-7100
Sr.LDH (U/L)	1495±724	1450 (830)			345-2960
D-Dimers (mg/dl)	-	44.7 (17.85)			2.0-6000
Pro-BNP (pg/ml)	3108±8198	399 (2146)			5-35000

Note: Because of skewness, the numeric variables are presented as Mean+SD and Median, and IQR along with their Range.

Table 2: Post admission complications in COVID-19 ICU.

	Complications	n (%)
NIV	Skin necrosis	0
(n=41)	Conjunctivitis	0
	Nasal irritation	0
	Aspiration	0
	Hypotension	0
	Discomfort	2/41(4.87)
IV	Hypotension	8/31(26)
(n=31)	Hypercarbia	12/31(39)
(due to PEEP)	Renal impairment	2/31(6.4)
Complications leading to mortality in the non-survivors	While Intubation	7/55 (12.7)
(n=55)	Sudden cardiac arrest	13/55 (23.6)
	Refractory Hypoxia	18/55 (32.7)
	Septic Shock	13/55 23.6)
	Renal failure	4/55 (7.27)

Discussion

In our retrospective cohort study, we tried to establish an association between patients' outcome and the modes of ventilation and oxygenation therapies, in the outbreak of COVID-19. The results obtained are in favor of NIV as compare to IV for respiratory support for these patients.

In a retrospective cohort by Zhou F et al in Wuhan in the early period of outbreak of this pandemic, it was found that among 191 COVID-19 patients, mortality was less in the patients who received NIV as compared to the patients who had received invasive ventilation (92% vs. 96% respectively).[7]

In another study conducted in Wuhan China by Namendys-Silva showed a 79% mortality rate among patients of NIV group vs. 86% in mechanically ventilated (IV) patients during this pandemic, thus favoring our study results.[18]

In a research letter published in BMC, by Hua J et al**,** in Wuhan China, shows a decrease in mortality rate where NIV was used in COVID-19 patients for acute hypoxic respiratory failure vs. mechanically ventilated (IV) patients (40.8% vs. 92% respectively).[19] This difference was statistically significant (p <0.001). Although it does not affect the total duration of ICU stay. They suggested in their study to avoid invasive ventilation and to utilize NIV at the early stage of respiratory failure until invasive ventilation is inevitable. This strengthens our study findings.

In the Korean journal of Anesthetist (KJA) in a letter to the editor, Abhishek Singh has strongly

advocated the use of NIV for respiratory failure in COVID-19 patients by citing reference of a number of studies in this favor.[20] He concluded his letter by suggesting the use of NIV strategy in a certain population of COVID-19 patients with respiratory failure like a younger age group with lesser co-morbidities. Whereas in our study there was no statistically significant difference found, in the outcome of patients with and without co-morbidities.

In a study by Ferguson et al, age-related mortality was found to be more in the old age group i.e. 2.2% at age 60 and increasing to 9.3% at age 80 that is much relatable to our study results.[21] Thus agreeing upon this point, in our study age-related mortality was likewise more among the old age group 89% vs. middle age 76%.

According to a study in northeast China, conducted by Wan S et al, it was found that NIV was prioritized over invasive ventilation in COVID-19 patients with respiratory complications, which lead to a higher rate of patients discharge from ICU[10] which is similar to our study results.

Meng L et al in a very recently published study in June 2020 has estimated a very high mortality rate among invasively ventilated COVID-19 patients with ARDS. This finding again favors our study results.[11]

Burns GP et al has shown in their study that using CPAP and BiPAP has reduced ICU stay among hypoxemic COVID-19 patients as compared to patients who received invasive ventilation.[22] Though in our study, duration of ICU stay differs as a subjective variation in NIV group, ranging from 1 day to 26 days in total. And our study showed that there was no effect on total duration of ICU stay by any of the modes of ventilation.

It was reported that metabolic acidosis and severe hypoxemia is a predictor of poor prognosis when using NIV. This was not a case in our study.[14] Nasibova EM also quoted some studies which described complications of using NIV like skin necrosis, conjunctivitis, nasal irritation, general discomfort, and most importantly aerosol generation leading to the spread of infection among health care professionals.[14] These findings were contradictory to our study results as there is no evidence of such complications associated with the use of NIV at our setup.

Patel BK has written regarding the controversial role of NIV among COVID-19 patients with ARDS or hypoxic respiratory failure.[15] He cited reference to a large clinical trial involving more than 700 patients; found that NIV did not significantly improved survival. Rather it may lead to exacerbation of lung injury. The association of NIV with lower mortality was found to be no more statistically significant, which differs from our study.

We concluded that NIV should be prioritized in ICUs for early management of acute hypoxic respiratory failure associated with COVID-19, as NIV is more effective than invasive mechanical ventilation. All age groups with and without co-morbidities can be benefited from these non-invasive strategies and rate of mortality can be reduced. Our sample size was small so some questions could not be answered.

More studies are required with larger sample size to reach a clear cut-off mark, addressing the issues like when to initiate non-invasive ventilation, when to safely switch between the two modes, by terminating non-invasive ventilation and initiating invasive ventilation in AHRF among COVID-19 patients.

Conflict of interest: None declared.

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