

ORIGINAL ARTICLE

AN OBSERVATIONAL STUDY ON THE EFFECTS OF IMPROVISED CPAP (iCPAP) IN CARDIOVASCULAR DISEASES WITH ACUTE RESPIRATORY FAILURE

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Objectives: This study describes three surges of COVID-19 hypoxemic respiratory failure and our experience with using iCPAP in patients with cardiovascular diseases at a tertiary cardiac care centre.

Methodology: This observational study was conducted from March 23rd 2020 to May 31st 2021, at The National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan. This is an analysis of data from the PRICE Network Registry. Data was collected for all adult patients with cardiovascular diseases admitted with acute hypoxemic respiratory failure and a confirmed diagnosis of SARS CoV-2.

Results: Among 362 patients with 'severe' or 'critical' COVID-19 were hospitalized; 163 (45%) in the 1st surge, 92 (25.4%) in the 2nd and 107 (29.6 %) in the 3rd surge. All-cause mortality was 118 (32.6%). iCPAP was used in 39% (141) patients, 19% (69) patients required oxygen only, 25.4% (92) were on BiPAP support and 16.6% (60) were intubated. 'iCPAP failure' occurred in 48/141 (34%) patients. iCPAP failure occurred in patients with higher APACHE II scores (16.3 ± 5.7 vs 21.3 ± 6 , $p \leq 0.001$), lower ROX index on admission (5.0 ± 2.2 vs. 10.4 ± 5.4 , $p \leq 0.001$), lesser degree of improvement in ROX index at 48 hours (Day 3 ROX 18.7 ± 8.9 vs. 9.9 ± 6.3 , $p \leq 0.001$). Mortality rate on iCPAP was 44 (31.2%).

Conclusion: COVID-19 outcomes in a resource-limited setting in patients having cardiovascular diseases, appear comparable to global reports. A modification of standard CPAP (iCPAP) appeared to be safe and effective. This modification of standard CPAP (iCPAP) identifies an option for resource-limited or resource-exhausted critical care units.

Keywords: Heart failure, influenza vaccine, knowledge of influenza, attitude

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INTRODUCTION

The first COVID-19 surge struck Pakistan in March 2020. According to a pre-pandemic national survey in 2020, Pakistan had 0.71 ventilator beds per 100,000 population (1473 ventilated beds), a proportion far lower than that of neighboring countries; Sri Lanka (2.3), Nepal (2.8) and India (2.3).¹ Enormous demands for oxygen, ventilators and ICU beds have left even well-equipped ICUs crippled worldwide causing higher mortalities than expected.² In light of these unprecedented needs, health organizations have urged finding innovative methods in optimizing respiratory support, and these have served as ripe times to 'relook' at non-invasive ventilatory (NIV) support, and in turn minimizing invasive mechanical ventilation (IMV), for the critically-ill.

NIV is well-established to reduce mortality in cardiogenic pulmonary edema (CPE) and chronic obstructive pulmonary disease (COPD). Positive airway pressure (PAP), delivered via an interface (usually a full-face mask (FFM)), in the context of 'acute respiratory failure' (ARF), optimizes interacting pressures around the heart, lungs, and inside the thoracic cavity.³ AHRF secondary to acute respiratory distress syndrome (ARDS)) evolves as a complex 'inflammatory insult' causing diffuse alveolar damage (DAD), damaging pulmonary vasculature (endotheliitis) and inciting an intrapulmonary and/or a systemic inflammatory cascade known as cytokine release syndrome (CRS). Resolution of illness is also expected over days to weeks, rather than hours. Hence any NIV device used for AHRF must be effective, and safe, such that applications over extended durations are not accompanied with skin breakdown or other patient

discomfort. Second, NIV devices used for AHRF must also allow rescue maneuvers, such as ‘awake-proning’, that improve ventilation-perfusion (VQ) relationships and relieve hypoxemia.

Current guidelines recommend NIV be used as a preventive strategy for avoiding intubation in AHRF only when performed by experienced teams in highly selected cooperative patients with ‘early ARDS’ & without any associated major organ dysfunction.⁴ In recent years, high-flow oxygen (HFO) delivered via especially designed nasal cannulas (HFNCs) are shown to have equivalent, if not better, outcomes (reduced intubation rates & 90-day mortality) for patients with AHRF.⁵

In practical terms, PAP improves FRC, prevents alveolar recruitment, and relieves hypoxemia by improved VQ mismatch, and both NIV and HFNC systems reduce dead-space and provide PAP.⁶ Additionally, use of a NC allows humidification, oral nutrition, is tolerated better by patients than a FFM, facilitates awake-proning, and has lower risks of facial pressure ulcerations seen with tighter fitting interfaces, allowing it to be used for longer periods.

Lung injury from COVID-19 appears to be an even more complex and multifaceted insult. Extensive parenchymal damage alone may occur in some, much as in ‘typical ARDS’, while an intense abolition of hypoxic pulmonary vasoconstriction (HPV), anomalous angiogenesis or endothelial damage/micro- and macrovascular thrombosis may predominate in other atypical ones causing higher shunt fraction.⁷ In resource-limited setups, where few IMV options exist and oxygen must be rationed, this individualized approach may translate into a very careful titration of both PAP and HFO to optimize individual needs; that is to say, some may benefit from lower PAP but higher fractions of inspired oxygen (FiO₂) or vice versa. Both observational studies^{8,9} and society guidelines recommend either NIV or HFNC as reasonable options for respiratory support in COVID-19 AHRF.¹⁰

Our hospital, a 650-bedded, public-sector, government-supported, primarily cardiovascular disease facility, receives an overwhelming number of COVID-19 patients with each local surge. In the absence of readily-available invasive ventilation and with the proven benefits of noninvasive ventilation, for all critically-ill patients who present to our center, we have improvised combining & optimizing the non-invasive benefits of HFNC and a PAP device (termed ‘improvised CPAP’ or ‘iCPAP’) and applied this to our COVID-19 patients. Our hospital critical care administration has previously approved application of

iCPAP in AHRF. With surges of patients with COVID-19, we began to triage patients to iCPAP so as to support as many patients as possible and save up ventilators for those with refractory hypoxia.

The objective of this study was to describe our experience with severe and critical COVID-19 hypoxemic respiratory failure during three surges of the pandemic.

METHODOLOGY

This study is reported following the STROBE statement checklist for observational studies. The conduct of this study was actively supported and made possible by the Pakistan Registry of Intensive Care (PRICE), a founding member of the Wellcome Trust funded Crit Care Asia network.¹¹

The National Institute of Cardiovascular Diseases (NICVD) Ethical Research Committee approved the study (ERC approval number ERC-13/2020) and waived the need for obtaining informed consent because data were collected as part of routine quality improvement activities and no direct patient interactions, or post-discharge follow-up occurred. No compensation or incentives were offered for participation. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. No individual patient data is presented.

This study is a retrospective analysis of center-specific data from the Severe Acute Respiratory Illness (SARI) dataset of the PRICE Network Registry. Details of the registry have been previously described.¹² The period described is from March 23rd, 2020, to May 31st, 2021. Patient information was extracted from the medical records by trained abstractors using standardized definitions and entered into a database. Additional data on respiratory support, oxygenation, and derived respiratory variables, was also collected. Patients were admitted to a dedicated COVID unit, with merged high dependency unit (HDU) and intensive care unit (ICU) capabilities. The healthcare team comprised senior critical care attending physicians, critical care trainees, cardiology trainees, cardiology attending physicians, an infectious diseases consultant physician and critical care nursing. Data was collected for all patients aged 18 years and older having cardiovascular diseases, admitted to the COVID unit with AHRF with a confirmed diagnosis of SARS CoV-2 by a reverse transcriptase polymerase chain reaction (RT-PCR) only

We excluded patients with contraindication to the use of positive pressure (PAP) therapy (i.e., pneumothorax/ subcutaneous emphysema, fluctuating or depressed mental status, arrhythmias).

For all participants, we followed an algorithm where all patients with resting room air pulse oximetry saturation (SpO₂) < 92% initially received supplemental oxygen via conventional nasal cannula (NC) or a Venturi Face Mask (VFM), to achieve (and maintain) target SpO₂ of 90-94%. If the patient's oxygen requirement consistently exceeded > 5 L/min (to maintain SpO₂ 90-94%), and the patient remained hemodynamically stable, with no contraindications to PAP, iCPAP trial was given, with a target SpO₂ of 90-94%. All other routine care and therapeutics as per COVID-19 treatment guidelines were continued, including awake-proning. Patients underwent continuous monitoring for vital signs, pulse oximetry, routine laboratory investigations, and arterial blood gases (ABGs) (initially at 1 hour, then at 4-6 hours and then twice daily and as needed).

iCPAP delivery system was assembled using the ResMed Lumis™ 150 VPAP ST-A Unit with a heated humidifier connected to the distensible, wide-bore, nasal cannula (Respicare HFNC). This system used standard CPAP (noninvasively applied continuous positive airway pressure) delivered through a modified nasal interface (nasal cannula instead of a mask) and had previously been tested and approved by the relevant institutional departments for use. iCPAP therapy is intended to combine and optimize the beneficial effects of humidified, high flow (and a resultant low dose of positive pressure) of a HFNC, with the benefits of continuous positive airway pressure (CPAP) delivered via wide-bore, soft binasal prongs to patients with ARDS, which were better tolerated hence improved patient compliance, ability to converse and maintain oral intake, and the likelihood of less delirium and ease of performing secondary maneuvers such as awake-proning.

'iCPAP failure' was defined as failure to maintain target SpO₂, and subsequent advancement to either

bilevel positive airway pressure (BiPAP) by full facemask or endotracheal intubation (ETT), at any time during ICU admission.

'Acute Coronary Syndrome (ACS)' was defined as evidence of acute myocardial ischemia or infarction. Patients presenting with cardiogenic shock or arrest were presumed to have ACS.

Continuous data was tested for normality; measures of central tendency were compared as means ± standard deviations (SD) using the Student's t-test for normally distributed variables and as medians (interquartile range, IQR) using the Mann-Whitney U test for skewed data. Categorical variables were compared using the chi-squared test or the Fisher's exact test for n < 5. Logistic regression analysis was performed to determine the predictive ability of variables for predefined outcomes. Univariate and multivariate analyses were used, and for multivariate regression, a backward mode with a threshold 0.10 was used for elimination. Multivariate associations were reported as Odds Ratio (OR); Exp (B) with 95% confidence intervals. A two-sided p value of < 0.05 was considered as statistically significant. All analyses were carried out using IBM SPSS software version 22.0.

RESULTS

A total of 362 patients with 'severe' or 'critical' COVID-19 respiratory failure were hospitalized between March 23rd, 2020, and May 31st, 2021. Of all COVID-19 cases, 163 (45%) hospitalized in 1st surge (March-July 2020) 92 (25.4%) in the 2nd surge (August-December 2020) and 107 (29.6%) in the 3rd surge (January-May 2021). Mean age was 56.2 ± 14.4 years, 248 (68.5%) were male and 44 (12.1%) were healthcare workers (HCWs). Mean APACHE II score at admission was 18.6 ± 6.2. The most common presenting symptoms reported were shortness-of-breath (SOB) (46.8%), cough (17.6%), and chest pain (17.6%), with a median of 4 days (IQR 2-7) of symptoms (Table 1).

Table 1: Clinical characteristics of patients with COVID-19 and comparison between surges

Characteristics	Total	COVID-19 Surges			P-value
		Surge 1	Surge 2	Surge 3	
N (%)	362	163 (45%)	92 (25.4%)	107 (29.6%)	-
Male	68.5% (248)	71.8% (117)	66.3% (61)	65.4% (70)	0.475
Female	31.5% (114)	28.2% (46)	33.7% (31)	34.6% (37)	
Age (years)	56.2 ± 14.4	54 ± 15	54.5 ± 14.5	61 ± 12.1	<0.001
Symptom Duration (d)	4 [2-7]	4 [2-6]	3 [2-6]	4 [2-7]	0.317
Chronic lung disease	19.1% (69)	33.7% (55)	10.9% (10)	3.7% (4)	<0.001
Hypertension	42.3% (153)	37.4% (61)	31.5% (29)	58.9% (63)	<0.001
Diabetes	25.1% (91)	10.4% (17)	23.9% (22)	48.6% (52)	<0.001
CKD	11% (40)	12.9% (21)	8.7% (8)	10.3% (11)	0.565

CHF	13.8% (50)	6.1% (10)	16.3% (15)	23.4% (25)	<0.001	
CAD	33.7% (122)	27.6% (45)	33.7% (31)	43% (46)	0.033	
Valvular heart disease	5.5% (20)	2.5% (4)	8.7% (8)	7.5% (8)	0.064	
NSTEMI	36.2% (131)	44.2% (72)	38% (35)	22.4% (24)	<0.001	
STEMI	33.4% (121)	22.1% (36)	25% (23)	57.9% (62)		
Unstable angina	11.6% (42)	17.8% (29)	10.9% (10)	2.8% (3)		
Decompensated CHF	9.1% (33)	8% (13)	14.1% (13)	6.5% (7)		
Valvular dysfunction	2.2% (8)	0.6% (1)	2.2% (2)	4.7% (5)		
Heart Block/Arrhythmia	4.4% (16)	3.7% (6)	6.5% (6)	3.7% (4)		
Cardiogenic shock	1.7% (6)	1.8% (3)	2.2% (2)	0.9% (1)		
Others*	1.4% (5)	1.8% (3)	1.1% (1)	0.9% (1)		
Ejection Fraction (%)	35 [25-45]	40 [30-55]	35 [25-45]	35 [25-45]		0.231
APACHE II	18.6 ± 6.2	19.2 ± 5.8	19.9 ± 6.7	16.5 ± 5.8		<0.001
Oxygen only	19% (69)	14.7% (24)	21.7% (20)	23.3% (25)	0.15	
NIV	64.3% (233)	61.3% (100)	67.3% (62)	66.3% (71)	0.54	
Invasive ventilation	16.5% (60)	23.9% (39)	10.8% (10)	10.2% (11)	0.003	
Respiratory rate	20.62 ± 5.83	20.24 ± 6.61	20.7 ± 5.7	21.13 ± 4.51	0.467	
SBP	118.6 ± 21.4	118.8 ± 17.5	119.6 ± 24.8	117.4 ± 23.8	0.775	
DBP	71.21 ± 14.2	73.2 ± 13.2	71.4 ± 16.0	67.7 ± 13.5	0.008	
Shock index	0.81 ± 0.2	0.79 ± 0.2	0.8 ± 0.2	0.86 ± 0.2	0.097	
Hemodynamic support	19.6% (71)	13.5% (22)	21.7% (20)	27.1% (29)	0.019	
Creatinine (mg/dl)	1.38 ± 1.02	1.33 ± 1.21	1.48 ± 0.91	1.38 ± 0.74	0.579	
Absolute Lymphocyte Count	1955.5 ± 1779.7	2014.8 ± 2384.1	1752 ± 1172	2029.6 ± 1242.8	0.808	
Blood Glucose mg/dl	198.7 ± 93.6	199.5 ± 108.7	196.8 ± 86.8	199.4 ± 83.2	0.986	
CRP (mg/dl)	12.8 ± 17.0	15.1 ± 22.1	11.23 ± 12.7	10.7 ± 9.9	0.209	
CRP on day 2 (mg/dl)	2.5 ± 6.2	1.9 ± 5.2	2 ± 6.5	3.7 ± 7.2	0.056	
Ferritin	878.5 ± 518.9	980.4 ± 659.7	639.5 ± 356.2	964.2 ± 525.4	0.507	
d-Dimer (FEU)	3.1 ± 3	2.3 ± 3.3	4.2 ± 0	3.2 ± 3.1	0.826	
Proned	62.2% (225)	65.6% (107)	64.1% (59)	55.1% (59)	0.198	
Tocilizumab	24.3% (88)	6.1% (10)	39.1% (36)	39.3% (42)	<0.001	
Remdesivir	42.8% (155)	23.9% (39)	46.7% (43)	68.2% (73)	<0.001	
Steroids	90.1% (326)	81.6% (133)	96.7% (89)	97.2% (104)	<0.001	
AKI	24.6% (89)	29.4% (48)	21.7% (20)	19.6% (21)	0.142	
Mortality	32.6% (118)	31.9% (52)	33.7% (31)	32.7% (35)	0.957	
ICU Length of Stay	4.17 ± 4.3	4.68 ± 4.7	3.91 ± 4.81	3.52 ± 2.74	0.089	

Data is reported as means (± SD) or medians (IQR) for skewed distributions or as proportions. *Myocarditis, "stuck" valve, ruptured sinus of Valsalva.

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; NIV, non-invasive ventilation; CHF, congestive heart failure

A total of 295 (81.2%) were admitted with an ACS, of which 121 (33.4%) had an ST elevation MI (STEMI), 131 (36.2%) had a non-ST elevation MI (NSTEMI), 42 (11.6%) had unstable angina (UA). 71 (19.6%) patients presented in cardiogenic shock requiring vasopressor support. Systemic steroids (dexamethasone 6 mg/day or equivalent) were administered to 326 (90.1%) patients, 225 (62.2%) patients underwent awake-proning, 155 (42.8%) patients received remdesivir, 88 (23.4%) patients received tocilizumab and 11 (3%) patients received convalescent plasma. Overall (all-cause) mortality was 118 (32.6%). Organ-dysfunction that occurred included: acute kidney injury (AKI) in 89 (24.6%), venous thromboembolism (VTE) in 25 (6.9%), liver dysfunction in 12 (3.3%) and major bleeding (gastrointestinal and hematoma causing compartment syndrome) in 2 (0.6%) patients. Median length of ICU stay was 4.1 ± 4.3 days.

Comparing survivors v/s non-survivors, the latter tended to be older (mean age 61.5 ± 12.3 v/s 53.6 ± 14.6 years, p < 0.001), have higher serum creatinine (1.75 ± 1.4 v/s 1.2 ± 0.66, p < 0.001), serum glucose (224.2 ± 108.6 v/s 182.6 ± 79.1, p = 0.003), more likely to require vasopressors (41.55 v/s 9%, p < 0.001) and have a higher Shock Index (0.93 ± 0.3 v/s 0.76 ± 0.1, p < 0.001) at admission (Table 2).

Overall, 69 (19%) patients received oxygen only (via NC or VFM), 92 (25.4%) received BiPAP (mean IPAP was 17.2 ± 3.4 cm H₂O and mean EPAP 11 ± 4 cm H₂O). 141 (39%) patients received iCPAP (mean CPAP applied was 12 ± 4.5 cm H₂O). 60 (16.6%) required IMV.

Mean FiO₂ at admission was 0.65 ± 0.33 for patients on BiPAP compared to 0.59 ± 0.29 for those on iCPAP, p = 0.11. Of note, in comparison to the 1st surge, fewer patients received IMV in the 2nd and 3rd surge (23.9% v/s 10.8% v/s 10.2%), and a higher

proportion of patients were managed with oxygen only, or NIV (iCPAP or BiPAP) support.

Table 2: Comparison of COVID-19 AHRF ‘survivors’ and ‘non-survivors’

Characteristics	Mortality		P-value
	No	Yes	
Total (N)	244	118	
Age (years)	53.62 ± 14.65	61.56 ± 12.39	<0.001
Duration of symptoms	4.8 ± 3.8	4.4 ± 3.3	0.271
Ejection fraction (%)	40 ± 14.1	34 ± 10.4	0.074
APACHE II score	18.3 ± 6.4	19 ± 5.7	0.346
Creatinine (mg/dL)	1.2 ± 0.66	1.75 ± 1.45	<0.001
Absolute lymphocyte count	2074.6 ± 1992.7	1655.6 ± 1041.4	0.286
Blood Glucose (mg/dL)	182.6 ± 79.1	224.2 ± 108.6	0.003
CRP (mg/dL)	12.9 ± 15.6	12.6 ± 19.8	0.915
CRP on Day 2	2.4 ± 6.2	2.7 ± 6.3	0.663
Shock index (Heart rate/ Systolic BP)	0.76 ± 0.1	0.93 ± 0.3	<0.001
Chronic respiratory disease	20.5% (50)	16.1% (19)	0.319
Hypertension	40.2% (98)	46.6% (55)	0.245
Diabetes	23% (56)	29.7% (35)	0.168
Chronic kidney disease	11.5% (28)	10.2% (12)	0.71
Coronary artery disease	32% (78)	37.3% (44)	0.315
Pronation	57.4% (140)	72% (85)	0.007
Cardiovascular support	9% (22)	41.5% (49)	<0.001
Tocilizumab	26.2% (64)	20.3% (24)	0.221
Remdesivir	44.3% (108)	39.8% (47)	0.424
Steroids	89.8% (219)	90.7% (107)	0.783
AKI	10.2% (12)	31.6% (77)	<0.001
STEMI	37.7% (92)	33.1% (39)	0.388
NSTEMI	34% (83)	32.2% (38)	0.732

AKI Acute Kidney Injury, STEMI ST Elevation myocardial infarction, NSTEMI Non-ST Elevation myocardial infarction, CRP C-reactive protein

A total of 141 (39%) patients received iCPAP during their stay. All patients on iCPAP received continuous PAP in a 24-hour period. Mean PAP applied was 12 ± 4.5 cm H₂O. Median ROX index at initiation of iCPAP was 7.2 (IQR 4.4-11.7), with a follow-up median index of 15.6 (IQR 7.7-23) at 24 hours. All oxygenation variables including FiO₂, PaO₂, SpO₂, RR, ROX index and PF ratios significantly improved at 48 hours (Day 3) of iCPAP therapy (Table 3).

iCPAP failure’ occurred in 48/141 (34%) patients; of whom 43 (30.4%) were escalated to BiPAP support and 5 (3.5 %) to IMV (refer to Table-4). Patients were more likely to fail iCPAP if they had higher APACHE

II scores (16.3 ± 5.7 v/s 21.3 ± 6, p < 0.001), lower systolic (121 ± 21.9 v/s 103 ± 19.8, p < 0.001) and diastolic blood pressures (74 ± 13.3 v/s 63 ± 11, p < 0.001), worse shock indices (0.79 ± 0.2 v/s 0.9 ± 0.2, p < 0.001) and a lower cardiac ejection fraction (31% ± 9.9 v/s 37% ± 12.7) on admission.

Table 3: Oxygenation variables of patients on iCPAP

	Admission	Day 3	P-value
FiO ₂	0.60 (IQR 0.36-0.95)	0.30 (IQR 0.21-0.62)	<0.001
PaO ₂	78 (IQR 63-91.5)	95.5 (IQR 76-110)	<0.001
SpO ₂	94 (IQR 91-96)	97 (IQR 94-100)	<0.001
Respiratory Rate	24 (IQR 22-26)	20 (IQR 20-24)	<0.001
ROX score	7.2 (IQR 4.43-11.7)	15.6 (IQR 7.7-23.3)	<0.001
PaO ₂ / FiO ₂ Ratio	148 (IQR 86-238)	229 (IQR 136.4-238)	<0.001

ROX index = SpO₂ / (FiO₂/100) / respiratory rate

Patients were also more likely to fail iCPAP if they had a lower ROX index on admission (5 ± 2.2 v/s 10.4 ± 5.4, p < 0.001) and a lesser degree of stabilization or improvement on iCPAP at 48 hours (Day 3 ROX 18.7 ± 8.9 v/s 9.9 ± 6.3, p < 0.001). In addition, our analysis showed that patients with moderate-severe ARDS (PF ratio < 150) were less likely to improve with iCPAP, in comparison with patients who had mild-moderate ARDS (PF ratio > 200) on admission. Even though patients with moderate-severe ARDS had a larger improvement in oxygenation at Day 3 (PF ratio improved from 109 ± 65 to 189.5 ± 116 compared to 212 ± 111.3 to 244 ± 125.7), this improvement in oxygenation did not prevent iCPAP failure for this severity of illness (Table 4).

Overall mortality for patients managed on iCPAP alone was 44 (31.2%). Patients who failed iCPAP and needed to be transitioned to continuous BiPAP (43/48 (89.5%)) or IMV (5/48 (10.4%)) had a combined mortality of 54% (BiPAP; 12 (28%), IMV; 4 (80%) patients.

DISCUSSION

In this study, we describe outcomes of one of the largest cohorts of critically-ill COVID-19 patients from Pakistan and highlight key & innovative aspects of managing COVID-19 AHRF. First, for all of our 362 severe/critical patients, with report a mortality of 32.6%, is comparable to regional and global mortality reports. Pakistan-wide mortality rates for ‘severe’ and ‘critical’ COVID-19 AHRF are approximately 41.5%, with 76.3% for those on IMV (PRICE Registry,

unpublished data). Similarly, ICU-mortality rates reported from around the world include: 31.5% from Critical Care Asia (Sri Lanka, India, Pakistan, Nepal, Bangladesh, Malaysia, Vietnam),¹³ 37.9% (ICNARC report, England, Wales and Northern Ireland),¹⁴ and 37.7%, Standardized Mortality Ratio (SMR) of 1.86, from Brazil (ICUs Project, UTIsbrasileiras).¹⁵

Table 4: Oxygenation variables of patients on iCPAP

Characteristics	iCPAP Failure		P-value
	No	Yes	
Total (N)	93	48	-
Chronic respiratory disease	20.4% (19)	25% (12)	0.388
Hypertension	44.1% (41)	39.6% (19)	0.732
Valvular heart disease	6.5% (6)	12.5% (6)	0.732
Diabetes	33.3% (31)	39.6% (19)	0.732
Chronic kidney disease	17.2% (16)	12.5% (6)	0.732
Congestive heart failure	31.2% (29)	33.3% (16)	0.732
APACHE II score	16.3 ± 5.7	21.3 ± 6	<0.001
RR at admission	23.7 ± 3.9	24.8 ± 4.9	<0.001
RR at Day 3	20.7 ± 3.7	22.7 ± 4.5	<0.001
ROX score at admission	10.4 ± 5.4	5 ± 2.2	<0.001
ROX score at Day 3	18.7 ± 8.9	9.9 ± 6.3	<0.001
PF Ratio at admission	211.9 ± 111.3	109 ± 65	<0.001
PF Ratio at Day 3	243.7 ± 125.7	189.5 ± 116.2	<0.001
SBP at admission	120.7 ± 21.9	103.3 ± 19.8	<0.001
DBP at admission	73.9 ± 13.3	62.8 ± 11	<0.001
Shock Index	0.79 ± 0.23	0.93 ± 0.28	<0.001
STEMI	9.7% (9)	41.7% (20)	0.732
NSTEMI	28% (26)	10.4% (5)	0.732
Ejection Fraction	37.2 ± 12.74	31.04 ± 9.89	<0.001
Shock	34.4% (32)	58.3% (28)	<0.001
Antibiotics	33.3% (31)	64.6% (31)	0.732
Length of stay	5.49 ± 3.43	4.65 ± 3.68	<0.001

Shock Index = heart rate/ systolic BP. ROX index = SpO₂ / (FiO₂/100) / respiratory rate

iCPAP improvised continuous positive airway pressure support.

Second, our cohort displayed a spectrum of comorbidities/‘risk factors for critical illness’ similar to those observed in other populations, including hypertension (HTN), 42.3%, diabetes mellitus (DM) (25.1%), and chronic kidney disease (CKD), 11%.¹⁶ We did, however, have a larger proportion of patients with cardiovascular disease (CVD) (53%), since this is a major tertiary-care cardiovascular referral site. Our patients were also younger (mean age 56 years). Within this cohort, we found higher mortality was associated with age (> 60 years), renal dysfunction, hemodynamic decompensation, ARDS, and IMV. This is similar to other reports, including those earliest from Wuhan, China (December 2019-January 2020; 52 critically-ill patients), where overall mortality was

61.5%; and highest for older patients and those who required IMV (‘survivors’ v/s ‘non-survivors’; 64.6 years vs 51.9 years, and 94% vs 35%, respectively).¹⁷

Third, for the first time, we describe patterns/changes in disease intensity, and treatment prescription, over the course of three surges in Pakistan. Patients were younger (54 v/s 61 years), had more severe illness (APACHE II), less likely to receive steroids (81% vs 97%), and have a longer duration of ICU-stay (4.68 to 3.52 days, $p = 0.089$), in the initial surge. We also describe an increased utilization of NIV over IMV for critically-ill patients, across the three surges. This in turn, may represent an increasing ‘physician familiarity or comfort’, or a ‘learning-curve’ during the pandemic, for the progressive adoption of NIV in critical-illness. Our observations are supported by others; where Wang et al., at the start of the pandemic (January-February 2020), described that of 344 patients admitted to the Tongji Hospital ICU (China) only 20% patients received NIV, whereas 30% received IMV.¹⁸ Later, in March-April 2020, in an audit on 688 patients, Forrest et al. reported that as many as 78% received NIV, while 22% received IMV.¹⁹ And in China, 17.6% (of 239) patients were described to receive IMV, whilst 52.1% received NIV.²⁰ In our cohort, 64.3% received NIV, and 16.5% were intubated (IMV).

It is also important to note, that despite a progressively higher usage of NIV, our mortality rates remained consistent across surges (~ 30%, Table 1). This emulates observations globally; for instance, a multicenter cohort study across 5 hospitals (March-April 2020) reported that 83% patients of those IMV died, while only 32% in the NIV subset died (unadjusted OR=10, 95% CI 6.7–17).¹⁹ In a case series reported by Chand et al. 274 (91.3%) patients received IMV; and 55.8% died, and 26 patients managed with a HFNC had a much lower 30-day mortality (15.4%).²¹ In a systematic review and meta-analysis of 10,150 patients across Asia, Europe and North America, Armstrong et al. describe a combined ICU mortality of 41.6% (34.0–49.7%), with a reduction over time seen in post-hoc analysis. Pooled ICU mortality was 59.5% (39.8–76.5%) in studies published before the end of March 2020, and 41.6% (34.0–49.7%) for all included studies to the end of June 2020.²² Possible explanations for these trends include a widespread incorporation of systemic steroid therapy after publication of the landmark RECOVERY trial (July 2020),²³ and likely a more equitable triage of ICU resources, including increased reliance on NIV methods, in both resource-plentiful and resource-constrained settings.

Given these encouraging results with the use of NIV, faced with a massive influx of critically-ill patients in a resource-constrained setting, we developed an improvised CPAP delivery system using available supplies. CPAP/BiPAP delivery devices are readily available even in resource-limited countries,^{11,12} whereas HFNCs are newer, more expensive, and not available widely. We developed iCPAP because we did not have/could not get a HFO delivery system and wanted to combine the benefits of a comfortable patient-ventilator interface, HFO with PAP delivery. Therefore, we modified our interface to use that designed to accommodate high flow rates. We were able to obtain NCs designed for use with high-flow systems but unfortunately not the delivery systems. With rising cases, we triaged patients to iCPAP so as to support as many patients as possible and save up ventilators for those with refractory hypoxia. Our system is somewhat similar to that of a ‘bubble CPAP’ used in pediatrics. The bubble CPAP delivery system uses short nasal prongs as the patient interface. Small pressure oscillations are created by running oxygen through a tube submerged in a container of water. When the oxygen runs out of the tube, the ensuing bubbling produces oscillations in airway pressure. When these oscillations are transmitted to the patient’s lungs, the result is improved gaseous exchange and lung function.²⁴

We postulate that delivery of titrated CPAP via NC may have several potential benefits in managing COVID-19 AHRF; a) clinicians may reserve the ability to carefully fine-tune PAP and HFO separately, based on individual patient needs/physiology. For instance, a patient with severe hypoxemia and bilateral infiltrates/atelectasis on imaging, poor compliance (‘typical ARDS’) may benefit from a higher PAP (and/or awake-proning) to stent open collapsed airways (improve FRC), but not necessarily very HFO. On the other hand, another patient with a similar degree of hypoxemia, high MVE, but not as much loss of aeration on imaging (‘atypical ARDS’) may have a relatively preserved lung compliance (particularly in early ‘mild-moderate’ ARDS) and may not need higher PAP but only support with HFO. Since lung compliance is relatively preserved in such patients, a higher PAP (as delivered with BiPAP), may not improve oxygenation or may do so only at the unnecessary risk of barotrauma. A lower PAP may be sufficient, in fact protective, as it avoids unnecessary overdistention or ‘ventilation-induced lung injury’ (VILI). Hence, iCPAP may allow clinicians to carefully modulate both low-moderate intensities of PAP and HFO, tailored to patients, in a non-invasive fashion; b) Use of a distensible, wide-bore nasal tubing may minimize increased work-of-breathing

associated with high-resistance interfaces and narrow expiratory tubing; c) an undeniable benefit of a comfortable interface is that it can be tolerated for days to weeks as facial decubiti are a frequent complication with tight, occlusive interfaces; d) improved patient comfort in turns improves compliance with maneuvers such as awake-proning which make a significant difference, as it is recognized that COVID-19 AHRF responds well to awake-proning and may require several days of PAP support; and finally e) noninvasive and especially HFNC support requires lesser sedative use, allows for more generous nurse-patient ratios and permits patients to actively participate in their care.

In this study, we demonstrate that iCPAP can be a safe alternate to standard NIV (BiPAP) in patients with COVID-19 AHRF. Patients on iCPAP have a similar/lower mortality in comparison to standard NIV (BiPAP). In addition, there were no adverse events (i.e., pneumothorax, pneumomediastinum), as are all too commonly observed with ‘physiologically-inappropriate’ application of high PAP (BiPAP).²⁵ In our study, patients who received iCPAP were successfully oxygenated, and respiratory indices improved consistently in most (ROX index etc., Table-3)), with ‘iCPAP failure’ occurring in a small, but identifiable, group.

The strengths of this study include that this is a large cohort of COVID-19 patients from a low-income country having cardiovascular diseases, information that is needed to complete our understanding of the global burden of this pandemic. We share our experience of a modification in the interface of a standard CPAP respiratory support system, which appears to have been effective and with low failure and mortality rates comparable to those reported from resource replete ICUs.

Our report is limited in that this study was not pre-emptively designed to demonstrate the efficacy of iCPAP, therefore we do not have detailed oxygenation and ventilation data, nor head-to-head comparison of standard NIV (CPAP or BiPAP) in mild-moderate ARDS.

CONCLUSION

COVID-19 outcomes in patients having cardiovascular diseases in a resource-limited setting appear comparable to global reports. A modification of standard CPAP (iCPAP) appeared to be safe and effective. This modification of standard CPAP (iCPAP) identifies an option for resource-limited or resource-exhausted critical care units.

AUTHORS' CONTRIBUTION

MW, JA, and NS: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. LT, MH, KB, UI, MIA, SNH, MA, and MU: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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REFERENCES

- Hashmi M, Taqi A, Memon MI, Ali SM, Khaskheli S, Sheharyar M, et al. A national survey of critical care services in hospitals accredited for training in a lower-middle income country: Pakistan. *J Crit Care.* 2020;60:273-8.
- Sprung CL, Joynt GM, Christian MD, Truog RD, Rello J, Nates JL. Adult ICU Triage During the Coronavirus Disease 2019 Pandemic: Who Will Live and Who Will Die? Recommendations to Improve Survival. *Crit Care Med.* 2020;48(8):1196-202.
- Pinsky MR. Cardiopulmonary Interactions: Physiologic Basis and Clinical Applications. *Ann Am Thorac Soc.* 2018;15(Suppl 1):S45-S8.
- Rochweg B, Brochard L, Elliott MW, Hess D, Hill NS, Nava S, et al. Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J.* 2017;50(2):1602426.
- Frat JP, Thille AW, Mercat A, Girault C, Ragot S, Perbet S, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med.* 2015;372(23):2185-96.
- Moller W, Feng S, Domanski U, Franke KJ, Celik G, Bartenstein P, et al. Nasal high flow reduces dead space. *J Appl Physiol (1985).* 2017;122(1):191-7.
- Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. *N Engl J Med.* 2020;383(2):120-8.
- Goury A, Moussanang JA, Bard M, Champenois V, Julien G, Dupont V, et al. Predictive factors associated with high-flow nasal cannula success for COVID-19-related acute hypoxemic respiratory failure. *Health Sci Rep.* 2021;4(2):e287.
- Rahim F, Amin S, Noor M, Bahadur S, Gul H, Mahmood A, et al. Mortality of Patients With Severe COVID-19 in the Intensive Care Unit: An Observational Study From a Major COVID-19 Receiving Hospital. *Cureus.* 2020;12(10):e10906.
- Baldomero AK, Melzer AC, Greer N, Majeski BN, MacDonald R, Linskens EJ, et al. Effectiveness and Harms of High-Flow Nasal Oxygen for Acute Respiratory Failure: An Evidence Report for a Clinical Guideline From the American College of Physicians. *Ann Intern Med.* 2021;174(7):952-66.
- Crit Care A. Establishing a critical care network in Asia to improve care for critically ill patients in low- and middle-income countries. *Crit Care.* 2020;24(1):608.
- Hashmi M, Beane A, Taqi A, Memon MI, Athapattu P, Khan Z, et al. Pakistan Registry of Intensive CarE (PRICE): Expanding a lower middle-income, clinician-designed critical care registry in South Asia. *J Intensive Care Soc.* 2019;20(3):190-5.
- Linking of Global Intensive Care (LOGIC) (2020) Table Data COVID19. Characteristics and outcomes of COVID-19 and suspected COVID-19 patients in national registries. <https://www.icubenchmarking.com/wp-content/uploads/2020/08/Tabledata-covid19-july20-1-1.pdf> [Accessed on: 1st September 2021].
- ICNARC report on COVID-19 in Critical Care: England WaNI, 3. <https://www.icnarc.org/Our-Audit/Audits/Cmp/Our-National-Analyses/2020/05/08/Report-On-Patients-Critically-Ill-With-Covid-19> [Accessed on: 28th August 2021].
- The Brazilian ICUs project UR. <http://www.utisbrasileiras.com.br/en/covid-19/benchmarking-covid-19/> [Accessed on: 28th August 2021].
- Liu D, Cui P, Zeng S, Wang S, Feng X, Xu S, et al. Risk factors for developing into critical COVID-19 patients in Wuhan, China: A multicenter, retrospective, cohort study. *EclinicalMedicine.* 2020;25:100471.
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020;8(5):475-81.
- Wang Y, Lu X, Li Y, Chen H, Chen T, Su N, et al. Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19. *Am J Respir Crit Care Med.* 2020;201(11):1430-4.
- Forrest IS, Jaladanki SK, Paranjpe I, Glucksberg BS, Nadkarni GN, Do R. Non-invasive ventilation versus mechanical ventilation in hypoxemic patients with COVID-19. *Infection.* 2021;49(5):989-97.
- Xu J, Yang X, Yang L, Zou X, Wang Y, Wu Y, et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. *Crit Care.* 2020;24(1):394.
- Chand S, Kapoor S, Orsi D, Fazzari MJ, Tanner TG, Umeh GC, et al. COVID-19-Associated Critical Illness-Report of the First 300 Patients Admitted to Intensive Care Units at a New York City Medical Center. *J Intensive Care Med.* 2020;35(10):963-70.
- Armstrong RA, Kane AD, Cook TM. Outcomes from intensive care in patients with COVID-19: a systematic review and meta-analysis of observational studies. *Anaesthesia.* 2020;75(10):1340-9.
- Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med.* 2021;384(8):693-704.
- Baldursdottir S, Falk M, Donaldsson S, Jonsson B, Drevhammar T. Basic principles of neonatal bubble CPAP: effects on CPAP delivery and imposed work of breathing when altering the original design. *Arch Dis Child Fetal Neonatal Ed.* 2020;105(5):550-4.
- Sethi SM, Ahmed AS, Hanif S, Aqeel M, Zubairi ABS. Subcutaneous emphysema and pneumomediastinum in patients with COVID-19 disease; case series from a tertiary care hospital in Pakistan. *Epidemiol Infect.* 2021;149:e37.

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