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CASE REPORT

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Successful prolonged use of non-invasive ventilation in severe COVID-19 patients: a case series.

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ABSTRACT

BACKGROUND: The Coronavirus disease-19 (COVID-19) primarily affects respiratory system leading to acute hypoxemic respiratory failure. Invasive mechanical ventilation has been a gold standard in the respiratory therapy of patients with acute respiratory distress syndrome (ARDS). It requires advanced ventilators, qualified intensivists and trained intensive care unit (ICU) staff to manage, which is not readily available and of which there has been a perpetual shortage during the current pandemic. Non-invasive ventilation (NIV) is one of the bridging non-invasive respiratory supports to avoid invasive intubation intended to improve oxygenation and ventilation in severe COVID-19 patients where conventional oxygen therapy fails.

CASE: The authors report a series of four cases where prolonged NIV was used under expert supervision in patients with severe COVID-19 disease.

CONCLUSIONS: This case series showed that NIV can be prolonged successfully under supervision in severe COVID-19 patients that can avoid intubation and its complications.

KEY WORDS: COVID-19 disease, COVID-19 pandemic, acute hypoxemic respiratory failure, non-invasive ventilation, endotracheal intubation, coronavirus, case report.

INTRODUCTION

SARS-COV-2 is a virus that has caused the ongoing pandemic of COVID-19 that originated in Wuhan, China in December 2019 and has spread rapidly across the globe [1]. These patients frequently develop refractory hypoxemia which can either be caused by intrapulmonary shunting or ventilation–perfusion mismatch. Oxygen therapy remains the mainstay of management in these patients. Various modalities of oxygen therapy in severely hypoxemic patients include High Flow Nasal Cannula (HFNC), Non-invasive ventilation (NIV) or invasive mechanical ventilation. Guidelines recommend invasive mechanical ventilation in patients with PaO_2/FiO_2 (P/F) ratio <150 [2]. However, during COVID-19 pandemic there is an immense pressure on healthcare setup with acute shortage of ICU beds, equipments and adequate staff. The management of patients on invasive mechanical ventilation further increases the workload and thereby compromises the efficient care of increasing number of ICU patients. In view of the above shortcomings, the invasive ventilation may be avoided by using non-invasive modalities like HFNC or NIV during the pandemic. Many experts believe that NIV leads to aerosol generation that can cause risk of virus transmission to health care staff. However recent studies have shown that NIV with tight fitting mask and use of proper personal protective equipment (PPE) does not cause significant transmission of infection [3]. The literature regarding the prolonged use of NIV in COVID-19 is scarce.

The authors hereby report a series of four cases of severe COVID-19 pneumonia which were successfully managed on prolonged use of NIV thus avoiding intubation and its complications.

CASE REPORT 1

Patient Information: A 62-year male with BMI of 30, a known case of Hypertension and type 2 Diabetes Mellitus on regular treatment was admitted with complaints of sore throat for 4 days, fever 3 days, and breathlessness 1day after his nasopharyngeal swab for reverse transcriptase-polymerase chain reaction (RT-PCR) tested positive.

Clinical Findings: On admission he was conscious, oriented with heart rate (HR) 96/min, blood pressure (BP) 152/92mmHg, respiratory rate (RR) 32/min, temperature 99.2°F and SpO_2 92% on 15L/min oxygen via non-rebreathing mask (NRM).

Diagnostic Assessment: His arterial blood gas analysis (ABG) showed pH of 7.44, pCO_2 30 mmHg, pO_2 83 mmHg, HCO^{3-} 22.7mmol/L and SO_2 97%, P/F ratio 92. His laboratory findings are shown in table 1. On arrival to ICU he was started on NIV with FiO_2 1.0, CPAP 10 cm H_2O and pressure support (PS) 5 cm H_2O in view of increasing respiratory distress and desaturation. FiO_2 was reduced to 0.6 in the next 2 hours to maintain SpO_2 92-94%. P/F ratio improved to 111. His chest X-ray showed airspace opacification in bilateral lung fields predominantly in right middle zone suggestive of pneumonic consolidation (Figure 1A). His HRCT thorax revealed patchy areas of ground glass opacities in bilateral lung parenchyma (CT severity score 18/25).

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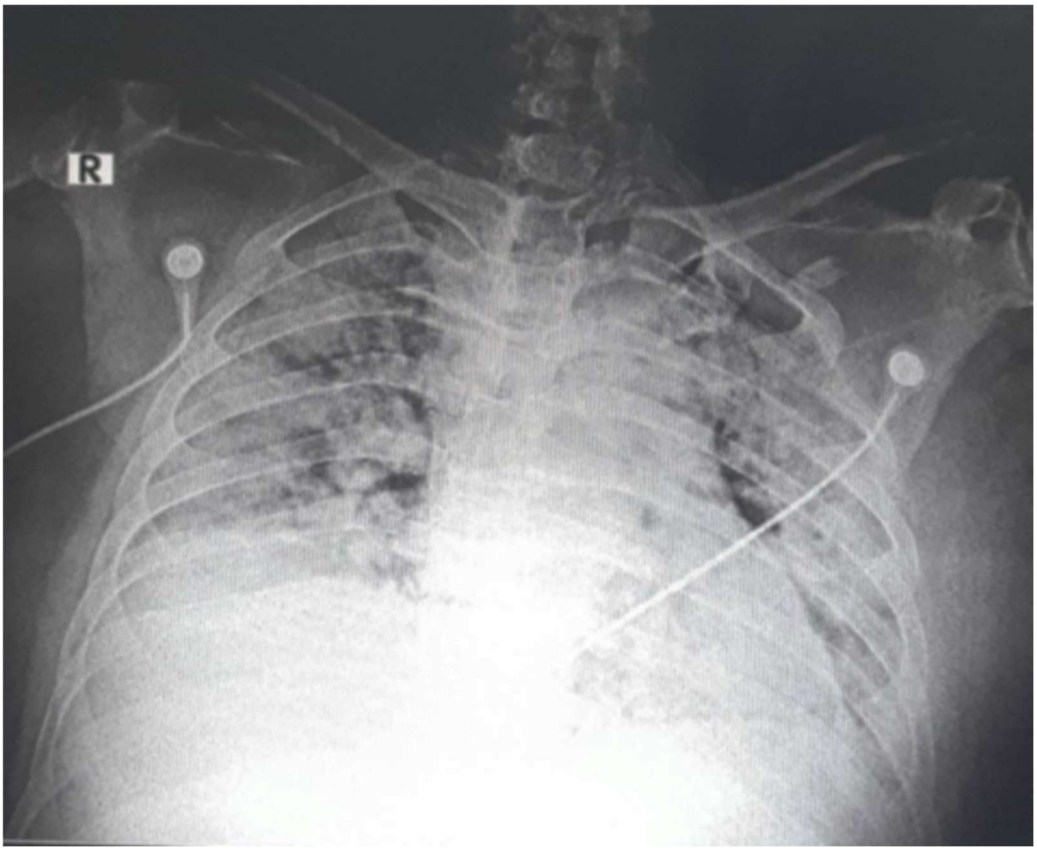

Figure 1A. Baseline anterior-posterior view (AP) chest radiographs of case 1.

Table 1. Baseline investigations of all the cases.

Laboratory parameter	Case 1	Case 2	Case 3	Case 4
TLC (*10^9/L)	12.0	10.6	5.8	12.0
N:L Ratio	18.6	8	9	8.7
Urea (mg/dl)	23	28	24	103
Creatinine (mg/dl)	1.1	1.3	1.2	1.2
Glucose (mg/dl)	280	174	278	223
Calcium (mg/dl)	8.5	8.3	8.5	8.3
Albumin (g/dl)	4.2	2.5	2.3	2.7
PCT (ng/ml)	0.230	0.052	0.236	0.10
CRP (mg/L)	>90	24.3	>90	>90
Ferritin (ng/ml)	57.4	127	903	565
D-dimer (mcg/ml)	0.45	0.99	0.88	5.7
IL-6 (pg/ml)	1321	39	300	-
PaO_2/FiO_2 Ratio	92	74	57	81

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Therapeutic Intervention: He was started on remdesivir, doxycycline, ivermectin, dexamethasone, subcutaneous low molecular weight heparin, insulin infusion. One unit of convalescent plasma was transfused. NIV was continued with intermittent HFNC during feeding.

On day three his oxygen requirement further increased to 80% and he remained tachypneic, had a P/F ratio of 84 (Figure 2) and respiratory rate of 34/min. Injection tocilizumab was given and 2nd unit of plasma transfused. The patient was continued on NIV with CPAP 10 and PS increased to 8 cm of H_2O. After this he was stabilized between day 4 and day 8.

On day 9 his oxygenation and ventilatory parameters improved, he was placed on alternate NIV and HFNC. Mobilization was started, gradually his requirement of NIV decreased and he was taken off from NIV on day 15. He was thereafter continued on HFNC with flow 30L/min and FiO_2 0.5 for the next 4 days. Incentive spirometry, physiotherapy and mobilization continued. On day 21 he was shifted to facemask (flow 5L/min) and transferred to isolation ward.

Follow-up and Outcome: His SARS-CoV-2 RT-PCR for nasopharyngeal swab came negative and he was ultimately discharged from the hospital on day 25.

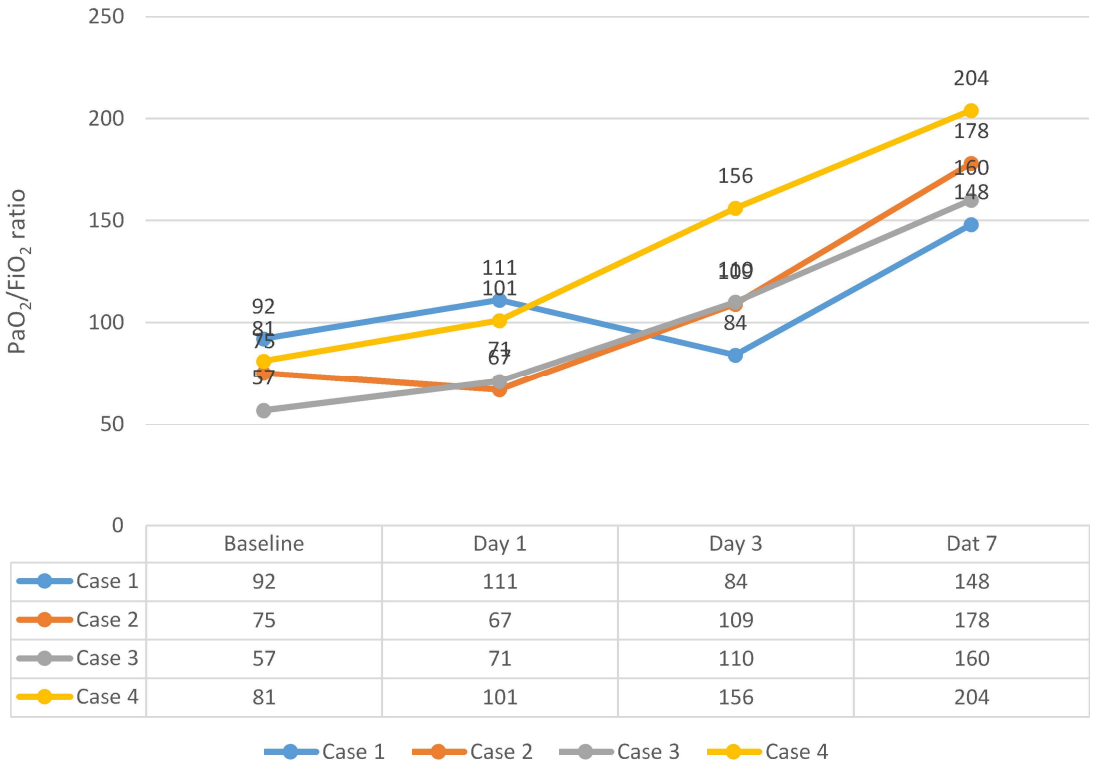

Figure 2. Trends in PaO_2 /FiO_2 ratio.

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CASE REPORT 2

Patient Information: A 75 years old female with BMI 24kg/m^2 presented with chief complaints of fever and difficulty in breathing for 7 days. Patient was a known case of Hypertension since 20 years and on regular medications.

Clinical Findings: On examination in triage, her HR was 72/min, BP 132/72 mmHg, RR 20/min, temperature 98.4^{o}F and SpO_2 94% on NRM with oxygen flow 10 litres/min. RTPCR for COVID 19 was tested positive.

Diagnostic Assessment: Her laboratory findings are shown in table 1. Her ABG showed pH of 7.47, pCO_2 43 mmHg, pO_2 52 mmHg, HCO^- 31.9 mmol/L and SO_2 87%, P/F ratio 74. A chest radiograph showed multiple bilateral peripheral infiltrates in the lower zones (Figure 1B).

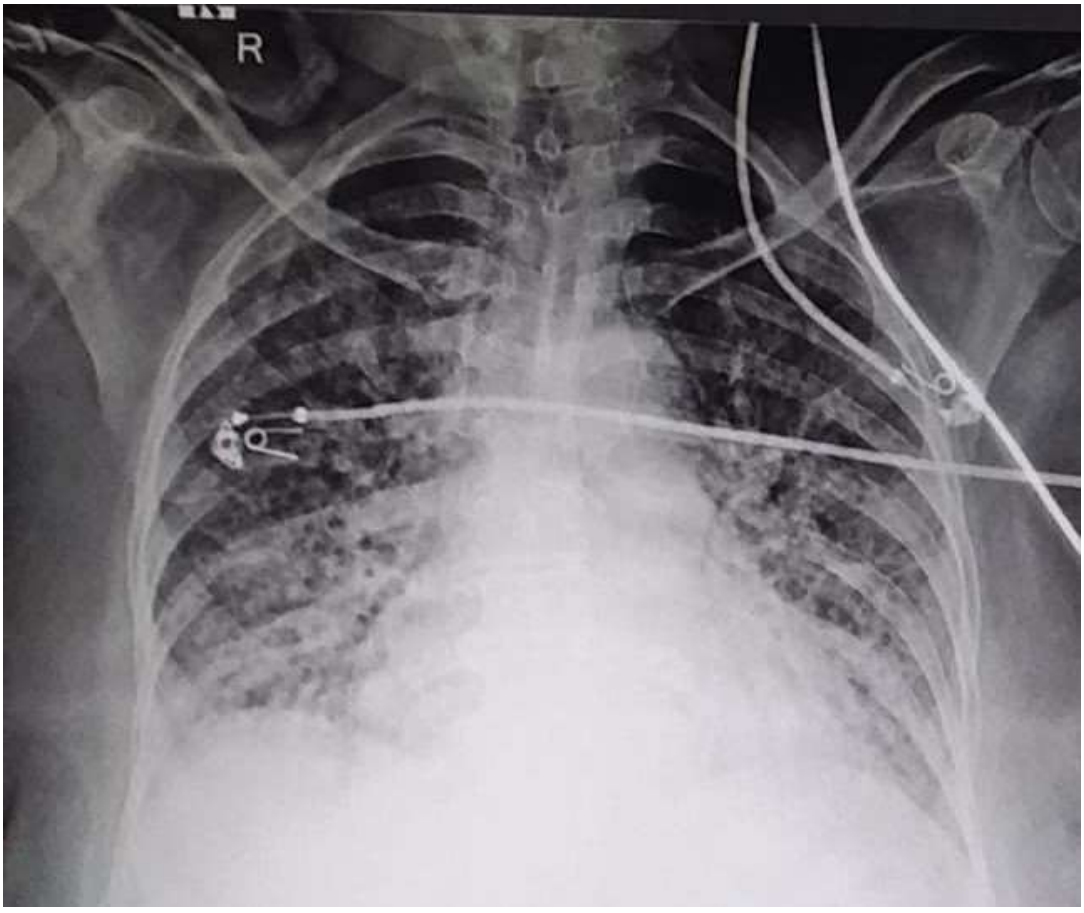

Figure 1B. Baseline anterior-posterior view (AP) chest radiographs of case 2.

Therapeutic Intervention: On admission to ICU, patient was maintaining SpO_2 92-94 % on NRM 15L/min oxygen flow. Awake self proning was advised. Patient was started on remdesivir, ivermectin, doxycycline, dexamethasone, subcutaneous low molecular weight heparin.

Her clinical condition worsened on the second day with an increasing respiratory distress, P/F ratio of 99, SpO_2 86%. She was started on NIV with initial settings of FiO_2 1.0, PEEP 10 cm H_2O and PS above PEEP of 7 cm H2O, PEEP and FiO_2 were titrated to maintain SpO_2 92-94%. On day 5, as the clinical condition of patient started deteriorating again with rising inflammatory markers, she was started on tocilizumab injection and the second dose was repeated 24 hours later. Over the time there was gradual improvement in the clinical condition and P/F ratio also increased to 160 (Figure 2).

Follow-up and Outcome: The NIV was gradually weaned off and patient was placed on NRM at 15L/min on day 23 of admission. She was mobilized, and shifted to ward on Day 25 of hospital admission. The patient's RTPCR for SARS-CoV-2 was negative so she was discharged from hospital on day 30 to non-COVID centre on facemask (oxygen 5L/min).

CASE REPORT 3

Patient Information: A 53 years old male with BMI 26kg/m2, known case of hypertension for 6 years, on regular medication was admitted to the hospital with 3 days history of high grade fever, dry cough and shortness of breath since 2 days.

Clinical Findings: On examination he was conscious, oriented with PR 90 beats/minute, BP-130/80 mmHg, RR- 20/min, maintaining SpO_2 of 85 – 90 % on 10 litres/min oxygen through NRM. Patient was shifted to HDU. Awake self proning was advised, he was continued on NRM and maintaining SpO_2 of 92 – 94%.

Diagnostic Assessment: Laboratory findings are shown in table 1. His chest X-ray showed bilateral infiltrates more on the right side (Figure 1C). ABG showed PH-7.41, pCO_2- 42mmHg, pO_2- 76mmhg, HCO_3- 25.4, Lactate- 1.6, PaO_2/FiO_2 ratio of 57 mm Hg.

Therapeutic Intervention: Treatment was started with remdesivir, ivermectin, doxycycline, dexamethasone and subcutaneous LMWH.

On day 3 of admission his respiratory rate increased to 40/min and saturation dropped to 86% despite 15L/min oxygen by NRM. He was shifted to ICU and started on HFNC on FiO_2- 1.0 and flow of 60 L/min but patient's condition didn't improve with increase in respiratory distress. The patient was then started on NIV with initial settings of FiO_2 1.0, CPAP 10 cmH20, PS 5 cmH_20. FiO_2 was titrated to maintain SpO_2 92-94%. There was progressive improvement in respiratory pattern and oxygenation (P/F 110). The patient remained on NIV from day 3 to day 18 with HFNC during feeding.

There was gradual improvement in the clinical condition with his P/F ratio increasing to 150 mmHg (Figure 2). On Day 19 patient was placed on HFNC with FiO_2 of 0.6 and flow of 50L/min. He was mobilized, started on incentive spirometry and gradually weaned off from HFNC over the next 3 days. He was then shifted back to HDU on NRM with 10L/min Oxygen flow.

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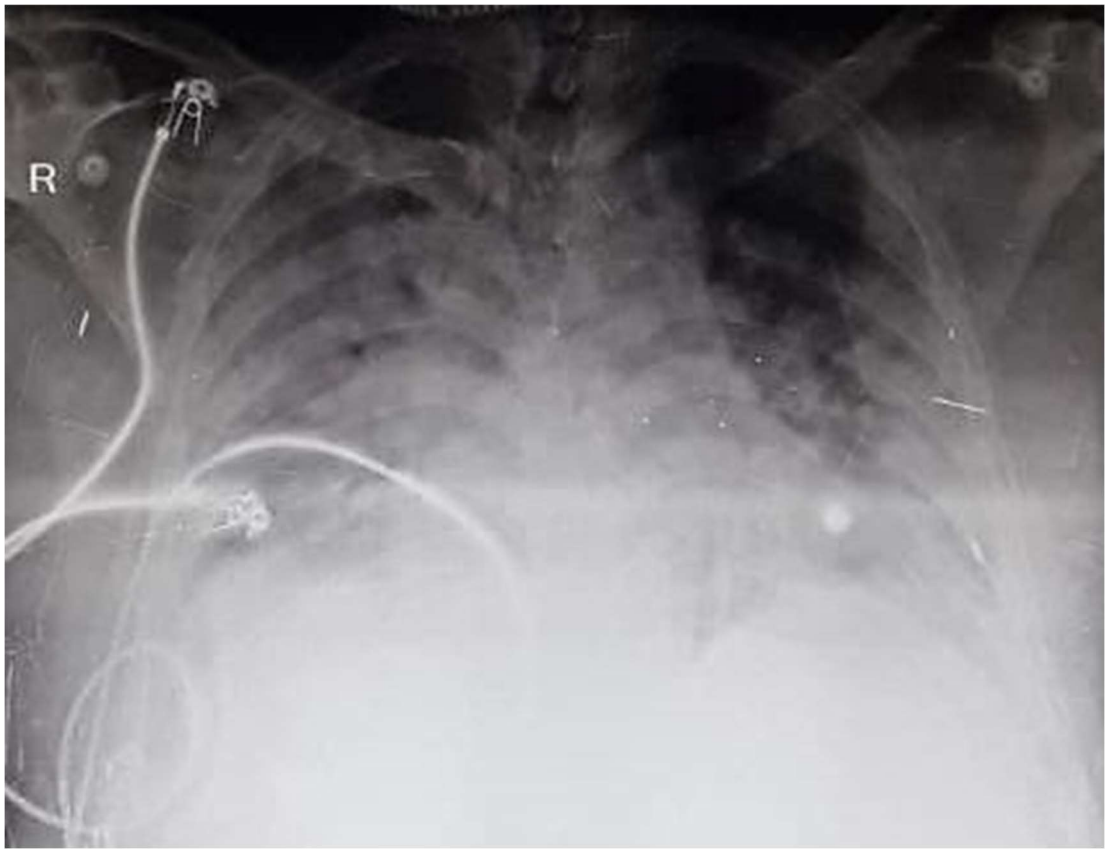

Figure 1C. Baseline anterior-posterior view (AP) chest radiographs of case 3.

Follow-up and Outcome: He was gradually weaned from NRM and on Day 26 he was ultimately discharged from the hospital in a stable condition when his RT-PCR for nasopharyngeal swab came negative.

CASE REPORT 4

Patient Information: A 54-year-old female admitted to ICU with COVID-19 pneumonia, was a known case of obstructive sleep apnea (OSA) since 15 years on home CPAP during sleep, hypertension 12 years, hypothyroidism 6 years and type 2 Diabetes Mellitus 4 years, on regular treatment. She presented with history of fever for 5 days, cough 3 days and shortness of breath 1 day.

Clinical Findings: On examination in triage she was conscious, PR 70/min, BP 140/80, RR 28/min and SpO_2 91% on CPAP of 12 cm of H_2O (Home CPAP device).

Diagnostic Assessment: Chest X-ray showed patchy air space opacification in bilateral lung fields (Figure 1D). Laboratory findings as shown in table 1. ABG showed pH 7.44, pO_2 81, pCO_2 42, HCO_3- 27.8, SO_2 88%, P/F 81.

Therapeutic Intervention: Patient was started on treatment with remdesivir, ivermectin, doxycycline, subcutaneous low molecular weight heparin along with her regular medications. She was shifted to ICU and was continued on NIV with CPAP of 12cm H_2O, FiO_2 0.6 targeting SpO_2 of 88-90%.

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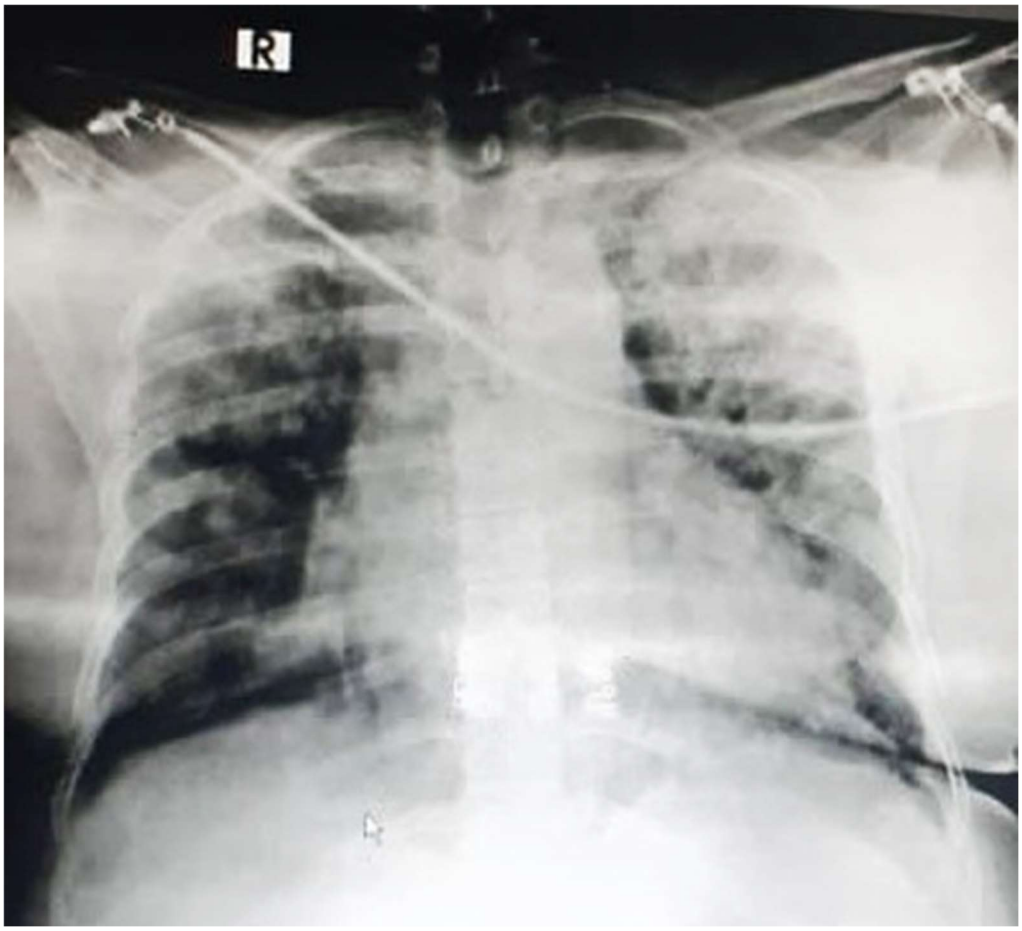

Figure 1D. Baseline anterior-posterior view (AP) chest radiographs of case 4.

On Day 4 her P/F improved to 180 (Figure 2). Her FiO2 was reduced to 0.4 and CPAP to 10cm H_2O. Intermittent HFNC was used during feeds. She remained on continuous NIV with CPAP for next 16 days. On day 20 she was placed on NRM at 12L/min during day time. She was continued on her usual night time CPAP.

Follow-up and Outcome: On Day 21 her nasopharyngeal RTPCR came negative and she was transferred to non-COVID hospital in stable condition.

DISCUSSION

All the cases in this case series had severe COVID-19 infection with P/F ratio <150 (Figure 2). All were successfully managed on NIV although the course of NIV was prolonged. NIV is an established modality of respiratory support in acute exacerbation of chronic obstructive lung disease (COPD) and cardiogenic pulmonary oedema. However, its role in hypoxemic respiratory failure and ARDS is still controversial. The ATS/ERS guidelines suggest NIV use for de novo acute respiratory failure (ARF) as a preventive measure to avoid intubation [4]. NIV was tried successfully in Hong Kong in 2003 in patients of ARF secondary to Severe Acute Respiratory Syndrome (SARS) outbreak [3]. It has also been used in ARF due to H1N1 and had a success rate of 15%-25% [5].

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There was an immense pressure on healthcare systems with increasing number of COVID-19 patients being admitted to ICU. The overburdened healthcare system may cause more patients to be treated with NIV despite absence of any strong evidence supporting its use [6]. During the initial outbreak, reports from China had favoured early invasive mechanical ventilation to NIV. However, reports from Italy showed NIV with CPAP to be a promising modality in COVID-19. The duration of NIV trial is not well defined. Abbas et al, reported a case where a severe COVID-19 patient with hypoxemic respiratory failure was successfully managed by prolonged use of NIV. Invasive mechanical ventilation was avoided and the patient was discharged to home on day 14 [7]. Similarly, Singh et al reported a case of severe COVID 19 which was managed on NIV from day 2 to day 14 and was discharged on day 22 [8]. Our patients also required relatively prolonged duration of NIV (Figure 3).

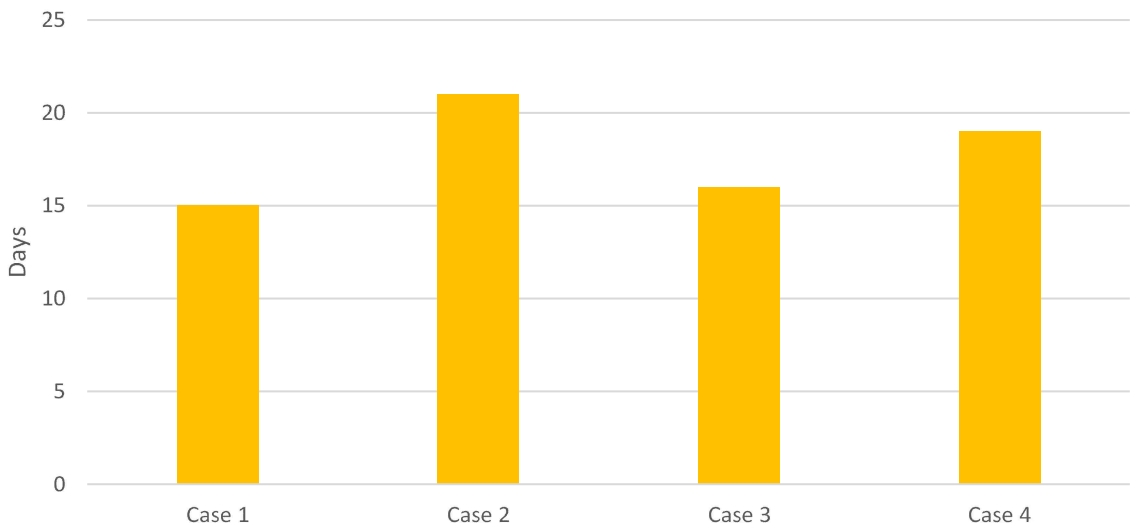

Figure 3. Duration of non-invasive ventilation (NIV) used.

Recent evidence favours the use of NIV to prevent patient deterioration and need of invasive mechanical ventilation. A study by Menzella et al concluded that use of NIV avoided intubation in almost half of the cases [9]. A systematic review and meta-analysis by Ferreyro et al showed that the treatment with non-invasive oxygenation therapies prevent invasive mechanical ventilation and were associated with lower risk of death [10]. A sub analysis of HOPE study in COVID-19 patients concluded that more than half of the patients on NIV survived without the need of intubation and NIV could prove to be a reasonable strategy in an overcrowded and resource limited setting [11].

Surviving sepsis campaign also recommends that in absence of HFNC, NIV can be used with close observation for signs of respiratory failure [12]. We however prefer a trial of NIV to avoid invasive mechanical ventilation despite the patient not maintaining saturation on HFNC as seen in case number 3. He was given a trial of NIV and gradually improved thereafter. Intubation was avoided and patient was successfully managed, although prolonged NIV support was required.

Invasive mechanical ventilation has its own sets of problem. The patient needs to be sedated and may need paralysis. The intubated patient is at increased risk of ventilator associated pneumonia (VAP), acute hypoxemic insult as a result of tube misplacement, increased risk of delirium, critical illness neuromyopathy which increases the length of ICU stay and mortality. The burden on the healthcare workers is thus increased. NIV is preferred over invasive mechanical ventilation to avoid these complications. Although we prefer to prolong the NIV, this under no circumstances delays the decision to go for invasive mechanical ventilation the moment it is warranted.

Choice of NIV interface is very important and the same depends on patient tolerance, fitting of NIV mask and staff training. However, nasal masks are not preferred due to predominant mouth breathing. Oro-nasal masks are most frequently used worldwide. Helmet masks offer more advantages like better patient tolerance and better airway clearance [13]. A study by Patel et al had shown that the use of Helmet NIV in ARDS reduces the need of invasive mechanical ventilation and thereby mortality rate when compared to the NIV face masks [14]. Helmet NIV can deliver higher level of PEEP, reduces inspiratory efforts and hence can reduce patient self-induced lung injury (PSILI) [15]. NIV was well tolerated by all four patients we are reporting here and no NIV related complications were seen.

CONCLUSIONS

To our knowledge this is the largest case series reported where judicious prolonged use of NIV under expert supervision led to recovery of the patients who presented with severe COVID-19 symptoms. Meticulous use of NIV in these patients led to avoidance of intubation and successful outcome. We believe that this case series will provide guidance to the treating physicians to manage severe COVID-19 patients on NIV and avoid intubation and its complications. However, prompt recognition of NIV failure is must and under no circumstances should the decision to go for invasive mechanical ventilation be delayed.

SUPPLEMENTARY INFORMATION

Funding: *This research received no external funding.*
Institutional Review Statement: *The study was conducted according to the guidelines of the Declaration of Helsinki.*
Informed Consent Statement: *Informed consent was obtained from all subjects involved in the study.*
Data Availability Statement: *The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.*
Conflicts of Interest: *The authors declare no conflicts of interest.*

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