Original Article

An observational study on the timing of intubation and outcome in COVID-19 ARDS patients who were treated with high flow nasal oxygen prior to invasive mechanical ventilation: A time series analysis (InOutHFNO trial)

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ABSTRACT

Background and Aims: Prolonged high flow nasal oxygen (HFNO) application might delay intubation and increase mortality in acute hypoxemic respiratory failure (AHRF) patients. Intubation in coronavirus disease 2019 (COVID-19) AHRF (CAHRF) patients 24 to 48 hours after HFNO initiation has been associated with increased mortality in previous studies. This cut-off period is variable in previous studies. A time series analysis could reflect more robust data on outcome in relation to HFNO duration before intubation in CAHRF. **Methods:** A retrospective study was conducted at 30-bedded ICU of a tertiary care teaching hospital from July 2020 to August 2021. The study cohort comprised 116 patients who required HFNO and were subsequently intubated following HFNO failure. A time series analysis of patient outcomes on each day of HFNO application prior to invasive mechanical ventilation (IMV) was done. **Results:** ICU and hospital mortality was 67.2%. Beyond day 4 of HFNO application, there was a trend towards increased risk-adjusted ICU and hospital mortality for each day delay in intubation of CAHRF patients on HFNO [OR 2.718; 95% CI 0.957–7.721; *P* 0.061]. This trend was maintained till day 8 of HFNO application, after which there was 100% mortality. Taking day four as a cut-off in the timeline of HFNO application, we have observed an absolute mortality benefit of 15% with early intubation despite a higher APACHE-IV score than the late intubation group. **Conclusion:** IMV beyond the 4th day of HFNO initiation in CAHRF patients increases mortality.

Key words: COVID-19, HFNO failure, mechanical ventilation

INTRODUCTION

High flow nasal oxygen (HFNO) has been increasingly used in coronavirus disease 2019 (COVID-19) patients with acute hypoxemic respiratory failure (AHRF, defined as PF ratio of 300 or less with a respiratory rate >25/min) during the pandemic. During the initial period of the COVID-19 pandemic, the use of HFNO was usually avoided due to the notion of risk of nosocomial airborne transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Subsequently, it was realized that this concern was minimal and could be avoided with proper preventive measures.[1] In AHRF, HFNO has been associated with lower risk of invasive mechanical ventilation (IMV) in both COVID-19 and non-COVID-19 patients.[2] In non-COVID-19 AHRF,

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randomized controlled trials (RCTs) have shown the mortality advantage of HFNO compared to conventional oxygen and non-invasive ventilation (NIV).[3] This evidence made clinicians rely more on HFNO to manage CAHRF, resulting in patients being subjected to prolonged HFNO to avoid intubation and mechanical ventilation. It has been observed among non-COVID-19 AHRF patients on HFNO for an extended period that they suffer the worst outcome when they ultimately fail HFNO and get IMV.[4] Similar data have emerged from CAHRF patients treated with prolonged HFNO and NIV.[5] Thus, the timing of intubation in this patient population has become a subject of active research. Studies looking at the timing of intubation in patients on non-invasive respiratory support (NIRS) and outcome have defined 'early' and 'delayed' intubation with a variable cut-off period which was selected arbitrarily or based on previous studies in this field.[6-12] We have conducted a systematic observation and time series analysis of the outcome of patients who got intubated during the HFNO trial before IMV without defining a definite cut-off of early vs delayed intubation, thereby addressing a knowledge gap in this area. We would form the accrued data of the time period after which intubated patients' mortality starts increasing; and analyze the subgroup of these patients before and after this period. The hypothesis was to demonstrate a difference in clinical outcome based on the duration of HFNO before intubation in CAHRF patients requiring IMV.

METHODS

This study was approved by the institutional ethical committee, and informed consent was waived due to the observational nature of the study (AMRI-EC/AP-72/2021-22).

This observational study was conducted at intensivist-led 30-bedded dedicated COVID ICU of a 250-bedded tertiary care teaching hospital from July 2020 to August 2021. This was a retrospective analysis of prospectively collected data. Data was collected for all consecutive patients admitted to the ICU with a confirmed diagnosis of COVID-19 by RT-PCR during the study period. We included all consecutive patients who required HFNO and subsequently received IMV following the failure of the HFNO trial during the study period. The decision to intubate was taken in consultation with the senior intensivist. Senior intensivists decided to intubate predominantly based on trends of five parameters: SpO2, respiratory rate, PF ratio, work of breathing and flow rate on HFNO. We excluded patients who did not require HFNO during their ICU stay or required HFNO only after IMV or who did not require IMV after HFNO, or who required HFNO and IMV multiple times. We also excluded patients requiring NIV before or after IMV to maintain the homogeneity of the sample. We also excluded patients in whom life support was withdrawn at the family's request and patients who were taken discharge against medical advice [Figure 1]. We used Fisher and Paykel Airvo™ HFNO device for all patients. The data collected in patients who met inclusion criteria were age, gender, APACHE IV, co-morbidities, days on HFNO prior to IMV, mortality outcome of IMV after HFNO failure, ICU length of stay and hospital length of stay. The sample included patients with malignancy (not terminal malignancy) who had predicted survival of at least 5 years. The data were collected by ICU data entry operators who were not part of the treating team. A time series analysis of mortality for each day of HFNO application prior to IMV was calculated. The primary outcome was to detect any difference in mortality of CAHRF patients depending upon the duration of HFNO before intubation.

The data are expressed as mean ± standard deviation (SD) or numbers. Categorical and continuous variables were analysed using the Chi-square test and independent sample *t*-test, respectively. The odds ratio for mortality and ICU and hospital length of stay were calculated by logistic regression analyses adjusting with the severity of illness. All statistical analyses were done in SPSSv22, and a two-tailed *P* value of <0.05 was considered significant.

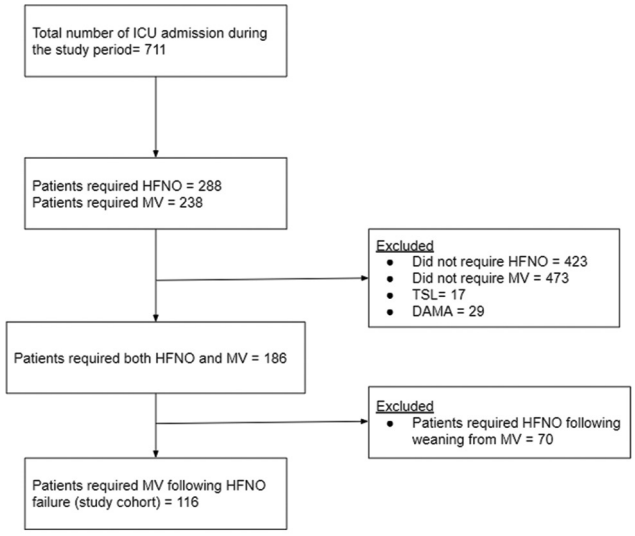

Figure 1: Study flowchart

RESULTS

The total number of COVID-19 patients admitted to the ICU during the study period was 711, out of which 288 patients required HFNO and 238 patients required mechanical ventilation. The total number of patients on HFNO who were subsequently ventilated was 116 [Figure 1].

The demographics and study parameters are summarised in Tables 1 and 2.

Most of the patients who got tracheally intubated were found to be clustered on day 1 of HFNO application (n = 48; 41.37%) [Figure 2]. There was only minor variability in crude and risk-adjusted mortality in patients who got ventilated from day 1 to day 4 of HFNO application [Figures 2 and 3, Table 3]. Beyond day 4 of HFNO application, there was a trend towards increased crude and risk-adjusted ICU and hospital mortality for each day of delay in intubation [Figures 2 and 3]. The odds ratio of increased mortality was 2.718 times after day four as compared to before [Table 4]. This trend was maintained till day 8 of HFNO application, after which the mortality reached 100% [Figures 2 and 3].

Table 1: Demographics of the study cohort

Parameters	Frequencies
Age	64.13±12.83
Male	74 (63.8%)
Female	42 (36.2%)
Co-morbidity	
Hypertension	64 (55.17%)
Diabetes	50 (43.10%)
COPD/Asthma	13 (11.2%)
Malignancy/Immunocompromised	14 (12.06%)
IHD	20 (17.24%)
APACHE IV	67.25±27.89

We further divided the study cohort into two groups called 'early' and 'late HFNO failure group' or 'early' and 'late intubation group', using day 4 as a cut-off timeline of HFNO application [Table 2]. Absolute crude mortality was lower by 15% in the early HFNO failure group (63.6% vs 78.6%) despite severity scores like APACHE-IV being higher in the early HFNO failure group [Table 2]. Risk-adjusted regression analysis showed delaying IMV beyond the 4th day of the HFNO trial is associated with an increased risk of mortality [OR 2.718; 95% CI 0.957-7.721; *P* 0.085] [Table 4]. Cox regression analysis [Figure 4] revealed that hazard increases as the days on HFNO increase.

ICU length of stay and hospital length of stay is higher in the late group [Table 2]. But, when subgroup analysis for survivors was done, no statistically significant difference was observed with respect to ICU length of stay, hospital length of stay and even ventilator days between the early and late HFNO failure group [Table 5]. Non-survivors had higher days on ventilation than survivors, though statistically insignificant [Table 6].

DISCUSSION

In this study, we observed that CAHRF patients who

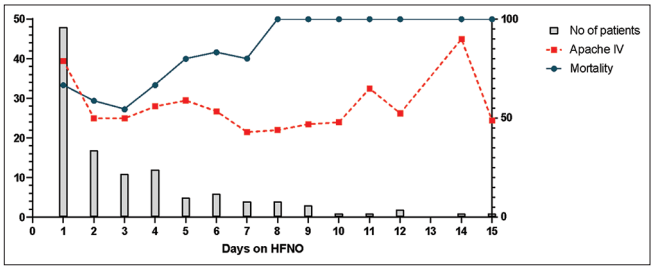

Figure 2: Number of patients getting intubated post HFNO failure, APACHE-IV on admission and crude mortality with respect to days on HFNO

Table 2: Outcome analysis using cut-off 4 days

Variables	Total *n*=116	Early HFNO failure (≤4 days) *n*=88; 75.9%	Late HFNO failure (>4 days) *n*=28; 24.1%	*P*
Age (years)	64.13±12.83	63.39±13.84	65.55±10.68	0.392
Male *n* (%)	74 (63.8)	61 (65.6)	13 (56.5)	0.282
Female *n* (%)	42 (36.2)	32 (34.4)	10 (43.5)	
Hypertension *n* (%)	64 (55.17)	50 (56.81)	28 (50)	0.314
Diabetes *n* (%)	50 (43.10)	35 (39.77)	15 (53.57)	0.228
APACHE IV	67.25±27.89	73.09±29.93	56.15±19.47	0.002*
ICU mortality *n* (%)	78 (67.2)	56 (63.6)	22 (78.6)	0.108
Hospital mortality *n* (%)	78 (67.2)	48 (63.2)	30 (75)	0.139
No. of days on ventilation	10.59±9.72	10.30±9.69	11.50±9.95	0.574
ICU length of stay (Day)	16.07±11.42	14.02±10.90	19.97±11.50	0.007*
Hospital length of stay (Day)	19.06±11.61	17.06±11.44	22.87±11.10	0.010*

ICU-Intensive care unit, APACHE - Acute physiology and chronic health evaluation

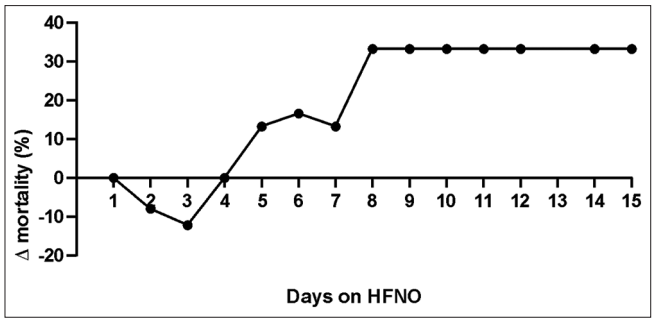

Figure 3: Variation of crude mortality with days on HFNO trial

Table 3: Comparison of risk-adjusted mortality among the first 3 days

Variables	Risk-adjusted OR	95% CI	*P*
Day 1 vs day 2	1.181	0.329-4.233	0.799
Day 2 vs day 3	0.869	0.185-4.084	0.858
Day 1 vs day 3	1.005	0.231-4.367	0.994

OR - Odds Ratio, CI - Confidence interval

Table 4: Risk-adjusted mortality odds ratio taking a cut-off 2 days, 3 days, 4 days

Variables	Risk-adjusted OR	95% CI	*P*
Mortality (cut-off 1 day)	1.555	0.616-3.933	0.350
Mortality (cut-off 2 days)	1.738	0.738-4.091	0.206
Mortality (cut-off 3 days)	2.198	0.896-5.392	0.085
Mortality (cut-off 4 days)	2.718	0.957-7.721	0.061

OR - Odds Ratio, CI - Confidence interval

needed IMV after the 4th day of HFNO application had higher mortality than those requiring IMV before that; none of our patients survived who got intubated after the 8th day of HFNO application. The ICU mortality of our entire study cohort of ventilated patients was 67.2%, which is similar (68.7%) to other study populations reported from Indian ICUs[6] but higher than that reported from the west (26%).[13] Previous studies have addressed a similar advantage of early intubation both in CAHRF and non-COVID-19 AHRF patients on HFNO, but the time period of intubation varied from 24 to 48 hours.[6-12] The advantages of HFNO in AHRF are a decrease in work of breathing, proper humidification of inhaled gases, possibility of prone positioning while on this device, decrease in anatomical dead space and generation of positive airway pressure. On the other hand, this can lead to a false sense of security among clinicians, because of which some clinicians might use HFNO for an unnecessarily prolonged period to avoid intubation and IMV. But previous studies have shown that those patients who fail lengthy HFNO application and ultimately land up in IMV have high mortality.[4,5] Prolong HFNO trial increases the duration of spontaneous respiration in AHRF patients, which

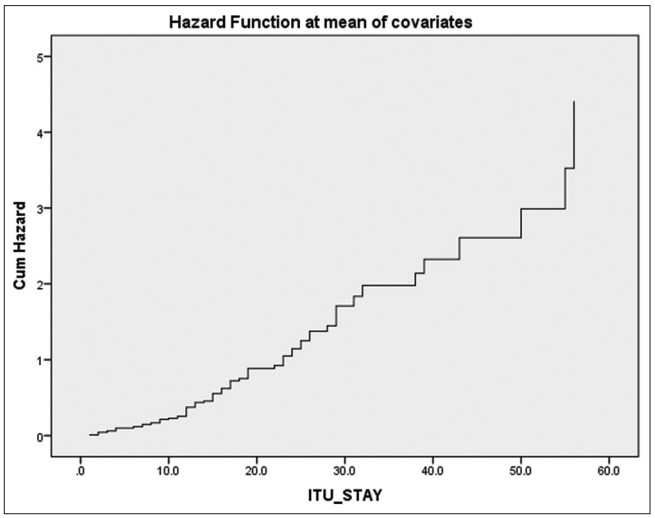

Figure 4: Cox regression analysis

amplifies the lung damage by perpetuating the process called patient's self-inflicting lung injury (P-SILI), where increased negative intrapleural pressure due to increased work of breathing creates an unduly high transpulmonary pressure resulting in increased stress and strain in an already injured COVID lung.[14] In conjunction with increased respiratory rate, this phenomenon further damages the COVID-19 lung by a process called 'Ergo trauma', typically described in patients with IMV.[15] This leads to a poorer outcome when patients are intubated late during HFNO application. We conducted a time series analysis of patients on HFNO who failed and required IMV as opposed to many previous studies, which have an arbitrary cut-off of 24 to 48 hours and analysed patient outcomes before and after that period. Late intubation or late HFNO failure in our study cohort could be defined as intubation after four days of HFNO trial as the mortality started increasing after this time period. This period was variably reported in previous studies from 24 to 48 hours.[6-12]

Furthermore, an increase in mortality in CAHRF patients requiring IMV after the 4th day and no survival after the 8th day of HFNO application was a distinctive finding from our study which has not been described previously.

In this study, overall ICU and in-hospital mortality is 67.2%, comparable to a recent study from western India, which reported an ICU mortality of 68.7% in a cohort of 147 severe COVID-19 patients requiring invasive mechanical ventilation.[5] The strength of our study is the time period analysis of HFNO failure and outcome without considering an arbitrary

Table 5: Subgroup analysis of survivors (*n*=38; 32.75% of the study cohort)			
Parameters	**Early HFNO failure (≤4 days) (*n*=32; 84.2%)**	**Late HFNO failure (>4 days) (*n*=6; 15.8%)**	***P***
Number of days on ventilation	8.37±6.72	6.66±3.66	0.552
ICU length of stay (days)	12.90±7.23	16.16±8.03	0.099
Hospital length of stay (days)	19.09±8.73	20.33±9.41	0.326

ICU-Intensive care unit

Table 6: Comparison of the number of days on ventilation between survivors and non-survivors			
Parameters	**Survivors (*n*=38; 32.75%)**	**Non-survivors (*n*=78; 67.25%)**	***P***
Number of days on ventilation	8.10±6.33	11.80±10.83	0.054

cut-off period to define early and late intubation, a reasonable sample size during the early days of HFNO failure and an exclusive intensive care population. Being a single-centre study, the homogeneity of caregivers during the study period ensures a uniform protocol for intubating an HFNC failure patient. On the other hand, the limitation of our study is a reduction in sample size in later days of HFNO application, exclusion of patients on other NIRS like NIV and not using ROX index for intubation. ROX index is a predictor of HFNO failure in non-COVID AHRF patients. But it was not validated in CAHRF patients on HFNO when the study was initiated. Two meta-analyses revealed that its prediction efficacy is moderate, and the cut-off varies from 2.7 to 9.2. Moreover, it is not applicable beyond 12 hours of HFNO application due to its declining prediction efficacy.[16,17]

CONCLUSION

COVID-19 AHRF patients requiring IMV beyond the 4th day of HFNO application had higher mortality. An absolute mortality benefit of 15% was observed when IMV was initiated in the first four days of HFNO application. Patients getting intubated after the 8th day of HFNO application had 100% mortality.

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Conflicts of interest

There are no conflicts of interest.

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