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(Citation)
The Kobe journal of the medical sciences,69(1):33-39

(Issue Date)
2023

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

(JaLCDOI)
https://doi.org/10.24546/0100482088

(URL)
https://hdl.handle.net/20.500.14094/0100482088

Kobe J. Med. Sci., Vol. 69, No. 1, pp. E33-E39, 2023

In-hospital Mortality among Patients with High-flow Nasal Cannulas in the General Ward

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Received January 12, 2023/Accepted March 23, 2023

Keywords: High flow nasal cannula, ROX index, In-hospital mortality, Quality of life

High-flow nasal cannulas (HFNCs) have become common devices for patients with respiratory failure who are treated in general wards. Few reports have been published on in-hospital mortality associated with the ratio of oxygen saturation (ROX) index, measured by pulse oximetry/fraction of inspired oxygen to respiratory rate, in patients treated with HFNCs. We aimed to examine in-hospital mortality and associated factors in patients who initiated HFNC use in a general ward. Sixty patients who initiated HFNC use in general wards at Kobe University Hospital between December 2016 and October 2020 were retrospectively enrolled. We assessed in-hospital mortality, comorbidities, and ROX index. The in-hospital mortality was 48.3%, and ROX index values were significantly lower in patients who died than in those who did not (at HFNC oxygen therapy initiation; 6.93 [2.73–18.5] vs. 9.01 [4.62–18.1], p = 0.00861). Although the difference was not statistically significant, the change in ROX index values between HFNC initiation and 12 hours after initiation tended to be greater in the patients who died in the hospital (0.732 [−2.84–3.5] vs. −0.35[−4.3–2.6], p = 0.0536). Lower ROX index values may be associated with the in-hospital death of patients who are treated with HFNCs in general wards.

INTRODUCTION

A high-flow nasal cannula (HFNC) is a device used for oxygen therapy in which a high flow of heated and humidified air/oxygen blends through a nasal cannula and delivers gas (1). HFNC oxygen therapy can reduce respiratory dead space by removing nasopharyngeal carbon dioxide (CO_2) (2, 3) and decreasing respiratory effort (4). Humidification improves mucociliary clearance and reduces discomfort associated with dry conditions (5–7). Moreover, HFNC oxygen therapy has advantages that improve the quality of life (QOL), such as enabling oral intake and conversation (8). Randomized controlled trials have reported that the mortality rate in patients treated with HFNC oxygen therapy in the intensive care unit (ICU) was lower than that with non-invasive ventilation (NIV) (9). Roca et al. reported that in ICU patients with acute respiratory failure who were treated with HFNC oxygen therapy, the ROX index (defined as the ratio of oxygen saturation as measured by pulse oximetry [SpO_2]/fraction of inspired oxygen [FiO_2] to a respiratory rate value greater than or equal to 4.88) was consistently associated with a lower risk of intubation (10). The ROX index can be easily and quickly evaluated in hospital general wards as an indicator of the need for intubation in patients with respiratory failure.

HFNCs have also become common devices used in general wards by patients who have a do-not-intubate (DNI) order, cannot tolerate NIV, and/or need palliative care. Reports have been published on the rate of escalation from HFNC to ventilators in general wards (11, 12), and the effect of HFNCs on the reduction in respiratory rate (13). Limited data exist regarding the association between the ROX index and HFNC treatment success in general wards (14). However, a poor prognosis is predicted for patients using HFNCs in general wards due to their severe respiratory status. Few studies have reported on the association between the ROX index and in-hospital mortality of patients who are treated with HFNCs in general wards. In addition, only a few studies have reported on the association between comorbidities and in-hospital mortality. In this study, we examined the in-hospital mortality and risk factors associated with the in-hospital death of patients who were treated with HFNCs in a general ward.

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MATERIALS AND METHODS

Study design

This single-center, retrospective, and observational study assessed the in-hospital mortality of patients treated with HFNC oxygen therapy in general wards. The study included patients in the general wards of Kobe University Hospital departments between December 2016 and October 2020, who were clinically diagnosed as requiring HFNC oxygen therapy for respiratory failure. Specifically, SpO_2, respiratory rate, or forced respiration did not improve with a nasal cannula or mask in these patients. If respiratory failure worsened and the patients did not have DNI orders, they were escalated to NIV or invasive mechanical ventilation (IMV). Patients with severe vital signs or requiring intubation were transferred to the ICU. Pediatric and postoperative patients requiring HFNC were excluded from the study. We used the opt-out method, which meant that participants were included in the study unless they refused to participate after being notified of the study content via the hospital website. The study was approved on December 28, 2021 by the Institutional Ethics Committee of Kobe University Hospital (approval no. B210243). This study conformed to the Declaration of Helsinki. The HFNCs were prepared by Fisher and Paykel Healthcare (Auckland, New Zealand).

Data collection

Demographics including age, sex, comorbidities, and DNI orders at the initiation of HFNC oxygen therapy were collected. HFNC-related data included initial oxygen flow rates of HFNC, ROX index values (calculated from FiO_2, SpO_2, and respiratory rate at HFNC oxygen therapy initiation and at 12 hours [8–12 hours allowed] after initiation), escalation to IMV or NIV, and discontinuation based on patient intolerability. Clinical outcomes, such as in-hospital death, discharge to home, duration of HFNC use, length of hospital stay, ICU transfer, and home oxygen therapy (HOT) at discharge were recorded. The length of hospital stay was measured from the date of HFNC oxygen therapy initiation to the date of discharge or death. The primary endpoint was in-hospital mortality among patients who received HFNC in a general ward. The secondary endpoints were the rate of transfer to the ICU and escalation to IMV or NIV, ROX index, comorbidities, oral intake, and conversation.

Statistical analysis

Quantitative variables are expressed as the mean ± standard deviation (SD) or median (range). Categorical variables are described as frequencies and percentages. The nonparametric Mann-Whitney U test was used to analyze continuous variables, and Fisher's exact test was used for categorical variables. Continuous variables were compared using two-sample t-tests. The Wilcoxon rank-sum test was used to compare the ROX index values at HFNC oxygen therapy initiation and 12 h after initiation. Receiver operating characteristic (ROC) curve analysis was performed to determine the sensitivity and specificity of the ROX index in predicting in-hospital death. The cutoff ROX index value for predicting in-hospital mortality was also calculated. Logistic regression was used for multivariate analysis to compute the odds ratios (ORs) and 95% confidence intervals (CIs). In all tests, two-tailed p values of <0.05 were considered statistically significant. All statistical analyses were performed using EZR, version 1.51 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (15).

RESULTS

Patient characteristics

Sixty patients in the general ward received HFNC oxygen therapy for respiratory failure. The baseline characteristics are summarized in Table I.

Table I. Patient characteristics

	All n = 60	In-hospital death n = 29	Alive n = 31	p value
Age (years of age, median [range])	74 (45–92)	73 (49–87)	74 (45–92)	0.894
Male	42 (70.0%)	23 (79.3%)	19 (61.3%)	0.164
Home oxygen therapy before admission	11 (18.3%)	5 (17.2%)	6 (19.4%)	1
Body Mass Index (mean ± SD)	20.9 ± 3.22	21.2 ± 2.91	20.6 ± 3.52	0.474
With a Do-not-intubate order	39 (65%)	22 (75.9%)	17 (54.8%)	0.109
Oxygen flow before HFNC initiation (L/min, median [range])	8.5 (1–15)	9.5 (2–15)	7.5 (1–15)	0.133
Gas flow at HFNC initiation (L/min median [range])	40 (30–60)	40 (30–60)	40 (30–50)	0.682
FiO_2 at HFNC initiation (median [range])	0.5 (0.25–1)	0.6 (0.3–1)	0.5 (0.25–1)	0.0235
Comorbidities				
Interstitial lung disease	35 (58.3%)	21 (72.4%)	14 (45.2%)	0.0396
Lung cancer	18 (30%)	11 (37.9%)	7 (22.6%)	0.262
COPD	10 (16.7%)	3 (10.3%)	7 (22.6%)	0.302
Heart failure	15 (25%)	8 (27.6%)	7 (22.6%)	0.769
Duration of HFNC (days, median [range])	6 (1–40)	6 (1–40)	6 (2–14)	0.085
Length of hospital stay (days, median [range])	21 (1–92)	12 (1–92)	28 (3–90)	<0.01

Abbreviations: SD, standard deviation; HFNC, high-flow nasal cannula; COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen. Each parameter is expressed as the number (percentage) of patients, median (range), or mean ± standard deviation.

The median (range) age in the study was 74 (45–92) years, 42 males were included (70%), the mean BMI was 20.9 ± 3.2, the median (range) oxygen flow before HFNC oxygen therapy initiation was 8.5 (1–15) L/min, 4 (6.7%) patients initiated HFNC following NIV use in the general ward, and 39 (65.0%) patients had DNI orders. Interstitial lung disease (ILD) was the most common comorbidity. The median (range) gas flow at HFNC oxygen therapy initiation was 40 (30–60) L/min, and the median (range) FiO_2 at HFNC oxygen therapy initiation was 0.50 (0.25–1.0). The median (range) duration of HFNC use was 6 (1–40) days and the median (range) length of hospital stay was 21 (1–92) days.

In-hospital mortality

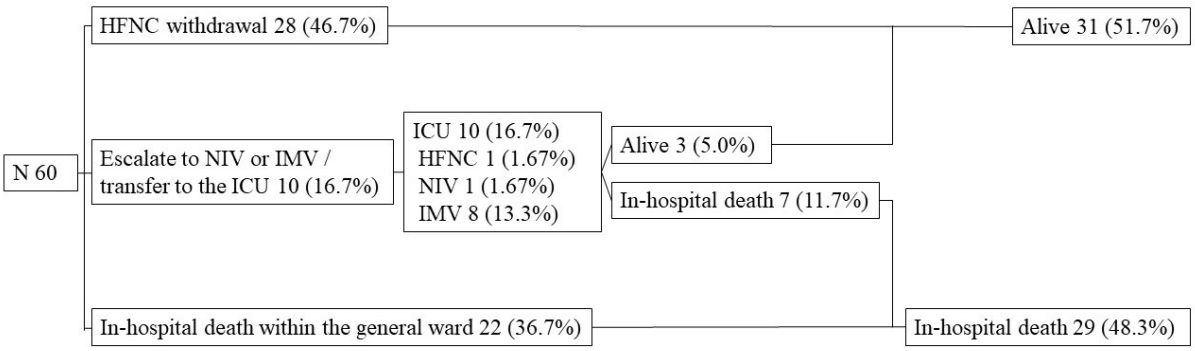

Figure 1. Outcomes of patients using HFNC.
Abbreviations: HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; IMV, invasive mechanical ventilation; ICU, intensive care unit. Each parameter is expressed as the number (percentage) of patients.

The outcomes of patients using HFNCs are shown in Figure 1. The overall in-hospital death was 29 (48.3%). Twenty-eight patients (46.7%) withdrew from HFNC. Ten (16.7% of all patients and 47.6% of patients without DNI orders) were transferred to the ICU, eight (13.3% of all patients and 38.1% of patients without DNI orders) were escalated to IMV, and one patient was escalated to NIV. Among the 10 patients who were transferred to the ICU, seven (11.7% of all patients and 33.3% of patients without DNI orders) died in the hospital. Twenty-two patients (36.7 %) in the general ward died in the hospital. Of 31 patients who survived, 14 (23.3%) were discharged. Only one patient discontinued HFNC because of nose discomfort. That patient required 4–7 L/min of oxygen instead of HFNC, and was transferred to a long-term chronic care hospital. Eighteen (36.7%) of the 49 patients without HOT before admission required oxygen therapy when they were discharged or transferred to long-term chronic care hospitals, and six (12.2%) patients were discharged without HOT.

Association between ROX index and in-hospital death

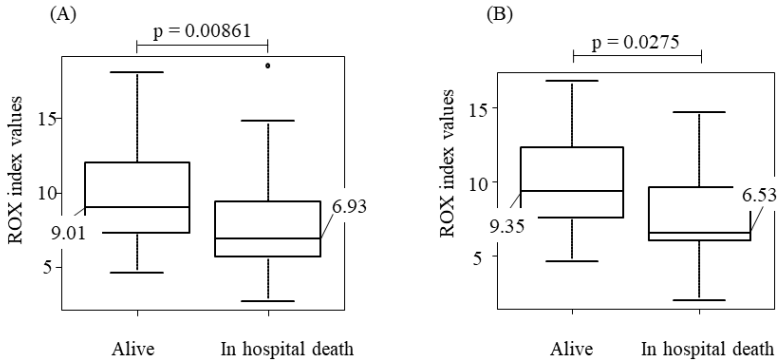

Figure 2. ROX index values at HFNC oxygen therapy initiation (A) and at 12 hours after HFNC oxygen therapy initiation (B). Abbreviations: ROX index, an index combining respiratory rate and oxygenation; HFNC, high-flow nasal cannula.
P values were calculated using the Mann-Whitney U test. A p value <0.05 was considered significant.

As shown in Figure 2, ROX index values at HFNC therapy initiation and 12 hours after initiation were significantly lower in patients who died in the hospital than in those who were discharged alive (at HFNC oxygen therapy initiation: 6.93 [2.73–18.5] vs. 9.01 [4.62–18.1], p = 0.00861; and 12 hours after HFNC oxygen therapy initiation: 6.53 [1.98–14.7] vs. 9.35 [4.62–16.8], p = 0.0275). Among the patients who were discharged, the ROX index values significantly increased 12 h after HFNC oxygen therapy initiation (p = 0.0464). Although the difference was not statistically significant, the change in patient ROX index values from therapy initiation to 12 h after initiation in patients who remained alive tended to be greater than that in patients who died in the hospital (0.732 [−2.84–3.5] vs. −0.35[−4.3–2.6] p = 0.0536) (Figure 3).

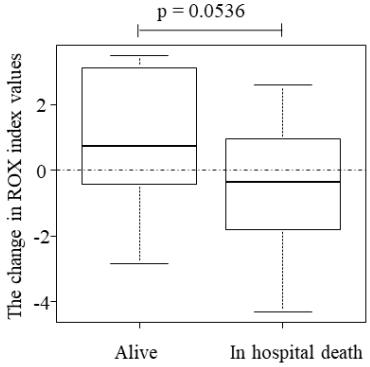

Figure 3. The change in ROX index values between HFNC oxygen therapy initiation and after 12 hours.
Abbreviations: ROX index, an index combining respiratory rate and oxygenation; HFNC, high-flow nasal cannula. P values were calculated using the Mann-Whitney U test. A p value <0.05 was considered significant.

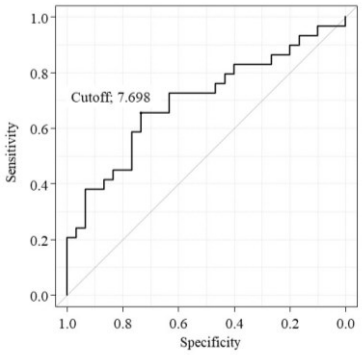

Figure 4. The ROC curve of ROX index values at HFNC oxygen therapy initiation used to predict in-hospital death. Abbreviations: ROC, receiver operating characteristic; ROX, index combining respiratory rate and oxygenation; HFNC, high-flow nasal cannula.

The cutoff ROX index value (calculated from the ROC curve analysis of the relationship between the ROX index at HFNC oxygen therapy initiation and in-hospital death) used to predict in-hospital death was 7.698 (sensitivity, 0.733; specificity, 0.655; area under the curve [AUC], 0.698; 95% confidence interval [CI], 0.561 to 0.835) (Figure 4).

Analysis of ILD patients and multivariable analysis

Next, we evaluated other associated factors. Table I shows a comparison of the characteristics between patients who died in the hospital and those who remained alive.

Significantly more patients with ILD died in the hospital than those without ILD (21 of 35 [60.0%] patients with ILD vs. 8 of 25 [32.0%] patients without ILD; p = 0.0396). Fifteen of the 24 (62.5%) patients with ILD who had DNI orders died in the hospital. Thirty of 35 (85.7%) patients initiated or increased steroids for ILD, and 17 of 30 (56.7%) patients treated with steroids for ILD died in the hospital.

However, we found no significant difference between patients with or without ILD in ROX index values at HFNC oxygen therapy initiation (7.81 [3.59–18.1] vs. 8.62 [2.73–18.5], p = 0.403).

Table II. Multivariable analysis of in-hospital mortality

	Odds ratio (95% CI)	p value
ROX index values at HFNC oxygen therapy initiation	0.848 (0.711–1.01)	0.0651
Interstitial lung disease	2.770 (0.874–8.75)	0.0834
DNI order	1.940 (0.575–6.55)	0.285

Abbreviations: ROX, index combining respiratory rate and oxygenation; HFNC, high-flow nasal cannula; DNI, do-not-intubate; CI, Confidence interval. A p value <0.05 was considered significant.

We performed a multivariate analysis of in-hospital mortality by incorporating the ROX index at HFNC oxygen therapy initiation, ILD, and DNI. Although the difference was not statistically significant, the ROX index tended to be associated with a decreased odds ratio (0.884 [0.711–1.01], p = 0.0651). Similarly, ILD was not significantly associated with an increased odds ratio (2.770 [0.874–8.75], p = 0.0834) (Table II).

DISCUSSION

In this retrospective study investigating the in-hospital mortality of patients who were treated for respiratory failure with HFNC oxygen therapy in general wards, we clarified the association between the ROX index and in-hospital mortality. No reports have been published to date on the association between ROX index values and in-hospital patient mortality within general wards. In this study, the ROX index values at HFNC therapy initiation and after 12 h were significantly higher in patients who did not die in the hospital. Moreover, the difference between ROX index values at HFNC therapy initiation and after 12 h tended to be greater in patients who died. This result was similar to that reported in a previous study showing a smaller increase in the ROX index over 12 h in patients who required IMV (10). Considering these results, the ROX index may be a useful predictor of in-hospital death in patients who are treated with HFNC oxygen therapy in general wards. Zemach et al. reported that higher ROX index values were associated with an improved rate of successful treatment outside the ICU (ROX index: success, 8.2 ± 3.6 vs. failure, 5.1 ± 1.9, p < 0.001). In that study, the rate of successful treatment in patients

without DNIs was 50% (14). Successful treatment was defined as the absence of intubation, ICU admission, or hospital discharge. In our study, the no-intubation rate and ICU admission was 52.4%; however, the no-intubation rate, ICU admission, and hospital discharge rate was 28.6%. This finding might be related to the backgrounds of the patients included in this study.

In previous reports, 35–44% of patients, including those receiving palliative care, died in the hospital, and 43–45% were discharged from the general ward and ICU (11, 16). Among patients with DNI orders, 78–93% of the patients died in the hospital (8, 11, 14) and 13% were discharged (11). In our study, in-hospital mortality, with or without DNI orders, was similar to that in the previous studies (11, 16), but fewer patients were discharged. The lower number of discharged patients in our study might have resulted from the exclusion of postoperative patients.

The in-hospital mortality of patients with DNIs who were treated with HFNC for respiratory failure associated with ILD was 62.5% in this study and 79.6 % in previous reports (8). Although ILD was associated with in-hospital death, in this study we found no significant difference between patients with or without ILD in ROX index values at HFNC therapy initiation. This finding could indicate that more patients with ILD die not because of poor respiratory status at HFNC therapy initiation, but because of poor response to treatment for ILD (17–19).

This study had several limitations. The design was a single-center retrospective study with some data limitations. Additionally, the study lacked a cost-effectiveness analysis. Future studies on patient characteristics associated with better clinical outcomes, cost-effectiveness, and QOL are warranted.

A lower ROX index may be associated with the in-hospital mortality of patients who are treated with HFNC therapy in general wards.

ACKNOWLEDGMENTS

The authors thank all patients and medical staff who contributed to this study.

CONFLICTS OF INTEREST

MT received funding from Teijin Pharma Ltd., Tokyo, Japan. The authors declare no conflicts of interest.

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