Risk Factors for Non-invasive Ventilation Failure in Influenza Infection with Acute Respiratory Failure in Emergency Department

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Research

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Abstract

Background

Non-invasive ventilation (NIV) has been widely used in hypoxemic acute respiratory failure (ARF) due to influenza pneumonia in emergency department (ED). However, the benefit of NIV in decreasing intubation rate remains controversial. Previous studies have reported that prolonged use of NIV was associated with increased mortality. Our study aims to identify risk factors for NIV failure in influenza infection with acute respiratory failure in ED.

Method

We perform a retrospective cohort observational study. Enrolled patients older than 18 years who used NIV due to influenza infection with ARF between 1 January 2017 to 31 December 2018 in Ramathibodi Emergency Department. Patients characteristics, comorbidity, clinical and laboratory outcome, chest imaging, NIV setting and parameter were recorded. We follow the outcome success or failure of the NIV used.

Results

162 patients were enrolled, 72 (44%) suffered NIV failure in influenza infection with ARF. We used univariate and multivariate logistic analyses to assess risk factors for NIV failure. The ability of risk factor to predict NIV failure was analyzed using the area under the receiver operating characteristic (AUROC). Risk factors of NIV failure included sequential organ failure assessment (SOFA) score (P = 0.001), PaO2/FiO2 (PF) ratio (P = 0.001) and quadrant infiltrations in chest x-rays (CXR) (P = 0.001). SOFA score, PF ratio and number quadrant infiltrations in chest radiography have good ability to predict NIV failure, AUROC 0.894 (0.839 - 0.948), 0.828 (0.764 - 0.892) and 0.792 (0.721 – 0.863), respectively and no significant difference in the ability to predict NIV failure between three parameters. Use of PF ratio plus number quadrant infiltrations in chest radiography demonstrated higher predictive ability for NIV failure in influenza infection with ARF.

Conclusions

SOFA score, PF ratio and quadrant infiltrations in chest radiography were good predictors of NIV failure in influenza infection with ARF.

Background

Influenza infection is a course of acute respiratory failure (ARF). In patients with acute respiratory failure due to influenza infection admitted to intensive care unit (ICU), the intubation rate is high (60%) and mortality rate after intubation of up to 50% (1–4).

Use of non-invasive mechanical ventilator (NIV) has proved effective in chronic obstructive pulmonary disease (COPD) and acute decompensated heart failure (5, 6). In these patients, NIV has achieved reduction in endotracheal intubation rate, ventilator-association pneumonia and mortality rate. NIV is widely used in several clinical settings, nevertheless the benefit of NIV use in patients with hypoxemic ARF remain controversial (7–9). The effectiveness of NIV use in ARF due to viral pneumonia is controversial and has a high failure rate compared with other causes of ARF. In previous studies, unsuccessful NIV use was found a risk of increased mortality and a complication in patients with ARF (10, 11). Therefore, selecting patients with ARF due to influenza infection that might benefit from NIV use is challenging.

Risk factors are important for physicians to closely monitor if switching to invasive mechanical ventilation is necessary. The aim of this study was to identify risk factors associated NIV failure in ARF due to influenza infection in ED.

Methods

Design and Setting

This retrospective cohort observational study was conducted at Ramathibodi hospital, a tertiary care and university hospital in Bangkok, Thailand, and was approved by the Ethics Committee of Ramathibodi hospital, Mahidol University. The trial was registered in Thai Clinical Trial Registry identifier TCTR 20200506005

Populations

Patients who visited the Ramathibodi Emergency Department with influenza infection from 1 January 2017 to 31 December 2018 were determined with database software (RAMAEMR) and recruited.

Inclusion Criteria and exclusion Criteria

The inclusion criteria included: 1) patients older than 18 years who visited the Ramathibodi emergency department 2) patients receiving NIV due to influenza infection with ARF. The exclusion criteria included: 1) patients and family members who signed do-not-attempt-resuscitation orders. 2) patients who were transferred to other hospitals. 3) patients who were transferred in and had received medical treatment by another hospital prior to emergency department arrival. 4) patients with missing data

Definitions

Influenza infection was defined by laboratory confirmed detection of influenza A and B from nasopharyngeal swab rapid antigen test or PCR test. Acute respiratory failure (ARF) was defined by: (1) respiratory rate $\geq$ 25 breaths per minute with accessory muscle use and pulse oximetry $\leq$ 90% at room air or (2) partial arterial oxygen $\leq$ 60 mmHg at room air or PF ratio $\leq$ 300 mmHg with PEEP $\geq$ 5 cmH_20 or

partial arterial carbon dioxide ≥ 50 mmHg at room air. NIV failure was defined by patients switching from NIV to endotracheal intubation in the first 48 hours.

Data collection and clinical endpoints

Patients who met the inclusion criteria and excluded by exclusion criteria were included in this study. All patients were evaluated by emergency medicine residents, emergency medical staff and internal medicine residents. Patient demographic information, vital signs (systolic blood pressure, respiratory rate), oxygen saturation at triage, SOFA score, APACHE score, PF ratio, arterial blood gas (pH, PaCO2, HCO3, lactate level), NIV setting (mode, initial inspire pressure, PEEP), NIV parameter (Expire tidal volume) and quadrant infiltration in chest radiography were recorded. Data record forms entered in database software (RAMA-EMR) were used. Research was done on all patients who used NIV due to influenza infection with ARF for data collection.

Clinical endpoint was success or failure of the NIV used in the first 24 hours. This study aimed to identify risk factors associated NIV failure in ARF due to influenza infection in ED.

Sample sizes and Statistical Analyses

To evaluate the outcome, patients were divided into 2 groups: (1) those with NIV failure and (2) those who used NIV successfully.

Sample size calculation was aimed at analyzing predictor risks for NIV failure. From our previous hospital data on influenza infection with ARF NIV failure. Our calculation revealed that around 60 patients with influenza infection with ARF who failed NIV and 92 patients with influenza infection with ARF with successful NIV in the emergency department were required to provide an adequate sample size for this study (80% power, 5% alpha error).

Categorical variables were expressed as absolute values and percentages and continuous variables as medians and interquartile ranges (IQRs). Categorical variables were compared using the chi-squared test or with Fisher exact test when appropriate, while continuous variables were compared using the Mann–Whitney U test. The area under the receiver operating characteristic (AUROC) curve and odds ratio from logistic regression were used to assess predicting risk factor for NIV failure in influenza infection with ARF in ED. The model calibration was also assessed using the Hosmer–Lemeshow (X2) test with $P < 0.05$ suggesting imperfective calibration.

Data were recorded using Microsoft Excel 365, while Stata version 14.0 and SPSS version 18.0 were used for statistical analyses.

Results

A total of 1453 patients with confirmed influenza infection in ED over a 2-year period were initially recruited. After reviewing electronic medical records, 180 patients met inclusion criteria and 18 patients

were excluded by exclusion criteria (14 patients and family members who signed do-not-attempt-resuscitation orders and 4 patients who were transferred to other hospitals), resulting in final inclusion of 162 patients.

Among these 162 patients, there were 72 patients (44%) who failed NIV use, 64 patients (88.9%) were intubated in 24 hours, average time to intubation was 12 hours (95%CI 11-18) and 12 patients died after being intubated post NIV failure. NIV setting: all patients used BiPAP ST mode and no significant differences in tidal volume and initial PEEP. Significant differences in patient characteristics, including SOFA score, PF ratio and new quadrant infiltration in chest radiography were observed between NIV failure group and NIV success group. The patient's demographic data are show in Table 1.

Table 1 Demographics and baseline characteristics

Variable	NIV failure group (N = 72)	NIV success group (N = 90)	*P* value
Age (year), median (IQR)	79 (74-82)	77 (75-81)	0.920
Male sex, *N (%)*	34 (47.2)	32 (35.6)	0.327
Comorbidities, *N (%)*			
Hypertension	60 (83.3)	66 (73.3)	0.367
Diabetic mellitus	36 (50.0)	36 (40.0)	0.417
Chronic Obstructive Pulmonary Disease	12 (16.7)	24 (26.7)	0.262
Asthma	16 (8.3)	8 (8.9)	0.905
Coronary artery disease	34 (47.2)	34 (37.8)	0.44
Heart failure	30 (41.7)	26 (28.9)	0.26
End stage renal disease	14 (19.4)	10 (11.1)	0.319
Neuromuscular disease	2 (2.8)	12 (13.3)	0.122
Immunosuppression	12 (16.7)	4 (4.4)	0.10
Malignancy	8 (11.1)	14 (15.6)	0.537
Influenza, *N (%)*			
Influenza A	50(69.4)	54 (60.0)	
Influenza B	22 (30.6)	36 (40.0)	
Systolic blood pressure, median (IQR) mmHg	147 (137-156)	142 (135-148)	0.552
Respiratory rate, median (IQR) bpm	26 (24-28)	24 (24-26)	0.556
**SpO_2 (%), median (IQR)	93 (92-94)	92 (92-94)	0.373
***APACHE Score, median (IQR)	15 (13-16)	14 (12-15)	0.499
****SOFA Score, median (IQR)	6 (6-7)	1 (1-2)	0.001
*****PF ratio (mmHg), median (IQR)	168.7 (150-189)	270.5 (260-300)	0.001
*******PF ratio level, median (IQR)	2(2-3)	1(0-1)	0.001
Arterial blood gas			
pH, median (IQR)	7.44 (7.40-7.45)	7.43 (7.41-7.45)	0.654
$PaCO_2$, median (IQR) mmHg	36.1 (33-39)	35 (34-38)	0.271
		24 (23-25.2)	0.449

HCO_3, median (IQR) mEq/L	24.2 (22.9-254.)	1.65 (1.4-2.0)	0.918
Lactate level, median (IQR) mmol/L	1.55 (1.5-1.8)		
Number infiltrated quadrant on chest radiography, median (IQR)	2 (1-2)	1 (1-2)	0.001
Non-invasive setting			
Tidal volume (ml)	436 (430-450)	430 (430-440)	0.408
Tidal volume (ml/kg)	7.4 (6.4-8.2)	7.2 (6.2-7.9)	0.542
********Initial PEEP (cmH_2O)	8 (6-8)	8 (6-8)	0.526

**SpO_2; Oxygen saturation, ***APACHE Score; Acute Physiology and Chronic Health Evaluation Score, ****SOFA Score; Sequential Organ Failure Assessment Score, *****PF ratio; Ratio of arterial oxygen partial pressure to fractional inspired oxygen

******PF ratio level; 0 = PF ratio > 200 mmHg with non-PEEP, 1 = PF ratio ≤ 200 mmHg with non-PEEP or ≤ 300 mmHg with PEEP ≥ 5 cmH_2O, 2 = PF ratio ≤ 100 mmHg with non-PEEP or ≤ 200 mmHg with PEEP ≥ 5 cmH_2O, 3 = PF ratio ≤100 mmHg with PEEP ≥ 5 cmH_2O

********PEEP; Positive end-expiratory pressure

Predicting performance of risk factor for NIV failure in influenza infection with ARF

NIV failure group had lower PF ratio than NIV success group (168.7 vs 317.5; *P* = 0.001), higher SOFA score (6 vs 1; *P* = 0.001) and higher number infiltrated quadrant on chest radiography (2 vs 1; *P* = 0.001). Univariate analysis found SOFA score (OR = 2.275, 95% CI 1.809-2.861, *P* = 0.001), PF ratio level (OR = 6.385, 95% CI 3.649 – 11.172, p = 0.001) and number infiltrated quadrant on chest radiography (OR = 5.614, 95% CI 3.124 – 10.089, *P* = 0.001) as dependent risk factors for NIV failure (Table 2).

Multivariate analysis model identified SOFA score (OR = 2.163, 95% CI 1.577 – 2.968, *P* = 0.001) and number infiltrated quadrant on chest radiography (OR = 6.487, 95% CI 2.692 – 15.627, *P* = 0.001) as independent factors associated with NIV failure in influenza infection with ARF (Table 2).

Table 2. Univariate and multivariate analyses of NIV failure in influenza infection with ARF.

Factor analysis	***OR	*P* value	****aOR	*P* value
*SOFA score	2.275 (1.809-2.861)	0.001	2.163 (1.577 – 2.968)	0.001
**PF ratio level	6.385 (3.649 – 11.172)	0.001	2.053 (0.990 – 4.635)	0.083
Number infiltrated quadrant on chest radiography	5.614 (3.124 – 10.089)	0.001	6.487 (2.692 – 15.627)	0.001

***OR; odds ratio

****aOR; adjusted odds ratio; adjusted for neuromuscular disease patients, immunosuppression patients, SOFA score, PF ratio level, number infiltrated quadrant on chest radiography, tidal volume and initial PEEP.

*SOFA Score; Sequential Organ Failure Assessment Score

**PF ratio level; 0 = PF ratio > 200 mmHg with non-PEEP, 1 = PF ratio ≤ 200 mmHg with non-PEEP or ≤ 300 mmHg with PEEP ≥ 5 cmH_2O, 2 = PF ratio ≤ 100 mmHg with non-PEEP or ≤ 200 mmHg with PEEP ≥ 5 cmH_2O, 3 = PF ratio ≤100 mmHg with PEEP ≥ 5 cmH_2O

Hosmer–Lemeshow (X2) test was *P* value of 0.758.

SOFA score, PF ratio level and number infiltrated quadrant on chest radiography provided good ability to predict NIV failure in influenza infection with ARF by AUROC 0.894 (95% CI 0.839 - 0.948), 0.828 (95% CI 0.764 - 0.892) and 0.792 (0.721 – 0.863), respectively (Figure 1). We converted PF ratio level number infiltrated quadrant on chest radiography to rubric scales shown in Table 3. The cut-off points of predicting factors were SOFA score ≥4 (sensitivity 86.1%, specificity 84.1%; LR = 5.4), PF ratio level ≥2 (sensitivity 66.7%, specificity 86.4%; LR = 4.9) and number infiltrated quadrant on chest radiography ≥2 (sensitivity 50%, specificity 95.5%; LR =11.1).

Table 3. rubric scale for PF ratio and number infiltrated quadrant on chest radiography (PFCXR score)

Score	0	1	2	3
PF ratio	>200	≤ 200 with non-PEEP or ≤ 300 with PEEP ≥ 5	≤ 100 with non-PEEP or ≤ 200 with PEEP ≥ 5	≤100 with PEEP ≥ 5
Number quadrant infiltration on chest radiography	0	1	2	≥3

Survival analysis: Probability of NIV success in 24-hour

Probability of NIV success by Kaplan-Meier curve, PF ratio level ≥2, number infiltrated quadrant on chest radiography ≥2, and SOFA score ≥ 4 had low probability of NIV success in 24-hour than lower group, log rank *P* value of 0.017, 0.018 and 0.983, respectively (Figure 2).

Discussion

In this study, of the162 patients who visited the ED with influenza infection with ARF from 1 January 2017 to 31 December 2018, 72 patients (44%) had NIV failure in first 48 hours. Our study showed that SOFA score, PF ratio level and number infiltrated quadrant on chest radiography had the ability to predict NIV failure in influenza infection with ARF. SOFA score had higher accuracy than PF ratio level and number infiltrated quadrant on chest radiography. However, there was no statistically significant difference in ability to predict NIV failure between three parameters.

Many studies have shown an increase in NIV use, both overall or in a specific group such as pneumonia. The benefits of NIV use in ARF due to viral infection remain controversial. ARF with influenza infection (H1N1) during the pandemic of 2009 had a high failure rate in NIV, which was associated with high mortality (2–4). Several studies have tried to identify predictive factors for NIV failure in ARF due to influenza infection. As a result, many predicting factors have been found.

In previous studies, lower PF ratio and increased number infiltrated quadrant on chest radiography were independent factors associated with NIV failure in influenza infection with ARF in 48 h (2, 7–9, 11–17). Our study showed PF ratio level ≥2 (PF ratio ≤ 100 mmHg with non-PEEP or ≤ 200 mmHg with PEEP ≥ 5 cmH_2O), number infiltrated quadrant on chest radiography ≥2 and SOFA score ≥4 were required on invasive mechanical ventilator (IMV) in 24-hour higher than lower group. However, PF ratio level and number infiltrated quadrant on chest radiography predicted patients who needed to be closely monitored for early required IMV or not considered for NIV in 24-hour statistically significant differences (Figure. 2) and average time to NIV failure was 12-hour. We were found 12 patients (7.4%) died and all of them were found in NIV failure group (16.7%). In recent study, tidal volume greater than 9.5 mL/kg was associated

with NIV failure (18). Our study was found no significant differences in tidal volume and initial PEEP between NIV failure (tidal volume 7.4 ml/kg (95%CI 6.4-8.2), PEEP 8 (95%CI 6-8)) and NIV success (tidal volume 7.2 ml/kg (95%CI 6.2-7.9), PEEP 8 (95%CI 6-8)).

In this study, the ability of each individual predictor for NIV failure was effective and SOFA score had the greatest ability but many parameters are required to calculate SOFA score. We tried to combine PF ratio level and number infiltrated quadrant on chest radiography into a new score, named PFCXR. We create scales with logistic regression to weight parameters. Finally, we summarized this score by rubric scales (Table 3).

PFCXR score showed AUROC 0.881 (Figure 3), higher than PF ratio level and number infiltrated quadrant on chest radiography alone. The cut-off points of PFCXR score $\geq$3 for predicted NIV failure in ARF with influenza infection was sensitivity 66.7%, specificity 93.2 % and positive likelihood ratio 9.81. Patients with higher score of PFCXR score had higher rate failed NIV and needed to be closely monitored for early intubation in 24 hours (Figure 2).

This study has some limitations. First, this was a retrospective and single center study. Second, the management of NIV and identification of NIV failure were based on attending physicians in the ED. However, emergency medicine residents, emergency medical staff and internal medicine residents had been trained in resuscitation care. This variability in shift to shift in medical decision is a part of real life in the emergency department and NIV setting such as mode, initial PEEP and Tidal volume was not clinically and statistically different in this study. Third, data in some confounding variable were not collected in this study such as number of sputum suction and cough reflex. Finally, loss of larger sample sizes due to identification of influenza infection was not performed in all patients who presented with respiratory infection with ARF. Nevertheless, our study showed a strong risk factor to predict NIV failure in influenza infection with ARF and adequate sample size to find primary outcome.

Conclusion

SOFA score, PF ratio and quadrant infiltrations in chest radiography were good predictors for NIV failure in influenza infection with ARF. The combination of PF ratio level and quadrant infiltrations in chest radiography can be used as a predictor for NIV failure in influenza infection and awareness for intubation. Every physician choosing with NIV should be aware of these risk factors and need closely monitored for early intubate. In pandemic influenza infection or viral infection with acute respiratory failure, resource of mechanical ventilator and intensive care unit were limited therefor used predictors for triage or choosing who need that resource. Further study needs to validate the results in time to failed NIV and mortality.

Abbreviations

NIV: non-invasive ventilator, ED: emergency department, ARF: acute respiratory failure, CXR: chest x-rays, SpO_2: Oxygen saturation, APACHE Score: Acute Physiology and Chronic Health Evaluation Score, SOFA Score: Sequential Organ Failure Assessment Score, PF ratio: Ratio of arterial oxygen partial pressure to fractional inspired oxygen, PEEP: Positive end-expiratory pressure, ICU: intensive care unit, OR: odds ratio aOR; adjusted odds ratio, PFCXR: Ratio of arterial oxygen partial pressure to fractional inspired oxygen and chest x-rays score

Declarations

Ethical Approval and Consent to participate

This study was approved by the ethics committee of Faculty of Medicine Ramathibodi hospital Mahidol University (IRB MURA2019/52 Date 15 January 2019)

Consent for publication

“Not applicable”

Availability of supporting data

The datasets analyzed in this study are not publicly available due to privacy issues, but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

“Not applicable”

Authors' contributions

KS and PS designed this study and protocol development. KS and JB were responsible for the data collection. KS, JB and PS were responsible for data analysis. KS and JB conducted the manuscript writing. KS and PS provided final approval for this version to be published. KS and PS agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Figures

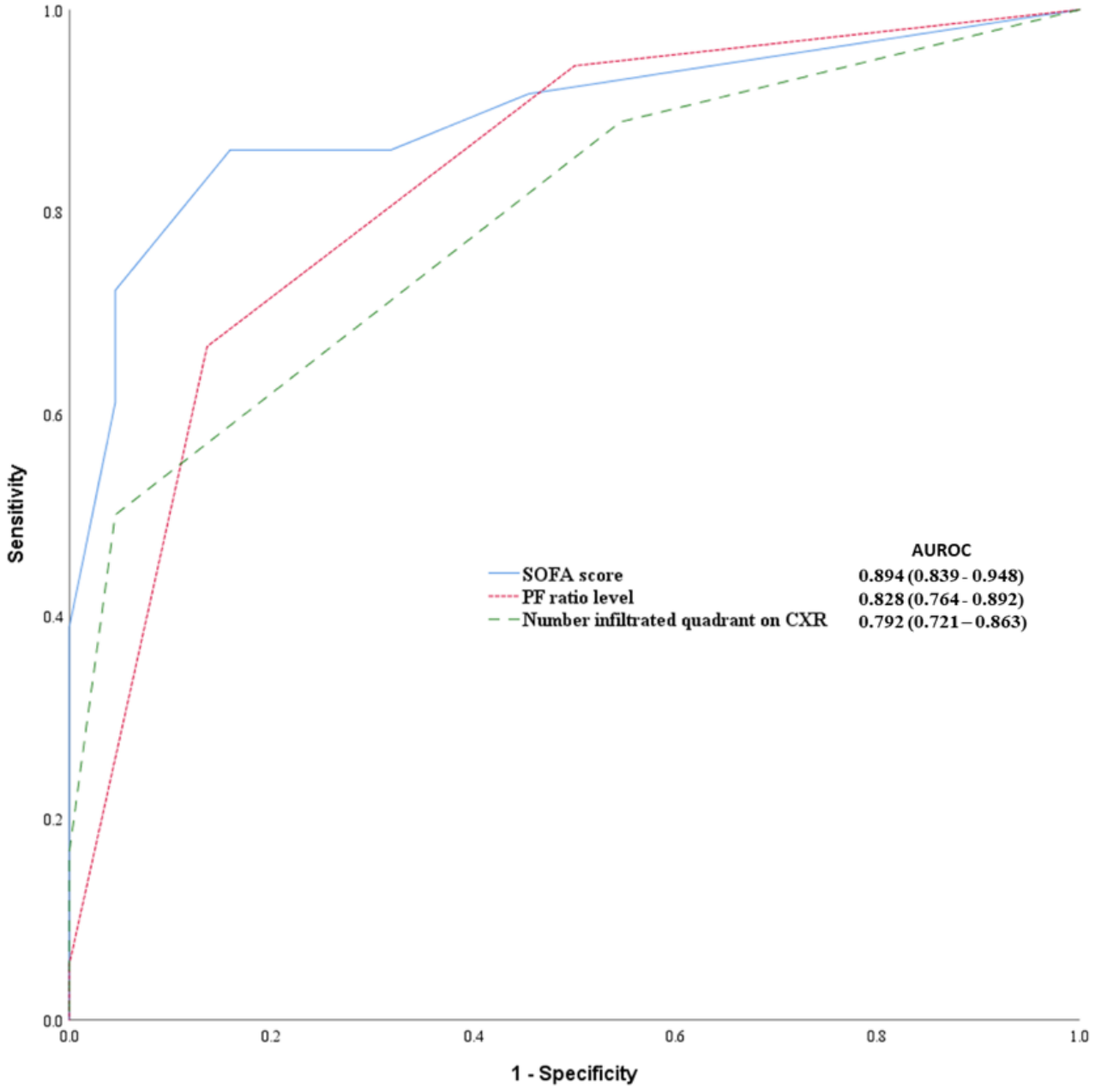

Figure 1

Performance of predicting factor for NIV Failure in influenza infection with ARF. AUROC, area under the receiver operating characteristic, AUROC of SOFA score, PF ratio level and number quadrant infiltration on chest radiography were 0.894 (95% CI 0.839 - 0.948), 0.828 (95% CI 0.764 - 0.892) and 0.792 (95% CI 0.721 – 0.863), respectively. However, no significant difference in ability to predict NIV failure.

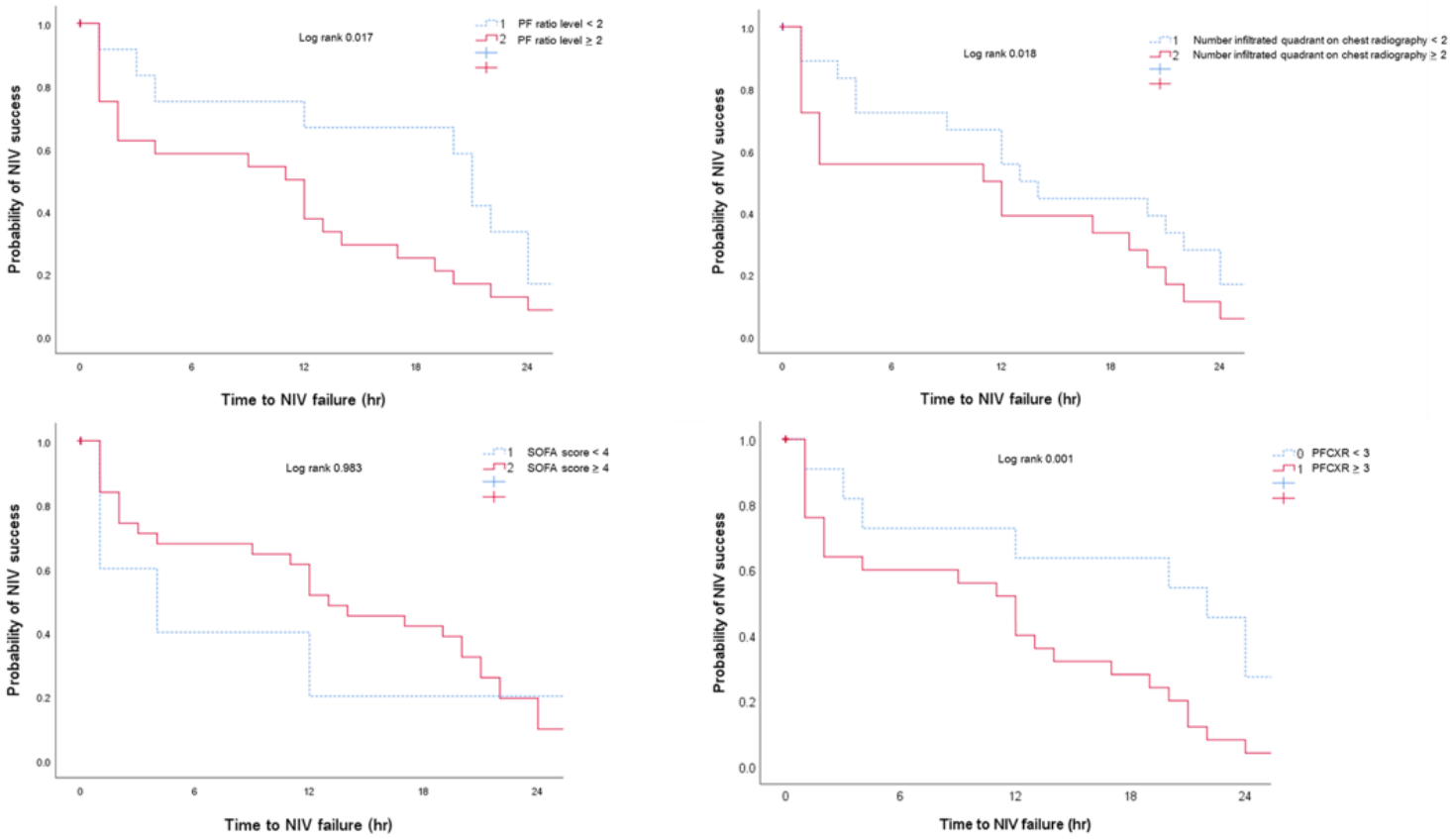

Figure 2

Kaplan-Meier survival analysis for 24 hour non-invasive ventilation in influenza infection with ARF.

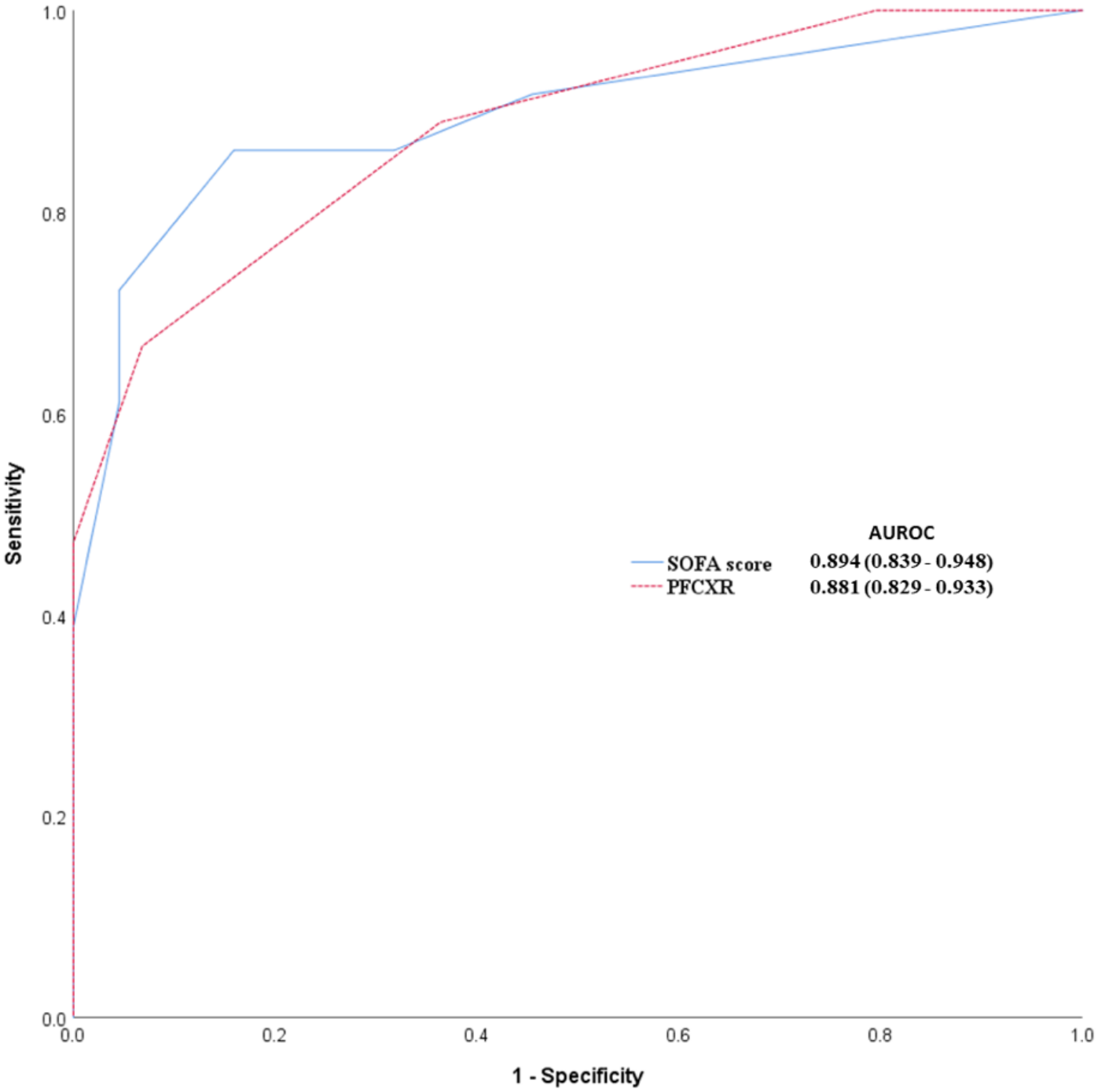

Figure 3

ROC curves of PFCXR and SOFA score for NIV Failure in Influenza infection with ARF. AUROC; area under the receiver operating characteristic, PFCXR; PF ratio level plus number quadrant infiltration on chest radiography. AUROC of SOFA score and PFCXR were 0.894 (95% CI 0.839 - 0.948) and 0.881 (95% CI 0.829 - 0.933), respectively. However, no significant difference in ability to predict NIV failure