Bedside risk stratification for mortality in patients with acute respiratory failure treated with noninvasive ventilation

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ABSTRACT

Our hypothesis was that patients managed with noninvasive ventilation (NIV) on the wards could be risk-stratified with initial pulse oximetry/fraction of inspired oxygen ($\text{SpO}_2/\text{FiO}_2$) ratios and tidal volumes (Vte). A prospective study of consecutive patients with acute respiratory failure requiring NIV on the wards was conducted. A multivariate logistic regression model and a negative binomial regression model were used. A total of 403 patients (55.8% women) had a mean age of 65.0 ± 14.9 years with a mean body mass index of $32.1 \pm 11.1 \text{ kg/m}^2$. The 28-day mortality was 14.1%, and the intubation rate was 16.1%. Pneumonia was associated with the highest 28-day mortality (22.5%) and rate of intubation (36.7%) when compared with chronic obstructive pulmonary disease (4.4% and 7.3%) or congestive heart failure (22.2% and 13.4%). The $\text{SpO}_2/\text{FiO}_2$ groups were <214 (26.6%), $214 - 357$ (66.0%), and ≥ 357 (7.4%). Those in the $\text{SpO}_2/\text{FiO}_2 < 214$ group had a higher 28-day mortality rate (odds ratio [OR] = 8.19; 95% confidence interval [CI] 1.02 -65.7), intubation rate (OR = 3.7; 95% CI 1.1 -12.1), intensive care unit admission rate (OR = 2.9; 95% CI 1.2 -7.4), and length of stay (relative risk = 2.0; 95% CI 1.3 -3.0). A Vte/predicted body weight $< 7.7 \text{ mL/kg}$ was associated with increased intubations (OR = 3.1; 95% CI 1.3 -7.4), intensive care unit admissions (OR = 2.5; 95% CI 1.3 -4.6), and 30-day readmissions (OR = 2.9; 95% CI 1.2 -6.8). In conclusion, in patients without acute respiratory distress syndrome who had acute respiratory failure managed with noninvasive ventilation on the wards, severe hypoxemia as assessed by a simple $\text{SpO}_2/\text{FiO}_2 \leq 214$ was associated with poor outcomes.

KEYWORDS Intubation; mortality; noninvasive ventilation; $\text{SpO}_2/\text{FiO}_2$ ratio; tidal volume

The use of noninvasive ventilation (NIV) to treat acute respiratory failure is increasing.^{1–3} NIV use decreases the rate of endotracheal intubation and mortality in patients with chronic obstructive pulmonary disease (COPD) exacerbations^{4–6} and reduces the rate of endotracheal intubation in patients with cardiogenic pulmonary edema.^{4,7–9} NIV is commonly used to treat acute respiratory failure on the wards.^{10,11}

The benefits of tidal volume (Vte) reduction may be present in critically ill patients without acute respiratory distress syndrome (ARDS).^{12,13} However, an optimal expiratory Vte strategy in NIV for acute respiratory failure has not been well

established, except perhaps in patients with acute hypoxemic respiratory failure.⁴ Carreaux et al¹⁴ explored the feasibility of a low Vte strategy using NIV in acute hypoxemic respiratory failure and found that higher Vte was associated with failure defined as need of intubation. Frat et al showed that Vte $> 9 \text{ mL/kg}$ predicted body weight (PBW) and severe hypoxemia as indicated by a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) $\leq 200 \text{ mm Hg}$ in patients spontaneously breathing with acute hypoxemic respiratory failure was associated with a higher rate of intubation and mortality.¹⁵

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Figure 1. Patients screened for study inclusion. CPAP indicates continuous positive airway pressure; DNR/DNI, do not resuscitate/do not intubate; NIV, noninvasive ventilation.

More recently, the ratio of oxygen saturation by pulse oximetry/fraction of inspired oxygen ($\text{SpO}_2/\text{FiO}_2$) has been comparable to $\text{PaO}_2/\text{FiO}_2$ values^{16,17} in evaluating the degree of hypoxemia in patients with acute respiratory failure. The clinical characteristics and outcomes appear similar in patients with ARDS diagnosed with $\text{SpO}_2/\text{FiO}_2$ or $\text{PaO}_2/\text{FiO}_2$ ratios.¹⁸ We hypothesized that patients with acute respiratory failure supported with NIV on the wards could be initially risk-stratified using the $\text{SpO}_2/\text{FiO}_2$ ratio and Vte/PBW with lower $\text{SpO}_2/\text{FiO}_2$ ratios.

METHODS

This was a prospective observational study at a 680-bed academic hospital in Central Texas over a year and a half. The study was approved by the institutional review board. Consent was waived due to the observational nature of the study.

Consecutive patients receiving NIV were entered into the study after the primary medical team ordered NIV for any cause of acute respiratory failure. Patients were excluded from the study if they had a do not resuscitate status, were under the age of 18, received NIV after extubation, were on chronic NIV therapy for previously diagnosed sleep apnea or obesity hypoventilation syndrome, used NIV only immediately postoperatively, had a diagnosis of ARDS, were managed with continuous positive airway pressure, or were previously admitted and enrolled in this study (Figure 1).

NIV was delivered via Respironics V60, Vision, Focus, or STD 30 using an oral-nasal mask. Clinicians determined

bilevel NIV pressure settings based on their assessment of the patient and managed the patients on the general medical floor assisted by respiratory therapists. In our hospital, the respiratory therapy protocol includes titrating FiO_2 to a goal SpO_2 of 92%. Furthermore, pressure changes were made at the physician's discretion based on SpO_2 , blood gases, and clinical response. Escalation of care to the intensive care unit (ICU) was determined by consultation with the ICU team. Patient information collected included demographics, age, gender, height, weight, and calculated body mass index. The patient's PBW was calculated using the same formula used in the ARDSnet Trial.¹⁰ During each 4-hour period, according to our usual practice, the respiratory therapist would document NIV data including the Vte , positive airway pressures, and clinical data, including patients' SpO_2 and FiO_2 . This information was recorded prospectively. We recorded Vte to reduce the leak error inherent to inspiratory Vte and better represent patients' actual Vte . The Charlson Comorbidity Index was calculated for each patient based on a validated International Classification of Diseases–9 scoring system.^{19,20}

We used the initial Vte to place patients into quartiles: <7.7 mL/kg PBW, ≥ 7.7 – 9.2 mL/kg PBW, ≥ 9.2 – 11.0 mL/kg PBW, and ≥ 11.0 mL/kg PBW. The initial $\text{SpO}_2/\text{FiO}_2$ ratio was used to classify patients into three validated groups derived from $\text{PaO}_2/\text{FiO}_2$ ratios of <200 , ≥ 200 – 300 , and ≥ 300 that had equivalent $\text{SpO}_2/\text{FiO}_2$ ratios of <214 , ≥ 214 – 357 , and ≥ 357 . All analyses of variables were determined a priori. The primary outcome studied was 28-day

mortality. Secondary outcomes were ICU admission, endotracheal intubation, length of stay (LOS), and 30-day readmission rate.

Means and frequencies were calculated for patient characteristics, treatment, and outcomes. Bivariate analyses assessed underlying differences by group status. Chi-square analyses (Fisher's exact for small expected counts) compared categorical characteristics and outcomes across groups. The nonparametric Kruskal-Wallis test assessed differences for continuous measures between patient groups.

Multivariable logistic regression analyses were used to examine the association between SpO₂/FiO₂ ratio and Vte/PBW with the outcomes of 28-day mortality, intubation, ICU admission, and 30-day readmission, adjusting for patient age, gender, and comorbidities. A generalized linear model assuming a negative binomial distribution and log link was used to assess the relationship between SpO₂/FiO₂ ratio and Vte/PBW with hospital LOS, adjusted for the same confounders. In all models, age was divided by 10 to assess a decade effect, and a type I error of $\alpha = 0.05$ was assumed throughout. All analyses were performed using SAS, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 1880 consecutive patients who received NIV for any reason were evaluated for entry into the study, and 403 patients were included (*Figure 1*). We recorded 5,721 4-hour periods, with a median of 8.4 (interquartile range [IQR] 2–11) periods per patient. The mean age of the patients was 65.0 ± 14.9 years, the mean body mass index was 32.1 ± 11.1, and 55.8% were female. The median Vte/PBW was 8.9 (IQR 7.3–11.3) mL/kg, with a median inspiratory positive airway pressure of 12 cm H₂O (IQR 10–12) and median expiratory positive airway pressure of 6 cm H₂O (IQR 5–6). The 28-day mortality was 14.1%, 16.1% were intubated, 39.2% were admitted to the ICU, the median LOS was 5 days (IQR 3–9), and the 30-day readmission rate was 16.1% (*Table 1*). The most common cause of death was pneumonia followed by septic shock (*Supplementary Table 2*).

There was an average of 1.7 respiratory diagnoses per patient. The most common diagnoses were COPD (40.4%), congestive heart failure (CHF) (39.5%), and pneumonia (39.0%), with only a minority having pneumonia as the only diagnosis (n = 49, 12.2%). When comparing those patients who had only one diagnosis, patients with pneumonia had the highest 28-day mortality (22.5%) compared to patients with COPD (4.4%) or CHF (22.2%); in addition, they had the highest intubation rate (36.7%) compared to COPD (7.3%) or CHF (13.4%), the highest ICU admission rate (55.1%) compared to COPD (18.8%) or CHF (40.2%), and the longest LOS (6 days; IQR 4–14) compared to COPD (3 days; IQR 2–6) or CHF (5 days; IQR 3–9) (*Table 2, Supplementary Figure 1*).

Table 1. Characteristics of patients at baseline (N = 403)

Variable	Result ^a
Age (years)	65 (14.9)
Male	178 (44.2%)
Female	225 (55.8%)
White	294 (73%)
Black	61 (15%)
Other race	48 (12%)
Body mass index (kg/m ²)	32.1 (11.1)
Charlson comorbidity index	4.3 (2.8)
Bilevel NIV	
Vte (mL)	553 (445–683)
Vte/PBW (mL/kg)	8.9 (7.3–11.3)
IPAP (cm H ₂ O)	12.0 (10.0–12.0)
EPAP (cm H ₂ O)	6.0 (5.0–6.0)
Vte/PBW quartile groups	
<7.7 mL/kg PBW (N = 100)	6.5 (1.5)
≥7.7–9.2 mL/kg PBW (N = 101)	8.6 (1.5)
≥9.2–11.0 mL/kg PBW (N = 101)	9.8 (1.8)
≥11.0 mL/kg PBW (N = 101)	12.7 (2.9)
SpO ₂ /FiO ₂ groups	
<214 (n = 107, 26.6%)	154.9 (43.3)
214–<357 (n = 266, 66%)	272.6 (37.0)
≥357 (n = 30, 7.4%)	438.9 (35.6)
Outcomes	
28-day mortality ^a	56 (14.1%)
Intubation	65 (16.1%)
ICU admission	158 (39.2%)
Length of stay (days)	5.0 (3.0–9.0)
30-day readmission	65 (16.1%)

^aSample size of 398 patients (1% missing).

EPEP indicates expiratory positive airway pressure; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IPAP, inspiratory positive airway pressure; IQR, interquartile range; NIV, noninvasive ventilation; PBW, predicted body weight; SD, standard deviation; SpO₂, oxygen saturation by pulse oximetry; Vte, tidal volume. Data presented as N (%), mean (standard deviation), or median (interquartile range).

Irrespective of underlying diagnosis, the distribution of SpO₂/FiO₂ ratios was <214, 26.6%; ≥214–<357, 66.0%; and ≥357, 7.4%. The 28-day mortality rate was highest in patients with an SpO₂/FiO₂ ratio <214 (27.4%) when compared with those with 214–<357 (9.9%) or ≥357 (3.3%). An SpO₂/FiO₂ ratio <214 had the highest rates of ICU admission and endotracheal intubation (51.4% and 29.9%) when compared with those with 214–<357 (35.3% and 10.9%) or ≥357 (30.0% and 13.3%). The median LOS was

Table 2. Effect of respiratory diagnosis on outcomes (*N* = 403)

Variable	<i>N</i> (%) or median (quartile 1–3)				<i>P</i> value
	COPD ^a	CHF ^a	Pneumonia ^a	Other ^b	
Exclusive diagnosis ^c	69 (17.1%)	82 (20.3%)	49 (12.2%)	72 (18.9%) ^b	0.04
Total diagnoses ^d	163 (40.4%)	159 (39.5%)	157 (39.0%)	207 (51.4%)	
Exclusive outcome					
28-day mortality	3 (4.4%)	18 (22.2%)	11 (22.5%)	7 (9.9%)	0.004
Intubation	5 (7.3%)	11 (13.4%)	18 (36.7%)	8 (11.1%)	<0.0001
ICU admission	13 (18.8%)	33 (40.2%)	27 (55.1%)	23 (31.9%)	0.0005
LOS median (min-max)	3 (2–6)	5 (3–9)	6 (4–14)	3 (2–7.5)	0.0001
30-day readmission	11 (15.9%)	8 (9.8%)	5 (10.2%)	12 (16.7%)	0.49

^aSee Supplementary Figure 1.^bNot COPD, CHF, or pneumonia.^cCOPD without CHF, pneumonia, or other; CHF without COPD, pneumonia, or other; pneumonia without COPD, CHF, or other; other without COPD, CHF, or pneumonia.^dIncluding COPD, CHF, pneumonia, and other diagnoses.

COPD indicates chronic obstructive pulmonary disease; CHF, congestive heart failure; ICU, intensive care unit; LOS, length of stay.

longest with SpO₂/FiO₂ ratio <214 (7 days; IQR 4–12) compared to 214–<357 (5 days; IQR 3–8) or ≥357 (4 days; IQR 2–6). The 30-day readmission rate did not vary with the severity of hypoxemia (Table 3). The Bland-Altman plot showed a good level of agreement between the SpO₂/FiO₂ ratio and PaO₂/FiO₂ ratio and outcomes in 266 patients with initial arterial blood gases (Supplemental Figure 2).

The Vte/PBW were placed in quartiles of <7.7 mL/kg PBW (25%); ≥7.7–9.2 mL/kg PBW (25%); ≥9.2–11.0 mL/kg PBW (25%); and ≥11.0 mL/kg PBW (25%). Patients with Vte <7.7 mL/kg PBW had a higher ICU admission rate (47%), median LOS (6 days; IQR 4–10), and 30-day readmission rate (21%) compared to patients with Vte ≥7.7–9.2 mL/kg PBW (34%, 5 days, 11%); ≥9.2–11.0 mL/kg PBW (49%, 5 days, 24%); and ≥11.0 mL/kg PBW (28%, 4 days, 9%). The 28-day mortality and intubation rate was not significantly different over all quartiles of Vte/PBW.

In terms of the primary outcome, in the multivariable logistic regression models, severe hypoxemia (SpO₂/FiO₂ ≤214) was associated with increased odds of 28-day mortality (odds ratio [OR] = 8.19; 95% confidence interval [CI] 1.02–65.7). For every decade of increase in age, the odds of 28-day mortality increased (OR = 1.51; 95% CI 1.17–1.93) (Table 4).

In terms of secondary outcomes, in the multivariate logistic regression model, severe hypoxemia (OR = 3.7; 95% CI 1.1–12.1) and lower age in decades (OR = 0.7; 95% CI 0.6–0.9) were associated with failure of NIV (intubation). Severe hypoxemia (OR = 2.9; 95% CI 1.2–7.4) and Vte/PBW <7.7 mL/kg and ≥9.2–11.0 mL/kg PBW were associated with ICU admission (OR = 2.5; 95% CI 1.3–4.6 and OR = 2.6; 95% CI 1.4–4.8). Greater comorbidity per Charlson score was associated with a higher 30-day readmission (OR = 1.1; 95% CI 1.0–1.2) (Supplementary Table 1).

DISCUSSION

In our cohort of patients with non-ARDS acute respiratory failure managed with bilevel NIV on the wards, we found that the initial bedside SpO₂/FiO₂ ratio in patients with hypoxemic respiratory failure was associated with a higher mortality rate, intubation rate, ICU admission rate, and LOS. This is in concordance with the findings of Frat et al in which a PaO₂/FiO₂ < 200 at 1 h of NIV use in acute hypoxemic respiratory failure predicted intubation (OR 4.26; 95% CI 1.62–11.1, *P* = 0.003).¹⁵ Even as the use of NIV increases on the wards for acute respiratory failure,¹⁵ delays in intubation have been associated with higher mortality.²¹ Obtaining timely arterial blood gases may be challenging on the wards. Thus, a bedside tool to predict poor outcomes may alert clinicians to pursue earlier escalation of care, including intubation.

A second major finding was that patients with pneumonia had higher mortality, higher intubation rates, increased admissions to the ICU, and longer LOS compared with patients with COPD and CHF. In acute hypoxemic respiratory failure, NIV failure leads to a high mortality.^{22,23} This is of particular concern in patients with ARDS, which is why we excluded such patients from this study.^{2,4,23–26} Our intubation rate of 16.1% was far lower than the 50% reported in hypoxemic-only respiratory failure¹⁴ as a result of our case mix of patients, which included pneumonia (39.0%), COPD (40.4%), and CHF (39.5%). NIV use has proven benefits in patients with COPD and CHF exacerbations.^{4,5,27}

The SpO₂/FiO₂ ratio has been used in lieu of the PaO₂/FiO₂ ratio.^{16–18} Because we did not have patients with an SpO₂/FiO₂ < 89 or a PaO₂/FiO₂ < 100, a group with a severe degree of hypoxemia could not be analyzed. We used the initial SpO₂/FiO₂ ratios, but these outcomes were similar when the initial SpO₂/FiO₂ ratios were compared to the average SpO₂/FiO₂ ratios during NIV utilization.

Table 3. Effect of SpO₂/FiO₂ ratio severity group on outcomes (N = 403)

Variable	SpO ₂ /FiO ₂ value			P value ^a
	<214	214–<357	≥357	
N	107 (26.6%)	266 (66%)	30 (7.4%)	
Initial SpO ₂ /FiO ₂ ratio	154.9 (43.3)	272.6 (37.0)	438.9 (35.6)	
Age (years)	67.2 (13.7)	65.0 (15.2)	56.2 (14.1)	0.002
Women	54 (50.5%)	149 (56.0%)	22 (73.3%)	0.08
Charlson score	3.8 (2.5)	4.5 (2.9)	4.4 (2.8)	0.09
Body mass index (kg/m ²)	28.9 (9.4)	32.9 (11.2)	35.7 (13.1)	0.001
4-hour periods	5 (2–11)	5 (2–11)	5 (2–7)	0.98
Bilevel Vte/PBW (mL/kg)	9.1 (7.8–10.4)	9.2 (7.6–11.3)	9.4 (8.9–10.9)	0.30
28-day mortality ^b	29 (27.4%)	26 (9.9%)	1 (3.3%)	<0.0001
Intubation	32 (29.9%)	29 (10.9%)	4 (13.3%)	<0.0001
ICU admission	55 (51.4%)	94 (35.3%)	9 (30.0%)	0.009
Length of stay	7 (4–12)	5 (3–8)	4 (2–6)	<0.0001
30-day readmission	13 (12.2%)	48 (18.1%)	4 (13.3%)	0.34

^aChi-square analyses for categorical variables and Kruskal-Wallis/ANOVA test for continuous variables, assuming a type I error rate of $\alpha = 0.05$.

^bSample size of N = 398 patients (1% missing): SpO₂/FiO₂ < 214–106 patients (1% missing), 214 ≤ SpO₂/FiO₂ < 357–262 patients (1.5% missing), SpO₂/FiO₂ ≥ 357–30 patients (0% missing).

FiO₂ indicates fraction of inspired oxygen; ICU, intensive care unit; PBW, predicted body weight; SpO₂, oxygen saturation by pulse oximetry; Vte, tidal volume. Data presented as N (%), mean (standard deviation), or median (interquartile range).

Table 4. Multivariate logistic regression analysis for the primary outcome of 28-day mortality

Variables	Odds ratio	95% CI	P value
Age (decade effect)	1.51	1.17–1.93	0.001
Female	1.08	0.58–2.01	0.81
Charlson Comorbidity Index	1.09	0.99–1.21	0.09
SpO ₂ /FiO ₂ ≤ 214	8.19	1.02–65.7	0.05
SpO ₂ /FiO ₂ > 214<357	2.11	0.27–16.9	0.48
<7.7 mL/kg PBW	2.05	0.85–4.97	0.11
≥7.7–9.2 mL/kg PBW	1.45	0.57–3.67	0.43
≥9.2–11.0 mL/kg PBW	0.83	0.31–2.27	0.72

CI indicates confidence interval; FiO₂, fraction of inspired oxygen; PBW, predicted body weight; SpO₂, oxygen saturation by pulse oximetry.

Our data limitation didn't allow us to look at the change in SpO₂/FiO₂ ratios with the application of NIV and the subsequent impact on outcomes, including the median times to intubation.

We found a low Vte/PBW was not associated with mortality or intubation. However, a Vte/PBW of <7.7 mL/kg PBW was associated with higher odds of ICU admission and an increased risk of prolonged LOS. A “dose escalation” effect with sequentially higher Vte quartiles was not found. This is in contrast to the findings of Frat et al who showed a 50%

intubation rate with a Vte/PBW > 9 mL/kg (OR 3.14; 95% CI 1.22–8.06, $P = 0.02$) and a higher 90-day mortality.¹⁵ Notably, their study comprised only patients with acute hypoxemic respiratory failure managed with NIV, unlike our heterogeneous cohort of non-ARDS acute respiratory failure. It is possible that patients with low Vte/PBW may have had decreased lung compliance because of more severe underlying cardiopulmonary disease. However, the degree of hypoxemia did not account for this difference in our analysis. It is also possible that low Vte/PBW may have been a surrogate marker for a rapid shallow breathing pattern not amenable to capture with NIV. Due to the nature of this pragmatic study, we didn't have all the respiratory rates in these patients.

In our “real-life” study with non-ARDS acute respiratory failure on the wards, we carefully excluded patients who only continued use of home NIV, needed NIV after extubation, had care limitations imposed by advance directives, and received NIV in the immediate postoperative period. Our study is unique in that we suggest using easily available parameters such as the SpO₂/FiO₂ ratio to risk-stratify those managed with NIV.

Our limitations include lack of severity of illness information such as Simplified Acute Physiology Score (SAPS) or Acute Physiology and Chronic Health Evaluation (APACHE) scores, which are not collected in patients admitted on the general medical floors. An observational study makes the determination of cause and effect difficult. Although we used the SpO₂/FiO₂ ratio for simplicity, we acknowledge that its accuracy would be lower in quantifying

hypoxemia in the presence of high FiO₂ compared to the PaO₂/FiO₂ ratio. Lastly, it is possible that certain indications for NIV or clinician experience with NIV management and patient selection may have introduced bias in our data.

In conclusion, in non-ARDS patients with acute respiratory failure managed on bilevel NIV, severe hypoxemia as assessed by a quick bedside SpO₂/FiO₂ ≤ 214 was associated with a high 28-day mortality, intubation rate, and ICU admission rate in patients irrespective of etiology. In these patients, a diagnosis of pneumonia was associated with worse outcomes compared with COPD, CHF, or pneumonia with COPD or CHF.

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1. Esteban A, Ferguson ND, Meade MO, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med*. 2008;177(2):170–177. doi:10.1164/rccm.200706-893OC.
2. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med*. 2007;35(1):18–25. doi:10.1097/01.CCM.0000251821.44259.F3.
3. Maheshwari V, Paioli D, Rothaar R, Hill NS. Utilization of noninvasive ventilation in acute care hospitals: a regional survey. *Chest*. 2006;129(5):1226–1233. doi:10.1378/chest.129.5.1226.
4. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet*. 2009;374(9685):250–259. doi:10.1016/S0140-6736(09)60496-7.
5. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*. 2000;355(9219):1931–1935. doi:10.1016/S0140-6736(00)02323-0.
6. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ*. 2003;326(7382):185. doi:10.1136/bmj.326.7382.185.
7. Masip J, Roque M, Sánchez B, Fernández R, Subirana M, Expósito JA. Noninvasive ventilation in acute cardiogenic pulmonary edema: systematic review and meta-analysis. *JAMA*. 2005;294(24):3124–3130. doi:10.1001/jama.294.24.3124.
8. Masip J, Betbesé AJ, Páez J, et al. Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. *Lancet*. 2000;356(9248):2126–2132. doi:10.1016/S0140-6736(00)03492-9.
9. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J; 3CPO Trialists. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med*. 2008;359(2):142–151. doi:10.1056/NEJMoa0707992.
10. Raurell-Torredà M, Argilaga-Molero E, Colomer-Plana M, Ródenas-Francisco A, Ruiz-García MT, Muntanya JU. Optimising non-invasive mechanical ventilation: Which unit should care for these patients? A cohort study. *Aust Crit Care*. 2017;30(4):225–233. doi:10.1016/j.aucc.2016.08.005.
11. Ozsancak Ugurlu A, Sidhom SS, Khodabandeh A, et al. Where is noninvasive ventilation actually delivered for acute respiratory failure? *Lung*. 2015;193(5):779–788. doi:10.1007/s00408-015-9766-y.
12. Serpa Neto A, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA*. 2012;308(16):1651–1659. doi:10.1001/jama.2012.13730.
13. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369(22):2126–2136. doi:10.1056/NEJMr1208707.
14. Carteaux G, Millán-Guilarte T, De Prost N, et al. Failure of noninvasive ventilation for de novo acute hypoxemic respiratory failure: role of tidal. *Crit Care Med*. 2016;44(2):282–290. doi:10.1097/CCM.0000000000001379.
15. Frat JP, Ragot S, Coudroy R, et al. Predictors of intubation in patients with acute hypoxemic respiratory failure treated with a noninvasive oxygenation strategy. *Crit Care Med*. 2018;46(2):208–215. doi:10.1097/CCM.0000000000002818.
16. Festic E, Bansal V, Kor DJ, Gajic O; US Critical Illness and Injury Trials Group: Lung Injury Prevention Study Investigators (USCIITG-LIPS). SpO₂/FiO₂ ratio on hospital admission is an indicator of early acute respiratory distress syndrome development among patients at risk. *J Intensive Care Med*. 2015;30(4):209–216. doi:10.1177/0885066613516411.
17. Sanz F, Dean N, Dickerson J, et al. Accuracy of PaO₂/FiO₂ calculated from SpO₂ for severity assessment in ED patients with pneumonia. *Respirology*. 2015;20(5):813–818. doi:10.1111/resp.12560.
18. Rice TW, Wheeler AP, Bernard GR, et al; National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network. Comparison of the SpO₂/FiO₂ ratio and the PaO₂/FiO₂ ratio in patients with acute lung injury or ARDS. *Chest*. 2007; 132(2):410–417. doi:10.1378/chest.07-0617.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8.
20. Li B, Evans D, Faris P, Dean S, Quan H. Risk adjustment performance of Charlson and Elixhauser comorbidities in ICD-9 and ICD-10 administrative databases. *BMC Health Serv Res*. 2008;8(1):12. doi:10.1186/1472-6963-8-12.
21. Cabrini L, Esquinas A, Pasin L, et al. An international survey on non-invasive ventilation use for acute respiratory failure in general non-monitored wards. *Respir Care*. 2015;60(4):586–92. doi:10.4187/respcare.03593.
22. Bellani G, Laffey JG, Pham T, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788–800. doi:10.1001/jama.2016.0291.
23. Carrillo A, Gonzalez-Diaz G, Ferrer M, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Med*. 2012;38(3):458–466. doi:10.1007/s00134-012-2475-6.
24. Thille AW, Contou D, Fragnoli C, et al. Non-invasive ventilation for acute hypoxemic respiratory failure: intubation rate and risk factors. *Crit Care*. 2013;17(6):R269. doi:10.1186/cc13103.
25. Rana S, Jenad H, Gay PC, Buck CF, Hubmayr RD, Gajic O. Failure of non-invasive ventilation in patients with acute lung injury: observational cohort study. *Crit Care*. 2006;10(3):R79. doi:10.1186/cc4923.
26. Hess DR. Noninvasive ventilation for acute respiratory failure. *Respir Care*. 2013;58(6):950–972. doi:10.4187/respcare.02319.
27. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526–2533. doi:10.1001/jama.2012.5669.
28. Cabrini L, Landoni G, Oriani A, et al. Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and metaanalysis of randomized controlled trials. *Crit Care Med*. 2015; 43(4):880–888. doi:10.1097/CCM.0000000000000819.