Analysis of Noninvasive Ventilation in Subjects With Sepsis and Acute Respiratory Failure

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BACKGROUND: Acute respiratory failure is among the sequelae of complications that can develop in response to severe sepsis. Research into sepsis-related respiratory failure has focused on ARDS and invasive mechanical ventilation. We studied the factors associated with success and failure of noninvasive ventilation (NIV) in the treatment of sepsis-related acute respiratory failure. METHODS: This retrospective study included 136 subjects with a diagnosis of acute respiratory failure and intrapulmonary or extrapulmonary sepsis who were placed on NIV. Subjects were divided into 2 groups based on the need for intubation from NIV: NIV failure (n = 70) and NIV success (n = 66). Demographic, clinical, and outcome data were collected and compared between groups, with the development of multivariate models to predict NIV failure and mortality. RESULTS: The overall NIV failure rate in subjects with a diagnosis of sepsis was 51%. There were no between-group differences in demographic or baseline characteristics. However, there were significant differences in clinical variables, with higher SOFA scores (NIV failure: 6.4 [± 3.0] vs NIV success: 4.9 [± 2.1]; P = .002), 2nd lactate levels (NIV failure: 2.6 [1.7 – 4.3] vs NIV success: 1.9 [1.4 – 2.6] mmol/L; P = .007), and initial NIV F_{IO_2} settings (NIV failure: 0.50 [0.40 – 0.70] vs NIV failure: 0.40 [0.35 – 0.50]; P = .003) in subjects who failed NIV. There were also more subjects in the NIV failure group who had a lactate ≥ 4 mmol/L prior to NIV start compared to those who succeeded on NIV (33% vs 15%, P = .02). At NIV start, subjects in the NIV failure group had lower mean arterial pressure (85 mm Hg [IQR 74–96] vs 91.7 mm Hg [IQR 78–108], P = .042) and Glasgow coma scale scores (14 [IQR 13–15] vs 15 [IQR 14–15], P < .002), while fewer subjects in the NIV failure group received a fluid bolus in the 24 h prior to NIV start (33% vs 53%, P = .02) or had signs of volume overload (36% vs 64%, P < .001). Multivariate analysis indicated that age (odds ratio 1.05 [95% CI 1.01–1.09], P = .02), SOFA score (odds ratio 1.49 [95% CI 1.15–1.94], P = .002), first systolic blood pressure (odds ratio 0.97 [95% CI 0.95–0.99], P = .02), signs of volume overload (odds ratio 0.23 [95% CI 0.07–0.68], P = .008], fluids prior to NIV (odds ratio 0.08 [95% CI 0.02–0.31], P < .001), and initial F_{IO_2} on NIV (odds ratio 1.04 [95% CI 1.01–1.08, P = .002) independently predicted NIV failure with an area under the curve of 0.88. Only NIV failure independently predicted death in multivariate analysis (area under the curve = 0.70). CONCLUSIONS: NIV failure in sepsis-related acute respiratory failure was independently predicted by patient acuity, first systolic blood pressure after sepsis alert, initial F_{IO_2} settings on NIV, fluid resuscitation, and signs of volume overload. However, only NIV failure independently predicted death in this cohort of subjects. *Key words: sepsis; noninvasive ventilation; NIV; early goal-directed therapy; mechanical ventilation; shock.*
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Introduction

Sepsis is defined as a systemic inflammatory response to multiple possible causes of infection.[1] The disorder results from a dysregulated immune system response to infection and can lead to life-threatening organ dysfunction. Acute respiratory failure (ARF) is among the clinical sequelae that can develop secondary to overwhelming systemic inflammation leading to pulmonary endothelial and microcirculatory dysfunction (ie, extrapulmonary sepsis), or direct lung injury from inflammatory cell migration into pulmonary tissue (ie, intrapulmonary sepsis).[2] Recent

quality standards, including those recommended by Centers for Medicare and Medicaid Services (CMS),[3] promote the use of early management bundles to reduce morbidity and mortality. These guidelines include prompt lactate and blood-culture draws, antibiotic administration, and fluid resuscitation for sepsis-associated hypotension. While fluids are thought to address sepsis-associated hypotension, the role of fluid administration in the development of ARF in this patient population is less clear. However, researchers have posited that fluid balance may be related to worsening pulmonary edema, use of fluid-related medical interventions, development of acute lung injury, and fewer ventilator-free days.[4-6]

Sepsis is also a known risk factor for the development of ARDS[7] on the basis of the "2-hit" model, advanced from preclinical studies and the subsequent validation of lung-injury prediction scores.[8] Research into sepsis-induced ARF has mainly focused on ARDS and invasive mechanical ventilation.[6,8-10] Consequently, the Surviving Sepsis Campaign guidelines[11] only provide recommendations for invasive mechanical ventilation related to sepsis-induced ARDS, while offering no standards for noninvasive ventilation (NIV) or respiratory failure, which does not meet criteria for severe lung injury.

Research shows that NIV can be effective and improve outcomes in certain diagnoses, such as COPD or heart failure exacerbations.[12] Relevant literature contains NIV studies of heterogeneous populations with some subsets of septic subjects, but this group has not been the primary focus. For example, Agarwal et al[13] reported a 50% failure rate with mortality of 35% in a meta-analysis of NIV for acute lung injury/ARDS, which included subjects with sepsis. Other studies of acute hypoxemic respiratory failure have reported that sepsis predisposed subjects to NIV failure,[14] along with other factors including ARDS, de novo respiratory failure, baseline disease severity, and clinical variables such as encephalopathy, breathing frequency, P_{aO_2}/F_{IO_2}, and tidal volume (V_T).[15-17]

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QUICK LOOK

Current knowledge

Acute respiratory failure is among the sequelae of complications that can develop in response to severe sepsis. Failure of NIV in ARDS is related to mental status, severity of illness and shock. Further understanding the causes of NIV failure in non-ARDS is important to avoid consequences of delayed intubation.

What this paper contributes to our knowledge

NIV failed in a significant portion of subjects with sepsis and was independently associated with subject acuity, fluid administration, hemodynamic parameters, age, and initial F_{IO_2} on NIV. The only significant predictor of mortality in this patient population was NIV failure after controlling for SOFA scores, first systolic blood pressure after sepsis alert, mean arterial pressure at NIV start, fluid administration prior to NIV, and any lactate $>$ 4 mmoL/L prior to initiation of NIV. Larger cohort studies, with additional data related to fluid administration and balance, are needed to confirm these results.

We found only 1 study that explicitly studied a group of subjects with sepsis who were placed on NIV. Razlaf et al[18] studied immunocompromised subjects with intra- or extrapulmonary sepsis and reported an overall NIV success rate of 45%, although the presence of ARDS was not discerned. No research was found examining NIV use in a general population of patients with ARF related to sepsis. Consequently, there is no information to guide patient selection or alert clinicians to variables that potentially indicate poor outcomes. Therefore, this study sought to review the clinical course, failure rates, and factors that may predict NIV failure in patients with a diagnosis of sepsis and ARF who are placed on NIV.

Methods

Subjects

This was a retrospective study of all patients admitted to MedStar Washington Hospital Center (MWHC) from July 2017 to July 2018 and placed on NIV for ARF with a diagnosis of sepsis. The study cohort was obtained from Vizient, one of the institution's data repositories, with information extracted from a hospital-wide sepsis database and the electronic medical record using a standardized format. All patients with discharge coding for a sepsis diagnosis, documentation of infection and organ dysfunction, and procedural coding for NIV were reviewed for inclusion. Subjects'

electronic medical records were reviewed for both SEP-1 and SEP-3 sepsis criteria. Exclusion criteria included obstructive sleep apnea, palliative care or do-not-intubate orders, extubation to NIV, or NIV use in postextubation respiratory failure. This study was approved by MedStar's institutional review board (2018-142).

Clinical Protocols

NIV was provided to all subjects using either the Vision or V60 ventilator (Philips Respironics, Murrysville, Pennsylvania) with use of a vented, full-face mask (Fisher & Paykel, Auckland, New Zealand). Settings were established by the respiratory therapist based on the Respiratory Therapy Department's hospital-approved NIV protocol. Protocol goals following the initiation of NIV include pressure and F_{IO_2} titration to achieve a breathing frequency $\leq$ 25 breaths/min, $S_{pO_2} \geq 92\%$, and V_T 6–8 mL/kg/ideal body weight, with minimal to no work of breathing, as assessed by use of accessory muscles of ventilation. The initial NIV order and decision to intubate in these subjects were at the discretion of the treating provider. In general, criteria to intubate at the hospital includes excessive work of breathing or severe blood-gas derangements unrelieved by maximal NIV, inadequate ventilatory drive (eg, apnea, bradypnea), shock, and cardiac arrest.

MWHC implemented a sepsis program consisting of a hospital-wide committee and dedicated response team for patients with signs of systemic inflammatory response syndrome (SIRS)/sepsis to provide high-quality, efficient, and timely treatment. Sepsis definitions and classifications were evaluated using both the CMS Early Management Bundle Severe Sepsis/Septic Shock SEP-1[3] criteria and the newer Surviving Sepsis Campaign guideline (SEP-3) criteria.[19] According to SEP-1, sepsis is classified as a presumed or known infection plus $\geq$ 2 SIRS criteria. Severe sepsis is defined as the presence of sepsis plus $\geq$ 1 sign of end-organ dysfunction or lactate $>$ 2 mmol/L, whereas septic shock is defined as sepsis with refractory hypotension or indications of tissue hypoperfusion (initial lactate $\geq$ 4 mmol/L). Per the Surviving Sepsis Campaign SEP-3 guidelines, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, with organ dysfunction operationalized using SOFA scores.[19] Of note, CMS does not follow the updated Third International Consensus Definitions for Sepsis and Septic Shock, known as Sepsis-3.[19]

Identification of patients with possible sepsis included clinical suspicion based on medical history or presentation and the use of an automated clinical decision-making tool embedded in the hospital's electronic medical record. The St. John Sepsis Surveillance Agent (Table 1) alerts clinicians of the documented presence of SIRS/sepsis criteria in both in-patients and emergency patients as defined by CMS' sepsis core measures, but also includes measures of organ dysfunction as recommended in SEP-3. Upon trigger of a sepsis alert, the response team assesses the patient as quickly as possible and begins treatment based on the diagnosis and classification of sepsis. At MWHC, sepsis is diagnosed subsequent to a documented source of infection following a workup (eg, microbiologic testing, imaging) and acute organ dysfunction as assessed through laboratory values and clinical assessment, prior to antibiotic administration. These encounters were recorded immediately in the medical record using a template with required fields.

Table 1. St. John Sepsis Surveillance Agent

SIRS CRITERIA	SEPSIS CRITERIA
≥3 of the following modifications • Temperature <36.0 or ≥38.4°C • Heart rate ≥91 beats/min • Frequency ≥21 breaths /min • WBCs ≥ 12.1K or <4K or Bands ≥10.1% • Glucose >140 mg/dL and <200 mg/dL	2 SIRS criteria AND any 1 end organ dysfunction modification • SBP <90 mm Hg, or MAP <65 mm Hg, or a SBP decrease of >40 mm Hg • Lactate ≥2.1 mmol/L • Creatinine ≥2.0 mg/dL AND increase of 0.5 mg/dL over 72 h • Bilirubin > 2 mg/dL, ≤10 mg/dL • Platelet count <100,000 • INR >1.5 (not on anticoagulant) or PTT >60 s

SIRS = systemic inflammatory response syndrome
WBC = white blood cell count
SBP = systolic blood pressure
MAP = mean arterial pressure
INR = international normalized ratio
PTT = partial thromboplastin time

Treatment of sepsis at MWHC during the study period was based on the SEP-1, 3- and 6-h bundled care with early goal-directed therapy. CMS has not adopted the Surviving Sepsis Campaign's 2018 update, which created a single "hour-1 bundle"; however, we evaluated the timing recommended by this update for all measures to assess outcomes according to how rapidly treatment was delivered.[20] Three-hour early goal-directed therapy for severe sepsis included lactate measurement, blood cultures prior to antibiotics, and administration of broad-spectrum antibiotics. Six-hour early goal-directed therapy included 30 mL/kg crystalloid administration for hypotension (systolic blood pressure [SBP] $<$ 90 mm Hg, decline in SBP $>$ 40 mm Hg, or mean arterial pressure [MAP] $<$ 70 mm Hg) or lactate $\geq$ 4 mmol/L; use of vasopressors for refractory hypotension despite fluid resuscitation to maintain MAP $\geq$ 65 mm Hg; and lactate remeasurement if initial values were $\geq$ 2 mmol/L. One-hour goal-directed therapy includes all of the above, although the Surviving Sepsis Campaign guidelines acknowledge that time for delivery may exceed the stated 1-h goal (https://www.sccm.org/getattachment/SurvivingSepsisCampaign/Guidelines/Adult-

Patients/Surviving-Sepsis-Campaign-Hour-1-Bundle.pdf?lang=en-US, *Accessed January 4, 2021*).

Data Analysis

Demographic, baseline, clinical, and outcome data were extracted from the medical record, with additional information obtained from a hospital-wide sepsis database with documentation on CMS core measure-related values. Demographic data included age and sex. Baseline information included body mass index; acuity measures SOFA within 24 h of NIV initiation, and the Charlson comorbidity index); past medical history; presence of immunosuppression (by provider documentation and ICD-10 discharge coding for immunodeficiency disorders, immunodeficiency secondary to medications, hematologic malignancies, HIV disease); sepsis source (intra- or extrapulmonary, or mixed per provider notes); NIV indication; time from sepsis alert to NIV initiation; and the hospital unit where NIV was started. Clinical and outcome data such as lactate levels, hemodynamics, fluid requirements based on lactate or blood pressure, fluid administration (total fluids at 6 h after sepsis alert; and any fluids administered within 3 h after alert), use of vasopressors, signs of fluid overload (ie, chest radiograph interpretation of pulmonary edema or pulmonary venous congestion by the radiologist, and other clinical indicators including documentation of jugular venous distention, lower-extremity edema, crackles), time to antibiotic initiation from sepsis alert, Glasgow coma scores at NIV start, pre-NIV F_{IO_2} and S_{pO_2} serum CO_2, initial NIV settings, post-NIV response (breathing frequency and exhaled V_T), post-NIV arterial blood gas, NIV duration, diagnosis of ARDS in the medical record, and mortality were also collected.

All continuous data are presented as either mean ± SD or median (interquartile range), and categorical values are presented as number (%). Between-group comparisons were made using chi-square testing for categorical information, and Student *t* test or Wilcoxon rank-sum test for quantitative data, depending on normality testing using Shapiro-Wilk. Univariate logistic regression was also performed, and all variables with $P \leq .10$ were examined in a backward, step-wise, multivariate logistic regression model following log transformation of all non-normally distributed continuous data. Data were imported into SAS 9.4 (SAS Institute, Cary, North Carolina) and analyzed with $P < .05$ indicating statistical significance.

Results

There were 2,514 patients admitted to MWHC with sepsis during the study period (Fig. 1). Of these patients, 210 were placed on NIV and thus were screened for study inclusion. We excluded 74 subjects (ie, due to obstructive sleep apnea, extubation to NIV, postextubation respiratory failure, palliative or do-not-resuscitate orders), leaving 136 subjects with sepsis-related ARF (Fig. 1), with 70 subjects in the NIV failure group (ie, required intubation from NIV) and 66 subjects in the NIV success group (ie, no intubation from NIV). The overall failure rate for NIV in subjects with a diagnosis of sepsis was 51%, and documented reasons for failure are shown in the supplementary materials (available at http://www.rcjournal.com).

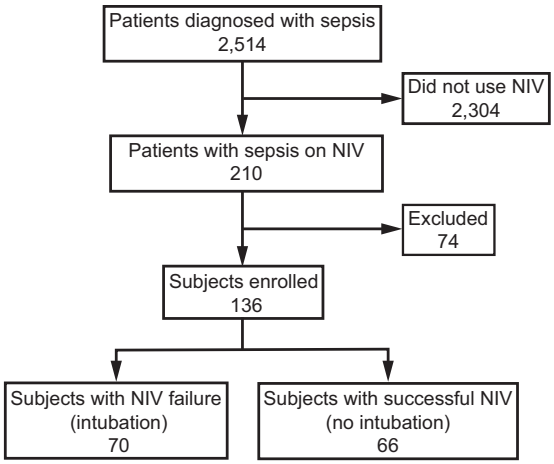

Fig. 1. Flow chart. NIV = noninvasive ventilation.

Demographic and baseline characteristics between groups are shown in Table 2, and documented infection sources are shown in Table 3. There were no statistically significant differences between groups for age ($P = .23$), sex ($P = .94$), body mass index ($P = .40$), Charlson comorbidity index ($P = .11$), immunosuppression ($P = .72$), sepsis source ($P = .78$), history of chronic respiratory failure ($P = .87$), heart failure ($P = .95$), renal failure ($P = .32$), hospital unit where NIV was started ($P = .66$), or time to NIV initiation after sepsis alert ($P = .37$). However, SOFA scores were higher in subjects who failed NIV compared to those in the NIV success group (6.4 ± 3.0 vs 4.9 ± 2.1, $P = .002$).

Clinical parameters included pre-NIV S_{pO_2} and F_{IO_2}, lactate, hemodynamic variables, use of vasopressors, fluid administration, Glasgow coma score, initial NIV settings, and post-NIV arterial blood gas, breathing frequency, and exhaled V_T (Table 4). Subjects in the NIV failure group required higher median (interquartile range [IQR]) values for F_{IO_2} (0.45 [IQR 0.35–1] vs 0.40 [IQR 0.28–0.50], $P = .01$) to achieve similar S_{pO_2} values (95% [IQR 90–98] vs 95% [IQR 91–97], $P = .95$) prior to NIV start compared to those in the NIV success group. First lactate levels following the initial sepsis alert were similar between groups ($P = .57$), and there was no difference in the number of subjects who required a second lactate ($P = .32$). However, second lactate levels (2.6 [IQR 1.7–4.3] vs 1.9 [IQR 1.4–2.6] mmol/L, $P = .007$) were higher in the NIV failure group, and the lactate value trended downward (from first to second test) in fewer of these subjects ($P = .042$). There were also more subjects in the NIV

Table 2. Baseline Characteristics of Subjects With Sepsis Placed on NIV for Acute Respiratory Failure

Variable	NIV Failure ($n = 70$)	NIV Success ($n = 66$)	P
Age, y	66.5 (57.3–75)	65 (49–71)	.23
Male/female	36/34	34/32	.94
Body mass index, kg/m^2	26.6 (23.2–31.6)	27.5 (23.1–32.2)	.4
Charlson comorbidity index	5 (3–6)	5 (4–7)	.11
SOFA score	6.3 ± 3.0	4.9 ± 2.11	.002
Immunosuppression	8 (12)	9 (14)	.72
Past medical history of			
Chronic respiratory disease	20 (29)	20 (30)	.87
CKD/ESRD	13 (19)	16 (24)	.32
Heart failure	30 (43)	27 (41)	.95
Source			.78
Intrapulmonary	33 (47)	33 (50)	
Extrapulmonary	28 (40)	21 (32)	
Mixed	9 (13)	12 (18)	
Sepsis alert to NIV start, h	1.0 (–0.90 to 21.03)	3.77 (–0.75 to 29.3)	.37
Indications for NIV			.22
Hypoxemic respiratory failure	41	28	
Hypercapnic respiratory failure	1	2	
Mixed hypoxemic/hypercapnic respiratory failure	14	14	
Work of breathing	14	22	
S_{pO_2} prior to NIV start, %	95 (90–98)	95 (91–97)	.95
F_{IO_2} prior to NIV start	0.45 (0.35−1.0)	0.40 (0.28−0.50)	.01
Hospital unit where NIV was started			.66
General care	18 (26)	12 (18)	
ICU	13 (19)	16 (24)	
Emergency department	35 (50)	35 (53)	
Other	3 (4)	3 (5)	

Data presented as mean ± SD, median (interquartile range), or n (%). Data were analyzed with Student t test or Wilcoxon rank sum test following normality testing for quantitative variables, or with chi-square test for categorical information.
NIV = noninvasive ventilation
SOFA = Sequential Organ Failure Assessment
CKD = chronic kidney disease
ESRD = end-stage renal disease

Failure group that had a lactate ≥ 4 mmol/L (33% vs 14%, $P = .02$) prior to NIV start compared to those who succeeded on NIV. Hemodynamics also varied, with both the first SBP after the sepsis alert (122 [IQR 97–139] vs 137 [IQR 105.5–158.5] mm Hg, $P = .02$) and MAP at NIV start (85 [IQR 74–96] vs 91.7 [IQR 78–108.7] mm Hg, $P = .042$) being significantly lower in the NIV failure group. Patterns in blood pressure values did not differ between groups, nor did heart rate ($P = .77$) or use of vasopressors ($P = .14$) at NIV start.

A similar number of subjects in both groups required fluid resuscitation (80% vs 71% in the NIV failure and NIV success groups, respectively, $P = .23$), and there were no significant between-group differences in the time to the start of fluid administration from the sepsis alert if fluids were provided (NIV failure: 0 h [IQR –0.77 to 2.49] vs NIV success: –0.33 h [IQR –1.70 to 1.4], $P = .58$), with fluids given coinciding with the sepsis alert or prior to the alert, thus meeting the 1-h bundle goals. The NIV failure group and the NIV success group were also statistically similar regarding the total amount of fluids received (37 [IQR 16–53] vs 39.5 [23.2–57.0] mL/kg/body weight, respectively, $P = .41$) and the number of subjects who received ≥ 4 L of fluids (23% vs 32%, respectively, $P = .31$). However, fewer subjects ($P = .001$) in the NIV failure group (39 of 56, 70%) who required fluid resuscitation received any fluids within the first 6 h following the sepsis alert compared with those in the NIV success group (42 of 47, 89%). In addition, subjects in the NIV failure group were less likely to have signs of volume overload (35% vs 64%, $P < .001$) or receive any fluid resuscitation in the 24 h prior to NIV start (29% vs 79%, $P = .02$). In the NIV failure group, 17 (55%) subjects with a history of heart failure or chronic renal failure had signs of volume overload compared to 27 (75%) in the NIV success group, although this difference was not statistically significant ($P = .12$). Fewer subjects ($P = .02$) in the NIV failure

Table 3. Documented Source of Infection

Sepsis Source	NIV Failure ($n = 70$)	NIV Success ($n = 66$)
Bacteremia	4 (6)	4 (6)
Cellulitis	0 (0)	2 (3)
Endocarditis	4 (6)	2 (3)
Liver		
Cholangitis	0 (0)	2 (3)
Cholecystitis	2 (3)	2 (3)
Mediastinitis	2 (3)	0 (0)
Necrotizing fasciitis	4 (6)	0 (0)
Osteomyelitis	1 (2)	1 (2)
Pancreatitis	2 (3)	2 (3)
Pericarditis	1 (2)	1 (2)
Peritonitis	3 (4)	1 (2)
Vascular dialysis catheter	3 (4)	3 (5)
Pneumonia	33 (47)	33 (50)
Urinary tract infection	15 (21)	15 (23)

Data are presented as *n* (%). Some subjects may have had > 1 diagnosis.
NIV = noninvasive ventilation

group with heart failure or chronic renal failure received recommended fluids (45%) following the sepsis alert compared to the NIV success group (78%).

Glascow coma scores at NIV start were also lower in the NIV failure group than in the NIV success group (14 [IQR 13–15] vs 15 [IQR 14–15], $P = .002$) (Table 3). Initial NIV settings were similar between groups for inspiratory positive airway pressure ($P = .14$), expiratory positive airway pressure ($P = .24$), and pressure-support level ($P = .30$), but F_{IO_2} was significantly higher in the NIV failure group than in the NIV success group (0.50 [IQR 0.40–0.70] vs 0.40 [IQR 0.35–0.50], $P = .003$). Arterial blood gas results were available within 4 h of NIV start in 45 (64%) subjects in the NIV failure group, and in 40 (61%) subjects in the NIV success group (Table 5). After the initiation of NIV, P_{aO_2}/F_{IO_2} was significantly lower in the NIV failure group than in the NIV success group (186.6 [IQR 106.3–235] vs 198.3 [IQR 148.5–298.9], $P = .039$), but there were no differences in pH ($P = .18$), P_{aCO_2} ($P = .78$), or HCO_3^- ($P = .69$). Exhaled V_T was similar between both groups, but there were significant differences between the NIV failure group and the NIV success group for breathing frequency (30 breaths/min [IQR 23–36] vs 25 breaths/min [IQR 20–29], $P < .001$), NIV duration (5.9 h [IQR 1.7–20.9] vs 12.3 h [IQR 4.8–34.8], $P = .02$), development of ARDS (22% vs 5%, $P = .003$), and mortality (42% vs 11%, $P < .001$), respectively.

Age, SOFA score, first SBP after sepsis alert, MAP at start of NIV, lactate ≥ 4 mmol/L prior to NIV, Glasgow coma score, fluids prior to NIV, signs of volume overload prior to NIV, and initial NIV F_{IO_2} were significant in the univariate analysis and thus were entered as independent variables into a backward, step-wise multiple logistic regression analysis with "NIV failure" as the dependent variable. Results indicated that age (odds ratio [OR] 1.05 [95% CI 1.01–1.09], $P = .02$), SOFA score (OR 1.49 [95% CI 1.15–1.94], $P = .002$), first SBP (OR 0.97 [95% CI 0.95–0.99], $P = .02$), signs of volume overload (OR 0.23 [95% CI 0.07–0.68], $P = .008$], fluids prior to NIV (OR 0.08 [95% CI 0.02–0.31], $P < .001$), and initial NIV F_{IO_2} (OR 1.04 [95% CI 1.01–1.08], $P = .002$) independently predicted NIV failure. Receiver operating curve analysis found an area under the curve of 0.88 (Fig. 2). When SOFA scores and initial SBP after sepsis alert were eliminated from the model, the area under the curve was 0.85. Further analysis revealed a sensitivity of 42% and specificity of 82% for the continuous variables in the model using the Youden J Index to determine specific cut points for age (65 y), initial SBP (119.5 mm Hg), SOFA score (7), and F_{IO_2} (0.45).

Significant univariate results with "mortality" as the dependent variable included age, first SBP after sepsis alert, MAP at NIV start, lactate ≥ 4 mmol/L prior to NIV, fluid administration prior to NIV, SOFA scores, and NIV failure. However, only NIV failure (OR 5.28 [95% CI 1.92–14.3], $P = .001$) independently predicted death in multivariate analysis with area under the curve of 0.70 (Fig. 3).

Discussion

The results of this retrospective cohort study in subjects placed on NIV for sepsis-related ARF include a high failure rate (50%), which was independently predicted by age, degree of organ failure, signs of volume overload, fluid administration prior to NIV, initial F_{IO_2} on NIV, and initial SBP after sepsis alert, with a good overall model fit (area under the curve = 0.88). However, there was poor sensitivity and moderate specificity at cut points for continuous model variables. Also of note, NIV failure was the only variable that independently predicted mortality after controlling for age, SOFA score, initial SBP after sepsis alert, MAP at NIV start, fluid administration prior to NIV, and lactate > 4 mmol/L prior to NIV, with the model explaining a fair amount of the variance (area under the curve = 0.70).

NIV research has included specific and heterogeneous patient populations, but few studies have examined subjects with sepsis as a distinct group. Two published, full-text manuscripts were found reviewing the use of NIV in subjects with sepsis. Duan et al[14] conducted a prospective multi center observational study of 519 subjects with acute hypoxemic respiratory failure in 16 ICUs; of these subjects, 70% ($n = 365$) were diagnosed with sepsis. NIV failed in 38% of subjects with sepsis and > 60% of those with septic

Table 4. Clinical Parameters at Initiation of NIV

Variable	NIV Failure ($n = 70$)	NIV Success ($n = 66$)	P
First lactate after sepsis alert, mmol/L	2.5 (1.5–3.9)	2.5 (.53–3.1)	.57
Second lactate, mmol/L*	2.6 (1.7–4.3)	1.9 (1.4–2.6)	.01
Lactate trending down (first – second)	29 (51)	36 (69)	.042
Any lactate > 4 mmol/L	23 (33)	9 (14)	.02
First SBP after sepsis alert, mm Hg	122 (97–139)	137 (105.5–158.5)	.02
Heart rate at NIV start, beats/min	113 ± 2.9	111.6 ± 23.3	.43
MAP at NIV start, mm Hg	85 (74–96)	91.7 (78–108)	.042
Lowest MAP in 24 h prior to NIV start, mm Hg	77 ± 16	79 ± 18	.51
Lowest SBP in 24 h prior to NIV start, mm Hg	107 ± 28	112 ± 28	.31
SBP decreased > 40 mm Hg prior to NIV	33 (47)	27 (41)	.36
Use of vasopressors in 24 h prior to NIV	6 (9)	2 (3)	.14
Required fluid resuscitation†	56 (80)	47 (71)	.23
Total fluids, mL/kg/BW	37 (16–55)	39.5 (23.2–57.0)	.41
Received/started fluids in 24 h prior to NIV start‡	16 (29)	37 (79)	.02
Required fluids/received fluids	36 (64)	42 (89)	< .001
Received fluids within 6 h of sepsis alert	39 (70)	42 (89)	< .001
Signs of volume overload at NIV start	24 (35)	42 (64)	< .001
Time to first antibiotic, min	28 (–320 to 82.5)	47.5 (–93 to 95)	.46
Glasgow coma score at NIV start	14 (13–15)	15 (14–15)	.001
Serum CO_2	21 (17–26)	23 (19–25)	.20
Initial NIV settings			
Inspiratory positive airway pressure, cm H_2O	15 (12–15)	13 (12–15)	.14
Expiratory positive airway pressure, cm H_2O	5 (5–7.5)	5 (5–6)	.24
Pressure support, cm H_2O	8 (7–10)	7 (5–10)	.30
F_{IO_2}	0.50 (0.40–0.70)	0.40 (0.35–0.50)	.003

Data presented as mean ± SD, median (interquartile range), or n (%). Data were analyzed with Student t test or Wilcoxon rank sum test following normality testing for quantitative variables, or with chi-square test for categorical information.
* NIV Failure: $n = 58$; NIV Success: $n = 52$.
† Based on CMS criteria for lactate and/or BP.
‡ NIV Failure: $n = 56$; NIV Success: $n = 47$.
NIV = noninvasive ventilation
SBP = systolic blood pressure
MAP = mean arterial pressure

shock, compared to 23% of subjects without sepsis. Multivariate analysis indicated that sepsis and septic shock were independently associated with NIV failure, with similar rates between pulmonary and nonpulmonary origins. Not surprisingly, NIV failure in the study by Duan et al[14] was also higher in subjects with greater organ dysfunction as measured by SOFA, with a rate of 53% corresponding to scores of 5–6. Our results concur with these findings, as the NIV failure rate was 50%, and subjects in the NIV failure group had a higher mean SOFA score of 6.3 ± 3.0 compared to 4.9 ± 2.1 in the NIV success group. More subjects in the NIV failure group also had a lactate ≥ 4 mmoL/L, a definition used by CMS to define septic shock, although there were no between-group differences in vasopressor use. MAP was also lower at NIV start in subjects who failed NIV (85 mm Hg [IQR 73–96]) compared to subjects in the NIV success group (91.6 mm Hg [IQR 78–108.6], $P = .042$), but these values were well above those considered hypotensive. We found no between-group differences for NIV failure corresponding to source in accordance with Duan et al.[14]

Razlaf et al[18] studied 120 immunocompromised subjects with intrapulmonary or extrapulmonary sepsis and reported an NIV failure rate of 55%. High APACHE II scores, use of catecholamines, and poorer oxygenation were predictive of NIV failure, with no difference in sepsis source. Our study included few immunocompromised subjects, but we noted a comparable failure rate of 50% in a mixed population of subjects with sepsis. Patient acuity was higher as noted previously, and there were significant between-group differences for P_{aO_2}/F_{IO_2} after NIV initiation, with lower values in those who failed NIV, along with higher initial NIV F_{IO_2} settings.

The presence of ARDS was not discerned in the studies by Razlaf et al[18] or Duan et al,[14] though sepsis is a risk factor for the development of severe lung injury and other studies have shown an association between ARDS and unsuccessful treatment with NIV,[21] particularly in more severe categories.

Table 5. Clinical Outcomes After NIV Initiation

Variable	NIV Failure ($n = 70$)	NIV Success ($n = 66$)	P
ABG ≤ 4 h after NIV start, n	45	40	
pH	7.39 (7.27–7.43)	7.40 (7.34–7.45)	.18
P_{aCO_2}	32 (26–45)	34 (29–43)	.78
HCO_3^-	22 ± 12	21.9 ± 5	.69
P_{aO_2}/F_{IO_2}	186.6 (106.3–235)	198.3 (148.5–298.9)	.039
V_T after NIV start, mL/kg/IBW	9 ± 3	8.0 ± 2.48	.14
Breathing frequency after NIV start, breaths/min	30 (23–36)	25 (20–29)	< .001
NIV duration, h	5.9 (1.7–20.9)	12 (4.8–34.8)	.02
ARDS	15 (22)	3 (5)	.003
In-hospital mortality	30 (43)	7 (11)	< .001

Data presented as mean ± SD, median (interquartile range), or n (%). Data were analyzed with Student t test or Wilcoxon rank sum test following normality testing for quantitative variables, or with chi-square test for categorical information.
NIV = noninvasive ventilation
ABG = arterial blood gas
V_T = tidal volume
IBW = ideal body weight

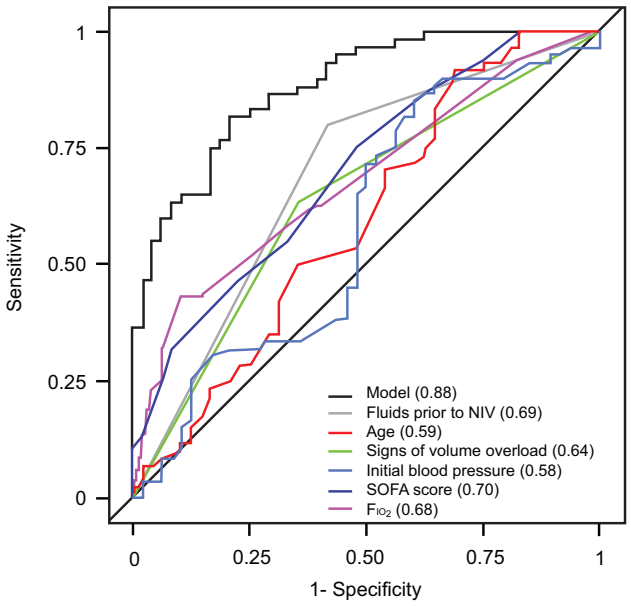

Fig. 2. Receiver operating characteristic curves for independent predictors of NIV failure in subjects with sepsis. Area under the curve values are shown in parentheses. NIV = noninvasive ventilation, SOFA = Sequential Organ Failure Assessment.

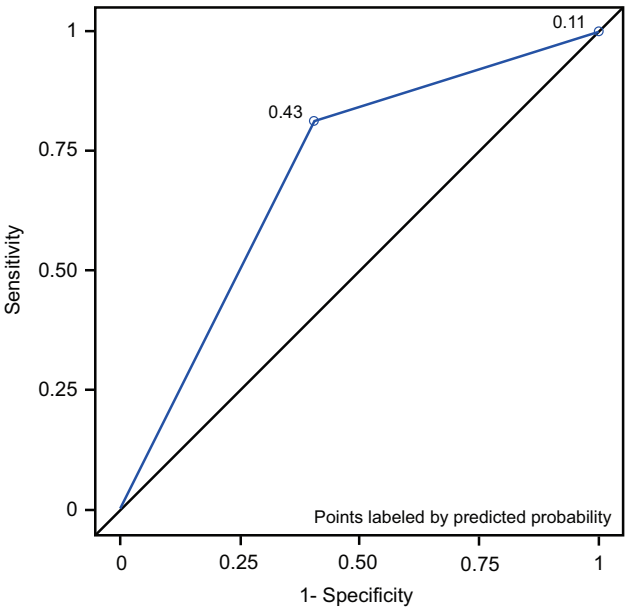

Fig. 3. Receiver operating characteristic curve for independent predictors of mortality in subjects with sepsis placed on noninvasive ventilation. Area under the curve = 0.7034.

ARDS was not diagnosed during NIV in any subject in our study, and fewer patients in the NIV success group were identified with the disorder. The Berlin definition[22] requires the use of 5 cm H_2O PEEP to consider ARDS, and subjects were placed on NIV emergently, with a relatively short duration of therapy. These issues may have left little time for the requisite appearance of bilateral infiltrates or the ability to document and rule out the potential contribution of heart failure to chest radiograph findings.

Higher patient acuity is a recurrent theme in research reviewing the therapeutic success of NIV in specific diagnoses or patient populations. In studies of subjects with heart failure, COPD, immunosuppression, pneumonia, and acute hypoxemic respiratory failure,[21] NIV failure has been associated with greater illness severity measured using a variety of standardized scoring systems. While the SOFA score[23] is a useful gauge of illness severity, calculating this value is time consuming and the required tests are not

always ordered or available. Faster bedside indicators may be more useful in making decisions regarding appropriate patient selection for the use of NIV in patients with sepsis. When SOFA was eliminated from our model, the area under the curve was 0.85, maintaining an acceptable explanation of the variance.

Research has shown improved outcomes with use of early goal-directed therapy in sepsis, although fluid management in these patients is still controversial.[24-26] While fluid resuscitation is recommended as part of SEP-1 guidelines[20] to increase cardiac output and counteract hypoxia thought to result from tissue hypoperfusion, the literature is mixed regarding outcomes. Fixed-fluid doses in sepsis are often criticized secondary to the potential development of complications, particularly in patients with a history of heart or renal failure. We noted that subjects who received more than the recommended amount of fluids prior to NIV initiation and had signs of volume overload were more likely to succeed on NIV, whereas subjects who did not receive the recommended amount of fluids at 6 h after sepsis alert, or did not receive any fluid resuscitation, were more likely to require endotracheal intubation. Subjects with heart or renal failure who failed NIV were also less likely to receive the recommended amount of fluids. The limited available literature regarding fluid management in high-risk subjects with sepsis has been contradictory. Kuttab et al[27] reported that subjects ($n = 509$), including those with heart failure, end-stage renal disease, or documented volume overload, were less likely to be given 30 mL/kg/body weight fluids, and this was associated with greater odds of mortality. In a retrospective, propensity score-matched cohort study of subjects with sepsis or septic shock ($n = 208$), Khan et al[28] reported no difference in intubation rates in subjects with sepsis and heart failure, end-stage renal disease, or cirrhosis given $\geq$ 30 mL/kg or $<$ 30 mL/kg intravenous fluid volumes. The Surviving Sepsis Campaign guidelines and SEP-1 make no exceptions for fluid volumes based on past medical history.

Overall, our results support sepsis guidelines (CMS, Surviving Sepsis Campaign)[3,20] for fluid management, but there is no high-level evidence showing improvements in the rate of adverse events with fluid administration in adults, apart from its combination with other bundle elements.[29] Both retrospective and prospective studies have shown better mortality rates with rapid and adequate fluid resuscitation.[11,30] It should be noted, however, that while both groups received a median amount that exceeded a dose of 30 mL/kg actual body weight recommended by guidelines, the total median fluids in the NIV failure group and the NIV success group (2.5 L [IQR 1.001–3.922] vs 2.9 L [IQR 1.998–4.996], respectively) were below those considered as large volumes ($>$ 4–5 L) in the literature.[31] Further, there were no significant differences in the number of subjects who received $\geq$ 4 L of total fluids for resuscitation within 6 h after sepsis alert. Administration of large volumes of fluids have been associated with pulmonary edema, pleural effusions, hypoxia, increased work-of-breathing, and prolonged duration of mechanical ventilation in patients with sepsis.[31] A further distinction can also be made between fluid administration for resuscitation and a cumulative, long-term positive fluid balance (related to a cap or tapering of total fluids). The latter is associated with lung injury, ARDS, and greater mortality,[32] whereas the former is linked to the occurrence of pulmonary venous congestion and acute pulmonary edema.[33]

Indeed, there is growing evidence that large fluid boluses and cumulative fluid balance are associated with increased mortality. However, we did not find an association between increased mortality and initial resuscitation with fluids of $\geq$ 30 mL/kg/body weight and volume overload, which runs counter to a variety of recent research.[32-40] Most of these studies showing poor outcomes with volume overload in subjects with sepsis have focused on a positive and persistent long-term fluid balance, starting on the first day in the ICU. Our study concentrated on initial resuscitation, and we do not have information on ongoing fluid balance. Nevertheless, we postulate that some of the discrepancy in findings may lie in the total amount of initial fluids provided, which was less than that considered to be aggressive or large volumes, despite exceeding SEP-1 mandates. Conversely, our study does support previous research showing NIV failure as an independent predictor of death.[17] In fact, after controlling for potential confounders, including hemodynamic variables, patient acuity, lactate levels, and fluid administration, NIV failure was the only significant predictor of mortality, although the model explained only a fair amount of the variance (area under the curve = 0.70).

Strengths and Limitations

To our knowledge, we are the first to review NIV outcomes in a general population of subjects with sepsis using SEP-1 guidelines mandated by CMS as an evaluation framework. Previous studies[41-43] have reviewed factors independently associated with NIV failure, including comorbid sepsis and other factors, but none have analyzed the application of bundled care to outcomes with NIV during ARF in sepsis. Additional strengths of our preliminary study include access to our hospital-wide database, which included detailed data on sepsis response, clinical management, and outcomes for all patients admitted to our institution. We also included all patients admitted with sepsis and placed on NIV for ARF during the study period when there was consistent treatment for the disorder, as mandated by protocolized care. In addition to our analyses based on sepsis-core measures, we reviewed other confounding variables such as comorbidities, NIV settings, and physiologic

data, information lacking in other studies that describe NIV use in subjects with sepsis.

However, there are several limitations to this research. The study was retrospective and used data extracted from the electronic medical record, which may be subject to documentation or extraction errors. The overall sample size in each group was relatively small, and the research was conducted in a single institution, which may limit generalization to other patient populations with different clinical management of sepsis.

Further, we did not record certain therapeutic information, including the type of fluid used for resuscitation (although crystalloids are a standing order), fluid response based on hemodynamic parameters in individual subjects, and infusion rates. We also do not have more accurate information on fluid balance, including inferior vena cava collapse, input/output data, or total fluids administered following the initial bundle window of 1–6 h. More detailed data on initial fluid balance were unavailable for a large portion of subjects, often because they were recently admitted to the hospital and emergently placed on NIV and then intubated, without the opportunity for full diagnostic workups or adequate time for comparative data acquisition. However, rapid bedside determination of factors associated with NIV failure may be helpful to clinicians during an emergent situation, and ascertaining whether the patient is septic and has received or started fluid resuscitation requires a relatively simple query. Last, chest radiographs may not be sensitive in detecting fluid overload, although we also collected data regarding other clinical signs related to volume status.[44]

Conclusions

Our results indicate that NIV failed in a significant portion of subjects with sepsis and was independently associated with patient acuity, fluid administration, hemodynamic parameters, age, and initial F_{IO_2} on NIV. The only significant predictor of mortality in this patient population was NIV failure after controlling for SOFA scores, first SBP after sepsis alert, MAP prior to sepsis, fluid administration prior to NIV, and any lactate $>$ 4 mmol/L prior to NIV. Larger cohort studies, with additional data related to fluid administration and balance, are needed to confirm these results.

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