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The Comparative Effectiveness of Noninvasive and Invasive Ventilation in Patients with Pneumonia

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Abstract

Purpose—To compare the outcomes of patients hospitalized with pneumonia treated with noninvasive ventilation (NIV) and invasive mechanical ventilation (IMV).

Materials and Methods—Using the HealthFactsmultihospital electronic medical record database, we included patients hospitalized with a diagnosis of pneumonia and treated with NIV or IMV. We developed a propensity model for receipt of initial NIV and assessed the outcomes in a propensity-matched cohort, and though covariate adjusted and propensity score weighted models.

Results—Among 3971 ventilated patients, 1109 (27.9%) were initially treated with NIV. Patients treated with NIV were older, had lower acuity of illness score, and were more likely to have congestive heart failure andchronic pulmonary disease. Mortality was 15.8%, 29.8% and 25.9.0% among patients treated with initial NIV, initial IMV and among those with NIV failure. In the propensity matched analysis, the risk of death was lower in patients treated with NIV (relative risk:

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Author Contributions: Drs. Stefan, Lindenauer, Pekow, Steingrub, Lagu and Hill conceived and designed the study. Dr. Stefan acquired the data used in the analysis. Drs. Stefan, Priya, Nathanson, Lindenauer, Lagu, Steingrub, and Hill were involved in the analysis and interpretation of the data. Dr. Stefan drafted the manuscript and Drs. Lindenauer, Priya, Pekow, Lagu, Steingrub, Nathanson, Pekow and Hill reviewed and contributed to revisions prior to submission.

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0.71, 95% CI: 0.59–0.85). Subgroup analysis showed that NIV was beneficial among patients with cardiopulmonary comorbidities (relative risk 0.59, 95% CI: 0.47–0.75) but not in those without (relative risk 0.96, 95% CI: 0.74–0.1.25)NIV failure was significantly (p=0.002) more common in patients without cardiopulmonary conditions (21.3%) compared to those with these conditions (13.8%).

Conclusions—Initial NIV was associated with better survival among the subgroup of patients hospitalized with pneumonia who had COPD or heart failure. Patients who failed NIV had high in-hospital mortality, emphasizing the importance of careful patient selection monitoring when managing severe pneumonia with NIV.

Keywords

pneumonia; noninvasive ventilation; mechanical ventilation; noninvasive ventilation failure

Background

Each year in the United States, nearly one million patients with acute respiratory failure (ARF) are treated with invasive mechanical ventilation (IMV).[1] Up to 40% of mechanically ventilated patients die in the hospital,[2,3] and some of these deaths are directly attributable to complications of the ventilator.[4] In selected groups of patients with ARF, noninvasive mechanical ventilation (NIV) reduces the need for endotracheal intubation leading to better outcomes. While most of the published evidence on the effectiveness of NIV to avoid intubation applies to patients with acute COPD exacerbation[5–8] or acute cardiopulmonary edema,[9,10] NIV has become a common treatment in patients with ARF regardless of etiology.[11–14]

Pneumonia is the leading infectious cause of hospitalization in U. S. and results in over one million admissions annually. Between 58% and 87% of patients with severe pneumonia develop ARF. Mortality among patients with pneumonia who require intensive care unit admission ranges from 15 to 51%. The effectiveness of NIV in pneumonia is controversial since it is associated with high treatment failure rates compared to other causes of ARF[15,16] and because mortality rate associated with NIV failure is high. [17] This risk is particularly concerning for patients with no prior respiratory or cardiac condition (known as ‘de novo’ acute respiratory failure).[14,17–19] In addition, several studies have found that pneumonia is an independent risk factor for NIV failure in patients hospitalized with acute COPD exacerbation or asthma.[8,20,21] Thus, professional guidelines recommend caution in using NIV in immunocompetent patients with ARF due to pneumonia given insufficient evidence of its efficacy.[22]

Only one other study has examined the role of NIV in patients with pneumonia needing ventilatory assistance, however it included only patients older than 65 years of age admitted to an intensive care unit.[23] Therefore, we aimed to compare the outcomes of patients with pneumonia initially treated with NIV to those initially treated with IMV using a large multihospital electronic medical record database that contains results of laboratory testing.

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Methods

Design and setting

We conducted a retrospective cohort study of patients hospitalized between January 1, 2009 and December 31, 2012 using Cerner HealthFacts (Cerner Corporation, Kansas City). Data in HealthFacts Facts is extracted directly from the EMR from hospitals in which Cerner has a data use agreement. Encounters may include pharmacy, clinical and microbiology laboratory, admission and billing information. All admissions, medication orders and dispensing, laboratory orders and specimens are date and time stamped, providing a temporal relationship between treatment patterns and clinical information. Cerner Corporation has established Health Insurance Portability and Accountability Act-compliant operating policies to establish de-identification for Health Facts. The dataset was used extensively for research.[24,25] (Additional details about HealthFacts database in eAppendix)

Study population

The inclusion/exclusion criteria aimed to identify a cohort of patients with pneumonia eligible for either NIV or IMV for whom laboratory and medication data was available. This reduced the risk of misclassification from criteria based only on ICD-9 codes and allowed us to calculate a severity risk score at admission. From a cohort of patients with a principal discharge diagnosis of pneumonia or a secondary diagnosis of pneumonia when accompanied by a principal diagnosis of acute respiratory failure or sepsis, we included patients who were 18 years or older and received NIV or IMV on the day of admission. (ICD-9 codes in eAppendix 2) To increase the specificity of the diagnosis of pneumonia, we restricted the analysis to those patients treated with antibiotics within 48 hours of admission. Since the dataset does not contain information about advance directives, we excluded patients older than 80 years and patients on palliative care or hospice at the time of admission, as they are less likely to be intubated if NIV is unsuccessful. We verified this assumption by analyzing this cohort of patients separately. (Results in eAppendix). Since we wanted to estimate mortality risk at the time of admission, we excluded patients who did not have results of WBC testing within 24 hours of admission, and patients without laboratory data. We also excluded patients with obstructive sleep apnea since it would not be possible to differentiate chronic use of NIV from treatment for acute respiratory failure; and patients with a contraindication for NIV. We further excluded patients transferred to or from another facility because their initial form of ventilation and their outcomes could not be ascertained. For patients with multiple eligible admissions during the study period, we randomly selected 1 admission for inclusion into the study cohort.

Treatment variable—We defined initial NIV and initial IMV based on the first method of ventilation and noted changes in ventilation therapy (if any) over time. We used ICD-9 procedure codes to identify ventilation modality (93.90 for NIV and 96.7x and 96.04 for IMV). Of note, ICD-9 procedure codes do not contain information about the number of hours per day that the ventilation method was used.

When NIV and IMV were recorded on the same day with neither recorded for the following day, we assumed IMV followed NIV.

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Patient and hospital characteristics

We recorded patient age, gender, and insurance status and the hospital characteristics (eg, teaching status, number of beds) of each hospitalization. We recorded chronic comorbidities based on the software provided by the Healthcare Costs and Utilization Project of the AHRQ.[26,27] We calculated an overall comorbidity score as described by Gagne et al.,[28]

We collected several variables to assess illness severity at the time of admission. First, we calculated the Laboratory Acute Physiology Score (LAPS), which uses the results of laboratory testing at the time of admission to quantify the risk of inpatient mortality. The LAPS has been internally and externally validated and has a high performance (c statistic of 0.83) in various subpopulations. It integrates 14 laboratory tests, including arterial blood gas results, into a single continuous score, which ranges between 0 and 256; higher LAPS scores are associated with greater likelihood of mortality (detailed information about LAPS in eAppendix).[29–31] We also collected information on the number of prior hospitalizations, NIV or IMV use in the year before the index admission; vasopressor use during first 24 hours of admission; and initial care venue including intensive care unit, intermediate care, or general medical ward (all treatments received in the emergency room are rolled in the admission encounter and can not be separately identified). We classified pneumonia as community acquired or healthcare associated using the methodology used by other authors.[32,33]

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes were NIV failure, length of hospital stay, and all-cause 30-day readmission among survivors.

NIV failure was defined as treatment with IMV following exposure to NIV. We required that NIV be followed by IMV on the same or subsequent day.

Using ICD-9 diagnosis codes, we identified complications that arose during hospitalization (not present at admission) which included myocardial infarction, cardiopulmonary arrest, and pneumothorax.

Statistical analysis

To describe the study population, we calculated frequencies and proportions for categorical data, means, standard deviations, or medians and interquartile ranges (IQR) for continuous variables. We compared characteristics of patients who received initial NIV or IMV using absolute standardized differences. All standardized differences > 10% were deemed important.

To assess the impact of initial mode of ventilation on outcomes, we first developed a propensity score for receipt of initial NIV using a GEE model accounting for patient clustering within hospitals. Predictor variables included patient demographics, comorbidities, prior admission status, prior use of NIV or IMV within one year, principal diagnosis, receipt of vasopressors within 24 hours of admission, community acquired versus healthcare associated pneumonia, and LAPS. We matched each initial NIV-treated patient to an initial IMV-treated patient of similar propensity using a Greedy Match algorithm. Our

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primary analysis was in the propensity-matched cohort using multivariable conditional logistic regression to account for matching and adjusting for remaining differences between the groups.

Using the full cohort, we also developed a series of hierarchical models including a hospital random effect, adjusting for propensity for treatment and other covariates to assess the independent effect of NIV on the outcomes. In-hospital mortality was frequent (>20%), so Poisson models with log link function were used to estimate the relative risk for this outcome. Logit link models were used for 30-day all-cause readmission and identity link models for length of stay which was winsorized at 5th and 99th percentile of its distribution to address skewness. Additionally, we evaluated two propensity weighting methods, stabilized inverse-probability-of-treatment weighting (SIPTW) and standardized mortality ratio weighting (SMRW).[34] (see eAppendix for details)

We performed two sensitivity analyses. First, we examined the association between the type of ventilation and outcomes among patients with a median acuity range (LAPS of 50 to 99) which excluded patients at extremes of illness severity. Second, using hospital preference for NIV as an instrument, we carried out an instrumental variable (IV) analysis in an attempt to address concerns about residual unmeasured confounding.[35] Hospitals with rates of NIV at or above the median rate were considered to prefer NIV over IMV. (Detailed description of IV analysis is included in eAppendix)

In addition, because prior studies showed that the patients with ‘de novo’ acute respiratory failure have worse outcomes, we performed a secondary analysis and assessed mortality and NIV failure rates in subgroups of patients with and without cardiopulmonary conditions. [18,19,36]

NIV Failure

Among the cohort of patients who were initially administered NIV, we identified factors predictive of NIV failure (intubation) using a GEE model and the predictors as in the models mentioned above.

All analyses were performed using the Statistical Analysis System (version 9.4, SAS Institute, Inc., Cary, NC) and STATA 13 (StataCorp. Inc., College Station, TX).

Results

A total of 3,971 patients from 81 hospitals were included in the analysis. 1,109 (27.9%) patients were initially managed with NIV and 2,862 (72.1%) received IMV. (Figure 1) Patients’ mean (SD) age was 61.7 (13.6) years, 51.7% were male, 72.5% were white and mean (SD) comorbidity score was 3.6 (2.6). Mean (SD) LAPS was 70.7 (28.7), 39.2% were admitted to the ICU and 45.2% had community acquired pneumonia. In-hospital mortality was 25.9%, mean (SD) length of stay was 10.4 days (8.5) and 30-day readmission rate was 15.2%.

Patients initially treated with NIV were older and more likely to be white than patients initially treated with IMV (mean age 64.0 vs 60.9 years). They were also more likely to have

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been treated with NIV in a prior admission (13.6% vs 3.7%), and to have had ≥ 2 admissions in the prior year. They had lower severity of illness at the time of admission (mean LAPS 59.4 vs 75.1), were less likely to have a principal diagnosis of sepsis or acute respiratory failure, or to be treated with vasopressors within 24 hours of admission (16.7% vs 45.7%), and to be initially admitted to the intensive care unit (24.8% vs 44.8%). Comorbidities such as congestive heart failure and chronic pulmonary disease were more frequent among those treated with NIV. In contrast, liver disease, weight loss, paralysis and other neurological disorders were more common among patients treated with IMV. Rates of community and health-care associated pneumonia were similar in the two groups. (Table 1)

In unadjusted analysis, in-hospital death occurred in 15.8% of patients treated with NIV and 29.8% of patients treated with IMV. The mean (SD) length of stay was 7.6 (5.6) days and 11.5 (9.1) days among those ventilated with NIV and IMV respectively. Among survivors, 62.4% of the NIV and 48.7% of IMV treated patients were discharged home. (Table 2)

Results of propensity-matched and multivariable adjusted models analyses

We matched 812 patients treated with NIV (73.2% of the initial NIV cohort) by their propensity score with patients treated with IMV. Race and the number of times a patient received NIV in the year prior to admission were the characteristics that differed between the two groups with an absolute standardized difference of 18% and 12.6% (See Table 1). In the conditional regression models which adjusted for unbalanced factors in the matched subset, the risk of death for patients treated with NIV was lower compared with those treated with IMV (relative risk: 0.71, 95% CI: 0.59–0.85). The results from the models in the full cohort (which adjusted for patient demographics, comorbidities, prior admission and ventilation therapy, LAPS, and propensity for NIV treatment) and the estimates based on SMR (average treatment effect in the treated) and SIPTW (the population average treatment effect) were similar but somewhat smaller (ie, closer to one).[34] (Figure 2)

In a sensitivity analysis of a cohort of 2453 patients with a LAPS of 50–99 we observed that the survival benefit of NIV was similar to the results in the full cohort (relative risk for death: 0.64; 95% CI: 0.51–0.81).

Instrumental variable (IV) analysis: the assessment of the instrument characteristics showed that the instrument was strong, but the Durbin-Wu-Hausman test indicated that the IV analysis did not achieve better adjustment of confounding than the standard multivariable regression. (Results are presented in eAppendix)

Secondary analysis—Mortality and NIV failure rates were significantly lower in patients with pneumonia and comorbid cardiopulmonary conditions (COPD or heart failure) than in those without (21.5% vs 32.7% and 13.8% vs 21.3%). In the multivariable mortality model, the interaction between early NIV and cardiopulmonary comorbidity was significant ($p = 0.005$). From stratified analysis, the relative risk of death of early NIV versus IMV was 0.59 (95% CI: 0.47, 0.75) in patients with COPD or heart failure comorbidities and 0.96 (95% CI: 0.74, 1.25) among patients without these conditions.

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Among survivors, use of NIV was associated with shorter length of hospital stay (3.3 days less, 95% CI: (−4.09, −2.48) in the matched sample). There was no significant association between the ventilation modality and all-cause 30-day readmission. (Figure 2)

NIV failure

NIV failure was recorded in 158 (15.8%) of those treated with NIV who were not on palliative care or discharged to hospice. Patients who failed NIV had higher hospital mortality than patients who were successfully treated with NIV (25.9% vs 9.7%, p <0.001). They also had higher rates of in-hospital complications, longer median hospital stay (10 vs 6 days) and were less likely to be discharged home (53.0% vs 67.7.2%). (eTable 2) In the multivariable analysis that adjusted for patient characteristics, the following factors were predictors of NIV failure: LAPS (1.26: 95% CI (1.16–1.37) for each 10 point increase in the LAPS), principal diagnosis of ARF (OR: 3.31, 95% CI 2.02, 5.41), weight loss (OR: 2.96; 95% CI 1.89, 4.63), use of vasopressors in the first 24 hours of admission (OR: 3.18; 95% 1.98, 5.12) and initial admission to ICU (OR: 2.23; 95% CI 1.454–3.434). (Table 3)

Among patients with NIV failure, mortality was higher in those without comorbid COPD or CHF than in those with these conditions (40.6% vs 25.05).

Discussion

In this retrospective study of nearly 4,000 patients hospitalized with pneumonia who required ventilation, we found that more than one fourth of the patients received NIV as the initial ventilation method. Patients treated with NIV tended to have lower severity of illness at admission as evidenced by lower LAPS scores and were more likely to have comorbid COPD, and heart failure.. In the propensity-matched cohort, NIV therapy was associated with a 29% relative reduction of in-hospital mortality compared with IMV. The survival advantage with NIV therapy remained significant in several modeling methods and sensitivity analyses. Patients treated with NIV had shorter hospital stay, and were more likely to be discharged home than patients treated with IMV but there were no significant differences in 30-day readmission rate. However, the subgroup analysis of patients with and without cardiopulmonary comorbidities demonstarted that the mortality benefit was limited to patients with a history of COPD or heart failure. Among patients who received NIV as first-line therapy, 15.9% ultimately failed and required IMV; these patients had similar mortality as those who were initially intubated. NIV failure was significantly (p=0.002) more common in patients without cardiopulmonary conditions (21.3%) compared to those with these conditions (13.8%).

When patients with pneumonia develop severe respiratory failure despite antibiotics and other supportive treatments, ventilatory support is necessary. Over the last decade, the use of NIV has significantly increased in patients with pneumonia[14] despite mixed evidence regarding its efficacy in preventing intubation.[19,36,6] In a recent randomized trial Frat et al found that in patients with acute hypoxemic respiratory failure, treatment with NIV, high-flow nasal cannula oxygen and conventional oxygen therapy did not result in significantly different intubation rates.[37] In another study which included immunocompromised patients admitted to the ICU with hypoxemic acute respiratory failure, early noninvasive ventilation

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compared with oxygen therapy alone did not reduce 28-day mortality.[38] Outside the clinical trials, only few observational studies have investigated the role on NIV in patients with pneumonia. [23,39,40] In a large retrospective study of Medicare beneficiaries hospitalized to the ICU with pneumonia and without associated COPD or cardiogenic pulmonary edema Valley et al found that 19% of the ventilated patients received NIV. The rate of NIV use is lower than in our study, probably reflecting a population without COPD that was directly admitted to a critical care unit. Using an instrumental variable analysis, they showed that among marginal patients with pneumonia there was no difference in mortality between NIV and IMV.[23] There are several reasons why our results are differed from those of Valley et. al.: first, our analysis was not restricted to the elderly and we included all ventilated patients regardless of their admission venue; second, we did not exclude patients with comorbid COPD or CHF which represented more than half of all patients with pneumonia in our sample; third, we reported on in-patient mortality not 30-day mortality and sicker patients with advanced directive limiting intubation are more likely to receive NIV and die soon after discharge; and lastly, our results apply to the average ventilated patient not to the marginal patient. Importantly, our results are similar to those reported by Valley et al in the cohort of patients without COPD or heart failure. Several other studies have shown that patients with ‘de novo’ ARF derived less benefit from NIV than those with cardiopulmonary comorbidities such as COPD or heart failure.[18,19,36] One possible explanation is that acute respiratory failure in patients with pneumonia superimposed on COPD or CHF may be evident earlier in the presence of these comorbid conditions, which in turn respond to NIV. In contrast, acute respiratory failure may represent a more severe case of pneumonia or signal the development of severe sepsis in patients without COPD or HF.

Patients who required endotracheal intubation after a trial of NIV had similar outcomes to those who were intubated at the time of admission. Patient selection is of paramount importance for NIV success. and when NIV is applied to patients with severe respiratory failure and close observation in an ICU is necessary for prompt intubation.[41] We have outlined some characteristics of the patients who are more likely to fail NIV including higher severity of illness at admission, sepsis as principal diagnosis, and comorbid weight loss, which may help physicians decide against NIV as first line therapy.

Our study has several strengths. It is one of the largest cohort studies to date on patients with pneumonia undergoing mechanical ventilation in US hospitals. Further, we used a rich EMR database that allowed us to adjust for severity of illness at admission based on a previously validated index that incorporates the results of laboratory testing. We also adjusted for multiple confounders and performed several sensitivity analyses using advanced statistical methods. Although our findings are notable, our results should be interpreted in light of several limitations. First, despite adjusting for numerous confounders and conducting several sensitivity analyses, thepotential for selection bias due to the retrospective design and unmeasured confounders remains a threat to the validity if our findings. Second, we used ICD-9 diagnosis codes to identify patients with pneumonia and included principal diagnosis of acute respiratory failure and secondary diagnosis of pneumonia rather than physician documentation and the results of chest radiology nd this may have resulted in some misclassification. We have attempted to reduce misclassification by restricting the analysis to those treated with antibiotics within 48 hours of admission. Third, we did not have

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information about advanced directive; patients with do not intubate status started on NIV could have died because they refused IMV. However, this will bias (increase) mortality rate in the NIV group. We have attempted to minimize this bias by excluding patients older than 80 and those with a hospice or palliative care status. Fourth, we used the LAPS to assess severity at admission and this score was not specifically developed and validated in patients with pneumonia. Nevertheless, LAPS has the advantage of using laboratory values including arterial blood gases and demonstrated high c stgatistic. Fifth, we used ICD-9 procedure code to identify NIV and IMV and the codes do not have information about the number of hours per day of use. Finally, although the Cerner database includes both teaching and non-teaching hospitals of diverse size and geography, the majority are urban and all have an electronic medical record system. Thus, they are not representative of all hospitals in the U.S.

In conclusion, initial NIV was associated with better survival to hospital discharge compared to initial IMV in patients hospitalized with pneumonia but only among patients with comorbid cardiopulmonary conditions. Patients who failed NIV had high in-hospital mortality. This highlights the need for the judicious use of NIV especially for those patients without comorbid COPD or CHF and for careful monitoring in an ICU when managing severe pneumonia with NIV to avoid delayed intubation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- One in four patients hospitalized with pneumonia and ventilated received NIV
- Patients treated with NIV were older and had lower severity of illness score
- NIV use was associated with lower risk of death in pneumonia patients with COPD or heart failure but not among those with without these comorbidities.

NIV failure was more common among patients without COPD and/or heart failure comorbidity

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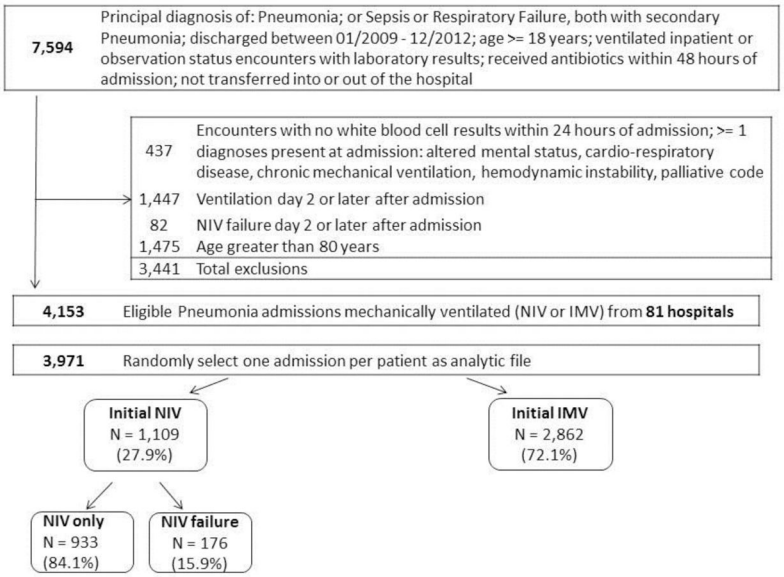

Figure 1.
Patient selection flowchart

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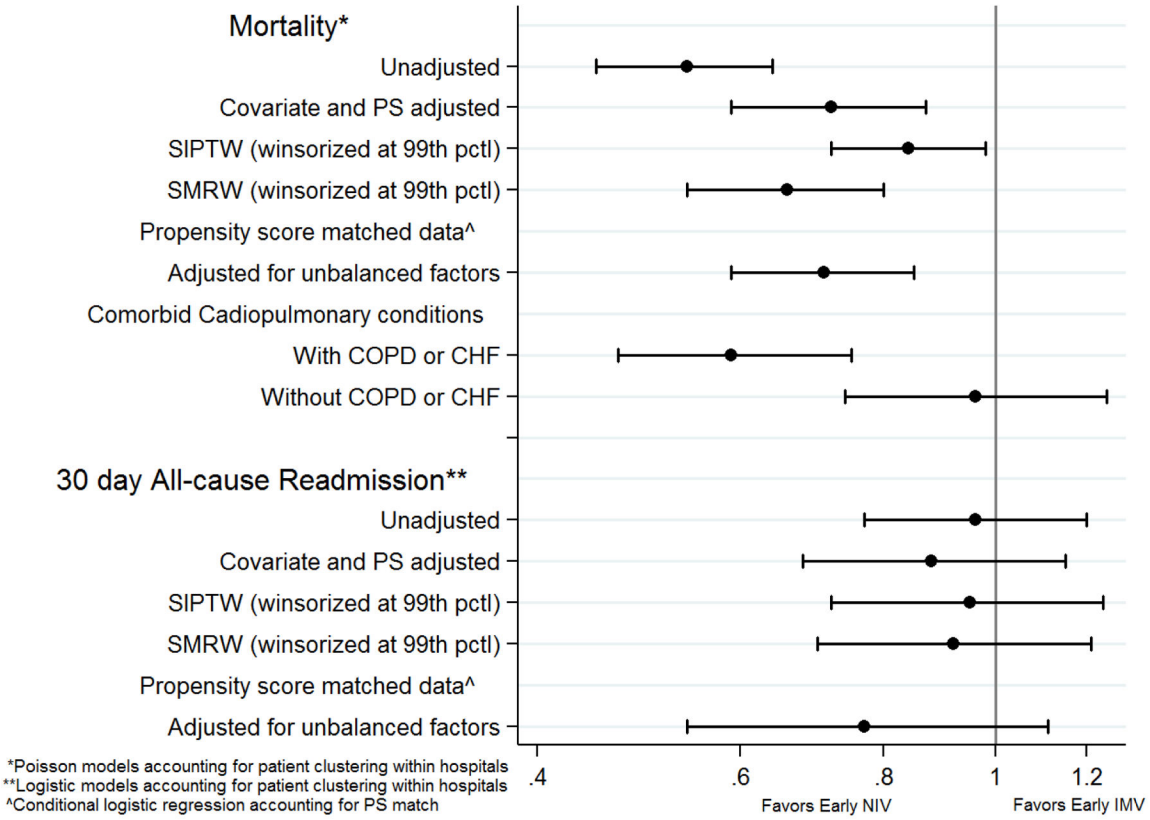

Figure 2.

Mortality and 30-day readmission Relative risk/Odds ratio (95% CI)

PS, Propensity Score; SIPTW, Stabilized Inverse Probability of Treatment Weighting; SMRW, Standardized Mortality Ratio Weighting; COPD, Chronic Pulmonary Disease; CHF, Congestive Heart Failure; NIV, Non-Invasive Ventilation; IMV, Invasive Mechanical Ventilation

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Table 1

Patient characteristics in full and propensity matched cohorts

Characteristics	Full Cohort			Propensity matched		
	Early NIV	**Early IMV**	**Absolute standardized difference***	**Early NIV**	**Early IMV**	**Absolute standardized difference***
	1109 (27.9)	**2862 (72.1)**	**%**	**812 (50)**	**812 (50)**	**%**
	percent of patients					
Age, Mean (SD), years	64.0 (12.8)	60.9 (13.8)	23.7	62.8 (13.1)	63.2 (12.9)	3.1
Gender						
Female	49.6	47.8	3.6	49.5	50.1	1.2
Race/Ethnicity			27.8			18.1
White	80.8	69.3		79.1	71.9	
Black	13.1	23.0		14.5	21.3	
Hispanic	1.5	1.7		1.8	1.8	
Insurance payer			25.9			4.7
Medicare	66.6	54.1		62.1	62.4	
Medicaid	6.8	8.7		8.5	7.3	
Transfer from SNIF	7.6	6.1	5.8	7.3	6.4	3.4
LAPS, Mean (SD)	59.4 (25.1)	75.1 (28.9)	58.3	63.1 (25.6)	62.7 (26.0)	1.4
LAPS categories			56.3			5.0
0 – 49	38.9	19.5		32.0	34.2	
50 – 74	34.1	31.7		35.8	35.3	
75 – 99	20.0	28.1		23.0	21.8	
>= 100	7.0	20.8		9.1	8.6	
Principal diagnosis			69.2			0.5
Pneumonia	46.3	16.5		34.4	34.5	
ARF	28.4	37.7		34.4	34.1	
Sepsis	25.2	45.8		31.3	31.4	
Gagne combined score, Mean (SD)	3.5 (2.6)	3.6 (2.5)	4.5	3.6 (2.6)	3.6 (2.6)	0.6
Comorbidities (selected)						

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Characteristics	Full Cohort			Propensity matched		
	Early NIV	Early IMV	Absolute standardized difference*	Early NIV	Early IMV	Absolute standardized difference*
	1109 (27.9)	2862 (72.1)	%	812 (50)	812 (50)	%
Congestive heart failure	34.1	28.8	11.4	33.1	34.9	3.6
Pulmonary circulation disease	10.6	7.6	10.5	9.9	10.0	0.4
Paralysis	5.9	8.4	9.8	6.8	6.8	0
Neurological disorders	13.6	18.8	14.0	16	16.4	1.0
Chronic pulmonary disease	61.5	43.5	36.6	56.9	56.0	1.7
Diabetes	31.5	31.8	0.6	30.9	35.3	9.4
Renal failure	18.1	17.8	0.8	18.3	18.3	0
Liver disease	2.3	5.6	17.3	3.1	2.8	1.5
Metastatic cancer/ Solid tumor w/out metastasis	11.7	9.7	6.5	11.3	11.2	0.4
Obesity	12.3	10.0	7.2	12.3	12.2	0.4
Morbid obesity	5.8	4.6	5.4	5.9	5.2	3.2
Depression/Psychoses	18.3	15.3	7.9	17.7	17.0	2.0
Hypertension	50.7	43.2	15.0	48.8	49.5	1.5
Smoking	42.2	28.1	29.9	38.5	36.7	3.8
Weight loss	11.1	18.8	21.7	13.7	14.2	1.4
Prior year IMV			9.2			2.1
None	92.6	90.0		91.0	90.4	
1 or more time	7.4	10.0		9.0	9.6	
Prior year NIV			35.6			12.6
None	86.4	96.3		89.3	92.9	
1 ore more time	13.6	3.7		10.7	7.1	
Prior year admissions			13.4			1.2
None	43.7	50.4		45.7	45.1	
1 or more time	56.3	49.6		54.3	54.9	
Vasopressors in first 24 hours of admission	16.7	45.7	66.0	22.7	23.4	1.8
Initial care venue			50.4			5.8
Ward	69.4	54.8		66.7	69.5	

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Characteristics	Full Cohort			Propensity matched		
	Early NIV	Early IMV	Absolute standardized difference*	Early NIV	Early IMV	Absolute standardized difference*
	1109 (27.9)	2862 (72.1)	%	812 (50)	812 (50)	%
Intensive Care Unit	24.8	44.8		31.8	29.2	
Intermediate care	5.8	0.5		1.5	1.4	
Pneumonia type						
Health-care associated	52.1	55.8	7.3	53.4	54.6	2.2
Community-acquired	47.9	44.2		46.6	45.4	
Hospital region			9.1			9.6
Midwest	16.1	17.3		14.4	17.2	
Northeast	34.4	30.1		33.1	29.7	
South	39.9	42.4		43.1	44.1	
West	9.6	10.2		9.4	9.0	
Hospital size			2.0			2.1
6 – 199 beds	15.6	14.9		15.5	14.8	
200 – 499 beds	55.5	56.3		53.9	54.3	
500 & more beds	28.9	28.8		30.5	30.9	
Hospital teaching status						
Teaching	72.9	79.8	16.1	74.5	80.3	13.9
Non-teaching	27.1	20.2		25.5	19.7	

NIV, Non-Invasive Ventilation; IMV, Invasive Mechanical Ventilation; SNIF, Skilled Nursing/Intermediate care Facility; LAPS, Laboratory Acute Physiology Score; ARF, Acute Respiratory Failure.

*A value >10% is seen as a large difference between the groups

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Table 2

Unadjusted outcomes in full and propensity matched cohorts

Outcomes	Early NIV	Early IMV	p-value *	Early NIV	Early IMV	p-value*
	1109 (27.9)	**2862 (72.7)**		**812 (50)**	**812 (50)**	
In-hospital mortality	15.8	29.8	<0.001	18.2	26.0	0.0003
LOS, Mean (SD), Days *	7.6 (5.6)	11.5 (9.1)	<0.001	8.1 (5.9)	11.1 (8.6)	<0.001
Readmitted within 30 days (among survivors)	14.8	15.3	0.72	13.6	15.5	0.29
AMI (Not POA)	2.6	6.7	<0.001	2.5	5.5	0.01
Cardiopulmonary arrest (Not POA)	1.1	6.2	<0.001	1.3	6.2	<0.001
Pneumothorax/Emphysema	0.7	2.6	0.001	1.0	2.5	0.04
Discharge disposition (among survivors)			<0.001			0.01
Home/Home-health	62.4	48.7		59.9	51.4	
SNF/ICF	31.4	41.0		33.6	39.6	
Hospice	5.0	6.8		5.0	6.2	
Other	1.2	3.5		1.5	2.8	

NIV, Non-Invasive Ventilation; IMV, Invasive Mechanical Ventilation; SNIF, Skilled Nursing/Intermediate care Facility; LOS, Length of Stay; AMI, Acute Myocardial Infarction; POA, Present on Admission.

* From Generalized Estimating Equations models accounting for patient clustering within hospitals

** From Conditional logistic regression accounting for propensity score matching

^ Winsorized at 5th and 99th percentile

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Table 3

Predictors of NIV failure (OR>1 predicts NIV failure; <1 otherwise)

Source	OR	LL	UL
Age in years *	0.77	0.66	0.89
Principal diagnosis			
Pneumonia	Reference group		
ARF	3.31	2.02	5.41
Sepsis	1.50	0.87	2.59
LAPS **	1.02	1.01	1.03
Chronic lung disease	0.53	0.35	0.81
Renal failure	0.52	0.30	0.88
Rheumatoid arthritis/collagen vascular disease	3.52	1.45	8.58
Weight loss	2.96	1.89	4.63
Prior year IMV			
None	Reference group		
1 time	2.33	1.17	4.63
2 or more times	0.93	0.27	3.19
Vasopressors within 24 hours of admission	3.18	1.98	5.12
Initial Care Venue			
Ward	Reference group		
Intensive Care Unit	2.23	1.45	3.43
Intermediate care	0.45	0.09	2.24

NIV, Non-Invasive Ventilation; IMV, Invasive Mechanical Ventilation; LAPS, Laboratory Acute Physiology Score; ARF, Acute Respiratory Failure.

*For every 10 year increase in age

**For every 10 point increase in Laboratory Acute Physiology Score (LAPS)