ORIGINAL RESEARCH

Comparative Effectiveness of Noninvasive Ventilation vs Invasive Mechanical Ventilation in Chronic Obstructive Pulmonary Disease Patients With Acute Respiratory Failure

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BACKGROUND: Limited evidence exists on the comparative effectiveness of noninvasive ventilation (NIV) vs invasive mechanical ventilation (IMV) in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) patients with respiratory failure.

OBJECTIVES: To characterize the use of NIV and IMV, and to compare the effectiveness of NIV vs IMV in AECOPD.

DESIGN AND PATIENTS: Retrospective cohort study using data from the 2006–2008 Nationwide Emergency Department Sample. Emergency department visits for AECOPD with acute respiratory failure were identified with codes from the International Classification of Diseases, Ninth Revision, Clinical Modification.

MEASURES: The outcome measures were inpatient mortality, hospital length of stay, hospital charges, and complications.

RESULTS: There were an estimated 101,000 visits annually for AECOPD with acute respiratory failure; 96% were admitted to the hospital. Of these, NIV use increased from 14% in 2006 to 16% in 2008 ($P=0.049$). Use of NIV, however, varied widely between hospitals, ranging from 0% to 100% with a median of 11%. Noninvasive ventilation was more often used in higher–case volume, Northeastern hospitals. In a propensity score analysis, NIV use, compared with IMV, was associated with lower inpatient mortality (risk ratio: 0.54, 95% confidence interval [CI]: 0.50-0.59), shortened hospital length of stay (-3.2 days; 95% CI: -3.4 to -2.9 days), lower hospital charges ($-\$35,012$; 95% CI: $-\$36,848$ to $-\$33,176$), and lower risk of iatrogenic pneumothorax (0.05% vs 0.5%, $P<0.001$).

CONCLUSIONS: Although NIV use is increasing in US hospitals, its adoption remains low and varies widely between hospitals. Our observational study suggests NIV appears to be more effective and safer than IMV for AECOPD in the real-world setting. *Journal of Hospital Medicine* 2013;8:165–172. © 2013 Society of Hospital Medicine

Chronic obstructive pulmonary disease (COPD) is now the third leading cause of death in the United States,[1] and its rising mortality trend is unique among the top 5 causes of death.[2] Acute exacerbations of COPD (AECOPD) are important events in the natural history of COPD, accounting for 1.5 million emergency department (ED) visits and 726,000 hospitalizations each year in the United States.[3,4] Given the significant morbidity and mortality from AECOPD, *Healthy People 2020* lists reducing deaths, hospitalizations, and ED visits as the key objectives for COPD.[5]

Over the past 2 decades, noninvasive ventilation (NIV) has emerged as a potentially useful treatment modality in AECOPD patients with acute respiratory failure. Noninvasive ventilation commonly refers to positive-pressure ventilatory support delivered through a nasal or full-face mask, such as bilevel positive airway pressure.[6] A number of randomized controlled trials[7–9] and meta-analyses[10] have suggested a mortality-reduction benefit with NIV use compared with standard medical care in AECOPD. To our knowledge, however, very few small randomized controlled trials compared NIV vs invasive mechanical ventilation (IMV) head-to-head,[11–13] and a recent evidence review found only 5 studies (405 subjects) on this topic.[14] Collectively, the limited evidence from randomized trials showed that NIV use resulted in similar intensive care unit (ICU) and in-hospital mortality, fewer complications (eg, ventilator-associated pneumonia and sepsis), and shorter hospital length of stays (LOS). Given that these trials have a smaller sample size and tend to exclude older patient (age >75 years) or patients with multiple comorbidities, there is a need to better understand the adoption and effectiveness of NIV treatment for AECOPD in a much larger patient population in the real-world setting using observational data.

To address these knowledge gaps in the literature, we analyzed data from a large, nationally representative ED and inpatient sample. The objective of the present analysis was 2-fold: (1) to characterize the use of NIV and IMV in AECOPD patients with acute

respiratory failure at a national level; and (2) to compare the effectiveness of NIV vs IMV in the real-world setting.

METHODS
Study Design and Setting
We conducted a retrospective cohort study using data from the 2006–2008 Nationwide Emergency Department Sample (NEDS),[15] a component of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. The NEDS is nationally representative of all community hospital–based EDs in the United States, defined by the American Hospital Association as all nonfederal, short-term, general, and other specialty hospitals.[16] Community hospitals include academic medical centers if they are nonfederal short-term hospitals. The NEDS was constructed using administrative records from the State Emergency Department Databases and the State Inpatient Databases. The former captures information on ED visits that do not result in an admission (ie, treat-and-release visits or transfers to another hospital); the latter contains information on patients initially seen in the ED and then admitted to the same hospital. Taken together, the resulting NEDS represents all ED visits regardless of disposition and contains information on short-term outcomes for patients admitted through the ED. In other words, the NEDS is the largest all-payer ED and inpatient database in the United States. The NEDS represents an approximately 20% stratified sample of US hospital-based EDs, containing more than 28 million records of ED visits from approximately 1000 hospitals each year. Additional details of the NEDS can be found elsewhere.[15,17] We received a waiver for this analysis from our institutional review board.

Study Population
Patient visits were included in this analysis if they carried any COPD-related diagnostic code (ie, International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code of 491.xx [chronic bronchitis], 492.xx [emphysema], or 496.xx [chronic airway obstruction, not elsewhere classified]) as their primary ED diagnosis and any acute respiratory failure code (ie, 518.81 [acute respiratory failure], 518.82 [pulmonary insufficiency not elsewhere classified, 518.84 [acute and chronic respiratory failure], or 799.1 [respiratory arrest]) as their secondary diagnosis. Patient visits with a primary diagnosis of acute respiratory failure and a secondary diagnosis of COPD were also included. Patients age <40 years were excluded, because they are much less likely to have COPD.[18]

Modes of Mechanical Ventilation
The primary exposure variable was mode of mechanical ventilation. To compare the effectiveness of differ-

ent ventilatory modes, patients were divided into 3 groups according to the ventilation mode they received: (1) NIV alone, (2) IMV alone, and (3) combined modes of NIV and IMV. The use of NIV was identified by using Current Procedural Terminology (CPT) code of 94660 or ICD-9 procedure code 93.90, whereas the use of IMV was identified by using CPT code of 31500 or ICD-9 procedure code 96.04 or 96.7x.

Patient-Level and Emergency Department–Level Variables
The NEDS contains information on patient demographics, national quartiles for median household income based on the patient's ZIP code, payment sources, ICD-9-CM diagnoses and procedures, ED disposition, hospital LOS, and hospital disposition. Hospital characteristics include annual visit volume, urban-rural status, ownership, teaching status, and US region. Geographic regions (Northeast, South, Midwest, and West) were defined according to Census Bureau boundaries.[19] To adjust for confounding by patient mix, Elixhauser comorbidity measures were derived based on the ICD-9 codes, using the Agency for Healthcare Research and Quality's Comorbidity Software.[20] This risk-adjustment tool has been derived and validated extensively.[21]

Outcome Measures
The outcome measures were all-cause inpatient mortality, hospital LOS, hospital charges, and ventilator-related complications. Three ventilator-related complications were identified using ICD-9 procedure codes: ventilator-associated pneumonia (997.31), facial injury (910.x), and iatrogenic pneumothorax (512.1).

Statistical Analysis
Summary statistics are presented as proportions (with 95% confidence intervals [CI]), means (with standard deviations [SD]), or medians (with interquartile ranges). Bivariate associations were examined using Student t tests, Kruskal-Wallis tests, and χ^2 tests, as appropriate. Emergency department and discharge weights were used to obtain national estimates at the ED and visit level. At all other times (eg, the propensity score and instrumental variable analyses), the unweighted cohort was analyzed, because survey weights are generally not advised for propensity score analysis using complex survey data.[22]

Propensity Score Analysis
To adjust for baseline patient and ED characteristics that may have confounded the relationship between ventilation mode and clinical outcomes, we performed propensity score and instrumental variable analyses. To compare the effectiveness of NIV vs IMV, a propensity score or predicted probability of NIV was estimated using a logistic-regression model with all
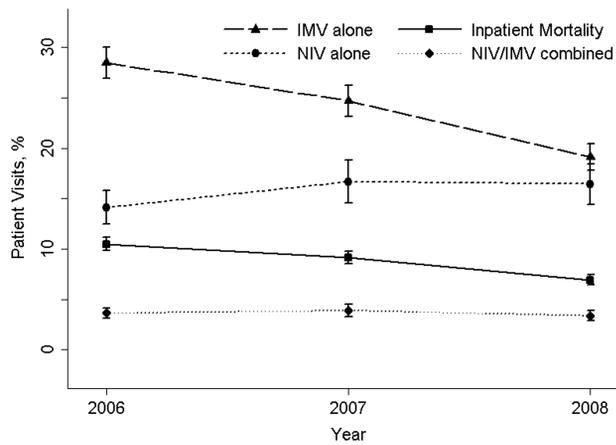
FIG. 1. Secular trends in use of noninvasive and invasive mechanical ventilation and inpatient mortality among patients with acute exacerbation of chronic obstructive pulmonary disease and acute respiratory failure in the United States, 2006–2008. Error bars represent 95% confidence intervals. Abbreviations: IMV, invasive mechanical ventilation; NIV, noninvasive ventilation.

patient characteristics (age, sex, quartiles for median household income, weekend admission, insurance status, season, calendar year, and comorbid conditions) and ED characteristics (urban/rural and teaching status, US region, annual ED volume, and annual volume of AECOPD with respiratory failure) as the independent variables. We then performed 1:1 propensity score matching based on a nearest-neighbor algorithm with caliper distance of 0.01. Although propensity score matching may result in a smaller sample, it provides a clinically relevant estimate of treatment effect because subjects in the matched sample are potential candidates for either treatment option.[23,24] An absolute standardized difference between characteristics of <10% was considered as adequate balance.[25]

Instrumental Variable Analysis

When hospitals always or nearly always use NIV or IMV, this suggests the choice is largely independent of patient characteristics, and it is possible to use the hospital preference as a proxy for the actual treatment choice (ie, an "instrument variable"). The instrumental variable analysis simulates a natural randomization of patients to 2 hospital groups with high and low NIV use.

The main difference between instrumental variable and propensity score analysis is that the former could potentially adjust for unmeasured confounders.[26] We used Stata procedure IVREG to estimate the outcome differences between NIV-preferring hospitals (NIV use in ≥90% of patients) and IMV-preferring hospitals (NIV use in ≤10% of patients).

All odds ratios (ORs) and β-coefficients are presented with 95% CIs. All analyses were performed using Stata 12.0 software (StataCorp, College Station, TX). All *P* values are 2-sided, with *P*<0.05 considered statistically significant.

Sensitivity Analyses

We conducted a sensitivity analysis to determine whether it was plausible that an unmeasured confounder could completely explain the observed results. The risk ratio of a hypothetical unmeasured confounder on study outcome and the exposure-confounder imbalance were both varied to see at what point the observed association was reduced to 1.0.[27]

RESULTS

Patient and ED Characteristics

The 2006–2008 NEDS sample contained 67,651 ED visits for AECOPD with acute respiratory failure from 1594 US EDs. After the weighting procedure, there were an estimated 101,000 visits annually for AECOPD with acute respiratory failure from approximately 4700 US EDs. In the weighted analysis, the mean patient age of these visits was 68 years, and 56% were made by women. Ninety-six percent were admitted to the hospital. Of these, the mortality rate was 9% and the mean hospital LOS was 7 days. Figure 1 shows the secular trends in NIV, IMV, and the combined use over the 3-year study period. Use of IMV decreased from 28% in 2006 to 19% in 2008 (*P*<0.001), whereas NIV use increased slightly from 14% in 2006 to 16% in 2008 (*P*=0.049); the combined use of both ventilation modalities remained stable (~4%). Inpatient mortality decreased from 10% in 2006 to 7% in 2008 (*P*<0.001).

Figure 2 shows that the frequency of NIV use (including combined use of NIV and IMV) varied widely between hospitals, ranging from 0% to 100% with a median of 11%. In the unweighted cohort of AECOPD with acute respiratory failure, 43% received some forms of ventilatory support. Table 1 shows the patient and hospital characteristics of the patients receiving ventilatory support: 36% received NIV, 56% received IMV, and 8% received combined use. In general, patients receiving combined use of NIV and IMV tended to have more comorbidities (eg,
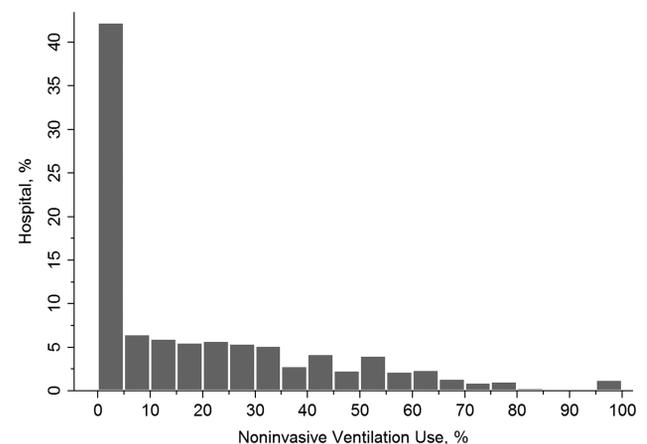
FIG. 2. Variation in hospital use of noninvasive ventilation in patients with acute exacerbation of chronic obstructive pulmonary disease and acute respiratory failure in the United States, 2006–2008.

TABLE 1. Patient and Hospital Characteristics According to Ventilatory Mode

	NIV Alone (A) (n=10,032)	IMV Alone (B) (n=15,427)	Combined Use (C) (n=2311)	*P* Value, A vs B	*P* Value, B vs C
Patient characteristics					
Age, y,				<0.001	0.64
40–49	5	5	5		
50–59	17	18	19		
60–69	31	33	33		
70–79	30	29	29		
≥80	17	15	13		
Female sex, %	57	53	54	<0.001	0.87
Quartile for median household income of patient ZIP code, $, %				<0.001	<0.001
1–38,999	30	34	29		
39,000–47,999	28	28	28		
48,000–62,999	24	22	24		
≥63,000	18	15	19		
Weekend admission, %	27	28	28	0.07	0.80
Insurance status, %				<0.001	0.91
Medicare	74	70	70		
Medicaid	9	12	12		
Private	12	13	13		
Self-pay	2	3	2		
Other	2	2	2		
Season, %				<0.001	0.16
Winter (January 1–March 31)	29	32	31		
Spring (April 1–June 30)	24	25	26		
Summer (July 1–September 30)	22	20	19		
Fall (October 1–December 31)	25	22	24		
No. of comorbidities, median (IQR)	4 (3–5)	4 (3–5)	4 (3–6)	<0.001	<0.001
Selected comorbidities, %					
Hypertension	56	55	55	0.01	0.65
CHF	38	40	44	0.001	<0.001
Fluid and electrolyte disorders	37	44	49	<0.001	<0.001
Diabetes, uncomplicated	27	26	29	0.04	0.002
Pneumonia	19	34	39	<0.001	<0.001
Deficiency anemia	16	19	19	<0.001	0.39
Obesity	18	12	17	<0.001	<0.001
Depression	15	11	11	<0.001	0.54
Pulmonary circulatory diseases	15	11	14	<0.001	<0.001
Hospital characteristics					
Annual ED visit volume, median (IQR)	42,704 (29,505–62,470)	44,119 (29,895–64,097)	46,695 (31,298–66,235)	0.02	0.0003
Annual ED volume of COPD exacerbation with respiratory failure, median (IQR)	45 (26–72)	42 (23–68)	38 (23–64)	<0.001	<0.001
Urban/rural and teaching status, %				<0.001	<0.001
Metropolitan nonteaching	53	52	47		
Metropolitan teaching	31	35	39		
Nonmetropolitan	16	13	13		
US region, %				<0.001	<0.001
Northeast	28	16	36		
Midwest	17	22	15		
South	41	45	32		
West	14	17	17		

NOTE: **Abbreviations:** CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; ED, emergency department; IMV, invasive mechanical ventilation; IQR, interquartile range; NIV, noninvasive ventilation.

congestive heart failure and pneumonia) compared with the NIV-alone or IMV-alone groups. With respect to hospital characteristics, NIV was used more often in hospitals with higher volumes of COPD exacerbation and respiratory failure, in nonmetropolitan hospitals, and in hospitals in the Northeast.

The unadjusted differences in outcomes are shown in Table 2. The combined-use group had the highest inpatient mortality, longest LOS, and highest charges, followed by the IMV and NIV groups. In general,

complications were few across all 3 groups, but the rate of iatrogenic pneumothorax was notably lower in the NIV group. Table 3 details the statistically significant predictors of NIV use in the propensity score model. Similar to the unadjusted analysis, older age, high-income neighborhoods, Medicare insurance, and some comorbidities were positively associated with NIV use (eg, pulmonary circulatory disorders and liver disease), whereas a few comorbidities were negatively associated with NIV use (eg, pneumonia, and alcohol

TABLE 2. Clinical Outcomes Among COPD Patients With Acute Respiratory Failure According to Ventilatory Mode

Outcome	NIV Alone (A) (n=10,032)	IMV Alone (B) (n=15,427)	Combined Use (C) (n=2311)	P Value. A vs B	P Value, B vs C
Inpatient mortality, n (%)	825 (8)	2,454 (16)	407 (18)	<0.001	0.04
Hospital length of stay, median (IQR), d	5 (4–8)	8 (5–13)	10 (7–16)	<0.001	<0.001
Hospital charge per visit, median (IQR), $	26,002 (15,747–44,638)	53,432 (31,998–92,664)	64,585 (39,024–110,336)	<0.001	<0.001
Complications*					
Ventilator-associated pneumonia, n (%)	≤10 (≤0.1)	≤10 (≤0.1)	≤10 (≤0.5)	0.09	1.00
Facial injury, n (%)	≤10 (≤0.1)	≤10 (≤0.1)	≤10 (≤0.5)	0.26	1.00
Iatrogenic pneumothorax, n (%)	≤10 (≤0.1)	90 (0.6)	14 (0.6)	<0.001	0.90

NOTE: **Abbreviations:** COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; IQR, interquartile range; NIV, noninvasive ventilation. *For privacy protection, we are not able to report cells in the tables ≤10 individual records.

and drug abuse). With respect to hospital characteristics, higher case volumes of COPD exacerbation/respiratory failure, Northeastern and nonmetropolitan hospitals, and more recent years were associated with NIV use.

In terms of propensity score distributions (see Supporting Information, Figure E1, in the online version of this article), there was sufficient overlap of the NIV and IMV groups. After matching on propensity score for the NIV and IMV groups, the differences in baseline characteristics were all balanced (see Supporting Information, Table E1, in the online version of this article), as indicated by <10% standardized differences in all covariates between the 2 groups. Finally, in the propensity score–matched cohort (see Supporting Information, Table E2, in the online version of this article), NIV use remained associated with significantly lower inpatient mortality (risk ratio: 0.54; 95% CI: 0.50-0.59, P<0.001), a shorter hospital LOS (mean difference, −3.2 days; 95% CI: −3.4 to −2.9 days, P<0.001), and lower hospital charges (mean difference, P<$35,012; 95% CI: −$36,848 to −$33,176, P<0.001), compared with IMV use. Use of NIV also was associated with a lower rate of iatrogenic pneumothorax than IMV use (0.05% vs 0.5%, P<0.001).

Using hospital preference for NIV vs IMV as an instrument, the instrumental analysis confirmed the benefits of NIV use, with a 5% reduction in inpatient mortality in the NIV-preferring hospitals (risk difference, P<5%; 95% CI: P<1.8% to P<8.3%).

In the sensitivity analysis to assess the impact of an unmeasured confounder, the confounder would have had to have a very strong impact on outcome (risk ratio: 5) and a severe exposure-confounder imbalance (odds ratio of exposure on confounder: 5) to reduce the observed association to 1.0. In other words, an individual unmeasured confounder is unlikely to explain the observed association.

DISCUSSION
In this nationally representative sample of 67,651 ED visits for AECOPD with acute respiratory failure, we found that NIV use was increasing from 2006 to 2008. However, the utilization of NIV remained low (16% in 2008) and varied widely by patient and hospital characteristic. As with all observational studies, causality cannot be inferred definitely; however, our study suggests that, NIV use—compared with IMV use—was associated with potentially important benefits: a reduction of inpatient mortality by 46%, shortened hospital LOS by 3 days, reduced hospital charges by approximately $35,000 per visit, and modestly reduced risk of iatrogenic pneumothorax.

A recent analysis using the US Nationwide Inpatient Sample has shown increasing use of NIV and concomitant decreasing mortality in AECOPD over time.[28] Our analysis confirmed these favorable trends in the United States using a much larger NEDS sample (28 million visits in the NEDS vs 8 million visits in the Nationwide Inpatient Sample per year). Despite these favorable trends, NIV was still underutilized for AECOPD with respiratory failure in the United States (16% in 2008) compared with major European countries (~40%).[29] Although our study lacked clinical details to arrive at the optimal rate of NIV use, the low rate of NIV use is concerning and suggests room for improvement in NIV use in appropriate patients as outlined by the current COPD guidelines.[18,30] Why is NIV not widely adopted, given its demonstrated efficacy? Previous surveys have identified several perceived reasons for low NIV use, including lack of physician knowledge, insufficient respiratory therapist training, inadequate equipment, and time required for setting up NIV.[29,31,32] Our study adds to the literature by showing the actual predictors of NIV use in the real world. Our data showed that the early adopters were hospitals with higher case volumes, and hospitals in the Northeast and in nonmetropolitan areas. A higher case volume has been linked with lower mortality in AECOPD (ie, practice makes perfect),[33] and frequent NIV use could explain the lower AECOPD mortality in high–case volume centers. Alternatively, smaller hospitals tend to have moonlighters working in EDs who may not be board certified in emergency medicine. Perhaps the logical next step is to conduct a qualitative study to understand the specifics of best practices and provider characteristics in these Northeastern, higher–case volume centers. Another incentive to promote NIV use in clinical practice is the cost-effectiveness associated with this intervention, as previous studies have shown that, compared with usual

TABLE 3. Statistically Significant Predictors of NIV Use Alone

Patient Characteristics	Adjusted OR (95% CI)*	P Value
Age, y		
40–49	1.00 (Reference)	
50–59	0.96 (0.84-1.11)	0.61
60–69	0.96 (0.84-1.10)	0.56
70–79	1.09 (0.94-1.25)	0.25
≥80	1.30 (1.12-1.52)	0.001
Quartile for median household income of patient ZIP code, $		
1–38,999	1.00 (Reference)	
39,000–47,999	1.13 (1.05-1.21)	0.001
48,000–62,999	1.21 (1.12-1.30)	<0.001
≥63,000	1.21 (1.11-1.32)	<0.001
Insurance status		
Medicare	1.00 (Reference)	
Medicaid	0.79 (0.72-0.88)	<0.001
Private	0.88 (0.81-0.96)	0.004
Self-pay	0.68 (0.56-0.82)	<0.001
Other	0.88 (0.73-1.07)	0.22
Season		
Winter (January 1–March 31)	1.00 (Reference)	
Spring (April 1–June 30)	1.06 (0.99-1.14)	0.11
Summer (July 1–September 30)	1.17 (1.08-1.26)	<0.001
Fall (October 1–December 31)	1.24 (1.15-1.33)	<0.001
Comorbidity		
CHF	0.90 (0.85-0.95)	<0.001
Pulmonary circulatory disorders	1.40 (1.29-1.52)	<0.001
Diabetes, complicated	1.25 (1.08-1.44)	0.002
Liver disease	1.79 (1.40-2.28)	<0.001
Coagulopathy	0.54 (0.46-0.63)	<0.001
Obesity	1.52 (1.41-1.65)	<0.001
Weight loss	0.50 (0.44-0.57)	<0.001
Fluid and electrolyte disorders	0.84 (0.80-0.89)	<0.001
Deficiency anemia	0.83 (0.78-0.90)	<0.001
Alcohol abuse	0.66 (0.58-0.76)	<0.001
Drug abuse	0.74 (0.62-0.88)	0.001
Psychoses	1.22 (1.10-1.37)	<0.001
Depression	1.45 (1.34-1.57)	<0.001
Pneumonia	0.48 (0.45-0.51)	<0.001
Valvular heart disease	0.87 (0.77-0.97)	0.01
Neurological disorders	0.89 (0.80-0.98)	0.02
RA/collagen vascular diseases	1.25 (1.02-1.53)	0.04
Blood-loss anemia	0.72 (0.53-0.97)	0.03
Hospital characteristics		
Annual ED visit volume, per 1000-visit increase	0.997 (0.996-0.998)	<0.001
Annual ED volume of COPD exacerbation with respiratory failure, per 10-visit increase	1.03 (1.02-1.03)	<0.001
Urban/rural and teaching status		
Metropolitan nonteaching	1.00 (Reference)	
Metropolitan teaching	0.91 (0.85-0.97)	0.006
Nonmetropolitan	1.30 (1.20-1.42)	<0.001
US region		
Northeast	1.00 (Reference)	
Midwest	0.44 (0.40-0.48)	<0.001
South	0.54 (0.50-0.58)	<0.001
West	0.51 (0.46-0.56)	<0.001
Calendar year		
2006	1.00 (Reference)	
2007	1.30 (1.22-1.39)	<0.001
2008	1.65 (1.54-1.76)	<0.001

NOTE: Abbreviations: AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; NIV, noninvasive ventilation; OR, odds ratio; RA, rheumatoid arthritis. *Propensity score model included the following patient and hospital characteristics: age, sex, median household income, insurance status, weekend admission, season, comorbid conditions, US region, urban/rural and teaching status, annual ED volume, annual ED volume of COPD with respiratory failure, and calendar year. Nonsignificant predictors that are not reported in the table include sex, weekend admission, and the following comorbid conditions: peripheral vascular disorders, paralysis, uncomplicated diabetes, hypothyroidism, renal failure, peptic ulcer disease excluding bleeding, hypertension, lymphoma, AIDS, solid tumor without metastasis, and metastatic cancer.

care, receiving NIV was associated with a reduction in costs, mainly through reduced use of the ICU.[34,35]

Some patient factors associated with NIV use may be well justified. For example, older AECOPD patients may have an advance directive describing their treatment wishes (eg, do-not-intubate order),[36] and therefore NIV was preferred to IMV. Also, our data suggested AECOPD patients with a suspected pneumonia component were less likely to be placed on NIV, which is consistent with COPD guideline recommendations.[18,30] As outlined in the current guidelines, the major contraindications to NIV include impending respiratory arrest, excessive respiratory secretions, massive gastrointestinal bleeding, recent facial trauma, or altered mental status.[18,30] By contrast, some factors associated with NIV use may be targeted for intervention, such as lower rates of NIV use in the uninsured, patients who live in low-income neighborhoods, and hospitals in US regions other than the Northeast.

Current guidelines recommend using NIV in AECOPD patients with early signs of respiratory failure, such as arterial pH of 7.25–7.35 or pCO_2 ≥45 mm Hg.[18,30] When NIV is considered as the modality of ventilatory support, it should probably be used as early as possible,[37] because evidence suggests that delayed use of NIV may lead to severe respiratory acidosis and increased mortality.[38] Other than in ICUs, NIV can be used on general wards and in EDs that have adequate staff training and experience, because the success rates of NIV in these settings are similar to those reported in ICU studies.[8,36,39] In addition, NIV is more cost-effective when performed outside the ICU.[35] In fact, studies have found a substantial portion of patients had NIV started in the ED (one-fourth) and on the general ward (one-fourth).[31,40] Given the shortage of intensivists in the United States, hospitalists begin to play an important role in provision of critical care outside the ICU.[41] Once NIV is used, it is important to ensure that it is delivered effectively and monitored closely because NIV failure has been shown to be associated with high mortality.[28,42]

This study has some potential limitations. First, we used administrative claims that lack clinical details such as data on arterial blood gases and severity scores, and thus potential residual confounding may exist. In our study, the IMV group may be sicker than the NIV group, which could partially explain the increased mortality with IMV. However, the propensity scores overlap to a great extent between the 2 study groups, suggesting that a strong confounding bias is less likely, given the observed covariates. Furthermore, the instrumental variable and sensitivity analyses taking into account unmeasured confounders still suggested the benefits of NIV. Second, the NEDS does not contain data on the location where NIV was initiated (eg, ED, ward, or ICU) or the timing of initiating NIV or IMV. As a result, for the combined-use group, we could not further distinguish the group

switching from NIV to IMV (ie, NIV failure)[42] or from IMV to NIV (ie, NIV as a weaning strategy).[43] Accordingly, we chose to focus on the comparativeness effectiveness of NIV vs IMV. Third, although the NEDS data have undergone quality-control procedures,[44] some misclassification may exist in identifying patient population and interventions. Finally, the analysis may not reflect the most recent trend in NIV use, as the 2010 NEDS data have just been released. In addition, although the study is the largest to date on this topic, our findings may not be generalizable to EDs that were not part of the NEDS.

In summary, in this nationally representative ED and inpatient database, NIV use is increasing for AECOPD with acute respiratory failure; however, its adoption remains low and varies widely between US hospitals. Our observational study suggests that NIV appears to be more effective and safer than IMV in the real-world setting. There is an opportunity to increase the use of NIV as recommended in guidelines and to promote the use NIV in replacement of IMV in patients with severe AECOPD. Given the increasing mortality burden of COPD, such a strategy may help reduce COPD mortality at the population level, thereby fulfilling the objectives of *Healthy People 2020*.

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