Noninvasive Ventilation in Patients with Asthma and Chronic Obstructive Lung Disease:

Outcomes and Trends in Use

A thesis

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ABSTRACT

Noninvasive positive pressure ventilation (NIV) had transformed the concept of mechanical ventilation with the main advantage of avoiding invasive mechanical ventilation (IMV) in selected patients. Clinical trials have shown that NIV improves outcomes in patients with hypercapnic respiratory failure due to COPD and several studies have reported an increase in NIV use in patients with COPD worldwide. However, there is a significant uncertainty about the efficacy of NIV in patients with asthma despite reports that the use of NIV in patients with asthma had increased.

The goal of this proposal was to examine current ventilation management practices and outcomes in patients with asthma and COPD in a large registry of hospitals and assess patient and hospital characteristics associated with the use of NIV in clinical practice. We hypothesized that the adoption of NIV as an alternative to IMV as initial ventilation strategy will vary substantially across hospitals and according to patient characteristics, and that, after adjusting for differences between patients, treatment with NIV will be associated with better clinical outcomes compared to IMV.

In the first aim of the proposal we examined trends in the use of NIV among more than 700, 000 patients with acute exacerbation of COPD over the period 2001 - 2011 in a large and representative network of 475 US hospitals and identified patient factors influencing its use. We found that initial NIV use increased (from 5.9% to 14.8%), and initial IMV declined (from 8.7% to 5.9%). Elderly patients had higher odds of receiving NIV, while blacks and Hispanics were less likely to be treated with NIV than whites.

Cases with a high burden of comorbidities and those with concomitant pneumonia had high rates of NIV failure and were more likely to receive initial IMV.

For the second and third aim of the proposal we conducted a retrospective cohort study of more than 13,000 hospitalizations for an exacerbation of asthma at 100 hospitals using a detailed electronic medical record database. We found that NIV use had doubled in 4 years; similar with patients with COPD, elderly patients with asthma were more likely to receive initial NIV while those with higher acuity and those with concomitant pneumonia were less likely to receive NIV. Use of NIV was associated with significantly lower in-patient risk of dying and shorter lengths of stay. Patients with NIV failure had the highest mortality and pneumonia was a risk factor for failure. We found large variation in hospital use of NIV for patients with an acute exacerbation of asthma and hospitals with higher NIV rates did not have lower IMV rates suggesting an expansion in the use of assisted ventilation.

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LIST OF ABBREVIATIONS

ACPE = Acute Cardiogenic Pulmonary Edema

AE-COPD = Acute Exacerbation of COPD

ARDS = Acute Respiratory Distress Syndrome

ARF = Acute Respiratory Failure

CHF= Congestive Heart Failure

COPD = Chronic Obstructive Pulmonary Disease

IMV = Invasive Mechanical Ventilation

IQR= Interquartile Range

LAPS = Laboratory Acute Physiology Score

LOS=length of stay

NIV = Noninvasive Ventilation

OD= Odds Ratio

POA= present on admission

RCT = Randomized Controlled Trial

RS=risk standardized

US=United States

INTRODUCTION

Acute Respiratory Failure (ARF) is a potentially life threatening dysfunction of the respiratory system. In the US, approximately 800,000 patients with ARF per year require respiratory support with invasive mechanical ventilation,(Wunsch et al.) with in-hospital death rates ranging from 20% to 40%. In 2009, ARF accounted for approximately 320,000 deaths and more than $50 billion of spending in the US hospitals.("HCUPnet, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample ", 2011)

Acute respiratory failure is a potential complication of several common medical conditions including acute cardiogenic pulmonary edema (ACPE), acute exacerbations of COPD, pneumonia, asthma, and acute respiratory distress syndrome (ARDS). When supplemental oxygen and other treatments are ineffective, patients with ARF have traditionally been managed with invasive mechanical ventilation (IMV). While many ARF patients benefit from IMV, the mortality rate of these patients is close to 20- 40%, with a number of these deaths directly attributable to complications associated with IMV.

Beginning in the 1990s, the noninvasive alternative approach gradually emerged for treating patients with acute respiratory failure with the major benefit of avoiding IMV in selected patients and thereby preventing associated complications.(Bott et al., 1993; Hill, 1993, 1994; Meduri, Conoscenti, Menashe, & Nair, 1989) The major difference between noninvasive (NIV) and invasive (IMV) ventilation relies on the type of interface connecting the patient to the ventilator. The noninvasive interface, a tight mask instead of the endotracheal tube, is the major determinant of the advantages of NIV, such as eliminating the risk for heavy sedation, decreasing the risk of infections in general and

for ventilator-associated pneumonia in particular. Several randomized controlled trials (RCTs) reported that in selected patients with ARF, NIV avoids most of the complications of IMV while retaining similar efficacy.(Brochard et al., 1995; Girou et al., 2000; Nourdine et al., 1999) A meta-analysis of 8 RCTs, which included a total of 364 patients with hypoxemic ARF, concluded that the addition of NIV to standard care reduced the rate of endotracheal intubation by 23%, and reduced in-hospital mortality by 17%.(Keenan, Sinuff, Cook, & Hill, 2004) Although there is significant evidence to support the efficacy of NIV in ARF due to exacerbation of COPD(Agarwal, Gupta, Aggarwal, & Gupta, 2008; Brochard et al., 1995; Corrado et al., 1998; Hill, 2000, 2003; Scala et al., 2007; Squadrone et al., 2004) and ACPE,(Collins et al., 2006; L'Her et al., 2004) there is a knowledge gap for patients with ARF due to other conditions such as pneumonia,(Confalonieri et al., 1999; Hill, 2001) ARDS,(Garpestad & Hill, 2006; Garpestad, Schumaker, & Hill, 2007) and asthma.(Meduri, Cook, Turner, Cohen, & Leeper, 1996; Soroksky, Stav, & Shpirer, 2003)

Therapy with NIV is considered successful if endotracheal intubation is avoided. Conversely, the term “NIV failure” is used when a patient is initially treated with NIV but is subsequently placed on IMV. The failure rate of NIV ranges from 5-50% depending on the severity/etiology of ARF(Antonelli et al., 2001; Chandra et al.; Hill, 2001, 2004; Hill, Brennan, Garpestad, & Nava, 2007) and patients who fail NIV may have an increased risk of mortality compared to those started directly on IMV.(Chandra et al.; Esteban et al., 2004) Thus, proper identification of patients who may benefit from NIV as an alternative to IMV is essential for optimizing the use of NIV and improving the outcomes of patients with ARF. Understanding whether treatment effects vary by

patient and clinical characteristics can help target patients most likely to benefit from NIV, supporting the practice of personalized medicine.

Despite the substantial morbidity and costs associated with ARF, surprisingly little is known about current ventilation management practices in the US and the extent to which NIV has replaced IMV, particularly in conditions other than COPD or ACPE. More importantly only 5 RCTs, representing a total of 405 patients, have compared NIV with IMV, and only 39 patients had ARF due to conditions other than COPD or ACPE; (Antonelli et al., 1998; Conti et al., 2002; Honrubia et al., 2005; Jurjevic et al., 2009; Matic et al., 2007) thus there is significant uncertainty about the efficacy of NIV for other groups of patients. The evidence supporting the efficacy of NIV in patients with an acute exacerbation of asthma is far less clear. A Cochrane review of 5 trials and 206 patients found that compared to usual care alone, NIV improves respiratory rate and lung function and increases the number of patients discharged from emergency departments but no benefit was found on the risk of intubation or mortality.(Lim et al.) Despite the lack of data on efficacy and safety, a recent analysis of the Nationwide Inpatient Sample showed that rates of NIV use among patients with asthma had increased five-fold between 2000 and 2008.(Akinbami et al.)

Therefore, the goals of this dissertation research was to examine current ventilation management practices in patients with ARF secondary to asthma exacerbation in a large registry of patients from more than 100 hospitals throughout the U.S. and to compare the effectiveness of NIV and IMV among patients with asthma exacerbation. In addition we examined trends in the use of NIV among patients with COPD and identify patient factors influencing its use.

1.1 Trends in Mechanical Ventilation among Patients Hospitalized with Acute Exacerbations of COPD in the United States, 2001 to 2011

Chronic obstructive pulmonary disease (COPD) is responsible for approximately one million admissions annually to U.S. hospitals and is the third most common cause of death in United States.("FASTSTATS; Chronic Lower Respiratory Disease," ; "NHLBI Morbidity and Mortality Chartbook,") In patients hospitalized for an acute exacerbation of COPD (AE-COPD), usual care consists of supplemental oxygen, bronchodilators, corticosteroids, and antibiotics; in severe cases, ventilatory support with noninvasive (NIV) or invasive ventilation (IMV) is required.(Todisco et al., 2004)

Multiple small randomized controlled trials and two meta-analyses have demonstrated that, when added to standard therapy, NIV reduces the need for IMV and improves survival in carefully selected patients with acute respiratory failure due to COPD.(Brochard et al., 1995; Keenan et al., 1997; Lightowler, Wedzicha, Elliott, & Ram, 2003) Consequently, NIV has been endorsed by several national and international societies as a first-line treatment in these patients.("International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute Respiratory failure," 2001; Keenan et al., 2011; "Non-invasive ventilation in acute respiratory failure," 2002) Information about the use of NIV is beginning to emerge and several studies have reported an increase in NIV utilization in patients with COPD worldwide.(Chandra et al.; Demoule, Girou, Richard, Taille, & Brochard, 2006; Tsai, Lee, Delclos, Hanania, & Camargo, 2013; A. J. Walkey & Wiener)

Little is known, however, about the patient characteristics associated with NIV use in routine clinical practice and whether factors, such as age, sex, race and comorbidities, influence the likelihood that a patient receives NIV or IMV as an initial ventilation therapy.

Using data from a geographically and structurally diverse sample of US hospitals, we examined decade-long trends (2001-2011) in the use of NIV and IMV among patients hospitalized for an AE-COPD and assessed the influence of patient factors on receipt of NIV and IMV. We hypothesized that use of NIV has increased over this period but that the increase has varied significantly across hospitals and patient groups. Specifically, we expected that there will be less increase among older patients, and those with a high burden of comorbidity.

1.2 Hospital Patterns of Use of Noninvasive Ventilation in Patients with Asthma Exacerbation

In the United States, an estimated 25.7 million individuals have asthma.(Akinbami et al.) There are approximately 500,000 hospitalizations annually with an asthma exacerbation and 4% of these hospitalizations are treated with invasive mechanical ventilation (IMV).(Krishnan et al., 2006) Asthma patients requiring IMV have an in-hospital death rate ranging from 15 to 22%(Afessa, Morales, & Cury, 2001; Gupta, Nath, Agarwal, & Behera) and mortality associated with asthma has changed little over the last decade due to lack of significant advances in treatment.(Akinbami et al.)

There is strong evidence that noninvasive mechanical ventilation (NIV) reduces risk of intubation and mortality in patients with acute exacerbations of COPD.(Brochard et al., 1995; Carlucci, Richard, Wysocki, Lepage, & Brochard, 2001; Ram, Lightowler, & Wedzicha, 2003) The pathophysiology of acute respiratory failure in asthma is in many ways similar to that of acute respiratory failure in COPD, giving reasons to believe that NIV could also be successful in patients with severe acute asthma. However, there is a paucity of data on the efficacy of NIV in asthma exacerbation. A Cochrane systematic review published in 2013 compared usual care with usual care plus NIV in patients hospitalized with asthma and found only five randomized controlled trials with a total of 206 patients. The review concluded that NIV improves the respiratory rate and lung function and decreases hospitalizations when used in the emergency department, but the limited data did not permit any conclusions to be made with regards to its effects on intubation or mortality.(Lim et al.) The most recent guidelines from the Global Initiative for Asthma recognizes that using NIV in patients with asthma exacerbation is controversial despite an increase in its use in clinical practice.("Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2014," 2014)

Data on the hospital utilization of NIV in patients with an acute exacerbation of asthma are lacking. It is unclear if hospitals that have higher use of NIV achieve better patient outcomes including lower use of IMV and better survival. The purpose of this large observational study was to describe the hospital patterns of mechanical ventilation for patients hospitalized with asthma exacerbations in a large network of U.S. hospitals. We also analyzed the relationship between hospital use of NIV and hospital-level IMV and death rates. We hypothesized that preferences for assisted ventilation will vary

across hospitals, and the variation will be associated with certain hospital characteristics such as size, teaching status and location.

1.3 Outcomes of Noninvasive and Invasive Ventilation in Patients Hospitalized with Asthma Exacerbation

Asthma is a common disorder which affects upwards of 1 in every 10 adults in the United States. It accounts for nearly 2 million emergency department visits per year("National Hospital Ambulatory Medical Care Survey: 2010 Emergency Summary Tables," 2010) and 20-30% of these patients require hospitalization. Asthma exacerbations are characterized by progressive worsening of dyspnea and wheezing and most exacerbations respond to treatment with supplemental oxygen, bronchodilators and steroids. Despite aggressive management, some patients fail to improve and require admission to the intensive care unit and endotracheal intubation. Intensive care admissions and intubation rates vary from 10 to 30% depending on the population studied(McFadden, 2003; Pendergraft et al., 2004) and 8-22% of patients who are intubated do not survive.(Gupta et al.; Shapiro, 2001)

The use of noninvasive ventilation (NIV) in patients with acute respiratory failure has increased dramatically during the last decade regardless of the etiology (A.J Walkey & Wiener, 2012) although the supporting evidence varies largely depending on the primary underlying condition. For patients hospitalized with moderate to severe COPD exacerbation, systematic reviews and meta-analysis suggest that noninvasive ventilation is effective in reducing the risk of intubation and short-term mortality.(Ram et al., 2003)

However the evidence supporting the efficacy of NIV in patients with an acute exacerbation of asthma is far less clear. A Cochrane review of 5 trials and 206 patients found that compared to usual care alone, NIV improves respiratory rate and lung function and increases the number of patients discharged from emergency departments but no benefit was found on the risk of intubation or mortality.(Lim et al.) Despite the lack of data on efficacy and safety, a recent analysis of the Nationwide Inpatient Sample showed that rates of NIV use among patients with asthma had increased five-fold between 2000 and 2008.(Akinbami et al.)

Using data from a large multihospital electronic medical record database that contains laboratory data we examined factors associated with the choice of ventilation in patients hospitalized with asthma exacerbation and compared the clinical outcomes of noninvasive (NIV) and invasive mechanical ventilation (IMV) in these patients.

We expected that after adjusting for patient and hospital characteristics and severity of illness at admission, patients treated with NIV as initial ventilation strategy will have lower mortality and lower resource utilization compared to patients initially treated with IMV.

In this proposal we took advantage of a unique multi-hospital database, derived from hospital electronic medical records, that contain physiologic and laboratory data enabling us to examine factors not available within other datasets. Our investigation made use of Cerner's Health Facts database, a unique resource containing highly detailed records from a geographically and structurally diverse sample of more than 100 US hospitals. In addition to containing all of the elements found in standard hospital claims, Health Facts contains time stamped information of therapies administered and tests

results (e.g., arterial blood gases). The availability of detailed patient-level timed physiological and laboratory data from this registry allowed us to more rigorously compare the effectiveness of NIV versus IMV, minimizing the potential confounding by indication effect of the severity.

MATERIALS AND METHODS

2.1 Trends in Mechanical Ventilation among Patients Hospitalized with Acute Exacerbations of COPD in the United States, 2001 to 2011

Design, study setting, and subjects

We used data from the Premier Inpatient Database, a dataset which has been used extensively for health services research; (Lindenauer et al., 2006; Lindenauer et al., 2005)its details have been described previously.(Lindenauer, Pekow, Wang, Gutierrez, & Benjamin, 2004; Safavi et al., 2013) In brief, this dataset contains a date-stamped log of all items and services charged to the patient or their insurer, including medications, laboratory, and ventilation therapies at the individual patient level. Hospitals in the dataset represent all regions of the United States, are predominantly small to medium-sized non-teaching facilities, and serve mostly urban patient populations.

We included hospitalizations of patients ≥40 years of age with a principal discharge diagnosis of COPD (International Classification of Disease, 9th Revision, ICD-9 codes: 491.21, 492.22, 491.8, 491.9, 492.8, 496) or a principal diagnosis of acute respiratory failure (518.81, 518.82, 518.84) paired with a secondary diagnosis of COPD who were discharged between 01/01/2001 and 06/30/2011. We excluded admissions transferred from or to another facility (because we did not have information about their initial ventilation therapy or outcomes), hospitalizations <2 days, admissions to a hospice bed and those with a diagnosis of obstructive sleep apnea because we could not distinguish whether NIV was used for sleep apnea or for acute respiratory failure.

For each admission we recorded demographic information, insurance coverage, number of COPD admissions in prior year and diagnosed comorbidities. We calculated a single numeric comorbidity score using the method described by Gagne et al. and grouped this score into tertiles for analysis.(Gagne, Glynn, Avorn, Levin, & Schneeweiss, 2010) For each hospital we assessed the number of beds, teaching status, whether it served an urban or rural population, and geographic region. We included only hospitals which were in the Premier dataset for a minimum of a full year between 2001 and 2011 and had patients eligible for the study.

Outcomes

The primary study outcome was the initial form of ventilation (NIV or IMV) administered at any point during the hospital course. We defined NIV failure as transition to IMV after an initial period of NIV. An additional composite outcome was defined as NIV failure or death.

Administration of NIV and IMV was identified using two approaches. First, we reviewed ICD-9 procedure codes and the date associated with the receipt of each procedure. Second, we used charges generated by the respiratory therapist for NIV or IMV use. We considered a patient to have received NIV or IMV during the admission if there was an ICD-9 procedure code or a charge for the procedure or service. We validated this approach in a single hospital chart audit of 200 patients hospitalized with a diagnosis of acute respiratory failure between 2010 and 2012. We found that ICD-9 procedure codes had a sensitivity of 86% for identifying NIV use compared with 99% when both ICD-9 and respiratory therapist charge codes were used. Specificity for NIV use was 96% for both procedure and billing codes.(M.S. Stefan et al., 2014)

Ventilation strategy	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
NIV procedure code	86.5 (80.9 - 92.2)	91.5 (84.4 - 98.6)	96.1 (92.7 - 99.4)	74.0 (63.9 - 84.0)
NIV billing	96.4 (93.4 - 99.5)	96.6 (92.0 - 100.0)	98.5 (96.6 - 100.0)	91.9 (85.2 - 98.7)
NIV billing or procedure	99.3 (97.9 - 100.0)	91.5 (84.4 - 98.6)	96.5 (93.6 - 99.5)	98.2 (94.6 - 100.0)
IMV procedure code	100	99.2 (97.6 - 100)	98.7 (96.2 - 100.0)	100
IMV billing	100	94.3 (90.2 - 98.4)	91.7 (85.8 - 97.6)	100
IMV billing or procedure	100	94.3 (90.2 - 98.4)	91.7 (85.8 - 97.6)	100

Data analysis

We calculated summary statistics at the admission-level for all variables using frequencies and proportions for categorical data and means, medians, and interquartile ranges, for continuous variables.

Hierarchical generalized linear models with a random hospital effect using SAS PROC GLIMMIX were used to examine relative changes over time in the use and outcomes of NIV and IMV while controlling for several patient- and hospital characteristics. The population at risk varied with the outcome. We modeled use of any ventilation, initial NIV, and initial IMV among all admissions (all admitted patients eligible to receive ventilation therapy) to evaluate trends over time in use of ventilation and type of ventilation. The use of NIV as the initial ventilation method as a percentage of all ventilation starts was modeled among admissions of patients receiving ventilation to evaluate relative change over time in choice of ventilation mode. NIV failure, defined as transition to IMV after a trial of NIV as well as a composite outcome of NIV failure or

death was modeled among admissions started on NIV (eligible for NIV failure) to evaluate trends in outcome following initial NIV use. Year was included as a linear term in all models.

Initial models included pre-specified interaction terms of patient characteristics with study year (2001- 2011) to identify trends in ventilation use related to patient characteristics that were significantly associated with ventilation outcomes. Interaction terms with $p > 0.05$ were dropped from final models.

All analyses were performed using the Statistical Analysis System (version 9.3, SAS Institute, Inc., Cary, NC) and STATA (StataCorp, 2011, Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Because the data do not contain identifiable information, the Institutional Review Board at Baystate Medical Center determined that this study did not constitute human subjects research.

2.2 Hospital Patterns of Use of Noninvasive Ventilation in Patients with Asthma Exacerbation

Study design and setting

We performed a cross-sectional analysis using Cerner's Health Facts database, which contains electronic medical records from a geographically and structurally diverse sample of more than 100 US hospitals. In addition to all of the elements found in standard hospital claims databases, Health Facts contains comprehensive medication records and laboratory results. Details about the Health Facts database have been

previously described.(Amin et al.; Kosiborod, 2008; Kosiborod et al., 2009) We included patients discharged from a hospital contributing data to Health Facts from January, 2009 to December, 2012. Patients were included if they were aged 18 years or older, and received a principal diagnosis of asthma (International Classification of disease, 9th Revision, Clinical Modification code,("ICD-9-CM coding and reporting official guidelines. American Hospital Association, American Medical Record Association, Health Care Financing Administration, National Center for Health Statistics," 1990) ICD-9 codes 493.0x, 493.1x 493.9x 493.2x, 493.8x) or of acute respiratory failure (ICD-9 codes: 518.81, 518.82, 518.84, 518.4) and secondary diagnosis of asthma. Overall algorithms to identify persons with asthma based on ICD-9 diagnostic code and hospital and ambulatory visits have sensitivity of 72% and specificity of 87%.(Wakefield & Cloutier, 2006) To increase the specificity of the diagnosis, we restricted the cohort to patients treated with short-acting bronchodilators and systemic steroids, medications which are expected to be used in any admission with an asthma exacerbation. We excluded patients without laboratory results since these variables were used to calculate the severity of illness score at admission or without medication data because we used treatment variables to define the cohort. We also excluded patients with obstructive sleep apnea since it is not possible to differentiate chronic use of NIV from treatment specifically for acute respiratory failure. We also excluded patients who were transferred from or to another hospital because their initial form of ventilation and their outcomes could not be ascertained. Hospitals with less than 45 eligible admissions with asthma during the study period were excluded to provide stable hospital rate estimates. To

derive this threshold, we calculated that for a rate of NIV use of 5%, 45 admissions would give a hospital a 90% chance of having at least one patient treated with NIV.

For this study, patient data were de-identified in accordance with the Health Insurance Portability and Accountability Act and hospitals were identified by a random identifier assigned by Cerner. The Institutional Review Board at Baystate Medical Center Committee reviewed the protocol for this study and determined that it is not considered to be Human Subjects Research as defined by the Office of Human Research Protections.

Patient and Hospital Information

Covariates of interest included patient socio-demographic characteristics, several comorbidities, prior admission, NIV or IMV use in the prior year, ICD-9 for chronic obstructive asthma and coexistent pneumonia. Comorbidities were assessed using the Healthcare Cost and Utilization software("Heathcare Cost and Utilization Project (HCUP). Overview of the Nationwide Inpatient Sample,") and also using the combined Charlson/Romano/Gagne comorbidities software.(Gagne et al., 2010) To assess the severity of illness we used the Laboratory-based Acute Physiology Score (LAPS) which integrates information from 14 laboratory tests recorded at admission into a single continuous variable with a value that can range between a minimum of 0 and a theoretical maximum of 256. The LAPS is similar to many existing severity of illness scores, but it has a specific algorithm with respect to imputation based on an initial assessment of predicted mortality risk.(Escobar, Gardner, Greene, Draper, & Kipnis; Escobar et al., 2008; van Walraven, Escobar, Greene, & Forster) In addition, we adjusted for prior hospitalization for asthma, NIV or IMV use in the year prior to the index admission. We also utilized information collected on several hospital characteristics including number of

beds, teaching status, if the hospital serves a rural or urban community, and its geographical region.

Noninvasive and Invasive Ventilation

The primary variable of interest was the initial ventilation, NIV or IMV, defined as the first method of ventilation used during hospitalization. We used ICD-9 CM procedure codes 93.90 to define NIV exposure and 96.04, 96.70-96.72 for IMV exposure. NIV failure was defined as IMV used after NIV. We assumed that NIV preceded IMV in the rare cases where there were procedure codes for both NIV and IMV on the same day.

Outcomes

The primary study outcomes were hospital-level risk standardized rates of initial NIV or initial IMV, in-patient case fatality rate, and length of stay (in hours). We also calculated hospital risk standardized rates of any IMV, which included IMV after NIV (NIV failure).

Statistical analysis

Descriptive statistics included frequencies and percentiles for categorical factors and means and percentile distributions for continuous factors. For each hospital we calculated the rates of use for NIV and IMV among all admissions with an asthma exacerbation.

To estimate hospital-level risk standardized (RS) NIV rates we used the same statistical modeling techniques employed by CMS for reported readmission and mortality rates.(Harlan M. Krumholz et al., 2008; H. M. Krumholz et al., 2006) We developed hierarchical generalized logistic models (HGLM) with hospital level random effects to

account for the clustering of patients within hospitals (allowing for correlation within sites due to common practices or institutional culture) and adjusted for patient characteristics, chronic comorbidities, the LAPS score, and hospital characteristics as fixed effect. This approach simultaneously models two levels (patient and hospital) to account for the variance in patient outcomes within and between hospitals. The hospital *predicted* NIV rate was calculated as the sum of the individual risk probabilities for each patient within a given hospital and reflects the NIV rate at that hospital using the hospital specific random effect given the patient case mix. The *expected* NIV rate reflects a particular hospital's patient mix, but replaces the hospital specific effect with the average hospital effect. Then the RS-NIV was calculated as the ratio between the hospital predicted and hospital expected NIV rate multiplied by the overall unadjusted NIV rate for all admissions.

The approach is based on a less familiar concept for the readers and differs in some respects of the usual observed/expected rates. However, if the O/E is used, when the number of events used in a direct estimate is small, the estimate is unstable with a relatively large standard error and poor statistical performance. The RS approach uses a hierarchical model as an effective method to account for clustering of admissions within hospitals, supports valid and effective risk adjustment and produces stabilized estimates thereby reducing regression to the mean effects. The hierarchical modeling shrinkage effect has the advantage of reducing reported variation of hospital data and stabilizing highly variable estimates. Even after risk adjustment for case mix differences, inherent unpredictability causes directly estimated hospital effects and relative rates (observed/expected ratio) for some hospitals to vary more than the systematic effects are

to be identified. This is especially true for hospitals with low volume for which the rates will have very wide confidence intervals. The RS methodology reduces the variation.

We used similar methods to calculate hospital RS-IMV rate and the hospital RS-mortality rate. For the mortality outcome, one random admission was selected if the patient had multiple admissions because mortality can occur only once during the last hospitalization.

The correlations between the hospital RS-NIV rates and RS-IMV and RS-case-fatality rates were evaluated with the Spearman correlation coefficient. We also grouped hospitals in quartiles of the initial RS-NIV rate and compared initial RS-IMV, RS-case-fatality rates, and RS-Length of Stay (LOS) across quartiles of RS-NIV using the Kruskal Wallis test and Cuzick's test for trend. Stata/MP 13.1 for Windows (StataCorp, College Station, TX) was used for statistical analyses.

2.3 Outcomes of Noninvasive and Invasive Ventilation in Patients Hospitalized with Asthma Exacerbation

Data source

We conducted a retrospective cohort study using a comprehensive electronic medical record (EMR) dataset, Cerner HealthFacts (Cerner Corporation, Kansas City) from January, 2009 to December, 2012. In addition to the information contain in a hospital claim file, Health Facts contains detailed clinical, pharmacy and laboratory results, all time-stamped as well. Health Facts is a HIPAA-compliant comprehensive source of de-identified data. Cerner aggregates the data provided by participating

facilities and uses stringent quality assurance processes to ensure the ongoing integrity of the information. The dataset is described elsewhere in detail.(Amin et al.; Kosiborod, 2008; Kosiborod et al., 2009)

Study cohort

Patients were included if they were 18 years or older and they had a principal diagnosis of asthma (International Classification of disease, 9th Revision, Clinical Modification code, ICD-9 codes 493.0x, 493.1x 493.9x 493.2x, 493.8x) or principal diagnosis of acute respiratory failure (ICD-9 codes: 518.81, 518.82, 518.84, 518.4) combined with a secondary diagnosis of asthma.(*International Classification of Diseases, 9th Revision, Clinical Modification*, 2004) We took advantage of the presence of pharmacy data to restrict the analysis to patients treated with short-acting bronchodilators and systemic steroids because we felt that any patient hospitalized with asthma exacerbation of moderate severity would have been treated with this combination of medications; as such, patients without medication data were excluded. We excluded patients without laboratory results because these data were used to calculate an acuity score and patients with obstructive sleep apnea since it would not be possible to differentiate chronic use of NIV from treatment specifically for acute respiratory failure. We further excluded patients who were transferred to or from another facility because their initial form of ventilation and their outcomes could not be ascertained. We also excluded patients with a contraindication for NIV including cardiac arrest, acute myocardial infarction, facial trauma, significant arrhythmia and hemodynamic instability present at admission.

Independent variables

For each hospitalization data were recorded on patients age, gender, race, insurance status and we calculated an overall comorbidity score based on the method described by Gagne.(Gagne et al., 2010) We also used the software provided by the Healthcare Costs and Utilization Project of the Agency for Healthcare Research and Quality to classify comorbidities based on the method described by Elixhauser.(Elixhauser, Steiner, Harris, & Coffey, 1998)

To assess the severity of disease at the time of hospital admission we used the Laboratory Acute Physiology Score (LAPS) which was developed by Escobar et al in an electronic medical record dataset to predict short-term mortality.(Escobar et al., 2008) The LAPS uses data from admission and integrates 14 laboratory tests (albumin, anion gap, arterial pH, bicarbonate, bilirubin, blood urea nitrogen, creatinine, glucose, hematocrit, lactate, $PaCO_2$, PaO_2, sodium, troponin, total white blood cell count), into a single continuous variable which ranges between 0 and a theoretical 256. The variables included in the LAPS are collected directly from the EMR and do not require chart abstraction. The LAPS is similar to many existing severity of illness scores, but it has an important difference with respect to missing data, where it employs two steps for point assignment. First, a regression model is used to subdivide the population into two risk groups, with a predicted mortality risk of $< 6\%$ and $\geq 6\%$. Among patients with a low risk of death missing data are imputed to normal, as is the customary convention in many severity scores. Patients with a predicted risk of death $\geq 6\%$, ("high risk") have a different imputation approach and points are assigned for missing data for several important test results based on the beta coefficients from the regression model. The

LAPS score had been validated externally and has been used in other studies.(Escobar et al., 2008; van Walraven et al.)

Type of Ventilation

We used ICD-9 procedure codes to identify patients receiving NIV (code 93.90) or IMV (code 96.7x).("ICD-9-CM coding and reporting official guidelines. American Hospital Association, American Medical Record Association, Health Care Financing Administration, National Center for Health Statistics," 1990) Since the dataset includes date-stamped procedure codes we were able to determine the day when the ventilation was initiated and the sequence of ventilation. We recorded the initial form of ventilation, defined as the first method of ventilation started after hospital admission as initial NIV or initial IMV. For the rare cases where NIV and IMV were recorded the same day, we assumed that NIV preceded IMV. NIV failure was defined as treatment with IMV after initial exposure to NIV.

Outcomes

The outcomes were the initial method of ventilation, in patient case-fatality and hospital length of stay. We also assessed the rates and outcomes of NIV failure as a secondary analysis.

Statistical Analysis

To describe the study population we calculated counts and percentages for categorical variables and means, medians, and percentiles for continuous variables. The association of patient or hospital characteristics with the three ventilation strategies of no

ventilation, initial NIV, or initial IMV was assessed via the chi-square test or one-way analysis of variance.

To assess the impact of initial NIV versus IMV on in-hospital risk of death and length of stay, we first developed a regression model to estimate the probability that patients who were ventilated would receive NIV initially. Propensities for NIV were obtained from a hierarchical (multi-level) mixed effects logistic regression model where hospitals were treated as random effects and hospital characteristics, patient demographics, comorbidities, and the LAPS were treated as fixed effects. We then matched patients treated with NIV and IMV on propensity using a Greedy Match algorithm, and evaluated the outcomes in the propensity matched cohort. Propensity scores were also used to estimate treatment effects using Inverse Probability Weighting.(Brookhart, Sturmer, Glynn, Rassen, & Schneeweiss; Brookhart, Wyss, Layton, & Sturmer) This approach, unlike matching does not results in a reduction of the sample size. The IPTW is defined at the inverse of the estimated PS for treated patients and the inverse of 1- the estimated PS for the comparison group. Patients who receive an unexpected treatment are weighted up to account for patients like them who did receive treatment and those patients who receive a typical treatment are weighted down because they are overrepresented in the data. As such, this approach creates a pseudo-population which is representative of patients' characteristics in the overall population. The results of IPTW are generalizable to the entire population from which the observed sample was taken and the treatment effect is referred to as the population average treatment effect.

We then developed a hierarchical generalized linear model adjusting for patient characteristics including a random hospital effect and assessed the effect of NIV on the

study outcomes. Logit link models were used for mortality and logarithmic link function for length of stay. In all analyses that assessed mortality, if a patient had multiple eligible admissions during the study period we randomly chose one encounter because the mortality outcome can occur only in the last hospitalization.

Next, we identified factors predictive of NIV failure by first restricting the cohort to those started on NIV while using the same hierarchical regression model structure and the same predictors as in the other models.

In an additional, secondary analysis we restricted the cohort to patients without concomitant pneumonia at admission and excluding all patients with cardiac arrest or other contraindications for NIV irrespective of the presence on admission indicator and performed the same analyses.

We performed several analyses to characterized patients with missing data and their outcomes and compared them with the cohort included in the analysis.

RESULTS

3.1 Trends in Mechanical Ventilation among Patients Hospitalized with Acute Exacerbations of COPD in the United States, 2001 to 2011

Patient and hospital characteristics

A total of 723,560 hospitalizations with an AE-COPD from 475 hospitals were included and189 hospitals participated in the dataset all 11 years of the study

The median age at admission was 70 years (IQR 61-79), 60% of admissions were females, and 72% white patients. The median Gagne comorbidity score (CS) was 2 (IQR 1-3) and the most common comorbidities were hypertension, heart failure, and diabetes. One-third of cases had at least one admission for COPD during the prior year, and 18% of admissions had a concomitant diagnosis of pneumonia present at admission. Approximately half of the admissions were to hospitals located in the South, 68% to non-teaching facilities, and 84% to hospitals located in urban areas.

Table 1.1: Characteristics of admissions for exacerbation of COPD, 2001 - 2011

Characteristics	**N**	**%**
Total COPD Admissions	723560	100.00
Female	431455	59.63
Age (years)		
<65	242196	33.47
65-74	210980	29.16
75-84	198120	27.38
≥85	72264	9.99
Race/ Ethnicity		
White	524328	72.47

Black	73703	10.19
Hispanic	26010	3.59
Other	99519	13.75
Comorbidity Score		
Low (≤1)	312439	43.18
Median (2-3)	233775	32.31
High (≥4)	177346	24.51
Concomitant Pneumonia	128464	17.75
Number of COPD Admissions in Prior Year		
None	497223	68.72
1	125365	17.33
2	48797	6.74
≥3	52175	7.21
Hospital Characteristics		
Bed Size		
Small (<200)	136463	18.86
Medium (200–400)	301069	41.61
Large (>400)	286028	39.53
Region		
Midwest	144208	19.93
Northeast	131441	18.17
South	355285	49.10
West	92626	12.80
Population Served		
Rural	118473	16.37
Urban	605087	83.63
Teaching Hospital	229546	31.72

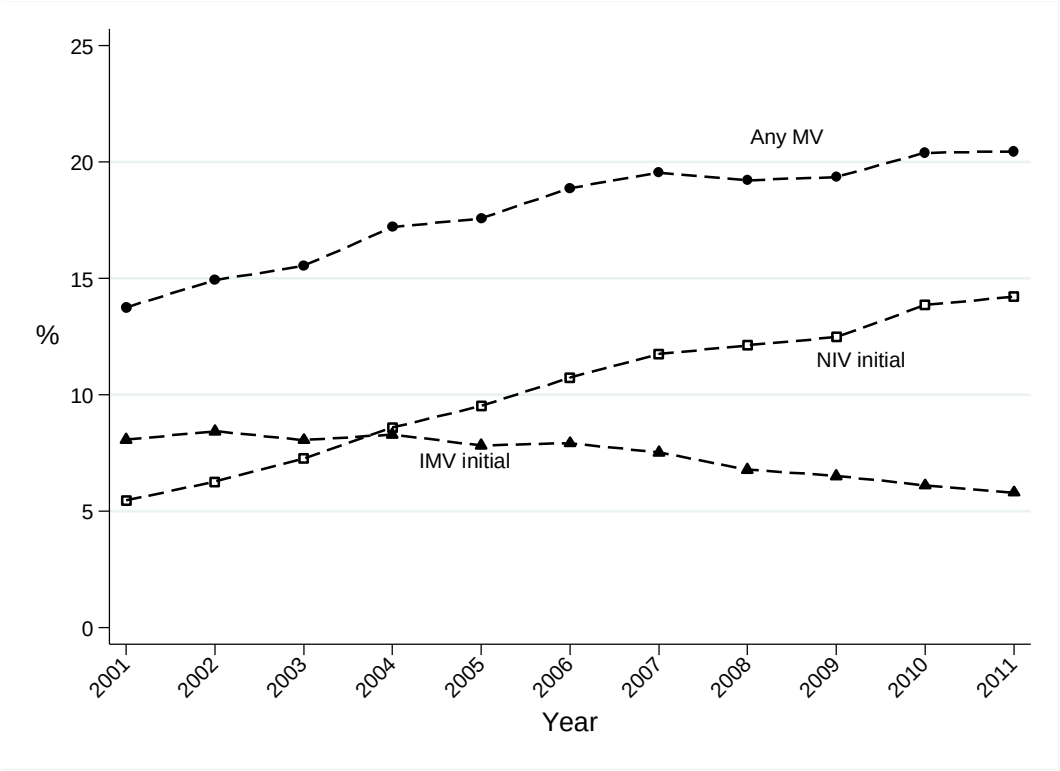
Use of NIV and IMV between 2001 and 2011

Overall, in 18.2% of admissions, patients were mechanically ventilated (IMV or NIV) at some point during their hospitalization; in 10.6% of admissions, patients were initially started on NIV (59.2% of all admissions with ventilation); in 7.3% of admissions, patients were started on IMV; in a small number of admissions (0.4%) the order of ventilation could not be determined. In all, 16.6% of the admissions initially started on NIV resulted in subsequent intubation (i.e. NIV failure).

Trends in the use of noninvasive and invasive ventilation between 2001 and 2011

After adjusting for changes in hospital and patient characteristics during the years under study, exposure to any form of mechanical ventilation had a relative increase of 4.4% annually (from 14.1% in 2001 to 20.3% in 2011). The annual rate of initial NIV increased on average 15.1% (from 5.9% to 14.8%); use of initial IMV declined an average 3.2% per year (from 8.7% to 5.9%) and by 2004, the rate of initial NIV was higher than that of initial IMV. (Figure 1.1) Between 2001 and 2011, the percentage of ventilator starts that were non-invasive increased an average of 8.0% per year (from 39.9% to 71.7%) and the annual rates of NIV failure declined by 0.7% (from 17.9% to 16.7%). Patient characteristics and ventilation management over time are described in eTable 1.1.

Figure 1.1: Trends in use of mechanical ventilation, overall, and by initial ventilation strategy



eTable 1.1: Patient Characteristics and Ventilation Management Over Time

CHARACTERISTIC or VENTILATION MANAGEMENT		YEAR										
		2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Total COPD Admissions		43,421	51,173	59,249	56,689	64,295	71,057	73,016	86,039	86,345	83,161	49,115
Gender	Female	58.20%	58.20%	59.10%	59.40%	59.80%	59.70%	59.80%	59.70%	60.20%	60.30%	60.30%
	Male	41.80%	41.80%	40.90%	40.60%	40.20%	40.30%	40.20%	40.30%	39.80%	39.70%	39.70%
Age (years)	Median, IQR	71,62-78	71,61-78	71,61-78	71,61-78	71,62-79	71,61-79	71,61-79	71,61-79	70,60-79	70,60-79	70,61-79
	<65	32.00%	32.60%	32.90%	32.50%	32.60%	33.10%	33.20%	33.10%	35.30%	35.10%	34.30%
	65-74	32.00%	31.00%	30.20%	29.80%	29.20%	28.50%	28.60%	28.10%	28.50%	28.40%	28.70%
	75-84	27.90%	28.40%	28.50%	28.60%	28.60%	28.40%	27.90%	27.60%	25.60%	25.30%	25.60%
	≥85	8.10%	8.00%	8.40%	9.00%	9.60%	10.10%	10.30%	11.20%	10.60%	11.20%	11.50%
Race/Ethnicity	White	76.70%	73.20%	74.00%	73.20%	72.80%	71.50%	70.90%	70.80%	70.60%	71.80%	75.80%
	Black	7.60%	8.80%	9.60%	10.50%	10.30%	10.50%	10.80%	10.60%	11.00%	10.50%	10.30%
	Hispanic	2.20%	3.80%	4.60%	3.20%	3.40%	3.50%	3.60%	4.10%	4.20%	3.80%	2.20%
	Other	13.60%	14.20%	11.90%	13.10%	13.60%	14.40%	14.80%	14.60%	14.20%	13.90%	11.70%
Combined Comorbidity Score	Median, IQR	2,1-3	2,1-3	2,1-3	2,1-3	2,1-3	2,1-3	2,1-4	2,1-4	2,1-4	2,1-4	2,1-4
	Low (≤1)	48.40%	47.80%	47.70%	46.40%	45.60%	43.10%	41.80%	40.50%	40.40%	39.50%	39.50%
	Median (2-3)	33.70%	33.00%	33.30%	33.10%	32.70%	32.20%	31.90%	32.00%	31.60%	31.50%	31.70%
	High (≥4)	17.90%	19.20%	19.00%	20.50%	21.70%	24.80%	26.30%	27.40%	28.00%	29.00%	28.90%
History of Concomitant Pneumonia		9.20%	10.50%	12.90%	13.90%	15.30%	15.60%	17.50%	23.50%	22.80%	21.90%	23.80%
Number of COPD Admissions in Prior Year	None	70.50%	70.40%	70.50%	68.40%	69.70%	69.50%	68.00%	68.20%	66.80%	66.70%	70.00%
	1	16.80%	17.00%	16.80%	17.60%	17.00%	16.90%	17.40%	17.60%	17.80%	17.80%	17.00%
	2	6.40%	6.40%	6.60%	6.80%	6.60%	6.60%	6.90%	6.80%	7.20%	7.20%	6.30%
	≥3	6.20%	6.20%	6.20%	7.20%	6.70%	6.90%	7.70%	7.50%	8.10%	8.30%	6.80%
Hospital Characteristics												
Bed Size	Small (<200)	18.30%	19.20%	18.70%	16.00%	17.70%	17.30%	17.90%	18.80%	19.90%	20.30%	23.40%
	Medium (200-400)	41.50%	42.30%	41.50%	41.80%	41.30%	41.30%	40.80%	41.30%	42.00%	42.20%	41.90%
	Large (>400)	40.20%	38.50%	39.90%	42.20%	40.90%	41.40%	41.30%	39.90%	38.00%	37.60%	34.70%
Region	Midwest	20.90%	20.60%	17.80%	19.20%	20.50%	20.20%	20.20%	20.40%	19.70%	19.70%	20.20%
	Northeast	9.30%	10.10%	17.30%	19.80%	20.40%	19.70%	19.90%	20.40%	19.70%	19.00%	17.90%

	South	57.90%	57.30%	55.20%	51.30%	48.80%	46.30%	45.80%	45.70%	45.80%	46.70%	48.00%
	West	11.80%	12.00%	9.80%	9.70%	10.30%	13.80%	14.10%	13.40%	14.70%	14.60%	13.90%
Population Served	Rural	21.90%	19.60%	17.50%	15.00%	15.80%	15.30%	14.60%	14.90%	15.00%	16.30%	18.40%
	Urban	78.10%	80.40%	82.50%	85.00%	84.20%	84.70%	85.40%	85.10%	85.00%	83.70%	81.60%
Teaching Hospital		29.60%	30.30%	32.40%	33.90%	32.70%	31.90%	30.80%	31.20%	32.00%	32.00%	31.60%
Nature of Ventilation	No Ventilation	86.47%	85.30%	84.69%	83.12%	82.65%	81.35%	80.72%	81.09%	81.00%	80.04%	79.98%
	NIV Initially	5.46%	6.27%	7.26%	8.59%	9.52%	10.73%	11.75%	12.13%	12.48%	13.86%	14.21%
	IMV Initially	8.07%	8.44%	8.06%	8.29%	7.83%	7.92%	7.52%	6.78%	6.52%	6.11%	5.80%
	Any Ventilation	13.53%	14.70%	15.31%	16.88%	17.35%	18.65%	19.28%	18.91%	19.00%	19.96%	20.02%
Death		3.90%	3.90%	3.50%	3.50%	3.10%	3.10%	2.80%	2.60%	2.20%	2.00%	2.20%

Table 1.2: Patterns of ventilation use according to patient characteristics 2001-2011

Outcome: ventilation type/ Patient population	**Any ventilation/ All patients**	**NIV initial/ All patients**	**IMV initial/ All patients**	**NIV proportion/ Ventilated patients**	**NIV Failure/ NIV patients**
Variable	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Year (annual change)	1.06 (1.05-1.07)	1.14 (1.12-1.17)	0.95 (0.94-0.96)	1.19 (1.17-1.21)	0.96 (0.93-0.98)
Female	0.99 (0.98-1.01)	1.01 (1.00-1.03)	0.96 (0.95-0.98)	1.05 (1.02-1.08)	0.98 (0.94-1.02)
Age					
65-74	0.93 (0.89-0.96)	0.97 (0.92-1.01)	0.92 (0.88-0.96)	1.06 (0.99-1.14)	0.87 (0.76-0.98)
75-84	0.66 (0.64-0.69)	0.76 (0.72-0.8)	0.67 (0.63-0.7)	1.12 (1.04-1.21)	0.75 (0.64-0.85)
≥85	0.43 (0.41-0.46)	0.56 (0.52-0.6)	0.45 (0.41-0.48)	1.22 (1.07-1.38)	0.50 (0.37-0.62)
Age by Year interaction					
65-74	1.00 (0.99-1.01)	1.00 (1.00-1.01)	0.99 (0.98-1.00)	1.01 (1.00-1.02)	0.99 (0.97-1.00)
75-84	1.01 (1.00-1.01)	1.01 (1.00-1.02)	0.98 (0.98-0.99)	1.03 (1.02-1.04)	0.97 (0.95-0.99)
≥85	1.02 (1.01-1.03)	1.02 (1.01-1.03)	0.99 (0.97-1.00)	1.04 (1.02-1.06)	0.98 (0.94-1.01)
Race					
Hispanic	0.89 (0.81-0.97)	0.90 (0.85-0.94)	0.93 (0.82-1.05)	0.90 (0.82-0.98)	0.98 (0.83-1.12)
Black	1.11 (1.05-1.17)	0.99 (0.96-1.02)	1.20 (1.12-1.29)	0.86 (0.82-0.90)	1.02 (0.94-1.10)
Other	1.13 (1.07-1.20)	1.00 (0.97-1.04)	1.15 (1.06-1.24)	0.91 (0.86-0.96)	1.01 (0.92-1.10)
Race by Year interaction					
Hispanic	1.00 (0.99-1.02)	--	1.01 (0.99-1.03)	--	--
Black	0.99 (0.98-1.00)	--	0.99 (0.98-1.00)	--	--
Other	0.99 (0.98-1.00)	--	0.99 (0.98-1.01)	--	--
Comorbidity score					
Medium:2-3	2.02 (1.95-2.09)	1.68 (1.60-1.76)	2.04 (1.99-2.09)	0.88 (0.81-0.94)	1.39 (1.19-1.59)
High:≥4	4.04 (3.89-4.19)	2.66 (2.53-2.79)	4.01 (3.91-4.11)	0.73 (0.68-0.79)	2.11 (1.81-2.41)
Comorbid score by Year Interaction					
Medium:2-3	0.98 (0.98-0.99)	0.99 (0.98-1.00)	--	0.98 (0.97-0.99)	1.01 (0.99-1.04)
High:≥4	0.97 (0.96-0.97)	0.98 (0.97-0.99)	--	0.97 (0.96-0.98)	1.03 (1.01-1.05)
Pneumonia	5.62 (5.43-5.81)	2.75 (2.62-2.88)	5.88 (5.64-6.13)	0.55 (0.54-0.57)	2.6 (2.47-2.72)
Pneumonia by Year	0.88 (0.87-0.88)	0.92 (0.91-0.93)	0.90 (0.90-0.91)	--	--

interaction					
COPD Prior Admit					
1	1.25 (1.21-1.30)	1.47 (1.44-1.50)	1.04 (0.99-1.10)	1.39 (1.28-1.49)	0.85 (0.80-0.90)
2	1.39 (1.32-1.47)	1.79 (1.74-1.84)	0.96 (0.89-1.04)	1.71 (1.52-1.90)	0.86 (0.79-0.93)
3+	1.66 (1.58-1.75)	2.21 (2.15-2.27)	1.16 (1.07-1.24)	1.70 (1.52-1.89)	0.72 (0.66-0.78)
COPD Prior Admit by Year Interaction					
1	1.01 (1.01-1.02)	--	1.00 (1.00-1.01)	--	--
2	1.02 (1.01-1.03)	--	1.02 (1.01-1.03)	--	--
3+	1.02 (1.01-1.03)	--	1.00 (0.99-1.01)	--	--

Ventilation type refers to the ventilation therapy administered during admission. Patient population refers to the population which was eligible for each type of ventilation. Any ventilation = any NIV or IMV during hospitalization and population eligible =all admissions included in the analysis.

NIV or IMV initial = ventilation type which was employed first and population eligible= all admissions included in the analysis. NIV % of all ventilator starts = NIV was employed first as the ventilatory therapy and population eligible=admissions among all ventilated patients. NIV failure=transition to IMV after a trial of NIV and population eligible = admissions among all patients ventilated with NIV initial

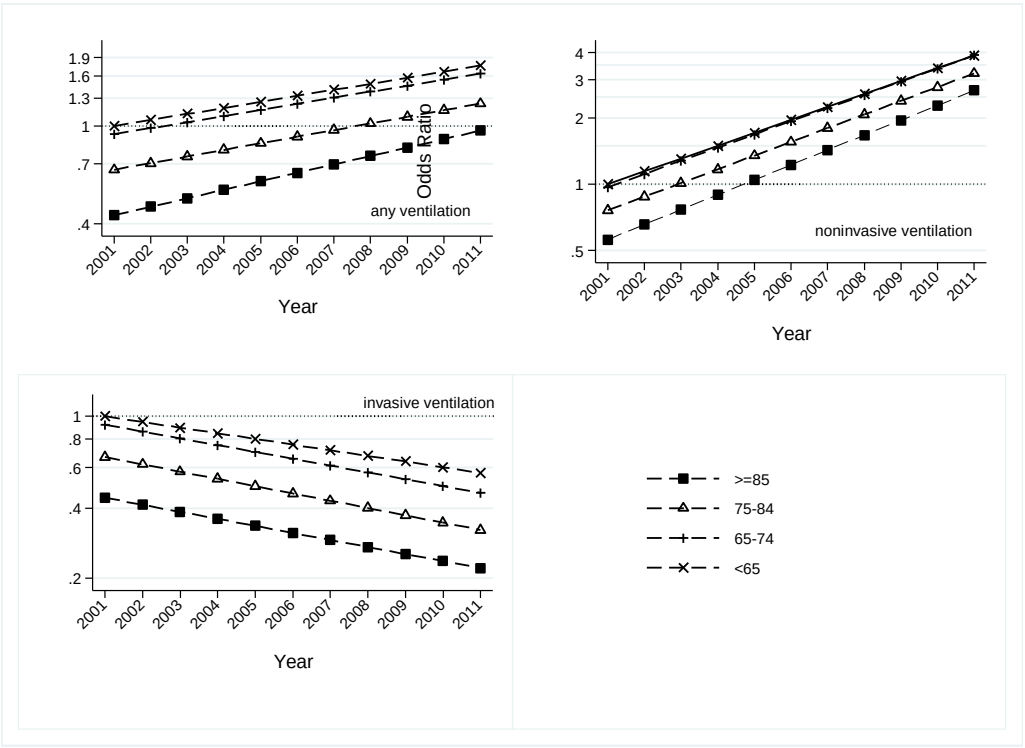
All models are adjusted for year, gender, age group, race, combined comorbidity score, concomitant pneumonia, COPD prior admission, and hospital characteristics (i.e., number of beds, teaching status, urban/rural, geographical area). Initial models evaluated interaction terms for year with gender, age group, race, comorbidity score, concomitant pneumonia and prior COPD admissions. Non-significant interaction terms ($p>0.05$) were dropped from final models reported here. For NIV proportion and NIV failure we also adjusted for annual hospital ventilation rate.

Main effect OR estimates apply to baseline year 2001. Multiply by the year interaction effect for each subsequent year. For example the OR 4.04 (3.89-4.19) indicates that in 2001, patients with high comorbidity burden were 4.04 times more likely to be ventilated than patients with low comorbidity burden. The interaction effect with year, OR 0.97 (0.96-0.97), indicates that the odds of ventilation for patients with high comorbidity burden decreases by a factor of 0.97 times per year, so that 10 years later, by 2011, they are $4.04 \times 0.97^{10} = 2.98$ times more likely to be ventilated than those with a low comorbidity burden.

Patterns of ventilation use according to patient characteristics

After adjusting for other patient and hospital characteristics, older patients (≥75) were significantly less likely than the youngest patients (40-64) to receive any form of mechanical ventilation and when ventilated, were more likely to be started on NIV; NIV failure was lower in older patients compared to the youngest, but there was no difference in the combined outcome of NIV failure or death. Over the 10 years of the study, use of NIV increased faster in older relative to the youngest patients by a factor of 1.02 times per year, while use of IMV decreased more among the oldest relative to the youngest by a factor of 0.99 times per year. For example, in 2001 the oldest patients were 44% less likely than the youngest to be started on NIV (OR=0.56); but by 2011 were 32% less likely to be started on NIV (OR=0.68). (Table 1.2 and eFigure 1.1a)

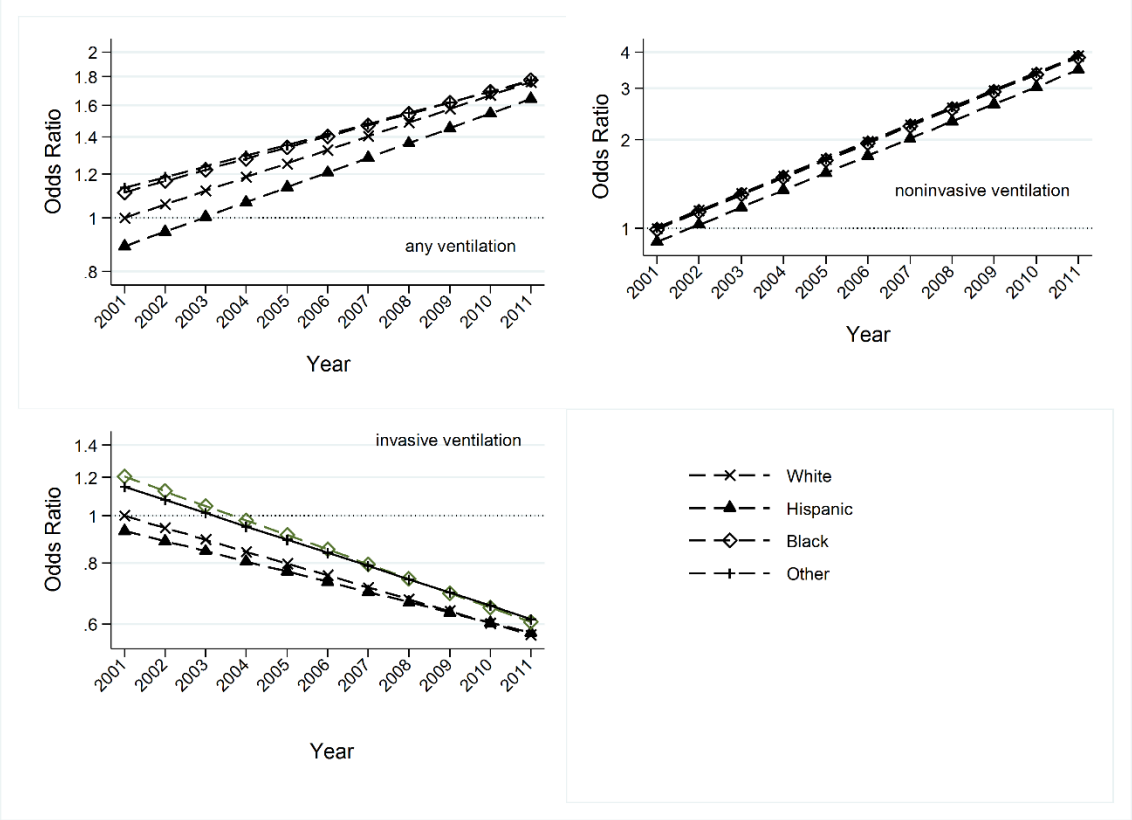
eFigure 1.1a Trends of ventilation use in COPD by age groups, 2001-2011



ORs plotted are relative to referent group, admissions of patients <65, in 2001

In 2001, compared to admissions of white patients, Hispanics were less likely to receive any ventilation (OR=0.89). In contrast, blacks were more likely than whites to be ventilated (OR=1.11 in 2001) and more likely to be started on IMV (OR=1.20 in 2001). However across the 10 year period use of IMV decreased among black relative to white patients, and increased among Hispanic relative to white patients, so that by 2011 use was similar in Hispanic and white patients (Table 1.2 and eFigure 1.1b) NIV failure rates were similar across race groups.

eFigure 1.1b Trends of ventilation use in COPD by race groups, 2001-2011

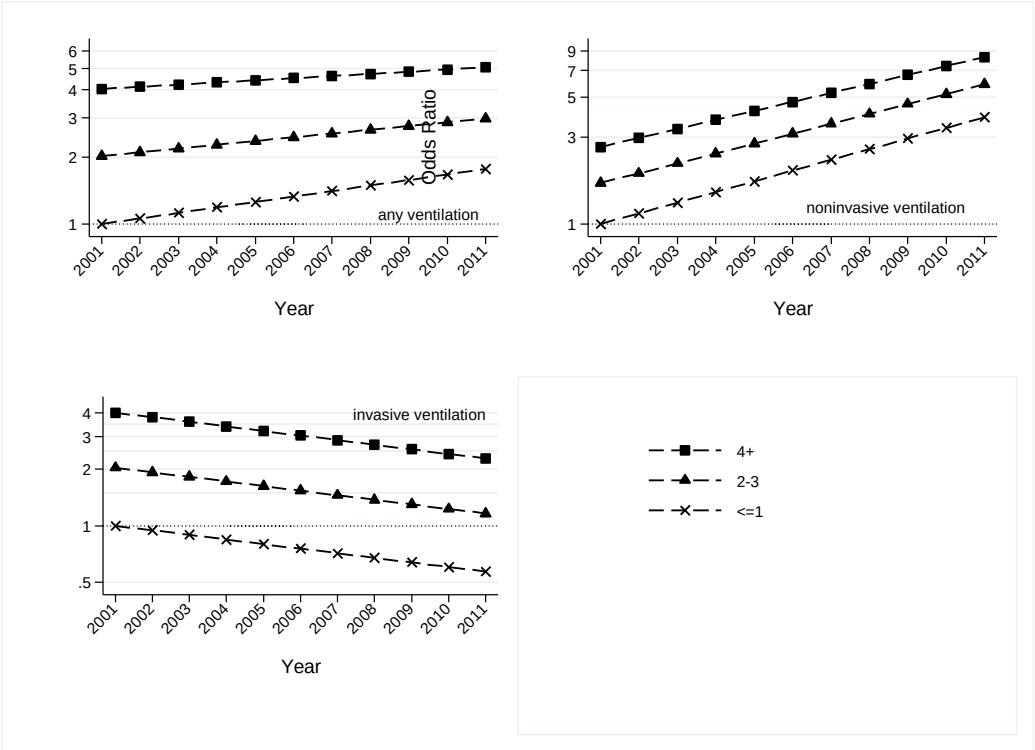


ORs plotted are relative to referent group, admissions of white patients, in 2001

Admissions of patients with high levels of comorbidity (Gagne CS≥4) were 4 times more likely to lead to any form of ventilation than those of patients with the lowest

levels of comorbidity (Gagne CS≤1) in 2001. Among hospitalizations with ventilation, those of patients with high comorbidity scores were less likely to lead to NIV starts and more likely to have NIV failure than those of patients with a lower comorbidity burden. Although NIV use increased over time in all hospitalizations, the annual rate of increase among those with a higher comorbidity burden was lower than in those with the lowest comorbidity burden. For example, patients with high comorbidity score were 4.04 times more likely to be ventilated in 2001 than those with low score but only 2.98 times more likely to get ventilated than those with low score in 2011. (Table 1.2 and eFigure 1.1c)

eFigure 1.1c Trends of ventilation use in COPD by comorbidity score, 2001-2011

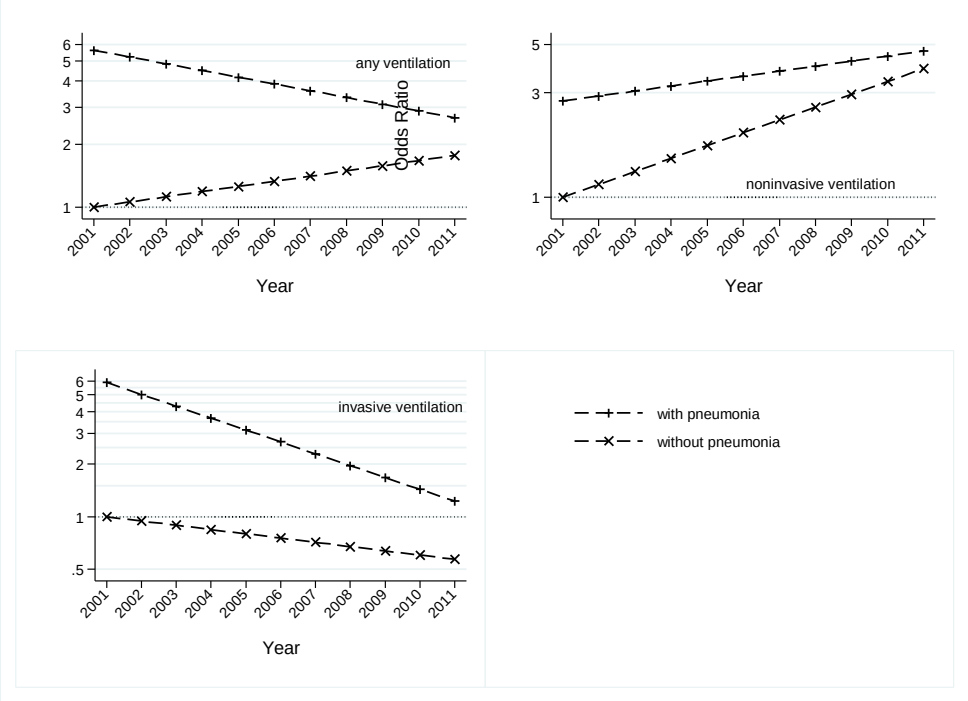


ORs plotted are relative to referent group, admissions of patients with low comorbidity score, in 2001

Compared to admissions without pneumonia, those with AE-COPD and pneumonia were more likely to lead to any ventilation, especially IMV initiation, and to experience NIV failure. Over the 10 year study period overall ventilation use decreased

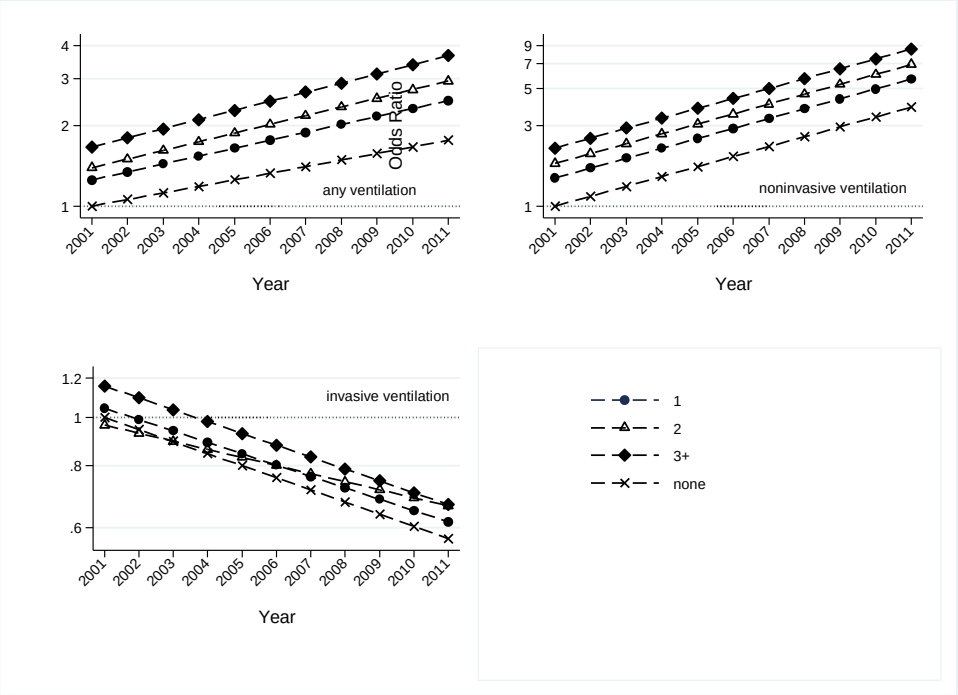
among admissions of COPD with concomitant pneumonia, while ventilation use increased among those without pneumonia though overall odds of ventilation were still higher in those with pneumonia than without (OR=1.57 in 2011). While NIV use increased among both groups of patients, the rate of increase was greater among those without pneumonia. At the same time IMV use decreased in both groups, but the rate of decline was greater among admissions of pneumonia patients. (Table 1.2 and Figure 1.2) The trends of ventilation use in COPD by numbers of prior COPD admissions are illustrated in eFigure 1.1d.

Figure 1.2: Trends of ventilation use in COPD with and without pneumonia, 2001-2011



ORs plotted are relative to referent group, admissions of patients without concomitant pneumonia, in 2001

eFigure 1.1d: Trends of ventilation use in COPD by prior number of COPD admissions, 2001-2011



ORs plotted are relative to referent group, admissions of patients without prior hospitalization for COPD

3.2 Hospital Patterns of Use of Noninvasive Ventilation in Patients with Asthma Exacerbation

Patient and Hospital Characteristics

We identified a total of 24,372 admissions (inpatient or observation status) for asthma exacerbations in 132 hospitals between 2009 and 2012; 10,319 hospitalizations were excluded based on patient-level exclusion criteria. After excluding hospitals with less than 45 eligible encounters, the cohort for analysis included 13,588 admissions from 58 hospitals.

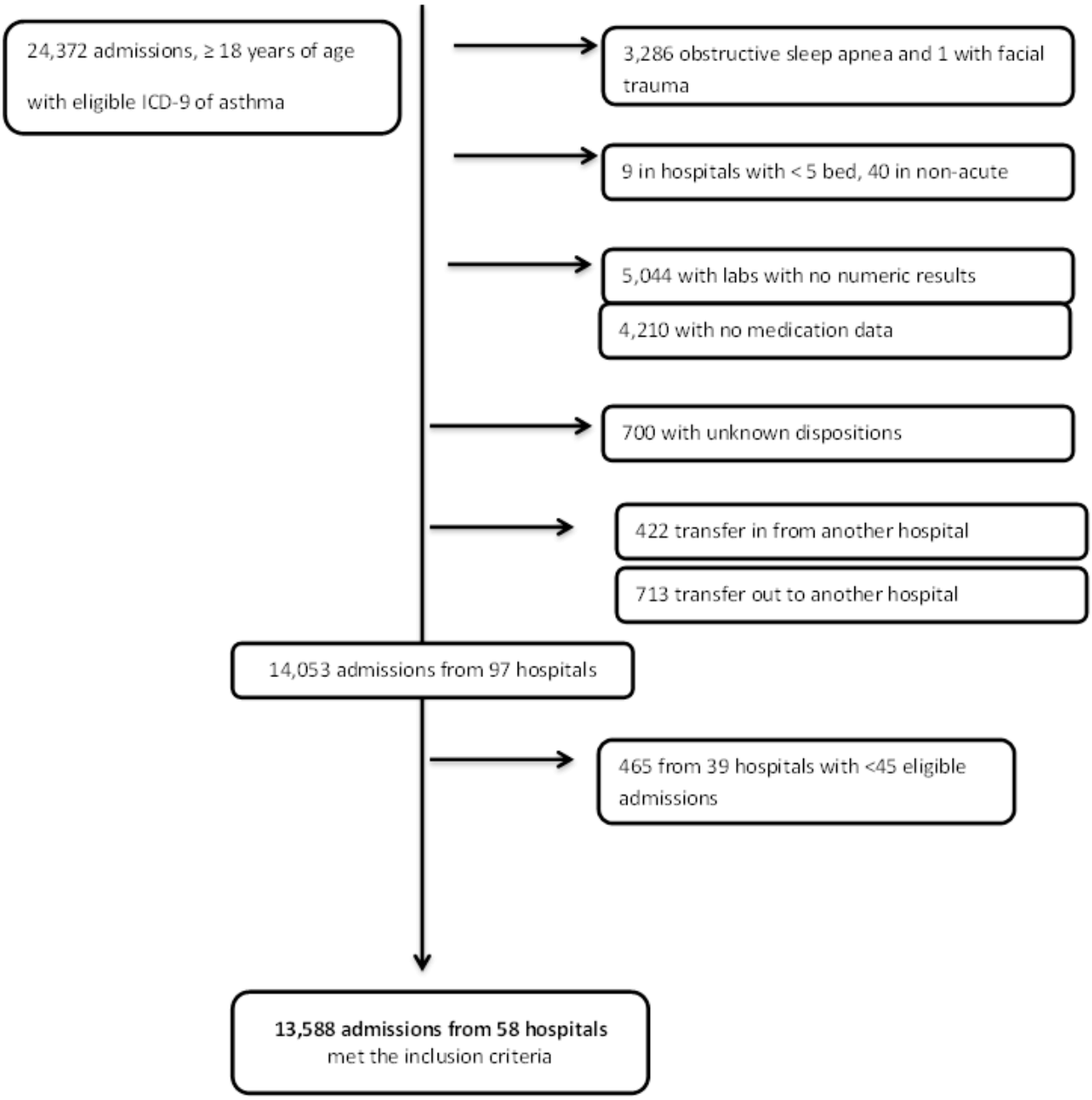
All 58 hospitals were urban, 36 (62%) were teaching and 29 (50%) had between 200 and 499 beds. The median volume of admissions with asthma per hospital over the study period was 325 [200, 445].

The median age of the study population was 52 years, 79.9% were female and 53.4% were white. The median comorbidity score was 1 [1, 2], 25.0% had diabetes mellitus, 11.9% had heart failure and 16.7% were obese. The median LAPS score was 26 [20, 38]. The median length of stay of the population was 73 [44, 120] hours, and 1.2% patients died during hospitalization.

Of all hospitalizations with an acute exacerbation of asthma, most, 12,268 (90.3%) were not ventilated; 546 (4.0%) were initially treated with NIV and 774 (5.7%) with IMV; 4.9% of all patients ventilated with NIV were intubated (NIV failure). The use of NIV as the first method of ventilation increased from 2.3% in 2009 to 4.8% in 2012. The in-hospital case-fatality rate was 0.3% in patients who were not ventilated,

2.6% in patients initially treated with NIV, 15.6% in patients initially treated with IMV and 21.4% in patients with NIV failure.

Figure 2.1: Study cohort flow chart

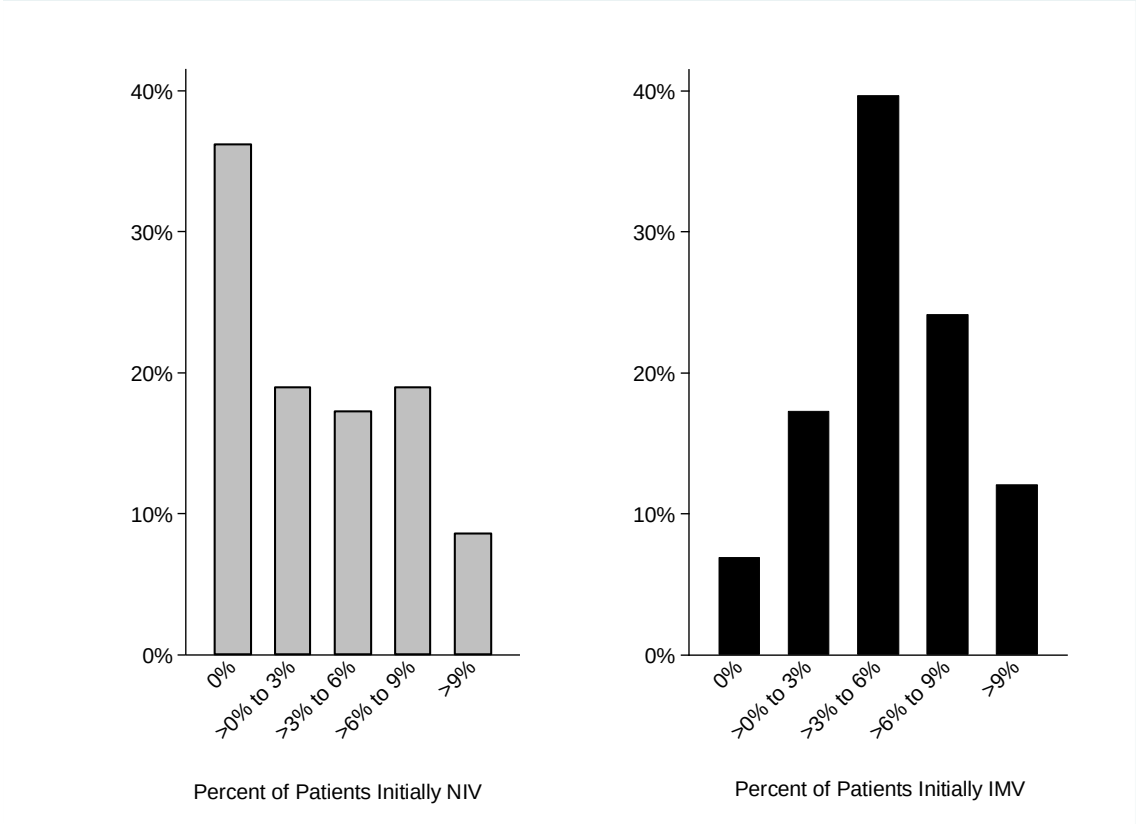


*the criteria are not mutually exclusive
ICD-9: International Classification of disease, 9th Revision, Clinical Modification code
NIV or IMV initial refers to the first method of ventilation during hospitalization

Hospital use of Noninvasive and Invasive Ventilation

The unadjusted initial NIV hospital rates ranged from a minimum of 0% to a maximum of 16.3%, with an unweighted mean of 3.4%. Overall, 38% (22 out of 58) of the hospitals did not use NIV in any admission with asthma during the study period. The initial IMV rate varied between 0% and 14.5% with an unweighted mean of 5.0%.

Figure 2.2: Distribution of observed initial noninvasive and invasive ventilation rate among hospitals included in the analysis



NIV= non-invasive ventilation, IMV= invasive mechanical ventilation
NIV or IMV initial refers to the first method of ventilation during hospitalization
Hospitals rates of NIV and IMV are grouped in equally spaced categories by stratifying by 3% increments

Hospital initial RS-NIV rates ranged from a 0.4% to 33.1% and hospital initial RS-IMV rates from 3.5% to 10.1%. The interquartile range (i.e., the 25th and 75th percentiles) of RS-NIV was [1.2%, 14.1 %] versus [4.9% to 6.6%] for RS-IMV. We observed no significant trend among hospital characteristics (number of beds, teaching status, census region) and either RS-NIV or RS-NIV. However, using the variance F-test, there was more variation in RS-NIV overall compared to RS-IMV ($p<0.001$).

Table 2.1: Risk-standardized initial noninvasive ventilation rates by characteristics of hospitals included in the analysis

Overall	Number of Hospitals	RS-initial NIV % Median [IQR]	RS-initial IMV % Median [IQR]
Hospital Size			
<199 Beds	18	4.4 [1.3, 9.9]	5.5 [4.9, 6.6]
200 to 499	29	4.0 [1.1, 16.1]	5.7 [4.7, 6.5]
500+	11	8.7 [0.7, 8.9]	5.6 [4.2, 6.9]
Teaching Status			
Teaching Hospital	36	4.3 [1.3, 15.8]	5.6 [4.6, 6.7]
Non-Teaching Hospital	22	6.2 [1.1, 13.2]	5.7 [4.9, 6.6]
Region			
Midwest	11	8.8 [0.9, 18.1]	5.7 [4.9, 6.8]
Northeast	21	4.0 [1.3, 15.6]	5.5 [4.7, 6.6]
South	21	4.6 [1.3, 9.9]	5.2 [4.9, 6.6]
West	5	5.8 [1.3, 9.1]	6.0 [5.7, 6.3]

RS-NIV= risk-standardized non-invasive ventilation, RS-IMV= risk-standardized invasive mechanical ventilation, IQR= inter-quartile range
NIV or IMV initial refers to the first method of ventilation during hospitalization

In addition, the likelihood ratio tests comparing the hierarchical models predicting either initial NIV or initial IMV compared to a logistic regression model that did not use hospitals as random effects were significant ($p<0.001$ for both models). This indicates that there was significant variation at the hospital level in the use of either ventilation type. Patient characteristics were similar among the quartiles of RS-NIV.

Table 2.2: Patient characteristics by quartiles of risk-standardized initial noninvasive ventilation

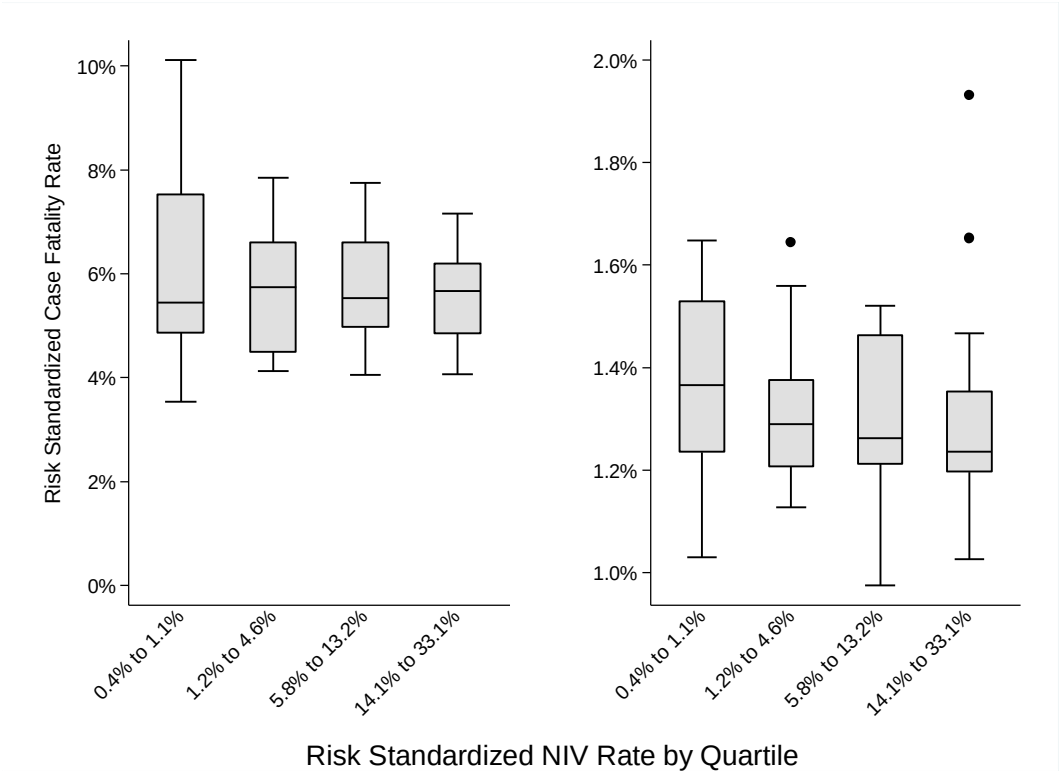
	Risk-standardized Initial NIV				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P-value for trend**
Age	56 [54, 58]	54 [51, 60]	53 [49, 55]	55 [51, 58]	0.23
% Female	74 [70, 76]	74 [69, 78]	73 [68, 75]	74 [72, 76]	0.87
% Black	13 [6, 43]	24 [12, 45]	18 [5, 55]	13 [4, 30]	0.67
LAPS	30 [29, 31]	30 [28, 33]	30 [29, 32]	32 [29, 34]	0.13

RS-NIV= risk-standardized non-invasive ventilation, LAPS= Laboratory acuity physiology score
NIV initial refers to the first method of ventilation during hospitalization
Numbers in each row express the median and inter-quartile range

Relationship between Hospital Risk Standardized initial NIV Rates and Outcomes

There was no significant correlation between the hospital initial RS-NIV rate and hospital RS-initial IMV rate (rho = -0.10, p=0.45). There was a modest, non-significant negative correlation with RS-NIV and the RS-case-fatality rate (rho =-022, p=0.09). Box plots illustrating these relationships are in Figure 2.3.

Figure 2.3: Correlation between risk standardized initial noninvasive ventilation rate and risk standardized initial invasive ventilation rate and in-hospital case fatality rate



NIV= non-invasive ventilation, IMV= invasive mechanical ventilation
NIV or IMV initial refers to the first method of ventilation during hospitalization
Each range represents the minimum and maximum risk adjusted rates for each quartile at the hospital level. In other words, we calculate the RS-NIV for each hospital. Then we took 4 equal sized groups at the hospital level (N =15 or 14 in each group) and then calculate the box plots at the hospital level.

Outcomes stratified by RS-NIV quartiles are shown in Table 2.3. There was no clear pattern of risk-standardized initial IMV use across RS-NIV quartiles and hospitals in the highest quartile of RS-NIV did not have lower RS-initial IMV use (median Q4 vs. Q1: 5.4% vs 5.7%, p= 0.60). Results were similar for hospital rates of any IMV (initial IMV plus IMV after NIV). Hospitals did have lower adjusted length of stay (p-value for trend = 0.01) when stratified by adjusted RS-NIV quartiles. There was **no** statistically

significant decline in risk standardized case fatality across RS-NIV quartiles (test for trend p = 0.10).

Table 2.3: Hospital risk standardized rates of invasive mechanical ventilation, case-fatality rate and length of stay by quartiles of risk standardized initial noninvasive ventilation

	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	**P-Value (Kruskal -Wallis)**	**P-Value for trend**
RS-initial NIV %	0.6 [0.5, 0.7]	1.5 [1.3, 2.5]	8.8 [7.8, 9.1]	18.1 [16.1, 22.6]	NA	NA
RS- initial IMV %	5.4 [4.9, 7.5]	5.7 [4.5, 6.6]	5.5 [5.0, 6.6]	5.7 [4.9, 6.2]	0.95	0.58
RS-Total IMV%	5.6 [5.0, 7.5]	5.9 [4.6, 6.8]	5.7 [5.2, 6.7]	5.9 [5.2, 6.7]	0.99	0.83
RS-case fatality rate %	1.4 [1.2, 1.5]	1.3 [1.2, 1.4]	1.3 [1.2, 1.5]	1.2 [1.2, 1.4]	0.41	0.10
RS-LOS (hours)	102 [98, 113]	106 [95, 113]	91 [84, 95]	94 [78, 112]	0.02	0.01

RS= risk-standardized, NIV= non-invasive ventilation, IMV= invasive mechanical ventilation, LOS=length of stay
NIV or IMV initial refers to the first method of ventilation during hospitalization
Numbers in each row express the median and inter-quartile range
The Kruskal Wallis Test compares all 4 quartiles. It tests if the 4 quartiles are the same (it ranks the values rather than computes a mean) versus the hypothesis that at least one is different. The p-value test for trend look

Figure 2.3 shows that as the hospital RS-NIV increased, the risk adjusted rate of initial IMV varied only slightly. Comparing mean values in the highest quartile of RS-NIV use to the lowest, we saw that there was an absolute difference in total ventilation of 19.5% implying that approximately an additional 20 out of 100 patients were ventilated in these hospitals. Moreover, there was a substantial, non-linear increase in the risk-

standardized total rate of initial mechanical ventilation with the rate in the highest quartile of RS-NIV being 3.8 times the rate in the lowest quartile and 1.8 times the rate of the third highest quartile.

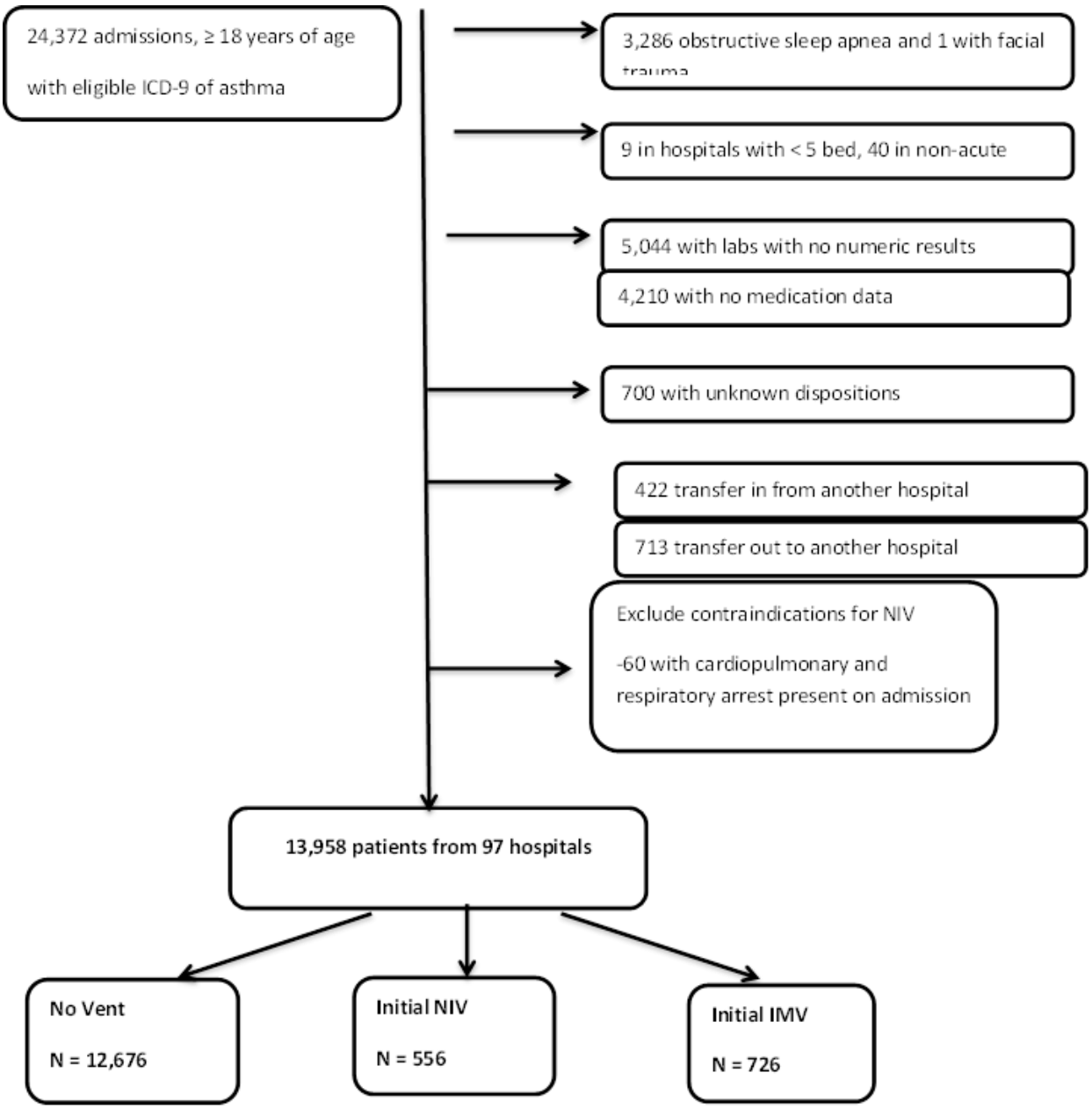
3.3 Outcomes of Noninvasive and Invasive Ventilation in Patients Hospitalized with Asthma Exacerbation

Patient and Hospital Characteristics

We identified a total of 13,958 hospitalizations at 97 hospitals which met our inclusion criteria. (eFigure 3.1) The median [IQR] age of our study population was 53 years [42, 67], 73.0% were female, 54.3% were Caucasian and 34.9% were black. In 1,261 (9.0%) admissions there was a secondary diagnosis of pneumonia present at admission.

Of the 97 hospitals included in the study, 91 (93.4%) were urban. There were 50 (51.5%) teaching hospitals and 43 (44.3%) hospitals had between 200 and 499 beds while 11 (11.3%) had 500 or more beds. The median [interquartile range] volume of admissions with asthma per hospital over the study period was 64 [13, 227].

eFigure 3.1: Study cohort flow chart



*the criteria are not mutually exclusive
ICD-9: International Classification of disease, 9th Revision, Clinical Modification code
NIV or IMV initial refers to the first method of ventilation during hospitalization

Table 3.1: Characteristics and outcomes of the patients included in the study

Variable	**No Vent** **N = 12,676** **(90.8%)**	**Initial NIV** **N = 556** **(4.0%)**	**Initial IMV** **N = 726** **(5.2%)**	**P-value**
Patient Characteristics				
Age, Median (IQR), years	53 [42, 67]	53 [43, 68]	53 [40, 64]	0.12
Female (%)	73.6	69.2	66.3	<0.001
Race/Ethnicity				
Caucasian	54.8	51.3	49.4	
Black	34.5	37.9	41.2	
Hispanic	4.3	4.0	3.0	<0.001
Asian/Other	4.8	6.7	4.5	
Unknown	1.7	0.2	1.8	
Smoking	36.8	47.1	40.1	<0.001
Combined Score	1 [1,2]	2 [1, 3]	2 [1,4]	<0.001
Comorbidities				
CHF	10.5	23.0	24.1	<0.001
Valvular Disease	3.3	6.7	4.4	<0.001
Pulm. Circ. Disease	0.7	6.7	6.1	<0.001
Neuro Disorders	5.3	4.5	13.2	<0.001
Diabetes Mellitus	24.6	27.2	23.7	0.32
Hypothyroidism	9.3	9.0	6.1	0.01
Renal Failure	5.6	7.6	9.6	<0.001
Obesity	16.6	19.1	16.5	0.30
Morbid Obesity	6.5	9.2	5.9	0.03
Anemia	9.9	13.7	17.1	<0.001
Alcohol Abuse	2.4	5.9	6.3	<0.001
Drug Abuse	5.8	11.5	13.8	<0.001
Psychoses	5.4	7.6	7.2	0.02

Hypertension	40.2	39.0	35.8	0.06
Pneumonia POA	8.0	13.1	24.2	<0.001
Status Asthmaticus	0.8	5.6	14.6	<0.001
LAPS				
0 to 19	12.9	7.2	2.3	
20 to 24	27.6	15.0	11.8	
25 to 30	22.0	10.9	6.1	<0.001
31 to 41	22.7	22.0	12.4	
42+	14.9	44.9	67.5	
Complications[b]	0.2	0.5	3.4	<0.001
LOS in Days	2.9 [1.8, 4.7]	4.1 [2.7, 6.9]	6.7 [3.8, 11.5]	<0.001
Inpatient Case Fatality Rate	0.2%	2.3%	14.2%	<0.001

[a] Additional comorbidities present in less than 5% of the sample: peripheral vascular disease; liver disease; peptic ulcer disease with bleeding; AIDS; lymphoma; metastatic cancer; solid tumor without metastasis; rheumatoid arthritis; coagulopathy.
[b] Complications include: pneumothorax, subcutaneous emphysema and subcutaneous emphysema from procedure
CHF= congestive heart failure, LAPS= laboratory acute physiology score, LOS= length of stay, POA= present on admission, LAPS= laboratory acute physiology score, NIV= noninvasive ventilation, IMV=invasive mechanical ventilation

Among the 13,958 hospitalizations, 12,676 (90.8%) were not ventilated, 556 (4.0%) were initially treated with NIV and 726 (5.2%) with IMV. NIV failure was recorded in 4.7% (n = 26) of all admissions initially treated with NIV. (See Table 3.1 for patient characteristics and outcomes by ventilation type). The in-hospital case-fatality rate was 2.3%, 14.2% and 15.4% among those initially ventilated with NIV, initially IMV, and among those with NIV failure respectively. Median length of stay in the hospital was 4.1 days, 6.7 days, and 10.9 days for patients ventilated with NIV, IMV and NIV failure respectively. (See eTable 3.1 for the outcomes of patients treated only with NIV, only with IMV and NIV failure).

eTable 3.1: Unadjusted outcomes by ventilation strategies

Ventilation Pathway	Percent of Patients	Inpatient Case Fatality Rate	LOS in Days
No Ventilation	90.8%	0.2%	2.9 [1.8, 4.7]
NIV Only	3.8%	1.7%	4.0 [2.6, 6.6]
IMV Only	4.6%	14.7%	6.7 [3.7, 11.8]
NIV Failure	0.2% (4.7% of NIV)	15.4%	10.9 [5.9, 18.5]

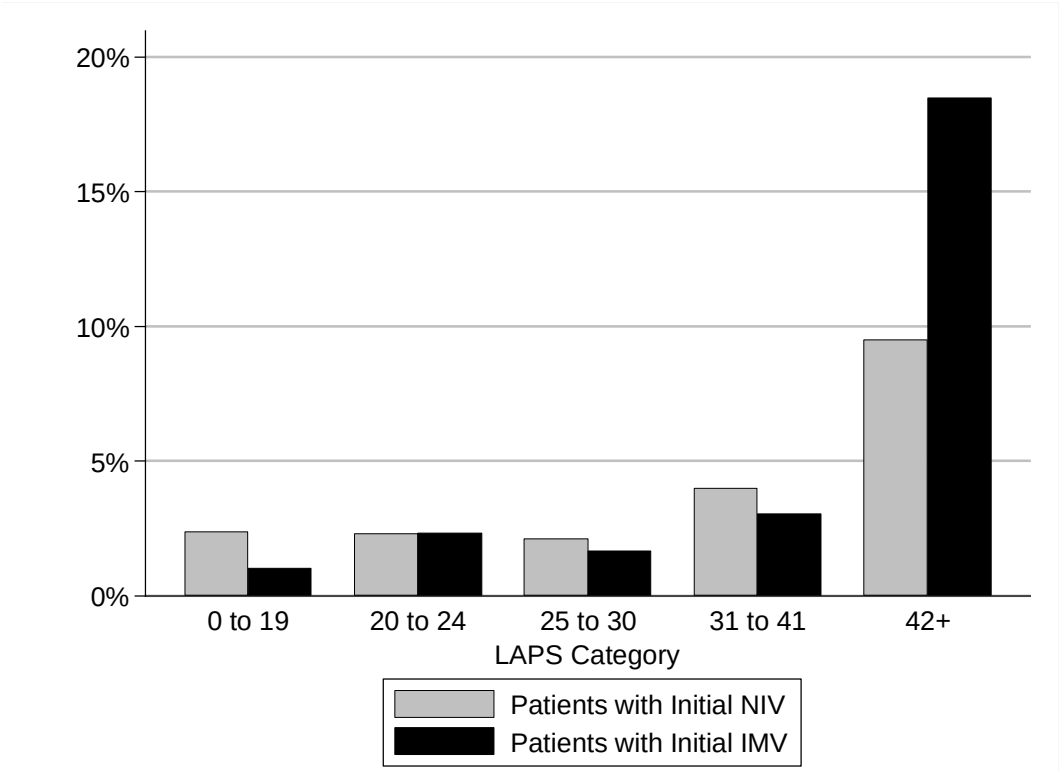
NIV= noninvasive ventilation, IMV=invasive mechanical ventilation,
NIV failure = NIV followed by IMV

Predictors for Initial Use of NIV

Figure 3.1 shows that the LAPS Score was significantly higher in admissions initially receiving IMV than admissions receiving NIV. In the regression analysis on ventilated patients, we found that older patients were more likely to receive initial NIV, while patients with higher acuity at admission, status asthmaticus, comorbid weight loss and neurological disorders were less likely to receive NIV. Patients with concomitant diagnosis of pneumonia had twice the odds of being receiving initial IMV than patients without concomitant pneumonia (odds ratio: 0.50; 95% CI (0.34, 0.74).

A likelihood ratio test comparing the hierarchical model to a logistic regression model without hospitals was highly significant ($p<0.001$) indicating that the hospital where the patient was treated had a significant association with the type of ventilation received. Moreover, the c-statistic (area under the ROC curve) of the model improved from 0.76 (the logistic regression model without hospital level effects) to 0.88 in the hierarchical model, indicating a strong institutional effect after adjusting for patient case mix.

Figure 3.1: Ventilation strategies by LAPS score



LAPS= laboratory acute physiology score, NIV= noninvasive ventilation, IMV=invasive mechanical ventilation
NIV or IMV initial refers to the first method of ventilation during hospitalization
NIV initial includes NIV failure
Each box plot represents the % of patients in that category of LAPS score.
For example, in the category of LAPS 0-19: approximately 2.4% of patients treated with NIV had this score and 1.1% with IMV, and 96.6 of those not ventilated (not-ventilated are not show)

Table 3.2: Predictors for initial noninvasive versus invasive mechanical ventilation for the patients included in the study

Variable	**Odds Ratio**	**P-Value**
Age (per 5 years)	1.05; (1.01 to 1.10)	0.03
Prior Admission within past 12 months		
0	1	
1	0.94; (0.063 to 1.40)	0.77
2+	1.69; (1.06 to 2.67)	0.03
Prior NIV within past 12 months	2.30; (1.32 to 4.00)	0.003

Prior IMV within past 12 months	0.36; (0.21 to 0.62)	<0.001
LAPS Score (per 5 units)	0.84; (0.81 to 0.87)	<0.001
Status Asthmaticus	0.30; (0.18 to 0.51)	<0.001
Pneumonia POA	0.50; (0.34 to 0.74)	<0.001
Neurological Disorders	0.24; (0.14 to 0.43)	<0.001
Weight Loss	0.20; (0.08 to 0.51)	0.001
Diabetes Mellitus (with and without complications)	1.69; (1.07 to 2.18)	0.02

LAPS= laboratory acute physiology score
POA= present on admission
NIV initial refers to the first method of ventilation during hospitalization
NIV initial includes NIV failure
Odds ratios > 1 mean the risk is higher for receiving NIV, odds ratios < 1 mean that if the variable is present, the patient is more likely to receive IMV.

Comparison of NIV and IMV Therapy Adjusted Outcomes

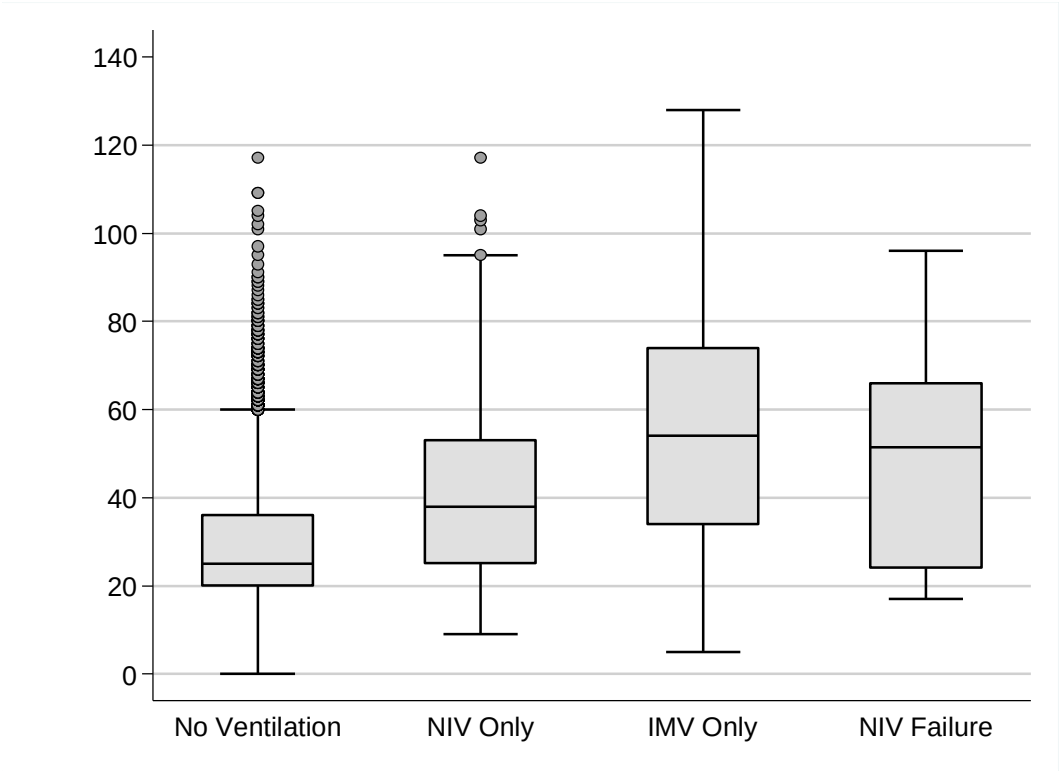
In the propensity score matching, there were 216 matched pairs (38.8% of the NIV cohort) to assess mortality and 260 matched pairs (46.8%) to assess length of stay. The LAPS score, hospital characteristics (i.e., bed size and teaching status), demographics and comorbidities were non-significantly different between NIV and IMV admissions after matching. Use of NIV was associated with significantly lower in-patient risk of dying (Relative Risk Ratio = 0.12; 95% CI (0.04, 0.40) and shorter lengths of stay (3.9 days less; 95% (2.5, 5.3)). The results from the analyses which used hierarchical regression modeling with hospitals as random effects and with inverse-probability weighting (IPW) were similar.

Table 3.3: Adjusted outcomes of initial noninvasive and invasive ventilation for the patients included in the study

Statistical Method	**NIV initial Case Fatality Rate**	**IMV initial Case Fatality Rate**	**Relative Risk Ratio** (95% CI)	**P-value**
Greedy Matched (216 matched pairs)	1.4%	11.6%	0.12 (0.04, 0.40)	0.001
Hierarchical Logistic Regression model with Hospitals as Random Effects	2.5sdc%	14.3%	0.18 (0.07, 0.29)	0.002
Inverse Probability Weighting	2.3%	14.8%	0.15 (0.05, 0.26)	<0.001
Statistical Method	**NIV Mean LOS (days)**	**IMV Mean LOS (days)**	**Difference in LOS (95% CI)**	**P-value**
Greedy Matched (260 matched pairs)	5.4	9.3	3.9 (2.5, 5.3)	<0.001
Hierarchical Generalized Linear Regression model with Hospitals as Random Effects and a logarithmic link function	4.4	9.4	5.0 (4.2, 5.9)	<0.001
Inverse Probability Weighting	5.8	9.6	3.8 (2.8, 4.8)	<0.001

NIV= noninvasive ventilation, IMV=invasive mechanical ventilation, LOS=length of stay, CI=confidence interval
NIV or IMV initial refers to the first method of ventilation during hospitalization
NIV initial includes NIV failure
Relative Risks below 1 mean that NIV is protective (is associated with less mortality than IMV).

eFigure 3.2 LAPS score by ventilation strategy and for noninvasive ventilation failure



LAPS= laboratory acute physiology score, NIV= noninvasive ventilation, IMV=invasive mechanical ventilation, NIV failure = NIV followed by IMV
NIV or IMV only = only this ventilation method was used. NIV failure is not included in NIV only or in IMV only

eTable 3.2: Characteristics and outcomes of the patients with initial noninvasive ventilation, noninvasive ventilation failure and invasive ventilation included in the study

Variable	Initial NIV Only N = 530 (95.32%)	NIV Failure N = 26 (4.68%)	Initial IMV N = 726 (4.64%)	P-value
Patient Characteristics				
Age, Median (IQR), years	53 [43, 68]	61 [47, 73]	53 [40, 64]	0.09
Female (%)	69.1	73.1	66.3	0.480
Race/Ethnicity				
Caucasian	51.5	46.2	49.4	
Black	37.4	50.0	41.2	
Hispanic	4.2	0.0	3.0	0.07
Asian/Other	6.8	3.9	4.5	
Unknown	0.2	0.0	1.8	
Smoking	47.9	30.8	40.1	0.009
Combined Score	2 [1, 3]	3 [2,4]	2 [1,4]	<0.001
Comorbidities				
CHF	21.9	46.2	24.1	0.02
Valvular Disease	6.8	3.9	4.4	0.16
Pulm. Circ. Disease	6.8	3.9	6.1	0.88
Per. Vasc. Disease	1.7	7.7	3.0	0.06
Neuro Disorders	5.2	11.5	13.2	<0.001
Diabetes Mellitus	25.9	53.9	23.7	0.002
Hypothyroidism	8.5	19.2	6.1	0.04
Renal Failure	7.7	3.9	9.6	0.43
Liver Disease	3.0	7.7	2.2	0.14
Coagulopathy	3.0	15.4	4.4	0.02
Obesity	18.3	34.6	16.5	0.05
Morbid Obesity	9.0	11.5	5.9	0.05
Weight Loss	1.3	3.9	8.3	<0.001
Anemia	13.6	15.4	17.1	0.23

Alcohol Abuse	5.9	7.7	6.3	0.78
Drug Abuse	11.3	15.4	13.8	0.36
Psychoses	7.6	7.7	7.2	0.88
Hypertension	39.1	38.5	35.8	0.50
Pneumonia POA	12.1	34.6	24.2	<0.001
Status Asthmaticus	5.3	11.5	14.6	<0.001
LAPS				
0 to 19	7.4	3.9	2.3	
20 to 24	14.7	23.1	11.7	
25 to 30	11.1	7.7	6.6	<0.001
31 to 41	23.2	0	13.0	
42+	43.6	65.4	66.4	
Complications[b]	0.6	0.0	3.4	0.001
Inpatient Case Fatality Rate(%)	1.7	15.4	14.2	<0.001

[a] Additional comorbidities present in less than 5% of the sample: peptic ulcer disease with bleeding; AIDS; lymphoma; metastatic cancer; solid tumor without metastasis; rheumatoid arthritis.
[b] Complications include: pneumothorax and subcutaneous emphysema
NIV= noninvasive ventilation, IMV=invasive mechanical ventilation, NIV failure = NIV followed by IMV
CHF= congestive heart failure, LAPS= laboratory acute physiology score, LOS= length of stay
NIV or IMV only = only this ventilation method was used. NIV failure is not included in NIV only or in IMV only

NIV failure

NIV failure was uncommon as 26 out of 556 (4.7%) patients treated with initial NIV were later intubated. Supplemental eFigure 3.2 shows that patients with NIV failure had admission LAPS scores that more closely approximated the scores of patients treated initially with IMV than those treated with NIV. Characteristics of patients treated only with NIV, with NIV failure and with initial IMV are presented in eTable 3.2. These patients had the highest death rate of all patients ventilated (15.4%) and the longest hospital stay (10.9 days, IQR [5.9, 18.5]. After multivariable adjustment, we derived a parsimonious model of factors that were most associated with NIV failure. These

included the number of prior admissions within the last 12 months, diabetes mellitus, and the coexistence of pneumonia.

Table 3.4: Predictors for noninvasive ventilation failure

Variable	NIV Failure Odds Ratio N = 26(4.7%)	P-value
Number of Prior Admissions within the last year		
0	1	
1	0.51;(0.10 to 2.59)	0.42
2+	2.76; (1.04 to 7.27)	0.04
CHF	2.23;(0.86 to 6.81)	0.10
Diabetes mellitus (with or without complications)	2.73;(1.10 to 6.81)	0.03
Pneumonia POA	5.68;(2.04 to 15.86)	0.001

CHF= congestive heart failure, POA= present on admission, NIV failure= IMV after NIV
Odds ratios > 1 mean that if the variable is present, the patient is more likely to have NIV Failure (the odds of NIV Failure are 2.74 times greater for example with CHF than without)

Patients with and without Concomitant Pneumonia

Patients with a diagnosis of an asthma exacerbation and pneumonia were more likely to be ventilated with either NIV or IMV and among those treated with NIV, there was a higher NIV failure rate. (eTable 3.3) We also saw higher case fatality rates and longer lengths of stay in patients with pneumonia than in those without concomitant pneumonia. (eTable 3.4 and eTable 3.5)

eTable 3.3: Initial ventilation and NIV failure in the cohort with and without pneumonia diagnosis

Ventilation Pathway	Full Cohort N= 13,958	Cohort without pneumonia POA N= 12,697	Pneumonia cohort N= 1,261	P-value
No Ventilation	90.8%	91.9%	80.3%	
NIV Initial	4.0%	3.8%	5.8%	<0.001
IMV Initial	5.2%	4.3%	14.0%	
NIV failure (% of NIV)	0.2% (4.7% of NIV)	0.14% (3.5% of NIV)	0.71% (12.3% of NIV)	<0.001

NIV= noninvasive ventilation, IMV=invasive mechanical ventilation, NIV failure = NIV followed by IMV
NIV or IMV Initial refers to the first method of ventilation during hospitalization

eTable 3.4: Unadjusted outcomes for the full cohort and for the cohort without pneumonia

Initial Ventilation	**CFR Full Cohort**	**CFR Cohort without Pneumonia**	**CFR Pneumonia Cohort**	**LOS full Cohort (hours)**	**LOS Cohort without Pneumonia (hours)**	**LOS Pneumonia Cohort (hours)**
No Vent	0.2%	0.2%	0.7%	70 [42, 113]	69 [41, 109]	93 [61,140]
NIV	2.3%	1.7%	6.8%	99 [65, 165]	95 [61, 159]	137 [86, 180]
IMV	14.2%	13.5%	16.5%	160 [92, 277]	134 [81, 224]	267 [169, 447]

NIV= noninvasive ventilation, IMV=invasive mechanical ventilation, LOS= length of stay,
CFR= case-fatality rate

eTable 3.5: Adjusted outcomes for the full cohort and for the cohort without pneumonia and in sensitivity analysis

	Full Cohort Case Fatality		**Cohort without pneumonia Case Fatality**		**Cohort in sensitivity analysis Case Fatality**	
Statistical Method	*Relative Risk Ratio (95% CI)*	*P-value*	*Relative Risk Ratio (95% CI)*	*P-value*	*Relative Risk Ratio (95% CI)*	*P-value*
Greedy Matched (239 matched pairs)	0.21 (0.10, 0.48)	<0.001	0.12 (0.04, 0.37) 226 matched pairs	<0.001	0.19 (0.07, 0.56) 211 matched pairs	0.002
Hierarchical Logistic Regression model with Hospitals as Random Effects	0.17 (0.09, 0.32)	<0.001	0.16 (0.08, 0.32)	<0.001	0.17 (0.09, 0.35)	<0.001
Inverse Probability Weighting	0.20 (0.07, 0.34)	0.004	0.14 (0.2, 0.25)	<0.001	0.17 (0.06, 0.27)	<0.001
Statistical Method	*Difference in*	*P-value*	*Difference in*	*P-*	*Difference in*	*P-value*

	LOS (95% CI)		*LOS (95% CI)*	*value*	*LOS (95% CI)*	
Greedy Matched	3.8 (2.3, 5.2) 278 matched pairs	<0.001	3.0 (1.8, 4.3) 201 matched pairs	<0.001	4.4 (2.9, 5.9) 253 matched pairs	<0.001
Hierarchical Generalized Linear Regression model with Hospitals as Random Effects and a logarithmic link function	4.8 (4.0, 5.6)	<0.001	3.3 (2.5, 4.2)	<0.001	5.1 (4.2, 6.0)	<0.001
Inverse Probability Weighting	3.7 (2.8, 4.5)	<0.001	2.6 (1.6, 3.6)	<0.001	3.9 (2.9, 5.0)	<0.001

NIV= noninvasive ventilation, IMV=invasive mechanical ventilation, LOS= length of stay
CI = confidence interval

We performed a secondary analysis and compared the characteristics of the admissions included in the analysis and those excluded from the analysis because of the missing data (laboratory results, medication information). We found that these 2 groups were similar in their characteristics and outcomes.

DISCUSSION

This dissertation sought to examine current ventilation management practices in patients hospitalized with an acute exacerbation of asthma and an acute exacerbation of COPD. It also aimed to compare the effectiveness of NIV and IMV among patients with asthma exacerbation.

4.1 Trends in Mechanical Ventilation among Patients Hospitalized with Acute Exacerbations of COPD in the United States, 2001 to 2011

We began by examining the trends in the use of NIV among 723,560 hospitalizations with acute exacerbation of COPD at 475 hospitals over the period 2001 - 2010 in a large and representative network of US hospitals and identified patient factors influencing its use. We found that there was a steady and dramatic increase in the use of NIV, a substantial decline in the use of IMV, an overall increase in the use of mechanical ventilation, and a slight decrease in the frequency of NIV failure. Advanced age, race, comorbidity burden, and concomitant pneumonia were important determinants of whether a patient received mechanical ventilation and influenced the annual rate of change in the use of various ventilation strategies. Elderly patients had higher odds of receiving NIV, while blacks and Hispanics were less likely to be treated with NIV than were whites. Cases with a high burden of comorbidities and those with concomitant pneumonia had high rates of NIV failure and were more likely to receive initial IMV.

Our results are consistent with trends in ventilation use reported in a study by Chandra et al that analyzed data from the Nationwide Inpatient Sample and found a significant increase in NIV use from 1998 to 2008.(Chandra et al.) The NIV rates

reported in our study are considerably higher than these rates (e.g.,14.0% vs. 4.5% in 2008) most likely due to the more sensitive approach we used for identifying NIV and a more specific set of ICD-9 codes that restricted the cohort to admissions with more severe exacerbations of COPD. When limiting the identification of NIV to the same methodology used in the study by Chandra, we obtained comparable rates (e.g., 5.4% in 2008). Our observed rates are more similar to those from an audit in the United Kingdom that assessed the in-hospital care of 9,700 patients with COPD in 2008, finding that NIV was used in 11% of these patients.(Roberts, Stone, Buckingham, Pursey, & Lowe, 2011)

In this study, the overall increase in NIV as an initial ventilation strategy between 2001 and 2011 was offset mostly by a decrease in IMV use. However, there was also an increase in all ventilator starts, suggesting that NIV was progressively used in patients who might not in the past have received any ventilation.

By providing data on patient factors related to the utilization of NIV, and more precise estimates of NIV utilization, our results extend the findings of earlier studies. We have demonstrated that factors such as age, race, comorbidity burden, and concomitant pneumonia influence whether a patient receives NIV or IMV as initial ventilator therapy. While there was an increase in the use of NIV and corresponding declines in the use of IMV during the years under study in all hospitalizations, the rate of change varied by patient characteristics. Patients older than 85 years of age had 57% lower odds of receiving any form of mechanical ventilation compared to the youngest patients and were more likely to receive NIV than IMV when they were ventilated. These results are consistent with the findings from other studies suggesting that intensity of treatment decreases with advancing age and it is likely influenced by patient and or physician

preference to withhold more aggressive treatments, such as IMV.(Hamel et al., 2001; Hamel et al., 1999; Lagu et al., 2012) The NIV growth rate was highest in the admissions of oldest compared with the youngest patients; these trends may reflect the diffusion of the results of several studies reporting that NIV has a good success rate in older patients.(Nava et al.; Riario-Sforza, Scarpazza, Incorvaia, & Casali; Scarpazza, Incorvaia, Amboni, et al.; Scarpazza et al., 2008; Scarpazza, Incorvaia, Melacini, et al.)

Black patients had higher rates of ventilation compared with white patients and were more likely to be invasively ventilated, even after adjusting for the hospital where care was received. Several prior studies have shown that black patients are more likely to prefer and receive life-sustaining treatments, including IMV, compared with white patients.(Bayer, Mallinger, Krishnan, & Shields, 2006; Cannon et al., 2009; Lagu et al., 2012) It is also possible that black patients are delaying hospitalization and present with more severe disease than white patients.

Our results provide new information about the role of comorbidity burden and concomitant pneumonia in the ventilatory management of patients with COPD. We found that patients with a higher disease burden were more likely to be ventilated and to receive initial IMV treatment than patients with a lower comorbidity burden; they also had the highest rate of NIV failure. Similar ventilation patterns were observed for patients with pneumonia. The respiratory deterioration found in these patients may be less easily reversible and these patients may more often deteriorate to the point where they have to be intubated. Of interest, although the use of NIV increased in all admissions with COPD during the years under study, the annual rate of increase was lower for those with a high comorbidity burden and for those with pneumonia. These findings suggest that providers

may have become more cautious about NIV use among patients at high risk of requiring subsequent intubation.

The strengths of our study include the large and diverse set of hospitals included in the analysis, increasing the generalizability of our findings, and the detailed charge data to which we had access which enabled us to provide more accurate estimates of NIV use than would be obtained from ICD-9 procedure codes alone. We also examined trends over time, which provides perspective on how the ventilatory management of patients with COPD is evolving. In addition, we used robust statistical methods to identify patient factors associated with the adoption of NIV over time and possible changes in these factors over a decade-long perspective.

Our study has a number of limitations. First, we relied on ICD-9 codes to identify cases of acute COPD exacerbation and, therefore, we cannot exclude disease misclassification. However, we used a previously validated set of ICD-9 codes that were shown to have reasonable sensitivity and specificity. Second, hospitals that participate in Premier are not completely representative of US hospitals (predominantly small to medium size and serving urban populations) and the results may not be entirely generalizable. Third, we did not have physiology data on the severity of acute respiratory failure and we could therefore not determine if the threshold for applying mechanical ventilation has changed over time. Forth, we excluded patients with a diagnosis of obstructive sleep apnea because we were not able to distinguish if NIV was used for sleep apnea or for respiratory failure. Finally, the dataset does not contain information on patients' decisions about life sustaining treatments and the decrease in NIV failure may reflect a larger number of patients withholding aggressive treatment at the end of life.

4.2 Hospital Patterns of Use of Noninvasive Ventilation in Patients with Asthma Exacerbation

In this large observational study of over 13,000 admissions with an asthma exacerbation, we found a wide variation in the use of NIV among a diverse group of hospitals in the United States. Twelve (21%) of hospitals had risk standardized NIV rates less than 1.0% while fourteen (24%) had risk-standardized rates >15%. Notably, we observed that hospitals with higher rates of NIV did not have lower rates of IMV and their overall rates of ventilation were higher. This suggests that NIV was not being used in place of IMV but rather that hospitals were expanding the use of ventilatory assistance and lowered the threshold for initiating ventilation. There was not an association between hospital initial RS-NIV rates and hospital RS-case-fatality rate, though the p-value for trend was borderline non-significant and mortality was rare making it hard to detect significant variation.

Despite the lack of strong evidence on efficacy or endorsement from professional societies, the use of NIV in patients hospitalized with an asthma exacerbation is increasing. A large study using data from the Nationwide Inpatient Sample from 2000 to 2008, found that the utilization of NIV in admissions with asthma had increased from 0.3% to 1.9% (a 5 fold increase), leading to an overall increase in mechanical ventilation.(Nanchal et al.) Our study conducted at the hospital-level supports these findings. We found an initial NIV use of 2.3% in 2009 and 4.8% in 2012 and greater overall ventilation rates in hospitals with the highest use of NIV.

In our study, the large variation across hospitals in the use of NIV in patients with an asthma exacerbation was not explained by hospital characteristics or the hospitals' case-mix suggesting that the source of variation may be at the institution and/or provider levels. There was substantially more variation in the hospital risk standardized NIV rates than the IMV rates. One possible reason for the variability in institutional and/or provider practices is the limited evidence on the efficacy of NIV in asthma and the uncertainty of the guidelines on NIV use. Although the Global Initiative for Asthma has specific criteria for defining patients with severe asthma exacerbation who may require IMV, the guidelines are ambiguous about NIV use.("Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2014," 2014) Similar to our findings, single-center studies which described NIV use in asthma included a very heterogeneous population of patients, from moderate asthma attacks to status asthmaticus(Diehl & Guerot; Scala) and reported a large range of use of NIV.(Fernandez, Villagra, Blanch, & Fernandez, 2001; Meduri et al., 1996; Murase et al.) Two small retrospective studies which included patients with asthma admitted to ICU found that NIV was used between 2%(Peters et al.) and 67%19 of the ventilated patients.

Our results showed that hospitals in the highest quartiles of NIV use had higher overall rates of ventilation. The expansion in NIV use in these hospitals suggests that clinicians used NIV in patients with asthma of lower severity to prevent acute respiratory failure and not in patients with moderate to severe asthma as an alternative to intubation. In addition, hospital-level factors including hospital use of NIV for conditions that have stronger evidenced based recommendations such as COPD or acute pulmonary edema,

presence of respiratory therapists, and availability of NIV devices may all influence the use of NIV.

Variation in practices of NIV use across hospitals had been reported in COPD and in acute decompensation of heart failure.(Kulkarni et al.; Lindenauer et al.) In a large study of NIV use among patients hospitalized with COPD between 2009 and 2011, Lindenauer et al found that interquartile range of initial NIV was [10.2% to 19.4%] versus [2.3% to 6.4%] for initial IMV among all patients hospitalized with COPD.(Lindenauer et al.) In contrast to our study, the authors observed that hospitals with greater use of NIV for COPD had lower rates of invasive mechanical ventilation, confirming the results from clinical trials in a real-world population.

In the absence of strong evidence about the comparative effectiveness of NIV use versus other ventilation strategies including usual care, high-flow oxygen and IMV, the likelihood of a patient being treated with NIV seems primarily dependent on the hospital to which the patient is admitted. Death is rare in the large majority of patients hospitalized with an asthma exacerbation but those who are intubated and mechanically ventilated have a high death rate ranging from16 to 22%.(Afessa et al., 2001; Gupta et al.) In this study, we did not find a significant survival benefit for hospitals with a higher use of NIV which is understandable in the face of lack of decrease in the IMV use. Since the use of invasive mechanical ventilation in patients with asthma is associated with increased morbidity and mortality(Afessa et al., 2001; Gupta et al.) and that there is a rationale for the use of NIV in asthma,(Murase et al.) large randomized controlled trials should explore if there is a benefit of using NIV in selected patients with asthma.

Study strength and limitations

Our study had several strengths. We used a multihospital dataset which included data on laboratory results and medications and we used a validated severity illness score to adjust for differences in patient case mix. We restricted the analysis to hospitals with a minimum of 45 admissions to obtain more stable estimates of hospital rates and we calculated hospital risk standardized outcome rates accounting for variance in patient outcomes within and between hospitals.

However, the results of this study need to be interpreted in the context of several limitations. First, we used ICD-9 diagnostic codes for selecting patients with asthma. However, we reduced the chance of misclassification of the diagnosis by only including patients treated with steroids and bronchodilators. Second, to assess ventilation type, we used ICD-9 procedure codes and there may be variation in coding across hospitals. We have validated the NIV procedure codes in a single center study by retrospective chart review of 100 patients with acute respiratory failure from 2010 to 2011. The ICD-9 codes had a sensitivity of 86% (95% CI, 81-92%) and a specificity of 92% (95% CI, 84%-98%).(M.S. Stefan et al., 2014) Third, although our regression models adjusted for illness severity still the potential of unmeasured patient and hospital-level confounders remain. Nevertheless the hospital-level analysis is less likely to be affected by confounding by indication and patient case mix differences between hospitals would have to be quite large to change the results. Fourth, the hospitals included in the analysis tended to be larger teaching hospitals in an urban environment that invested in an electronic medical system between 2009 and 2012. Thus, our results may not be applicable to all hospitals in US. Finally, we were able to study only in-hospital mortality

and there is a possibility that the impact of mechanical ventilation may go beyond hospitalization.

In conclusion, we found a wide variation in the hospital use of NIV for patients with an acute exacerbation of asthma; however institutions with higher NIV rates did not have lower use of IMV suggesting an expansion in the use of assisted ventilation. These results indicate a need to understand contextual and organizational factors contributing to this variability.

4.3 Outcomes of Noninvasive and Invasive Ventilation in Patients with Asthma Exacerbation

In the third study of almost 14,000 patients with asthma in 97 hospitals in the US, we found that despite scant evidence for the efficacy of NIV in patients with asthma, this type of ventilation was used in 4.0% of all hospitalized patients with asthma and in 43.4% of the ventilated patients. Compared with patients treated with IMV, patients treated with NIV were older, were less likely to have concomitant pneumonia, and had a lower severity of illness score at admission. Patients receiving NIV had much lower mortality and a shorter length of stay than those receiving IMV and these differences remained in the propensity matched analysis. Although these findings were similar in the sensitivity analyses the large difference in mortality suggests possible residual confounding by indication, with physicians using IMV in patients who are sicker. The better outcomes in patients treated with NIV were likely related to and greater severity of illness as characterized by the LAPS score in those treated with IMV. We found that NIV failure was uncommon, but was associated with the highest mortality and resource

utilization. Patients with concomitant pneumonia were more likely to be ventilated with NIV or IMV and had the worst outcomes.

Over the last 15 years NIV has become standard of care in the management of acute exacerbation of COPD and cardiogenic pulmonary edema.(Hill et al., 2007; Keenan et al., 2011) Nevertheless, NIV use has increased irrespective of the etiology of the acute respiratory failure, for conditions where the supporting evidence is weak, including asthma. (Nanchal et al.; A. J. Walkey & Wiener; A.J Walkey & Wiener, 2012) A recent large study which used the Nationwide Inpatient Dataset reported that the proportion of admissions with asthma exacerbation for which NIV was used increased from 0.3% in 2000 to 1.9% in 2008. In our cohort, which included admissions from 2009 to 2012 the rate of NIV therapy was 2.3% in 2009 and 4.7% in 2012 confirming the steady increase in its use. The growing use of NIV may be due to clinicians recognizing the pathophysiologic similarities between an asthma attack and COPD exacerbation rather than based on empirical evidence in the literature. The improved familiarity and comfort of physicians and respiratory therapists with NIV might also contribute to its use outside of the evidence-supported indications.

Our findings of much better outcomes of patients treated with NIV versus those treated with IMV should be interpreted with caution. Although we performed robust statistical analysis using several different statistical methods to derive the results and a validated illness severity score which includes laboratory results, the large difference in mortality between the two ventilation types suggests possible selection bias, with physicians using NIV in patients who are less sick. As clinicians choose to use NIV in patients who do not require immediate intubation and therefore have lower severity of

illness, patients treated with NIV are expected to have better outcomes. Still the magnitude of difference in mortality found in this study raises the possibility that clinicians may have had a low threshold to initiate NIV.

Theoretically, NIV can be used in an episode of asthma exacerbation in 3 different scenarios: 1) as an alternative to intubation in patients with severe acute respiratory failure (ie "mandatory ventilation"), 2) to prevent intubation in patients with mild to moderate respiratory failure who do not need immediate respiratory support (ie "supportive ventilation"), and 3) to prevent acute respiratory failure in patients without significant gas exchange abnormalities (ie 'prophylactic ventilation). One explanation for the large difference in the observed short-term outcomes in our study, is that NIV may have been used mainly prophylactic and not in the borderline patients who failed standard medical therapy.(Scala; Soroksky et al.) The difference in mortality in patients with an asthma exacerbation treated with NIV or IMV in our study was much larger than those reported in patients with COPD exacerbation. A recent large retrospective cohort study which compared the outcomes of patients with COPD treated with NIV or IMV, found that mortality rates were 5.3% and 7.2% among those initially treated with NIV and IMV respectively.(Lindenauer et al.)

The rate of NIV failure in our study was 4.7% of all patients ventilated with NIV, which is in contrast with the rate of 19.4% reported in a small study of 98 patients with an acute asthma exacerbation treated with NIV in the emergency department. However, the population in that study was more consistently selected to represent those with severe asthma exacerbation who failed routine treatment, explaining the higher rate of NIV failure.(Ganesh, Shenoy, Doshi, Rishi, & Molnar)

Consistent with studies in patients with COPD we found that patients with NIV failure had worse outcomes than patients who were initially intubated (Lindenauer et al.; M. S. Stefan et al.; Tsai et al., 2013) and that pneumonia was a risk factor for worse outcomes and for NIV failure.(Confalonieri et al., 1999; Honrubia et al., 2005; Lindenauer et al.) Patients who failed NIV were more similar in their characteristics with patients who were intubated raising the possibility that NIV may have been used in some patients who should have been intubated initially. These findings have substantial implications because patients with asthma can deteriorate rapidly and those at risk for NIV failure require close monitoring in an intensive care unit. If this is not possible, intubation may be a more sound decision.

Strengths and limitations

This study has several strengths. This appears to be the largest cohort of patients with asthma studied to date which provides estimates regarding ventilation strategies and their outcomes. The EMR dataset contains detailed laboratory data which allowed better adjustment for the severity of illness than in other observational studies with large administrative datasets. Given the lack of national clinical registries in patients hospitalized with asthma these results give a glimpse into real-world practice patterns.

However, one needs to evaluate the observed findings of this study to understand the inherent limitations of the dataset. First, we used ICD-9 diagnosis and procedure codes to define our cohort and the type of ventilation and there may be variability in the way hospitals use these codes driven by reimbursement policies. We supplemented the diagnosis codes with the requirement for specific treatments used in asthma exacerbation to increase the specificity of the diagnosis. Second, we excluded a large number of

patients because they did not have laboratory or medication data or their disposition was unknown; however when we analyzed the admissions included and excluded from the cohort, the characteristics and outcomes were similar. Third, as with all observational studies in comparative effectiveness research, it is possible that there are still unmeasured confounders at the patient and hospital level which biased the results. Fourth, the decision to place a patient on NIV or IMV is per clinical judgment of the physician and we were not able to discern if some hospitals have a standardized pathway for treating this group of patients. Finally, although the Cerner hospitals include a mixture of teaching and nonteaching, small and large hospitals, the majority of the hospitals were urban and all had an electronic medical record system and as such they may not be entirely representative of all hospitals in the US.

In summary, the results of this dissertation research have enriched our understanding of the ventilation patterns of use of NIV in patients hospitalized with an asthma exacerbation or with COPD. These series of investigations, using rich datasets, generated important new knowledge about current ventilation management practices and associated patient outcomes, and identified predictive factors for the NIV utilization in two common medical conditions. There is a pressing need for large multicenter clinical trials to study the use of NIV in patients with asthma exacerbation before routine clinical use of NIV can be recommended in these patients. Future research should aim to identify criteria for patients with asthma exacerbation most likely to benefit from NIV and identify patients at risk for NIV failure for any patient with acute respiratory failure treated with NIV. Decision supports tools to help providers to select patients for NIV,

IMV or high flow nasal cannula therapy and how to monitor these patients may improve the outcomes of patients with acute respiratory failure.

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