Online Data Supplement

Evidence-Based Utilization of Non-Invasive Ventilation and Patient Outcomes

Anuj B Mehta MD, Ivor S Douglas, Allan J Walkey MD MSc

Table of Contents

Online Supplemental Methods:

Patients: Using the Healthcare Cost and Utilization Project's California State Inpatient Database (CA SID)(1, 2) we performed a retrospective cohort study on adult patients (≥18 years of age) who required ventilatory support. The CA SID contains administrative discharge data for 100% of discharges from non-federal hospitals in the state of California and, uniquely, includes information about patient early do-not-resuscitate (DNR) status (within 24 hours of admission).(3, 4) Our primary patient cohort consisted of patients who received initial ventilatory treatment with NIV identified by previously validated *International Classification of Disease, 9th edition, Clinical Modification (ICD9-CM)* billing code 93.90(5). Patients were considered to have a strong evidence condition for NIV if they were admitted for an acute exacerbation of COPD or HF (**eTable 1** for *ICD9-CM* codes to identify disease cohorts).(5-7). We excluded patients who had a DNR order as they could be started on NIV but may not be eligible for IMV, patients transferred to or from another acute care hospital as it would be unclear which hospital practices contributed to NIV outcomes, patients with obstructive sleep apnea (*ICD9-CM* code 327.2 and 780.57) as they would potentially receive NIV for sleep disordered breathing rather than respiratory failure, and patients admitted to hospitals that treated fewer than 25 patients with NIV during 2011 given the instability of individual hospital estimates for hospitals with fewer than 25 patients (**Figure 1**).

Exposures and Outcomes: The primary exposure was the hospital-level rate of NIV for strong evidence conditions (NIV-SEC), calculated as the number of patients who received NIV for strong evidence conditions divided by the total number of patients treated with NIV. Because of non-linear association between NIV-SEC rates and outcomes, hospital NIV-SEC rate was divided into quartiles. The primary outcome was NIV failure [initial treatment with NIV

followed by treatment with IMV (*ICD9-CM* code 96.7x(7, 8))]. NIV failure was selected as the primary outcome because patients who suffer NIV failure have a higher risk of death compared to those treated initially with IMV.(9-11) Using the hospital procedure start day, NIV failure was identified as hospitalizations where IMV was initiated on the same day or after NIV was started as previously described.(9-11) Patients who received NIV after IMV were not included in our primary cohort. In-hospital mortality for patients receiving NIV was a secondary outcome.

Statistical Analysis: We compared continuous variables using Student's t test, Wilcoxon Rank sum test, and linear regression as appropriate and categorical variables with Chi-Square and Cochrane Armitage tests for trends. We describe hospital variation in evidence based patient selection for NIV by calculating the median odds ratio which describes the odds of a patient with a strong evidence condition receiving NIV at hospital with more evidence-based practices compared to hospitals with less evidence-based patient selection.(12) To evaluate the association between hospital NIV-SEC rates and patient outcomes, we used multivariable hierarchical logistic regression(13) with hospital level random intercepts to 1) determine the association of patient diagnosis (strong evidence condition or not) with patient outcomes (NIV failure and NIV in-hospital mortality), 2) calculate hospital risk-adjusted NIV failure and hospital risk-adjusted mortality rates from random effects output, and 3) determine the association between hospital NIV-SEC rates and patient outcomes. These models were adjusted for patient demographics (age, gender, race/ethnicity, median income of the patient's Zip Code), individual Elixhauser comorbidities(14, 15), acute organ failures (**Table E2**)(16, 17) present on admission(3, 18), and cause of respiratory failure (COPD, HF, pneumonia, non-pneumonia sepsis, asthma or other)(**Table E3**). To determine the association between hospital NIV-SEC rates and hospital

risk-adjusted NIV failure and mortality rates we used Spearman's correlation test with Penalized B-spline regression(19) to visualize the relationship.

Sensitivity and Exploratory Analyses: Controversy exists about the benefits of NIV for immunocompromised patients with acute respiratory failure with some studies showing a mortality benefit and others showing potential harm.(20-24) As such, we conducted a sensitivity analysis in which immunocompromised patients (*ICD9-CM* code 279.0, 279.1, 279.2, 279.3, and 288.0) were defined as having a strong evidence condition for NIV use.

Additionally, given previous work demonstrating an inverse relationship between NIV case-volume and outcomes(11), we conducted an exploratory analysis investigating the relationship between hospital evidence-based NIV case-selection, NIV case-volume, and NIV outcomes. We created four hospital groupings based on NIV case-volume and NIV-SEC rate: Group 1 – low hospital NIV case-volume and high hospital NIV-SEC rate, Group 2 - low hospital NIV case-volume and low hospital NIV-SEC rate, Group 3 – high hospital NIV case-volume and high hospital NIV-SEC rate, and Group 4 - high hospital NIV case-volume and low hospital NIV-SEC rate. High and low levels were defined as being above or below the median case-volume or NIV-SEC rate. We compared NIV failure rates across hospital groups using the Analysis of Variance test with the post-hoc Tukey test for pairwise comparisons.

All statistical testing was two-tailed and performed at a critical alpha=0.05 and conducted with SAS v9.4 (Cary, NC). The study was deemed to be exempt from review by the National Jewish Health Institutional Review Board (Denver, CO).

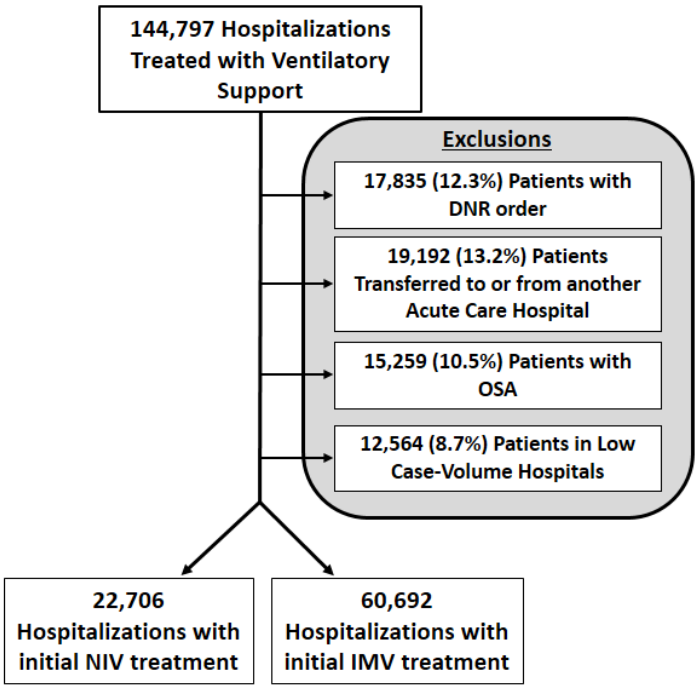

Figure E1 Study Design: We identified patients ≥ 40 years old who received initial ventilatory treatment with NIV. We excluded patients who had a DNR order, were transferred to or from another acute care hospital, had obstructive sleep apnea, and patients admitted to hospitals that treated fewer than 25 patients with NIV in 2011 (low case-volume). Abbreviations: DNR – do-not-resuscitate. OSA – obstructive sleep apnea. NIV – non-invasive ventilation. IMV – invasive mechanical ventilation.

Table E1: *ICD9-CM* Codes for Strong Evidence Conditions

COPD		
	Principal Diagnosis	Secondary Diagnoses POA
Criteria 1	490.x or 491.x or 492.x or 496.x	N/A
Criteria 2	518.81 or 518.82 or 518.84 or 799.1	491.21 or 491.22
Heart Failure		
	Principal Diagnosis	Secondary Diagnoses POA
Criteria 1	402.01 or 402.11 or 402.91 or 404.01 or 404.03 or 404.13 or 404.91 or 428.x	N/A
Criteria 2	518.81 or 518.82 or 518.84 or 799.1	428.21 or 428.83 or 428.31 or 428.33 or 428.41 or 428.43

Abbreviations: *ICD9-CM – International Classification of Disease, 9th Edition Clinical Modification*. POA – present on admission

Table E2: *ICD9-CM* Codes for Acute Organ Failures Present on Admission

Respiratory Failure	518.81, 518.82, 518.84, 799.1x
Cardiovascular Failure/Shock	458.0, 458.8, 458.9, 785.5, 785.51, 785.52, 785.59 796.3
Renal Failure	584.x
Neurological Failure	293.x, 348.1, 348.3, 780.01, 780.09
Hematological Failure	287.3, 287.4, 287.5, 286.9, 286.6
Hepatic Failure	570.x, 572.2, 573.3, 573.4
Acidosis	276.2

Abbreviations: *ICD9-CM – International Classification of Disease, 9th Edition Clinical Modification*.

Table E3: *ICD9-CM* Codes for Pneumonia, Non-Pneumonia Sepsis, and Asthma

Pneumonia		
	Principal Diagnosis	Secondary Diagnoses POA
Criteria 1	480.x or 481.x or 482.x or 483.x or 484.x or 485.x or 486.x or 487.x or 488.x or 507.x	N/A
Criteria 2	518.81 or 518.82 or 518.84 or 799.1	480.x or 481.x or 482.x or 483.x or 484.x or 485.x or 486.x or 487.x or 488.x or 507.x
Criteria 3	038.x	480.x or 481.x or 482.x or 483.x or

		484.x or 485.x or 486.x or 487.x or 488.x or 507.x
Non-Pneumonia Sepsis*		
	Principal Diagnosis	Secondary Diagnoses POA
Criteria 1	402.01 or 402.11 or 402.91 or 404.01 or 404.03 or 404.13 or 404.91 or 428.x	N/A
Criteria 2	518.81 or 518.82 or 518.84 or 799.1	428.21 or 428.83 or 428.31 or 428.33 or 428.41 or 428.43
Asthma		
	Principal Diagnosis	Secondary Diagnoses POA
Criteria 1	493.x	N/A
Criteria 2	518.81 or 518.82 or	493.01 or 493.02 or

	518.84 or 799.1	493.11 or 493.12 or 493.21 or 493.22 or 493.91 or 493.92

*Excludes patients with a secondary diagnosis of pneumonia POA

Abbreviations: *ICD9-CM – International Classification of Disease, 9th Edition Clinical Modification*. POA – present on admission

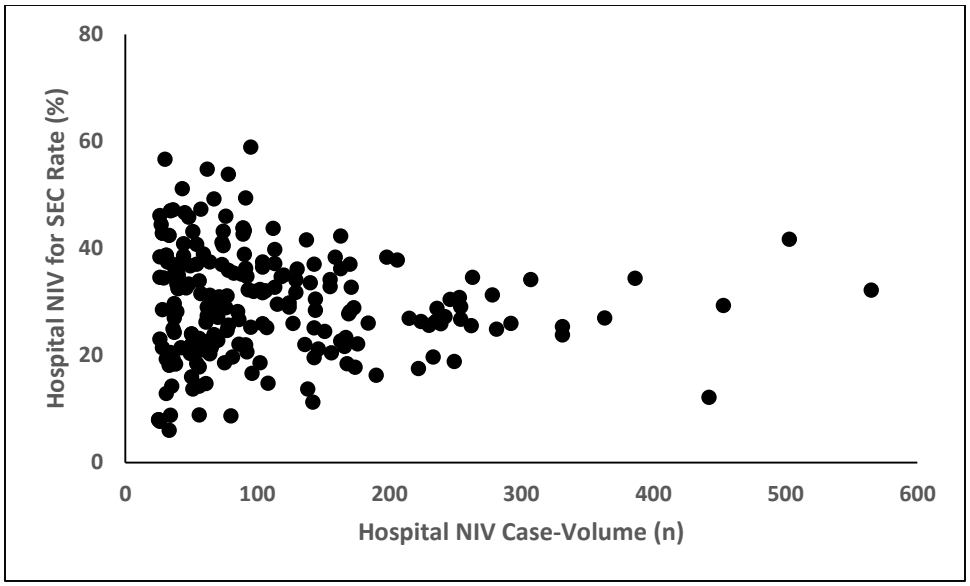

Figure E2: Association of Hospital NIV Case-Volume with NIV-SEC Rate. Hospital NIV case-volume was not associated with hospital NIV-SEC rate (# of NIV for SEC/total # of NIV) (ρ=-0.05, p=0.47). Abbreviations: NIV – non-invasive ventilation. SEC – strong evidence condition.

References

(1) Agency for Healthcare Research and Quality. Overview of the state inpatient databases (SID). http://www.hcup-us.ahrq.gov/sidoverview.jsp Last Updated January 20, 2016. Accessed February 2, 2016.

(2) Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project. Introduction to the HCUP State Inpatient Databases. https://www.hcup-us.ahrq.gov/db/state/siddist/Introduction_to_SID.pdf Last Updated February 2016. Accessed July 16, 2016.

(3) L. E. Goldman, P. W. Chu, C. Prothro and D. Osmand. Office of Statewide Health Planning and Development. Accuracy of condition present on admission, do not resuscitate, and e-codes in California Patient Discharge Data: prepared for the Office of Statewide Health Planning and Development , Healthcare Outcomes Center. http://www.oshpd.ca.gov/HID/Products/PatDischargeData/ResearchReports/PDDValidation/PDD_Validation_Study.pdf Last Updated Spring 2011. Accessed January 19, 2016.

(4) Goldman LE, Chu PW, Osmond D, Bindman A. Accuracy of do not resuscitate (DNR) in administrative data. *Med Care Res Rev* 2013;70:98-112.

(5) Lindenauer PK, Stefan MS, Shieh MS, Pekow PS, Rothberg MB, Hill NS. Outcomes Associated With Invasive and Noninvasive Ventilation Among Patients Hospitalized With Exacerbations of Chronic Obstructive Pulmonary Disease. *JAMA Intern Med* 2014;174:1982-1993.

(6) Stein BD, Bautista A, Schumock GT, Lee TA, Charbeneau JT, Lauderdale DS, Naureckas ET, Meltzer DO, Krishnan JA. The validity of International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for identifying patients hospitalized for COPD exacerbations. *Chest* 2012;141:87-93.

(7) Mehta AB, Syeda SN, Wiener RS, Walkey AJ. Epidemiological trends in invasive mechanical ventilation in the United States: A population-based study. *J Crit Care* 2015;30:1217-1221.

(8) Quan H, Parsons GA, Ghali WA. Validity of procedure codes in International Classification of Diseases, 9th revision, clinical modification administrative data. *Med Care* 2004;42:801-809.

(9) Chandra D, Stamm JA, Taylor B, Ramos RM, Satterwhite L, Krishnan JA, Mannino D, Sciurba FC, Holguin F. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med* 2012;185:152-159.

(10) Walkey AJ, Wiener RS. Use of noninvasive ventilation in patients with acute respiratory failure, 2000-2009: a population-based study. *Ann Am Thorac Soc* 2013;10:10-17.

(11) Mehta AB, Douglas IS, Walkey AJ. Hospital Non-Invasive Ventilation Case-Volume and Outcomes for Acute Exacerbations of Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2016.

(12) Merlo J, Chaix B, Ohlsson H, Beckman A, Johnell K, Hjerpe P, Rastam L, Larsen K. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of

clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;60:290-297.

(13) Houchens R, Chu B, Steiner C. Hierarchical Modeling using HCUP Data. HCUP Methods Series Report # 2007-01 Online. Online: U.S. Agency for Healthcare Research and Quality.; 2007. 2007-01.

(14) Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8-27.

(15) Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-1139.

(16) Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med* 2007;35:1244-1250.

(17) Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003;348:1546-1554.

(18) Courtright KR, Raneses E, Harhay MO, Kipnis P, Escobar GJ, Halpern SD, Kerlin MP. External Validation of a Claims-Based ICU Risk-Adjustment Methodology. In: American Thoracic Society; 2016. p. A3620-A3620.

(19) SAS Institute, Inc. SAS Proc Transreg: Penalized B-Spline. http://support.sas.com/documentation/cdl/en/statug/68162/HTML/default/viewer.htm#statug_transreg_details07.htm Last Updated November 2, 2015. Accessed December 18, 2016.

(20) Hilbert G, Gruson D, Vargas F, Valentino R, Gbikpi-Benissan G, Dupon M, Reiffers J, Cardinaud JP. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001;344:481-487.

(21) Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, Gasparetto A, Meduri GU. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA* 2000;283:235-241.

(22) Lemiale V, Mokart D, Resche-Rigon M, Pene F, Mayaux J, Faucher E, Nyunga M, Girault C, Perez P, Guitton C, Ekpe K, Kouatchet A, Theodose I, Benoit D, Canet E, Barbier F, Rabbat A, Bruneel F, Vincent F, Klouche K, Loay K, Mariotte E, Bouadma L, Moreau AS, Seguin A, Meert AP, Reignier J, Papazian L, Mehzari I, Cohen Y, Schenck M, Hamidfar R, Darmon M, Demoule A, Chevret S, Azoulay E, Groupe de Recherche en Reanimation Respiratoire du patient d'Onco-Hematologie (GRRR-OH). Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2015;314:1711-1719.

(23) Schnell D, Timsit JF, Darmon M, Vesin A, Goldgran-Toledano D, Dumenil AS, Garrouste-Orgeas M, Adrie C, Bouadma L, Planquette B, Cohen Y, Schwebel C, Soufir L, Jamali S, Souweine B, Azoulay E. Noninvasive mechanical ventilation in acute respiratory failure: trends in use and outcomes. *Intensive Care Med* 2014;40:582-591.

(24) Adda M, Coquet I, Darmon M, Thiery G, Schlemmer B, Azoulay E. Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Crit Care Med* 2008;36:2766-2772.