# Title Page:

Venous or Arterial Blood Gas Diagnosis of Hypercapnic Respiratory Failure Among Inpatients

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Conflicts of Interest:

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JF

IP

SMB

Author contributions:

B.W.L Study concept design, Data acquisition/analysis, Manuscript drafting/revision/editing, Literature Review, Statistics, Guarantor of integrity of the entire study

**\*\*\***

A portion of this research was presented in abstract form:

**Keywords**: \*\*\*

Word count

Abstract: \*\*\*

Manuscript: \*\*\*

**Abbreviations:**

**\*\*\***

# Abstract:

Purpose:

Methods:

Results:

Conclusions:

# Introduction:

**Question: Are people using VBG to make the diagnosis? Should they?**

**ABG: PaCO2 > 45 calendar day of admit**

**VBG: VBG PCO2 > 50 calendar day of admit**

**VBG\_corr (Farkas): If VBG SO2 < 90%, then PCO2 - 0.2 (difference in A-V O2 sats)**

# Methods:

TriNetX research network database. The study was exempted by the University of Utah Institutional Review Board (University of Utah IRB #¬00152089).

The TriNetX (TriNetX, LLC) research network, which provides de-identified individual-level patient data from roughly 80 medical centers across the US pertaining to roughly 100 million patients. Details on the harmonization and linkage processes are provided in the Supplemental Index. Data was requested on 6/4/2024.

Spectrum:

We requested an enriched sample for the presence of hypercapnic respiratory failure all inpatient encounters occurring during calendar year 2022. The first encounter occurring where a patients met any of the following inclusion criteria were included: patients who received a diagnostic code for any respiratory failure, patients who had a condition known to cause hypercapnia, patients who received a procedure code for non-invasive or invasive ventilation, patients who had an arterial blood gas or venous blood gas obtained on the first day of the encounter, and patients with severe obesity. Patients were excluded if there was evidence of incomplete data (for example, any of: no procedure codes, no diagnoses, no vital signs, no medications submitted to TriNetX for the encounter of interest).

Full Data cleaning methods are discussed in the supplement. All analyses were cross-sectional on the encounter of interest to avoid relying on the completeness of linkages between encounters or institutions. No imputation for missing data was performed to mirror the amount of missing data that would be present in practice.

Outcomes:

Distributions of demographics and comorbidities selected by each method.

Draw clear distinction between “things about the data” and ”things about the patient”

* Lenth of Stay
* Rate of Critical Care Services and Intubation
* Change in diagnosis from ED->discharge?
* Unable, at this point, to do mortality, readmission rate
  + These rely on continuous data, and thus I expect the data completeness to drop (if nothing else, because people go to different hospitals)
* Also: distributions of disease stability of clustering, physiologic plausibility are outcomes, though not explained.

- For use case 2 and 3 - it wouldn’t be possible to verify the status - but could be possible to summarize who those patients are and make a case for future verification.

## Statistical Analysis: -- could this go as a letter? (Maybe to JCSM?)

[ ] Adjust this to make sure we’re not self plagarizing.

Propensity weighting \*\*\* of both

For analysis that use only predictors that are available in certain data-sets, predictions can be verified by evaluating against the arterial blood gasses that are “held out” but were obtained in clinical practice. However, it would be very useful to estimate which patients would have hypercapnia *if a blood gas was checked*, though this quantity is not directly verifiable. However, to the extent that which patients receive an arterial blood gas can be modeled, estimates can be calculated. This method, termed “inverse propensity weighting”, relies on the intuition that if a patient was very unlikely to have had a blood gas drawn – but it was and it showed hypercapnia – then presumably there are many similar patients for whom arterial blood gas sampling was not performed (unobserved). Thus, a pseudopopulation that approximates if arterial blood gasses were obtained at the usual rate, balanced across the factors in the propensity score, what factors would correlate with hypercapnia? As an exploratory analysis, we performed inverse propensity weighting to predict which patients may have had hypercapnia, but were not recognized. Details on the methods of the inverse propensity weighting are found in the supplemental materials.

# Results:

## Description of the TriNetX cohort:

Perhaps minimize this talk… as we’re not necessarily interested in the “entire” cohort – so much as we are interested in the features identified by different ethods

‘Missing’ Data Rates:

* + ABG: \*\*%; VBG \*\*%
  + BMP, CBC elements \*\*%
  + Triage VS: \*\*% (BP) -\*\*% (SpO2)

Control outcomes: [ ] update these descriptions

* Receive paralytic → IMV code? \*\*
* AECOPD/Asthma → Systemic Steroid? \*\*
* Pneumonia dx code → CAP Antibiotic? \*\*%
* \*\*% have critical care services billed
* \*\*% with acidemia (<7.35 pH); higher likelihood of critical care (OR 1.77)
  + CHF (OR 0.82) and OSA (OR 0.93) less likely acidemic

COPD (OR 1.16), CKD (1.21), and OUD (1.10) more likely

“

# Discussion

In this literature review and analysis of a large, aggregated dataset of US health records, we find that currently used cohort definitions aiming to select “all comers” with hypercapnia use criteria that select different patients who vary in characteristics that would be expected to influence both prognosis and response to various treatments. This findings suggests that the interpretability of future research findings might be improved if standardized definitions were utilized.

We then showed that most patients who have an ICD-code for hypercapnic respiratory failure have either an arterial blood gas diagnostic of hypercapnia, or a highly suggestive venous blood gas. This suggests that ICD-code based criteria are specific for non-iatrogenic, community-onset hypercapnia. However, we find that that vast minority of patients with a venous or arterial blood gas suggesting hypercapnia receive a diagnostic code, and that patients who are billed as hypercapnia are different from those who aren’t. In the US, billing codes are often applied by coders who rely on clinician’s documentation and, in cases where the diagnosis is ambiguous, supporting evidence. In the case of hypercapnia, it is not clear if clinicians are recognizing the presence of hypercapnia but not viewing it as a primary diagnosis, failing to recognize and thus bill for hypercapnia, or if billing is not capturing the clinician’s intent. However, the differences between the two groups suggests that studies that enroll patients who are only billed as having hypercapnia will select a subset of patients that may not be representative of all patients with hypercapnia.

Thus – if population health, referrals, or quality improvement projects rely on

\*\*\* specifically, do more of the blood gas types have multiple diagnosis? (there is probably a missing data problem here to work against)

The concept of computable phenotypes, referring to algorithms that use various types of data to identify specific types of patients, have been proposed to address the problem of incomplete information in secondary use datasets. For example, ICD code-based identification of idiopathic pulmonary fibrosis has been shown to be insufficiently sensitive or specific for use in studies. Accordingly, studies utilizing different criteria – such as multiple billing codes, temporal relationships between clinical events, natural-language processing of radiology reports, or machine learning applied to images \*\*\* - have been shown to improve the accuracy of cohort creation, which is expected to lead to more reliable research, practice improvement, and QI initiatives. Only select subsets of patients with hypercapnic respiratory failure, such as those with hypercapnia resulting only from chronic obstructive pulmonary disease (COPD), cystic fibrosis, or amyotrophic trophic lateral sclerosis, have management supported by randomized evidence. Patients with other causes of hypercapnia, and especially those with multiple contributing conditions, also face high morbidity and mortality but scant evidence informs their management.

If a large portion of patients with multi-causal hypercapnia are at high risk of readmission yet have little evidence to guide their management, this would represent an important gap in the literature.

Last, we evaluated several potential enrollment criteria that could improve the capture rate and representativeness of cohorts of patients with hypercapnia. When just utilizing the elements present in the CDC HCUPS databases (such as the Inpatient Sample and Readmissions Databases), we find that \*\*\* With just billing codes, procedures, and demographics - it does not seem like we have a good enough accuracy for a usable approach. --- laboratory values are, in general, far more predictive than other elements we evaluated. Thus, the sensitivity or specificity of any definition will be limited in datasets such as the HCUPs NIS that do not contain laboratory information.

When using a broad range of features we find that \*\*\*

Lastly, we explore the potential to use inverse propensity weighting to predict which patients would have had hypercapnia if they had a blood gas checked to verify their blood CO2 status. Reference-standard diagnosis for hypercapnic respiratory requires obtaining an arterial blood gas, which is painful for patients, and is infrequently variably obtained in routine care. Hypercapnia has presents with nonspecific symptoms and data suggests it is frequently missed. Thus, cohorts that only include patients who have received this gold-standard test may select only a specific subset of patients with the syndrome that may not represent all patients with hypercapnia. Additionally, many datasets (such as National Inpatient Sample) do not contain blood gas results, and therefore studies using incomplete data-sets may be required to use other operational definitions. Therefore, it is possible that the specific method used to enroll patients, including requiring the reference study lab test, would lead to spurious estimates of prevalence, importance, or treatment responsiveness that limits the interpretability of this research paradigm.

While strengths of this study include the broad inclusion criteria of medical systems across the country, which likely provides a national average of clinician and billing behavior, it is worth noting that local variation may influence the accuracy of the analyzed data-elements.

• All single-encounter data (cross-sectional) due to data quality

Can’t evaluate readmissions, mortality, subsequent outpatient management.

We focused on inpatient hypercapnic respiratory failure, though some patients are identified in outpatient or emergency care settings (though data from emergency encounters that led to inpatient admission were included) . We sought to focus on the inpatient setting because the ascertainment of arterial blood gasses is even less frequent and more indiosyncratic, and we believe most newly identified hypercapnic respiratory failure is managed inpatient – though this is not universally true, such as for patients who have OHS. Conversely, patients who are identified as stable outpatients tend to have better outcomes, and thus focusing on the inpatient admissions may address the biggest unmet research need.

Another limitation involves the lack of verification for many patients who do not receive blood gasses. Thus, while inverse propensity weighting can allow estimation of how predi9ctive various features are of blood gas ascertainment, prospective verification is needed. Additionally, due to limitations with the data we are unable to confirm exactly which patients may have received procedures that introduced (iatrogenic) hypercapnia – though we attempted to restrict our analysis to hospital day 0.

* Predictive modeling for other medical conditions, including respiratory conditions such as chronic cough and ILD, has been much improved by the integration of unstructured data – such as notes, radiology reports, or images. We were unable to assess these predictors, but future work may be able to improve the classification accuracy of these algorithms by including this data. Performance of different types of data elements? A limitation of the current approach is the absence of unstructured data, which contains many features pertinent to the likelihood of hypercapnia being present (signs, symptoms, historical features of the current presentation)
* We utilized an enriched sample which introduces several caveats. "Sensitivity depends on the spectrum of disease in the sample, specificity depends on the sample of non-disease"" — thus, because we have requested a data-set that restricted “non-disease” - the true specificity may be even higher than reported. citation for spectrum bias: Cite this as: BMJ 2016;353:i3139 http://dx.doi.org/10.1136/bmj.i3139
* This analysis will treat hypercapnia as an acute condition, where we want to identify each “incident” case as a new event, as opposed to something like diabetes where once someone “has it”, they are considered to still have it.
* There will be people in the cohort who a.) have incidental hypercapnia (ie. They are chronically hypercapnic but hospitalized for another reason) and some who have b.) iatrogenic hypercapnia (caused by interventions). Including a. Is fine though not prioritized, not aiming to include b.
* Lastly, improvement in disease identification with computable phenotypes addresses only one of several threats to the validity of health-record based research. Other problems, such as missing event and covariate data, time of event determination (immortal time), and confounding will require altnerative approaches to address.

In sum, we show that EHR-based cohorts investigating patients with hypercapnic respiratory failure have used a variety of definitions to select patients, and that these methods create groups of patients that differ in ways expected to influence both their prognosis and their potential response to medical interventions. Further work utilizing unstructured data-elements and prospective verification of CO2 status in patients who may normally be missed in clinical practice are needed for more reliable and applicable methods are needed to improve the robustness and interpretability of future health-record based identification of patients with hypercapnic respiratory failure.

# Tables and Figures;

## Table 1

|  |  |  |
| --- | --- | --- |
| Test on Day-0? | No VBG | Had VBG |
| No ABG | 16.6% | 13.2% |
| Had ABG | 39.9% | 30.3% |

## Table 2: Sample Characteristics Using various cohort definitions

|  |  |  |  |
| --- | --- | --- | --- |
| Test sugg. ↑ CO2 (vs all others) | ABG | VBG | VBG Corr |
| OR of +ICD | 6.5 | 5.6 | 6.1 |
| (Inv. Prob BG Wt) | 5.7 | 5.7 | 6.1 |
| +Abs % Increase | 10.3% | 9.8% | 10.2% |
| OR of subsequent events during hosp | | | |
| Steroid | 1.51\* | 1.13 | 1.2 |
| Crit Care | 1.83 | 1.74 | 1.86 |
| NIV or IMV | 2.6 | 2.02 | 2.29 |

Expand this to cover most of them.

## Figure 1: Inclusion Flow Diagram.

## Figure 2: Coefplots (replacing table 2?)

# References:

# Supplementary Materials

## TriNetX Information [maybe just say this has been explained in detail elsewhere?]

The data used in this study was collected 6/4/2023 from the TriNetX Research Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 110 million patients from 80 healthcare organizations. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA), the US federal law which protects the privacy and security of healthcare data, and any additional data privacy regulations applicable to the contributing HCO. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule. Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform, only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. Because this study used only de-identified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from Institutional Review Board approval

TriNetX:

Publication guidelines; https://trinetx.com/real-world-resources/publications/trinetx-publication-guidelines/

"Mostly large AMCs" - average 7 years of historical data. 80% refresh >= every 4 weeks.

Linkage analysis - the TriNetX team attempts to map local or atypical terminologies onto shared Terminologies (HL7, ICD-10-CM, CPT, RxNORM + OMOP, LOINC)

-TriNetX, aggregated health record data summarizing ~115 million patients who received care at one of ~75 US medical centers during calendar year 2022

-Enrichment sample (~2 million; ~850k after data quality checks to ensure all needed data was being submitted) with some reason a provider would consider hypercapnia:

a respiratory or confusion complaint, a historical diagnosis of a predisposing condition, and diagnosis for a related condition (e.g. respiratory failure), obesity.

would not use whether they obtained an ABG or VBG as a method for inclusion to avoid incorporation bias

Relevant Codes:

## Data request details:

Encounter Table -> Type: We are interested in care settings: Ambulatory (AMB), Emergency (EMER), Inpatient Encounter

(IMP).

* We’re not interested in:  Home Health (HH), Inpatient Non-acute (NONAC), Observation (OBSENC), Pre-admission (PRENC), Short Stay (SS),

There are now several different criteria that a patient could meet to be included. I’ll call these “reasons for suspsicion” (RFS). Definitions for these are below. (these are analagous to the 3 criteria we initially had, but expanded)

* RFS: ABG
* RFS: VBG
* RFS: Resp Failure Dx
* RFS: obesity
* RFS: Vent Support
* RFS: Predisposition

I think the way to do this that has the least chance of us needing to go back and adjust (because I could always cut back in the refined data) would be:

to select the first encounter of each Care Setting by RFS permutation (so, theoretically up to 18 encounters - 3 care settings and 6 reasons for suspicion- per patient… though in reality I expect much less).

All the data-elements (not mean-imputed; not dropping variables with high missingness) for each encounter as we have in the current code would be perfect. Would need a patient ID and a date so that I can tell which are from the same patient and which were first.

**RFS: ABG**

\*Any value OK (e.g. it does NOT need to be above 45, like previously)

LOINC 2019-8 Arterial CO2

LOINC 2026-3 Arterial CO2

LOINC 32771-8 Arterial CO2

**RFS: VBG**

\*Any value OK

LOINC 115577-6 CO2 in blood

LOINC 2021-4 CO2 in venous blood

**RFS: Resp Failure Dx**

Either

J96.\*   (Any Respiratory failure dx code; e.g. including J96.00, J96.10, J96.92, etc. etc. )

or

E66.2 Morbid obesity with alveolar hypoventilation

**RFS: obesity**

E66.01 Dx Code Morbid Obesity due to excess calories

Z68.41 Dx code BMI 40.0-44.9 dx code

Z68.42 Dx Code BMI 45-49.9 dx code

LOINC 39156-5 Body Mass Index greater than or equal to 40

**RFS: Vent Support**

Any of the following codes:

ICD PCS 5A09459 - Assistance with respiratory ventilation negative airway pressure

ICD PCS 5A0945B - Assistance with respiratory ventilation intermittent negative airway pressure

ICD PCS 5A09559 - Asstiance with respiratory ventilation continuous neg airway pressure

ICD PCS 5A0955B - Asstiance with respiratory ventilation continuous neg airway pressure

ICD PCS 5A09359 - Asstiance with respiratory ventilation continuous neg airway pressure

ICD PCS 5A0935B - Asstiance with respiratory ventilation intermittent neg airway pressure

ICD PCS 5A09358 Intermittant CPAP 24

ICD PCS 5A09458 Intermittant CPAP 24-96

ICD PCS 5A09558 Intermittant CPAP 96+

ICD PCS 5A09357  Assistance with Respiratory Ventilation, Less than 24 Consecutive Hours, Continuous Positive Airway Pressure

ICD PCS 5A09457 Assistance with Respiratory Ventilation, 24-96 Consecutive Hours, Continuous Positive Airway Pressure

ICD PCS 5A09557 Assistance with Respiratory Ventilation, Greater than 96 Consecutive Hours, Continuous Positive Airway Pressure

ICD PCS 5A0935Z - assistance with respiratory ventilation less than 24 consecutive hours

ICD PCS 5A0945Z - assistance with respiratory ventilation 24-96 consecutive hours

ICD PCS 5A0955Z - assistance with respiratory ventilation greater than 96 consecutive hours

ICD PCS 5A1945Z - Respiratory Ventilation

ICD PCS 5A1935Z Resp Vent <24

ICD PCS 5A1945Z Resp Vent 24-96

ICD PCS 5A1955Z Resp Vent 96+

CPT 1015098 - Vent management

CPT 1014859 Vent assist and management

CPT 94002 Vent assist and management, controlled

CPT 94003 Vent assist and management, controlled subsequent

CPT 94660 CPAP initiation and mgmt

**RFS: Predisposition** (For all diagnoses, include sub-categories (e.g. I27.1\* rather than I27.1 only)

Any of:

I27.1 Dx code Kyphoscoliotic heart disease

I27.9 Dx code Pulmonary Heart disease

I27.81 Dx Code Cor Pulmonale (chronic)

I27.2 Dx Code Other secondary pulmonary hypertension

G47.3 Dx Code Sleep Apnea

G95 Dx Code Other and unspecified diseases of spinal cord

G71 Dx Code Primary disorders of muscles

G35 Dx Code Demyelinating diseases of the central nervous system

G36 Dx Code Demyelinating diseases of the central nervous system

G37 Dx Code Demyelinating diseases of the central nervous system

G70 Dx Code Myasthenia Gravis

G12.21 Dx Code Amyotrophic lateral sclerosis

S14.101 Dx Code Unspecified injury at C1 level of cervical spinal cord

S14.102 Dx Code Unspecified injury at C2 level of cervical spinal cord

S14.103 Dx Code Unspecified injury at C3 level of cervical spinal cord

S14.104 Dx Code Unspecified injury at C4 level of cervical spinal cord

S14.105 Dx Code Unspecified injury at C5 level of cervical spinal cord

S14.106 Dx Code Unspecified injury at C6 level of cervical spinal cord

S14.107 Dx Code Unspecified injury at C7 level of cervical spinal cord

S14.15 Other incomplete lesions of the spinal cord

S14.12 Central cord syndrome of cervical spinal cord

S14.109 Dx Code Unspecified injury at unspecified level of cervical spinal cord

S14.10 Dx Code Unspecified injury at unspecified level of cervical spinal cord

S14.1 Dx Code Other and Unspecified Injuries of the spinal cord

D75.1 Dx Code Secondary Polycythemia

F11 Dx Code - opioid related disorders

T40 Dx code Poisoning by narcotics and psychedleics

E84 Dx Code - cystic fibrosis

J45 Dx code - asthma

J44 Dx Code - COPD

J43 Dx Code - emphysema

I50 Dx Code - heart failure

TrinetX

• De-identified, patient-level data (not PHI, though recommended to be treated as such)

• Federated data from medical center EHRs

70 Healthcare Organizations; mostly (but not exclusively) AMCs

Requested 6/4/2023

• Time: Jan 1 2022 to Dec 31 2022

• Aim: identify all patients who a reasonable clinician would suspect might have hypercapnia (whether or not they actually do)

• Outpatient, ER, Inpatient (+/- ICU)

• Select the time a patient met any criteria for each setting

• Include encounter type, and which criteria they met

• There are now several different criteria that a patient could meet to be included. I’ll call these “reasons for suspsicion” (RFS). Definitions for these are below. (these are analagous to the 3 criteria we initially had, but expanded)

• RFS: ABG

• RFS: VBG

• RFS: Resp Failure Dx

• RFS: obesity

• RFS: Vent Support

• RFS: Predisposition

select the first encounter of each Care Setting by RFS permutation

To ensure adequate data quality, the following data-processing steps were taken:

- Data cleaning: removing physiologically improbable values (see appendix)

- Visualized all proportions and distributions

o Exclude Likely data entry errors (reconcile units such as C vs F, etc)

• Compared to proportions of other comparable populations [e.g. cohorts]

• Added data fidelity check (last slide)

• Calculation of positive (ie expected) and negative (expected to be absent) correlations?

• E.g. procedure codes and parlaytics; diagnosis of pneumonia and receipt of antibiotics.

• Other things that always or never happen? Steroids COPD?

TODO

• Could you validate things like: who are the patients where opiates are an outpatient medication but not an inpatient medication? (indicative of a side effect)

• bicarbonate -> compensation status. —> negative control outcome? (Or a summary of the amount of variation)

## Data cleaning and data representation

No missing data imputation was performed for the following reason: data may be incomplete (rather than missing) as a result of:

- Clinically, the lab value wasn’t checked

- The parameter was not recorded in the EHR

- The documented parameter was not recorded in a utilizable field

- The value was present in the EHR, but not reported to TriNetX

Of the mechaanisms of incompleteness, only the last is a threat to the validity of our analysis – because incomplete data by the other methods will be problematic for algorithms using health record data recorded by methods similar to those participating in TriNetX

Checklist:

"1. How complete are the data?

2. How were the data collected and handled?

3. What were the specific data types?

4. Did the analysis account for EHR variability?

5. Are the data and analytic code transparent?

6. Was the study appropriately multidisciplinary?"

(And of course, RECORD statement) - https://www.record-statement.org/

How to treat missing data? (Not checked)

Good key Citations:

https://www.thelancet.com/journals/landig/article/PIIS2589-7500(22)00154-6/fulltext#section-3d6acba1-acea-4be2-8dc9-b7e14e5b6583

Citation synopsis: 6 pitfalls

1. considering how the chosen inclusion criteria might influence the cohort

2. Imprecise definitions that may not actually reflect true underlying physiology

1. example: billing code data may only reflect not is billable, not what is done.

3. Relying on data that is not available at the time it is needed

4. Informed presence bias - simple imputation may not be sufficient: https://pubmed.ncbi.nlm.nih.gov/22081062/

5. not modeling the reasons why patients receive treatments/exposures of interest

6. Model overfitting / lack of generalizability

Relatedly: ATS data quality standards - https://www.atsjournals.org/doi/full/10.1513/AnnalsATS.201309-300RM

MI: 10-100 - BMI is truncated at 50 to avoid identifying notable patients.

RR: 2-75 --- // whats going on with respiratory rates below 4?  - do we think these are coding errors or peri-arrest? — seems like they are preferentially in the ventilation procedure code group… perhaps this is an error in how IMV vs spontaneous breaths are coded in the dataset? I think nothing to do here yet.

Temp(F): 30 - 110

Sys BP: 30 - 350

Dia BP: (15 on revamp) 20 - 250

SpO2: 50-100

HR: 15 - 300

Temp: outside 70F - 110F;  20c - 43c

\*\*\* If temperature is between 20-43, can be assumed to represent C and converted to Fahrenheit

Several data control methods were applied, explained in detail in the Supplemental Material. Encounters were required to have at least 1 data element of each type (ensuring participating centers were submitting all categories of data during the time), variables outside physiologic ranges were removed, and positive/negative control measures were developed (findings that should always or never co-occur, such as a code for invasive mechanical ventilation when neuromuscular blockade is used). Distributions of covariates were examined after each exclusion to assess the plausibility of the missing-at-random assumption for key covariates. Outcomes and characterizations were all performed within the same encounter of interest to minimize the risk of data discontinuity.

For the respiratory failure codes - just keep as is and include each individually

Code groupings:I think several groups can be near-synonymous and could be lumped

* “Dyspnea diagnosis”  (1 if any, 0 if none, then drop individual components): has\_r060 has\_r06 has\_r0600  has\_r0602 has\_r0603 has\_r0609
* “Upper Airway” (1 if any, 0 if none, then drop individual components): has\_r061 has\_r062 has\_r0683
* “Other respiratory abnormality” (1 if any, 0 if none, then drop individual components): has\_r065 has\_r066 has\_r067 has\_r068 has\_r0689 has\_r069 has\_r0681 has\_r063 has\_r064 has\_r0682
* “Pulm Edema” (1 if any, 0 if none, then drop individual components): has\_j81 has\_r0601
* “Pneumonia” (1 if any, 0 if none, then drop individual components): has\_j9 has\_j10 has\_j11 has\_j12 has\_j13 has\_j14 has\_j15 has\_j16 has\_j17 has\_j18
* “AECOPD”  (1 if any, 0 if none, then drop individual components): has\_j440 has\_j441 has\_j21
* “Resp Depressant”  (1 if any, 0 if none, then drop individual components): has\_z79891 has\_e9352 has\_f1110 has\_t40 has\_f19982
* “Connective Tissue Disease” (1 if any, 0 if none, then drop individual components): has\_m05 has\_m06 has\_m30 has\_m31 has\_m32 has\_m33 has\_m34 has\_m35 has\_m36
* “Dementia” (1 if any, 0 if none, then drop individual components): has\_f01 has\_f02 has\_f03 has\_f04 has\_f05 has\_f06 has\_f07 has\_f08 has\_f09
* “Diabetes” (1 if any, 0 if none, then drop individual components): has\_e08 has\_e09 has\_e10 has\_e11 has\_e12 has\_e13
* “Neuromuscular Disease”  (1 if any, 0 if none, then drop individual components): has\_g12 has\_g14 has\_g70 has\_g35 has\_g71 has\_g95 has\_g36 has\_g37
* “Nicotine Dependence” (1 if any, 0 if none, then drop individual components): has\_f17 has\_f12 has\_f18

Length of stay: los

-Critical Care time: has\_99291 (critical care services)

-Intuation Rate… combine the following as “Invasive Mech Ventilation” (1 if any, 0 if none - then drop individual components.): has\_94002 has\_94003 has\_5a1945z has\_5a1935z has\_5a1955z has\_5a19054.

-Need for non-invasive support…. Combine the following as “Noninvasive Ventilation” (1 if any, 0 if none, then drop individual components): has\_5a09358 has\_5a09458 has\_5a09558 has\_5a09357 has\_5a09457 has\_5a09557

## Statistical Supplement

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| *Example Calculation* | **ICD code = ‘Prediction’** | | | |
| **Blood gas = reference standard** |  | ICD Code for Hypercapnic RF | No ICD code for Hypercapnic RF |  |
| PaCO2 >= 45mmHg | True Positive | False Negative | Sensitivity  TP / (TP + FN)  (=Recall) |
| PaCO2 < 45mmHg (or no ABG) | False Positive | True Negative  [Huge Number, not very informative] | Specificity  TN / (TN + FP) |
|  | PPV  TP / (TP + FP)  (=Precision) | NPV  TN / (TN + FN) |  |

Considerations for a definition:

|  |  |  |  |
| --- | --- | --- | --- |
| **Study Aim** | **Efficacy Trial** | **Determine Burden of Disease** | **Improve Processes of Care** |
| Ideal Characteristic | Select a population with severe disease, homogeneous in characteristic that predicts treatment responsiveness | Capture all patients who suffer from the adverse consequences of hypercapnic respiratory failure | Identify all patients who will benefit from instituting certain management pathways |
| Example | Severe COPD, no other cause of CO2, severe air trapping, PaCO2 > 52 mmHg | More sensitive definition?  (If only use PaCO2, you will miss patients and skew toward people with classic/severe presentation) | |

## Inverse Propensity weighting

Logistic Regression Based

Missing indicator method.