# Assessing Natural History, Drug Use and Treatment Impact for COVID-19 in the Sentinel System

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5-14-2020

# FDA/Center for Drug Evaluation and Research Use Cases

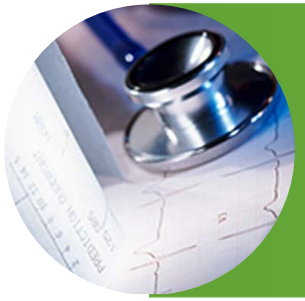
- Monitor for shortages of drugs used for treatment of COVID-19 and its complications in hospitalized patients
- COVID-19 natural history cohorts
  - To aid interpretation of, or as external control for, single-arm clinical trials
  - Serve as a basis for creating cohorts for studies of impact of drug use on COVID-19 outcomes
    - —Cohort of hospitalized patients to study drug treatment impact
      - e.g. hydroxychloroquine
    - —Cohort of hospitalized patients using certain drugs chronically to evaluate whether use of these drugs predict COVID-19 outcomes
      - e.g. ACE inhibitors
    - —Subcohorts with unique characteristics, e.g. cancer patients

# Sentinel System

Launched in 2008 in response to the FDA Amendments Act (FDAAA) 2007

- Numerous data partnerships with private and public data holders
- Access to healthcare claims, EHRs, medical records
- Network with academia, health insurers, research organizations

*NETWORK OF COLLABORATORS*



- >300 million patient identifiers
- 70 million members currently accruing new data
- Data partners retain physical and operational control of their data behind their own firewalls

*DATA AT A GLANCE*

- Rapid, parameterizable, flexible, reusable tools
- Propensity score and other advanced analytics
- Capable of signal detection, refinement, and evaluation

*METHODS*

# Sentinel System Projects

- **Drug shortages**
  - The goal of the first Sentinel COVID-19 project is to set up a sequential drug monitoring capability with an emphasis on in-hospital (especially critical care) drugs in up to 20 data partners for drug use data for 60 priority drugs by state and week.
    - —Partners with inpatient EHR data can generate counts of prescriptions/administrations by day/week by state
- **Natural history cohorts**
  - **HCA Healthcare** cohort using inpatient EHR data from large hospital system
    - —Get a first, descriptive look at characteristics and outcomes of hospitalized COVID-19 patients
  - **TriNetX**
    - —Data can be queried interactively in real-time to investigate COVID-19 treatment, natural hx, medical care use, and outcomes
  - **In development**
    - —Integrated Data Systems, PCORnet, and other EHR partners

# Sentinel System Projects

- **Question** to help understand likely demand for drugs for serious COVID-19 patients
  - For a cohort of hospitalized COVID-19 patients what are the proportions of patients with tachypnea (respiratory rate ≥ 24 breaths/min) or requiring supplemental oxygen or a SpO2 ≤ 94% on room air, or requiring mechanical ventilation?
    - —The greatest interest is for patients requiring supplemental oxygen and requiring mechanical ventilation


# TRINETX AND COVID-19: CODING, DATA, AND OUTCOMES

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May 14, 2020

TriNetX


## REAL-WORLD DATA

- Demographics
- Diagnoses
- Procedures
- Medications
- Lab Results
- Vitals
- Oncology
- Genomics
- Cardiology
- Pulmonology
- Patient Location
- Mortality

## USE CASES

### Clinical Trial Optimization

- Protocol Design
- Site Identification
- Path to Patients

### Real-World Evidence Generation

# TRINETX'S APPROACH TO REAL-WORLD DATA CAPTURE



## VARIOUS AND DISPARATE DATA

Demographics
Diagnoses
Procedures
Lab Results
Vitals
Medications
Cardiology
Genomics
Oncology
Pulmonology
Patient Location
Mortality

## MAPPED TO INDUSTRY STANDARD TERMINOLOGIES

Healthcare Org.

3rd Party Data

BYOD

TriNetX

- HL7
- ICD-10, ICD-9
- CPT
- RxNorm, NDF-RT
- LOINC
- NAACCR, ICD-O
- HGNC, HGVS, ClinVar, dbSNP

## MASTER TERMINOLOGY / INTELLIGENT SYNONYM SEARCH

MUST Have: HbA1c

CANNOT Have: Search Term…

| Code | | Term Description | Patients |
|---|---|---|---|
| TNX:LAB:9037 | L | Hemoglobin a1c/hemoglobin.total in blood | 3,294,500 |

ADD TO QUERY

D Demographics | Dx Diagnoses | L Labs
M Medications | P Procedures | G Genomics

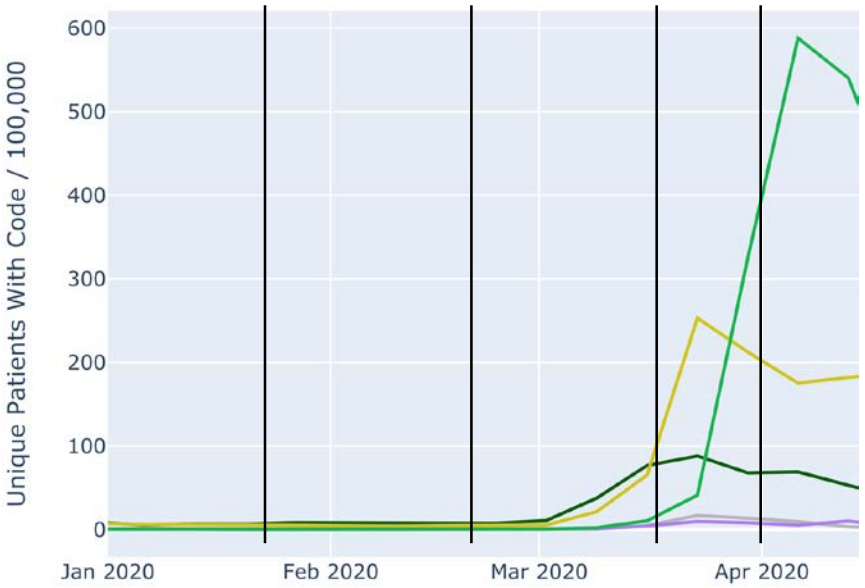
# COVID-19 CODING TRENDS

# PATIENTS WITH COVID-19-RELATED DIAGNOSES PER 100,000 PERSONS PER WEEK IN THE USA NETWORK



## January 1, 2019 through April 15, 2020


## January 1, 2020 through April 15, 2020




- B34.2 – Coronavirus infection, unspecified
- B97.21 – SARS-associated coronavirus as the cause of diseases classified elsewhere
- B97.29 – Other coronavirus as the cause of diseases classified elsewhere
- J12.81 – Pneumonia due to SARS-associated coronavirus
- U07.1 – COVID-19

January 21 – First confirmed case of COVID-19 in the US

February 20 – CDC releases guidance around coding COVID-19-related encounters

March 18 – CDC announces new ICD-10-CM diagnosis code “U07.1” effective April 1

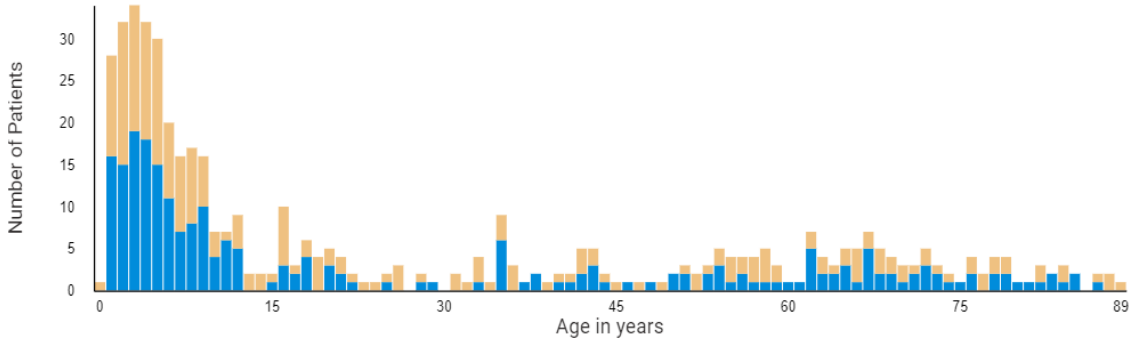
April 1 – Effective date for new “U07.1” code for reporting COVID-19

# CHANGES IN AGE DISTRIBUTIONS OF DIAGNOSED PATIENTS



The age distributions of patients coded with non-specific COVID-19-related diagnoses, such as diagnosis codes B34.2, B97.29, and J12.81, substantially changed in 2020. Below, we can see that J12.81 was more commonly used among pediatrics before January 1, 2020. After January 1, 2020, adults make up the majority of the J12.81-defined population.

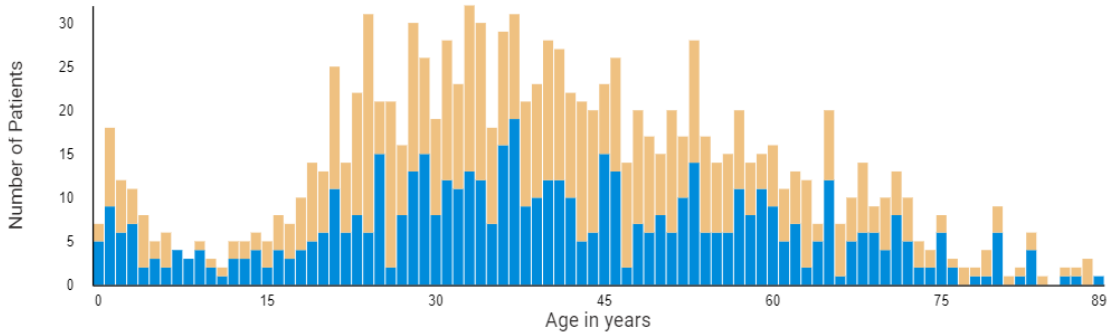
## Before January 1, 2020




*Patients 90 and Older: 11*

| Total Patients | Minimum Age | Maximum Age | Mean Age | Standard Deviation |
|---|---|---|---|---|
| 480 | 0 | 90 | 28 | 29 |

## After January 1, 2020



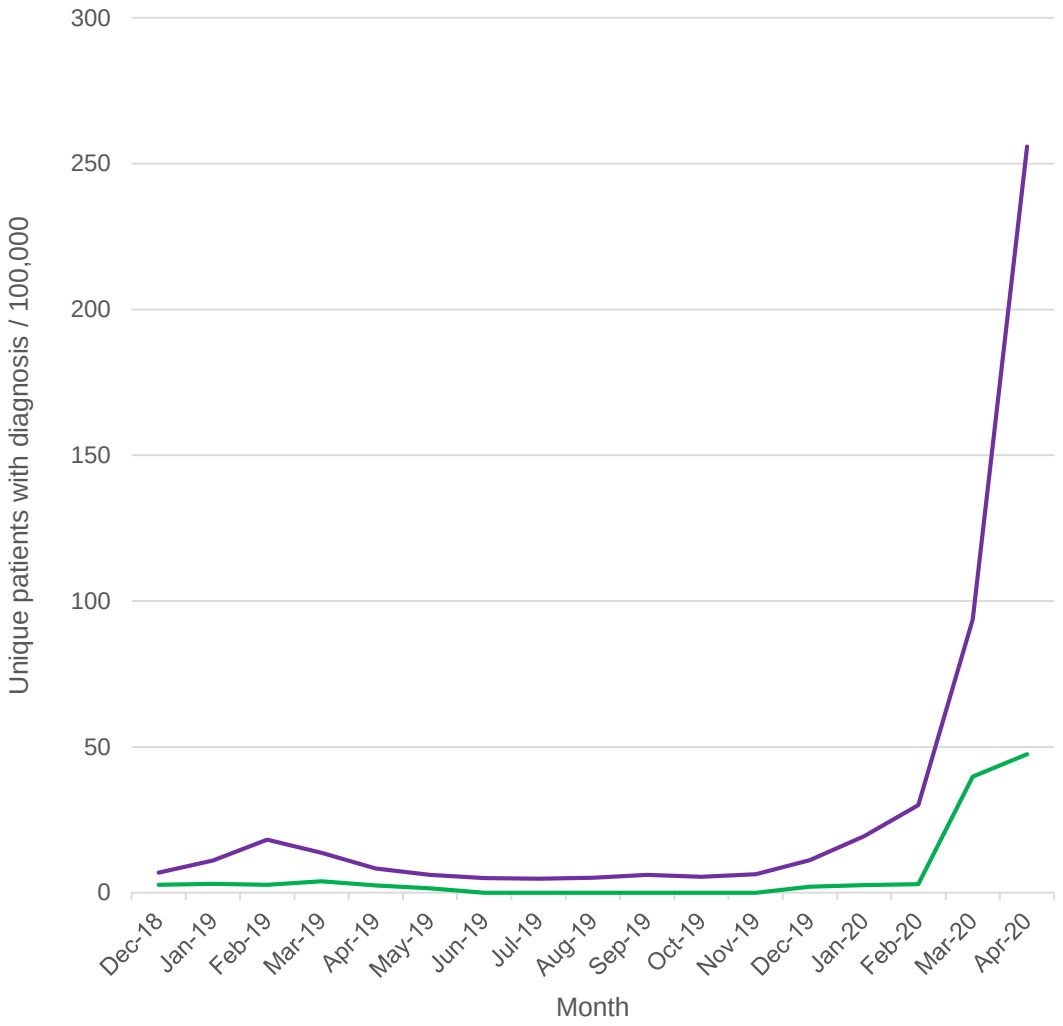

*Patients 90 and Older: 3*

| Total Patients | Minimum Age | Maximum Age | Mean Age | Standard Deviation |
|---|---|---|---|---|
| 1,220 | 0 | 90 | 40 | 19 |

J12.81 – Pneumonia due to SARS-associated coronavirus

# PATIENTS WITH COVID-19-RELATED DIAGNOSES PER 100,000 PERSONS PER MONTH IN THE USA NETWORK






Patients with B97.29, used to diagnose other coronavirus as the cause of diseases classified elsewhere, recorded along with a specific respiratory related diagnosis:

- J20 Acute bronchitis
- OR
- J12.89 Other viral pneumonia
- OR
- J22 Unspecified acute lower respiratory infection
- OR
- J98.8 Other specified respiratory disorders
- OR
- J80 Acute respiratory distress syndrome

Patients with Z20.828, used to code for suspected exposure to a viral communicable disease, coupled with a key symptom:

- R05 Cough
- OR
- R06.02 Shortness of breath
- OR
- R07.1 Chest pain on breathing
- OR
- R07.89 Other chest pain
- OR
- R50.9 Fever, unspecified
- OR
- R07.9 Chest pain, unspecified

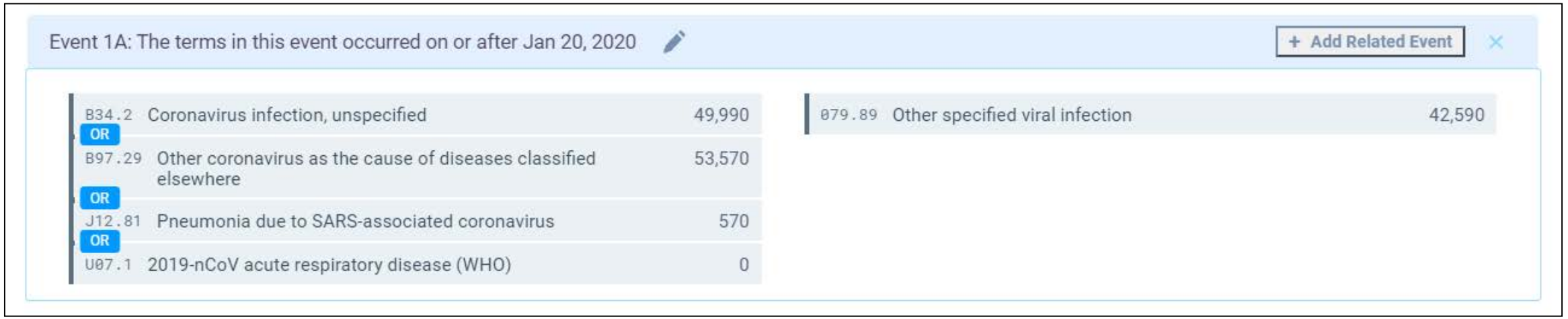
# COVID-19
# IDENTIFYING PATIENTS

# BASE QUERY FOR COVID-19 PATIENT IDENTIFICATION



Initial query logic used by TriNetX as of April 3, 2020:

| Network | Number of Patients |
|---|---|
| USA | 1,330 |




**Inclusion requirements: coronavirus codes used in EMRs for COVID-19**

- B34.2 and J12.81 used more before CDC guidelines
- B97.29 used more after CDC guidelines released
- U07.1 new code specific to COVID-19
- Any code must be present Jan 20, 2020 or after to yield patients

**Exclusion requirement: ICD-9 other specified viral infection code**

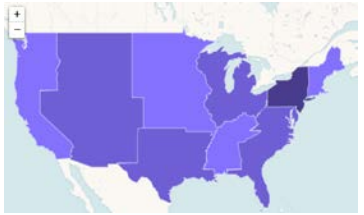
- Mapped to B34.2 and B97.29
- Still used occasionally as ‘catch all’ code for 50+ viral infections

# BASE QUERY FOR COVID-19 PATIENT IDENTIFICATION



Current query logic used by TriNetX as May 13, 2020:

| Network | # of Patients |
|---|---|
| USA | 31,070 |



Event 1A: The terms in this event occurred on or after Jan 20, 2020 + Add Related Event

| | | |
|---|---|---|
| B34.2 | Coronavirus infection, unspecified | 53,030 |
| OR | | |
| B97.29 | Other coronavirus as the cause of diseases classified elsewhere | 76,560 |
| OR | | |
| J12.81 | Pneumonia due to SARS-associated coronavirus | 650 |
| OR | | |
| U07.1 | 2019-nCoV acute respiratory disease (WHO) | 17,890 |
| OR | | |
| U07.2 | COVID-19, virus not identified (WHO) | 0 |
| OR | | |
| 9088 | SARS coronavirus 2 and related RNA [Presence] | 132,350 |
| | Positive, Ever | |

079.89 Other specified viral infection 42,880

**Inclusion requirements: coronavirus codes used in EMRs for COVID-19**

- Same inclusions as prior query
- Added new U07.1 and U07.2 diagnosis codes
- Many lab tests ‘rolled up’ as 9088 and added

**Exclusion requirement: ICD-9 other specified viral infection code**

- Same exclusion as prior query

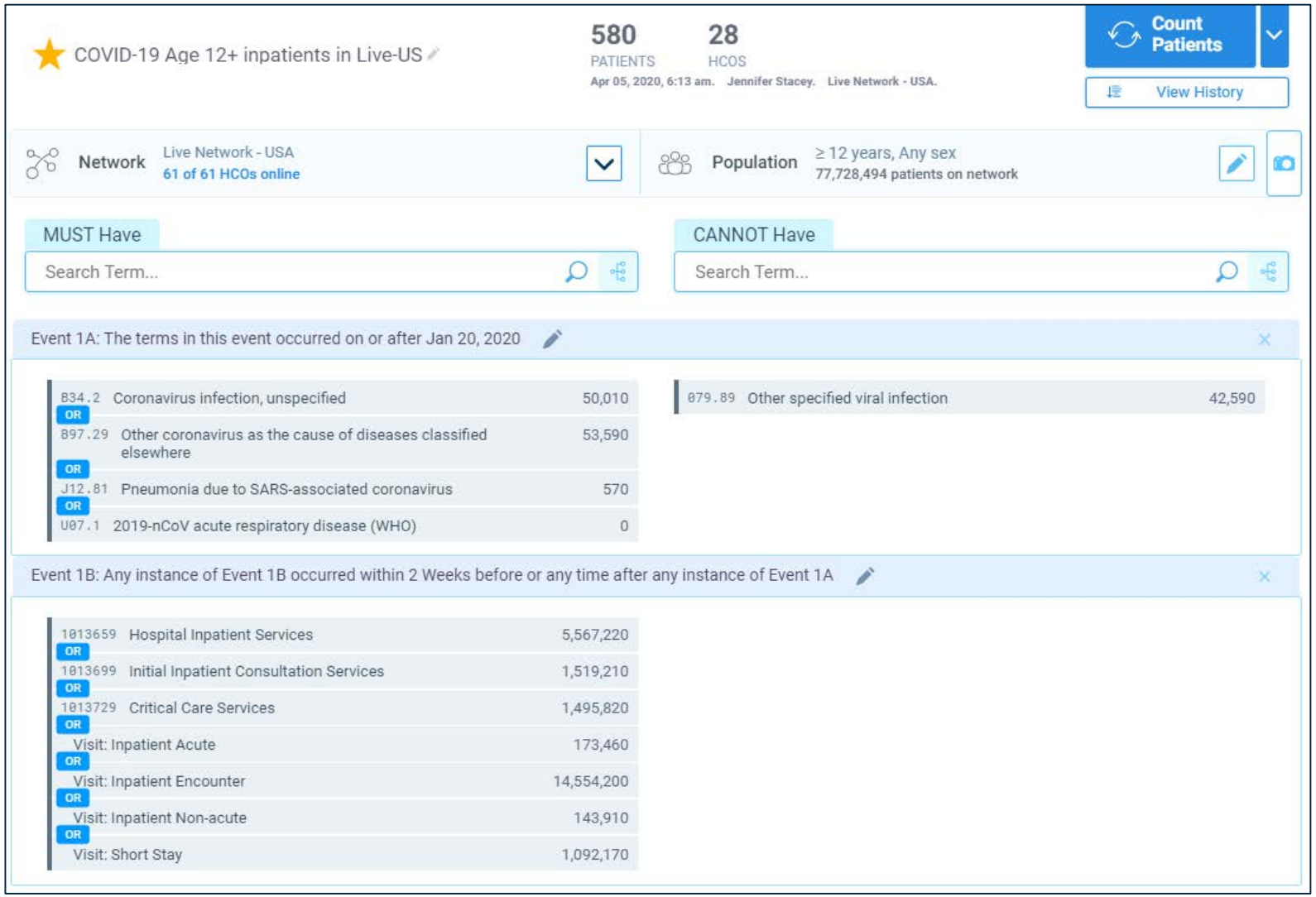
# COVID-19 USE CASES

## #1 – INPATIENT QUERY & VENTILATION OUTCOMES

APRIL 5, 2020

# SPECIFIED COVID-19 QUERY: INPATIENT COHORT






## ID's 580 patients

- US Network
- Age ≥12 years
- Same base query logic
- Inpatient code required 2 weeks before or anytime after COVID-19 diagnosis

# INPATIENT COHORT OUTCOME: MECHANICAL VENTILATION



## Selected inputs:

- Mechanical ventilation CPT or ICD-10-PCS codes

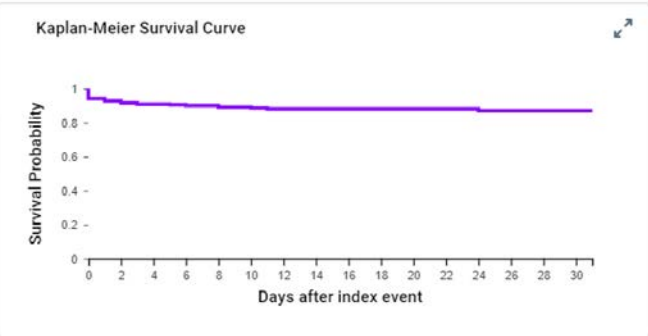
- Must occur on the same day to 1 month after both COVID-19 diagnosis and inpatient status

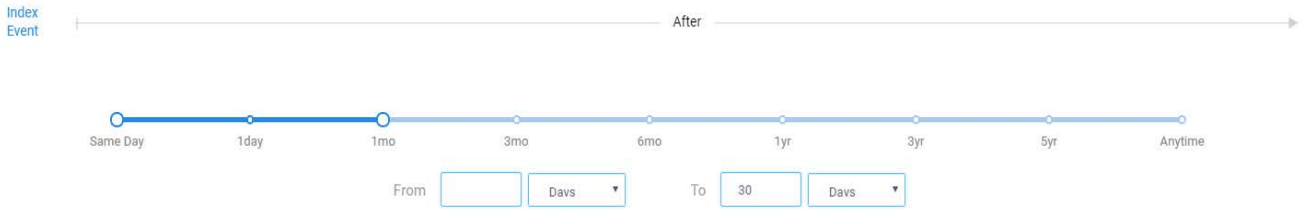
## Results:

**1a : Risk**

| Cohort | Cohort Statistics: Patients in Cohort | Patients with Outcome | Risk |
|---|---|---|---|
| 1 COVID-19 Age 12+ inpatients in... | 570 | 60 | 10.526% |

**1b : Kaplan-Meier Analysis**




MUST Have

Search Term...

| | | |
|---|---|---|
| 31500 | Intubation, endotracheal, emergency procedure | 246,630 |
| OR | | |
| 1015098 | Ventilator Management | 421,320 |
| OR | | |
| 5A1935Z | Respiratory Ventilation, Less than 24 Consecutive Hours | 306,610 |
| OR | | |
| 5A1945Z | Respiratory Ventilation, 24-96 Consecutive Hours | 348,300 |
| OR | | |
| 5A1955Z | Respiratory Ventilation, Greater than 96 Consecutive Hours | 254,250 |
| OR | | |
| 0BH17EZ | Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening | 413,830 |
| OR | | |
| 0BH18EZ | Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening Endoscopic | 270,770 |
| OR | | |
| 0BH13EZ | Insertion of Endotracheal Airway into Trachea, Percutaneous Approach | 110 |
| OR | | |
| 1022227 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician | 7,070 |
| OR | | |
| 39.65 | Extracorporeal membrane oxygenation [ECMO] | 4,720 |

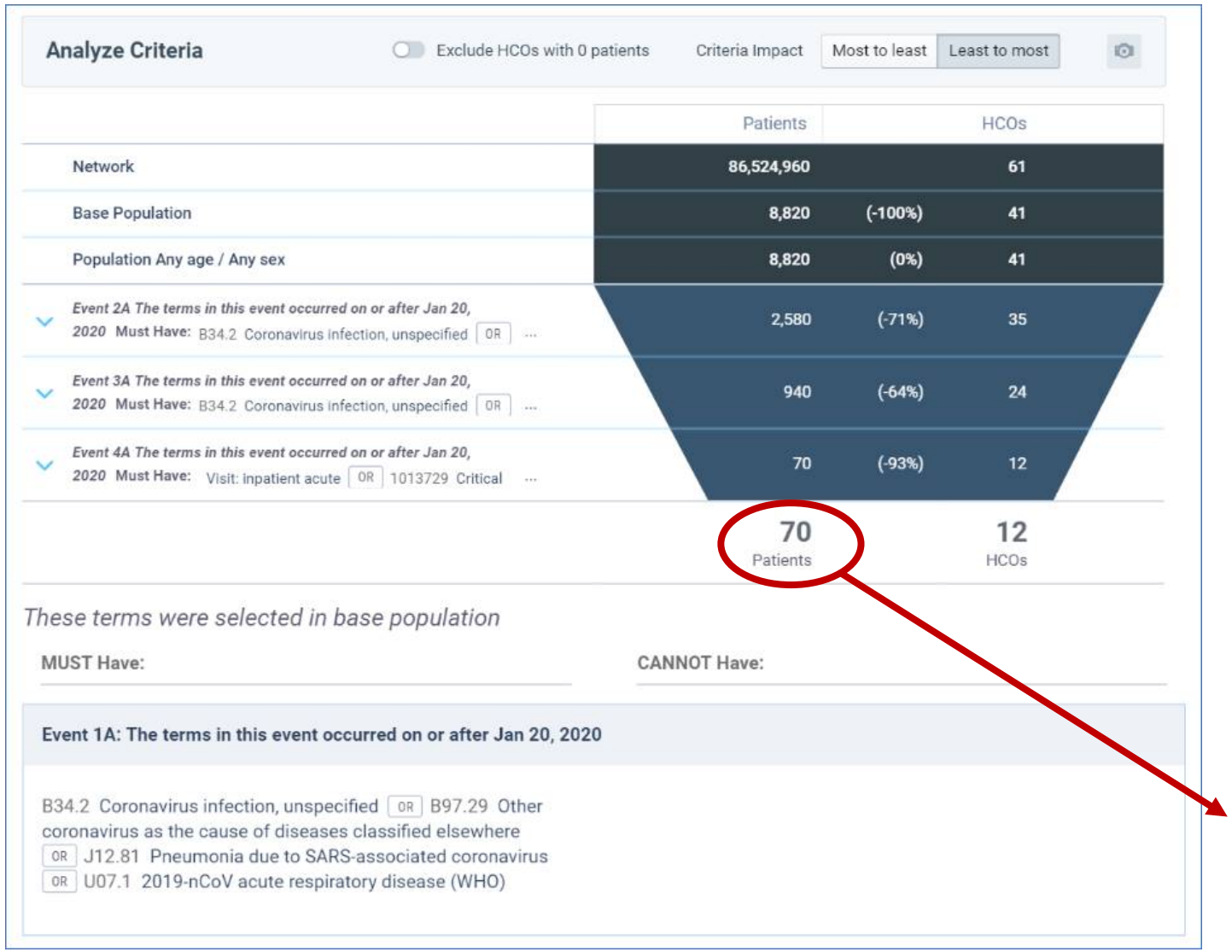
# COVID-19 USE CASES

## #2 – ASSESSING POSSIBLE DIALYSATE SHORTAGES DUE TO UNEXPECTED KIDNEY FAILURE OUTCOMES

APRIL 19, 2020

# DIALYSIS PATIENT ATTRITION FUNNEL






**COVID patients**

- 8,820 patients as of April 19, 2020

**COVID patients with an inpatient visit**

- 2,580 patients (Cohort #1)

**Of cohort #1, how many have evidence of an ICU stay?**

- 940 patients (Cohort #2)

**Of cohort #1, how many patients have evidence of continuous renal replacement therapy?**

- 170 patients

**How many of #2 (COVID+ICU) have evidence of dialysis in the ICU?**

- 70 patients

*Inpatient status may be enough vs getting more granular with ICU status considering the overcrowding and other unit conversions to handle the intensive care demands.

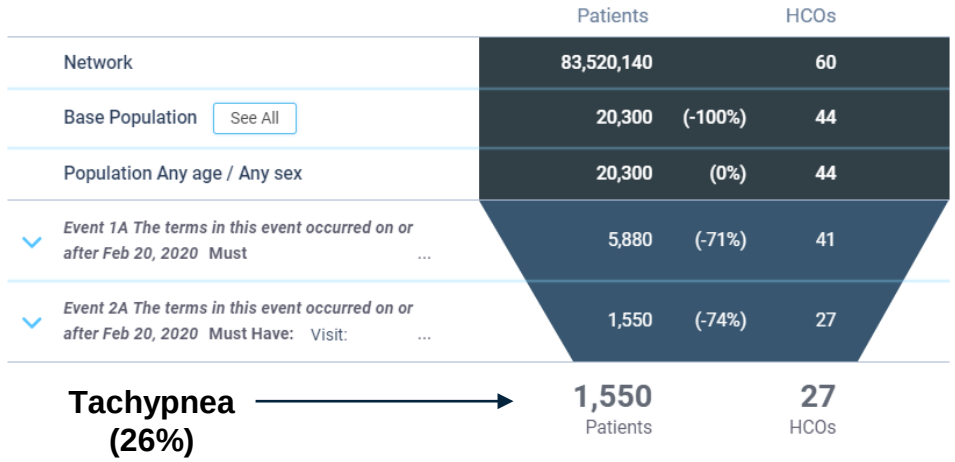
# COVID-19 USE CASES

## #3 – ASSESSING SUPPLEMENTAL O2 USE
## MAY 1, 2020 & MAY 13, 2020

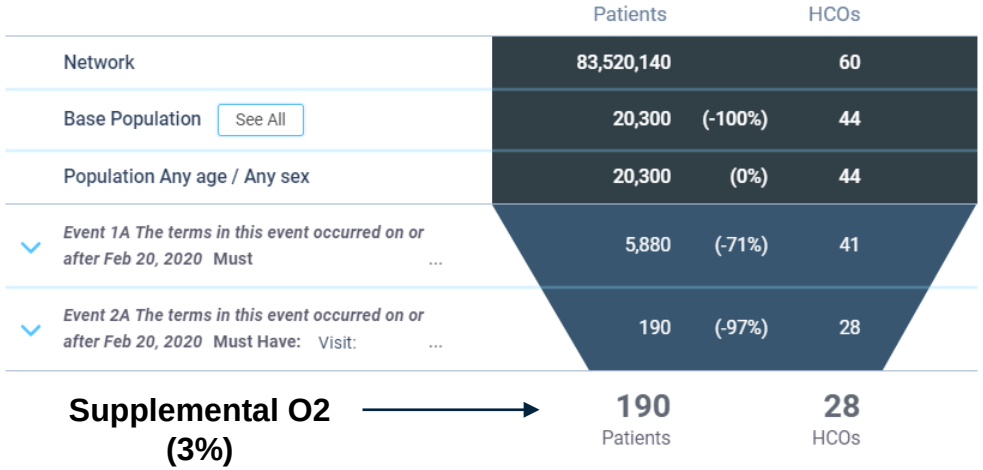
# RESPIRATORY SUB COHORT ATTRITION FUNNELS



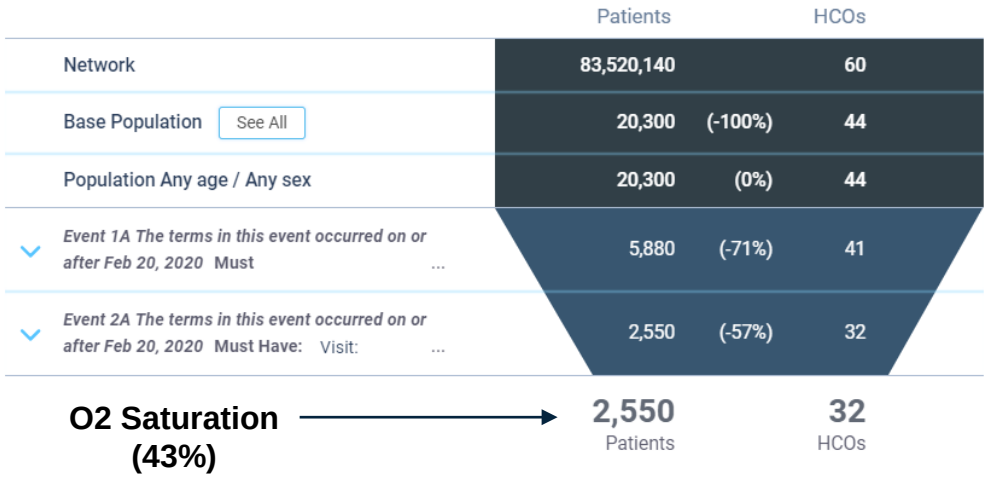
For a cohort of hospitalized COVID patients can we get counts on tachypnea (respiratory rate ≥ 24 breaths/min) or requiring supplemental oxygen or a SpO2 ≤ 94% on room air, or requiring mechanical ventilation?



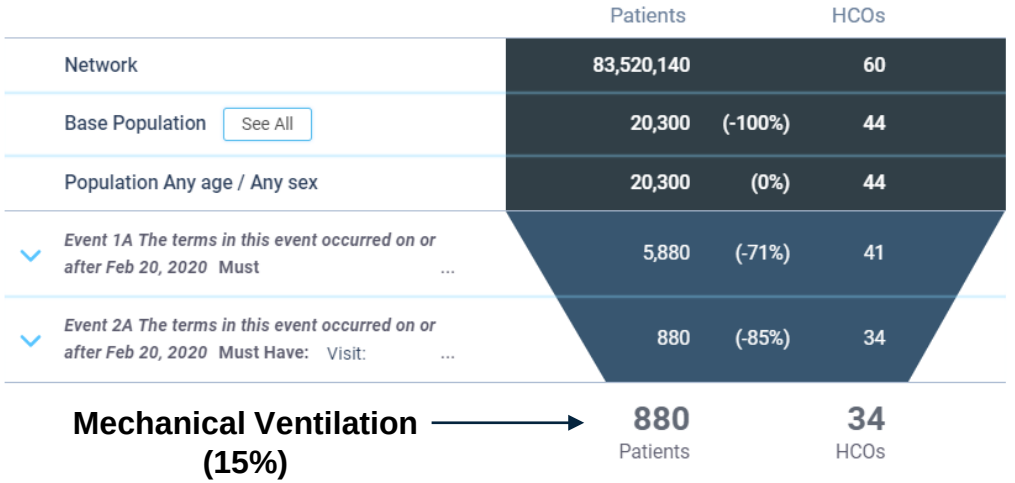

**Tachypnea (26%)** → 1,550 Patients, 27 HCOs




**Supplemental O2 (3%)** → 190 Patients, 28 HCOs




**O2 Saturation (43%)** → 2,550 Patients, 32 HCOs




**Mechanical Ventilation (15%)** → 880 Patients, 34 HCOs

# IDENTIFYING PATIENTS ON SUPPLEMENTAL OXYGEN

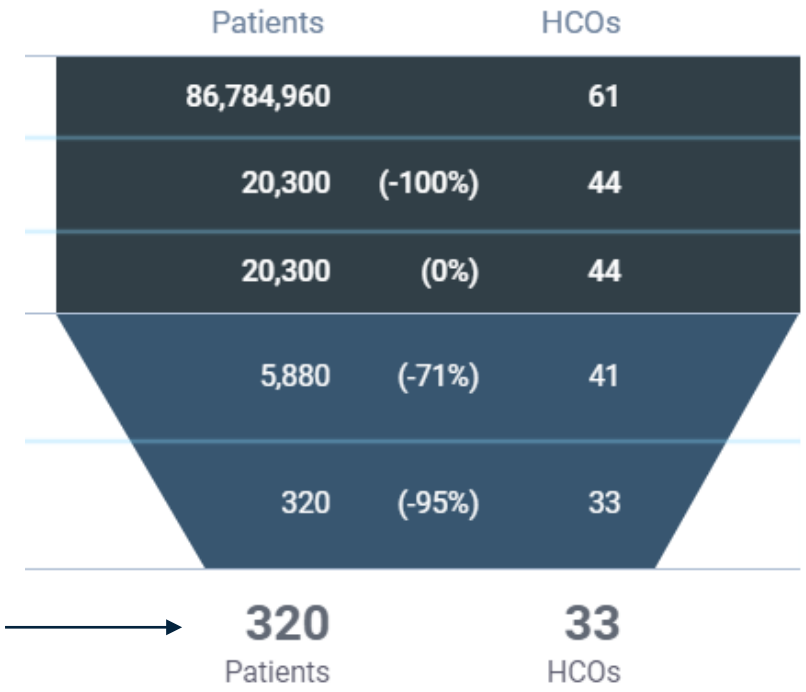


- Initial codes used the following diagnosis to identify 190 patients:

| | | |
|---|---|---|
| Z99.81 | Dependence on supplemental oxygen | 453,690 |
| OR | | |
| 7806 | Oxygen | 10,780 |

- Expanded codes list used the following diagnosis to now identify 320 patients

| | | |
|---|---|---|
| Z99.81 | Dependence on supplemental oxygen | 453,690 |
| OR | | |
| 7806 | Oxygen | 10,780 |
| OR | | |
| E1390 | Oxygen concentrator, single delivery port, capable of delivering 85 percent or greater oxygen concentration at the prescribed flow rate | 48,510 |
| OR | | |
| S8120 | Oxygen contents, gaseous, 1 unit equals 1 cubic foot | 380 |
| OR | | |
| S8121 | Oxygen contents, liquid, 1 unit equals 1 pound | 70 |
| OR | | |
| E1391 | Oxygen concentrator, dual delivery port, capable of delivering 85 percent or greater oxygen concentration at the prescribed flow rate, each | 20 |
| OR | | |
| 5A09 | Physiological Systems / Assistance / Respiratory | 305,290 |
| OR | | |
| 94660 | Continuous positive airway pressure ventilation (CPAP), initiation and management | 326,760 |
| OR | | |
| 5A19054 | Respiratory Ventilation, Single, Nonmechanical | 1,670 |
| OR | | |
| E0601 | Continuous positive airway pressure (cpap) device | 58,580 |

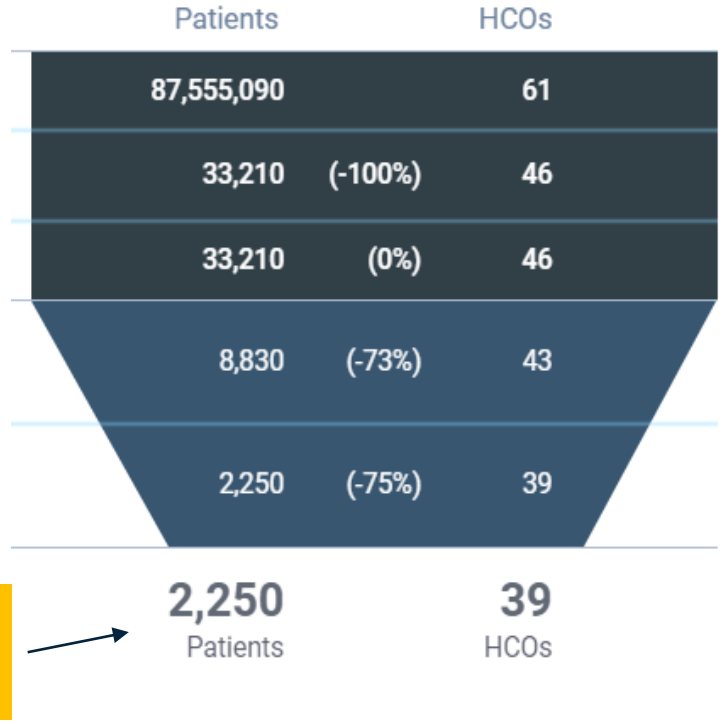


# RATIONALE FOR SUPPLEMENTAL OXYGEN CODING



Supplemental oxygen may not be coded in a patients EHR accurately and/or in structured manner

- Initial query did not include non-invasive ventilation codes (i.e. – CPAP) for supplemental O2 as they don't specify if an oxygen condenser was used or not, but making assumption along with additional codes increased patients on O2 from 3% to 5% of cohort
- Adding ***hypoxia*** is another consideration. While not specifically stating O2 was administered, added to the query it identifies that 25% of patients in the cohort were *in need of* supplemental O2.




**Further Updated Supplemental O2 (25%)**

Reality of RWD may be that oxygen supplementation may be noted in the patient's chart instead of being coded, especially if it's not a long-term supplement

Sentinel

# Reagan-Udall Foundation - Covid-19 Lab Presentation

*Translating early observations to scalable RWD/RWE*

May 14, 2020

# Proportion of patients requiring supplemental oxygen

**TABLE 2. Health care use, interventions, and outcomes in adults hospitalized with COVID-19 (N = 305), by age group and race/ethnicity* — eight hospitals, Georgia, March 2020**

| Characteristic of hospitalization | Total no. (%) (N = 305) | Age group (yrs) No. (%) 18–49 (n = 89) | 50–64 (n = 99) | ≥65 (n = 117) | P-value§ | Race/Ethnicity*,† No. (%) Black (n = 247) | Other (n = 50) | P-value§ |
|---|---|---|---|---|---|---|---|---|
| **Health care use** | | | | | | | | |
| Median hospital duration, days¶ | 8.5 (5.0–14.0) | 7.0 (4.3–11.8) | 8.0 (5.0–12.8) | 10.0 (6.0–16.0) | 0.001 | 8.0 (5.0–13.8) | 8.0 (4.0–14.0) | 0.084 |
| Any supplemental oxygen | 232 (76.1) | 58 (65.2) | 70 (70.7) | 104 (88.9) | <0.001 | 186 (75.3) | 40 (80.0) | 0.59 |
| Nasal cannula | 220 (72.1) | 57 (64.0) | 67 (67.7) | 96 (82.1) | 0.007 | 177 (71.7) | 37 (74.0) | 0.86 |
| Noninvasive ventilation | 11 (3.6) | 2 (2.2) | 4 (4.0) | 5 (4.3) | 0.80 | 10 (4.0) | 0 (—) | 0.22 |
| High-flow nasal cannula | 69 (22.6) | 13 (14.6) | 17 (17.2) | 39 (33.3) | 0.002 | 55 (22.3) | 14 (28.0) | 0.37 |
| **ICU admission and interventions** | | | | | | | | |
| Admitted to ICU | 119 (39.0) | 24 (27.0) | 32 (32.3) | 63 (53.8) | <0.001 | 96 (38.9) | 21 (42.0) | 0.75 |
| Median ICU duration, days¶ | 8.0 (5.0–12.0) | 7.0 (4.0–14.0) | 8.0 (6.0–11.0) | 9.0 (5.0–12.0) | 0.74 | 8.0 (5.0–12.0) | 9.0 (6.0–11.0) | 0.92 |
| Invasive mechanical ventilation | 92 (30.2) | 17 (19.1) | 27 (27.3) | 48 (41.0) | 0.003 | 75 (30.4) | 16 (32.0) | 0.87 |
| Median ventilator days¶ | 9.0 (5.0–12.0) | 8.5 (5.0–13.3) | 9.0 (5.5–10.5) | 10.0 (6.0–12.0) | 0.74 | 9.0 (5.0–11.5) | 9.5 (6.3–13.3) | 0.20 |
| Acute renal replacement therapy | 23 (7.5) | 2 (2.2) | 8 (8.1) | 13 (11.1) | 0.037 | 19 (7.7) | 3 (6.0) | >0.99 |
| Vasopressor support | 84 (27.5) | 13 (14.6) | 21 (21.2) | 50 (42.7) | <0.001 | 70 (28.3) | 13 (26.0) | 0.86 |
| Cardiopulmonary resuscitation | 13 (4.3) | 2 (2.2) | 3 (3.0) | 8 (6.8) | 0.25 | 11 (4.5) | 2 (4.0) | >0.99 |
| **Outcome** | | | | | | | | |
| Discharged alive | 233 (76.4) | 85 (95.5) | 83 (83.8) | 65 (55.6) | <0.001 | 192 (77.7) | 34 (68.0) | 0.15 |
| Still hospitalized | 24 (7.9) | 1 (1.1) | 7 (7.1) | 16 (13.7) | 0.002 | 18 (7.3) | 6 (12.0) | 0.26 |
| Died** | 48 (17.1) | 3 (3.4) | 9 (9.8) | 36 (35.6) | <0.001 | 37 (16.2) | 10 (22.7) | 0.28 |
| Invasive mechanical ventilation or death** | 86 (30.6) | 16 (18.2) | 22 (23.9) | 48 (47.5) | <0.001 | 69 (30.1) | 16 (36.4) | 0.48 |

**Abbreviations:** COVID-19 = coronavirus disease 2019; ICU = intensive care unit; IQR = interquartile range.

* Black was defined as non-Hispanic black race/ethnicity; other includes all other racial/ethnic groups.

† Eight patients were excluded from race comparisons because race and ethnicity data were missing.

§ P-values were calculated using Fisher's exact tests for proportions and the Wilcoxon rank-sum test or the Kruskal-Wallis H test for medians.

¶ Continuous variables are presented as median (IQR).

** Among 281 total patients who were no longer hospitalized, 88 (31.3%) were aged 18–49 years, 92 (32.7%) were aged 50–64 years, and 101 (35.9%) were aged ≥65 years; among 273 patients with available race/ethnicity data who were no longer hospitalized, 229 (83.9%) were non-Hispanic black, and 44 (16.1) were of other race/ethnicity.

Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Early Release / Vol. 69 April 29, 2020

Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19 — Georgia, March 2020

- 8 Georgia hospitals (7 in Atlanta); data summarized via medical record–abstraction for adult patients with laboratory-confirmed COVID-19 admitted in March 2020.

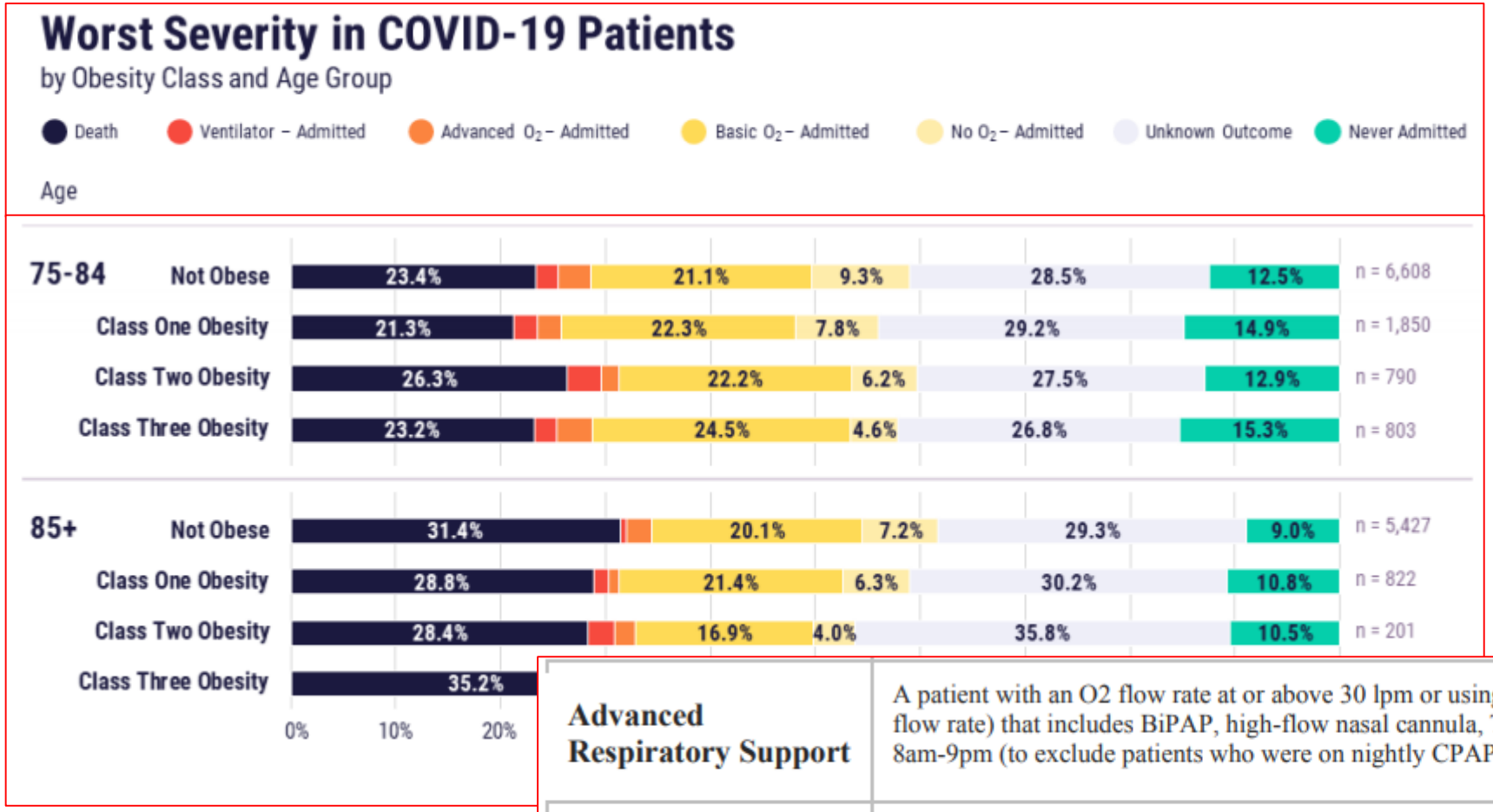
- Any supplemental oxygen: 76%
- Nasal cannula: 72%
- Non-invasive ventilation: 3.6%
- Invasive mechanical ventilation: 30%

# Oxygen Support – Preliminary Results from Inpatient EHRs

| **Oxygen delivery** | Hospitalizations with coronavirus or COVID-19 diagnosis codes (B97.29, U07.1, or B34.2) (N=360) | | Hospitalizations with CDC recommended COVID-19 codes (B97.29 or U07.1) (N=339) | |
|---|---|---|---|---|
| | 1/1/20 – 4/6/20 | 2/20/20 – 4/6/20 | 1/1/20 – 4/6/20 | 2/20/20 – 4/6/20 |
| Supplemental O2 on admission* | 28.5% | 15.8% | 27.6% | 15.9% |
| Supplemental O2 after admission* | 43.5% | 25.3% | 42.1% | 24.8% |
| Mechanical ventilation on admission* | 8.5% | 4.4% | 8.2% | 4.7% |
| Mechanical ventilation after admission* | 13.9% | 12.5% | 14.2% | 13.3% |
| Any mechanical ventilation during the hospitalization** | 18.4% | 15.0% | 18.5% | 15.9% |

*One hospitalization could contribute to both rows if the patient had relevant codes ‘on admission’ and also ‘after admission’
**There is no “any supplemental oxygen during the hospitalization” in the current report

# Proportion of patients requiring supplemental oxygen




- Focus on obesity, not $O_2$ supplementation
- Includes all patients, not just hospitalized
- Different definitions of $O_2$ supplementation

(Modified from the Epic report)

| | |
|---|---|
| **Advanced Respiratory Support** | A patient with an O2 flow rate at or above 30 lpm or using a high flow oxygen delivery device (regardless of O2 flow rate) that includes BiPAP, high-flow nasal cannula, T-piece, blow-by, or CPAP if administered between 8am-9pm (to exclude patients who were on nightly CPAP for apnea). |
| **Basic Respiratory Support** | A patient on supplementary oxygen with a flow rate under 30 lpm, or using any oxygen delivery device that is not a ventilator or high-flow oxygen device (e.g., ETT, LMA, CPAP, BiPAP, high-flow nasal cannula, T-piece, or blow-by). |

https://ehrn.org/obesity-and-covid-19-severity/
https://ehrn.org/wp-content/uploads/Obesity-and-COVID-19.pdf

# How to make sense of all the Covid-19 Data?

- COVID-19 creates a perfect storm for the promise and perils of real-world data
- Rapid and real-time information versus definitive studies
- Inpatient electronic health records (EHRs) were initial focus
- Registries and ambulatory EHRs now contributing
- Can health insurance billing data help?
- Easy availability of RWD enabled rapid and prolific generation of real-world information
- **But how can we make sense of it all? Which analyses are right? How can the data be used?**

# Pieces of the Puzzle

- It’s all right and it might all be wrong
- Hard to see all the puzzle pieces or to know what is missing
- Gathering data quickly is akin to organizing the pieces
- Current information helps us ask better questions - putting the puzzle together…*together*
- Flexibility and transparency are critical: Understand what was done
- **Formal analyses should focus on matching the right data to right methods to the intended use**