Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

# CBER Surveillance Program

## Biologics Effectiveness and Safety Initiative

# A Structured Review of Electronic Coding Algorithms for Acute Respiratory Distress Syndrome (ARDS) Using Administrative Claims and Electronic Health Records

## Final Report

May 24, 2021

**Prepared by:** Patrick Saunders-Hastings,[1] Sze Wing Heong,[1] Pradeep Rajan,[1] Timothy Burrell,[2] Jeff Beers,[3] Judith Cope,[4] Deborah Thompson,[4] Cindy Ke Zhou[4]

**Author Affiliations:**

[1] Gevity Consulting Inc., Ottawa, Ontario, Canada
[2] IBM Watson Health, Cambridge, Massachusetts, United States of America
[3] IBM Global Business Services, Issaquah, Washington, United States of America
[4] Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, United States of America

*This page is intentionally left blank*

**Table of Contents**

## Table of Tables



## Table of Figures

# List of Acronyms

| | |
|---|---|
| AECC | American-European Consensus Conference |
| AFHSB | United States Armed Forces Health Surveillance Branch |
| AHRQ | Agency for Healthcare Research and Quality |
| ALI | Acute Lung Injury |
| ARDS | Acute Respiratory Distress Syndrome |
| BEST | Biologics Effectiveness and Safety |
| CBER | Center for Biologics Evaluation and Research |
| CI | Confidence Interval |
| CMS | Centers for Medicare and Medicaid |
| CPAP | Continuous Positive Airway Pressure |
| CPT | Current Procedural Terminology |
| EHR | Electronic Health Record |
| FDA | Food and Drug Administration |
| GEM | General Equivalence Mapping |
| HCPCS | Healthcare Common Procedure Coding System |
| ICD-9-CM | International Classification of Diseases, Ninth Revision, Clinical Modification |
| ICD-10-CM | International Classification of Diseases, Tenth Revision, Clinical Modification |
| ICU | Intensive Care Init |
| LOINC | Logical Observation Identifiers Names and Codes |
| MeSH | Medical Subject Headings |
| NIS | Nationwide Inpatient Sample |
| NDC | National Drug Code |
| NPV | Negative Predictive Value |
| $PaO_2/FiO_2$ | Arterial Partial Pressure of Oxygen to Fraction of Inspired Oxygen |
| PAWP | Pulmonary Artery Wedge Pressure |
| PEEP | Positive end Expiratory Pressure |
| PICO | Population, Intervention, Comparator, Outcome |
| PPV | Positive Predictive Value |
| SME | Subject Matter Expert |
| TRALI | Transfusion-Related Acute Lung Injury |

# A Summary

The United States (U.S.) Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative conducted a structured literature review (through June 9, 2020) to identify validated coding algorithms for ascertaining cases of acute respiratory distress syndrome (ARDS) in large administrative healthcare databases. The studies selected for this targeted review used billing codes in claims or electronic health record (EHR) databases to derive ARDS coding algorithms. Three studies with varying performance measures (positive predictive value [PPV], negative predictive value [NPV], sensitivity, or specificity) were found.[1-3] A comprehensive algorithm was developed leveraging findings from all relevant papers identified in the literature review and further reviewed and refined by clinical subject matter experts (SMEs).

No validation studies for coding algorithms identified in administrative claims, nor studies using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes were found. However, we identified three U.S.-based studies that validated electronic coding algorithms derived from billing codes in electronic health records (EHR). First, a study used International Classification of Diseases, Ninth Revision, Clinical Modification (ICM-9-CM) codes from hospital discharge records to identify cases of ARDS in patients admitted into the intensive care unit (ICU), followed with medical chart review per American-European Consensus Conference (AECC) criteria.[1] This validation study reported a specificity of 99.6% and a sensitivity of 6.2% for the EHR-based coding algorithm.[1] Another study validated ARDS and acute lung injury (ALI) ICD-9-CM diagnosis and procedure codes in patients admitted to a study hospital.[3] The algorithm performance varied depending on the AECC criteria applied, with a sensitivity of 53–71%, specificity of 73–100%, and PPV of 90–100%; these findings highlight the importance of selecting an ARDS clinical case definition most relevant to the research question of interest.[3] The third study validated ARDS ICD-9-CM diagnosis codes from hospital discharge records in ICU patients aged 12 years or over in six general acute care hospitals in Utah.[2] The authors reported a sensitivity of 85%, specificity of 98%, PPV of 7%, and NPV of over 99.9%.[2]

The algorithm developed and proposed herein leveraged approaches reported across these three publications to build a comprehensive draft algorithm, which was then refined by clinical SMEs from IBM (TB, JB), FDA Center for Biologics Evaluation and Research (CBER) (JC, DT), and Acumen. The proposed algorithm uses both ICD-9-CM and ICD-10-CM codes, the latter of which were translated from ICD-9-CM codes via forward-backward mapping using the General Equivalence Mappings (GEMs) for reference.[i] Several options were included in the proposed algorithm so the specificity and sensitivity of the algorithm can be modified by adding or excluding code groups; this was done to support additional analytical flexibility in tailoring the algorithm specifications to the research question of interest or user priorities (i.e., with respect to sensitivity and specificity).

As an initial step in assessing the feasibility of using the algorithm to identify cases of ARDS, the algorithm was applied in the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), a collection of commercially insured individuals in the U.S. Statistics describing the frequency and proportions of ARDS codes included in the algorithm were generated, with results reported below.

[i] Additional information about GEMs and the methodology for forward and backward mapping can be found at Centers for Medicaid and Medicare Services. (2017). 2018 ICD-10-CM and GEMs. Available at https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs. Researchers used the following website to map ICD-9-CM codes to ICD-10-CM: https://www.icd10data.com.

## B Background

Among other responsibilities, the U.S. FDA is mandated to protect the public health by ensuring the safety and efficacy of drugs, biologics, and medical devices.[ii] In support of this mandate, the FDA Center for Biologics Evaluation and Research (CBER) has a mission to conduct policy and regulatory reviews of biologics and related products, including blood products, vaccines, allergenics, tissues, and cellular and gene therapies. CBER assesses the risks and benefits of new biologic products, as well as previously approved products that have been proposed for new indications. The CBER process emphasizes the pursuit of the maximum public benefit while minimizing risks to the public for each biologic product. The BEST Initiative is a program initiated by CBER whose objective is to assess the safety and effectiveness of biologic products using large datasets of administrative healthcare data.

Acute respiratory distress syndrome (ARDS) is a serious condition caused by direct or indirect insult to the lung which leads to an acute and intense inflammatory response that can result in low blood oxygen levels, abnormal lung physiology, and death.[3,4] Symptoms include dyspnea, rapid and shallow respiration, dry cough, confusion, restlessness, and crackling, rattling or wheezing lung sounds.[5] Recent studies suggest that the incidence of ARDS in the U.S. ranges from 15.3–58.7 cases per 100,000 person-years.[6] Another study estimated the total number of annual cases to be 190,600, which were associated with 74,500 deaths and 2.2 million intensive care unit (ICU) days in the U.S.[7,8] ARDS is also a source of significant healthcare expenditure in the U.S., associated with an estimated $5 billion in healthcare costs yearly.[5,9]

Important risk factors for ARDS include sepsis, pneumonia, inhalation injury, drug overdose, and transfusions.[10] Additionally, ARDS has been identified as a potential complication associated with coronavirus disease 2019 (COVID-19), and may represent an outcome of interest for future studies of COVID-19 epidemiology and vaccine safety and effectiveness assessment.[11] It may also be of interest to identify ARDS in relation to other products under the CBER mandate.

The objective of this review was to assess and understand the validity of electronic coding algorithms using billing codes for identifying ARDS from administrative claims and electronic health records (EHR). These coding algorithms can draw from a variety of classification systems, including International Classification of Diseases (ICD), Healthcare Common Procedure Coding System (HCPCS), Current Procedural Terminology (CPT), National Drug Code (NDC), and Logical Observation Identifiers Names and Codes (LOINC).

A structured literature review of coding algorithms for identifying potential cases of ARDS was conducted, leveraging findings from U.S. and international studies to inform the development of an algorithm. The focus of the review was on algorithms derived from administrative claims data (i.e., claims-based), while algorithms derived from EHRs that used standardized billing codes (i.e., EHR-based) were also considered. The draft algorithm was then reviewed by clinical SMEs and tested in the MarketScan® Research Databases (Commercial and Medicare Supplemental), a large collection of administrative claims data accessed via the Treatment Pathways online analytic platform. **Section C** summarizes the literature review methodology and findings. **Section D** provides clinical case definitions for ARDS, which could be of value in further assessing the performance of the proposed algorithm via chart review validation studies; **Sections E** and **F** present the algorithm and its associated assumptions and decisions, respectively; **Section G** presents the approach for and results of an initial application of the algorithms to characterize the population with ARDS in a claims database; and **Section H** provides discussion and concluding thoughts.

[ii] U.S. Food and Drug Administration. What We Do. March 28, 2018. https://www.fda.gov/aboutfda/whatwedo/

# C Literature Review

## C1 Methods

A literature review search strategy was developed for the BEST Initiative, based on the Population, Intervention, Comparator, Outcome (PICO) framework. The PICO framework used can be summarized as follows:

- **Population:** *any population group (human)*
- **Intervention:** *any intervention or no intervention*
- **Comparator:** *any comparator, placebo*
- **Outcome:** *Acute Respiratory Distress Syndrome*

The setting for eligible studies was any clinically observable environment that led an individual to seek care.

The literature review process started with a comprehensive search of existing publications available in the CBER[iii] and Center for Drug Evaluation and Research Sentinel[iv] databases. A review of the academic literature was then conducted using a structured search method. Only publications available in English were included for review. PubMed and Google Scholar were used to identify relevant resources through to June 2020 (date of search). The search strategy, which is not case-sensitive, is summarized below:

- ***Search 1 (PubMed):*** "acute respiratory distress syndrome" AND ICD – **retrieved 17 articles**
- ***Search 2 (Google Scholar):*** "acute respiratory distress syndrome" AND validate AND ICD – **retrieved 2750 results**

Targeted and *ad hoc* searches of the gray literature were conducted, including clinical guidelines and reports from organizations such as the United States Armed Forces Health Surveillance Branch (AFHSB) and the Agency for Healthcare Research and Quality (AHRQ). A snowballing technique was also applied, wherein the bibliographies of relevant studies were scanned for additional publications. Abstract review was subsequently conducted for these publications. The literature search was conducted between June 4, 2020, and June 9, 2020.

Publications that met the above search criteria were screened. Articles that did not report a claims- or EHR-based definition for ARDS were excluded. All abstracts were reviewed, and 15 articles were reviewed in full text. Of these, five were retained for extraction and informed algorithm design. A Microsoft® Excel spreadsheet was developed to extract relevant data. The data elements collected are provided in **Table 1**.

A relevance ranking was assigned based on the judgement of the reviewer and the available information on study location (“Country”), the algorithm specifications (“Algorithm”), and the measures of validity and diagnostic accuracy (e.g., sensitivity and specificity). Relevance rankings were assigned based on the following criteria:

- ***Ranking 1:*** U.S. claims- or EHR-based validation study (i.e., reporting measures of validity and diagnostic accuracy)
- ***Ranking 2:*** U.S. study that reported a claims- or EHR-based coding algorithm but no independent validation OR a non-U.S. validation study
- ***Ranking 3:*** Non-U.S. study that reported a claims- or EHR-based coding algorithm but no independent validation

[iii] U.S. Food and Drug Administration. Innovation and Regulatory Science. July 10, 2020. https://www.fda.gov/vaccines-blood-biologics/science-research-biologics/innovation-and-regulatory-science
[iv] Sentinel. Publications and Presentations. https://www.sentinelinitiative.org/communications/publications

***Table 1. Data elements recorded in the extraction spreadsheet.***

| Data Element |
|---|
| Author |
| Publication Year |
| Article Relevance (Ranking 1-3) |
| Full Citation |
| Country of Study |
| Data Source |
| Years Included |
| Population Eligibility Criteria |
| Validation Method |
| Disease Definition |
| Algorithm Incidence Rules |
| ICD-9/ICD-9-CM Codes |
| ICD-10/ICD-10-CM Codes |
| Other Codes |
| PPV % (95% Confidence Interval [CI]) |
| NPV % (95% CI) |
| Other Performance Measures |
| Comments |

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; PPV, Positive predictive value; NPV, Negative predictive value; 95% CI, 95% confidence interval

## *C2 Results*

Following title and abstract screening, full-text review, and data extraction; a total of five U.S. publications were identified as being of particular relevance for identifying ARDS using EHRs (additional information in **Appendix A**).[1-4,12] One study was identified from the CBER research database. No studies reported the use of ICD-10 codes. Of the five studies, three were subject to validation and included varying measures of performance such as positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity.[1-3] We summarized literature below with respect to the data source from which each coding algorithm was derived (i.e., claims or EHRs), validation with medical charts (i.e., yes or no), and the location of the study (i.e., U.S. or international).

### 2.a Claims-based Algorithms with Validation

No claims-based algorithms that reported measures of diagnostic accuracy were found.

### 2.b Medical Records-based Algorithms with Validation

Howard and colleagues sought to validate ARDS diagnosis codes in patients admitted to the ICU.[1] Every patient admitted to the ICU during the study period was evaluated daily to determine whether they met the American-European Consensus Conference (AECC) criteria for ARDS within a 24-hour period. Patient charts and discharge summaries were reviewed for any mention of ARDS. Patients who met the AECC criteria had cardiogenic pulmonary edema excluded using pulmonary artery catheter or echocardiogram. Using ICD-9-CM codes 518.82 (other pulmonary insufficiency, not elsewhere classified) and 518.85 (pulmonary insufficiency following trauma and surgery) from discharge records, the authors reported that their algorithm had a specificity of 99.6% and a sensitivity of 6.2% (no 95% confidence interval [CI] reported). The authors hypothesized that the low sensitivity could be due to misinterpretation of patient charts leading to coding error or medical coding specialists not coding for ARDS due to lack of mention of the term in physician notes.

Rincon and colleagues sought to validate ARDS and acute lung injury (ALI) identified by ICD-9-CM codes in the Nationwide Inpatient Sample (NIS).[3] They included all patients admitted to one hospital with ARDS and/or ALI codes in their discharge records. ICD-9-CM codes included 518.5 (pulmonary insufficiency following trauma and surgery) and 518.82 (other pulmonary insufficiency, not elsewhere classified), as well as ICD-9 procedural codes 96.70 (continuous invasive mechanical ventilation of unspecified duration), 96.71 (continuous invasive mechanical ventilation for less than 96 consecutive hours), and 96.72 (continuous invasive mechanical ventilation for 96 consecutive hours or more). ARDS and ALI were determined to be present if AECC criteria were met.[3] Using the AECC criteria of arterial partial pressure of oxygen to fraction of inspired oxygen ($PaO_2/FiO_2$) and chest x-rays as the reference method, the authors reported a sensitivity of 71%, specificity of 100%, and PPV of 100% (no NPV or 95% CI reported) for the coding algorithm.[3,10] Algorithm performance was reduced when adding an additional AECC criterion of having normal echocardiography, with a sensitivity of 53%, specificity of 73%, and PPV of 90% (no NPV or 95% CI reported). This change in performance highlights the importance of applying the most suitable ARDS case definition for each research question of interest. The authors noted that algorithm performance was better than what has been reported in previous studies. They speculated that the better performance may have been due to the single-center bias in case ascertainment and differing prevalence of ARDS and ALI across studies. However, the better performance may also be due to the addition of codes related to mechanical ventilation. It is important to note that the study algorithm was applied to both ARDS and ALI, and the performance of the algorithm is likely to differ from one considering ARDS alone.

Thomsen and Morris sought to validate ICD-9-CM diagnosis codes from discharge records for ARDS in six acute care hospitals in Utah.[2] The presence of ARDS ICD-9-CM codes 518.5 (pulmonary insufficiency following trauma and surgery), 518.81 (acute respiratory failure), and 518.82 (other pulmonary insufficiency, not elsewhere classified) diagnoses were identified from ICU discharge records among patients aged 12 years or older. The ICU records were reviewed per the AECC criteria for severe ARDS to validate those diagnosis codes. The authors had previously applied their algorithm to a single hospital, reporting a sensitivity of 88%, specificity of 99%, PPV of 11% and NPV of over 99.9% (no 95% CI reported).[2,13] In the current study, five additional hospitals were added along with the hospital from the prior study. The authors tested the performance of the algorithm both including and excluding the hospital from the prior study. Including only the five new sites resulted in a slightly poorer performance (sensitivity of 79%, specificity of 98%, PPV of 4%, and NPV of over 99.9%, no 95% CI reported), compared with the single site-based study. Combining six sites resulted in a similar performance with a sensitivity of 85%, specificity of 98%, PPV of 7%, and NPV of over 99.9% (no 95% CI reported). The authors highlight the importance of consistent coding between facilities and note that the low PPV may be due to the ARDS being an infrequent condition.

## 2.c Algorithm Application Without Validation

Two additional U.S.-based studies — both derived coding algorithms from billing codes of EHRs — were identified and considered in efforts to develop a comprehensive list of codes for ARDS.[4,12]

Reynolds and colleagues used data from the Maryland Health Services Cost Review Commission to estimate the incidence and mortality rates for ARDS.[12] Their study population of interest were patients over the age of 12 years who were discharged with ICD-9-CM codes 518.5x (pulmonary insufficiency following trauma and surgery) or 518.82 (other pulmonary insufficiency, not elsewhere classified) and had at least one procedure code for ventilatory support, which included ICD-9-CM procedure codes 96.70 (continuous invasive mechanical ventilation of unspecified duration), 96.71 (continuous invasive mechanical ventilation for less than 96 consecutive hours), and 96.72 (continuous invasive mechanical ventilation for 96 consecutive hours or more). Furthermore, ventilatory support was required for four days or more unless the patient died within that time period or required ventilatory support for an unspecified duration. This approach was based on a previous study examining the incidence of ARDS in Utah, summarized above.[2]

Eworuke and colleagues used an EHR-based algorithm to estimate the national incidence rates and risk factors for ARDS among the NIS database.[4] The authors used ICD-9-CM diagnosis codes 518.5x (pulmonary insufficiency following trauma and surgery), 518.82 (other pulmonary insufficiency, not elsewhere classified), and 518.81 (acute respiratory failure) in the first or second diagnosis position, in addition to ICD-9-CM procedure codes 96.70 (continuous invasive mechanical ventilation of unspecified duration), 96.71 (continuous invasive mechanical ventilation for less than 96 consecutive hours), and 96.72 (continuous invasive mechanical ventilation for 96 consecutive hours or more) to identify ARDS related hospital discharges. Additionally, to align with the Berlin criteria for ARDS, patients had to have at least one risk factor for ARDS. Patients at risk for left atrial hypertension and those without an ARDS risk factor were excluded. Risk factors included pneumonia, sepsis, trauma, pancreatitis, shock, transfusion, aspiration of gastric contents, pulmonary contusion, and drowning; these were identified using a separate list of ICD-9-CM codes.

## D ARDS Clinical Case Definition

Two robust case definitions were noted in the literature review. Definitions created by the AECC and the ARDS Definition Task Force demonstrated notable similarities but differed in their complexity.[10,14] The optimal case definition may depend on the priorities of a particular research or validation study and data available. Should a validation study of the proposed ARDS algorithm be executed, these definitions could be used to inform chart review and adjudication.

The AECC ARDS definition was the most commonly identified in the literature. First introduced in 1994, the definition classifies ARDS as the most severe end of the ALI spectrum.[14] For example, all ARDS patients have ALI but patients with ALI may not have ARDS.[14] As such, the definition for ARDS builds upon the definition for ALI and includes the following criteria, differing only in the relevant $PaO_2/FiO_2$ thresholds:[14]

Criteria for ALI:[14]

1) Acute onset
2) $PaO_2/FiO_2 \leq 300$ mmHg regardless of positive end expiratory pressure (PEEP) level [10]
3) Frontal chest radiograph shows bilateral infiltrates
4) Pulmonary artery wedge pressure (PAWP) ≤ 18 mmHg OR no evidence of left atrial hypertension

Criteria for ARDS:[14]

1) Acute onset
2) $PaO_2/FiO_2 \leq 200$ mmHg regardless of PEEP level[10]
3) Frontal chest radiograph shows bilateral infiltrates
4) PAWP ≤ 18 mmHg OR no evidence of left atrial hypertension

The Berlin definition was created by the ARDS Definition Task Force in 2012 to address the reliability, validity, and limitation issues of the AECC definition.[10] The Berlin definition includes an acute time frame, three severity subgroups, risk factors, clarified radiograph criteria, and minimal PEEP requirements as well as the removal of ALI terminology and PAWP requirements.[10] The resulting definition is:[10]

1) Onset within one week of known clinical insult or new/worsening respiratory symptoms
2) Chest radiograph or computed tomography scan showing bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
3) Edema/respiratory failure not fully explained by cardiac failure or fluid overload. If the patient does not have a risk factor, hydrostatic edema must be excluded using objective assessment. Direct risk factors include pneumonia, aspiration of gastric contents, inhalation injury, pulmonary

contusion, pulmonary vasculitis, and drowning. Indirect risk factors include non-pulmonary sepsis, major trauma, pancreatitis, severe burns, non-cardiogenic shock, drug overdose, multiple transfusions, or transfusion-associated ALI.

4) Three severity levels determined using oxygenation as determined by $PaO_2/FiO_2$, PEEP, and continuous positive airway pressure (CPAP).
    a) Mild ARDS: "200 mmHg < $PaO_2/FIO_2 \leq$ 300 mmHg with PEEP or CPAP ≥5 cm $H_2O$"[10]
    b) Moderate ARDS: "100 mmHg < $PaO_2/FIO_2 \leq$ 200 mmHg with PEEP ≥5 cm $H_2O$"[10]
    c) Severe ARDS: "$PaO_2/FIO_2 \leq$ 100 mmHg with PEEP ≥5 cm $H_2O$"[10]

## E ARDS Coding Algorithm

The aim of this review was to develop an algorithm to identify cases of ARDS that could be of potential interest following exposure to a biologic product. To form a comprehensive list of ARDS codes for clinical consideration, all codes used to identify ARDS were extracted from the articles identified in the literature review (**Appendix A**). To expand the draft code list and reflect current coding practice, ICD-10-CM diagnosis codes were generated from ICD-9-CM codes using forward-backward mapping via the Centers for Medicare and Medicaid Services (CMS) GEMs files.[v] The expanded draft code list, which included ICD-9-CM and ICD-10-CM codes, was subsequently reviewed by clinical SMEs from IBM (TB, JB), FDA CBER (JC, DT), and Acumen.

The final algorithm is presented in **Table 2**. As informed by previously published studies, the workgroup has developed an algorithm that includes diagnosis codes for ARDS, along with an option to include relevant procedural codes. This algorithm may be subject to refinements for future specific research questions. For example, recognizing that users may have different priorities regarding algorithm specificity and sensitivity, four different algorithm iterations have been offered, ranging from most specific (Option 1) to most sensitive (Option 4). Annual counts of patients with specific diagnosis codes are provided in **Appendix B**.

Specific decisions and assumptions related to construction of the algorithm are summarized in **Section F**. Overall, the clinical SMEs recommended the inclusion of additional codes or exclusion of codes from the expanded draft code list based on clinical relevance and optimizing the balance between specificity and sensitivity. A list of excluded codes is provided in **Appendix C**. These codes were ultimately determined by the clinical SMEs to be too general and could potentially increase the risk of misclassification. As such, while they were not applied as exclusion criteria, the codes in **Appendix C** were left out of the algorithm options to identify cases of ARDS.

We proposed four coding algorithms in the order of descending specificity and increasing sensitivity, and summarized them as follows:

**INCLUDE: ANY** ("either–or" logic) of the codes listed below, regardless of health care setting or coding position (only one code required).

**Option 1**: ≥1 diagnosis code for ARDS in Category 1 AND ≥1 procedure code in Category 0.5 within the same encounter
**Option 2**: ≥1 diagnosis code for ARDS in Category 1
**Option 3**: ≥1 diagnosis code for ARDS in Categories 1 or 1.5
**Option 4**: ≥1 diagnosis code for ARDS in Categories 1, 1.5 or 2

[v] Additional information about GEMs and the methodology for forward and backward mapping can be found at Centers for Medicaid and Medicare Services. (2017). 2018 ICD-10-CM and GEMs. Available at https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs. Researchers used the following website to map ICD-9-CM codes to ICD-10-CM: https://www.icd10data.com.

***Table 2. ARDS algorithm.***

| Code | Description | Code Cat | Code Type | Category |
|---|---|---|---|---|
| 518.82 | Other pulmonary insufficiency, not elsewhere classified | DX | 9 | 1 |
| J80 | Acute respiratory distress syndrome | DX | 10 | 1 |
| 518.51 | Acute respiratory failure following trauma and surgery | DX | 9 | 1.5 |
| 518.52 | Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery | DX | 9 | 1.5 |
| 518.7 | Transfusion related acute lung injury (TRALI) | DX | 9 | 1.5 |
| 518.81 | Acute respiratory failure | DX | 9 | 1.5 |
| J95.1 | Acute pulmonary insufficiency following thoracic surgery | DX | 10 | 1.5 |
| J95.2 | Acute pulmonary insufficiency following nonthoracic surgery | DX | 10 | 1.5 |
| J95.821 | Acute postprocedural respiratory failure | DX | 10 | 1.5 |
| J95.84 | Transfusion-related acute lung injury (TRALI) | DX | 10 | 1.5 |
| J96.00 | Acute respiratory failure, unspecified whether with hypoxia or hypercapnia | DX | 10 | 1.5 |
| J96.01 | Acute respiratory failure, with hypoxia | DX | 10 | 1.5 |
| J96.02 | Acute respiratory failure, with hypercapnia | DX | 10 | 1.5 |
| J96.90 | Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia | DX | 10 | 1.5 |
| J96.91 | Respiratory failure, unspecified, with hypoxia | DX | 10 | 1.5 |
| J96.92 | Respiratory failure, unspecified, with hypercapnia | DX | 10 | 1.5 |
| R06.03 | Acute respiratory distress | DX | 10 | 1.5 |
| J95.822 | Acute and chronic postprocedural respiratory failure | DX | 10 | 2 |
| 518.84 | Acute and chronic respiratory failure | DX | 9 | 2 |
| 518.53 | Acute and chronic respiratory failure following trauma and surgery | DX | 9 | 2 |
| J96.20 | Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia | DX | 10 | 2 |
| J96.21 | Acute and chronic respiratory failure, with hypoxia | DX | 10 | 2 |
| J96.22 | Acute and chronic respiratory failure, with hypercapnia | DX | 10 | 2 |
| 96.70 | Continuous mechanical ventilation of unspecified duration | PCS | 9 | 0.5 |
| 96.71 | Continuous mechanical ventilation for < 96 h consecutively | PCS | 9 | 0.5 |
| 96.72 | Continuous mechanical ventilation for ≥96 h consecutively | PCS | 9 | 0.5 |
| 5A1522F | Extracorporeal Oxygenation, Membrane, Central | PCS | 10 | 0.5 |
| 5A1522G | Extracorporeal Oxygenation, Membrane, Peripheral Veno-arterial | PCS | 10 | 0.5 |
| 5A1522H | Extracorporeal Oxygenation, Membrane, Peripheral Veno-venous | PCS | 10 | 0.5 |
| 5A1935Z | Respiratory Ventilation, Less than 24 Consecutive Hours | PCS | 10 | 0.5 |
| 5A1945Z | Respiratory Ventilation, 24-96 Consecutive Hours | PCS | 10 | 0.5 |
| 5A1955Z | Respiratory Ventilation, Greater than 96 Consecutive Hours | PCS | 10 | 0.5 |
| 94002 | Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing, hospital inpatient/observation, initial day | CPT | 4 | 0.5 |
| 94003 | Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing, hospital inpatient/observation, each subsequent day | CPT | 4 | 0.5 |
| 94004 | Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing, nursing facility, each day | CPT | 4 | 0.5 |
| 94660 | Continuous positive airway pressure ventilation (CPAP), initiation and management | CPT | 4 | 0.5 |
| 33946 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-venous | CPT | 4 | 0.5 |
| 33947 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; initiation, veno-arterial | CPT | 4 | 0.5 |
| 33948 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; daily management, each day, veno-venous | CPT | 4 | 0.5 |

| Code | Description | Code Cat | Code Type | Category |
|---|---|---|---|---|
| 33949 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; daily management, each day, veno-arterial | CPT | 4 | 0.5 |
| 33951 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), percutaneous, birth through 5 years of age (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |
| 33952 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |
| 33953 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), open, birth through 5 years of age | CPT | 4 | 0.5 |
| 33954 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of peripheral (arterial and/or venous) cannula(e), open, 6 years and older | CPT | 4 | 0.5 |
| 33955 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of central cannula(e) by sternotomy or thoracotomy, birth through 5 years of age | CPT | 4 | 0.5 |
| 33956 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; insertion of central cannula(e) by sternotomy or thoracotomy, 6 years and older | CPT | 4 | 0.5 |
| 33957 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition peripheral (arterial and/or venous) cannula(e), percutaneous, birth through 5 years of age (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |
| 33958 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition peripheral (arterial and/or venous) cannula(e), percutaneous, 6 years and older (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |
| 33959 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition peripheral (arterial and/or venous) cannula(e), open, birth through 5 years of age (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |
| 33962 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition peripheral (arterial and/or venous) cannula(e), open, 6 years and older (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |
| 33963 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition of central cannula(e) by sternotomy or thoracotomy, birth through 5 years of age (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |
| 33964 | Extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS) provided by physician; reposition central cannula(e) by sternotomy or thoracotomy, 6 years and older (includes fluoroscopic guidance, when performed) | CPT | 4 | 0.5 |

Abbreviations: CPT, Current Procedural Terminology; DX, ICD-CM Diagnosis; PCS, ICD procedure coding system.

## F Assumptions and Decisions

The algorithm presented above was reviewed internally and with CBER stakeholders and partners. Decisions and assumptions relevant to the algorithm are listed below. Some of the decisions may be modified depending on the study research question.

- There is no ARDS-specific ICD-9-CM code. As such, users may consider applying a procedure code requirement for ICD-9-CM queries but not ICD-10-CM queries to add specificity. However, differences in application of the algorithm between ICD-9-CM and ICD-10-CM time periods could introduce other sources of misclassification and limit comparability across time periods.
- Category 1.5 lists codes that are related to ARDS (i.e., on the ALI continuum), while Category 2 lists codes not specified as acute or chronic. Application of these categories will depend on the priorities of the user and the specific research question.
- Procedure codes (Category 0.5) have been provided for users wishing to specify the algorithm further. The inclusion of procedure codes for intubation was discussed, but these codes were ultimately excluded out of concern that they may not be as reliably reported in facility claims data and the assumption that patients being intubated would already be captured by the ventilation codes included in Category 0.5. Both ICD procedural codes and CPT ventilation codes have been included, based on the clinical judgement that different databases would be likely to preferentially use one of these two standards and to give users the flexibility to adapt the algorithm to the relevant database.
- For users looking to specify the algorithm further (regardless of the Inclusion Category being used), codes for chronic respiratory distress/failure may be used as an exclusion criterion (e.g., exclude all individuals with a chronic code in the previous six months).
- ARDS can be viewed as a more severe form of TRALI, and the two may not be clinically distinguishable except by history or etiology, so TRALI has been added to the more inclusive category 1.5.
- The inclusion of acute pulmonary edema in Category 1.5 was discussed. However, it was believed that acute pulmonary edema could be due to many causes and may not be associated with increased capillary permeability due to ARDS. Further, coding for ARDS is typically done in an inpatient setting and is quite reliable, whereas coding for acute pulmonary edema happens in a variety of care settings and can be more variable. Lastly, cases of acute pulmonary edema that have/manifest ARDS may also receive an ARDS code included in the algorithm. Given these considerations, the code has been excluded from algorithm Options 1–4 but has been tested in the MarketScan Research Databases to establish frequency of use relative to ARDS codes. (**Appendix C)**
- Risk windows used to determine the association of ARDS with a particular exposure should be determined based on the particular research question and exposure of interest.

## G Algorithm Characterization

### *G1 Methods*

To characterize ARDS among a commercially insured population in the U.S., the workgroup used the IBM MarketScan Research Databases (Commercial and Medicare Supplemental), accessed via the Treatment Pathways[vi] online analytic platform, to query and analyze the codes included in the ARDS algorithm (**Table 2**). The analyses below reflect a broader, more sensitive application of the algorithm, and characterize Algorithm Option 3 (i.e., ≥1 diagnosis code for ARDS in categories 1 or 1.5). For Option 3, Category 0.5 was left out due to concern that this could improperly exclude true cases of ARDS, while Category 2 was excluded as these codes include both acute and chronic cases. In order to gather the broadest range of ARDS cases to support a descriptive analysis, the analyses presented herein did not require exposure to a biologic product and did not restrict based on diagnosis coding position. It is

[vi] IBM MarketScan Research. Insight for Better Healthcare. https://marketscan.truvenhealth.com/marketscanportal/Portal.aspx

recommended that the proposed algorithm(s) undergo a validation study prior to use and future analytical studies should tailor the algorithm specifications according to the study priorities and the research question of interest.

The figures presented below have been drawn from the study period of January 1, 2014–December 31, 2018. For all analyses, ICD-9-CM codes were queried for January 1, 2014–September 30, 2015, and ICD-10-CM codes were queried for October 1, 2015–December 31, 2018. This was done out of recognition of the transition to ICD-10-CM on October 1, 2015, and to exclude codes reported in error.

Counts of individual patients who had at least one diagnosis code related to ARDS, rather than counts of ARDS codes, were presented. As such, counts relate to the first diagnosed ARDS event for an individual during a given surveillance period (e.g., January 1–December 31, 2014), and individuals could only be counted once per surveillance period. Since we did not estimate the incidence of ARDS in the study population no washout period was applied.

Individuals had to be continuously enrolled to be included in the analysis for a particular year. For example, patients had to be continuously enrolled from January 1 to December 31, 2014, to be included in the “2014” dataset. Age is calculated in Treatment Pathways as if each individual was born on July 1 of their given year of birth. Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under one year old), this population group has been left out of the two charts that depict the proportions of individuals with ARDS by age. Infants under one year of age were not excluded from queries of the absolute number of patients receiving an ARDS diagnosis.

Age- and gender-specific data on the MarketScan Research Databases enrollment and counts of individuals receiving a diagnostic code for ARDS were extracted. Code-specific queries are described in **Section E** and summarized in **Appendix B**. In addition to the code-specific queries, the authors executed queries that aggregated all ICD-9-CM codes, all ICD-10-CM codes, and all codes (ICD-9-CM and ICD-10-CM) for ARDS.

## *G2 Results*

Of the codes included in the ARDS algorithm, codes for acute respiratory failure (ICD-9-CM 518.81[other pulmonary insufficiency, not elsewhere classified]; ICD-10-CM J96.00 [acute respiratory failure, unspecified whether with hypoxia or hypercapnia], J96.01 [acute respiratory failure, with hypoxia]) were the most frequently used (**Appendix B**). Of those receiving at least one ARDS diagnosis between 2014 and 2018 (n=452,732), 32.1% (n=145,118), 24.6% (n=111,587), and 38.0% (n=172,007) had at least one 518.81, J96.00, and J96.01 code, respectively.

**Table 3** provides a summary of aggregate counts for ICD-9-CM and ICD-10-CM codes, suggesting that approximately 3.5–3.8 individuals per 1,000 individuals included in the MarketScan Research Databases received a code associated with ARDS each year. Among the cohort of 46,153,898 patients that were continuously enrolled for at least one calendar year between January 1, 2014, and December 31, 2018, 452,732 individuals (0.98% of the cohort) had at least one ICD-9-CM or ICD-10-CM diagnosis code for ARDS.

***Table 3. Counts of patients with ARDS by code set and year.***

| Code/ Description | Year | | | | |
|---|---|---|---|---|---|
| | 2014 | 2015[a] | 2016 | 2017 | 2018 |
| ICD-9-CM | 102,292 | 62,139 | | | |
| ICD-10-CM | | 29,489 | 82,705 | 70,159 | 67,471 |
| ICD-9-CM OR ICD-10-CM | 102,292 | 84,968 | 82,705 | 70,159 | 67,471 |
| MarketScan Research Databases Enrollment[b] | 28,407,959 | 22,117,235 | 21,616,291 | 19,563,847 | 19,371,891 |
| Proportion of Patients with ARDS per 1,000 Enrolled Population[c] | 3.6 | 3.8 | 3.8 | 3.6 | 3.5 |

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

[a] In 2015, queries combining ICD-9-CM and ICD-10-CM codes returned lower patient counts than when codes were queried individually. This is because of cases in which both ICD-9-CM and ICD-10-CM codes were reported for the same individual, in the January–September and October–December timeframe, respectively.

[b] Individuals included in this row are those who were enrolled for the full calendar year (January 1–December 31) for 2014, 2015, 2016, 2017, and 2018, respectively.

[c] Proportions were calculated using the counts in the “ICD-9-CM OR ICD-10-CM” row.

The workgroup assessed whether the 2015 transition to ICD-10-CM and any associated changes in coding practices resulted in notable shifts in the frequency of ARDS. **Figure 1** illustrates the proportion of the enrolled population with an ARDS diagnosis and suggests that the transition did not result in a substantial change to the proportion of individuals receiving an ARDS diagnosis.

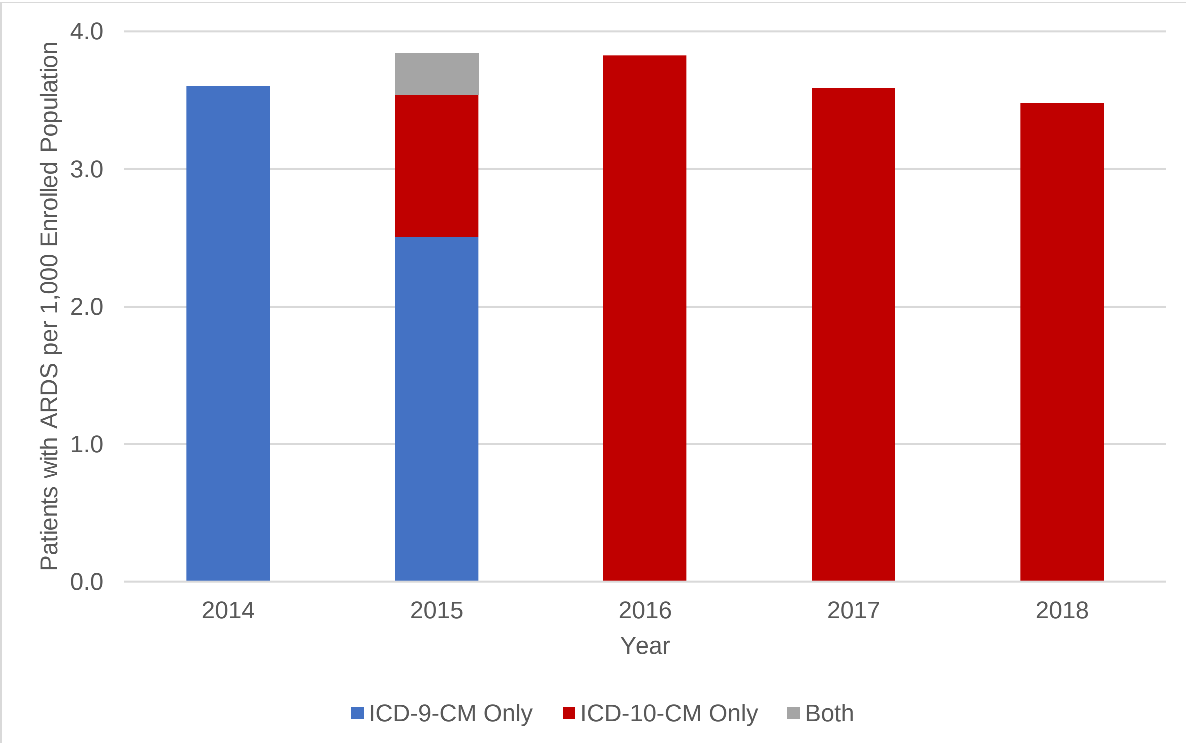


***Figure 1. Proportion of patients with ARDS code per 1,000 enrolled, by year (2014–2018).***

Note: In 2015, a patient could receive both an ICD-9-CM and an ICD-10-CM diagnosis, in the January–September and October–December timeframe, respectively.

**Figure 2** presents counts of patients with a relevant ICD-9-CM ARDS code (as listed in **Table 2**), stratified by age group. Counts were calculated for the timeframe of January 1, 2014, to September 30, 2015, among the cohort of 33,216,843 patients who were continuously enrolled for at least one calendar year between January 1, 2014, and December 31, 2015. There were 181,101 (0.6%) individuals with at least one ICD-9-CM code for ARDS between January 1, 2014, and September 30, 2015, with an average age (calculated at the first event) of 59 years.

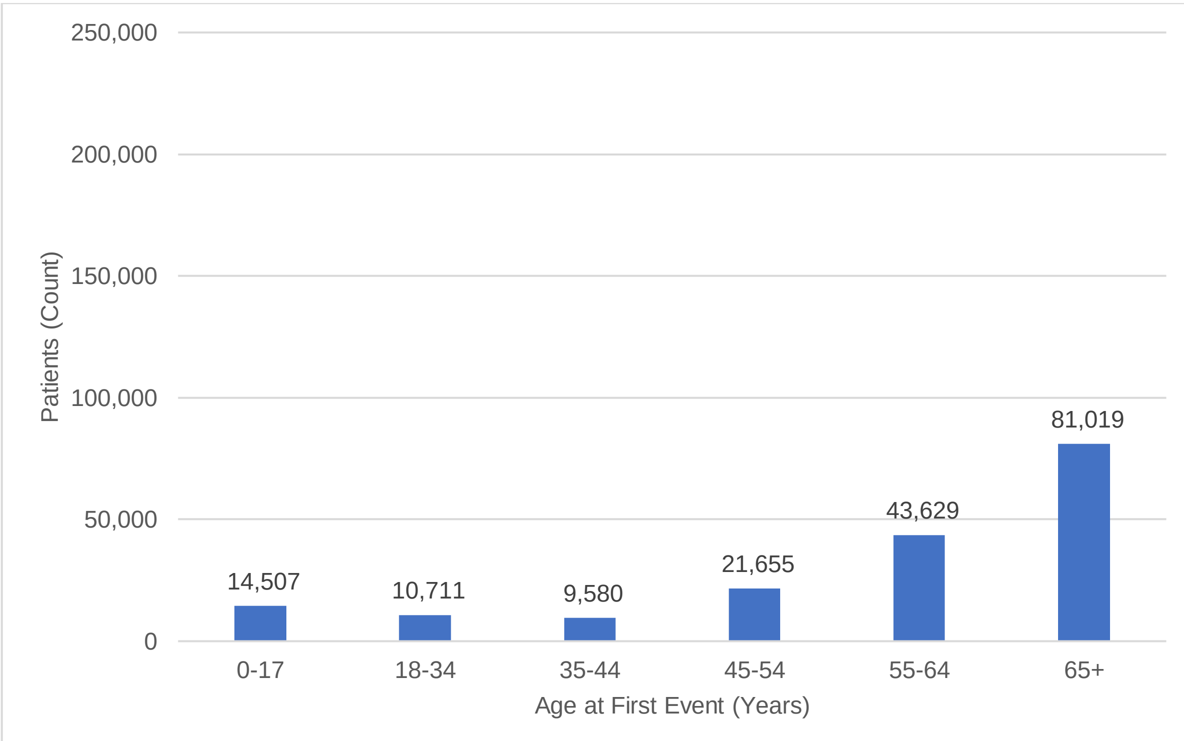


***Figure 2. Patients with at least one diagnosis code for ARDS defined by ICD-9-CM codes, January 1, 2014–September 30, 2015, stratified by age.***

**Figure 3** presents counts of patients with an ICD-10-CM ARDS code (as listed in **Table 2**), stratified by age group. Counts were calculated using a cohort of 35,337,738 patients who were continuously enrolled for at least one calendar year between 2015 and 2018 (i.e., January 1–December 31 for at least one of 2015, 2016, 2017, or 2018), while the ICD-10-CM diagnoses were queried for the ICD-10-CM time period (October 1, 2015–December 31, 2018). Among 291,831 individuals (0.8%) with at least one ICD-10-CM code for ARDS between October 1, 2015, and December 31, 2018, the average age at first event was 58 years.

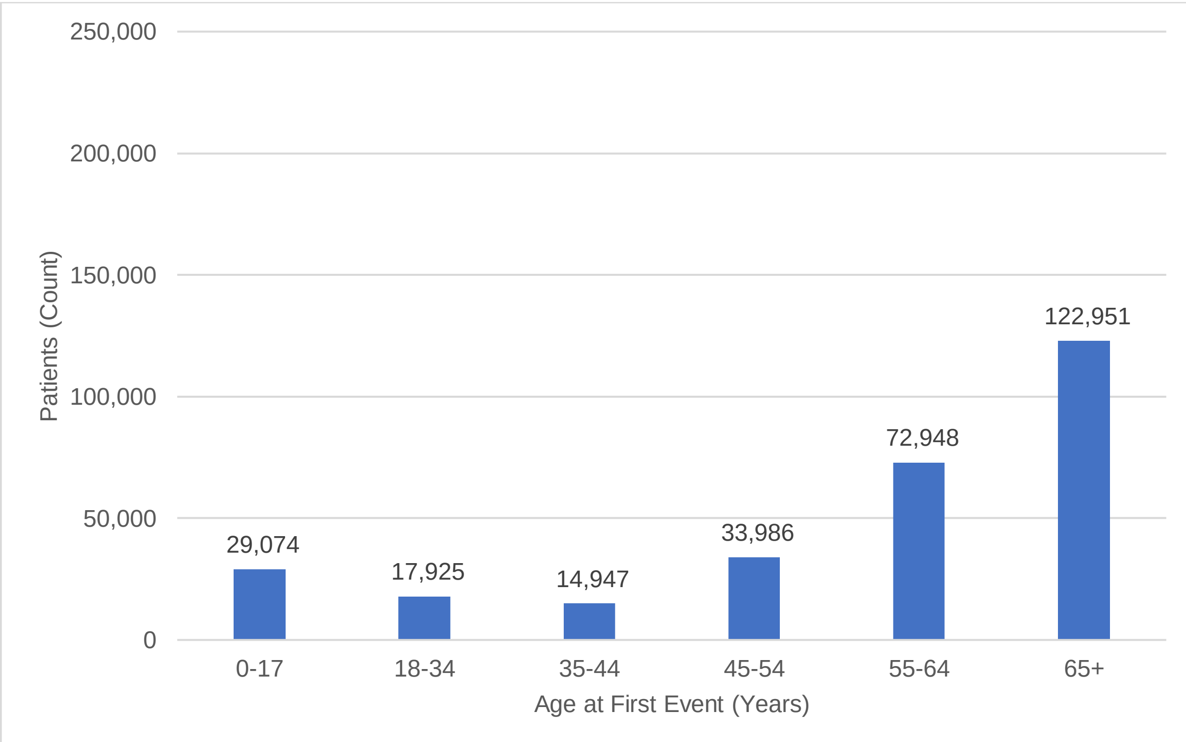


***Figure 3. Patients with at least one diagnosis code for ARDS defined by ICD-10-CM codes, October 1, 2015–December 31, 2018, stratified by age.***

**Figure 4** presents counts of patients with either an ICD-9-CM or ICD-10-CM code for ARDS among a cohort of 46,153,898 individuals who were continuously enrolled for at least one calendar year between 2014 and 2018. Among 452,732 individuals (1.0%) who received a diagnosis code for ARDS between January 1, 2014, and December 31, 2018, the average age at the first event was 58 years. Absolute patient counts were highest in the age group of 65+ years.

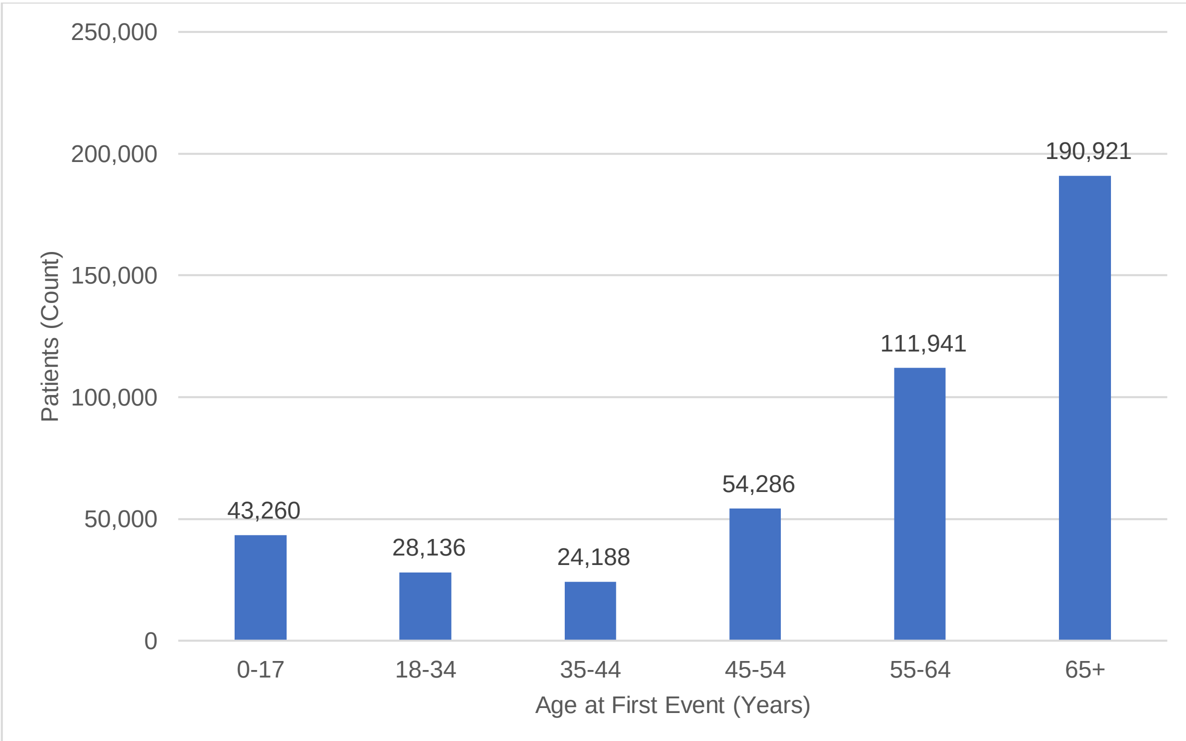


***Figure 4. Patients with at least one diagnosis code for ARDS (ICD-9-CM or ICD-10-CM), January 1, 2014–December 31, 2018, stratified by age.***

**Figure 5** presents the proportion of the population (aged 1-85+ years) with at least one ICD-9-CM or ICD-10-CM code for ARDS (per 1,000 population with continuous enrollment in the MarketScan Research Databases) between January 1, 2014, and December 31, 2018, by age and gender. Individuals were required to be enrolled for at least one calendar year between 2014 and 2018 but were not required to be enrolled for the full five-year period to be included in the calculations. Patients 85 years of age and older were grouped to minimize the effect of unstable estimates due to the smaller enrolled population sizes available in this age range in the commercially insured population. Results suggest that the proportion of patients with ARDS increases with age and that a higher proportion of older (≥65 years) men than women experience ARDS. There is also a small peak in children 1–5 years of age where the proportion boys receiving an ARDS diagnosis code (7.2 per 1,000 enrolled) is slightly higher than that in girls (5.0 per 1,000 enrolled). The proportion of individuals developing ARDS seems to begin increasing around 30–35 years of age and increases rapidly after about 65 years of age.

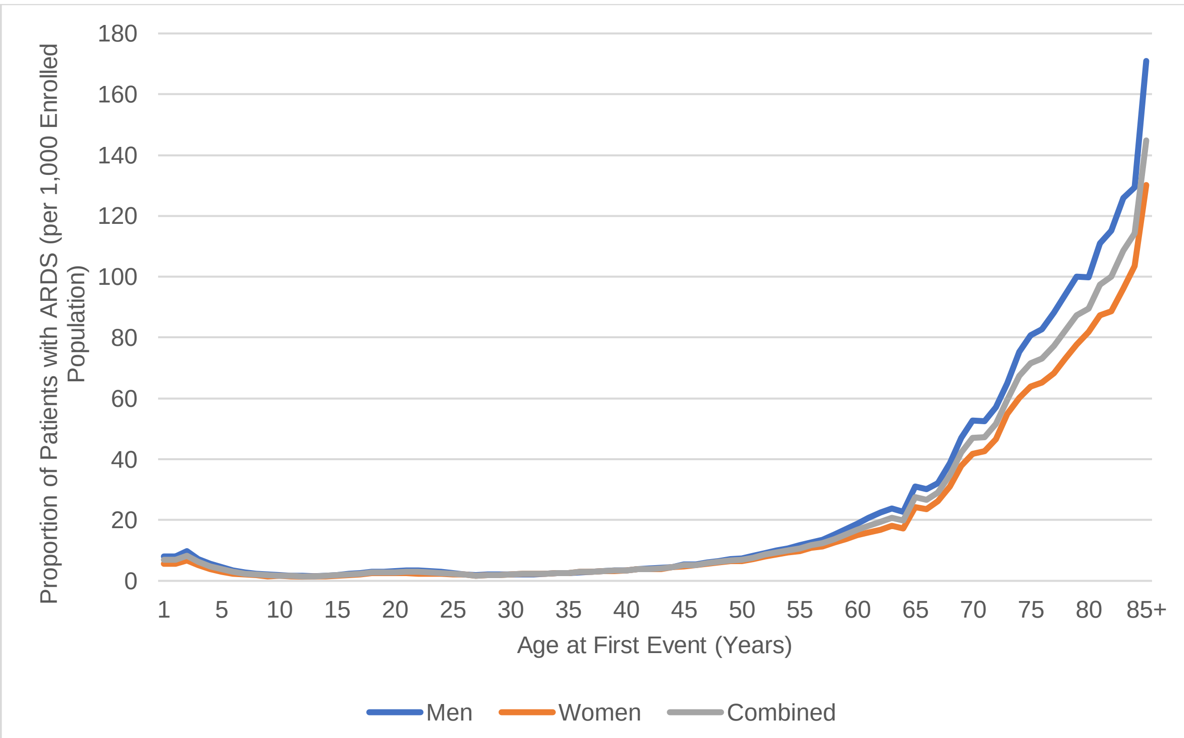


***Figure 5. Proportion of patients (1-85+)* with at least one diagnosis code for ARDS (ICD-9-CM or ICD-10-CM) per 1,000 enrolled population, by age and gender (January 1, 2014–December 31, 2018).***

* Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under 1 year old), the proportion of those under 1 year old experiencing ARDS is excluded from the chart.

The workgroup also assessed whether there was notable variation in the proportion of patients with ARDS by calendar year of diagnosis. **Figure 6** presents the annual proportions of patients with ARDS for ages 1–85+ years and suggests that observed rates did not vary substantially from year-to-year except for 2018 where the proportion of individuals between the ages of 1-5 with ARDS was higher than other years. It should be noted that the proportions presented in **Figure 6** are substantially lower than those in **Figure 5**, where ARDS encounters were queried for the entire 2014–2018 period instead of for a single year.

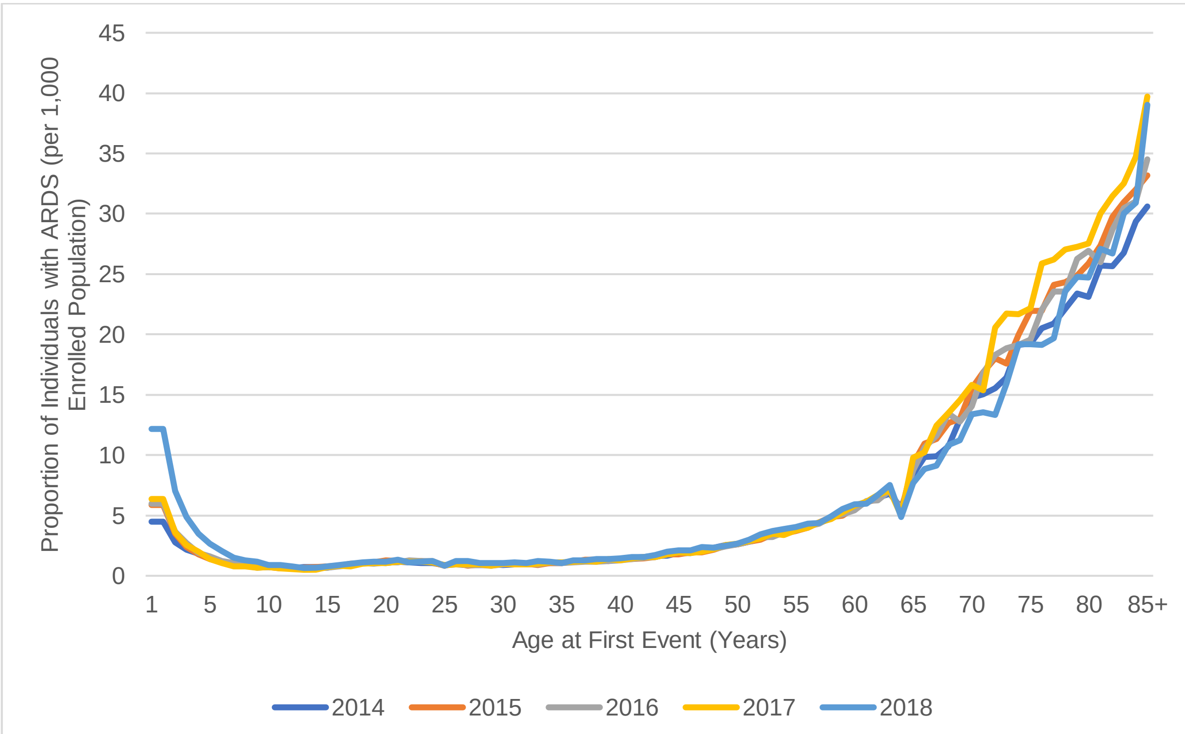


***Figure 6. Proportion of patients (1–85+)* with at least one diagnosis for* ARDS *(ICD-9-CM or ICD-10-CM) per 1,000 enrolled population, by age and calendar year (January 1, 2014–December 31, 2018).***

*Out of concern that the minimum continuous enrollment requirement could impact the inclusion of infants (i.e., those under 1 year old), the proportion of those under 1 year old experiencing ARDS is excluded from the chart.

Analyses were also conducted to test whether a temporal association in the occurrence or reporting of ARDS according to the time of the year. To test this, enrollment and ARDS encounter data for January 1–June 30 and July 1–December 31 were queried for each year. As presented in **Table 4** and **Figure 7**, there did not appear to be a substantial difference in the proportion of patients experiencing ARDS during the first and second halves of the calendar year.

***Table 4. Counts and proportions of patients experiencing ARDS[b], defined by ICD-9-CM and ICD-10-CM codes, stratified by time of year (2014–2018).***

| Description | Year | | | | |
|---|---|---|---|---|---|
| | 2014 | 2015 | 2016 | 2017 | 2018 |
| Jan–June Patient Count | 63,700 | 54,975 | 54,061 | 44,122 | 42,985 |
| July–Dec Patient Count | 63,344 | 50,470 | 52,664 | 42,933 | 40,753 |
| Jan–June Enrollment | 31,110,014 | 24,094,695 | 23,531,649 | 21,406,675 | 21,225,754 |
| July–Dec Enrollment | 30,867,380 | 23,759,879 | 23,759,879 | 20,866,148 | 20,866,232 |
| **January–June proportion (per 1,000 enrolled)** | **2.1** | **2.3** | **2.3** | **2.1** | **2.0** |
| **July–December proportion (per 1,000 enrolled)** | **2.1** | **2.1** | **2.2** | **2.1** | **2.0** |

[b] A patient can be counted in both time periods when queries are run separately, whereas they would be counted only once when the query spans the full year. Therefore, the sum of the proportions presented here will exceed those presented for full calendar years.

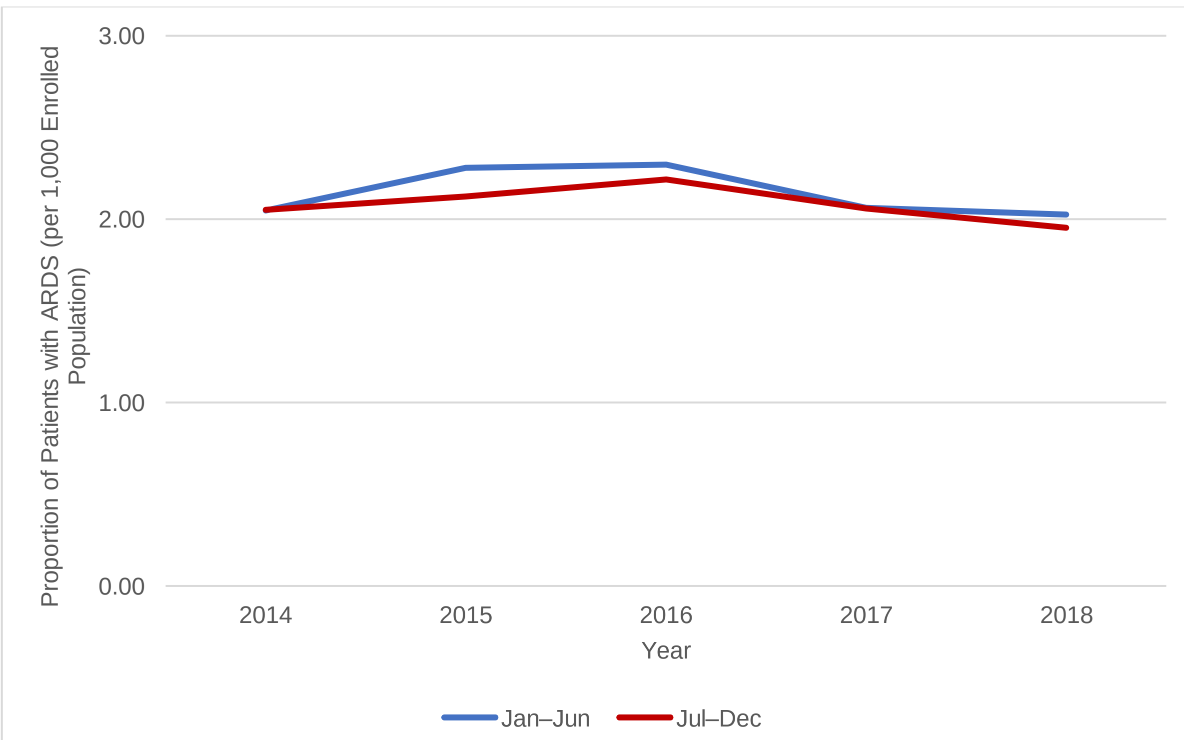


**Figure 7. Proportion of patients with at least one diagnosis for ARDS (ICD-9-CM or ICD-10-CM), stratified by time of year (2014–2018).**

## H Discussion and Conclusion

The objective of this structured review was to assess and understand the validity of electronic coding algorithms for identifying ARDS from administrative claims and EHRs using billing codes. It is unclear how diagnostic code-based algorithms would perform differently in EHR compared to claims databases, beyond the differences that already occur within different databases of either EHR or claims.

A structured literature review found no validation studies for claims-based algorithm or applications of ICD-10-CM coding algorithm. However, three validation studies for algorithms using EHRs billing codes (i.e., EHR-based) were identified.[1-3] Measures of the algorithm performance of ARDS varied across these three studies.[1-3] Using the data extracted from the literature of interest, four algorithms were developed within varying focus on sensitivity and specificity, followed by refinements through consultation with clinical SMEs.

The feasibility of one algorithm (i.e., Option 3 in **Section E**) was tested by conducting descriptive analyses in the MarketScan Treatment Pathways, a U.S. database covering commercially insured patients. Counts of patients with specific diagnosis codes associated with ARDS were queried and are presented in **Appendix B**. The resulting counts suggest that the majority of the aggregate counts are represented by codes related to respiratory failure: 518.81 (acute respiratory failure), J96.00 (acute respiratory failure, unspecified whether with hypoxia or hypercapnia), J96.01 (acute respiratory failure, with hypoxia), and J96.90 (respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia).

Additional analyses were performed to further characterize the epidemiology of the disease amongst the database population. The findings suggest that approximately 3.5–3.8 individuals per 1,000 individuals received a diagnosis code related to ARDS each year. A small decreasing trend in the proportion of individuals receiving an ARDS diagnosis code was observed between 2016 and 2018, despite the small absolute change. The lowest proportion (3.5 per 1,000 enrollees) was observed in 2018, though it is not clear if this is meaningfully different from the proportions observed in the other four years of study (3.6–3.8 individuals per 1,000). This may have been partly due to a younger enrolled population in 2018 (average age 60 years compared to 62–63 years in the other four years of study). Also, it was reported that the incidence of ARDS decreased over time from 82.4 to 38.8 cases per 100,000 between 2001 and 2008 in Olmsted County, Minnesota; this was attributed to a reduction in hospital-acquired ARDS by implementing changes in hospital practice including improved treatment of sepsis and pneumonia, changing mechanical ventilation practices, and increased staffing.[6]

The average age at the time of first diagnosis was 58 years, with cases distributed fairly evenly between males and females until the age of about 65 years, after which more men than women are affected. There was also a higher proportion those 1–5 years of age receiving an ARDS diagnosis code, especially among boys. This became more obvious for those at age one year in 2018. However, we cannot rule out the possibility that data point in 2018 was an outlier, as there were more cases in 2018 (n=2,148) than in 2014–2017 (n=1,135–1,167).

We compared our findings to a recent study that used the U.S. NIS to generate descriptive statistics on patients with ARDS, which reported an incidence rate ranging from 1.8 to 2.2 cases per 1,000 between 2006 and 2014, with a mean age of 62.0 and 49.1 years for individuals with and without ARDS risk factors, respectively.[4] The higher proportion of individuals receiving an ARDS diagnosis code in the present study may be due to a more sensitive algorithm application and inclusion of codes reported as part of the diagnostic/testing process (i.e., cases that were eventually ruled out as not being ARDS). In this study, females represented 45.6% and 49.5% of those with and without ARDS risk factors, respectively.[4] The increase with age that we observed in the proportion of patients with ARDS is consistent with findings from previous studies conducted in the U.S. and Spain.[8,15] The proportion of patients diagnosed with ARDS did not substantially differ between January to June and July to December, consistent with findings from another study conducted in Australia that did not find seasonal variation in the incidence of ARDS.[16]

Strengths of this study are the development of ARDS algorithms with a presumed range of sensitivity and specificity using ICD-9-CM and ICD-10-CM coding standards, based on a structured review of coding definitions and active engagement with clinical SMEs. To assess the plausibility of the algorithm, it was applied in a large administrative claims database to characterize ARDS in the commercially insured U.S.

population and generate descriptive statistics. Limitations of this review include the absence of validated ICD-10-CM or claims-based algorithms, as well as the variable performance of EHR-based ARDS algorithms used to inform the proposed algorithm — with PPV ranging from 4% to 100%.[1-3] As a result, the performance of the algorithm proposed herein is unknown without a validation study in claims data with access to medical records. Further, the analyses conducted in the MarketScan Research Databases should be viewed as exploratory and generalizable to the U.S. population that is commercially insured, and additional studies among populations with different insurance coverage would be required to validate the results and observations stemming from these queries.

## I Acknowledgements

Development of the ARDS algorithm and review report benefitted from significant engagement with the FDA CBER team members and their partners. We thank them for their contributions and feedback. Additional feedback on the proposed algorithm and draft report was provided by IBM Watson Health, Acumen (Laurie Feinberg, Nirmal Choradia) and Epi Excellence LLC.

## J References

1. Howard AE, Courtney-Shapiro C, Kelso LA, Goltz M, Morris PE. Comparison of 3 methods of detecting acute respiratory distress syndrome: clinical screening, chart review, and diagnostic coding. *Am J Crit Care.* 2004;13(1):59-64.
2. Thomsen GE, Morris AH. Incidence of the adult respiratory distress syndrome in the state of Utah. *Am J Respir Crit Care Med.* 1995;152(3):965-971.
3. Rincon F, Ghosh S, Dey S, et al. Impact of acute lung injury and acute respiratory distress syndrome after traumatic brain injury in the United States. *Neurosurgery.* 2012;71(4):795-803.
4. Eworuke E, Major JM, Gilbert McClain LI. National incidence rates for Acute Respiratory Distress Syndrome (ARDS) and ARDS cause-specific factors in the United States (2006-2014). *J Crit Care.* 2018;47:192-197.
5. Taylor MM. ARDS diagnosis and management: implications for the critical care nurse. *Dimens Crit Care Nurs.* 2005;24(5):197-207; quiz 208-199.
6. Li G, Malinchoc M, Cartin-Ceba R, et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmsted County, Minnesota. *Am J Respir Crit Care Med.* 2011;183(1):59-66.
7. Griffiths MJD, McAuley DF, Perkins GD, et al. Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res.* 2019;6(1):e000420.
8. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *The New England journal of medicine.* 2005;353(16):1685-1693.
9. Martin GS, Bernard GR. Airway and lung in sepsis. *Intensive Care Med.* 2001;27 Suppl 1:S63-79.
10. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *Jama.* 2012;307(23):2526-2533.
11. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? *Crit Care.* 2020;24(1):198.
12. Reynolds HN, McCunn M, Borg U, Habashi N, Cottingham C, Bar-Lavi Y. Acute respiratory distress syndrome: estimated incidence and mortality rate in a 5 million-person population base. *Crit Care.* 1998;2(1):29-34.
13. Thomsen G, Morris A, Danino J, Ellsworth J, Wallace C. Accuracy of ICD-9 coding in the diagnosis of ARDS. *Am Rev Respir Dis.* 1992;145:A81.
14. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. *Intensive Care Med.* 1994;20(3):225-232.
15. Manzano F, Yuste E, Colmenero M, et al. Incidence of acute respiratory distress syndrome and its relation to age. *J Crit Care.* 2005;20(3):274-280.
16. Bersten AD, Edibam C, Hunt T, Moran J. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. *Am J Respir Crit Care Med.* 2002;165(4):443-448.

## Appendix A. Literature Review Summary

**Table A1** below includes a summary of the data extraction table used to extract data from papers of interest.

***Table A1. Data Extraction Table***

| Author, Year | Title | Country | Summary | Disease Definition | Algorithm/Criteria | Validity | Claims/EHR-based Algorithm[vii] |
|---|---|---|---|---|---|---|---|
| Eworuke, 2018 | National incidence rates for Acute Respiratory Distress Syndrome (ARDS) and ARDS cause-specific factors in the United States (2006-2014). | U.S. | Study used ICD-9-CM codes to determine the incidence of ARDS and risk factors in the U.S. in all ARDS hospital discharges. | Berlin definition | ICD-9-CM diagnosis codes in primary or secondary position: 518.5, 518.82, 518.81 AND procedure code: 96.70-2 | NA | EHR |
| Howard, 2004 | Comparison of 3 methods of detecting acute respiratory distress syndrome: clinical screening, chart review, and diagnostic coding. | U.S. | Calculated sensitivity and specificity for ICD-9 ARDS codes in medical ICU patients. | AECC definition | ICD-9-CM discharge codes: 518.82, 518.85 | Sensitivity: 6.2%, Specificity: 99.6% | EHR |
| Reynolds, 1998 | Acute respiratory distress syndrome: estimated incidence and mortality rate in a 5-million-person population base. | U.S. | The study used ICD-9 codes to investigate the incidence and mortality rate for ARDS in patients over the age of 12. | NA | ICD-9-CM codes: 518.5, 518.82 AND procedure code: 96.70, 96.71, 96.72 | NA | EHR |

[vii] Each publication reported on a either a claims-based (i.e., ARDS codes derived from insurance claims) or EHR-based (i.e., ARDS codes derived from administrative medical records) algorithm.

| Author, Year | Title | Country | Summary | Disease Definition | Algorithm/Criteria | Validity | Claims/EHR-based Algorithm[vii] |
|---|---|---|---|---|---|---|---|
| Rincon, 2012 | Impact of acute lung injury and acute respiratory distress syndrome after traumatic brain injury in the U.S. | U.S. | Calculated PPV, specificity, and sensitivity for ICD-9-CM ARDS codes in patients admitted into a hospital with ARDS/ALI using different AECC criteria. | AECC definition | ICD 9-CM codes: 518.5, 518.82,<br>96.70, 96.71, 96.72 | Depending on AECC criteria used:<br>PPV: 90-100%<br>Sensitivity: 53-71%<br>Specificity: 73-100% | EHR |
| Thomsen, 1995 | Incidence of the adult respiratory distress syndrome in the state of Utah. | U.S. | Calculated PPV, NPV, specificity and sensitivity for ICD-9 codes for patients aged 12 and over in the ICU. | Following criteria had to be met:<br>1) Pao2/PAo2 ≦ 0.2<br>2) Chest radiograph showing bilateral lung infiltrates<br>3) No evidence of heart failure or fluid overload or if available, pulmonary wedge pressure ≦ 15 mm Hg)<br>4) Total static thoracic compliance 50 ml/cm H20 or over<br>5) Age 12 and over | ICD-9-CM discharge diagnosis codes: 518.5, 518.81, 518.82 | PPV: 7%<br>NPV: >99.9%<br>Sensitivity: 85%<br>Specificity: 98% | EHR |

Abbreviations: AECC, American-European Consensus Conference; EHR, electronic health record; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NA, not applicable; U.S., United States

## Appendix B. Counts of Patients with Specific Codes Proposed for the Algorithm

As an initial test of the proposed algorithm, the workgroup ran code-specific queries for ARDS inclusion categories 1 and 1.5 (i.e., Algorithm Option 3) in a large U.S. administrative claims dataset. Researchers used the MarketScan Research Databases (Commercial, Medicare Supplemental), accessed via the Treatment Pathways online analytic platform, querying the past five full years of available data. Results are presented in **Table B1**. Because the transition between International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM to ICD-10-CM) occurred on October 1, 2015, ICD-9-CM codes were queried for January 1, 2014–September 30, 2015, and ICD-10-CM codes were queried for October 1, 2015–December 31, 2018.

Subtotal rows and total columns may be smaller than the sum of individual cells, because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience an ARDS event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and experience an ARDS event, then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2016 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

Of the codes included in the ARDS algorithm, codes for acute respiratory failure (ICD-9-CM 518.81; ICD-10-CM J96.00, J96.01) and respiratory failure (ICD-10-CM J96.90) were the most frequently used during the study period. Of those receiving at least one ARDS diagnosis between 2014 and 2018 (n=452,732), 32.1% (n=145,118) had received an ICD-9-CM 518.81 code (acute respiratory failure). Meanwhile, 38.0% (n=172,007), 24.6% (n=111,587), and 17.9% (n=80,838) received ICD-10-CM code J96.01 (acute respiratory failure, with hypoxia), J96.00 (acute respiratory failure, unspecified whether with hypoxia or hypercapnia), and J96.90 (respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia), respectively.

***Table B1. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes proposed for inclusion in ARDS algorithm (January 1, 2014–December 31, 2018).***

| Code | Code Description | Year | | | | | | | | | | Total (Count) | Total (% of Total) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2014 (Count) | 2014 (% of Total) | 2015 (Count) | 2015 (% of Total) | 2016 (Count) | 2016 (% of Total) | 2017 (Count) | 2017 (% of Total) | 2018 (Count) | 2018 (% of Total) | | |
| **ICD-9-CM** | | | | | | | | | | | | | |
| 518.51 | Acute respiratory failure following trauma and surgery | 10,417 | 10.2% | 5,522 | 6.5% | | | | | | | 18,003 | 4.0% |
| 518.52 | Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery | 6,604 | 6.5% | 3,596 | 4.2% | | | | | | | 11,395 | 2.5% |
| 518.53 | Acute and chronic respiratory failure following trauma and surgery | 729 | 0.7% | 351 | 0.4% | | | | | | | 1,216 | 0.3% |
| 518.7 | Transfusion related acute lung injury (TRALI) | 65 | 0.1% | 33 | 0.0% | | | | | | | 115 | 0.0% |
| 518.81 | Acute respiratory failure | 79,309 | 77.5% | 48,626 | 57.2% | | | | | | | 145,118 | 32.1% |
| 518.82 | Other pulmonary insufficiency, not elsewhere classified | 25,419 | 24.8% | 14,463 | 17.0% | | | | | | | 44,697 | 9.9% |
| 518.84 | Acute and chronic respiratory failure | 17,317 | 16.9% | 11,111 | 13.1% | | | | | | | 31,756 | 7.0% |
| **ICD-9-CM Subtotal** | | **102,292** | **100.0%** | **62,139** | **73.1%** | | | | | | | **183,431** | **40.5%** |
| **ICD-10-CM** | | | | | | | | | | | | | |
| J80 | Acute respiratory distress syndrome | | | 5,130 | 6.0% | 15,096 | 18.3% | 8,922 | 12.7% | 5,105 | 7.6% | 43,019 | 9.5% |
| J95.1 | Acute pulmonary insufficiency following thoracic surgery | | | 285 | 0.3% | 1,149 | 1.4% | 1,024 | 1.5% | 866 | 1.3% | 3,693 | 0.8% |
| J95.2 | Acute pulmonary insufficiency following nonthoracic surgery | | | 244 | 0.3% | 1,054 | 1.3% | 942 | 1.3% | 699 | 1.0% | 3,356 | 0.7% |
| J95.821 | Acute postprocedural respiratory failure | | | 1,798 | 2.1% | 5,379 | 6.5% | 3,897 | 5.6% | 3,157 | 4.7% | 17,106 | 3.8% |
| J95.822 | Acute and chronic postprocedural respiratory failure | | | 232 | 0.3% | 638 | 0.8% | 261 | 0.4% | 147 | 0.2% | 1,599 | 0.4% |
| J95.84 | Transfusion-related acute lung injury (TRALI) | | | 23 | 0.0% | 44 | 0.1% | 31 | 0.0% | 34 | 0.1% | 179 | 0.0% |
| J96.00 | Acute respiratory failure, unspecified whether with hypoxia or hypercapnia | | | 12,332 | 14.5% | 30,600 | 37.0% | 23,495 | 33.5% | 18,764 | 27.8% | 111,587 | 24.6% |
| J96.01 | Acute respiratory failure, with hypoxia | | | 13,230 | 15.6% | 44,290 | 53.6% | 41,943 | 59.8% | 38,315 | 56.8% | 172,007 | 38.0% |
| J96.02 | Acute respiratory failure, with hypercapnia | | | 2,405 | 2.8% | 7,744 | 9.4% | 7,420 | 10.6% | 6,068 | 9.0% | 31,643 | 7.0% |
| J96.20 | Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia | | | 3,418 | 4.0% | 7,508 | 9.1% | 5,560 | 7.9% | 3,811 | 5.6% | 24,864 | 5.5% |
| J96.21 | Acute and chronic respiratory failure, with hypoxia | | | 4,244 | 5.0% | 12,375 | 15.0% | 11,179 | 15.9% | 8,712 | 12.9% | 44,646 | 9.9% |
| J96.22 | Acute and chronic respiratory failure, with hypercapnia | | | 1,577 | 1.9% | 4,375 | 5.3% | 3,872 | 5.5% | 3,214 | 4.8% | 16,281 | 3.6% |

| Code | Code Description | Year | | | | | | | | | | Total (Count) | Total (% of Total) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2014 (Count) | 2014 (% of Total) | 2015 (Count) | 2015 (% of Total) | 2016 (Count) | 2016 (% of Total) | 2017 (Count) | 2017 (% of Total) | 2018 (Count) | 2018 (% of Total) | | |
| J96.90 | Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia | | | 8,423 | 9.9% | 21,555 | 26.1% | 16,532 | 23.6% | 13,094 | 19.4% | 80,838 | 17.9% |
| J96.91 | Respiratory failure, unspecified, with hypoxia | | | 2,385 | 2.8% | 6,970 | 8.4% | 5,631 | 8.0% | 4,473 | 6.6% | 25,322 | 5.6% |
| J96.92 | Respiratory failure, unspecified, with hypercapnia | | | 621 | 0.7% | 1,553 | 1.9% | 1,274 | 1.8% | 996 | 1.5% | 5,874 | 1.3% |
| R06.03 | Acute respiratory distress | | | 0 | 0.0% | 0 | 0.0% | 3,223 | 4.6% | 15,549 | 23.0% | 21,835 | 4.8% |
| **ICD-10-CM Subtotal** | | | | **29,489** | **34.7%** | **82,705** | **100.0%** | **70,159** | **100.0%** | **67,471** | **100.0%** | **295,753** | **65.3%** |
| **Total** | | **102,292** | **100.0%** | **84,968** | **100.0%** | **82,705** | **100.0%** | **70,159** | **100.0%** | **67,471** | **100.0%** | **452,732** | **100.0%** |

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

Note: Codes highlighted in yellow represent those that accounted for at least 10% of the overall count among the 2014-2018 cohort.

## Appendix C. Codes Excluded from the Proposed Algorithm

The diagnosis codes listed in **Table C1** were considered based on literature review and consultation with clinical SMEs (JB, TB, JC, DT), but excluded from the algorithm. They were not used to identify patients with a relevant ARDS diagnosis.

***Table C1. Excluded codes potentially relevant to ARDS identified from the literature or GEMs mappings.***

| Code | Description | Code Category | Code Type |
|---|---|---|---|
| 518.0 | Pulmonary collapse | DX | 9 |
| 518.1 | Interstitial emphysema | DX | 9 |
| 518.2 | Compensatory emphysema | DX | 9 |
| 518.3 | Pulmonary eosinophilia | DX | 9 |
| 518.4 | Acute edema of lung, unspecified | DX | 9 |
| 518.6 | Allergic bronchopulmonary aspergillosis | DX | 9 |
| 518.83 | Chronic respiratory failure | DX | 9 |
| 518.89 | Other diseases of lung, not elsewhere classified | DX | 9 |
| B44.81 | Allergic bronchopulmonary aspergillosis | DX | 10 |
| J81.0 | Acute pulmonary edema | DX | 10 |
| J81.1 | Chronic pulmonary edema | DX | 10 |
| J82 | Pulmonary eosinophilia, not elsewhere classified | DX | 10 |
| J95.00 | Unspecified tracheostomy complication | DX | 10 |
| J95.01 | Hemorrhage from tracheostomy stoma | DX | 10 |
| J95.02 | Infection of tracheostomy stoma | DX | 10 |
| J95.03 | Malfunction of tracheostomy stoma | DX | 10 |
| J95.04 | Tracheo-esophageal fistula following tracheostomy | DX | 10 |
| J95.09 | Other tracheostomy complication | DX | 10 |
| J95.3 | Chronic pulmonary insufficiency following surgery | DX | 10 |
| J95.4 | Chemical pneumonitis due to anesthesia | DX | 10 |
| J95.5 | Postprocedural subglottic stenosis | DX | 10 |
| J95.61 | Intraoperative hemorrhage and hematoma of a respiratory system organ or structure complicating a respiratory system procedure | DX | 10 |
| J95.62 | Intraoperative hemorrhage and hematoma of a respiratory system organ or structure complicating other procedure | DX | 10 |
| J95.71 | Accidental puncture and laceration of a respiratory system organ or structure during a respiratory system procedure | DX | 10 |
| J95.72 | Accidental puncture and laceration of a respiratory system organ or structure during other procedure | DX | 10 |
| J95.811 | Postprocedural pneumothorax | DX | 10 |
| J95.812 | Postprocedural air leak | DX | 10 |
| J95.830 | Postprocedural hemorrhage of a respiratory system organ or structure following a respiratory system procedure | DX | 10 |
| J95.831 | Postprocedural hemorrhage of a respiratory system organ or structure following other procedure | DX | 10 |
| J95.850 | Mechanical complication of respirator | DX | 10 |
| J95.851 | Ventilator associated pneumonia | DX | 10 |
| J95.859 | Other complication of respirator [ventilator] | DX | 10 |
| J95.860 | Postprocedural hematoma of a respiratory system organ or structure following a respiratory system procedure | DX | 10 |
| J95.861 | Postprocedural hematoma of a respiratory system organ or structure following other procedure | DX | 10 |
| J95.862 | Postprocedural seroma of a respiratory system organ or structure following a respiratory system procedure | DX | 10 |
| J95.863 | Postprocedural seroma of a respiratory system organ or structure following other procedure | DX | 10 |

| Code | Description | Code Category | Code Type |
|---|---|---|---|
| J95.88 | Other intraoperative complications of respiratory system, not elsewhere classified | DX | 10 |
| J95.89 | Other postprocedural complications and disorders of respiratory system, not elsewhere classified | DX | 10 |
| J96.10 | Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia | DX | 10 |
| J96.11 | Chronic respiratory failure, with hypoxia | DX | 10 |
| J96.12 | Chronic respiratory failure, with hypercapnia | DX | 10 |
| J98.01 | Acute bronchospasm | DX | 10 |
| J98.09 | Other diseases of bronchus, not elsewhere classified | DX | 10 |
| J98.11 | Atelectasis | DX | 10 |
| J98.19 | Other pulmonary collapse | DX | 10 |
| J98.2 | Interstitial emphysema | DX | 10 |
| J98.3 | Compensatory emphysema | DX | 10 |
| J98.4 | Other disorders of lung | DX | 10 |
| J98.51 | Mediastinitis | DX | 10 |
| J98.59 | Other diseases of mediastinum, not elsewhere classified | DX | 10 |
| J98.6 | Disorders of diaphragm | DX | 10 |
| J98.8 | Other specified respiratory disorders | DX | 10 |
| J98.9 | Respiratory disorder, unspecified | DX | 10 |
| R06.00 | Dyspnea, unspecified | DX | 10 |
| R06.01 | Orthopnea | DX | 10 |
| R06.02 | Shortness of breath | DX | 10 |
| R06.09 | Other forms of dyspnea | DX | 10 |
| R06.1 | Stridor | DX | 10 |
| R06.2 | Wheezing | DX | 10 |
| R06.3 | Periodic breathing | DX | 10 |
| R06.4 | Hyperventilation | DX | 10 |
| R06.5 | Mouth breathing | DX | 10 |
| R06.6 | Hiccough | DX | 10 |
| R06.7 | Sneezing | DX | 10 |
| R06.81 | Apnea, not elsewhere classified | DX | 10 |
| R06.82 | Tachypnea, not elsewhere classified | DX | 10 |
| R06.83 | Snoring | DX | 10 |
| R06.89 | Other abnormalities of breathing | DX | 10 |
| R06.9 | Unspecified abnormalities of breathing | DX | 10 |

Abbreviation: DX, ICD-CM diagnosis.

Authors also ran code-specific queries in the MarketScan Research Databases (Commercial and Medicare Supplemental) during January 1, 2014–December 31, 2018, to assess the number of patients with diagnosis codes above that were ultimately excluded. This was done to understand how many patients will be excluded as a result of each code being omitted from the algorithm; however, it should be noted that patients with excluded codes may be included in the analysis if they *also* have a code that was included in the algorithm. Results are presented in **Table C2**.

The transition from ICD-9-CM to ICD-10-CM occurred October 1, 2015; no ICD-9-CM codes were queried after this date and no ICD-10-CM codes were queried prior to this date. The code standard-specific subtotal rows were calculated by querying all codes for a particular code standard together. The "Total (Count)" column was calculated by querying the individual code in a cohort of patients who were enrolled for at least one calendar year between 2014 and 2018.

Subtotal rows and Total columns may be smaller than the sum of individual cells because patients with multiple codes in a single year and with more than one of the same diagnosis codes in different years will only be counted once in these rows and columns. As a result, the sum of all "% of Total" cells in a single column may exceed 100%. However, the "Total" column could also be larger than the sum of individual years, as a result of situations where an individual is only enrolled for part of the year that they experience an ARDS event but is then continuously enrolled for a separate year. For example, an individual could be continuously enrolled for a few days, weeks, or months in 2016 and have a diagnosis code of interest (per **Table C1**), then be continuously enrolled for all of 2017. This event would not be captured in the column for the 2016 (as the individual would be excluded from that cohort) but would be captured in the "Total" column.

Acute edema of lung, unspecified (ICD-9-CM 518.4; ICD-10-CM J81.0) was noted as being of interest. Researchers queried the frequency with which these codes were reported among individuals in three contexts related to ARDS codes:

1. Independent of ARDS codes (Algorithm Option 3: categories 1 and 1.5 in **Table 2)**
2. Inclusive of ARDS codes (Algorithm Option 3: categories 1 and 1.5 in **Table 2**)
3. Exclusive of ARDS codes (Algorithm Option 3: categories 1 and 1.5 in **Table 2**)

The same query period — determined by calendar year and ICD-CM transition dates — was used to query both ARDS and acute edema of lung, unspecified. In other words, an individual that received an ARDS diagnosis code in 2016 and an acute edema of lung code in 2018 would be captured in categories 1 and 3 in the 2016 column but would be captured in categories 1 and 2 in the Total column, where the query boundaries are larger.

Results (**Table C2**) suggest that nearly half of individuals receiving a diagnostic code for acute edema of the lung, unspecified (518.4) or acute pulmonary edema (J81.0) did not also receive a diagnostic code for ARDS. This supports the clinical judgment that acute pulmonary edema has clinical causes other than ARDS (e.g., cardiogenic pulmonary edema). Acute pulmonary edema is only found in the presence of ARDS about half of the time and is not a major component of the ARDS case definition, supporting its exclusion from the ARDS algorithm.

***Table C2. Annual patient counts and proportions for ICD-9-CM and ICD-10-CM diagnosis codes of interest excluded from the ARDS algorithm (2014–2018).***

| Code | Code Description | Year | | | | | | | | | | Total (Count) | Total (% of Total) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 2014 (Count) | 2014 (% of Total) | 2015 (Count) | 2015 (% of Total) | 2016 (Count) | 2016 (% of Total) | 2017 (Count) | 2017 (% of Total) | 2018 (Count) | 2018 (% of Total) | | |
| **ICD-9-CM** | | | | | | | | | | | | | |
| 518.4 | Acute edema of lung, unspecified | 9,071 | 100.0% | 5,380 | 61.7% | | | | | | | 16,557 | 29.3% |
| 518.4 Including ARDS Codes | Acute edema of lung, unspecified including ARDS code categories 1, 1.5 | 5,000 | 55.1% | 2,827 | 32.4% | | | | | | | 9,741 | 17.2% |
| 518.4 Excluding ARDS Codes | Acute edema of lung, unspecified excluding ARDS code categories 1, 1.5 | 4,071 | 44.9% | 2,553 | 29.3% | | | | | | | 6,816 | 12.1% |
| **ICD-9-CM Subtotal** | | **9,071** | **100.0%** | **5,380** | **61.7%** | | | | | | | **16,557** | **29.3%** |
| **ICD-10-CM** | | | | | | | | | | | | | |
| J81.0 | Acute pulmonary edema | | | 3,577 | 41.0% | 11,587 | 100.0% | 10,103 | 100.0% | 8,306 | 100.0% | 41,024 | 72.6% |
| J81.0 Including ARDS Codes | Acute pulmonary edema, including ARDS code categories 1, 1.5 | | | 1,859 | 21.3% | 6,232 | 53.8% | 5,560 | 55.0% | 4,591 | 55.3% | 25,495 | 45.1% |
| J81.0 Excluding ARDS Codes | Acute pulmonary edema, excluding ARDS code categories 1, 1.5 | | | 1,718 | 19.7% | 5,355 | 46.2% | 4,543 | 45.0% | 3,715 | 44.7% | 15,529 | 27.5% |
| **ICD-10-CM Subtotal** | | | | **3,577** | **41.0%** | **11,587** | **100.0%** | **10,103** | **100.0%** | **8,306** | **100.0%** | **41,024** | **72.6%** |
| **Total*** | | **9,071** | **100.0%** | **8,722** | **100.0%** | **11,587** | **100.0%** | **10,103** | **100.0%** | **8,306** | **100.0%** | **56,522** | **100.0%** |

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

*Total and subtotal rows denote counts for acute edema of lung, unspecified (ICD-9-CM 518.4; ICD-10-CM J81.0)