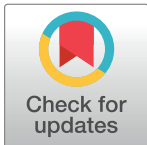


RESEARCH ARTICLE

Acute respiratory distress syndrome after SARS-CoV-2 infection on young adult population: International observational federated study based on electronic health records through the 4CE consortium

Bertrand Moal^{1*}, Arthur Orioux², Thomas Ferté³, Antoine Neuraz⁴, Gabriel A. Brat⁵, Paul Avillach⁵, Clara-Lea Bonzel⁵, Tianxi Cai⁵, Kelly Cho⁶, Sébastien Cossin⁷, Romain Griffier⁸, David A. Hanauer⁹, Christian Haverkamp¹⁰, Yuk-Lam Ho⁸, Chuan Hong⁵, Meghan R. Hutch¹¹, Jeffrey G. Klann¹², Trang T. Le¹³, Ne Hooi Will Loh¹³, Yuan Luo¹⁴, Adeline Makoudjou¹⁵, Michele Morris⁵, Danielle L. Mowery⁵, Karen L. Olson¹⁶, Lav P. Patel¹⁴, Malarkodi J. Samayamuthu⁵, Fernando J. Sanz Vidorreta¹⁷, Emily R. Schriver¹⁸, Petra Schubert¹⁹, Guillaume Verdy¹, Shyam Visweswaran⁵, Xuan Wang⁵, Griffin M. Weber⁵, Zongqi Xia²⁰, William Yuan⁵, Harrison G. Zhang⁵, Daniela Zöller²¹, Isaac S. Kohane⁵, The Consortium for Clinical Characterization of COVID-19 by EHR (4CE)^{5†}, Alexandre Boyer², Vianney Jouhet⁸



OPEN ACCESS

Citation: Moal B, Orioux A, Ferté T, Neuraz A, Brat GA, Avillach P, et al. (2023) Acute respiratory distress syndrome after SARS-CoV-2 infection on young adult population: International observational federated study based on electronic health records through the 4CE consortium. *PLoS ONE* 18(1): e0266985. <https://doi.org/10.1371/journal.pone.0266985>

Editor: Robert Jeenchen Chen, Stanford University School of Medicine, UNITED STATES

Received: April 5, 2022

Accepted: November 9, 2022

Published: January 4, 2023

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0266985>

Copyright: © 2023 Moal et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

1 IAM Unit, Bordeaux University Hospital, Bordeaux, France, **2** Medical Intensive Care Unit, Bordeaux University Hospital, Bordeaux, France, **3** Inserm Bordeaux Population Health Research Center UMR 1219, Inria BSO, Team SISTM, University of Bordeaux, Bordeaux, France, **4** Department of Biomedical Informatics, Hôpital Necker-Enfants Malade, Assistance Publique Hôpitaux de Paris (APHP), University of Paris, Paris, France, **5** Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts, United States of America, **6** Population Health and Data Science, MAVERIC, VA Boston Healthcare System, Boston, Massachusetts, United States of America, **7** INSERM Bordeaux Population Health ERIAS TEAM, Bordeaux University Hospital / ERIAS - Inserm U1219 BPH, Bordeaux, France, **8** Institute of Digitalization in Medicine, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany, **9** IAM Unit, INSERM Bordeaux Population Health ERIAS TEAM, Bordeaux University Hospital / ERIAS - Inserm U1219 BPH, Bordeaux, France, **10** Department of Learning Health Sciences, University of Michigan, Ann Arbor, Michigan, United States of America, **11** Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, Massachusetts, United States of America, **12** Department of Preventive Medicine, Northwestern University, Chicago, Illinois, United States of America, **13** Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **14** Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany, **15** Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States of America, **16** Department of Anaesthesia, National University Health System, Singapore, Singapore, **17** Computational Health Informatics Program, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, United States of America, **18** Department of Internal Medicine, Division of Medical Informatics, University of Kansas Medical Center, Kansas City, Kansas, United States of America, **19** Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, United States of America, **20** Data Analytics Center, University of Pennsylvania Health System, Philadelphia, Pennsylvania, United States of America, **21** Department of Neurology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America

† Membership of the author group can be found in the Acknowledgments.

* bertrandmoal@gmail.com

Data Availability Statement: All relevant data are available at: https://github.com/covidclinical/ARDS_aggregated_data_Public.

Funding: KC is supported by VA MVP000 and CIPHER. DAH is supported by National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) UL1TR002240. YL is supported by NIH/NCATS U01TR003528 and NIH National Library of Medicine (NLM) 1R01LM013337. MM is supported by Clinical and Translational Science Award (CTSA) UL1TR001857. DLM is supported by NIH/NCATS CTSA UL1-TR001878 (University of Pennsylvania). LPP is supported by CTSA Award UL1TR002366. SV is supported by NIH/NLM R01LM012095 and NIH/NCATS UL1TR001857. GMW is supported by NIH/NCATS UL1TR002541, NIH/NCATS UL1TR000005, NIH/NLM R01LM013345, and NIH National Human Genome Research Institute (NHGRI) 3U01HG008685-05S2. ZX is supported by NIH National Institute of Neurological Disorders and Stroke (NINDS) R01NS098023. Funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: 4CE, Consortium for Clinical Characterization of COVID-19 by EHR; ARDS, acute respiratory distress syndrome; EHR, electronic health records; HS, healthcare systems; ICD, international classification diseases; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Abstract

Purpose

In young adults (18 to 49 years old), investigation of the acute respiratory distress syndrome (ARDS) after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been limited. We evaluated the risk factors and outcomes of ARDS following infection with SARS-CoV-2 in a young adult population.

Methods

A retrospective cohort study was conducted between January 1st, 2020 and February 28th, 2021 using patient-level electronic health records (EHR), across 241 United States hospitals and 43 European hospitals participating in the Consortium for Clinical Characterization of COVID-19 by EHR (4CE). To identify the risk factors associated with ARDS, we compared young patients with and without ARDS through a federated analysis. We further compared the outcomes between young and old patients with ARDS.

Results

Among the 75,377 hospitalized patients with positive SARS-CoV-2 PCR, 1001 young adults presented with ARDS (7.8% of young hospitalized adults). Their mortality rate at 90 days was 16.2% and they presented with a similar complication rate for infection than older adults with ARDS. Peptic ulcer disease, paralysis, obesity, congestive heart failure, valvular disease, diabetes, chronic pulmonary disease and liver disease were associated with a higher risk of ARDS. We described a high prevalence of obesity (53%), hypertension (38%-although not significantly associated with ARDS), and diabetes (32%).

Conclusion

Trough an innovative method, a large international cohort study of young adults developing ARDS after SARS-CoV-2 infection has been gather. It demonstrated the poor outcomes of this population and associated risk factor.

Introduction

Acute respiratory distress syndrome (ARDS) [1], is a frequent complication after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. According to studies, it appears in 3.4% of the population with a laboratory positive PCR confirmation of infection to the SARS-CoV-2 [2], up to 31% of hospitalized patients [3–5], and 92% of patients admitted to the intensive care unit [4] (ICU).

ARDS has a severe impact on patient outcomes. In a cohort study carried out in New York City on COVID-19 patients, the mortality of ARDS patients reached 39% [4]. ARDS has been frequently associated with long-term disabilities [6–10] and represents a heavy care burden for health systems [11] due to long ICU stays and extended rehabilitation [7, 9].

Age is an important risk factor for developing ARDS [3]. However, young adults (18–49 years old) represented a third of hospitalized patients [12] and a quarter of patients admitted

to the ICU [4]. Based on the Premier Healthcare Database, which includes 1,030 hospitals in the United States, Cunningham et al. [13] reported that 21% of young adults (aged 18 to 34 years) hospitalized with COVID-19 disease were admitted to the ICU and 10% required mechanical ventilation. Similarly, in a separate cohort, young adults represented more than 20% of the patients admitted to ICUs for COVID-19 infection with ARDS [3].

Few studies [12–15] have investigated the young adult population, mostly were single-center analyses, all exclusively in the U.S. population and none focused on ARDS patients. To our knowledge, there have been no specific studies on ARDS after SARS-CoV-2 infection in the young adult population among an international cohort. This may be due to the difficulty in obtaining a large sample of this population. Key questions remain related to the risk factors of ARDS in young adults, and the difference, in terms of outcomes, compared to an older population.

In this study, we investigate the risk of ARDS among young adults hospitalized with COVID-19 using an international cohort from the international Consortium for Clinical Characterization of COVID-19 (4CE) [16–21]. This international consortium collects data from 342 hospitals in 6 countries and develops an innovative federated approach for electronic health records (EHR) analysis.

Through a federated analysis, the objectives were to evaluate the risk factors for developing ARDS following infection with SARS-CoV-2 and hospitalization in young adults and to compare characteristics, care, and outcomes between this population and an older population (greater than 49 years old) who similarly developed ARDS during their COVID-19 hospitalization.

Patients and methods

The 4CE consortium [16–21] has developed a framework to extract and standardize data directly from the EHRs of participating healthcare systems (HS) and to streamline federated analyses without sharing patient-level data. A common data model for structuring patient-level data was adopted to enable identical analyses across all participating HS. Fig 1 presents the workflow from 4CE data collection to ARDS analysis.

Common 4CE data collection by HS

As previously described [16], each participating HS were responsible for and obtained ethics approval, as needed, from the appropriate ethics committee at their institution. IRB protocols were reviewed and approved at APHP (IRB00011591, Project CSE-20-29_ClinicalCOVID),

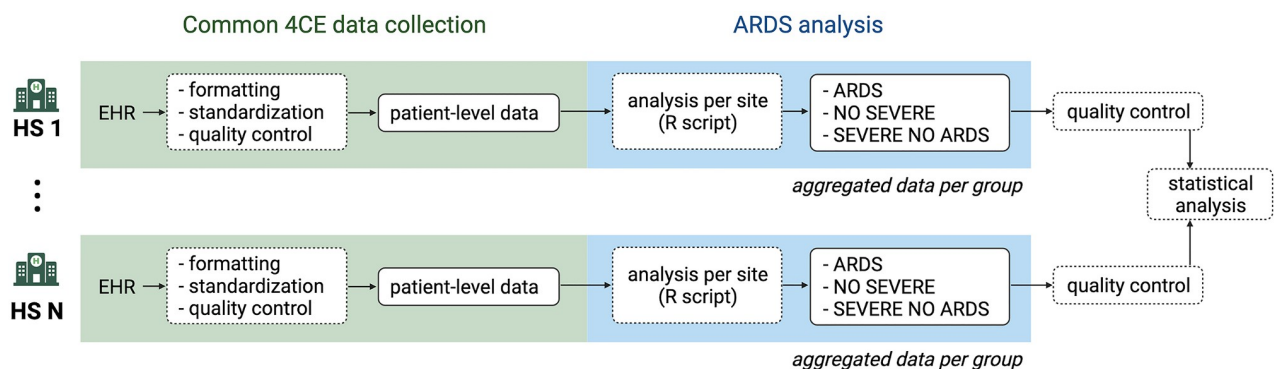


Fig 1. Study workflow. From EHR extraction to ARDS analysis on aggregated data (HS: healthcare system).

<https://doi.org/10.1371/journal.pone.0266985.g001>

Bordeaux University Hospital (Registration #CHUBX2020RE0253), Mass General Brigham (IRB#2020P001483), Northwestern University (IRB# STU00212845), University of Kansas (STUDY00146505), University of Freiburg (Application #255/20, Process #210587), and at VA North Atlantic, Southwest, Midwest, Continental, and Pacific (IRB # 3310-x).

The research was determined to be exempt at University of Michigan (IRB# HUM00184357), Beth Israel Deaconess Medical Center (IRB# 2020P000565), University of Pittsburgh (STUDY20070095), and University of Pennsylvania (IRB#842813). University of California Los Angeles determined that this study does not need IRB approval because research using limited data sets does not constitute human subjects research.

Cohort identification. Across each participating HS, we included all hospitalized patients within 7 days before and up to 14 days after a positive PCR SARS-CoV-2 test. The first hospital admission date within this time window was considered day 0 (the index date). Note that although all patients had a positive PCR test near their admission date, it is possible that for some patients the hospitalization was for reasons other than COVID-19.

Patient-level data collection by HS. Patient-level data were collected by HSs, which can represent one or several hospitals. At each HS, data were extracted directly from the EHR and consisted of time to admission and discharge, survival status, sex and age group [18–25, 26–49, 50–69, 70–79, and 80+ years old]. Diagnoses were collected from the first 3 digits of the billing code using [international classification disease \(ICD\) version 10](#). This 3-digit rollup was adopted to account for finer-grained differences in coding practices across hospitals. Procedures related to endotracheal tube insertion or invasive mechanical ventilation were collected and were denoted as severe procedures [17]. Medications administered were collected at the class level (as per the [ATC standard nomenclature](#) [22], [S1 Appendix](#)). Severe medication [17] refers to sedatives/anesthetics or treatment for shock (classes: SIANES, SICARDIAC).

All patient-level data were standardized to a common format, then stored and analyzed locally at each HS. Several quality controls were conducted iteratively at each HS to ensure the quality of the data.

ARDS analysis

Data aggregation by HS for ARDS analysis. Final data extraction was completed on 30th August 2021 and included patient hospitalizations occurring from 1st January 2020 to 28th February 2021. All patients of 18 years or older were included in the analysis. ARDS patients were identified using the ICD10 code, J80—Acute respiratory distress syndrome.

Using patient-level data, each HS ran an [R script](#) locally to classify patients into 3 groups as follows:

- ARDS: Patients with an ARDS ICD code
- NO_SEVERE: Patients without an ARDS ICD code, severe medication or severe procedure
- SEVERE_NO_ARDS: Patients with severe medication or severe procedure but without an ARDS ICD code

For the analysis, the cohort was divided into two age groups: patients aged 18 to 49 years and patients older than 49 years ([Fig 2](#)). For each group, the number of patients was aggregated in terms of:

- Age, sex, mortality at 90 days after the admission
- Each ICD code, Elixhauser index (23) and complication class ([S2](#) and [S3](#) Appendices)

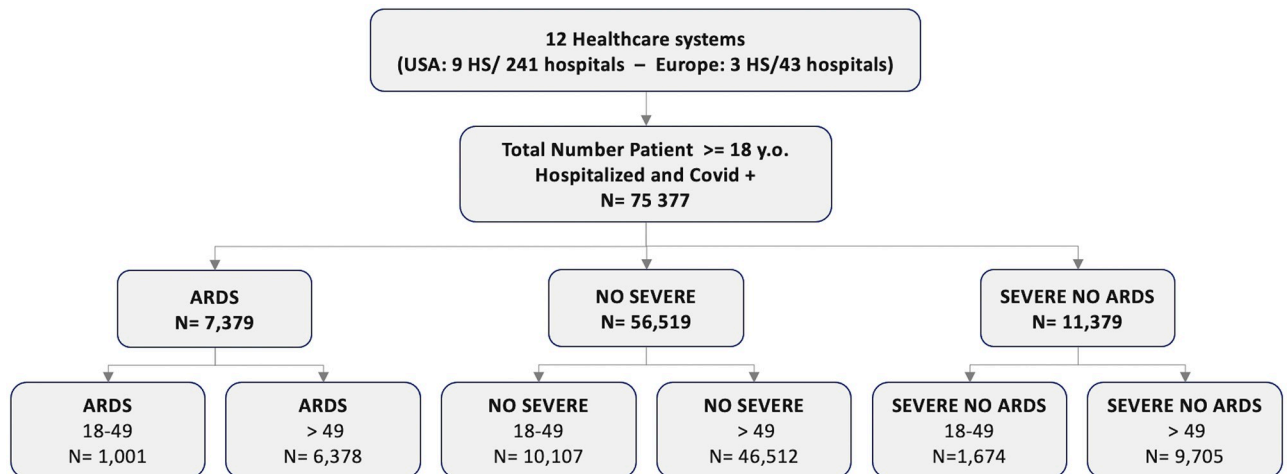


Fig 2. Flow chart. Distribution of patients per group (y.o. = years old).

<https://doi.org/10.1371/journal.pone.0266985.g002>

Aggregate data were centrally collected, and several quality controls were executed before pooling the aggregated data together. Descriptive analysis was presented [S1 Table](#).

Statistical analysis. Risk factor: comparison between young patients with and without ARDS.

To identify the risk factors associated with an ARDS after SARS-CoV-2 infection and hospitalization, we compared the young patients with ARDS and the young non severe patients. Patients classified in the “SEVERE_NO_ARDS” group were excluded from this analysis.

For comorbidities classified by the Elixhauser Comorbidity Index [23], risk ratios with confidence intervals were calculated from a univariable analysis considering diagnoses recorded between 365 days before (-365) the admission and 90 days after (+90) the admission. First univariable analysis was performed at each HS and aggregated through a random effect meta-analyses to account for heterogeneity between HS. In addition, comorbidities associated with ARDS in this meta univariable analysis and sex were selected for a multivariable analysis. Multivariable analysis was performed at each HS and then aggregated through another meta-analysis with random effect.

Complications and mortality: comparison between young and old adults with ARDS.

The proportion of patients per sex were evaluated and compared between young adults and older adults with ARDS. Complications were identified as novel diagnoses established between the day of admission and +90 days after the admission. To compare complications between young and older patients with ARDS, we performed a univariable analysis and reported estimated risk ratios with confidence intervals. Moreover, mortality was evaluated for both groups at 90 days after the index admission.

Statistical analyses were performed locally at each HS and then aggregated via meta-analysis with the R package metafor [24].

Results

12 HS participated in the analysis: 9 U.S. HS representing 241 hospitals, two French HS representing 42 hospitals, and one German HS representing 1 hospital ([Table 1](#)). 75,377 hospitalized patients with biological confirmation of COVID were included in the analysis.

Table 1. Name, city, country, number of hospitals per HS, number of beds and inpatient discharges/year per HS.

Healthcare System	City	Country	Hospitals	Beds	Inpatient discharges/year
Assistance Publique—Hôpitaux de Paris	Paris	France	39	20,098	1,375,538
Bordeaux University Hospital	Bordeaux	France	3	2,676	130,033
Medical Center, University of Freiburg	Freiburg	Germany	1	1,660	71,500
Beth Israel Deaconess Medical Center	Boston, MA	USA	1	673	40,752
Mass General Brigham (Partners Healthcare)	Boston, MA	USA	10	3,418	163,521
University of Pennsylvania	Philadelphia, PA	USA	5	2,469	118,188
University of Michigan	Ann Arbor, MI	USA	3	1,000	49,008
Northwestern University	Chicago, IL	USA	10	2,234	103,279
University of California, LA	Los Angeles, CA	USA	2	786	40,526
University of Pittsburgh / UPMC	Pittsburgh, PA	USA	39	8,085	369,300
University of Kansas Medical Center	Kansas City, KS	USA	1	794	54,659
Veteran affairs	Multiple cities	USA	170	13,801	680,687

<https://doi.org/10.1371/journal.pone.0266985.t001>

About 7.8% (1001/12,782, HS range: 1.6 to 15%) of hospitalized young adults with COVID developed ARDS compared to 10.2% (6378/62595, HS range: 1.8 to 21.2%) of older patients. Young patients represented 13.4% (1001/7379) of ARDS patients (HS range: 6.5% to 24.5%).

Risk factors: Comparison between young adults with ARDS and young non severe patients (Table 2)

For the risk factor analysis, young ARDS patients (n = 1001) were compared to young non severe patients (n = 10,107). Among young ARDS patients, 43/1001 (4.3%) were aged between 18 to 25 years old. In an univariable analysis, patients aged 26 to 49 years old had an increased risk of developing ARDS compared to those aged 18 to 25 years old (RR = 2.94; 95% CI: [2.11; 4.1]). Due to the low proportion of patients between 18 to 25 years, age class was not included in the multivariable analysis.

In the multivariable analysis, compared to women, men had a higher risk for developing ARDS (RR = 1.71; 95% CI: [1.20; 2.43]) and the following comorbidities were significantly associated with ARDS: Peptic ulcer disease (RR = 3.66; 95% CI: [2.01; 6.49]), Paralysis (RR = 3.73; 95% CI: [2.52; 5.51]), Obesity (RR = 2.82; 95% CI: [2.06; 3.95]), Congestive heart failure (RR = 2.2; 95% CI: [1.36; 3.57]), Valvular disease (RR = 1.89; 95% CI: [1.08; 3.29]), Diabetes (RR = 1.85; 95% CI: [1.44; 2.38]), Chronic pulmonary disease (RR = 1.62; 95% CI: [1.34; 1.96]) and Liver disease (RR = 1.61; 95% CI: [1.12; 2.31]). Hypertension was not significantly associated (RR = 1.36 [0.98; 1.89]).

Peripheral vascular disease, and renal failure were associated with developing ARDS in univariable analysis, but not in multivariable analysis. AIDS/HIV, alcohol abuse, cancer, drug abuse, hypothyroidism, and psychosis were not associated with higher risk. Nicotine dependency was not associated with a higher risk (p = 0.138).

In the young ARDS population, we observed a high prevalence of comorbidities including obesity 533/1001 (53.3%), diabetes 382/1001 (38.2%), and hypertension 322/1001 (32.2%).

Complications and mortality: Comparison between young and old adult population with ARDS

6378 patients aged > 49 with ARDS were compared to the young adult population with ARDS. The percentage of males was 67.1% (672/1001) and 75.2% (4797/6378) for the

Table 2. Number and percentage of patients per age groups, per sex, per Elixhauser comorbidities for young adult patients with ARDS and non severe young adult patients. Risk ratio associated in uni- and multivariable analysis.

Variables	ARDS	NO SEVERE	Univariable analysis		Multivariable analysis	
	ages 18–49	ages 18–49	Risk Ratio with CI (95%)	p-value	Risk Ratio with CI (95%)	p-value
	n = 1001 n (%)	n = 10107 n (%)				
Age groups, reference: 18 to 25 years old						
18to25	43 (4.3)	1207 (11.9)	2.9 [2.1; 4.1]	<0.001	not include	
26to49	966 (96.5)	8900 (88.1)				
Sex, reference: female						
female	327 (32.7)	4427 (43.8)	1.7 [1.3; 2.2]	<0.001	1.71 [1.2; 2.4]	0.003
male	672 (67.1)	5680 (56.2)				
Comorbidities (Elix Hauser class), ICD code from -365 days before to + 90 days after admission						
AIDS/HIV	12 (1.2)	121 (1.2)	1 [0.5; 1.9]	0.987	not include	
Alcohol abuse	59 (5.9)	895 (8.9)	1 [0.7; 1.4]	0.92	not include	
Cancer	37 (3.7)	280 (2.8)	1.3 [0.9; 1.7]	0.164	not include	
Chronic pulmonary disease	219 (21.9)	1406 (13.9)	1.8 [1.6; 2.1]	<0.001	1.6 [1.3; 2.0]	<0.001
Congestive heart failure	143 (14.3)	532 (5.3)	3.4 [2.6; 4.4]	<0.001	2.2 [1.4; 3.6]	0.001
Diabetes	322 (32.2)	1691 (16.7)	2.5 [2; 3.1]	<0.001	1.9 [1.4; 2.4]	<0.001
Drug abuse	65 (6.5)	828 (8.2)	1 [0.8; 1.3]	0.997	not include	
Hypertension	382 (38.2)	2274 (22.5)	2.5 [2; 3.2]	<0.001	1.4 [0.98; 1.9]	0.062
Hypothyroidism	45 (4.5)	431 (4.3)	1.4 [1; 2.1]	0.077	not include	
Liver disease	179 (17.9)	960 (9.5)	2.1 [1.6; 2.8]	<0.001	1.6 [1.1; 2.3]	0.01
Obesity	533 (53.2)	2759 (27.3)	2.9 [2.2; 3.9]	<0.001	2.8 [2.0; 4.0]	<0.001
Paralysis	64 (6.4)	162 (1.6)	2.9 [2.3; 3.6]	<0.001	3.7 [2.5; 5.5]	<0.001
Peptic ulcer disease	36 (3.6)	60 (0.6)	4.2 [2.9; 6]	<0.001	3.7 [2.1; 6.5]	<0.001
Peripheral vascular disease	37 (3.7)	184 (1.8)	2.7 [1.7; 4.2]	<0.001	1.2 [0.7; 2.1]	0.485
Psychoses	52 (5.2)	599 (5.9)	1.1 [0.8; 1.4]	0.513	not include	
Renal failure	131 (13.1)	590 (5.8)	2.4 [1.9; 2.9]	<0.001	1.3 [0.9; 1.8]	0.158
Valvular disease	92 (9.2)	346 (3.4)	2.9 [2.1; 4]	<0.001	1.9 [1.1; 3.3]	0.025

<https://doi.org/10.1371/journal.pone.0266985.t002>

young population and the old population, respectively, without significant difference ($p = 0.457$).

Complications (Table 3). Young ARDS patients had a lower risk of developing the following complications: Acute kidney failure (RR = 0.76; 95% CI: [0.68; 0.85]); cardiac rhythm/conduction disorder (RR = 0.59; 95% CI: [0.47; 0.73]), disorders of fluid, electrolyte and acid-base balance (RR = 0.95; 95% CI: [0.88; 0.99]); and stroke (RR = 0.35; 95% CI: [0.23; 0.53]). However, they had a higher risk of developing pneumonia due to *Streptococcus pneumoniae* (RR = 1.78; 95% CI: [1.16; 2.75]), and Streptococcal sepsis (RR = 1.58; 95% CI: [1.08; 2.31]). More than half of the young ARDS patients had Respiratory bacterial superinfection (538/1001 (53.8%)) during their hospitalization. No significant differences were found for the occurrence of pulmonary embolism ($p = 0.671$), affecting one in 10 patients in both groups with ARDS.

Mortality

90 days after admission, 16.2% (162/1001) of the young ARDS patients were deceased (HS range [11.2%; 36.8%]). In the older adult population with ARDS patients, the mortality was 41.1% (2619/6378, HS range [24.3%; 76.7%]).

Table 3. Proportion and associated risk ratio of complication classes for the young compared to old adult with ARDS.

Complications	ARDS (ages 18–49)	ARDS (ages > 49)	Risk Ratio with CI (95%)	p-value
	n = 1001	n = 6378		
	n (%)	n (%)		
Acute kidney failure	403 (40.3)	3431 (53.8)	0.8 [0.7; 0.9]	<0.001
Cardiac arrest	57 (5.7)	455 (7.1)	1.1 [0.8; 1.5]	0.691
Cardiac complication	255 (25.5)	2195 (34.4)	0.8 [0.6; 0.9]	0.01
Cardiac Rhythm/conduction disorder	310 (31)	2847 (44.6)	0.6 [0.5; 0.7]	<0.001
Digestive complication	393 (39.3)	2643 (41.4)	1 [0.9; 1.1]	0.907
Disorders of fluid, electrolyte and acid-base balance	546 (54.5)	3730 (58.5)	0.9 [0.9; 1]	0.02
Haematological disorder	388 (38.8)	2440 (38.3)	1 [0.9; 1]	0.528
Hemodynamic disorder	271 (27.1)	1852 (29)	1 [0.8; 1.1]	0.573
Arterial embolism and thrombosis	14 (1.4)	100 (1.6)	1.1 [0.6; 1.9]	0.737
Stroke	25 (2.5)	509 (8)	0.4 [0.2; 0.5]	<0.001
Phlebitis and thrombophlebitis	180 (18)	777 (12.2)	1.3 [1; 1.6]	0.078
Pulmonary embolism	105 (10.5)	695 (10.9)	1 [0.8; 1.2]	0.637
Respiratory complication (excluding ARDS)	857 (85.6)	5502 (86.3)	1 [0.9; 1]	0.202
Pressure ulcer	115 (11.5)	818 (12.8)	1 [0.8; 1.2]	0.875
Viral reactivation	29 (2.9)	177 (2.8)	1.2 [0.8; 1.8]	0.356
Infections				
Aspergillosis	26 (2.6)	164 (2.6)	0.7 [0.5; 1.2]	0.179
Candidiasis	64 (6.4)	421 (6.6)	1.2 [0.9; 1.5]	0.182
Other fungal infection	21 (2.1)	111 (1.7)	1.1 [0.6; 1.9]	0.768
Bacterial infection	528 (52.7)	3366 (52.8)	0.9 [0.9; 1]	0.187
Bacterial intestinal infection	41 (4.1)	242 (3.8)	1.2 [0.9; 1.6]	0.299
Respiratory bacterial superinfection	538 (53.7)	3507 (55)	1 [0.9; 1.1]	0.869
Pneumonia due to <i>Streptococcus pneumoniae</i>	34 (3.4)	107 (1.7)	1.8 [1.2; 2.7]	0.009
Streptococcal sepsis	41 (4.1)	145 (2.3)	1.6 [1.1; 2.3]	0.018

<https://doi.org/10.1371/journal.pone.0266985.t003>

Data

The aggregated data per site are available [here](#). Sites were anonymized.

Discussion

In a large international EHR-based cohort, we employed a novel federated approach including 241 hospitals in the United States and 43 in Europe, to describe comorbidities, complications, and mortality of young adults developing ARDS after SARS-CoV-2 infection. Even though young patients with ARDS represent a small proportion of hospitalized patients with COVID (HS range: [0.4%; 3.3%]), we were able to gather a large cohort thanks to this innovative method and demonstrated the poor outcome of young ARDS patients with notable mortality (16.2%).

Mortality and complications

Independently on the etiology, in-hospital mortality for ARDS patients has been reported to be between 30 to 40% [7, 25, 26]. Mortality at 30 days for ARDS patients of any age with COVID-19 was reported at 39% [4] and corresponds to the mortality for the older ARDS population in our study. The young ARDS population's mortality at 90 days was smaller, around 16.2% with large variability between HS [11.2; 36.8%]. Importantly, it was not possible to assess

the attributable COVID-19 mortality from our data. However the mortality appeared high for this young population; in a 2018 study conducted in France, all-cause mortality of ICU patients in the same age range was estimated to be less than 10% [27]. The relatively higher risk of developing pneumonia due to *Streptococcus pneumoniae* and Streptococcal sepsis in young adults is probably related to their greater survival rate compared to older patients. The high frequency of complications in this young population emphasizes the major impact of ARDS on poor outcomes and mortality.

Risk factors

Although the proportion of the general population is low, ARDS appears in 7.8% of young hospitalized adults with COVID. These percentages are in agreement with those reported by Cummings et al. [3] and Cunningham et al. [13]. Among those young ARDS patients only 4.3% were aged between 18- and 25-years old. Patients developing ARDS in this young adult population had a high prevalence of obesity (53%), hypertension (38%) and diabetes (32%).

A limitation of relying on billing codes to identify comorbidities is the challenge of accurately distinguishing comorbidities from complications. In our analysis, comorbidities were considered as those diagnoses from billing codes assigned up to one year before and up to 90 days after the admission. In electronic health records, each code is attached to one specific hospitalization visit. For patients with prior hospitalizations, comorbidities are easily identified with the codes attached to those previous hospitalization. However, for patient without previous hospitalization, the fact that electronic health records do not contains any code, do not mean that patient did not have comorbidities. For example, an obese patient without prior hospitalization would be identified as “obese” only if we take into account the code associated with the index hospitalization. This approach is more sensitive, but it can lead to considering complications as comorbidities. It is particularly true for peptic ulcer disease or paralysis which was identified as a comorbidity associated with ARDS but which is also known to be a common complication of mechanical ventilation [28, 29] or prolonged ICU admission. We perform a complementary univariable analysis on the sub population who had previous hospital visits and considering only the ICD code related to those previous visits as comorbidities (one year and– 14 days before the admission). In this univariable analysis presented in [S2 Table](#), ARDS was associated with the presence of peptic ulcer disease or paralysis in a previous hospitalization, which explained our choice to keep both in the main multivariable analysis that means considering them as comorbidities. “Paralysis” regroup is related a large diversity of diagnoses. including encephalitis, myelitis and encephalomyelitis, hereditary ataxia, cerebral palsy, hemiplegia and hemiparesis, paraplegia (paraparesis) and quadriplegia (quadriparesis), and other paralytic syndromes ([S2 Appendix](#)); but a common co-occurrence is reduced lung capacity which could contribute to its association with ARDS. The association with peptic ulcer as comorbidities remains unclear and requires additional investigations.

Obesity has been identified as a risk factor for poor outcome for ARDS [30] and for SARS-CoV-2 infection [3, 14, 15, 31] and it also appears in this analysis as a risk factor in this young adult population. Diabetes has a controversial association with ARDS [32–34] but appears in this population as a risk factor and has also been associated with the severity of SARS-CoV-2 infection in other studies [3, 14, 15, 31]. Despite its association with poor outcomes in several cohorts of COVID-19 patients [2, 15], hypertension was not significantly associated with ARDS in our study, possibly due to the choice of the variable included in the multivariable analysis and/or a lack of power.

Congestive heart failure, valvular disease, chronic liver disease, and chronic pulmonary disease are not associated with ARDS in the literature, however, their associations with

COVID-19 have been identified as a risk factor for poor outcomes [3, 14, 15, 31]. Through our analysis, it seems that most of the comorbidities associated with ARDS in the young adult population are similar to the ones associated with poor outcomes after SARS-CoV-2 infection in the general population. However, for most of them, it is unclear whether they are truly related to the onset of ARDS or just general comorbidities. Further analysis needs to be carried out to eliminate confounding factors and better understand the potential mechanisms of those associations.

Limitations

Our major limitation is that group membership, comorbidities, and complication analyses are based on billing codes, procedures, and medications directly extracted from EHR. Variation in billing coding practices, especially across international healthcare systems, may result in missing data and related biases [35]. However, multiple quality controls have been established to reduce those potential biases. For the detection of ARDS patients, a correct sensibility is expected as billing code is related to reimbursement in most countries and ARDS is associated with heavy care. Regarding the relation between ARDS and COVID-19 infection, patients included in our analysis had positive reverse transcription PCR tests for SARS-CoV-2 infection 7 days before to 14 days after the date of admission. This inclusion criterion allows us to ensure that included patients had the COVID-19 infection at least at the beginning of the hospitalization. Even if it is not possible to establish a clear temporal relationship or causality between ARDS and COVID-19 with ICD codes, it would be extremely rare that the development of ARDS during the hospitalization of a COVID-19 positive patient had no relation to COVID-19 infection. It is possible that COVID-19 infection was not the primary cause of the ARDS but most likely had an impact on the ARDS development.

To identify comorbidities associated with ARDS following hospitalization with COVID, a comparison was performed considering only non severe patients. Patients with mechanical ventilation, sedatives/anesthetics, or treatment for shock but without ARDS code were not included, which could generate a selection bias. This choice was conducted to eliminate potential miscoded ARDS patients and patients with severe disease or care not related to SARS-CoV-2 infection but with a concomitant infection. Those patients could have been included in the ARDS population, but the objective of this study was to focus precisely on ARDS patients, and this grouping would have resulted in a significant measurement bias. Especially because the number of young SEVERE_NO_ARDS patients is greater than the one of ARDS patients. In addition, we believe that the descriptive analysis of the SEVERE_NO_ARDS brings credit to this choice (S1 Table). Compared to the other groups, SEVERE_NO_ARDS population had the higher percentage of women (52.2%) and of patients with previous contact with the health-care system (72%). In addition, 15.1% of those patients had a billing code associated with pregnancy and 36.1% with long-term drug therapy. These results suggest that the COVID-19 infection was simply concomitant but not the main cause of these hospitalizations.

Treatment like the use of mechanical ventilation, ECMO or even ICU admission were not collected. The collection of treatment data, described by specific codes in EHR, has proven to be too partial and largely heterogeneous between health systems (even from the same country) to be collected. It also appears that the accuracy of ICU admission in EHR data was poor. It was particularly true at the beginning of the pandemic, where hallways were converted into ad hoc ICUs to support the surge of sick patients, without notification in the chart. This issue has already been discussed in a previous article from the consortium [17].

More detailed analysis on age's threshold was not possible because age was intentionally not collected by the 4CE consortium as a continuous variable. This choice was made to ensure

greater security/de-identification on the data collection process which allowed for an easier regulatory process for international aggregated data sharing.

Conclusion

We federated a large EHR-based international cohort of young adults developing ARDS after COVID-19. ARDS appears in 7.8% of hospitalized young patients with COVID and was associated with high mortality (16.2%). Young adults developing ARDS presented a high prevalence of comorbidities, particularly obesity, hypertension (although not being associated with ARDS), and diabetes. ARDS development was associated with peptic ulcer disease, paralysis, obesity, congestive heart failure, valvular disease, diabetes, chronic pulmonary disease, and liver disease.

Supporting information

S1 Appendix. Medication class.

(DOCX)

S2 Appendix. Elixhauser comorbidities.

(DOCX)

S3 Appendix. Complication classification.

(DOCX)

S1 Table. Number and percentage of patients per age groups, per sex, per Elixhauser comorbidities for all groups.

(DOCX)

S2 Table. Number and percentage of patients per Elixhauser comorbidities for young adult patients with ARDS and non severe young adult patients. Risk ratio associated in univariable analysis for the sub population which had previous hospital visits and considering only the ICD code related to those previous visits (one year and– 14 before the admission).

(DOCX)

Acknowledgments

The Consortium for Clinical Characterization of COVID-19 by EHR (4CE)

Lead author: Isaac S Kohane MD, PhD

James R Aaron MHA¹, Giuseppe Agapito PhD², Adem Albayrak³, Giuseppe Albi MS⁴, Mario Alessiani MD, FACS⁵, Anna Alloni PhD⁶, Danilo F Amendola MSc⁷, François Angoulvant MD, PhD⁸, Li L.L.J Anthony⁹, Bruce J Aronow PhD¹⁰, Fatima Ashraf MS¹¹, Andrew Atz MD¹², Paul Avillach MD, PhD¹³, Vidul Ayakulangara Panickan MS¹³, Paula S Azevedo MD, PhD¹⁴, James Balshi¹⁵, Ashley Batugo BS¹⁶, Brett K Beaulieu-Jones PhD¹³, Brendin R Beaulieu-Jones MD, MBA¹³, Douglas S Bell¹⁷, Antonio Bellasi MD, PhD¹⁸, Riccardo Bellazzi MS, PhD⁴, Vincent Benoit PhD¹⁹, Michele Beraghi MS²⁰, José Luis Bernal-Sobrino MS²¹, Mélodie Bernaux²², Romain Bey¹⁹, Surbhi Bhatnagar PhD²³, Alvar Blanco-Martínez MS²¹, Martin Boecker²⁴, Clara-Lea Bonzel MSc¹³, John Booth MSc²⁵, Silvano Bosari Prof.²⁶, Florence T Bourgeois MD, MPH²⁷, Robert L Bradford²⁸, Gabriel A Brat MD¹³, Stéphane Bréant²⁹, Nicholas W Brown MEng¹³, Raffaele Bruno MD³⁰, William A Bryant PhD²⁵, Mauro Bucalo MS⁶, Emily Bucholz MD, PhD, MPH³¹, Anita Burgun³², Tianxi Cai ScD¹³, Mario Cannataro M.Sc.³³, Aldo Carmona³⁴, Anna Maria Cattelan MD³⁵, Charlotte Caucheteux³⁶, Julien Champ³⁷, Krista Y Chen BS³⁸, Jin Chen PhD³⁹, Luca Chiovato MD, PhD⁴⁰, Lorenzo Chiudinelli PhD⁴¹, Kelly

Cho PhD, MPH⁴², James J Cimino MD⁴³, Tiago K Colicchio PhD, MBA⁴³, Sylvie Cormont²⁹, Sébastien Cossin⁴⁴, Jean B Craig PhD⁴⁵, Juan Luis Cruz-Bermúdez PhD²¹, Jaime Cruz-Rojo MD²¹, Arianna Dagliati MS, PhD⁴⁶, Mohamad Daniar MSIS⁴⁷, Christel Daniel⁴⁸, Priyam Das PhD¹³, Batsal Devkota⁴⁹, Audrey Dionne MD³¹, Rui Duan PhD⁵⁰, Julien Dubiel²⁹, Scott L DuVall PhD⁵¹, Loic Esteve⁵², Hossein Estiri PhD⁵³, Shirley Fan⁵⁴, Robert W Follett BS¹⁷, Thomas Ganslandt MD⁵⁵, Noelia García-Barrio MS²¹, Lana X Garmire PhD⁵⁶, Nils Gehlenborg¹³, Emily J Getzen MS⁵⁷, Alon Geva MD, MPH⁵⁸, Tomás González González MD²¹, Tobias Gradinger MD, BSc⁵⁵, Alexandre Gramfort³⁶, Romain Griffier⁴⁴, Nicolas Griffon⁴⁸, Olivier Grisel³⁶, Alba Gutiérrez-Sacristán PhD¹³, Pietro h guzzi PhD⁵⁹, Larry Han PhD⁵⁰, David A Hanauer MD, MS⁶⁰, Christian Haverkamp MD⁶¹, Derek Y Hazard MSc⁶², Bing He PhD⁵⁶, Darren W Henderson BS¹, Martin Hilka²⁹, Yuk-Lam Ho MPH⁶³, John H Holmes MS, PhD^{64,16}, Jacqueline P Honerlaw RN, MPH⁶³, Chuan Hong PhD^{65,13}, Kenneth M Huling HS¹³, Meghan R Hutch BS⁶⁶, Richard W Issitt DClintP²⁵, Anne Sophie Jannot⁶⁷, Vianney Jouhet MD, PhD⁴⁴, Ramakanth Kavuluru PhD⁶⁸, Mark S Keller¹³, Chris J Kennedy PhD⁶⁹, Kate F Kernan MD⁷⁰, Daniel A Key BEng²⁵, Katie Kirchoff MSHI⁷¹, Jeffrey G Klann MEng, PhD⁵³, Isaac S Kohane MD, PhD¹³, Ian D Krantz⁷², Detlef Kraska Dr.⁷³, Ashok K Krishnamurthy PhD⁷⁴, Sehi L'Yi PhD¹³, Trang T Le PhD⁶⁴, Judith Leblanc⁷⁵, Guillaume Lemaitre³⁶, Leslie Lenert MD, MS⁴⁵, Damien Leprovost⁷⁶, Molei Liu PhD⁷⁷, Ne Hooi Will Loh MBBS⁷⁸, Qi Long PhD⁷⁹, Sara Lozano-Zahonero PhD⁸⁰, Yuan Luo PhD⁶⁶, Kristine E Lynch PhD⁵¹, Sadiqa Mahmood³, Sarah E Maidlow AA⁸¹, Adeline Makoudjou MD⁶², Simran Makwana MS¹³, Alberto Malovini PhD⁸², Kenneth D Mandl MD, MPH⁸³, Chengsheng Mao PhD⁶⁶, Anupama Maram MS⁸⁴, Monika Maripuri MBBS, MPH⁶³, Patricia Martel⁸⁵, Marcelo R Martins MSc⁸⁶, Jayson S Marwaha MD⁸⁷, Aaron J Masino PhD⁸⁸, Maria Mazzitelli MD, PhD³⁵, Diego R Mazzotti PhD⁸⁹, Arthur Mensch⁹⁰, Marianna Milano PhD⁹¹, Marcos F Minicucci MD, PhD⁹², Bertrand Moal MD, PhD⁹³, Taha Mohseni Ahooyi PhD⁹⁴, Jason H Moore PhD⁹⁵, Cinta Moraleta MD, PhD⁹⁶, Jeffrey S Morris⁹⁷, Michele Morris BA⁹⁸, Karyn L Moshal⁹⁹, Sajad Mousavi PhD¹³, Danielle L Mowery PhD⁶⁴, Douglas A Murad¹⁷, Shawn N Murphy MD, PhD¹⁰⁰, Thomas P Naughton BA¹⁰¹, Carlos Tadeu Breda Neto⁷, Antoine Neuraz MD, PhD¹⁰², Jane Newburger MD, MPH³¹, Kee Yuan Ngiam MBBS, FRCS¹⁰³, Wanjiku FM Njoroge MD¹⁰⁴, James B Norman¹³, Jihad Obeid MD, FAMILA⁴⁵, Marina P Okoshi PhD⁹², Karen L Olson PhD¹⁰⁵, Gilbert S. Omenn MD, PhD¹⁰⁶, Nina Orlova²⁹, Brian D Ostasiewski BS¹⁰⁷, Nathan P Palmer PhD¹³, Nicolas Paris²⁹, Lav P Patel MS¹⁰⁸, Miguel Pedrera-Jiménez MS²¹, Ashley C Pfaff MD¹⁰⁹, Emily R Pfaff PhD¹¹⁰, Danielle Pillion MS¹³, Sara Pizzimenti MS²⁶, Tanu Priya BS¹¹¹, Hans U Prokosch¹¹², Robson A Prudente PhD¹¹³, Andrea Prunotto PhD⁸⁰, Víctor Quirós-González MS²¹, Rachel B Ramoni¹¹⁴, Maryna Raskin³, Siegbert Rieg MD¹¹⁵, Gustavo Roig-Domínguez MS²¹, Pablo Rojo MD, PhD⁹⁶, Paula Rubio-Mayo MS²¹, Paolo Sacchi MD³⁰, Carlos Sáez PhD¹¹⁶, Elisa Salamanca²⁹, Malarkodi Jebathilagam Samayamuthu MD⁹⁸, L. Nelson Sanchez-Pinto MD, MBI¹¹⁷, Arnaud Sandrin²⁹, Nandhini Santhanam MSc⁵⁵, Janaina C.C Santos MS¹¹⁸, Fernando J Sanz Vidorreta¹⁷, Maria Savino MS¹¹⁹, Emily R Schriver MS¹²⁰, Petra Schubert MPH⁶³, Juergen Schuettler¹²¹, Luigia Scudeller MD, MSc²⁶, Neil J Sebire MD, FRCPath¹²², Pablo Serrano-Balazote MD, MS²¹, Patricia Serre²⁹, Arnaud Serret-Larmande MD¹²³, Mohsin Shah MSc²⁵, Zahra Shakeri Hossein Abad PhD¹²⁴, Domenick Silvio¹²⁵, Piotr Sliz¹²⁶, Jiyeon Son MD¹²⁷, Charles Sondag¹²⁸, Andrew M South MD, MS¹²⁹, Francesca Sperotto MD, PhD³¹, Anastasia Spiridou PhD²⁵, Zachary H. Strasser MD⁵³, Amelia LM Tan BSc, PhD¹³, Bryce W.Q. Tan MBBS¹³⁰, Byorn W.L. Tan MBBS¹³⁰, Suzana E Tanni PhD⁹², Deanne M Taylor PhD¹³¹, Ana I Terriza-Torres MS²¹, Valentina Tibollo MS⁸², Patric Tippmann MSc¹³², Emma MS Toh¹³³, Carlo Torti PhD¹³⁴, Enrico M Treçarichi PhD¹³⁴, Andrew K Vallejos¹³⁵, Gael Varoquaux¹³⁶, Margaret E Vella MPH¹³, Guillaume Verdy MSc⁹³, Jill-Jénn Vie¹³⁷, Shyam Visweswaran MD, PhD⁹⁸, Michele Vitacca MD, PhD¹³⁸, Kavishwar B Waghlikar

MBBS, PhD¹³⁹, Lemuel R Waitman¹⁴⁰, Xuan Wang PhD¹³, Demian Wassermann³⁶, Griffin M Weber MD, PhD¹³, Martin Wolkewitz PhD¹³², Scott Wong¹³⁰, Zongqi Xia MD, PhD¹⁴¹, Xin Xiong MS⁵⁰, Ye Ye BMED, MSPH, PhD¹⁴², Nadir Yehya MD, MSCE¹⁴³, William Yuan PhD¹³, Joany M Zachariasse MD, PhD¹³, Janet J Zahner BS¹⁴⁴, Alberto Zambelli¹⁴⁵, Harrison G Zhang BA¹³, Daniela Zöller PhD⁸⁰, Valentina Zuccaro MD³⁰, Chiara Zucco PhD⁹¹

¹Department of Biomedical Informatics, University of Kentucky, Lexington, KY, United States. ²Department of Legal, Economic and Social Sciences, University Magna Graecia of Catanzaro, Italy, Catanzaro, Italy. ³Health Catalyst, INC., Cambridge, MA, United States. ⁴Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Italy, Pavia, Italy. ⁵Department of Surgery, ASST Pavia, Lombardia Region Health System, Pavia, Italy. ⁶BIOMERIS (BIOMedical Research Informatics Solutions), Pavia, Italy. ⁷Clinical Research Unit of Botucatu Medical School, São Paulo State University, Botucatu, Brazil, Clinical Research Unit of Botucatu Medical School, São Paulo State University, Botucatu, Brazil, Botucatu, Brazil. ⁸Pediatric emergency Department, Hôpital Necker-Enfants Malades, Assistance Public-Hôpitaux de Paris, Paris, Paris, France. ⁹National Center for Infectious Diseases, Tan Tock Seng Hospital, Singapore, Singapore, Singapore. ¹⁰Departments of Biomedical Informatics, Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, United States. ¹¹BIG-ARC, The University of Texas Health Science Center at Houston, School of Biomedical Informatics, Houston, TX, United States. ¹²Department of Pediatrics, Medical University of South Carolina, Charleston, SC, United States. ¹³Department of Biomedical Informatics, Harvard Medical School, Boston, MA, United States. ¹⁴Internal Medicine Department, Botucatu Medical School, São Paulo State University, Botucatu, Brazil, Botucatu, Brazil. ¹⁵Department of Surgery, St. Luke's University Health Network, Bethlehem, PA, Bethlehem, PA, United States. ¹⁶Institute for Biomedical Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States. ¹⁷Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States. ¹⁸Department of Medicine, Division of Nephrology, Ente Ospedaliero Cantonale, Lugano, Switzerland, Lugano, Switzerland. ¹⁹IT Department, Innovation & Data, APHP Greater Paris University Hospital, Paris, France. ²⁰IT Department, ASST Pavia, Voghera, Italy. ²¹Health Informatics, Hospital Universitario 12 de Octubre, Madrid, Spain, Madrid, Spain. ²²Strategy and Transformation Department, APHP Greater Paris University Hospital, Paris, France. ²³Department of Biomedical Informatics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, United States. ²⁴Technical University of Munich, Munich, Germany. ²⁵Digital Research, Informatics and Virtual Environments (DRIVE), Great Ormond Street Hospital for Children, UK, London, United Kingdom. ²⁶Scientific Direction, IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy. ²⁷Department of Pediatrics, Harvard Medical School, Boston, MA, United States. ²⁸North Carolina Translational and Clinical Sciences (NC TraCS) Institute, UNC Chapel Hill, Chapel Hill, NC, United States. ²⁹IT department, Innovation & Data, APHP Greater Paris University Hospital, Paris, France. ³⁰Division of Infectious Diseases I, Fondazione I.R.C.C.S. Policlinico San Matteo, Italy, Pavia, Italy. ³¹Department of Cardiology, Boston Children's Hospital, Harvard Medical School, Boston, MA, United States. ³²Department of Biomedical Informatics, HEGP, APHP Greater Paris University Hospital, Paris, France. ³³Department of Medical and Surgical Sciences, Data Analytics Research Center, University Magna Graecia of Catanzaro, Italy, Catanzaro, Italy. ³⁴Department of Anesthesia, St. Luke's University Health Network, Bethlehem, PA, Bethlehem, PA, United States. ³⁵Dipartimento di Medicina dei Sistemi, Infectious and Tropical Disease Unit, Padua University Hospital, Padua, Italy. ³⁶Université Paris-Saclay, Inria, CEA, Palaiseau, France. ³⁷INRIA Sophia-Antipolis-ZENITH team, LIRMM, Montpellier, France, Montpellier, France. ³⁸Computational Health Informatics Program, Boston Children's Hospital, Boston, MA, United States.

³⁹Department of Internal Medicine, University of Kentucky, Lexington, KY, United States. ⁴⁰Unit of Internal Medicine and Endocrinology, Istituti Clinici Scientifici Maugeri SpA SB IRCCS, Pavia, Italy. ⁴¹UOC Ricerca, Innovazione e Brand reputation, ASST Papa Giovanni XXIII, Bergamo, Bergamo, Italy. ⁴²Population Health and Data Science, MAVERIC, VA Boston Healthcare System, Boston, MA, United States. ⁴³Informatics Institute, University of Alabama at Birmingham, Birmingham, AL, United States. ⁴⁴IAM unit, INSERM Bordeaux Population Health ERIAS TEAM, Bordeaux University Hospital / ERIAS—Inserm U1219 BPH, Bordeaux, France. ⁴⁵Biomedical Informatics Center, Medical University of South Carolina, Charleston, SC, United States. ⁴⁶Department of Electrical Computer and Biomedical Engineering, University of Pavia, Italy, Pavia, Italy. ⁴⁷Clinical Research Informatics, Boston Children’s Hospital, Boston, MA, United States. ⁴⁸IT department, Innovation & Data (APHP), UMRS1142 (INSERM), APHP Greater Paris University Hospital, INSERM, Paris, France. ⁴⁹Department of Biomedical and Health Informatics, Children’s Hospital of Philadelphia, Philadelphia, PA, United States. ⁵⁰Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, United States. ⁵¹VA Informatics and Computing Infrastructure, VA Salt Lake City Health Care System, Salt Lake City, UT, United States. ⁵²SED/SIERRA, Inria Centre de Paris, Paris, France. ⁵³Department of Medicine, Massachusetts General Hospital, Boston, MA, United States. ⁵⁴Health Information Technology & Services, University of Michigan, Ann Arbor, MI, United States. ⁵⁵Heinrich-Lanz-Center for Digital Health, University Medicine Mannheim, Heidelberg University, Mannheim, Germany. ⁵⁶Department of Computational Biology and Bioinformatics, University of Michigan, Ann Arbor, MI, United States. ⁵⁷Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States. ⁵⁸Department of Anesthesiology, Critical Care, and Pain Medicine and Computational Health Informatics Program, Boston Children’s Hospital, Boston, MA, United States. ⁵⁹Department of Surgical Medical Sciences, University of Catanzaro, Catanzaro, Italy. ⁶⁰Department of Learning Health Sciences, University of Michigan Medical School, Ann Arbor, MI, Ann Arbor, MI, United States. ⁶¹Institute of Digitalization in Medicine, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany. ⁶²Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany. ⁶³Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), VA Boston Healthcare System, Boston, MA, United States. ⁶⁴Department of Biostatistics, Epidemiology, and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States. ⁶⁵Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, United States. ⁶⁶Department of Preventive Medicine, Northwestern University, Chicago, IL, United States. ⁶⁷Department of Biomedical Informatics, HEGP, APHP Greater Paris University Hospital, Paris, France. ⁶⁸Division of Biomedical Informatics (Department of Internal Medicine), University of Kentucky, Lexington, KY, United States. ⁶⁹Center for Precision Psychiatry, Massachusetts General Hospital, Boston, MA, United States. ⁷⁰Department of Critical Care Medicine, Children’s Hospital of Pittsburgh, Pittsburgh, PA, United States. ⁷¹Medical University of South Carolina, Charleston, SC, United States. ⁷²Department of Pediatrics, Division of Human Genetics, The Children’s Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States. ⁷³Center for Medical Information and Communication Technology, University Hospital Erlangen, Erlangen, Germany. ⁷⁴Renaissance Computing Institute/Department of Computer Science, University of North Carolina, Chapel Hill, Chapel Hill, NC, United States. ⁷⁵Clinical Research Unit, Saint Antoine Hospital, APHP Greater Paris University Hospital, Paris, France. ⁷⁶Clevy.io, Paris, France. ⁷⁷Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, MA, United States. ⁷⁸Department of Anaesthesia, National University Health System, Singapore, Singapore, Singapore. ⁷⁹Department of Biostatistics,

Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States. ⁸⁰Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Freiburg, Germany. ⁸¹Michigan Institute for Clinical and Health Research (MICHR) Informatics, University of Michigan, Ann Arbor, MI, United States. ⁸²Laboratory of Informatics and Systems Engineering for Clinical Research, Istituti Clinici Scientifici Maugeri SpA SB IRCCS, Pavia, Italy., Pavia, Italy. ⁸³Computational Health Informatics Program, Boston Children's Hospital, Boston, MA, United States. ⁸⁴Harvard Catalyst, Harvard Medical School, Boston, MA, United States. ⁸⁵Clinical Research Unit, Paris Saclay, APHP Greater Paris University Hospital, Boulogne-Billancourt, France. ⁸⁶Medical Informatics Center, Hospital das Clínicas, Faculty of Medicine of Botucatu, Clinics hospital of the Botucatu Medical School, São Paulo State University, Botucatu, Brazil, Botucatu, Brazil. ⁸⁷Department of Surgery, Beth Israel Deaconess Medical Center, Boston, MA, United States. ⁸⁸Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, PA, United States. ⁸⁹Department of Internal Medicine, Division of Medical Informatics, University of Kansas Medical Center, Kansas City, KS, United States. ⁹⁰ENS, PSL University, Paris, France. ⁹¹Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, Italy, Catanzaro, Italy. ⁹²Internal Medicine Department of Botucatu Medical School, São Paulo State University, Botucatu, Brazil, Botucatu, Brazil. ⁹³IAM unit, Bordeaux University Hospital, Bordeaux, France. ⁹⁴Department of Biomedical Health Informatics, Children's Hospital of Philadelphia, Philadelphia, PA, United States. ⁹⁵Department of Computational Biomedicine, Cedars-Sinai Medical Center, West Hollywood, United States. ⁹⁶Pediatric Infectious Disease Department, Hospital Universitario 12 de Octubre, Madrid, Spain, Madrid, Spain. ⁹⁷Department of Biostatistics, Epidemiology, and Informatics, Institute for Biomedical Informatics, University of Pennsylvania Perelman School of Medicine, Berwyn, United States. ⁹⁸Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA, United States. ⁹⁹Department of Infectious Diseases, Great Ormond Street Hospital for Children, UK, London, United Kingdom. ¹⁰⁰Department of Neurology, Massachusetts General Hospital, Boston, MA, United States. ¹⁰¹Harvard Catalyst | The Harvard Clinical and Translational Science Center, Harvard Medical School, Boston, MA, United States. ¹⁰²Department of biomedical informatics, Hôpital Necker-Enfants Malade, Assistance Publique Hôpitaux de Paris (APHP), University of Paris, Paris, France. ¹⁰³Department of Biomedical informatics, WiSDM, National University Health System Singapore, Singapore, Singapore. ¹⁰⁴Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States. ¹⁰⁵Computational Health Informatics Program and Department of Pediatrics, Boston Children's Hospital and Harvard Medical School, Boston, MA, United States. ¹⁰⁶Dept of Computational Medicine & Bioinformatics, Internal Medicine, Human Genetics, and School of Public Health, University of Michigan, Ann Arbor, MI, United States. ¹⁰⁷CTSI, WFBMI, Wake Forest School of Medicine, Winston Salem, NC, United States. ¹⁰⁸Department of Internal Medicine, Division of Medical Informatics, University Of Kansas Medical Center, Kansas City, KS, United States. ¹⁰⁹Department of Surgery, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States. ¹¹⁰NC TraCS Institute, UNC Chapel Hill, Chapel Hill, NC, United States. ¹¹¹Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, United States. ¹¹²Department of Medical Informatics, University of Erlangen-Nürnberg, Erlangen, Germany. ¹¹³Clinical Research Unit São Paulo State University, Brazil, Clinical Research Unit São Paulo State University, Brazil, Botucatu, Brazil. ¹¹⁴Office of Research and Development, Department of Veterans Affairs, Department of Veterans Affairs, Washington, DC, United States. ¹¹⁵Division of Infectious Diseases, Department of Medicine II, Medical Center—University of Freiburg, Faculty of Medicine, Freiburg, Germany. ¹¹⁶Biomedical Data Science Lab, ITACA

Institute, Universitat Politècnica de València, Spain, Valencia, Spain. ¹¹⁷Department of Pediatrics (Critical Care), Northwestern University Feinberg School of Medicine, Chicago, IL, United States. ¹¹⁸Nurse department of FMB—medicine school of Botucatu, Clinical Research Unit of Botucatu Medical School, São Paulo State University, Botucatu, Brazil, Botucatu, Brazil. ¹¹⁹ASST Pavia, Lombardia Region Health System, Management Engineer, Direction, Pavia, Italy. ¹²⁰Data Analytics Center, University of Pennsylvania Health System, Philadelphia, PA, United States. ¹²¹Department of Anesthesiology, University Hospital Erlangen, FAU Erlangen-Nürnberg, Germany, Erlangen, Germany. ¹²²Digital Research, Informatics and Virtual Environments (DRIVE), Great Ormond Street Hospital for Children NIHR BRC, UK, London, United Kingdom. ¹²³Department of Biostatistics and Biomedical Informatics, Hôpital Saint-Louis, APHP Greater Paris University Hospital, Paris University, Paris, France. ¹²⁴Dalla Lana School of Public Health, University of Toronto, Toronto, Canada. ¹²⁵MICHR Informatics, University of Michigan, Ann Arbor, MI, United States. ¹²⁶CHIP, Boston Children's Hospital, Boston, MA, United States. ¹²⁷Department of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, United States. ¹²⁸Critical Care Medicine, Department of Medicine, St. Luke's University Health Network, Bethlehem, PA, Bethlehem, PA, United States. ¹²⁹Department of Pediatrics-Section of Nephrology, Brenner Children's, Wake Forest University School of Medicine, Winston Salem, NC, United States. ¹³⁰Department of Medicine, National University Hospital, Singapore, Singapore, Singapore. ¹³¹Department of Biomedical Health Informatics and the Department of Pediatrics, The Children's Hospital of Philadelphia and the University of Pennsylvania Perelman Medical School, Philadelphia, PA, United States. ¹³²Institute of Medical Biometry and Statistics, Institute of Medical Biometry and Statistics, Medical Center, University of Freiburg, Freiburg, Germany. ¹³³Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore. ¹³⁴Department of Medical and Surgical Sciences, Infectious and Tropical Disease Unit, University Magna Graecia of Catanzaro, Italy, Catanzaro, Italy. ¹³⁵Clinical & Translational Science Institute, Medical College of Wisconsin, Milwaukee, United States. ¹³⁶Université Paris-Saclay, Inria, CEA, Montréal Neurological Institute, McGill University, Palaiseau, France. ¹³⁷SequeL, Inria Lille, Villeneuve-d'Ascq, France. ¹³⁸Respiratory Department, ICS S. Maugeri IRCCS Pavia Italy, Lumezzane (Bs), ITALY. ¹³⁹Department of Medicine, Massachusetts General Hospital, Boston, MA, USA. ¹⁴⁰Department of Health Management and Informatics, University of Missouri, Columbia, MO, Columbia, MO, United States. ¹⁴¹Department of Neurology, University of Pittsburgh, Pittsburgh, PA, United States. ¹⁴²Department of Veterans Affairs, 1100 First Street, NW, Washington, DC 20420, University of Pittsburgh, Pittsburgh, PA, United States. ¹⁴³Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA, United States. ¹⁴⁴Departments of Information Services, Biomedical Informatics, Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, United States. ¹⁴⁵Department of Oncology, ASST Papa Giovanni XXIII, Bergamo, Bergamo, Italy

Author Contributions

Conceptualization: Bertrand Moal, Romain Griffier, Isaac S. Kohane, Alexandre Boyer, Vianney Jouhet.

Data curation: Bertrand Moal, Kelly Cho, Romain Griffier, David A. Hanauer, Christian Haverkamp, Yuk-Lam Ho, Meghan R. Hutch, Jeffrey G. Klann, Trang T. Le, Yuan Luo, Adeline Makoudjou, Michele Morris, Danielle L. Mowery, Lav P. Patel, Malarkodi J.

Samayamuthu, Fernando J. Sanz Vidorreta, Emily R. Schriver, Petra Schubert, Shyam Visweswaran, Griffin M. Weber, Zongqi Xia, Alexandre Boyer, Vianney Jouhet.

Formal analysis: Bertrand Moal, Antoine Neuraz, Gabriel A. Brat, Paul Avillach, Clara-Lea Bonzel, Tianxi Cai, Kelly Cho, Romain Griffier, Yuk-Lam Ho, Chuan Hong, Ne Hooi Will Loh, Adeline Makoudjou, Michele Morris, Lav P. Patel, Shyam Visweswaran, Xuan Wang, Zongqi Xia, William Yuan, Daniela Zöller, Alexandre Boyer, Vianney Jouhet.

Investigation: Bertrand Moal, Arthur Orioux, Sébastien Cossin.

Methodology: Bertrand Moal.

Validation: Bertrand Moal, Arthur Orioux, Sébastien Cossin.

Visualization: Arthur Orioux.

Writing – original draft: Bertrand Moal, Thomas Ferté, Antoine Neuraz, Gabriel A. Brat, Paul Avillach, Romain Griffier, David A. Hanauer, Meghan R. Hutch, Trang T. Le, Ne Hooi Will Loh, Yuan Luo, Adeline Makoudjou, Danielle L. Mowery, Karen L. Olson, Guillaume Verdy, Xuan Wang, Griffin M. Weber, Zongqi Xia, William Yuan, Harrison G. Zhang, Isaac S. Kohane, Alexandre Boyer, Vianney Jouhet.

Writing – review & editing: Bertrand Moal, Arthur Orioux, Thomas Ferté, Antoine Neuraz, Gabriel A. Brat, Paul Avillach, Sébastien Cossin, Romain Griffier, David A. Hanauer, Meghan R. Hutch, Trang T. Le, Ne Hooi Will Loh, Yuan Luo, Adeline Makoudjou, Danielle L. Mowery, Karen L. Olson, Guillaume Verdy, Xuan Wang, Griffin M. Weber, Zongqi Xia, William Yuan, Harrison G. Zhang, Isaac S. Kohane, Alexandre Boyer, Vianney Jouhet.

References

1. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994; 149: 818–824. <https://doi.org/10.1164/ajrccm.149.3.7509706> PMID: 7509706
2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020; 382: 1708–1720. <https://doi.org/10.1056/NEJMoa2002032> PMID: 32109013
3. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *The Lancet*. 2020; 395: 1763–1770. [https://doi.org/10.1016/S0140-6736\(20\)31189-2](https://doi.org/10.1016/S0140-6736(20)31189-2) PMID: 32442528
4. Chand S, Kapoor S, Orsi D, Fazzari MJ, Tanner TG, Umeh GC, et al. COVID-19-Associated Critical Illness—Report of the First 300 Patients Admitted to Intensive Care Units at a New York City Medical Center. *J Intensive Care Med*. 2020; 35: 963–970. <https://doi.org/10.1177/0885066620946692> PMID: 32812834
5. Patel U, Malik P, Usman MS, Mehta D, Sharma A, Malik FA, et al. Age-Adjusted Risk Factors Associated with Mortality and Mechanical Ventilation Utilization Amongst COVID-19 Hospitalizations—A Systematic Review and Meta-Analysis. *SN Compr Clin Med*. 2020; 2: 1740–1749. <https://doi.org/10.1007/s42399-020-00476-w> PMID: 32904541
6. Luyt C-E. Long-term Outcomes of Pandemic 2009 Influenza A(H1N1)-Associated Severe ARDS.: 10.
7. Matthay MA. Acute respiratory distress syndrome. 2019; 22.
8. Chiumello D, Coppola S, Froio S, Gotti M. What's Next After ARDS: Long-Term Outcomes. *Respir Care*. 2016; 61: 689–699. <https://doi.org/10.4187/respcare.04644> PMID: 27121623
9. Khalid I, Alraddadi BM, Dairi Y, Khalid TJ, Kadri M, Alshukairi AN, et al. Acute Management and Long-Term Survival Among Subjects With Severe Middle East Respiratory Syndrome Coronavirus Pneumonia and ARDS. *Respir CARE*. 2015; 9. <https://doi.org/10.4187/respcare.04325> PMID: 26701365
10. Bein T, Weber-Carstens S, Apfelbacher C. Long-term outcome after the acute respiratory distress syndrome: different from general critical illness? *Respir Syst*. 2017; 23: 6.

11. Cooke CR. Economics of Mechanical Ventilation and Respiratory Failure. *Crit Care Clin.* 2012; 28: 39–55. <https://doi.org/10.1016/j.ccc.2011.10.004> PMID: 22123098
12. Owusu D, Kim L, O'Halloran A, Whitaker M, Piasecki AM, Reingold A, et al. Characteristics of Adults aged 18–49 Years without Underlying Conditions Hospitalized with Laboratory-Confirmed COVID-19 in the United States, COVID-NET—March–August 2020. *Clin Infect Dis.* 2020 [cited 17 Dec 2020]. <https://doi.org/10.1093/cid/ciaa1806> PMID: 33270136
13. Cunningham JW, Vaduganathan M, Claggett BL, Jering KS, Bhatt AS, Rosenthal N, et al. Clinical Outcomes in Young US Adults Hospitalized With COVID-19. *JAMA Intern Med.* 2021; 181: 379. <https://doi.org/10.1001/jamainternmed.2020.5313> PMID: 32902580
14. Sandoval M, Nguyen DT, Vahidy FS, Graviss EA. Risk factors for severity of COVID-19 in hospital patients age 18–29 years. *PLOS ONE.* 2021. <https://doi.org/10.1371/journal.pone.0255544> PMID: 34329347
15. Altonen BL, Arreglado TM, Leroux O, Murray-Ramcharan M, Engdahl R. Characteristics, comorbidities and survival analysis of young adults hospitalized with COVID-19 in New York City. Tan W, editor. *PLOS ONE.* 2020; 15: e0243343. <https://doi.org/10.1371/journal.pone.0243343> PMID: 33315929
16. Brat GA, Weber GM, Gehlenborg N, Avillach P, Palmer NP, Chiovato L, et al. International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. *Npj Digit Med.* 2020; 3: 109. <https://doi.org/10.1038/s41746-020-00308-0> PMID: 32864472
17. Klann JG, Weber GM, Estiri H, Moal B, Avillach P, Hong C, et al. Validation of a Derived International Patient Severity Algorithm to Support COVID-19 Analytics from Electronic Health Record Data. *Health Informatics.* 2020 Oct. <https://doi.org/10.1101/2020.10.13.20201855>
18. Hutch MR, Liu M, Avillach P, Consortium for Clinical Characterization of COVID-19 by EHR (4CE), Luo Y, Bourgeois FT. National Trends in Disease Activity for COVID-19 Among Children in the US. *Front Pediatr.* 2021; 9: 700656. <https://doi.org/10.3389/fped.2021.700656> PMID: 34307261
19. Bourgeois FT, Gutiérrez-Sacristán A, Keller MS, Liu M, Hong C, Bonzel C-L, et al. International Analysis of Electronic Health Records of Children and Youth Hospitalized With COVID-19 Infection in 6 Countries. *JAMA Netw Open.* 2021; 4: e2112596. <https://doi.org/10.1001/jamanetworkopen.2021.12596> PMID: 34115127
20. International Comparisons of Harmonized Laboratory Value Trajectories to Predict Severe COVID-19: Leveraging the 4CE Collaborative Across 342 Hospitals and 6 Countries: A Retrospective Cohort Study | medRxiv. [cited 22 Dec 2020]. <https://www.medrxiv.org/content/10.1101/2020.12.16.20247684v1>
21. Kohane IS, Aronow BJ, Avillach P, Beaulieu-Jones BK, Bradford RL, Brat GA, et al. What Every Reader Should Know About Studies Using Electronic Health Record Data but May Be Afraid to Ask. *J Med INTERNET Res.* 9. <https://doi.org/10.2196/22219> PMID: 33600347
22. WHO Anatomical Therapeutic Chemical (ATC) Classification. <https://pubchem.ncbi.nlm.nih.gov/source/11950>
23. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity Measures for Use with Administrative Data: *Med Care.* 1998; 36: 8–27. <https://doi.org/10.1097/00005650-199801000-00004> PMID: 9431328
24. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw.* 2010; 36. <https://doi.org/10.18637/jss.v036.i03>
25. Rubenfeld GD, Weaver J, Stern EJ. Incidence and Outcomes of Acute Lung Injury. *N Engl J Med.* 2005; 9. <https://doi.org/10.1056/NEJMoa050333> PMID: 16236739
26. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA.* 2016; 315: 788. <https://doi.org/10.1001/jama.2016.0291> PMID: 26903337
27. Atramont A, Lindecker-Cournil V, Rudant J, Tajahmady A, Drewniak N, Fouard A, et al. Association of Age With Short-term and Long-term Mortality Among Patients Discharged From Intensive Care Units in France. *JAMA Netw Open.* 2019; 2: e193215. <https://doi.org/10.1001/jamanetworkopen.2019.3215> PMID: 31074809
28. Siddiqui F, Ahmed M, Abbasi S, Avula A, Siddiqui AH, Philipose J, et al. Gastrointestinal Bleeding in Patients With Acute Respiratory Distress Syndrome: A National Database Analysis. *J Clin Med Res.* 2019; 11: 42–48. <https://doi.org/10.14740/jocmr3660> PMID: 30627277
29. the SUP-ICU co-authors, Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med.* 2015; 41: 833–845. <https://doi.org/10.1007/s00134-015-3725-1> PMID: 25860444
30. Hibbert K, Rice M, Malhotra A. Obesity and ARDS. *Chest.* 2012; 142: 785–790. <https://doi.org/10.1378/chest.12-0117> PMID: 22948584

31. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. *BMJ*. 2020; m1966. <https://doi.org/10.1136/bmj.m1966> PMID: [32444366](https://pubmed.ncbi.nlm.nih.gov/32444366/)
32. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury: *Crit Care Med*. 2009; 37: 2455–2464. <https://doi.org/10.1097/CCM.0b013e3181a0fea5> PMID: [19531947](https://pubmed.ncbi.nlm.nih.gov/19531947/)
33. Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome: *Crit Care Med*. 2000; 28: 2187–2192. <https://doi.org/10.1097/00003246-200007000-00001> PMID: [10921539](https://pubmed.ncbi.nlm.nih.gov/10921539/)
34. on behalf of the LUNG SAFE Investigators, the ESICM Trials Group, Boyle AJ, Madotto F, Laffey JG, Bellani G, et al. Identifying associations between diabetes and acute respiratory distress syndrome in patients with acute hypoxemic respiratory failure: an analysis of the LUNG SAFE database. *Crit Care*. 2018; 22: 268. <https://doi.org/10.1186/s13054-018-2158-y> PMID: [30367670](https://pubmed.ncbi.nlm.nih.gov/30367670/)
35. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. *Adv Ther*. 2018; 35: 1763–1774. <https://doi.org/10.1007/s12325-018-0805-y> PMID: [30357570](https://pubmed.ncbi.nlm.nih.gov/30357570/)