Validation of an Internationally Derived Patient Severity Phenotype to Support COVID-19 Analytics from Electronic Health Record Data

Jeffrey G Klann, Laboratory of Computer Science, Department of Medicine, Massachusetts General Hospital; and Harvard Medical School - Boston, United States

Griffin M Weber Department of Biomedical Informatics, Harvard Medical School; and Department of Medicine, Beth Israel Deaconess Medical Center - Boston, United States

Hossein Estiri, Laboratory of Computer Science, Department of Medicine, Massachusetts General Hospital; and Harvard Medical School - Boston, United States

Bertrand Moal, Bordeaux University Hospital, Bordeaux, France

Paul Avillach, Department of Biomedical Informatics, Harvard Medical School, Boston, United States

Chuan Hong, Department of Biomedical Informatics, Harvard Medical School, Boston, United States

Victor Castro, Research Information Science and Computing, Mass General Brigham, Boston, United States

Thomas Maulhardt, Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center Freiburg, University of Freiburg, Germany

Amelia LM Tan, Department of Biomedical Informatics, Harvard Medical School, Boston, United States

Alon Geva, Department of Anesthesiology, Critical Care, and Pain Medicine and Computational Health Informatics Program, Boston Children's Hospital - Boston, United States

Brett K Beaulieu-Jones, Department of Biomedical Informatics, Harvard Medical School, Boston, United States

Alberto Malovini, IRCCS ICS Maugeri, Pavia, Italy

Andrew M South, Department of Pediatrics, Section of Nephrology, Brenner Children’s Hospital, Wake Forest School of Medicine, Winston Salem, United States

Shyam Visweswaran, Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, United States

Gilbert S Omenn, Department of Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, United States

Kee Yuan Ngiam, National University Health Systems Singapore, Singapore

Kenneth D Mandl, Computational Health Informatics Program, Boston Children’s Hospital, Boston, United States

Martin Boeker, Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany

Karen L Olson, Computational Health Informatics Program, Boston Children’s Hospital, Boston, United States

Danielle L Mowery, Department of Biostatistics, Epidemiology, and Informatics, Institute for Biomedical Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States

Michele Morris, Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, United States

Robert W Follett, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, United States

David A Hanauer, Department of Pediatrics, University of Michigan Medical School, Ann Arbor, United States

Riccardo Bellazzi, Department of Electrical, Computer and Biomedical Engineering, University of Pavia, Italy and IRCCS ICS Maugeri, Pavia, Italy

Jason H Moore, Department of Biostatistics, Epidemiology, and Informatics, Institute for Biomedical Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States

Ne-Hooi Will Loh, Division of Critical Care, National University Health System, Singapore

Douglas S. Bell, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, United States

Kavishwar B Wagholikar, Department of Medicine, Massachusetts General Hospital, Boston, United States

Luca Chiovato, IRCCS ICS Maugeri, Pavia and Department of Internal Medicine and Medical Therapy, University of Pavia, Pavia, Italy

Valentina Tibollo, IRCCS ICS Maugeri, Pavia, Italy

Siegbert Rieg, Division of Infectious Disease, Department of Medicine II, Faculty of Medicine and Medical Center, University of Freiburg, , Freiburg, Germany

Anthony L.L.J. Li, National Center for Infectious Diseases, Tan Tock Seng Hospital, Singapore

Vianney Jouhet, Bordeaux University Hospital/ ERIAS-Inserm U1219 BPH, Bordeaux, France

Emily Schriver, Data Analytics Center, Penn Medicine, University of Pennsylvania Health System, Philadelphia, Pennsylvania, United States

Malarkodi J Samayamuthu, Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, United States

Zongqi Xia, Department of Neurology, University of Pittsburgh, Pittsburgh, United States

Meghan Hutch, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, United States

Yuan Luo, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, United States

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

Isaac S Kohane, Department of Biomedical Informatics, Harvard Medical School, Boston, United States

Gabriel A Brat, Department of Biomedical Informatics, Harvard Medical School, Boston, United States

Shawn N Murphy, Department of Neurology, Massachusetts General Hospital; and, Research Information Science and Computing, Mass General Brigham - Boston, United States

Correspondence: Jeffrey G. Klann; jeff.klann@mgh.harvard.edu; 50 Staniford St., Suite 750, Boston, MA 02114

Keywords: novel coronavirus; disease severity; computable phenotype; medical informatics; data networking; data interoperability

Word Count: 4,270

ABSTRACT

Introduction. The Consortium for Clinical Characterization of COVID-19 by EHR (4CE) is an international collaboration addressing COVID-19 with federated analyses of electronic health record (EHR) data.

Objective. We sought to develop and validate a computable phenotype for COVID-19 severity.

Methods. Twelve 4CE sites participated. First we developed an EHR-based severity phenotype consisting of six code classes, and we validated it on patient hospitalization data from the 12 4CE clinical sites against the outcomes of ICU admission and/or death. We also piloted an alternative machine-learning approach and compared selected predictors of severity to the 4CE phenotype at one site.

Results. The full 4CE severity phenotype had pooled sensitivity of 0.73 and specificity 0.83 for the combined outcome of ICU admission and/or death. The sensitivity of individual code categories for acuity had high variability - up to 0.65 across sites. At one pilot site, the expert-derived phenotype had mean AUC 0.903 (95% CI: 0.886, 0.921), compared to AUC 0.956 (95% CI: 0.952, 0.959) for the machine-learning approach. Billing codes were poor proxies of ICU admission, with as low as 49% precision and recall compared to chart review.

Discussion. We developed a severity phenotype using 6 code classes that proved resilient to coding variability across international institutions. In contrast, machine-learning approaches may overfit hospital-specific orders. Manual chart review revealed discrepancies even in the gold-standard outcomes, possibly due to heterogeneous pandemic conditions.

Conclusion. We developed an EHR-based severity phenotype for COVID-19 in hospitalized patients and validated it at 12 international sites.

BACKGROUND AND SIGNIFICANCE

The coronavirus disease 2019 (COVID-19) pandemic has stretched healthcare systems around the world to capacity. The need for actionable and reliable data has highlighted the value of the electronic health record (EHR). In particular, practice patterns and patient outcomes recorded in the EHR can be rapidly aggregated and analyzed to promote learning, discovery, and clinical feedback. [1] Despite large international investments to build such research networks [2–4], progress has been slow [5]; COVID-19 has challenged our informatics infrastructures and highlighted continued weaknesses. [6]

The Consortium for Clinical Characterization of COVID-19 by EHR (4CE) is a recently convened volunteer consortium of over 340 international hospitals that are leveraging EHR data and clinical expertise to develop robust informatics-driven investigations into COVID-19. The approach relies on shared analytics scripts supporting two common research analytics formats where analysis is local and aggregation is central. [7,8] By leveraging investments in standard analytic models while respecting data governance and patient privacy, we completed the initial phase of the study within two months of the pandemic's beginning, characterizing COVID-19 comorbidities and laboratory test values from 96 hospitals worldwide. [9]

To understand patient disease courses and investigate outcomes using EHR data, reliable and robust measures of disease severity are critical. Intuitively, outcomes such as ICU admission and in-hospital death seemed to be good correlates of severity. Early work in 4CE attempted to use these outcomes as severity measures, but it became apparent that these data are not reliably available in all environments. Therefore, 4CE sought to develop a reasonable proxy measure of worse outcomes in hospitalized patients with COVID-19 based on widely available EHR data such as medication, diagnosis, and lab codes. This combination of codes is essentially a computable phenotype, which is commonly used in medical informatics to detect the presence of a disease

state through proxy measures when no single validated data element for a disease exists or when individual diagnosis codes are mediocre predictors of actual disease presence. [10–13]

The most common method for defining a computable phenotype is through clinical and informatics expertise, wherein terms are specified that correlate clinical experience with the phenotype. However, a phenotype can make sense clinically yet have poor performance due to coding anomalies and variation between sites. Alternatively, it is possible to define phenotypes using a data-driven approach that uses statistical algorithms to find predictors of the desired outcomes directly from the data. These can also exhibit generalization problems due to overfitting. Thus, an important next step for either approach is to validate the phenotype, which can be done by comparing the concordance between the derived phenotype and the desired outcome - for which it is a proxy - at multiple sites. Although a variety of methods for defining an outcome are possible, the most reliable method of validating a computable phenotype is to perform chart review, which is considered the gold standard of truth about the patient. [14,15] For example, identification of ICU admissions is not always accurate, especially in a pandemic, where formal protocols are not always followed. In hospitals where hallways were converted into ad-hoc ICUs to support the surge of sick patients, standardized EHR data elements such as 'transfer to ICU' would not be properly recorded. Manual chart review (and perhaps natural language processing (NLP) in the near future) would be the only method to discover a patient's ICU status.

Existing Severity Measures

There has been heightened interest in disease severity measures since the outbreak of COVID-19. [16] We performed a review of 26 early COVID-19 studies. Five used ICU admission as the severity measure, one used American Thoracic Society criteria for severity of community-acquired pneumonia [17], and the rest used the World Health Organization (WHO) definition [18]. Other severity measures have been suggested [19]; however, they are not widely used or well validated.

The WHO broadly defines “severe” disease as fever or suspected respiratory infection, plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or arterial oxygen saturation measured by pulse oximeter (SpO2) ≤93% while breathing room air. [18] The WHO definition includes patients admitted to the hospital with pneumonia who can be managed on medical wards and are not critically ill. Best evidence suggests that about 85% of such patients will never progress to critical illness such as acute respiratory distress syndrome (ARDS). [20]

ICU admission cannot be used as a severity measure in 4CE because many sites do not have these data available in their EHRs. 4CE is only collecting common EHR data classes (demographics, diagnoses, medications, labs, and International Classification of Diseases (ICD) procedure codes), and thus a 4CE severity measure must include only these classes. The WHO definition has the same issue and is also very inclusive. It is most accurately a proxy for hospital admission (moderate disease) rather than a difficult hospital course (severe disease). As such, the WHO definition is too sensitive for 4CE’s goal of identifying patients with severe disease.

Objective

We set out to develop an EHR-driven severity phenotype as a proxy for worse clinical course in hospitalized patients with COVID-19 and validate it against the outcomes ICU admission and/or death in a subset of the global 4CE consortium. Because outcome data had uncertain accuracy, we performed a focused chart review to better understand validation performance. Finally, we compared a data-driven algorithm at one site to the expert-derived 4CE phenotype to understand the strengths and weaknesses of the two approaches.

MATERIALS AND METHODS

Defining Severity

First, we developed a 4CE severity phenotype that is both clinically reasonable and possible to identify across our diverse sites. To do this, we needed to limit severity to the EHR data classes that 4CE is collecting: demographics, diagnoses, medications, labs, and ICD procedure codes. We did not use outcomes (e.g., ICU admission), symptoms (e.g., wheezing), or vital signs (e.g., respiratory rate), as these are not widely or reliably available in EHRs.

We used the WHO severity definition as a starting point and two authors (GW and GB) identified a much more specific diagnosis group: patients who required invasive mechanical ventilation for acute respiratory failure or vasoactive medication infusions for shock.

We created a value set of EHR data elements that suggest these disease states, based on commonly available data classes:

- **Lab Test:** PaCO2 or PaO2
- **Medication:** sedatives/anesthetics or treatment for shock
- **Diagnosis:** ARDS, ventilator-associated pneumonia
- **Procedure:** endotracheal tube insertion or invasive mechanical ventilation [21]

These data elements correlate with many individual standard codes. To identify standard codes, we cross-referenced the i2b2 ontology in the ACT network. [2] This is a comprehensive terminology dictionary of 2.5 million codes found in many EHRs, with individual codes arranged hierarchically in folders describing the above concepts. The result was a list of ~100 codes in the International Classification of Diseases versions 9 and 10 (ICD-9 and ICD-10), Logical Observation Identifiers Names and Codes (LOINC), and RxNorm format, which are international standards used for research. These are listed in Table A1 in the Appendix, and on the Github sites for 4CE data extraction and the ACT COVID ontology. [22,23]

Local sites expanded these standard codes to match their local codes. Often, this was assisted with previous mappings from i2b2 where local items were a child folder of the standard code. [24] When mappings were not straightforward, the terms that most closely matched the definition were used, maximizing semantic equivalence across sites. For example, some US sites had both Current Procedural Terminology (CPT) and ICD procedure codes; the CPT codes were not added when ICD was available. In contrast, because some European sites do not use the US Clinical Modifications of ICD-10, other coding systems like Operation and Procedure Classification (OPS) codes were added to identify invasive mechanical ventilation.

Because the presence of any of these codes suggest severe disease, patients were assigned the severity phenotype if any code in the value set was generated during the hospital course. This makes the algorithm robust to practice variation - if one site does not include e.g., medication codes, then the severity phenotype can still be assigned through other code categories. Note that for laboratory tests, the phenotype uses the *existence* of these codes and not the associated value, because performing the test (e.g., PaO_2) suggests disease severity. Similarly, medication administration, regardless of the dose, indicates severe illness.

Network-Wide Analysis: 4CE Severity Validation

To validate the 4CE severity phenotype (and discover whether it actually works in practice), a subset of 12 sites with the necessary data identified patients who were admitted to the ICU and/or who died. Although not a perfect equivalence to severe disease or hospital course, ICU admission and death are objective measures that can be gleaned from patient data. We defined three options for confirming ICU admission, in order from most to least accurate:

1) **Chart Review.** This is considered the gold standard for identifying outcomes like ICU admission and could have been particularly useful in crisis situations like the COVID-19

pandemic. Nonetheless, chart review is time-consuming and laborious, so this option was impractical without substantial human resources.

2) **Local Hospital Data.** Hospital systems have idiosyncratic methods of determining ICU status, but they tend to be fairly accurate because they are used to determine admission, discharge, and transfer (ADT) status and to manage hospital bed allocation. However, not all sites had access to local hospital data, and expertise was required to incorporate this information into a data warehouse. Such limitations underscored the rationale for development of the severity phenotype.
3) **Specific ICU CPT Procedure Codes.** In the US, healthcare providers and hospitals use CPT codes to bill for provided critical care services. CPT codes for billing time spent providing critical care (99291, 99292) provide a third option for defining ICU admission. These CPT codes were not used to define the severity phenotype.

Each site computed a set of 2x2 tables comparing the 4CE severity phenotype to three outcomes (death only, ICU only, and ICU-or-death) (Table A2) for all patients in the 4CE Cohort. The 4CE Cohort included all hospitalized patients with a positive test for SARS-CoV-2 from 7 days before to 14 days after the hospitalization. Sites calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1-score from these tables. We used a fixed-effects meta-analysis model to estimate pooled scores over all sites. Sites then calculated the performance of individual code classes by computing the sensitivity for the same set of three outcomes. This analysis gave further insight into the components of the phenotype's performance at each site. Sensitivity would be highest for the full phenotype, as the trait is assigned when any code in the 4CE severity value set is present. Additionally, each site reported its approach for confirming ICU admission, total number of ICU beds (to give a sense of site capacity), and any variation from the standard 4CE severity definition or cohort definition. Sites performed these analyses between August 5, 2020, and September 18, 2020, reflecting cases that were recorded from March through August 2020.

To understand the practical differences between methods of defining ICU admission, we performed a limited analysis at two sites. We used a set of chart-reviewed ICU admission data among 866 confirmed COVID-19 patients from Massachusetts General Hospital (MGH) between March 8, 2020, and June 3, 2020. Extensive manual chart reviews were completed by trained reviewers, including physicians, pharmacists, research nurses, and clinical research coordinators. [25] University of Freiburg Medical Center in Germany (UKFR) provided a set of ICU admission flags obtained from manual chart review of 168 patients in their 4CE COVID-19 cohort that were directly related to their COVID-19 hospitalization. We compared coded ICU admissions to the chart-reviewed data at MGH and UKFR for patients in the 4CE Cohort. These overlapping data sets allowed us to compare the two definitions of ICU admission with the 4CE severity phenotype. We also compared the performance of the chart-reviewed definition to CPT code-based ICU admission (99291 and 99292) using MGH data.

Data-Driven Pilot Analysis

It is possible to define a phenotype using a data-driven (rather than expert-driven) approach. To better understand the differences between a data-driven vs. expert-driven severity phenotype, we undertook a machine-learning approach at a single site, Mass General Brigham (MGB), using an existing computable phenotyping pipeline.

First, we evaluated the classification performance of the 4CE severity phenotype. Second, we performed automated computable phenotyping using the Minimize Sparsity Maximize Relevance (MSMR) dimensionality reduction algorithm to select codes from among all possible data elements. [26,27] In both approaches, we applied generalized linear models (GLM) with a logit link, binomial distribution, and component-wise functional gradient boosting [28,29] to develop the computational models. We used the 4CE Cohort with ICU admission and/or death as the target for prediction. We trained and tested the models using an 80-20 train-test split, which we iterated 9 times to capture potential variability in performance metrics due to sampling. Model tuning was

performed via 5-fold cross-validation. To evaluate the two computable phenotyping models, we calculated the area under the receiver operating characteristic curve (AUC ROC) on the held-out test sets.

RESULTS

4CE Severity Analysis

Twelve sites participated in this analysis. The site names, locations, number of hospital beds, number of ICU beds (not reflecting surge capacity), and total 4CE Cohort size (rounded to the nearest 10) are shown in Table 1. We also included the data source used for ICU admission and whether the site's code mapping included any significant additions to the severity value set. (For example, European sites do not use the US ICD-10-CM, so additional standard codes were needed.) In further results, site names were replaced by a randomly assigned region identifier (either USAx for sites in the United States or GLOBALx for others).

Healthcare System	City	Country	No. of Hospitals	Total Beds	ICU Beds	ICU Data Source	4CE Cohort Size	Additional Codes in Value Set
Mass General Brigham (Partners Healthcare)	Boston, MA	USA	10	3418	292	Hospital data	3290	None
University of Pennsylvania	Philadelphia, PA	USA	5	2469	515	Hospital data	2330	Hospital data for intubation and ventilation
University of Pittsburgh	Pittsburgh, PA	USA	39	8400	589	CPT code and hospital location	990	CPT codes for intubation and ventilation
Beth Israel Deaconess Medical Center	Boston, MA	USA	1	673	77	Hospital data	690	None
University of Michigan	Ann Arbor, MI	USA	3	1043	141	CPT code and hospital location	420	None
University of California, Los Angeles	Los Angeles, CA	USA	2	786	192	Hospital data	430	None
Bordeaux University Hospital	Bordeaux	France	3	2676	180	Hospital data	360	CCAM (French procedure codes)
Istituti Clinici Scientifici Maugeri	Pavia, Lumezzane / Brescia, Milan	Italy	3	775	0	N/A (rehab hospital - no ICU)	260	None

Medical Center, University of Freiburg	Freiburg	Germany	1	1660	132	Hospital data	190	ICD-10 GM and OPS codes
Boston Children's Hospital	Boston, MA	USA	1	404	107	ICU note type	60	None
National University Hospital	Singapore	Singapore	1	1556	65	Hospital data	260	SNOMED codes for diagnoses; TOSP billing codes for procedures
St. Luke's University Health Network	Bethlehem, PA	USA	12	1700	287	Hospital data	1230	None

Table 1: Participating 4CE sites and metadata on ICU and 4CE coding definitions, number of beds, and 4CE Cohort size (rounded to the nearest 10).

The demographic characteristics of the cohorts (all patients vs. all patients with the severity phenotype) across the twelve sites are shown in Table 2.

Category	Group	All Patients n=10,340	Severe Phenotype Patients n=3,800	% Severe
Age	0-25	450 (4%)	90 (3%)	21%
	26-49	2180 (21%)	630 (17%)	29%
	50-69	3740 (36%)	1580 (42%)	42%
	70-79	1820 (18%)	800 (21%)	44%
	80+	2070 (20%)	650 (17%)	32%
Sex	Female	4930 (47%)	1610 (42%)	33%
	Male	5410 (52%)	2190 (58%)	41%
Race	White	4210 (42%)	1520 (41%)	36%
	Black	2550 (25%)	1000 (27%)	39%
	Other	3360 (33%)	1220 (33%)	36%

Table 2: Demographic characteristics of all patients vs. all patients with the severity phenotype, across the twelve sites. (Numbers are rounded to the nearest 10.)

Sites reported the sensitivity, specificity, PPV, and NPV of the 4CE severity phenotype for the outcome of ICU admission and/or death. The pooled F-score over 12 sites was estimated as 0.72 (95% CI: 0.63, 0.80) using a fixed-effect meta-analysis model. The pooled sensitivity was 0.73 (95% CI: 0.64, 0.82) with mean 0.73 (range 0.56). The pooled specificity was 0.83 (95% CI: 0.76, 0.91) with mean 0.80 (range 0.5). The sensitivity, specificity, PPV, NPV, and F-score by site can be seen in Table 3. Sites also computed these measures separately for ICU admission and death. The pooled specificity went down for the individual outcomes (0.79 for ICU and 0.67 for death),

but sensitivity was higher (0.77 for ICU, 0.76 for death). The statistics for the individual outcomes can be seen in Table A3 in the Appendix.

	Higher Specificity								
	GLO1	**GLO2**	**USA5**	**USA8**	**USA1**	**USA3**	**USA6**	**GLO5**	**USA4**
Sensitivity	0.35	0.74	0.58	0.66	0.76	0.75	0.73	0.83	0.67
Specificity	0.96	0.93	0.86	0.87	0.89	0.89	0.79	0.96	0.68
PPV	0.55	0.90	0.80	0.75	0.82	0.71	0.73	0.74	0.54
NPV	0.92	0.82	0.68	0.82	0.85	0.91	0.79	0.98	0.79
F-Score	0.43	0.81	0.67	0.70	0.79	0.73	0.73	0.78	0.60
F-Score CI	[0.26, 0.60]	[0.74, 0.88]	[0.65, 0.69]	[0.68, 0.73]	[0.74, 0.83]	[0.55, 0.91]	[0.70, 0.76]	[0.67, 0.90]	[0.65, 0.69]

			Higher Sensitivity						
			USA7	**USA2**	**GLO3**	**Meta-analysis**			
		Sensitivity	0.91	0.86	0.88	0.73 [0.64, 0.82]			
		Specificity	0.50	0.64	0.46	0.83 [0.76, 0.91]			
		PPV	0.70	0.70	0.63	0.73 [0.63, 0.82]			
		NPV	0.80	0.82	0.79	0.83 [0.75, 0.91]			
		F-Score	0.79	0.77	0.73	0.72 [0.63, 0.80]			
		CI	[0.75, 0.83]	[0.74, 0.82]	[0.68, 0.78]				

Table 3. The sensitivity, specificity, PPV, NPV, and F1-score of the 4CE severity phenotype for the outcome ICU admission and/or death, at each site in the United States (USA) and outside the US (GLObal). Estimates of the pooled scores were computed using a fixed-effect meta-analysis model.

Sites computed the sensitivity of individual code classes to understand how each contributed to the performance of the overall metric. Code classes demonstrated high variability of sensitivity across sites (Figure 1). For example, the anesthetic medication class had sensitivity ranging from 0.15 to 0.76. Code class sensitivity for the separate outcomes of ICU admission and death can be seen in Figures A1-A3 in the Appendix. Figure 2 shows the percentage of all severe patients

with a code in each class. Figure 3 shows the overlap of high-level code classes in a Venn Diagram.

Comparison of ICU Definitions

We computed the precision and recall of code-defined ICU admission using chart review as the reference at MGH and UKFR. At MGH, we found agreement for ICU admission with 97% precision and 83% recall. At UKFR, we measured 78% precision and 85% recall. At MGH, we also compared agreement of CPT-code ICU admission definition to chart-reviewed ICU admission and found a 49% precision and 49% recall.

We also recomputed summary statistics of the performance of our 4CE severity phenotype for the outcome of ICU admission and/or death using the chart-reviewed definition of ICU. At MGH and UKFR, the sensitivity was higher using the chart-reviewed definition (MGH: 0.80 vs 0.58 using hospital codes; UKFR: 0.85 vs. 0.74 using hospital codes). Specificity went down at MGH (0.75 vs 0.86 using hospital codes), while it went up slightly at UKFR (0.96 vs 0.93 using hospital codes).

The differences between UKFR and MGH (lower agreement precision and higher specificity performance at UKFR) are likely due to UKFR identifying only COVID-19-related ICU admissions, while MGH identified all ICU admissions during the COVID-19 hospitalization.

The full sets of summary statistics are reported in Tables 4 and A4.

	MGH: hospital	MGH: chart	UKFR: hospital	UKFR: chart
Sensitivity	0.58	0.80	0.74	0.85
Specificity	0.86	0.75	0.93	0.96
PPV	0.80	0.57	0.90	0.93
NPV	0.68	0.90	0.82	0.91

Table 4. Comparing the performance of the 4CE severity phenotype when using chart-reviewed ICU admission data or hospital codes at MGH and UKFR. The hospital column is repeated from Table 2 for clarity.

Data-Driven Pilot

The GLM model trained using the 4CE severity codes performed with a mean AUC ROC 0.903 (0.886, 0.921) on the MGB COVID-19 cohort. The GLM model trained on MSMR-selected codes (from among all possible diagnosis, medication, and LOINC codes) resulted in a mean AUC ROC of 0.956 (95% confidence interval: 0.952, 0.959). See Figure 4.

The MSMR-based algorithm's top ten codes (by odds ratio) fell into the following categories:

- Similar to the 4CE definition: PaCO2, PaO2, ARDS, sedatives
- Reflective of ICU ordering patterns: d-dimer, immature granulocytes, albumin
- Surprising proxies of severity: chlorhexidine, glycopyrrolate, palliative care encounter

DISCUSSION

When using EHR-derived data for research, we often adopt proxies for outcomes, especially if these outcomes are infrequently or poorly recorded in the EHR. Validation of these proxies is essential so that we can understand their strengths and limitations. Furthermore, to perform research on a network and especially at global scale, the outcome proxies must use data types broadly available through most EHRs and also be validated at multiple sites to account for differences in coding patterns. Examining subgroup performance of the codes can further improve our ability to understand cross-site differences.

In this study, our primary aim was to develop and validate an EHR-based severity phenotype for the international 4CE consortium to enable network-wide research on COVID-19 across heterogeneous sites. The EHR proxies we used to test for severity included commonly available elements in the EHR: diagnosis codes, laboratory orders, medication orders, and procedure codes. These elements improve our ability to infer the presence of respiratory distress and shock, which presumably are serious enough to lead to ICU admission, if available, and/or death.

This study highlights the frequent presence of coding differences between sites, as demonstrated by the remarkable variation in sensitivity by code class. Moreover, the codes captured for the severity phenotype at each site were very different. For example, some sites had a very high prevalence of mechanical ventilation codes and blood gas orders, whereas others had a low prevalence of these same measures, likely due to practice variation and code extraction differences. We compensated for this limitation by employing a logical OR method that accounts for this issue by assigning the phenotype if any code class is present. If a local practice tends not to use e.g., invasive mechanical ventilation (some sites might have favored non-invasive ventilation [30]), a severe patient could instead be flagged due to e.g., a PaO2 test. This also highlights the importance of expert-derived proxies for accurate EHR-based analysis. Clinicians among the 4CE leadership who understood the vagaries of hospital coding helped several sites to improve their data extraction and analysis, thereby enhancing the data quality of the 4CE initiative.

Given that the codes were a proxy for illness severity, the PPVs we obtained in the range of 0.7 to 0.9 and the NPVs in the range of 0.68 to 0.98 are indicative of the model's overall success. At three sites, the 4CE severity phenotype was more sensitive than specific. The phenotype captured ICU transfer or patient mortality but also patients without those outcomes. At most sites (9/12), the phenotype had higher specificity than sensitivity; it flagged mostly ICU or deceased patients but missed a small number of patients likely admitted to the ICU for monitoring. This study also highlights the challenges in selecting a gold standard for validation. There is no measurable assessment of a patient's actual complexity, so we chose ICU admission or mortality, as they are commonly used and generally accepted gold standards. However, ICU admission is not always clearly defined, especially during the pandemic. We evaluated 3 ways of identifying ICU admission, with accuracy improving from CPT codes to hospital code ICU designation to chart review by clinical experts. Our separate analysis of ICU admission definition suggests that the particular approach to coding ICU admission could impact measured performance. It also

validated our prioritization of choices for defining ICU admission: chart review was preferred, followed by hospital codes, and then billing data. The gold standard for validation is chart review, and the differences between what is actually recorded in a patient's chart and what data elements are available in the EHR are not always appreciated. In our analysis, chart review as compared to hospital data had precision of 97% (MGH) / 78% (UKFR) and recall of 83% (MGH) / 85% (UKFR), due largely to ICU admissions missed in hospital codes. This is probably due to pandemic conditions, where non-traditional spaces were converted into ICUs to support the surge of sick patients. The 4CE severity phenotype performed better overall when using chart review-based ICU admission and was able to correctly identify more severe patients. Sensitivity increased by 0.22 at MGH and 0.11 at UKFR. Change in specificity was mixed, but this was likely influenced by the different ICU admission targets at the two sites (all ICU admissions at MGH vs. COVID-related ICU admissions at UKFR). Billing codes were significantly less precise, missing many ICU admissions, yielding 49% precision and 49% recall. In the next phase of our work, it will be important to validate our findings with the addition of clinical notes at additional sites.

We explored a machine-learning data-driven approach at a single site and compared the results to our expert-derived phenotype. Among the top ten features identified by the data-driven model, four were conceptually similar to the expert-derived phenotype. Three were labs that occurred more frequently in the ICU than on the floor, which reflect ordering pattern biases rather than clinically meaningful data points. [31] The remaining orders were interesting proxies of the ICU (e.g., chlorhexidine, an antibacterial agent used for cleaning the skin). These proxies may be less generalizable than expert-curated codes.

Limitations

Our data-driven computable exploration was only performed at one site. In the future, we hope to engage a larger sample of sites in a data-driven analysis, which would allow us to pool together

a list of common codes to better discern generalizability. This will become possible as the 4CE network expands its computational infrastructure.

Additionally, the data analysis was conducted at sites during a surge in the COVID-19 pandemic, which could create unanticipated bias in the results.

Conclusion

We developed an EHR-based severity phenotype that can be used when longer-term outcomes data are not readily or reliably available. We validated this at 12 international 4CE sites and confirmed its good performance, due largely to its inclusiveness and breadth. We discovered many coding differences in individual EHR elements across sites. Additionally, we explored the comparison of an expert-derived proxy to a data-driven acuity score that maximized performance at individual sites. Finally, we found differences in ICU admission definitions, revealing that chart review captured information that was not reliable in hospital administrative data.

INFORMED CONSENT/IRB STATEMENT

Each institution reported obtaining proper institutional review board approval for data sharing. Certifications of waivers or approval were collected by the consortium. As data were transmitted in aggregate, no patient level data were available from any site.

ACKNOWLEDGEMENTS

Thanks to all members of the 4CE Consortium (see list in the Appendix) and all the effort and hard work of the local teams at the 12 sites. Thanks also to Brigitta Gough and Margaret Vella for their help in preparing this manuscript for submission, which was itself a massive undertaking.

CONTRIBUTIONS

Murphy, Brat, and Kohane contributed equally. Klann led the study and writing the manuscript. All authors approved the manuscript and contributed substantially. A table including full contributions is listed in Appendix B (Table B1).

COMPETING INTERESTS

RB and AM are shareholders of Biomeris s.r.l. KDM is an advisor to Medal, Inc.

DATA SHARING

All data collected for this study is presented in the manuscript or appendix. The 4CE Consortium provides additional visualizations and data for other consortium projects: https://covidclinical.net

FUNDING

This work was supported in part by the grants in the table below.

Grant Name	Funder	Grant #
Integrating EHR and Genomics to Predict Multiple Sclerosis Drug Response	NIH National Institute of Neurological Disorders and Stroke	R01NS098023
Pediatric Critical Care and Trauma Scientist Development Program	NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development	K12 HD047349
The Role of Angiotensin-(1-7) in Hypertension and Hypertension-Induced Heart and Kidney Damage	NIH Heart, Lung, and Blood Institute	K23-HL148394
Angiotensin-(1-7) Contributes to Hypertension and Hypertension-Induced Heart and Kidney Damage	NIH Heart, Lung, and Blood Institute	L40-HL148910
Instrumenting the Delivery System for a Genomics Research Information Commons	NIH National Center for Advancing Translational Sciences	U01TR002623
Wake Forest Clinical and Translational Science Institute	NIH National Center for Advancing Translational Sciences	UL1-TR001420

UPenn Institutional Clinical and Translational Science Award	NIH National Center for Advancing Translational Sciences	UL1-TR001878
Michigan Institute for Clinical and Health Research (Michr)	NIH National Center for Advancing Translational Sciences	UL1TR002240
UCLA Clinical and Translational Science Award	NIH National Center for Advancing Translational Sciences	UL1TR001881
University Of Pittsburgh Clinical And Translational Science Institute	NIH National Center for Advancing Translational Sciences	UL1 TR00185705
Harvard Catalyst CTSA/ACT Grant	NIH National Center for Advancing Translational Sciences	5UL1TR001857-05
Development and Evaluation of a Learning Electronic Medical Record System	NIH National Library of Medicine	R01 LM012095
Biases introduced by filtering electronic health records for patients with "complete data"	NIH National Library of Medicine	R01LM013345
Developing i2b2 into a Health Innovation Platform for Clinical Decision Support in the Genomics Era	NIH National Human Genome Research Institute	5R01HG009174-04
Data Fusion: A Sustainable, Scalable, Open Source Registry Advancing PVD Research	NIH National Heart, Lung, and Blood Institute	U01HL121518
Medical Informatics Funding Scheme, MIRACUM Consortium	German Federal Ministry of Education and Research	FKZ 01ZZ1801B

REFERENCES

1 Friedman CP, Allee NJ, Delaney BC, *et al.* The science of Learning Health Systems: Foundations for a new journal. *Learn Health Syst* 2017;**1**:e10020.

2 Visweswaran S, Becich MJ, D'Itri VS, *et al.* Accrual to Clinical Trials (ACT): A Clinical and Translational Science Award Consortium Network. *JAMIA Open* 10/2018;**1**:147–52.

3 Collins FS, Hudson KL, Briggs JP, *et al.* PCORnet: turning a dream into reality. *J Am Med Inform Assoc* 2014;**21**:576–7.

4 SPHN - Swiss Personalized Health Network (SPHN). https://sphn.ch/ (accessed 3 Sep 2020).

5 Budrionis A, Bellika JG. The Learning Healthcare System: Where are we now? A systematic review. *J Biomed Inform* 2016;**64**:87–92.

6 Surma V, Kudchadkar S, Bembea M, *et al.* The Critical Care Learning Healthcare System: Time to Walk the Walk. *Crit Care Med* 2020;**48**:1907–9.

7 Hripcsak G, Duke JD, Shah NH, *et al.* Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Stud Health Technol Inform* 2015;**216**:574–8.

8 Murphy SN, Weber G, Mendis M, *et al.* Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2). *J Am Med Inform Assoc* 2010;**17**:124–30.

9 Brat GA, Weber GM, Gehlenborg N, *et al.* International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. *NPJ Digit Med* 2020;**3**:109.

10 Shivade C, Raghavan P, Fosler-Lussier E, *et al.* A review of approaches to identifying patient phenotype cohorts using electronic health records. *J Am Med Inform Assoc* 2014;**21**:221–30.

11 Hripcsak G, Albers DJ. Next-generation phenotyping of electronic health records. *J Am Med Inform Assoc* 2013;**20**:117–21.

12 Rasmussen LV, Thompson WK, Pacheco JA, *et al.* Design patterns for the development of electronic health record-driven phenotype extraction algorithms. *J Biomed Inform* 2014;**51**:280–6.

13 Yu S, Ma Y, Gronsbell J, *et al.* Enabling phenotypic big data with PheNorm. *J Am Med Inform Assoc* 2018;**25**:54–60.

14 Newton KM, Peissig PL, Kho AN, *et al.* Validation of electronic medical record-based phenotyping algorithms: results and lessons learned from the eMERGE network. *J Am Med Inform Assoc* 2013;**20**:e147-54.

15 Rubbo B, Fitzpatrick NK, Denaxas S, *et al.* Use of electronic health records to ascertain, validate and phenotype acute myocardial infarction: A systematic review and recommendations. *Int J Cardiol* 2015;**187**:705–11.

16 Guan W-J, Ni Z-Y, Hu Y, *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 2020;**382**:1708–20.

17 Li H-Y, Guo Q, Song W-D, *et al.* Modified IDSA/ATS Minor Criteria for Severe Community-Acquired Pneumonia Best Predicted Mortality. *Medicine* 2015;**94**:e1474.

18 World Health Organization, Others. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. World Health Organization 2020. https://apps.who.int/iris/bitstream/handle/10665/331446/WHO-2019-nCoV-clinical-2020.4-chi.pdf (accessed 17 Jun 2020).

19 Diagnosis When There Is No Testing. https://www.acep.org/corona/covid-19-field-guide/diagnosis/diagnosis-when-there-is-no-testing/ (accessed 3 Sep 2020).

20 Ye Z, Rochwerg B, Wang Y, *et al.* Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidence-based guideline. *CMAJ* Published Online First: 29 April 2020. doi:10.1503/cmaj.200648

21 Tobin MJ. Advances in mechanical ventilation. *N Engl J Med* 2001;**344**:1986–96.

22 Visweswaran S. *ACT-COVID-Ontology*. Github 2020. https://github.com/shyamvis/ACT-COVID-Ontology (accessed 5 Jan 2021).

23 4CE Consortium. *4CE Phase 1.1 Data Extraction*. Github 2020. https://github.com/covidclinical/Phase1.1SqlDataExtraction (accessed 5 Jan 2021).

24 Klann JG, Abend A, Raghavan VA, *et al.* Data interchange using i2b2. *J Am Med Inform Assoc* 2016;**23**:909–15.

25 MGH COVID-19 Registry. 2020.https://rc.partners.org/about/projects-initiatives/new-covid-19-research-tools-researchers/covid-19-external-data-sets#mgh-covid-registry (accessed 8 Sep 2020).

26 Estiri H, Strasser ZH, Klann JG, *et al.* Transitive Sequencing Medical Records for Mining Predictive and Interpretable Temporal Representations. *Patterns (N Y)* 2020;**1**:100051.

27 Hossein Estiri, Sebastien Vasey, Shawn N Murphy. Transitive sequential pattern mining for discrete clinical data. In: Martin Michalowski RM, ed. *Artificial Intelligence in Medicine*. Springer 2020.

28 Hothorn T, Bühlmann P, Kneib T, *et al.* Model-based Boosting 2.0. *J Mach Learn Res* 2010;**11**:2109–13.

29 Hothorn T, Bühlmann P, Kneib T, *et al.* mboost: Model-based boosting. *R package version* 2012;:2–1.

30 Essay P, Mosier J, Subbian V. Rule-Based Cohort Definitions for Acute Respiratory Failure: Electronic Phenotyping Algorithm. *JMIR Med Inform* 2020;**8**:e18402.

31 Agniel D, Kohane IS, Weber GM. Biases in electronic health record data due to processes within the healthcare system: retrospective observational study. *BMJ* 2018;**361**:k1479.

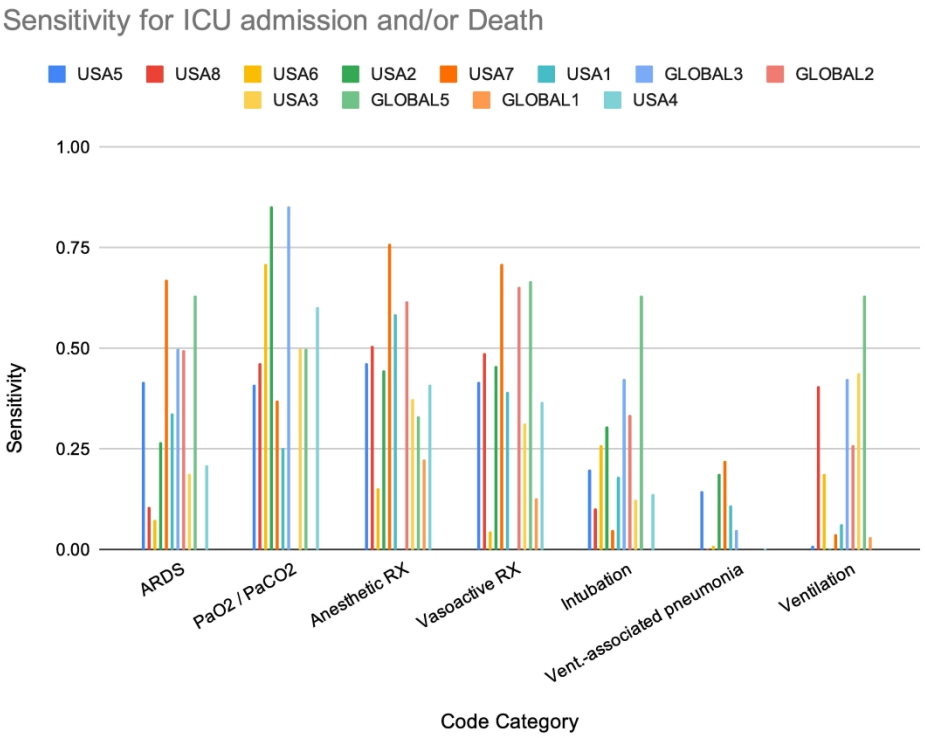
FIGURE CAPTIONS

Figure 1. Sensitivity of code classes to identify ICU admission and/or death.

Figure 2. Percentage of patients identified by the 4CE severity phenotype, broken down by code class.

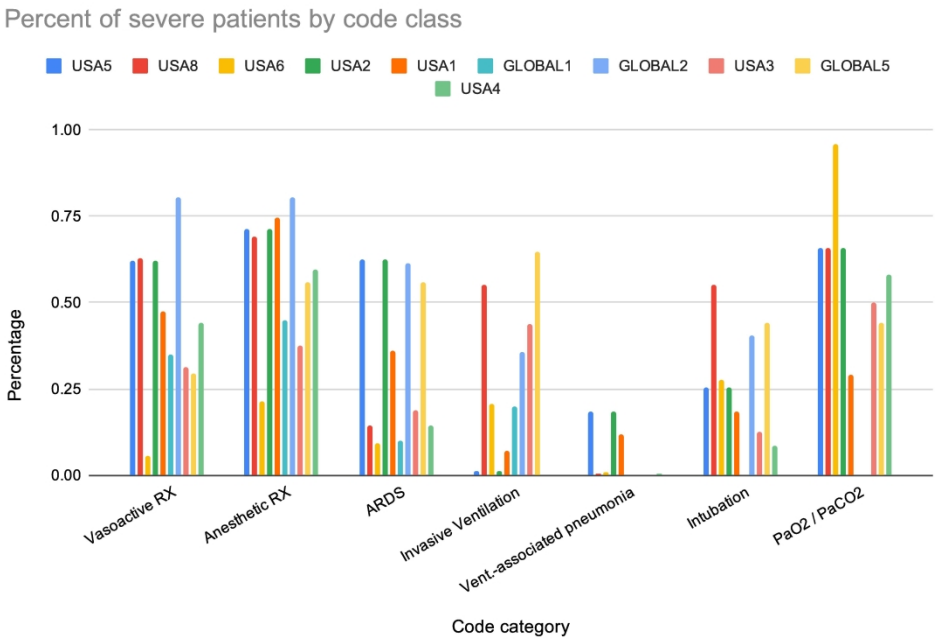
Figure 3. Venn diagram showing overlap of code classes among patients with the 4CE severity phenotype. (Nine sites reporting.)

Figure 4. ROC curves when using a GLM boost algorithm on 4CE-defined features vs. a data-driven approach.



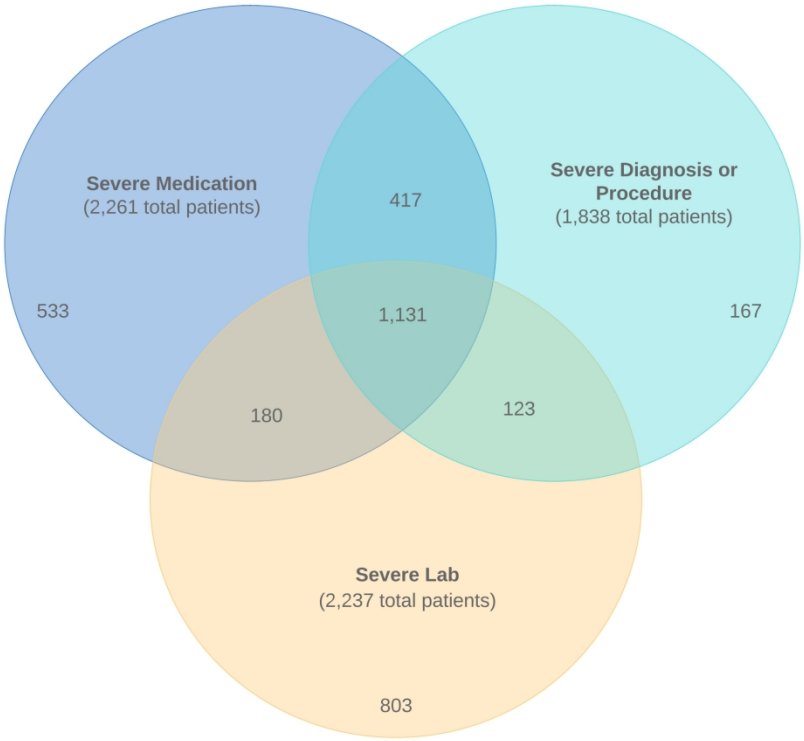
Sensitivity of code classes to identify ICU admission and/or death.

183x149mm (600 x 600 DPI)



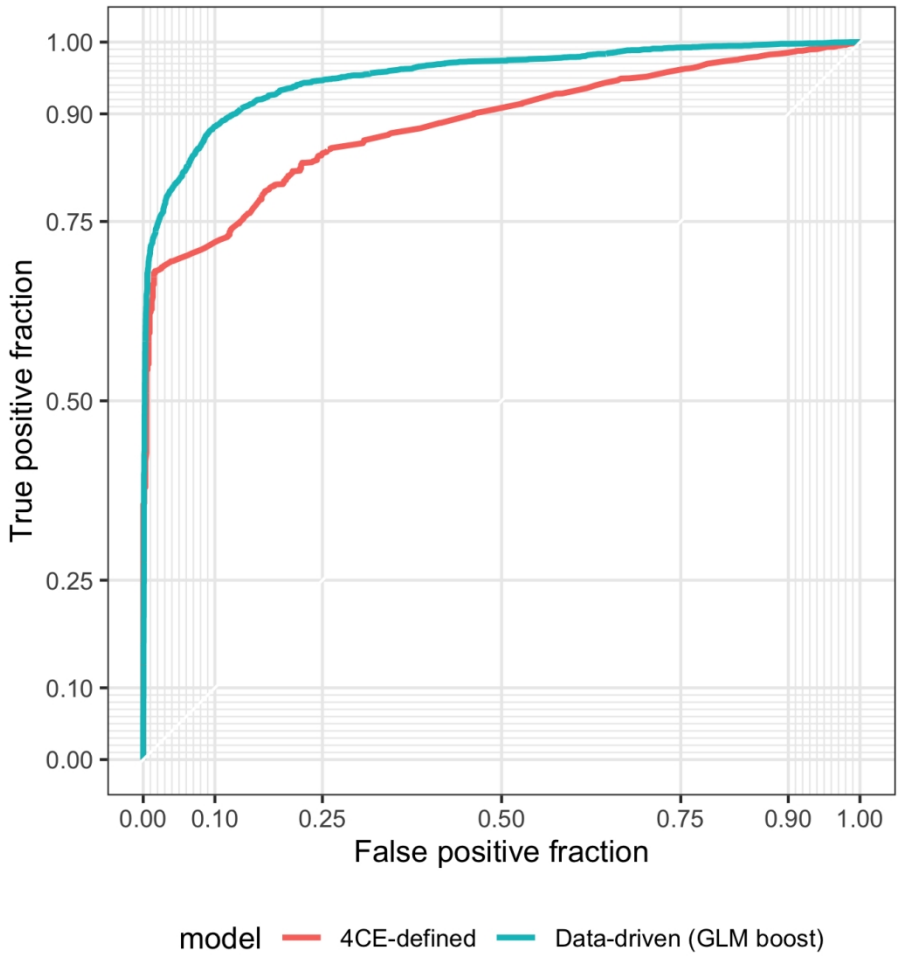
Percentage of patients identified by the 4CE severity phenotype, broken down by code class.

215x152mm (600 x 600 DPI)



Venn Diagram showing overlap of code classes among patients with the 4CE Severe Phenotype. (Nine sites reporting.)

216x177mm (600 x 600 DPI)



ROC curves when using a GLM boost algorithm on 4CE-defined features vs. a data-driven approach.

529x529mm (72 x 72 DPI)

APPENDIX A: ADDITIONAL METHODS AND RESULTS

4CE Detailed Severity Definition

The codification of the following data elements results in ~100 codes in ICD-9, ICD-10, LOINC, and RxNorm format, international standards used for research.

- **Lab Test:** PaCO2 or PaO2
- **Medication:** sedatives/anesthetics or treatment for shock
- **Diagnosis:** ARDS, ventilator-associated pneumonia
- **Procedure:** endotracheal tube insertion or invasive mechanical ventilation

These 100 elements are listed in Table A1 below, and can also be found in the 4CE Data Extraction file description (https://github.com/covidclinical/Phase1.1SqlDataExtraction) and as part of the ACT COVID Ontology v3.0 (https://github.com/shyamvis/ACT-COVID-Ontology/tree/master/ontology).

Table A1: 4CE Severity Codes [26]

Labs (PAO2)	
PaCO2	LOINC 2019-8
PaO2	LOINC 2703-7
Diagnoses and Procedures	
Acute respiratory distress syndrome (ARDS)	ICD-10: J80; ICD-9: 518.82
Ventilator associated pneumonia (pneumonia)	ICD-10: J95.851; ICD-9: 997.31
Insertion of endotracheal tube (intubation)	ICD-10: 0BH17EZ; ICD-9: 96.04
Invasive mechanical ventilation (vent)	ICD-10: 5A093*, 5A094*, 5A095*; ICD-9: 96.70, 96.71, 96.72
Anesthesia Medications (SIANES)	
Ketamine	RxNorm:6130,206967,206970,206972,238082,238083,238084,372528,631205,1087926,1301259,1486837,1605773
Propofol	RxNorm:8782,207793,312674,377483,884675,1188478,1808216,1808217,1808219,1808222,1808223,1808224,1808225,1808234,1808235,1862110,2050125
Midazolam	RxNorm:6960,106517,199775,311700,311701,311702,372922,379133,404091,404092,422410,446503,998210,998211,1313988,1551393,1551395,1666776,1666777,1666797,1666798,1666800,1666814,1666821,1666823,2057964
Cisatracurium	RxNorm:199211,199212,210676,210677,319864,377135,1730193,1730194,1730196
Rocuronium bromide	RxNorm:68139,198383,207901,375623,584528,584530,82858

	9,828591,830752,1234995,1242617
Vecuronium	RxNorm:71535,240606,376856,404136,859437
Dexmetotomidine	RxNorm:48937,259859,284397,309710,377219,897073,897077,1249681,1373737,1535224,1535226,1535228,1535230,1718899,1718900,1718902,1718906,1718907,1718909,1718910,1732667,1732668,1732674,1788947
Emergency Cardiac Medications (SICARDIAC)	
Dobutamine	RxNorm:3616,204395,309985,309986,309987,1812167,1812168,1812170
Dopamine	RxNorm:3628,238217,238218,238219,310011,310012,310013,727842,727843,727844,1114874,1114880,1114888,1292716,1292731,1292740,1292751,1292887,1743862,1743869,1743871,1743877,1743879,1743938,1743941,1743950,1743953
Epinephrine	RxNorm:3992,106779,106780,141848,198620,198621,204843,212343,244284,245317,247596,310116,310117,310127,310132,313967,372029,372030,372031,377281,727310,727316,727345,727347,727373,727386,727410,746206,746207,880658,883806,891437,891438,1305268,1305269,1490057,1546216,1546217,1658178,1660013,1660014,1660016,1661387,1721536,1870205,1870207,1870225,1870230,1870232,1989112,1989117,1991328,1991329
Norepinephrine	RxNorm:7512,209217,242969,1745276
Phenylephrine	RxNorm:8163,106686,198786,198787,198788,211704,211709,211712,211714,211715,212770,212771,212772,212773,238230,238996,238997,238999,239000,239001,241033,247940,260687,312395,312398,314175,351701,351702,351982,359907,373368,373369,373370,373372,373375,374570,376521,379042,387789,392099,393309,477358,477359,542391,542655,542674,562592,584580,584582,584584,584588,602511,603259,603276,603915,617785,669267,672683,672685,672891,692479,700414,704955,705163,705164,705170,827706,864089,1045470,1049182,1049184,1052767,1087043,1087047,1090087,1117374,1232651,1232653,1234563,1234569,1234571,1234576,1234578,1234579,1234581,1234584,1234585,1234586,1251018,1251022,1299137,1299141,1299145,1299879,1300092,1307224,1358843,1363777,1363785,1363786,1363787,1366958,1542385,1547926,1548673,1549386,1549388,1666371,1666372,1666374
Angiotensin II	RxNorm:1999003,1999006,1999007,1999012
Nitric oxide	RxNorm:7442
Milrinone	RxNorm:52769,311705,347930,404093,1791839,1791840,1791842,1791854,1791859,1791861,1939322
Epoprostenol	RxNorm:8814,211199,211200,562501,562502,1009216,1302755,1789858
Vasopressin	RxNorm:11149,313578,374283,1593738,2103181,2103182,2103184

Network-Wide Analyses: Individual Outcomes

As described in the main text, participating sites identified patients who were admitted to the ICU and/or who died, in order to validate the 4CE severity phenotype. Each site computed a set of 2x2 tables comparing the 4CE severity phenotype to three outcomes (death only, ICU only, and ICU-or-death) (Table A2, below) and then calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and F1-score from these tables (Table 3 and A3, below). Code class sensitivity for the outcomes of ICU admission and/or death can be seen in Figures 1 and A1-A3, below.

Table A2. Severity Analysis 2x2 tables design

	ICU and/or Death	No ICU or Death
Severe phenotype	`Phenotype and outcome`	`Phenotype only`
No severe phenotype	`Outcome only`	`Neither phenotype nor outcome`

Table A3. Sensitivity, Specificity, PPV, and NPV by outcome (ICU admission and/or death, ICU, and death)

Outcome	Measure	Meta-analysis	Mean	USA5	USA8	USA6	USA2	USA7	USA1	GLOB3	GLOB1	GLOB2	USA3	GLOB5	USA4
ICU/ DEATH	Sensitivity	0.73 [0.64, 0.82]	0.73	0.58	0.66	0.73	0.86	0.91	0.76	0.88	0.35	0.74	0.75	0.83	0.67
ICU	Sensitivity	0.77 [0.68, 0.87]	0.79	0.62	0.75	0.74	0.88	0.91	0.78	0.89	n/a	0.81	0.75	0.83	0.71
DEATH	Sensitivity	0.76 [0.64, 0.87]	0.78	0.59	0.66	0.78	0.91	0.90	0.80	0.91	0.35	0.76	1.00	1.00	0.73
ICU/ DEATH	Specificity	0.83 [0.76, 0.91]	0.79	0.86	0.87	0.79	0.64	0.50	0.89	0.46	0.96	0.93	0.89	0.96	0.68
ICU	Specificity	0.79 [0.71, 0.87]	0.75	0.85	0.85	0.78	0.62	0.45	0.88	0.41	n/a	0.89	0.89	0.96	0.67
DEATH	Specificity	0.67 [0.60, 0.75]	0.64	0.70	0.74	0.60	0.47	0.31	0.67	0.32	0.96	0.75	0.74	0.88	0.60
ICU/ DEATH	PPV	0.73 [0.63, 0.82]	0.71	0.80	0.75	0.73	0.70	0.70	0.82	0.63	0.55	0.90	0.71	0.74	0.54

ICU	PPV	0.67 [0.58, 0.77]	0.68	0.75	0.68	0.71	0.67	0.63	0.81	0.52	n/a	0.81	0.71	0.74	0.47
DEATH	PPV	0.24 [0.15, 0.33]	0.25	0.29	0.32	0.16	0.29	0.24	0.20	0.19	0.55	0.45	0.06	0.03	0.25
ICU/ DEATH	NPV	0.83 [0.75, 0.91]	0.83	0.68	0.82	0.79	0.82	0.80	0.85	0.79	0.92	0.82	0.91	0.98	0.79
ICU	NPV	0.86 [0.79, 0.94]	0.86	0.75	0.89	0.81	0.86	0.82	0.86	0.84	n/a	0.89	0.91	0.98	0.85
DEATH	NPV	0.97 [0.93, 1.02]	0.95	0.89	0.92	0.97	0.96	0.93	0.97	0.95	0.92	0.92	1.00	1.00	0.93

Figure A1. Sensitivity of code classes to identify ICU admission.

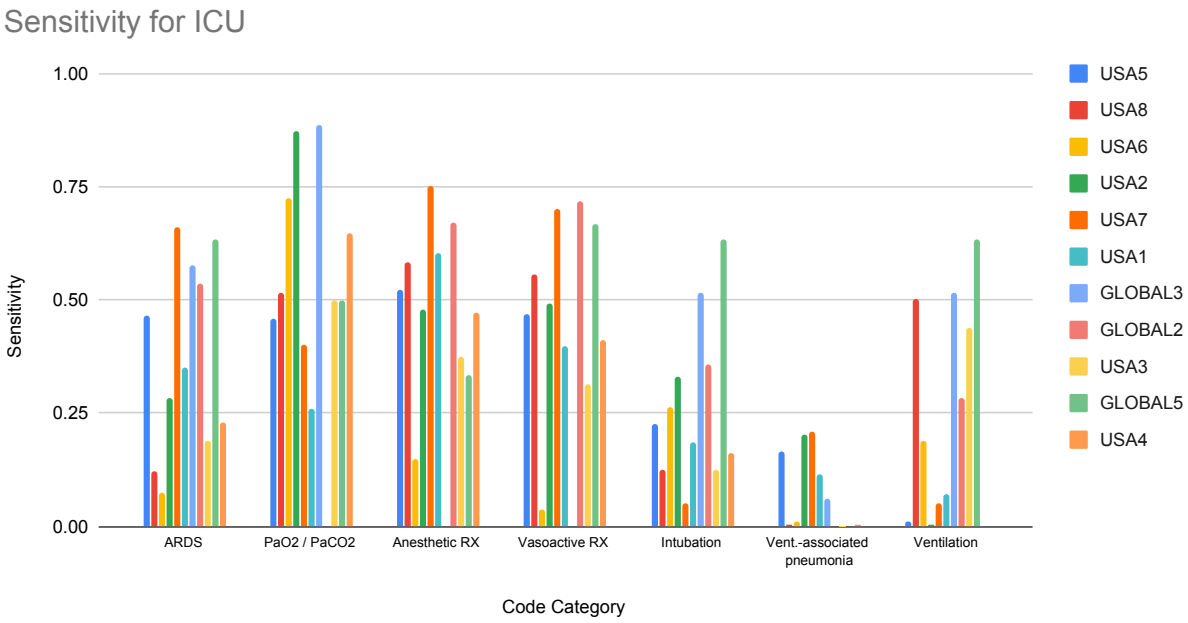


Figure A2. Sensitivity of code classes to identify death. (Sites close to 1.00 were biased by small populations.)

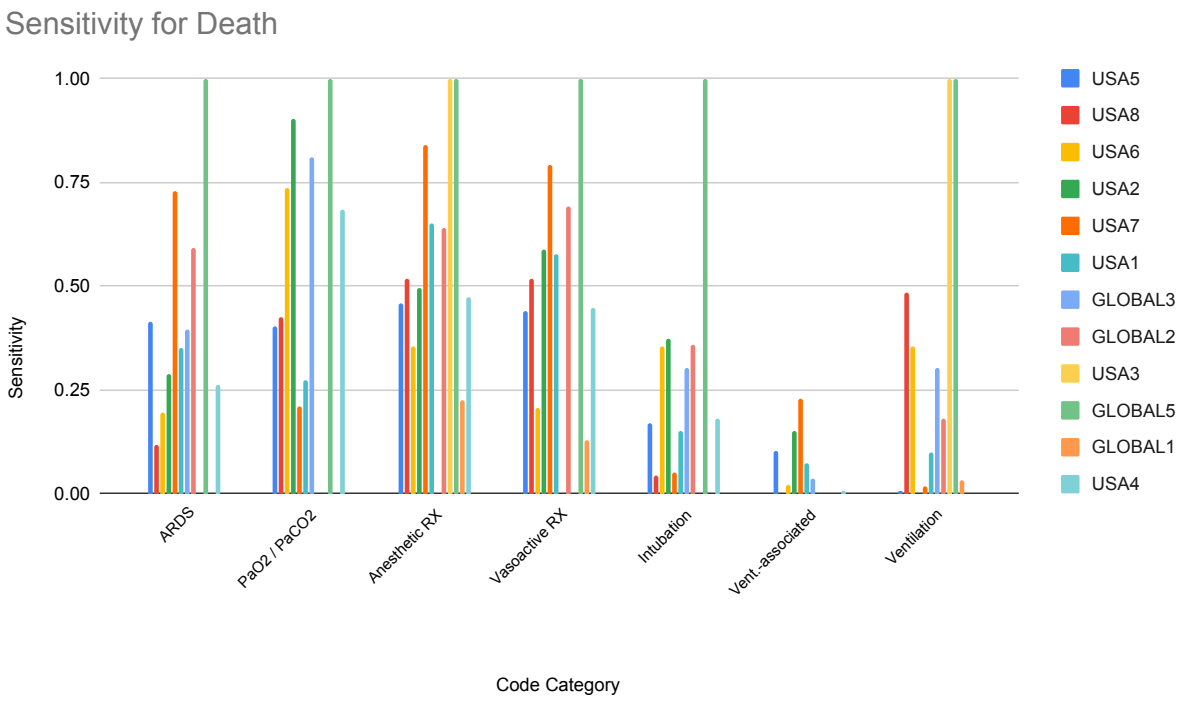
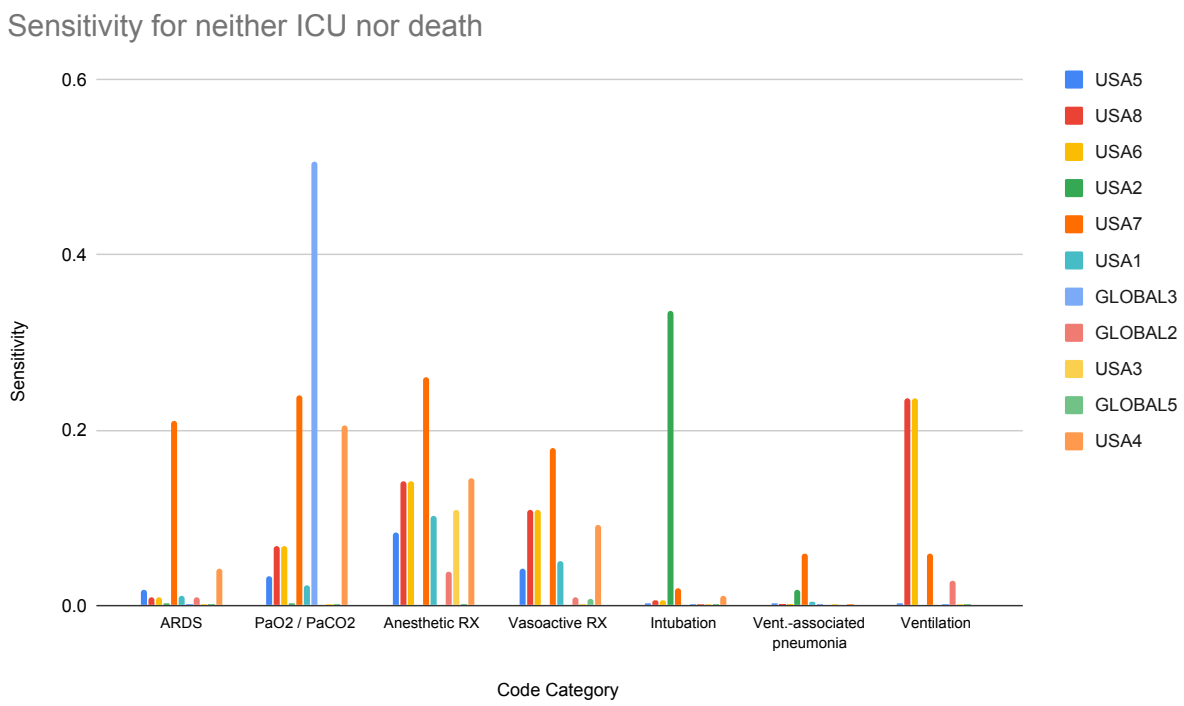


Figure A3. Sensitivity of code classes to identify no ICU admission nor death



Comparison of ICU Definitions

Table A4. Comparing chart-reviewed ICU admission data to other standards for finding ICU admission: hospital codes and CPT codes. This was done at Massachusetts General Hospital using the 4CE COVID-19 cohort and at UKFR using a manually chart reviewed subset of the 4CE COVID-19 cohort.

	MGH: CPT	MGH: Hospital	UKFR: Hospital
Sensitivity	0.49	0.83	0.85
Specificity	0.99	0.99	0.88
PPV	0.49	0.97	0.78
NPV	0.59	0.92	0.93

APPENDIX B: ADDITIONAL AUTHORSHIP INFORMATION

Figure B1. 4CE Consortium Members

Adem Albayrak; Danilo F Amendola; Anthony L.L.J Li; Bruce J Aronow; Andrew Atz; Paul Avillach; Brett K Beaulieu-Jones; Douglas S Bell; Antonio Bellasi; Riccardo Bellazzi; Vincent Benoit; Michele Beraghi; José Luis Bernal Sobrino; Mélodie Bernaux; Romain Bey; Alvar Blanco Martínez; Martin Boeker; Clara-Lea Bonzel; John Booth; Silvano Bosari; Florence T Bourgeois; Robert L Bradford; Gabriel A Brat; Stéphane Bréant; Mauro Bucalo; Anita Burgun; Tianxi Cai; Mario Cannataro; Aize Cao; Charlotte Caucheteux; Julien Champ; Luca Chiovato; James J Cimino; Tiago K Colicchio; Sylvie Cormont; Sébastien Cossin; Jean Craig Juan Luis Cruz Bermúdez; Arianna Dagliati; Mohamad Daniar; Christel Daniel; Anahita Davoudi; Batsal Devkota; Julien Dubiel; Scott L DuVall; Loic Esteve; Robert W Follett; Paula S.A Gaiolla; Thomas Ganslandt; Noelia García Barrio; Nils Gehlenborg; Alon Geva; Tobias Gradinger; Alexandre Gramfort; Romain Griffier; Nicolas Griffon; Olivier Grisel; Alba Gutiérrez-Sacristán; David A Hanauer; Christian Haverkamp; Martin Hilka; John H Holmes; Chuan Hong; Petar Horki; Meghan R Hutch; Richard Issitt; Anne Sophie Jannot; Vianney Jouhet; Mark S Keller; Katie Kirchoff; Jeffrey G Klann; Isaac S Kohane; Ian D Krantz; Detlef Kraska; Ashok K Krishnamurthy; Sehi L'Yi; Trang T Le; Judith Leblanc; Guillaume Lemaitre; Leslie Lenert; Damien Leprovost; Molei Liu; Ne Hooi Will Loh; Yuan Luo; Kristine E Lynch; Sadiqa Mahmood; Sarah Maidlow; Alberto Malovini; Kenneth D Mandl; Chengsheng Mao; Patricia Martel; Aaron J Masino; Michael E Matheny;

Thomas Maulhardt; Michael T McDuffie; Arthur Mensch; Bertrand Moal, Jason S Moore; Jeffrey S Morris; Michele Morris; Karyn L Moshal; Sajad Mousavi; Danielle L Mowery; Douglas A Murad; Shawn N Murphy; Kee Yuan Ngiam; Jihad Obeid; Marina P Okoshi; Karen L Olson; Gilbert S Omenn; Nina Orlova; Brian D Ostasiewski; Nathan P Palmer; Nicolas Paris; Lav P Patel; Miguel Pedrera Jimenez; Hans U Prokosch; Robson A Prudente; Rachel B Ramoni; Maryna Raskin; Siegbert Rieg; Gustavo Roig Dominguez; Elisa Salamanca; Malarkodi J Samayamuthu; Arnaud Sandrin; Emily Schriver; Juergen Schuettler; Luigia Scudeller; Neil Sebire; Pablo Serrano Balazote; Patricia Serre; Arnaud Serret-Larmande; Domenick Silvio; Piotr Sliz; Jiyeon Son; Andrew M South; Anastasia Spiridou; Amelia L.M. Tan; Bryce W.Q. Tan; Byorn W.L. Tan; Suzana E Tanni; Deanne M Taylor; Valentina Tibollo; Patric Tippmann; Andrew K Vallejos; Gael Varoquaux; Jill-Jênn Vie; Shyam Visweswaran; Kavishwar B Wagholikar; Lemuel R Waitman; Demian Wassermann; Griffin M Weber; Yuan William; Zongqi Xia; Alberto Zambelli; Aldo Carmona; Charles Sonday; James Balshi

Table B1. 4CE Authorship Contributions

Contribution	Conception or design of the work	Acquisition of data	Analysis or Interpretation of data	Drafting	Manuscript Approval
Authors' Initials	JK, GW, HE, PA, AM, GO, IK, GB, SM	JK, GW, HE, BM, PA, VC, TM, AM, AG, BB, AM, SV, GO, NY, KM, MB, KO, DM, MM, RF, DH, RB, JM, NL, DB, LC, VT, SR, AL, VJ, ES, MS, ZX, YL, MH, IK	JK, GW, HE, BM, PA, CH, VC, TM, AM, AG, BB, AM, AS, KM, MB, KO, DM, MM, RF, VT, SR, AL, VJ, ES, ZX, IK, SM	JK, HE, BM, PA, TM, AG, BB, AS, SV, KM, MB, NL, KW, ZX, IK, GB, SM	JK, GW, HE, BM, PA, CH, VC, TM, AM, AG, BB, AM, AS, SV, GO, NY, KM, MB, KO, DM, MM, RF, DH, RB, JM, NL, DB, KW, LC, VT, SR, AL, VJ, ES, MS, ZX, YL, MH, IK, GB, SM

Table B2. IRB Boards that Approved This Study

Institutional Review Board	IRB Approval
Mass General Brigham	Exempt
University of Pennsylvania	Exempt
University of Pittsburgh	Exempt
Beth Israel Deaconess Medical Center	Exempt
University of Michigan	Exempt
University of California, Los Angeles	Exempt
Bordeaux University Hospital	Exempt
Istituti Clinici Scientifici Maugeri	Waived
Medical Center, University of Freiburg	Exempt
Boston Children’s Hospital	Exempt
National University Hospital	Waived
St. Luke's University Health Network	Waived