Research and Applications

Towards clinical data-driven eligibility criteria optimization for interventional COVID-19 clinical trials

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ABSTRACT

Objective: This research aims to evaluate the impact of eligibility criteria on recruitment and observable clinical outcomes of COVID-19 clinical trials using electronic health record (EHR) data.

Materials and Methods: On June 18, 2020, we identified frequently used eligibility criteria from all the interventional COVID-19 trials in ClinicalTrials.gov (n = 288), including age, pregnancy, oxygen saturation, alanine/aspartate aminotransferase, platelets, and estimated glomerular filtration rate. We applied the frequently used criteria to the EHR data of COVID-19 patients in Columbia University Irving Medical Center (CUIMC) (March 2020–June 2020) and evaluated their impact on patient accrual and the occurrence of a composite endpoint of mechanical ventilation, tracheostomy, and in-hospital death.

Results: There were 3251 patients diagnosed with COVID-19 from the CUIMC EHR included in the analysis. The median follow-up period was 10 days (interquartile range 4–28 days). The composite events occurred in 18.1% (n = 587) of the COVID-19 cohort during the follow-up. In a hypothetical trial with common eligibility criteria, 33.6% (690/2051) were eligible among patients with evaluable data and 22.2% (153/690) had the composite event.

Discussion: By adjusting the thresholds of common eligibility criteria based on the characteristics of COVID-19 patients, we could observe more composite events from fewer patients.

Conclusions: This research demonstrated the potential of using the EHR data of COVID-19 patients to inform the selection of eligibility criteria and their thresholds, supporting data-driven optimization of participant selection towards improved statistical power of COVID-19 trials.

Key words: real-world data, clinical trial, eligibility criteria, COVID-19, criteria optimization
INTRODUCTION
Background and significance
The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been spreading worldwide rapidly since late 2019. The number of confirmed COVID-19 cases and deaths globally exceeded 15 million and 600 thousand, respectively, as of July 22, 2020. Despite the rocketing number of confirmed cases and deaths, there is no consensus on a definitive therapy for COVID-19 as of late July 2020. Meanwhile, many clinical trials have been launched to evaluate the efficacy and safety of experimental agents. As COVID-19 clinical trials are being created rapidly, concerns regarding the robustness of trial designs have been raised, particularly related to insufficient power or sample sizes, inadequate statistical adjustments, and inconsistent definitions for endpoints. However, no one yet has evaluated the influence of the eligibility criteria of the COVID-19 studies on these issues.

Clinical trials on investigational agents test efficacy upon a sample of patients who meet the eligibility criteria. Results from trials with restrictive eligibility criteria do not provide evidence regarding the risks and benefits of tested drugs for patients who were excluded from the trials and may not generalize to real-world patients with the target condition. On the other hand, applying overly permissive eligibility criteria may include heterogeneous patients and reduce the probability of detecting the drug’s true effect. Thus, it is vital to balance the tradeoff between internal validity and external validity during eligibility criteria definition. Better understanding of the baseline characteristics and the events of interest among potentially eligible patients could inform optimal definition of eligibility criteria for COVID-19 interventional trials.

Objective
Towards this understanding, we aimed to measure the influence of eligibility criteria on patient recruitment and outcome event observation in this retrospective cohort study. We first identified the frequently used eligibility criteria in COVID-19 trials. Then, using electronic health record (EHR) data, we assessed the influence of individual eligibility criteria based on the number of patients that could be included or excluded by each criterion. The outcome events were compared between the included and excluded groups to estimate how eligibility criteria could be modified to optimize the balance between internal and external validity.

MATERIALS AND METHODS
Selection and processing of eligibility criteria for evaluation
Eligibility criteria and descriptive trial information were obtained from the Aggregative Analysis of ClinicalTrials.gov (AACT) database. AACT provides a copy of ClinicalTrials.gov, updated daily, with some postprocessing and data formatting, enabling users to easily analyze multiple aspects of clinical trials in a structured format. A total of 288 COVID-19 interventional trials with at least 1 recruiting site in the US were registered in ClinicalTrials.gov as of June 18, 2020. Two researchers (AMB, LAS) shared the workload for the annotation of these trials and independently annotated 457 eligibility criteria from a common set of 32 trials manually and mapped them to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). For example, in the exclusion criterion “Exclude patients with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal,” aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were annotated as measurement entities and > 3 times upper limit of normal was annotated as a value entity. Corresponding values were retrieved from the Columbia University Irving Medical Center (CUIMC) OMOP database using the OMOP concept identifier for AST, 3013721.

The COVID-19 cohort in Columbia University Irving Medical Center (CUIMC)
The EHR of CUIMC was transformed to the OMOP CDM v5.3 in May 2020, henceforth referred to as the CDM. The operational definition of the COVID-19 cohort was based on the cohort definition developed during the Observational Health Data Sciences and Informatics (OHDSI) study-a-thon, namely “a persons hospitalized with COVID-19 narrow, with no prior observation required.” Cohort enrollment date was defined as the admission date of a person hospitalized with COVID-19 after March 1, 2020. We included each patient with a confirmed diagnosis of COVID-19 within 3 weeks prior to or during hospitalization. Using the OMOP CDM, the occurrence of outcome events was identified in patients with COVID-19. The event of interest was the composite of mechanical ventilation, tracheostomy, and in-hospital death, corresponding to the severity score of ≥ 6 of the World Health Organization ordinal scale for clinical improvement.

Measurements, including glomerular filtration rate, liver function tests, blood oxygen saturation, and platelet counts, were extracted from the OMOP CDM. The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation for patients with age ≥ 18 and Schwartz equation for patients with age < 18, respectively. Measurements of oxygen saturation and supplemental oxygen requirements were also extracted from the EHR narratives along with their values using natural language processing. Primary terminology related to oxygen saturation or supplemental oxygen delivery was recognized in the Emergency Department provider notes and then data were manually reviewed to identify oxygen saturation and the requirement of supplemental oxygen. Measured values at the time of cohort enrollment date ± 1 day were used as the initial presenting characteristics to evaluate the simulated eligibility of patients to COVID-19 interventional clinical trials, selecting the earliest measure in the case of multiple measurements. A validated algorithm was used to identify pregnancy episodes in the CUIMC OMOP database. The OMOP concepts and corresponding concept codes that were used to identify the occurrence of events are presented in Supplementary Table 1. This study was approved by the CUIMC institutional review board.

Evaluation of the impact of single or multiple criteria
The impact of the most frequently used eligibility criteria from COVID-19 clinical trials was evaluated using EHR data from COVID-19 patients hospitalized at CUIMC. The joint influence of multiple criteria was estimated using synthetic eligibility criteria, designed using the most commonly used cutoff values. The number of potentially eligible patients, the proportion of patients with events during the follow-up period, and the required sample size to detect 20% reduction of composite events with 80% power and a significance level alpha of 0.05 were compared among synthetic trials with different thresholds for the same set of criteria.

Statistical analysis
In the case of a censored event, the observation is censored on the last date for which EHR data are available from the CUIMC.

References:
1. The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been spreading worldwide rapidly since late 2019.
2. As COVID-19 clinical trials are being created rapidly, concerns regarding the robustness of trial designs have been raised.
3. The operational definition of the COVID-19 cohort was based on the cohort definition developed during the Observational Health Data Sciences and Informatics (OHDSI) study-a-thon.
4. The event of interest was the composite of mechanical ventilation, tracheostomy, and in-hospital death.
5. The glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation for patients with age ≥ 18 and Schwartz equation for patients with age < 18.
6. The OMOP concepts and corresponding concept codes that were used to identify the occurrence of events are presented in Supplementary Table 1.
7. This study was approved by the CUIMC institutional review board.

Abbreviations:
AST: aspartate aminotransferase
ALT: alanine aminotransferase
COVID-19: coronavirus disease 2019
EHR: electronic health record
OMOP: Observational Medical Outcomes Partnership
CDM: Common Data Model
CUIMC: Columbia University Irving Medical Center
OHDSI: Observational Health Data Sciences and Informatics
AACT: Aggregative Analysis of ClinicalTrials.gov
OMOP database. For time-to-event analysis, the cumulative incidence was compared among different subgroups stratified by criteria. Log-rank test with post-hoc adjustment with false discovery rate was used to test the significance of difference in survival analysis. Cohort generation and descriptive analysis were done using Python v3.5. Plotting figures and sample size calculation were done using R v4.0.

RESULTS

Frequently used medical concepts in eligibility criteria

There were 288 interventional trials (301 cohorts; analysis was done at the cohort level hereafter) targeting COVID-19 in the United States as of June 18, 2020. Frequently used exclusion criteria of COVID-19 trials are presented in Supplementary Table 2. Medical concepts that belong to the condition, drug, and measurement domains of the OMOP CDM were frequently used in the eligibility criteria of COVID-19 trials. We evaluated the inter-annotator agreement as an F1 score on instance-level in a subset (32/288) of annotated trials. The instance-level F1 scores for condition, drug, and measurement concepts were 0.789, 0.845, and 0.884, respectively. We evaluated the following frequently used criteria: 1) age, 2) pregnancy, 3) oxygen saturation, 4) liver function (AST, ALT), 5) platelet counts, and 6) estimated glomerular filtration rate (eGFR). The most frequent minimum age was 18 years, with 261 trials (86.7%) using this criterion. Only 24 trials (8.0%) included pediatric patients. Six trials excluded patients over 65. The next most frequent exclusion criteria were pregnancy, oxygen saturation, hepatic impairment, requiring mechanical ventilation, ratio of arterial oxygen tension to inspired oxygen fraction, platelet counts, and renal impairment. Criteria concerning mechanical ventilation and ratio of arterial oxygen tension to inspired oxygen fraction were not evaluated because those are related to composite events in the study cohort.

The COVID-19 cohort in CUIMC

A total of 3251 COVID-19 patients were identified from the CUIMC EHR. The baseline characteristics of patients are presented in Table 1. More events were observed in males (20.1%, 355/1767) than females (15.6%, 232/1483) and in patients with age over 65 (28.8%, 464/1609) than in adults ≤ 65 (7.9%, 120/1510) or pediatric patients (2.3%, 3/132). While the composite events occurred in 10.8% of patients with eGFR ≥ 60 mL/min/1.73m², more than 30% of patients with eGFR < 30 mL/min/1.73m² had events. Although the number of patients with AST or ALT > 5 times ULN was small, the proportions of patients with composite events were higher in these groups (17/47 [36.2%] in ALT > 5 times ULN; 43/120 [35.8%] in AST > 5 times ULN). Patients with room-air oxygen saturation ≤ 93% or supplemental oxygen had more events (266/969 [27.5%]). No events were observed in pregnant patients.

Figure 2 shows the cumulative incidence of composite events over the duration of follow-up period stratified by age groups, eGFR levels, and oxygen saturation. Overall, the difference in the occurrence of composite events was statistically significant for different age groups, renal functions, and oxygen saturation levels (Figure 2). Patients with age > 65 had a higher risk for the occurrence of composite events when compared to adult patients with age ≤ 65 (Hazard ratio [HR] 4.24, 95% confidence interval [CI] 3.47–5.19, Figure 2A). Cumulative incidences of composite events over the duration of follow-up period according to a different age with more detailed groupings are presented in Figure 2B. Patients with eGFR ≥ 60 mL/min/1.73m² had significantly lower risk for the occurrence of composite events in comparison to eGFR < 60 mL/min/1.73m² (Figure 2C). Patients with oxygen saturation at room-air > 93% had significantly lower incidence of composite events than those with supplemental oxygen requirement or oxygen saturation ≤ 93% (Figure 2D).

Estimation of the collective influence of multiple hypothetical eligibility criteria

The number of eligible patients and corresponding incidence of composite events were modeled using a synthetic clinical trial with the following inclusion criteria: 1) Age ≥ 18; 2) eGFR ≥ 30 mL/min/1.73m²; 3) AST/ALT ≤ 5 times the ULN; 4) not pregnant; 5) Oxygen saturation at room air ≤ 93% or requirement of supplemental oxygen; and 6) platelets ≥ 50 x10³/μL, and 2051 COVID-19 patients with available eGFR, AST/ALT, platelets, and oxygen saturation levels was used in the estimation. In the synthetic trial, 33.6% (690/2051) of patients were eligible and 22.2% (135/690) of eligible patients had composite events (Table 2). Patients were mostly ineligible because of the oxygen saturation (n = 1153) followed by the renal function (n = 405). Ineligible patients showed comparable risks regarding the incidence of composite events when compared to potentially eligible patients (Figure 3; HR 0.92 (95% CI 0.75–1.12),
The number of eligible patients, composite events, and sample size required to detect 20% reduction in event rates according to different set of eligibility criteria are presented in Table 2. With modifying the thresholds for age, renal, and liver functions, more patients were potentially eligible for the trials and more events could be observed during the follow-up. Selected alternative sets of eligibility criteria that enable study sponsors to decrease the required sample size are presented in Table 2. We recommend sponsors use “Age ≥ 50” instead to enrich the event rates. Sponsors could adopt 15 mL/min/1.73m² and 10x ULN as thresholds for renal and liver functions to enrich the event rates, respectively. Alternatives that have shown more accrual and more event rates are presented in Supplementary Table 3.

**DISCUSSION**

The number of interventional COVID-19 clinical trials is growing rapidly. Without knowing the baseline characteristics and incidence

| Characteristics                                    | Number of patients (n, %) | Number of events (n, %) |
|---------------------------------------------------|---------------------------|-------------------------|
| Overall                                           | 3251                      | 587 (18.1%)             |
| Age, category                                     |                           |                         |
| Median (IQR)                                      | 65 (50–77)                |                         |
| < 18                                              | 132 (4.1%)                | 3 (2.3%)                |
| 18–29                                             | 171 (5.2%)                | 1 (0.6%)                |
| 30–39                                             | 257 (7.9%)                | 11 (4.3%)               |
| 40–49                                             | 256 (7.9%)                | 15 (5.9%)               |
| 50–59                                             | 496 (15.3%)               | 44 (8.9%)               |
| 60–69                                             | 688 (21.2%)               | 115 (16.7%)             |
| 70–79                                             | 615 (18.9%)               | 173 (28.1%)             |
| 80–89                                             | 465 (14.3%)               | 157 (33.8%)             |
| ≥ 90                                               | 171 (5.2%)                | 68 (39.8%)              |
| Sex                                               |                           |                         |
| Male                                              | 1767 (54.4%)              | 355 (20.1%)             |
| Female                                            | 1483 (45.6%)              | 232 (15.6%)             |
| eGFR, mL/min/1.73m²                               |                           |                         |
| No.                                               | 3076                      |                         |
| ≥ 60                                              | 1716 (55.8%)              | 185 (10.8%)             |
| 45–59                                             | 433 (14.1%)               | 98 (22.6%)              |
| 30–44                                             | 357 (11.6%)               | 106 (29.7%)             |
| 15–29                                             | 298 (9.7%)                | 101 (33.9%)             |
| < 15                                              | 272 (8.8%)                | 90 (33.1%)              |
| ALT, U/L<sup>a</sup>                              |                           |                         |
| No.                                               | 2893                      |                         |
| Median (IQR)                                      | 29 (18–51)                |                         |
| ≤ 1x ULN                                          | 2169 (75.0%)              | 396 (18.3%)             |
| 1x ULN–< 3x ULN                                   | 618 (21.4%)               | 124 (20.1%)             |
| 3x ULN–< 5x ULN                                   | 59 (2.0%)                 | 12 (20.3%)              |
| > 5x ULN                                          | 47 (1.6%)                 | 17 (36.2%)              |
| AST, U/L<sup>b</sup>                              |                           |                         |
| No.                                               | 2911                      |                         |
| Median (IQR)                                      | 42 (28–70)                |                         |
| ≤ 1x ULN                                          | 1276 (43.8%)              | 166 (13.0%)             |
| 1x ULN–≤ 3x ULN                                   | 1314 (45.1%)              | 280 (21.3%)             |
| 3x ULN–≤ 5x ULN                                   | 201 (6.9%)                | 66 (32.8%)              |
| > 5x ULN                                          | 120 (4.1%)                | 43 (35.8%)              |
| Oxygen saturation                                 |                           |                         |
| No.                                               | 2259                      |                         |
| ≤ 93% or on supplemental oxygen                  | 969 (42.9%)               | 266 (27.5%)             |
| > 93%                                             | 1290 (57.1%)              | 204 (15.8%)             |
| Platelets, 10³/µL                                 |                           |                         |
| No.                                               | 3150                      |                         |
| Median (IQR)                                      | 207 (157–271)             |                         |
| < 50                                              | 19 (0.6%)                 | 3 (15.8%)               |
| ≥ 50                                              | 3131 (99.4%)              | 569 (18.2%)             |
| Currently pregnant                                | 49 (1.5%)                 | 0                       |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ULN, upper limit of normal.

<sup>a</sup>The ULN of ALT was 50 U/L.

<sup>b</sup>The ULN of AST was 37 U/L.
of events of interest of COVID-19 patients, the protocols of previous clinical trials and drug monographs were the only knowledge sources for clinical trial designers when they specified eligibility criteria. With the availability of real-world data on COVID-19 patients, it is possible to better estimate the influence of eligibility criteria on accrual and outcome rates and to develop data-driven criteria design. The influence of eligibility criteria for age, renal function, liver function, oxygen saturation, platelets, and pregnancy on patient selection and event observation for COVID-19 trials was evaluated. For the criteria concerning age, renal function, and oxygen saturation, the adoption of certain cutoff values could lead to the exclusion of a significant number of patients and observable events as well as to the inclusion of patients who do not contribute much information. 

Regarding the age range, the most common age range criterion was “18 years or older.” While patients most vulnerable to COVID-19 (ie, those with age over 65), qualified for most of the trials, pediatric patients were largely excluded from most ongoing trials. In our cohort, 2.3% (3/132) of pediatric patients experienced the composite events, implying pediatric patients were less likely to have severe pulmonary events when compared to adults but are not completely free of risks. Recently, a multisystem inflammatory syndrome in children has been reported and the association with COVID-19 is being investigated. Clinical presentation and severe outcomes commonly involved the intestines and heart, with very distinctive features from acute COVID-19 progression in adults. Therefore, pediatric patients should be studied in trials tailored to the unique progression of COVID-19 in children rather than being excluded or being included in trials recruiting all age ranges. 

Among the measurements, oxygen saturation was the most commonly used eligibility criterion of the COVID-19 trials. However, the way in which each clinical trial formulated criteria related to oxygen saturation varied. Some trials simply mentioned the numerical

![Figure 1](image-url)
cutoff for oxygen saturation, while others provided more information about the delivery methods or flow rates. In some cases, other respiratory indexes including respiratory rates and ratio of arterial oxygen tension to inspired oxygen fraction ratio were also added to form a combined criterion in order to enroll patients meeting at least 1 of the criteria. Regardless of the complexity of eligibility criteria, patients with low oxygenation status had more opportunities to participate in clinical trials. Patients with supplemental oxygen requirement or oxygen saturation ≤ 93% had significantly higher incidence of severe events in our evaluation. Observable events could be enriched by excluding patients with room-air oxygen saturation above 93%.

Only 1.5% (49/3251) of the cohort was pregnant at enrollment; composite events were not observed among them. When compared to nonpregnant patients, pregnancy does not seem to confer additional risk regarding the clinical outcome of the COVID-19.21–23 Given the relatively small number of pregnant patients hospitalized in each institution, a collaborative approach with a multisite clinical trial or registry is more feasible to generate COVID-19-related clinical trial evidence in pregnant patients.24

Figure 2. Cumulative incidence of mechanical ventilation, tracheostomy, or in-hospital death by (A-B) different age groups, (C) different renal functions, and (D) oxygen saturation.

Abbreviation: eGFR, estimated glomerular filtration rate.
When the occurrence of events was evaluated stratified by eGFR, the rate of the composite event drops for patients with eGFR \( \geq 60 \) mL/min/1.73m\(^2\). To enrich the study population, sponsors should consider enrolling patients with moderate renal impairment, although it will depend upon the tolerability and pharmacokinetic properties of the interventional agent. For example, remdesivir, baricitinib, and tocilizumab are currently being tested for treatment of COVID-19 and can be administered to patients with eGFR \( \geq 30 \) mL/min/1.73m\(^2\). Using the eGFR criteria of \( \geq 30 \) or 45 mL/min/1.73m\(^2\) would have the dual benefit of expanding the pool of eligible patients and enriching the trial with a group of patients who have a greater need for a potentially effective drug. For patients with eGFR < 30 mL/min/1.73m\(^2\), retrospective evaluation could be an alternative if it is not feasible to include these patients as trial participants considering the fragile clinical state in this subgroup.}

**Table 2.** The number of eligible patients, composite events, and sample size required to detect 20% reduction in event rates according to different sets of eligibility criteria

| Hypothetical trial                      | Eligible number of patients\(^a\) | Composite events (n, %) | Sample size required to detect 20% reduction in event rates\(^b\) |
|-----------------------------------------|-----------------------------------|-------------------------|---------------------------------------------------------------|
| **Joint of commonly used criteria**     |                                   |                         |                                                               |
| – Age \( \geq 18 \)                     | 690                               | 153 (22.2%)             | 2548                                                          |
| – eGFR \( \geq 30 \) mL/min/1.73m\(^2\) |                                   |                         |                                                               |
| – AST/ALT \( \leq 5 \times \text{ULN} \) |                                   |                         |                                                               |
| – Nonpregnant                           |                                   |                         |                                                               |
| – Room-air saturation \( \leq 93\% \) or on supplemental oxygen |   |                         |                                                               |
| – Platelets \( \geq 50 \times 10^3/\mu\) L |   |                         |                                                               |
| **Selected alternative scenarios**      |                                   |                         |                                                               |
| Scenario with more events               | 693                               | 187 (27.0%)             | 1980                                                          |
| – Age \( \geq 50 \)                     |                                   |                         |                                                               |
| – eGFR \( \geq 15 \) mL/min/1.73m\(^2\) |                                   |                         |                                                               |
| – AST/ALT \( \leq 10 \times \text{ULN} \) |                                   |                         |                                                               |
| – Nonpregnant                           |                                   |                         |                                                               |
| – Room-air saturation \( \leq 93\% \) or on supplemental oxygen |   |                         |                                                               |
| – Platelets \( \geq 50 \times 10^3/\mu\) L |   |                         |                                                               |
| Scenario with more eligible patients    | 933                               | 214 (22.9%)             | 2442                                                          |
| – Age \( \geq 50 \)                     |                                   |                         |                                                               |
| – eGFR \( \geq 15 \) mL/min/1.73m\(^2\) |                                   |                         |                                                               |
| – AST/ALT \( \leq 10 \times \text{ULN} \) |                                   |                         |                                                               |
| – Nonpregnant                           |                                   |                         |                                                               |
| – Room-air saturation \( \leq 95\% \) or on supplemental oxygen |   |                         |                                                               |
| – Platelets \( \geq 50 \times 10^3/\mu\) L |   |                         |                                                               |

Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; ULN: upper limit of normal.

**Note:** The ULN of AST and ALT were 37 U/L and 50 U/L, respectively.

\(^a\)Measurements were available in a total of 2051 patients.

\(^b\)power = 80%, alpha = 0.05 events were treated as dichotomous.

![Figure 3. Cumulative incidence of mechanical ventilation, tracheostomy, or in-hospital death by eligibility to a hypothetical clinical trial using common eligibility criteria. Inclusion criteria for this hypothetical trial are as follows: 1) Age \( \geq 18 \); 2) eGFR \( \geq 30 \) mL/min/1.73m\(^2\); 3) AST/ALT \( \leq 5 \times \text{ULN} \); 4) not pregnant; 5) Oxygen saturation at room air \( \leq 93\% \) or requirement of supplemental oxygen; and 6) platelets \( \geq 50 \times 10^3/\mu\) L. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal.](image-url)
patients. Previous studies indicated that COVID-19 treatment outcome could be influenced by the availability of medical resources or ethnicity.26,27 The baseline characteristics of our study population were comparable to the patient characteristics in other studies (Supplementary Table 4).29,31 In an international study that included 95 hospitals across 5 countries, the laboratory trajectories including hepatic and renal function were consistent on the day of COVID-19 diagnosis.30 However, the characteristics of the COVID-19 patient population may be evolving as the pandemic progresses and its epicenters move geographically. Further studies are warranted to test the generalizability of the results to cohorts with different demographics or comorbidities. Our analytical software was based on the OMOP CDM and can be easily run on other OMOP CDM-compliant clinical databases, enabling future studies like this in different institutions. Secondly, we focused our evaluation of the influence of eligibility criteria against severe events. A better understanding of patient cases who progress from mild to moderate is as important as that of severe cases. Future research is needed to evaluate the impact of eligibility criteria on the occurrences of moderate-level events. Thirdly, this retrospective cohort study used the CUIMC OMOP database as a primary data source for the analysis. Event of deaths that might have occurred outside the hospital were not able to be included in the analysis. During the early period of the pandemic, the location of death was unknown or not specified in 26.5% of the decedents.31 Linking to death registry or claims data would lead to a more precise estimate of the death rate. In addition, the stored EHR data might be incomplete and/or inconsistent, and the data collection process could be biased.32 The conversion of EHR data to OMOP can introduce additional data quality issues; however, the conversion process involves several data quality checks, and other multicenter observational studies using this database have shown consistency between CUIMC and other healthcare databases.33 Fourth, the values of measurements are dynamic in nature. The eligibility status of patients could be temporal and hence change as the patients are being followed-up. Future research is needed to address the impact of dynamic changes in clinical characteristics on patients’ eligibility.

CONCLUSION
We present a novel use of electronic health records data for estimating the influence of eligibility criteria of COVID-19 trials on patient accrual and the incidence of severe events using EHR and provide data-driven recommendations for the thresholds for age, oxygen saturation, kidney and liver function, achieving potential COVID-19 trials with greater power without increasing sample sizes. This method promises to improve feasibility and efficiency for COVID-19 clinical trial recruitment.

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AUTHOR CONTRIBUTIONS
JHK wrote the manuscript; JHK, CNT, CS, CL, AMB, JRR, HL, SML, MSVE, and CW edited the manuscript; JHK, CS, and CW designed the research; JHK analyzed the data; JHK, AO, CNT, CL, JL, and HL acquired and interpreted the data; PBR defined the phenotype; AMB and LAS manually reviewed the eligibility criteria; LE contributed to the natural language processing of notes in the electronic health records.

SUPPLEMENTARY MATERIAL
Supplementary material is available at Journal of the American Medical Informatics Association online.

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CONFLICT OF INTEREST STATEMENT
None declared.

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