**Study Protocol**

**External validation of an existing model named COVID Vulnerability Index for hospitalization amongst adult patients presenting with flu or flu-like symptoms: a rapid network study to inform the management of COVID-19**

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# List of Abbreviations

|  |  |
| --- | --- |
| Abbreviation | Phrase |
| AUROC | Area Under the Receiver Operating Characteristic Curve |
| CDM | Common Data Model |
| O | Outcome Cohort |
| OHDSI | Observational Health Data Sciences & Informatics |
| OMOP | Observational Medical Outcomes Partnership |
| T | Target Cohort |
| TAR | Time at Risk |

# Executive Summary

The objective of this study is to perform a large-scale external validation of an existing patient-level prediction model, name the COVID Vulnerability Index, that was developed to identify patients who are likely to be severe or critical when infected with COVID-19. We will validate the model in a situation that mimics patients’ initial interactions with the healthcare system for COVID-19. Specifically, for patients that visit a general practitioner (GP), the emergency room (ER), or other outpatient care (OP) with Covid-19, flu or flu-like symptoms and had no symptoms of pneumonia 60 days prior to the visit. The outcome being predicted is hospitalizations with pneumonia with a time of risk of 30 days from the initial visit (including the day of the visit).

# Rationale & Background

**General description of COVID-19**

The Corona Virus Disease 2019 (COVID-19), which started in late 2019 as an epidemic in Wuhan, Hubei Province, China, has been declared a pandemic and a public health emergency of international concern by the World Health Organization (WHO) in January 2020 (1). The growing number of infections by COVID-19 has resulted in an unprecedented pressure on healthcare systems worldwide, and a large number of casualties at a global scale. Diagnosis of COVID-19 currently relies on the detection of SARS-CoV-2 nucleic acid (2), but no medical treatment or vaccine is available yet. Common symptoms presented by patients include fever, cough, and dyspnea, signaling the onset of pneumonia (3). Although the majority of people have uncomplicated or mild illness (81%), some will develop severe illness requiring hospitalization and oxygen support (14%) or intensive care unit treatment (5%) (4).

**Problem definition**

At initial disease presentation it is difficult to determine which suspected COVID-19 patients are likely to develop secondary infections, such as pneumonia or acute respiratory distress syndrome (ARDS), and therefore require hospitalization. Currently, patients are admitted based on a simple age and health risk assessment. The WHO Risk Communication Guidance distinguishes two distinct categories of patients at high risk of severe disease: those older than 60 years and those with “underlying medical conditions” which is non-specific (5). Early identification of patients who will require hospital care will ensure these patients have the best chance of receiving optimal care. Further interventions assessed earlier on can reduce the severity of symptoms and as such reduce the resources required for each patient. Moreover, reducing hospital admissions that are not strictly necessary avoids burden on the already stressed healthcare system and prevents unnecessary medical interventions. A recently developed model is the COVID Vulnerability Index (6) that aims to predict which Patients are likely to be severe when infected with COVID-19.

**Study aims**

The objective of this study is to inform the triage and early management of patients with diagnosed or suspected COVID-19 by validating the COVID Vulnerability Index, as this has not been extensively validated. In addition, the COVID Vulnerability Index was not evaluated on COVID-19 patients, but the OHDSI contains COVID-19 patient data and can determine whether the model transports to the COVID-19 population.

**Clinical use case**

The model aims to identify the short-term risk of hospitalization due to COVID-19 but was developed amongst non-COVID patients. Due to the rapid onset of the COVID-19 pandemic a current barrier to validation is the low number of patients that are available to study in EHR and claims systems. As such, in data without COVID-19 patients, we have chosen to use flu or flu-like symptoms as a proxy for COVID-19. This is due to the fact that both disease types share some similarities, for example symptom presentation at onset and it appears that similar groups of patients are at risk of negative outcomes in both disease trajectories, although COVID-19 does appear to have higher associated risks (7). We will evaluate the existing model on patients with flu and flu-like symptoms in addition to the COVID-19 patient datasets as they become available. If the COVID Vulnerability Index is shown to be transportable to COVID-19 patients then this will increase the speed at which it can be disseminated and as such have a greater impact on the attempt to control the most negative impacts of the pandemic.

**How the study is performed**

We will convert the COVID Vulnerability Index to use the Observational Health Data Sciences and Informatics (OHDSI) Patient-Level Prediction framework. The OHDSI collaboration is a network of researchers working towards a common goal of standardizations and best practice frameworks for analysing observational data in healthcare. The OHDSI collaboration relies on researchers mapping their datasets into the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM). This, along with the Patient-Level Prediction framework, allows for rapid model development and validation following accepted best practices (8), which provides a unique opportunity to make a difference in the current crisis. We will perform external validation of the model across the OHDSI network. The main advantage of our approach is that we have access to some COVID-19 data and will externally validate the models on recent COVID-19 data to evaluate whether the models transport to this similar patient population.

# Objective

The objective is to validate the COVID Vulnerability Index model for the task of predicting hospitalization amongst adult patients presenting with flu or COVID-19 or flu-like symptoms:

1. To assess if the COVID Vulnerability Index model, transports across the OHDSI network spanning multiple countries.
2. To assess whether the COVID Vulnerability Index model transports to COVID-19 patients.

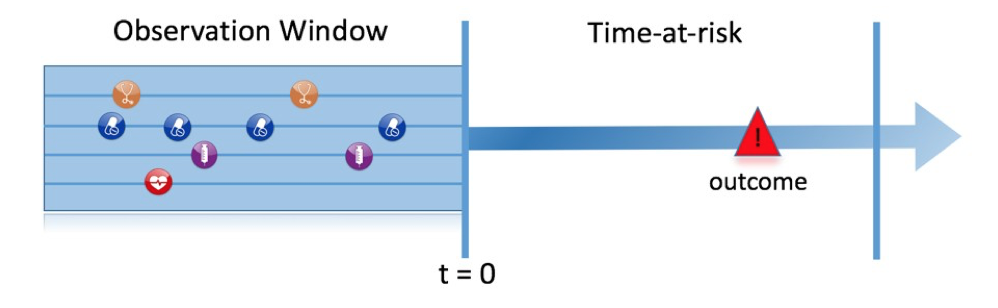
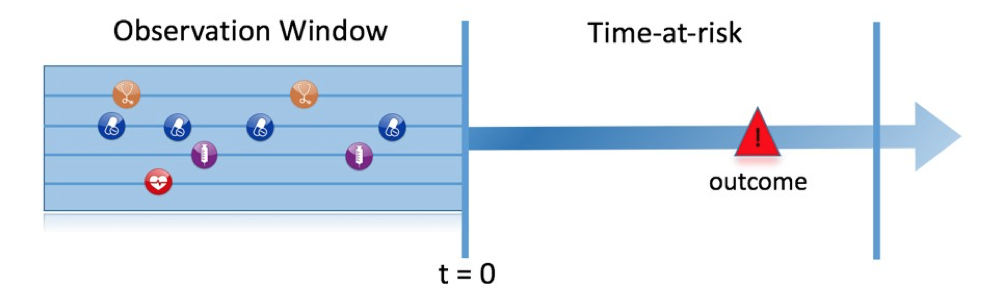
|  |  |  |
| --- | --- | --- |
| **Target Cohorts** | **Outcome Cohorts** | **Time at Risk** |
| [COVID ID13 v1] GP/OP/ER visits of patients presenting with Covid flu or flu-like symptoms AND no symptoms or pneumonia in prior 60d | [COVID19 ID25 V1] Hospitalizations with pneumonia | [Time at Risk Settings #1] Risk Window Start: 0, Add Exposure Days to Start: FALSE, Risk Window End: 30, Add Exposure Days to End: FALSE |
| GP/OP/ER visits of patients presenting with Covid, flu or flu-like symptoms AND no symptoms or pneumonia in prior 60d during 2020 | [COVID19 ID25 V1] Hospitalizations with pneumonia | [Time at Risk Settings #1] Risk Window Start: 0, Add Exposure Days to Start: FALSE, Risk Window End: 30, Add Exposure Days to End: FALSE |
| GP/OP/ER visits of patients presenting with Covid or flu-like symptoms AND no symptoms or pneumonia in prior 60d during 2020 no flu in prior 60 days | [COVID19 ID25 V1] Hospitalizations with pneumonia | [Time at Risk Settings #1] Risk Window Start: 0, Add Exposure Days to Start: FALSE, Risk Window End: 30, Add Exposure Days to End: FALSE |
| GP/OP/ER visits of patients presenting with COVID AND no symptoms or pneumonia or flu in prior 60d during 2020 | [COVID19 ID25 V1] Hospitalizations with pneumonia | [Time at Risk Settings #1] Risk Window Start: 0, Add Exposure Days to Start: FALSE, Risk Window End: 30, Add Exposure Days to End: FALSE |

# Methods

## Study Design

This study will follow a retrospective, observational, patient-level prediction design. We define 'retrospective' to mean the study will be conducted using data already collected prior to the start of the study. We define 'observational' to mean there is no intervention or treatment assignment imposed by the study. We define 'patient-level prediction' as a modelling process wherein an outcome is predicted within a time at risk relative to the target cohort start and/or end date. Prediction is performed using a set of covariates derived using data prior to the start of the target cohort.

Figure 1 illustrates the prediction problem we will address. Among a population at risk, we aim to predict which patients at a defined moment in time (t = 0) will experience some outcome during a time-at-risk (TAR). Prediction is done using only information about the patients in an observation window prior to that moment in time.



***Figure 1: The prediction problem***

We follow the PROGRESS best practice recommendations for model development and the TRIPOD guidance for transparent reporting of the model results (9, 10).

## Data Source(s)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Source Full Name** | **Country Code** | **Data Provenance** | **Source Short Name** | **Patient Count** | **History** | **Patient Type** |
| Optum® de-identified Electronic  Health Record Dataset | US | EMR | Optum EHR - EMR, US | 96m | 2006- | EHR / Privately Insured |
| Optum© De-Identified Clinformatics® Data Mart Database – Date of Death | US | Claims | Optum DOD | 88m | 2000-2018 | Insurance claims data (inpatient/outpatient medical conditions and drug dispensing plus some laboratory data) for patients aged between 0 and 90 |
| Add… |  |  |  |  |  |  |

## Study Populations

### Target Cohort(s) [T]

|  |  |  |
| --- | --- | --- |
| **Cohort ID** | **Cohort Name** | **Description** |
| 5894 | [COVID ID13 v1] GP/OP/ER visits of patients presenting with Covid flu or flu-like symptoms AND no symptoms or pneumonia in prior 60d | TBD |
| 556 | [COVID ID65 v1] GP/OP/ER visits of patients presenting with Covid or flu-like symptoms AND no influenza AND no symptoms or pneumonia in prior 60d | TBD |
| 557 | [COVID ID66 v1] GP/OP/ER visits of patients presenting with Covid AND no influenza AND no symptoms or pneumonia in prior 60d | TBD |

### Outcome Cohorts(s) [O

|  |  |  |
| --- | --- | --- |
| **Cohort ID** | **Cohort Name** | **Description** |
| 5892 | [COVID19 ID25 V1] Hospitalizations with pneumonia | TBD |

**Full descriptions:**

The JSON files describing for all the outcome cohorts are available at:

* https://github.com/ohdsi-studies/Covid19PredictionStudies/tree/master/CovidVulnerabilityIndex/inst/cohorts

In order to convert these to a human readable form, import the JSON into a new cohort definition in any instance of ATLAS and reload.

### Time at Risk

The table below describes the Time at Risk (TAR) window start and end for each of the analyses that are executed.

|  |
| --- |
| **Time at Risk** |
| [Time at Risk Settings #1] Risk Window Start: 0, Add Exposure Days to Start: FALSE, Risk Window End: 30, Add Exposure Days to End: FALSE |

### Additional Population Settings

The final study population in which we will develop our model is a subset of the target cohort, because we may for example apply criteria that are dependent on the outcome, or we want to perform sensitivity analyses with sub-populations of the target cohort. For this we have to answer the following questions:

* ***What is the minimum amount of observation time we require before the start of the target cohort?***This choice could depend on the available patient time in the training data, but also on the time we expect to be available in the data sources we want to apply the model on in the future. The longer the minimum observation time, the more baseline history time is available for each person to use for feature extraction, but the fewer patients will qualify for analysis. Moreover, there could be clinical reasons to choose a short or longer look-back period.
* ***Can patients enter the target cohort multiple times?*** In the target cohort definition, a person may qualify for the cohort multiple times during different spans of time, for example if they had different episodes of a disease or separate periods of exposure to a medical product. The cohort definition does not necessarily apply a restriction to only let the patients enter once, but in the context of a particular patient-level prediction problem we may want to restrict the cohort to the first qualifying episode.
* ***Do we allow persons to enter the cohort if they experienced the outcome before?*** Do we allow persons to enter the target cohort if they experienced the outcome before qualifying for the target cohort? Depending on the particular patient-level prediction problem, there may be a desire to predict incident first occurrence of an outcome, in which case patients who have previously experienced the outcome are not at risk for having a first occurrence and therefore should be excluded from the target cohort. In other circumstances, there may be a desire to predict prevalent episodes, whereby patients with prior outcomes can be included in the analysis and the prior outcome itself can be a predictor of future outcomes.
* ***How do we define the period in which we will predict our outcome relative to the target cohort start?***We have to make two decisions to answer this question. First, does the time-at-risk window start at the date of the start of the target cohort or later? Arguments to make it start later could be that we want to avoid outcomes that were entered late in the record that actually occurred before the start of the target cohort or we want to leave a gap where interventions to prevent the outcome could theoretically be implemented. Second, we need to define the time-at-risk by setting the risk window end, as some specification of days offset relative to the target cohort start or end dates.
* ***Do we require a minimum amount of time-at-risk?*** We have to decide if we want to include patients that did not experience the outcome but did leave the database earlier than the end of our time-at-risk period. These patients may experience the outcome when we no longer observe them. For our prediction problem we decide to answer this question with “yes,” requiring a minimum time-at-risk for that reason. Furthermore, we have to decide if this constraint also applies to persons who experienced the outcome, or we will include all persons with the outcome irrespective of their total time at risk.

In our study three population settings are defined as described below:

***Population Settings***

|  |  |
| --- | --- |
| **Item** | **Settings** |
| minTimeAtRisk | 1 |
| requireTimeAtRisk | FALSE |
| addExposureDaysToStart | FALSE |
| riskWindowStart | 0 |
| washoutPeriod | 365 |
| addExposureDaysToEnd | FALSE |
| includeAllOutcomes | TRUE |
| priorOutcomeLookback | 99999 |
| binary | TRUE |
| removeSubjectsWithPriorOutcome | FALSE |
| riskWindowEnd | 30 |
| firstExposureOnly | FALSE |

## Statistical Analysis Method(s)

### COVID Vulnerability Index

The model is a logistic regression with the following predictors:

|  |  |
| --- | --- |
| **Covariate Name** | **Coefficient** |
| Pneumonia (except caused tuberculosis) | 0.117 |
| Other and ill-defined heart disease | -0.111 |
| Heart failure | -0.271 |
| Acute rheumatic heart disease | -0.008 |
| Coronary atherosclerosis and other heart disease | -0.529 |
| Pulmonary heart disease | -0.005 |
| Chronic rheumatic heart disease | -0.014 |
| Diabetes mellitus with complication | -0.273 |
| Diabetes mellitus without complication | -0.496 |
| Chronic obstructive pulmonary disease and bronchiectasis | -0.269 |
| Other specified and unspecified lower respiratory disease | -0.02 |
| Pneumonia (except caused tuberculosis) X Age | 0.01 |
| Other and ill-defined heart disease X Age | 0.003 |
| Heart failure X Age | 0.009 |
| Acute rheumatic heart disease X Age | 0.003 |
| Coronary atherosclerosis and other heart disease X Age | 0.011 |
| Pulmonary heart disease X Age | 0 |
| Chronic rheumatic heart disease X Age | -0.001 |
| Diabetes mellitus with complication X Age | 0.007 |
| Diabetes mellitus without complication X Age | 0.009 |
| Chronic obstructive pulmonary disease and bronchiectasis X Age | 0.013 |
| Other specified and unspecified lower respiratory disease X Age | 0.006 |
| Age | -0.014 |
| Male | -0.212 |
| Number of visits 365 days | 0.186 |

The json phenotypes of each of the predictors can be found here:

https://github.com/ohdsi-studies/Covid19PredictionStudies/tree/master/CovidVulnerabilityIndex/inst/cohorts

### Performance Evaluation

The following evaluations will be performed on the model:

|  |  |
| --- | --- |
| Evaluation | Description |
| Box Plots | The prediction distribution boxplots are box plots for the predicted risks of the people in the test set with the outcome (class 1: blue) and without the outcome (class 0: red). |
| Calibration Plot | The calibration plot shows how close the predicted risk is to the observed risk. The diagonal dashed line thus indicates a perfectly calibrated model. The ten (or fewer) dots represent the mean predicted values for each quantile plotted against the observed fraction of people in that quantile who had the outcome (observed fraction). The straight black line is the linear regression using these 10 plotted quantiles mean predicted vs observed fraction points. The two blue straight lines represented the 95% lower and upper confidence intervals of the slope of the fitted line. |
| Demographic Summary Plot | This plot shows for females and males the expected and observed risk in different age groups together with a confidence area. |
| Precision Recall Plot | The precision-recall curve is valuable for dataset with a high imbalance between the size of the positive and negative class. It shows the trade-off between precision and recall for different threshold. High precision relates to a low false positive rate, and high recall relates to a low false negative rate. High scores for both show that the classifier is returning accurate results (high precision), as well as returning a majority of all positive results (high recall). A high area under the curve represents both high recall and high precision. |
| Prediction Distribution Plots | The preference distribution plots are the preference score distributions corresponding to i) people in the test set with the outcome (red) and ii) people in the test set without the outcome (blue). |
| ROC Plot | The ROC plot plots the sensitivity against 1-specificity on the test set. The plot shows how well the model is able to discriminate between the people with the outcome and those without. The dashed diagonal line is the performance of a model that randomly assigns predictions. The higher the area under the ROC plot the better the discrimination of the model. |
| Smooth Calibration Plot | Similar to the traditional calibration shown above the Smooth Calibration plot shows the relationship between predicted and observed risk. the major difference is that the smooth fit allows for a more fine-grained examination of this. Whereas the traditional plot will be heavily influenced by the areas with the highest density of data the smooth plot will provide the same information for this region as well as a more accurate interpretation of areas with lower density. the plot also contains information on the distribution of the outcomes relative to predicted risk. However, the increased information game comes at a computational cost. It is recommended to use the traditional plot for examination and then to produce the smooth plot for final versions. |
| Test-Train Similarity Plot | The test-train similarity is presented by plotting the mean covariate values in the train set against those in the test set for people with and without the outcome. |
| Variable Scatter Plot | The variable scatter plot shows the mean covariate value for the people with the outcome against the mean covariate value for the people without the outcome. The size and colour of the dots correspond to the importance of the covariates in the trained model (size of beta) and its direction (sign of beta with green meaning positive and red meaning negative), respectively. |

## Quality Control

The PatientLevelPrediction package itself, as well as other OHDSI packages on which PatientLevelPrediction depends, use unit tests for validation. More information can be found in the Book of OHDSI at: <https://ohdsi.github.io/TheBookOfOhdsi/SoftwareValidity.html>

## Tools

To create the study package, ATLAS will be used to specify the cohorts, time-at-risk, covariate and population settings as well as which models will be analysed. Information on this is available in the Book of OHDSI at: <https://ohdsi.github.io/TheBookOfOhdsi/OhdsiAnalyticsTools.html#atlas>

The package developed in ATLAS will utilise the Patient-Level Prediction R package to run the analysis. More information on this is available at: <https://ohdsi.github.io/TheBookOfOhdsi/PatientLevelPrediction.html>

This study will be designed using OHDSI tools and run with R (11). More information about the tools can be found in the Appendix 'Study Generation Version Information'.

# Diagnostics

Reviewing the incidence rates of the outcomes in the target population prior to performing the analysis will allow us to assess its feasibility. The full table can be found in the 'Table and Figures' section under 'Incidence Rate of Target & Outcome'. Additionally, reviewing the characteristics of the cohorts provides insight into the cohorts being reviewed.

# Data Analysis Plan

## Model Evaluation

The external validity of the models will be assessed across the OHDSI network, including on recent COVID-19 data. We will use the area under the receiver operating characteristic curve (AUROC) to evaluate the discriminative performance of the models and plot the predicted risk against the observed fraction to visualize the calibration. See 'Performance Evaluation' section for more detailed information about additional model evaluation metrics.

## Analysis Execution Settings

For the study there is 4 target cohorts evaluated for 1 outcomes over 1 model. In total there are 4 analyses performed.

# Strengths & Limitations

Strength

* The analysis can help gain insight into the clinical usefulness of the model by identifying whether it is transportable.

Limitations

* The external validation datasets may not have a sufficient number of (some of) the different outcomes to be used in the analysis.
* Although the CDM standardizes the vocabularies of the datasets, the concept recording distributions are likely to differ between databases and it is unknown how much this will limit model transportability.

# Protection of Human Subjects

For this study, participants from various countries will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

All the databases used in this study have a well-developed mechanism to ensure that regulations dealing with ethical use of the data and adequate privacy control are adhered to.

If required, the protocol has been reviewed by the Institutional Review Boards of the respective databases.

# Plans for Disseminating & Communicating Study Results

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles, presentations at conferences, etc.).

We will add the results of the study within a publicly accessible shiny app available at data.ohdsi.org.

# Tables & Figures

## Incidence Rate of Target & Outcome

***Feasibility assessment training data***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| T | O | TAR start | TAR end | T size | O count | O incidence |

***Feasibility assessment validation data***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Database | O | TAR | T size | O count | O incidence |

# Appendices

## Study Generation Version Information

Skeleton Version: PatientLevelPredictionStudy - v0.0.1

Identifier / Organization: OHDSI

# References

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