RESEARCH PROTOCOL:

Association of proton-pump inhibitor (PPI) and histamine 2-receptor antagonist (H2RA) on coronavirus disease (COVID-19) incidence and complications

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# 1. List of Abbreviations

|  |  |
| --- | --- |
| PPI | Proton Pump Inhibitor |
| H2RA | Histamine 2 Receptor Antagonist |
| ARDS | Acute respiratory distress syndrome |
| CDM | Common data model |
| COVID-19 | Coronavirus disease 2019 |
| ECMO | Extracorporeal membrane oxygenation |
| MACE | Major acute cardiovascular event |
| OMOP | Observational Medical Outcomes Partnership |
| OHDSI | Observational Health Data Science and Informatics |
| RxNorm | US-specific terminology in medicine that contains all medications available on the US market |
| SNOMED | Systematized Nomenclature of Medicine |

# 2. Responsible Parties

## 2.1. Investigators and Authors

|  |  |
| --- | --- |
| **Investigator/Author** | **Institution/Affiliation** |
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## 2.2 Sponsor

This study was undertaken Observational Health Data Science and Informatics (OHDSI), an open collaboration. This study received grant funding from the Korean Ministry of Health & Welfare and from the Korean Ministry of Trade, Industry & Energy.

# 3. Abstract

This study will evaluate the effect of PPI or H2RA exposure on the risk of contracting COVID-19 infection and the risk of experiencing respiratory failure, pneumonia, acute kidney injury, and death in COVID-19 patients. The analysis will be undertaken across a federated multi-national network of electronic health records and administrative claims from primary care and secondary care that have been mapped to the Observational Medical Outcomes Partnership Common Data Model in collaboration with the Observational Health Data Sciences and Informatics (OHDSI). We will use a prevalent user cohort design to estimate the relative risk of each outcome using an on-treatment analysis of monotherapy comparisons. In the analysis of respiratory failure, pneumonia, acute kidney injury, and death, we will conduct separate analyses assessing prevalent use of PPI and H2RA at the time of any diagnosis with COVID-19 or at the time of an inpatient admission with COVID-19 diagnosis. Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. Large-scale propensity score matching and stratification strategies that allow balancing on a large number of baseline potential confounders will be used in addition to negative control outcomes to allow for evaluating residual bias in the study design as a whole as a diagnostic step.

# 4. Amendments and Updates

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Number** | **Date** | **Section of study protocol** | **Amendment or update** | **Reason** |
| None |  |  |  |  |
|  |  |  |  |  |

|  |  |
| --- | --- |
| **Key Dates and Milestones** | **Planned / Estimated Date** |
| Start of analysis | April 7, 2020 |
| End of analysis |  |
| Presentation of results |  |

# 5. Rationale and Background

Since January 2020, a growing number of infections caused by coronavirus SARS-Cov2, COVID-19 has resulted in unprecedented pressure on healthcare systems worldwide, and a great number of casualties on a global scale. With an approximate 4% mortality based on data from China where the outbreak originated, there is a paucity of data on an international level surrounding the factors associated with disease severity or morbidity/mortality.Recent studies have reported increased mortality and complications, including acute respiratory distress syndrome (ARDS), among SARS-CoV-2 infected patients [1, 2].

Acid-suppressants including proton pump inhibitor (PPI) and histamine 2 receptor antagonist (H2RA) are the most frequently prescribed medications for patients with acid-related disorders. However, PPI can be the risk factor for the pneumonia and viral diseases [3, 4]. Moreover, recent studies reported that PPI can worsen the clinical outcomes of COVID-19 infected patients [5]. On the other hand, PPI and H2RA are not influencing the infection of the virus. However, the evidence is still controversy and requires reliable and feasible evidence from various institutions.

This protocol outlines a study in the Observational Health Data Science and Informatics (OHDSI) community with federated access to international data assets mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [6]. This infrastructure provides a unique opportunity to address this question across a number of populations and contribute valuable insights that will inform the key clinical and policy decisions of the risk of acid-suppressant treatment during the current SARS-Cov2, COVID-19 pandemic.

# 6. Study Objectives

***Objective 1:***  To estimate the association of prevalent use of a) proton pump inhibitor (PPI)  and b) histamine II receptor antagonist (H2RA) on the risk of contracting COVID-19 infection.

***Objective 2:*** To estimate the association of prevalent use of a) proton pump inhibitor (PPI)  and b) histamine II receptor antagonist (H2RA) on the risk of respiratory failure, pneumonia, acute kidney injury, and death in patients diagnosed with COVID-19. As a secondary objective focused on potential benefits, estimate the association among prevalent users and differences in the risk of major acute cardiovascular events (MACE), including acute myocardial infarction, congestive heart failure, stroke or sudden cardiovascular death.

# 7. Research Methods

## Data Sources

A South Korean national claims database have already begun accumulating COVID-19 patients and have tested the operability of our analysis package at their sites (**Table 1**).

The study will be conducted using data from real world data sources that have been mapped to the OMOP Common Data Model in collaboration with the Observational Health Data Sciences and Informatics (OHDSI). The OMOP Common Data Model (<https://github.com/OHDSI/CommonDataModel/wiki>) includes a standard representation of health care experiences (such as information related to drug utilization and condition occurrence), as well as common vocabularies for coding clinical concepts and enables consistent application of analyses across multiple disparate data sources.

**Table 1**. Data sources formatted to the OMOP CDM that currently include COVID-19 patients.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Data source** | **Source population** | **Sample size** | **Data type** | **Longitudinal history** |
| South Korea: Health Insurance and Review Assessment (HIRA) | All citizens in South Korea | ≈ 50 million | Administrative fee-for-service claims data collected for healthcare reimbursement, including healthcare services such as treatments, pharmaceuticals, procedures, and diagnoses. | 5-years of available look-back (data older than 5-years is deleted from the database) |

## Hypothesis 1

### Patient Cohort

To test hypothesis 1, the cohort will consist of adult patients aged 18 years and over who receive at least one eligible prescription for an exposure drug between 1st November 2019 and 31st January 2020 (with index date set as the last prescription in this window) and are observable in each database for at least 180 days prior to the index date. Cohort exit will be the earliest of: the occurrence of an outcome event; the end of exposure; death; loss or deregistration from the database; or date of last data collection.

### Exposures

The exposures of interest are the primary (target) exposure of interest being PPI and H2RA medications. Drug exposure will first be defined as: a patient issued or dispensed at least one eligible prescription (with index date set as the last prescription in this window). For the analysis restricting to patients on monotherapy, we will require the absence of any other of the primary or secondary medication class treatments for patients prescribed with acid-suppressant drugs between –180 days and 0 days prior to the index date. Only patients who maintained the same drug for 7 days or more were enrolled in the cohort. Continuous drug exposures will be defined from the start of follow-up by grouping sequential prescriptions that have fewer than 30 days gap between prescriptions. End of exposure will be defined as the end of the last prescription’s drug supply.

### Controls or Comparators

An active comparator control population will be created consisting of patients prescribed the other monotherapy medication to minimize confounding by indication. Absence of treatment by multiple drug classes will follow the definition as above. However, residual differences may still remain as suggested by difference in clinical practice around the choice of first-line acid-suppressant treatment class, which will be addressed by applying statistical methods for confounding adjustment.

### Outcomes

The primary outcomes of interest to test hypothesis 1 will be an incident COVID-19 infection diagnosis using both a broad and narrow definition, hospitalization with pneumonia, and hospitalization with pneumonia or ARDS or acute kidney injury or resulting in death. Up to 76 negative control outcome experiments will be performed examining the risk of residual confounding.

### Covariates

Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. These will include: gender, age group (10-year deciles), index month, conditions (SNOMED concepts and descendants) any time prior to index, conditions in the 180 days prior to index, conditions in the 30 days prior to index, drugs (ATC classes and RxNorm ingredients) any time prior to index, drugs in the 180 days prior to index, drugs in the 30 days prior to index, procedures any time prior to index, procedures in the 180 days prior to index, procedures in the 30 days prior to index, devices any time prior to index, devices in the 180 days prior to index, devices in the 30 days prior to index, measurements any time prior to index, measurement in the 180 days prior to index, measurements in the 30 days prior to index, measurement values in the last 180 days, CHADS2Vasc, Diabetes Comorbidity Severity Index, and Charlson index.

### Analysis

We will estimate the relative risk of each outcome using an on-treatment analysis for the following class exposure comparisons in patients with prescribed with PPI and H2RA. We will describe patient characteristics (prevalence) for each cohort comparison and data source. To adjust for measured confounding, propensity score models for each class pair and data source will be created using a data-driven process using regularized logistic regression when target and comparator cohorts contain at least 500 patients within each data source. This process allows the data to decide which combinations of baseline patient characteristics, including demographics and previous conditions, drug exposures, procedures, and health-service-use behaviors are most predictive of treatment assignment. For cohorts with fewer than 500 patients, we will build propensity score models using gender and age categorized in deciles, and index month examining for any heterogeneity.

Patients will be stratified by propensity score or 1:1 matched to ensure sufficient balance is achieved if all after-adjustment baseline characteristics return absolute standardized mean differences of less than 0.1. We will make the choice for matching or stratification based on sufficient exposure cohort size. Cox proportional hazards models will be used to estimate hazard ratios (HRs) between target and comparator treatment cohorts for the risk of each outcome in each data source. We will aggregate HRs across data sources to produce meta-analytic estimates using a random-effects meta-analysis.

For each effect estimate, we will evaluate associations using negative control outcome experiments. We will use the empirical null distributions to calibrate each HR estimate, its 95% CI, and the p value to reject the null hypothesis of no differential effect. A HR will be considered significantly different from the null value when its calibrated 95% CI does not include this value (and corresponds to a calibrated p of less than 0.05 without correcting for multiple testing).

The following additional calculations will be performed: power calculations estimating minimum detectable relative risk; preference score (a transformation of propensity score that adjusts for prevalence differences between populations) distributions to evaluate empirical equipoise and population generalizability; patient characteristics to evaluate cohort balance before and after propensity score adjustment; negative-control calibration plots to assess residual bias; and Kaplan-Meier plots to examine HR proportionality assumptions.

If sufficient numbers of patients are available, a sensitivity analysis will be performed restricted to recent initiators of PPI or H2RA and their active comparators. Recent initiators will be defined if the first ever PPI or H2RA prescription is recorded between –60 days and 0 days prior to index.

## Hypothesis 2

### Patient Cohort

To test hypothesis 2, the cohort will consist of adult patients aged 18 years and over who receive at least one eligible prescription for an exposure drug between 1st November 2019 and 31st January 2020 (with index date set as the last prescription in this window) and are observable in each database for at least one year prior to the index date. Cohort exit will be the earliest of: the occurrence of an outcome event; the end of exposure; death; loss or deregistration from the database; or date of last data collection.

### Exposures

The exposures of interest are the primary (target) exposure of interest being PPI and H2RA medications. Drug exposure will first be defined as: a patient issued or dispensed at least one eligible prescription (with index date set as the last prescription in this window). For the analysis restricting to patients on monotherapy, we will require the absence of any other of the primary or secondary medication class treatments prescribed between –180 days and 0 days prior to the index date. Only patients who maintained the same drug for 7 days or more were enrolled in the cohort. Continuous drug exposures will be defined from the start of follow-up by grouping sequential prescriptions that have fewer than 30 days gap between prescriptions. End of exposure will be defined as the end of the last prescription’s drug supply.

### Controls or Comparators

An active comparator control population will be created consisting of patients prescribed the other monotherapy medication to minimize confounding by indication. Absence of treatment by multiple drug classes will follow the definition as above. However, residual differences may still remain as suggested by difference in clinical practice around the choice of first-line PPI/H2RA treatment class, which will be addressed by applying statistical methods for confounding adjustment.

### Outcomes

The primary outcomes of interest for hypothesis 2 will be the occurrence of a composite intensive respiratory intervention, consisting of mechanical ventilation, tracheostomy, extracorporeal membrane oxygenation (ECMO) or death. A secondary outcome aimed at informing benefit-risk will examine major acute cardiovascular events (MACE) including acute myocardial infarction, congestive heart failure, stroke or sudden cardiovascular death. Seventy-six negative control outcome experiments will be performed examining the risk of residual confounding [7].

### Covariates

Data driven approaches will be used to identify potential covariates for inclusion in matched or stratified propensity score models identified using regularized logistic regression. These will include: gender, age group (10-year deciles), index month, conditions (SNOMED concepts and descendants) any time prior to index, conditions in the 180 days prior to index, conditions in the 30 days prior to index, drugs (ATC classes and RxNorm ingredients) any time prior to index, drugs in the 180 days prior to index, drugs in the 30 days prior to index, procedures any time prior to index, procedures in the 180 days prior to index, procedures in the 30 days prior to index, devices any time prior to index, devices in the 180 days prior to index, devices in the 30 days prior to index, measurements any time prior to index, measurement in the 180 days prior to index, measurements in the 30 days prior to index, measurement values in the last 180 days, CHADS2Vasc, Diabetes Comorbidity Severity Index, and Charlson index.

### Analysis

We will estimate the relative risk of each outcome using an on-treatment analysis for the following class exposure comparisons in patients prescribed with PPI and H2RA. We will describe patient characteristics (prevalence) for each cohort comparison and data source. To adjust for measured confounding, propensity score models for each class pair and data source will be created using a data-driven process using regularized logistic regression when target and comparator cohorts contain at least 500 patients within each data source. This process allows the data to decide which combinations of baseline patient characteristics, including demographics and previous conditions, drug exposures, procedures, and health-service-use behaviors are most predictive of treatment assignment. For cohorts with fewer than 500 patients, we will build propensity score models using gender and age categorized in deciles, and index month examining for any heterogeneity.

Patients will be stratified by propensity score or 1:1 matched to ensure sufficient balance is achieved if all after-adjustment baseline characteristics return absolute standardized mean differences of less than 0.1. We will make the choice for matching or stratification based on sufficient exposure cohort size. Cox proportional hazards models will be used to estimate hazard ratios (HRs) between target and comparator treatment cohorts for the risk of each outcome in each data source. We will aggregate HRs across data sources to produce meta-analytic estimates using a random-effects meta-analysis.

For each effect estimate, we will evaluate associations using negative control outcome experiments. We will use the empirical null distributions to calibrate each HR estimate, its 95% CI, and the p value to reject the null hypothesis of no differential effect. A HR will be considered significantly different from the null value when its calibrated 95% CI does not include this value (and corresponds to a calibrated p of less than 0.05 without correcting for multiple testing).

The following additional calculations will be performed: power calculations estimating minimum detectable relative risk; preference score (a transformation of propensity score that adjusts for prevalence differences between populations) distributions to evaluate empirical equipoise and population generalizability; patient characteristics to evaluate cohort balance before and after propensity score adjustment; negative-control calibration plots to assess residual bias; and Kaplan-Meier plots to examine HR proportionality assumptions.

If sufficient numbers of patients are available, a sensitivity analysis will be performed restricted to recent initiators of PPI or H2RA and their active comparators. Recent initiators will be defined if the first ever PPI or H2RA prescription is recorded between –60 days and 0 days prior to index.

# 8. Sample Size and Study Power

See previous section.

# 9. Strengths and Limitations

Comparative cohort studies allow direct estimation of relative incident event rates following exposures of interest and control for observed confounding in these rate estimates by contrasting balanced populations of subjects. This protocol employs large-scale propensity score matching and stratification strategies that allow balancing on a large number of baseline potential confounders and have been shown to also balance on important unobserved confounders. Further, the use of negative control outcomes allows for evaluating the study design as a whole in terms of residual bias as a diagnostic step to help ensure casual validity of estimates.

In the interest of generating actionable evidence that can address the urgent public health need, we have incorporated several study-design features that allow us to run this analysis as immediately as possible. We acknowledge, however, that there are also limitations to this analysis which need to be understood in order to properly interpret the results. To date, longitudinal healthcare data to study patients with COVID-19 is still accumulating, and there are only small samples available in limited contexts and these samples are held by independent data partners who cannot pool patient-level data across sites.

Ideally, a comparative cohort analysis estimating the effect of acid-suppressant drugs on incidence of COVID-19 (hypothesis 1) would be undertaken using a new user cohort design.38 In a new user cohort design, all patients are aligned at the point of their drug initiation (which is referred to as the index date) and the variables included in adjustment models include only those that preceded initiation of the drug. A new user design, however, would require a larger number of patients than a prevalent user design and a long history of longitudinal data (capturing both inpatient and outpatient care) that is not available for all study sites. Similar arguments hold for evaluating the effect of acid-suppressant use on outcomes of COVID-19 infection and severity of disease.

To help overcome data limitations and increase sample size, we have elected for a prevalent user design. To address hypothesis 1 under this design, we define the index date and align patients on a specific point in calendar time (a prescription between 1st November 2019 and 31st January 2020) at which point they became “at-risk” for COVID-19. For the analysis addressing hypothesis 2, we define the index date as the day patients are clinically recognized as having COVID-19. Of chief concern is that mediators on the causal pathway between exposure (to acid-suppressant medications) and the outcome (H1: COVID-19 infection, H2: COVID-19 outcomes) may be included in the adjustment since true exposure begins before the “at-risk” study period. One possible mediator is duration of prior acid-suppressant treatment. While prior treatment duration is difficult to ascertain in a prevalent user design, prior treatment remains highly correlated with many baseline features that our large-scale propensity model considers when balancing patients and can provide some protection against this design bias.

The prevalent user design was originally developed to address the challenge of having limited available data when comparing new-to-market drugs with established drugs.[8] In the original publication describing the prevalent user design, the authors highlight multiple sources of bias that are likely to arise in that context. Here, we use the prevalent user design to address the problem of not having sufficient data on a new illness (COVID-19), which affects all of our comparators equally. Thus, we assert that multiple forms of bias that arise in the new-to-market vs. traditional comparison (e.g. substantially longer duration of prior exposure among users of the established drug compared to users of the new-to-market drug, or unidirectional switching from the established drug to the new-to-market drug) are less likely to produce meaningful bias in our analysis.

Misclassification of study variables is unavoidable in observational analyses of secondary health data. It is possible that we misclassify our exposures by failing to observe medication use when a patient is actually taking it or, more commonly, seeing medication prescriptions in the data that the patient is not actually taking. However, we do not expect misclassification will be strongly differential with respect to the treatments being compared or with respect to outcome status. Thus, bias due to exposure misclassification will most likely be toward the null (i.e. increase the likelihood of a type II error).

Outcome misclassification is also an important concern, particularly in the analysis of hypothesis 1, since the COVID-19 outcome will be under diagnosed due to limited availability of testing resources and the fact that many infected patients may remain asymptomatic or not require observed healthcare utilization. It is important to note that the extent of underdiagnosis will likely vary by site due to differences in national testing strategies. Furthermore, classification of the outcome could also vary with respect to calendar time, since underdiagnosis could become more or less frequent over the course of the pandemic. To address this inherent limitation, we have included a hospitalization-based COVID-19 outcome which will be well-classified in these data to provide additional context. We do not expect outcome misclassification to be differential with respect to these exposure groups. Thus, bias due to outcome misclassification will also most likely be toward the null.

# 10. Protection of Human Subjects

The study uses only de-identified data. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians.

# 11. Management and Reporting of Adverse Events and Adverse Reactions

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse events reports. The study results will be assessed for medically important results.

# 12. Plans for Disseminating and Communicating Study Results

This study protocol will be registered at the EU PAS Register and study results will be posted on the OHDSI website after completion of the study. At least one paper describing the study and its results will be written and submitted for publication to a peer-reviewed scientific journal. The results will also be presented at the OHDSI in-person events.

# 13. List of Tables and Figures

**Table 1.** Data sources formatted to the OMOP CDM that currently include COVID-19 patients.

# 14. References

1. Andersen, K.G., et al., *The proximal origin of SARS-CoV-2.* Nature medicine, 2020. **26**(4): p. 450-452.

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8. Suissa, S., E.E. Moodie, and S. Dell'Aniello, *Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores.* Pharmacoepidemiol Drug Saf, 2017. **26**(4): p. 459-468.

# 16. Appendix 1: Target, Comparator, and Outcome Cohort Definitions

## 16.1 Exposure Cohort Definitions

1. [JMPark] PPI users, hospitalized with COVID-19

Initial Event Cohort

People having any of the following:

* a visit occurrence of Inpatient Visit
  + occurrence start is after 2019-12-01

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a measurement of SARS-CoV-2 positive test measurement pre-coordinated5

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

* or at least 1 occurrences of a measurement of SARS-CoV-2 test measurement6
  + value as concept is any of: Detected, Detected, Positive, Positive, Present, Present

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

* or at least 1 occurrences of an observation of SARS-CoV-2 test measurement6
  + value as concept is any of: Detected, Detected, Positive, Positive, Present, Present

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

* or at least 1 occurrences of a condition occurrence of COVID-19 conditions1

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

Limit cohort of initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: age >=18

Having all of the following criteria:

* with the following event criteria:
  + with age >= 18

Inclusion Criteria #2: has >=180d of prior observation

Having all of the following criteria:

* at least 1 occurrences of an observation period

where event starts between all days Before and 180 days Before index start date and event ends between 0 days Before and all days After index start date

Inclusion Criteria #3: Has T/C drug drug era overlapping day -30 or a drug exposure in the last 60 days

Having any of the following criteria:

* at least 1 occurrences of a drug era of PPI drugs4

where event starts between all days Before and 1 days Before index start date and event ends between 30 days Before and all days After index start date

* or at least 1 occurrences of a drug exposure of PPI drugs4

where event starts between 60 days Before and 1 days Before index start date

Inclusion Criteria #4: No exposure to any other H2RA blocker drugs within 180 days before start-date

*This inclusion criteria varies depending on which T/C drug is being assessed (since that one will not be excluded)*

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of H2RA drugs2

where event starts between 180 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

2. [JMPark] H2RA users, hospitalized with COVID-19

Initial Event Cohort

People having any of the following:

* a visit occurrence of Inpatient Visit3
  + occurrence start is after 2019-12-01

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having any of the following criteria:

* at least 1 occurrences of a measurement of SARS-CoV-2 positive test measurement pre-coordinated5

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

* or at least 1 occurrences of a measurement of SARS-CoV-2 test measurement6
  + value as concept is any of: Detected, Detected, Positive, Positive, Present, Present

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

* or at least 1 occurrences of an observation of SARS-CoV-2 test measurement6
  + value as concept is any of: Detected, Detected, Positive, Positive, Present, Present

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

* or at least 1 occurrences of a condition occurrence of COVID-19 conditions1

where event starts between 21 days Before and all days After index start date and event starts between all days Before and 0 days After index end date

Limit cohort of initial events to: **earliest event per person.**

Inclusion Rules

Inclusion Criteria #1: age >=18

Having all of the following criteria:

* with the following event criteria:
  + with age >= 18

Inclusion Criteria #2: has >=180d of prior observation

Having all of the following criteria:

* at least 1 occurrences of an observation period

where event starts between all days Before and 180 days Before index start date and event ends between 0 days Before and all days After index start date

Inclusion Criteria #3: Has T/C drug drug era overlapping day -30 or a drug exposure in the last 60 days

Having any of the following criteria:

* at least 1 occurrences of a drug era of H2RA drugs2

where event starts between all days Before and 1 days Before index start date and event ends between 30 days Before and all days After index start date

* or at least 1 occurrences of a drug exposure of H2RA drugs2

where event starts between 60 days Before and 1 days Before index start date

Inclusion Criteria #4: No exposure to any other PPI drugs within 180 days before start-date

*This inclusion criteria varies depending on which T/C drug is being assessed (since that one will not be excluded)*

Having all of the following criteria:

* exactly 0 occurrences of a drug exposure of PPI drugs4

where event starts between 180 days Before and 1 days Before index start date

Limit qualifying cohort to: **earliest event per person.**

End Date Strategy

No end date strategy selected. By default, the cohort end date will be the end of the observation period that contains the index event.

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 0 days.

Appendix 1: Concept Set Definitions

1. COVID-19 conditions

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 439676 | Coronavirus infection | Condition | SNOMED | NO | YES | NO |
| 4100065 | Disease due to Coronaviridae | Condition | SNOMED | NO | YES | NO |
| 37311060 | Suspected disease caused by severe acute respiratory coronavirus 2 | Condition | SNOMED | NO | YES | NO |
| 37311061 | Disease caused by severe acute respiratory syndrome coronavirus 2 | Condition | SNOMED | NO | YES | NO |

2. H2RA drugs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 950696 | Nizatidine | Drug | RxNorm | NO | YES | NO |
| 953076 | Famotidine | Drug | RxNorm | NO | YES | NO |
| 961047 | Ranitidine | Drug | RxNorm | NO | YES | NO |
| 997276 | Cimetidine | Drug | RxNorm | NO | YES | NO |
| 43009003 | lafutidine | Drug | RxNorm Extension | NO | YES | NO |

3. Inpatient Visit

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |

4. PPI drugs

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 904453 | Esomeprazole | Drug | RxNorm | NO | YES | NO |
| 911735 | rabeprazole | Drug | RxNorm | NO | YES | NO |
| 923645 | Omeprazole | Drug | RxNorm | NO | YES | NO |
| 929887 | lansoprazole | Drug | RxNorm | NO | YES | NO |
| 948078 | pantoprazole | Drug | RxNorm | NO | YES | NO |
| 19039926 | dexlansoprazole | Drug | RxNorm | NO | YES | NO |
| 43009052 | ilaprazole | Drug | RxNorm Extension | NO | YES | NO |

5. SARS-CoV-2 positive test measurement pre-coordinated

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 37310282 | 2019 novel coronavirus detected | Measurement | SNOMED | NO | YES | NO |

6. SARS-CoV-2 test measurement

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 756055 | Measurement of severe acute respiratory syndrome coronavirus 2 | Measurement | OMOP Extension | NO | YES | NO |
| 37310281 | 2019 novel coronavirus not detected | Measurement | SNOMED | YES | YES | NO |

## 16.2 Outcome Cohort Definitions

1. [JMPark] Occurrence of a composite intensive respiratory intervention during hospitalization

Initial Event Cohort

People having any of the following:

* a procedure of [covid19 v1] Mechanical ventilation2
* a procedure of [Covid19 v1] Extracorporeal membrane oxygenation (ECMO) procedure1
* a procedure of [COVID19 v1] tracheostomy3
* a measurement of [covid19 v1] Mechanical ventilation2
* an observation of [covid19 v1] Mechanical ventilation2

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

For people matching the Primary Events, include:

Having all of the following criteria:

* at least 1 occurrences of a visit occurrence of [OHDSI Covid19 v1] Inpatient Visit4

where event starts between all days Before and 0 days After index start date and event ends between 0 days Before and all days After index start date

Limit cohort of initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 30 days.

2. [JMPark] COVID-19 diagnosis

Initial Event Cohort

People having any of the following:

* a condition occurrence of COVID-19 (including asymptomatic)1

with continuous observation of at least 0 days prior and 0 days after event index date, and limit initial events to: **all events per person.**

Limit qualifying cohort to: **all events per person.**

End Date Strategy

Date Offset Exit Criteria

This cohort defintion end date will be the index event's start date plus 1 days

Cohort Collapse Strategy:

Collapse cohort by era with a gap size of 90 days.

Appendix 1: Concept Set Definitions

1. [Covid19 v1] Extracorporeal membrane oxygenation (ECMO) procedure

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 1531630 | Extracorporeal Oxygenation, Membrane, Peripheral Veno-venous | Procedure | ICD10PCS | NO | NO | NO |
| 1531631 | Extracorporeal Oxygenation, Membrane, Peripheral Veno-arterial | Procedure | ICD10PCS | NO | NO | NO |
| 1531632 | Extracorporeal Oxygenation, Membrane, Central | Procedure | ICD10PCS | NO | NO | NO |
| 2002247 | Extracorporeal membrane oxygenation [ECMO] | Procedure | ICD9Proc | NO | YES | NO |
| 2787820 | Extracorporeal Supersaturated Oxygenation, Intermittent | Procedure | ICD10PCS | NO | NO | NO |
| 2787821 | Extracorporeal Hyperbaric Oxygenation, Continuous | Procedure | ICD10PCS | NO | NO | NO |
| 4052536 | Extracorporeal membrane oxygenation | Procedure | SNOMED | NO | YES | NO |
| 4338595 | Cardiac support using extracorporeal membrane oxygenation circuitry | Procedure | SNOMED | NO | NO | NO |
| 44515635 | Extracorporeal membrane oxygenation | Procedure | OPCS4 | NO | YES | NO |
| 44811012 | Fluoroscopy guided percutaneous insertion of cannula for extracorporeal membrane oxygenation | Procedure | SNOMED | NO | NO | NO |
| 46257586 | Extracorporeal Membrane Oxygenation or Extracorporeal Life Support Services and Procedures | Procedure | CPT4 | NO | YES | NO |

2. [covid19 v1] Mechanical ventilation

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 765576 | Orotracheal intubation using bougie device | Procedure | SNOMED | NO | YES | NO |
| 2108641 | Glossectomy; complete or total, with or without tracheostomy, without radical neck dissection | Procedure | CPT4 | YES | YES | NO |
| 2108642 | Glossectomy; complete or total, with or without tracheostomy, with unilateral radical neck dissection | Procedure | CPT4 | YES | YES | NO |
| 2745440 | Insertion of Endotracheal Airway into Trachea, Percutaneous Approach | Procedure | ICD10PCS | NO | YES | NO |
| 2745444 | Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening | Procedure | ICD10PCS | NO | YES | NO |
| 2745447 | Insertion of Endotracheal Airway into Trachea, Via Natural or Artificial Opening Endoscopic | Procedure | ICD10PCS | NO | YES | NO |
| 4006318 | Respiratory assist, manual | Procedure | SNOMED | YES | YES | NO |
| 4013354 | Insertion of endotracheal tube | Procedure | SNOMED | NO | YES | NO |
| 4021786 | Fear of disconnection from ventilator | Condition | SNOMED | YES | YES | NO |
| 4031379 | Artificial ventilation finding | Condition | SNOMED | YES | YES | NO |

3. [COVID19 v1] tracheostomy

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 2110486 | Transoral approach to skull base, brain stem or upper spinal cord for biopsy, decompression or excision of lesion; requiring splitting of tongue and/or mandible (including tracheostomy) | Procedure | CPT4 | YES | YES | NO |
| 2743216 | Removal of Tracheostomy Device from Trachea, Via Natural or Artificial Opening | Procedure | ICD10PCS | NO | YES | NO |
| 2794811 | Medical and Surgical @ Respiratory System @ Change @ Trachea @ External @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2829384 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Percutaneous Endoscopic @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2829386 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Via Natural or Artificial Opening @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2831237 | Medical and Surgical @ Respiratory System @ Bypass @ Trachea @ Open @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2836115 | Medical and Surgical @ Respiratory System @ Bypass @ Trachea @ Percutaneous @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2862930 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Open @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 2870619 | Medical and Surgical @ Respiratory System @ Revision @ Trachea @ Percutaneous @ Tracheostomy Device | Procedure | ICD10PCS | NO | YES | NO |
| 4195473 | Temporary tracheostomy | Procedure | SNOMED | NO | YES | NO |

4. [OHDSI Covid19 v1] Inpatient Visit

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Excluded** | **Descendants** | **Mapped** |
| 262 | Emergency Room and Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9201 | Inpatient Visit | Visit | Visit | NO | YES | NO |
| 9203 | Emergency Room Visit | Visit | Visit | NO | YES | NO |

# 17. Appendix 3: ENCePP Checklist for Study Protocols

We have filled out the ENCePP Checklist for Study Protocols (Revision 4) which was adopted by the ENCePP Steering Group on October 15, 2019. A link to the completed form is provided below:

