Pragmatic Trial Exploring Impact of Patient Positioning in the Management of Patients Infected with COVID-19: Supine vs. Prone

Statistical Analysis Plan

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Introduction

This document describes the statistical analysis plan for a pragmatic trial designed to investigate the use of the prone positioning (PP) as compared to supine positioning to increase oxygenation and improve clinical outcomes in patients hospitalized with oxygen support for Covid-19. Prone positioning has long been used to combat hypoxemia in acute respiratory distress syndrome (ARDS). PP has shown to reduce lung over inflation and bolsters alveolar recruitment. PP also promotes uniformity of vertical pleural pressure gradients resulting in more uniform alveolar size. This trial hypothesizes that because PP serves to balance stress and strain within the lungs of COVID-19 positive patients requiring supplemental oxygen, PP will lead to improved outcomes compared to traditional supine positioning. This statistical analysis plan briefly describes the approach to the design and analysis of this study and is intended to provide enough information for an independent statistician to pursue our approach.

Population and Design Considerations

This study enrolls patients hospitalized for Covid-19 who are in receipt of supplemental oxygen but who are not mechanically ventilated. This study is designed as a pragmatic, parallel group, randomized controlled trial comparing clinical status at 5 days post randomization between patients randomized to a proning intervention and patients randomized to usual care. Eligible patients are allocated to study group based on their medical record number. Assignment of MRNs is considered random.

At the time of designing this study, insufficient data were available on the WHO Ordinal Outcome Scale to understand its measurement properties for detailed sample size analyses. In addition, we modified the endpoint to be more granular and thus expect it to provide greater power for discriminating differences between study groups. Based on the clinical course of patients admitted with oxygen at our institution, we estimated the distribution of potentially eligible patients across the WHO ordinal scale at day five for patients with no intervention. Assuming that discharging an additional 20% of participants by day 5 (i.e. scoring lower in on the WHO scale), then 150 patients per group would have over 90% power to detect this difference. If we reduce the need for oxygen among a similar proportion of patients but only discharge an additional 10%, then 175 patients per group will have over 80% power to detect the difference. We therefore originally planned to enroll 250 participants per study arm. When 50 patients were enrolled, or 25 patients per arm, we pre-specified and interim look at the distribution of the outcome variable (blinded to study arm). Following this interim look, we estimated that with our planned 250 patients per arm, we would be able to detect an OR of 1.6 with 80% power for the modified WHO ordinal scale at day 5. Due to concern over some missing data, potential crossover between arms, and to allow for a supplementary study that is using body position sensors to objectively measure exposure to proning, an additional 10% of the sample size will be enrolled for a planned total of 550 patients.

Interventions

This study is to evaluate the effectiveness of a simple, pragmatic intervention of 'provider-directed proning'. That is, a provider writes an order that the patient is recommended to prone, the patient is provided instructions and/or help on proning, and subsequently the patient is reminded to prone as healthcare personnel attend the patient. The alternative is no order to prone, and no instructions to the patient, which is usual care. Thus our two groups are

a) Intervention: Provider-directed Prone Positioniong
b) Control: Usual care

Endpoints

Primary Endpoint:

The primary endpoint as an ordinal variable that quantifies provision of oxygen as the main measure of clinical status measured on the fifth day of enrollment. The basis of the outcome is the World Health Organization Ordinal Covid-19 Outcome Scale, and this has been combined with data concerning the intensity of oxygen requirements. Patients are first ranked by categories of oxygenation strategies from the least invasive to the most invasive. Then, within rank, they are assigned a score based on the oxygen delivery settings as follows:

- Death
- ECMO
- Mechanical ventilation (ranked by mean FIO2 for the day)
- Non-invasive ventilation such as BIPAP (ranked by mean FIO2 for the day)
- High flow nasal cannula (ranked by mean FIO2 for the day, estimated from the %FIO2 recorded on the device)
- Standard nasal cannula (ranked by mean FIO2 for the day, FIO2 on standard nasal cannula or face mask is estimated as 21 + 3 x liters per minute (LPM) O2 flow)
- Room air

To minimize missingness on this primary outcome, we use the approach of last value carried forward for patients who are not observed for the full five days. Patients discharged home are at the bottom end of the scale (generally room air) while those who die will be scored the worst possible outcome. Patients discharged to a long-term care facility or similar have their oxygen needs at transfer recorded as their final requirements. Not many patients are expected in this category because the endpoint is being measured relatively close in time to the intervention (5 days), and when transfers occur in this population, they are likely to occur after much later in the clinical course.

Secondary Endpoints:

The secondary endpoint is constructed the same way as the primary endpoint, but measured on each of the first five days of randomization.

Exploratory Endpoints:

A number of exploratory endpoints have been proposed for this trial, and additional outcome may be proposed as understanding of the underlying disease and treatment course evolves. Below, we list the pre specified exploratory outcomes. For newly proposed endpoints, the analytical approaches will generally be similar to those described below.

- Length of Stay
- ICU Length of Stay
- Intubation yes/no

- Ventilator-free days (VFDs) to 28 days, calculated as a backwards count of whole days from day 28 to the last day in receipt of mechanical ventilation.
- Oxygen Levels
  - Maximum FIO2 for each day 1-5 after enrollment
- Maximum modified WHO ordinal scale score observed during 28 days of hospitalization, the modification is as follows:
  1. Death
  2. Hospitalized on invasive mechanical ventilation or ECMO
  3. Hospitalized on non-invasive ventilation or high flow nasal cannula
  4. Hospitalized on supplemental oxygenation
  5. Hospitalized not on supplemental oxygen
  6. Discharged/not-hospitalized (regardless of symptoms or organ support needs)
- Modified WHO COVID-19 ordinal scale measured at day 14

Safety endpoints:

- Incidence of Complications related to Positioning (e.g. accidental line displacement, vomiting, falls)

Datasets

Main Analysis

The main analysis for this study will be conducted using an intention-to-treat, or as assigned. All participants who met inclusion criteria and were randomized will be included. Participants will be grouped according to the arm to which they were allocated.

Safety Analysis

A safety analysis will be conducted to explore events associated with proning. This analysis will included all participants and events related to proning will be described regardless of study arm.

Other analyses

Neither a per protocol or complete case analysis is expected. A per protocol analyses might be justified if the number of major protocol deviations (including cross overs) exceeds about five in both arms combined.

Sensitivity analysis

This study was originally designed as a single-center pragmatic randomized controlled effectiveness trial. As the Covid-19 case waxed and waned across the country, and as demand for evidence for proning increased, the decision was made to open additional sites. One additional site was opened, which contributed less than 10% of participants to the dataset. We will repeat our main analyses excluded this additional site. If there are considerable differences, then we will report single site data.

Statistical Approach

Descriptive Analysis

Initially, we will describe the study cohort, both overall and grouped by intervention assignment. To characterize the study sample, demographic, clinical, and lab data will be described overall

and by group. Groups will not be formally compared used statistical tests; differences and confidence intervals of differences may be reported. All categorical variables will be described using frequencies and proportions, and continuous variables will be described using mean, standard deviation, and percentiles (i.e. 25^{th} , 50^{th} , 75^{th}). Missingness will be recorded for each variable. To further assess the distribution of variables, graphical summaries will be displayed using box-plots, dot-plots, violin-plots, and/or histograms. At a minimum, the following baseline variables will be described:

- Age (years)
- Sex (Male, Female, Not reported)
- BMI – kg/m^2
    - Obesity (None, Stage I BMI 30.0 -34.9; Stage II BMI 35.0 – 39.9; Stage III BMI>=40.0, Not reported)
- Race (American Indian/Alaska Native, Asian, Black/African American, White, Other, Not reported)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported)
    - Ethnicity may be combined with race
- Elixhauser Score
- Number of coexisting conditions (None; One; Two or more)
- Coexisting conditions (Yes/No)
    - Any
    - Diabetes
    - Hypertension
    - Underlying Respiratory Disease
    - Heart Disease
    - Renal Disease
    - Malignancies
- Smoking Status (as documented in the EMR)
- Renal replacement therapy required at enrollment (Yes/No)
- Vasopressors required at enrollment (Yes/No)
- Score on ordinal scale at enrollment (Hospitalized on low flow supplemental oxygen; Hospitalized on high flow supplemental oxygen; Hospitalized on non-invasive ventilation)

Subsequent to characterizing the cohort at baseline, we will explore and describe the outcome variables overall and grouped by study arm. We will take the same approach as for the cohort descriptors, using comprehensive summary statistics and graphical representations as appropriate. For depicting clinical course, alluvial or Sankey plots maybe be used.

We will describe fidelity of the intervention using the 'dose' of proning. This will be characterized primarily using nursing estimates of the number of hours a patient spent proned during a shift. Briefly, each nursing shift lasts for 12 hours, running from 7am to 7pm. After each shift, the nurse was asked to estimate for how many hours enrolled participants were proned, regardless of which study arm they were in. We will characterize the time spent proned as estimated total time, proportion of time, average time per shift. We note that a supplementary study included more formal objective measurements of proning. The accuracy of the nursing estimate of proning may be estimable and reported as a result of that supplementary study.

Main Analysis

Our main analysis will be a covariate-adjusted proportional odds (PO) regression model with the main predictor being group assignment. Suppose the outcome Yi for participant i can take one of the J ordered level of responses j = 1, 2; … ; J. The PO logistic regression models the logit as a linear function of the randomization groups and a set of pre-specified covariates:

$$\text{Log}\left(\frac{\Pr(Y \leq j)}{1-\Pr(Y \leq j)}\right) = \alpha_j + \beta_1 X_1 + \cdots + \beta_p X_p\,, \quad \text{for } j = 1, 2, \ldots, J-1 \qquad (1)$$

where X_1 is an indicator variable that defines the treatment groups, X_2 represents the important baseline covariate of severity, and the remaining X_s represent the additional covariates.

In the proportional odds model we assume that the relationship between each level in the outcome variable is proportional, so the effect that describes the relationship between the lowest category versus all higher categories of the outcome variable is the same as the relationship that describes the next lowest category and all higher categories. The proportionality assumptions will be explored graphically e.g. the logit of the empirical cumulative distribution function of the outcome should be parallel among categories of covariate Xj, and a partially proportional odds model may be pursued. The covariates that will be included in the model are those listed in the descriptive analyses, which include the important variable of baseline severity. Duplication of comorbidity variables will be avoided; only the Elixhauser score will be used. To check other model assumptions, the approaches described in Regression Modeling Strategies (Harrell 2015, 2nd ed.) will be used, i.e. we will assess the model fits, residual plots, partial effect plots, and/or anova plots (Wald minus the d.f.) will be displayed. Model results will be summarized with point estimates, 95% C.I., and p-values displayed in tabular form or graphically, along with model fit statistics.

Secondary Analysis

We have specified a single primary endpoint, and so we are not adjusting for multiplicity. Since our secondary endpoint should be more sensitive than the primary for changes in the outcomes, we are not employing a gatekeeping strategy. We will proceed with the secondary analysis regardless. With up to 5 outcome measurements per patient, a proportional odds model will be specified to include the random effect of patient and we will include number of days since enrollment. We will additionally include the time by treatment interaction to determine whether there is a differential treatment effect of proning over the observational window.

For exploratory outcomes, binary outcomes will be modeled assuming a logit link function, and ordinal and discrete outcomes will be modeled using a proportional odds model. Similar approaches will be used to modeling as for the main analyses.

Missingness

We do not expect missingness on our primary outcome. There may be missingness on covariates or on secondary or exploratory outcomes. We will not exclude cases with missing covariates. We will use multiple imputation with predicted mean matching. Cases with missing outcomes may also have the outcomes imputed

Subgroup analyses and differential treatment effects

To determine whether effects of treatment depend on any of the baseline characteristics, we will test the interaction between the characteristic and treatment effect in the PO model. Only if it is significant will we conduct a separate subgroup analysis. In this case, we will be liberal when considering whether a potential effect modifier has an interaction with the treatment, using a p-value of <0.2. For continuous variables, of which age is the primary variable of interest, we will not create artificial groups but instead we will present the partial effect plots demonstrating how the treatment effect changes over age. If warranted, a subgroup analysis may be conducted using the same model as for the primary outcome, but with the subgroup-defining variable removed from the model. We will not adjust subgroup analyses for multiplicity, but all data reports will clearly indicate the potential for false positive findings. We will focus these subgroup analyses on estimates of potential group specific effects rather than significance testing. Any findings will be subject to further confirmatory studies. Subgroup analyses will be performed using the intention to treat sample.

Summary

The analyses described here are those necessary to answer the trial's primary question of whether advising patients to prone is more effective than usual care in improving clinical status five days after being hospitalized for Covid-19 with requirements for supplemental oxygen. Beyond our analysis exploring the effect of treatment on primary, secondary, and exploratory endpoints, we expect there to be multiple additional exploratory analyses conducted, in particular as they relate to the supplementary study and understanding the association between objective measures of proning and moment-to-moment oxygen levels. It is not possible to predetermine the nature of such analyses. However, we are committed to preserving rigor and reproducibility and will pre-specify each subsequent analysis in the context of the specific question to be answered, cognizant of bias and missingness in the data.