# Lo(fex) and Behold: Extending Previous Analyses of Lofexidine's Efficacy for Opiate Withdrawal Symptoms

**Abstract**

This paper analyzes the National Institute on Drug and Abuse efficacy trial titled, *A Phase III Placebo-Controlled, Double-Blind Multi-Site Trial of Lofexidine for Opiate Withdrawal*. We extend the analysis of Yu et al., 2008 [1] on the relationship between lofexidine and opiate withdrawal symptoms as measured by the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS). We present a Bayesian hierarchical model to examine the relationship between MHOWS score, treatment, and participant-level covariates. We additionally conduct a mediation analysis to explore how lofexidine, which is commonly used to alleviate hypertension, may influence MHOWS beyond reducing blood pressure. Finally, we introduce a Cox proportional hazards model to predict participant dropout. From the hierarchical model, we find that treatment results in a statistically significant decrease in peak MHOWS scores as compared to placebo, holding all other covariates constant. However, our mediation analysis challenges this result, finding that lofexidine is no longer significant when systolic blood pressure is excluded from the considered symptoms. In the survival analysis, we find that lofexidine reduces the risk of trial dropout.

# 1 Introduction

## 1.1 Motivation

The United States is confronting an unprecedented opioid crisis. From 1999 to 2021, nearly 645,000 people died from an overdose involving opioids [2], with a more than 600% increase in fatalities occurring between 1999 and 2021 [3]. At the individual level, increased dependence on opioids has manifested in severe ways, including premature mortality, increased healthcare costs, and challenging opiate withdrawal experiences [4]. On a societal scale, the effects are equally dire, marked by increased unemployment rates and a heightened strain on healthcare resources [5]. These profound consequences underscore the urgency of developing effective treatment strategies for opioid use disorder.

In this context, lofexidine—a nonopiate historically used in hypertension treatment—has emerged as a candidate for alleviating opioid withdrawal symptoms, a critical component of opioid use disorder treatment. Usage in over 75,000 opiate detoxification cases in the United Kingdom, as well as preclinical research in mice studies in the United States, provide a basis for exploring the efficacy of alpha2-adrenergic agents such as lofexidine in treating and reducing the effects of opiate withdrawal; the success of such trials allowed for the Phase III trial that formed the basis for Yu et al.'s analysis. [6]. Our analysis aims to strengthen the methodology and re-evaluate the findings of Yu et al [1]. We extend alternative models for modeling lofexidine efficacy and patient dropout, enabling us to answer the following questions:

1. Does lofexidine have a statistically significant relationship with opiate withdrawal symptoms experienced—as measured by MHOWS—after controlling for relevant patient-level covariates?

2. Does lofexidine have a statistically significant relationship with a patient's likelihood to drop out of the study ("early termination") after controlling for relevant patient-level covariates?

3. Does controlling for the potentially confounding effects of lofexidine's prior usage as an anti-hypertensive treatment alter its observed impact on alleviating opiate withdrawal symptoms?

## 1.2 Trial Description

To investigate the efficacy of lofexidine, the National Institute on Drug and Abuse (NIDA) developed a Phase III, placebo-controlled, double-blind, randomized trial in an inpatient setting [1]. The trial studied 68 opiate-dependent individuals with 35 randomized to the lofexidine treatment and 33 to the placebo. The study was conducted at three different research sites across the country in Los Angeles, CA, New York, NY, and Philadelphia, PA [1].

Yu et al.'s experiment consists of three phases: first, on Days 1-3, the opioid agonist stabilization phase occurs, where all patients are given a standardized amount of

morphine to reset the timeline of the psychological effects of withdrawal. Second, on Days 4-8, patients are given either the placebo or lofexidine treatment, and an array of medical data is collected. Finally, starting on Day 9, all patients receive the placebo treatment for two days. On Day 11, all subjects are discharged [1].

The primary outcome measure for the study was the Modified Himmelsbach Opiate Withdrawal Scale (MHOWS) on Day 5, which is the second day of opioid detoxification treatment [1]. MHOWS was approved by the FDA in 1999 as the primary outcome measure for this trial based upon its objectivity and reliability in measuring treatment efficacy for opiate withdrawal in clinical trials [6]. The usage of a standardized dose of initial morphine during the initial phase of the trial satisfies the prerequisite for usage of MHOWS as an opiate withdrawal metric for this clinical trial [6].

### 1.3 Data Description

The data for our extended analysis comes from 38 forms collected by physicians and other study administrators to track individual patient medical readings and withdrawal systems over the trial period. The data was aggregated for each patient and stored as IMC01 through IMC36 with two supplementary forms (IMCENR and FNLPKRES). The full data dictionary can be found in the NIDA-CSP-1020 Protocol [7].

Exploratory data analysis was conducted on the potential covariates, as well as their relations with our target variables MHOWS and dropout day denoted in the research questions. This analysis is detailed in Appendix 4.5.

## 2 Methodology

### 2.1 Data Processing

To make the data suitable for modeling, we first aggregated the datasets of interest based on patient ID number and site, since the data of interest were collected on multiple separate forms.

Three form questions track whether a patient is a heroin, hydromorphone, or morphine user, and another three track how much the patients use those opiates on a daily basis. Since we are primarily interested in the severity of opiate dependency (regardless of the actual opiate being used), we chose to combine these variables into one comprehensive covariate: morphine milligram equivalents (MME), which converts the potency of each of these drugs into units of morphine. This standardizes the opiate potency across several drugs and consolidates our covariates into a singular standardized measure of prior drug use severity. MME is an accepted tracker of opioid potency as per the CDC [8] and HHS [9]. Standard MME scales do not have a conversion for heroin, so we equate 1mg of heroin to 2 units of morphine as heroin has been found to have approximately two times the potency of morphine [10].

In the process of replacing missing data, we made the assumption that data missing not at random (MNAR) could be treated as a negative response. For instance, some questions about opiate use had only positive or missing responses. Since every

participant in the study filled out at least some part of each form, we assumed that a non-response could be treated as a negative response. We subsequently imputed the remaining missing data using Multiple Imputation by Chained Equations (MICE) [11]. MICE requires that missing data be missing at random (MAR). After addressing the MNAR data, we assume all remaining missingness is random and proceed with MICE.

We then calculated the MHOWS scores for each patient using the formula reference in the study protocol, which is detailed in Table 5 in Appendix 4.1. Consistent with the study protocol [6], we made several assumptions about the data in order to calculate MHOWS, including carrying forward data from patients who dropped out on Day 4 and averaging Day 4 and Day 6 data from patients who were not evaluated on Day 5. This process is detailed in Appendix 4.1.

## 2.2 Modeling MHOWS

Bayesian modeling offers several advantages over traditional linear regression or mixed modeling (as implemented by the previous analysis). Incorporating prior knowledge into the model allows for a probabilistic framework and a more nuanced understanding of distributions over possible values. By providing a full probability distribution over our parameters and predictions, Bayesian regression allows us to further quantify our uncertainty. This approach can lead to more robust predictions, especially in cases where data is scarce or noisy. With the scarcity (n = 68) in our dataset, we argue that incorporating a Bayesian model is justified.

To address the first research question, we chose to proceed with a Bayesian hierarchical model. In many clinical settings, including the NIDA trial, subject data is often drawn from population clusters. This may violate the independence assumption, as people within clusters might be more similar to each other than people between clusters. Hierarchical models allow us to isolate this bias and capture the variation of predictors across different groups. In our case, we identified testing site as a level in the hierarchical model to account for potential differences between patients, doctors, and general medical treatment across different testing sites. This is consistent with the analysis of many multisite trials [12] and the frequentist mixed-modeling approach of Yu et al.

Since we anticipate the random effect captures much of the unseen variability, we leave the remaining $\beta$ values for our covariates of interest untouched across the three sites. This implies that we do not expect that age, weight, race, etc. will affect MHOWS differently across different sites and that the differences between trial sites will be captured solely in varying the intercept.

In addition to a Bayesian hierarchical approach, we also formulate a Bayesian pooled approach without grouping by site. This serves as a straightforward, non-hierarchical baseline model. This comparative analysis allows us to gauge whether the additional complexity introduced by the hierarchical model is justified by its performance. The assumptions for Bayesian modeling are met and are detailed in Appendix Section 4.3.

### 2.2.1 Hierarchical Model Framework

In our hierarchical model, we model the variability of predictors between and within different testing sites. First, we define

- $X_{i,j} \in \mathcal{R}^n$: the vector containing $n$ predictors for the $i^{th}$ subject in site $j$.
- $Y_{i,j} \in \mathcal{R}$: MHOWS score for the $i^{th}$ subject in site $j$.

**2.2.1.1 Variability within Sites** For each site $j$, each subject's MHOWS score is normally distributed with mean, $\mu_{i,j}$. We then model each subject's $\mu_{i,j}$ as a linear relationship between a subject's predictors.

$$Y_{i,j}|\beta_{0j}, \beta, \sigma_y \sim N(\mu_{i,j}, \sigma_y^2) \text{ where } \mu_{i,j} = \beta_{0j} + \beta X_{i,j}$$

- $\beta_{0j}$: intercept of the model for site $j$. In a varying intercepts model, this is group-specific.
- $\beta = [\beta_1, \beta_2, ..., \beta_n]$: a vector of coefficients for the predictors in the data.
- $\sigma_y$: within-site variability.

**2.2.1.2 Variability between Sites** In our model, since we are focused on modeling the variability of intercepts between sites, we will look to define how these intercepts are distributed. We will assume that site-specific intercepts will vary normally around a global intercept.

$$\beta_{0j} \mid \beta_0, \sigma_0 \sim N(\beta_0, \sigma_0^2)$$

- $\beta_0$: the global average intercept across all sites. It defines what the expected average site's baseline MHOWS score is.
- $\sigma_0$: between-site variability

### 2.2.2 Prior Elucidation and Sensitivity Analysis

We have defined global parameters: $\beta_0$, $\sigma_0$, $\beta$, and $\sigma_y$. We need to establish priors for each of these parameters.

$$\begin{array}{cc} \beta_0 \sim N(m_0, s_0^2), & \beta \sim N(m_1, s_1^2) \\ \sigma_y \sim \text{Exp}(\lambda_y), & \sigma_0 \sim \text{Exp}(\lambda_0) \end{array}$$

- $\beta_0$: This is the global intercept, or the mean MHOWS score when all covariates are held at zero or reference. The protocol notes that MHOWS scores are known to be normally distibruted.[6] We were able to determine that MHOWS scores vary from approximately 0 to 133 (see 4.6) through an analysis of the individual components in the computation. As determined through extensive prior elucidation work (see Appendix 4.7), data from Phase II was taken to determine a collection of justifiable,

informative priors for $\beta_0$. A non-informative prior was also considered, centering the distribution at the mean of 0 and 133 with a large variance.

We conducted a sensitivity analysis to determine how robust the model was to changes in the prior mean and variance. We tested multiple prior means and iterated across a range of variances to examine the effect these incremental changes had on posteriors. Conducting a sensitivity analysis on variance was particularly important given that while our priors are based primarily off of data from Phase II, we add a term to our prior variance as an additional expression of uncertainty, which is also detailed in Appendix 4.7.

- $\beta$: We were not able to gather conclusive information on how changes in each predictor affect MHOWS, so we initialize weakly informative normal priors centered around 0 with autoscaling. The `rstanarm` package internally adjusts the scales of our priors based on the observed standard deviation.

- $\sigma_y$ and $\sigma_0$: Standard deviations between and within groups are strictly positive, so we choose to initialize each of these priors as an exponential distribution with mean 1 with autoscaling.

### 2.2.3 MHOWS Model Covariates

To answer the first research question regarding lofexidine's relationship to MHOWS, we look at the beta parameter for a lofexidine treatment indicator variable. This parameter represents the expected difference in MHOWS for a participant, as conditioned on the statistics of said participant (a difference in conditional expectation). This can otherwise be expressed as the expected difference in MHOWS for a given participant with the specific covariates of the participant being analyzed.

The final covariates used for our MHOWS hierarchical model were treatment (lofexidine vs. placebo, our primary covariate of interest), age, gender, weight, race, MME (taken over the preceding 30 days), cigarettes smoked by the patient (in the last 24 hours), and use of a nicotine patch. We justify our inclusion of each covariate within our model in Table 6 in Appendix 4.4.

### 2.2.4 MHOWS Model Metrics

After establishing covariates, we iteratively conditioned on each of our prior distribution subsets to generate 9 posterior distributions for our model. To evaluate the performance of our models on predicting MHOWS, we calculated the median absolute error (MAE) for each of the 9 fitted models. MAE was selected as it is more resilient to outliers than other common metrics such as mean squared or mean absolute error. MAE describes the median difference between the observed MHOWS scores and the posterior predictive means. We took the model with the lowest median absolute errors and performed further analysis, including posterior predictive checks and p-direction analysis.

## 2.3 Modeling Survival

In the context of this secondary outcome model, survival represents someone who has made it through eight days of the study. This data is right censored. Dropping out from the study (early termination) before eight days is thus considered as not survival.

### 2.3.1 Kaplan-Meier Estimate and Log-Rank Test

In the original study, the authors used a Kaplan-Meier curve for survival analysis and conducted a log-rank test for differences in time to early termination between placebo and lofexidine patients [1]. We replicate their statistical tests and find the same results. As per the log-rank test, there is a statistically significant difference between the expected dropouts between the lofexidine and placebo groups ($p = 0.02$).

Table 1: Observed and Expected Values for Treatment Groups

| **Treatment** | **N** | **Observed** | **Expected** | **(O-E)ˆ2/E** | **(O-E)ˆ2/V** |
|---|---|---|---|---|---|
| *LOFEXIDINE* | 35 | 23 | 29.7 | 1.53 | 5.35 |
| *PLACEBO* | 33 | 28 | 21.3 | 2.14 | 5.35 |

Chisq= 5.3 on 1 degree of freedom, p= 0.02

### 2.3.2 Cox Model

In modeling survival, we extend the original authors' survival analysis with our Cox proportional hazards (CPH) model. Whereas the original CPH model only relates dropout to the treatment (lofexidine vs. placebo), our model has the following form:

$$\lambda(t) = \lambda_0(t)exp(\beta_1\text{Treatment} + \beta_2\text{Age} + \beta_3\text{Is male} + \beta_4\text{Is other race} + \beta_5\text{Is white} + \beta_6\text{Weight} + \beta_7\text{Uses nicotine patch} + \beta_8\text{Cigarettes smoked} + \beta_9\text{MME over 30 days} + \beta_{10}\text{Baseline Systolic Blood Pressure} + \beta_{11}\text{Need for Psychiatric Treatment} + \mu_{Testing\ Center})$$

where $\lambda_0(t)$ represents the baseline hazard for when our covariates are equal to 0 (with no assumed shape) and $\mu_{Site}$ is a random effect for the testing site. The baselines for the categorical variables of gender, race, treatment, and nicotine patch usage are female, Black, lofexidine treatment, and active user respectively.

These covariates are the same as our Bayesian hierarchical model, with the addition of a numeric variable that tracks how many cigarettes the patient smoked in the preceding 24 hours (from when the MHOWS measurements were taken), a categorical variable indicating whether a patient currently uses a nicotine patch, and a numeric variable that records an interview's opinion on the patient's need for psychiatric treatment, recorded on a scale from 1-10. The former two covariates are included because a patient's nicotine dependency could affect their likelihood of remaining in the study; as per the study protocol, patients were offered financial compensation to stop smoking and use a nicotine patch. As such, we were interested in the impact of the patient's nicotine usage on their overall likelihood of remaining in the study, something that the original analysis does

not consider. The latter covariate is included as a metric of discomfort, as a participant being susceptible to psychological problems may make them more likely to drop out of the study.

### 2.4 Mediation Analysis

Prior studies have demonstrated that lofexidine lowers blood pressure (Montgomery et. al). The NIDA-CSP-1020 protocol describes the MHOWS calculation in detail, which includes a systolic blood pressure measurement where 1 point is allocated for each 2 mm Hg. rise up to 30mm. Thus, in directly modeling MHOWS, we capture this known effect of lofexidine. For any participant that comes in with high blood pressure, we can expect that on average, their blood pressure measurement will decrease, explicitly reducing that part of the MHOWS calculation. However, we do not know how it will associate with the other opiate withdrawal symptoms.

We offer an auxiliary analysis in which we remove the systolic blood pressure measurement from the MHOWS score, producing a new target variable: MMHOWS (Modified MHOWS, or MHOWS without blood pressure). For this auxiliary analysis, we directly modify the dependent variable to isolate the known effect of lofexidine from unknown effects. We define the unknown effects to be lofexidine's impact on other withdrawal symptoms. Thus, this analysis seeks to determine the extent to which lofexidine relates to withdrawal symptoms on the MHOWS scale other than blood pressure.

We view this framework in the context of mediation analysis, exploring unknown mediated pathways between lofexidine and other opiate withdrawal symptoms in the MHOWS score. Within a mediation analysis framework, our MHOWS model represents the total effect (c-path), establishing the overall effect of lofexidine on opiate withdrawal symptoms. Our auxiliary model for MMHOWS then models the direct effect (c'-path), capturing the effect of lofexidine on MHOWS that is not mediated by blood pressure. The mediated effect (ab-path) can then be captured within the difference of the total and direct effect, such that we come to understand the proportion of lofexidine's impact on withdrawal severity that operates through its known effect on blood pressure. In order to ensure a robust Bayesian model, we make use of rstanarm's autoscale such that we can use our research about priors for MHOWS mean and variance in the MMHOWS model after scaling them. Our mediation analysis was preceded by testing the classical assumptions for mediation analysis, as seen in Appendix 4.9.

## 3 Results

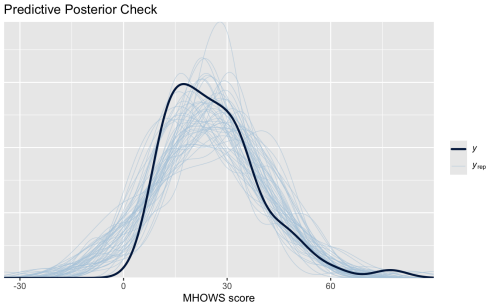
### 3.1 Bayesian hierarchical models

After performing Bayesian estimation via Markov chain Monte Carlo (MCMC) algorithms, the median absolute errors of the posterior distributions faceted by global intercept prior are shown below.

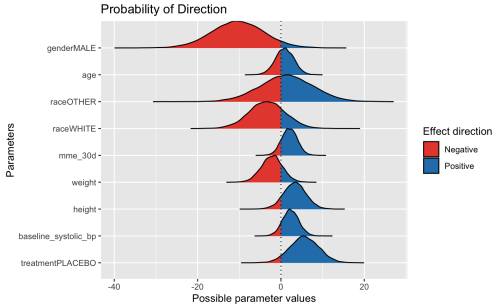
As shown in Table 2, the a global intercept prior of mean 19.3 and standard deviation of 2 resulted in the lowest MAE, and the complete pooled model performed the worst

Table 2: Median Absolute Errors

| **Model Intercept Prior** | **MAE** | **Scaled MAE** |
|---|---|---|
| $N(19.3, 2^2)$ | 7.36 | 0.510 |
| $N(19.3, 5^2)$ | 7.75 | 0.542 |
| $N(19.3, 7^2)$ | 7.98 | 0.558 |
| $N(19.3, 10^2)$ | 8.20 | 0.565 |
| $N(30.3, 2^2)$ | 8.24 | 0.570 |
| $N(30.3, 5^2)$ | 8.20 | 0.568 |
| $N(30.3, 7^2)$ | 8.26 | 0.560 |
| $N(30.3, 10^2)$ | 8.12 | 0.559 |
| $N(66.5, 20^2)$ | 8.32 | 0.569 |
| Complete Pooled | 8.35 | 0.574 |




(a) Posterior Predictive Checking




(b) p-direction areas for all covriates

in terms of median absolute error. This suggests that testing site might indeed have an effect on MHOWS scores, and we cannot assume independence between and within testing groups.

Furthermore, there is also an observable positive correlation between intercept standard deviation prior and MAE. In fact, the weakly informative prior centered around the mean of all possible MHOWS scores had the second worse MAE score of 8.32. Considering we have an empirical understanding of possible MHOWS scores from previous trials, this observation seems sensible.

Finally, after plotting the posterior predictive check for the $N(19.32^2)$ prior model in Figure 1a, we see that our model reasonably approximates the shape of the observed distribution and the variability of MHOWS scores. The ranges of our posterior prediction MHOWS scores appear to be within the range of the actual MHOWS scores.

### 3.1.1 Intercept Variability

The intercept row in Table 3 compares intercepts between the three sites. With posterior mean intercepts of 37.26, 39.11 and 39.09 for testing sites 1, 162, and 733 respectively, site 1 seems to have a lower baseline MHOWS score compared to the other two. Thus, with all other covariates held equal, we would expect site 1 to have a roughly 2-unit lower MHOWS score than sites 162 and 733. This supports our initial claim that there might be variation between testing sites in this lofexidine study.

Table 3: Bayesian Hierarchical Linear Model

| **Covariate** | **Coefficient** | **95% HDI** | **p-direction** |
|---|---|---|---|
| *Intercept* | 34.70 | 21.20, 47.23 | 1.00 |
| CENTER:1 | +2.56 | — | — |
| CENTER:162 | +4.41 | — | — |
| CENTER:733 | +4.39 | — | — |
| *Treatment* | | | |
| Placebo | — | — | — |
| Lofexidine | -5.60 | -12.48, | 0.9510 |
| *Age* | 0.842 | -3.38, 5.31 | 0.6532 |
| *Race* | | | |
| African-American | — | — | — |
| Other | 1.40 | -11.16, 13.97 | 0.5884 |
| White | -3.35 | -11.83, 5.26 | 0.7782 |
| *Weight* | -2.15 | -7.23, 2.90 | 0.8053 |
| *Height* | 3.32 | -2.00, 8.67 | 0.8880 |
| *Gender* | | | |
| Female | — | — | — |
| Male | -10.27 | -21.99, 2.23 | 0.9531 |
| *Baseline Systolic Blood Pressure* | 2.36 | -1.58, 6.24 | 0.8832 |
| *MME (Over 30 days)* | 2.04 | -1.77, 5.61 | 0.8610 |

HDI = High Density Interval, p-direction = probability of direction

### 3.1.2 Treatment Group Analysis

Our results indicate that individuals within the lofexidine treatment group are expected to have a 5.60-unit lower MHOWS score, on average, than subjects in the placebo treatment group, when holding all other covariates constant and having a variable intercept based on testing site.

We evaluate the statistical confidence of this covariate effect. In a Bayesian approach, there is no notion of a p-value, as we are dealing with distributions and uncertainty rather than point estimates. In this analysis, we consider "probability of direction," which describes the probability that a certain effect (or covariate) is positive or negative. A simulation study by Makowski et al., 2019 [13] notes this the probability of direction (p-direction) metric is the closest statistical equivalent to the frequentist p-value. It has a mathematical correspondence with the p-value, denoted p-value $= 2(1 -$ p-direction).

Based on this methodology, we calculate the p-value of the lofexidine treatment covariate to be roughly 0.098. Thus, at a significance level of 0.10, taking lofexidine results in a statistically significant decrease in Day 5 MHOWS scores as compared to placebo. The presence of this significance leads us to question lofexidine's historical use as an anti-hypertensive medication and whether that affects the statistical significance of lofexidine treatment in opiate withdrawal. We explore this question in depth in Section 3.3.

### 3.1.3 Sensitivity Analysis

The results of our sensitivity analysis can be found in Appendix 4.8. They show that our $\beta$ coefficients are robust to various sets of priors.

## 3.2 Survival

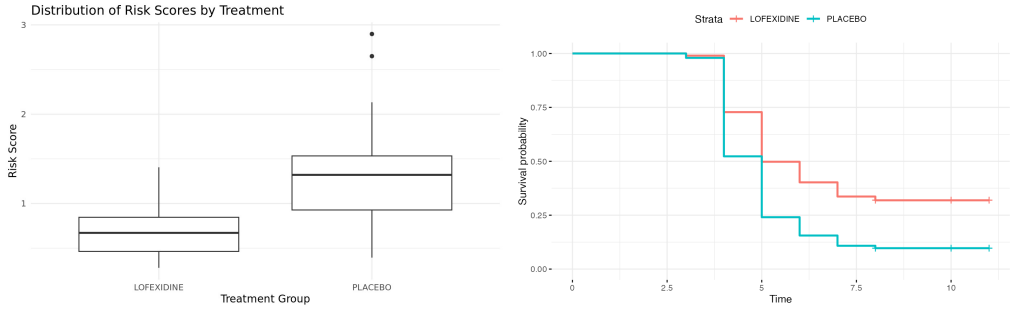
Table 4: Hazard Ratios for Various Characteristics

| **Characteristic** | **HR** | **95% CI** | **p-value** |
|---|---|---|---|
| *Treatment* | | | |
| Lofexidine | — | — | — |
| Placebo | 1.81 | 0.98, 3.37 | 0.060 |
| *Age* | 1.05 | 1.00, 1.10 | 0.037 |
| *Race* | | | |
| African-American | — | — | |
| Other | 0.54 | 0.19, 1.54 | 0.3 |
| White | 0.86 | 0.41, 1.82 | 0.7 |
| *Weight* | 1.00 | 0.99, 1.01 | 0.6 |
| *Gender* | | | |
| Female | — | — | — |
| Male | 0.41 | 0.15, 1.14 | 0.089 |
| *Cigarettes smoked (last 24 hours)* | 1.00 | 0.89, 1.13 | ¿0.9 |
| *Nicotine Patch* | | | |
| Used at All Times | — | — | — |
| Not Used | 3.92 | 1.01, 15.2 | 0.049 |
| *Baseline Systolic Blood Pressure* | 0.99 | 0.96, 1.01 | 0.3 |
| *MME (Over 30 days)* | 1.00 | 1.00, 1.00 | 0.2 |
| *Need for Psychiatric Treatment* | 1.04 | 0.93, 1.16 | 0.5 |

1 HR = Hazard Ratio, CI = Confidence Interval

Table 4 contains the results from our mixed-effects CPH model. We find that the treatment a patient receives has an association with an increased hazard ratio that is statistically significant at the $\alpha = 0.1$ level but not at the $\alpha = 0.05$ level ($p = 0.06$). A hazard ratio of 1.81 implies that it is nearly two times as likely that a patient receiving a placebo drops out than a patient receiving lofexidine, all else held constant.

Age is another covariate that is statistically significant. ($p = 0.037$). The HR of 1.05 implies that a one-year increase in age, all else held constant, is associated with a 5% increase in the hazard (chance of failing to complete the study). Additionally, being male is associated with an HR of 0.41, implying that all else held constant, men are much less likely to drop out of the trial than women. This statistic is also significant only at the $\alpha = 0.1$ level ($p = 0.089$). However, we caveat this finding by emphasizing the small sample size and the even smaller number of female patients upon which the model was developed. Finally, the non-usage of a nicotine patch was statistically significant ($p = 0.049$) and was associated with a HR of 3.92, meaning those not using a patch were nearly 400% more likely to drop out, all other covariates held constant. Again, we reiterate that only a small subset of patients wore a nicotine patch, but this suggests




(a) Individual risk scores, stratified by treatment

(b) Predicted survival from Cox mixed-effects model

that the financial incentive associated with remaining in the study while using only a nicotine patch might have affected an individual's likelihood to drop out.

Our findings on treatment significance are further supported by risk scores and predicted survival curves, which show clear visual distinctions between the patients receiving lofexidine and those receiving the placebo. Figure 2a shows the risk scores, or the individual predicted hazards for each patient given their treatment and covariates; patients receiving the placebo have a higher 25th percentile risk, a higher median risk, and a higher 75th percentile risk. Figure 2b shows the predicted survival curves from the CPH model. For each day, the probability that patients receiving lofexidine "survive" (continue in the trial) is higher than their counterparts receiving placebo. As such, both figures support our findings that treatment has a significant impact on individual hazard.

Overall, we find that age, use of a nicotine patch, treatment, and gender are associated with a change in the hazard of an individual patient, and that the remaining covariates appear to have a hazard ratio close to 1, indicating that they have little impact on total survival. Although we do not find the treatment to be statistically significant at the same level as the original analysis, we still see that placebo is associated with a higher hazard (thus implying that lofexidine is associated with a lower hazard), reinforcing the findings of Yu et al [1].

### 3.3 Mediation Analysis

Upon changing our variable of interest from MHOWS to MMHOWS, we find that the indicator for treatment is no longer statistically significant at the $\alpha = 0.1$ level. This finding implies that without the inclusion of systolic blood pressure in MHOWS, lofexidine may no longer have as strong an association with lowered MHOWS scores. As such, we leave our discussion of the first research question open to the possibility that lofexidine does not alleviate the other symptoms of opiate withdrawal nearly as much as it reduces blood pressure. However, the findings of our survival model still support the claim that lofexidine was correlated with a much lower hazard, which implies that neither model alone tells the entire story.

### 3.4 Limitations and Future Work

The main limitations of our MHOWS analysis are small dataset size and the risk of overfitting. Given the relatively small number of data points (n = 68), our analysis has relatively low power and significance, and would likely benefit from being applied to a study with more patients. We thus see in our uncertainty quantification that we have wide distributions for our estimates of the beta values for our covariates. Our choice of Bayesian hierarchical modeling is sensible in that it is more robust to overfitting in that the Bayesian posterior penalizes more complex model structure ("shrinkage"). However, it is still possible to overfit the data, especially with our small dataset size. Finally, in choosing to do a Bayesian analysis, our model is computationally intensive and is subject to the influence of priors. While this can be helpful, a bad choice of priors can lead to poor model convergence and less accurate estimates of the beta coefficients in our model. Though our sensitivity analyses indicate robustness, additional examination may be warranted.

Cox Survival Analysis also has a few limitations. Similar to our MHOWS model, in using so many covariates with a small dataset, there is certainly a risk of overfitting. Additionally, the model is semiparametric, which means we do not define a baseline hazard. This can make it difficult to obtain absolute risk estimates over time, limiting the model's ability to provide complete predictions of survival probabilities. It would have been ideal to compare against another semiparametric model, such as the Buckley-James estimator, as well as parametric models, in order to have a fair and effective baseline to understand how well our CPH model fit the data.

Opting for a Bayesian approach, we were able to obtain a more holistic view of lofexidine's efficacy for opioid withdrawal. We find the 3.2mg dose of lofexidine, as compared to the placebo, causes a statistically significant reduction in MHOWS scores and makes patients less likely to withdraw from the trial.

Using the Cox model, we were also able to show that users using a nicotine patch were far less likely to withdraw from the trial, all else held constant. We cannot unable to determine exactly why this might be—financial incentive may have altered behavior in the trial, but it may also be that patients attempting to quit nicotine concurrently might be more determined to surmount their addiction. In any case, this finding is notable and may have implications for trial design in the substance withdrawal space moving forward, particularly when multiple substances are interacting.

Our findings from the mediation analysis suggest that the impact of systolic blood pressure changes on MHOWS may impact clinical perceptions of its usefulness in treating opiate withdrawal and requires future research. In particular, extended research on lofexidine's impact on withdrawal symptoms beyond blood pressure would be beneficial.

# 4 Appendix

## 4.1 MHOWS Calculation

The score for any day is the sum of the points outlined in Table 5 [6].

Table 5: Scoring System for Symptoms

| **Symptom** | **Points** |
|---|---|
| Emesis | 0 points if the number of emesis is 0 or missing for the day;<br>5 points if the number of emesis is 1 for the day;<br>10 points if the number of emesis is 2 for the day;<br>15 points if the number of emesis is >3 for the day; |
| Yawning | 1 point if observed on the day |
| Lacrimation | 1 point if observed on the day |
| Rhinorrhea | 1 point if observed on the day |
| Perspiration | 1 point if observed on the day |
| Tremor | 3 points if observed on the day |
| Goose-flesh | 3 points if observed on the day |
| Anorexia | 3 points if appetite is coded as "poor" or "none" for any meal that day |
| Restlessness | 5 points if observed on the day |
| Pupil dilation | 1 point for each 0.1 mm increase in pupil size |
| Temperature | 1 point for each 0.1 degree C. rise |
| Respiration | 1 point for each respiration per minute increase |
| Systolic BP | 1 point for each 2 mm Hg. rise (up to 30 mm) |
| Weight | 1 point for each pound loss |

Though our variable of interest is Day 5 MHOWS scores, several considerations were made in the study protocol to allow for score calculations in the presence of data missingness. In particular, if a patient is missing any or all of the data on Day 5, the study proposes imputating the arithmetic mean of Day 4 and Day 6 metrics [6]. In the event that the patient dropped out on Day 4 but was evaluated on this day, these Day 4 values are carried forward.

## 4.2 Miscellaneous Data Cleaning

During our analysis, we discovered a clerical error in the height column. One patient has a listed height of 5.9 inches, far less than the height of the shortest adult ever recorded. We reasonably assume that the patient is actually 5 foot 9 inches, or the decimal was added by accident and the patient is 59 inches. We used a CDF of heights from the U.S. National Center for Health Statistics and found that the probability of a given 39-year-old, 160 lbs male patient being 59 inches tall is less than 0.001. As such, we presume the person is truly 5 foot 9 inches, (69 inches). We replace this height accordingly for the remainder of our analysis, noting that this value may be inaccurate.

## 4.3 Bayesian Model Assumptions

To model our data using a hierarchical model, the following assumptions are satisfied.

- Structure of Data: Outcomes $Y_{i,j}$ of any group are independent of those from another group. However, within group, there may be correlations.
- Linear Relationship: Within any group $j$, the outcome and predictors have a linear relationship.
- Variability within Groups: Observed outcomes $Y_{i,j}$ vary normally around a mean and standard deviation for that group.
- Variability between Groups: Group-specific parameters (the baseline) vary normally around a global intercept and standard deviation.

### 4.4 Covariate Justification

Table 6: Data Description and Justification for Inclusion

| **Field Label** | **Justification** |
|---|---|
| Treatment | Treatment is the primary variable of interest in this MHOWS model. |
| Age | Difference in age accounts for various physical and mental differences, including pharmacokinetic and pharmacodynamic differences such as how one's body metabolizes and responds to opiates and their withdrawal [14]. |
| Sex | Biological differences between sexes can account for pharmacokinetic and pharmacodynamics differences, including how one's body metabolizes and responds to opiates and withdrawal [15]. |
| Site Number | The location at which a participant is admitted may carry information about local opiates or geographic factors that may influence one's withdrawal. |
| Race | While race is a complex spectrum, one's genetic makeup can lead to pharmacodynamic differences in how the body responds to opiates [16]. |
| MME (Over 30 days) | Recency and severity of opiate use are direct indicators of potential dependence and tolerance in participants. Participants are standardized at the beginning of the study with an identical dose of morphine. However, this variable seek to capture if there is any additional variability in MHOWS that results from differences in the severity of their opiate addiction between participants prior to the study, standardizing each opiate based on potency. |
| Cigarette Smoking | Prior studies have shown that smoking before or during treatment was associated with increased opiate withdrawal discomfort [17]. |
| Weight | Height/Weight may impact the effect of the dosages and can lead to pharmacodynamic differences in how one's body responds to opiates and withdrawal [18]. |
| Psychiatric Treat. Need | Psychological factors including neuroticism have been shown to be associated with distress of patient, which could lead to this as an effective covariate for our survival analysis [19]. |

### 4.5 Exploratory Data Analysis

In Figure 3, we see the distribution of MHOWS has an interquartile range from about 15 to 36 and a mean of about 26 as observed in the data.

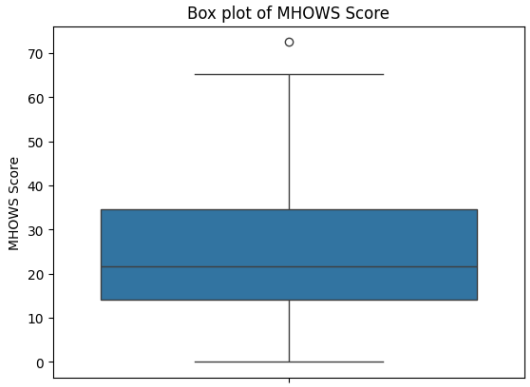



Figure 3: Box Plot of MHOWS in Patients in NIDA-CSP-1020

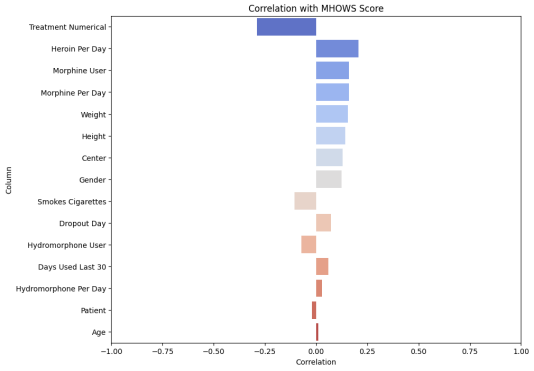



Figure 4: Correlation Plots of Covariates with Treatment

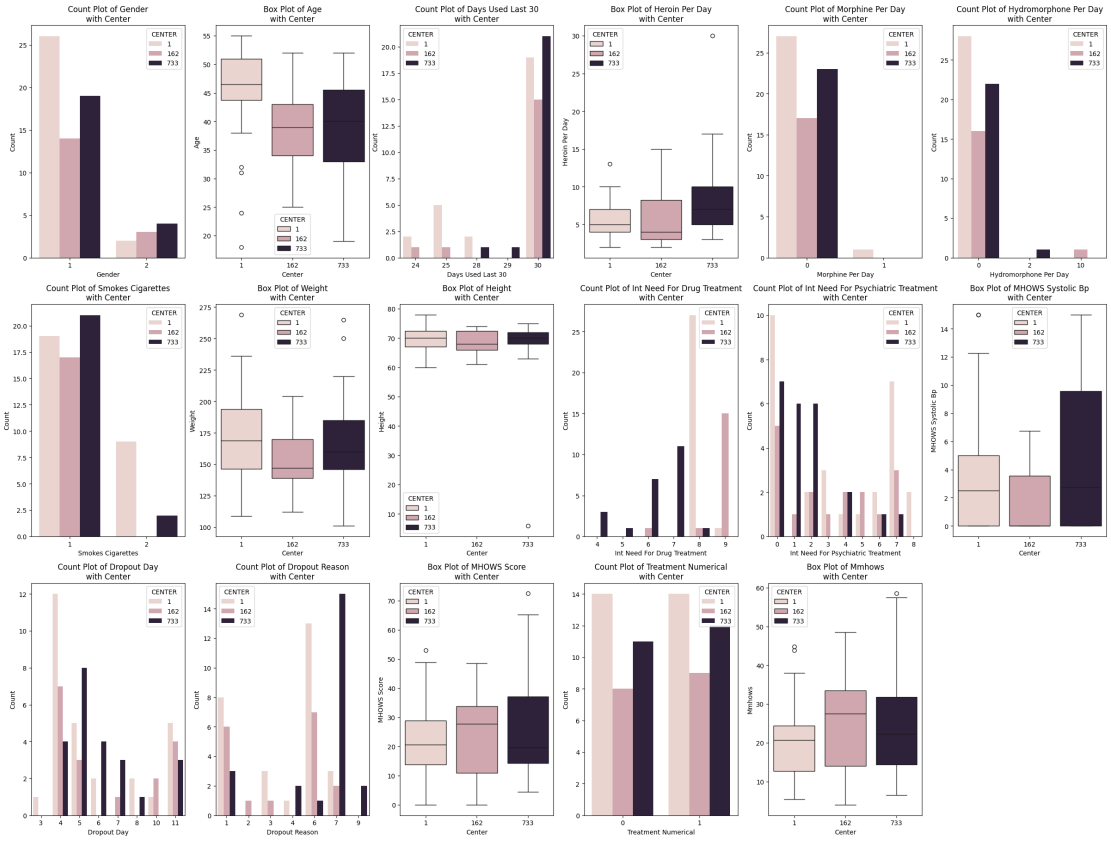



Figure 5: Box Plots and Count Plots of Covariates varied by Site

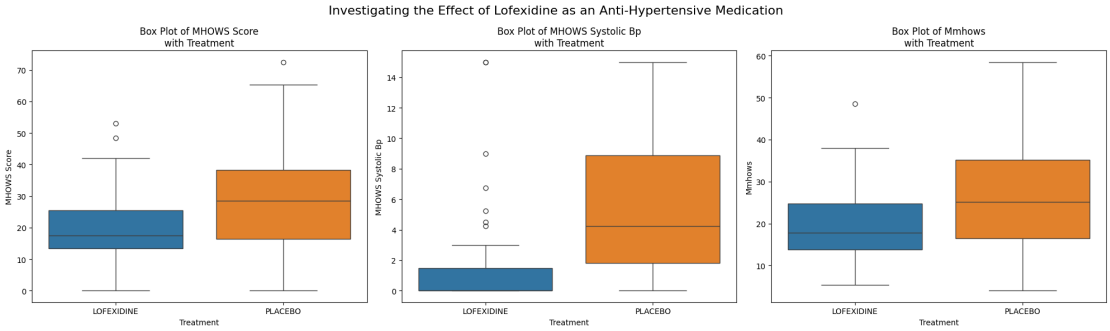



Figure 6: Box Plots of Treatment with Blood Pressure, MHOWS, and MMHOWS (MHOWS minus systolic blood pressure)

In Figure 4, we find strong correlations between MHOWS and treatment, as well as several variables related to opiate use, justifying our interest in MME or opiate usage generally as a covariate of interest.

In Figure 5, we see that several covariates vary significantly across the three treatment sites, supporting the decision of Yu et al. [6] to incorporate site as a random effect.

In Figure 6, the left box plot shows the difference in MHOWS scores; the middle-box plot shows the difference in systolic blood pressure (showcasing lofexidine's anti-hypertensive effects). Lofexidine appears to significantly reduce blood pressure, thereby greatly reducing MHOWS score. We seek to isolate its effect on other opiate withdrawal symptoms in the MHOWS calculation in addition to it reducing blood pressure.

### 4.6 Distribution of MHOWS Scores

The calculations for the MHOWS score are noted in Table 5. The discontinuous signs of withdrawal include Yawning, Lacrimation, Rhinorrhea, Perspiration, Tremor, Gooseflesh, Anorexia, Restlessness, and Emesis. The total number of emesis episodes in a 24-hour period was recorded daily. In theory, the lowest possible score from the discontinuous signs is 0 (no signs recorded), and the maximum is 133.

The continuous signs of withdrawal include Pupil Dilation, Temperature, Respiration, Systolic Blood Pressure, and Weight. Each of these were compared to the baseline value measured earlier in the study. The minimum possible score from this section is 0, which means no changes from baseline. The maximum is harder to quantify, as changes from baseline can range over a variety of values. We use the following estimations:

- **Pupil dilation score**: Based on previous studies on pupil dilation during withdrawal [20], pupils dilate on average 1.4mm during withdrawal, with maximum increases of almost 2mm. Thus, we can assume the max points from this assessment is 20 points.

- **Temperature**: Normal body temperature is 37 degrees Celsius. Based on a study of temperature during withdrawal, the maximum temperature increase during

withdrawal for subjects was nearly 3 degrees (to 40 degrees) [21]. The maximum points from this section is 30 points.

- **Respiration**: Respiration increases by roughly 16 breaths per minute [22]. We can say the maximum score from this assessment is 20.
- **Systolic blood pressure**: There is a max 30mmHG increase, so the maximum score from this section is 15.
- **Weight Loss**: Losing 15 pounds of weight at max is a reasonable estimate for a short time-frame opiate withdrawal. The maximum score is 15 points.

Based on these estimations, we can reasonably estimate that MHOWS scores can range from 0 to 133.

### 4.7 Justification For Explored $\beta_0$ Priors

As noted in the protocol, previous studies provide information about possible MHOWS score distributions on the morning of the second day lofexidine treatment[23] [24] [25]. We will include these findings in our assumptions when constructing prior distributions. Importantly, we have that Day 5 MHOWS scores assume a distribution that is approximately normal, so we will choose a normal prior. The following priors were considered during the model-building and sensitivity analysis processes:

- **Observed MHOWS scores from Phase II 3.2 mg/day lofexidine patients**:

  Since we aim to understand the effect of lofexidine versus placebo in reducing Day 5 MHOWS scores, we decided that our prior distribution for the treatment beta coefficient will be centered at 0, such that we are not biasing the results by immediately assuming the efficacy of lofexidine. As such, even though our global intercept—which can be interpreted as the mean MHOWS score when all predictors are held at reference—has placebo as the reference treatment, we can assume the distribution of MHOWS scores for lofexidine treatment to be similar. From the Phase II lofexidine study, patients receiving 3.2 mg of lofexidine per day had a mean MHOWS score of 19.3 with a standard deviation of 5.7 (n=6) on the second day of treatment. We will thus set mu = 19.3. Our variance will account for the observed within-group standard deviation as well as additional variance. Since the study conditions are not exactly the same and it is possible that the distributions of MHOWS scores are likely different between groups, we hope the additional variance will better allow the observed data to shape our posterior. Given an observed $\sigma$ of 5.7, we have $\beta_0 \sim N(19.3, 5.7^2 + \tau)$ where $\tau$ is an additional expression of uncertainty that we will vary in our sensitivity analysis.

- **Observed MHOWS scores from Phase II 1.6 mg/day lofexidine patients**:

  Yu E et al. make the "conservative" assumption that of all of the treatments in Phase II, 1.6mg of lofexidine a day most closely resembles a placebo treatment,

using this fact in their Phase III power calculation [6]. We can proceed similarly, using the mean and standard deviation of 1.6 mg/day MHOWS to form our normal prior, once again factoring in additional uncertainty. Given an observed $\mu = 30.3$ and $\sigma = 11.1$, we have $\beta_0 \sim N(30.3, 11.1^2 + \tau)$ where $\tau$ is an additional expression of uncertainty that we will vary in our sensitivity analysis.

- **A weakly informative prior for the global intercept**:

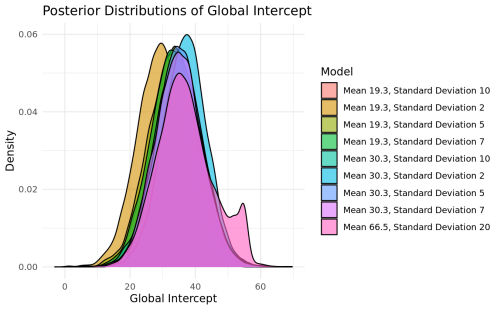
  Acknowledging that Phase II has an extremely small sample size, we can proceed relying heavily on our idea that MHOWS scores lie between 0 and 133. We can set a $\mu$ at the center of this distribution (66.5) with a large enough $\sigma^2$ such that the prior doesn't give us much information outside of that ($20^2$).

### 4.8 Sensitivity Analysis Results

Table 7: The Impact of Global Prior Mean and SD on Posterior Estimates

| Mean | SD | Estimate | SE | Conf. Interval |
|---|---|---|---|---|
| 19.3 | 2 | 29.12 | 6.99 | [17.55, 40.63] |
| 19.3 | 5 | 32.70 | 7.16 | [20.67, 44.32] |
| 19.3 | 7 | 33.21 | 7.06 | [21.40, 44.74] |
| 19.3 | 10 | 33.71 | 7.16 | [21.73, 45.60] |
| 30.3 | 2 | 36.87 | 6.61 | [25.70, 47.44] |
| 30.3 | 5 | 35.03 | 6.89 | [23.78, 46.60] |
| 30.3 | 7 | 34.84 | 7.08 | [23.13, 46.66] |
| 30.3 | 10 | 34.66 | 7.27 | [22.73, 46.85] |
| 66.5 | 20 | 36.32 | 8.20 | [23.77, 54.16] |

Figure 7: Posterior Distributions from Sensitivity Analysis of Global Intercept




### 4.9 Mediation Analysis Assumptions

In performing a mediation analysis, we must satisfy the following assumptions: (1) The exposure influences the mediator and the exposure and mediator both influence the outcome and (2) There is no uncontrolled confounding [26].

In addressing (1), we first mention that the exposure is known to influence the mediator from previous clinical research proving lofexidine to be an effective hypertension treatment in reducing blood pressure [6]. We then measure the effect of the exposure on the outcome via our model and know the mediator (blood pressure) directly influences the outcome via its inclusion in the MHOWS calculation [6]. We thus satisfy the first classical assumption for our mediation analysis.

In addressing (2) to ensure there is no uncontrolled confounding, we must consider the confounding in all relationships that can be confounded: exposure–outcome, exposure–mediator, and mediator–outcome. Given that the data is based on a clinical trial with a randomized treatment exposure, the exposure-outcome and exposure-mediator

relationships meet our assumption [26]. Furthermore, in our MHOWS model, we control for relevant data including demographics, physical and psychological health, and addiction severity. After then using our systolic blood pressure measurement for our auxiliary MHOWS model with these covariates, we have controlled for sources of bias in pre-existing differences in our mediator, meeting the no uncontrolled confounding assumption for the mediator-outcome relationship.

### 4.10 Cox Model Assumptions

In order to use the CPH model, we must adhere to the proportional hazards (PH) assumption, which asserts that the hazards are proportional and constant over time for different covariate levels (strata).

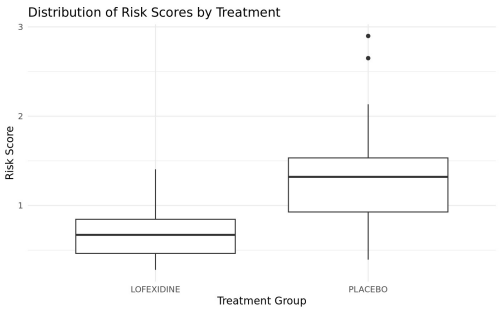
We argue that this assumption is likely to hold for our set of covariates. All of our covariates being used are time-invariant after being measured at the beginning of the study. As such, we would not expect their relative effect on different groups or individuals to change or violate the PH assumption. Ultimately, however, this will need to be rigorously checked with the given data by analyzing the Schoenfeld residuals of the fitted Cox model. For the Schoenfeld residuals to demonstrate the PH assumption has been met for our covariate, we expect to see them randomly distributed around zero with no pattern, in order to demonstrate that the PH assumption has been met for each covariate. The log-hazard ratio can also be analyzed; large values of a log-hazard ratio global chi-squared test imply deviation from the proportional hazards assumption.

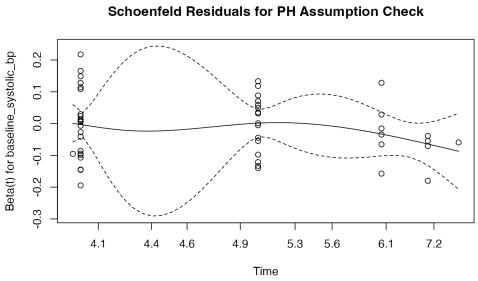
The results from a Chi-squared test of log-hazard ratios and plotting Schoenfeld residuals for each of the covariates used in our CPH model are shown below. We find that each of the covariates have a non-significant p-value, indicating a proportionality of hazards, and that the Schoenfeld residuals are randomly distributed about zero, indicating that the PH assumption holds.

Table 8: Chi-Square Test Results

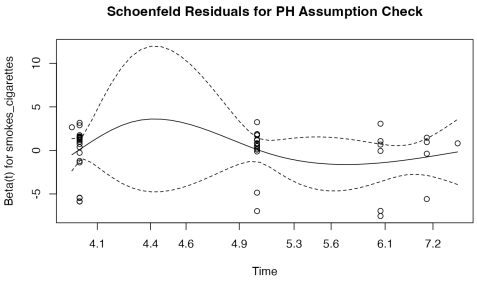
| **Characteristic** | **Chisq** | **df** | **p** |
|---|---|---|---|
| *Treatment* | 9.78e-01 | 1 | 0.32 |
| *Age* | 6.97e-05 | 1 | 0.99 |
| *Race* | 1.98e+00 | 2 | 0.37 |
| *Weight* | 6.17e-02 | 1 | 0.80 |
| *Gender* | 1.49e-02 | 1 | 0.90 |
| *Smokes Cigarettes* | 1.17e+00 | 1 | 0.28 |
| *Baseline Systolic BP* | 1.36e+00 | 1 | 0.24 |
| *MME over 30 days* | 9.14e-02 | 1 | 0.76 |
| *Need for Psychiatric Treat.* | 1.89e+00 | 1 | 0.17 |
| *GLOBAL* | 9.14e+00 | 10 | 0.52 |

Figure 8: Risk Scores by Treatment

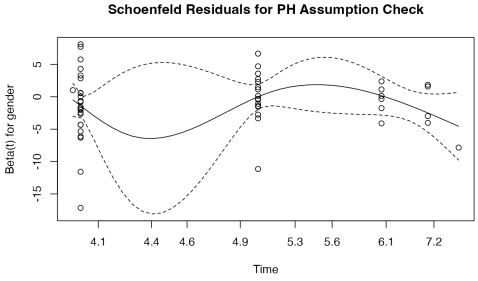




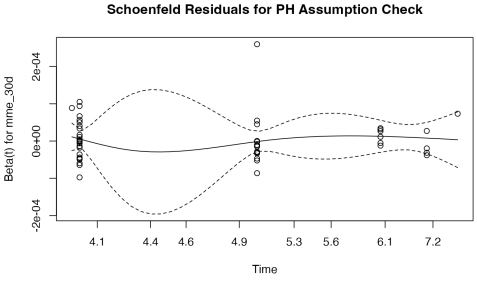

(a) Schoenfeld residuals for systolic BP



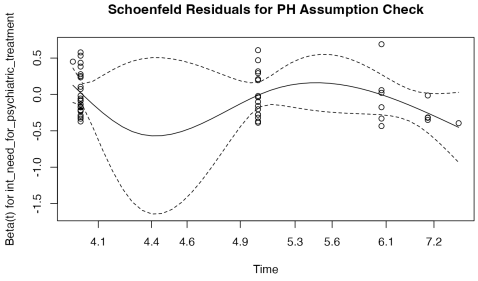

(b) Schoenfeld residuals for cigarettes



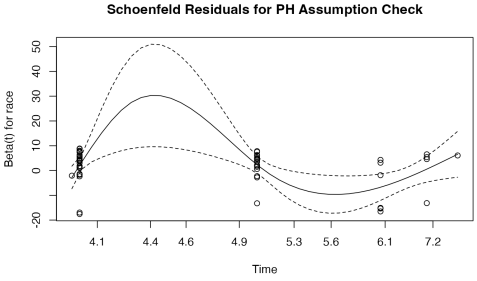

(c) Schoenfeld residuals for gender



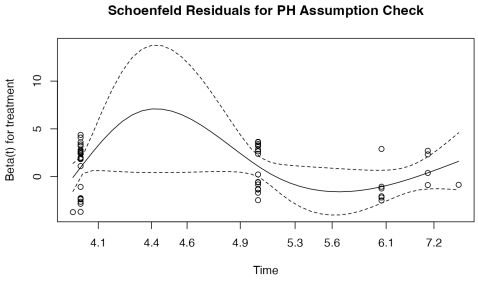

(d) Schoenfeld residuals for MME 30d



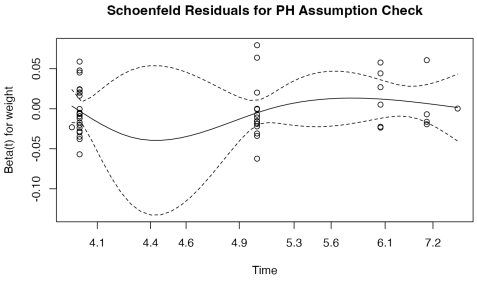

(e) Schoenfeld residuals for psych. treat.




(f) Schoenfeld residuals for race




(g) Schoenfeld residuals for treatment




(h) Schoenfeld residuals for weight

Figure 9: Schoenfeld residuals for various factors

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