# Pharmacoepidemiology, Machine Learning and COVID-19: An intent-to-treat analysis of hydroxychloroquine, with or without azithromycin, and COVID-19 outcomes amongst hospitalized US Veterans

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Running head: Hydroxychloroquine and azithromycin for COVID-19

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ABSTRACT

Hydroxychloroquine (HCQ) was proposed as an early therapy for coronavirus disease 2019 (COVID-19) after *in vitro* studies indicated possible benefit. Previous *in vivo* observational studies have presented conflicting results, though recent randomized clinical trials have reported no benefit from HCQ amongst hospitalized COVID-19 patients. We examined the effects of HCQ alone, and in combination with azithromycin, in a hospitalized COVID-19 positive, United States (US) Veteran population using a propensity score adjusted survival analysis with imputation of missing data. From March 1, 2020 through April 30, 2020, 64,055 US Veterans were tested for COVID-19 based on Veteran Affairs Healthcare Administration electronic health record data. Of the 7,193 positive cases, 2,809 were hospitalized, and 657 individuals were prescribed HCQ within the first 48-hours of hospitalization for the treatment of COVID-19. There was no apparent benefit associated with HCQ receipt, alone or in combination with azithromycin, and an increased risk of intubation when used in combination with azithromycin [Hazard Ratio (95% Confidence Interval): 1.55 (1.07, 2.24)]. In conclusion, we assessed the effectiveness of HCQ with or without azithromycin in treating patients hospitalized with COVID-19 using a national sample of the US Veteran population. Using rigorous study design and analytic methods to reduce confounding and bias, we found no evidence of a survival benefit from the administration of HCQ.

KEYWORDS:

hydroxychloroquine, covid-19, treatment outcome, propensity score, gradient boosting, pharmacoepidemiology, survival analysis

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ABBREVIATIONS:

CI, Confidence interval; HCQ, Hydroxychloroquine; HR, Hazard ratio; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; US, United States; VA, Veterans Affairs Healthcare Administration

In the swell of the coronavirus disease 2019 (COVID-19) pandemic, the world rushed to find therapeutic and prophylactic treatments, and hydroxychloroquine (HCQ) became an early front-runner(1, 2). HCQ is a common anti-malarial/-rheumatologic drug with immunosuppressive functions. Early *in vitro* studies suggested HCQ might be repurposed to treat infections with a strong immune component(1, 3, 4), such as COVID-19. This was appealing considering its low cost and widespread availability. The United States (US) Food and Drug Administration issued an emergency use authorization for HCQ on March 28, 2020(5) prior to the completion of a randomized controlled trial, only to revoke it less than 3 months later, following concerns about HCQ associated adverse events reported by observational studies(6, 7).

Around the same time as the US Food and Drug Administration's retraction, several randomized controlled trials, ORCHID, RECOVERY and SOLIDARITY discontinued their HCQ arms due to interim analyses showing no benefit in reducing COVID-19 inpatient mortality (8-10). These trials recently made their results public (11-13). While randomized controlled trials are a gold standard for evaluating the effectiveness of a drug(14), none of those investigating HCQ treatment explored the combination with azithromycin in their study design. Azithromycin has also been given

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to COVID-19 positive patients, and one small observational study hypothesized that the combination of the two drugs reduced viral load (1).

Results from observational studies of HCQ in treating COVID-19 have been inconsistent, and subject to bias(15-19). Early studies claiming a benefit were from small samples with limited data and little control of potential confounders. Timing of treatment during hospitalization was often poorly defined, no studies appeared to control for secular trends in the timing of treatment, and several studies used data from HCQ use prior to the US Food and Drug Administration's initial emergency use authorization(20). Particularly, the study design and analytic techniques may not have been able to account for the various sources of potential and residual confounding(21-23).

In a recent meta-analysis of HCQ and mortality in patients hospitalized with COVID-19(16), 25 of the 29 studies used observational data, and 10 of these peer-reviewed and pre-print publications used some form of propensity adjustment. One main goal of propensity analysis is to balance confounding factors in order to emulate a randomized controlled trial setting(24). Recent studies on propensity scoring have found that machine learning methods can achieve better balance than traditional regression methods in observational studies (25-29). Gradient boosted modeling using decision trees allows for interactions among the variables used in propensity score calculation and makes no assumptions about the shape of the relationship between the confounder and treatment received(25).

In this paper we apply careful study design and statistical analytic approaches, leveraging machine learning methods to evaluate the effectiveness of HCQ, with or

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without azithromycin, in the treatment of COVID-19 in the US Veteran population. We empirically assess the bias of the results by considering *a priori*-defined clinical confounders and a range of sensitivity analyses. Finally, we compare our analytic results to existing literature on HCQ effectiveness for COVID-19 and draw conclusions about the implications surrounding confounding in the context of an evolving pandemic.

## METHODS

### Veteran Affairs Healthcare cohort

The Veteran Affairs Healthcare Administration (VA) is the largest single-payer US healthcare system, with 6 million Veterans under care in the last two years. Structured electronic health records in a Corporate Data Warehouse include all clinical encounters. Record domain include demographics, laboratory results, vital signs, health factors, pharmacy prescription fills, hospitalizations, and outpatient visits. A COVID-19-specific research database was constructed in the Knowledge, Discovery, and Innovation computing environment at the Department of Energy's Oak Ridge National Laboratory. The work for this analysis under the US Food and Drug Administration-led COVID-19 Insights Partnership projects was approved by both Department of Energy and VA institutional review boards and is a joint activity involving VA and Department of Energy investigators.

### Study design

We designed our study cohort to mimic criteria that might be expected in a clinical trial setting (Figure 1). Key variables, index date, and exposure criteria are illustrated following a template developed for communicating reproducible observational study designs in pharmacoepidemiology(30). Day 0 or index date was classified as the

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day of first hospitalization on the same day or after first positive diagnosis for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Identification of COVID-19 cases

The VA COVID-19 research cohort includes individuals who were tested for SARS-CoV-2 inside or outside of a VA facility. We used the VA's National Surveillance Tool, the authoritative data source for defining positive and negative SARS-CoV-2 cases(31), to identify Veterans who had a positive diagnosis as our study COVID-19 cases.

Inclusion criteria

We restricted the sample to individuals hospitalized within the VA only due to limited HCQ use and outcomes data for patients outside of VA hospitals. The base cohort included COVID-19 cases prior to April 30, 2020, when HCQ usage dramatically decreased (Figure 2). We included cases where onset of infection was no later than hospital admission or June 1, 2020. We excluded patients who had received HCQ or azithromycin for non-COVID-19 illnesses, i.e., anyone using HCQ in the year prior to or using azithromycin within 14 days before the index date. Additionally, we excluded patients who were discharged, intubated, or died within 48 hours of admission, to avoid immortal time bias. We removed patients who received care at hospitals that were not prescribing HCQ to ensure all individuals had a non-zero probability of receiving treatment.

Exposure assessment

Initiation was defined as the date of first inpatient prescription fill from index date until the end of follow-up. For an intention-to-treat analysis, we classified individuals into

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four groups (Both: HCQ + azithromycin, HCQ alone, azithromycin alone, and neither drug) based on initiating one or both of the drugs within the first 48 hours following hospitalization. For example, any individuals that started only HCQ within the 48-hour window, but who were later prescribed azithromycin after 48 hours, were considered HCQ alone.

Outcomes assessment

*Outcome: mortality* - VA all-cause mortality information was based on the Beneficiary Identification Records Locator Subsystem, clinical records and social security death index data(32). Time-to-death was measured from index date, and censored anyone who remained alive at 30 days.

*Outcome: invasive ventilation/intubation* - We considered only invasive ventilation using diagnostic International classification of diseases series 10 (0BH13EZ, 0BH17EZ, 0BH18EZ, 5A1935Z, 5A1945Z, 5A1955Z) and current procedural terminology (31500) codes. Amongst COVID-19 positive hospitalized patients, over 95% of the intubations occurred within 21 days of admission, thus we analyzed the outcome using time-to-intubation during this 21-day period, with censoring at death or discharge.

Covariates and confounders

Potential confounders were assembled in clinically meaningful identification time frames (Figure 1). For uncommon laboratory tests that were measured acutely (lactate dehydrogenase, c-reactive protein, d-dimer, and ferritin), we used evidence of measurement as the covariate of interest. Patient demographics (age, sex, region of the US, urbanicity), height and weight, smoking status, alcohol use disorder, and evidence of recent long-term care were taken from data prior to index date. Additional variables

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considered as potential confounders of treatment and both primary outcomes were chronic medications, concurrent inpatient treatments (for COVID-19 or HCQ contraindications), chronic conditions (based on diagnostic codes and including a frailty score(33)), and acute laboratory results and vital signs (those related to acute illness). All potential confounders were included in the propensity model. Complete descriptions of diagnostic and medication codes can be found in Web Tables 1-2 and Web Appendix 1.

Statistical analyses

All analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria)(34) and publicly available packages.

*Missing data* - Missing covariate information was imputed using the multiple imputation from chained equations "**mice**" package in R(35, 36). Ten imputed data sets were generated, analyzed separately, and the final results were subsequently combined using Rubin's rules to determine final effect sizes and confidence intervals(37).

*Propensity score calculation* - Propensity scores for each treatment were estimated from a Gradient Boosting Machine (GBM)(38), an ensemble of models that take baseline measures and characteristics as inputs and outputs the patient's predicted probability (or propensity score) for receiving each treatment (Both, HCQ alone, azithromycin alone, or neither). We employed decision trees as base learners for GBM, using the "**gbm**" and "**WeightIt**" R packages to fit our models(39, 40). The hyperparameters were set as: interaction depth of 4, maximum of 5000 trees, and shrinkage of 0.1. We optimized the maximum of standardized mean differences between potential confounders across the treatment arms.

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For each patient, the propensity score was converted to a stabilized inverse probability of treatment weight. We evaluated the propensity scores using the "**cobalt**" package in R to look at the distributions of average standardized mean differences between each pair of treatments(41). The relative influence(42) was calculated as the normalized amount of change in the balance metric for each variable when it was used to split a node.

*Outcome models* - The stabilized inverse probability of treatment weights from the propensity modeling steps were included as subject-level weights in Cox proportional hazards multivariable models for estimating treatment effects on mortality and intubation using the "**survival**" package(43) in R. An alpha level of 0.05 was used.

Sensitivity analyses

We assessed design assumptions and data restrictions with a series of sensitivity analyses to address questions regarding timing, analytic design, and methods. To consider whether timing of treatment initiation made a difference in survival, we considered a shorter 24-hour exposure window, with corresponding adjustments in exclusions and outcomes. We explored the effect of the secular prescribing trend(s) by limiting analyses to time windows framed by regulatory guidelines and patterns of use within the VA. The final set of sensitivity analyses focused on the statistical and machine learning methods and assumptions. We additionally considered a set of doubly-robust models, where select confounders were included in both the propensity and outcome models(44, 45). Complete details about cohort restrictions and sensitivity analyses performed can be found in Web Table 3 and Web Appendix 2.

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## RESULTS

### Characteristics of users

As of April 30, 2020 there were 7,193 SARS-CoV-2 positive cases out of 64,055 individuals tested overall(46), yielding an analytic cohort of 1,769 individuals (Figure 3). The mean number of days between a positive laboratory result and hospitalization was 2.1 days (Web Figure 1). In the first 48 hours of hospitalization, 429 (24%) individuals initiated HCQ and azithromycin, 228 (13%) HCQ alone, and 342 (19%) azithromycin alone, while 770 (44%) were not prescribed either of these two treatment strategies (Table 1, Web Table 4).

Those who initiated azithromycin alone or in combination with HCQ, in the first 48 hours of hospitalization, were younger (mean 67.6 and 67.8 years of age, respectively), compared to those initiating HCQ alone (70.2 years) or neither treatment (71.5 years) in the same exposure time-frame. Non-Hispanic blacks were more likely to receive at least one treatment than other race/ethnicity groups, and those in urban settings were more likely to be prescribed some form of HCQ. Those coming from long-term care or nursing facilities were less likely to initiate either treatment within the first 48 hours of admission. Acute laboratory measurements, such as lactate dehydrogenase and C-reactive protein, were more commonly available on those initiating both treatments.

### Propensity model

Before weighting, the exposure groups differed with respect to multiple covariates (Table 1). Overall, the GBM was able to balance a large majority of the variables in the primary analysis model. Complete love and balance plots can be found in Web Figures 2-15. The week of admission variable did not achieve the recommended

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threshold of 0.1(47), nor even 0.2 for the average standardized mean difference comparing those initiating Both treatments to any of the others. Similarly, the average standardized mean difference for week of admission comparing HCQ alone to Neither or azithromycin alone groups was approximately 0.2. Figure 4 displays the average relative importance or influence of a given predictor in the primary propensity model. Notably total station size and week of admission were the most important factors across all imputations and sensitivity analyses (Web Figures 16-18).

Primary analysis

Of the 429 individuals initiating both HCQ and azithromycin in the first 48 hours following VA hospital admission, 90 (21%) died within 30 days after admission and 64 (15%) were intubated within 21 days of admission (Table 2, Web Table 5). After weighting, those initiating both treatments had a 22% increased hazard of death (HR=1.22, 95% CI: 0.91, 1.63) and 55% increased hazard of intubation (HR=1.55, 95% CI: 1.07, 2.24), compared to those on neither treatment within the first 48 hours after hospitalization.

Comparing those exposed to HCQ alone versus neither treatment in the 48 hours following admission, there were non-statistically significant increased risks of both mortality within 30 days of index (HR=1.21, 95% CI: 0.82, 1.76) and intubation within 21 days of index (HR=1.33, 95% CI: 0.82, 2.15). Meanwhile, those initiating azithromycin alone in the first 48 hours had similar hazards for death (HR=0.90, 95% CI: 0.64, 1.27) and intubation (HR=1.03, 95% CI: 0.66, 1.61) compared to neither treatment. None of these analyses indicated a benefit of HCQ or azithromycin.

Sensitivity analyses

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There were few measurable changes in the effect estimates and confidence intervals of the two comparisons (Both vs. neither; HCQ alone vs. neither) for many of the sensitivity analyses. Figure 5 summarizes the average treatment effect HR (95% CI) for those initiating any combination of HCQ compared to neither treatment in the 48 hours following admission. Complete results, including event counts and number exposed, from all sensitivity analyses can be found in Web Tables 6-7.

Censoring at change in treatment (adding either azithromycin or HCQ after 48 hours post-hospitalization) produced substantially different results for mortality (HCQ vs. Neither HR: 1.42, 95% CI 0.92-2.18; Both vs. Neither HR: 1.63, 1.18-2.25; Figure 5A). This corresponded to 75 fewer “cases”, mostly from the neither group. A similar pattern of inflated hazard ratios and fewer cases can be seen for the intubation outcome (Figure 5B).

Dropping the index dates that occurred prior to Pharmacy Benefits Management’s guidelines for HCQ emergency use authorization posted on March 30, 2020, left just over two-thirds of the total sample (N=1,218). This did not affect the intent-to-treat hazard ratio for HCQ alone versus neither drug in terms of mortality, but it did shift the final estimate for Both vs. neither away from the null (HR: 1.41, 95% CI 0.98-2.03), indicating greater harm. For the intubation outcome, the HR shifted again, however, these may not be interpretable due to the small number of cases.

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## DISCUSSION

### Key findings

We found no benefit in COVID-19 mortality and intubation from HCQ alone or in combination with azithromycin when administered shortly after hospital admission. The direction of the effect was consistent across all models, and comparable to recent studies of HCQ for the treatment of SARS-CoV-2 infection in the inpatient hospital setting(11, 12, 48-50).

### Research in context

A previous analysis of HCQ effectiveness amongst veterans demonstrated no evidence of benefit for those prescribed HCQ with or without azithromycin, with indication of harm from HCQ alone(20). The sample size was small (N=807), with a restricted follow-up window for certain individuals.

In contrast, a study from the Henry Ford hospital system estimated that any form of HCQ led to significant reductions for in-hospital mortality (HCQ vs. neither HR=0.66; Both vs. neither HR=0.71)(51). The study differed in population demographics, size and by the use of a multivariate modeling approach that included a limited number of confounders in the models. This study was criticized for insufficiently controlling for confounding by indication, i.e. sicker patients were less likely to receive HCQ(52). Additionally, the Henry Ford study did not account for secular trends, which we demonstrate are an important factor to include in analyses.

### Methodological differences

Using a sample twice the size of the prior VA study (1,769 vs. 807), we found similar average treatment effects of HCQ with or without azithromycin compared to neither treatment. Those differences that exist in our findings can likely be explained by

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our use of an adjudicated algorithm-based case definition (National Surveillance Tool) that captures laboratory-identified cases as well as those not in the VA system. However, given the 95% agreement between COVID-19 case definitions based on VA laboratory test only and National Surveillance Tool positive definitions, it is also possible that the search terms used in the prior paper were not able to capture all SARS-CoV-2 positive cases. Magagnoli *et al*. additionally restricted follow-up through April 29, 2020, meaning that the outcomes of those hospitalized towards the end of April would not have had enough time to be observed.(20) In a sensitivity analysis using a similar enrollment restriction (hospitalized on or before April 30), but with adequate follow-up time for all individuals, we saw no change in our results or conclusions.

Strengths

Relative to other observational cohorts in the US, the VA has more longitudinal data, with limited loss to follow-up. This allows for a more complete assessment of patients' comorbidities and outcomes.

Chronological bias(53) is a challenging feature of research related to HCQ. It can be introduced by variable prescribing patterns for the drug(54), in conjunction with the geographic spread of the disease(55) and a constantly-evolving knowledgebase about the disease and its therapeutics(52). We explored multiple sensitivity analyses that demonstrated consistent results when timing of hospitalization and hospital size and capacity were accounted for in the models.

We considered the importance of timing of treatment with a sensitivity analysis setting the exposure window to 24 hours, as in other studies (48, 56). This resulted in similar estimates to the primary analysis for mortality (HCQ vs. neither HR=1.24, Both

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vs. neither HR=1.15). Given that 11% of the sample added one or more of the treatments in the 24-48 hour window, our use of the 48-hour window may be preferable as it more effectively avoids misclassification. We excluded individuals who died, were intubated, or discharged within the 48 hours, because the patients would not have had enough time to experience benefit or harm from HCQ. While this ensured the circumvention of immortal time bias when defining the group with neither treatment, we recognize that this may present additional limitations.

Limitations

Our results may not generalize to those intubated prior to receiving treatment nor to those with less severe illness who are discharged almost immediately. Compared to the overall US population, VA users are older, mostly male, with more comorbidities and lower socioeconomic status (55). Our results may differ from studies of younger and healthier populations with a higher proportion of women. However, older, male and sicker individuals are at higher risk for severe COVID-19, which warranted the study of this drug early-on, despite historical data indicating that these might also be the individuals most at risk for adverse events from HCQ (3).

Propensity weighting was unable to completely eliminate covariate imbalance across the treatment groups. To address this limitation, we performed a series of doubly-robust models(44, 45) (as described in Web Appendix 1), where covariates were included in both the propensity and outcome models. The estimated HRs and confidence intervals were similar to the primary analysis, further confirming the lack of benefit from HCQ.

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Our analysis did not account for any changes in HCQ or azithromycin status following the 48-hour exposure assessment, such as new prescriptions or treatment discontinuation. We attempted to address the change in treatment after 48 hours through a sensitivity analysis censoring at the addition of another treatment. This per-protocol on-treatment analysis has been shown to confer bias in the clinical trial setting(57), thus is not preferred over the intention-to-treat method used. In fact, we observed this bias in the shifted HRs and confidence intervals that made HCQ (both with and without azithromycin) appear harmful compared to neither treatment.

After 48 hours from index date, approximately 25% of the combination treatment patients were in the intensive care unit, compared to 5% in the neither group, 19% in the azithromycin alone group, and 13% for those on HCQ alone. We did not look at this particular outcome or adjust for it as a confounder in the propensity models. However, in a sensitivity analysis removing these individuals, the HRs for both mortality and intubation of the combined treatment group, relative to neither treatment, shifted completely to the null, indicating that HCQ may have been seen as a “rescue” therapy in intensive care unit patients. Of note, even with this restriction, there is no evidence of benefit.

Despite our array of sensitivity analyses, we acknowledge that there is still a possibility of some unmeasured and residual confounding that we were unable to account for. However, the GBM approach allowed us to control for many variables, and any remaining unmeasured confounders would likely require strong associations with both the treatment assignment and outcomes, to explain away the null relationship observed in the data.

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Implications

In the early months of the pandemic, there was much uncertainty surrounding risk factors of COVID-19 and subsequent deaths, which translated to inconsistent results and conclusions from studies with moderate to severe levels of bias(16). With our best attempts to adjust for possible confounding, we found confirmatory evidence for an increased risk of intubation for those who were treated with the combination of HCQ and azithromycin for COVID-19 in a hospital setting. We found no inpatient survival benefit to the administration HCQ, with or without concomitant azithromycin.

Our study reflects the challenges of modeling effectiveness during the start of a pandemic and demonstrates that consistent data over a period of time are critical for disentangling the effects of confounding by indication. While we are unable to account for compassionate use of HCQ, we do show that sensitivity analyses in both study design and modeling can allow researchers to account for a large number of potential confounders using electronic health record data when *a priori* relationships are not well established.

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All authors contributed equally to this work.

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Conflicts of Interest: Nothing to disclose

Data Availability: The data used in this paper cannot be shared outside the VA, except as authorized under VA policy with respect to the Freedom of Information Act (FOIA). Formal mechanisms of request for anonymized data, analytic codebooks and programs, must be approved by the VHA Office of Research Oversight.

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BIBLIOGRAPHY


1. Andreani J, Le Bideau M, Duflot I, et al. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. Microb Pathog. 2020;145:104228.
2. Kupferschmidt K, Cohen J. Race to find COVID-19 treatments accelerates. Science. 2020;367(6485):1412-3.
3. Oscanoa TJ, Romero-Ortuno R, Carvajal A, et al. A pharmacological perspective of chloroquine in SARS-CoV-2 infection: An old drug for the fight against a new coronavirus? Int J Antimicrob Agents. 2020;56(3):106078.
4. Tarek M, Savarino A. Pharmacokinetic Basis of the Hydroxychloroquine Response in COVID-19: Implications for Therapy and Prevention. Eur J Drug Metab Pharmacokinet. 2020;45(6):715-23.
5. Bright R. Letter of Authorization - chloroquine phosphate and hydroxychloroquine sulfate. 2020. (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f398f8a9-92f3-47cb-81c2-6078806a464d). (Accessed October 20, 2020).
6. Disbrow GL. Letter revoking EUA for chloroquine phosphate and hydroxychloroquine sulfate, 6/15/2020. 2020. (https://www.fda.gov/media/138945/download). (Accessed October 20, 2020).
7. U. S. Food Drug Administration. FDA Drug Safety Communication: FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. 2020:4-7. (https://www.fda.gov/safety/medical-product-safety-information/hydroxychloroquine-or-chloroquine-covid-19-drug-safety-communication-fda-cautions-against-use). (Accessed October 20, 2020).
8. Kiley JP. NIH halts clinical trial of hydroxychloroquine. 2020. (https://www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine). (Accessed: October 20, 2020).
9. Recovery Collaborative Group. Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June 2020. 2020. (https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf). (Accessed: October 20, 2020).
10. World Health Organization (WHO). WHO discontinues hydroxychloroquine and lopinavir/ritonavir treatment arms for COVID-19. 2020. (https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19). (Accessed: October 20, 2020).
11. Pan H, Peto R, Karim QA, et al. Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results [preprint]. *medRxiv*. 2020. (doi:10.1101/2020.10.15.20209817). Accessed November 01, 2020.
12. Recovery Collaborative Group, Horby P, Mafham M, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;383(21):2030-40.


ORIGINAL UNEDITED MANUSCRIPT

13. Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020;doi: 10.1001/jama.2020.22240.
14. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med. 2000;342(25):1878-86.
15. Alexander PE, Debono VB, Mammen MJ, et al. COVID-19 coronavirus research has overall low methodological quality thus far: case in point for chloroquine/hydroxychloroquine. J Clin Epidemiol. 2020;123:120-6.
16. Fiolet T, Guihur A, Rebeaud ME, et al. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. Clin Microbiol Infect. 2020;doi: 10.1016/j.cmi.2020.08.022.
17. Singh AK, Singh A, Singh R, et al. Hydroxychloroquine in patients with COVID-19: A Systematic Review and meta-analysis. Diabetes Metab Syndr. 2020;14(4):589-96.
18. Hernandez AV, Roman YM, Pasupuleti V, et al. Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review. Ann Intern Med. 2020;173(4):287-96.
19. Patil VM, Singhal S, Masand N. A systematic review on use of aminoquinolines for the therapeutic management of COVID-19: Efficacy, safety and clinical trials. Life Sci. 2020;254:117775.
20. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with COVID-19. Med (N Y). 2020;doi: 10.1016/j.medj.2020.06.001.
21. Kim AHJ, Sparks JA, Liew JW, et al. A Rush to Judgment? Rapid Reporting and Dissemination of Results and Its Consequences Regarding the Use of Hydroxychloroquine for COVID-19. 2020;172:819-21.
22. Pottegard A, Kurz X, Moore N, et al. Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic. Pharmacoepidemiol Drug Saf. 2020;29(8):825-31.
23. Zhai MZ, Lye CT, Kesselheim AS. Need for Transparency and Reliable Evidence in Emergency Use Authorizations for Coronavirus Disease 2019 (COVID-19) Therapies. JAMA Intern Med. 2020;180(9):1145-6.
24. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.
25. Lee BK, Lessler J, Stuart EA. Improving propensity score weighting using machine learning. Stat Med. 2010;29(3):337-46.
26. McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. Psychol Methods. 2004;9(4):403-25.
27. Setodji CM, McCaffrey DF, Burgette LF, et al. The Right Tool for the Job: Choosing Between Covariate-balancing and Generalized Boosted Model Propensity Scores. Epidemiology. 2017;28(6):802-11.

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28. Yang JY, Webster-Clark M, Lund JL, et al. Propensity score methods to control for confounding in observational cohort studies: a statistical primer and application to endoscopy research. Gastrointest Endosc. 2019;90(3):360-9.
29. Westreich DJ, Lessler J, Jonsson Funk M. Propensity Score Estimation: Machine Learning and Classification Methods As Alternatives To Logistic Regression. Journal of Clinical Epidemiology. 2011;63(8):826-33.
30. Schneeweiss S, Rassen JA, Brown JS, et al. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med. 2019;170(6):398-406.
31. Chapman AB, Peterson KS, Turano A, et al. A Natural Language Processing System for National COVID-19 Surveillance in the US Department of Veterans Affairs. *Proceedings of the 1st Workshop on NLP for COVID-19 at ACL 2020*. Online: Association for Computational Linguistics, 2020. (https://www.aclweb.org/anthology/2020.nlpcovid19-acl.10). (Accessed October 20, 2020).
32. Sohn MW, Arnold N, Maynard C, et al. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr. 2006;4:2.
33. Orkaby AR, Nussbaum L, Ho YL, et al. The Burden of Frailty Among U.S. Veterans and Its Association With Mortality, 2002-2012. J Gerontol A Biol Sci Med Sci. 2019;74(8):1257-64.
34. R Core Team. R: A Language and Environment for Statistical Computing, release 3.6.1. Vienna, Austria: R Foundation for Statistical Computing; 2019.
35. Doove LL, Van Buuren S, Dusseldorp E. Recursive partitioning for missing data imputation in the presence of interaction effects. Computational Statistics & Data Analysis. 2014;72:92-104.
36. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations. (R package version 3.11.0). https://cran.r-project.org/package=mice. Published August 5, 2020. Accessed October 20, 2020.
37. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med. 1991;10(4):585-98.
38. Hastie T, Tibshirani R, Friedman J. Boosting and Additive Trees. *The Elements of Statistical Learning*, 2009:1-51.
39. Greenwell B, Boehmke B, Cunningham J, et al. gbm: Generalized Boosted Regression Models. (R package version 2.1.8). https://cran.r-project.org/package=gbm. Published July 15, 2020. Accessed October 1, 2020.
40. Greifer N. WeightIt: Weighting for Covariate Balance in Observational Studies. (R package version 0.10.2). https://cran.r-project.org/package=WeightIt. Published August 27, 2020. Accessed October 20, 2020.
41. Greifer N. cobalt: Covariate Balance Tables and Plots. (R package version 4.2.3). https://cran.r-project.org/package=cobalt. Published August 31, 2020. Accessed October 20, 2020.
42. Natekin A, Knoll A. Gradient boosting machines, a tutorial. Front Neurorobot. 2013;7(DEC):21.
43. Therneau TM. survival: A Package for Survival Analysis in S. (R package version 3.2-3). https://cran.r-project.org/package=survival. Published June 13, 2020. Accessed October 20, 2020.

ORIGINAL UNEDITED MANUSCRIPT

44. McCaffrey DF, Griffin BA, Almirall D, et al. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013;32(19):3388-414.
45. Nguyen TL, Collins GS, Spence J, et al. Comparison of the ability of double-robust estimators to correct bias in propensity score matching analysis. A Monte Carlo simulation study. Pharmacoepidemiol Drug Saf. 2017;26(12):1513-9.
46. VA Access to Care: COVID-19 National Summary. https://www.accesstocare.va.gov/Healthcare/COVID19NationalSummary. (Accessed August 20, 2020).
47. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-79.
48. Rosenberg ES, Dufort EM, Udo T, et al. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. JAMA. 2020;323(24):2493-502.
49. Rivera DR, Peters S, Panagiotou OA, et al. Utilization of COVID-19 Treatments and Clinical Outcomes among Patients with Cancer: A COVID-19 and Cancer Consortium (CCC19) Cohort Study. Cancer Discov. 2020;10(10):1514-27.
50. Sbidian E, Josse J, Lemaitre G, et al. Hydroxychloroquine with or without azithromycin and in-hospital mortality or discharge in patients hospitalized for COVID-19 infection: a cohort study of 4,642 in-patients in France [preprint]. *medRxiv*. 2020. (doi:10.1101/2020.06.16.20132597). Accessed October 20, 2020.
51. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. Int J Infect Dis. 2020;97(0):396-403.
52. Lee TC, MacKenzie LJ, McDonald EG, et al. An observational cohort study of hydroxychloroquine and azithromycin for COVID-19: (Can't Get No) Satisfaction. Int J Infect Dis. 2020;98:216-7.
53. Spencer EA. Chronological Bias. 2017. https://catalogofbias.org/biases/chronological-bias/. (Accessed October 2, 2020).
54. Bull-Otterson L, Gray EB, Budnitz DS, et al. Hydroxychloroquine and Chloroquine Prescribing Patterns by Provider Specialty Following Initial Reports of Potential Benefit for COVID-19 Treatment - United States, January-June 2020. MMWR Morb Mortal Wkly Rep. 2020;69(35):1210-5.
55. Rentsch CT, Kidwai-Khan F, Tate JP, et al. Patterns of COVID-19 testing and mortality by race and ethnicity among United States veterans: A nationwide cohort study. PLoS Med. 2020;17(9):e1003379.
56. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020;382(25):2411-8.
57. Greenland S, Lanes S, Jara M. Estimating effects from randomized trials with discontinuations: the need for intent-to-treat design and G-estimation. Clin Trials. 2008;5(1):5-13.

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Table 1. Select Baseline Characteristics of a National Sample of Hospitalized US Veterans with COVID-19 Between March 1, 2020 and April 30, 2020 by 48-Hour Treatment Exposure

| Baseline Characteristic [a] | Neither drug (N = 770) | | | Azithromycin alone (N = 342) | | | HCQ alone (N = 228) | | | HCQ + Azithromycin (N = 429) | | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | Median (IQR) | N | % | Median (IQR) | N | % | Median (IQR) | N | % | Median (IQR) | |
| Demographics and Lifestyle | | | | | | | | | | | | | |
| Age | 71.47 (13.12) | | | 67.64 (13.55) | | | 70.24 (12.80) | | | 67.81 (13.22) | | | <0.001 |
| Male | 736 | 95.6 | | 322 | 94.2 | | 219 | 96.1 | | 413 | 96.3 | | 0.527 |
| Race/Ethnicity | | | | | | | | | | | | | <0.001 |
| Non-Hispanic White | 321 | 41.7 | | 107 | 31.3 | | 65 | 28.5 | | 139 | 32.4 | | |
| Non-Hispanic Black | 341 | 44.3 | | 190 | 55.6 | | 138 | 60.5 | | 225 | 52.4 | | |
| Hispanic | 77 | 10.0 | | 21 | 6.1 | | 15 | 6.6 | | 42 | 9.8 | | |
| Other | 31 | 4.0 | | 24 | 7.0 | | 10 | 4.4 | | 23 | 5.4 | | |
| Days to admission [b] | 2.6 (8.1) | | | 0.8 (4.4) | | | 1.0 (2.3) | | | 0.6 (2.3) | | | <0.001 |
| Week of admission | 15.3 (2.1) | | | 14.0 (1.9) | | | 14.5 (1.4) | | | 14.0 (1.2) | | | <0.001 |
| Total station size | 61485 (31509) | | | 64346 (31385) | | | 49902 (20603) | | | 57189 (28718) | | | <0.001 |
| Urban | 707 | 91.8 | | 310 | 90.6 | | 217 | 95.2 | | 408 | 95.1 | | 0.031 |
| Coming from LTC facility [c] | 130 | 16.9 | | 18 | 5.3 | | 23 | 10.1 | | 20 | 4.7 | | <0.001 |
| In ICU at 48 hours | 134 | 17.4 | | 77 | 22.5 | | 41 | 18.0 | | 124 | 28.9 | | <0.001 |
| Smoking status [d, e] | | | | | | | | | | | | | 0.042 |
| Never | 167 | 30.1 | | 90 | 35.3 | | 50 | 35.2 | | 111 | 39.5 | | |
| Current | 239 | 43.1 | | 85 | 33.3 | | 54 | 38.0 | | 104 | 37.0 | | |
| Former | 148 | 26.7 | | 80 | 31.4 | | 38 | 26.8 | | 66 | 23.5 | | |
| Prior Laboratory Measures [f] | | | | | | | | | | | | | |
| Hemoglobin (g/dL) | | | 12.8 (11.1, 14.1) | | | 13.5 (12.0, 14.6) | | | 13.2 (11.4, 14.3) | | | 13.4 (12.2, 14.6) | <0.001 |
| HbA1c [g] (percent) | | | 6.2 (5.6, 7.3) | | | 6.1 (5.6, 7.1) | | | 6.2 (5.7, 7.4) | | | 6.2 (5.7, 7.1) | 0.733 |

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| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LDL-C (mg/dL) | | | 78.0 (58.0, 102.5) | | | 90.3 (69.0, 121.4) | | | 81.0 (59.0, 108.6) | | | 87.0 (64.0, 110.0) | <0.001 |
| Lymphocyte count (K/cmm) | | | 1.6 (1.3, 2.2) | | | 1.7 (1.4, 2.2) | | | 1.7 (1.4, 2.1) | | | 1.7 (1.4, 2.2) | 0.617 |
| Acute Laboratory Measures [h] | | | | | | | | | | | | | |
| eGFR (mL/min) | | | 63.1 (38.5, 85.1) | | | 61.6 (39.7, 83.8) | | | 55.2 (32.2, 81.8) | | | 62.7 (41.8, 82.6) | 0.156 |
| WBCs (K/cmm) | | | 6.0 (4.6, 7.9) | | | 6.1 (4.9, 8.4) | | | 6.1 (4.5, 8.1) | | | 6.3 (4.9, 8.2) | 0.383 |
| ALT (U/L) | | | 24.0 (16.0, 39.0) | | | 28.0 (18.0, 44.0) | | | 30.0 (20.0, 44.0) | | | 33.0 (22.5, 49.0) | <0.001 |
| C-reactive protein [i] (mg/dL) | | | 19.0 (6.3, 71.7) | | | 11.4 (5.5, 44.2) | | | 21.6 (8.3, 75.3) | | | 15.4 (8.5, 42.4) | 0.009 |
| Missing | 251 | 32.6 | | 108 | 31.6 | | 61 | 26.8 | | 81 | 18.9 | | |
| D-dimer [i] (ug/mL) | | | 13 (3, 2199) | | | 6 (3, 3600) | | | 1004 (4, 2195) | | | 1411 (3, 3071) | 0.555 |
| Missing | 664 | 86.2 | | 296 | 86.5 | | 190 | 83.3 | | 348 | 81.1 | | |
| Acute Vitals [j] | | | | | | | | | | | | | |
| Body mass index [k] $\geq$ 30 kg/m$^2$ | 282 | 37.0 | | 152 | 44.6 | | 107 | 46.9 | | 209 | 48.7 | | <0.001 |
| Oxygen saturation [l] $\leq$ 93% | 131 | 18.1 | | 67 | 20.8 | | 52 | 24.0 | | 116 | 28.2 | | 0.001 |
| Respiratory rate [k] > 22/min | 82 | 11.0 | | 45 | 13.2 | | 37 | 16.6 | | 76 | 17.9 | | 0.006 |
| Temperature [l] $\geq$ 100.4 F | 117 | 15.6 | | 64 | 18.8 | | 43 | 19.2 | | 97 | 22.8 | | 0.023 |
| Prior Medications [m] | | | | | | | | | | | | | |
| Any ACE or ARB [n] | 309 | 40.1 | | 137 | 40.1 | | 88 | 38.6 | | 182 | 42.4 | | 0.784 |
| Any Anticoagulant | 107 | 13.9 | | 38 | 11.1 | | 26 | 11.4 | | 43 | 10.0 | | 0.213 |
| In-hospital Medications [o] | | | | | | | | | | | | | |
| Dexamethasone | 2 | 0.3 | | 0 | 0.0 | | 1 | 0.4 | | 7 | 1.6 | | 0.007 |
| Methylprednisolone | 10 | 1.3 | | 5 | 1.5 | | 9 | 3.9 | | 19 | 4.4 | | 0.002 |
| Remdesivir | 12 | 1.6 | | 1 | 0.3 | | 1 | 0.4 | | 0 | 0.0 | | 0.014 |
| Comorbidity Scores [p] | | | | | | | | | | | | | |

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| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Charlson comorbidity index [g] | 4.84 (3.42) | | 4.13 (2.90) | | 4.61 (3.24) | | 4.10 (2.84) | | 0.005 |
| Frailty index | 0.31 (0.17) | | 0.24 (0.16) | | 0.27 (0.17) | | 0.24 (0.15) | | <0.001 |
| 5-year Cardiovascular Diseases | | | | | | | | | |
| Coronary heart disease | 301 | 39.1 | 107 | 31.3 | 80 | 35.1 | 119 | 27.7 | 0.001 |
| Cerebrovascular accident | 212 | 27.5 | 78 | 22.8 | 58 | 25.4 | 74 | 17.2 | 0.001 |
| Peripheral vascular disease | 212 | 27.5 | 64 | 18.7 | 59 | 25.9 | 100 | 23.3 | 0.014 |
| Prior conditions [q] | | | | | | | | | |
| Diabetes | 395 | 51.3 | 151 | 44.2 | 123 | 53.9 | 205 | 47.8 | 0.065 |
| Hypertension | 616 | 80.0 | 246 | 71.9 | 179 | 78.5 | 312 | 72.7 | 0.004 |
| Any lung disease [r] | 269 | 34.9 | 104 | 30.4 | 68 | 29.8 | 124 | 28.9 | 0.12 |
| Dementia | 176 | 22.9 | 40 | 11.7 | 30 | 13.2 | 44 | 10.3 | <0.001 |

[a] Values are expressed as mean (standard deviation)
[b] Days between a SARS-CoV-2 positive laboratory result and hospital admission
[c] Any prior admissions to or from a long-term care, skilled nursing, or community housing facility up to six months before hospitalization
[d] Smoking taken as mode from health factors data. Number missing omitted from table.
[e] Proportions may not sum to 100 due to rounding
[f] Prior laboratory measures timing: Two years up to 7 days prior to hospitalization (HbA1c, Hemoglobin, Lymphocytes), Five years up to 7 days prior to hospitalization (LDL-C)
[g] Variable not used in propensity score model(s)
[h] Acute laboratory measures timing: Seven days prior to hospitalization up to date of first medication or 48 hours, whichever came first (ALT, eGFR, WBC count), Any measure 48 hours prior up through 48 hours after hospital admission (C-reactive protein, D-dimer)
[i] Rare laboratory measures fed into PS model using indicator of collection (C-reactive protein, lactate dehydrogenase, ferritin, and d-dimer)
[j] Vitals timing was within two days of index date, except for height and weight, which were from the closest measure before index.
[k] Variable included in PS model as a continuous measure only
[l] Variable included as both indicator and continuous measure in PS model
[m] Prior medications: Prescribed in the year prior to index through outpatient only
[n] Indicators for any ACE and any ARB were included separately in the PS model
[o] In-hospital medications: received at any point in first 48 hours of hospitalization based on inpatient pharmacy data

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[p] Comorbidity scores timing: Charlson comorbidity index two years prior to hospitalization, Frailty index in three years prior to hospitalization
[q] Prior conditions timing: Any 1 inpatient code or 2 outpatient codes in the two years up to seven days prior to hospitalization
[r] Asthma, bronchitis and chronic obstructive pulmonary disease (COPD) were entered into PS model as separate indicators
Abbreviations: ACE: Angiotensin converting enzyme inhibitor; ALT: Alanine aminotransferase; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; HbA1c: Glycosylated hemoglobin; ICU: Intensive Care Unit; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; LTC: long-term care; PS: Propensity score; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SD: Standard deviation; WBC: White blood cell

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Table 2. Effect of HCQ with or Without Azithromycin on Mortality Over 30 days and Intubation Over 21 Days in a National Sample of Hospitalized US Veterans with COVID-19 Between March 1, 2020 and April 30, 2020

| Drug | No. Exposed | Death | | | | Intubation | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. of Cases | No. of Person-Days | HR | 95% CI | No. of Cases | No. of Person-Days | HR | 95% CI |
| Neither drug | 770 | 141 | 20,376 | 1.00 | (ref) | 69 | 7,241 | 1.00 | (ref) |
| Azithromycin alone | 342 | 56 | 9,174 | 0.90 | 0.64, 1.27 | 39 | 2,625 | 1.03 | 0.66, 1.61 |
| HCQ alone | 228 | 49 | 5,853 | 1.21 | 0.82, 1.76 | 32 | 1,897 | 1.33 | 0.82, 2.15 |
| HCQ and azithromycin | 429 | 90 | 11,153 | 1.22 | 0.91, 1.63 | 64 | 3,370 | 1.55 | 1.07, 2.24 |

Abbreviations: CI: Confidence interval; HCQ: Hydroxychloroquine; HR: Hazard ratio

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Figure 1.

Title: Study Design Diagram National Sample of Hospitalized US Veterans with COVID-19 Between March 1, 2020 and April 30, 2020

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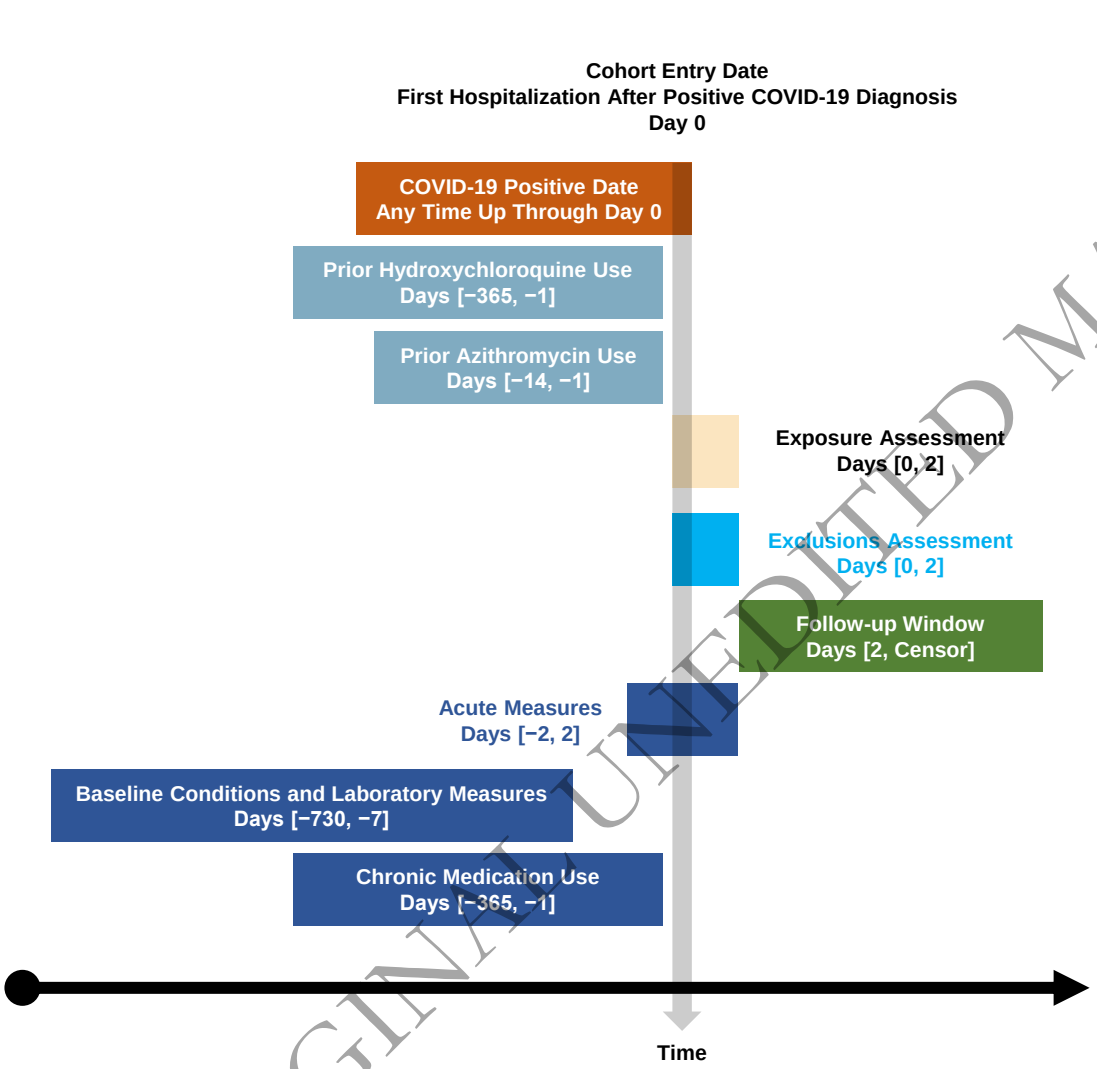


Hospitalizations occurring after or on the same day as COVID-19 case date

Washout windows

Exposure assessment window: Initiation of hydroxychloroquine (HCQ) or azithromycin

Exclusions include early outcomes of death, intubation, or discharge

Censoring at earliest time point of death or 30 days for the primary analysis, and earliest time point of intubation, discharge, or 21 days for the secondary analysis

Covariate assessment windows

Acute measures- vitals, autoimmune disease laboratory measures, HCQ contraindications

Baseline conditions- cardiovascular diseases, chronic lung diseases, immunocompromising conditions, cancers, diabetes

Baseline laboratory measures- complete blood count, lipid and metabolic panels

Chronic medication use- angiotensin receptor blockers, angiotensin converting enzyme inhibitors, steroids, antiplatelet therapies, anticoagulants

Exceptions to time-frames:
Lipid panel laboratory measures days [-1826, -7]
Vascular baseline conditions days [-1826, -7]

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Figure 2.

Title: New-User Hydroxychloroquine Prescriptions Over Time in a National Sample of Hospitalized US Veterans with COVID-19 Between March 1, 2020 and April 30, 2020

Important dates as annotated on the plot: a) March 18, 2020: Pharmacy Benefits Management (PBM) Literature Summary of Off-Label COVID-19 Therapeutic Options Posted; b) March 23, 2020: PBM Hydroxychloroquine (HCQ) Prioritization Criteria Posted; c) March 28, 2020: US Food and Drug Administration (FDA) Approves HCQ Under Emergency Use Authorization (EUA); d) March 30, 2020: PBM HCQ Safety Document Posted; e) April 20, 2020: PBM HCQ Prioritization Criteria Archived (Lack of Effectiveness Data); f) April 23, 2020: PBM HCQ Safety Document Updated; g) April 24, 2020: FDA Drug Safety Communication

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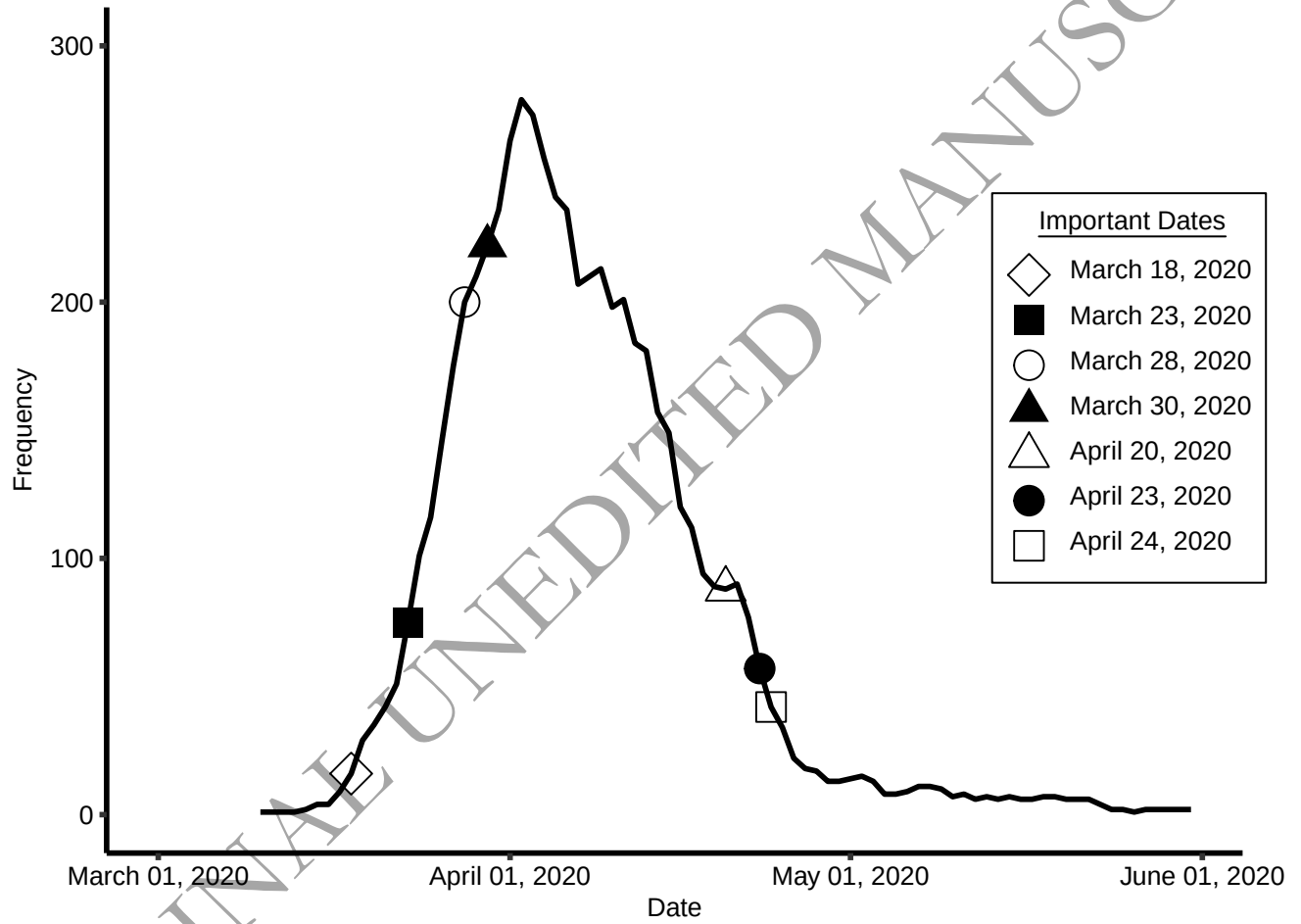


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Figure 3.

Title: Study Inclusion and Exclusion Criteria for the Primary Analysis National Sample of Hospitalized US Veterans with COVID-19 Between March 1, 2020 and April 30, 2020

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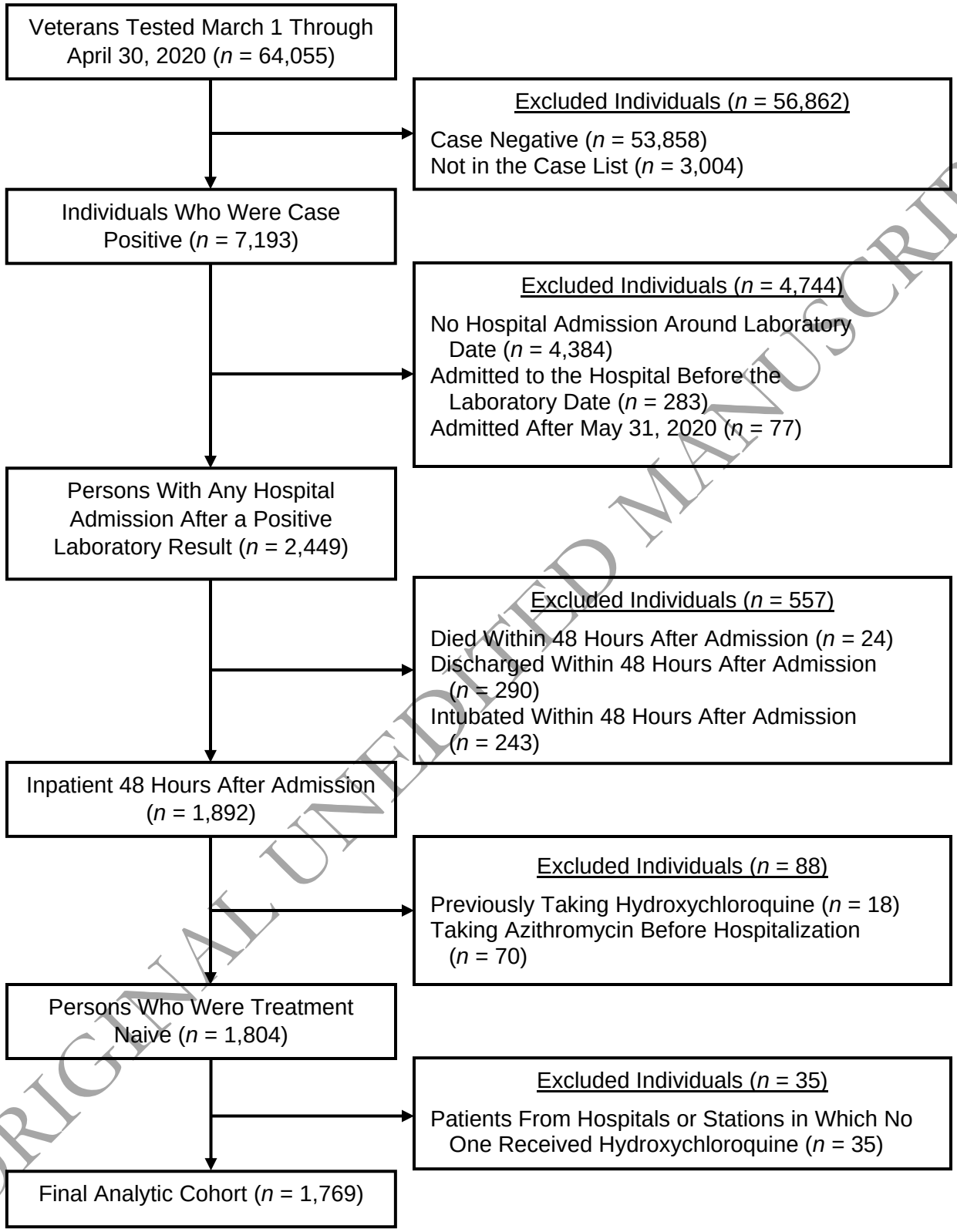


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Figure 4.

Title: Relative Influence Plot of Variables Included in Propensity Model (Primary Analysis)

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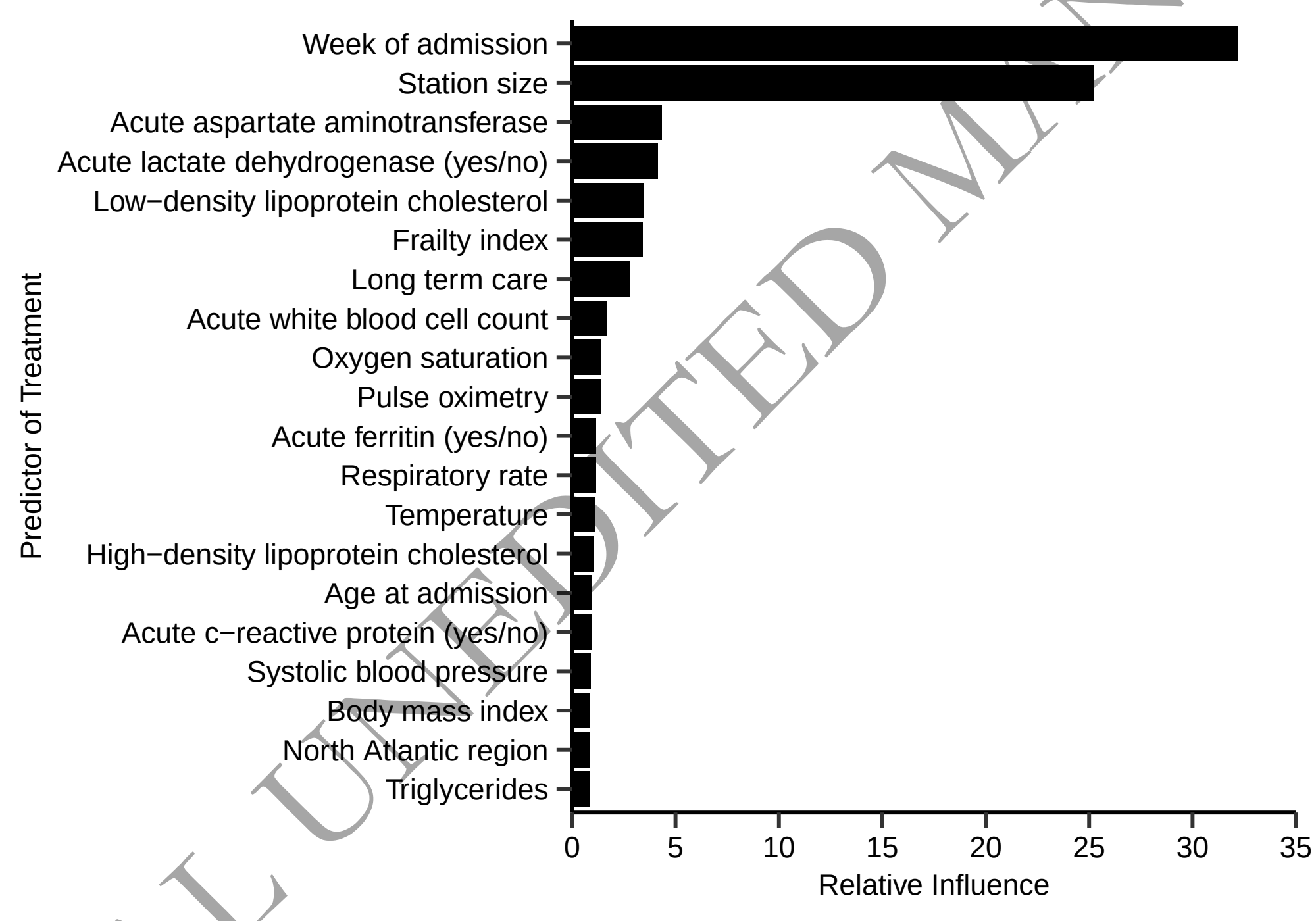


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Figure 5.

Title: Forest Plots Comparing Mortality (A) and Intubation (B) Hazard Ratios Across Sensitivity Analyses

Figure Legend:

Squares with solid lines and diamonds with dashed lines represent the hazard ratios and 95% confidence intervals corresponding to the average treatment effects of hydroxychloroquine (HCQ) and HCQ with azithromycin (Both) compared to neither treatment, respectively. Sensitivity analyses – Differences from Primary Analysis: Censoring – Censoring when subjects add HCQ or azithromycin after 48-hour exposure window; 24-Hour Exposure Window – Using a 24-hour window (from hospitalization) for exposure definition and corresponding exclusions; Excluding Azithromycin – Removing the azithromycin alone group prior to propensity modeling; Laboratory Positive Only – Restricting the cohort to only those with a positive laboratory test result in the VA laboratory records; Excluding Alternate Treatments – Removing individuals on dexamethasone, lopinavir-ritonavir, remdesivir, or tocilizumab in the 48-hour exposure window; Index After March 30, 2020 – Restricting index dates to after March 30, 2020 (or post-issuance of emergency use authorization for HCQ use); Index Before May 1, 2020 – Restricting index dates to April 30, 2020 or earlier; No Intensive Care Unit – Removing any individuals admitted to an intensive care unit within the 48-hour exposure assessment window

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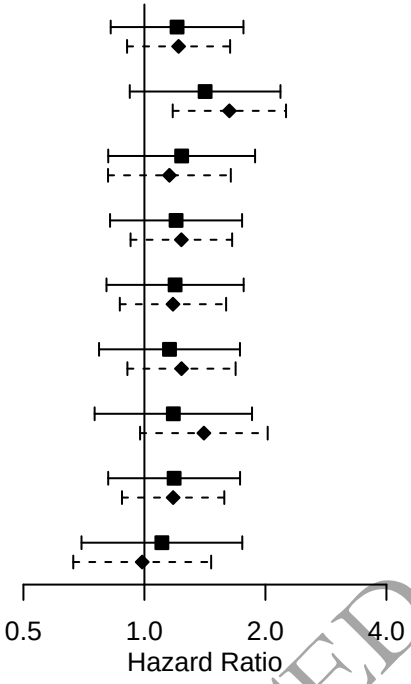
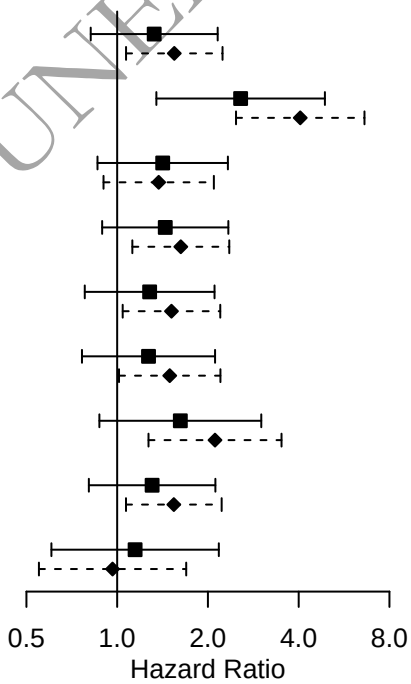
| Scenario | HCQ HR (95% CI) | Both HR (95% CI) |
|---|---|---|
| Primary analysis | 1.21 (0.82, 1.76) | 1.22 (0.91, 1.63) |
| Censoring analysis | 1.42 (0.92, 2.18) | 1.63 (1.18, 2.25) |
| 24−hour exposure window | 1.24 (0.81, 1.88) | 1.15 (0.81, 1.64) |
| Excluding azithromycin | 1.20 (0.82, 1.75) | 1.24 (0.92, 1.65) |
| Laboratory positive only | 1.19 (0.80, 1.77) | 1.18 (0.87, 1.60) |
| Excluding alternate treatments | 1.15 (0.77, 1.73) | 1.24 (0.91, 1.69) |
| Index after March 30, 2020 | 1.18 (0.75, 1.85) | 1.41 (0.98, 2.03) |
| Index before May 1, 2020 | 1.19 (0.81, 1.73) | 1.18 (0.88, 1.58) |
| No intensive care unit | 1.11 (0.70, 1.75) | 0.99 (0.67, 1.47) |




| Scenario | HCQ HR (95% CI) | Both HR (95% CI) |
|---|---|---|
| Primary analysis | 1.33 (0.82, 2.15) | 1.55 (1.07, 2.24) |
| Censoring analysis | 2.57 (1.35, 4.89) | 4.05 (2.48, 6.61) |
| 24−hour exposure window | 1.42 (0.86, 2.33) | 1.37 (0.90, 2.09) |
| Excluding azithromycin | 1.44 (0.89, 2.34) | 1.63 (1.12, 2.35) |
| Laboratory positive only | 1.28 (0.78, 2.10) | 1.51 (1.04, 2.20) |
| Excluding alternate treatments | 1.27 (0.76, 2.11) | 1.49 (1.01, 2.20) |
| Index after March 30, 2020 | 1.62 (0.87, 3.01) | 2.11 (1.27, 3.51) |
| Index before May 1, 2020 | 1.31 (0.81, 2.12) | 1.54 (1.07, 2.22) |
| No intensive care unit | 1.15 (0.61, 2.17) | 0.97 (0.55, 1.69) |




ORIGINAL UNEDITED MANUSCRIPT