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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Abbreviations:

ASMD, average standardized mean difference; BMI, Body mass index; CI, Confidence interval; CPT, Current procedural terminology; CRP, C-reactive protein; DOE, Department of Energy; EUA, Emergency use authorization; FDA, Food and drug administration; HCQ, Hydroxychloroquine; HR, Hazard ratio; ICD, International classification of diseases; ICU, Intensive care unit; LDH, Lactate dehydrogenase; NST, National surveillance tool; PBM, VA department of pharmacy benefits management; PS, Propensity score; RCT, randomized controlled trial; SD, Standard deviation; sIPTW, Stabilized inverse probability of treatment weight; VA, Veterans Affairs Healthcare Administration

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ABSTRACT

Hydroxychloroquine (HCQ) was proposed as an early therapy for 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, US Veteran population using a propensity score adjusted survival analysis with imputation of missing data. As of April 30, 2020, 64,055 US Veterans were tested for COVID-19. From 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 [HR 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

In the swell of the 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 the novel coronavirus disease, COVID-19. This was appealing considering its low cost and widespread availability. The US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for HCQ on March 28, 2020(5) prior to the completion of a randomized controlled trial (RCT), 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 FDA's retraction, several RCTs, 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 RCTs 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 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 FDA's initial

EUA(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 an RCT 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 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 (DOE) Oak Ridge National Laboratory. The work for this analysis under the FDA-led COVID-19 Insights Partnership projects was approved by both DOE and VA institutional review boards and is a joint activity involving VA and DOE 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 day of first hospitalization on the same day or after first SARS-CoV-2 positive diagnosis.

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 (NST), 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 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 ICD-10 (0BH13EZ, 0BH17EZ, 0BH18EZ, 5A1935Z, 5A1945Z, 5A1955Z) and CPT procedure (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 (LDH), C-reactive protein (CRP), 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 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 ICD-10 codes and including a frailty score(33)), and acute lab results and vital signs (those related to acute illness). All potential confounders were included in the propensity model.

Statistical analyses

Missing data - Missing covariate information was imputed using the multiple imputation from chained equations "**mice**" package in R(34-36). 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.

For each patient, the propensity score was converted to a stabilized inverse probability of treatment weight (sIPTW). We evaluated the propensity scores using the "**cobalt**" package in R to look at the distributions of average standardized mean differences (ASMD) 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 sIPTWs 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 in R(43). 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 the supplementary material (Table s5).

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). 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, Supplemental Table S1).

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 lab measurements, such as LDH and CRP, 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 balance plots can be found in the supplementary material. The week of admission variable did not achieve the recommended threshold of 0.1(47), nor even 0.2 for the ASMD comparing those initiating Both treatments to any of the others. Similarly, the ASMD 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.

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). 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

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. Figures 5a and 5b summarize the event counts, number of subjects, and average treatment effect HR (95% CI) for those initiating any combination of HCQ compared to neither

treatment in the 48 hours following admission. Complete tables with results from all sensitivity analyses can be found in the supplementary material.

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 (PBM) guidelines for HCQ EUA 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.

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 our use of an adjudicated

algorithm-based case definition (NST) 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 NST 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(54) is a challenging feature of research related to HCQ. It can be introduced by variable prescribing patterns for the drug(55), in conjunction with the geographic spread of the disease(53) 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 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 (53). 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) (supplemental material), 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.

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 ICU, 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 ICU 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.

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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Conflicts of Interest:

Nothing to disclose

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TABLES

Table 1. Select Baseline Characteristics by 48-Hour Treatment Exposure

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P
Demographics and Lifestyle					
Age (mean (SD))	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[1] (mean (SD))	2.6 (8.1)	0.8 (4.4)	1.0 (2.3)	0.6 (2.3)	<0.001
Week of admission (mean (SD))	15.3 (2.1)	14.0 (1.9)	14.5 (1.4)	14.0 (1.2)	<0.001
Total station size (mean (SD))	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[2] (%)	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[3] (%)					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[4] Labs (median [IQR])					
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[5] (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
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

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P
Acute[6] Labs (median [IQR])					
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[7] (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
N missing (%)	251 (32.6)	108 (31.6)	61 (26.8)	81 (18.9)	
D-dimer[7] (ug/mL)	13 [3, 2199]	6 [3, 3600]	1004 [4, 2195]	1411 [3, 3071]	0.555
N missing (%)	664 (86.2)	296 (86.5)	190 (83.3)	348 (81.1)	
Acute[8] Vitals (%)					
Body mass index[9] $\geq$ 30 kg/m^2	282 (37.0)	152 (44.6)	107 (46.9)	209 (48.7)	<0.001
Oxygen saturation[10] $\leq$ 93%	131 (18.1)	67 (20.8)	52 (24.0)	116 (28.2)	0.001
Respiratory rate[9] > 22/min	82 (11.0)	45 (13.2)	37 (16.6)	76 (17.9)	0.006
Temperature[10] $\geq$ 100.4*F	117 (15.6)	64 (18.8)	43 (19.2)	97 (22.8)	0.023
Prior[11] Medications (%)					
Any ACE or ARB[12]	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[13] Medications (%)					
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[14] (mean (SD))					
Charlson comorbidity index[5]	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

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P
Prior conditions[15] (%)					
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[16]	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

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; SD: standard deviation; WBC: White blood cell

[1] Days between a SARS-CoV-2 positive laboratory result and hospital admission

[2] Any prior admissions to or from a long-term care, skilled nursing, or community housing facility up to six months before hospitalization

[3] Smoking taken as mode from health factors data.

[4] Prior labs timing: Two years up to 7 days prior to hospitalization (HbA1c, Hemoglobin, Lymphocytes), Five years up to 7 days prior to hospitalization (LDL-C)

[5] Variable not used in propensity score model(s)

[6] Acute labs 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)

[7] Rare labs fed into PS model using indicator of collection (C-reactive protein, lactate dehydrogenase, ferritin, and D-dimer)

[8] Vitals timing was within two days of index date, except for height and weight, which were from the closest measure before index.

[9] Variable included in PS model as a continuous measure only

[10] Variable included as both indicator and continuous measure in PS model

[11] Prior medications: Prescribed in the year prior to index through outpatient only

[12] Indicators for any ACE and any ARB were included separately in the PS model

[13] In-hospital medications: received at any point in first 48 hours of hospitalization through IV or BCMA

[14] Comorbidity scores timing: Charlson comorbidity index two years prior to hospitalization, Frailty index in three years prior to hospitalization

[15] Prior conditions timing: Any 1 inpatient code or 2 outpatient codes in the two years up to seven days prior to hospitalization

[16] Asthma, bronchitis and chronic obstructive pulmonary disease (COPD) were entered into PS model as separate indicators

Table 2. sIPTW Hazard Ratios for Mortality and Intubation – Primary Analysis

	Neither drug	Azithromycin alone	HCQ alone	HCQ + Azithromycin
N exposed	770	342	228	429
Mortality				
Cases/Person-Days	141/20,376	56/9,174	49/5,853	90/11,153
HR (95% CI)	1.00 (ref)	0.90 (0.64, 1.27)	1.21 (0.82, 1.76)	1.22 (0.91, 1.63)
Intubation				
Cases/Person-Days	69/7,241	39/2,625	32/1,897	64/3,370
HR (95% CI)	1.00 (ref)	1.03 (0.66, 1.61)	1.33 (0.82, 2.15)	1.55 (1.07, 2.24)

Abbreviations: CI: Confidence interval; HCQ: Hydroxychloroquine; HR: Hazard ratio; sIPTW: Stabilized inverse probability of treatment weighted

FIGURES

Figure 1. Study Design Diagram

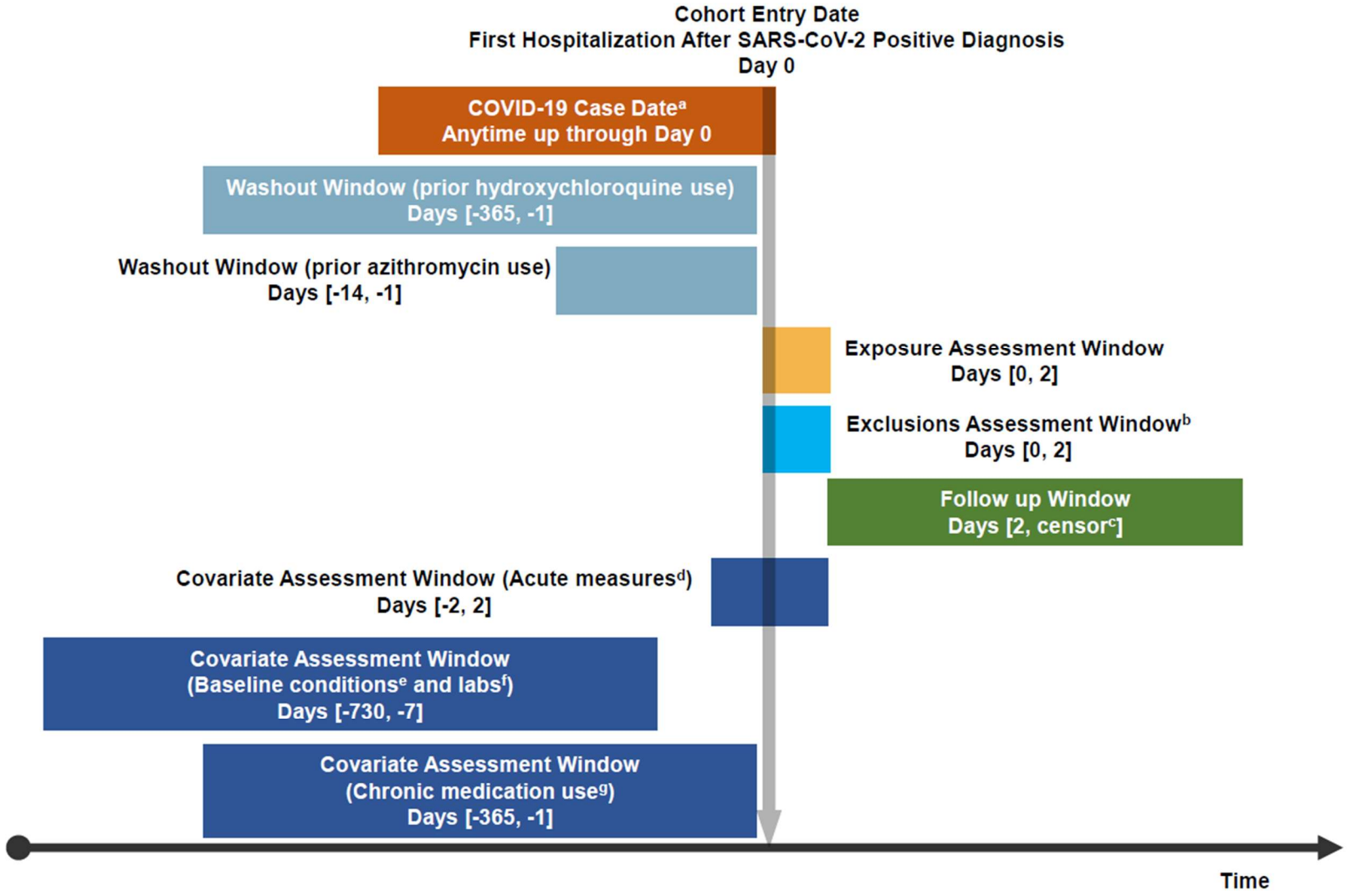


Figure Footnotes:

a. Hospitalizations occurring after or on the same day as COVID-19 case date.
b. Exclusions: Early outcomes of death, intubation or discharge
c. Earliest time point of death or 30 days [primary analysis], and earliest time point of intubation, discharge or 21 days [secondary analysis]
d. Acute measures include vitals (blood pressure, oxygen, pulse, respiratory rate, temperature), selected labs (C-reactive protein, Ferritin, D-Dimer, Lactate Dehydrogenase, alanine aminotransferase, aspartate aminotransferase, estimated glomerular Filtration rate, white blood cell count, and Platelets), use of inpatient HCQ contraindications, use of possible alternative COVID treatments (lopinavir/ritonavir, remdesivir, dexamethasone, methylprednisolone, or tocilizumab) and VA station. Additional measures collected over time were alcohol use (as measured by AUDIT-C), smoking status, and demographic information.
e. Baseline conditions included one inpatient or two outpatient visits with diagnosis codes for: acute myocardial infarction (AMI), cardiomyopathy (CARD), congestive heart disease (CHD), heart failure (HF), cerebrovascular accident (CVA), ischemic stroke, peripheral vascular disease (PVD), hypertension, chronic kidney disease, cancer, severe liver disease, asthma, chronic obstructive pulmonary disease, bronchitis, alcohol use disorder, diabetes, dementia, rheumatoid arthritis, venous thromboembolism, arterial disease, lupus, and multiple sclerosis
f. Labs included: blood urea nitrogen, high-density lipoprotein cholesterol (HDL-C), hemoglobin, low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglycerides, sodium, and neutrophils and lymphocytes count
g. Chronic medication use includes outpatient fills for angiotensin receptor blockers, angiotensin converting enzyme inhibitors, steroids, antiplatelet therapy, and anticoagulants

Covariate exceptions:

- Lipids (HDL-C, LDL-C, Triglycerides) and Total Cholesterol looking back up to five years, i.e. Days [-1826, -7]
- Vascular diseases (AMI, CARD, CHD, HF, CVA, PVD) looking back up to five years, i.e. Days [-1826, -7]

Figure 2. New-User HCQ Prescriptions Over Time Amongst COVID-19 Positive Cases

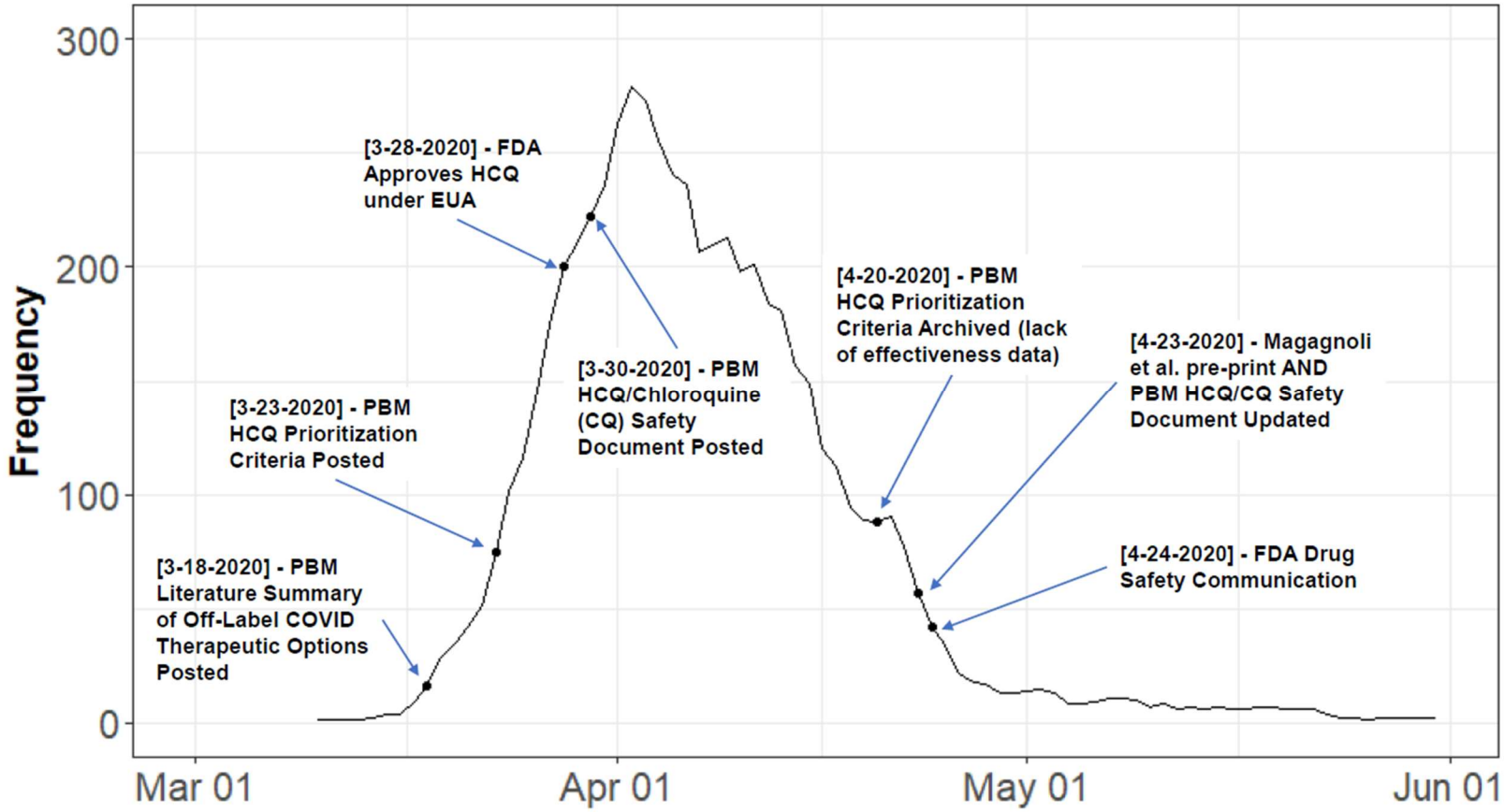


Figure Abbreviations:

CQ - Chloroquine; EUA - Emergency use authorization; FDA - Food and drug administration; HCQ - Hydroxychloroquine; PBM - VA Pharmacy Benefits Management

Figure 3. Study Inclusion and Exclusion Criteria for the Primary Analysis

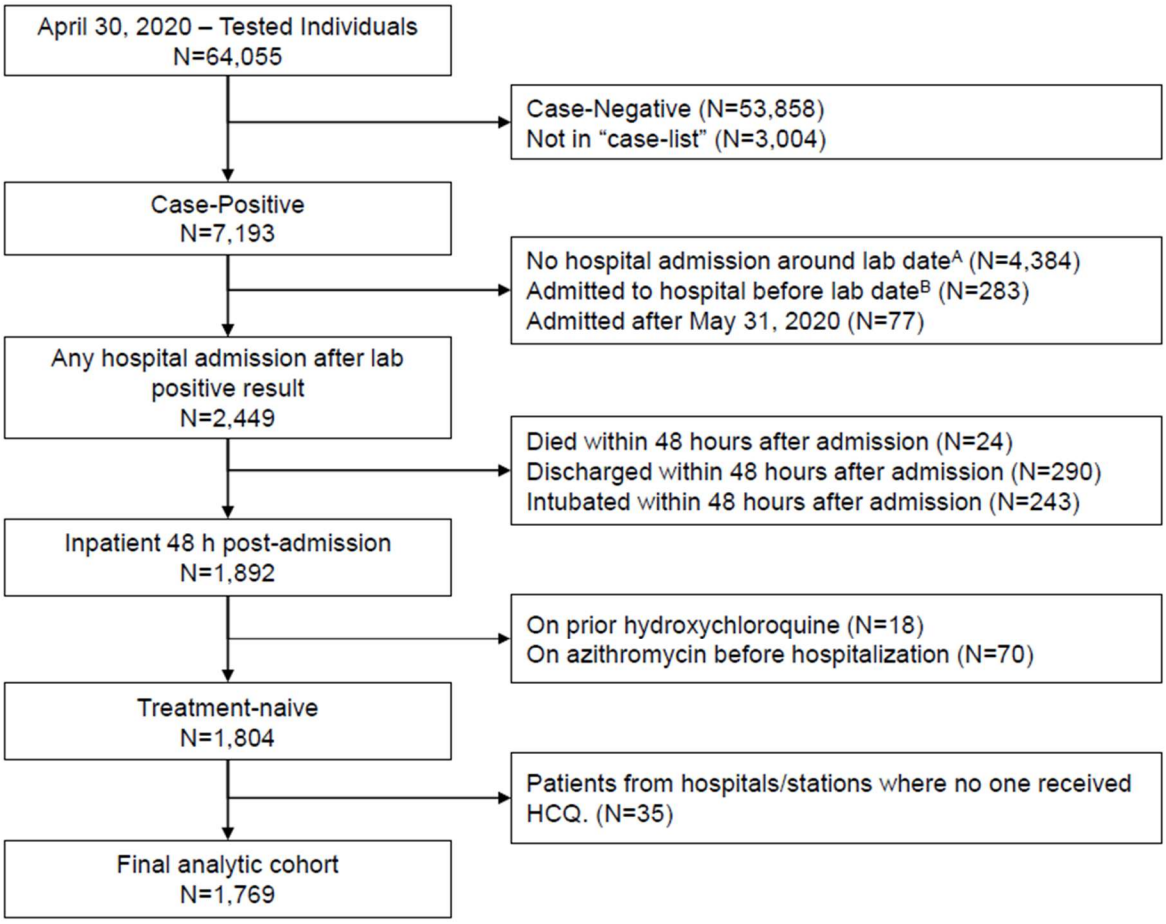


Figure footnotes:

[A] Includes hospital admissions with a discharge date prior to COVID-19 case date
[B] Admissions with no discharge date or discharge date after COVID-19 case date

Figure 4. Relative Influence Plot of Variables Included in Propensity Model (Primary Analysis)

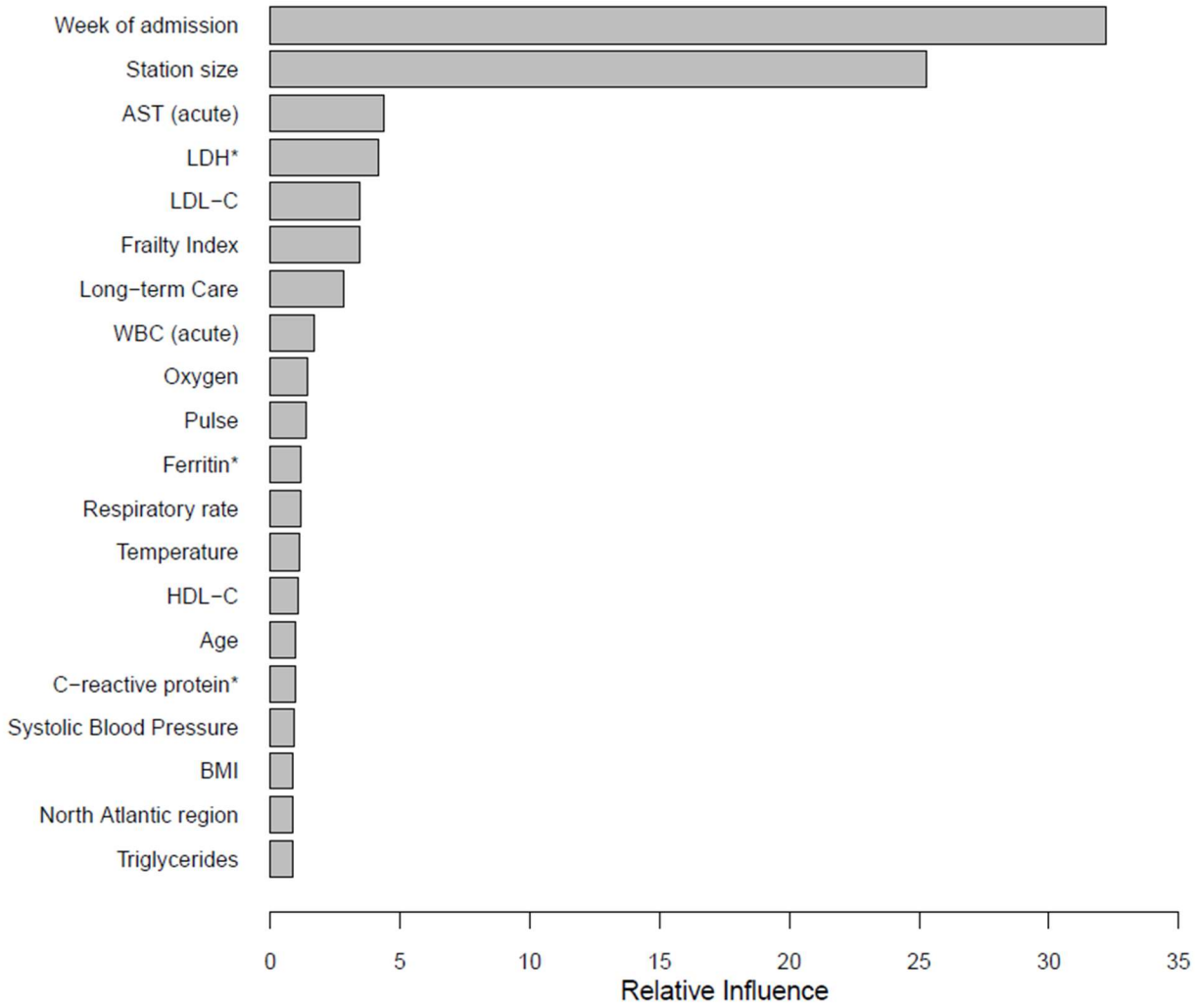


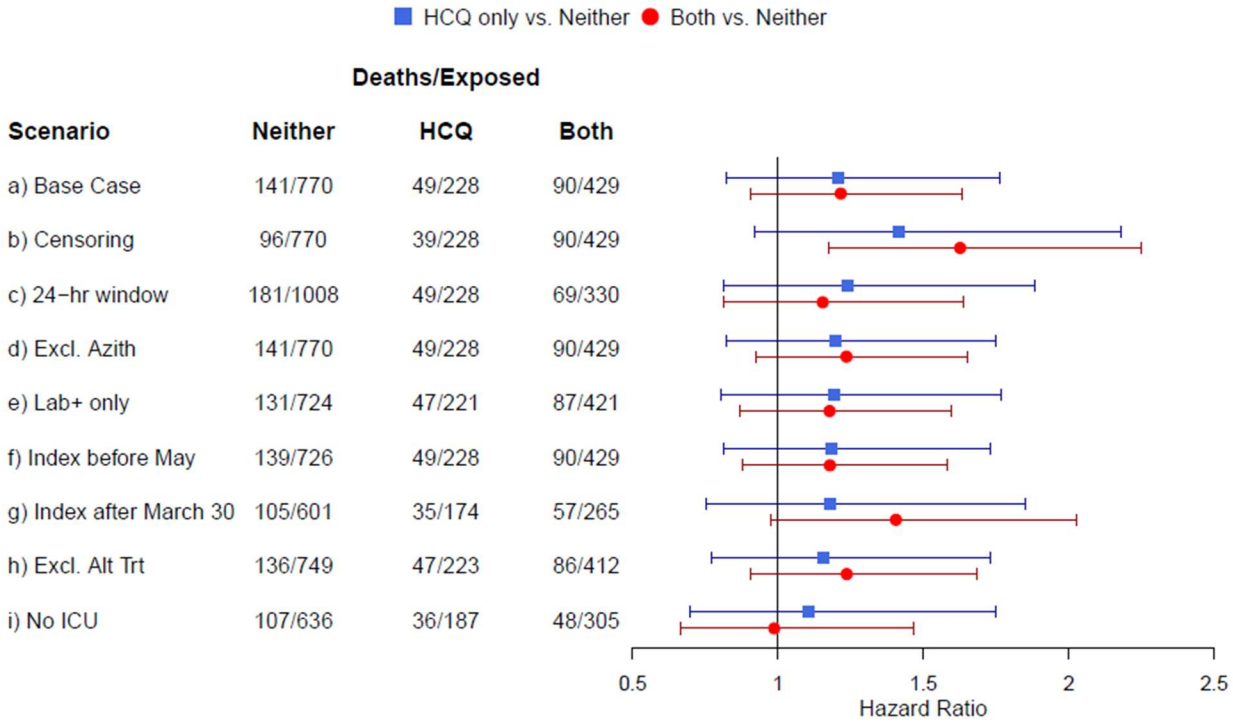
Figure Abbreviations:

AST - Aspartate aminotransferase; BMI - Body mass index; HDL-C - High-density lipoprotein cholesterol; LDH - Lactate dehydrogenase; LDL-C - Low-density lipoprotein cholesterol; WBC - White blood cell count

Figure footnote:

* Modeled using an indicator for the particular lab was measured at some point in the first 48-hours following hospital admission.

Figure 5. Forest Plots Comparing Mortality (a) and Intubation (b) Hazard Ratios Across Sensitivity Analyses



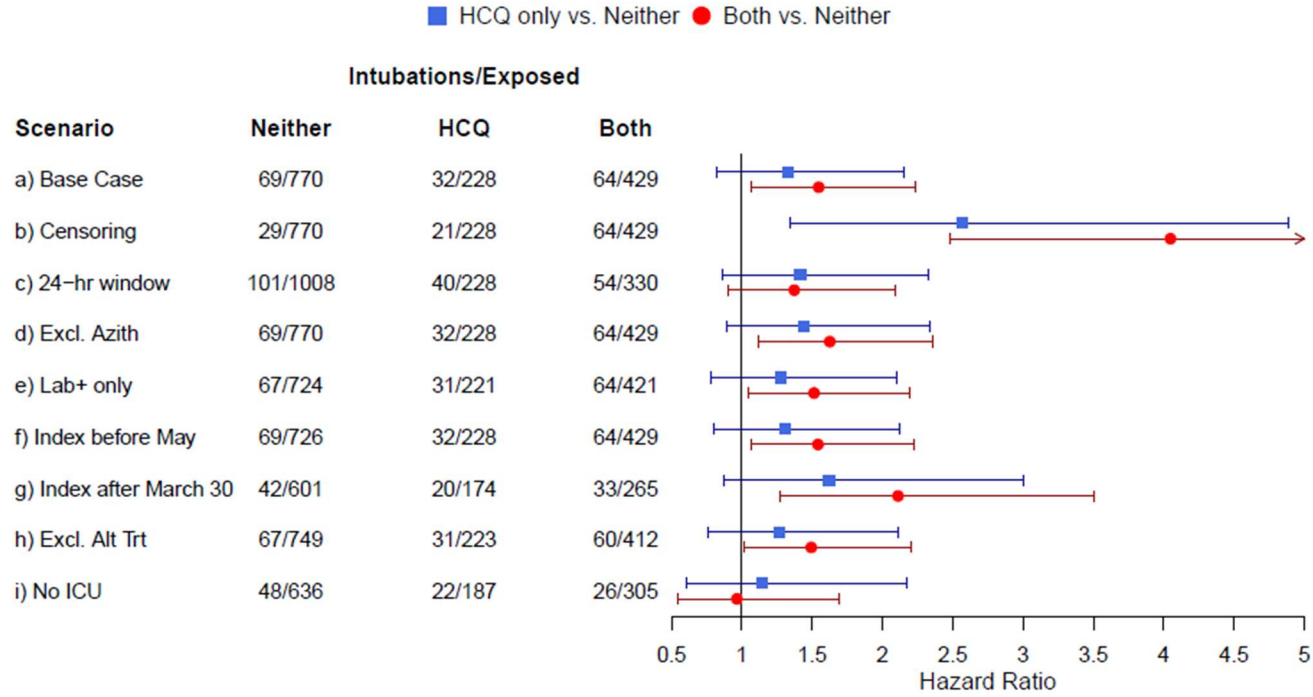


Figure Abbreviations:

FDA - Food and drug administration; HCQ - Hydroxychloroquine; ICU - Intensive care unit; PBM - VA Pharmacy Benefits Management; rt-PCR - Reverse transcription polymerase chain reaction

Figure Footnotes:

Sensitivity analyses – Difference from Primary Analysis:

a) Base Case – Primary analysis
b) Censoring – Censoring when subjects add HCQ or azithromycin after 48-hour exposure window
c) 24-hr window – Using 24-hour window from hospitalization for exposure definition and exclusions
d) Excl. Azith – Removing the azithromycin alone group prior to propensity modeling
e) Lab+ only – Restricting cohort to those with positive SARS-CoV-2 rt-PCR test result in the VA laboratory records
f) Index before May – Restricting index dates to April 30, 2020 or earlier
g) Index after March 30 – Restricting index dates to after March 30, 2020 (PBM/FDA guidelines date)
h) Excl. Alt Trt – Removing individuals on dexamethasone, lopinavir-ritonavir, remdesivir, or tocilizumab in the 48-hour exposure window
i) No ICU – Removing any individuals admitted to the ICU within the 48-hour exposure assessment window

Supplementary Materials – Table of Contents

Table s1. Supplemental Table 1

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P	Base case PS variable
Demographics and Lifestyle						
Age (mean (SD))	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[1] (mean (SD))	2.6 (8.1)	0.8 (4.4)	1.0 (2.3)	0.6 (2.3)	<0.001	
Total station size[2] (mean (SD))	61485 (31509)	64346 (31385)	49902 (20603)	57189 (28718)	<0.001	*
Week of admission[3] (%)					<0.001	*
9: 2020-02-26	0 (0)	1 (0.3)	0 (0)	0 (0)		
10: 2020-03-04	1 (0.1)	2 (0.6)	0 (0)	0 (0)		
11: 2020-03-11	17 (2.2)	13 (3.8)	0 (0)	2 (0.5)		
12: 2020-03-18	59 (7.7)	50 (14.6)	18 (7.9)	40 (9.3)		
13: 2020-03-25	92 (11.9)	98 (28.7)	36 (15.8)	122 (28.4)		
14: 2020-04-01	107 (13.9)	57 (16.7)	54 (23.7)	126 (29.4)		
15: 2020-04-08	110 (14.3)	39 (11.4)	64 (28.1)	88 (20.5)		
16: 2020-04-15	141 (18.3)	39 (11.4)	38 (16.7)	46 (10.7)		
17: 2020-04-22	170 (22.1)	33 (9.6)	16 (7)	3 (0.7)		
18: 2020-04-29	43 (5.6)	7 (2)	2 (0.9)	2 (0.5)		
19: 2020-05-06	8 (1)	1 (0.3)	0 (0)	0 (0)		
20: 2020-05-13	7 (0.9)	1 (0.3)	0 (0)	0 (0)		
21: 2020-05-20	10 (1.3)	1 (0.3)	0 (0)	0 (0)		
22: 2020-05-27	5 (0.6)	0 (0)	0 (0)	0 (0)		
In ICU at 48 hours[4] (%)	134 (17.4)	77 (22.5)	41 (18.0)	124 (28.9)	<0.001	
Urban (%)	707 (91.8)	310 (90.6)	217 (95.2)	408 (95.1)	0.031	*
Coming from LTC[5] facility (%)	130 (16.9)	18 (5.3)	23 (10.1)	20 (4.7)	<0.001	*

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P	Base case PS variable
Demographics and Lifestyle						
Region (%)					<0.001	*
North Atlantic	372 (48.3)	108 (31.6)	107 (46.9)	194 (45.2)		
Southeast	79 (10.3)	50 (14.6)	22 (9.6)	48 (11.2)		
Midwest	159 (20.6)	97 (28.4)	53 (23.2)	124 (28.9)		
Continental	83 (10.8)	42 (12.3)	37 (16.2)	47 (11.0)		
Pacific	77 (10.0)	45 (13.2)	9 (3.9)	16 (3.7)		
Alcohol use disorder (AUDIT-C)						*
N missing (%)	17 (2.2)	8 (2.3)	5 (2.2)	10 (2.3)		
4-level group (%)					<0.001	
Abstinent	537 (71.3)	201 (60.2)	144 (64.6)	242 (57.8)		
Non-hazardous	170 (22.6)	105 (31.4)	65 (29.1)	147 (35.1)		
Hazardous	30 (4.0)	21 (6.3)	11 (4.9)	27 (6.4)		
Severe	16 (2.1)	7 (2.1)	3 (1.3)	3 (0.7)		
Smoking status[6]						*
N missing (%)	216 (28.1)	87 (25.4)	86 (37.7)	148 (34.5)		
3-level group (%)					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 Labs[7]						
HbA1c in percentage						
median [IQR]	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	
N missing (%)	132 (17.1)	64 (18.7)	34 (14.9)	68 (15.9)		
Serum BUN in mg/dL						*
median [IQR]	18.0 [14.0, 26.0]	16.0 [13.0, 22.0]	18.6 [13.0, 25.8]	17.0 [13.0, 22.0]	<0.001	
N missing (%)	41 (5.3)	27 (7.9)	10 (4.4)	26 (6.1)		
HDL-C in mg/dL						*
median [IQR]	43.0 [36.0, 51.0]	44.0 [37.5, 55.0]	42.0 [36.9, 53.0]	43.0 [35.0, 52.0]	0.092	
N missing (%)	45 (5.8)	25 (7.3)	11 (4.8)	26 (6.1)		

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P	Base case PS variable
Prior Labs[7]						
Hemoglobin in g/dL						*
median [IQR]	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	
N missing (%)	48 (6.2)	27 (7.9)	10 (4.4)	32 (7.5)		
LDL-C in mg/dL						*
median [IQR]	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	
N missing (%)	47 (6.1)	25 (7.3)	11 (4.8)	26 (6.1)		
Lymphocyte count in K/cmm						*
median [IQR]	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	
N missing (%)	176 (22.9)	128 (37.4)	44 (19.3)	101 (23.5)		
Serum sodium in mmol/L						*
median [IQR]	139.0 [137.0, 141.0]	140.0 [138.0, 141.0]	139.0 [137.0, 141.0]	140.0 [138.0, 142.0]	0.001	
N missing (%)	40 (5.2)	25 (7.3)	7 (3.1)	24 (5.6)		
Total cholesterol in mg/dL						*
median [IQR]	148.0 [124.0, 179.0]	164.0 [135.2, 195.8]	155.5 [128.8, 182.0]	159.0 [135.5, 185.0]	<0.001	
N missing (%)	70 (9.1)	36 (10.5)	12 (5.3)	38 (8.9)		
Triglycerides in mg/dL						*
median [IQR]	111.0 [78.0, 155.0]	106.0 [73.0, 168.8]	116.0 [80.0, 174.0]	115.0 [79.0, 167.0]	0.308	
N missing (%)	48 (6.2)	28 (8.2)	11 (4.8)	27 (6.3)		
Acute Labs[8]						
ALT in U/L						*
median [IQR]	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	
N missing (%)	81 (10.5)	72 (21.1)	34 (14.9)	82 (19.1)		
AST in U/L						*
median [IQR]	33.0 [22.0, 51.2]	37.0 [27.0, 52.0]	40.0 [27.0, 58.0]	43.0 [32.0, 64.0]	<0.001	
N missing (%)	102 (13.2)	81 (23.7)	41 (18)	112 (26.1)		
C-reactive protein[9] in mg/dL						*
median [IQR]	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	
N missing (%)	251 (32.6)	108 (31.6)	61 (26.8)	81 (18.9)		

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P	Base case PS variable
Acute Labs[8]						
D-dimer[9] in ug/mL						*
median [IQR]	13.4 [2.9, 2198.8]	6.1 [3.2, 3600.2]	1003.5 [3.5, 2194.8]	1411.0 [2.8, 3071.0]	0.555	
N missing (%)	664 (86.2)	296 (86.5)	190 (83.3)	348 (81.1)		
eGFR in mL/min						*
median [IQR]	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	
N missing (%)	31 (4)	48 (14)	21 (9.2)	53 (12.4)		
Ferritin[9] in ng/mL						*
median [IQR]	432.6 [193.4, 862.2]	563.8 [285.1, 972.6]	637.1 [290.5, 1167.8]	634.7 [336.0, 1079.1]	<0.001	
N missing (%)	271 (35.2)	126 (36.8)	53 (23.2)	94 (21.9)		
LDH[9] in U/L						*
median [IQR]	266.5 [196.8, 363.5]	292.0 [230.0, 391.0]	305.5 [233.0, 403.5]	357.0 [264.0, 486.5]	<0.001	
N missing (%)	322 (41.8)	127 (37.1)	66 (28.9)	94 (21.9)		
Platelet count in K/cmm						*
median [IQR]	188.5 [142.2, 248.8]	186.5 [154.2, 242.8]	181.0 [149.0, 235.0]	192.0 [147.0, 250.8]	0.749	
N missing (%)	20 (2.6)	28 (8.2)	7 (3.1)	39 (9.1)		
WBC count in K/cmm						*
median [IQR]	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	
N missing (%)	53 (6.9)	36 (10.5)	7 (3.1)	46 (10.7)		
Acute Vitals[10]						
BMI[3] in kg/m^2						*
median [IQR]	27.8 [23.7, 33.1]	29.1 [25.1, 33.7]	29.6 [25.0, 33.2]	29.7 [25.9, 34.2]	<0.001	
N missing (%)	7 (0.9)	1 (0.3)	0 (0)	0 (0)		
$\geq$30 (%)	282 (37.0)	152 (44.6)	107 (46.9)	209 (48.7)	<0.001	
Oxygen saturation[11] in percent						*
median [IQR]	96.0 [94.0, 98.0]	96.0 [94.0, 98.0]	96.0 [94.0, 97.0]	95.0 [93.0, 97.0]	<0.001	
N missing (%)	45 (5.8)	20 (5.8)	11 (4.8)	18 (4.2)		
$\leq$93 (%)	131 (18.1)	67 (20.8)	52 (24.0)	116 (28.2)	0.001	

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P	Base case PS variable
Acute Vitals[10]						
DBP in mmHg						
median [IQR]	74.0 [66.0, 82.0]	74.0 [67.0, 84.0]	75.0 [66.0, 81.8]	74.0 [65.0, 82.0]	0.711	
N missing (%)	22 (2.9)	2 (0.6)	6 (2.6)	5 (1.2)		
SBP in mmHg						*
median [IQR]	131 [117, 148]	128 [116, 143]	132 [119, 148]	129.5 [117, 145]	0.129	
N missing (%)	22 (2.9)	2 (0.6)	6 (2.6)	5 (1.2)		
Pain on a 0-10 scale						*
median [IQR]	0.0 [0.0, 3.0]	0.0 [0.0, 5.0]	0.0 [0.0, 3.0]	0.0 [0.0, 3.0]	0.249	
N missing (%)	37 (4.8)	9 (2.6)	9 (3.9)	15 (3.5)		
Pulse in beats/min						*
median [IQR]	84.0 [73.0, 97.0]	87.0 [76.0, 98.0]	88.0 [78.5, 98.0]	88.0 [78.0, 100.0]	<0.001	
N missing (%)	21 (2.7)	3 (0.9)	5 (2.2)	3 (0.7)		
Respiratory rate[3] /min						*
median [IQR]	18.0 [18.0, 20.0]	19.0 [18.0, 20.0]	20.0 [18.0, 20.5]	19.0 [18.0, 22.0]	0.001	
N missing (%)	23 (3)	2 (0.6)	5 (2.2)	5 (1.2)		
>22 (%)	82 (11.0)	45 (13.2)	37 (16.6)	76 (17.9)	0.006	
Temperature[11] in degrees F						*
median [IQR]	98.7 [98.0, 99.8]	98.8 [98.2, 100.0]	99.0 [98.3, 100.1]	99.1 [98.3, 100.2]	<0.001	
N missing (%)	20 (2.6)	2 (0.6)	4 (1.8)	4 (0.9)		
$\geq$100.4 (%)	117 (15.6)	64 (18.8)	43 (19.2)	97 (22.8)	0.023	
Prior Medications[12]						
Any ACE or ARB (%)	309 (40.1)	137 (40.1)	88 (38.6)	182 (42.4)	0.784	
Any ACE-inhibitor (%)	201 (26.1)	94 (27.5)	56 (24.6)	122 (28.4)	0.696	*
Any ARB (%)	122 (15.8)	44 (12.9)	32 (14.0)	70 (16.3)	0.503	*
Any Anticoagulant (%)	107 (13.9)	38 (11.1)	26 (11.4)	43 (10.0)	0.213	*
Any Antiplatelet (%)	57 (7.4)	19 (5.6)	25 (11.0)	27 (6.3)	0.08	*
Any Steroid (%)	255 (33.1)	129 (37.7)	94 (41.2)	147 (34.3)	0.103	*

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P	Base case PS variable
In-hospital Medications[13]						
HCQ contraindication (%)					0.579	*
No contraindicated medication	97 (12.6)	49 (14.3)	33 (14.5)	67 (15.6)		
Moderate	103 (13.4)	43 (12.6)	32 (14.0)	63 (14.7)		
Serious	570 (74.0)	249 (72.8)	163 (71.5)	299 (69.7)		
Severe	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)		
Dexamethasone (%)	2 (0.3)	0 (0.0)	1 (0.4)	7 (1.6)	0.007	*
Lopinavir/Ritonavir (%)	4 (0.5)	2 (0.6)	0 (0.0)	1 (0.2)	0.614	*
Remdesivir (%)	12 (1.6)	1 (0.3)	1 (0.4)	0 (0.0)	0.014	*
Methylprednisolone (%)	10 (1.3)	5 (1.5)	9 (3.9)	19 (4.4)	0.002	*
Tocilizumab (%)	3 (0.4)	2 (0.6)	4 (1.8)	10 (2.3)	0.009	*
5-year Cardiovascular Diseases						
Acute myocardial infarction (%)	81 (10.5)	23 (6.7)	16 (7.0)	27 (6.3)	0.031	*
Cardiomyopathy (%)	100 (13.0)	32 (9.4)	14 (6.1)	37 (8.6)	0.008	*
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	*
Heart failure (%)	216 (28.1)	73 (21.3)	56 (24.6)	74 (17.2)	<0.001	*
Peripheral vascular disease (%)	212 (27.5)	64 (18.7)	59 (25.9)	100 (23.3)	0.014	*
Any vascular disease (%)	448 (58.2)	157 (45.9)	122 (53.5)	179 (41.7)	<0.001	*
Comorbidity Scores[14]						
CCI mean (SD)	4.84 (3.42)	4.13 (2.90)	4.61 (3.24)	4.10 (2.84)	0.005	
Frailty Index (mean (SD))	0.31 (0.17)	0.24 (0.16)	0.27 (0.17)	0.24 (0.15)	<0.001	*
Prior conditions[15]						
Arterial disease (%)	121 (15.7)	37 (10.8)	42 (18.4)	53 (12.4)	0.028	*
Diabetic arterial disease (%)	67 (8.7)	16 (4.7)	27 (11.8)	21 (4.9)	0.001	*
Ischemic stroke (%)	92 (11.9)	32 (9.4)	17 (7.5)	24 (5.6)	0.003	*
Venous thromboembolism (%)	66 (8.6)	12 (3.5)	15 (6.6)	22 (5.1)	0.008	*
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 cancer (%)	142 (18.4)	49 (14.3)	47 (20.6)	71 (16.6)	0.198	*

	Neither drug (N = 770)	Azithromycin alone (N = 342)	HCQ alone (N = 228)	HCQ + Azithromycin (N = 429)	P	Base case PS variable
Prior conditions[15]						
Chronic kidney disease (%)	252 (32.7)	88 (25.7)	81 (35.5)	102 (23.8)	0.001	*
Severe liver disease (%)	12 (1.6)	5 (1.5)	1 (0.4)	5 (1.2)	0.604	*
Dementia (%)	176 (22.9)	40 (11.7)	30 (13.2)	44 (10.3)	<0.001	*
Any lung disease (%)	269 (34.9)	104 (30.4)	68 (29.8)	124 (28.9)	0.12	
Asthma (%)	58 (7.5)	23 (6.7)	12 (5.3)	24 (5.6)	0.484	*
Bronchitis (%)	81 (10.5)	33 (9.6)	30 (13.2)	35 (8.2)	0.226	*
COPD (%)	212 (27.5)	73 (21.3)	52 (22.8)	95 (22.1)	0.062	*
Alcohol use disorder (%)	122 (15.8)	35 (10.2)	26 (11.4)	55 (12.8)	0.05	*
Any immunodeficient disease (%)	21 (2.7)	14 (4.1)	7 (3.1)	10 (2.3)	0.515	
Lupus (%)	6 (0.8)	2 (0.6)	0 (0.0)	1 (0.2)	0.398	*
Multiple sclerosis (%)	4 (0.5)	1 (0.3)	2 (0.9)	2 (0.5)	0.815	*
Rheumatoid arthritis (%)	14 (1.8)	13 (3.8)	5 (2.2)	7 (1.6)	0.156	*

ACE: Angiotensin converting enzyme inhibitor; ALT: Alanine aminotransferase; ARB: Angiotensin receptor blocker; AST: Aspartate aminotransferase; BMI: Body mass index; BUN: Blood urea nitrogen; CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disorder; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; F: Farenheit; HbA1c: Glycosylated hemoglobin; HCQ: Hydroxychloroquine; ICU: Intensive Care Unit; IQR: Interquartile range; LDL-C: Low-density lipoprotein cholesterol; LDH: Lactate dehydrogenase; LTC: long-term care; PS: Propensity score; SBP: Systolic blood pressure; SD: Standard deviation; WBC: White blood cell

[1] Days between a SARS-CoV-2 positive laboratory result and hospital admission

[2] Based on number of Veterans with at least one inpatient or two outpatient visits at a VA facility during calendar years 2018 and 2019

[3] Variable included in PS model as a continuous measure only

[4] Does not incorporate timing of treatment initiation

[5] Any prior admissions to or from a long-term care, skilled nursing, or community housing facility up to six months before hospitalization

[6] Smoking taken as mode from health factors data

[7] Prior labs timing: Two years up to 7 days prior to hospitalization (HbA1c, Serum BUN, Hemoglobin, Lymphocyte count, Serum sodium), Five years up to 7 days prior to hospitalization (LDL-C, HDL-C, Total cholesterol, Triglycerides)

[8] Acute labs timing: Seven days prior to hospitalization up to date of first medication or 48 hours, whichever came first (ALT, AST, eGFR, Platelet count, WBC count), Any measure 48 hours prior up through 48 hours after hospital admission (C-reactive protein, D-dimer, Ferritin, LDH)

[9] Rare labs fed into PS model using indicator of collection (C-reactive protein, LDH, ferritin, and D-dimer)

[10] Vitals timing was within two days of index date, except for height and weight, which were from the closest measure before index

[11] Variable included as both indicator and continuous measure in PS model

[12] Prior medications: Prescribed in the year prior to index through outpatient only

[13] In-hospital medications: received at any point in first 48 hours of hospitalization through IV or BCMA

[14] Comorbidity scores timing: Charlson comorbidity index any time prior to hospitalization, Frailty index in three years prior to hospitalization

[15] Prior conditions timing: Any 1 inpatient code or 2 outpatient codes in the two years up to seven days prior to hospitalization; Prior conditions defined using ICD-10 codes only

Table s2. International Classification of Diseases Codes (ICD) for Underlying Conditions

Condition	**ICD10 codes/*ICD 9***
Acute Myocardial Infarction (AMI)	I21.X (not including I21.AX), I22.X *410.X-412.X, 429.7X*
Cardiomyopathy	I42.X, I43.X *425.X*
Coronary Heart Disease (CHD)	I20.X, I21.X, I24.X, I25.10, I25.110, I25.2, I25.3, I25.41, I25.42, I25.5, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.810, I25.811, I25.812, I25.82, I25.83, I25.84, I25.89, I25.9 *410.X-414.X, 429.X, 996.03X, V45.81X, V45.82X*
Heart Failure (HF)	I11.0, I13.0, I13.2, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.814, I50.9, I50.1, I50.810, I50.811, I50.812, I50.813, I50.82, I50.83, I50.84, I50.89 *428.X*
Cerebrovascular Accident (CVA)	I600.X-I69.X, G45.X, G46.X, H34.0 *430.X-438.X, 346.6X, V12.54X*
Peripheral Vascular Disease (PVD)	I70.X, I71.X, I73.9, Z95.8, Z95.9, I73.1, I73.8, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9 *440.X-448.X, 557.X, 785.4X, V43.4X*
Any Vascular disease	Any ICD from the following conditions: AMI, CARD, CHD, HF, CVA, or PVD
Hypertension	I10.X-I13.X, I15.X, I16.X
Diabetes	E08.X, E10.X, E11.X, E13.X
Asthma	J45.X
Chronic Obstructive Pulmonary Disease (COPD)	J41.0X, J41.1X, J41.8X, J42.X, J43.0X, J43.1X, J43.2X, J43.8X, J43.9X, J44.0X, J44.1X, J44.9X
Bronchitis	J20.X, J21.X, J40.X, J41.X, J42.X
Alcohol Use Disorder	F10.120X, F10.121X, F10.129X, F10.150X, F10.151X, F10.159X, F10.180X, F10.181X, F10.182X, F10.188X, F10.220X, F10.221X, F10.229X, F10.230X, F10.231X, F10.232X, F10.239X, F10.250X, F10.251X, F10.259 X, F10.280X, F10.281X, F10.282X, F10.288X, F10.10X, F10.11X, F10.14X, F10.19X, F10.20X, F10.21X, F10.24X, F10.25X, F10.26X, F10.27X, F10.29X
Chronic Kidney Disease	I12.0, I13.1, N03.2X-N03.7X, N18.X, N19.X, N05.2X-N05.7X, N25.0, Z49.0X - Z49.2X, Z94.0, Z99.2
Cancer	C00.X-C43.X, C45.X-C76.X, C80.X-C96.X, C7A
Severe Liver Disease	K72.1X, K72.9X, K76.6X, K76.7X, I85.0X, I85.9X, I86.4X, I98.2X, K70.4X, K71.1X, K76.5X
Dementia	F00.X, F01.X, F02.X, F03.X, G30.X, F05.1X, G31.1X
Systemic Lupus Erythematosus (Lupus)	H01.1X, L93.X, M32.X
Rheumatoid Arthritis (RA)	M05.X, M32.X, M34.X, M06.0X, M06.1X, M06.2X, M06.3X, M06.4X, M06.8X, M06.9X, M31.5X, M33.2X, M35.3X, M33.0X, M33.1X, M33.9X, M35.1X, M36.0X
Multiple Sclerosis (MS)	G35.X
Ischemic Stroke	I63.X, I66.X

Condition	**ICD10 codes/*ICD 9***
Venous Thromboembolism (VTE)	I26.X, I80.1X, I80.2X, I80.3X, I80.8X, I80.9X, I82.0X, I82.1X, I82.2X, I82.3X, I82.4X, I82.5X, I82.6X, O87.1X
Arterial Disease	I73.9X, I73.89X, I70.20X, I70.21X, I70.22X, I70.23X, I70.24X, I70.26, I70.29, M62.2X, R23.1X, R23.0X, T69.1X, N28.0X, M30.3X
Diabetes with Underlying Circulatory Disease	E08.5X, E09.5X, E10.5X, E11.5X, E13.5X

Table s3. Medications Considered

Medication Type	Names/Classes included	Timing, Source
Anti-platelet	Clopidogrel, Ticagrelor, Prasugrel, Fipyridamole, Ticlopidine, Eptifibatide	Chronic, Outpatient
Anti-coagulants	Heparin, Warfarin, Rivaroxaban, Dabigatran, Apixaban, Edoxaban, Edoxaparin, Fondparinux	Chronic, Outpatient
ACE Inhibitors (ACE)	Fosinopril, Lisinopril, Lisinopril-Hydrochlorothiazide, Captopril, Benazepril, Benazepril-Amlodipine, Ramipril, Enalapril	Chronic, Outpatient
Angiotensin Receptor Blockers (ARB)	Candesartan, Valsartan, Valsartan-Sacubitril, Losartan-Hydrochlorothiazide, Olmesartan, Valsartan-Hydrochlorothiazide	Chronic, Outpatient
Steroids	Names: Beclomethasone, Betamethasone, Budecort refill canister, Budesonide, CMI study Dexamethasone, Cortisone, Dexamethasone, Fludrocortisone, Flunisolide, Fluticasone, Formoterol, Hydrocortisone, Methylprednisolone, Mometasone, Prednisolone, Prednisone, Triamcinolone Drug classes: glucocorticoids, mineralocorticoids, nasal anti-inflammatories, anti-asthmatics	Chronic, Outpatient
Dexamethasone	Dexamethasone	Acute, Inpatient
Steroids	Methylprednisolone	Acute, Inpatient
Lopinavir-Ritonavir	Lopinavir, Ritonavir, Kaletra	Acute, Inpatient
Remdesivir	Remdesivir	Acute, Inpatient
Tocilizumab	Tocilizumab, Actemra	Acute, Inpatient

Inpatient Medication Capture:

The VA system logs all inpatient medications through a centralized Bar Code Medication Administration (BCMA) system, which was implemented across the VA hospitals in the early 2000s. This method of electronically documenting transactional processes has been shown to decrease medication administration errors[1] and is the clinical record of medication administration. As such it is closely monitored for accuracy. The BCMA dispensing of HCQ and other drugs are done on a per-person, per-dose basis.

Table s4. Crude Event Counts

	Neither	Azithromycin alone	HCQ alone	HCQ + Azithromycin
N on treatment	770	342	228	429
#Added Azithromycin or HCQ after 48 hours (%)	128 (17)	86 (25)	20 (9)	------
Admitted to ICU during exposure window (%)	134 (17)	77 (23)	41 (18)	124 (29)
#In ICU prior to treatment initiation	------	64	30	106
Admitted to ICU after 48 hours (% [a])	202 (28)	56 (20)	48 (24)	65 (20)
21-day Intubation (%)	69 (9)	39 (11)	32 (14)	64 (15)
#Died [b] after intubation	49	23	26	43
#Discharged [c] after intubation	18	16	5	23
30-day Discharge (%)	547 (71)	271 (79)	166 (73)	324 (76)
#Died [b] after discharge	28	14	7	18
30-day Death (%)	141 (18)	56 (16)	49 (22)	90 (21)
#Died [d] inpatient on initial hospitalization	128	49	46	78

Abbreviations: HCQ – Hydroxychloroquine; ICU – Intensive care unit

[a] Proportion out of those not in ICU at 48 hours

[b] Not restricted to deaths within 30 days

[c] Regardless of later deaths

[d] 30-day inpatient mortality, all deaths in this row represent a subset of the preceding row

Table s5. Sensitivity Analyses Descriptions

Short Description	Sensitivity Type	Exposure window	Total N	Total 30-Day Deaths	Total 21-Day Intubation	Variables in Propensity Model	Change from primary analysis (Base Case)
Base Case	-	48-hour	1769	336	204	Base Case	-
Censoring	Analytic	48-hour	1769	261	133	Base Case	Censoring subjects at addition of HCQ/Azithromycin after 48-hr window
24-hr window	Cohort definition	24-hour	2029	378	265	Base Case	Using 24-hr window for exposure definition and exclusions
Excl. Azith	Analytic + Cohort	48-hour	1427	280	165	Base Case	Removing the Azithromycin alone group prior to propensity modeling
Lab+ only	Cohort definition	48-hour	1705	320	201	Base Case	Restricting to rt-PCR laboratory positive individuals only
Index before May	Cohort definition	48-hour	1721	334	204	Base Case	Restricting index dates to April 30th and earlier
Index after March 30	Cohort definition	48-hour	1218	225	165	Base Case	Restricting index dates to after March 30th
Excl. Alt Trt	Cohort definition	48-hour	1721	324	197	Base Case	Removing individuals on dexamethasone, lopinavir-ritonavir, remdesivir, or tocilizumab in the 48-hour window
No ICU	Cohort definition	48-hour	1393	228	112	Base Case	Removing those admitted to the ICU within the 48-hour window

Short Description	Sensitivity Type	Exposure window	Total N	Total 30-Day Deaths	Total 21-Day Intubation	Variables in Propensity Model	Change from primary analysis (Base Case)
DR1	Analytic	48-hour	1769	336	204	Base Case	Outcome model: include station size as covariate
DR2	Analytic	48-hour	1769	336	204	Base Case	Outcome model: include week of admission as covariate
DR3	Analytic	48-hour	1769	336	204	Base Case	Outcome model: include station size and week of admission as covariates
DR4	Analytic	48-hour	1769	336	204	Base Case	Outcome model: stratify on VA station
DR5	Analytic	48-hour	1769	336	204	Base Case	Outcome model: stratify on VA station and add week of admission as covariate
PM1	Analytic	48-hour	1769	336	204	Base Case - station size	Different PM variable list
PM2	Analytic	48-hour	1769	336	204	Base Case - station size - week	Different PM variable list
PM3	Analytic	48-hour	1769	336	204	Base Case + time-to-admission	Different PM variable list
PM4	Analytic	48-hour	1769	336	204	Base Case + time-to-admission + Albumin (acute and prior) + ALT/AST/eGFR/Platelet/WBC (prior) + station size quartile + Lymphocytes fraction (acute)	Different PM variable list
PM5	Analytic	48-hour	1769	336	204	Base Case - station size (continuous) + station size quartile	Different PM variable list

Sensitivity Analyses Rationale:

- Censoring: To address potential misclassification bias, we explored a scenario that censors those individuals who added HCQ or azithromycin as a treatment during the follow-up window. While this is not recommended in practice, we wanted to illustrate that any study which employs this approach is likely to see biased results.
- 24-hr window: In order to examine the effect of using a 48-hour exposure assessment period prior to starting follow-up, we performed analyses using a shorter, 24-hour period. This also allowed us to determine whether the timing of initiating HCQ (with or without Azithromycin) affected the results.
- Excl. Azith: In order to more accurately estimate the effects of HCQ, we conducted an analysis removing all individuals exposed to Azithromycin alone in the 48-hour exposure window. A propensity model for three treatments (rather than four) would better balance confounders over the HCQ and control groups, thereby improving accuracy of the estimate HCQ effect.
- Lab+ only: We performed one analysis restricting the cohort to only individuals with a positive laboratory SARS-CoV-2 PCR test in the EHR, given that most studies and hospitals use this case definition, solely, and we would like our results to be generalizable.
- Index before May: As the last HCQ initiation amongst those hospitalized with COVID-19 occurred on April 30, 2020, in our sample, we considered a scenario removing any individuals hospitalized after that date, to ensure that the HCQ unexposed comparators represent the appropriate counterfactual (positivity assumption).
- Index after March 30: To assess whether FDA and PBM guidelines for EUA timing made a difference, we restricted the primary cohort to individuals hospitalized after March 30, 2020. This analysis also poses the opportunity to address potential positivity violations in the earlier weeks of the pandemic, before HCQ usage rose.
- Excl. Alt Trt: Similar to the approach taken by Sbidian *et al*.[2], we looked at the effect of restricting the sample to those who were not on other inpatient COVID-19 treatments in the same exposure window. These included dexamethasone, lopinavir/ritonavir, tocilizumab and remdesivir. This is another positivity assumption analysis, as the RCT protocols were listing other COVID-19 treatments as contraindications.
- No ICU: At the start of the pandemic, individuals were often admitted to the ICU for the purposes of negative pressure isolation, which is why we did not explore this end-point as an outcome. Similarly, we did not adjust the propensity or survival models for ICU, as the group was thought to be overly heterogeneous. To better understand whether ICU additionally confounded the relationship between HCQ use and the two outcomes, we were interested in those individuals that were not admitted to the ICU within the first 48 hours of hospitalization, or the exposure window.
- PM: For the primary analysis, we selected parameters that were clinically relevant, and selected those that had at least two individuals with a feature in the HCQ group. We also explored a series of sensitivity analyses with different combinations of parameters in the propensity score model. These would be interpreted as the confounders that were observed and needing balance. A complete list of variables in the propensity models can be found in Table s1. For the sensitivity analyses, we did the following:
    1. We initially included station size as a potential confounder and possible determinant of treatment choice. In sensitivity analyses, we removed station size from the list as well as having models with quartile of station size in the model.
    2. To account for changing indications for treatment over time, we initially included calendar week as a predictor and have removed it in sensitivity analyses.

3. We initially included all risk factors thought to determine the choice of treatment. In sensitivity analyses, we removed conditions where any treatment arm had fewer than 2 subjects with the condition, which included lupus, MS, and severe liver disease.

- DR: After the first series of primary analyses, we observed some remaining imbalance in two variables, week and total station size. In order to account for residual confounding, we considered a post-hoc doubly-robust method, employed by McCaffrey et al[3], of adding imbalanced variables into the outcome model. The following final models were evaluated:
    1. including total station size as a covariate in the Cox model
    2. including week as a covariate in the Cox model
    3. including total station size and week as covariates in the Cox model
    4. stratify the Cox model by VA station - allows for different baseline hazards by station
    5. stratify the Cox model by VA station and adjust for week as a covariate

Table s6. Case Counts and Adjusted Hazard Ratios for Sensitivity Analyses of Mortality

	Neither drug	Azithromycin alone	Hydroxychloroquine alone	Hydroxychloroquine + Azithromycin
Primary Analysis				
N exposed	770	342	228	429
Cases/Person-Days	141/20376	56/9174	49/5853	90/11153
HR (95% CI)	1 (ref)	0.90 (0.64, 1.27)	1.21 (0.82, 1.76)	1.22 (0.91, 1.63)
Censoring at change*				
Cases/Person-Days	96/17926	36/7261	39/5544	90/11153
HR (95% CI)	1 (ref)	1.03 (0.68, 1.57)	1.42 (0.92, 2.18)	1.63 (1.18, 2.25)
No Azithromycin alone*				
Cases/Person-Days	141/20376	-	49/5853	90/11153
HR (95% CI)	1 (ref)	-	1.2 (0.82, 1.75)	1.24 (0.92, 1.65)
24-hour exposure window				
N exposed	1008	463	228	330
Cases/Person-Days	181/26719	79/12266	49/5832	69/8682
HR (95% CI)	1 (ref)	0.96 (0.71, 1.31)	1.24 (0.81, 1.88)	1.15 (0.81, 1.64)
Lab positive only				
N exposed	724	339	221	421
Cases/Person-Days	131/19192	55/9109	47/5679	87/10984
HR (95% CI)	1 (ref)	0.92 (0.65, 1.3)	1.19 (0.8, 1.77)	1.18 (0.87, 1.6)
Index dates before May 1				
N exposed	726	338	228	429
Cases/Person-Days	139/19098	56/9054	49/5854	90/11153
HR (95% CI)	1 (ref)	0.9 (0.64, 1.27)	1.19 (0.81, 1.73)	1.18 (0.88, 1.58)
Index dates after March 30				
N exposed	601	178	174	265
Cases/Person-Days	105/15991	28/4790	35/4505	57/6838
HR (95% CI)	1 (ref)	0.78 (0.47, 1.30)	1.18 (0.75, 1.85)	1.41 (0.98, 2.03)
Removing alternate treatment individuals				
N exposed	749	337	223	412
Cases/Person-Days	136/19854	55/9051	47/5752	86/10703
HR (95% CI)	1 (ref)	0.88 (0.62, 1.26)	1.15 (0.77, 1.73)	1.24 (0.91, 1.69)
Removing individuals admitted to ICU within 48-hour window				
N exposed	636	265	187	305
Cases/Person-Days	107/17021	37/7242	36/4911	48/8227
HR (95% CI)	1 (ref)	0.87 (0.57, 1.33)	1.11 (0.70, 1.47)	0.99 (0.67, 1.47)
Statistical model sensitivity analyses HR (95% CI)**				
DR1	1 (ref)	0.90 (0.64, 1.27)	1.18 (0.80, 1.72)	1.20 (0.90, 1.62)
DR2	1 (ref)	0.90 (0.64, 1.27)	1.20 (0.82, 1.76)	1.20 (0.89, 1.62)
DR3	1 (ref)	0.90 (0.64, 1.27)	1.17 (0.80, 1.72)	1.19 (0.88, 1.61)
DR4	1 (ref)	1.08 (0.75, 1.55)	1.22 (0.82, 1.83)	1.43 (1.02, 1.99)
DR5	1 (ref)	1.05 (0.73, 1.52)	1.21 (0.81, 1.81)	1.38 (0.99, 1.93)
PM1	1 (ref)	0.89 (0.62, 1.26)	1.23 (0.84, 1.80)	1.28 (0.95, 1.72)
PM2	1 (ref)	0.93 (0.64, 1.34)	1.21 (0.80, 1.83)	1.22 (0.89, 1.66)
PM3	1 (ref)	0.90 (0.64, 1.27)	1.21 (0.83, 1.76)	1.21 (0.90, 1.62)
PM4	1 (ref)	0.90 (0.64, 1.27)	1.20 (0.82, 1.76)	1.21 (0.90, 1.62)
PM5	1 (ref)	0.89 (0.63, 1.27)	1.13 (0.76, 1.69)	1.28 (0.95, 1.72)

PM: Propensity model; DR: Doubly-robust; CI: Confidence interval

*Number exposed the same as the primary analysis.

**Number exposed and cases/person-days are the same as the primary analysis for DR and PM analyses.

DR1: outcome = trt + tot_station; DR2: outcome = trt + week; DR3: outcome = trt + week + tot_station; DR4: outcome = trt + strata(station); DR5: outcome = trt + strata(station) + week

PM1: excluding tot_station; PM2: excluding tot_station and week; PM3: adding tt_admit; PM4: kitchen sink; PM5: station quartile instead of size

Table s7. Case Counts and Adjusted Hazard Ratios for Sensitivity Analyses of Intubation

	Neither drug	Azithromycin alone	Hydroxychloroquine alone	Hydroxychloroquine + Azithromycin
Primary Analysis				
N exposed	770	342	228	429
Cases/Person-Days	69/7241	39/2625	32/1897	64/3370
HR (95% CI)	1 (ref)	1.03 (0.66, 1.61)	1.33 (0.82, 2.15)	1.55 (1.07, 2.24)
Censoring at change*				
Cases/Person-Days	29/6629	19/2236	21/1840	64/3370
HR (95% CI)	1 (ref)	1.65 (0.85, 3.2)	2.57 (1.35, 4.89)	4.05 (2.48, 6.61)
No Azithromycin alone*				
Cases/Person-Days	69/7241	-	32/1897	64/3370
HR (95% CI)	1 (ref)	-	1.44 (0.89, 2.34)	1.63 (1.12, 2.35)
24-hour window				
N exposed	1008	463	228	330
Cases/Person-Days	101/8373	70/3187	40/1583	54/2391
HR (95% CI)	1 (ref)	1.25 (0.87, 1.78)	1.42 (0.86, 2.33)	1.37 (0.90, 2.09)
Lab positive only				
N exposed	724	339	221	421
Cases/Person-Days	67/6783	39/2587	31/1838	64/3319
HR (95% CI)	1 (ref)	1.03 (0.66, 1.61)	1.28 (0.78, 2.1)	1.51 (1.04, 2.2)
Index dates before May 1				
N exposed	726	338	228	429
Cases/Person-Days	69/6872	39/2578	32/1897	64/3370
HR (95% CI)	1 (ref)	1.05 (0.67, 1.63)	1.31 (0.81, 2.12)	1.54 (1.07, 2.22)
Index dates after March 30				
N exposed	601	178	174	265
Cases/Person-Days	42/5860	13/1494	20/1533	33/2137
HR (95% CI)	1 (ref)	1.07 (0.52, 2.20)	1.62 (0.87, 3.01)	2.11 (1.27, 3.51)
Removing alternate treatment individuals				
N exposed	749	337	223	412
Cases/Person-Days	67/7034	39/2576	31/1848	60/3216
HR (95% CI)	1 (ref)	1.04 (0.66, 1.64)	1.27 (0.76, 2.11)	1.49 (1.01, 2.2)
Removing individuals admitted to ICU within 48-hour window				
N exposed	636	265	187	305
Cases/Person-Days	48/5934	16/2070	22/1537	26/2360
HR (95% CI)	1 (ref)	0.53 (0.26, 1.09)	1.15 (0.61, 2.17)	0.97 (0.55, 1.69)
Statistical model sensitivity analyses HR (95% CI)**				
DR1	1 (ref)	1.03 (0.66, 1.61)	1.34 (0.82, 2.17)	1.55 (1.07, 2.24)
DR2	1 (ref)	0.96 (0.62, 1.50)	1.30 (0.80, 2.10)	1.37 (0.95, 1.99)
DR3	1 (ref)	0.96 (0.62, 1.51)	1.30 (0.80, 2.12)	1.38 (0.95, 1.99)
DR4	1 (ref)	1.08 (0.67, 1.74)	1.24 (0.74, 2.08)	1.60 (1.06, 2.43)
DR5	1 (ref)	0.95 (0.59, 1.54)	1.23 (0.73, 2.06)	1.42 (0.93, 2.15)
PM1	1 (ref)	1.05 (0.67, 1.64)	1.28 (0.78, 2.09)	1.43 (0.98, 2.09)
PM2	1 (ref)	1.23 (0.78, 1.94)	1.25 (0.73, 2.15)	1.39 (0.93, 2.07)
PM3	1 (ref)	1.04 (0.67, 1.62)	1.33 (0.82, 2.16)	1.56 (1.08, 2.25)
PM4	1 (ref)	1.05 (0.68, 1.64)	1.34 (0.82, 2.18)	1.56 (1.08, 2.25)
PM5	1 (ref)	1.08 (0.69, 1.69)	1.24 (0.75, 2.07)	1.47 (1.01, 2.15)

PM: Propensity model; DR: Doubly-robust; CI: Confidence interval

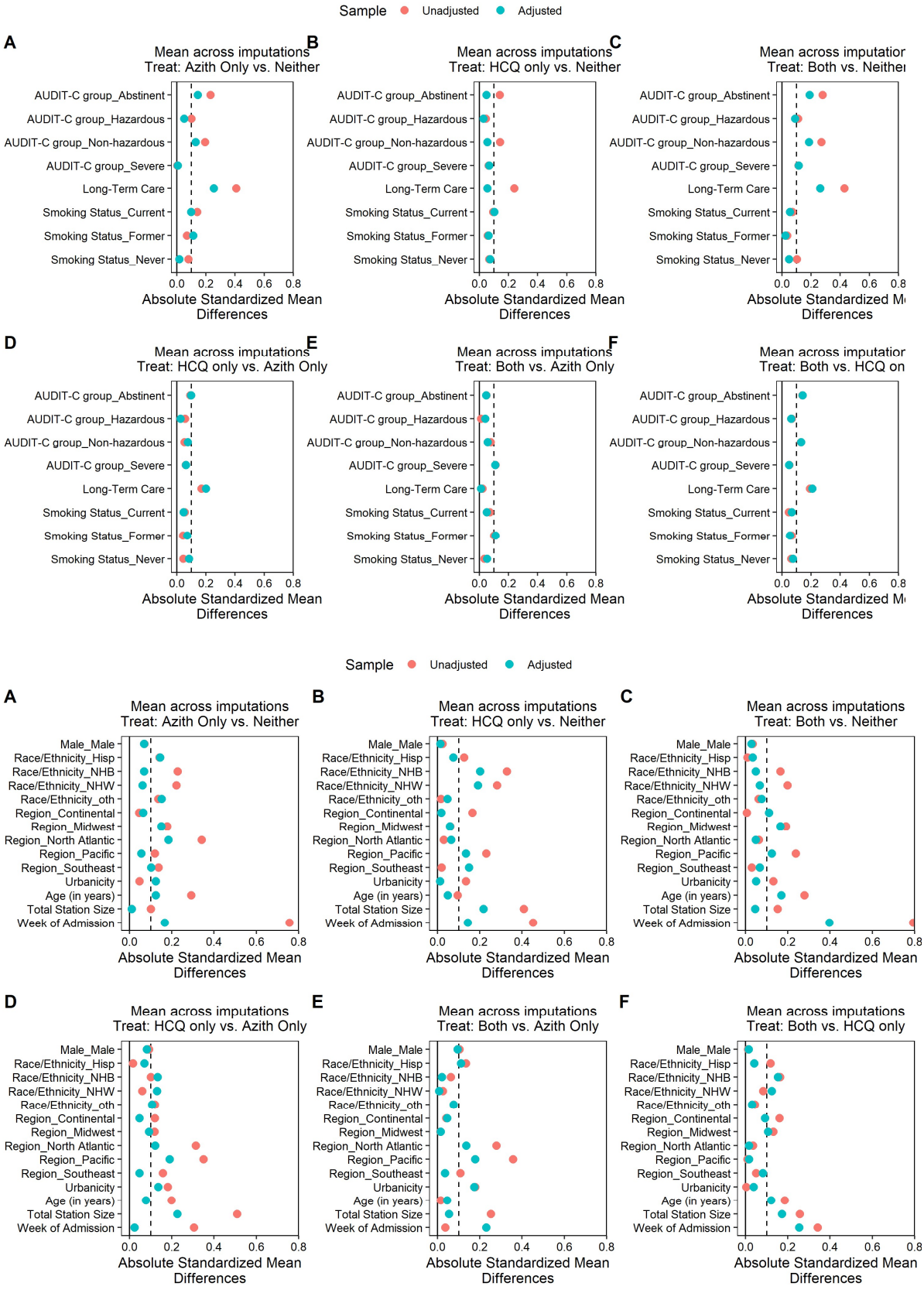
*Number exposed the same as the primary analysis.

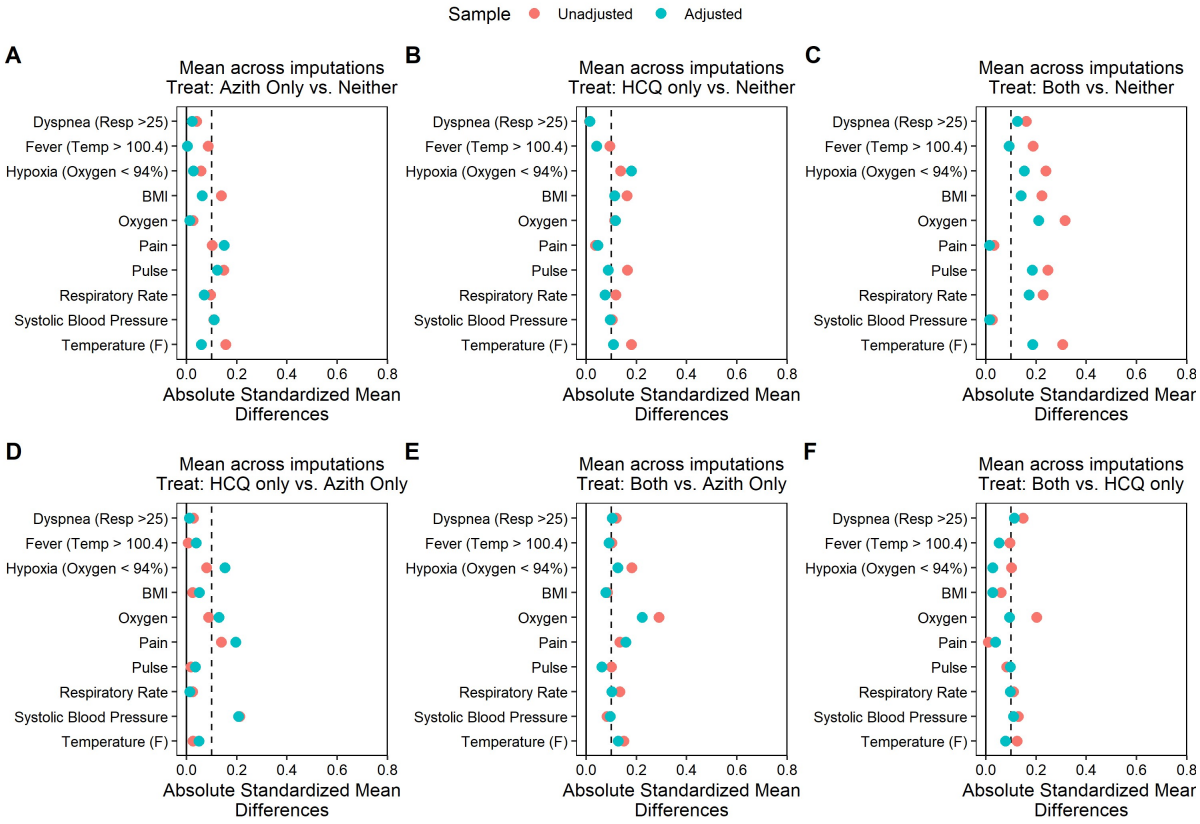
**Number exposed and cases/person-days are the same as the primary analysis for DR and PM analyses.

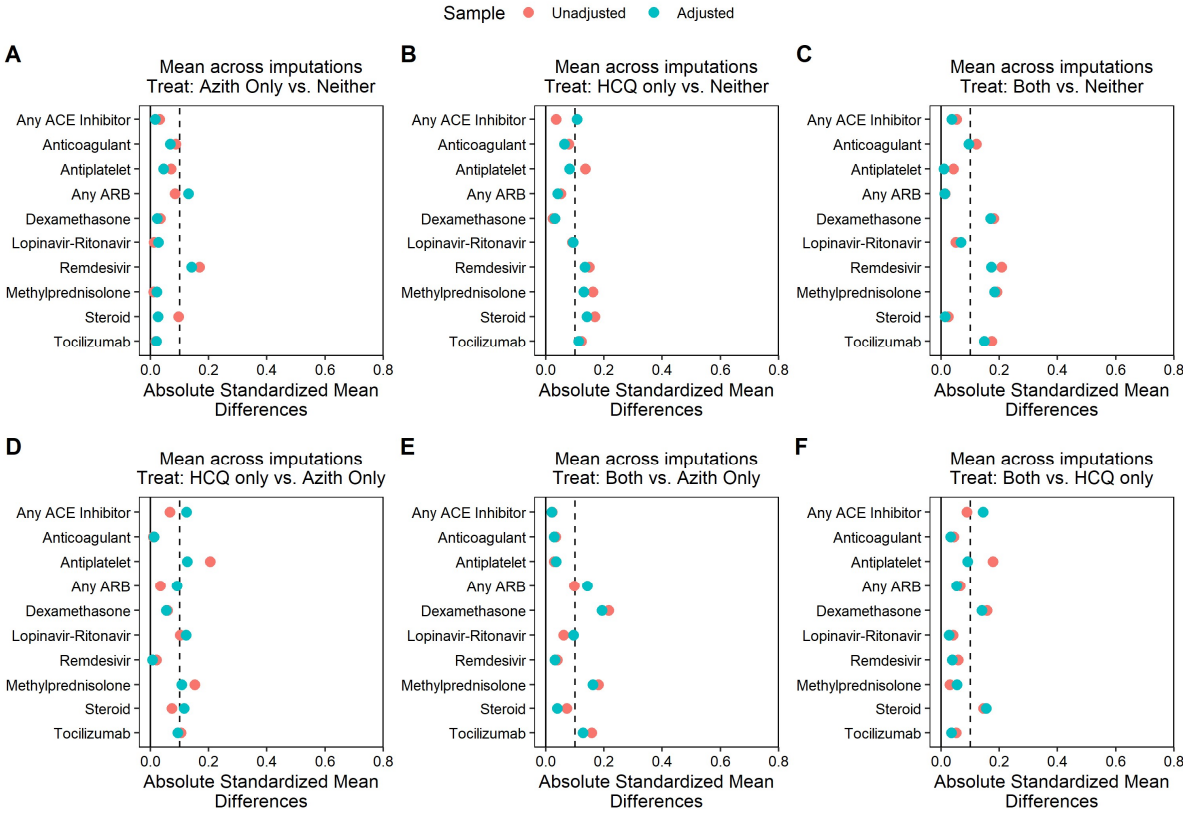
DR1: outcome = trt + tot_station; DR2: outcome = trt + week; DR3: outcome = trt + week + tot_station; DR4: outcome = trt + strata(station); DR5: outcome = trt + strata(station) + week

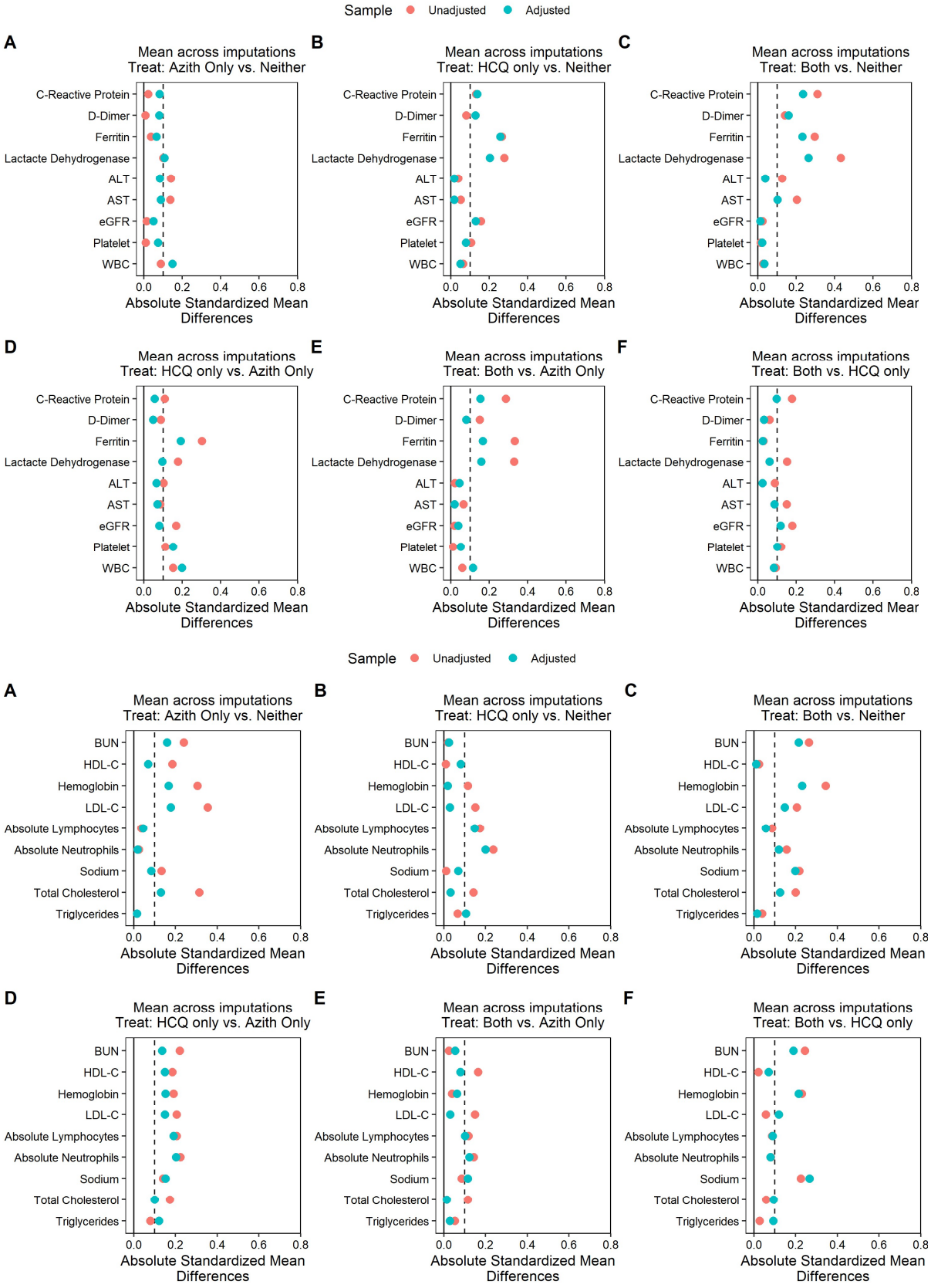
PM1: excluding tot_station; PM2: excluding tot_station and week; PM3: adding tt_admit; PM4: kitchen sink; PM5: station quartile instead of size

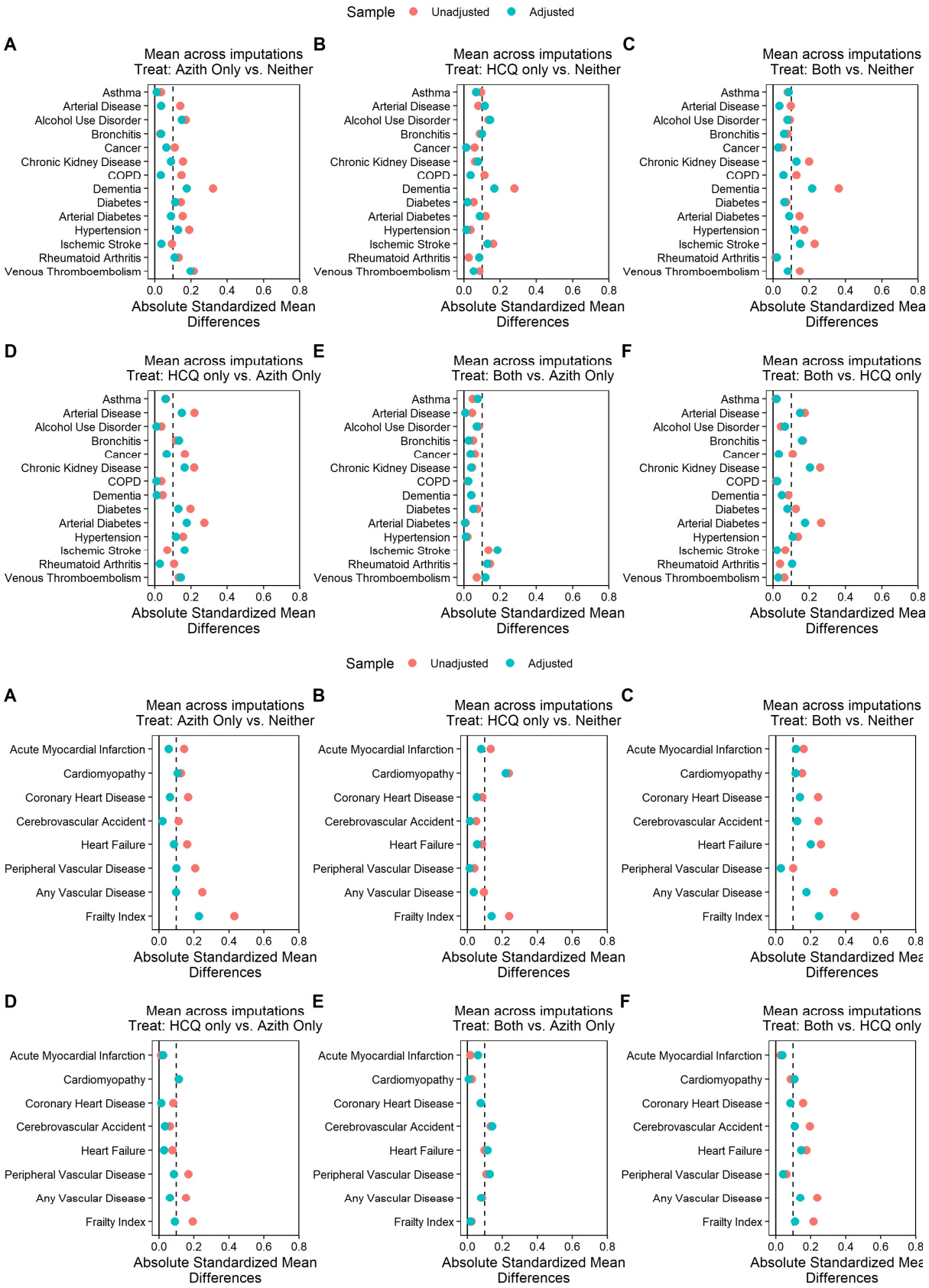
Figure s1. Love Plots for Primary Analysis Balance Assessment




Sample
Unadjusted
Adjusted
A
Mean across imputations
Treat: Azith Only vs. Neither
B
Mean across imputations
Treat: HCQ only vs. Neither
C
Mean across imputations
Treat: Both vs. Neither
D
Mean across imputations
Treat: HCQ only vs. Azith Only
E
Mean across imputations
Treat: Both vs. Azith Only
F
Mean across imputations
Treat: Both vs. HCQ only
Dyspnea (Resp >25)
Fever (Temp > 100.4)
Hypoxia (Oxygen < 94%)
BMI
Oxygen
Pain
Pulse
Respiratory Rate
Systolic Blood Pressure
Temperature (F)
0.0
0.2
0.4
0.6
0.8
Absolute Standardized Mean Differences


Sample
Unadjusted
Adjusted
A
Mean across imputations
Treat: Azith Only vs. Neither
B
Mean across imputations
Treat: HCQ only vs. Neither
C
Mean across imputations
Treat: Both vs. Neither
D
Mean across imputations
Treat: HCQ only vs. Azith Only
E
Mean across imputations
Treat: Both vs. Azith Only
F
Mean across imputations
Treat: Both vs. HCQ only
Any ACE Inhibitor
Anticoagulant
Antiplatelet
Any ARB
Dexamethasone
Lopinavir-Ritonavir
Remdesivir
Methylprednisolone
Steroid
Tocilizumab
0.0
0.2
0.4
0.6
0.8
Absolute Standardized Mean Differences


Sample Unadjusted Adjusted
A
Mean across imputations
Treat: Azith Only vs. Neither
B
Mean across imputations
Treat: HCQ only vs. Neither
C
Mean across imputations
Treat: Both vs. Neither
D
Mean across imputations
Treat: HCQ only vs. Azith Only
E
Mean across imputations
Treat: Both vs. Azith Only
F
Mean across imputations
Treat: Both vs. HCQ only
C-Reactive Protein
D-Dimer
Ferritin
Lactacte Dehydrogenase
ALT
AST
eGFR
Platelet
WBC
0.0 0.2 0.4 0.6 0.8
Absolute Standardized Mean Differences
Sample Unadjusted Adjusted
A
Mean across imputations
Treat: Azith Only vs. Neither
B
Mean across imputations
Treat: HCQ only vs. Neither
C
Mean across imputations
Treat: Both vs. Neither
D
Mean across imputations
Treat: HCQ only vs. Azith Only
E
Mean across imputations
Treat: Both vs. Azith Only
F
Mean across imputations
Treat: Both vs. HCQ only
BUN
HDL-C
Hemoglobin
LDL-C
Absolute Lymphocytes
Absolute Neutrophils
Sodium
Total Cholesterol
Triglycerides
0.0 0.2 0.4 0.6 0.8
Absolute Standardized Mean Differences


Sample
Unadjusted
Adjusted
A
Mean across imputations
Treat: Azith Only vs. Neither
B
Mean across imputations
Treat: HCQ only vs. Neither
C
Mean across imputations
Treat: Both vs. Neither
D
Mean across imputations
Treat: HCQ only vs. Azith Only
E
Mean across imputations
Treat: Both vs. Azith Only
F
Mean across imputations
Treat: Both vs. HCQ only
Asthma
Arterial Disease
Alcohol Use Disorder
Bronchitis
Cancer
Chronic Kidney Disease
COPD
Dementia
Diabetes
Arterial Diabetes
Hypertension
Ischemic Stroke
Rheumatoid Arthritis
Venous Thromboembolism
0.0
0.2
0.4
0.6
0.8
Absolute Standardized Mean Differences
Sample
Unadjusted
Adjusted
A
Mean across imputations
Treat: Azith Only vs. Neither
B
Mean across imputations
Treat: HCQ only vs. Neither
C
Mean across imputations
Treat: Both vs. Neither
D
Mean across imputations
Treat: HCQ only vs. Azith Only
E
Mean across imputations
Treat: Both vs. Azith Only
F
Mean across imputations
Treat: Both vs. HCQ only
Acute Myocardial Infarction
Cardiomyopathy
Coronary Heart Disease
Cerebrovascular Accident
Heart Failure
Peripheral Vascular Disease
Any Vascular Disease
Frailty Index
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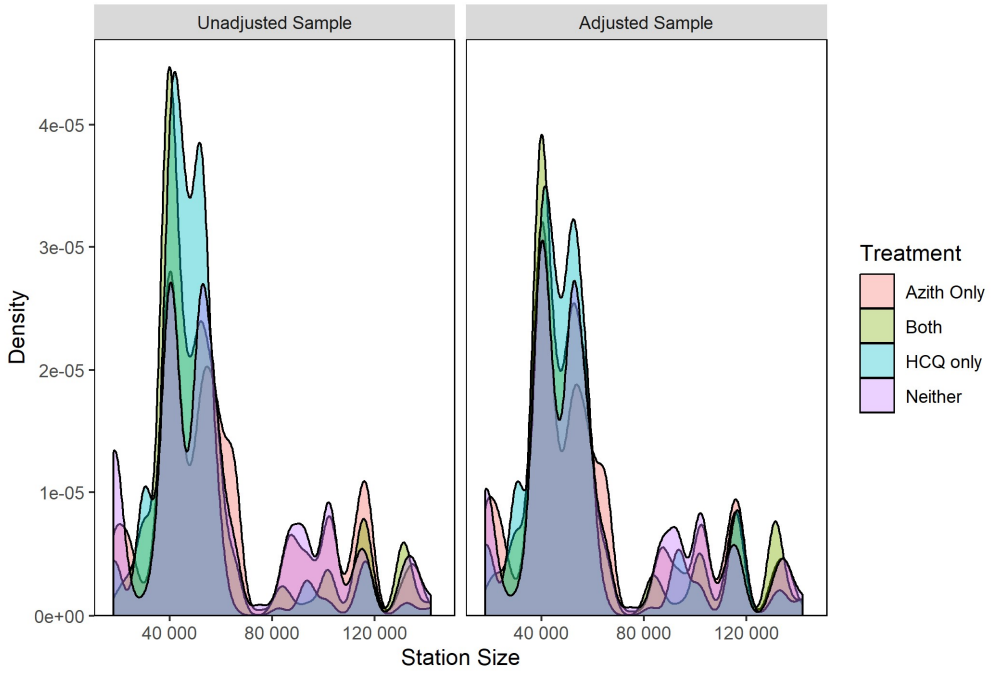
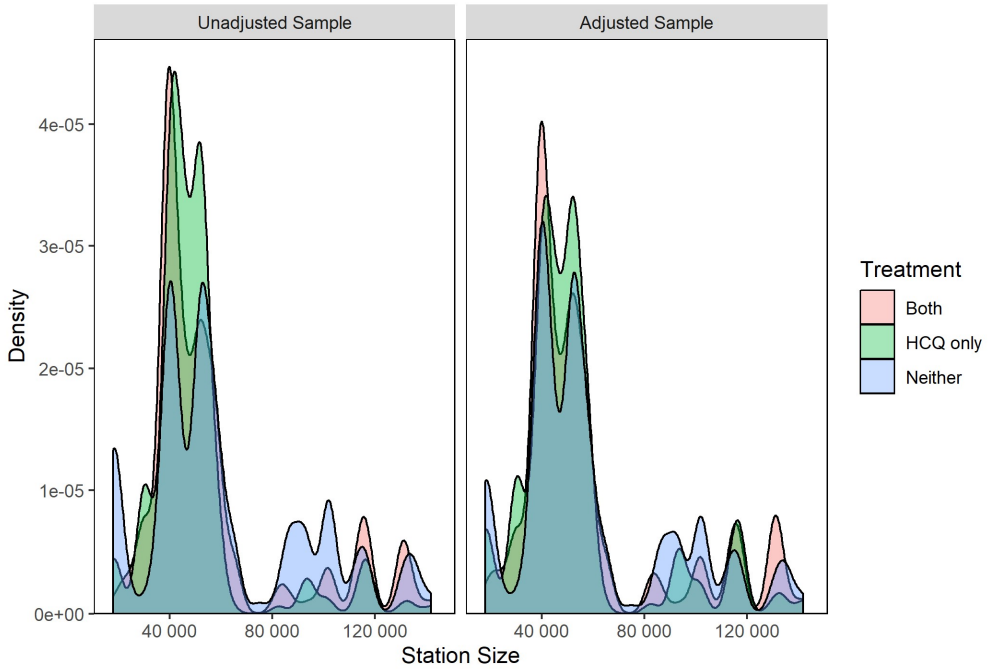
0.2
0.4
0.6
0.8
Absolute Standardized Mean Differences

Figure s2. Balance Plots for Key Variables by Sensitivity Analysis

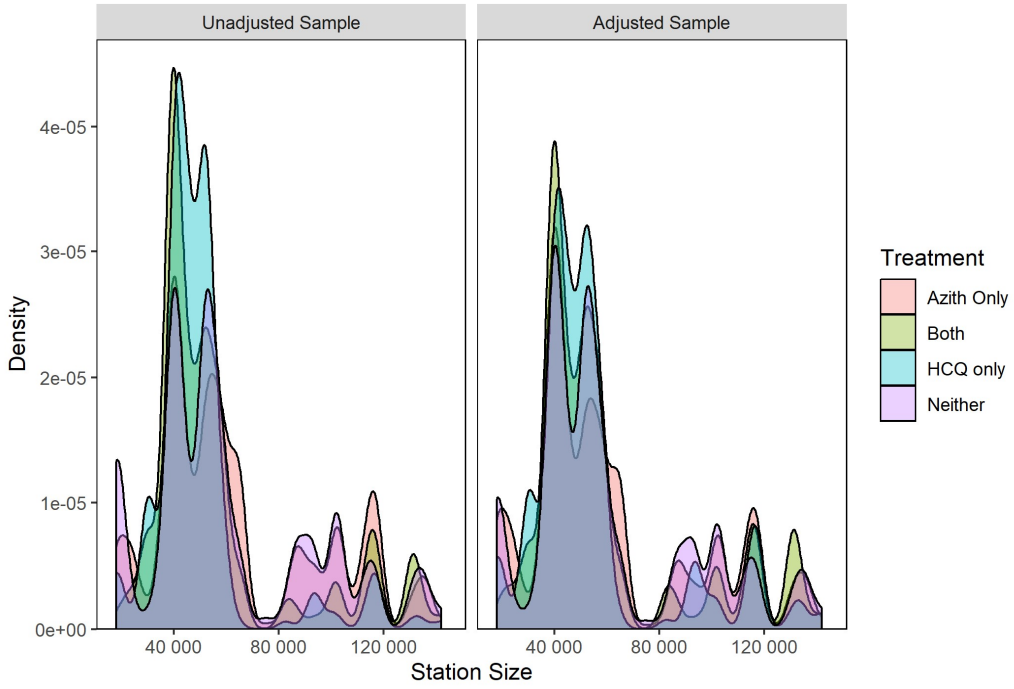
Station Size Balance Plot for Primary Analysis



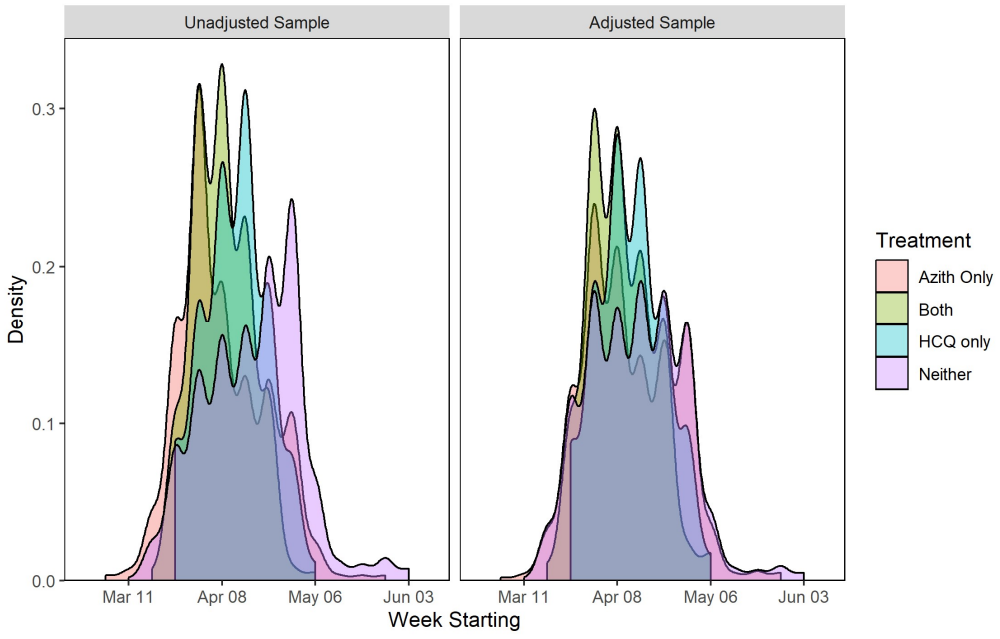
Station Size Balance Plot for Analysis Excluding Azithromycin Alone Group from GBM



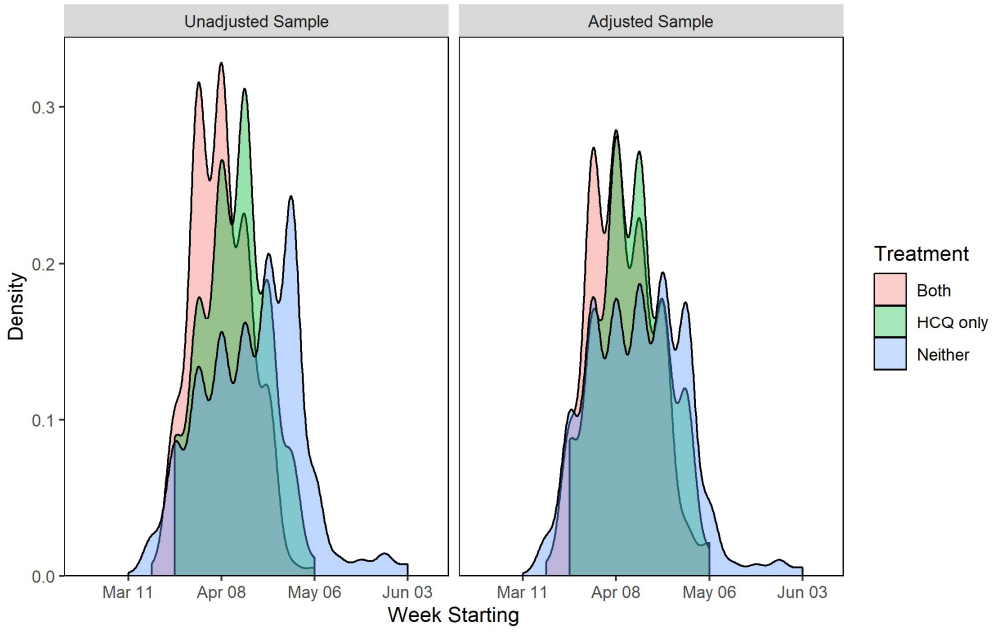
Station Size Balance Plot for Kitchen Sink Variable list



Week of Admission Balance Plot for Primary Analysis



Week of Admission Balance Plot for Analysis Excluding Azithromycin Alone Group from GBM



Week of Admission Balance Plot for Kitchen Sink Variable List

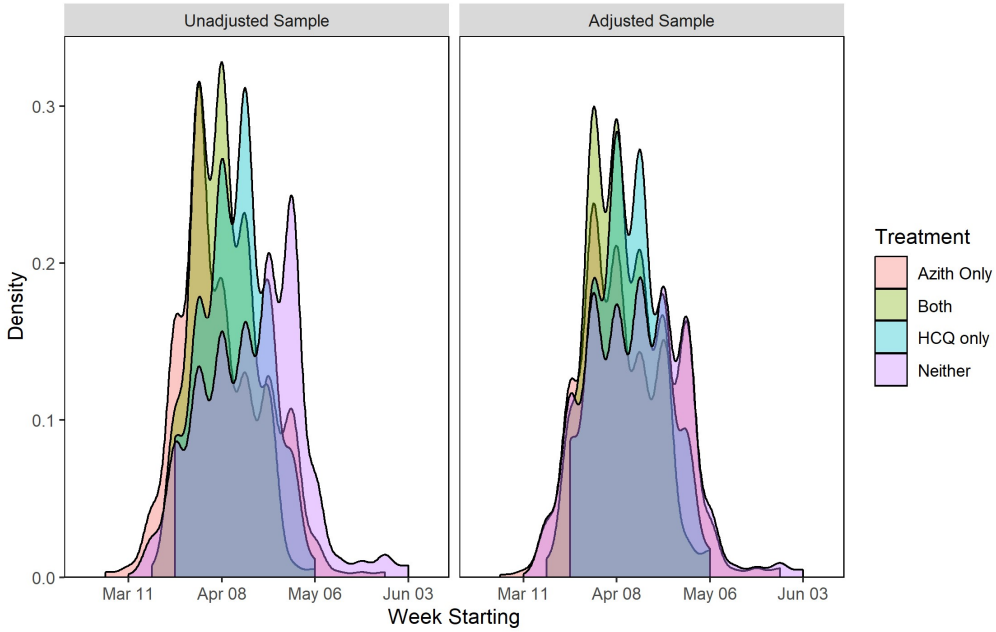
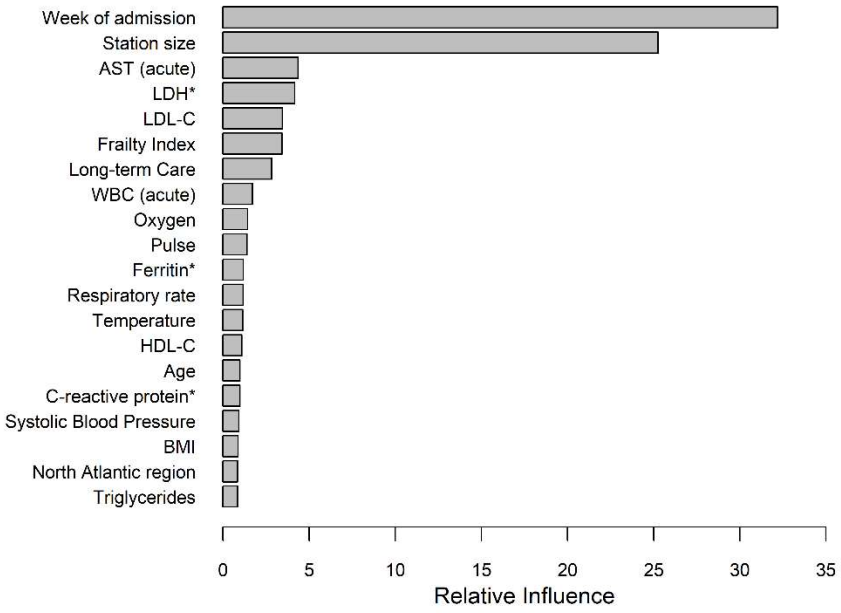


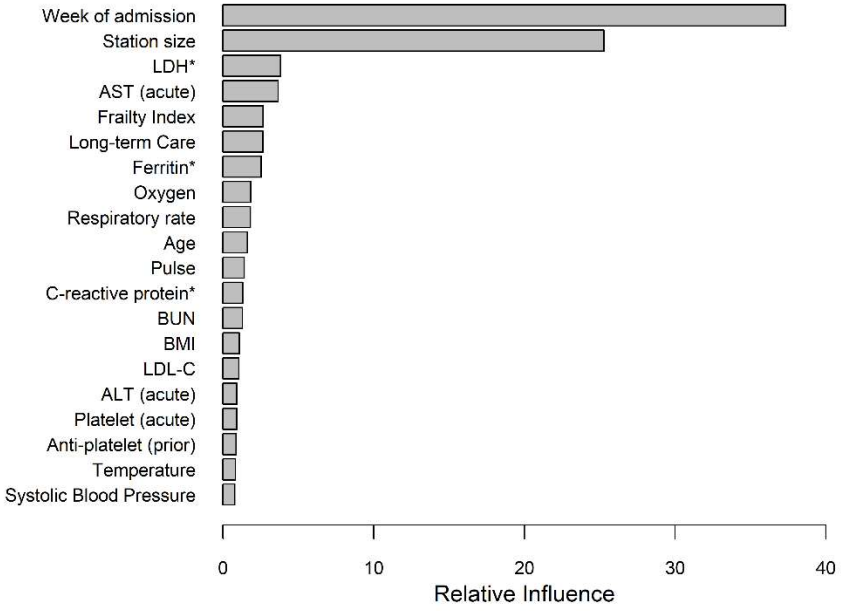
Figure s3. Variable Importance/Relative Influence Across Selected Sensitivity Analyses

Footnotes and abbreviations all the same as Figure 4 in main manuscript text.

Top 20 Variables from Primary Analysis



Top 20 Variables when Excluding Azithromycin Alone Group



Top 20 Variables from the Kitchen Sink Variables List

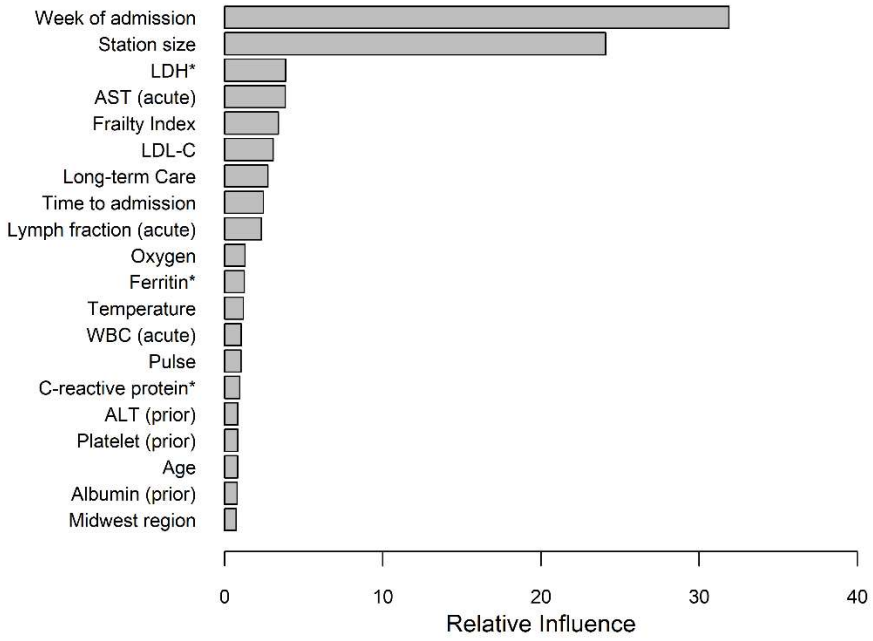
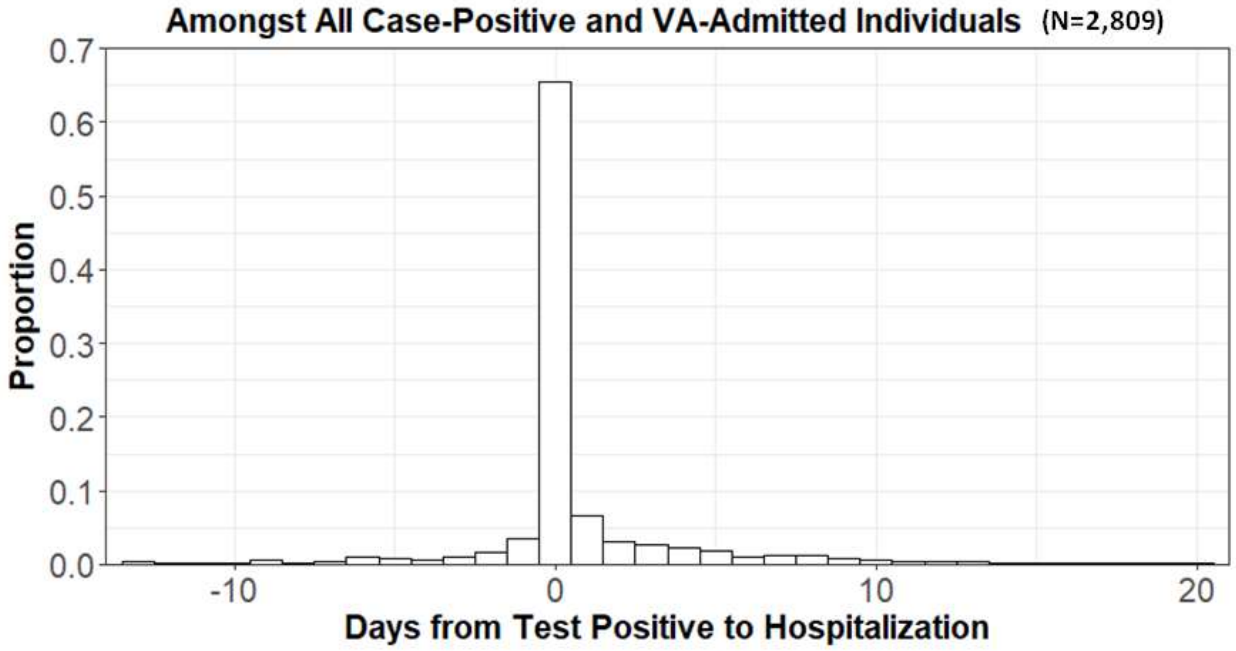


Figure s4. Time Between First Positive SARS-CoV-2 Test to Hospitalization



Between March 1, 2020 and May 1, 2020, the average time between sample collection and testing positive was 2.1 days. In our analytic sample, 89% had a primary ICD-10 code for COVID-19 listed, of which 87% had a corresponding date within 2 weeks of their index date. To account for instances when someone may have entered the hospital due to another illness with a later diagnosis of COVID-19, we restricted our hospitalized sample to only those who were admitted on or after their first diagnosis date. The following figure shows the distribution of days between first positive test and hospital admission, with less than 1% of the sample being hospitalized after one month following testing positive. The majority of our sample was admitted on the same day or within a week of their first positive SARS-CoV-2 test, strongly suggesting that the individuals were hospitalized and treated for COVID-19.

Supplement Bibliography

1. Coyle, G.A. and M. Heinen, *Evolution of BCMA within the Department of Veterans Affairs.* Nurs Adm Q, 2005. **29**(1): p. 32-8.
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3. McCaffrey, D.F., et al., *A tutorial on propensity score estimation for multiple treatments using generalized boosted models.* Stat Med, 2013. **32**(19): p. 3388-414.