Efficacy of hydroxychloroquine and tocilizumab in patients with COVID-19: A single-center retrospective chart review

Sohaib Roomi, Waqas Ullah, Faizan Ahmed, Soban Farooq, Usama Sadiq, Asad Chohan, Munnam Jafar, Maryum Saddique, Shristi Khanal, Robert Watson, Margot Boigon

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Sohaib RoomiMD, ; Waqas Ullah; Faizan Ahmed; Soban Farooq; Usama Sadiq; Asad Chohan; Munnam JafarMD, ; Maryum SaddiqueMD, ; Shristi Khanal; Robert Watson; Margot Boigon

Corresponding Author:
Sohaib RoomiMD,
Phone: +12674666985
Email: roomigujjar251@gmail.com

Abstract

Background: During the initial phases of the coronavirus disease 2019 (COVID-19)pandemic, there was an unfounded fervor surrounding the use of hydroxychloroquine (HCQ) and tocilizumab(TCZ): however, evidence on their efficacy and safety have been controversial.

Objective: We hypothesize that HCQ and TCZ use would be associated with a reduction in end-points of in-hospital mortality, upgrade to intensive care unit, mechanical ventilation, or acute renal failure necessitating dialysis. The objective of the study is to validate our hypothesis.

Methods: A retrospective cohort study was performed to determine the impact of HCQ and TCZ use on hard clinical outcomes during hospitalization. Independent t-test and multivariate logistic regression analysis were performed to calculate mean differences and adjusted odds ratios (aOR) with its 95% confidence interval (CI), respectively.

Results: A total of 176 hospitalized patients with confirmed COVID-19 were included. Patients were divided into two comparison groups HCQ vs. no-HCQ (n=144 vs. 32) and TCZ vs. no-TCZ (n=32 vs. n-144), respectively. The mean age, baseline comorbidities and other medications used during hospitalization were comparable among all the groups. The unadjusted odds ratio for patients upgraded to a higher level of care (OR 2.6, 95% CI 1.19-5.69, p=0.003) and reduction in C-reactive protein(CRP) level at day 7 of hospitalization (21% vs. 56%, OR 0.21, 95% CI 0.08-0.55, p=0.002) were significantly higher in the TCZ group compared to the control group. There was no significant difference in the odds of in-hospital mortality, upgrade to intensive medical care, need for invasive mechanical ventilation (IVM), acute kidney failure (AKI) necessitating dialysis, or discharge from the hospital after recovery in both TCZ and HCQ groups compared to their respective control groups. Adjusted odds ratios controlled for baseline comorbidities and medications closely followed the unadjusted estimates.

Conclusions: In this cohort of patients with COVID-19, neither TCZ nor HCQ offered a significant reduction in in-hospital mortality, upgrade to intensive medical care, invasive mechanical ventilation, or acute renal failure needing dialysis. These results are similar to the recently published preliminary results of HCQ arm of Recovery trial which showed no clinical benefit from the use of HCQ in hospitalized patients with COIVD-19 while TCZ arm of recovery trial is ongoing. Double-blinded randomized controlled trials are the need of the hour to further evaluate the impact of these drugs in bigger patient samples so that data-driven guidelines can be deduced to combat this global pandemic.

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Efficacy of hydroxychloroquine and tocilizumab in patients with COVID-19: A single-center retrospective chart review

Abstract:

Background:

During the initial phases of the coronavirus disease 2019 (COVID-19) pandemic, there was an unfounded fervor surrounding the use of hydroxychloroquine (HCQ) and tocilizumab(TCZ): however, evidence on their efficacy and safety have been controversial. The purpose of this study is to evaluate the overall clinical effectiveness of HCQ and TCZ in patients with COVID-19.

Methods:

A retrospective cohort study was performed to determine the impact of HCQ and TCZ use on hard clinical outcomes during hospitalization. Independent t-test and multivariate logistic regression analysis were performed to calculate mean differences and adjusted odds ratios (aOR) with its 95% confidence interval (CI), respectively.

Results:

A total of 176 hospitalized patients with confirmed COVID-19 were included. Patients were divided into two comparison groups HCQ vs. no-HCQ (n=144 vs. 32) and TCZ vs. no-TCZ (n=32 vs. n-144), respectively. The mean age, baseline comorbidities and other medications used during hospitalization were uniformly distributed among all the groups. (Insignificant P-values in table 1) The unadjusted odds ratio for patients upgraded to a higher level of care (OR 2.6, 95% CI 1.19-5.69, *P*=.003) and reduction in C-reactive protein(CRP) level at day 7 of hospitalization (21% vs. 56%, OR 0.21, 95% CI 0.08-0.55, *P*=.002) were significantly higher in the TCZ group compared to the control group. There was no significant difference in the odds of in-hospital mortality, upgrade to intensive medical care, need for invasive mechanical ventilation (IVM), acute kidney failure (AKI) necessitating dialysis, or discharge from the hospital after recovery in both TCZ and HCQ groups compared to their respective control groups. Adjusted odds ratios controlled for baseline comorbidities and medications closely followed the unadjusted estimates. (Table 2, Table 3)

Conclusion:

In this cohort of patients with COVID-19, neither TCZ nor HCQ offered a significant reduction in in-hospital mortality, upgrade to intensive medical care, invasive mechanical ventilation, or acute renal failure needing dialysis. These results are similar to the recently published preliminary results of HCQ arm of Recovery trial which showed no clinical benefit from the use of HCQ in hospitalized patients with COIVD-19 while TCZ arm of recovery trial is ongoing. Double-blinded randomized controlled trials are the need of the hour to further evaluate the impact of these drugs in bigger patient samples so that data-driven guidelines can be deduced to combat this global pandemic.

Introduction:

As of July 23, 2020, more than 4 million cases and one hundred forty thousand deaths from the novel coronavirus disease 2019 (COVID 19) have been reported in the United States. There is currently no proven medical therapy for this disease except low dose dexamethasone and remdesivir based on preliminary evidence with the mainstay of treatment being supportive care. [1]Multiple off-label and compassionate use therapies are currently being employed, targeting currently known pathophysiological mechanisms of this novel virus. Increasing social and economic devastation caused by COVID-19 has led the Federal Drug Administration (FDA) to issue Emergency use authorizations (EUA) for various drugs without proven benefits. [2] Although many of these drugs have revealed promising in vitro activity against coronaviridae including acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the translation of these in-vitro effects into clinical efficacy is a matter of debate. While, as physicians, we tend to assume that these drugs will do more good than harm when utilizing them as a last resort to severely ill patients, the fact remains that in the absence of randomized control trials there is no way to reliably judge the impact of these medications. Fortunately, this situation is being remedied, with evidence emerging, initially from China, and more recently from trials in the United States and Europe.

Amongst others, hydroxyquinoline (HCQ) and the interleukin-6 (IL-6) inhibitor, tocilizumab (TCZ) became popular options to treat COVID-19. There is no concrete evidence supporting their use and they were widely adopted across the world based on anecdotal data. Our hospital, following the guidelines of its parent enterprise, permitted the use of HCQ in COVID-19 patients who had respiratory insufficiency as indicated by low oxygen saturation. Similarly, TCZ was widely used in the cohort being studied for the patients meeting criteria for cytokine release syndrome (CRS) during the time frame of this study. The purpose of this study is to evaluate the overall clinical effectiveness of HCQ and TCZ in our hospital. Our study did not reveal a reduction in in-hospital mortality and the results were similar to the preliminary results of the HCQ arm of the Recovery trial which did not reveal a difference in 28-day mortality between HCQ group and usual care group. [3] However, in addition to mortality, we have also evaluated other secondary end-points and hypothesized that HCQ and TCZ use would be associated with a reduction in the end-points of an upgrade to intensive care unit (ICU), need for invasive mechanical ventilation (IMV), acute renal failure necessitating dialysis and reduction in D-dimer and C-reactive protein (CRP) at 7th day of hospitalization.

Methods:

Study design and participants:

This retrospective cohort study included adult inpatients (≥18 years old) from Abington Hospital - Jefferson Health, USA. All patients had a confirmed diagnosis of COVID-19 between March 1, 2020, and May 30, 2020. The study was approved by the Institutional Review Board and the requirement for informed consent was waived by the Research Ethics Committee.

Data collection:

All COVID-19 patients who were admitted to the hospital between March 1, 2020, and May

30, 2020, were included. All the data were extracted from electronic medical records (Sunrise) using a standardized data collection form. All authors contributed to data retrieval and an independent author adjudicated any difference in interpretation between the data extractors. SARS-CoV-2 was detected in respiratory specimens (nasopharyngeal or throat swabs) by real-time qualitative polymerase chain reaction (RT-qPCR) method. Routine blood work included complete blood count, serum electrolytes, renal function test, coagulation profile, serum ferritin, CRP, d-dimer level, lactate dehydrogenase (LDH), and myocardial enzymes (troponin T TnT) on presentation to the hospital and on the day 7 of hospitalization. Baseline comorbidities including hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), chronic obstructive lung disease (COPD) and coronary artery disease (CAD) were also recorded. The criteria of discharge from the hospital after recovery included resolution of fever, absence of symptoms for at least 1 day and substantial clinical or radiological improvement.

Statistical analysis:

A chi-square ($\chi 2$) test was used for comparison of categorical data and Fisher exact test was adopted if the expected count in more than 20% cells was less than 5. Continuous variables were presented as mean and standard deviations (SD) while categorical variables were reported in percentages and proportions. To quantify the association between the dichotomous categorical variables, an unadjusted odds ratio (OR) was obtained using a Cochran-Mantel-Haenszel method. To explore the risk factors and gauge the impact of potential effect modifiers (covariates) on our endpoints, (in-hospital mortality, ICU upgrade, IMV, dialysis, inflammatory marker level) binomial and multinomial logistic regression models were applied. The differences in the baseline comorbidities (DM, HTN, CAD, CKD, COPD) and medication use (HCQ, tocilizumab, remdesivir, therapeutic anticoagulation, steroid) were accounted for to obtain an adjusted odds ratio (aOR) for all outcomes. For normally and abnormally distributed continuous data, an independent sample t-test and Mann-Whitney U test were used, respectively. A one-way analysis of variance (ANOVA) was used to compare differences in the mean of continuous variables for multiple in-hospital complications. A two-sided α of less than 0.05 was considered statistically significant corroborating inference from a 95% confidence interval (CI). Statistical analyses were performed using the SPSS software (version 25, windows).

Results:

Demographics and Baseline Characteristics:

Our study population consisted of 176 patients who were hospitalized and had confirmed COVID-19 infection. All patients were divided into two comparison groups HCQ vs. no-HCQ (n=144 vs. 32) and TCZ vs. no-TCZ (n=32 vs. n-144), respectively. A table and a figure given below depict the underlying comorbidities and other medications used during hospitalization in both comparison groups (Figure 1, Table 1). The mean age in years for HCQ vs. no- HCQ groups was (63.75 vs. 65.87, *P*=.55) while for TCZ vs no-TCZ groups, it was (58.09 vs. 65.48, *P*=2.75) respectively. The most common underlying comorbidities in all the four groups were DM, HTN, CAD, CKD and COPD. Common medications used during hospitalization included steroids, anti-coagulants, HCQ and TCZ. These underlying comorbidities and medications used during hospitalization were non-significantly different between the comparison groups (*P*-value =>.05). The detailed percentages of group-wise comorbidities and demographics are given in Table 1.

Figure 1: Baseline comorbidities and medication use in the HCQ group, TCZ group, and control groups.

The X-axis represents sex, comorbidities, medications, CRP and D-dimer level at presentation
Y-axis represents the percentage of subjects

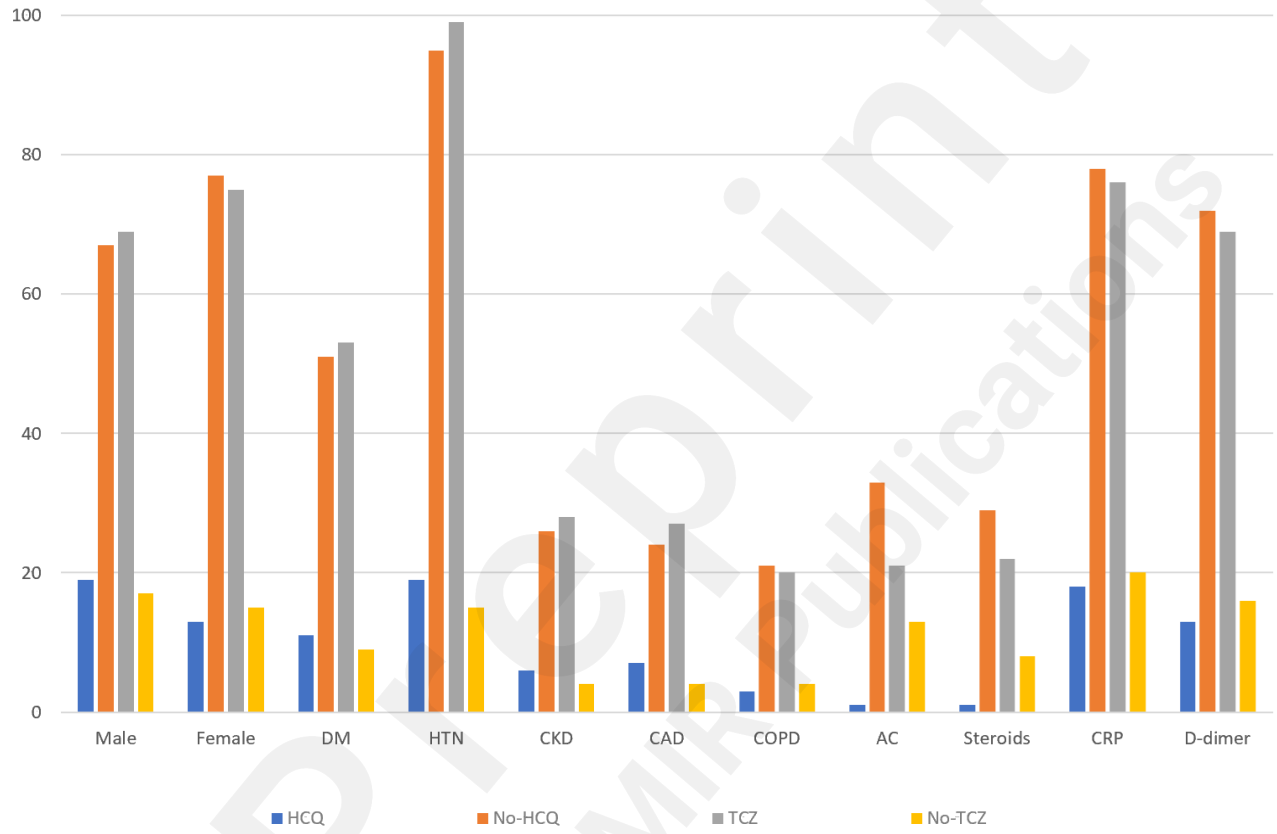

Table 1: Baseline characteristics of the included population across comparison groups.

		No-HCQ	HCQ	Sig	No-TCZ	TCZ	Sig
Age		65.87years	63.75years	P=.55	58.09years	65.48years	P=2.75=
Sex	Male	66 (80.50%)	16 (19.50%)	P=.167	23 (27.70%)	60 (72.30%)	P=.44
	Female	75 (88.20%)	10 (11.80%)		13 (14.90%)	74 (85.10%)	
DM	No	92 (85.20%)	16 (14.80%)	P=.716	23 (21.10%)	86 (78.90%)	P=.974
	Yes	49 (83.10%)	10 (16.90%)		13 (21.30%)	48 (78.70%)	
HTN	No	48 (80.00%)	12 (20.00%)	P=.237	14 (23.30%)	46 (76.70%)	P=.611

	Yes	93 (86.90%)	14 (13.10%)		22 (20.00%)	88 (80.00%)	
CAD	No	114 (82.60%)	24 (17.40%)	P=.16	30 (21.60%)	109 (78.40%)	P=.784
	Yes	27 (93.10%)	2 (6.90%)		6 (19.40%)	25 (80.60%)	
CKD	No	114 (83.80%)	22 (16.20%)	P=.65	28 (20.30%)	110 (79.70%)	P=.557
	Yes	27 (87.10%)	4 (12.90%)		8 (25.00%)	24 (75.00%)	
COPD	No	119 (83.20%)	24 (16.80%)	P=.29	32 (21.90%)	114 (78.10%)	P=.56
	Yes	22 (91.70%)	2 (8.30%)		4 (16.70%)	20 (83.30%)	
Steroids	No	115 (83.30%)	23 (16.70%)	P=.39	32 (22.90%)	108 (77.10%)	P=.247
	Yes	26 (89.70%)	3 (10.30%)		4 (13.30%)	26 (86.70%)	
AC	No	115 (85.80%)	19 (14.20%)	P=.318	25 (18.40%)	111 (81.60%)	P=.075
	Yes	26 (78.80%)	7 (21.20%)		11 (32.40%)	23 (67.60%)	

HCQ: hydroxychloroquine TCZ: tocilizumab Sig: significance DM: diabetes mellitus HTN: hypertension CKD: chronic kidney disease CAD: coronary artery disease COPD: chronic obstructive pulmonary disease AC: anticoagulation

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Odds Ratios of Outcomes:

The table and forest plots given below compares the above-mentioned outcomes between the TCZ group and no TCZ group. (Table 2, Figure 2, Figure 3) As shown, the unadjusted odds ratio for the patients requiring an upgrade to the intensive care unit (ICU) was significantly higher in patients who received TCZ compared to the control group (OR 2.6, 95% CI 1.19-5.69, *P*=.003). Similarly, patients who received TCZ had a significant reduction in the CRP levels at day 7 of hospitalization compared to the control group (21% vs. 56%, OR 0.21, 95% CI 0.08-0.55, *P*=.002). However, this reduction in the inflammatory markers did not translate into clinical benefits. There was no significant difference in the unadjusted odds of in-hospital mortality, invasive mechanical ventilation, acute renal failure necessitating dialysis, and discharge from the hospital after recovery between the two groups. The proportion of high d-dimer levels (>500ng/dL) and elevated CRP (>100ng/dL) on day 7 of hospitalization were also identical between TCZ and non TCZ groups, respectively. However, when we adjusted the observed odds ratios for baseline comorbidities and medications, including DM, HTN, CKD, CAD, COPD, use of anticoagulation at home, therapeutic anticoagulation during the hospital stay, steroid and HCQ use in the TCZ comparison group, the adjusted odds values were consistent with unadjusted odds ratios for all the outcomes except for an upgrade to medial ICU where there was no difference between TCZ group and no TCZ group, contrary to unadjusted odds which revealed more ICU upgrades in the TCZ group compared to no-TCZ group. (Table 2). Forest plots given below reveal the difference in unadjusted and adjusted odds between the TCZ group and the no-TCZ group. (Figure 2, 3)

Table 2: Tocilizumab regression analysis with the outcome

Outcome	TCZ	No TCZ	UOR (95%CI) *	*P*-value	aOR (95%CI) *	*P*-Value
IMV	47	31	1.94 (0.89-4.23)	.14	1.2(0.49-2.9)	.67
Upgrade	50	28	2.6(1.19-5.69)	.03	1.9(0.80-4.5)	.14
Dialysis	6	6	1.13(0.23-5.6)	.79	1.3(0.21-8.3)	.76
Mortality	6	13	0.44(0.97-1.99)	.43	0.28(0.05-1.4)	.13
Discharge	25	38	0.54(0.23-1.3)	.23	0.78(0.28-2.1)	.64
D-dimer day 1	50	52	0.93(0.43-2.01	.99	0.7(0.31-1.7)	.47
D-dimer day 7	77	64	1.92(0.76-4.9)	.24	1.4(0.52-4.2)	.45
CRP day 1	63	55	1.38(0.63-3.04)	.55	1.26(0.54-2.93)	.59
CRP day 7	21	56	0.21(0.08-0.55)	.002	0.17(0.05-0.50)	.001

TCZ: tocilizumab HCQ: hydroxychloroquine UOR: Unadjusted odds ratio aOR: Adjusted odds ratio
IMV: invasive mechanical ventilation

Figure 2: Forest Plot comparing unadjusted odds of outcomes between TCZ group and no-TCZ group.

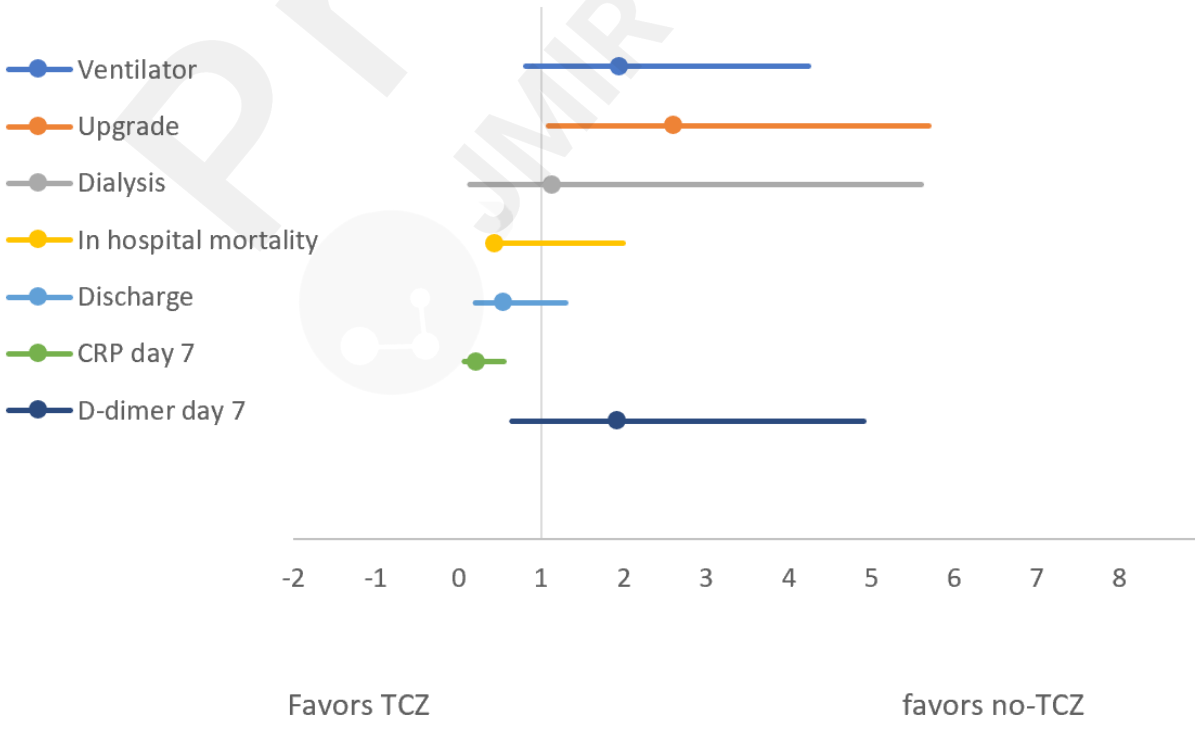
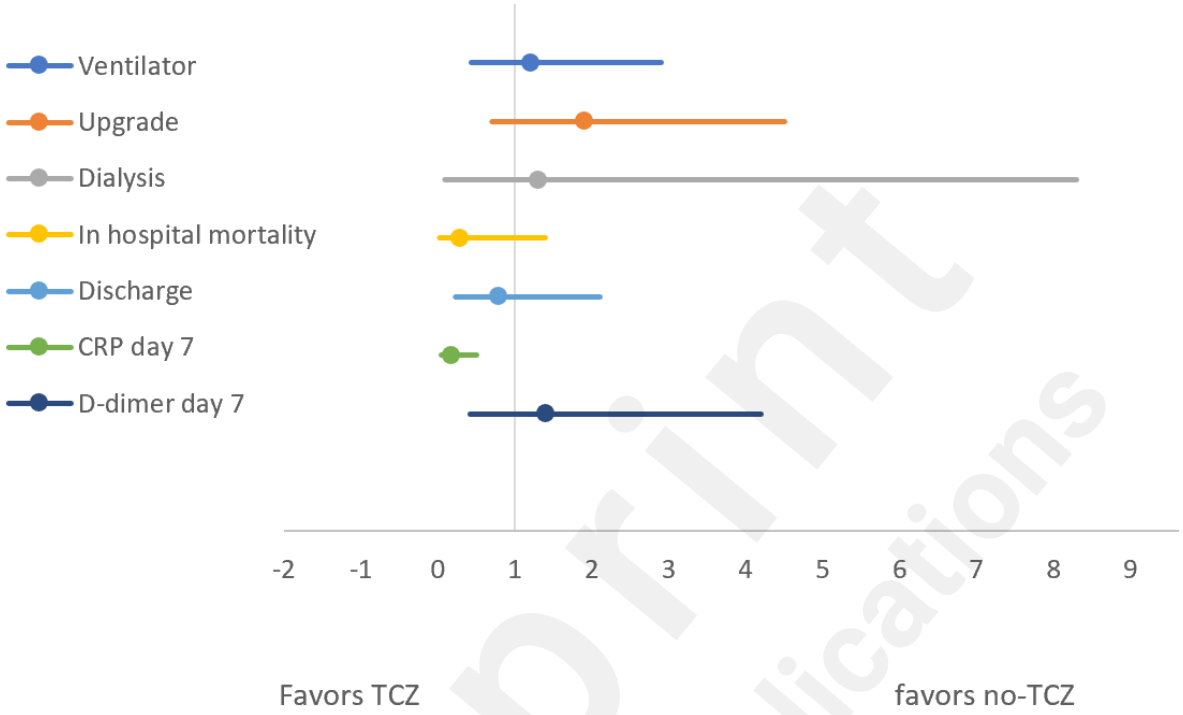


Figure 3: Forest Plot comparing adjusted odds of outcomes between TCZ group and no-TCZ group.



Similarly, the table and the forest plots given below compare the above-mentioned outcomes between the HCQ group and no HCQ group. (Table 3, Figure 4, Figure 5) As shown, the use of HCQ in patients with COVID-19 was not associated with a significant improvement in any of the outcomes. The unadjusted odds ratio of in-hospital mortality, upgrade to ICU, IMV, acute renal failure needing dialysis or discharge after recovery were identical between patients receiving HCQ vs. no-HCQ, respectively. Similarly, the proportion of high d-dimer and CRP levels on day-7 of the hospitalization was not significantly different between HCQ and no-HCQ groups. As with the TCZ comparison group, a multivariate regression analysis was used to adjust the observed odds ratios for baseline comorbidities and medications including TCZ in the HCQ comparison group. The adjusted odds values were consistent with unadjusted odds ratios for all the outcomes as having been depicted by similar forest plots given below. (Figure 4, 5)

Table 3: HCQ regression analysis with the outcome

Outcome	HCQ	No HCQ	UOR (95%CI) *	*P*-value	aOR (95%CI) *	*P*-Value
IMV	37	22	2.08(0.84-	.16	1.2(0.46-3.2)	.68

			5.14)			
Upgrade	33	25	1.5(0.63-3.59)	.48	0.9(0.35-2.3)	.84
Dialysis	5	9	0.57(0.12-2.02)	.57	0.34(0.06-1.7)	.19
Mortality	13	6	2.28 (0.5-10.3)	.43	1.6(0.33-7.9)	.54
Discharge	35	41	0.78(0.36-1.7)	.68	1.15(0.48-2.7)	.74
D-dimer day 1	51	54	0.89(0.37-2.10)	.95	0.80(0.3-1.9)	.63
D-dimer day 7	69	33	4.47(0.77-25)	.18	3.6(0.59-22.7)	.16
CRP day 1	55	62	0.75(0.33-1.69)	.62	0.64(0.27-1.51	.31
CRP day 7	49	29	2.42(0.45-12.95	.5	2.0(0.33-12.8)	.44

TCZ: tocilizumab HCQ: hydroxychloroquine UOR: Unadjusted odds ratio aOR: Adjusted odds ratio
IMV: invasive mechanical ventilation

Figure 4: Forest Plot comparing unadjusted odds of outcomes between HCQand no-HCQ group.

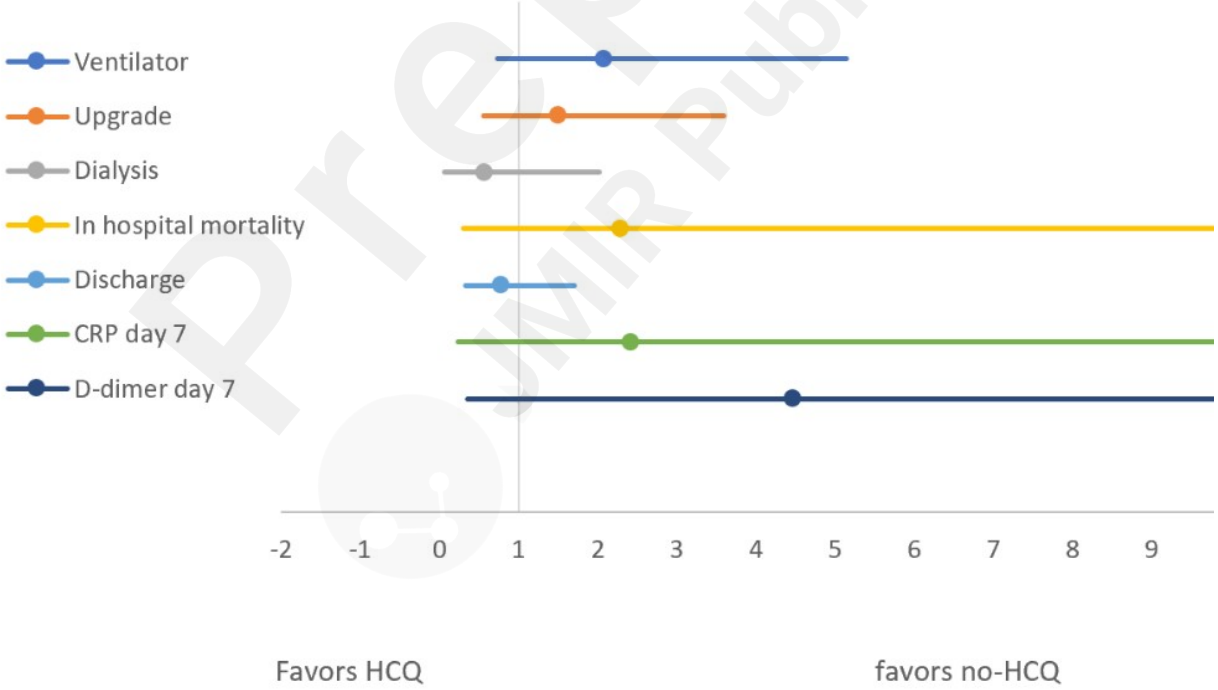
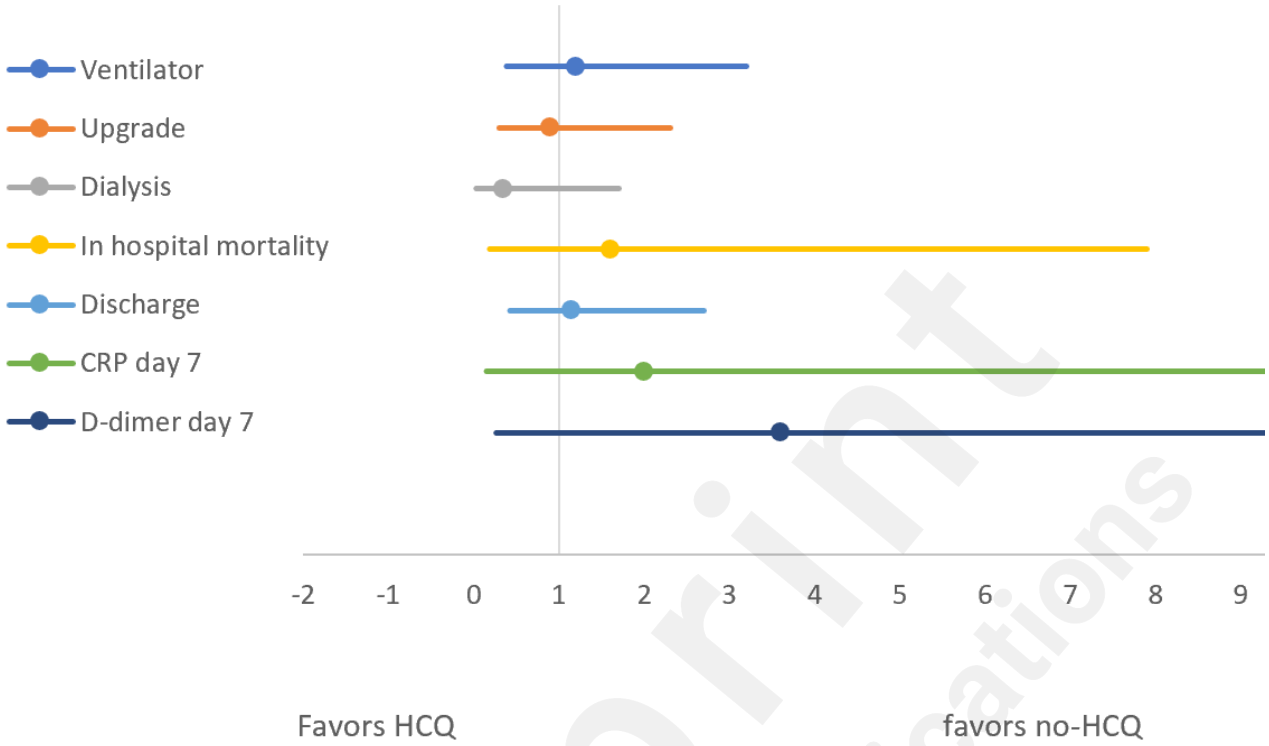


Figure 5: Forest Plot comparing adjusted odds of outcomes between HCQand no-HCQ group.



Discussion:

The purpose of this study is to evaluate the overall clinical effectiveness of HCQ and TCZ in our hospital and it reveals that both TCZ and HCQ had no role in improving hard clinical outcomes in the COVID-19 patients admitted to the hospital. Compared to patients in the control group, those who received either of these medications did not show a significant reduction in the rate of in-hospital mortality, upgrade to ICU, invasive mechanical ventilation (IMV), reduction in acute renal failure to the point of needing dialysis or discharge from the hospital after recovery. Though the patients who received TCZ appeared to have a higher rate of ICU upgrade, this trend seemed to be driven by multiple comorbidities in the TCZ group, as evidenced by an identical adjusted odds ratio on multivariate analysis. (Table 2, Figure 2,3) Partly contributing to this might be the higher use of TCZ in the sicker patients who fulfilled the criterion to receive the drug based on disease severity.

HCQ and TCZ, the major therapy for rheumatological diseases, have recently gained attention as one of the major cornerstone management approaches for COVID-19. The former is thought to work by inhibiting glycosylation of the host receptors, endosomal acidification and proteolytic processing thereby, blocking viral entry into host cells.[4-8] Tocilizumab, on the other hand is believed to counteract the misdirected immune response related to COVID-19 cytokine storm.[9] Being a monoclonal antibody directed against interleukin-6, tocilizumab is thought to dampen the immune response and potentially reduce the adverse outcomes related

to COVID-19.

A previous study by Xu et al. have shown a significant improvement in respiratory function (91% reduction in symptoms) and length of hospital stay of COVID-19 patients with a single dose of tocilizumab. [10] However, this study was underpowered (21 patients) and had no control arm.[10] Similarly, Luo and colleagues observed 80% survival in patients receiving tocilizumab. This study also was not followed by any large scale study and had several limitations.[11] A recently published retrospective cohort study that included 544 patients admitted in different hospitals of Italy revealed that after adjustment for sex, age, recruiting center, duration of symptoms, and SOFA score, TCZ treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p=0·020). [12] Our study consisted of 176 patients and it demonstrated that there were no major clinical benefits of tocilizumab use in COVID-19 patients. Although a significant reduction of CRP levels on day 7 of hospitalization was observed in the TCZ group compared to the control group yet this difference did not translate into clinical benefits in terms of a reduction in the in-hospital mortality, medical ICU upgrade or reduction in IMV. (Figure 2, 3) As mentioned in the study limitations below, a bigger patient population and randomized controlled design of the study might have demonstrated a clinical benefit parallel to this reduction in CRP level. Among other ongoing randomized, double blinded, controlled trials, Oxford-based Recovery trial is also recruiting participants into the tocilizumab arm of the trial who meet the eligibility criteria. [13]

Similarly, preliminary data from China reported that HCQ use was associated with a reduction in the viral load, duration of disease and resolution of COVID-19 pneumonitis on imaging. [14] A small nonrandomized open-label French study consisting of 36 patients also reported significant reduction in the viral load in the patients taking HCQ.[15] Major subsequent large-scale trials also reported its potential utility in reducing the need for IMV. However, the medical community was concerned regarding the potential cardiovascular adverse effects of off-label HCQ use. Despite all controversies surrounding HCQ, its use prevailed in the earlier part of the pandemic leading to stockpiling and shortage of HCQ in international markets, followed by a swift decline in its use. [16)

In our study, we systematically determined the impact of HCQ on the hard clinical outcomes in the COVID-19 cohort. Our mortality analysis showed a nonsignificant difference in the rate of in-hospital mortality in patients receiving HCQ group compared to those in the control group. It should be noted, however, that there was a two-fold higher risk of death in the HCQ arm. These findings are in line with a previous study by Magagnoli et al. that has also reported three times higher odds of death in patients receiving HCQ. [17] Following this, another French study consisting of 181 patients with diagnosed COVID-19 pneumonitis reported that HCQ use was of no benefit.[18] In terms of mortality, the results of our study are similar to recently published preliminary results of Recovery trial in which patients were randomized between the HCQ group (n 1542) and usual care group (n 3132). There was no significant difference in 28 day mortality between the two groups with a Hazard ratio of 1.11 95 % CI (0.98-1.26) p=.10. [3] Following these results, FDA revoked EUA for use of HCQ in COVID-19 patients on June, 15, 2020. [19]

The most debilitating complication of severe SARS-CoV-2 infection is acute respiratory failure necessitating the use of invasive mechanical ventilation and other concurrent resource-intensive needs in critical care units.[16] Previous studies have reported mixed results,

showing 11% to 44% use of invasive mechanical ventilation in patients receiving HCQ andTCZ. [14,20,21] Magagnoli et al. included sicker patients, who were more likely to receive HCQ on compassionate grounds and hence were more prone to have adverse outcomes and death, questioning its reliability.[18] By contrast, our analysis has adjusted the pooled estimate of IMV requirement in both HCQ and tocilizumab groups by identifying major potential confounders such as baseline comorbidities and other medications used during the hospital stay. By demonstrating a non-significant trend in all the above-mentioned outcomes, we recommend against the routine use of HCQ and tocilizumab in patients with COVID-19.

Limitations:

The findings of our study should be interpreted in light of its limitations. Due to the retrospective non-randomized nature of the study, a causal relationship could not be established. Although the overall findings were adjusted for covariates including baseline comorbidities and medications yet the impact of unmeasured confounders such as initiation of several complementary therapies at the treating physician's discretion, could not be determined. Based on our clinical experience, the average duration of any therapy for COVID-19 was less than seven days; therefore, we chose to use day-1 and day-7 laboratory values. However, given the variable frequency of laboratory specimen collection, it is not possible for us to ascertain if these values truly represented pre and post-treatment values accurately in all cases. The patients who received tocilizumab were mainly selected based on the availability of the drug (which was in short supply intermittently during the time frame of our study), and these patients were sicker with lower PaO2/FiO2 ratios. Moreover, by excluding patients still in the hospital, the case fatality ratio in our study cannot reflect the true mortality of COVID-19. Our study did show a trend of beneficial events in terms of the point estimate of the pooled effect size. However, there was an overlap in the confidence intervals and broad confidence intervals indicating that our study was underpowered to reach the level of significance. Although we adjusted the outcomes against demographics and underlying comorbidities, neither did we evaluate the contribution of underlying comorbidities to COVID-19 mortality via propensity score matching nor did our study evaluate the potentially harmful effects of these medications. We believe that a large scale study will determine the true merits of these medications and will also reveal the potentially harmful outcomes of these medications. Many questions remain open however, by adjusting the adult patients with the confirmed disease, we believe our population is the representative of the real-world cohort.

Conclusion:

Hydroxychloroquine and tocilizumab use was not associated with the reduction in end-points of in-hospital mortality, upgrade to medical ICU, need for invasive mechanical ventilation, acute renal failure necessitating dialysis or discharge from the hospital. Though there was a significant reduction in CRP level at day-7 of hospitalization in the patients receiving TCZ yet lack of improvement in hard clinical outcomes suggests that the large scale randomized control trials are the need of the hour to evaluate the efficacy of these drugs.

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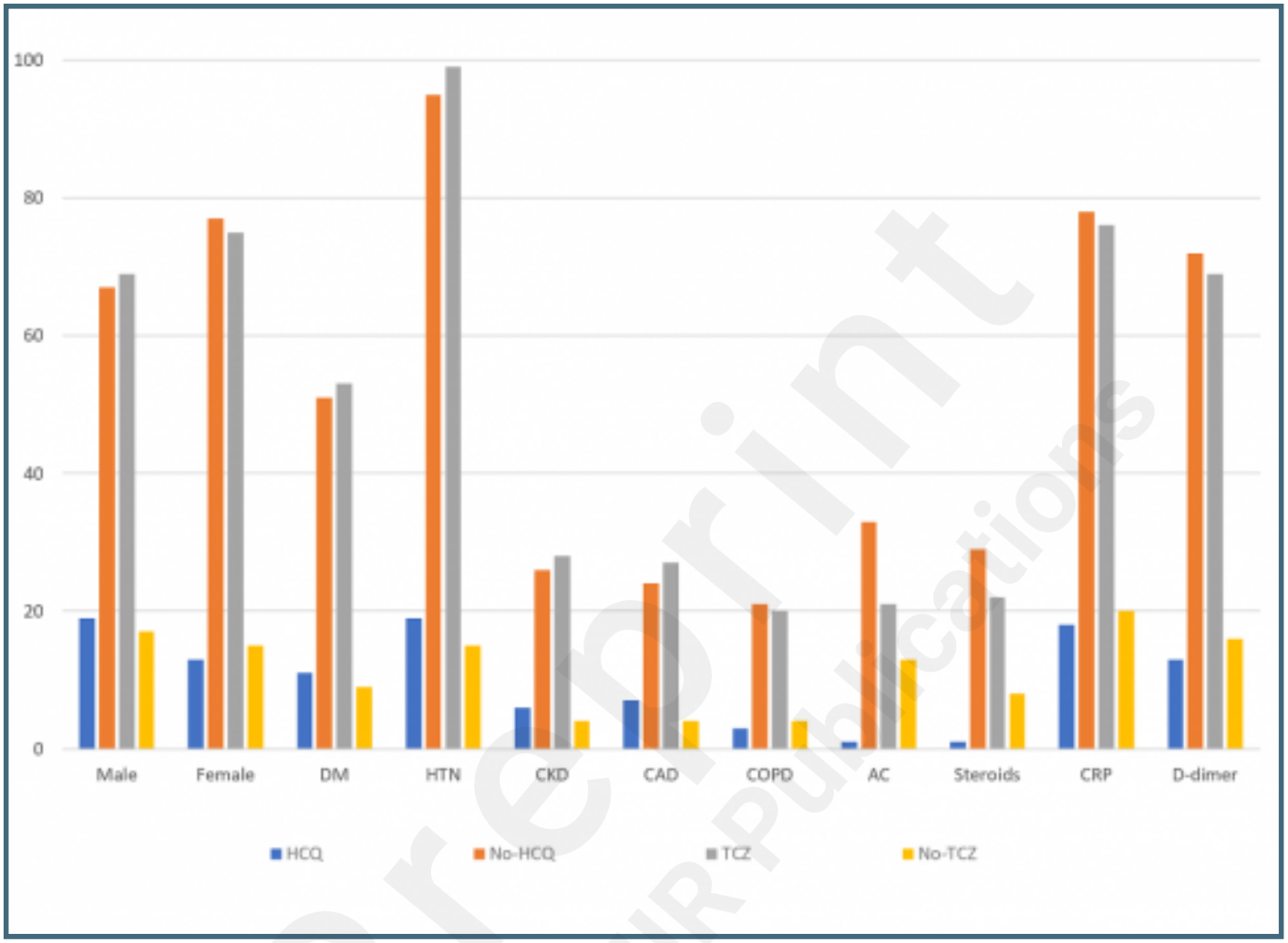
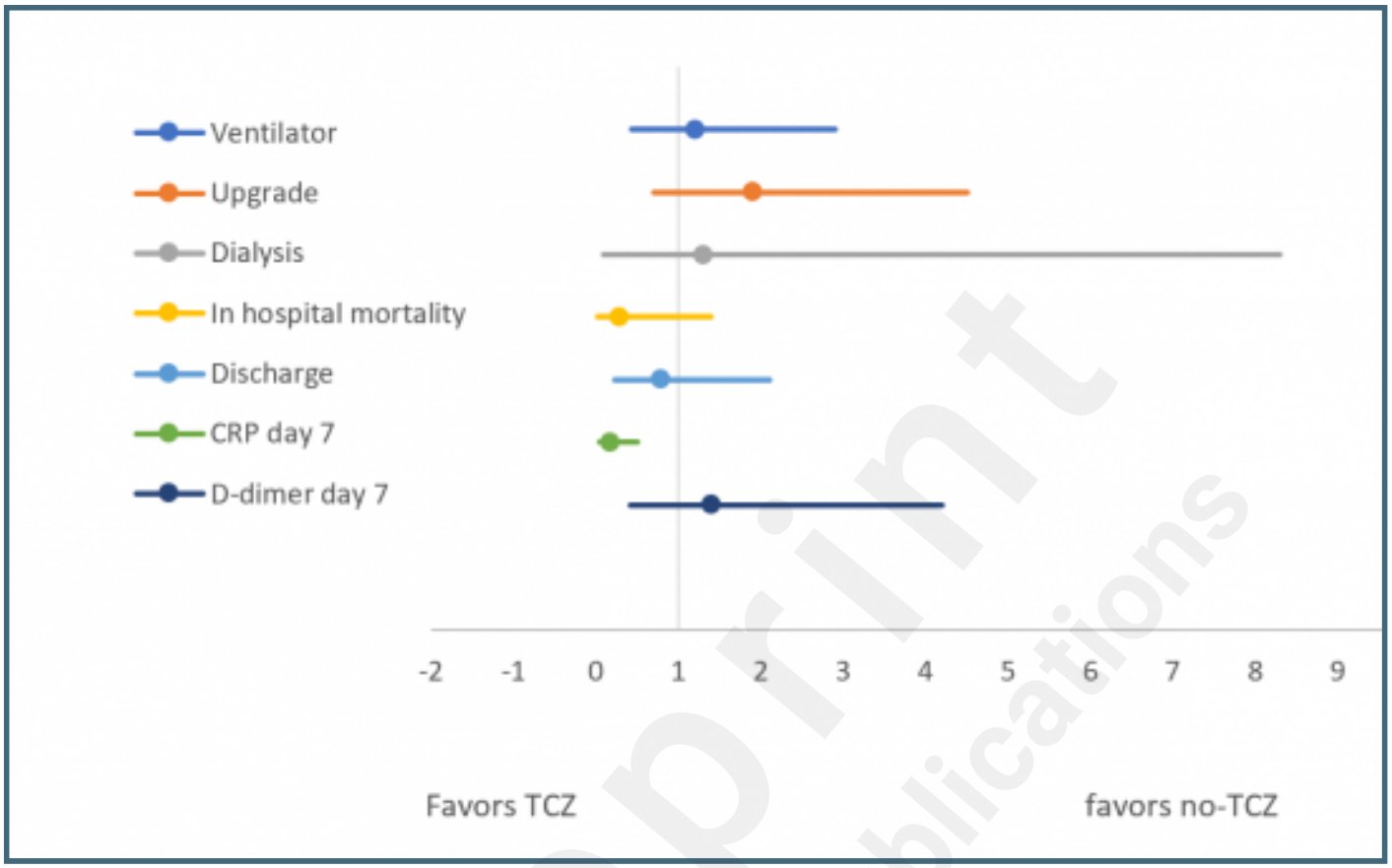
Supplementary Files

Figures

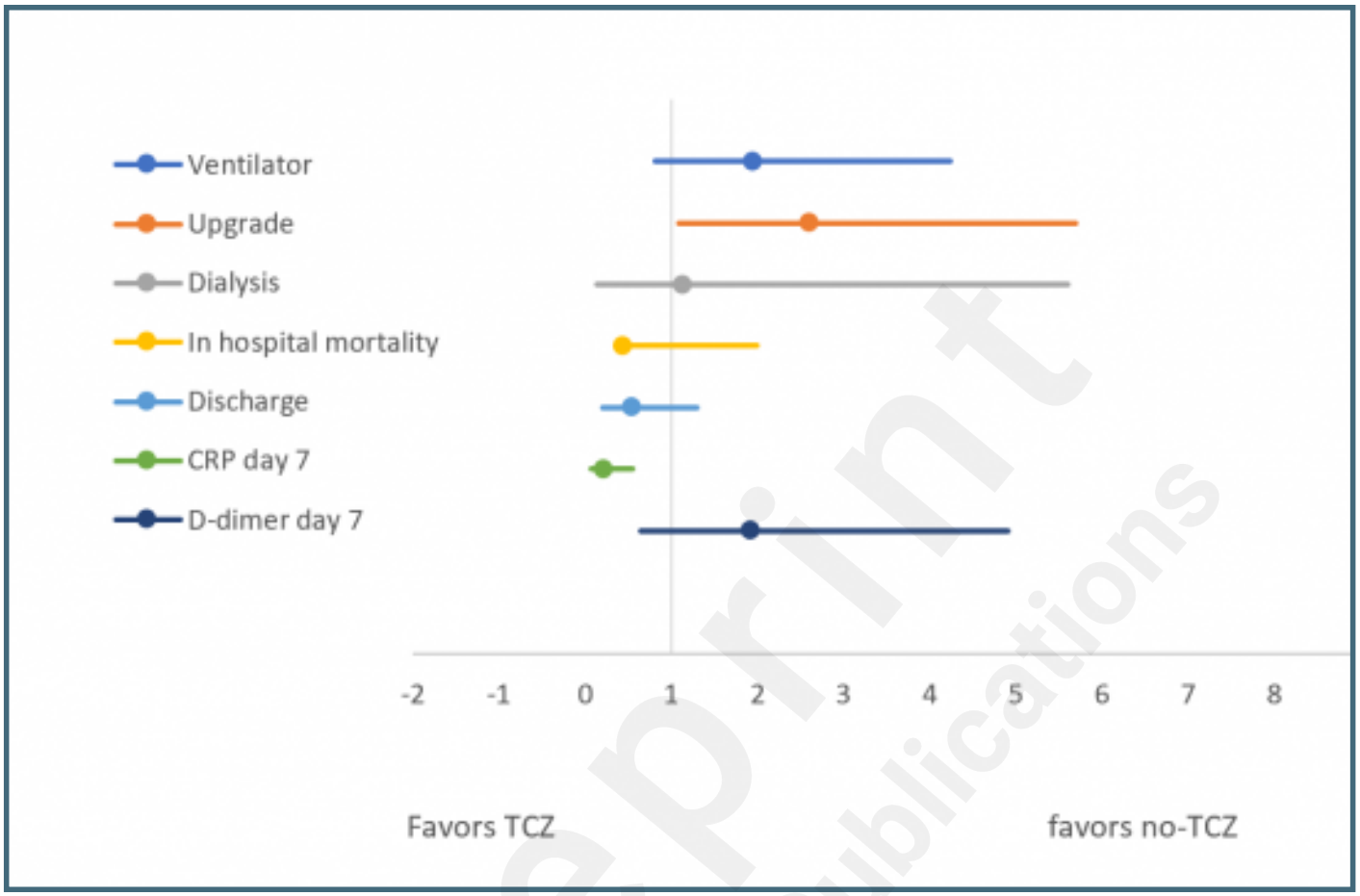
Baseline comorbidities and medication use in the HCQ group, TCZ group, and control groups. x-axis represents sex, comorbidities, medications, CRP and D-dimer level at presentation y-axis represents the percentage of subjects.



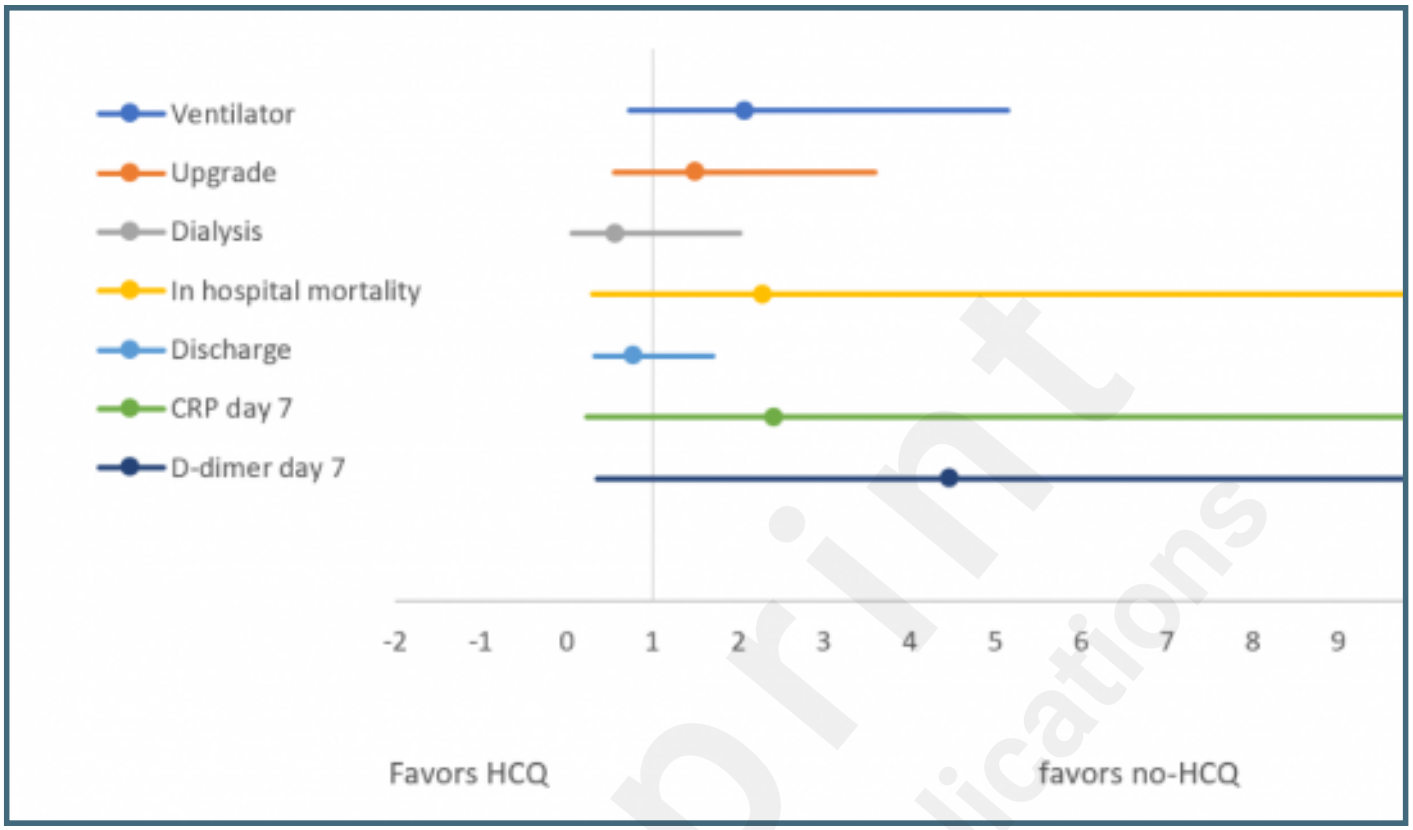
Forest Plot comparing adjusted odds of outcomes between the TCZ group and no-TCZ group.



Forest Plot comparing unadjusted odds of outcomes between the TCZ group and no-TCZ group.



Forest Plot comparing unadjusted odds of outcomes between HCQand no-HCQ group.



Forest Plot comparing the adjusted odds of outcomes between HCQ and no-HCQ group.