QUANTIFYING TREATMENT EFFECTS OF HYDROXYCHLOROQUINE AND AZITHROMYCIN FOR COVID-19: A SECONDARY ANALYSIS OF AN OPEN LABEL NON-RANDOMIZED CLINICAL TRIAL

A PREPRINT

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March 22, 2020

ABSTRACT

Human infections with a novel coronavirus (SARS-CoV-2) were first identified via syndromic surveillance in December of 2019 in Wuhan China. Since identification, infections (coronavirus disease-2019; COVID-19) caused by this novel pathogen have spread globally, with more than 250,000 confirmed cases as of March 21, 2020. An open-label clinical trial has just concluded, suggesting improved resolution of viremia with use of two existing therapies: hydroxychloroquine (HCQ) as a monotherapy, and in combinations with azithromycin (AZ). [1].

The results of this trial have major implications for global policy in the rapid scale-up and response to this pandemic. The authors present results with 'naked' p-values for differences in proportions between the study arms, but do not provide effect size estimates; and statistical significance may not be clinically significant.

To address this gap, more modern analytical methods including survival models, have been applied to theses data, and show modest to no impact of HCQ treatment, but more significant effects from the HCQ-AZ combination, potentially suggesting an important role for co-infections in COVID-19 pathogenesis.

The trial of Gautret and colleagues, with consideration of the effect sizes, and p-values from multiple models, does not provide sufficient evidence to support HCQ monotherapy for the treatment of COVID-19. However, these data do suggest further study of HCQ-AZ combination therapy should be prioritized with great haste.

Keywords COVID-19 · Emerging pathogens · Pharmaceutical therapies · Clinical trials · Secondary analyses

1 Introduction

Evidence-based public health programming is essential for global pandemic planning, and optimization of resources. However, unadjusted analysis may provide distorted estimates, or not full utilize scarce clinical data.

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2 Data and Analysis

All analyses was performed using Stata 16.1 (College Station, TX, USA). Standard 95% confidence interval were used; model parsimony was assessed using Akaike and Bayesian information criteria (AIC/BIC). All models were adjusted for age and sex. Assessing the predictive power of logistic models used Tjur's $R\hat{2}$. [2].

2.1 Data source

Data were obtained from [1], and the Supplemental Table 1 was digitized using Tabula software, with subsequent hand-validation.Data for the six patients who were lost-to-follow-up (LTF) were manually entered into a database.

2.2 Primary outcome

The primary outcome as reported by the authors "The primary endpoint was virological clearance at day-6 post-inclusion." An optimal analysis for this endpoints in a binary regression which avoids many of the potential biases in logistic models when outcomes are common [3].

2.3 Secondary outcome

The stated "Secondary endpoint was virological clearance overtime during the study period...." and standard Cox survival time models were used to capture time-to-first negative PCR (with a Ct threshold of >=35). The incorporation of the censored patients was as per standard methods.

3 Results

The sequence of confirmed viremia via PCR is shown in (Fig. 1), and the LFT patients are at the bottom of the figure.

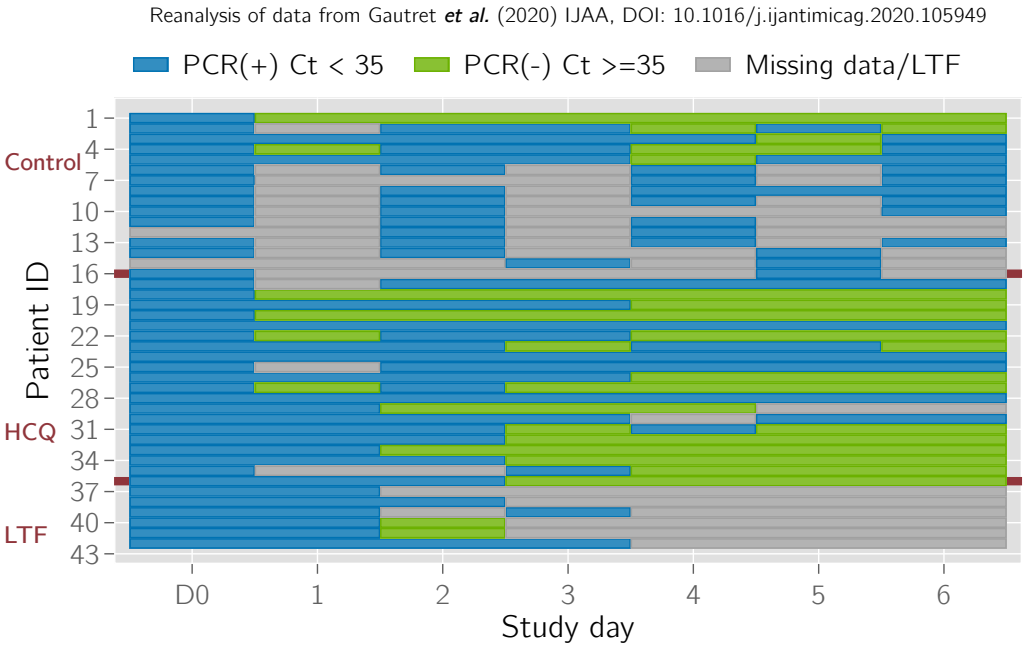

Figure 1: Sequence plot of enrolled patients. (N= 42).

The primary outcome was assessed using binary regressions to provide relative risks for clearance of viremia between the study arms. The main effect of interest (that of all combined HCQ-treated patients versus control), shows a marginally significant risk ratio of 3.84 (95 % CI 1.02 - 14.42, p= 0.047). Analysis of the separate HCQ and HCQ+AZ outcome was not possible due to quasi-separation of the model.

variable	RR	95% CI	p-value
Study Arm			
Control	reference	-	-
HCQ	3.836	1.020 - 14.42	0.047
Age Years	1.009	0.996 - 1.022	0.176
Sex			
Male	reference	-	-
Female	0.585	0.335 - 0.963	0.176

Table 1. Risk ratios for clearance of virema, by day six, using binary regression (Primary outcome). (N=30).

To address the limitations of these models, Firth penalized-likelihood model were used, which deal well with separation and quasiseparation. [4]

variable	OR	95% CI	p-value
Study Arm			
Control	reference	-	-
HCQ	5.216	0.797 - 34.143	0.085
HCQ+AZ	52.280	1.954 - 1,399.058	0.018
Age Years	0.981	0.939 - 1.025	0.399
Sex			
Male	reference	-	-
Female	0.971	0.168 - 5.622	0.974

Table 3. Odds ratios for clearance of virema, by day six, Firth penalized likelihood models (Primary outcome). (N= 30).

To assess the secondary outcome, Kaplan-Meier and Cox models were use to compare the time-to-event with adjustment for covariates,

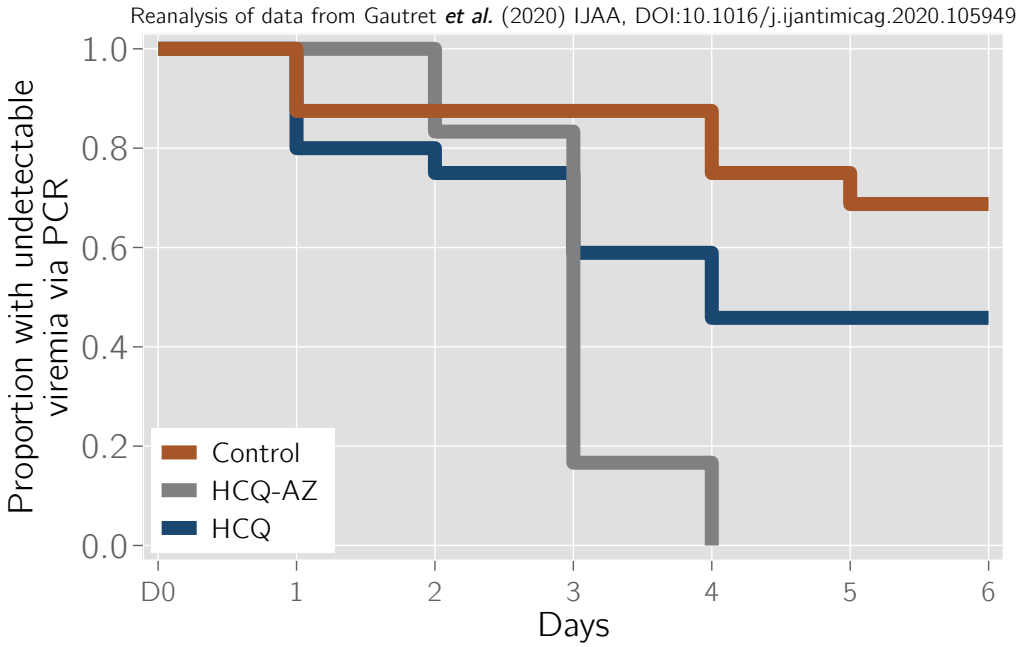

Figure 2: Unadjusted Kaplan-Meir plot of all enrolled patients (N= 42).

variable	HR	95% CI	p-value
Study Arm			
Control	reference	-	-
HCQ	2.887	0.874 - 9.541	0.082
HCQ+AZ	6.265	1.538 - 25.517	0.010
Age Years	0.984	0.957 - 1.011	0.246
Sex			
Male	reference	-	-
Female	1.058	0.382 - 2.927	0.914

Table 1. Hazard ratios for time to first negative PCR, using Cox PH models. (N=36).

4 Discussion and Conclusions

Together these results, especially in consideration of the loss to followup of six patients, do not provide sufficient evidence to support HCQ monotherapy for the treatment of COVID-19. However, these data do suggest further studies of HCQ-AZ combination therapy should be prioritized with great haste. The rapid increase in confirmed infections within the last few days suggests that the pandemic is accelerating, and there are major opportunity costs associated with all choices; and rapid science will be critical for progress.

References

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Revision History

Revision	**Date**	**Author(s)**	**Description**
1.0	17.1.21	AAL	created