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Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19

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This article is a preprint and has not been certified by peer review [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

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Abstract

BACKGROUND: Despite limited and conflicting data on the use of hydroxychloroquine in patients with Covid-19, the U.S. Food and Drug Administration has authorized the emergency use of this drug when clinical trials are unavailable or infeasible. Hydroxychloroquine, alone or in combination with azithromycin, is being widely used in Covid-19 therapy based on anecdotal and limited observational evidence. METHODS: We performed a retrospective analysis of data from patients hospitalized with confirmed SARS-CoV-2 infection in all United States Veterans Health Administration medical centers until April 11, 2020. Patients were categorized based on their exposure to hydroxychloroquine alone (HC) or with azithromycin (HC+AZ) as treatments in addition to standard supportive management for Covid-19. The two primary outcomes were death and the need for mechanical ventilation. We determined the association between treatment and the primary outcomes using competing risk hazard regression adjusting for clinical characteristics via propensity scores. Discharge and death were taken into account as competing risks and subdistribution hazard ratios are presented. RESULTS: A total of 368 patients were evaluated (HC, n=97; HC+AZ, n=113; no HC, n=158). Rates of death in the HC, HC+AZ, and no HC groups were 27.8%, 22.1%, 11.4%, respectively. Rates of ventilation in the HC, HC+AZ, and no HC groups were 13.3%, 6.9%, 14.1%, respectively. Compared to the no HC group, the risk of death from any cause was higher in the HC group (adjusted hazard ratio, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HC+AZ group (adjusted hazard ratio, 1.14; 95% CI, 0.56 to 2.32; P=0.72). The risk of ventilation was similar in the HC group (adjusted hazard ratio, 1.43; 95% CI, 0.53 to 3.79; P=0.48) and in the HC+AZ group (adjusted hazard ratio, 0.43; 95% CI, 0.16 to 1.12; P=0.09), compared to the no HC group. CONCLUSIONS: In this study, we found no evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalized with Covid-19. An association of increased overall mortality was identified in patients treated with hydroxychloroquine alone. These findings highlight the importance of awaiting the results of ongoing prospective, randomized, controlled studies before widespread adoption of these drugs.

Competing Interest Statement

COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

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Disclosure forms provided by the authors are available with the NEJM. JA is a co-founder of iVeena Holdings, iVeena Delivery Systems and Inflammasome Therapeutics, and has received consultancy fees from Allergan, Biogen, Boehringer Ingelheim, Immunovant, Janssen, Olix Pharmaceuticals, Retinal Solutions, and Saksin LifeSciences, all unrelated to this work. JA is named as an inventor on a patent application filed by the University of Virginia relating to Covid-19 but unrelated to this work. SSS has received research grants from Boehringer Ingelheim, Gilead Sciences, Portola Pharmaceuticals, and United Therapeutics, all unrelated to this work. The other authors declare no competing interests.

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Author Declarations

All relevant ethical guidelines have been followed; any necessary IRB and/or ethics committee approvals have been obtained and details of the IRB/oversight body are included in the manuscript.

Yes

All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

Yes

I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).

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Mike • 10 hours ago • edited

This was certainly an interesting paper. It's done a lot of work and the findings are notable. IMHO it warrants as much attention as the pro-HCQ study via Dr. Raoult. While it is entertaining, I will add that it is not conclusive, nor without fault. A double-blind study is still required, but it is worth the read.

Observations/Questions:

1. "hydroxychloroquine, with or without azithromycin, was more likely to be prescribed to patients with more severe disease"
2. "we cannot rule out the possibility of selection bias or residual confounding"
3. demographic: 100% male, 66% black, median age ~70 (59 youngest)
4. uses PSM, which despite a common practice, could be considered controversial (https://gking.harvard.edu/f...
5. Unless I missed it, I didn't see any specifics about how the treatments were administered.
- How long before death were patients treated?
- What was the quantity/frequency of the treatments?
- Were the treatments consistent between hospitals?

see more

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David B Joyce • 11 hours ago • edited

19 patient shifted fromNo HC to HC(7) or HC+AZ(12) after ventilation. Ventilation is obviously a sign of increasing severity and greater risk of death. If all of these ventilations resulted in death, then the pre ventilation treatment fatality statistics might look like 22% (HC), 13% (HC+Az) and 21% No HC. Need the data on individual outcomes. Also not impressed with the cohorts.

SPo2 >95: 63%(HC) 57.5%(HC+Az) 73.4%(No HC)
BP> 159: 19.6% 9.7% 9.5%
creatinine>5 17.5% 11.5% 7.6%

3 • Reply • Share ›

honesttalk David B Joyce • 10 hours ago

Why wasn't ZINC SULFATE included in the treatment? ZINC is what interferes with the viral load increase.

4 | Reply • Share ›

stickler • 11 hours ago

Every news media seems to be including this same sentence: "The nationwide study was not a rigorous experiment," which to trump supporters means that its conclusions are completely untrustworthy and it can be summarily disregarded as a politically motivated product of the deep state. In what way did this study lack rigor? Does there appear to be anything lacking in the design, methodology, data, analysis, interpretation or reporting of results, or is it more a matter of just awaiting peer review?.

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Michael Kyba • 12 hours ago

A cursory browse through Table 2 of the paper shows that the patients that would eventually comprise the HC group were the sickest upon admission, the HC+AZ patients were intermediate and the patients that would elect no HC group were the least sick. This is prior to intervention.

This sort of sampling bias highlights the importance of double blind randomization to determine efficacy. Such an a priori correlation might be due to sicker patients opting for experimental treatments at a higher rate. In any case, it would not be wise to interpret these data as indicating that the interventions cause the worse outcomes. The underlying health state is probably responsible.

Some examples follow, then a criticism of what the authors have written into their Results and Discussion.

Known risk factors include age, weight and blood pressure; and signs of severe disease include kidney damage.

Browsing through table 2 looking for parameters with lowish p-values:
Mean systolic blood pressure differences between groups showed a p-value of just under

see more

6 | Reply • Share ›

Mike Cee • 12 hours ago

This paper is flawed and should be withdrawn immediately.
1) This paper is flawed due to the limitation discussed on page 12 about the likelihood that the HCQ group, "However, hydroxychloroquine, with or without azithromycin, was more likely to be prescribed to patients with more severe disease, as assessed by baseline ventilatory status and metabolic and hematologic parameters."
Doctors working the front lines have already noted that patients at SYMPTOMS ONSET + 14 days should not be prescribed HCQ
2) The important grouping by number of days since SYMPTOM ONSET was left out of this study. Previous studies, while anecdotal, suggest that patients should be prescribed HCQ early because it is believed to prevent the virus from infecting the type 2 lung cell through the ACE2 receptor and thus stops the progression of the disease.
3) This study did not document the dosage given to the patients. That would have been a helpful inclusion so we could understand if the patients who died were actually poisoned by excessive the treatment.
4) HCQ prescribed in patients in the first week after SYMPTOMS ONSET to include a zinc supplement which anecdotal evidence suggests a dual function of the combination: The HCQ provides an avenue for the zinc to enter the Type 2 lung cell where it interferes with the virus replication process.

7 | Reply • Share ›

Eric H • 12 hours ago

The Hazard Ratio confidence intervals in Table 5 of the report shows that the findings of this study are not significant. That plus the uncertainties in the Propensity Score Matching method make it even worse. I noticed the HCQ group contained a substantially higher proportion of high blood pressure and diabetic w/complications than the control group. Worst of all, they apparently did not interview even one doctor to ascertain the range of Tx criteria used.

2 ^ | v • Reply • Share ›

docmeehan • 13 hours ago • edited

I'm not sure VA database born retrospective cohort analysis that declines to reveal drug dosing protocols contributes much to the science. Let's have those drug dosing protocols.

2 ^ | v • Reply • Share ›

deutsch • 13 hours ago

The group no HCQ had azihtromycine 31% !!!!

1 ^ | v • Reply • Share ›

Marv Goosen • 15 hours ago

The problem with this study is that it is retrospective and as the authors state in their discussion, patients in worse shape may have been put in the HC group which would also account for higher mortality. Unfortunately until a prospective study with severity matched controls is done, no conclusions can be made.

3 ^ | v • Reply • Share ›

Senad Hasanagic • 15 hours ago

Totally flowed retrospective analysis because baseline Clinical characteristics are missing (not reported) in significant number of patients. So adjustments not possible.

3 ^ | v • Reply • Share ›

Iyad Sultan • 15 hours ago

Patients who are sicker are more likely to get HQ or HQ+AZ and are more likely to die. Those who got the combination were 50% likely to get mech vent. The only message is that combination is superior and NO HQ alone. Otherwise, this is a biased study that misses the point - sorry!

3 ^ | v • Reply • Share ›

Savio • 16 hours ago

Cytokine bath or flooding is causing co-morbidity. HCQ can apparently reduce the inflammation in response to the virus but not counter the virus itself.

Here is a review paper describing the “Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology”.

https://www.nature.com/arti...

“Hydroxychloroquine and chloroquine are weak bases and have a characteristic ‘deep’ volume of distribution and a half-life of around 50 days. These drugs interfere with lysosomal activity and autophagy, interact with membrane stability and alter signalling pathways and transcriptional activity, which can result in inhibition of cytokine production and modulation of certain co-stimulatory molecules.”

1 ^ | v • Reply • Share ›

Roleigh Martin • 16 hours ago

Why was not Zinc added to the dosage, many clinical reports have been made about how critical Zinc level monitoring and Zinc supplementation is to successful use of this Rx.

3 ^ | v • Reply • Share ›

Brandon B • 17 hours ago

Risk of ventilation was 6.9% in HQ + AZ group and 14.1% in no Tx group. That is double. It was stated that these numbers are similar in the article. Not significant?

10 ^ | v 3 • Reply • Share ›

Rick ↗ Brandon B • 12 hours ago

And HQ+AZ actually gave lower death rate, if you group the patients only based on "pre-ventilation" treatment as in table 4. Grouping patients based on "overall hospital stay", as the analysis was done to draw their main conclusion, leads to inclusion of patients who were treated with HQ+AZ in later stage presumably because they were sicker. Based on presented stats on the clinical characteristics, the patients in HQ groups were overall sicker.

2 ^ | v • Reply • Share ›

Eric H ↗ Brandon B • 12 hours ago

Saw that too. I have to wonder if this was a typographical error. It contradicts the statement of conclusions. Which is wrong? They can't both be right.

1 | • Reply • Share ›

Diane Merriam ↗ Brandon B • 12 hours ago

HQ and no HQ were almost the same on ventilation numbers. The death rates for both the HQ and the HQ+AZ were both significantly higher than for the no HQ group.

The early studies that were claiming success with HQ were done only on very mild cases. 85% of them weren't even running a fever. A drug might help some that were barely sick to begin with get over it faster while not helping anyone with a full blown case. Even that one had three go to the ICU and one death. Since they couldn't obtain the samples they needed from cases in the ICU or dead, those people were dropped from the study altogether.

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vlodko62 ↗ Brandon B • 13 hours ago

The relative death rates for the three groups are not encouraging.

| • Reply • Share ›

Doctor Hawaii ↗ Brandon B • 15 hours ago

You might want to refresh your understanding of statistics. Look at the P values and the CIs in the analysis. So, not significant is correct.

| • Reply • Share ›

Pierre Balaz • 17 hours ago

Just to get all the details : which was the posology of then medications used ? (HCQ and AZT) ?

7 | 1 • Reply • Share ›

Brooklyn Ease ↗ Pierre Balaz • 14 hours ago

Dosing information is important in this study as the risk of hydroxychloroquine causing prolonged QTc and Tdp is higher with 600 mg than 400 mg dosages, if rhythm disturbance contributed to death.

1 | • Reply • Share ›

Eric H ↗ Pierre Balaz • 14 hours ago

What about the zinc? With a zinc deficiency (very common in elderly) the HCQ is almost worthless.

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Udub • 19 hours ago • edited

Quite strange study !!! What was the purpose ? .. retrospective study to see if people that were given drugs hcq or hcq + azt (likely people with worrying/severe form of covid at least enough to prescribe meds) died more than people for which it was decided not to give any particular medicine (likely less severe form of covid ... only 50 were given azt on the no hcq group)...

what were the criteria to give or not hcq ? Were hcq / hcq+azt given with the first symptoms or at an already adavanced stage ?

Comparing deaths between people who seemed really sick (they need medication) with people not needing particular medication is a bit confusing ... conclusions show either lack of analysis or partiality

9 | 4 • Reply • Share ›

Doctor Hawaii ↗ Udub • 15 hours ago

This isn't a strange study at all.
The purpose is to analyze the risks and benefits of a treatment that is currently getting widespread use despite no good evidence supporting that use. The results of this and RCTs currently occurring should help shape guidance on treatment so

that we don't wind up (needlessly) harming or killing more people than we help. And the clinical characteristics of the patients in each group were accounted for and factored into the results: "...competing risk hazard regression adjusting for clinical characteristics..."

4 • Reply • Share ›

Nom DePlume Udub • 15 hours ago

While is true we don't know how the patients were chosen for who received the meds and who did not, it seems reasonable that the sicker, more desperate were given the meds.

While that would bias the results of higher ventilation and/or death, this study DOES show that the drugs ARE NOT MIRACLE CURES OR GAME CHANGERS.

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