Letter About: Risk Factors for Mortality in Patients with COVID-19 in New York City

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Dear Editor,

We read with interest the study by Mikami et al.[1] about the association of hydroxychloroquine (HCQ) with mortality in 3708 patients hospitalized with COVID-19. The authors reported adjusted HRs from a Cox regression model with and without propensity score adjustment, respectively: 0.53, 95%CI (0.41–0.68) and 0.53, 95%CI (0.41–0.67). They concluded that treatment with HCQ was associated with reduced mortality. We appreciate that the authors appropriately tempered their interpretation of the results. Nonetheless, we are concerned that many readers may still overinterpret the impressive hazard ratios.

Moreover, we believe that the validity of the findings is weakened due to survivor bias, treatment selection bias, and reporting bias.

First, authors did not account for survivor bias in their analysis. Looking at their survival curves suggests that most deaths in the non-HCQ group occurred within 10 days of admission. We[2] and other investigators[3] have illustrated that survivor bias, which occurs because patients who live longer are more likely to receive treatment than those who die early, could change associations from benefit to harm. In a re-analysis of British hospital data from the Influenza Clinical Information Network study of 1391 patients with confirmed pandemic influenza A/H1N1 2009, authors observed that time bias can make Oseltamivir appear more effective (time-dependent bias), useless (competing risk bias), or even harmful (length bias).[3]

Second, surprisingly authors did not report on ICU care or ventilatory support in their cohort. Data from two large US cohorts[4,5] during the same months of the pandemic reported that many patients died outside the ICU without ventilatory support (Table 1). Including these patients in the analysis would certainly affect the validity of the results due to confounding by indication. No statistical method can account for this treatment selection bias.

Finally, authors did not report on cardiac toxicity of HCQ in their cohort. Our group[6] has recently conducted a meta-analysis on HCQ-induced cardiac toxicity in COVID-19 patients. We found that treatment with HCQ was associated with a clinically significant increased risk of QTc prolongation and discontinuation of drug due to QT prolongation. In addition, HCQ was associated with a clinically significant risk of torsades de pointes ventricular tachycardia (TdP) or monomorphic VT or cardiac arrest of 3 per 1000 (95%CI 0.0–21).

We call for investigators to comply with reporting guidelines and for more vigilance in interpreting findings from observational studies especially when they show results contradicting those of randomized trials.

In response to:

Mikami, T., Miyashita, H., Yamada, T. et al. Risk Factors for Mortality in Patients with COVID-19 in New York City. J GEN INTERN MED (2020). https://doi.org/10.1007/s11606-020-05983-z

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Table 1 Comparison of Three Large COVID-19 Cohorts in New York and Michigan, USA—March to April 2020

Arshad et al.	The Henry Ford Health System (6 hospitals) in Southeast Michigan: March 10, 2020 to May 2, 2020			
Variable	HCQ group ($n = 1985$)	Non-HCQ ($n = 556$)	$N = 2541$	Comment
ICU admission	26.9%	14.6%	24.2%	166/615 (27%) of those who died did not
Ventilatory support	20.2%	8.6%	17.7%	receive mechanical ventilation
Mortality	16.1%	25.4%	18.1%	
Richardson et al.	The Northwell Health System (12 hospitals) in New York City, Long Island, and Westchester County, New York: March 1, 2020, and April 4, 2020			
Variable	HCQ group	Non-HCQ	$N = 5700$	271/553 (49%) and 262/553 (47.4%) of those who
ICU admission	NA	NA	6.54%	died did not receive mechanical ventilation
Ventilatory support	NA	NA	14.2%	or ICU care, respectively
Mortality	NA	NA	9.7%	
Mikami et al.	The Mount Sinai Health System (8 hospitals) in New York City: March 13 and April 17, 2020			
Variable	HCQ group ($n = 2073$)	Non-HCQ ($n = 742$)	$N = 2815$	NR/NR (NR%) of those who died did
ICU admission	NR	NR	NR	not receive mechanical ventilation
Ventilatory support	NR	NR	NR	
Mortality	27.5%	31.1%	28.5%	

HCQ, hydroxychloroquine. NA, not applicable (did not examine HCQ). NR, not reported

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Compliance with Ethical Standards:

Conflict of Interest: *Authors report no conflict of interest.*

REFERENCES

1. **Mikami, T., Miyashita, H., Yamada, T. et al.** Risk Factors for Mortality in Patients with COVID-19 in New York City. J Gen Intern Med. 2020. https://doi.org/10.1007/s11606-020-05983-z.
2. **Tleyjeh IM, Ghomrawi HM, Steckelberg JM, et al.** Conclusion about the association between valve surgery and mortality in an infective endocarditis cohort changed after adjusting for survivor bias. J Clin Epidemiol. 2010;63(2):130-135. https://doi.org/10.1016/j.jclinepi.2008.06.022.
3. **Wolkewitz M, Schumacher M.** Survival biases lead to flawed conclusions in observational treatment studies of influenza patients. J Clin Epidemiol. 2017;84:121-129. https://doi.org/10.1016/j.jclinepi.2017.01.008.
4. **Arshad S, Nauriyal V, et al.** Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19. Int J Infect Dis. 0(0). https://doi.org/10.1016/j.ijid.2020.06.099.
5. **Richardson S, Hirsch JS, Narasimhan M, et al.** Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020;323(20):2052–2059. https://doi.org/10.1001/jama.2020.6775.
6. **Tleyjeh IM, Kashour Z, AlDosary O, et al.** The Cardiac Toxicity of Chloroquine or Hydroxychloroquine in COVID-19 Patients: A Systematic Review and Meta-regression Analysis. Mayo Clin Proc Innov Qual Outcomes. 2020. https://doi.org/10.1016/j.mayocpiqo.2020.10.005.