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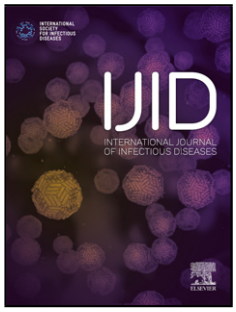

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Effectiveness of Hydroxychloroquine in COVID-19 disease: a done and dusted situation?

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Dear Sir,

Arshad *et al* show evidence for a reduced mortality in Covid-19 patients taking hydroxychloroquine alone or with azithromycin in an observational study in USA [1]. Data on effectiveness and toxicity of hydroxychloroquine are controversial [2-6].

A total of 539 COVID-19 hospitalised patients were included in our cohort in Milan, from February 24 to May 17,2020 of whom 174 died in hospital (day 14 probability of death: 29.5% - 95%CI: 25.5-34.0). We divided a subset of our cohort in three groups who started treatment a median of 1 day after admission: those receiving hydroxycholoroquine alone (N=197), those receiving hydroxycholoroquine+azithromycin (N=94), and those receiving neither (controls) (N=92). Of the latter group, 10 started HIV antivirals (boosted-lopinavir or –darunavir), 1 teicoplanin, 12 immunomodulatory drugs or corticosteroids, 23 heparin and 46 remained untreated. The percent of death in the 3 groups was 27%, 23% and 51%. Mechanical ventilation was used in 4.3% of hydoxychloroquine, 14.2% of hydroxycholoroquine+azithromycin and 26.1% of controls. Unweighted and weighted relative hazards of mortality are shown in Table 1. After adjusting for a number of key confounders (see table), the use of hydroxycholoroquine+azithromycin was associated with a 66% reduction in risk of death as compared to controls; the analysis also suggested a larger effectiveness of hydroxychloroquine in patients with less severe COVID-19 disease (PO2/FiO2>300, interaction p-value<.0001). Our results are remarkably similar to those shown by Arshad *et al*.

Some important weaknesses of the analysis by Arshad have been pointed out [7] but not all of these apply to our study. Our propensity scores include some of the potential confounders that were missing in the analysis by Arshad (e.g. calendar day of admission, disease severity, cardio-vascular disease (CVD), baseline plasma CRP); second, we have excluded people receiving other drugs which could have biased the effect of hydroxychloroquine when used in combination. Third, although residual confounding is a possibility (e.g. people with CVD were more frequent in control), people in the control group were more likely to undergo mechanical ventilation that is a conservative bias. These results from two different real-life settings (Italy and USA), are conflicting with those of two large randomised trials [8, 9]. Although unmeasured confounding remains the most likely explanation for the discrepancies, a robust meta-analysis is still lacking and we question whether hydroxychloroquine should be further tested. When best to start treatment is also a question that needs to be addressed in ad-hoc randomised studies.

Table 1- Unadjusted and adjusted marginal relative hazards of in-hospital mortality

	Unadjusted HR (95% CI)	p-value	Adjusted*£ HR (95% CI)	p-value
	All Patients			
Control# (n=92)	1.00		1.00	
Hydroxychloroquine (n=197)	0.43 (0.28, 0.64)	<.001	0.66 (0.39, 1.11)	0.118
Hydroxychloroquine +Azithromycin (n=94)	0.36 (0.21, 0.60)	<.001	0.44 (0.24, 0.82)	0.009
	&Baseline PO2/FiO2 0-300			
Control# (n=41)	1.00		1.00	
Hydroxychloroquine (n=83)	0.52 (0.31, 0.87)		0.71 (0.37, 1.35)	
Hydroxychloroquine +Azithromycin (n=28)	0.46 (0.23, 0.93)		0.59 (0.26, 1.35)	
				p-value for interaction
				<.001
	&Baseline PO2/FiO2 300+			
Control# (n=33)	1.00		1.00	
Hydroxychloroquine (n=100)	0.39 (0.15, 0.97)		0.49 (0.15, 1.63)	
Hydroxychloroquine +Azithromycin (n=60)	0.56 (0.21, 1.52)		0.62 (0.19, 1.97)	

*adjusted for age, gender, number of comorbidities,CVD (yes/no), duration of symptoms, date of admission, CRP and censoring using IPW

£the overall estimate was also adjusted for baseline COVID-19 disease severity

#Heparin, immuno-modulatory drugs, HIV antivirals, a combinations of these or no drugs at all

& 45 patients missing baseline PO2/FiO2 not included in the stratified analysis

Declarations of interest: none

Funding: none

Ethical Approval: This analysis is part of the study approved by Ethic Committee Area 1, Milan Italy (2020/ST/049 and 2020/ST/049_BIS, 11/03/2020).

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