We have carefully read the work by Pradelle et al. [1], which provides important information on the compassionate use of hydroxychloroquine (HCQ) and mortality inCovid-19 patients in the United States, Turkey, Italy and other three European countries during the first wave of the pandemics. Despite its relevance, we have identified methodological concerns that may have led to an inflation of the excess deaths attributable to the prescription of HCQ in hospitalized Covid-19 patients.

Firstly, the authors define the excessive number of deaths attributable to compassionate use of HCQ as Ndeath = Nhospitalised patients × Mortality rate × HCQ exposure × ORHCQ-mortality.

To achieve this, they use the total hospital mortality coefficient of each country to define the baseline mortality of Covid-19 hospitalized patients. However, this coefficient must be interpreted as a weighted average of the mortalities of patients exposed and not exposed to the drug. Otherwise, the number of deaths in the treatment groups may be overestimated. Namely, Mt = MeP + Mu (1 − P), where Mt Me and Mu are the mortality rates in the total, in the HCQ exposed and in the unexposed patients, respectively, and P is the prevalence of exposure to HCQ.

#Our reply

Indeed, there is collinearity among the mortality rate estimates. We had not anticipated such high prescription rates, which is unusual for compassionate use medications. Nevertheless, thanks to the formula (3) proposed by the authors, we can estimate the distortion in the mortality rate estimation of non-exposed patients to be around 1% in absolute terms.

$$M_u = \frac{M_t}{1 + [P(RR - 1)]} \quad (3)$$

For Italy, which has one of the highest mortality and exposure rate, using M_t=0.228, P=0.808, and RR=1.08:

$$\mathbf{M_u = 0.228 / (1 + 0.808 \times (1.08\text{-}1))}$$

$$\mathbf{M_u = 0.214}$$

Another factor in the equation raising concern is the measure used to quantify the effect of HCQ on mortality. The authors used the odds ratio (OR) as if it were a relative risk (RR). However, it is known that for the same outcome, the odds ratio tends to be higher than the relative risk, especially when the incidence of the outcome is high [2], as is the case with Covid-19 mortality. For example, the authors obtained the OR that quantifies the HCQ effect on mortality (1.11) from a previous meta-analysis [3] which had the RECOVERY trial [4] as the article with the highest weight. Mortality occurred in 25% of the control group patients from RECOVERY. Considering this value as Mu, and the formula [5]:

$$RR = OR /(1 - M_u + (M_u OR)) \quad (1)$$

we have that an OR of 1.11 corresponds to a RR of 1.08.

#Our reply

In medicine, it is common practice to use OR (odds ratios) and RR (relative risks) without converting between different measures of relative effect. Although ORs are

known to be prone to overestimation, this effect is typically minor in most cases when modeling treatment effects, given the size of risks and drug effects. A general rule suggests that ORs should be adjusted when the incidence of the studied outcome exceeds 10% especially if the OR is greater than 2.5 or less than 0.5 (1). Here, the OR is 1.11 for a risk >20%.
Consequently, we had not planned for any transformation.
In our modeling, this could lead to an 20% overestimation in excess mortality given an OR=1.11 and RR=1.08 for countries with the higher mortality rates.

Besides these issues, we consider that the calculation of excess deaths can be done with an updated estimate of HCQ effect on mortality. The meta-analysis used by authors as source of the OR for their calculations included trials published until 10/16/2020 [3]. However, more updated effect measures are available in the literature. A systematic review with meta-analysis by Siemieniuk et al. included trials up to 12/03/2021 and estimated an ORHCQ-mortality = 1.08 (95% CI: 0.92 - 1.27) [6]. This OR would correspond to a RR = 1.06 (95% CI: 0.94 - 1.19), considering a Mu = 25%.

Based on these premises, we recalculated the estimates of deaths attributable to HCQ by using RR from the meta-analyses aforementioned, calculated from the OR considering the baseline risk of the RECOVERY trial [4]. The number of deaths in HCQ patients in each country was calculated as:

$$D_{HCQ} = N_{\text{hospitalised patients}} \times P \times M_u \times RR \quad (2)$$

Where

$$M_u = M_t \times (1 + [P \times (RR - 1)])^{-1} \quad (3)$$

And the excess of deaths in HCQ patients = $D_{HCQ} - N_{\text{hospitalised patients}} P M_u$.

We observe that the excess deaths attributable to HCQ are lower than previously estimated, as shown in Table 1.
#Our reply
We recalculated the estimates using a fixed RR=1.08 and adjusted the mortality rate for HCQ exposure. We confirmed the estimate of 11,735 excess deaths, compared to 16,990. This estimation does not qualitatively challenge our study, with estimated uncertainty margins ranging between 6,267 and 19,256
Moreover, using adjusted RRs according to mortality rate (range 1.082-1.103 compared to 1.08), we found an excess of deaths of 12,485. This figure demonstrates the sensitivity of estimates depending on models and parameter uncertainties. That's why, in our study, we emphasized that "*... the present results should be viewed as rough estimates only*".
It is unclear how Viera et al. produced their 95% confidence interval. We hypothesize that Viera et al. might have used confidence intervals for the treatment effect of HCQ on mortality, which, as reported in our discussion, explains why estimates can vary greatly due to the uncertainty of this measure. As described in the methods of our study, we used the range of HCQ exposures to provide the range of our estimate (4,609 and 13,887).

Table 1. Excess deaths by compassionate use of HCQ in Covid-19 recalculated with updated parameters.
Fixed RR=1.08, adjusted RR were calculated using mortality rate for each country. Nb of hosp.: number of hospitalization; RR: relative risk; HCQ: hydroxychloroquine.

Country	Nb of hosp.	Rates of HCQ exposure	Crude mortality rate	Adjusted mortality rate	Fixed RR	Adjusted RR	Previous estimates	New estimates with fixed RR	New estimates using adjusted RRs
Belgium	19444	0.51	0.218	0.201	1.08	1.084	240	166	174
France	99997	0.156	0.116	0.115	1.08	1.096	199	143	172
Italy	89895	0.808	0.228	0.214	1.08	1.082	1822	1244	1289
USA	888037	0.621	0.210	0.200	1.08	1.084	12739	8826	9371
Spain	104715	0.835	0.197	0.185	1.08	1.086	1895	1291	1395
Turkey	21417	0.731	0.055	0.051	1.08	1.103	95	65	84
Total							16990	11735	12485

Moreover, based on the available evidence, it is not possible to rule out the null value of the association because the most updated RR is not statistically significant.

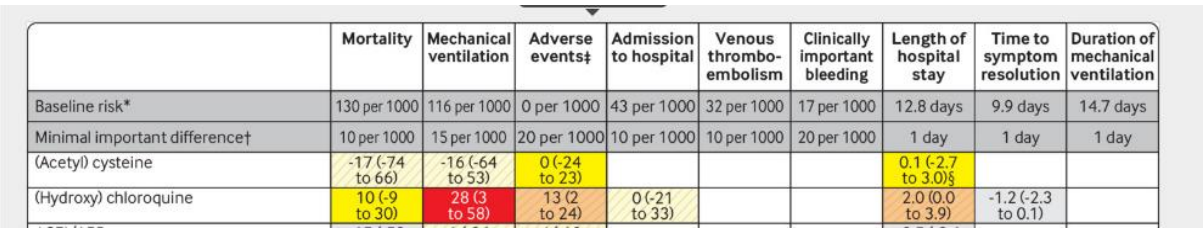
Meta-analyses	RR (95% CI)	Excess deaths	(95% CI)	
Axfors, 2021 [3]	1.08 (1.01 – 1.14)	11738	1534	19801
Siemieniuk, 2022 [6]	1.06 (0.94; 1.19)	8747	-9854	26053

#Our reply

The authors of this letter made two errors in interpreting the meta-analysis of Siemieniuk et al. published in the BMJ (1).

- **In this meta-analysis, the effects of chloroquine and hydroxychloroquine are pooled unlike in the meta-analysis by Axfors et al. (2). The methods section stated "*Treatments were grouped into common nodes based on molecule and not on dose or duration. For intervention arms with more than one drug, we created a separate node. Chloroquine and hydroxychloroquine were included in the same node for covid-19 specific effects and separated for disease independent adverse effects*."**

  In addition, the figures and tables were in accordance with the method's statement.



	Mortality	Mechanical ventilation	Adverse events‡	Admission to hospital	Venous thrombo-embolism	Clinically important bleeding	Length of hospital stay	Time to symptom resolution	Duration of mechanical ventilation
Baseline risk*	130 per 1000	116 per 1000	0 per 1000	43 per 1000	32 per 1000	17 per 1000	12.8 days	9.9 days	14.7 days
Minimal important difference†	10 per 1000	15 per 1000	20 per 1000	10 per 1000	10 per 1000	20 per 1000	1 day	1 day	1 day
(Acetyl) cysteine	-17 (-74 to 66)	-16 (-64 to 53)	0 (-24 to 23)				0.1 (-2.7 to 3.0)§		
(Hydroxy) chloroquine	10 (-9 to 30)	28 (3 to 58)	13 (2 to 24)	0 (-21 to 33)			2.0 (0.0 to 3.9)	-1.2 (-2.3 to 0.1)	

  Consequently, the estimate produced for (hydroxy)chloroquine (1.08, 95%CI 0.92 to 1.27) is not acceptable for our study. This does not affect the qualitative validity of our estimates, contrary to the authors' suggestion.

- **The meta-analysis of Siemieniuk et al. produced ORs, not RRs. Therefore, no transformation should be performed as done in this letter, and the estimations of excess deaths in Table 1 with transformed values (RR 1.06, 95%CI 0.94-1.19) are incorrected.**

It is worth mentioning that recent analyses suggest that a statistically significant increase in mortality in Covid patients treated with HCQ was only observed at high doses [7]. However, to accurately estimate the corresponding excess deaths attributable, it is necessary to know the frequency with which such doses were prescribed in the population.

#Our reply

The authors cite an unpublished meta-analysis, which suffers from four limitations: (i) the lack of peer review, (ii) the retrospective nature of the analysis, which contradicts the principle of the hypothetico-deductive method, (iii) the lack of power to demonstrate the absence of excess mortality with the lowest doses, and (iv) the absence of interaction between the two subgroups (lower vs higher doses).

Thus, while the point estimates suggested an excess of deaths in COVID-19 patients exposed, that amount seems to be smaller than reported by the authors. Furthermore, with the available evidence, this effect is not statistically significant. Finally, for analogous analyses, we recommend that RR be used instead of OR to calculate excess deaths, especially in scenarios of high incidence of the outcome.

#Our reply

We acknowledge that our model could potentially overestimate the number of deaths by 36%, and we appreciate the suggestions from the authors, which could be improved by the use of adjusted RR for HCQ effect.

However, we firmly disagree with the arguments presented regarding the misinterpretation of the meta-analysis of Siemieniuk et al. to justify a non-zero effect. Overall, this does not qualitatively challenge our results, as the estimate produced falls within the uncertainty margins of our study.

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