Supplementary material

1. Sensitivity analyses

Through additional statistical analyses we examined the potential impact on the main outcome (adjusted cause-specific in-hospital death hazard ratio for treatment) of several design features of the observed data base. Below, we thus accounted for further effects of (1) calendar time of entry (predictor of censoring), (2) continuous baseline confounders and (3) hospital membership, (4) of incomplete data (e.g. missing discharge data) with corresponding selection into the study population, and (5) of observed treatment group membership when treatment might be received several days past the starting date of the targeted survival time in this emulated trial (examining the so called *immortal time bias*).

The main cause-specific hazards model, M0, was performed to analyze time from in-hospital diagnosis until in-hospital death accounting for live discharge as the competing hazard, in the dataset with both admission and discharge data.

We used tenfold imputation assuming missing covariates were missing at random (using MICE package 3.8.0 with default options). The Cox proportional cause-specific hazards model from the R SURVIVAL library 3.1-12 was used with the Efron option to handle possibly tied event times, and robust standard errors allowing for clustering within hospitals. The treatment effect thus estimated varied very little across the different imputed datasets. This was also visually examined on the cumulative incidence plots that resulted in Figure 3. The model regressed the log cause-specific hazard linearly on baseline covariates as mentioned in the statistical analysis section: age, sex, comorbidities (cardiovascular disease, arterial hypertension, diabetes, chronic renal, liver and lung diseases, neurological and cognitive disorders, immunosuppressive conditions, malignancies, obesity and smoking status), laboratory parameters (LDH (≥ 350 U/L), CRP (≥ 150 mg/L) and paO2 (<60mmHg) at admission), clinical features (pneumonia diagnosis, acute respiratory distress syndrome, admission to intensive care unit within the 24h following admission, and the time from symptom onset to diagnosis) as well as calendar time of diagnosis. This yielded for HCQ adjusted in-hospital death **HR 0.684**, 95% CI 0.617–0.758.

Methods

In what follows we start from the model M0 above and either add additional covariates (make it more flexible) or drop or add additional (imputed) data depending on the presence of missing values (including also eligible patients who had admission data but no discharge data). Specifically, we performed the following additional analyses to evaluate sensitivity of the results to a number of assumptions made.

We evaluated the treatment effect in turn allowing for

1) an added interaction between treatment and calendar time of diagnosis
2) a more flexible (piecewise linear) effect of age and time from symptom onset to diagnosis
3) added the hospital membership as a fixed effect using the Firth correction
4) the M0 model fitted to the data subset with complete data (for all variables involved) only

5) adding the dataset of eligible patients with admission data but no discharge data (and hence no treatment indicator), NODISCHARGE. We performed two additional analyses on the thus augmented dataset
    a. Imputing treatment and outcome (through calendar time of diagnosis and time between diagnosis and discharge with discharge status) for NODISCHARGE data using the MICE package with the MAR (missing at random) assumption. Since we know that the true discharge times will tend to be longer by design in the dataset for which the discharge did not arrive prior to May 24, this underestimates the extent to which the `no-discharge data' cases are different from those entered in the main analysis. For this reason we performed a sensitivity analysis by adapting the NODISCHARGE outcome data next.
    b. Working with the same data as in a. we substituted the missing outcomes imputed above for the NODISCHARGE data by a discharge time exceeding May 24 and thus censored them on that date.
6) examination of immortal time bias by constructing emulated trials accounting for treatment timing.

In each of these analyses the estimated main effect of HCQ versus non-HCQ remained largely unchanged. Note that we did not allow for additional unmeasured confounders of treatment.

Results

1) A **linear interaction term between treatment and calendar time of diagnosis** was added to M0: A non-significant **interaction term (p=0.073) with HR = 1.009**, 95% CI 0.999 -1.018 suggesting a reduced HCQ effect for those entered more recently, accompanies an adjusted main effect of treatment HCQ versus non-HCQ (on the 31st of March = median calendar time considered): **HR 0.677**, 95% CI 0.611 - 0.751.

2) Inspection of martingale residuals on an imputed dataset suggested **a piecewise linear effect of age (with change point at age 55) and length of time between symptom onset and diagnosis (with change point at 10 days)** on the log cause-specific hazard scale. When both covariates were entered in addition to the other covariates of model M0, the HCQ effect was: **HR 0.693**, 95% CI 0.614 - 0.783.

3) The M0 model with **Firth correction to allow for additional fixed effects of individual hospitals** (95 dummy variables): **HR 0.661**, 95% CI 0.591-0.739. We also repeated this analysis with the exclusion of hospitals who treated 0% or 100% of their patients involved in our study, this excluded 18 hospitals (77 dummy variables remaining) which represented 20 patients: **HR 0.662**, 95% CI 0.592-0.740. In both analyses we used only the first imputed data set here.

4) The M0 model fitted to the data subset with **complete data** for all variables involved gave an adjusted HR for HCQ vs non-HCQ: **HR 0.691** with 95% CI 0.496-0.963.

5) The M0 model fitted on the **dataset augmented with those dropped out due to missing discharge data**, with different assumptions for the NODISCHARGE data:

a. MAR for treatment and outcome:
   adjusted HR for HCQ vs non-HCQ: **HR 0.661**, 95% CI 0.605-0.722
b. MAR for treatment + discharge time censored on May 24:
   adjusted HR for HCQ vs non-HCQ: **HR 0.704**, 95% CI 0.621-0.799

6) A stratified analysis has considered residual time to in-hospital death from treatment onwards. Each stratum consists of matching cohorts starting treatment (or not) at a given day post study entry to **avoid immortal time bias**. We considered starting days from 1 day earlier than the day of diagnosis up to 5 days after day of diagnosis. See Table S2 for an overview of the constructed data set. Emulating trials in this manner for 1 imputed dataset yields an **adjusted intention to treat HR for HCQ vs non-HCQ** using the same covariates and options as the M0 model but now stratified per trial: **HR 0.816**, 95% CI 0.751-0.887 [REF: Danaei et al. Stat Methods Med Res, 2013 22: 70 DOI: 10.1177/0962280211403603]

Table S2: *Overview of constructed emulated trials for the sensitivity analysis to asses "immortal time bias". After constructing these emulated trials the M0 model was again fitted but stratified according to the different starting date, with residual time to in-hospital death from `treatment start' onwards, the robust variance by clustering was no longer applied per hospital, but per patient.*

STRATA = the trials with the different starting days	starting HCQ treatment on day of strata	Considered COVID-19 Patients in the strata	Patients discharged dead	Patients discharged alive	Total follow up time (days)	Death rate (-)
-1	no	7215	1588	5627	86831	0.220
	yes	860	173	687	8339	0.201
	total	8075	1761	6314	95170	0.218
0	no	5380	1269	4111	60577	0.236
	yes	1835	319	1516	19039	0.174
	total	7215	1588	5627	79616	0.220
1	no	4337	1092	3245	44971	0.252
	yes	1002	163	839	10267	0.163
	total	5339	1255	4084	55238	0.235
2	no	3866	972	2894	37077	0.251
	yes	344	78	266	3684	0.227
	total	4210	1050	3160	40761	0.249
3	no	3500	872	2628	32005	0.249
	yes	136	18	118	1436	0.132
	total	3636	890	2746	33441	0.245
4	no	3103	759	2344	27587	0.245
	yes	101	15	86	1214	0.149
	total	3204	774	2430	28801	0.242
5	no	2748	650	2098	24059	0.237
	yes	75	12	63	705	0.160

	total	2823	662	2161	24764	0.235