Outcomes of 2,111 COVID-19 hospitalised patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a monocentric retrospective analysis

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ABSTRACT

Objectives We evaluated the 6-week mortality of SARS-CoV-2 hospitalised patients treated using a standardized protocol including systematic oxygen supplementation, broad spectrum antibiotics (NEWS-2 score >5), anticoagulation, combination hydroxychloroquine azithromycin (HCQ-AZ) if no contraindication, use of dexamethasone for severe patients and use of high-flow oxygen therapy in elderly patients non eligible for intensive care unit transfer.

Methods A retrospective monocentric cohort study was conducted in the standard hospital wards at the Institut Hospitalo-Universitaire Méditerranée Infection, between March and December 2020 in adults with PCR-proven infection.

Results Of the 2,111 hospitalised patients (median age, 67 [IQR 55-79] years; 1,154 [54.7%] men), 271 were transferred to the intensive care unit (12.8%) and 239 died (11.3%; the mean age of patients who died was 81.2 (±9.9)). Treatment with HCQ-AZ, used in 1,270 patients, was an independent protective factor against death (0.68 [0.52 – 0.88]). Zinc was independently protective against death (0.39 [0.23 – 0.67]), in a subgroup analysis of patients treated with HCQ-AZ. Dexamethasone was an independent factor associated with death for patients with CRP <100 mg/L (3.36, [2.09 – 5.40]) while no difference was observed for patient with CRP > 100mg/L. The use of high-flow oxygen therapy in elderly patients who were non eligible for intensive care unit transfer saved 19 patients (33.9%).

Conclusions Treating COVID-19 with HCQ-AZ is associated with lower mortality. The quality of care over time and analysed in large monocentric studies remains more valuable than randomised multicentric trials during new epidemics.

Highlights

- Treatment with HCQ-AZ was an independent protective factor against death
- Zinc was independently protective against death in patients treated with HCQ-AZ
- Monocentric studies are more valuable than multicentric trials during pandemics

INTRODUCTION

By 7 May 2021, SARS-CoV-2 outbreak had infected 156 million people and killed more than three million people (1). Worldwide management of the disease varied significantly in terms of indications for SARS CoV-2 testing of patients, therapeutic options and follow-up. Since March 2020, and based on preliminary Chinese data (2,3), at our hospital in Marseille, France, we decided upon a strategy including early massive screening by PCR and early treatment with hydroxychloroquine (HCQ) and azithromycin (AZ), as we had found that the association was effective against the virus on both *in vitro* and *in vivo* (4-7). Among the candidate treatments, only four main drugs (remdesivir, lopinavir-ritonavir, HCQ and dexamethasone) have been tested in large randomised studies. Lopinavir-ritonavir and remdesivir were associated with several and sometimes severe adverse events but did not demonstrate reproducible clinical efficacy (8, 9). Finally, corticosteroids (mainly dexamethasone) were then widely used to treat patients (10).

Broadly speaking, HCQ was associated with efficacy in terms of reducing viral shedding persistence in our preliminary study and improving clinical status in most of the observational studies. In contrast, no effect of HCQ was observed in most of the randomised studies (11-14). Importantly, most of the studies included inpatients and outpatients. In June 2020, we retrospectively reported the comparative clinical management of 3,737 outpatients and inpatients treated with HCQ-AZ or other treatments. HCQ-AZ was associated with a decreased risk of transfer to the ICU or with death (HR 0.19 0.12-0.29), a decreased risk of hospitalisation ≥10 days (odds ratios 95% CI 0.37 0.26-0.51) and shorter duration of viral shedding (time to negative PCR: HR 1.27 1.16-1.39). Recently, the need for early treatment using HCQ was demonstrated on large Iranian outpatient study (28,759 outpatients) and a Saudi Arabian study (5,541 outpatients) (15,16). In our outpatients cohort, we recently

reported a mortality rate of 0.15% among the 10,429 patients followed and a mortality rate of 0.06% among the 8,315 patients treated with HCQ-AZ (17).

Here, we report on a monocentric study performed in our institute involving the management of more than 2,111 patients treated in conventional hospital wards and observed by us, between 3 March and 31 December 2020, including those previously reported (7,8). The main outcome studied was death.

MATERIAL AND METHODS

Patients and study design

Our study was conducted at the Institut Hospitalo-Universitaire (IHU) Méditerranée Infection (https://www.mediterranee-infection.com/), which is home to the infectious and tropical diseases department of the Assistance Publique-Hôpitaux de Marseille (AP-HM), France (18). Our institute has 75 hospital beds. Since the beginning of the outbreak, we performed early massive PCR screening both on patients suspected of having COVID-19 and their contacts (18, 19). In addition, we proposed standardised treatment and follow-up for all individuals ≥18 years of age, with PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample in our outpatient ward, as previously described (19). The most severe patients could be hospitalised in five different ways at our institute: a) directly after screening in our day clinic, b) outpatients initially followed in our day clinic and then requiring hospitalisation, c) from the emergency department, d) from other hospital wards or nursing homes, e) from intensive care units. Data were collected from the patients hospitalised between 3 March and 31 December 2020 and were retrospectively analysed.

Clinical, biological and radiological data and follow-up

Demographic information (sex, age), and information on chronic conditions including cancer, diabetes mellitus, chronic heart disease, hypertension, chronic respiratory disease, obesity, hypothyroidism, asthma, obstructive sleep apnoea, and concomitant medications were

recorded. The Charlson index was recorded, as previously described (20). Clinical symptoms, including anosmia, ageusia, rhinitis, fever, cough, dyspnoea and thoracic pain, were systematically documented. Clinical severity was assessed using the National Early Warning Score adapted to COVID-19 patients (NEWS-2) upon hospital admission (21). Three categories of clinical deterioration were defined, as previously described: low score (NEWS-2=0-4), medium score (NEWS-2=5-6), and high score (NEWS-2≥7).

We recorded biological parameters including haemoglobin, lymphocyte, eosinophil and platelet counts; fibrinogen; D-dimer and other coagulation factors; electrolytes; zinc; lactate dehydrogenase (LDH); creatine phosphokinase (CPK); and C-reactive protein. Viral load was analysed by qPCR from nasopharyngeal swabs on admission and during the follow-up, and an indirect immunofluorescence quantitative assay was used to assess the serological status against SARS-CoV-2 (22). Viral culture was attempted for PCR-positive patients (23). A low dose CT-scan (LDCT) was proposed for all patients. Radiological lung lesions were classified into three categories: minimal, intermediate and severe involvement (18,24).

COVID-19 management

The first line treatment consisted of the combination of HCQ (200 mg of oral HCQ, three times daily for ten days) and AZ (500 mg on Day 1 followed by 250 mg daily for the next four days). This regimen was proposed as standard treatment for all patients without contraindications to these drugs. As previously detailed (17, 18), patients were informed of the off-label nature of the prescription of HCQ and AZ prior to receiving treatment. All patients underwent electrolyte analysis and an electrocardiogram (EKG) with corrected QT measurement (Bazett's formula) before starting treatment. EKGs with any abnormalities were systematically referred to a cardiologist for further assessment. From 15 April, following the preliminary results (25), we added the prescription of elemental zinc (15 mg, three times a day for 10 days).

In addition, broad-spectrum antibiotics (ceftriaxone or ertapenem) were included in the regimen for patients with pneumonia and/or NEWS scores ≥ 5. Since 5 April 2020, if they presented no contraindication, all patients were treated with an anticoagulant agent. The dosage of anticoagulant was decided according to the guidelines of the French Society of Anaesthesia and Resuscitation (Société française d'anesthésie et de réanimation) (26), with stratification according to level of oxygen administration, the patient's weight, D-dimers and fibrinogen dosage. For patients with a body mass index under 30 kg/m2, we prescribed enoxaparin 4000 UI a day. If the body mass index was higher than 30 kg/m2, or if high flow oxygen was used, we prescribed enoxaparin 4000 UI bid or 6000 UI bid. In cases of hypercoagulability marked by D Dimers higher than 3 µg/mL or fibrinogen higher than 8 g/L, we prescribed tinzaparin 175 UI/kg/d or enoxaparin 100 UI/kg/bid (regardless of weight or level of oxygen administration). In cases of renal impairment, sodic or calcic heparin was used. If patients were already receiving treatment with an anticoagulant agent upon admission, treatment was continued or adjusted for heparin, according to the recommendations of the clinician in charge (26).

Standard care included systematic oxygen supplementation. From June 2020 we used dexamethasone 6 mg for ten days, for patients outside the acute phase of the disease who required increased oxygen. Finally, from 15 September 2020, we used high-flow oxygen therapy devices for patients who were not eligible for intensive care due to their age and / or their comorbidities, and for whom transfer to the ICU was not possible (27).

Outcomes

The primary outcome was six-week mortality from admission date. Regarding the endpoint for clinical efficacy treatment analysis, we used two methods. Firstly, we performed an "intentionto-treat" analysis. Secondly, as previously described, we analysed the per

protocol outcome, selecting 72 hours after beginning the treatment for the evaluation (18). As a clinical outcome, we also evaluated transfer to the ICU as a secondary outcome.

Statistical analysis

Categorical variables were presented as n (%). We used the Wilcoxon Mann Whitney test, Student t-test, $\chi 2$ test, or Fisher's exact test to compare differences between groups of patients where appropriate. We performed multiple correspondence analysis (MCA) to investigate the associations between clinical data, biological data, radiological data, and the treatment received. In order to control for selection bias in comparing mortality between treatment groups, we used a propensity score weighting approach. The propensity score was calculated using a logistic regression with sex, age groups, NEWS-2 score, comorbidities and in-hospital treatment(s) (HCQ, AZ, Zinc and/or corticosteroids when appropriate) as covariates. The predicted probabilities from the propensity-score model were then used to calculate the stabilised inverse-probability-weighting weights (28). The association between treatment groups and mortality was then assessed using a weighted multivariable Cox models. Cox models were adjusted on the following variables: sex, age groups, NEWS-2 score, comorbidities and in-hospital treatment (HCQ, AZ, Zinc and/or corticosteroids where appropriate). Adjusted hazard ratios with 95% confidence intervals were calculated from the Cox regression coefficient estimates. Sensitivity analyses were performed by assessing whether observed effects were reproducible and consistent across subgroups according to age class, sex, comorbidities, disease severity, co-medications, and reasons for non-treatment. A two-sided α value of less than 0.05 was considered to be statistically significant. Analyses were carried out using SAS 9.4 statistical software (SAS Institute, Cary, NC).

Ethics statement

The data presented in this study were collected retrospectively from the routine care setting using the hospital's electronic health recording system. In France, at the time the study

was conducted, treatment of COVID-19 with HCQ for was approved off-label for hospital delivery only. As previously reported, for all patients, HCQ-AZ was prescribed either during complete hospitalisation or at day-care clinic by one of the physicians, after collegial decision based on their analysis of the most recent scientific data available and after assessment of the benefit/harm ratio of the treatment. In line with the European General Data Protection Regulation No 2016/679, patients were informed of the potential use of their medical data and that they could refuse the use of their data. The analysis of collected data followed the MR-004 reference methodology registered under No. 2020-152 in the AP-HM register. The non-interventional, retrospective nature of the study was approved by our institute's review board committee (Méditerranée Infection No.: 2021-015).

RESULTS

Overall characteristics of patients

From 3 March to 31 December 2020, 2,111 patients were hospitalised in our institute, 673 of whom we have previously reported on (13); 1,155 (54.7%) of them were male. The median age was 67 years, 682 patients (32.3%) were over 75 years of age and 146 (6.9%) were over 89 years of age (**Table 1**). Most of the patients were hospitalised from the emergency department (1.114, 52.8%), 496 patients (23.5%) directly after evaluation in our day clinic. 270 (12.8%) were first outpatients treated in our day clinic and then hospitalised, 193 patients (9.1%) came from other hospital wards and 38 patients (1.8%) were referred from the intensive care unit. A total of 1,270 (60.2%) patients received the combination of HCQ-AZ. Of the 841 patients not treated with this combination, 529 patients (62.9%) had a contraindication, the treatment was not proposed by the physician for 251 patients (29.9%), 33 refused the treatment (3.9%), and data was not available for 28 patients (3.3%) (**Table 2**). In addition, 1,302 (61.7%) patients were treated with zinc and 530 (25.1%) patients received dexamethasone.

Clinical, biological and radiological characteristics:

Underlying conditions and clinical symptoms are comprehensively described in **Table 1**. The mean Charlson index was 4.5 (±2.7). Most of the patients (796, 37.7%) had a NEWS-2 score ≥7 at the admission. A cough was the most frequent symptom (1,023, 48.5%), followed by dyspnoea (942, 44.6%), fever (601, 28.5%), anosmia (258, 12.2%), ageusia (255, 12.1%), thoracic pain (172, 8.1%) and rhinitis (127, 6%). Patients' biological characteristics upon admission of patients are comprehensively detailed in **Table 3**. The multiple correspondence analysis (MCA) allowed for the identification of different groups of patients depending on the outcome and highlighted the main clinical, biological and radiological involvement associated with death (**Figure 1**)

Adverse events associated with treatments

We listed 224 adverse events (**Table 4**). All adverse events were mild and included mostly gastrointestinal symptoms (74 cases of diarrhoea, 35 cases of nausea/vomiting and 29 cases of abdominal pain). We paid specific attention to QTc prolongation, which was observed in 38 patients (1.8%). Among them, only 11 patients had a QT > 500ms (0.52%). Among the 27 patients with QT < 500 ms, 13 patients (0.62%) had a QT expansion higher than 60 ms and 14 lower (0.66%). Thirty patients were treated with combination HCQ-AZ, 7 with AZ and 1 with HCQ. No cases of *torsade de pointe* or sudden death were observed.

Clinical outcomes

Of the 2,111 hospitalised patients, 271 (12.8%) were transferred into ICU (male, 73.8%). The mean age was 63.2(±11.0) years old (**Table 1, Figure 2**). A total of 239/2,111 (11.3%) patients, including those who were transferred to the ICU, died within six weeks (male, 61.9%). Their mean age was 81.2 (±9.9) years old. Almost two-thirds of patients with a fatal outcome were 80 year of age or older (152 patients, 63.6%, **Table 1**-**Table 5**). Nine patients with a fatal outcome were under 60 years old. Of these nine patients, six had severe

underlying conditions: two had Down's Syndrome with restrictive pulmonary syndrome, one had a mislabelled mental disability and chronic pulmonary insufficiency, one had late stage multiple sclerosis rendering him bedridden, one had a late stage inflammatory neurological disease, and one patient suffered from vasculitis, cardiomyopathy, renal chronic insufficiency, diabetes mellitus and chronic obstructive pulmonary disease. Only three patients who died had only moderate underlying conditions: one patient was a 49-year-old migrant with poorly stabilised type 1 diabetes, one 54-year-old patient was morbidly obese, and one 59-year-old patient had hypertension.

No patients under the age of 39 died, and the mortality rate was 1.2% for the 40–49 age group, 1.8% for 50–59, 4.9% for 60–69, 14% for 70–79, 27.6% for 80–89 and 32.2% for patients over the age of 89. Interestingly, the 90-day mortality rate of patients hospitalised in our institute was lower than national data in all age groups for the period from 1 March–15 June 2020 (**Figure 3**). Finally, mortality rates differed significantly depending on the mode of admission in our institute (2.2% for those who were first outpatients and were then hospitalised; 4.6% for patients who were directly hospitalised from our day clinic; 10.4% for patients transferred from other wards, and 17.1% for patients hospitalised from the emergency department (**Table 5**).

HCQ-AZ combination

The six-week mortality rate of patients treated with combination of HCQ-AZ was significantly lower than patients treated with other regimen whether in intention-to-treat (7.3% versus 17.4%, $p<0.001$) or per protocol including patients treated ≥3 days (5.9% versus 16.6%, $p<0.001$). In a weighted multivariate Cox proportional hazards model, HCQ-AZ was an independent protective factor against death (death hazard ratio (HR) 0.68, 95% confidence interval (95%CI) (0.52 – 0.88)) (Figures 4-5, **Tables S1-S2**). This effect was consistent for all subgroups of age, comorbidities, severity of the disease and comedications with zinc or

corticosteroids (**Figure 4**). Reasons for non-treatment (contraindication, non-proposition and refusal) were not confounding factors, as subgroup analyses excluding or including only these patients highlighted a similar protective effect **(Figure 4)**. This independent protective factor was confirmed in a 10 year age-stratified multivariable Cox proportional-hazards models from 55 to >80 years with hazard ratio ranging from 0.12 to 0.97 (**Figure S1**).

Zinc

Comparing the 1,302 patients treated with zinc to the 809 other patients not treated with zinc, using propensity weighted analysis, we did not demonstrate a reduction in death independently of age, comorbidities, severity of the diseases and other treatment (**Figure S2 Table S3**). Nevertheless, subgroup analyses evidenced that zinc was an independent protective factor against death among patients treated with HCQ-AZ without dexamethasone (n = 1,018, death hazard ratio (HR) , 0.39, 95%CI 0.23-0.67, p=0.0011; weighted multivariate Cox proportional hazards model) (**Figure S3**) and a trend for beneficial effect was observed in those treated with AZ only (n = 435, death hazard ratio (HR) , 0.64, 95%CI 0.39-1.06, p=0.0813).

Dexamethasone

Patients treated with dexamethasone were significantly older, more frequently male, had more severe symptoms and were significantly more likely to die (**Table S4**). Using a propensity weighted score to compare them, corticosteroids remained an independent factor associated with death for patients with CRP <100 mg/L (death hazard ratio (HR) 3.36, 95% confidence interval (2.09 – 5.40)) (**Table S5, Figure S4**). Conversely, for patient with CRP > 100mg/L, no difference in death outcome was observed between patients treated with or without corticosteroids (**Table S6, Figure S5**).

High-flow oxygen therapy

Fifty-six elderly patients who were not eligible for transfer to the ICU due to their age and comorbidities were treated in our institute using high-flow oxygen therapy. The mean age of these patients was 80.5 years (median 82.5) and 32 (57.1%) were male. These patients suffered from several underlying conditions (mean Charlson index: 6.8). Upon admission to our wards, clinical involvement was severe, with 80.4% of the patients having NEWS-2 score ≥ 7 (**Table S7**). Ultimately, 19 patients (33.9%) were weaned off HFNO and survived thanks to this technique.

DISCUSSION

In our institute, between February 2020 and May 2021, we implemented a widespread strategy of SARS-CoV-2 PCR screening of patients and their contacts who wanted to be tested. This led us to perform more than 600,000 PCRs, for 400,000 patients, of which 45,000 were positive. More than 20,000 were treated in our institute (21,000 in day clinic and 3,300 who were hospitalised). We previously reported the management of 3,700 out- and in-patients, where we described asymptomatic hypoxaemia, lung lesions on largely performed low dose CT-scan, biological factors (lymphocytopenia; eosinopenia; decrease in blood zinc; and increase in D-dimers, lactate dehydrogenase, creatinine phosphokinase, and C-reactive protein) associated with a poor clinical outcome (18). Finally, we demonstrated the role of the combination HCQ-AZ in decreasing morbidity, mortality and viral carriage (18). Since these earlier results, we have reported the outcome of more than 10,000 outpatients followed in 2020 in our centre (17). In this study, in addition to this recent work, we report our monocentric cohort of 2,111 patients hospitalised in 2020, and we confirmed the beneficial effect of HCQ-AZ after controlling for age, comorbidities and severity of the disease. This effect was consistent for all subgroups analyzed, and reasons for non-treatment (contraindication, non-proposition by the physician and refusal by the patient) were not confounding factors, as shown with subgroup analyses.

In this study, undoubtedly, the mortality rate that we observed was lower than in most studies including only hospitalised patients (11, 29, 30). The risk of death in patients was the same as that previously described in other series and patients over 80 years of age or with severe underlying conditions are particularly vulnerable. Conversely, the risk of death is extremely rare in patients under the age of 60 without comorbidities. As new information became available, we clearly demonstrated, in a cohort of hospitalised patients, the lower mortality of patients treated using the combination of HCQ-AZ. In addition, standard treatment has evolved. Since the beginning of April 2020 we added systematically anticoagulation for all patients. We also added the prescription of zinc. We demonstrated the interest of this for the first time, in reducing mortality in combination with HCQ-AZ. Finally, the equipment in the HFNO allowed us to propose a therapeutic treatment to patients who were not eligible for transfer to the ICU due to their age or comorbidities, which enabled us to save 19 lives in 2020. To date (May 2021), 43 elderly patients (32%) who were treated using HFNO were weaned off the treatment.

We think that our monocentric experience can help with the management of future outbreaks or new outbreaks linked to COVID-19, by showing that when patients are grouped in cohorts, daily observations allow standard care to be adjusted, leading to lower mortality rates. This phenomenon has also been observed in intensive care units where, initially, intubation was systematic and was then replaced where possible with non-intensive ventilation in the form of HFNO associated with ventral decubitus, which is less aggressive and corresponds more to the needs of this type of acute respiratory failure (31). For us, this series shows that there is no standardised solution for all infections and the treatment strategy must depend on the pathogen, and on the nature of the infected subjects, and that the protocols and recommendations must be established and modified as knowledge of the disease increases. This pragmatic approach is totally impossible in randomised trials. For example,

patients were not questioned about the presence of anosmia or ageusia in the first clinical trials (11). In some randomised trials, SARS-CoV-2 PCR testing was negative or was not performed because the laboratories were not equipped to do so, despite the fact that in our experience only 30% to 40% of individuals with suggestive clinical signs (other than anosmia) are positive for SARS-CoV-2 (32, 33). Consequently, the ability of the clinicians or the patients to decide that the clinical symptoms are caused by COVID-19 without PCR testing or anosmia, is in all likelihood extremely low.

Our experience has confirmed that the combination of HCQ-AZ gives significantly better results, as in many observational studies (15-17), excluding studies based on big data funded by the pharmaceutical industry (34). Finally, we did not demonstrate the benefit of corticosteroids on this disease, as reported in the Recovery trial (10), and which may have been part of the basic recommendations on the treatment of this disease. The Simpson effect cannot be excluded in the evaluation of corticosteroids, because the patients treated with corticosteroids had significantly more severe condition and were hospitalised at different stages of the disease (10, 35, 36). However, caution is essential especially in the acute phase of the disease or when there is no inflammatory syndrome during which the effect may be harmful.

In this type of epidemic, we believe that monocentric studies are more valuable than multicentric studies, due to the homogeneity of standard care (the “in our hands” phenomenon) (37). Moreover, the concentration in any given institute leads to a progression in the quality of care, which is linked to medical experience, the importance of which should not be neglected, in favour of evidence-based medicine. The quality of care remains a major element in patient care and observation remains a major element in reflecting on that care, particularly when it comes in new diseases.

371 **Table 1:** Baseline clinical characteristics (n=2,111)
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	All		ICU transfer		Deaths	
	n	%	n	%	n	%
n	2111		271		239	
Sex - Men	1154	54.7	200	73.8	148	61.9
Age - mean(std) Q1-median-Q3	65.8(17.2) 55-67-79		63.2(11.0) 56-64-72		81.2(9.9) 75-83-89	
Age 18-29	67	3.2	1	0.4	0	0
Age 30-39	118	5.6	6	2.2	0	0
Age 40-49	168	8	27	10	2	0.8
Age 50-59	380	18	60	22.1	7	2.9
Age 60-69	451	21.4	91	33.6	22	9.2
Age 70-79	401	19	73	26.9	56	23.4
Age 80-89	380	18	13	4.8	105	43.9
Age >89	146	6.9	0	0	47	19.7
Charlson index V1[b]- mean(std) Q1-median-Q3	4.5(2.7) 2-4-6		4.0(2.1) 2-4-5		6.9(2.2) 5-7-8	
Charlson index V2[b]- mean(std) Q1-median-Q3	1.4(1.7) 0-1-2		1.3(1.5) 0-1-2		2.4(2.0) 1-2-3	
Chronic condition(s)						
Hypertension	956	45.3	129	47.6	150	62.8
Diabetes mellitus	571	27	90	33.2	81	33.9
Cancer disease	246	11.7	32	11.8	42	17.6
Chronic respiratory diseases	393	18.6	47	17.3	62	25.9
Chronic heart diseases	520	24.6	59	21.8	116	48.5
Obesity	495	23.4	103	38	39	16.3
Hypothyroidism	210	9.9	22	8.1	31	13
Asthma	159	7.5	19	7	16	6.7
Obstructive sleep apnoea	112	5.3	21	7.7	15	6.3
Other inflammatory disease	97	4.6	12	4.4	16	6.7
Medications						
Metformin	336	15.9	50	18.5	34	14.2
Beta blocking agents	404	19.1	55	20.3	74	31.0
Verapamil	28	1.3	3	1.1	4	1.7
HMG CoA reductase inhibitors	418	19.8	57	21.0	64	26.8
Fibrates	26	1.2	3	1.1	6	2.5
Dihydropyridine derivatives	557	26.4	89	32.8	96	40.2
Angiotensin II receptor blockers	357	16.9	54	19.9	44	18.4
ACE inhibitors	251	11.9	34	12.5	30	12.6
Tobacco consumption	210	9.9	34	12.5	24	10.0
Pulmonary CT-scanner						
Missing	208	9.9	16	5.9	33	13.8
Normal	229	10.8	10	3.7	13	5.4
Minimal	496	23.5	22	8.1	31	13
Intermediate	717	34	90	33.2	69	28.9
Severe	461	21.8	133	49.1	93	38.9
Clinical symptoms						
Fever	601	28.5	112	41.3	67	28
Cough	1023	48.5	146	53.9	79	33.1
Rhinitis	127	6	8	3	3	1.3
Anosmia	258	12.2	39	14.4	9	3.8
Ageusia	255	12.1	42	15.5	10	4.2
Dyspnoea	942	44.6	171	63.1	134	56.1

Thoracic pain	172	8.1	13	4.8	5	2.1
NEWS score - mean(std) Q1-median-Q3	5.7(2.8) 4-6-8		7.0(2.5) 5-7-9		8.3(2.4) 7-8-10	
NEWS 0-4	735	34.8	41	15.1	11	4.6
NEWS 5-6	580	27.5	75	27.7	48	20.1
NEWS ≥7	796	37.7	155	57.2	180	75.3
Mode of hospitalisation						
Other wards	193	9.1	8	3	20	8.4
Firstly outpatient then hospitalisation	270	12.8	20	7.4	6	2.5
Directly from day clinic	496	23.5	58	21.4	23	9.6
From ICU	38	1.8	38	14	0	0
From emergency department	1114	52.8	147	54.2	190	79.5
Treatments						
HCQ-AZ	1270	60.2	158	58.3	93	38.9
Zinc	1302	61.7	170	62.7	161	67.4
Dexamethasone	530	25.1	169	62.4	121	50.6

373 a: Charlson index with age
374 b: Charlson index without age

Table 2. Patients not prescribed with hydroxychloroquine and azithromycin combination (n=841)

	n	%
Not proposed by the physician	251	29.9
Refused the combined treatment	33	3.9
Contraindication	529	62.9
Prolonged QTc	90	10.7
Other cardiac disorder	126	15.0
Risk of drug interactions	201	23.9
Ophthalmologic	5	0.6
Other contraindication	107	12.7
Other	28	3.3

Table 3. Baseline biological characteristics (n=2,111)

	All (n=2,111)			ICU Transfer (n=271)			Deaths (n=239)		
	n	mean	std	n	mean	std	n	mean	std
Potassium - mmol/L	1931	3.9	0.5	1931	3.9	0.5	1931	3.9	0.5
Lactate dehydrogenase - IU/L	1919	320	135	1919	320	135	1919	320	135
Creatine kinase - IU/L	1970	254	927	1970	254	927	1970	254	927
C-reactive protein - mg/L	2000	75.9	76.8	2000	75.9	76.8	2000	75.9	76.8
Troponin - IU/L	1322	27.9	80.7	1322	27.9	80.7	1322	27.9	80.7
Sodium - mmol/L	1966	138	4.4	1966	138	4.4	1966	138	4.4
Chlorides - mmol/L	1965	100	4.8	1965	100	4.8	1965	100	4.8
Proteins- g/L	1966	72.0	6.2	1966	72.0	6.2	1966	72.0	6.2
Creatinine - µmol/L	1966	89.4	62.2	1966	89.4	62.2	1966	89.4	62.2
Transaminases - ASAT IU/L	1966	50.9	96.3	1966	50.9	96.3	1966	50.9	96.3
Transaminases - ALAT IU/L	1966	40.6	48.7	1966	40.6	48.7	1966	40.6	48.7
GammaGT - IU/L	1971	71.0	84.6	1971	71.0	84.6	1971	71.0	84.6
Phosphatase - IU/L	1972	73.1	39.6	1972	73.1	39.6	1972	73.1	39.6
Bilirubin - µmol/L	1966	8.2	4.7	1966	8.2	4.7	1966	8.2	4.7
Zinc -	651	583	140	651	583	140	651	583	140
Eosinophils G/L - G/L	2037	0.0	0.1	2037	0.0	0.1	2037	0.0	0.1
Lymphocytes - G/L	2034	1.5	5.4	2034	1.5	5.4	2034	1.5	5.4
Platelets - G/L	2101	222	92.1	2101	222	92.1	2101	222	92.1
Fibrinogen - g/L	1992	5.7	1.6	1992	5.7	1.6	1992	5.7	1.6
D-dimers - µg/mL	1692	1.6	2.6	1692	1.6	2.6	1692	1.6	2.6
von Willebrand factor - IU/mL	366	7.1	18.2	366	7.1	18.2	366	7.1	18.2
TCK	349	1.8	0.6	349	1.8	0.6	349	1.8	0.6
Prothrombin - %	341	3.1	1.1	341	3.1	1.1	341	3.1	1.1

Table 4. List of adverse events (n=224)

	n	%
At least one adverse event	224	10.6
Diarrhoea	74	3.51
Prolonged QTc	38	1.8
- QT > 500 ms	11	0.52
- Expansion > 60 ms and QT < 500 ms	13	0.62
- Expansion < 60 ms and QT < 500 ms	14	0.66
Nausea / Vomiting	35	1.66
Abdominal pain / Other digestive troubles	29	1.37
Acute renal failure	21	0.99
Cytolysis / Cholestasis	20	0.95
Neuropsychiatric signs (mood disorder, insomnia, nervousness)	17	0.81
Skin disorders	16	0.76
Oral candidiasis	14	0.66
Headache	13	0.62
Anorexia	12	0.57
Fainting	9	0.43
Blurred vision and other visual disturbance	5	0.24
Dizziness	4	0.19
Palpitations / Tachycardia	4	0.19
Paraesthesia	2	0.09
Trembling	1	0.05

Tableau 5. Six-weeks mortality rates according to age and provenance (n=2,111)

	n	%
All (n=2,111)	239	11.3
Age		
Age 18-29 (n=67)	0	0.0
Age 30-39 (n=118)	0	0.0
Age 40-49 (n=168)	2	1.2
Age 50-59 (n=380)	7	1.8
Age 60-69 (n=451)	22	4.9
Age 70-79 (n=401)	56	14.0
Age 80-89 (n=380)	105	27.6
Age >89 (n=146)	47	32.2
Mode of hospitalisation		
Other wards(n=193)	20	10.4
Firstly outpatient then hospitalisation (n=270)	6	2.2
Directly from day clinic (n=496)	23	4.6
From ICU (n=38)	0	0.0
From emergency department (n=1114)	190	17.1

Figure 1. Baseline clinical and biological characteristics - Multiple Correspondence Analysis (n=2,111)

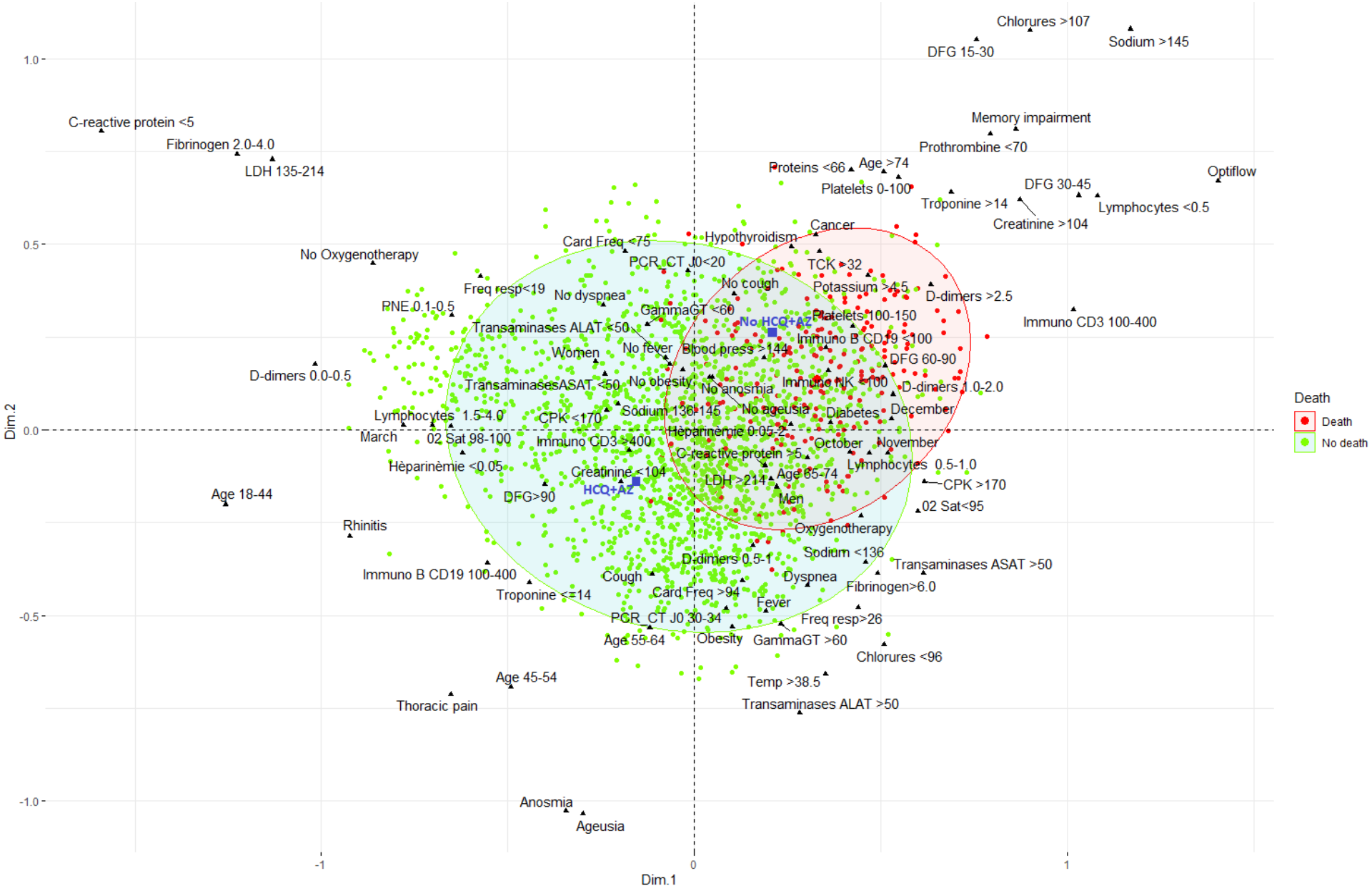


Figure 2: Number of ICU transfers and deaths according to age (n=2,111)

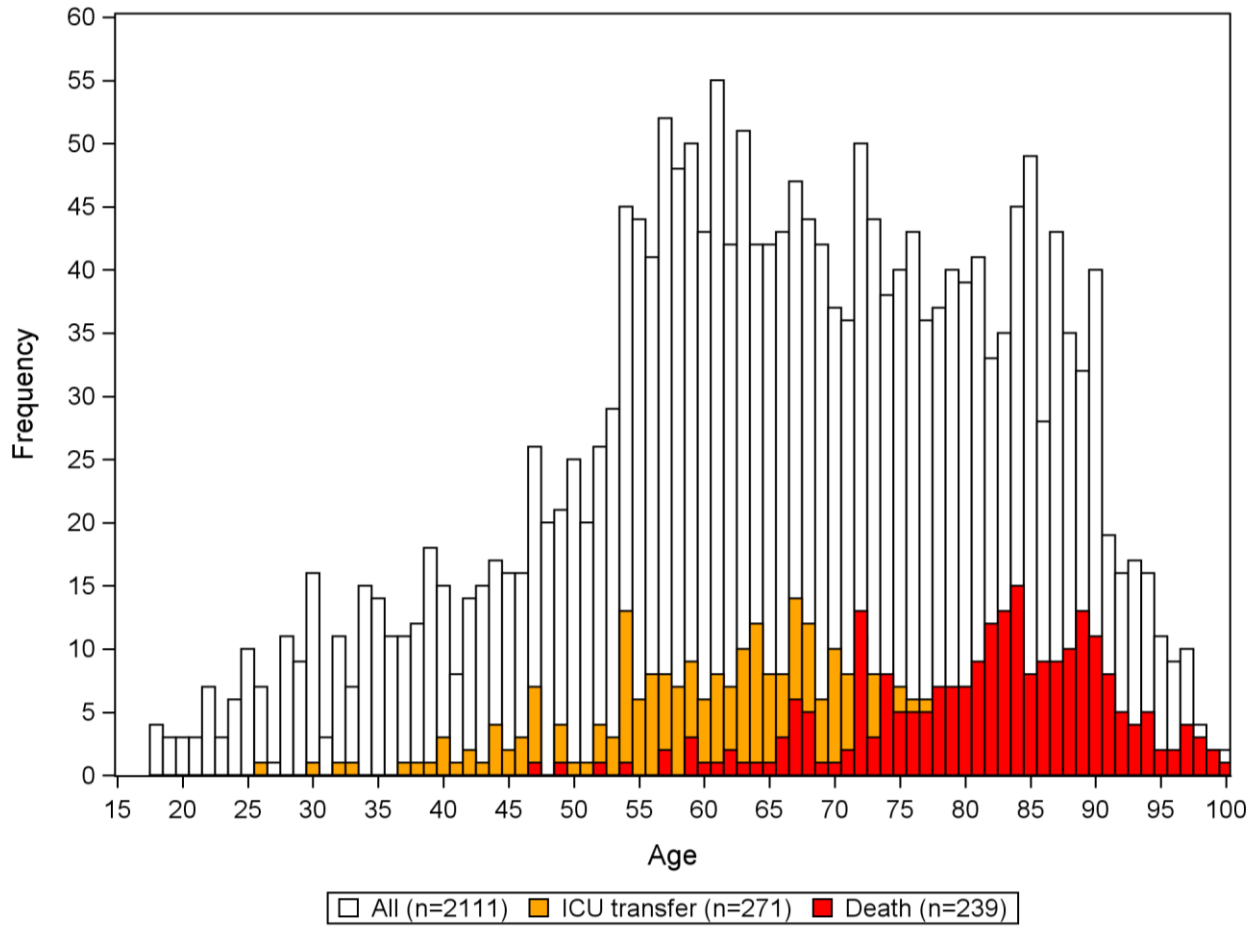
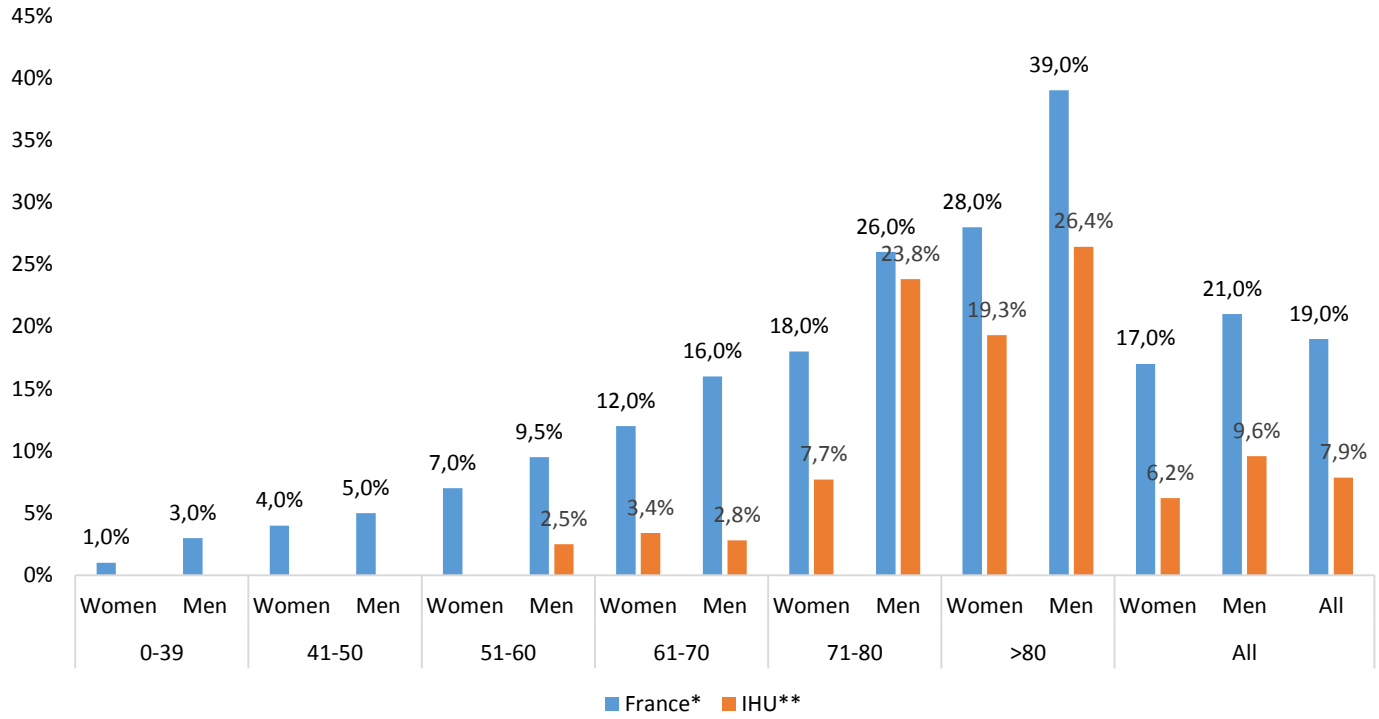


Figure 3: 90-day mortality rate during the first wave of COVID-19 - Comparison with French national estimates (n=700).



* 90,800 patients hospitalised between 1 March and 15 June in France.

** 700 patients hospitalised between 1 March and 15 June at IHU.

https://drees.solidarites-sante.gouv.fr/sites/default/files/2020-10/DD67.pdf

Figure 4: Association between treatment group (HCQ-AZ vs No HCQ-AZ) and death according to age, sex, comorbidities, severity and co-medications - Stratified multivariable Cox proportional-hazards models (n=2,111).

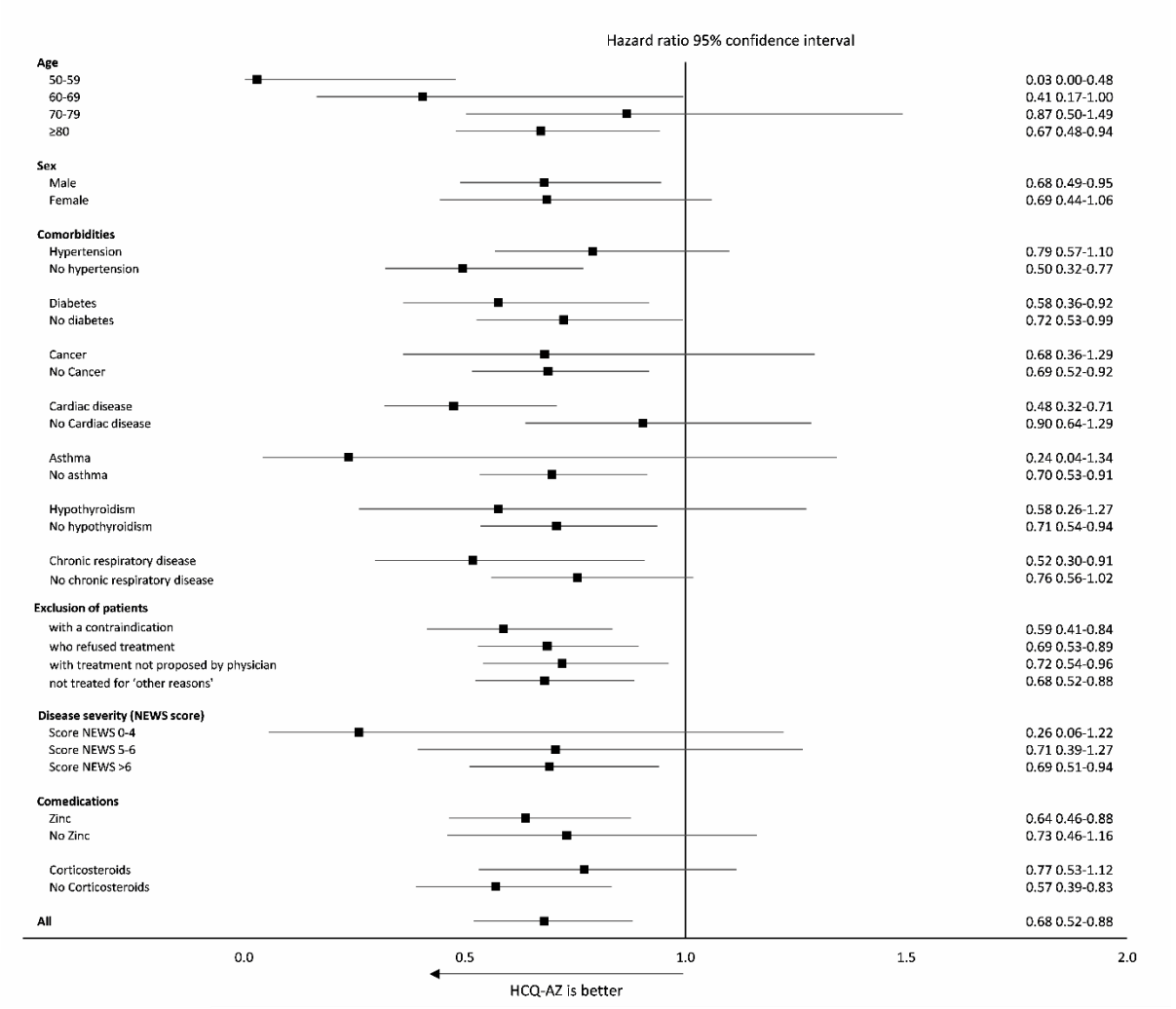
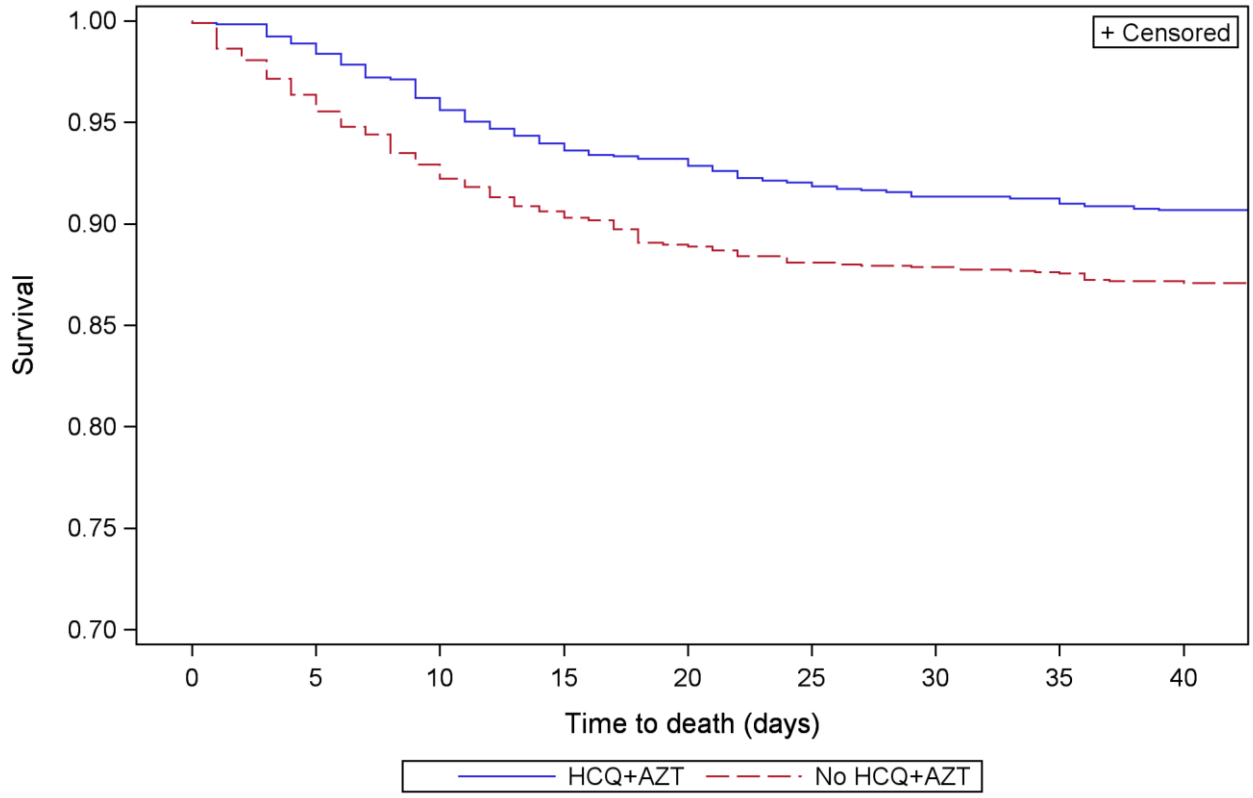


Figure 5. Kaplan-Meier curve of survival according to treatment groups (Propensity weighted sample, n = 2,111)



Log-rank test: p = 0.0135

Supplementary Material

Table S1. Comparison of treatment groups (HCQ-AZ vs No HCQ-AZ, n=2,111)

	Unweighted sample			Propensity weighted sample		
	HCQ-AZ	No HCQ-AZ		HCQ-AZ	No HCQ-AZ	
	N=1270	N=841	P*	N=1270	N=841	P*
Age mean(std)	63.0(16.7)	70.0(17.2)	<0.001	65.6(15.0)	65.1(21.4)	0.558
Men (%)	54.8%	54.5%	0.876	55.0%	55.6%	0.778
NEWS score						
0-4	38.3%	29.5%	<0.001	35.0%	35.5%	0.963
5-6	27.8%	27.0%		27.3%	26.8%	
>6	33.9%	43.5%		37.7%	37.7%	
Comorbidities						
Hypertension	40.3%	52.8%	<0.001	45.0%	44.8%	0.912
Diabetes mellitus	26.0%	28.7%	0.176	26.9%	26.5%	0.861
Cancer disease	11.3%	12.2%	0.489	12.0%	12.2%	0.853
Chronic respiratory diseases	16.2%	22.2%	0.001	18.6%	19.0%	0.820
Chronic heart diseases	17.4%	35.6%	<0.001	24.4%	24.5%	0.980
Obesity	22.9%	24.3%	0.476	23.2%	23.3%	0.969
Hypothyroidism	8.4%	12.2%	0.004	9.7%	9.6%	0.912
Asthma	7.3%	7.8%	0.655	7.6%	7.8%	0.875
Other inflammatory disease	3.9%	5.7%	0.047	4.6%	4.6%	0.977
Treatments (other than HCQ-AZ)						
Zinc	57.2%	68.5%	<0.001	61.9%	61.6%	0.888
Corticosteroids	19.8%	33.1%	<0.001	25.5%	25.6%	0.970

**: Chi-square/Fisher's exact or Student t-test where appropriate.*

Table S2 Association between treatment groups (HCQ-AZ vs No HCQ-AZ) and death - Multivariable Cox proportional-hazards model (n=2,111)

	HR	95% CI[a]	p
Treatment group (ref. No HCQ-AZ)	0.68	0.52-0.88	0.0037
Age (ref 18-54)			
55-64	2.59	0.83-8.09	0.1023
65-74	4.71	1.62-13.68	0.0044
>74	12.70	4.49-35.96	<.0001
Sex men (ref. women)	1.31	0.99-1.74	0.0566
NEWS score (ref. 0-4)			
5-6	3.28	1.65-6.55	0.0007
>6	6.13	3.15-11.95	<.0001
Number of comorbidities			
Hypertension	1.11	0.84-1.47	0.4697
Diabetes mellitus	1.01	0.76-1.35	0.9374
Cancer disease	1.10	0.78-1.55	0.5923
Chronic respiratory diseases	1.33	0.95-1.85	0.0925
Chronic heart diseases	1.56	1.19-2.04	0.0012
Obesity	0.66	0.45-0.95	0.0260
Hypothyroidism	1.15	0.77-1.71	0.4971
Asthma	1.14	0.64-2.03	0.6668
Other inflammatory disease	2.01	1.21 -3.35	0.0071
Treatments (other than HCQ-AZ)			
Zinc	0.63	0.47-0.84	0.002
Corticosteroids	2.56	1.92-3.40	<.0001

a: hazard ratio 95% CI

Table S3. Comparison of treatment groups (Zinc vs No Zinc, n=2,111)

	Unweighted sample			Propensity weighted sample		
	Zinc	No Zinc		Zinc	No Zinc	
	N=1302	N=809	p	N=1302	N=809	p
Age mean(std)	67.9(16.1)	62.4(18.5)	<0.001	65.9(15.5)	65.3(21.1)	0.476
Men (%)	56.8%	51.2%	0.011	52.0%	56.9%	0.024
NEWS score						
0-4	26.3%	48.5%	<0.001	34.7%	32.6%	0.187
5-6	30.2%	23.0%		27.8%	25.9%	
>6	43.5%	28.6%		37.6%	41.5%	
Comorbidities						
Hypertension	48.9%	39.6%	<0.001	45.6%	44.1%	0.509
Diabetes mellitus	30.4%	21.6%	<0.001	28.2%	30.0%	0.368
Cancer disease	11.8%	11.4%	0.751	11.8%	11.1%	0.613
Chronic respiratory diseases	20.4%	15.7%	0.007	18.9%	18.6%	0.841
Chronic heart diseases	27.3%	20.4%	0.000	25.3%	23.1%	0.243
Obesity	28.3%	15.6%	<0.001	24.6%	26.0%	0.487
Hypothyroidism	9.8%	10.3%	0.706	11.5%	9.1%	0.071
Asthma	8.1%	6.7%	0.240	8.1%	7.4%	0.520
Other inflammatory disease	4.6%	4.6%	0.970	5.5%	5.9%	0.662
Treatments (other than zinc)						
AZ	97.9%	83.6%	<0.001	91.1%	92.5%	0.231
HCQ	56.2%	71.3%	<0.001	61.3%	55.5%	0.007
Corticosteroids	36.2%	7.3%	<0.001	24.9%	28.0%	0.105

**: Chi-square/Fisher's exact or Student t-test where appropriate.*

Table S4. Characteristics of patients treated with corticosteroids (n=2,111)

	No corticosteroids N=1581	Corticosteroids N=530	p
Age mean(std)	64.5(18.1)	69.5(13.7)	<0.001
Men	50.8%	66.2%	<0.001
NEWS score mean(std)	5.2(2.7)	7.1(2.5)	<0.001
0-4	41.5%	14.9%	<0.001
5-6	27.7%	26.8%	
>6	30.8%	58.3%	
Death	7.5%	22.8%	<0.001

Table S5. Comparison of treatment groups among patients with baseline CRP<100 (Corticosteroids vs No Corticosteroids, n=1,073)

	Unweighted sample			Propensity weighted sample		
	No corticosteroids	Corticosteroids		No corticosteroids	Corticosteroids	
	N=858	N=215	p	N=858	N=215	p
Age mean(std)	65.2(18.5)	67.2(13.5)	0.085	65.6(14.5)	66.3(23.4)	0.593
Men (%)	46.7%	62.3%	<.0001	49.8%	44.3%	0.068
NEWS score						
0-4	44.6%	7.0%	<.0001	37.1%	38.6%	0.878
5-6	29.1%	27.0%		28.8%	27.9%	
>6	26.2%	66.1%		34.2%	33.5%	
Comorbidities						
Hypertension	46.6%	47.4%	0.829	46.7%	45.0%	0.578
Diabetes mellitus	27.5%	28.8%	0.697	27.8%	24.8%	0.262
Cancer disease	11.2%	9.3%	0.426	10.8%	14.9%	0.047
Chronic respiratory diseases	15.9%	19.5%	0.194	16.4%	12.4%	0.056
Chronic heart diseases	25.9%	19.5%	0.054	24.9%	25.3%	0.892
Obesity	22.0%	36.7%	<.0001	24.9%	21.2%	0.151
Hypothyroidism	11.5%	5.1%	0.006	10.2%	3.5%	<.0001
Asthma	5.2%	7.0%	0.323	5.6%	3.7%	0.151
Other inflammatory disease	3.5%	1.9%	0.221	3.1%	1.0%	0.014
Treatments (other than corticosteroids)						
AZ	93.0%	96.3%	0.078	93.7%	93.0%	0.651
HCQ	66.6%	50.7%	<.0001	63.3%	64.4%	0.710
Zinc	56.5%	91.6%	<.0001	63.7%	67.4%	0.195

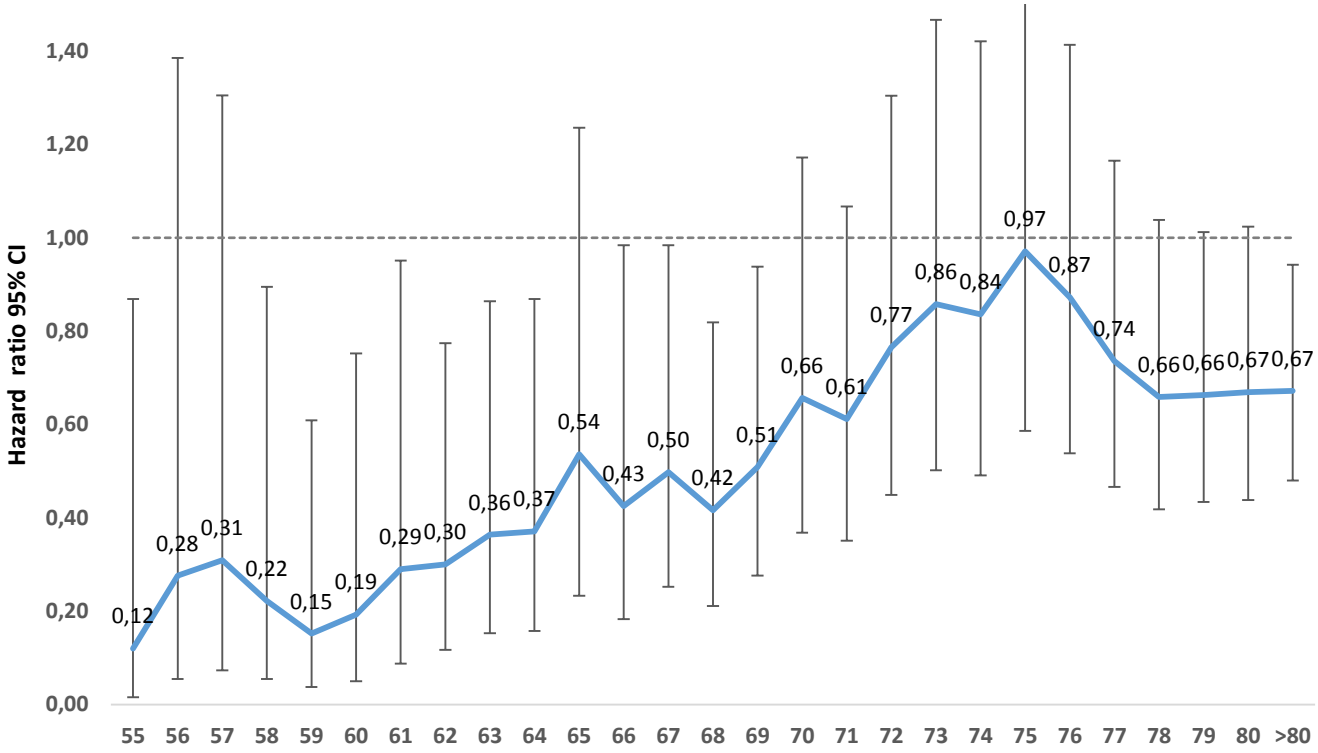
Table S6. Comparison of treatment groups among patients with baseline CRP≥100 (Corticosteroids vs No Corticosteroids, n=446)

	Unweighted sample			Propensity weighted sample		
	No corticosteroids	Corticosteroids		No corticosteroids	Corticosteroids	
	N=226	N=220	p	N=226	N=220	p
Age mean(std)	68.1(15.5)	70.5(13.0)	0.084	69.3(15.1)	68.9(12.8)	0.775
Men (%)	65.9%	69.6%	0.414	32.4%	27.5%	0.258
NEWS score						
0-4	16.8%	5.5%	<.0001	11.1%	14.0%	0.654
5-6	30.5%	18.2%		24.5%	23.2%	
>6	52.7%	76.4%		64.5%	62.9%	
Comorbidities						
Hypertension	50.0%	52.3%	0.631	51.4%	45.9%	0.241
Diabetes mellitus	31.0%	36.4%	0.228	33.6%	31.7%	0.661
Cancer disease	10.6%	12.3%	0.583	12.0%	11.3%	0.800
Chronic respiratory diseases	12.4%	21.8%	0.008	15.5%	16.0%	0.871
Chronic heart diseases	24.3%	31.8%	0.079	28.0%	25.8%	0.605
Obesity	19.0%	27.3%	0.039	21.0%	20.8%	0.961
Hypothyroidism	7.5%	9.1%	0.548	7.3%	7.1%	0.926
Asthma	4.0%	9.1%	0.029	5.4%	6.0%	0.801
Other inflammatory disease	5.3%	3.2%	0.266	4.2%	3.6%	0.720
Treatments (other than corticosteroids)						
AZ	93.4%	95.0%	0.461	94.9%	95.0%	0.966
HCQ	62.4%	49.6%	0.006	54.5%	55.5%	0.828
Zinc	52.2%	90.9%	<.0001	71.1%	69.8%	0.767

Table S7. Characteristics of patients treated with high-flow oxygen therapy (n=56)

	n	***%***
Sex – Men	32	57.1
Age - mean(std) Q1-median-Q3	80.5(9.3) 77.0-82.5-84.5	
NEWS score - mean(std) Q1-median-Q3	8.6(2.2) 7.0-9.0-10.0	
NEWS 0-4	2	3.6
NEWS 5-6	9	16.1
NEWS =>7	45	80.4
Charlson index - mean(std) Q1-median-Q3	6.8(2.2) 5.0-6.5-8.0	
Death	37	66.1

Figure S1. Association between treatment group (HCQ-AZ vs No HCQ-AZ) and death – 10 year age-stratified weighted multivariable cox proportional-hazards models (n=2,111)



a: The value reported on the X axis corresponds to the mid-point of the corresponding age stratum (ex: 55= between 50 and 60 years old).

Figure S2. Kaplan-Meier curve of survival according to treatment groups (Propensity weighted sample, n = 2,111)

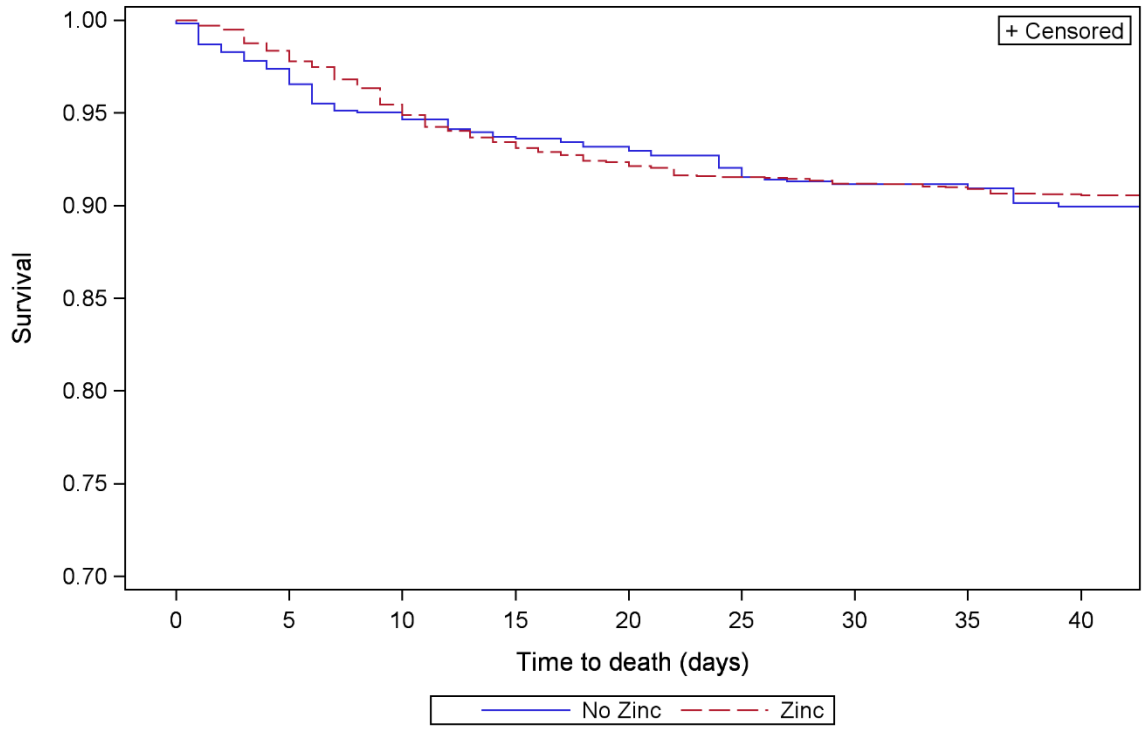
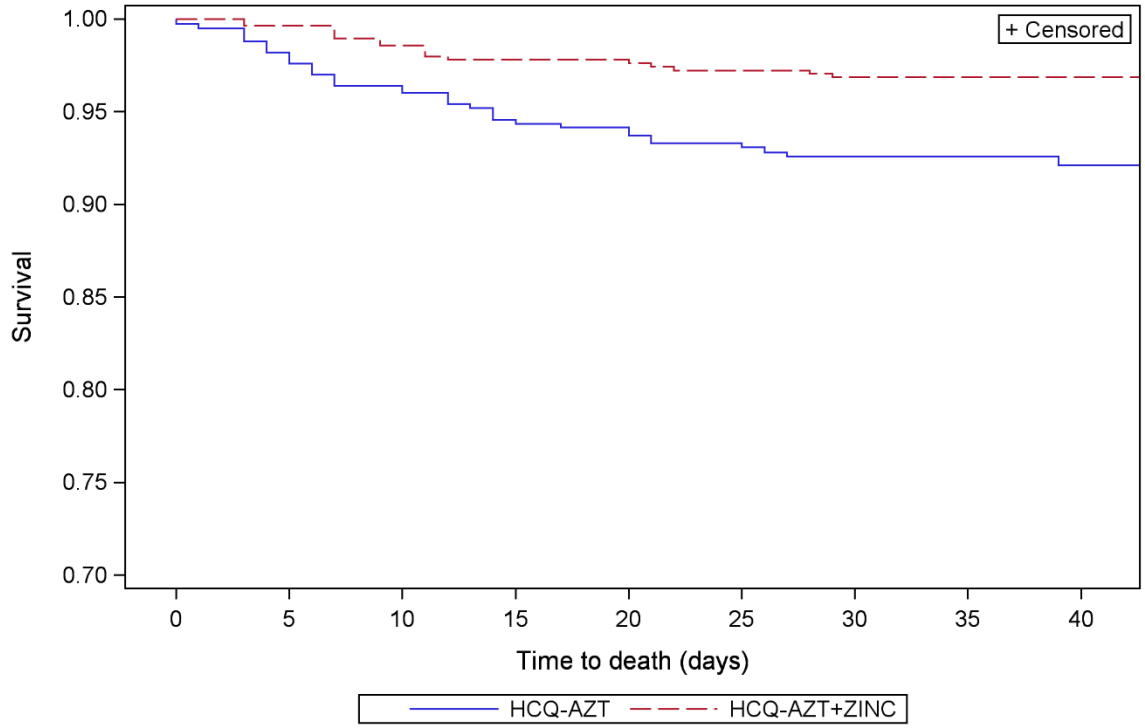
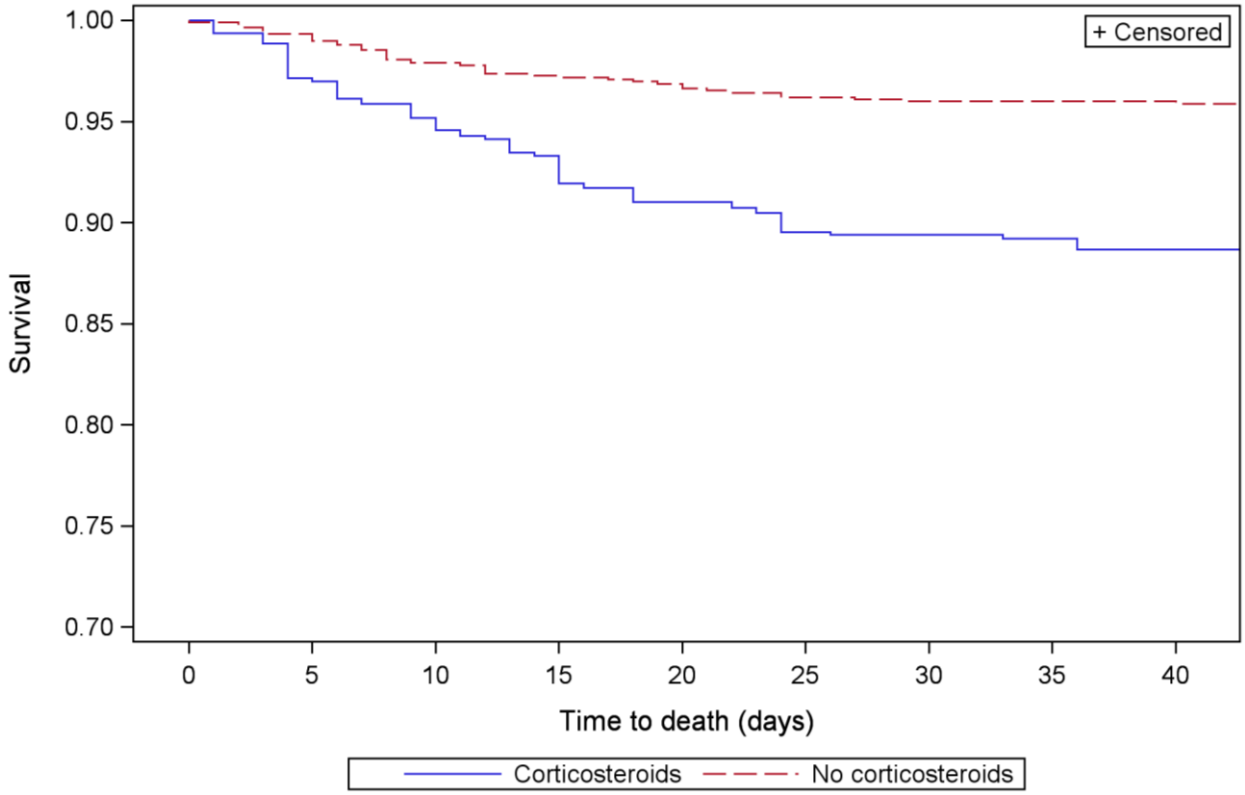


Figure S3. Kaplan-Meier curve of survival according to treatment groups (Propensity weighted sample, n = 1,018a)



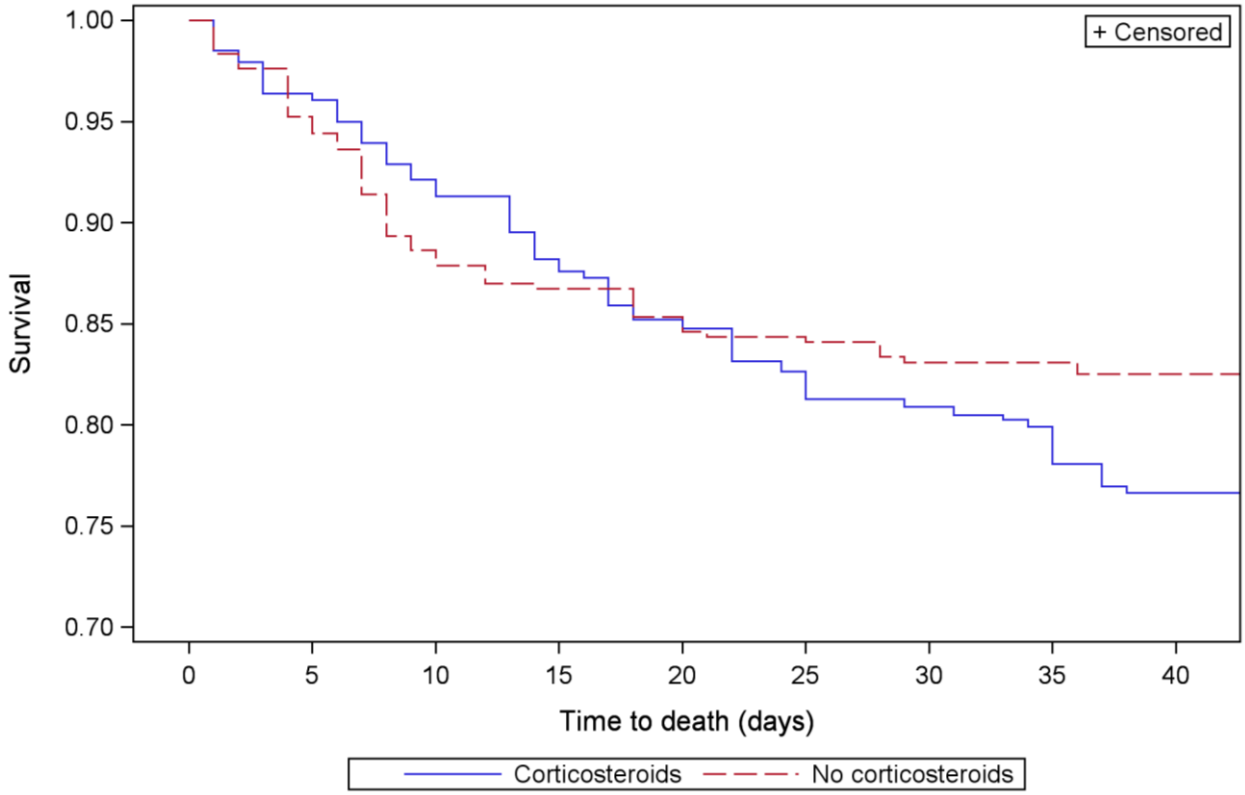
a: 1018 patients treated with HCQ-AZ (no corticosteroid)
Log-rank test: p=0.0011
Adjusted hazard ratio: 0.39 0.23-0.67 (p<0.001)

Figure S4. Kaplan-Meier curve of survival according to treatment groups among patients with baseline CRP<100 (Corticosteroids vs No Corticosteroids, Propensity weighted sample, n=1,073)



Log rank test: p=0.2019
Adjusted hazard ratio: 3.36 2.09-5.40 (p<0.001)

Figure S5. Kaplan-Meier curve of survival according to treatment groups among patients with baseline CRP≥100 (Corticosteroids vs No Corticosteroids, Propensity weighted sample, n=446)



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All authors read and approved the final manuscript

Declaration of competing interest

The authors declare no competing interests. Funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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