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Deaths induced by compassionate use of hydroxychloroquine during th first COVID-19 wave: an estimate

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ABSTRACT

Background: During the first wave VID-19 roxychloroquine (HCQ) was used off-label despite the absence of evidence enting its cl ts. Since then, a meta-analysis of randomised trials showed that HCQ use was a h an 11% increase in the mortality rate. We aimed to estimate the number of HCQ-related deaths w dwid
Methods and findings: stim the orldwide in-hospital mortality attributable to HCQ use by combining the mort rate, HCQ e, number of hospitalised patients, and the increased relative risk of death with HCQ lity rate ospitalised patients for each country was calculated using pooled prevalence esti- m by a m -analysis ublished cohorts. The HCQ exposure was estimated using median and extreme nates fr the same s matic review. The number of hospitalised patients during the first wave was t ted tabases. The systematic review included 44 cohort studies (Belgium: k = 1, France: k = 2 k = 12, Spain: k = 6, Turkey: k = 3, USA: k = 20). HCQ prescription rates varied greatly from one countr nother (range 16–84%). Overall, using median estimates of HCQ use in each country, we estimated that 16,9 Q-related in-hospital deaths (range 6267–19256) occurred in the countries with available data. The median mber of HCQ-related deaths in Belgium, Turkey, France, Italy, Spain, and the USA was 240 (range ot estimable), 95 (range 92–128), 199 (range not estimable), 1822 (range 1170–2063), 1895 (range 5–2094) and 12739 (3244– 15570), respectively.
C sions: Although our estimates are limited by their imprecision, these findings illustrate the hazard of drug repurposing with low-level evidence.

1. Introd on

In mber virus emerged in Wuhan, located in Hubei Province, [1] the e acute respiratory syndrome coronavirus 2 (SARS-C responsible for the Coronavirus disease 2019 (COVID-19). T NA-positive virus has caused a global pandemic. As of 2nd April 2023, ere were 764474387 confirmed cases of COVID-19 worldwide and 6915286 deaths [2].

Many treatments have been repurposed with varying degrees of success for patients, such as dexamethasone [3], hydroxychloroquine (HCQ) [4,5], remdesivir [4,6], or a combination of lopinavir and ritonavir [4,7], based on their effectiveness against other pathogens with similar structure or mechanism of action to SARS-CoV-2. For instance, remdesivir and lopinavir/ritonavir, which are prodrugs that form an analogue of adenosine triphosphate and inhibit viral RNA polymerase and replication, inhibit human and animal coronaviruses in vitro [8,9]. HCQ, a 4-aminoquinoline drug used to treat malaria and autoimmune rheumatic diseases, inhibits viral replication by increasing the pH of the

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endosome used for cell entry. In addition, HCQ may interfere with angiotensin-converting–enzyme 2 glycosylation, which is the cellular receptor of SARS-CoV-2 [10,11]. During the first wave of the pandemics, off-label use of HCQ has been proposed as a treatment option for COVID-19. Subsequent studies documented however an unfavourable risk-benefit balance, including the RECOVERY trial that showed a significant increase in cardiac mortality as well as a trend for increased all-cause mortality risk with HCQ [5]. In a meta-analysis of 14 trials testing HCQ in hospitalised patients with various doses, HCQ was associated with an 11% (95%CI 2–20%) increase in all-cause mortality [12].

The main objective of our study was to estimate the mortality attributed to compassionate use of HCQ in the context of COVID-19 before the publication of reliable randomised controlled trials (RCTs).

2. Methods

2.1. Outcomes

The main outcome was the estimated number of excess deaths amongst hospitalised patients for COVID-19 during the first wave of the pandemic attributable to HCQ worldwide.

2.2. Sources of data

2.2.1. Mortality rates and HCQ exposure

We conducted a systematic review and a meta-analysis of cohort studies to estimate the mortality rates and the proportion of HCQ exposure in hospitalised patients in each country represented in the available studies. We conducted a literature search to identify all published studies reporting the number of patients on all trea examined in COVID-19. We searched Pubmed, from 1st December 9, to 15th March 2021, using the keywords "coronavirus", "severe e respiratory syndrome 2 coronavirus", "SARS-CoV-2", "novel coron rus", "nCoV", "2019-nCoV" and "COVID-19" and "coh Pubme we selected studies according to the following i sion c ria: mu ticentre study, study size ≥ 500 patients to a centre ect. study reporting the treatments used in COVID-19 and nu treated with these drugs. Studies includi ly pa eceiving HCQ, receiving HCQ from August 2020 onw s, and patie eady treated with HCQ for autoimmune conditi excluded, as as studies from countries for which mortali data w lacking. Two authors (AP and JCL) reviewed the title bstracts and texts of all articles. If there was any doubt, a t reviewer (SM) i the final decision. When different studies e grou d in an article, we verified whether the studies had alre een i dually selected and if so, they were removed from our stu d not co der studies containing only ICU patients h e too l extern arameters could influence the results. Fr cted st authors (AP and SM) independently cted t type of s , inclusion dates, mortality rates, perce s of IC ions, countries of study, and the number of patients g HCQ contacted the authors of the included studies in ca e needed additional data.

2.2.2. Hospitalisa

We obtained the total number of hospitalisations by country from the dedicated databases [13–15]. We used hospitalisation data from the beginning of the pandemic in each country (mostly from March 2020 onward) until 17th July 2020 (i.e. date of publication of the RECOVERY trial[5]).

2.2.3. Relative HCQ effect on death

We used the odds ratio (OR) for HCQ-related mortality estimated from a previous meta-analysis of RCTs (i.e. OR=1.11) [12].

2.3. Statistical analysis

2.3.1. Mortality rates and HCQ exposure

The mortality rates for each country were estimated using a meta-analytic approach by pooling (random-effects model) the proportions reported in all included cohort studies. The HCQ exposure was estimated using median and extreme estimates from the same systematic review. A sensitive analysis was conducted using the estimate of mortality rate in hospitalised patients from other sources such as national surveillance report and regionwide analysis.

2.3.2. Number of excess deaths attributable t

We calculated the number of deaths i spitalise tients ($N_{hospitalised\ patients}$) by multiplying the n r of hospi d patients receiving HCQ by the mortality rate of country. T number of deaths (N_{deaths}) related to HCQ e ure was ined b ltiplying (i) the previously estimated nu of in-hospita r country and (ii) the OR of HCQ-relate ortality e main ce of uncertainty included in the model wa ran HCQ exposure, which was estimated using the me and e values inimum, maximum) reported in the incl d cohort st

$$N_{death} = N_{hos\ ed\ p} \times \text{mortality r} \times \text{HCQ exposure}_{median,\ min,\ max} \times OR_{HCQ\text{-}mortality}$$

W rmed statistica lysis with R (meta-package, *R Language a nvironment for Statistical Computing, Vienna, Austria*).

3. esults

3.1. eristics

e retrieved 7848 articles using the previously mentioned search ter reviewing titles, abstracts, and some full texts, we selected 44 studies totalizing 98406 patients (Fig. 1). The 44 included studies were conducted in Turkey (k = 3) [16–18], Belgium (k = 1) [19], France (k = 2) [20,21], Spain (k = 6) [22–27], Italy (k = 12) [28–39], and the USA (k = 20) [40–59] (Table 1). Out of the 44 studies, 5 studies were used only to estimate in-hospital all-cause mortality [21,29,39,58,59]. Among the 44 studies, 5 (11%) were prospective [20,22,32,38,43] and 32 (72%) included consecutive patients [16–18,20,22,24–28,30–32,34–36,41,42,44,45,47–54,56,57] (Table 1). The median number of patients included in each study was 1109 (range 348–15111), including 20% admitted to the ICU (range 0–68). The median age of the patients was 65 years (range 56–75), and 58% were men (range 47–96). The all-cause mortality was 21% (range 9–34%). Eleven studies (25%) were designed to report the treatment effect of compassionate drug use [19,22,23,28,39,46–48,55,58,59].

3.2. HCQ exposure, mortality rates and HCQ-related deaths

The number of patients treated with HCQ for COVID-19 for each country ranged from 10,018 to 551,417, with a heterogeneous exposure varying from 16% (France) to 84% (Spain). The mortality rates were calculated using data from one (Belgium) [19] to 20 cohorts (USA) (Fig. 2) [40–59]. The all-cause mortality of in-hospital patients ranged from 6% (Turkey) to 23% (Italy) (Table 2).

The median number of HCQ-related deaths in Belgium, Turkey, France, Italy, Spain, and the USA was 240 (range not estimable), 95 (range 92–128), 199 (range not estimable), 1822 (range 1170–2063), 1895 (range 1475–2094) and 12,739 (range 3244–15570), respectively. Overall, using median estimates of HCQ use in each country, we estimated that 16,990 HCQ-related in-hospital deaths (range 6420–20294) occurred in the countries with available data Table 3.

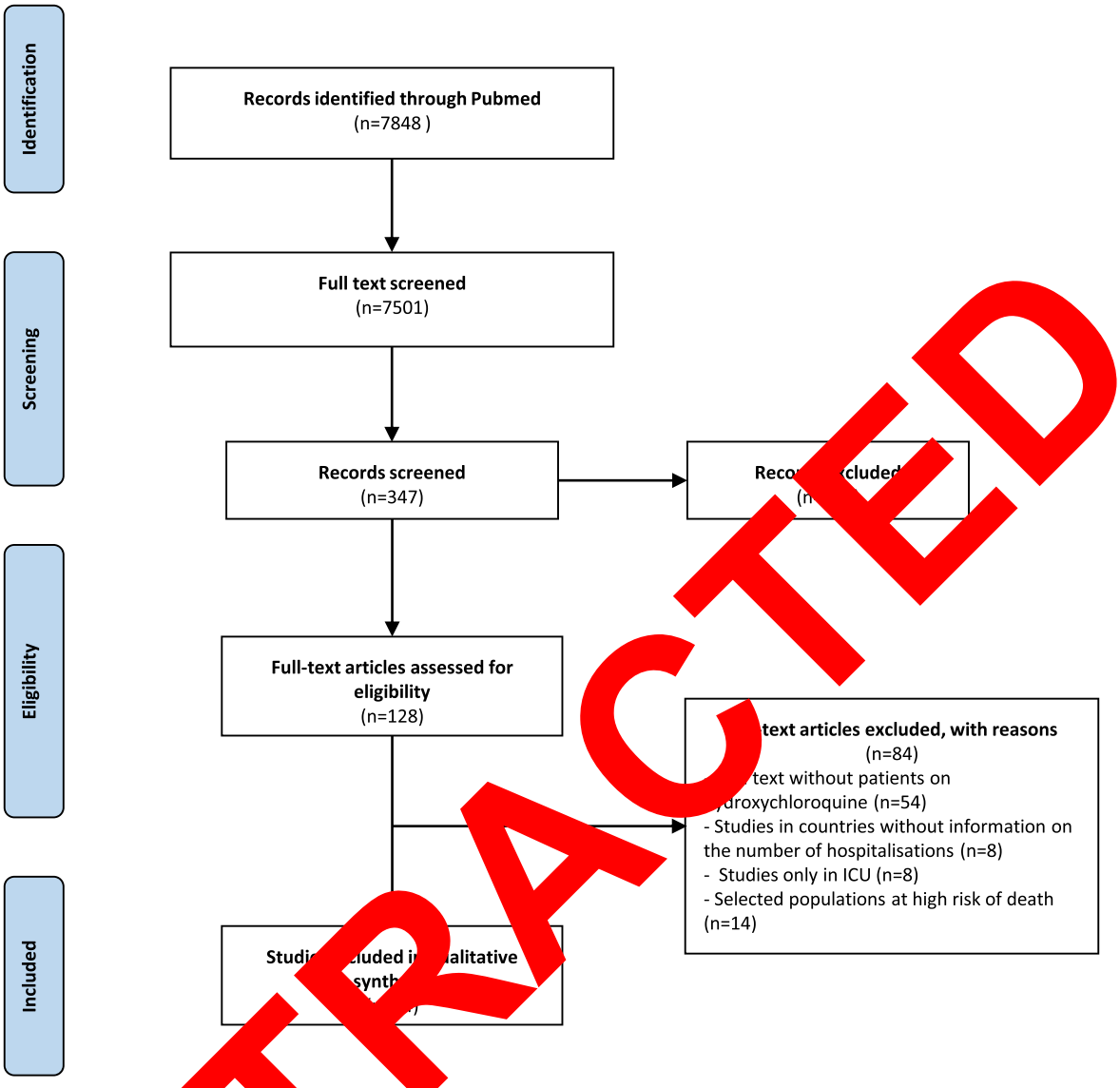

Fig. 1 chart of studies. HCQ: hydroxychloroquine, ICU: intensive care unit.

3.3. Sensitivity analysis

We extracted the in hospitalised patients with COVID-19 from the PREMIER ase for (12.5%) [60], nationwide sources for 17.4%], um (21.8%) [62], and Spain (29.1%) , and onwide s for Turkey (4.5%) [64] and Italy (28.0% 5].

Usi es, the median number of HCQ-related deaths in m, Turkey, France, Italy, Spain, and the USA was 240 (range not e ble), 77 (range 75–105), 299 (range not estimable), 2237 (range 14 533), 2799 (range 2179–3094) and 7583 (range 1990–9288), respectively. Using median estimates of HCQ use in each country, 13226 in-hospital deaths (range 6211–15530) may be related to HCQ prescription in the six assessed countries.

4. Discussion

The main finding of the present study is that HCQ might have been associated with an excess of 16990 deaths during the first wave of the COVID-19 pandemic in the six countries for which data were available. Given that reliable data on hospitalizations, HCQ use and in-hospital mortality for most countries, these numbers likely represent the tip of the iceberg only thus largely underestimating the number of HCQ-related deaths worldwide. Off-label prescribing may be appropriate when physicians judge they have enough evidence to suggest medication benefit. However, the first series reporting HCQ effect showed limited or no efficacy on mortality reduction [66]. Thus, the expected efficacy might be of modest magnitude at best, similar to other medications in the absence of obvious benefit. As a theoretical example, taking a 15% mortality rate in hospitalised patients and a 30% death reduction related to an effective drug administration, the number needed to treat would be ≈ 20 patients to prevent one death [67]. In other words, administrating off-label drugs to a given patient with COVID-19 outside a randomised study results in a slight individual benefit for them. Conversely, generating high-level evidence from powered and unbiased randomised controlled trials testing promising drugs, following Chalmers' principle to "randomize the first patient", has become increasingly urgent [68,69].

The toxicity of HCQ in patients with COVID-19 is partially due to cardiac side effects, including conduction disorders (ventricular tachycardia or fibrillation, and QT interval prolongation) [70–72]. In the RECOVERY trial, the risk of major cardiac arrhythmia related to HCQ in COVID-19 patients was 8.2% compared to 6.3% in the standard care group, with a 0.4% increased risk of death from cardiac causes [5]. The

Table 1
Characteristics of the included studies.

Study	Country	Prospective design	Consecutive inclusion	Study aim	Start of inclusions	End of inclusions	Study size	Mean age (years)	Men (%)	ICU (%)	All-cause mortality (%)	N. of patients on HCQ	HCQ exposure (%)
Catteau et al. [19]	Belgium	No	No	Treatment	14/03/2020	24/05/2020	8910	NA	55	6	22	4542	51
Kaeuffer et al.[20]	France	Yes	Yes	Prognosis	March 2020	March 2020	1045	66	59	32	11	163	16
Fauvel et al. [21]	France	No	Yes	Prognosis	26/02/2020	20/04/23	1240	64	58	15	12	NA	NA
Bartoletti et al.[37]	Italy	No	No	Treatment	22/02/2020	30/06/2020	513	71	66	23	34	445	87
Fumagalli et al.[36]	Italy	No	Yes	Prognosis	22/02/2020	10/04/2020	516	67	67	NA	2	[illegible]	52
Patti et al. [35]	Italy	No	Yes	Prognosis	01/03/2020	12/05/2020	522	NA	59	NA	[illegible]	398 from 456	76
Ameri et al. [34]	Italy	No	Yes	Prognosis	01/03/2020	09/04/2020	689	67	69	NA	24	57	83
Piano et al. [33]	Italy	No	No	Prognosis	22/02/2020	08/04/2020	565	66	[illegible]	15	17	12	73
Rinaldi et al. [32]	Italy	Yes	Yes	Prognosis	15/03/2020	30/04/2020	885	NA	67	[illegible]	22	811	92
Schiavone et al.[31]	Italy	No	Yes	Prognosis	23/02/2020	01/04/2020	844	[illegible]	62	[illegible]	[illegible]	681	81
Novelli et al. [30]	Italy	No	Yes	Prognosis	23/02/2020	14/03/2020	50[illegible]	66	72	19	34	332 from 444	65
Mitacchione et al.[29]	Italy	No	Yes	Prognosis	23/02/2020	31/0[illegible] 202	[illegible]42	64	6[illegible]	5	22	NA	NA
Guaraldia et al.[39]	Italy	No	No	Treatment[a]	21/02/2020	24[illegible] 20[illegible]	544	[illegible]	66	NA	16	NA	NA
Franco et al. [38]	Italy	Yes	No	Prognosis	01/03/2020	10/[illegible] 2020	670	[illegible]	69	0	27	263 from 321	39
CORIST[28]	Italy	No	Yes	Treatment	1[illegible]	[illegible]3/05/ 20[illegible]	3451	NA	62	NA	17	2634	76
Martínez-Sanz et al. [23]	Spain	No	No	Treatment	31/ 2020	[illegible] 20	1229	NA	62	7	15	1134	92
Gil-Rodrigo et al.[22]	Spain	Yes	Yes	[illegible]gnos[illegible]	01/03/2020	30/04/2020	1000	62	56	6	12	698	70
Casas-Rojo et al.[24]	Spain	No	Yes	Progno[illegible]	[illegible]7/03/	30/06/2020	15111	NA	57	8	21	12915 from 15084	85
Gutiérrez-Abejón et al.[25]	Spain	No	[illegible]	[illegible]is	01/03/2020	31/05/2020	7307	NA	57	NA	24	4746	65
Núñez-Gil et al.[27]	Spain	No	Yes	Prognosis	06/03/2020	02/04/2020	914	NA	59	NA	28	752 from 884	82
Pérez-Belmonte et al.[26]	Spain	[illegible]	Yes	Prognosis	01/03/2020	19/07/2020	2666	74.9	62	NA	NA	2185	82
Altuntas et al.[16]	Turkey	[illegible]	Ye[illegible]	Prognosis	11/03/2020	29/05/2020	994	NA	55	16	9	712	72
Yigenoglu et al.[1[illegible]	[illegible]	No	[illegible]s	Prognosis	11/03/2020	22/06/2020	1480	56	54	15	10.3	1049	71
Oztur[illegible] [18]	Tur[illegible]	No	Yes	Prognosis	17/04/2020	06/05/2020	1210	NA	55	22	14	1173 from 1199	97
Bahl et al. [40]	[illegible]SA	No	No	Prognosis	01/03/2020	31/03/2020	1461	NA	53	26	22	1073	73
Brar et al. [41]	[illegible]	No	Yes	Prognosis	03/03/2020	15/ 052020	585	NA	55	NA	22	333	57
Adrish et al. [42]	USA	No	Yes	Prognosis	09/03/2020	18/05/2020	1173	NA	61	NA	33	867	74
Frontera et al.[43]	USA	Yes	No	Prognosis	10/03/2020	20/05/2020	4491	NA	58	22	21	3015	67
Ionescu et al. [44]	USA	No	Yes	Prognosis	13/03/2020	05/05/2020	3480	65	49	18	15	2556	73
Kim et al. [45]	USA	No	Yes	Prognosis	12/03/2020	17/05/2020	510	64	66	68	32	381	75
Rosenberg et al.[46]	USA	No	No	Treatment	15/03/2020	28/03/2020	1438	NA	60	23	20	1006	70

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Prospective design	Consecutive inclusion	Study aim	Start of inclusions	End of inclusions	Study size	Mean age (years)	Men (%)	ICU (%)	All-cause mortality (%)	N. of patients on HCQ	HCQ exposure (%)
Arshad et al. [47]	USA	No	Yes	Treatment	10/03/2020	02/05/2020	2541	64	51	24	18	1202	47
Magagnoli et al.[48]	USA	No	Yes	Treatment	09/03/2020	29/04/2020	807	~70	96	NA	19	412	50
Kim et al. [49]	USA	No	Yes	Prognosis	01/03/2020	30/05/2020	867	57	55	23	14	222	26
Fried et al. [50]	USA	No	Yes	Prognosis	02/15/2020	20/04/2020	11721	NA	53	20	21	4232	36
Avery et al. [51]	USA	No	Yes	Prognosis	01/03/2020	21/08/2020	2472	NA	52	NA	11	[illegible]	17
Keller at al. [58]	USA	NA	NA	Treatment[b]	11/03/2020	13/04/2020	1806	62	47	NA	[illegible]	NA	NA
Ho et al.[52]	USA	No	Yes	Prognosis	07/03/2020	05/06/2020	4909	65	57	21	[illegible]	3304	67
Li et al.[59]	USA	No	NA	Treatment[a]	12/03/2020	17/06/2020	1938	65	53	26	15	NA	NA
Mikami et al. [53]	USA	No	Yes	Prognosis	13/03/2020	17/04/2020	3708	NA	NA	NA	22	[illegible]13	76
Laszkowska et al.[54]	USA	No	Yes	Prognosis	11/03/2020	28/04/2020	2804	63	56	[illegible]	19	1383	49
Yeramaneni et al. [55]	USA	No	No	Treatment	11//02/2020	08/05/2020	7158	[illegible]	49	[illegible]	[illegible]	2529	35
Piazza et al. [56]	USA	No	Yes	Prognosis	13/03/2020	03/04/2020	39[illegible]	62	57	43	14	279	70
El-Solh et al. [57]	USA	No	Yes	Prognosis	01/01/2020	01/05/2020	[illegible]4	69	[illegible]	50	29	747	46

HCQ: hydroxychloroquine, UK: United Kingdom, USA: United States of America, N.: [illegible]ber, NA: not applicable, ICU: intensive care unit

[a] tocilizumab

[b] glucocorticoids

[c] from a series including 1114 hospitalised patients and outpatients

increased risk of death from cardiac causes in RECOVERY corresp[illegible] to one half of the increase of the all-cause mortality, suggesting [illegible]e HCQ-related deaths are also related to non-cardiac causes. In a [illegible] conducted in Brazil, testing hydroxychloroquine (HC[illegible]or witho[illegible] azithromycin, an increase in hepatic and cardiac [illegible]effec[illegible]primarily manifesting as the prolonging of the correc[illegible]QT inte[illegible], was reported [73]. In this trial, the rate of fatal adve[illegible]ent reports of adverse events in the others ra[illegible]mized [illegible]testing HCQ in COVID-19 were scare [74]. In rheuma[illegible]arthritis, ti[illegible]g-term use of HCQ was associated with a higher [illegible]ajor adverse [illegible]iovascular events, including myocardial inf[illegible]ion, h[illegible]alisation for heart failure, all-cause and cardiovascular [illegible]rtality in pa[illegible]with a history of heart failure [71,72]. The anal[illegible]of the European [illegible]Vigilance database also reported the occu[illegible]e of HC[illegible]related non-cardiac side effects (in COVID-19 patients, [illegible]ding [illegible]titis, acute renal failure, hemolytic anemia and rhabdomy[illegible]). The [illegible]ght of other adverse events reported in p[illegible]ts tre[illegible]with H[illegible] such as acute eosinophilic pneumoni[illegible], [illegible]re blo[illegible]s such as thrombocytopenia [77], aplastic [illegible]mia [7[illegible] and agra[illegible]cytosis [77], seizures [77], psychiatric [illegible]rders [illegible] gastro-intestinal involvement [78,79], and hypogly[illegible] [illegible]wn.

In the a[illegible]e of restriction, the number of expected HCQ-related deaths is likel[illegible]e directly related to the promotion of its prescription by scientist[illegible]hysicians and health agencies. In February and March 2020, the use of this treatment was widely promoted based on preliminary reports suggesting a potential efficacy against COVID-19 [80]. For instance, the use of HCQ markedly increased from mid-March to mid-April 2020 [81,82] in France before a temporary recommendation supporting its use by the State Council was rapidly rejected [83]. Similarly, the Food and Drug Administration (FDA) granted a temporary emergency use authorisation for HCQ on March 28th 2020, which was finally revoked on June 15th 2020 [84]. In India, HCQ was also prescribed as a curative treatment to patients with COVID-19 and as a prophylactic treatment for front-line workers based on public authority guidance [85]. Conversely, the British government [illegible]moted HCQ use only within clinical trials, explaining the absence of [illegible]dies reporting the use of HCQ in the United Kingdom in the present study [86]. Consistently, a cohort of a multinational network showed a wide variation in the use of HCQ between countries, with 85% in Spain, 14% in the USA and less than 2% in China [80]. The rush to administer this treatment caused supply shortages in community pharmacies, forcing the implementation of dispensing restrictions [82]. Finally, the results of observational studies and randomized trials in May and June 2020, respectively, convincingly demonstrated that HCQ was ineffective and led to an increase in adverse events [4,5,12,66,73].

Our study showed a high proportion of prescriptions for HCQ even in countries which have restricted its use [84]. This result argues in favour of tightly regulating access to off-label prescriptions during future pandemics [87]. As an example, the issuance of the emergency use authorization for HCQ by the FDA, which permits distribution of the drug from the national stockpile for the treatment of hospitalized patients with COVID-19, was widely misinterpreted as an FDA approval for this indication [87]. The COVID-19 crisis has led to the implementation of a randomization platform enabling the rapid conduct of clinical trials [3]. Such a structure underscores even less justification for empiricism in off-label prescription. In addition, it is critical that representatives of public authorities should not, on the basis of their personal conviction, promote the prescription of medicines that have not been formally evaluated, thereby falsely raising hopes as to the existence of a solution to a complex health crisis [88–90]. Finally, it is important to bear in mind the risk of extrapolating the treatment effects in one condition to another, where the relevance of intermediate outcome (e.g. viral load) and the putative benefits are overestimated and the undesirable effects downplayed [91–93]. In the context of a new emerging infectious disease, the experience of COVID-19 argues in favour of confining expert advice to contextualising the results of preclinical and clinical studies, rather than generating "new results" from hazardous extrapolation [94].

Our study has some limitations. First, some of the results should be taken with caution, particularly the results obtained in France, Turkey and Belgium. For these countries, data concerning HCQ exposure were

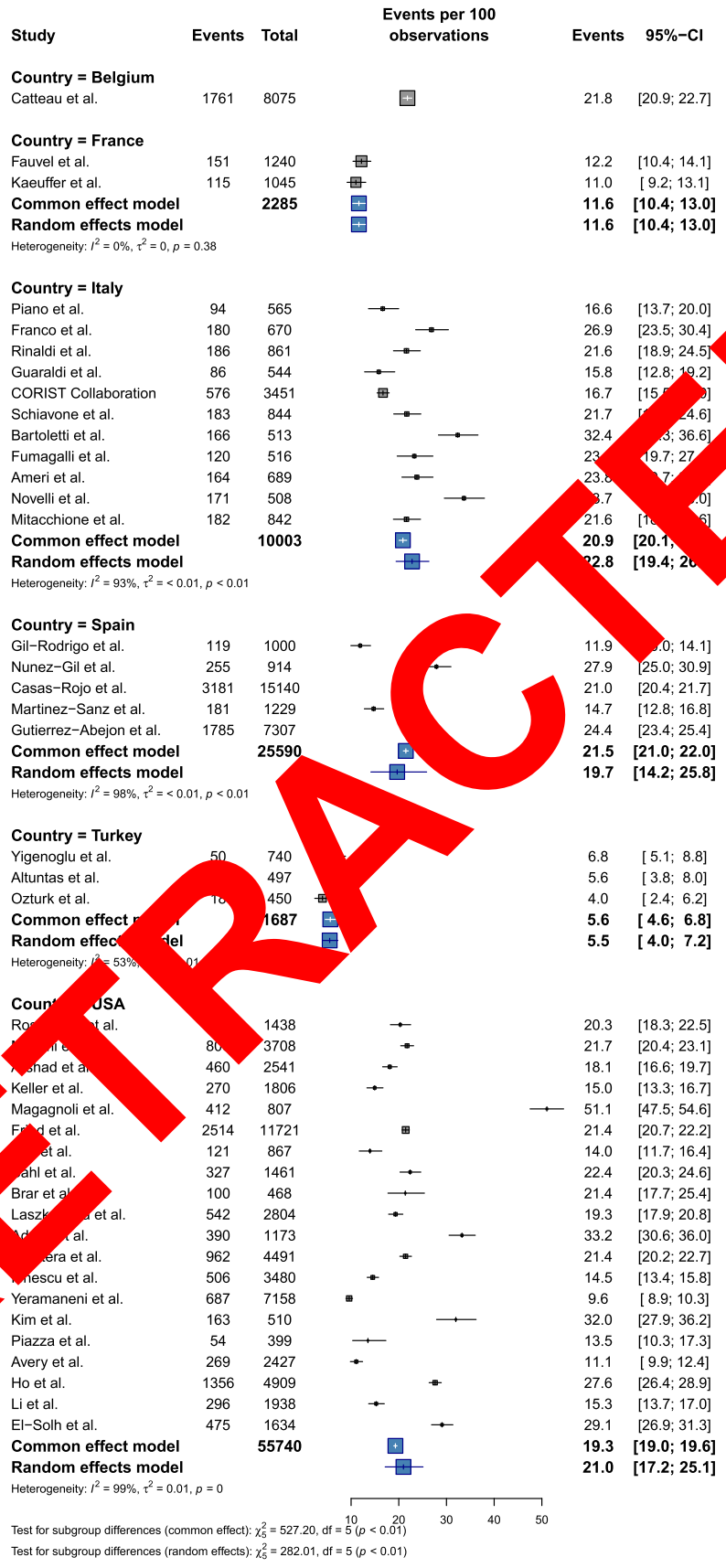

Fig. 2. Meta-analysis of mortality rates according to each country.

Table 2
Mortality induced by hydroxychloroquine by country using the estimate of mortality rate from meta-analysis of including cohorts.

Country	N. of hospitalisations	Rate of prescriptions (range)	N. of hospitalised patients exposed to HCQ (range)	Mortality rate	Odds ratio of treatment mortality	N. of patients who died on treatment (range)	N. of patients' excess mortality by treatment (range)
Belgium	19644	51.0[§]	10018	0.218	1.11	2424	**240**
France	99997	15.6[§]	15600	0.116	1.11	2009	**199**
Italy	89895	80.8 (51.9 - 91.5)	72635 (46656 - 82254)	0.228	1.11	18,383 (11808 - 20817)	**1822** (1170 - 2063)
Spain	104715	83.5 (65.0 - 92.3)	87437 (68065 - 96652)	0.197	1.11	19120 (14884 - 21135)	**1895** (1475 - 2094)
Turkey	21417	73.1 (70.8 - 99.1)	15656 (15163 - 21224)	0.055	1.11	956 (926 - 1296)	**95**
USA	888037	62.1 (16.3 - 75.9)	551471 (144750-674020)	0.210	1.11	128548 (33741 - 15711	**12** (3244 -)

HCQ: hydroxychloroquine, N.: number, USA: United States of America [§] Only one study reported the rate of hydroxychloroquine prescription

Table 3
Mortality induced by hydroxychloroquine by country using the estimate of mortality rate from other sources.

Country	N. of hospitalisations	Rate of prescriptions (range)	N. of hospitalised patients exposed to HCQ (range)	Mortality rate	Odds ratio of treatment mortality	N. of patients who died on treatment (range)	N. of patients' excess mortality by treatment (range)
Belgium	19644	51.0[§]	10018	0.210	1.11	2424	**231**
France	99997	15.6[§]	15600	0.116	1.11	2009	**299**
Italy	89895	80.8 (51.9 - 91.5)	72635 (46656 - 82254)	0.280	1.11	383 - 20817)	**2237** (1437 - 2533)
Spain	104715	83.5 (65.0 - 92.3)	87437 (68065 - 96652)	0.291[a]	1.11	19 (14884 - 21135)	**2799** (2179 - 3094)
Turkey	21417	73.1 (70.8 - 99.1)	15656 (15163 - 21224)	0.045	1.11	956 (926 - 1296)	**77** (75 - 105)
USA	888037	62.1 (16.3 - 75.9)	551471 (144750-674020)	0.125	1.11	119978 (31492 - 146640)	**7583** (1990 - 9268)

HCQ: hydroxychloroquine, N.: number, USA: United States of America udy reported the rate of hydroxychloroquine prescription
[a] The study included outpatients.

scarce. As a result, estimates in these countries are imprec Unfortunately, due to the lack of political determi ssess t effect of off-label prescriptions during the COVI crisis, unlikely that additional large-scale data will be genera rom th tries. Second, the data used were extracted d ectly hort s. However, a practice study carried out rance sho that HCQ prescription was highly heterogeneous largely influ by several factors, the most important b the esence of a stablished departmental procedure supporting its scription [95]. Taken together, these results sug a strong centr ct based, which may have biased the true HC xposure. Unfortuna hospital databases were not available t ecisely ermine the true HCQ exposure in deceased patients wi OVI . Third, we estimated the mortality of hospitalised patients u ata fro blished cohorts. Similarly, mortality ra ficanti ied s hospitals and regions, which may hav n in nced by e age, sex, comorbidities, ICU capacity provem in COVID-1 management, and trust of the population e system and pandemic-related policies [96–98]. supported by our sensitivity analysis using national surveillance from Spain and USA. However, the relative effect of HCQ exposure o comes was not modified. Fourth, we did not use all sources of uncertainties related to variables included in the models. We only included variables related to the HCQ treatment effect. Thus, HCQ-related deaths may be considerably over- or under-estimated. Indeed, the 95% confidence interval of the OR of all-cause mortality related to HCQ ranged from 2% to 20%. In other words, our results might be overestimated by a factor 5 (i.e. the actual number of deaths related to HCQ would be ≈3000 deaths) or underestimated by a factor 2 (i.e. the actual number of deaths related to HCQ would be ≈30000 deaths). Thus, the effect of HCQ on mortality was the main source of uncertainty for the proposed estimates. Finally, some estimates could not be calculated due to missing or incomplete information, such as the number of hospitalisations in China, South Korea, Russia and Qatar. The number of deaths related to HCQ worldwide was obviously underestimated because of the lack of studies in regions, such as East Europe, United Kingdom, Germany, Scandinavia, Africa, and South America. Since the number of inhabitants living in the countries included in the present study was ≈ 600 million, we might speculate that the real number of HCQ-induced deaths might be significantly higher given the wide use of HCQ during the first and subsequent waves in numerous countries [85,99,100]. In addition, the number of deceased outpatients exposed to HCQ is unknown. Accordingly, the present results should be viewed as rough estimates only.

In conclusion, the number of HCQ-related deaths is estimated at 16990, even though this number is probably underestimated because of the lack of data from most countries. More importantly, this study illustrates the limitations of treatment-effect extrapolation from chronic to severe conditions without accurate data and the need to produce quickly high-level evidence from RCTs in case of emergent diseases.

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Declaration of Competing Interest

No author declared conflict of interest.

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References

[1] E. Petersen, M. Koopmans, U. Go, et al., Comparing SARS-CoV-2 with SARS-CoV and influenza pandemics, Lancet Infect. Dis. 20 (9) (2020) e238–e244.

[2] W.H.O. Coronavirus (COVID-19) Dashboard [Internet]. [cited 2021 Jun 14]; Available from: ⟨https://covid19.who.int⟩.

[3] Dexamethasone in Hospitalized Patients with Covid-19, N. Engl. J. Med. 384 (8) (2021) 693–704.

[4] Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results, N. Engl. J. Med. 384 (6) (2021) 497–511.

[5] RECOVERY Collaborative Group, P. Horby, M. Mafham, et al., Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19, N. Engl. J. Med 383 (21) (2020) 2030–2040.

[6] J.H. Beigel, K.M. Tomashek, L.E. Dodd, et al., Remdesivir for the Treatment of Covid-19 — Final Report, N. Engl. J. Med. 383 (19) (2020) 1813–1826.

[7] RECOVERY Collaborative Group, Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, Lancet 396 (10259) (2020) 1345–1352.

[8] M.L. Agostini, E.L. Andres, A.C. Sims, et al., Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease, mBio 9 (2) (2018) e00221–18.

[9] V. Nukoolkarn, V.S. Lee, M. Malaisree, O. Aruksakulwong, S. Hannongbua, Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. J. Theor. Biol. 254 (4) (2008) 861–867.

[10] J. Fantini, H. Chahinian, N. Yahi, Synergistic antiviral effect of hydroxychloroquine and azithromycin in combination against SARS-CoV-2: What molecular dynamics studies of virus-host interactions reveal, Int J. Antimicrob. Agents 56 (2) (2020) 106020.

[11] S. Satarker, T. Ahuja, M. Banerjee, et al., Hydroxychloroquine in COVID-19: Potential Mechanism of Action Against SARS-CoV-2, Curr. Pharm. Rep. 6 (5) (2020) 203–211.

[12] C. Axfors, A.M. Schmitt, P. Janiaud, et al., Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials, Nat. Commun. 12 (1) (2021) 2349.

[13] National Data: Hospitalization [Internet]. The COVID Tracking Project. [cited 2023 Feb 10];Available from: ⟨https://covidtracking.com/data/national/hospitalization⟩.

[14] Mathieu E., Ritchie H., Rodés-Guirao L., et al. Coronavirus Pandemic (COV[illegible]19) [Internet]. Our World in Data. 2020 [cited 2023 Feb 10];Available from [illegible] ps://ourworldindata.org/covid-hospitalizations⟩.

[15] Saglik Bakanligi T. COVID-19 Bilgilendirme Platformu [Internet]. COVID-[illegible] Bilgilendirme Platformu. 2021 [cited 2021 Feb 18];Available from: ⟨https:/[illegible] d19.saglik.gov.tr/TR-66935/genelkoronavirus-tablosu.html⟩.

[16] F. Altuntas, N. Ata, T.N. Yigenoglu, et al., COVID-19 in h[illegible]tic cell transplant recipients, Bone Marrow Transpl. 56 (4) (20[illegible]

[17] T.N. Yigenoglu, N. Ata, F. Altuntas, et al., The outco[illegible] COVID[illegible] in patients with hematological malignancy, J. Med Virol. 93 [illegible]021) 10[illegible]104.

[18] S. Ozturk, K. Turgutalp, M. Arici, et al., Mortality a[illegible] of C[illegible] in chronic kidney disease, haemodialysis an[illegible]al tra[illegible]tients comp[illegible]d with patients without kidney disease: a n[illegible]wide ana[illegible]m Turkey, Nephrol. Dial. Transpl. 35 (12) (2020) [illegible]–2095.

[19] L. Catteau, N. Dauby, M. Montourc[illegible]w-dose hydroxy[illegible]quine therapy and mortality in hospita[illegible] patie[illegible]th COVID-19: a [illegible]tionwide observational study of 8075 participants, Int J[illegible]microb. Agents 56 (4) (2020) 106144.

[20] C. Kaeuffer, C. Le Hyari[illegible]abacher, et al., Clini[illegible]racteristics and risk factors associated wit[illegible]ere COVID-19: prospective [illegible]alysis of 1,045 hospitalised cases i[illegible]rth-Easte[illegible]ance, March 2020, Eur. Surveill. 25 (48) (2020) 2000895.

[21] C. Fauvel, O. Weizm[illegible]ille, et al[illegible]monary embolism in COVID-19 patients: a F[illegible]ch multi[illegible] cohort st[illegible]Eur. Heart J. 41 (32) (2020) 3058–3[illegible]

[22] A. G[illegible]rigo, [illegible]iró, P. P[illegible]., Analysis of clinical characteristics and o[illegible]es in pat[illegible] with COVI[illegible] based on a series of 1000 patients treated in [illegible]h emer[illegible]partments, Emergencias 32 (4) (2020) 233–241.

[23] J. [illegible]ez[illegible]Ron, et al., Effects of tocilizumab on mortality in hosp[illegible]atients with COVID-19: a multicentre cohort study, Clin. Microbiol Infect. 2[illegible](2021) 238–243.

[24] J.M. Casas[illegible] J.M. Antón-Santos, J. Millán-Núñez-Cortés, et al., Clinical characteristic[illegible]tients hospitalized with COVID-19 in Spain: Results from the SEMI-COVID-19 Registry, Rev. Clin. Esp. (Barc.) 220 (8) (2020) 480–494.

[25] E. Gutiérrez-Abejón, E. Tamayo, D. Martín-García, F.J. Álvarez, F. Herrera-Gómez, Clinical Profile, Treatment and Predictors during the First COVID-19 Wave: A Population-Based Registry Analysis from Castile and Leon Hospitals, Int J. Environ. Res Public Health 17 (24) (2020) 9360.

[26] L.M. Pérez-Belmonte, J.D. Torres-Peña, M.D. López-Carmona, et al., Mortality and other adverse outcomes in patients with type 2 diabetes mellitus admitted for COVID-19 in association with glucose-lowering drugs: a nationwide cohort study, BMC Med 18 (1) (2020) 359.

[27] I.J. Núñez-Gil, V. Estrada, C. Fernández-Pérez, I. Fernández-Rozas, F.J. Martín-Sánchez, C. Macaya, The COVID-19 curve, health system overload, and mortality, Emergencias 32 (4) (2020) 293–295.

[28] COVID-19 RISK and Treatments (CORIST) Collaboration, Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study, Eur. J. Intern Med 82 (2020) 38–47.

[29] G. Mitacchione, M. Schiavone, A. Curnis, et al., Impact of prior statin use on clinical outcomes in COVID-19 patients: data from tertiary referral hospitals during COVID-19 pandemic in Italy, J. Clin. Lipido 15 (1) (2021) 68–78.

[30] L. Novelli, F. Raimondi, A. Ghirardi, et al., At the peak of COVID-19 age and disease severity but not comorbidities are predictors of mortality: COVID-19 burden in Bergamo, Italy, Panminerva Med 63 (1) (2021) 51–61.

[31] M. Schiavone, A. Gasperetti, M. Mancone, et al., Oral anticoagulation and clinical outcomes in COVID-19: An Italian multicenter experience, Int J. Cardiol. 323 (2021) 276–280.

[32] M. Rinaldi, M. Bartoletti, L. Bussini, et al., COVID-19 in solid organ transplant recipients: No difference in survival compared to general population, Transpl. Infect. Dis. 23 (1) (2021) e13421.

[33] S. Piano, A. Dalbeni, E. Vettore, et al., Abnormal[illegible]tion tests predict transfer to intensive care unit and death in C[illegible]t 40 (10) (2020) 2394–2406.

[34] P. Ameri, R.M. Inciardi, M. Di Pasquale[illegible] Pulmonary em[illegible]m in patients with COVID-19: characteristics and outco[illegible] the Cardio-CO[illegible] Italy multicenter study, Clin. Res Cardi[illegible] 110 (7) [illegible] 1020–102[illegible]

[35] G. Patti, M. Mennuni, F. Della C[illegible] E. Spinoni[illegible]Sainagh[illegible]VID-UPO Clinical Team, Change over t[illegible] COVID-19 hos[illegible]tion in Northern Italy, Eur. J. Intern Med 8[illegible]20) 100[illegible]

[36] C. Fumagalli, R. Rozzin[illegible]anni[illegible], Clinical risk score to predict in-hospital mortality in COV[illegible]a retrospective cohort study, BMJ Open 10 (9) (2020) e04[illegible].

[37] M. Bartoletti, [illegible]coni, L. Sc[illegible] et al.[illegible]cy of corticosteroid treatment for hospitali[illegible]tients with seve[illegible] a multicentre study, Clin. Microbio[illegible]1) (2021) 105–[illegible]

[38] C. Fran[illegible] Fac[illegible]o, R. Tonelli, et al., Feasibility and clinical impact of out-of-ICU noninvasive [illegible]tory support in patients with COVID-19-related pn[illegible]onia, Eur. Respi[illegible] (5) (2020) 2002130.

[39] [illegible]ldi, M. Meschiari, [illegible]zzi-Lepri, et al., Tocilizumab in patients with severe COVID-19: a retrospective cohort study, Lancet Rheuma 2 (8) (2020) e474–e484.

[40] A. Bahl, M.N[illegible] Baalen, L. Ortiz, et al., Early predictors of in-hospital mortality in patients wi[illegible]VID-19 in a large American cohort, Intern Emerg. Med 15 (8) (2020) 1485–[illegible].

[41] [illegible]ar, L.C[illegible]eiro, M. Shusterman, et al., COVID-19 Severity and Outcomes in [illegible] Cancer: A Matched Cohort Study, J. Clin. Oncol. 38 (33) (2020) 3914–3924.

[42] M. Adrish, S. Chilimuri, N. Mantri, et al., Association of smoking status with [illegible]mes in hospitalised patients with COVID-19, BMJ Open Respir. Res 7 (1) (2020) e000716.

[43] J.A. Frontera, S. Sabadia, R. Lalchan, et al., A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City, Neurology 96 (4) (2021) e575–e586.

[44] F. Ionescu, I. Jaiyesimi, I. Petrescu, et al., Association of anticoagulation dose and survival in hospitalized COVID-19 patients: A retrospective propensity score-weighted analysis, Eur. J. Haematol. 106 (2) (2021) 165–174.

[45] J. Kim, A. Volodarskiy, R. Sultana, et al., Prognostic Utility of Right Ventricular Remodeling Over Conventional Risk Stratification in Patients With COVID-19, J. Am. Coll. Cardiol. 76 (17) (2020) 1965–1977.

[46] E.S. Rosenberg, E.M. Dufort, T. Udo, et al., Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State, JAMA 323 (24) (2020) 2493–2502.

[47] S. Arshad, P. Kilgore, Z.S. Chaudhry, et al., Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19, Int J. Infect. Dis. 97 (2020) 396–403.

[48] J. Magagnoli, S. Narendran, F. Pereira, et al., Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with COVID-19, Med (N. Y) 1 (1) (2020) 114–127.e3.

[49] D. Kim, N. Adeniji, N. Latt, et al., Predictors of Outcomes of COVID-19 in Patients With Chronic Liver Disease: US Multi-center Study, Clin. Gastroenterol. Hepatol. 19 (7) (2021) 1469–1479.e19.

[50] M.W. Fried, J.M. Crawford, A.R. Mospan, et al., Patient Characteristics and Outcomes of 11 721 Patients With Coronavirus Disease 2019 (COVID-19) Hospitalized Across the United States, Clin. Infect. Dis. 72 (10) (2021) e558–e565.

[51] R.K. Avery, T.P.-Y. Chiang, K.A. Marr, et al., Inpatient COVID-19 outcomes in solid organ transplant recipients compared to non-solid organ transplant patients: A retrospective cohort, Am. J. Transpl. 21 (7) (2021) 2498–2508.

[52] K.S. Ho, B. Narasimhan, J. Sheehan, L. Wu, J.Y. Fung, Controversy over smoking in COVID-19-A real world experience in New York city, J. Med Virol. 93 (7) (2021) 4537–4543.

[53] T. Mikami, H. Miyashita, T. Yamada, et al., Risk Factors for Mortality in Patients with COVID-19 in New York City, J. Gen. Intern Med 36 (1) (2021) 17–26.

[54] M. Laszkowska, A.S. Faye, J. Kim, et al., Disease Course and Outcomes of COVID-19 Among Hospitalized Patients With Gastrointestinal Manifestations, Clin. Gastroenterol. Hepatol. 19 (7) (2021) 1402–1409.e1.

[55] S. Yeramaneni, P. Doshi, K. Sands, M. Cooper, D. Kurbegov, G. Fromell, Famotidine Use Is Not Associated With 30-day Mortality: A Coarsened Exact Match Study in 7158 Hospitalized Patients With Coronavirus Disease 2019 From a Large Healthcare System, Gastroenterology 160 (3) (2021) 919–921.e3.

[56] G. Piazza, U. Campia, S. Hurwitz, et al., Registry of Arterial and Venous Thromboembolic Complications in Patients With COVID-19, J. Am. Coll. Cardiol. 76 (18) (2020) 2060–2072.

[57] A.A. El-Solh, Y. Lawson, M. Carter, D.A. El-Solh, K.A. Mergenhagen, Comparison of in-hospital mortality risk prediction models from COVID-19, PLoS One 15 (12) (2020) e0244629.

[58] M.J. Keller, E.A. Kitsis, S. Arora, et al., Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19, J. Hosp. Med 15 (8) (2020) 489–493.

[59] M. Li, E.J. Yoo, M. Baram, et al., Tocilizumab in the Management of COVID-19: A Preliminary Report, Am. J. Med Sci. 361 (2) (2021) 208–215.

[60] Centers for Disease Control and Prevention. COVID Data Tracker [Internet]. 2020 [cited 2023 Nov 27]; Available from: ⟨https://covid.cdc.gov/covid-data-tracker⟩.

[61] M. Souris, J.-P. Gonzalez, COVID-19: Spatial analysis of hospital case-fatality rate in France, PLoS One 15 (12) (2020) e0243606.

[62] Surveillance of covid-19 mortality in Belgium: Epidemiology and methodology during 1st and 2nd wave (March 2020 - 14 February 2021) [Internet]. [cited 2023 Nov 29];Available from: ⟨https://www.sciensano.be/sites/default/files/surveillance_of_covid-19_mortality_in_belgium.pdf⟩.

[63] L. Redondo-Bravo, M.J. Sierra Moros, Martínez, E.V. Sánchez, et al., The first wave of the COVID-19 pandemic in Spain: characterisation of cases and risk factors for severe outcomes, as at 27 April 2020, Eur. Surveill. 25 (50) (2020) 2001431.

[64] N. Kokturk, C. Babayigit, S. Kul, et al., The predictors of COVID-19 mortality in a nationwide cohort of Turkish patients, Respir. Med. 183 (2021) 106433.

[65] N. Mauer, G. Chiecca, G. Carioli, et al., The First 110,593 COVID-19 Patients Hospitalised in Lombardy: A Regionwide Analysis of Case Characteristics, Risk Factors and Clinical Outcomes, Int J. Public Health 67 (2022) 1604427.

[66] M. Mahévas, V.-T. Tran, M. Roumier, et al., Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data, BMJ 369 (2020) m1844.

[67] P. Sedgwick, What is number needed to treat (NNT)? BMJ 347 (2013) f4605.

[68] P. Janiaud, C. Axfors, J. van't Hooft, et al., The worldwide clinical trial research response to the COVID-19 pandemic - the first 100 days, F1000Res 9 (2020) 1193.

[69] T.C. Chalmers, Randomize the first patient!, N. Engl. J. Med 296 (2) (1977) 107.

[70] R. Muller, Systemic toxicity of chloroquine and hydroxychloroquine: prevalence, mechanisms, risk factors, prognostic and screening possibilities, Rheuma Int 41 (7) (2021) 1189–1202.

[71] Elvira D 'Andrea, R.J. Desai, M. He, et al., Cardiovascular Risks of Hydroxychloroquine vs Methotrexate in Patients With Rheumatoid Arth[illegible] J. Am. Coll. Cardiol. 80 (1) (2022) 36–46.

[72] J.C.E. Lane, J. Weaver, K. Kostka, et al., Risk of hydroxychloroquine alone a[illegible] combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study, Lancet Rheumatol. 2 (11) [illegible] e698–e7[illegible]

[73] A.B. Cavalcanti, F.G. Zampieri, R.G. Rosa, et al., Hydrox[illegible] with or without Azithromycin in Mild-to-Moderate Covid-19, [illegible]gl. J. [illegible] 383 (21) (2020) 2041–2052.

[74] MetaEvidence COVID-19, Living evidence synthes[illegible]t drug[illegible] safety [Internet]. [cited 2023 Nov 30];Availa[illegible]e fro[illegible] dence.org/viewPathology2.aspx?expositio[illegible]&path[illegible]5&comparator=0&endpoints=447,449,446,445,44[illegible]&displayOng[illegible]alse&optionG=O2&optionD=D1&selFocus=2&d[illegible]12&selSubgroup[illegible]

[75] D. Motola, G. Bonaldo, N. Montan[illegible]ofile of hydroxy[illegible]oquine used off-label for the treatment of pati[illegible]s with [illegible]19: A descriptive study based on EudraVigilance data, Fu[illegible]n. Clin. Pharm. [illegible] (2022) 1099–1105.

[76] Y. Ishiguro, Y. Muro, C. M[illegible]e, et al., Drug-indu[illegible]ute eosinophilic pneumonia due to hyd[illegible]loroquine in a chilblain[illegible]s patient, J. Dermatol. 46 (10) (2019) e35[illegible].

[77] PLAQUENIL (hyd[illegible]loroqu[illegible]lfate) tablets, for oral use Initial U.S. Approval: 1955 [In[illegible] 2023 Nov [illegible]0];Available from: ⟨https://www.accessdata.fda.gov/dr[illegible]docs/label[illegible]/009768s053lbl.pdf⟩.

[78] S. Marin[illegible]in Val, [illegible]ch Peli[illegible] et al., Safety of Short-Term Treat[illegible]al Chlor[illegible]ydroxychloroquine in Patients with and wit[illegible]COVID-[illegible]A Systema[illegible]ew, Pharm. (Basel) 15 (5) (2022) 634.

[79] [illegible]ng, Z. Ca[illegible] Han, et al., Hy[illegible]roxychloroquine in patients with mainly mild t[illegible]erate[illegible] 2019: open label, randomised controlled trial, BM[illegible]

[80] A. Pra[illegible]e, A.G. Sena, L.Y.H. Lai, et al., Use of repurposed and adjuvant drugs in hospita[illegible]nts with covid-19: multinational network cohort study, BMJ 373 (2021) n10[illegible]

[81] Covid-19: usage des médicaments de ville en France [Internet]. EPI-PHARE. 2020 [cited 2023 Feb 13];Available from: ⟨https://www.epi-phare.fr/rapports-detudes-et-publications/covid-19-usage-des-medicaments-de-ville-en-france-rapport4/⟩.

[82] R. Lutaud, D. Scronias, J. Ward, P. Verger, The hydroxychloroquine debate: a therapeutic dilemma for general practitioners, Eur. J. Public Health 31 (2) (2021) 283–285.

[83] Conseil d'État, 28 mars 2020, Demande de recommandation temporaire d'utilisation pour le Plaquenil (Covid-19) [Internet]. Conseil d'État. [cited 2023 Feb 13];Available from: ⟨https://www.conseil-etat.fr/decisions-de-justice/dernieres-decisions/conseil-d-etat-28-mars-2020-demande-de-recommandation-temporaire-d-utilisation-pour-le-plaquenil-covid-19⟩.

[84] U.S. Food and Drug administration. Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine [Internet]. FDA. 2020 [cited 2023 Feb 13];Available from: ⟨https://www.fda.gov/news-events/press-announcements/coronavir[illegible]update-fda-revokes-emergency-use-authorization-chloroquine-and⟩.

[85] Pulla P. India expands use of controversial [illegible]for corona[illegible]despite safety concerns. Nature [Internet] 2020 [cited [illegible]Feb 13];Availa[illegible]m: ⟨https://www.nature.com/articles/d41586–020[illegible]8⟩.

[86] Government of the United Kingdo[illegible]Chloroq[illegible]nd Hydroxy[illegible]roquine not licensed for coronavirus (COVID[illegible]treatment [illegible]et]. 20[illegible]ited 2023 Feb 13];Available from: ⟨https://[illegible]gov.uk/governm[illegible]oroquine-and-hydroxychloroquine-not-lic[illegible]for-coro[illegible]us-covid[illegible]tment⟩.

[87] J.J. Harrigan, R.A. Hub[illegible]S. Thom[illegible] al., Associati[illegible] Between US Administration Endorseme[illegible]Hy[illegible]ychloroqui[illegible] for COVID-19 and Outpatient Prescri[illegible], J. GE[illegible]RN MED 3[illegible] (2020) 2826–2828.

[88] Karni A., Thom[illegible] Trump Say[illegible] Takin[illegible]roxychloroquine, Prompting Warning Fr[illegible]lth Experts [Inte[illegible] T[illegible]ew York Times. 2020 [cited 2023 Nov 29];A[illegible]m: ⟨https://ww[illegible]es.com/2020/05/18/us/politics/trump-hy[illegible]ychlo[illegible]e-covid-coronav[illegible]us.html⟩.

[89] L'Observateur. Estro[illegible]rise le recours à la chloroquine au CHU de Nice [Int[illegible]et]. 2020 [cited [illegible]Nov 29]; Available from: ⟨https://www.nouvelobs.[illegible]onavirus-de-wuha[illegible]00322.OBS26427/estrosi-autorise-le-recours-a-la-chloroquine-au-chu-de-nic[illegible]html⟩.

[illegible] K. Niburski, O. Niburski, Impact of Trump's Promotion of Unproven COVID-19 Treatments a[illegible]bsequent Internet Trends: Observational Study, J. Med Internet Res 22 (11) ([illegible]) e20044.

[illegible] [illegible]J. Mezzio, [illegible]Nguyen, A. Kiselica, K. O'Day, Evaluating the Presence of [illegible]itive B[illegible] in Health Care Decision Making: A Survey of U.S. Formulary [illegible]ers, J. Manag Care Spec. Pharm. 24 (11) (2018) 1173–1183.

[92] G. Saposnik, D. Redelmeier, C.C. Ruff, P.N. Tobler, Cognitive biases associated with medical decisions: a systematic review, BMC Med Inf. Decis. Mak. 16 (2016)

[93] [illegible]Chalmers, R. Matthews, What are the implications of optimism bias in clinical research? Lancet 367 (9509) (2006) 449–450.

[94] A. Lavazza, M. Farina, The Role of Experts in the Covid-19 Pandemic and the Limits of Their Epistemic Authority in Democracy, Front. Public Health [Internet] (2020) [cited 2023 Nov 29];8. Available from: ⟨https://www.frontiersin.org/articles/10.3389/fpubh.2020.00356⟩.

[95] A. Bosquet, C. Affo, L. Plaisance, G. Poenou, E. Mortier, I. Mahé, Outside any therapeutic trial prescription of hydroxychloroquine for hospitalized patients with covid-19 during the first wave of the pandemic: A national inquiry of prescription patterns among French hospitalists, PLOS ONE 17 (1) (2022) e0261843.

[96] J. Gaudart, J. Landier, L. Huiart, et al., Factors associated with the spatial heterogeneity of the first wave of COVID-19 in France: a nationwide geo-epidemiological study, Lancet Public Health 6 (4) (2021) e222–e231.

[97] M.W. Sun, D. Troxell, R. Tibshirani, Public health factors help explain cross country heterogeneity in excess death during the COVID19 pandemic, Sci. Rep. 13 (1) (2023) 16196.

[98] L. Villani, M. McKee, F. Cascini, W. Ricciardi, S. Boccia, Comparison of Deaths Rates for COVID-19 across Europe During the First Wave of the COVID-19 Pandemic, Front. Public Health [Internet] (2020) [cited 2023 Dec 11];8. Available from: ⟨https://www.frontiersin.org/articles/10.3389/fpubh.2020.620416⟩.

[99] L.C.L. Correia, C. Sette, M. Santos, C.A.S. Magliano, F.S. Toscas, Brazil's COVID-19 guidelines: political hijack of public health, Lancet 399 (10331) (2022) 1223.

[100] Monde Le, Coronavirus: l'Algérie ne compte pas renoncer à l'hydroxychloroquine [Internet], Le. Monde Fr. (2020) [cited 2023 Feb 13];Available from: ⟨https://www.lemonde.fr/afrique/article/2020/05/27/coronavirus-l-algerie-ne-compte-pas-renoncer-a-l-hydroxychloroquine_6040901_3212.html⟩.