Risk of COVID-19 hospitalization and mortality in rheumatic patients treated with hydroxychloroquine or other conventional DMARDs in Italy

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Abstract

Objectives: To ascertain if hydroxychloroquine (HCQ)/chloroquine (CLQ) and other conventional disease-modifying anti-rheumatic drugs (cDMARDs) use, and rheumatic diseases per se, may be associated with COVID-19-related risk of hospitalization and mortality.

Methods: This case-control study nested within a cohort of cDMARD users was conducted in the Lombardy, Veneto, Tuscany and Lazio regions and Reggio Emilia province. Claims databases were linked to COVID-19 surveillance registries. Risk of COVID-19-related outcomes was estimated using a multivariate conditional logistic regression analysis, comparing HCQ/CLQ vs methotrexate, vs. other cDMARDs and vs. non-use of these drugs. Presence of rheumatic diseases vs. their absence in a non-nested population was investigated.

Results: 1275 cases hospitalized due to COVID-19 were matched to 12,734 controls. Compared to recent use of methotrexate, no association between HCQ/CLQ monotherapy and COVID-19 hospitalization (OR 0.83 [95%CI, 0.69-1.00]) or mortality (OR 1.19 [95%CI, 0.85-1.67]) was observed. A lower risk was found when comparing HCQ/CLQ use to the concomitant use of other cDMARDs and glucocorticoids. HCQ/CLQ was not associated with COVID-19 hospitalization as compared with non-use. An increased risk for recent use of either methotrexate monotherapy (OR 1.19 [95% CI, 1.05-1.34]) or other cDMARDs (OR 1.21 [95% CI, 1.08-1.36]) vs non-use was found. Rheumatic diseases were not associated with COVID-19-related outcomes.

Conclusion: HCQ/CLQ use in rheumatic patients was not associated with a protective effect against COVID-19-related outcomes. Use of other cDMARDs was associated with an increased risk when compared to non-use, and, if concomitantly used with glucocorticoids, also vs. HCQ/CLQ, probably to be ascribed to immunosuppressive action.

Keywords: Hydroxychloroquine, Chloroquine, Antirheumatic agents, COVID-19, outpatients

Key messages

- Exposure to hydroxychloroquine/chloroquine is not associated with a protective effect against COVID-19-related outcomes
- Exposure to other cDMARDs is associated with an increased risk of COVID-19-related outcomes
- Concomitant use of glucocorticoids and cDMARDs might increase the risk of COVID-19-related outcomes

Introduction

Between the end of December 2019 and March 11th 2021, the global coronavirus disease 2019 (COVID-19) pandemic due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) caused more than 2.5 million deaths and more than 117.1 million infected patients [1].

To accelerate the identification of drugs potentially preventing or curing COVID-19, there has been a great interest in repositioning drugs that have already been approved for other indications. Among these drugs, chloroquine (CLQ) and hydroxychloroquine (HCQ), two molecules with a long-standing history in the prophylaxis and treatment of malaria and the treatment of chronic inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) gained particular attention. *In vitro* studies demonstrated that these drugs may exert antiviral activity against several viruses, such as Zika virus [2], Ebola virus [3] and also SARS-CoV-2, probably by blocking endosomal transport [4,5], even though there was no evidence that HCQ/CLQ were beneficial in any acute viral infection in humans. In addition, a recently published *in vivo* study questioned the actual antiviral effect of HCQ/CLQ against SARS-CoV-2 [6].

Nevertheless, it has been hypothesized that HCQ/CLQ may be effective in the COVID-19 treatment also thanks to its immunomodulatory activity by reducing cytokine production, especially interleukin (IL)-1 and IL-6, and inhibiting toll-like receptor signaling [7–9]. However, an increasing body of evidence derived from both experimental and observational studies seems to suggest that HCQ/CLQ are not beneficial (or may be even detrimental) in COVID-19 treatment [10–12], including among COVID-19 hospitalized patients [13,14] and outpatients, [15,16] as well as high-risk patients recently exposed to SARS-CoV-2, where HCQ was used as post-exposure prophylaxis [17–20].

Three recent cohort studies investigated the effects of HCQ on the prevention of SARS-CoV-2 infection[21,22] and COVID-19 mortality [21,23] in patients who received this drug for the treatment of rheumatic diseases before the pandemic. These studies reported conflicting findings regarding the role of HCQ in preventing mortality due to COVID-19 [21,23].

Despite the controversial evidence on the efficacy of HCQ/CLQ in the COVID-19 treatment and prevention and their known side effects (e.g. retinopathy, hypoglycemia and cardiomyopathy), these drugs have been used also as self-medication during the first wave of the pandemic [24]. Moreover, HCQ/CLQ self-medication is particularly hazardous in patients for whom HCQ/CLQ are contraindicated, such as patients with glucose-6-phosphate dehydrogenase deficiency, in whom these drugs can trigger hemolytic crises.

On the other hand, it has been demonstrated that the exposure to other conventional disease-modifying anti-rheumatic drugs (cDMARDs) in patients with autoimmune diseases is associated with an increased risk of COVID-19-related hospitalization and mortality [25]. Likewise, an increased risk of COVID-19 hospitalization has been reported with moderate-high doses of glucocorticoids in patients with rheumatic diseases [25], as a result of an immunosuppressant action. Therefore, the aim of the present study was to investigate the potential decrease in risk of COVID-19-related hospitalization and mortality in patients with rheumatic diseases or other immune-mediated inflammatory diseases treated with HCQ/CLQ as compared to other cDMARDs. Secondary objectives of this study were to explore the risk of COVID-19-related hospitalization and

mortality related to HCQ/CLQ or other cDMARDs for rheumatic diseases or immune-mediated inflammatory diseases vs. non-use as well as the presence of rheumatic diseases vs. absence.

Patients and Methods

A large-scale nested case-control study in a cohort of cDMARD users was conducted in the Lombardy, Veneto, Tuscany and Lazio regions and the Reggio Emilia (Emilia Romagna) Local Health Unit (LHU) that cover an overall population of 25.1 million persons (42% of the Italian population).

Data Source

In Italy, residents have access to universal health care services that are provided by the National Health System (NHS). Use of these services is retrievable through administrative claims databases that are widely used for clinical research. The claims data used in this study were routinely collected, using systems that were in place prior to the start of the study. These databases provide information on hospital admissions, copayment exemptions and pharmacy claims. The latter were updated as of 31st December 2019 in all catchment areas. Medical diagnoses were coded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-CM-9). Exposure to cDMARDs was assessed using pharmacy claims in the last available 12 months. Drug data were recorded using the Anatomical Therapeutic Chemical (ATC) classification system and the National Drug Code (NDC) and the Defined Daily Dose (DDD) was used as the unit of measure for drug exposure. Copayment exemption databases were also searched to identify diseases exempting patients from healthcare copay. All these claims databases were linked to regional/local COVID-19 surveillance registries available in each catchment area through unique fully-anonymized patient identifiers. These registries were used to identify patients testing positive for SARS-CoV-2 RNA by polymerase chain reaction (PCR) on nasopharyngeal/throat swabs, and who were hospitalized or subsequently died due to COVID-19. Registries' data were updated to May 21st 2020 for Lombardy, Veneto, Lazio and Reggio Emilia and June 10th 2020 for Tuscany. To perform distributed analyses, the Italian National Institute of Health developed *TheShinISS*, an R-based tool tailored for the main epidemiological multi-database study designs: descriptive, cohort, case-control, case-cohort, self-controlled-case-series. TheShinISS was employed by each centre for elaborating and processing, at local level, data on COVID-19 patients and health archives through a common data model, performing data quality control, matching cases and controls, executing record-linkage, and finally creating the anonymized dataset to be shared for the centralized data analyses (Supplementary figure S1) [26–28].

Study Cohort

The study cohort comprised patients aged ≥18 years who received at least 1 prescription of cDMARDs for rheumatic diseases or other immune-mediated inflammatory diseases including: mycophenolic acid (ATC: L04AA06), leflunomide (ATC: L04AA13), sulfasalazine (ATC: A07EC01), cyclosporine (ATC: L04AD01), methotrexate (MTX) (ATC: L04AX03; L01BA01), azathioprine (ATC: L04AX01), auranofin (ATC: M01CB03), sodium aurotiosulfate (ATC: M01CB02), tacrolimus (ATC:

L04AD02), chloroquine (ATC: P01BA01) and HCQ (ATC: P01BA02) in the period between 1st January 2019 and 31st December 2019 within the catchment areas of the centers participating in the study.

Cases and Controls

From the study cohort, we identified as cases those testing positive for SARS-CoV-2 RNA by PCR on nasopharyngeal/throat swabs, and who were hospitalized due to COVID-19 as recorded in the COVID-19 surveillance registries. In addition, as primary outcome we specifically evaluated those patients who died within 30 days since hospital admission due to COVID-19. For each case, up to ten controls were randomly selected from the cohort of cDMARD users not affected by COVID-19 and matched for catchment area, sex and age at the date of hospital admission of the case.

Exposure Definition

Exposure of interest was the use of any cDMARD, grouped into the following mutually exclusive categories: (1) HCQ/CLQ monotherapy; (2) MTX monotherapy (main comparator); (3) other cDMARDs, except for HCQ/CLQ (secondary comparator); (4) other cDMARDs, except for MTX and HCQ/CLQ; (5) other cDMARDs plus MTX or HCQ/CLQ. Patients were considered to be exposed to each of these categories if they had at least 1 pharmacy claim within 3 months prior to 31st December 2019, i.e. the index date (ID). In addition, we classified patients exposed to the study drugs only during a period ranging from 12 to 3 months prior to ID as past users of any cDMARDs. Exposure to corticosteroids was assessed in the 3 months prior to the ID (October 2019 to December 2019). Corticosteroids were classified as high cumulative doses (>40 DDD) and low cumulative doses (≤40 DDD) during the exposure period.

Covariates

The following covariates were considered: age, sex, catchment area (matching factors); Charlson index, evaluated within 10 years prior to the ID; number of drug claims in the last 12 months; number of hospitalizations in the last 10 years; prior use of drugs for acid related disorders, lipid modifying agents, anticoagulants, platelet aggregation inhibitors, antiarrhythmics, antibiotics, anti-HIV drugs, anti-Parkinson drugs, antiepileptics, antipsychotics and antidepressants; recent use of nonsteroidal anti-inflammatory drugs, corticosteroids, target DMARDs (tDMARDs) and biological DMARDs (bDMARDs); chronic comorbidities (e.g. cerebro- and cardiovascular diseases, hepatopathies, diabetes, dementia, hypertension, chronic kidney failure, chronic obstructive pulmonary disease, cancer) and rheumatic diseases (overall and specifically restricted to those approved for HCQ/CLQ treatment, i.e. RA and SLE). Information on comorbidities was extracted from hospital discharge, copayment exemption and pharmacy claims databases within the last 10 years available (Supplementary table S1). Prior and recent drug use was considered as having drug claims within the last available 12 and 3 months, respectively.

Statistical Analysis

Categorical and continuous variables were reported as frequencies and medians along with interquartile ranges (IQRs). We compared the characteristics of cases and controls through descriptive analysis. In the primary analysis, risks of COVID-19 hospitalization and/or mortality were estimated as odds ratios (ORs) along with 95% confidence intervals (CIs), using a multivariate conditional logistic regression analysis, by comparing HCQ/CLQ versus MTX (primary comparator) and other cDMARDs (secondary comparator). Covariates significantly associated with COVID-19-related outcomes (potential confounders) were selected following a stepwise procedure based on the Akaike's Information Criterion method and subsequently included in the final multivariate models. All statistical analyses were performed using STATA version 16 (StataCorp LLC, College Station, TX, USA) and R version 3.6 (The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set up at $p<0.05$

Subgroup and Sensitivity Analyses

To evaluate the consistency of the results and to better assess the potential confounding effects on the risk estimates, we conducted a number of subgroup and sensitivity analyses. First, we restricted the analysis to patients with RA or SLE only, approved indications for HCQ/CLQ. Second, we assessed risk estimates in those patients concomitantly treated with corticosteroids (as either any use or high cumulative dosage, i.e. > median cumulative defined daily dose within 3 months prior to ID). Moreover, in a sensitivity analysis we conducted a case-control study in the general population (i.e. not nested in a cohort of cDMARD users) of Lombardy, Veneto and Lazio regions and Reggio Emilia LHU to evaluate COVID-19-related outcomes associated to: recent use of HCQ/CLQ, MTX and other cDMARDs (individually) vs. non-use and presence of rheumatic diseases (RA and SLE specifically) vs. absence of these diseases.

Results

Overall, from 21st February 2020 (date of first COVID-19 diagnosed patient in Italy) to 21st May 2020 in Lombardy, Veneto, Lazio and Reggio Emilia and to 10th June 2020 in Tuscany, 1275 cases were included in the study, with Lombardy accounting for 78.9% of them. Cases were matched to 12,734 controls (Figure 1). The median (IQR) age at ID was 70.0 (60.0-78.0) years and 51% were women (matching factors).

Overall, cases were more likely to have worse preexisting health conditions as documented by a more frequent history of hospitalizations, and higher frequency of Charlson index ≥3 and of several relevant comorbidities such as cardiovascular diseases (e.g. heart failure and ischemic heart disease), chronic pulmonary diseases and chronic kidney disease. Moreover, among others, recent use of corticosteroids, as well as past use of drugs for acid related disorders, lipid modifying agents, platelet aggregation inhibitors, antiarrhythmics, antibiotics, antidepressants, were also associated to COVID-19-related hospitalization and mortality (Table 1).

In the primary analysis, we found a trend toward a lower risk of COVID-19 hospitalization associated with recent HCQ/CLQ monotherapy vs. recent use of MTX (OR 0.83 [95% CI, 0.69 to 1.00]), which did not reach statistical significance. Instead, a statistically significant slight reduction of COVID-19 hospitalization risk with HCQ/CLQ as monotherapy was observed when comparing

recent use of HCQ/CLQ vs. recent use of other cDMARDs (OR 0.82 [95% CI, 0.69 to 0.98]). Nevertheless, recent use of HCQ/CLQ was not associated with any difference in the risk for COVID-19-related mortality as compared both to recent use of MTX (OR 1.19 [95% CI, 0.85 to 1.67]) or other cDMARDs (OR 1.08 [95% CI, 0.79 to 1.46]). Similarly, we found no increased risk for COVID-19 mortality when HCQ/CLQ was compared both to MTX as monotherapy and other cDMARDs (Table 2).

In the subgroup analysis restricted to patients with RA or SLE, we did not observe any statistical significant difference in the risk of COVID-19 hospitalization or mortality associated to recent use of HCQ/CLQ as compared to either recent MTX monotherapy (OR 0.82 [95% CI, 0.57 to 1.16] and OR 1.65 [95% CI, 0.80 to 3.40], respectively) or recent use of other cDMARDs (OR 0.75 [95% CI, 0.54 to 1.06] and OR 1.73 [95% CI, 0.84 to 3.56], respectively), even though an opposite trend for the two outcomes was reported. The restriction of the analysis to patients concomitantly treated with high doses of corticosteroids before 3 months of the ID showed that, compared to MTX monotherapy, HCQ/CLQ monotherapy was associated with a statistically significant reduction of COVID-19 hospitalization (OR 0.68 [95% CI, 0.51 to 0.92]) (Table 3).

The sensitivity analysis carried out in the general population showed no increased risk of COVID-19 hospitalization among recent users of HCQ/CLQ as compared with non-use, whereas a mild statistically significant increased risk for recent use of both MTX as monotherapy (OR 1.19 [95% CI, 1.05 to 1.34]) or other cDMARDs, except MTX or HCQ/CLQ (OR 1.21 [95% CI, 1.08 to 1.36]) vs non-use was found. The slight increase in the risk also for mortality was confirmed only for recent use of other cDMARDs, except MTX or HCQ/CLQ, vs. non-use (OR 1.43 [95% CI, 1.12 to 1.82]). Finally, we found that rheumatic diseases in general and RA/SLE specifically were not associated with the risk of COVID-19 hospitalization (vs. absence: OR 0.98 [95% CI, 0.89 to 1.07]) as well as mortality (vs. absence: OR 0.88 [95% CI, 0.74 to 1.05]) (Table 4).

Discussion

The main finding of this large-scale Italian nested case-control study was that recent exposure to HCQ/CLQ was not associated with a protective effect regarding COVID-19-related hospitalization and mortality compared to MTX monotherapy in rheumatic patients. This finding was confirmed when assessing those risks in association to HCQ/CLQ vs. non-use in non-nested population. The absence of a protective effect of HCQ/CLQ against COVID-19-related severe outcomes is in line with a large body of evidence from both in- and out-patient settings cumulated so far [29], especially in rheumatic patients [21,23].

Conversely, we observed an increased risk of COVID-19-related hospitalization and mortality among other cDMARDs users vs. HCQ/CLQ, as well as vs. MTX. Other cDMARDs include several compounds which are used also in indications other than autoimmune disease such as transplanted patients who may also be more likely to develop severe COVID-19. Accordingly, differences in risk of COVID-19-related negative outcomes between HCQ/CLQ and other cDMARDs disappeared when the analysis was restricted to RA/SLE patients. The association between the use of other cDMARDs and the increased risk of COVID-19-related hospitalization and mortality has also been documented in a recent systematic review and meta-analysis of both experimental and observational studies assessing the risk and prognosis of COVID-19 in immune-mediated

inflammatory diseases [25] and in a Danish observational study that found an increased risk of being hospitalized for COVID-19 in patients treated with cyclosporine, tacrolimus and thiopurines [30].

Nevertheless, we found a statistically significant marginal increase in risk of COVID-19-related hospitalization (and mortality only for other cDMARDs) with both MTX as well as other cDMARDs when compared to non-use in the general population. This finding may be due to the immunosuppressive effects of these drugs which are known to be associated with increased risk of infections [31]. Instead, no increase in such a risk with HCQ/CLQ was observed, as these drugs exert immunomodulatory and not immunosuppressant action. Accordingly, a statistically significant protective effect against COVID-19-related hospitalization and mortality for HCQ/CLQ vs MTX and other cDMARDs in rheumatic patients was only observed in patients who were concomitantly treated with high cumulative dosages of corticosteroids, thus emphasizing an even more pronounced risk of severe COVID-19 in presence of synergistic immunosuppressant effects, as reported by several recently published papers [30,32–35].

In general, being affected by rheumatic diseases and RA/SLE specifically was not found to be a risk factor for COVID-19 hospitalization and mortality, thus indicating the absence of confounding by indication, when assessing the risks associated with drugs used for the treatment of these diseases. However, MTX and other cDMARDs may be used in more severe forms of rheumatic diseases (and other immune-mediated inflammatory diseases) than HCQ/CLQ and as such we cannot rule out that the slight increased risk of COVID-19 hospitalization vs. non-use is partly due to confounding by severity and not only to immunosuppressive effect.

The strengths of our study include the use of a large multicenter database network with real-world data for more than 200,000 cDMARD users from five Italian regions. This wide sample size allowed us to perform a number of subgroup and sensitivity analyses increasing the robustness of our findings. The use of the COVID-19 patient registries, which are daily updated by the Italian NHS, leverages accurately collected data on patients testing positive for SARS-CoV-2 RNA by PCR on nasopharyngeal/throat swabs. Linking Italian claims databases to the COVID-19 registries at individual patient level, we were able to adjust the analyses for a large number of potential confounders. Furthermore, since MTX is the reference drug in the treatment of arthropathies and it has a similar use pattern as HCQ/CLQ, we selected this drug as the main comparator as well as carrying out a subgroup analysis in patients with SLA/RE (approved indications for HCQ) to better control for confounding effects. However, this study has also some limitations. As we assessed drug exposure until 31st December 2019 and identified COVID-19 cases until June 2020, we may have misclassified drug exposure if patients stopped/switched therapies in the period preceding COVID-19-related hospitalization or mortality. However, it is reasonable to suppose that it is unlikely that patients with rheumatic diseases had changed or stopped the treatment after the beginning of the pandemic, as recommended by the current guidelines of international societies of rheumatology [36,37]. Information on known risk factors for death in COVID-19 patients such as obesity and smoking was not available; however, the adjustment of the analysis for comorbidities strongly correlated to these variables (e.g. diabetes mellitus and chronic obstructive pulmonary disease), potentially accounted for their confounding effect. Moreover, since some chronic

comorbidities are not frequent cause of hospitalization, they may have been partly underestimated as they were mainly identified from hospital discharge diagnoses.

Conclusion

In this large Italian nested-case control study recent exposure to HCQ/CLQ in rheumatic patients was not associated with a protective effect against COVID-19-related hospitalization and mortality, in comparison with MTX. A slight statistically significant increased risk for recent use of both MTX as monotherapy or other cDMARDs, except MTX or HCQ/CLQ, when compared to non-use was found. Furthermore, when compared to HCQ/CLQ, we observed an increased risk of COVID-19 hospitalization and mortality in patients receiving other cDMARDs, especially if concomitantly treated with high dose glucocorticoids. This is likely attributable to a synergistic immunosuppressive effect of those drugs, leading to increased risk of severe SARS-CoV-2 infection rather than to HCQ/CLQ protective effect.

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Conflict of interest

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Ethics Approval

This study was approved by the Ethics Committee of the Italian National Institute of Health.

Data availability statement

The dataset generated for the present study is not available for sharing.

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Figure 1. Selection of cases and controls from cDMARD users identified in the data sources used in the study

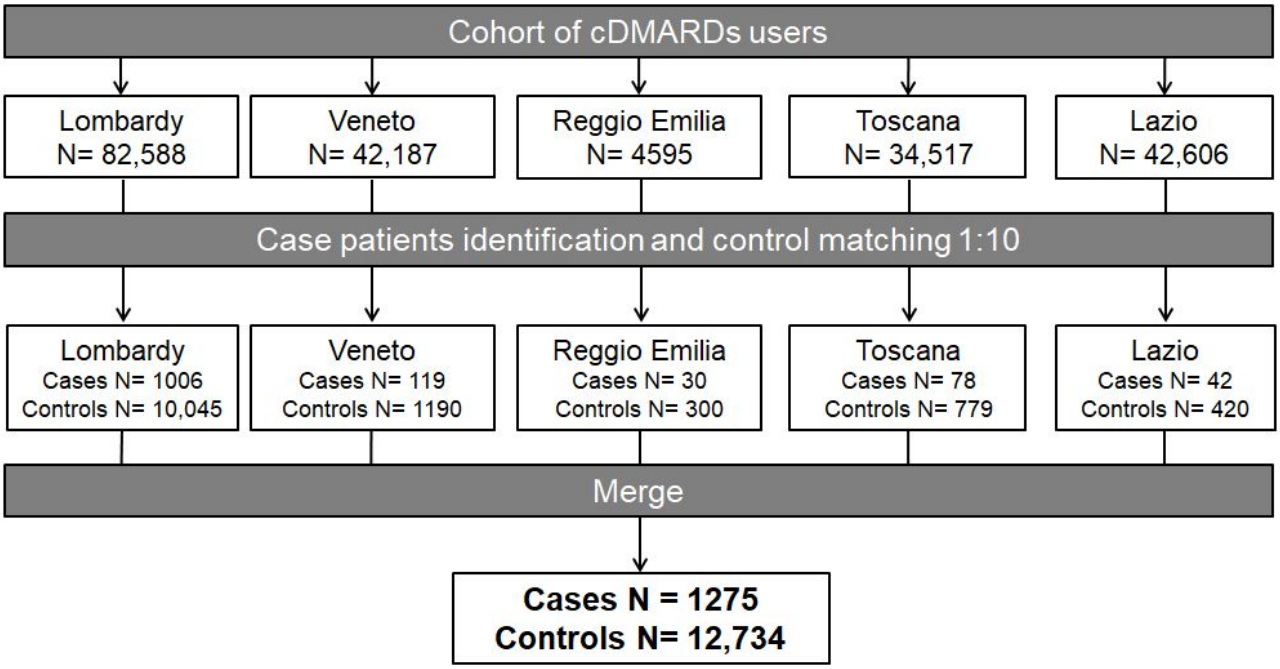

Table 1. Demographic and clinical characteristics of patients who were hospitalized or died because of COVID-19 and their matched controls

	COVID-19-related hospitalization			COVID-19-related mortality		
	Cases (N= 1275)	**Controls (N= 12,734)**	**Odds Ratio (95% CI)**	**Cases (N= 369)**	**Controls (N= 3,684)**	**Odds Ratio (95% CI)**
Centre – N (%)			*Matching factor*			*Matching factor*
Lombardy	1006 (78.9)	10,045 (78.9)		302 (81.8)	3014 (81.8)	
Lazio	42 (3.3)	420 (3.3)		8 (2.2)	80 (2.2)	
Reggio Emilia	30 (2.4)	300 (2.4)		11 (3.0)	110 (3.0)	
Tuscany	78 (6.1)	779 (6.1)		21 (5.7)	210 (5.7)	
Veneto	119 (9.3)	1190 (9.3)		27 (7.3)	270 (7.3)	
Gender – N (%)			*Matching factor*			*Matching factor*
Females	650 (51.0)	6,496 (51.0)		160 (43.4)	1599 (43.4)	
Age, median [IQR]	70.0 [60.0-78.0]	70.00 [60.0-78.0]		76.0 [60.0-82.0]	76.0 [69.0-82.0]	
Age, year – N (%)			*Matching factor*			*Matching factor*
18-49	108 (8.5)	1076 (8.4)		2 (0.5)	20 (0.5)	
50-59	194 (15.2)	1939 (15.2)		29 (7.9)	289 (7.8)	
60-69	307 (24.1)	3066 (24.1)		68 (18.4)	679 (18.4)	
70-79	389 (30.5)	3885 (30.5)		136 (36.9)	1356 (36.8)	
80-89	257 (20.2)	2568 (20.2)		124 (33.6)	1240 (33.7)	
≥90	20 (1.6)	200 (1.6)		10 (2.7)	100 (2.7)	
Charlson index – N (%)						
0	602 (47.2)	8030 (63.1)	*ref.*	143 (38.8)	2158 (58.6)	*ref.*
1-2	511 (40.1)	3989 (31.3)	1.75 (1.54-1.98)	155 (42)	1262 (34.3)	1.88 (1.48-2.38)
≥3	162 (12.7)	715 (5.6)	3.17 (2.60-3.80)	71 (19.2)	264 (7.2)	4.41 (3.02-5.67)
N. of hospitalizations in the previous 2 years – N (%)						
0	677 (53.1)	8822 (69.3)	*ref.*	178 (48.2)	2472 (67.1)	*ref.*
1	258 (20.2)	2139 (16.8)	1.59 (1.37-1.85)	72 (19.5)	626 (17.0)	1.6 (1.20-2.13)
≥2	340 (26.7)	1773 (13.9)	2.53 (2.20-2.92)	119 (32.2)	586 (15.9)	1.82 (2.20-3.61)
Comorbidities – N (%) in the previous 10 years						
Cerebrovascular diseases	94 (7.4)	736 (5.8)	1.31 (1.04-1.64)	41 (11.1)	290 (7.9)	1.47 (1.04-2.08)
Ischemic heart disease	161 (12.6)	1043 (8.2)	1.66 (1.38-1.99)	67 (18.2)	366 (9.9)	2.06 (1.54-2.75)

Atrial fibrillation	84 (6.6)	596 (4.7)	1.45 (1.14.1.85)	32 (8.7)	232 (6.3)	1.42 (0.96-2.01)
Heart failure	117 (9.2)	529 (4.2)	2.38 (1.92-2.94)	59 (16)	194 (5.3)	3.49 (2.54-4.8)
Hypertension	964 (75.6)	8187 (64.3)	1.87 (1.62-2.16)	312 (84.6)	2678 (72.7)	2.15 (1.6-2.9)
Hepatopathies	64 (5.0)	466 (3.7)	1.40 (1.07-1.84)	19 (5.1)	119 (3.2)	1.65 (1-2.73)
Chronic kidney disease	222 (17.4)	1001 (7.9)	2.54 (2.16-2.99)	67 (18.2)	282 (7.7)	2.75 (2.04-3.71)
Diabetes mellitus	296 (23.2)	2223 (17.5)	1.45 (1.26-1.67)	110 (29.8)	779 (21.1)	1.59 (1.26-2.02)
Chronic pulmonary disease	193 (15.1)	772 (6.1)	2.82 (2.38-3.35)	74 (20.1)	246 (6.7)	3.59 (2.68-4.8)
Cancer	260 (20.4)	1895 (14.9)	1.48 (1.28-1.71)	87 (23.6)	635 (17.2)	1.49 (1.15-1.92)
Dementia	25 (2.0)	156 (1.2)	1.63 (1.06-2.50)	13 (3.5)	65 (1.8)	2.06 (1.12-3.79)
Rheumatic diseases approved for HCQ/CLQ use[^]	463 (36.3)	5075 (39.9)	0.85 (0.75-0.96)	127 (34.4)	1420 (38.5)	0.83 (0.66-1.04)
Other rheumatic diseases[§]	153 (12.0)	1569 (12.3)	0.97 (0.81-1.16)	34 (9.2)	404 (11.0)	0.82 (0.57-1.19)
N. of drug claims in the previous year, median [IQR]	49 [29.00-74.00]	34 [19.00-54.00]	1.01 (1.01-1.02)	53 [37-81]	40 [24-59]	1.02 (1.01-1.02)
Prior drug use – N (%)*						
Drugs for acid related disorders	970 (76.1)	7933 (62.3)	1.99 (1.73-2.28)	297 (80.5)	2473 (67.1)	2.07 (1.58-2.71)
Lipid modifying agents	486 (38.1)	3711 (29.1)	1.54 (1.36-1.74)	148 (40.1)	1230 (33.4)	1.35 (1.08-1.68)
Anticoagulants	300 (23.5)	2042 (16.0)	1.64 (1.42-1.88)	99 (26.8)	686 (18.6)	1.62 (1.27-2.08)
Platelet aggregation inhibitors	406 (31.8)	3172 (24.9)	1.44 (1.26-1.63)	143 (38.8)	1117 (30.3)	1.47 (1.18-1.85)
Antiarrhythmics, class I and III	72 (5.6)	484 (3.8)	1.53 (1.18-1.98)	29 (7.9)	177 (4.8)	1.71 (1.13-2.60)
Antibiotics	754 (59.1)	6392 (50.2)	1.44 (1.28-1.62)	224 (60.7)	1860 (50.5)	1.52 (1.22-1.89)
Anti HIV drugs	46 (3.6)	285 (2.2)	1.65 (1.20-2.28)	12 (3.3)	84 (2.3)	1.45 (0.78-2.07)
Anti-Parkinson drugs	24 (1.9)	169 (1.3)	1.43 (0.93-2.21)	8 (2.2)	58 (1.6)	1.4 (0.66-2.94)
Antiepileptics	164 (12.9)	1166 (9.2)	1.47 (1.23-1.75)	46 (12.5)	352 (9.6)	1.35 (0.97-1.88)
Antipsychotics	38 (3.0)	295 (2.3)	1.30 (0.92-1.83)	15 (4.1)	89 (2.4)	1.73 (0.98-3.03)
Antidepressants	240 (18.8)	1969 (15.5)	1.28 (1.10-1.49)	73 (19.8)	590 (16.0)	1.32 (0.99-1.74)
Recent drug use – N (%)[#]						
NSAIDs	192 (15.1)	1803 (14.2)	1.08 (0.91-1.27)	49 (13.3)	514 (14.0)	0.94 (0.69-1.30)
Corticosteroids for systemic use	544 (42.7)	3882 (30.5)	1.71 (1.52-1.92)	163 (44.2)	1240 (33.7)	1.56 (1.26-1.94)
tDMARDs	11 (0.9)	122 (1.0)	0.90 (0.48-1.67)	3 (0.8)	32 (0.9)	0.93 (0.28-3.10)
bDMARDs	61 (4.8)	732 (5.7)	0.82 (0.63-1.08)	12 (3.3)	172 (4.7)	0.68 (0.37-1.24)

Abbreviations: bDMARDs = biologic disease-modifying antirheumatic drugs; cDMARDs = conventional disease-modifying antirheumatic drugs;; IQR = interquartile range; NSAIDs = non-steroidal anti-inflammatory drugs; tDMARDs = target disease-modifying antirheumatic drugs

^ Hospitalization or exemption code: rheumatoid arthritis, systemic lupus erythematosus, other connectivitis (i.e. systemic sclerosis and unspecified diffuse connective tissue disease)

§ Hospitalization or exemption code: giant cells arteritis, polymyalgia rheumatica, psoriatic arthropathy, ankylosing spondylitis and other inflammatory spondylopathies

* Evaluated using pharmacy claims within the last available 12 months prior ID

Evaluated using pharmacy claims within the last available 3 months prior ID

Table 2. Association between recent use of HCQ/CLQ vs MTX and other cDMARDs and COVID-19-related hospitalization and mortality

	COVID-19-related hospitalization				COVID-19-related mortality			
	Cases (N= 1275)	**Controls (N= 12,734)**	**Unadjusted* OR (95% CI)**	**Adjusted^ OR (95% CI)**	**Cases (N = 369)**	**Controls N = 3,684**	**Unadjusted* OR (95% CI)**	**Adjusted^ OR (95% CI)**
Recent use of:								
MTX monotherapy	300 (23.5)	3335 (26.2)	*ref.*	*ref.*	75 (20.3)	1084 (29.4)	*ref.*	*ref.*
HCQ/CLQ monotherapy	225 (17.6)	2773 (21.8)	0.88 (0.73-1.05)	0.83 (0.69-1.00)	81 (22.0)	864 (23.5)	1.32 (0.95-1.84)	1.19 (0.85-1.67)
Other cDMARDs (except MTX or HCQ/CLQ)	400 (31.4)	2716 (21.3)	1.70 (1.45-2.00)	1.15 (0.96-1.37)	112 (30.4)	700 (19.0)	2.40 (1.75-3.28)	1.46 (1.02-2.08)
Other cDMARDs (with MTX or HCQ/CLQ)	67 (5.3)	541 (4.2)	1.37 (1.04-1.82)	1.20 (0.90-1.60)	18 (4.9)	134 (3.6)	1.93 (1.12-3.33)	1.78 (1.02-3.10)
Past use of any cDMARDs	283 (22.2)	3369 (26.5)	0.94 (0.79-1.11)	0.93 (0.78-1.10)	83 (22.5)	902 (24.5)	1.33 (0.96-1.85)	1.19 (0.86-1.67)
Recent use of:								
Other cDMARDs (except HCQ/CLQ)	712 (55.8)	4546 (69.3)	*ref.*	*ref.*	191 (70.2)	1347 (68.5)	*ref.*	*ref.*
HCQ/CLQ monotherapy	225 (17.6)	2016 (30.7)	0.69 (0.58-0.81)	0.82 (0.69-0.98)	81 (29.8)	619 (31.5)	0.93 (0.70-1.24)	1.08 (0.79-1.46)

Abbreviations: cDMARDs = conventional disease-modifying antirheumatic drugs; CLQ = chloroquine; HCQ = hydroxychloroquine; MTX = methotrexate; OR = odds ratio;

* Univariate conditional logistic model matched for centre, age and gender

^ Multivariate conditional logistic regression model (stepwise forward based on Akaike's Information Criterion K=3.8415) matched for centre, age and gender and adjusted for the following eligible variables:, number of hospitalizations, Charlson index, number of prescriptions, drugs for peptic ulcer, anticoagulants, platelet aggregation, lipid modifying agents, antibiotics, anti-HIV drugs, anti-Parkinson drugs, antiepileptics, antipsychotics, antidepressants, antiarrhythmics, NSAIDs, corticosteroids, tDMARDs, bDMARDs, hypertension, cerebrovascular diseases, hepatopathies, diabetes, dementia, chronic kidney failure, COPD, neoplasms, artery cardiac disease, rheumatic diseases (with or without indication for cDMARDs)

Table 3. Subgroup analysis of the risk of COVID-19-realted hospitalization and mortality associated to recent use of HCQ/CQL vs. MTX and other cDMARDs

	COVID-19-related hospitalization				COVID-19-related mortality			
	Cases	**Controls**	**Unadjusted* OR (95% CI)**	**Adjusted^ OR (95% CI)**	**Cases**	**Controls**	**Unadjusted* OR (95% CI)**	**Adjusted^ OR (95% CI)**
Patients affected by RA or SLE								
MTX monotherapy	132 (60.3)	543 (58.6)	*ref.*	*ref.*	29 (47.5)	155 (59.6)	*ref.*	*ref.*
HCQ/CQL monotherapy	87 (39.7)	383 (41.4)	0.87 (0.61-1.22)	0.82 (0.57-1.16)	32 (52.5)	105 (40.4)	1.60 (0.84-3.06)	1.65 (0.80-3.40)
Other cDMARDs	167 (68.2)	441 (62.7)	*ref.*	*ref.*	38 (55.9)	123 (64.4)	*ref.*	*ref.*
HCQ/CQL monotherapy	78 (31.8)	262 (37.3)	0.77 (0.56-1.07)	0.75 (0.54-1.06)	30 (44.1)	68 (35.6)	1.33 (0.74-2.04)	1.73 (0.84-3.56)
Recent use of corticosteroids[#]								
MTX as monotherapy	143 (61.9)	509 (55.8)	*ref.*	*ref.*	42 (55.3)	183 (58.8)	*ref.*	*ref.*
HCQ/CQL monotherapy	88 (38.1)	404 (44.2)	0.83 (0.58-1.17)	0.78 (0.54-1.13)	34 (44.7)	128 (41.2)	1.35 (0.73-2.49)	1.23 (0.63-2.37)
Other cDMARDs	306 (78.1)	686 (68.2)	*ref.*	*ref.*	85 (72.0)	227 (69.4)	*ref.*	*ref.*
HCQ/CQL monotherapy	86 (21.9)	320 (31.8)	0.63 (0.48-0.85)	0.68 (0.51-0.92)	33 (28.0)	100 (30.6)	0.94 (0.58-1.54)	0.92 (0.53-1.57)
Recent use of high-dose corticosteroids (>40 DDD)[#]								
MTX as monotherapy	61 (67.8)	106 (54.1)	*ref.*	*ref.*	15 (60.0)	29 (57.7)	*ref.*	*ref.*
HCQ/CQL monotherapy	29 (32.2)	90 (45.9)	0.52 (0.26-1.06)	0.37 (0.15-0.93)	10 (40.0)	25 (46.3)	0.62 (0.11-3.34)	§
Other cDMARDs	129 (83.8)	175 (70.6)	*ref.*	*ref.*	34 (81.0)	51 (72.9)	*ref.*	*ref.*
HCQ/CQL monotherapy	25 (16.2)	73 (29.4)	0.41 (0.23-0.72)	0.45 (0.23-0.86)	8 (19.0)	19 (27.1)	0.45 (0.13-1.60)	§

Abbreviations: cDMARDs = conventional disease-modifying antirheumatic drugs; CLQ = chloroquine; DDD = defined daily dose; HCQ = hydroxychloroquine; MTX = methotrexate; OR = odds ratio; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus

* Univariate conditional logistic model matched for centre, age and gender

^ Multivariate conditional logistic regression model (stepwise forward based on Akaike's Information Criterion K=3.8415) matched for centre, age and gender and adjusted for the following eligible variables:, number of hospitalizations, Charlson index, number of prescriptions, drugs for peptic ulcer, anticoagulants, platelet aggregation, lipid modifying agents, antibiotics, anti HIV drugs, anti-parkinson drugs, antiepileptics, antipsychotics, antidepressants, antiarrhythmics, NSAIDs, corticosteroids, tDMARDs, bDMARDs, hypertension, cerebrovascular diseases, hepatopathies, diabetes, dementia, chronic kidney failure, COPD, neoplasms, artery cardiac disease, rheumatic diseases (with or without indication for cDMARDs)

[#]Exposure to corticosteroids was assessed from October 2019 to December 2019

§ Multivariate model not converged or too few discordant observations

Table 4. Sensitivity analysis of the association between risk of COVID-19-related hospitalization/mortality and HCQ/CLQ, MTX or other cDMARDs use (vs. non-use) and presence of rheumatic diseases or RA/SLE specifically (vs. absence) in the population based cohort

	COVID-19-related hospitalization				**COVID-19-related mortality**			
	Cases N= 60,175	**Controls N= 601,750**	**Unadjusted* OR (95% CI)**	**Adjusted^ OR (95% CI)**	**Cases N= 14,171**	**Controls N= 141,710**	**Unadjusted* OR (95% CI)**	**Adjusted^ OR (95% CI)**
No cDMARDs	59,113 (98.2)	596,110 (99.1)	*ref.*	*ref.*	13,883 (98.0)	140,262 (99.0)	*ref.*	*ref.*
HCQ/CQL as monotherapy	245 (0.4)	1759 (0.3)	1.41 (1.23-1.61)	1.04 (0.91-1.20)	87 (0.6)	508 (0.4)	1.73 (1.38-2.18)	1.27 (1.00-1.61)
MTX as monotherapy	320 (0.5)	2000 (0.3)	1.62 (1.44-1.82)	1.19 (1.05-1.34)	73 (0.5)	540 (0.4)	1.37 (1.07-1.75)	0.99 (0.77-1.27)
Other cDMARDs (except MTX or HCQ/CLQ)	436 (0.7)	1540 (0.3)	2.86 (2.57-3.18)	1.21 (1.09-1.36)	111 (0.8)	315 (0.2)	3.57 (2.87-4.44)	1.43 (1.13-1.82)
Other cDMARDs (with MTX or HCQ/CLQ)	61 (0.1)	341 (0.1)	1.81 (1.38-2.37)	1.19 (0.90-1.57)	17 (0.1)	85 (0.1)	2.02 (1.20-3.41)	1.30 (0.76-2.24)
Rheumatic disease, no	58,739 (97.6)	592,181 (98.4)	*ref.*	*ref.*	13,758 (97.1)	139,100 (98.2)	*ref.*	*ref.*
Rheumatic disease, yes	1436 (2.4)	9569 (1.6)	1.52 (1.43-1.60)	1.00 (0.94-1.07)	413 (2.9)	2610 (1.8)	1.60 (1.44-1.78)	0.94 (0.83-1.06)
RA or SLE, no	58,739 (98.8)	592,181 (99.2)	*ref*.	*ref*.	13,758 (98.5)	139,100 (99.0)	*ref.*	*ref.*
RA or SLE, yes	741 (1.2)	4934 (0.8)	1.53 (1.41-1.65)	0.98 (0.89-1.07)	211 (1.5)	1351 (1.0)	1.59 (1.37-1.84)	0.88 (0.74-1.05)

Abbreviations: cDMARDs = conventional disease-modifying antirheumatic drugs; CLQ = chloroquine; HCQ = hydroxychloroquine; MTX = metotrexate; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus

* Univariate conditional logistic model matched for centre, age and gender

^ Multivariate conditional logistic regression model (stepwise forward based on Akaike's Information Criterion K=3.8415) matched for centre, age and gender and adjusted for the following eligible variables:, number of hospitalizations, Charlson index, number of prescriptions, drugs for peptic ulcer, anticoagulants, platelet aggregation, lipid modifying agents, antibiotics, anti-HIV drugs, anti-parkinson drugs, antiepileptics, antipsychotics, antidepressants, antiarrhythmics, non-steroidal anti-inflammatory drugs, corticosteroids, tDMARDs, bDMARDs, hypertension, cerebrovascular diseases, hepatopathies, diabetes, dementia, chronic kidney failure, chronic obstructive pulmonary disease, neoplasms, artery cardiac disease, rheumatic diseases (with or without indication for cDMARDs).