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Off-Label Use of Hydroxychloroquine in COVID-19: Analysis of Reports of Suspected Adverse Reactions From the Italian National Network of Pharmacovigilance

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Abstract

This study aimed to characterize adverse drug reactions (ADRs) to hydroxychloroquine in the setting of COVID-19, occurring in Italy in the period March to May 2020. The analysis of the combination therapy with azithromycin or/and lopinavir/ritonavir as well as a comparison with ADRs reported throughout 2019 was performed. ADRs collected by the Italian National Network of Pharmacovigilance were analyzed for their incidence, seriousness, outcome, coadministered drugs, and Medical Dictionary for Regulatory Activities classification. A total of 306 reports were gathered for the quarter of 2020: 54% nonserious and 46% serious, and half of the latter required either the hospitalization or its prolongation. However, most of them were either completely recovered (26%) or in the process of recovery (45%), except for 9 fatal cases. Throughout 2019, 38 reports were collected, 53% nonserious and 47% serious, but no deaths had been reported. Diarrhea, prolonged QT interval, and hypertransaminasemia were the most frequently ADRs reported in 2020, significantly higher than 2019 and specific for COVID-19 subjects treated with hydroxychloroquine. The logistic regression analyses demonstrated that the likelihood of serious ADRs, QT prolongation, and diarrhea significantly increased with hydroxychloroquine dosage. Coadministration of lopinavir/ritonavir and hydroxychloroquine showed a positive correlation with diarrhea and hypertransaminasemia and a negative relationship with the ADR seriousness. The combination therapy with azithromycin was another independent predictor of a serious ADR. Off-label use of hydroxychloroquine for COVID-19, alone or in combination regimens, was associated with increased incidence and/or seriousness of specific ADRs in patients with additional risk factors caused by the infection.

Keywords

adverse drug reactions, azithromycin, COVID-19, hydroxychloroquine, lopinavir/ritonavir

Hydroxychloroquine (HCQ) is an antimalarial agent, currently used for the treatment of autoimmune diseases, such as rheumatoid arthritis[1] and systemic lupus erythematosus.[2] HCQ was one of the first drugs "off-label" repurposed for the prevention and the therapeutic management of COVID-19, as in vitro data demonstrated its efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) in Vero E6 cells.[3,4]

Due to its weak basic properties, HCQ accumulates within acidic vesicles, such as lysosomes and endosomes,[5] increasing their pH and preventing endocytosis, exosome release, and phagolysosomal fusion.[6] Moreover, like its structural analog chloroquine, it can impair the SARS-Cov-2 attachment and entry in the host cell through the inhibition of the N-glycosylation of the cell surface viral receptor ACE2,[7,8] and it may additionally prevent SARS-CoV-2 from binding with gangliosides.[9] Besides its antiviral activity, HCQ modulates innate and adaptive immune cell activation, cytokine response, and inflammation.[5,8]

Based on these findings, the negligible cost, the ease of administration and the known safety profile of HCQ within the approved indications, a considerable number of clinical trials have been launched to evaluate its effectiveness against COVID-19. The results obtained so far are controversial, and a number of potential biases and confounding factors limit their robustness.

Early clinical studies conducted in China[10] and in France[11,12] suggested that HCQ use was associated with a short time to clinical recovery and to viral load

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reduction/disappearance in patients with COVID-19, and its effect is reinforced by azithromycin.

On the basis of these preliminary results, HCQ has been prescribed worldwide.

Several retrospective observational studies[13–16] suggested that treatment with either HCQ alone or in combination with azithromycin is associated with reduction in COVID-19 mortality, better clinical outcome, and more rapid virus clearance when compared to other treatments.

Conversely, 3 multicenter, randomized controlled trials[17–19] and some large observational studies[20–23] found a nonsignificant association between HCQ administration and clinical end points like intubation or death or in-hospital mortality.

The widespread use of HCQ began to dwindle after the publication of a multinational registry analysis[24] demonstrating an increased risk of in-hospital mortality and ventricular arrhythmia associated with the use of HCQ with or without a macrolide, then retracted due to the nonguarantee of the veracity of the primary data sources.[25]

Afterwards, the multicenter RECOVERY,[26] ORCHID,[27] and Solidarity[28] trials halted enrollment of patients with COVID-19 in the HCQ arm based on interim analysis showing no evidence of benefit or harm.

Serious concerns have been raised regarding HCQ safety use in the setting of SARS-Cov-2 disease, particularly QT prolongation and arrhythmias,[29,30] and several observational studies were published on the potentially arrhythmogenic effect of HCQ and its combination with azithromycin.[31–36] Both drugs are associated with known risk of torsade de pointes (TdP), even when taken as recommended.[37]

Furthermore, patients with COVID-19 are likely to have higher arrhythmic risks as a result of the metabolic and physiologic changes due to their illness and comorbidities, including myocardial injury, high-grade systemic inflammatory state, electrolyte imbalances, and concomitant QT-prolonging medications.[38–40]

Thus, the European Medicines Agency and Italian Medicines Agency established that HCQ should only be used in clinical trials for the treatment of COVID-19.[41,42]

Therefore, the aim of this study was a retrospective analysis of suspected adverse drug reaction (ADR) reports to HCQ, collected by the Italian National Network of Pharmacovigilance (NPP), between March 1, 2020, and May 31, 2020, the period of the first wave of COVID-19 in Italy.

Materials and Methods

The Italian NPP was queried for suspected ADRs associated with HCQ that occurred in Italy in the period March 1, 2020, to May 31, 2020, the first wave of the pandemic. Downloaded reports were compared to those collected throughout the year 2019 and, for each of them, age, sex, seriousness, outcomes, concomitant medications, source, and type of reporting were gathered.

Seriousness and outcomes have been classified according to the Eudravigilance criteria. A suspected adverse reaction was listed as serious if it resulted in death, was life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or resulted in a congenital anomaly/birth defect. The outcome, providing information on the last reported status of the suspected undesirable effect, was classified as resolved, resolving, resolved with sequelae, not resolved, fatal, or not specified.

ADRs were classified by group queries according to the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and System Organ Class (SOC)[43] and their seriousness and outcomes classified according to the Eudravigilance criteria.

Drugs used were listed according to the World Health Organization's Anatomical Therapeutic Chemical classification system.[44]

Analysis of the data were accomplished using Prism version 5.04 (GraphPad Software Inc., San Diego, California) and the open-source statistical software R, version 8.16 (R Foundation for Statistical Computing, Vienna, Austria).

Descriptive statistics were used to summarize data, expressed as mean ± standard error or frequency with percentage, where appropriate. The statistical association between variables was assessed using Fisher's exact test, as applicable.

Multivariate logistic regression analysis, based on the maximum likelihood ratio criterion,[45] was performed to identify which risk factors (independent variables) could have affected the likelihood of a serious ADR, QT prolongation, diarrhea, and hypertransaminasemia (dependent variables). Additionally, the impact of HCQ dosage on the dependent variables was explored while controlling for those independent variables that had shown a significant relationship in the previous models.

A value of $P < .05$ was considered significant.

Table 1. Outcome of Nonserious and Serious Reports of Adverse Reactions to Hydroxychloroquine During the Period March to May 2020 and January to December 2019

	Hydroxychloroquine				
	March to May 2020				
		Serious (n = 140)			
Outcome	Nonserious (n = 166)	Other Medically Important Conditions	Hospitalization (Initial or Prolonged)	Life Threatening	Death
Resolved	33	21	21	4	
Resolving	81	23	35	0	
Resolved with sequelae	2	0	1	0	
Not resolved	6	4	8	0	
Not specified	44	10	4	0	
Fatal	0	0	0	0	9
	January to December 2019				
		Serious (n = 18)			
Outcome	Nonserious (n = 20)	Other Medically Important Conditions	Hospitalization (Initial or Prolonged)		
Resolved	5	1	4		
Resolving	7	8	2		
Resolved with sequelae	0	0	0		
Not resolved	2	0	0		
Not specified	6	1	2		
Fatal	0	0	0		

Results

March to May 2020 Reports

Within the period March to May 2020, 306 reports featuring at least 1 ADR associated with HCQ were collected. Characteristics of reporters, patients, and HCQ daily dosage are shown in Tables S1, S2, and S3, respectively.

Of 306 reports, 54.2% were defined as nonserious and 45.8% serious; of the latter, 49.3% required either inpatient hospitalization or the prolongation of existing hospitalization, 41.4% were represented by other medically important conditions, and 2.9% by life-threatening reactions (Table 1). Nine cases of death were observed: 2 of unknown cause, 5 not due to HCQ, and 2 possibly related to HCQ use/associated with HCQ use. No report resulted in persistent or significant disability/incapacity or in a congenital anomaly/birth defect (Table 1). The patient's age did not affect the seriousness (mean age: nonserious reports, 63 ± 1.2 years; serious reports, 65 ± 1.4 years).

Regardless of the seriousness, 25.8% of patients were completely recovered, 45.4% in the process of recovery, 5.9% nonrecovered, and 1% recovered with sequelae at the time of reporting. The outcome was not available in 19% of reports and was fatal in 9 cases (Table 1).

A total of 506 MedDRA PTs, corresponding to 23 different SOCs were identified (Table 2). The most frequently reported ADRs were diarrhea, corrected QT interval (QTc) prolongation, and hypertransaminasemia (Table 3).

The 306 reports also included those of 11 patients who did not have COVID-19 who took HCQ for autoimmune diseases. None of the 3 ADRs, previously reported, were detected in these reports (Table 3).

Overall, 21% of all PTs associated with off-label use of HCQ were represented by cardiovascular ADRs (Table S4).

In 223 reports, HCQ was coded as suspected and in 83 as concomitant.

Polypharmacy (use of >5 drugs) was detected in 83 reports, 42 nonserious and 41 serious, including 8 deaths. Overall, 1044 drugs, consisting of 217 different medicinal products, were coadministered with HCQ (Tables S5 and S6). Of these coadministered medicines, 46 are broken into 4 categories that represent different levels of certainty, by Crediblemeds.org, the most reliable, up-to-date resource of drugs classified by their potential to cause QT prolongation and/or TdP[46] (Table S7). In 42 of the 54 cases of long QT,

Table 2. Distribution of ADRs That Occurred With HCQ Administration During March to May 2020 and January to December 2019 According to MedDra SOC Classification

	Number of Reported Reactions (MedDra PT)	
MedDra SOC	March to May 2020	January to December 2019
Blood and lymphatic system disorders	26	3
Cardiac disorders	37	3
Congenital, familial, and genetic disorders	1	
Ear and labyrinth disorders	1	2
Endocrine disorders	1	
Eye disorders	2	
Gastrointestinal disorders	87	6
General disorders and administration site conditions	26	11
Hepatobiliary disorders	24	
Immune system disorders	5	
Infections and infestations	18	4
Injury, poisoning, and procedural complications	6	1
Investigations	107	4
Metabolism and nutrition disorders	18	2
Musculoskeletal and connective tissue disorders	4	7
Nervous system disorders	16	4
Psychiatric disorders	6	4
Renal and urinary disorders	2	1
Reproductive system and breast disorders	1	
Respiratory, thoracic, and mediastinal disorders	17	
Skin and subcutaneous tissue disorders	95	18
Social circumstances	1	
Vascular disorders	5	2

ADRs, adverse drug reactions; HCQ, hydroxychloroquine; MEdDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SOC, System Organ Class.

Table 3. Most Frequent PTs Reported in 2020 (March to May) and Comparison With Corresponding Frequencies in 2019 (January to December)

PT	2020, n (%)	2019, n (%)	*P*	2020 No COVID, n (%)
Diarrhea	58/506 (11)	0/72	.0005	0/23
Electrocardiogram prolonged QT/LQTS	54/506 (11)	0/72	.0008	0/23
Hypertransaminasemia/ increased transaminase/increased ALT/ increased AST	45/506 (9)	0/72	.0036	0/23
Erythema	14/506 (3)	3/72 (4)	.45	2/23 (9)
Bradycardia/conduction disorders	13/506 (3)	0/72	.38	0/23

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LQTS, long QT syndrome; PTs, Preferred Terms
Differences between column 2020 and 2019 were evaluated by the Fisher exact test.

HCQ was associated with at least 1 other drug listed by Crediblemeds.

According to the Liverpool Drug Interactions website[47] providing information on the likelihood of interactions between HCQ and commonly prescribed comedications, 506 potential drug-drug interactions between HCQ and 77 different medicinal products have been found.

Adverse Drug Reactions Associated With a Combination of HCQ and Lopinavir/Ritonavir and/or Azithromycin

A deeper analysis of the ADRs associated with the coadministration of HCQ and lopinavir/ritonavir and/or azithromycin, the 2 most frequently prescribed comedications, was performed.

Among the reports, 131 (71% nonserious, 29% serious) included the combination HCQ plus lopinavir/ritonavir, 72 (33% nonserious, 67% serious) HCQ plus azithromycin, and 32 (56% nonserious, 44% serious) the triple therapy with HCQ plus lopinavir/ritonavir and azithromycin (Table 4). Most ADRs have been resolved or are in the process of being resolved, although 3 deaths were observed in the HCQ plus azithromycin group, which is the treatment regimen with the highest reporting seriousness (Table 4).

Indeed, the logistic regression analyses showed that the likelihood of serious ADRs significantly increased or decreased with coadministration of azithromycin and lopinavir/ritonavir, respectively (Table 5). Additionally, controlling for these 2 independent

Table 4. Outcomes of Nonserious and Serious Reports of Patients Treated With Several Combination Therapies (March to May 2020)

Hydroxychloroquine Plus Lopinavir/Ritonavir		
Outcome	Nonserious (n = 93)	Serious (n = 38)
Resolved	13	9
Resolving	55	22
Resolved with sequelae	0	0
Not resolved	1	2
Not specified	24	4
Fatal	0	1[a]
Hydroxychloroquine plus azithromycin		
Outcome	Nonserious (n = 24)	Serious (n = 48)
Resolved	1	15
Resolving	14	21
Resolved with sequelae	0	0
Not resolved	0	4
Not specified	9	5
Fatal	0	3[b]
Hydroxychloroquine plus lopinavir/ritonavir and azithromycin		
Outcome	Nonserious (n = 18)	Serious (n = 14)
Resolved	1	3
Resolving	10	9
Resolved with sequelae	0	0
Not resolved	0	0
Not specified	7	1
Fatal	0	1[c]

[a] One drug could have contributed.
[b] Two not due to drug and 1 drug could have contributed.
[c] One drug could have contributed.

variables (drugs coadministered), HCQ dosage was another independent predictor of a serious ADR (Table 5).

Three independent variables were associated with diarrhea: combination therapy with lopinavir/ritonavir and HCQ dosage (positive correlation), and age (negative correlation) (Table 5).

Moreover, lopinavir/ritonavir as well as age and HCQ dosage were positively associated with hypertransaminasemia and prolonged QT, respectively (Table 5).

January to December 2019 Reports

During 2019, 38 ADR reports associated with the use of HCQ (26 times coded as concomitant drug and 12 as suspected) were collected by the Italian NPP. Characteristics of reporters, patients, and HCQ daily dosage are shown in Tables S1, S2, and S3, respectively.

Of the serious reports, 44.4% led either to hospitalization or prolongation of existing hospitalization and 55.5% referred to other medically important conditions (Table 1). No ADR resulted in persistent or significant disability/incapacity, congenital anomaly/birth defect, life-threatening condition, or death. Considering that in 9 reports the outcome was not specified, overall most of the ADRs (71%) had a complete resolution or an improvement (Table 1).

A total of 72 PTs distributed in 14 different SOCs were reported (Table 2), and those at increased cardiovascular risk included 1 case of each of the following: syncope, tachycardia, cardiac failure, flushing, hematoma, and decreased blood pressure; and 2 cases of increased blood pressure. No cases of electrocardiographic ECG QT interval prolongation, diarrhea, and hypertransaminasemia have been reported.

Polypharmacy occurred in 18 reports, 8 nonserious, and 10 serious. A total of 169 drugs, consisting of 91 different medicinal products, including 15 listed by Crediblemeds, were coadministered with HCQ.

Analyses of the most reported ADRs during the pandemic revealed that diarrhea, QTc prolongation and hypertransaminasemia were significantly more frequent in 2020 than in 2019 ($P < .0005$; .0008 and .0036, respectively) but only when patients with COVID-19 were specifically considered (Table 3).

Discussion

This study demonstrates that in Italy during the first wave of pandemic, off-label use of HCQ in patients with COVID-19 was associated with higher reporting compared to the whole previous year. Diarrhea, QT prolongation, and hypertransaminasemia were the most frequently reported ADRs, specifically in subjects assuming HCQ for the treatment of COVID-19, in agreement with most frequent reported ADRs identified by Zekarias et al[48] through the analysis of 2573 reports on COVID-19–specific treatments from VigiBase, the World Health Organization's global ADR database.

Although there was no difference in patients' mean age, in the 2 periods studied, a sex difference was identified. In line with literature,[48,49] in a COVID-19 setting, ADRs were reported more frequently in men, consistent with the higher risk of severe disease and death in men than in women[50] but during HCQ label use, more frequently in women, in agreement with female predominance of autoimmune diseases.[51,52]

The percentage of serious and nonserious reports in the 2 periods analyzed was comparable, and no differences in outcomes were appreciated, except for pandemic ADRs that resolved with sequelae or were fatal.

Multivariate logistic regression analyses showed that, during 2020, unlike age and sex of patients, the HCQ dose and the coadministration of azithromycin were significantly associated with the seriousness of the

Table 5. Multivariate Logistic Regression Analysis

Dependent Variable	Variable	Regression Coefficient	Standard Error	*P* Value	Significance
Seriousness[a]	Intercept	–0.706750	0.528787	.181	
	Azithromycin	1.347767	0.311793	1.54e^{-05}	***
	Lopinavir/ritonavir	–1.254224	0.260452	1.47e^{-06}	***
	Sex[c]	–0.073800	0.253928	.771	
	Age	0.012571	0.007896	.111	
Seriousness[b]	Intercept	–1.540681	0.500124	.00207	**
	HCQ dosage	0.003995	0.001299	.00209	**
	Azithromycin	1.26824	0.322042	8.21e^{-05}	***
	Lopinavir/ritonavir	–1.270305	0.285786	8.79e^{-06}	***
Prolonged QT[a]	Intercept	–8.74928	1.31340	2.71e^{-11}	***
	Azithromycin	–0.18760	0.42762	.661	
	Lopinavir/ritonavir	0.18544	0.35092	.597	
	Sex[c]	–0.36532	0.34720	.293	
	Age	0.10390	0.01688	7.50^{e-10}	***
QT prolonged[b]	Intercept	–9.2182448	1.461614	2.85e^{-10}	***
	HCQ dosage	0.00334	0.001587	.0353	*
	Age	0.092247	0.016877	4.60e^{-08}	***
Diarrhea[a]	Intercept	–0.27223	0.63930	.67023	
	Azithromycin	–0.31381	0.38122	.41041	
	Lopinavir/ritonavir	1.47118	0.32859	7.56e-^{06}	***
	Sex[c]	0.34742	0.31981	.27733	
	Age	–0.03351	0.01024	.00106	**
Diarrhea[a]	Intercept	–1.941341	0.889942	.02915	*
	HCQ dosage	0.004884	0.001663	.00331	**
	Age	–0.037551	0.011453	.00104	**
	Lopinavir/ritonavir	1.807102	0.381181	2.13e^{-06}	***
Hypertransaminasemia[a]	Intercept	–2.16534	0.77305	.00509	**
	Azithromycin	0.44291	0.37742	.24058	
	Lopinavir/ritonavir	1.02188	0.35029	.00353	**
	Sex[c]	0.61502	0.36424	.09131	
	Age	–0.01070	0.01109	.33452	
Hypertransaminasemia[b]	Intercept	–1.371695	0.613908	.0255	*
	HCQ dosage	–0.002312	0.001635	.1573	
	Lopinavir/ritonavir	0.911559	0.361229	.0116	*

HCQ, hydroxychloroquine.
[a] A total of 306 observations.
[b] A total of 259 observations (HCQ dosage was missing in 47 reports; see Table S3).
[c] Sex was codified as a dummy equal to 1 in case of male, 0 instead.
* $P < .05$, ** $P < .01$, *** $P < .001$.

reports. Use of high doses of the antimalarial[53–55] and combination therapy with azithromycin[17,55] have been reported to increase the risk of serious adverse events. Additionally, it is noteworthy to consider the long half-life and the high volume of distribution characterizing the HCQ pharmacokinetics.[56] In this study, the combination therapy of HCQ with lopinavir/ritonavir, on the other hand, appeared to reduce the likelihood of seriousness, although, to date, no clinical or virological benefit has been demonstrated with this treatment compared to single agents in retrospective trials.[57]

According to MedDRA hierarchy, during a COVID-19 scenario, most ADRs belonged to SOC "investigations," followed by "skin and subcutaneous disorders" and "gastrointestinal disorders," whereas during the pre–COVID-19 period, the 3 most common symptom manifestations were dermatologic conditions, general disorder, and administration site conditions as well as musculoskeletal and connective disorders. In COVID-19 reports, half of the "investigations" were represented by the ECG prolonged QT, in addition to ECG repolarization abnormalities, long QT syndromes, ventricular

tachycardia, and bradycardia, which also occurred, all predisposing to TdP. It is noteworthy that no case of TdP was reported. Several studies demonstrated that the incidence of malignant life-threatening tachyarrhythmia is extremely low in a short period of either HCQ or HCQ plus azithromycin administration.[31–36] Conversely, no case of long QT was reported throughout 2019. Remarkably, the 306 reports from the COVID-19 era also included those of 11 patients without COVID-19 taking HCQ, as approved for autoimmune diseases. QT prolongation and more in general cardiovascular ADRs were not detected in any of these reports. HCQ was also associated with bradycardia/conduction disorders, although the incidence was lower and not significantly different when compared to 2019.

In patients with SARS-Cov-2, the 2 most frequently coadministered drugs with either possible or known risk of inducing long QT/TdP were lopinavir/ritonavir and azithromycin, respectively.

Several studies have shown that the combination of HCQ and azithromycin was associated with a greater increase in QT interval in patients with COVID-19[32,33] as well as with more serious cardiovascular ADRs in patients rheumatic disorders[58] when compared with monotherapy. Moreover, a recent prospective observational study demonstrated that patients treated with either HCQ plus azithromycin or HCQ plus azithromycin and lopinavir/ritonavir had prolonged QTc compared to baseline values, but patients with triple therapy did not show a greater increase in the QTc than those on double therapy.[59]

In our analysis, neither azithromycin nor lopinavir/ritonavir coadministration seemed to be associated with prolonged QT, but only the age of patients and the HCQ dose, in agreement with Bernardini et al[60] and Juurlink.[61]

Besides concomitant therapies, COVID-19 per se might be an important factor enhancing the risk of adverse reactions to HCQ. In fact, it is increasingly recognized that, in COVID-19, myocardial involvement is common, possibly due to multiple mechanisms including direct viral infection, hypoxia-induced apoptosis, and cytokine storm–related cell damage.[38,39] Moreover, regardless of the development of cardiac injury, inflammatory cytokines can also exert direct electrophysiological effects on the myocardium, promoting QTc prolongation.[62–64] In particular, it has been demonstrated that interleukin-6, which is commonly found at high levels in patients with COVID, directly inhibits the ether-à-go-go–related gene potassium channel channels and prolongs action potential duration in ventricular myocytes.[65]

These mechanisms may contribute to explain the high incidence of QTc prolongation that we observed in 2020, specifically in patients assuming HCQ for COVID-19.

Disease-specific considerations could also account for gastrointestinal and hepatic adverse reactions, similarly reported to an increased extent in 2020 in patients with COVID-19. Indeed, a recent pooled analysis of the available clinical data revealed an overall diarrhea rate of about 10% in patients with COVID-19,[66] a percentage overlapping that we observed in our HCQ-treated patients with COVID-19 in 2020, but significantly higher when compared to a previous study on HCQ in rheumatoid arthritis.[49]

Similarly, a large retrospective observational cohort study demonstrated that hypertransaminasemia is relatively common during active COVID-19,[67] while it was reported in <1% of patients with rheumatoid arthritis administered HCQ.[68]

However, regression logistic analyses revealed that age and coadministration of lopinavir/ritonavir showed a positive correlation with diarrhea and hypertransaminasemia, as recently reported by Giacomelli et al.[69] Moreover, the age of patients and the dose of HCQ were found to decrease and increase the likelihood of diarrhea, respectively, in agreement with Unim et al[70] and Munster et al.[54]

Conclusions

This study suggests that off-label use of HCQ for COVID-19, alone or in combination with lopinavir/ritonavir and/or azithromycin, was associated with an increased incidence and/or seriousness of specific ADRs, in patients with additional risk factors including the infection itself, notwithstanding biases and limitations of the pharmacovigilance analysis.

Indeed, though the spontaneous ADR reporting system represents the mainstay of pharmacovigilance, allowing the early detection of possible safety signals and the continuous monitoring and evaluation of potential safety issues, it suffers from several limitations and biases imbedded in the concept of voluntary reporting.[71] Shortcomings include multiplicity of reporters; retrospective and open collection of data, generating missing information, and thus potential uncertainties and distortions; underreporting or overreporting; absence of either naïve control patients or patients receiving the drug without ADRs, incompleteness of reports due to lack of exposure data and comorbidities.

Though these findings deserve further investigations and validation, they have important implications that impose cautiousness in HCQ indication, especially for

patients susceptible to cardiovascular as well as intestinal and hepatic toxicities.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Author Contributions

E.F., P.E.L., and S.S. wrote the article; A.V. and S.S. came up with the study concept; E.F., A.V., and S.S. designed the research; E.F., F.C., and S.S. performed the research; E.F., F.C., P.E.L., and S.S. performed the data analyses.

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