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Research Article

Cardiotoxicity of Drugs Used in the Management of the COVID-19 Patients: Single-Center Retrospective Study

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Abstract

Background: Since COVID-19 was declared a pandemic by the World Health Organization (WHO), there have been many changes in treatment protocols. With the rise of COVID-19 cases globally and the absence of any approved medicine for the treatment of (COVID-19), many drugs have been experimentally administered to patients, ignoring possible side effects. Some of these drugs have a background of potential cardiotoxicity that should be evaluated.

Methods: A retrospective study will be conducted on patients' admissions to (ICU) or (CCU) in Al-Noor Hospital in the Kingdom of Saudi Arabia to treat COVID-19. The effect of the drugs used in the management of COVID-19 on the cardiac parameters of patients will be evaluated and compared with COVID-19 medications that cause cardiotoxicity in patients.

Results: The patients were having Symptoms included arrhythmia (56.3%), murmur (43.0%), QT prolongation (54.3%), chest pain (54.3%), shortness of breath (55.0%), heart palpitation (45.7%), fluid retention (47.0%) and myocarditis (51.7%). ICU admission diagnoses in most patients were COVID exacerbation (51.7%) and pneumonia (38.4%). Different classes of antibiotics and antivirals were administered to the patients, and a high risk of cardiac manifestations was observed in patients using Ribavirin which was used in 51 patients (33.8%).

Conclusion: The study showed that cardiotoxic symptoms appear among patients using anti-COVID medications, especially Ribavirin. Therefore, there is a need to limit the use of medicines for COVID-19, which causes cardiotoxicity and change the protocol used in Saudi Arabia.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a highly contagious viral infection, has affected over 200 countries within a brief span and created an alarming global situation (Davies et al., 2020). It has been declared a pan-demic by the WHO. With the rise of coronavirus cases globally and the absence of any approved medicine to treat the infection, many drugs were experimentally administered to the infected patients, ignoring the possible side effects (Wan et al., 2020). No specific treatment protocol has been approved by (the FDA) for COVID-19 infection (Hick & Biddinger, 2020; Wenham et al., 2020). However, patients may experience potential side effects from the medications used to treat the infection (Gevers et al., 2020). Therefore, it is essential to assess the possible side effects of the medicines currently under consideration for managing this infection (Javorac et al., 2020). According to a study, hospitalized patients in Wuhan, China, experienced acute cardiac manifestations such as shock (8.7%), cardiac injury (7.2%), and arrhythmia (16.7%)

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(Kamp et al., 2020). Another study involved 799 patients, of whom 62% experienced hypertension and other cardiac complications, and 77% died due to cardiac injury (Iqubal et al., 2021). Many parts of the world extensively used the antimalarial drugs chloroquine and hy-droxychloroquine to treat COVID-19 infections (Gautret et al., 2020). However, thorough research tri- als on the efficacy of these antivirals in treating infections yielded minimal evidence, limiting their potential for management. The use of these antivirals has nearly ceased in most global healthcare settings due to potential side effects such as blurred vision, abdominal cramps, and other abnormalities (Ferner & Aronson, 2020; Geleris et al., 2020). The cardiotoxic effects such as atrioventricular blocks, cardiac arrest, sick sinus syndrome, and QT prolongation were observed after chloroquine and hydroxychloroquine (CQ/HCQ) (Khuroo , 2020). Other complications associated with CQ and HCQ include ventricular hypertrophy, heart failure, valvular dysfunction, and pulmonary hypertension (Bachhav et al., 2021).

Moreover, many studies reported that using azithromycin results in prolongation of the QT interval, ventricular tachycardia, and arterial fibrillation (Trifirò et al., 2017). The mechanism by which azithromycin causes cardiotoxicity has been investigation (Cheng et al., 2015). Remdesivir also showed some cardiotoxic effects.

According to a case study, a patient receiving remdesivir to treat the Ebola virus developed hypotension and cardiac arrest and died (Mulangu et al., 2019). Lopinavir/ritonavir, which is used in the treatment of HIV infection, recently became a potential candidate for the treatment of COVID-19 patients. Sinus arrest and atrioventricular blocks have been associated with its use (Chaubey et al., 2009). Interferon-Alpha is also a potential treatment for COVID-19, and its use has been associated with reports of pericardial effusion. So, we want to investigate some major cardiotoxic concerns. We have a history of underlying conditions like congenital long QT syndromes (LQTS) or electrolyte imbalances, especially with potassium and calcium. Furthermore, a population of particular interest includes patients receiving medications such as tricyclic antidepressants, antipsychotics, and even some antiemetics, as well as those with comorbid conditions that could potentially harbor COVID-19. This study will answer many questions about COVID-19 infection. The treatment regimen for COVID-19 infection causes electrical disturbances (QT interval prolongation) that result in a higher risk of arrhythmia. However, the medications used in COVID-19 patients cause cardiotoxicity. Patients with COVID-19 are increasingly reporting cardiovascular complications. However, there is limited data on the incidence of cardiac arrhythmia in affected patients. The incidence of arrhythmia in COVID-19 patients varies between 10% and 20%, with 7.3% indicating palpitations as a presenting symptom (Liu et al., 2020; Zhao et al., 2021). Cardiovascular complications encompass myocardial damage (21.2%), arrhythmia (15.3%), heart failure (14.4%), and acute coronary syndrome (1%), with mortality rates of 8.47% for arrhythmia and 7.61% for myocarditis (Hou et al., 2020). Arrhythmia is prevalent among critically ill patients, underscoring its substantial influence on COVID-19 outcomes. To limit the use of the medication for COVID-19 that causes cardiotoxicity, change the treatment protocols used in Saudi Arabia, and compare the profile of cardiac adverse events associated with medications used for COVID-19 infection.

The objective of our study is to observe and evaluate the cardiotoxic effect of the medicines used in the treatment of COVID-19 patients at Al-Noor Specialist Hospital, Makkah and the cardiotoxicity effect of drug use in COVID-19 on the management of COVID-19 patients and comparison between the impact of the drugs that cause cardiotoxicity.

MATERIALS AND METHODS

Study design and setting

This retrospective observational study was conducted on patients hospitalized with COVID-19 infection from December 2020 to November 2021. The study was per-formed at Al-Noor Specialist Hospital, Makkah, a 550 bedded referral teaching hospital delivering tertiary care throughout the Makkah region of Saudi Arabia. Al-Noor Specialist Hospital in Makkah was likely selected for its strategic location, advanced healthcare facilities, high patient volume, and role as a key center for COVID-19 management in a densely populated and diverse region.

Inclusion Criteria

The patients with laboratory-confirmed COVID-19 infection admitted to the intensive care unit (ICU) and cardiac care unit (CCU) were included. COVID-19 infection was confirmed in all included patients via real-time reverse transcription-polymerase chain reaction (PCR) on oropharyngeal or nasopharyngeal samples.

Exclusion Criteria

The patients with incomplete records were excluded from this study. Patients with arrhythmia, heart failure and coronary artery diseases were excluded from the study. Also, all immunocompromised patients with malignancy were excluded from the study.

Data collection

Our research team members reviewed patient records using the electronic medical record system (HIS) to collect demographic characteristics, initial symptoms, comorbid conditions, therapeutic interventions, complications during ICU or CCU stay, and laboratory indices of organ failure. Routine laboratory investigations included parameters of renal and liver functions, complete blood profile, arterial blood gases, cardiac param-

eters (cardiac markers, ECG, and arrhythmia) and inflammatory markers (Lactate dehydrogenase (LDH) and C-reactive protein (CRP)) and D-dimer levels.

Data Management

The study data were classified according to the data and classification of cardiotoxicity in each group.

Data Analysis Strategies

The categorical variables were described as frequency rates and percentages, and the continuous variables were defined using the mean, median, and interquartile range (IQR) values. Statistical tests were performed using SPSS version 26.0. chi-square test will be applied to observe the association of risk factors with demographic characteristics, clinical history, symptoms, and presence of chronic disease. For all analysis, P-values 0.05 was considered statistically significant. An odds ratio (OR) measures the association between an exposure and an outcome. The odds ratio (OR) represents the odds that a product will occur given a particular direction exposure compared to the odds of the work occurring in that absence. The hazard ratio compares the probability of events in a treatment group to the likelihood of events in a control group. It's used to see if patients receive treatment progress faster (or slower) than those not receiving it.

Ethical approval

The study protocol was approved institutional review board of the general directorate of Health, Ministry of Health (MOH), Makkah, Kingdom of Saudi Arabia. No study activities were initiated until an Institutional Re-view Board approval was obtained. The final ethical approval was obtained from UQU biomedical research ethics committee Approval No: HAPO-02-K012-2021-04-666.

RESULTS

The demographic characteristics of the patients are described in Figure 1 below. Most of the patients were male (71.5%), and their age was more than 50 years (62.3%).

The patients' medical status and cardiovascular disease (CVS) manifestations are described in Table 1. The patients were having symptoms of arrhythmia (56.3%), murmur (43.0%), QT prolongation (54.3%), chest pain (54.3%), shortness of breath (55.0%), heart palpitation (45.7%), fluid retention (47.0%) and myocarditis (51.7%). The days of onset of symptoms ranged from 1 to 6, but in most cases, it was either one (38.4%) or two days (25.2%). ICU admission diagnosis in most of the patients was COVID-19 exacerbation (51.7%) and pneumonia (38.4%). The patients have also presented with comorbidities. The most common comorbid conditions were diabetes mellitus (DM), cardiovascular diseases (CVD) and renal diseases.

Table 2 describes the detailed therapeutic protocol and treatment plan of the patients. The number of patients received antiviral drugs, antibacterial, and other supported treatments. The most commonly used antiviral drugs were hydroxychloroquine (38.4%), Remdesivir (73%) interferon (41.1%), tocilizumab (54.3%) and acyclovir (33.1%), whereas the most commonly used antibacterial drugs were azithromycin (64.2%), ceftriaxone (47.7%), cefepime (45.7%), meropenem (27.2%), piperacillin/ tazobactam (58.9%) and vancomycin (31.1%).

The patients were also provided with supportive treatment, including anticoagulants, proton pump inhibitors and antihypertensives. Oxygen support was also provided to the patients to avoid hypoxic death. As far as the clinical outcome was concerned, around 78% of patients were discharged, whereas 21.9% died.

A high risk of cardiac manifestations was observed in patients using Ribavirin which was used in 51 patients (33.8%). Arrhythmia was observed in 56.5% of patients taking Tocilizumab, 38.8% of patients taking Hydroxychloroquine, 42.4% of patients taking Interferon, and 72.9 % patients taking remdesivir and 64.7% of patients taking Azithromycin. Shortness of breath was observed in 37.3% of patients taking Hydroxychloroquine, 33.7% of patients taking Ribavirin, 42.2% of patients taking Interferon, and 78.3% of patients taking remdesivir, 53% of patients taking Tocilizumab, and 67.5% of patients taking Azithromycin. Details are given in table 3.

DISCUSSION

This study emphasized the cardiotoxicity of the drugs used to manage the COVID-19 disease. Different drug classes used in COVID-19 patients increase the risk of ventricular arrhythmias and comorbid disease increases the risk of ventricular arrhythmias. These drugs should neither be used as routine medication, and correction of electrolyte abnormalities could prevent the risk of ventricular arrhythmias (Cubeddu et al., 2022; El Kadri et al., 2022). Overall, COVID-19 infections cause abnormalities in the cardiovascular system (CVS) either directly or indirectly, which may lead to cardiac arrest, including acute cardiac injury, acute myocardial infarction, arrhythmias, myocarditis, and acute heart failure (Mavraganis et al., 2020). Severe COVID-19 infection may be associated with a higher prevalence of acute coronary syndromes (ACS), which lead to cardiac ar -rest, despite the ongoing pandemic's decrease in the number of patients with acute myocardial infarction (MI) (Mountantonakis et al., 2020; Stefanini et al., 2020).

Acute coronary syndromes (ACS) can be caused by the rupture of atherosclerotic plaque due to inflammation in the body, a high thrombotic tendency, virus-induced endothelium, and an imbalance of myocardial supply-demand due to hemodynamic or high cardiac metabolic

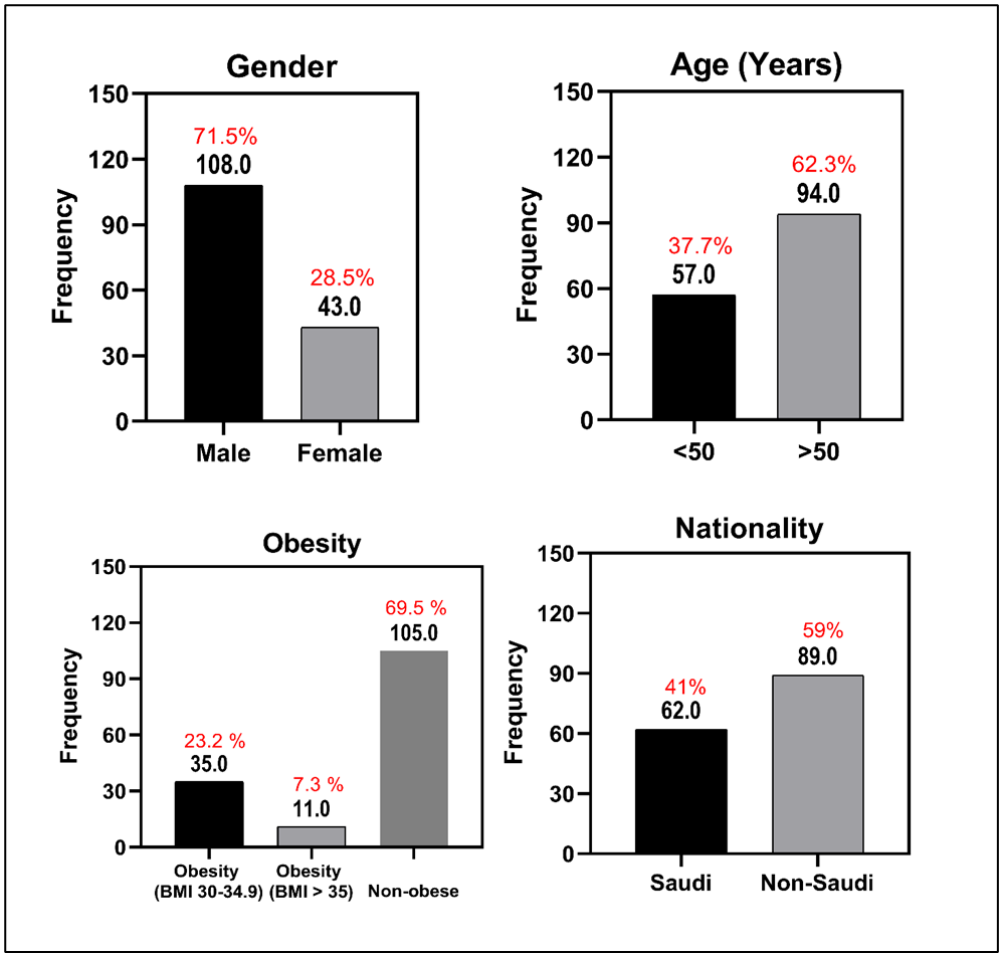

Figure 1: Demographic Characteristics of Patients

instability (Driggin et al., 2020). In our study, we frequently used antibiotics such as azithromycin and piperacillin/tazobactam, along with antivirals like hydroxychloroquine/chloroquine and remdesivir, for the management of COVID-19. Other potential mechanisms may include cardiac toxicity due to antivirals, steroids, and electrolyte abnormalities. The results of our study align with those of Kaliyaperumal et al., revealing a similar prevalence of heart palpitations (45.7%), QT-prolongation (54.3%), and arrhythmia (56.3%). Further, we have similar findings with another study by Brit Long; this group also found cardiovascular toxicities in COVID-19 patients, such as palpitations, atrial fibrillation, ventricular arrhythmias, QTc prolongation, and ST-T segment changes (Kaliyaperumal et al., 2022). Moreover, several studies documented the QT prolongation and Torsade De Pointes arrhythmias following azithromycin administration (Chorin et al., 2020; Foster et al., 2023). In addition to giving drugs, the coronavirus affects the renin-aldosterone system, which leads to electrolyte imbalances like low potassium, low calcium, and low magnesium levels. These imbalances contribute to QT prolongation and arrhythmias (Henry et al., 2021; Sandhu et al., 2021).

Our findings reported that most patients experienced shortness of breath after remdesivir administration. Before initiating the treatment, it is important to appropriately monitor the patients to prevent drug-associated adverse effects. We suggest assessing the QT interval in patients with suspected or confirmed COVID-19 via electrocardiogram (ECG) after the initiation of therapy, focusing on hyperkalemia , discontinuing the arrhythmic drugs, and supplementing with magnesium to reduce the potential risk of torsade de pointes (Lakkireddy et al., 2020).

To balance the risk-benefit ratio, it is important to closely monitor renal insufficiency, structural abnormalities, and functional cardiovascular abnormalities before treatment (Hendren et al., 2020). Amiodarone administration should be avoided in the case of ventricular tachycardia induced by hydroxychloroquine or azithromycin. Instead, procainamide, lidocaine, or esmolol should be administered intravenously (Mavraganis et al., 2020).

Our study aligns with the research on Hydroxychloroquine, which has been shown to increase the risk of cardiac arrest (cardiotoxicity) and cognitive dysfunction. Remdesivir influences cognitive dysfunction. These findings provide important information to change the protocol of COVID-19 medication for patients with COVID-19 (Izcovich et al., 2022).

Table 1: Clinical presentation according to the Medical Status/CVS Manifestation

	N	%
Arrhythmia	85	56.3 %
Troponemia	65	43.0 %
QT-prolongntion	82	54.3 %
Chest Pain	82	54.3 %
Shortness of breath	83	55 %
Heart palpitations	69	45.7 %
Fluid retention in the legs	71	47 %
Myocarditis	78	51.7 %
Days of onset of symptoms	N	%
1.0	58	38.4 %
2.0	38	25.2 %
3.0	15	9.9 %
4.0	8	5.3 %
5.0	16	10.6 %
6.0	16	10.6 %
ICU Admission Diagnosis	N	%
Covid Exacerbation	78	51.7 %
Pneumonia	58	38.4 %
Sepsis	46	30.4%
ARDS	2	1.3 %
MI	7	4.6 %
Heart Failure	1	0.7 %
G.I Bleeding	1	0.7 %
Comorbidities	N	%
D.M	87	57.6 %
CRD (Asthma)	59	39.1 %
CRD (COPD)	147	97.4 %
Hypokalemia	93	61.6 %
Bradycardia	89	58.9 %
Tuberculosis (T.B)	27	17.9 %
Chronic Kid. Disease	60	39.7 %
Acute kidney injury AKI	17	11.3 %
Liver Cirrhosis	11	7.3 %
Chronic Hepatitis B	2	1.3 %
Chronic Hepatitis C	4	2.6 %
Smoking History	75	49.7 %
Comorbidities (None)	37	24.5 %
Comorbidities = 1	38	25.2 %
Comorbidities >1	76	50.3 %

CONCLUSION AND RECOMMENDATION

Patients on antiviral therapy for coronavirus disease could have a high risk of cardiovascular side effects. It will be more prominent in patients with comorbidities, e.g., atrial fibrillation, heart failure, and coronary artery disease. Remdesivir has demonstrated in vitro activity against SARS-CoV-2. Additionally, its overdose can raise the threat of cardiac toxicity. The second important drug is Ribavirin. It has multiple administration strategies. Patients with chronic obstructive pulmonary disease and asthma, characterized by dyspnea and chest pain, place ribavirin in a higher risk category. However, there is a strong need for controlled trials to assess the safety of major COVID-19 medications in a larger population using large data registries. Additionally, if hydroxychloroquine or azithromycin therapy induces ventricular tachycardia, one must limit amiodarone.

We recommend incorporating the following considerations from our study into the COVID-19 management guidelines, based on our findings. Severe COVID-19-infected patients require careful monitoring of pharmacotherapy and its related side effects. COVID-19 pneumonia, the primary cause of admission among COVID-19 patients, has the potential to worsen a patient's condition if left untreated or improperly man-aged. Most patients receive antimicrobial therapy, including antiviral, antifungal, and antibiotic therapy. The most common antibiotics causing cardiovascular toxicities, including azithromycin and levofloxacin in such pa-

Table 2: Antimicrobials/Treatment Plan

Antivirals	**Treated**		**Untreated**	
	N	%	N	%
Remdesivir	111	73.5 %	40	26.5 %
Hydroxqloroqine	58	38.4 %	93	61.6 %
Ribavirin	51	33.8 %	100	66.2 %
Interferon	62	41.1 %	89	58.9 %
HCL/CL	84	55.6 %	67	44.4 %
Tocilizumab	82	54.3 %	69	45.7 %
Oseltamavir	31	20.5 %	120	79.5 %
Acyclovir	50	33.1 %	101	66.9 %
Antibacterials	Treated		Untreated	
	N	%	N	%
Azithromycin	97	64.2 %	54	35.8 %
Ceftrioxone and Ceftezidim	72	47.7 %	79	52.3 %
Cefepime	69	45.7 %	82	54.3 %
Meropenem	41	27.2 %	110	72.8 %
Piperacillin / tazobactam	89	58.9 %	62	41.1 %
Colistitimethate sodium	38	25.2 %	113	74.8 %
Levofloxacin	69	45.7 %	82	54.3 %
Vancomycin	47	31.1 %	104	68.9 %
Linzolide	58	38.4 %	93	61.6 %
Tegaclcyne	78	51.7 %	73	48.3 %
Daptomycin	57	37.7 %	94	62.3 %
Gentamycin	64	42.4 %	87	57.6 %
Amikacin	69	45.7 %	82	54.3 %
Clindamycin	89	58.9 %	62	41.1 %
Other Medications	Treated		Untreated	
	N	%	N	%
Enoxaprine	128	84.8 %	23	15.2 %
Heparine	62	41.1 %	89	58.9 %
Omeprazole	148	98 %	3	2 %
Hydrocortison / Prednisolon	101	66.9 %	50	33.1 %
Amlodipine	41	27.2 %	110	72.8 %
ACEI	37	24.5 %	114	75.5 %
ARAB	32	21.2 %	119	78.8 %
Oxygen Support				
			N	%
Room Air			79	52.3 %
High Flow O2			15	9.9 %
Intubation			57	37.7 %
Clinical Outcome				
			N	%
Discharged			118	78.1 %
Died			33	21.9 %

tients, cover all possible pathogens empirically causing covid pneumonia. Based on our findings, we recommend strict daily monitoring of the cardiovascular function of COVID patients and abruptly stopping these medications in case of any sign of QTC prolongations. Also, we recommend using other alternatives, e.g., beta-lactams and tetracyclines, in severe COVID-infected patients. Also, consistent monitoring of patient renal function is the key consideration to avoiding excessive drug accA doctor needs to stop giving all drugs that cause torsade de pointes VT, fix any problems with the patient's electrolytes, and give intravenous magnesium with isoproterenol or temporary transvenous pacing if the arrhythmia doesn't go away. persists. Also, using amiodarone concomitantly with proarrhythmic drugs, e.g., remdesivir, azithromycin, and hydroxychloroquine, could end up with incremental QTC prolongation.

AUTHOR CONTRIBUTION

Both authors are equal distributed in each steps of the manuscript.

Table 3: Risk of Cardiovascular Toxicity

CVS symptom * Drug	Patients					95% Confidence Interval	
	N	%	Pearson Chi-Square	Hazard Ratio	Odds Ratio	Lower	Upper
Arrhythmia * Tocilizumab	48	56.5	0.54	1.23	1.22	0.54	1.23
Arrhythmia * hydroxqloroqine	33	38.8	0.91	1.09	1.04	0.91	1.09
Arrhythmia * Ribavirin	36	42.4	0.011*	2.76	2.50	0.011*	2.76
Arrhythmia * Interferon	35	41.2	0.97	1.01	1.01	0.97	1.01
arrhythmia * Remdesivir	62	72.9	0.86	0.98	0.94	0.86	0.98
arrhythmia * Azithromycin	55	64.7	0.89	1.08	1.05	0.89	1.08
Troponemia * hydroxqloroqine	24	36.9	0.74	1.00	0.90	0.74	1.00
Troponemia * Ribavirin	22	33.8	0.99	1.89	1.01	0.99	1.89
Troponemia * Interferon	28	43.1	0.66	1.20	1.16	0.66	1.20
Troponemia * Remdesivir	51	78.5	0.23	1.68	1.58	0.23	1.68
Troponemia * Tocilizumab	38	58.5	0.37	1.22	1.34	0.37	1.22
Troponemia * Azithromycin	38	58.5	0.20	0.61	0.64	0.20	0.61
QT-prolongntion (ECG) * hydroxqloroqine	34	41.5	0.40	1.39	1.33	0.40	1.39
QT-prolongntion (ECG) * Ribavirin	28	34.1	0.92	1.12	1.04	0.92	1.12
QT-prolongntion (ECG) * Interferon	38	46.3	0.15	1.46	1.62	0.15	1.46
QT-prolongntion (ECG) * Remdesivir	58	70.7	0.40	0.99	0.73	0.40	0.99
QT-prolongntion (ECG) * Tocilizumab	40	48.8	0.14	0.10	0.61	0.14	0.10
QT-prolongntion (ECG) * Azithromycin	55	67.1	0.43	1.77	1.31	0.43	1.77
Chest Pain * hydroxqloroqine	28	34.1	0.24	0.07	0.67	0.24	0.07
Chest Pain * Ribavirin	23	28.0	0.11	0.68	0.57	0.11	0.68
Chest Pain * Interferon	34	41.5	0.91	1.57	1.04	0.91	1.57
Chest Pain * Remdesivir	57	69.5	0.23	0.93	0.63	0.23	0.93
Chest Pain * Tocilizumab	44	53.7	0.86	0.88	0.95	0.86	0.88
Chest Pain * Azithromycin	56	68.3	0.26	1.32	1.47	0.26	1.32
Shortness of breath * hydroxqloroqine	31	37.3	0.77	0.81	0.91	0.77	0.81
Shortness of breath * Ribavirin	28	33.7	0.99	0.89	1.00	0.99	0.89
Shortness of breath * Interferon	35	42.2	0.76	1.12	1.11	0.76	1.12
Shortness of breath * Remdesivir	65	78.3	0.14	1.10	1.73	0.14	1.10
Shortness of breath * Tocilizumab	44	53	0.73	0.12	0.89	0.73	0.12
Shortness of breath * Azithromycin	56	67.5	0.36	1.33	1.37	0.36	1.33
Heart palpitations * hydroxqloroqine	23	33.3	0.24	0.09	0.67	0.24	0.09
Heart palpitations * Ribavirin	21	30.4	0.43	0.77	0.76	0.43	0.77
Heart palpitations * Interferon	31	44.9	0.375.	1.31	1.34	0.375.	1.31
Heart palpitations * Remdesivir	51	73.9	0.92	1.10	1.04	0.92	1.10
Heart palpitations * Tocilizumab	39	56.5	0.62	1.98	1.18	0.62	1.98
Heart palpitations * Azithromycin	44	63.8	0.91	0.78	0.96	0.91	0.78
Myocarditis * hydroxqloroqine	29	37.2	0.75	0.81	0.90	0.75	0.81
Myocarditis * Ribavirin	27	34.6	0.82	1.92	1.08	0.82	1.92
Myocarditis * Interferon	30	38.5	0.50	0.11	0.80	0.50	0.11
Myocarditis * Remdesivir	60	76.9	0.33	1.48	1.44	0.33	1.48
Myocarditis * Tocilizumab	43	55.1	0.83	1.10	1.07	0.83	1.10
Myocarditis * Azithromycin	48	61.5	0.47	0.71	0.78	0.47	0.71

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DECLARATIONS

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose. The au-

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