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Analysis of the US FDA adverse event reporting system to identify adverse cardiac events associated with hydroxychloroquine in older adults

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Keywords:	hydroxychloroquine, adverse event, data signal, reporting odds ratio, elderly

Abstract:

Purpose The purpose of this study is to analyze the US FDA Adverse Event Reporting System (FAERS) to identify adverse cardiac events of hydroxychloroquine in older adults.

Method A case/non-case method was used to determine adverse events associated with hydroxychloroquine as the primary suspect drug between January 1, 2004, and December 31, 2019, for older adults (≥ 65 years). Adverse events are preferred terms (PTs) defined in MedDRA. We used frequentist approaches, including the reporting odds ratio (ROR) and the proportional reporting ratio (PRR) to measure disproportionality. We used Bayesian approaches to derive information component (IC) value and Empirical Bayesian Geometric Mean (EBGM) score. Signals were defined as the number of reports>3 and the lower limit of 95% confidence intervals (CI) of ROR ≥2, PRR ≥2, IC >0, EBGM>1

Results We identified 334 adverse cardiac events comprising 71 different MedDRA PTs from 2004 to 2019 for hydroxychloroquine in older adults. Strong disproportionality signals were noted for 'Restrictive cardiomyopathy' (ROR= 272.43 (138.09-537.47); EBGM= 149.78 (77.34-264.67), 'Right ventricular hypertrophy' (219.49 (85.32-564.70); 102.74 (39.67-222.81), 'Cardiac septal hypertrophy' (226.77 (78.65-653.80); 93.82 (32.19-219.81), 'Myocardial fibrosis' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and 'Cardiotoxicity' (43.90 (26.66-72.27); 40.28 (24.02-63.72).

Conclusions The risk of cardiomyopathy and myocardial disorders is high following exposure to hydroxychloroquine in older adults. Due to the current lack of safety data from randomized controlled trials as well as large observational studies to confirm the risk of adverse cardiac events associated with hydroxychloroquine, findings from analyses of post-marketing data may serve as interim guidance.

Analysis of the US FDA adverse event reporting system to identify adverse cardiac events associated with hydroxychloroquine in older adults

Response to reviewers

Nishtala et.al

Dear Editor

Thank you for the opportunity to revise our paper and clarify the comments raised by the reviewers. We are grateful for the useful comments provided by the reviewers to improve the manuscript, and the reviewers share our judgement that the findings of this study are interesting and important. Please see below, in blue, our detailed response to comments. All page numbers refer to the manuscript file with tracked changes

Reviewer 1:

Comments to the Author

Abstract

- RORs that high with a wide confidence interval represents a lack of sample size and very hard to interpret.

Response 1

We acknowledge this is a limitation of the study. However, the signals meet the criteria for a disproportionality signal- defined as the number of reports >3 and the lower limit of 95% confidence intervals (CI) of ROR ≥2, PRR value ≥2, IC value >0 and EBGM score >1.

We have also added the following sentence to the limitations paragraph of the Discussion on page

Page 7, Line 32-35: '*The ROR's for ADE's associated with hydroxychloroquine with a wide confidence interval represents a lack of sample size, and the safety signals must be interpreted with this limitation. The safety signals reported in this study with hydroxychloroquine do not impart causality."*

- Please rewrite the timeframe of the study such as January 1, 2004, etc. rather than the current format given the variability of dating convention worldwide.

Response 2

Page 4, Line 22-23: We agree with the reviewer and accordingly have changed the date format.

Introduction

Please reframe the message to NOT-TO-IMPART causality. FAERS database is meant for exploratory analyses – that is – to generate hypotheses rather than testing hypotheses.

Response 3.

We agree with the reviewer and appended the following sentence to the introduction:

Page 3, Line 32-33: *"The FAERS data is widely used in drug safety research for exploratory analyses to generate hypotheses and safety signals reported do not impart causality."*

Page 7, Line 32-35: *"The safety signals reported in this study with hydroxychloroquine do not impart causality."*

Methods

- Was the primary suspect outcomes were reported or primary OR secondary suspect outcomes were considered?

Response 4

Outcomes such as disability or hospitalisations were not analysed in the study.

We analysed all reported adverse events in older adults with hydroxychloroquine as the primary suspect drug. Concomitant drugs (secondary suspect drugs) were not included in the analyses.

- Were the authors able to identify for which indication hydroxychloroquine (HCQ) was prescribed? The method section mentions that. How many missing values were there? How it was relevant to the study?

Response 5

Indications were missing for 97 out of 1090 (8.9%) reports. The majority of the reports 430/1090 (39.4%) indicated hydroxychloroquine was used for rheumatic disorders (mainly rheumatoid arthritis) followed by 124/1090 (11.3%) reports for systemic lupus erythematosus.

We analysed all reported adverse events with hydroxychloroquine as the primary suspect drug in older adults regardless of the indication of its use during the study period. The missing indications for hydroxychloroquine did not have any impact on safety signals generated for hydroxychloroquine.

We appended the following sentence to the results:

Page 5, Line 9-13: *"Indications were missing for 97 out of 1090 (8.9%) reports. The majority of the reports 496/1090 (45.5%) indicated hydroxychloroquine was used for rheumatic disorders (mainly rheumatoid arthritis) followed by 124/1090 (11.3%) reports for systemic lupus erythematosus, and 199/1090 (18.3%) reports recorded hydroxychloroquine was used for an unknown indication."*

- How HCQ was identified? What string searches were used and/or how? How the misspellings (if any) were corrected?

Response 6

Data were retrieved from the Elsevier PharmaPendium database. The use of PharmaPendium for drug safety research is described elsewhere. The data is curated by an experienced team of data analysts at Elsevier and is made ready for analyses.

- How the duplicate reports were handled? Are these worldwide reports or just US reports?

Response 7

We identified duplicate reports based on CaseID, Primary Suspect Drugs, Gender, Age and Location. The analyses included reports from the USA and worldwide.

Results & Discussion

- Please describe why only older adults were chosen for the study. COVID-19 is causing major cardiac events in younger adults as well. This would be a very important clinical implication of this study.

Response 8

We have appended the following paragraph to the discussion to highlight the importance of COVID-19 related risks in older adults.

Page 5, Line 31-34 & Page 6, Line 1: "*The risk for severe illnesses from COVID-19 infection is age-related, with older adults aged 85 or older at highest risk. Underlying medical comorbidities, specifically underlying cerebrovascular and cardiovascular disease, including heart failure, coronary heart disease and cardiomyopathies, increases the risk of hospitalisations and intensive care unit admissions in older adults with COVID-19 infection.*"

- The authors should comment on the extremely high RORs and a wide confidence interval in terms of statistical consideration as well as clinical considerations. These are almost uninterpretable.

Response 9

Please note Response 1. We have discussed this as a study limitation.

- The authors should write the limitation of this study more precisely. There are many studies that provided a big description of the limitations of the FAERS database, and this current study should interpret and discuss the results based on the limitations. I would recommend depicting the limitation of this study and format the discussion. I am providing a citation for the authors' convenience –

Clin Drug Investig. 2017 Dec; 37(12): 1143–1152.

Response 10

We thank the reviewer for pointing us to this relevant citation. The study limitations outlined in the study conducted by Rahman et al. on the FAERS database are pertinent to our investigation. We have formatted our discussion based on the limitations discussed by Rahman et al.

We have revised the limitations section as follows.

Page 7, Line 17-35: *"There are database and several methodological limitations associated with this study. Adverse event reports are submitted voluntarily to FAERS, and this may potentially lead to underreporting. Although careful consideration was given to the removal of duplicated reports, there is a possibility that the AEs may be reported multiple times by various stakeholders including patients, manufacturers and physicians. Given the spontaneous nature of reporting, the drug exposure at a population level is unknown, hence the actual incidence rate for the AE cannot be established. Lack of information on comorbidities, family history, and incomplete dosage information is likely to bias the study findings. Characteristic*

of SRS is the potential for selective reporting of only serious adverse events. Specific methodological limitations include examining hydroxychloroquine as the primary drug of interest without ascertaining the impact of concomitant medications on the AE. Several of the AEs identified with hydroxychloroquine may be confounded by the severity of the underlying medical condition. For example, several autoimmune disorders treated with hydroxychloroquine are independently associated with adverse cardiac outcomes. It is important to note that we did not investigate a dose-dependent or a temporal relationship with AEs, as these are significant risk factors for cardiac AEs with hydroxychloroquine. Hence the safety signals reported with hydroxychloroquine do not impart causality."

Reviewer 2

This is an interesting paper and I have some comments for the authors consideration:

We appreciate the encouraging comment.

Abstract: Why are you examining cardiac events in hydroxychloroquine in older adults? Have clinical trials not examined this population? You need to be specific in the purpose of the study.

Response 11

We thank the reviewer for their suggestion. Given the word count limit in the abstract section, we have clarified the purpose of the study in the introduction.

Page 3, Line 15-29: "*COVID-19 disproportionately affects older adults. Given the repurposing of hydroxychloroquine has gained rapid interest for the treatment of COVID-19, understanding safety profile of hydroxychloroquine from post-marketing data is of paramount importance. This is particularly important as there is a lack of safety data for hydroxychloroquine from randomized controlled trials (RCTs) or observational studies (7). Specifically, there is a lack of safety data from RCTs for older adults using hydroxychloroquine for the treatment of COVID-19 infection caused by SARS-CoV-2 (8, 9). A recent RCT conducted in USA and Canada showed that hydroxychloroquine was not effective when offered as prophylaxis after COVID-19 exposure. In this RCT (N=821), the median age of the study population was 41 (IQR=33 to 51) years with no safety data reported for hydroxychloroquine use in older adults (9). A more recent RCT conducted over eight weeks that evaluated the efficacy and safety of hydroxychloroquine versus placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers showed no clinical benefit of hydroxychloroquine (10). The median age of the study population in this RCT was 33 (20-66), and there was no safety data for hydroxychloroquine reported in older adults.*"

Introduction, page 4, line 10: This drug candidate list seems slightly out of date now- lopinavir/ritonavir and ivermectin are not really leading candidates anymore. Perhaps use a more up to date reference. Remdesivir is also spelt incorrectly.

Response 12

We thank the reviewer for this suggestion and accordingly revised the sentence and updated the reference. We regret that we had misspelt Remdesivir. It is now amended in the revised manuscript.

Introduction: It may be worth mentioning that the FDA has subsequently withdrawn the emergency use authorisation. Also, be more specific about what data is lacking for hydroxychloroquine- data does exist for other indications aside from COVID. Is it that there is not RCT data for older adults using hydroxychloroquine at all (regardless of indication)? It is a generalisation to say they are usually excluded.

Response 13

We have updated the introduction to clarify that the FDA has withdrawn the emergency use authorisation of hydroxychloroquine.

There is limited RCT data for older adults using hydroxychloroquine, regardless of indication. We have appended the following paragraph in the introduction.

Page 3, Line 21-24: *"A recent RCT conducted in USA and Canada showed that hydroxychloroquine was not effective as postexposure prophylaxis after COVID-19 exposure. In this RCT, the median age of the study population (N=821) was 41(IQR=33 to 51) years with no safety data reported for hydroxychloroquine use in older adults [7]. "*

Discussion: The authors comment on the known cardiac effects of hydroxychloroquine. I think this could be expanded to explicitly state why older adults may be at greater risk, referring to prevalence of cardiac disease in this age group. Also, are they likely to experience more serious outcomes from these types of events e.g. death? The authors need to be clear why these events are of greater concern in older adults, as many of these events would be of concern among any age group.

Response 14

The risk for severe illness from COVID-19 increases with age, with older adults aged 85 or older at highest risk. Underlying medical comorbidities, specifically underlying cerebrovascular and cardiovascular disease including heart failure, coronary heart disease and cardiomyopathies means that an older adult with COVID-19 may require hospitalisation and subsequent admission to the intensive care unit.

We appended the following paragraph into the discussion.

Page 6, Line 15-23: *"Also, two recent studies have lighted the risk of QT interval prolongation in patients with COVID-19 infection treated with hydroxychloroquine. In a case series of intensive care unit patients (median age= 68 years (IQR, 58-74 years)) admitted for COVID-19 infection, those treated with hydroxychloroquine had an increased risk of QT prolongation. Similar findings were echoed in a cohort study conducted at a tertiary care hospital in Boston, Massachusetts, involving 90 patients with mean age 60 years (SD=16). In this cohort study, patients who received hydroxychloroquine for the treatment of pneumonia associated with*

COVID-19 were at high risk of QTc prolongation. The most common underlying comorbidities in this cohort included hypertension and diabetes."

Discussion: Regarding the novel findings, why are these events of concern? Are they more likely to result in death than the known events? Safety signals need to be discussed in terms of their importance, not just their presence

Response 15

We appreciate the importance of communicating the impact of safety signals on clinical outcomes. Accordingly, we have appended the following information to the discussion.

Page 6, Line 34-35 & Page 7 Line 1-4: *"Cardiac septal hypertrophy in older adults is associated with disturbance in intraventricular conduction and is an independent predictor of progression to atrial fibrillation in patients with hypertrophic cardiomyopathy. [23, 24]. Myocardial fibrosis is a significant risk factor for hypertrophic cardiomyopathy, and is associated with a myriad of severe adverse cardiovascular outcomes including sudden cardiac death, ventricular tachyarrhythmias, left ventricular dysfunction, and heart failure [25]."*

Discussion, limitations: Can the authors comment on whether masking of signals may be present and could have any influence on study results? The limitations should also explicitly state why causality cannot be inferred from these results.

Response 16

We did not explore whether the masking influenced the safety signals for hydroxychloroquine.

One study (*Wang HW, Hochberg AM, Pearson RK, Hauben M. An experimental investigation of masking in the US FDA adverse event reporting system database. Drug Saf. 2010 Dec 1;33(12):1117-33)* has reported that the prevalence of masking might be low in the Adverse Event Reporting System and is more likely to occur in pharmaceutical company databases. Another challenge is accurately identifying drug candidates in the FAERS that are likely to mask signals. We do not feel that this limitation is expected to be significant for the reasons outlined above. On balance, we cannot make a definitive comment if masking of signals influenced the study findings.

Please note our response 10 to reviewer 1 in which we have discussed the limitations of the study and the reasons causality cannot be inferred.

Conclusions: I agree that monitoring signals is important but they should also be investigated further where there is a concern, using other study methods where required. You mention screening in the conclusion but have not discussed this elsewhere- you should include a paragraph in the discussion outlining this recommendation in more detail. What screening is needed? Who will this help? How will this mitigate complications?

Response 17

We thank the reviewer for their valuable suggestion. We have appended the following paragraph in conclusion.

Page 8, Line 5-10: *"The American College of Cardiology's as well as the Canadian heart rhythm society recommendation is that patients with COVID-19 infection treated with hydroxychloroquine should undergo a careful assessment of baseline risk of QT prolongation, including baseline ECG, biochemical tests, and exclusion of concomitant drugs that have a potential to prolong QTc interval to mitigate further complications such as torsades de pointes [8]."*

Conclusions: You need to be clear that any lack of safety data is specifically for the age group (older adults) and the COVID indication. Hydroxychloroquine would not be authorised for other indications without sufficient safety data in these other populations. Please be clear on this throughout the manuscript.

Response 18

We thank the reviewer for pointing this out and have attempted to clarify this message throughout the manuscript.

We have appended the following sentence in the introduction

Page 3, Line 19-21: *"Specifically, there is a lack of safety data for older adults using hydroxychloroquine for the treatment of COVID-19 infection caused by SARS-CoV-2."*

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Analysis of the US FDA adverse event reporting system to identify adverse cardiac events associated with hydroxychloroquine in older adults

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Keywords: hydroxychloroquine, adverse event, data signal, reporting odds ratio, elderly

Word count: 2067 (excluding references)

Key points

1. The study found that the risk of cardiac cardiomyopathy and myocardial disorders is high following exposure to hydroxychloroquine in older adults.

2. Novel findings include the identification of a signal for cardiac septal hypertrophy.

Abstract

Purpose The purpose of this study is to analyze the US FDA Adverse Event Reporting System (FAERS) to identify adverse cardiac events of hydroxychloroquine in older adults.

Method A case/non-case method was used to determine adverse events associated with hydroxychloroquine as the primary suspect drug between January 1, 2004, and December 31, 2019, for older adults (≥ 65 years). Adverse events are preferred terms (PTs) defined in MedDRA. We used frequentist approaches, including the reporting odds ratio (ROR) and the proportional reporting ratio (PRR) to measure disproportionality. We used Bayesian approaches to derive information component (IC) value and Empirical Bayesian Geometric Mean (EBGM) score. Signals were defined as the number of reports>3 and the lower limit of 95% confidence intervals (CI) of ROR ≥2, PRR ≥2, IC >0, EBGM>1

Results We identified 334 adverse cardiac events comprising 71 different MedDRA PTs from 2004 to 2019 for hydroxychloroquine in older adults. Strong disproportionality signals were noted for *'Restrictive cardiomyopathy'* (ROR= 272.43 (138.09-537.47); EBGM= 149.78 (77.34-264.67), 'Right ventricular hypertrophy' (219.49 (85.32-564.70); 102.74 (39.67-222.81), '*Cardiac septal hypertrophy'* (226.77 (78.65-653.80); 93.82 (32.19-219.81), '*Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and *'Cardiotoxicity'* (43.90 (26.66-72.27); 40.28 (24.02-63.72).

Conclusions The risk of cardiomyopathy and myocardial disorders is high following exposure to hydroxychloroquine in older adults. Due to the current lack of safety data from randomized controlled trials as well as large observational studies to confirm the risk of adverse cardiac events associated with hydroxychloroquine, findings from analyses of post-marketing data may serve as interim guidance.

Introduction:

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has positioned drug repurposing research on the spotlight (1, 2). Drug repurposing is investigating existing drugs for new indications, and several drugs have emerged as candidates for repurposing to treat COVID-19. Among the several leading candidates chloroquine, hydroxychloroquine and remdesivir have generated massive interest in the USA as a potential *'game-changer'* in the treatment of COVID-19 (3, 4). Several clinical trials are being undertaken to generate evidence on the efficacy of hydroxychloroquine to treat COVID-19 patients (5). Based on the research evidence from ongoing clinical trials, the US FDA has removed the emergency use authorization for hydroxychloroquine and chloroquine for the treatment of COVID-19 given that the risks of using hydroxychloroquine for the treatment of COVID-19 infection outweigh any benefits (6). However, the uncertainty of the safety of hydroxychloroquine in older adults will endure given the historical evidence for the exclusion of older adults with comorbidities in clinical trials.

COVID-19 disproportionately affects older adults. Given the repurposing of hydroxychloroquine has gained rapid interest for the treatment of COVID-19, understanding safety profile of hydroxychloroquine from post-marketing data is of paramount importance. This is particularly important as there is a lack of safety data for hydroxychloroquine from randomized controlled trials (RCTs) or observational studies (7). Specifically, there is a lack of safety data from RCTs for older adults using hydroxychloroquine for the treatment of COVID-19 infection caused by SARS-CoV-2 (8, 9). A recent RCT conducted in USA and Canada showed that hydroxychloroquine was not effective when offered as prophylaxis after COVID-19 exposure. In this RCT (N=821), the median age of the study population was 41 (IQR=33 to 51) years with no safety data reported for hydroxychloroquine use in older adults (9). A more recent RCT conducted over eight weeks that evaluated the efficacy and safety of hydroxychloroquine versus placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers showed no clinical benefit of hydroxychloroquine (10). The median age of the study population in this RCT was 33 (20-66), and there was no safety data for hydroxychloroquine reported in older adults. The objective of this study is to analyze the US FDA Adverse Event Reporting System (FAERS), a publicly available database, to identify adverse cardiovascular events of hydroxychloroquine in older adults using analysis of disproportionality. The FAERS data is widely used in drug safety research for exploratory analyses to generate hypotheses and safety signals reported do not impart causality.

Method:

Ethics approval: The Departmental Research Ethical Officer at the University of Bath approved this study.

***Data source*:** Data was retrieved from the Elsevier PharmaPendium database (11). Data for 4667+ United States FDA and European Medicines Agency approved drugs, and 14+ million FAERS reports have been collected and stored in the PharmaPendium in the latest 2020.07 release. The use of PharmaPendium for drug safety research is described elsewhere (12, 13). Each FAERS report contains information on the drug and its role in the event, dose, frequency and route. The primary, secondary, concomitant and interacting drugs are reported.

Along with the adverse event experienced, the outcome, drug indication, reporter occupation, location of the event, manufacturer, patient gender and age are documented. Each report has an AERS report number and Case ID aiding with easy identification. The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify frequently implicated adverse drug events.

Adverse drug reaction definition

We used the preferred terms (PTs) recommended in the Medical Dictionary of Regulatory Activities (MedDRA v2.0) to define adverse events associated with hydroxychloroquine. Each PT is part of the hierarchal system, linking to a higher-level term (HLT), higher-level group term (HLGT) and system organ class (SOC).

Statistical Analyses

We selected hydroxychloroquine as the primary suspect drug and analyzed all reported adverse events in older adults from the start of January 1, 2004, to the end of December 31, 2019. The ratio of cases/non-cases for hydroxychloroquine was compared with the ratio of cases/non-cases for all other drugs for the same study period. We used the disproportionality analyses to calculate the reporting odds ratio (ROR) and the proportional reporting ratio (PRR) (14). We used the Bayesian approach to calculate information component (IC) values and Empirical Bayesian Geometric Mean (EBGM) scores. The criteria for a disproportionality signal was defined as the number of reports >3 and the lower limit of 95% confidence intervals (CI) of ROR ≥2, PRR value ≥2, IC value >0 and EBGM score >1. For secondary analyses, we mapped the PTs of adverse cardiovascular events to system organ class (SOC), high-level group term (HLGT) and high-level term (HLT). The analysis was conducted in R, version 3.6.1 (15).

Results

We retrieved a total of 7,247,902 drug-event pairs between January 1, 2004, and December 31, 2019, recorded in FAERS for adults aged ≥ 65 years by splitting multiple AEs reported for each case. Of which, 5327 adverse events (AEs) belonged to hydroxychloroquine. Amongst the 5327 AEs, we identified 334 adverse cardiac events comprising 71 different MedDRA PTs. The mean age of the patients within the reports (n=1090) for hydroxychloroquine is 71.77 (7.27) years, and 85.4 % were females. 56.1% of the reports were submitted by 'other healthcare professionals' followed by 20.3% from physicians and 20.5% from consumers. 90.4% of the reports were expedited. The country of origin of the reports was mostly from the USA. Indications were missing for 97 out of 1090 (8.9%) reports. The majority of the reports 430/1090 (39.4%) indicated hydroxychloroquine was used for rheumatic disorders (mainly rheumatoid arthritis) followed by 124/1090 (11.3%) reports for systemic lupus erythematosus, and 199/1090 (18.3%) reports recorded hydroxychloroquine was used for an unknown indication.

Figure 1. Mapping of hydroxychloroquine-associated all adverse drug events at different MedDRA levels: SOC: system organ class; HLGT: high-level group term; HLT: high-level term

Figure 2. Mapping of hydroxychloroquine-associated cardiovascular events at different MedDRA levels: SOC: system organ class; HLGT: high-level group term; HLT: high-level term. Yellow boxes include terms resulting in disproportionality signals; Grey boxes include terms without disproportionality; NEC: not elsewhere classified; MedDRA: Medical Dictionary for Regulatory Activities

Figure 3: RORs and EBGM scores with 95% CIs for PTs with hydroxychloroquine-associated cardiovascular events. ADR-adverse drug reaction; HCQ-hydroxychloroquine ROR- reporting odds ratio; EBGM-Empirical Bayesian geometric mean; CI confidence interval.

Strong disproportionality signals were noted for *'Restrictive cardiomyopathy'* (ROR= 272.43 (138.09-537.47); EBGM= 149.78 (77.34-264.67), *'Right ventricular hypertrophy'* (219.49 (85.32-564.70); 102.74 (39.67-222.81), '*Cardiac septal hypertrophy'* (226.77 (78.65-653.80); 93.82 (32.19-219.81), *'Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and *'Cardiotoxicity'* (43.90 (26.66-72.27); 40.28 (24.02-63.72).

Discussion

The risk for severe illnesses from COVID-19 infection is age-related, with older adults aged 85 or older at highest risk. Underlying medical comorbidities, specifically underlying cerebrovascular and cardiovascular disease, including heart failure, coronary heart disease and cardiomyopathies, increases the risk of hospitalizations and intensive care unit

admissions in older adults with COVID-19 infection (16). In this context, this study addressed the impending necessity emerging from the COVID-19 pandemic for understanding the safety of hydroxychloroquine in older adults.

Majority of the cardiovascular AEs reported in this study are related to cardiac conduction and myocardial disorders. These findings are consistent with a recent systematic review that concluded conduction disorders and myocardial hypertrophy as two major cardiac complications associated with hydroxychloroquine therapy (17).

Analyses of high-level MedDRA terms suggest that hydroxychloroquine therapy is associated with abnormal cardiac conduction, cardiac arrhythmias, and cardiomyopathy. Several case reports have described proarrhythmic effects and signs of long QT syndrome following hydroxychloroquine exposure in patients with systemic lupus erythematosus (18, 19). The interim guidance from the Canadian heart rhythm society to mitigate drug-induced arrhythmias is for performing baseline ECG testing in high-risk patients. The recommendation is to optimize drug treatments, and correct electrolytes, if QTc is moderately prolonged and to cease the drug if QTc is markedly prolonged (20). Also, two recent studies have lighted the risk of QT interval prolongation in patients with COVID-19 infection treated with hydroxychloroquine. In a case series of intensive care unit patients (median age= 68 years (IQR, 58-74 years)) admitted for COVID-19 infection, those treated with hydroxychloroquine had an increased risk of QT prolongation (21). Similar findings were echoed in a cohort study conducted at a tertiary care hospital in Boston, Massachusetts, involving 90 patients with mean age 60 years (SD=16). In this cohort study, patients who received hydroxychloroquine for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation (22). The most common underlying comorbidities in this cohort included hypertension and diabetes.

Hydroxychloroquine is known to cause direct myocardial toxicity and cardiomyopathy (23, 24). Yogasundaram *et al.* have shown that cardiomyopathy is a preventable complication and early withdrawal of hydroxychloroquine treatment can potentially result in a partial or complete reversal of cardiomyopathy (25).

Our analyses revealed several other cardiac adverse effects associated with hydroxychloroquine, including left and right ventricular hypertrophy and acute left ventricular failure. These are well recognized AEs of hydroxychloroquine. Prescribers should be aware that these serious adverse events can be pronounced in older adults with pre-existing cardiac disease. However, our novel findings include the identification of cardiac septal hypertrophy and myocardial fibrosis associated with hydroxychloroquine therapy, and these signals require further confirmation. Cardiac septal hypertrophy in older adults is associated with disturbance in intraventricular conduction and is an independent predictor of progression to atrial fibrillation

in patients with hypertrophic cardiomyopathy. (26, 27). Myocardial fibrosis is a significant risk factor for hypertrophic cardiomyopathy, and is associated with a myriad of severe adverse cardiovascular outcomes including sudden cardiac death, ventricular tachyarrhythmias, left ventricular dysfunction, and heart failure (28).

Strengths and limitations

This study used PharmaPendium, a database maintained by Elsevier that curates data from FAERS. PharmaPendium uses PTs, defined in MedDRA, to identify adverse events from FAERS. FAERS is a spontaneous reporting system (SRS) widely used for examining associations between marketed medicines and AEs. SRS is particularly useful when safety data from randomized controlled trials or observational studies are lacking. Analyses of SRS can potentially reveal new and clinically important drug-event associations. Rare safety events can be captured in SRS that is generally not identified in clinical trials. Notably, to our knowledge, no previous investigations have reported the safety profile of hydroxychloroquine in older adults.

There are database and several methodological limitations associated with this study. Adverse event reports are submitted voluntarily to FAERS, and this may potentially lead to underreporting (29). Although careful consideration was given to the removal of duplicated reports, there is a possibility that the AEs may be reported multiple times by various stakeholders including patients, manufacturers and physicians. Given the spontaneous nature of reporting, the drug exposure at a population level is unknown, hence the actual incidence rate for the AE cannot be established. Lack of information on comorbidities, family history, and incomplete dosage information is likely to bias the study findings. Characteristic of SRS is the potential for selective reporting of only serious adverse events. Specific methodological limitations include examining hydroxychloroquine as the primary drug of interest without ascertaining the impact of concomitant medications on the AE. Several of the AEs identified with hydroxychloroquine may be confounded by the severity of the underlying medical condition. For example, several autoimmune disorders treated with hydroxychloroquine are independently associated with adverse cardiac outcomes. It is important to note that we did not investigate a dose-dependent or a temporal relationship with AEs, as these are significant risk factors for cardiac AEs with hydroxychloroquine. The ROR's for ADE's associated with hydroxychloroquine with a wide confidence interval represents a lack of sample size, and the safety signals must be interpreted with this limitation. The safety signals reported in this study with hydroxychloroquine do not impart causality.

Conclusions

The risk of cardiac disorders is increased with hydroxychloroquine in older adults. Despite, the lack of causality in our findings, these safety signals must be monitored and where applicable appropriate screening to mitigate these complications is recommended. The American College of Cardiology's as well as the Canadian heart rhythm society recommendation is that patients with COVID-19 infection treated with hydroxychloroquine should undergo a careful assessment of baseline risk of QT prolongation, including baseline ECG, biochemical tests, and exclusion of concomitant drugs that have a potential to prolong QTc interval to mitigate further complications such as torsades de pointes (11). Due to the current lack of randomized controlled trials as well large observational studies to confirm the risk of AEs associated with hydroxychloroquine, findings from analyses of post-marketing data may serve as interim guidance until further robust data on safety becomes available.

Author Contributions

Study concept and design: PN, TC; Statistical analysis: PN, TC; Interpretation of data: All authors; Drafting of the manuscript: PN, SG; Critical revision of the manuscript for important intellectual content: All authors; Study supervision: PN.

Conflict of interest: The authors have no conflicts of interest to declare.

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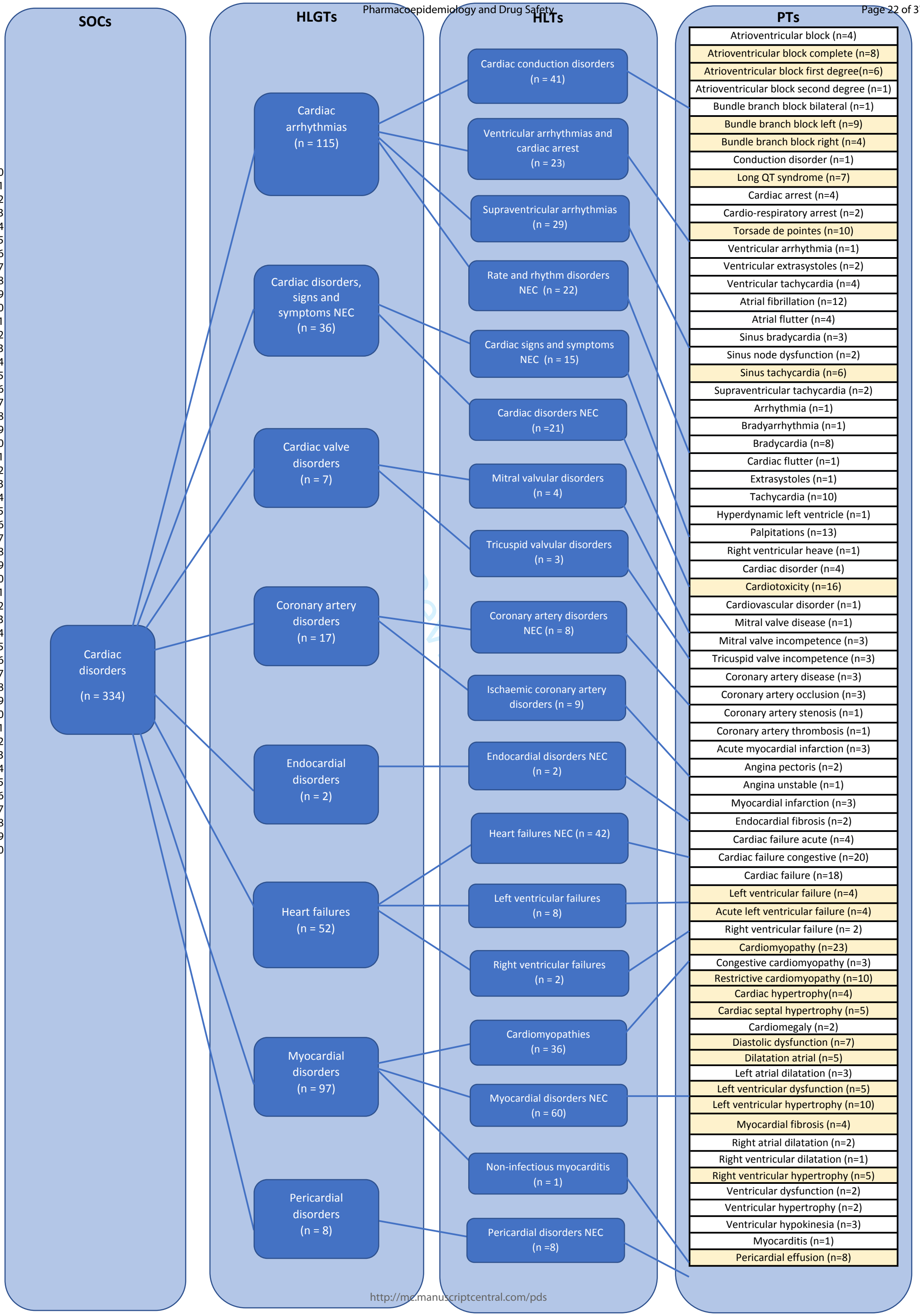
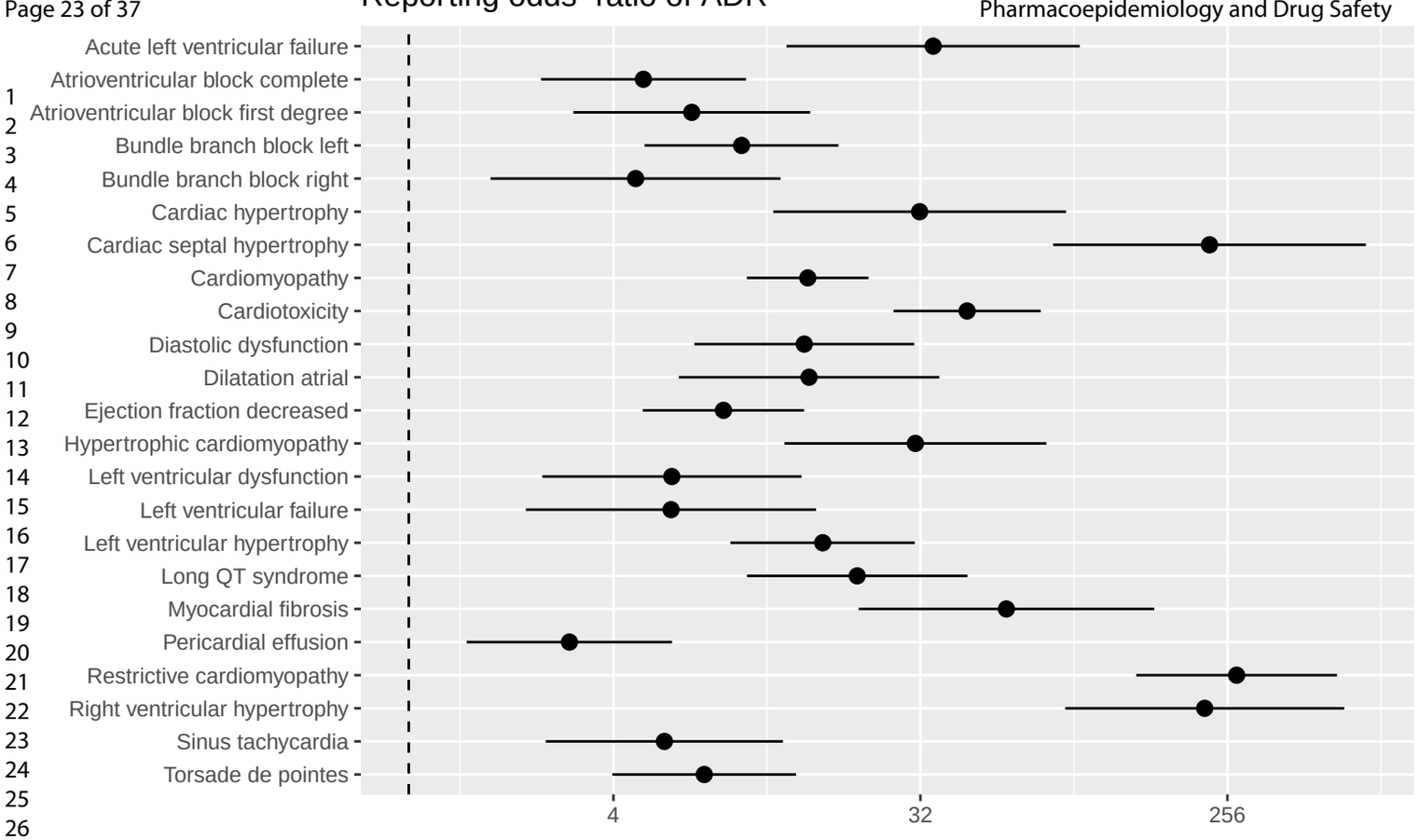
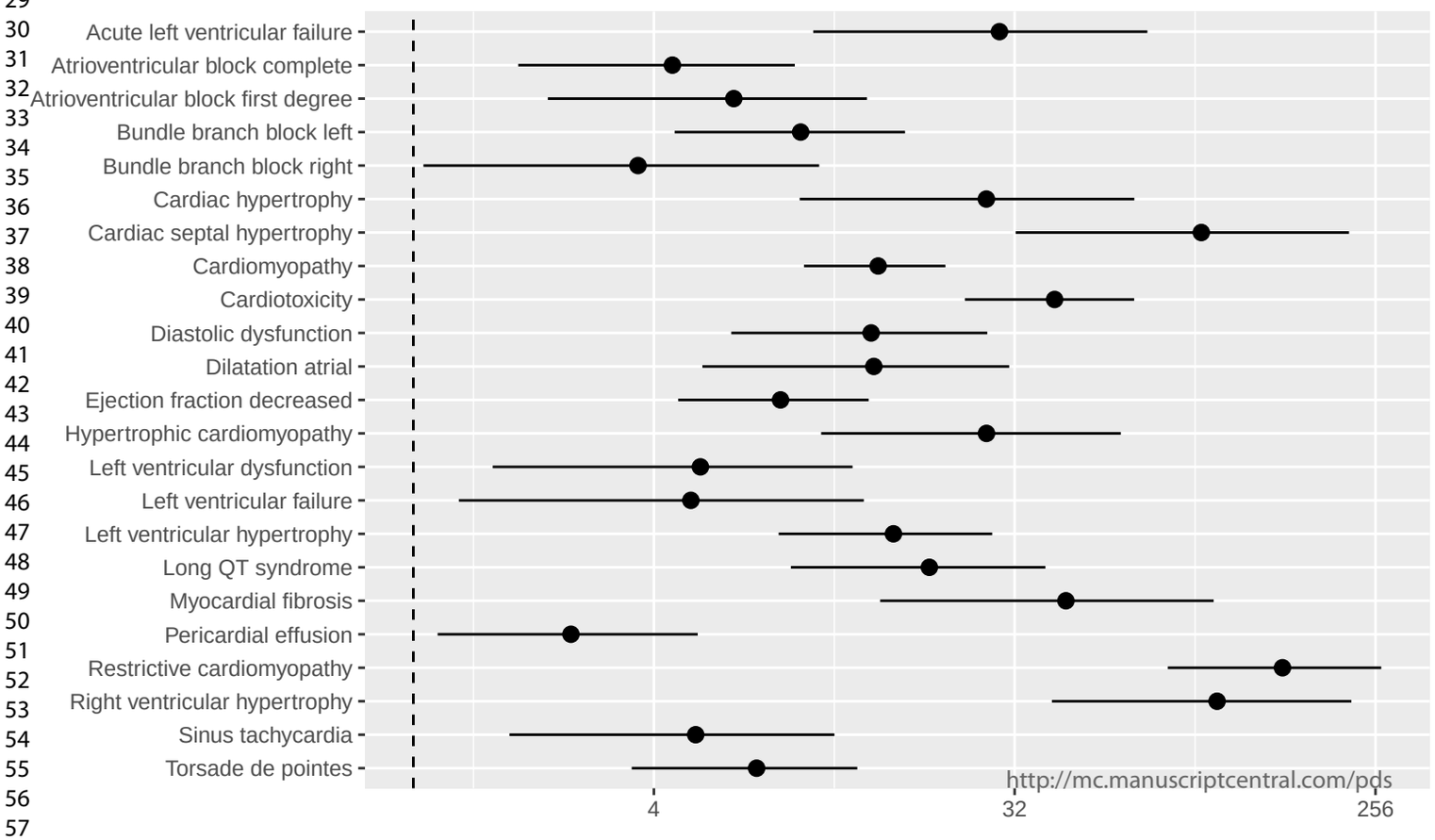
SOCs	HLGTs	HLTs	PTs
Blood and lymphatic system disorders (n = 110)	6	14	25
Cardiac disorders (n = 334)	8	18	71
Congenital, familial and genetic disorders (n = 11)	5	7	7
Ear and labyrinth disorders (n = 41)	4	5	11
Endocrine disorders (n = 4)	3	3	3
Eye disorders (n = 287)	11	26	66
Gastrointestinal disorders (n = 394)	15	35	70
General disorders and administration site conditions (n = 976)	6	23	88
Hepatobiliary disorders (n = 50)	3	10	20
Immune system disorders (n = 78)	4	6	14
Infections and infestations (n = 409)	7	42	119
Injury, poisoning and procedural complications (n = 137)	7	22	55
Investigations (n = 376)	18	46	133
Metabolism and nutrition disorders (n = 90)	10	18	29
Musculoskeletal and connective tissue disorders (n = 654)	8	29	76
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (n = 85)	19	29	37
Nervous system disorders (n = 304)	15	33	76
Psychiatric disorders (n = 132)	15	30	49
Renal and urinary disorders (n = 79)	5	10	25
Reproductive system and breast disorders (n = 4)	2	2	3
Respiratory, thoracic and mediastinal disorders (n = 256)	7	22	63
Skin and subcutaneous tissue disorders (n = 415)	7	29	79
Social circumstances (n = 39)	2	2	9
Vascular disorders (n = 62)	9	16	25


SOCs
HLGTs
HLTs
PTs
Cardiac disorders (n = 334)
Cardiac arrhythmias (n = 115)
Cardiac disorders, signs and symptoms NEC (n = 36)
Cardiac valve disorders (n = 7)
Coronary artery disorders (n = 17)
Endocardial disorders (n = 2)
Heart failures (n = 52)
Myocardial disorders (n = 97)
Pericardial disorders (n = 8)
Cardiac conduction disorders (n = 41)
Ventricular arrhythmias and cardiac arrest (n = 23)
Supraventricular arrhythmias (n = 29)
Rate and rhythm disorders NEC (n = 22)
Cardiac signs and symptoms NEC (n = 15)
Cardiac disorders NEC (n =21)
Mitral valvular disorders (n = 4)
Tricuspid valvular disorders (n = 3)
Coronary artery disorders NEC (n = 8)
Ischaemic coronary artery disorders (n = 9)
Endocardial disorders NEC (n = 2)
Heart failures NEC (n = 42)
Left ventricular failures (n = 8)
Right ventricular failures (n = 2)
Cardiomyopathies (n = 36)
Myocardial disorders NEC (n = 60)
Non-infectious myocarditis (n = 1)
Pericardial disorders NEC (n =8)
Atrioventricular block (n=4)
Atrioventricular block complete (n=8)
Atrioventricular block first degree(n=6)
Atrioventricular block second degree (n=1)
Bundle branch block bilateral (n=1)
Bundle branch block left (n=9)
Bundle branch block right (n=4)
Conduction disorder (n=1)
Long QT syndrome (n=7)
Cardiac arrest (n=4)
Cardio-respiratory arrest (n=2)
Torsade de pointes (n=10)
Ventricular arrhythmia (n=1)
Ventricular extrasystoles (n=2)
Ventricular tachycardia (n=4)
Atrial fibrillation (n=12)
Atrial flutter (n=4)
Sinus bradycardia (n=3)
Sinus node dysfunction (n=2)
Sinus tachycardia (n=6)
Supraventricular tachycardia (n=2)
Arrhythmia (n=1)
Bradyarrhythmia (n=1)
Bradycardia (n=8)
Cardiac flutter (n=1)
Extrasystoles (n=1)
Tachycardia (n=10)
Hyperdynamic left ventricle (n=1)
Palpitations (n=13)
Right ventricular heave (n=1)
Cardiac disorder (n=4)
Cardiotoxicity (n=16)
Cardiovascular disorder (n=1)
Mitral valve disease (n=1)
Mitral valve incompetence (n=3)
Tricuspid valve incompetence (n=3)
Coronary artery disease (n=3)
Coronary artery occlusion (n=3)
Coronary artery stenosis (n=1)
Coronary artery thrombosis (n=1)
Acute myocardial infarction (n=3)
Angina pectoris (n=2)
Angina unstable (n=1)
Myocardial infarction (n=3)
Endocardial fibrosis (n=2)
Cardiac failure acute (n=4)
Cardiac failure congestive (n=20)
Cardiac failure (n=18)
Left ventricular failure (n=4)
Acute left ventricular failure (n=4)
Right ventricular failure (n= 2)
Cardiomyopathy (n=23)
Congestive cardiomyopathy (n=3)
Restrictive cardiomyopathy (n=10)
Cardiac hypertrophy(n=4)
Cardiac septal hypertrophy (n=5)
Cardiomegaly (n=2)
Diastolic dysfunction (n=7)
Dilatation atrial (n=5)
Left atrial dilatation (n=3)
Left ventricular dysfunction (n=5)
Left ventricular hypertrophy (n=10)
Myocardial fibrosis (n=4)
Right atrial dilatation (n=2)
Right ventricular dilatation (n=1)
Right ventricular hypertrophy (n=5)
Ventricular dysfunction (n=2)
Ventricular hypertrophy (n=2)
Ventricular hypokinesia (n=3)
Myocarditis (n=1)
Pericardial effusion (n=8)



Reports (HCQ)	Reports (Other)	ROR	95% CI
4	156	34.89	(12.92−94.16)
8	2222	4.9	(2.45−9.82)
6	1201	6.8	(3.05−15.17)
9	1286	9.53	(4.94−18.37)
4	1171	4.65	(1.74−12.41)
4	171	31.83	(11.81−85.80)
4	24	226.77	(78.65−653.80)
23	2105	14.92	(9.88−22.52)
16	497	43.9	(26.66−72.27)
7	654	14.57	(6.92−30.70)
5	452	15.05	(6.23−36.36)
13	2101	8.43	(4.88−14.55)
5	220	30.93	(12.74−75.08)
5	1146	5.94	(2.47−14.30)
4	921	5.91	(2.21−15.78)
10	825	16.51	(8.84−30.82)
7	457	20.85	(9.88−44.01)
4	95	57.29	(21.06−155.85)
8	3665	2.97	(1.48−5.95)
10	50	272.43	(138.09−537.47)
5	31	219.49	(85.32−564.70)
6	1444	5.65	(2.53−12.61)
10	1841	7.4	(3.97−13.78)



Reports (HCQ)	Reports (Other)	EBGM	95% CI
4	156	29.31	(10.02−68.75)
8	2222	4.45	(1.83−9.01)
6	1201	6.34	(2.17−13.66)
9	1286	9.32	(4.51−17.01)
4	1171	3.65	(1.06−10.37)
4	171	27.18	(9.27−63.77)
4	24	93.82	(32.19−219.81)
23	2105	14.57	(9.50−21.46)
16	497	40.28	(24.02−63.72)
7	654	13.99	(6.25−27.33)
5	452	14.21	(5.29−31.00)
13	2101	8.3	(4.60−13.79)
5	220	27.2	(10.49−59.00)
5	1146	5.23	(1.58−12.57)
4	921	4.95	(1.30−13.41)
10	825	15.91	(8.21−28.11)
7	457	19.57	(8.81−38.19)
4	95	42.99	(14.74−100.75)
8	3665	2.48	(1.15−5.15)
10	50	149.78	(77.34−264.67)
5	31	102.74	(39.67−222.81)
6	1444	5.09	(1.74−11.32)
10	1841	7.23	(3.52−12.92)

Analysis of the US FDA adverse event reporting system to identify adverse cardiac events associated with hydroxychloroquine in older adults

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Keywords: hydroxychloroquine, adverse event, data signal, reporting odds ratio, elderly

Word count: 20671412 (excluding references)

Key points

1. The study found that the risk of cardiac cardiomyopathy and myocardial disorders is high following exposure to hydroxychloroquine in older adults.

2. Novel findings include the identification of a signal for cardiac septal hypertrophy.

Abstract

Purpose The purpose of this study is to ~~analyse~~ analyze the US FDA Adverse Event Reporting System (FAERS) to identify adverse cardiac events of hydroxychloroquine in older adults.

Method A case/non-case method was used to determine adverse events associated with hydroxychloroquine as the primary suspect drug between January 1, 2004,~~2004-01-01~~ and December 31, 2019,~~2019-12-01~~ for older adults (≥ 65 years). Adverse events are preferred terms (PTs) defined in MedDRA. We used frequentist approaches, including the reporting odds ratio (ROR) and the proportional reporting ratio (PRR) to measure disproportionality. We used Bayesian approaches to derive information component (IC) value and Empirical Bayesian Geometric Mean (EBGM) score. Signals were defined as the number of reports>3 and the lower limit of 95% confidence intervals (CI) of ROR ≥2, PRR ≥2, IC >0, EBGM>1

Results We identified 334 adverse cardiac events comprising 71 different MedDRA PTs from 2004 to 2019 for hydroxychloroquine in older adults. Strong disproportionality signals were noted for *'Restrictive cardiomyopathy'* (ROR= 272.43 (138.09-537.47); EBGM= 149.78 (77.34-264.67), 'Right ventricular hypertrophy' (219.49 (85.32-564.70); 102.74 (39.67-222.81), '*Cardiac septal hypertrophy*' (226.77 (78.65-653.80); 93.82 (32.19-219.81), '*Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and *'Cardiotoxicity'* (43.90 (26.66-72.27); 40.28 (24.02-63.72).

Conclusions The risk of cardiomyopathy and myocardial disorders is high following exposure to hydroxychloroquine in older adults. Due to the current lack of safety data from ~~randomised~~ randomized controlled trials as well as large observational studies to confirm the risk of adverse cardiac events associated with hydroxychloroquine, findings from analyses of post-marketing data may serve as interim guidance.

Introduction:

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has positioned drug repurposing research on the spotlight (1, 2). Drug repurposing is investigating existing drugs for new indications, and several drugs have emerged as candidates for repurposing to treat COVID-19. Among the several ~~The~~ leading candidates ~~are azithromycin,~~ chloroquine, hydroxychloroquine ~~, ivermectin, lopinavir/ritonavir~~ and rem~~e~~desivir have ~~. Amongst these, hydroxychloroquine has~~ generated massive interest in the USA as a potential ~~''~~*game-~~changer'~~ changer'* in the treatment of COVID-19 (3, 4). Several clinical trials are being undertaken to generate evidence on the efficacy of hydroxychloroquine to treat COVID-19 patients (5). Based on the research evidence from ongoing clinical trials, the US FDA has removed the emergency use authorization for hydroxychloroquine and chloroquine for the treatment of COVID-19 given that the risks of using hydroxychloroquine for the treatment of COVID-19 infection outweigh any benefits (6). However, the uncertainty of the safety of hydroxychloroquine in older adults will endure given the historical evidence for the exclusion of older adults with comorbidities in clinical trials.

COVID-19 disproportionately affects older adults. Given the repurposing of hydroxychloroquine has gained~~is gaining~~ rapid interest for the treatment of COVID-19, understanding safety profile of hydroxychloroquine from post-marketing data is of paramount importance. This is particularly important as there is a lack of safety data for hydroxychloroquine from ~~randomised~~ randomized controlled trials (RCTs) or observational studies (7). Specifically, there is a lack of safety data from RCTs for older adults using hydroxychloroquine for the treatment of COVID-19 infection caused by SARS-CoV-2 (8, 9). A recent RCT conducted in USA and Canada showed that hydroxychloroquine was not effective when offered as prophylaxis after COVID-19 exposure. In this RCT (N=821), the median age of the study population was 41 (IQR=33 to 51) years with no safety data reported for hydroxychloroquine use in older adults (9). A more recent RCT conducted over eight weeks that evaluated the efficacy and safety of hydroxychloroquine versus placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers showed no clinical benefit of hydroxychloroquin (10). The median age of the study population in this RCT was 33 (20-66), and there was no safety data for hydroxychloroquine reported in older adults. The objective of this study is to ~~analyse~~ analyze the US FDA Adverse Event Reporting System (FAERS), a publicly available database, to identify adverse cardiovascular events of hydroxychloroquine in older adults using analysis of disproportionality. The FAERS data is widely used in drug safety research for exploratory analyses to generate hypotheses and safety signals reported do not impart causality.

Method:

Ethics approval: The Departmental Research Ethical Officer at the University of Bath approved this study.

***Data source*:** Data was retrieved from the Elsevier PharmaPendium database (11). Data for 4667+ United States FDA and European Medicines Agency approved drugs, and 14+ million FAERS reports have been collected and stored in the PharmaPendium in the latest 2020.07 release. The use of PharmaPendium for drug safety research is described elsewhere (12, 13). Each FAERS report contains information on the drug and its role in the event, dose, frequency and route. The primary, secondary, concomitant and interacting drugs are reported~~.~~.

Along with the adverse event experienced, the outcome, drug indication, reporter occupation, location of the event, manufacturer, patient gender and age are documented. Each report has an AERS report number and Case ID aiding with easy identification. The Medical Dictionary for Regulatory Activities (MedDRA) was used to identify frequently implicated adverse drug events.

Adverse drug reaction definition

We used the preferred terms (PTs) recommended in the Medical Dictionary of Regulatory Activities (MedDRA v2.0) to define adverse events associated with hydroxychloroquine. Each PT is part of the hierarchal system, linking to a higher-level term (HLT), higher-level group term (HLGT) and system organ class (SOC).

Statistical Analyses

We selected hydroxychloroquine as the primary suspect drug and ~~analysed~~ analyzed all reported adverse events in older adults from the start of January 1, 2004,~~2004-01-01~~ to the end of December 31, 2019~~2019-12-31~~. The ratio of cases/non-cases for hydroxychloroquine ~~were~~ was compared with the ratio of cases/non-cases for all other drugs for the same study period. We used the disproportionality analyses to calculate the reporting odds ratio (ROR) and the proportional reporting ratio (PRR) (14). We used the Bayesian approach to calculate information component (IC) values and Empirical Bayesian Geometric Mean (EBGM) scores. The criteria for a disproportionality signal was defined as the number of reports >3 and the lower limit of 95% confidence intervals (CI) of ROR ≥2, PRR value ≥2, IC value >0 and EBGM score >1. For secondary analyses, we mapped the PTs of adverse cardiovascular events to system organ class (SOC), high-level group term (HLGT) and high-level term (HLT). ~~Analysis~~ The analysis was conducted in R, version 3.6.1 (15).

Results

We retrieved a total of 7,247,902 drug-event pairs between January 1, 2004, ~~2004-01-01~~ and December 31, 2019, ~~2019-12-31~~ recorded in FAERS for adults aged ≥ 65 years by splitting multiple AEs reported for each case. Of which, 5327 adverse events (AEs) belonged to hydroxychloroquine. Amongst the 5327 AEs, we identified 334 adverse cardiac events comprising 71 different MedDRA PTs. The mean age of the patients within the reports (n=1090) for hydroxychloroquine is 71.77 (7.27) years, and 85.4 % were females. 56.1% of the reports were submitted by ~~'~~'other healthcare ~~professionals'~~ professionals' followed by 20.3% from physicians and 20.5% from consumers. 90.4% of the reports were expedited. The country of origin of the reports was mostly from the USA. Indications were missing for 97 out of 1090 (8.9%) reports. The majority of the reports 430/1090 (39.4%) indicated hydroxychloroquine was used for rheumatic disorders (mainly rheumatoid arthritis) followed by 124/1090 (11.3%) reports for systemic lupus erythematosus, and 199/1090 (18.3%) reports recorded hydroxychloroquine was used for an unknown indication.

Figure 1. Mapping of hydroxychloroquine-associated all adverse drug events at different MedDRA levels: SOC: system organ class; HLGT: high-level group term; HLT: high-level term

Figure 2. Mapping of hydroxychloroquine-associated cardiovascular events at different MedDRA levels: SOC: system organ class; HLGT: high-level group term; HLT: high-level term. Yellow boxes include terms resulting in disproportionality signals~~,~~; Grey boxes include terms without disproportionality; NEC: not elsewhere classified; MedDRA: Medical Dictionary for Regulatory Activities

Figure 3: RORs and EBGM scores with 95% CIs for PTs with hydroxychloroquine-associated cardiovascular events. ADR-adverse drug reaction; HCQ-hydroxychloroquine ROR- reporting odds ratio; EBGM-Empirical Bayesian geometric mean; CI confidence interval.

Strong disproportionality signals were noted for *'Restrictive cardiomyopathy'* (ROR= 272.43 (138.09-537.47); EBGM= 149.78 (77.34-264.67), *'Right ventricular hypertrophy'* (219.49 (85.32-564.70); 102.74 (39.67-222.81), '*Cardiac septal hypertrophy'* (226.77 (78.65-653.80); 93.82 (32.19-219.81), '*Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and *'Cardiotoxicity'* (43.90 (26.66-72.27); 40.28 (24.02-63.72).

Discussion

The risk for severe illnesses from COVID-19 infection is age-related, with older adults aged 85 or older at highest risk. Underlying medical comorbidities, specifically underlying cerebrovascular and cardiovascular disease, including heart failure, coronary heart disease and cardiomyopathies, increases the risk of hospitalizations and intensive care unit admissions in older adults with COVID-19 infection (16). In this context, t~~T~~his study addressed the impending necessity emerging from the COVID-19 pandemic for understanding the safety of hydroxychloroquine in older adults.

Majority of the cardiovascular AEs reported in this study are related to cardiac conduction and myocardial disorders. These findings are consistent with a recent systematic review that concluded conduction disorders and myocardial hypertrophy as two major cardiac complications associated with hydroxychloroquine therapy (17).

Analyses of high-level MedDRA terms suggest that hydroxychloroquine therapy is associated with abnormal cardiac conduction, cardiac arrhythmias, and cardiomyopathy. Several case reports have described proarrhythmic effects and signs of long QT syndrome following hydroxychloroquine exposure in patients with systemic lupus erythematosus (18, 19). The interim guidance from the Canadian heart rhythm society to mitigate drug-induced arrhythmias is for performing baseline ECG testing in high-risk patients. The recommendation is to ~~optimise~~ optimize drug treatments, and correct electrolytes, if QTc is moderately prolonged and to cease the drug if QTc is markedly prolonged (20). Also, two recent studies have lighted the risk of QT interval prolongation in patients with COVID-19 infection treated with hydroxychloroquine. In a case series of intensive care unit patients (median age= 68 years (IQR, 58-74 years)) admitted for COVID-19 infection, those treated with hydroxychloroquine had an increased risk of QT prolongation (21). Similar findings were echoed in a cohort study conducted at a tertiary care hospital in Boston, Massachusetts, involving 90 patients with mean age 60 years (SD=16). In this cohort study, patients who received hydroxychloroquine for the treatment of pneumonia associated with COVID-19 were at high risk of QTc prolongation (22). The most common underlying comorbidities in this cohort included hypertension and diabetes.

Hydroxychloroquine is known to cause direct myocardial toxicity and cardiomyopathy (23, 24). Yogasundaram *et al.* have shown that cardiomyopathy is a preventable complication and early withdrawal of hydroxychloroquine treatment can potentially result in a partial or complete reversal of cardiomyopathy (25).

Our analyses revealed several other cardiac adverse effects associated with hydroxychloroquine, including left and right ventricular hypertrophy and acute left ventricular

failure. These are well ~~recognised~~ recognized AEs of hydroxychloroquine. Prescribers~~-~~ should be aware that these serious adverse events can be pronounced in older adults with pre-existing cardiac disease. However, our novel findings include the identification of cardiac septal hypertrophy and myocardial fibrosis associated with hydroxychloroquine therapy, and these signals require further confirmation. Cardiac septal hypertrophy in older adults is associated with disturbance in intraventricular conduction and is an independent predictor of progression to atrial fibrillation in patients with hypertrophic cardiomyopathy. (26, 27). Myocardial fibrosis is a significant risk factor for hypertrophic cardiomyopathy, and is associated with a myriad of severe adverse cardiovascular outcomes including sudden cardiac death, ventricular tachyarrhythmias, left ventricular dysfunction, and heart failure (28).

Strengths and limitations

This study used PharmaPendium, a database maintained by Elsevier that curates data from FAERS. PharmaPendium uses PTs, defined in MedDRA, to identify adverse events from FAERS. FAERS is a spontaneous reporting system (SRS) widely used for examining associations between marketed medicines and AEs. SRS is particularly useful when safety data from ~~randomised~~ randomized controlled trials or observational studies are lacking. Analyses of SRS can potentially reveal new and clinically important drug-event associations. Rare safety events can be captured in SRS that ~~are~~ is generally not identified in clinical trials. ~~Importantly~~Notably, to our knowledge, no previous investigations have reported the safety profile of hydroxychloroquine in older adults.

There are ~~several~~ database and several methodological limitations associated with this study. Adverse event reports are submitted ~~on a voluntary basis~~voluntarily to FAERS, and this may potentially lead to underreporting (29). Although careful consideration was given to the removal of duplicated reports, there is a possibility that the AEs may be reported multiple times by various stakeholders including patients, manufacturers and physicians. Given the spontaneous nature of reporting, the drug exposure at a population level is unknown, hence the actual incidence rate for the AE cannot be established. Lack of information on comorbidities, family history, and incomplete dosage information is likely to bias the study findings. Characteristic ~~to~~ of SRS is the potential for selective reporting of only serious adverse events. Specific methodological limitations include examining hydroxychloroquine as the primary drug of interest without ascertaining the impact of concomitant medications on the AE. Several of the AEs identified with hydroxychloroquine may be confounded by the severity of the underlying medical condition. For example, several autoimmune disorders treated with

hydroxychloroquine are independently associated with adverse cardiac outcomes. It is important to note that we did not investigate a dose-dependent or a temporal relationship with AEs, as these are significant risk factors for cardiac AEs with hydroxychloroquine. The ROR's for ADE's associated with hydroxychloroquine with a wide confidence interval represents a lack of sample size, and the safety signals must be interpreted with this limitation. The safety signals reported in this study with hydroxychloroquine do not impart causality.

Conclusions

The risk of cardiac disorders is increased with hydroxychloroquine in older adults. Despite, the lack of causality in our findings, these safety signals must be monitored and where applicable appropriate screening to mitigate these complications is recommended. The American College of Cardiology's as well as the Canadian heart rhythm society recommendation is that patients with COVID-19 infection treated with hydroxychloroquine should undergo a careful assessment of baseline risk of QT prolongation, including baseline ECG, biochemical tests, and exclusion of concomitant drugs that have a potential to prolong QTc interval to mitigate further complications such as torsades de pointes (11). Due to the current lack of ~~randomised~~ randomized controlled trials as well large observational studies to confirm the risk of AEs associated with hydroxychloroquine, findings from analyses of post-marketing data may serve as ~~an~~ interim guidance until further robust data on safety becomes available.

Author Contributions

Study concept and design: PN, TC; Statistical analysis: PN, TC; Interpretation of data: All authors; Drafting of the manuscript: PN, SG; Critical revision of the manuscript for important intellectual content: All authors; Study supervision: PN.

Conflict of interest: The authors have no conflicts of interest to declare.

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