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

Journal:	<i>Pharmacoepidemiology and Drug Safety</i>
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Complete List of Authors:	Nishtala, Prasad; University of Bath, Pharmacy and Pharmacology; University of Bath Gill, Sakirat; University of Bath, Pharmacy and Pharmacology Chyou, Te-yuan; University of Otago - Dunedin Campus, Biochemistry
Keywords:	hydroxychloroquine, adverse event, data signal, reporting odds ratio, elderly
Abstract:	<p>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.</p> <p>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 $ROR \geq 2$, $PRR \geq 2$, $IC > 0$, $EBGM > 1$.</p> <p>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).</p> <p>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.</p>

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3 **Analysis of the US FDA adverse event reporting system to identify adverse cardiac**
4 **events associated with hydroxychloroquine in older adults**
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6 **Response to reviewers**
7

8 **Nishtala et.al**
9

10 Dear Editor

11 Thank you for the opportunity to revise our paper and clarify the comments raised by the
12 reviewers. We are grateful for the useful comments provided by the reviewers to improve the
13 manuscript, and the reviewers share our judgement that the findings of this study are
14 interesting and important. Please see below, in blue, our detailed response to comments. All
15 page numbers refer to the manuscript file with tracked changes
16
17
18

19 **Reviewer 1:**
20

21 **Comments to the Author**
22

23 **Abstract**
24

25 **- RORs that high with a wide confidence interval represents a lack of sample size and**
26 **very hard to interpret.**
27

28 [Response 1](#)
29

30 We acknowledge this is a limitation of the study. However, the signals meet the criteria for a
31 disproportionality signal- defined as the number of reports >3 and the lower limit of 95%
32 confidence intervals (CI) of ROR ≥ 2 , PRR value ≥ 2 , IC value >0 and EBGM score >1.
33

34 We have also added the following sentence to the limitations paragraph of the Discussion on
35 page
36

37 *Page 7, Line 32-35: 'The ROR's for ADE's associated with hydroxychloroquine with a wide*
38 *confidence interval represents a lack of sample size, and the safety signals must be*
39 *interpreted with this limitation. The safety signals reported in this study with*
40 *hydroxychloroquine do not impart causality.'*
41
42

43
44 **- Please rewrite the timeframe of the study such as January 1, 2004, etc. rather than**
45 **the current format given the variability of dating convention worldwide.**
46

47 [Response 2](#)
48

49 Page 4, Line 22-23: We agree with the reviewer and accordingly have changed the date
50 format.
51
52

53 **Introduction**
54

55 **Please reframe the message to NOT-TO-IMPART causality. FAERS database is meant**
56 **for exploratory analyses – that is – to generate hypotheses rather than testing**
57 **hypotheses.**
58

59 [Response 3.](#)
60

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*

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3 of SRS is the potential for selective reporting of only serious adverse events. Specific
4 methodological limitations include examining hydroxychloroquine as the primary drug of
5 interest without ascertaining the impact of concomitant medications on the AE. Several of the
6 AEs identified with hydroxychloroquine may be confounded by the severity of the underlying
7 medical condition. For example, several autoimmune disorders treated with
8 hydroxychloroquine are independently associated with adverse cardiac outcomes. It is
9 important to note that we did not investigate a dose-dependent or a temporal relationship with
10 AEs, as these are significant risk factors for cardiac AEs with hydroxychloroquine. Hence the
11 safety signals reported with hydroxychloroquine do not impart causality.”
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20 Reviewer 2

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22
23 **This is an interesting paper and I have some comments for the authors consideration:**

24
25 We appreciate the encouraging comment.

26
27 **Abstract: Why are you examining cardiac events in hydroxychloroquine in older**
28 **adults? Have clinical trials not examined this population? You need to be specific in**
29 **the purpose of the study.**

30 Response 11

31
32 We thank the reviewer for their suggestion. Given the word count limit in the abstract
33 section, we have clarified the purpose of the study in the introduction.

34
35 Page 3, Line 15-29: “COVID-19 disproportionately affects older adults. Given the repurposing
36 of hydroxychloroquine has gained rapid interest for the treatment of COVID-19, understanding
37 safety profile of hydroxychloroquine from post-marketing data is of paramount importance.
38 This is particularly important as there is a lack of safety data for hydroxychloroquine from
39 randomized controlled trials (RCTs) or observational studies (7). Specifically, there is a lack
40 of safety data from RCTs for older adults using hydroxychloroquine for the treatment of
41 COVID-19 infection caused by SARS-CoV-2 (8, 9). A recent RCT conducted in USA and
42 Canada showed that hydroxychloroquine was not effective when offered as prophylaxis after
43 COVID-19 exposure. In this RCT (N=821), the median age of the study population was 41
44 (IQR=33 to 51) years with no safety data reported for hydroxychloroquine use in older adults
45 (9). A more recent RCT conducted over eight weeks that evaluated the efficacy and safety of
46 hydroxychloroquine versus placebo for pre-exposure SARS-CoV-2 prophylaxis among health
47 care workers showed no clinical benefit of hydroxychloroquine (10). The median age of the
48 study population in this RCT was 33 (20-66), and there was no safety data for
49 hydroxychloroquine reported in older adults.”
50
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53 **Introduction, page 4, line 10: This drug candidate list seems slightly out of date now-**
54 **lopinavir/ritonavir and ivermectin are not really leading candidates anymore. Perhaps**
55 **use a more up to date reference. Remdesivir is also spelt incorrectly.**

56 Response 12

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2
3 We thank the reviewer for this suggestion and accordingly revised the sentence and updated
4 the reference. We regret that we had misspelt Remdesivir. It is now amended in the revised
5 manuscript.
6
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9 **Introduction: It may be worth mentioning that the FDA has subsequently withdrawn**
10 **the emergency use authorisation. Also, be more specific about what data is lacking**
11 **for hydroxychloroquine- data does exist for other indications aside from COVID. Is it**
12 **that there is not RCT data for older adults using hydroxychloroquine at all (regardless**
13 **of indication)? It is a generalisation to say they are usually excluded.**
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17 Response 13

18
19 We have updated the introduction to clarify that the FDA has withdrawn the emergency use
20 authorisation of hydroxychloroquine.
21

22 There is limited RCT data for older adults using hydroxychloroquine, regardless of indication.
23 We have appended the following paragraph in the introduction.
24

25 Page 3, Line 21-24: *“A recent RCT conducted in USA and Canada showed that*
26 *hydroxychloroquine was not effective as postexposure prophylaxis after COVID-19 exposure.*
27 *In this RCT, the median age of the study population (N=821) was 41(IQR=33 to 51) years with*
28 *no safety data reported for hydroxychloroquine use in older adults [7]. ”*
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32 **Discussion: The authors comment on the known cardiac effects of**
33 **hydroxychloroquine. I think this could be expanded to explicitly state why older**
34 **adults may be at greater risk, referring to prevalence of cardiac disease in this age**
35 **group. Also, are they likely to experience more serious outcomes from these types of**
36 **events e.g. death? The authors need to be clear why these events are of greater**
37 **concern in older adults, as many of these events would be of concern among any age**
38 **group.**
39

40 Response 14

41
42 The risk for severe illness from COVID-19 increases with age, with older adults aged 85 or
43 older at highest risk. Underlying medical comorbidities, specifically underlying cerebrovascular
44 and cardiovascular disease including heart failure, coronary heart disease and
45 cardiomyopathies means that an older adult with COVID-19 may require hospitalisation and
46 subsequent admission to the intensive care unit.
47
48
49

50 We appended the following paragraph into the discussion.
51

52 Page 6, Line 15-23: *“Also, two recent studies have lighted the risk of QT interval prolongation*
53 *in patients with COVID-19 infection treated with hydroxychloroquine. In a case series of*
54 *intensive care unit patients (median age= 68 years (IQR, 58-74 years)) admitted for COVID-*
55 *19 infection, those treated with hydroxychloroquine had an increased risk of QT prolongation.*
56 *Similar findings were echoed in a cohort study conducted at a tertiary care hospital in Boston,*
57 *Massachusetts, involving 90 patients with mean age 60 years (SD=16). In this cohort study,*
58 *patients who received hydroxychloroquine for the treatment of pneumonia associated with*
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3 *COVID-19 were at high risk of QTc prolongation. The most common underlying comorbidities*
4 *in this cohort included hypertension and diabetes.”*
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8 **Discussion: Regarding the novel findings, why are these events of concern? Are they**
9 **more likely to result in death than the known events? Safety signals need to be**
10 **discussed in terms of their importance, not just their presence**
11

12 [Response 15](#)

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

15
16 Page 6, Line 34-35 & Page 7 Line 1-4: *“Cardiac septal hypertrophy in older adults is associated*
17 *with disturbance in intraventricular conduction and is an independent predictor of progression*
18 *to atrial fibrillation in patients with hypertrophic cardiomyopathy. [23, 24]. Myocardial fibrosis*
19 *is a significant risk factor for hypertrophic cardiomyopathy, and is associated with a myriad of*
20 *severe adverse cardiovascular outcomes including sudden cardiac death, ventricular*
21 *tachyarrhythmias, left ventricular dysfunction, and heart failure [25].”*
22
23
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25

26 **Discussion, limitations: Can the authors comment on whether masking of signals may**
27 **be present and could have any influence on study results? The limitations should**
28 **also explicitly state why causality cannot be inferred from these results.**
29

30 [Response 16](#)

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

32
33 One study (Wang HW, Hochberg AM, Pearson RK, Hauben M. *An experimental investigation*
34 *of masking in the US FDA adverse event reporting system database. Drug Saf. 2010 Dec*
35 *1;33(12):1117-33)* has reported that the prevalence of masking might be low in the Adverse
36 Event Reporting System and is more likely to occur in pharmaceutical company databases.
37 Another challenge is accurately identifying drug candidates in the FAERS that are likely to
38 mask signals. We do not feel that this limitation is expected to be significant for the reasons
39 outlined above. On balance, we cannot make a definitive comment if masking of signals
40 influenced the study findings.
41
42

43 Please note our response 10 to reviewer 1 in which we have discussed the limitations of the
44 study and the reasons causality cannot be inferred.
45
46
47

48 **Conclusions: I agree that monitoring signals is important but they should also be**
49 **investigated further where there is a concern, using other study methods where**
50 **required. You mention screening in the conclusion but have not discussed this**
51 **elsewhere- you should include a paragraph in the discussion outlining this**
52 **recommendation in more detail. What screening is needed? Who will this help? How**
53 **will this mitigate complications?**
54

55 [Response 17](#)

56 We thank the reviewer for their valuable suggestion. We have appended the following
57 paragraph in conclusion.
58
59
60

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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3 1 **Analysis of the US FDA adverse event reporting system to identify adverse cardiac**
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5 2 **events associated with hydroxychloroquine in older adults**
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45
46 17 **Keywords:** hydroxychloroquine, adverse event, data signal, reporting odds ratio, elderly
47
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49 18 **Word count:** 2067 (excluding references)
50
51

52 19 **Key points**

53
54 20 1. The study found that the risk of cardiac cardiomyopathy and myocardial disorders is high
55
56 21 following exposure to hydroxychloroquine in older adults.

57
58 22 2. Novel findings include the identification of a signal for cardiac septal hypertrophy.
59
60 23

1 Abstract

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

4 **Method** A case/non-case method was used to determine adverse events associated with
5 hydroxychloroquine as the primary suspect drug between January 1, 2004, and December 31,
6 2019, for older adults (≥ 65 years). Adverse events are preferred terms (PTs) defined in
7 MedDRA. We used frequentist approaches, including the reporting odds ratio (ROR) and the
8 proportional reporting ratio (PRR) to measure disproportionality. We used Bayesian
9 approaches to derive information component (IC) value and Empirical Bayesian Geometric
10 Mean (EBGM) score. Signals were defined as the number of reports >3 and the lower limit of
11 95% confidence intervals (CI) of $ROR \geq 2$, $PRR \geq 2$, $IC > 0$, $EBGM > 1$

12 **Results** We identified 334 adverse cardiac events comprising 71 different MedDRA PTs from
13 2004 to 2019 for hydroxychloroquine in older adults. Strong disproportionality signals were
14 noted for '*Restrictive cardiomyopathy*' (ROR= 272.43 (138.09-537.47); EBGM= 149.78
15 (77.34-264.67), '*Right ventricular hypertrophy*' (219.49 (85.32-564.70); 102.74 (39.67-
16 222.81), '*Cardiac septal hypertrophy*' (226.77 (78.65-653.80); 93.82 (32.19-219.81),
17 '*Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and '*Cardiotoxicity*' (43.90
18 (26.66-72.27); 40.28 (24.02-63.72).

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

24

1 Introduction:

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

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

34 Method:

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3 1 **Ethics approval:** The Departmental Research Ethical Officer at the University of Bath
4 2 approved this study.

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7 3 **Data source:** Data was retrieved from the Elsevier PharmaPendium database (11). Data for
8 4 4667+ United States FDA and European Medicines Agency approved drugs, and 14+ million
9 5 FAERS reports have been collected and stored in the PharmaPendium in the latest 2020.07
10 6 release. The use of PharmaPendium for drug safety research is described elsewhere (12, 13).
11 7 Each FAERS report contains information on the drug and its role in the event, dose, frequency
12 8 and route. The primary, secondary, concomitant and interacting drugs are reported.

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15 9 Along with the adverse event experienced, the outcome, drug indication, reporter occupation,
16 10 location of the event, manufacturer, patient gender and age are documented. Each report has
17 11 an AERS report number and Case ID aiding with easy identification. The Medical Dictionary
18 12 for Regulatory Activities (MedDRA) was used to identify frequently implicated adverse drug
19 13 events.

20 14 **Adverse drug reaction definition**

21 15 We used the preferred terms (PTs) recommended in the Medical Dictionary of Regulatory
22 16 Activities (MedDRA v2.0) to define adverse events associated with hydroxychloroquine. Each
23 17 PT is part of the hierarchal system, linking to a higher-level term (HLT), higher-level group
24 18 term (HLGT) and system organ class (SOC).

25 19 26 20 **Statistical Analyses**

27
28 21 We selected hydroxychloroquine as the primary suspect drug and analyzed all reported
29 22 adverse events in older adults from the start of January 1, 2004, to the end of December 31,
30 23 2019. The ratio of cases/non-cases for hydroxychloroquine was compared with the ratio of
31 24 cases/non-cases for all other drugs for the same study period. We used the disproportionality
32 25 analyses to calculate the reporting odds ratio (ROR) and the proportional reporting ratio (PRR)
33 26 (14). We used the Bayesian approach to calculate information component (IC) values and
34 27 Empirical Bayesian Geometric Mean (EBGM) scores. The criteria for a disproportionality
35 28 signal was defined as the number of reports >3 and the lower limit of 95% confidence intervals
36 29 (CI) of ROR ≥ 2 , PRR value ≥ 2 , IC value >0 and EBGM score >1. For secondary analyses, we
37 30 mapped the PTs of adverse cardiovascular events to system organ class (SOC), high-level
38 31 group term (HLGT) and high-level term (HLT). The analysis was conducted in R, version 3.6.1
39 32 (15).

40 33 41 34 **Results**

1 We retrieved a total of 7,247,902 drug-event pairs between January 1, 2004, and December
2 31, 2019, recorded in FAERS for adults aged ≥ 65 years by splitting multiple AEs reported for
3 each case. Of which, 5327 adverse events (AEs) belonged to hydroxychloroquine. Amongst
4 the 5327 AEs, we identified 334 adverse cardiac events comprising 71 different MedDRA PTs.
5 The mean age of the patients within the reports (n=1090) for hydroxychloroquine is 71.77
6 (7.27) years, and 85.4 % were females. 56.1% of the reports were submitted by 'other
7 healthcare professionals' followed by 20.3% from physicians and 20.5% from consumers.
8 90.4% of the reports were expedited. The country of origin of the reports was mostly from the
9 USA. Indications were missing for 97 out of 1090 (8.9%) reports. The majority of the reports
10 430/1090 (39.4%) indicated hydroxychloroquine was used for rheumatic disorders (mainly
11 rheumatoid arthritis) followed by 124/1090 (11.3%) reports for systemic lupus erythematosus,
12 and 199/1090 (18.3%) reports recorded hydroxychloroquine was used for an unknown
13 indication.

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

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

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

25 Strong disproportionality signals were noted for '*Restrictive cardiomyopathy*' (ROR= 272.43
26 (138.09-537.47); EBGM= 149.78 (77.34-264.67), '*Right ventricular hypertrophy*' (219.49
27 (85.32-564.70); 102.74 (39.67-222.81), '*Cardiac septal hypertrophy*' (226.77 (78.65-653.80);
28 93.82 (32.19-219.81), '*Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and
29 '*Cardiotoxicity*' (43.90 (26.66-72.27); 40.28 (24.02-63.72).

30 Discussion

31 The risk for severe illnesses from COVID-19 infection is age-related, with older adults aged
32 85 or older at highest risk. Underlying medical comorbidities, specifically underlying
33 cerebrovascular and cardiovascular disease, including heart failure, coronary heart disease
34 and cardiomyopathies, increases the risk of hospitalizations and intensive care unit

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3 1 admissions in older adults with COVID-19 infection (16). In this context, this study addressed
4 2 the impending necessity emerging from the COVID-19 pandemic for understanding the safety
5 3 of hydroxychloroquine in older adults.

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8 4 Majority of the cardiovascular AEs reported in this study are related to cardiac conduction and
9 5 myocardial disorders. These findings are consistent with a recent systematic review that
10 6 concluded conduction disorders and myocardial hypertrophy as two major cardiac
11 7 complications associated with hydroxychloroquine therapy (17).

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15 8 Analyses of high-level MedDRA terms suggest that hydroxychloroquine therapy is associated
16 9 with abnormal cardiac conduction, cardiac arrhythmias, and cardiomyopathy. Several case
17 10 reports have described proarrhythmic effects and signs of long QT syndrome following
18 11 hydroxychloroquine exposure in patients with systemic lupus erythematosus (18, 19). The
19 12 interim guidance from the Canadian heart rhythm society to mitigate drug-induced arrhythmias
20 13 is for performing baseline ECG testing in high-risk patients. The recommendation is to optimize
21 14 drug treatments, and correct electrolytes, if QTc is moderately prolonged and to cease the
22 15 drug if QTc is markedly prolonged (20). Also, two recent studies have lighted the risk of QT
23 16 interval prolongation in patients with COVID-19 infection treated with hydroxychloroquine. In
24 17 a case series of intensive care unit patients (median age= 68 years (IQR, 58-74 years))
25 18 admitted for COVID-19 infection, those treated with hydroxychloroquine had an increased risk
26 19 of QT prolongation (21). Similar findings were echoed in a cohort study conducted at a tertiary
27 20 care hospital in Boston, Massachusetts, involving 90 patients with mean age 60 years
28 21 (SD=16). In this cohort study, patients who received hydroxychloroquine for the treatment of
29 22 pneumonia associated with COVID-19 were at high risk of QTc prolongation (22). The most
30 23 common underlying comorbidities in this cohort included hypertension and diabetes.

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36 24 Hydroxychloroquine is known to cause direct myocardial toxicity and cardiomyopathy (23, 24).
37 25 Yogasundaram *et al.* have shown that cardiomyopathy is a preventable complication and early
38 26 withdrawal of hydroxychloroquine treatment can potentially result in a partial or complete
39 27 reversal of cardiomyopathy (25).

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48 28 Our analyses revealed several other cardiac adverse effects associated with
49 29 hydroxychloroquine, including left and right ventricular hypertrophy and acute left ventricular
50 30 failure. These are well recognized AEs of hydroxychloroquine. Prescribers should be aware
51 31 that these serious adverse events can be pronounced in older adults with pre-existing cardiac
52 32 disease. However, our novel findings include the identification of cardiac septal hypertrophy
53 33 and myocardial fibrosis associated with hydroxychloroquine therapy, and these signals require
54 34 further confirmation. Cardiac septal hypertrophy in older adults is associated with disturbance
55 35 in intraventricular conduction and is an independent predictor of progression to atrial fibrillation

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3 1 in patients with hypertrophic cardiomyopathy. (26, 27). Myocardial fibrosis is a significant risk
4 2 factor for hypertrophic cardiomyopathy, and is associated with a myriad of severe adverse
5 3 cardiovascular outcomes including sudden cardiac death, ventricular tachyarrhythmias, left
6 4 ventricular dysfunction, and heart failure (28).
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11 6 *Strengths and limitations*

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14 7 This study used PharmaPendium, a database maintained by Elsevier that curates data from
15 8 FAERS. PharmaPendium uses PTs, defined in MedDRA, to identify adverse events from
16 9 FAERS. FAERS is a spontaneous reporting system (SRS) widely used for examining
17 10 associations between marketed medicines and AEs. SRS is particularly useful when safety
18 11 data from randomized controlled trials or observational studies are lacking. Analyses of SRS
19 12 can potentially reveal new and clinically important drug-event associations. Rare safety events
20 13 can be captured in SRS that is generally not identified in clinical trials. Notably, to our
21 14 knowledge, no previous investigations have reported the safety profile of hydroxychloroquine
22 15 in older adults.
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30 17 There are database and several methodological limitations associated with this study. Adverse
31 18 event reports are submitted voluntarily to FAERS, and this may potentially lead to
32 19 underreporting (29). Although careful consideration was given to the removal of duplicated
33 20 reports, there is a possibility that the AEs may be reported multiple times by various
34 21 stakeholders including patients, manufacturers and physicians. Given the spontaneous
35 22 nature of reporting, the drug exposure at a population level is unknown, hence the actual
36 23 incidence rate for the AE cannot be established. Lack of information on comorbidities, family
37 24 history, and incomplete dosage information is likely to bias the study findings. Characteristic
38 25 of SRS is the potential for selective reporting of only serious adverse events. Specific
39 26 methodological limitations include examining hydroxychloroquine as the primary drug of
40 27 interest without ascertaining the impact of concomitant medications on the AE. Several of the
41 28 AEs identified with hydroxychloroquine may be confounded by the severity of the underlying
42 29 medical condition. For example, several autoimmune disorders treated with
43 30 hydroxychloroquine are independently associated with adverse cardiac outcomes. It is
44 31 important to note that we did not investigate a dose-dependent or a temporal relationship with
45 32 AEs, as these are significant risk factors for cardiac AEs with hydroxychloroquine. The ROR's
46 33 for ADE's associated with hydroxychloroquine with a wide confidence interval represents a
47 34 lack of sample size, and the safety signals must be interpreted with this limitation. The safety
48 35 signals reported in this study with hydroxychloroquine do not impart causality.
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6 2**Conclusions**

7 3 The risk of cardiac disorders is increased with hydroxychloroquine in older adults. Despite, the
8 4 lack of causality in our findings, these safety signals must be monitored and where applicable
9 5 appropriate screening to mitigate these complications is recommended. The American
10 6 College of Cardiology's as well as the Canadian heart rhythm society recommendation is that
11 7 patients with COVID-19 infection treated with hydroxychloroquine should undergo a careful
12 8 assessment of baseline risk of QT prolongation, including baseline ECG, biochemical tests,
13 9 and exclusion of concomitant drugs that have a potential to prolong QTc interval to mitigate
14 10 further complications such as torsades de pointes (11). Due to the current lack of randomized
15 11 controlled trials as well large observational studies to confirm the risk of AEs associated with
16 12 hydroxychloroquine, findings from analyses of post-marketing data may serve as interim
17 13 guidance until further robust data on safety becomes available.
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Author Contributions

28 15
29 16 Study concept and design: PN, TC; Statistical analysis: PN, TC; Interpretation of data: All
30 17 authors; Drafting of the manuscript: PN, SG; Critical revision of the manuscript for important
31 18 intellectual content: All authors; Study supervision: PN.

32 19 **Conflict of interest:** The authors have no conflicts of interest to declare.

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34 21 **Acknowledgements:** The study authors thank the Bridge Pharmacovigilance (BridgePV)
35 22 Team for completing the MedDRA hierarchy analysis and mapping.
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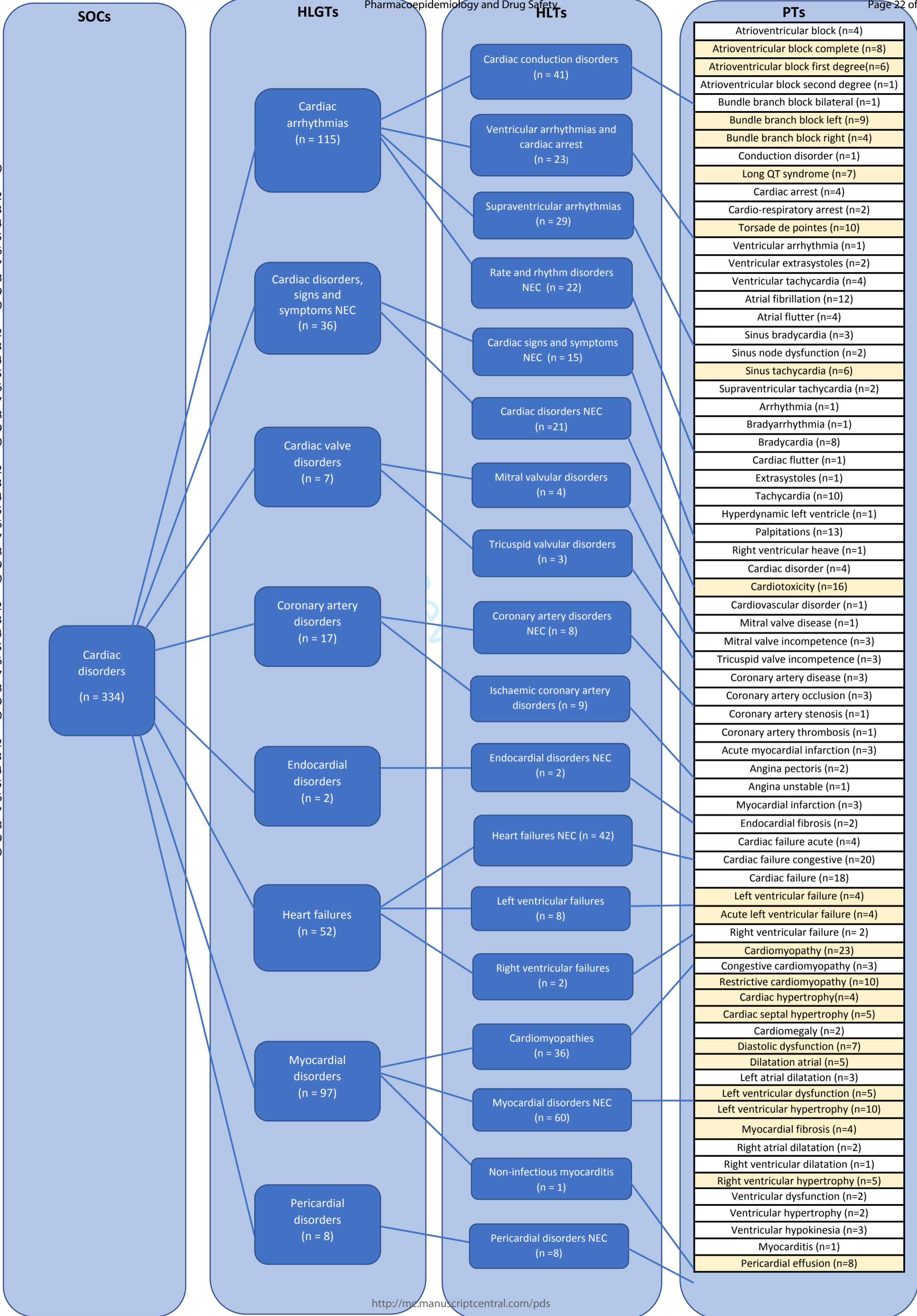
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	SOCs	HLGTs	HLTs	PTs
1				
2				
3	Blood and lymphatic system disorders (n = 110)	6	14	25
4				
5	Cardiac disorders (n = 334)	8	18	71
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7	Congenital, familial and genetic disorders (n = 11)	5	7	7
8				
9				
10	Ear and labyrinth disorders (n = 41)	4	5	11
11				
12	Endocrine disorders (n = 4)	3	3	3
13				
14	Eye disorders (n = 287)	11	26	66
15				
16	Gastrointestinal disorders (n = 394)	15	35	70
17				
18	General disorders and administration site conditions (n = 976)	6	23	88
19				
20				
21				
22	Hepatobiliary disorders (n = 50)	3	10	20
23				
24	Immune system disorders (n = 78)	4	6	14
25				
26				
27	Infections and infestations (n = 409)	7	42	119
28				
29	Injury, poisoning and procedural complications (n = 137)	7	22	55
30				
31				
32	Investigations (n = 376)	18	46	133
33				
34	Metabolism and nutrition disorders (n = 90)	10	18	29
35				
36	Musculoskeletal and connective tissue disorders (n = 654)	8	29	76
37				
38	Neoplasms benign, malignant and unspecified (incl cysts and polyps) (n = 85)	19	29	37
39				
40				
41	Nervous system disorders (n = 304)	15	33	76
42				
43	Psychiatric disorders (n = 132)	15	30	49
44				
45	Renal and urinary disorders (n = 79)	5	10	25
46				
47	Reproductive system and breast disorders (n = 4)	2	2	3
48				
49	Respiratory, thoracic and mediastinal disorders (n = 256)	7	22	63
50				
51	Skin and subcutaneous tissue disorders (n = 415)	7	29	79
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53	Social circumstances (n = 39)	2	2	9
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55	Vascular disorders (n = 62)	9	16	25
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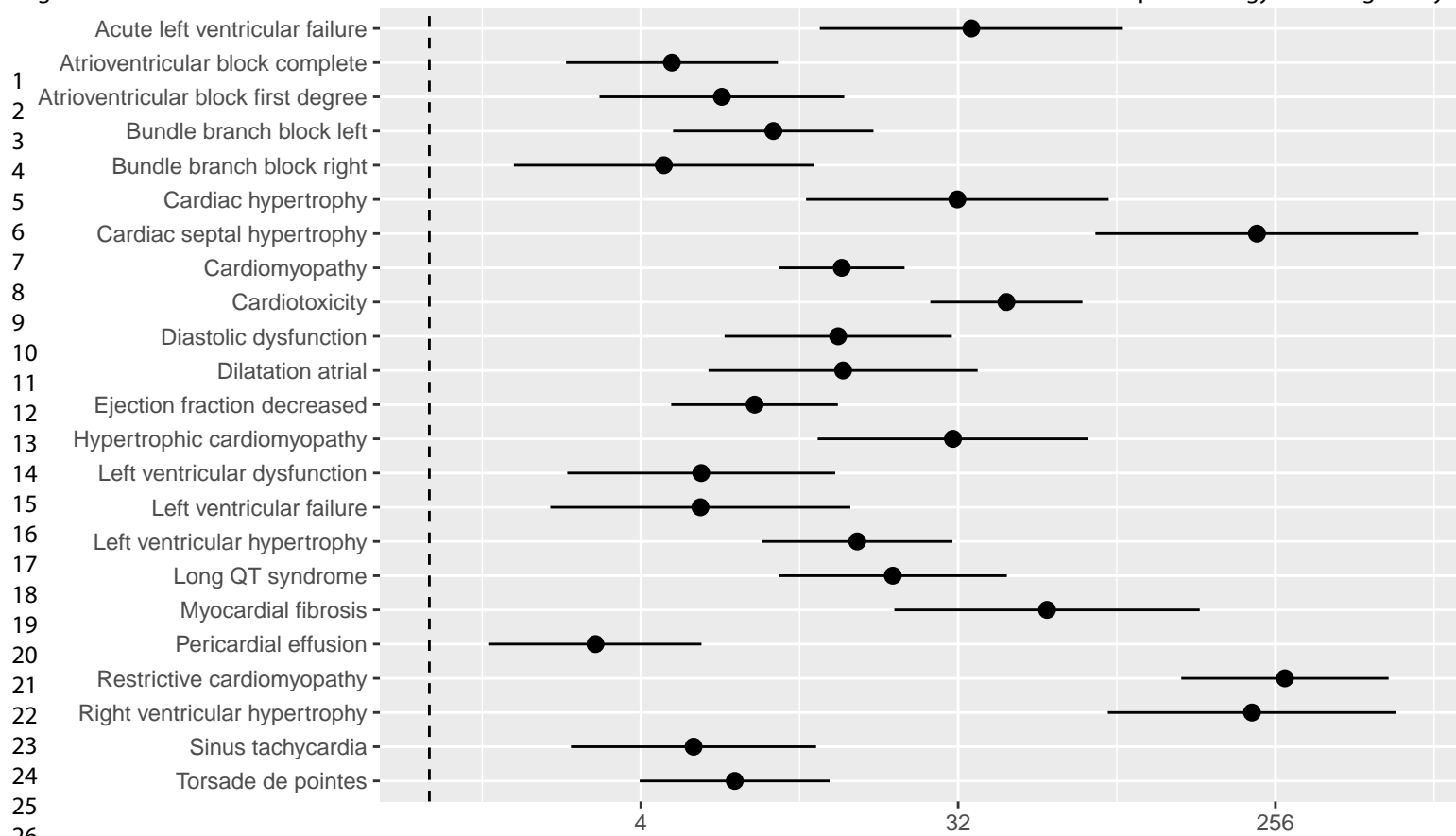
Reporting odds-ratio of ADR

Reports (HCQ)

Reports (Other)

ROR

95% CI



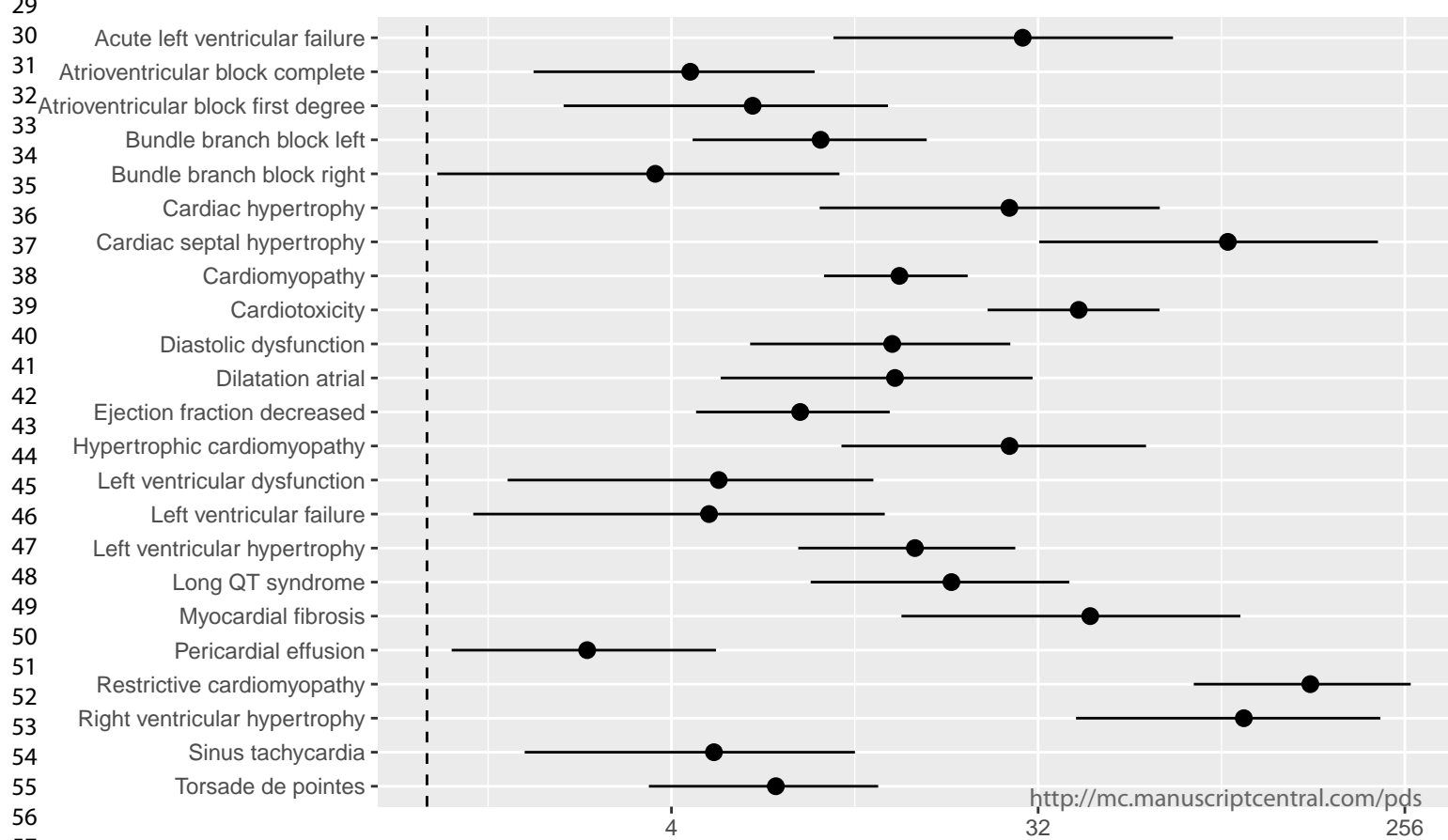
EBGM score of ADR

Reports (HCQ)

Reports (Other)

EBGM

95% CI



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3 1 **Analysis of the US FDA adverse event reporting system to identify adverse cardiac**
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5 2 **events associated with hydroxychloroquine in older adults**
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27 10 **Running title:** Adverse cardiac events associated with hydroxychloroquine
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46 17 **Keywords:** hydroxychloroquine, adverse event, data signal, reporting odds ratio, elderly
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49 18 **Word count:** 20671412 (excluding references)
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52 19 **Key points**

53
54 20 1. The study found that the risk of cardiac cardiomyopathy and myocardial disorders is high
55 21 following exposure to hydroxychloroquine in older adults.

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57 22 2. Novel findings include the identification of a signal for cardiac septal hypertrophy.
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1 Abstract

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

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

13 **Results** We identified 334 adverse cardiac events comprising 71 different MedDRA PTs from
14 2004 to 2019 for hydroxychloroquine in older adults. Strong disproportionality signals were
15 noted for '*Restrictive cardiomyopathy*' (ROR= 272.43 (138.09-537.47); EBGM= 149.78
16 (77.34-264.67), '*Right ventricular hypertrophy*' (219.49 (85.32-564.70); 102.74 (39.67-
17 222.81), '*Cardiac septal hypertrophy*' (226.77 (78.65-653.80); 93.82 (32.19-219.81),
18 '*Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and '*Cardiotoxicity*' (43.90
19 (26.66-72.27); 40.28 (24.02-63.72).

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

1 Introduction:

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

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

1
2
3 **1 Method:**

4
5 **2 Ethics approval:** The Departmental Research Ethical Officer at the University of Bath
6 approved this study.
7

8
9 **4 Data source:** Data was retrieved from the Elsevier PharmaPendium database (11). Data for
10 4667+ United States FDA and European Medicines Agency approved drugs, and 14+ million
11 FAERS reports have been collected and stored in the PharmaPendium in the latest 2020.07
12 release. The use of PharmaPendium for drug safety research is described elsewhere (12, 13).
13 Each FAERS report contains information on the drug and its role in the event, dose, frequency
14 and route. The primary, secondary, concomitant and interacting drugs are reported.

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

15 **Adverse drug reaction definition**

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

20
21 **Statistical Analyses**

22 We selected hydroxychloroquine as the primary suspect drug and ~~analysed~~analyzed all
23 reported adverse events in older adults from the start of ~~January 1, 2004,2004-01-01~~ to the
24 end of ~~December 31, 20192019-12-31~~. The ratio of cases/non-cases for hydroxychloroquine
25 ~~were~~was compared with the ratio of cases/non-cases for all other drugs for the same study
26 period. We used the disproportionality analyses to calculate the reporting odds ratio (ROR)
27 and the proportional reporting ratio (PRR) (14). We used the Bayesian approach to calculate
28 information component (IC) values and Empirical Bayesian Geometric Mean (EBGM) scores.
29 The criteria for a disproportionality signal was defined as the number of reports >3 and the
30 lower limit of 95% confidence intervals (CI) of ROR ≥ 2 , PRR value ≥ 2 , IC value >0 and EBGM
31 score >1. For secondary analyses, we mapped the PTs of adverse cardiovascular events to
32 system organ class (SOC), high-level group term (HLGT) and high-level term (HLT). **Analysis**
33 The analysis was conducted in R, version 3.6.1 (15).

1 Results

2 We retrieved a total of 7,247,902 drug-event pairs between January 1, 2004, 2004-01-01 and
3 December 31, 2019, 2019-12-31 recorded in FAERS for adults aged ≥ 65 years by splitting
4 multiple AEs reported for each case. Of which, 5327 adverse events (AEs) belonged to
5 hydroxychloroquine. Amongst the 5327 AEs, we identified 334 adverse cardiac events
6 comprising 71 different MedDRA PTs. The mean age of the patients within the reports
7 (n=1090) for hydroxychloroquine is 71.77 (7.27) years, and 85.4 % were females. 56.1% of
8 the reports were submitted by 'other healthcare professionals' followed by
9 20.3% from physicians and 20.5% from consumers. 90.4% of the reports were expedited. The
10 country of origin of the reports was mostly from the USA. Indications were missing for 97 out
11 of 1090 (8.9%) reports. The majority of the reports 430/1090 (39.4%) indicated
12 hydroxychloroquine was used for rheumatic disorders (mainly rheumatoid arthritis) followed
13 by 124/1090 (11.3%) reports for systemic lupus erythematosus, and 199/1090 (18.3%) reports
14 recorded hydroxychloroquine was used for an unknown indication.

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

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

22
23 **Figure 3:** RORs and EBGM scores with 95% CIs for PTs with hydroxychloroquine-
24 associated cardiovascular events. ADR-adverse drug reaction; HCQ-hydroxychloroquine
25 ROR- reporting odds ratio; EBGM-Empirical Bayesian geometric mean; CI confidence
26 interval.

27 Strong disproportionality signals were noted for '*Restrictive cardiomyopathy*' (ROR= 272.43
28 (138.09-537.47); EBGM= 149.78 (77.34-264.67), '*Right ventricular hypertrophy*' (219.49
29 (85.32-564.70); 102.74 (39.67-222.81), '*Cardiac septal hypertrophy*' (226.77 (78.65-653.80);
30 93.82 (32.19-219.81), '*Myocardial fibrosis*' (57.29 (21.06-155.85); 42.99 (14.74-100.75), and
31 '*Cardiotoxicity*' (43.90 (26.66-72.27); 40.28 (24.02-63.72).

32 Discussion

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1 The risk for severe illnesses from COVID-19 infection is age-related, with older adults aged
2 85 or older at highest risk. Underlying medical comorbidities, specifically underlying
3 cerebrovascular and cardiovascular disease, including heart failure, coronary heart disease
4 and cardiomyopathies, increases the risk of hospitalizations and intensive care unit
5 admissions in older adults with COVID-19 infection (16). In this context, ~~t~~This study addressed
6 the impending necessity emerging from the COVID-19 pandemic for understanding the safety
7 of hydroxychloroquine in older adults.

8
9 Majority of the cardiovascular AEs reported in this study are related to cardiac conduction and
10 myocardial disorders. These findings are consistent with a recent systematic review that
11 concluded conduction disorders and myocardial hypertrophy as two major cardiac
12 complications associated with hydroxychloroquine therapy (17).

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

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

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

1 failure. These are well ~~recognised~~recognized AEs of hydroxychloroquine. Prescribers should
2 be aware that these serious adverse events can be pronounced in older adults with pre-
3 existing cardiac disease. However, our novel findings include the identification of cardiac
4 septal hypertrophy and myocardial fibrosis associated with hydroxychloroquine therapy, and
5 these signals require further confirmation. Cardiac septal hypertrophy in older adults is
6 associated with disturbance in intraventricular conduction and is an independent predictor of
7 progression to atrial fibrillation in patients with hypertrophic cardiomyopathy. (26, 27).
8 Myocardial fibrosis is a significant risk factor for hypertrophic cardiomyopathy, and is
9 associated with a myriad of severe adverse cardiovascular outcomes including sudden
10 cardiac death, ventricular tachyarrhythmias, left ventricular dysfunction, and heart failure (28).
11

12 *Strengths and limitations*

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

22
23 There are ~~several~~ database and several methodological limitations associated with this study.
24 Adverse event reports are submitted ~~on a voluntary basis~~voluntarily to FAERS, and this may
25 potentially lead to underreporting (29). Although careful consideration was given to the
26 removal of duplicated reports, there is a possibility that the AEs may be reported multiple times
27 by various stakeholders including patients, manufacturers and physicians. Given the
28 spontaneous nature of reporting, the drug exposure at a population level is unknown, hence
29 the actual incidence rate for the AE cannot be established. Lack of information on
30 comorbidities, family history, and incomplete dosage information is likely to bias the study
31 findings. Characteristic ~~to of~~ SRS is the potential for selective reporting of only serious adverse
32 events. Specific methodological limitations include examining hydroxychloroquine as the
33 primary drug of interest without ascertaining the impact of concomitant medications on the AE.
34 Several of the AEs identified with hydroxychloroquine may be confounded by the severity of
35 the underlying medical condition. For example, several autoimmune disorders treated with

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

7

8 **Conclusions**

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

20

21 **Author Contributions**

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

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

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28 Team for completing the MedDRA hierarchy analysis and mapping.

29

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1. Some or all of the data that were used in this study were provided by a company with a vested interest in the product being studied. n/a
2. The sponsor of this project had the right of commenting but the authors retained the right to accept or reject comments or suggestions. n/a
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4

- 5
- 6 • been paid as a consultant (or in a similar capacity) by a company with a vested interest in the
7 product being studied, on issues related to the product being studied; n/a
 - 8 • been paid as a consultant (or in a similar capacity by a company with a vested interest in the
9 product being studies, on issues unrelated to the product being studied; n/a
 - 10 • received research or educational support from a company with a vested interest in the product(s)
11 being studied. n/a
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16 7. A company whose product is being studied has provided funding to support the work on this
17 project. n/a
18

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20
21 If you have answered YES to any of the above questions, or if you have additional personal, commercial or
22 academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been
23 reimbursed by Safe Drug Ltd. for international conference attendance.
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29
30 8. Manuscript title (first six words are sufficient)

31
32 Analysis of the US FDA adverse event reporting system to identify adverse cardiac events associated
33 with hydroxychloroquine in older adults
34
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36 9. Author's full name (a separate form must be submitted for each author)

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38 Prasad S Nishtala
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4. I, my spouse, or one of my dependent children is an employee of a company whose product is being studied. No
5. I, my spouse, or one of my dependent children has significant equity interest (>USD 10,000) in the company that owns the product being studied. No

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3 6. In the past three years I have:
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- 5 • been paid as a consultant (or in a similar capacity) by a company with a vested interest in the
6 product being studied, on issues related to the product being studied; No
7
8 • been paid as a consultant (or in a similar capacity by a company with a vested interest in the
9 product being studies, on issues unrelated to the product being studied; No
10
11 • received research or educational support from a company with a vested interest in the product(s)
12 being studied. No
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16 7. A company whose product is being studied has provided funding to support the work on this
17 project. No
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20
21 If you have answered YES to any of the above questions, or if you have additional personal, commercial or
22 academic conflicts of interest, please draft a statement to publish with the article. e.g., AB has been
23 reimbursed by Safe Drug Ltd. for international conference attendance.
24

25 n/a
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30 8. Manuscript title (first six words are sufficient)

31
32 Analysis of the US FDA adverse event reporting system to identify adverse cardiac events associated
33 with hydroxychloroquine in older adults
34

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36 9. Author's full name (a separate form must be submitted for each author)

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38 Sakirat Gill
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40 10. In checking this box, I confirm I have completed this form to the best of my knowledge.
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58 September 2016