Gender Differences in Adverse Drug Events of Hydroxychloroquine: Analysis of Spontaneous Reports Submitted to FAERS

Huan-huan JI

Children's Hospital of Chongqing Medical University

Lin SONG

Children's Hospital of Chongqing Medical University

Yun-tao JIA (✉ jiayuntaomail@hospital.cqmu.edu.cn)

Children's Hospital of Chongqing Medical University

Research Article

Keywords: Hydroxychloroquine, Adverse drug events, gender difference, Data-mining, FDA Adverse Event Reporting System

Posted Date: February 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-155861/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Several studies have investigated gender as a risk factor for the occurrence of adverse drug events (ADEs) and found that females are more likely to experience ADEs than male. Today, there is a poor knowledge about gender differences in safety profile of ADEs to hydroxychloroquine (HCQ). Identifying those gender differences in ADEs could reduce the experience of ADEs for patients with HCQ. Therefore, the aim of this explorative study was to investigate whether differences exist in reported ADEs of HCQ for male and female in the database of FDA Adverse Event Reporting System (FAERS).

Methods We performed a descriptive gender-related analysis and disproportionality analysis of HCQ safety data, obtained from the FAERS. Reporting odds ratio (ROR) and 95% confidence interval (CI) were calculated to quantify the signals of gender differences for specific drug-event combinations at system organ class (SOC) and preferred term (PT) level.

Results Disproportionality analysis indicated that 8 SOCs with 12 ADEs were statistically significantly more reported in female than male, including electrocardiogram Qt prolonged, retinal toxicity, musculoskeletal disorder, hypersensitivity, anaphylactic reaction, among others, and 5 SOCs with 11 ADEs were reported more in male than female, including cardiac failure, renal failure, completed suicidal, photosensitivity reaction. Common adverse events are similar between female and male. However, serious ADEs were more frequently reported in males.

Conclusions Therefore, the recognition of gender differences in ADEs may be helpful in prescribing medications, e.g. greater caution should be taken when prescribing HCQ to female with conduction disorder.

Introduction

HCQ approved by the FDA that have been used for many years to prevent and treat malaria and certain inflammatory conditions. Although HCQ well-established, they possess the potential to cause numerous side effects and should be used with caution in those with cardiovascular, neurological or vision disorders [1]. However, the HCQ FDA-approved labeling does not include sufficient information regarding safety issues in gender factor. So far, increasing evidence has shown that female is more likely to experience adverse drug events (ADEs) than male [2], but it is unknown whether gender differences exist in the ADEs pattern of HCQ. Identifying those gender differences in ADEs could reduce the experience of ADEs for patients and could be conducive to the development of personalized medicine for both male and female. In order to provide additional guidance to HCQ prescription, we analyzed the ADEs in HCQ treatment aiming to find some gender-based differences using the FDA Adverse Event Reporting System (FAERS) database.

Data-mining techniques, such as signal detection algorithms, are increasingly being used to explore medical databases and analyze large volumes of accumulated data to identify potential associations between drugs and ADEs that may have escaped detection in clinical trials [3]. Data from FAERS are

publicly available and routinely used by the FDA, health systems, clinical scientists, and pharmaceutical manufacturers to identify potential safety signals. Thus, provided us a unique data source to conduct research for ADEs gender differences of HCQ.

Methods

Data source

The fastest and easiest approach (though not the best one) for the assessing of the safety profile of drugs is the Adverse Drug Reaction Spontaneous Reporting System. Despite its limitations, spontaneous reporting could represent actually a valuable tool to assess gender differences in the onset of suspected ADEs. Pharmacovigilance databases can be used to assess a drug's safety by evaluating disproportional associations between the drug and one or more ADEs. The data for this study were retrieved from the public release of the FAERS database. The FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA from all over the world. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

In FAERS database, each report is coded using preferred term (PT) in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. To identify drug-event pairs that did not reach the signal threshold with single-term analysis, and to correct for underestimation of drug-event pair significance due to variability in the terms chosen to describe essentially the same ADE, disproportionality analysis was performed firstly using SOC, which combine similar clinically relevant PT. After gathering this overall picture, further disproportionality analysis in PT level was based on target ADEs from HCQ label be approved by FDA.

Statistical methods

A ratio of reports concerning female versus male was calculated for all of the SOCs or PTs included in FDA label for HCQ. Instead of testing whether the ratio of the occurrences of an adverse event for male and female patients was the same as the baseline ratio (i.e., ratio of drug use), which was unavailable from the database, we tested whether the proportion of a target adverse event, among all reported events, was the same between the males and females. The effects of disproportionality analysis were evaluated using the established pharmacovigilance index reporting odds ratio (ROR). Then, a 2*2 contingency table was used to detect the gender-differential drug-event combinations (Tab 1). ROR value was used to quantify the difference (i.e., effect size) between the female and male gender for a specific SOC or adverse event.

We first tested the gender difference in drug-event combination frequency distributions summarized at SOC level. Thus, if the lower limit of the ROR 95% CI greater than 1, we considered the overall ADEs in this SOC to be reported statistically significantly more often in female than male. When the upper limit of the

ROR 95% CI less than 1, we considered the overall ADEs in this SOC to be reported statistically significantly more often in male than female.

A similar ROR test for a 2*2 contingency table was used to detect the gender differences at PT level for target ADEs listed in label. To correct for multiple testing and provide a strong control of the family-wise error rate, the P values were adjusted using Bonferroni correction. Drug-event combinations with at least 50 overall occurrences altogether in both genders [4] and the number of female or male related ADE should be greater than 3 [5]. ROR value greater than 2 and the lower limit of the 95% CI greater than 1 indicates that the female patients are more likely to report a given adverse event than male patients. On the other hand, when the ROR value is less than 0.5 and the upper limit of the 95% CI less than 1, male patients tend to report the adverse event more frequently.

At adverse events level, we manually selected target ADEs from HCQ label be approved by FDA [1]. These adverse reactions have been identified during post-approval use of hydroxychloroquine or other 4-aminoquinoline compounds. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These target ADEs involved 15 different SOCs with a total of 89 preferred terms according to the MedDRA Terminology.

Tab 1. Two-by-two contingency table for disproportional analysis

	Target SOCs or Adverse Events	All Other SOCs or Adverse Events	Total
Female	a	b	a + b
Male	c	d	c + d

$$ROR=(a/c)/(b/d) =ad/bc; 95\% \text{ CI}= e^{\ln (ROR)\pm 1.96\sqrt{(1/a+1/b+1/c+1/d)}}$$

a: the number of female patients with target drug-events combinations. b: the number of female patients with HCQ but not target events. c: the number of male patients with target drug-events combinations. d: the number of male patients with HCQ but not target events.

Results

Descriptive analysis

Up to 2020, FAERS received 25619 reports in which HCQ was reported as a suspect or interacting drug. Table 2 lists the demographic data of HCQ reports. More than three-quarters ratio of the reports concerned female (76.61%) exclude the unknown gender. The overall female to male ratio reported in these reports is 4.97:1 and that for adults (18–64 years) is 5.25:1. Patients age distribution was similar for male and female in different age groups and mainly concentrated in the 18–64 years age group. There are peaks in the 40–50 and 60–70 age groups regardless of gender or not (Fig. 1). One possible

explanation for this concentration of ADEs in patients may be related to the age-specific incidence rates of most common therapeutic indications (e.g. rheumatoid arthritis and lupus erythematosus) [6]. The number of reports was consistently low before 2010, whereas a remarkable rise was observed from 2015 to 2019, with a difference in the male and the female groups in particular from 2015 (Fig. 2). This can be explained by the use of HCQ is increased due to a growing list of clinical indications, and subsequently growing side effects being under recognized and reported. Almost two-thirds of the cases reporter region derived from foreign area and there is basically no difference in the proportion considered each area for both genders. In the United States, the male to female ratio is 5.23:1. Healthcare professionals were responsible for 64.92% of the reports, while 24.57% were reported by consumer regardless of gender. Reporter distribution was similar for male and female.

The distribution of ADEs outcomes between male and female seemed to be similar. Both genders more frequently reported hospitalized and other outcomes. However, in terms of seriousness, the proportion of serious cases is higher in male than in female including death and life-threatening cases (5.40%, 4.76% in males and 2.91%, 2.31% in females). This finding can be partially explained by the fact that female report more physical symptoms and use more medical services compared to male [7].

At PT level, the most frequently reported ADEs, regardless of gender or not, were drug ineffective, rheumatoid arthritis, drug intolerance, and pain. Table 3 lists the first 30 most-reported ADEs for each gender, which account for 41.37% of all ADEs reported by female and 38.83% of those reported by male. Other events had a very similar distribution between genders. Obviously, some ADEs reports are drug indications or original diseases related symptoms for HCQ, such as rheumatoid arthritis, joint swelling and arthragia. FDA does not require that a causal relationship between a product and event be proven, so these ADEs have also been reported.

Table 2
Demographic data of hydroxychloroquine

	Female Patients NO (%)	Male Patients NO (%)	Female to Male Ratio
Age Category			
0–17 Years	407 (2.07%)	121(3.07%)	3.36:1
18–34 Years	9551 (48.66%)	1820 (46.12%)	5.25:1
65–85 Years	3585 (18.27%)	733 (18.58%)	4.89:1
More than 85 Years	96 (0.49%)	29 (0.73%)	3.31:1
Not Specified	5988 (30.51%)	1244 (31.53%)	4.82:1
Reporter Region			
Domestic	6162 (31.40%)	1179 (29.88%)	5.23:1
Foreign	13407 (68.31%)	2755 (69.82%)	4.87:1
Not Specified	58 (0.30%)	12 (0.30%)	4.83:1
Reporter Type			
Healthcare professional	13745 (70.03%)	2888 (73.19%)	4.76:1
Consumer	5358 (27.30%)	936 (23.72%)	5.72:1
Other	11 (0.06%)	0	-
Not specified	513 (2.61%)	122 (3.09%)	4.20:1
Serious Category			
Serious	16460 (83.86%)	3482 (88.24%)	4.73:1
Non-Serious	3167 (16.14%)	464 (11.76%)	6.83:1
Outcomes Category			
Died	572 (2.91%)	213 (5.40%)	2.69:1
Hospitalized	3643 (18.56%)	945 (23.95%)	3.86:1
Life threatening	454 (2.31%)	188 (4.76%)	2.41:1
Disabled	881 (4.49%)	189 (4.79%)	4.66:1
Required intervention	81 (0.41%)	23 (0.58%)	3.52:1
Other outcomes	13915 (70.90%)	2650 (67.16%)	5.25:1

Percentage calculated based on the total number of reported cases for the female gender (n = 19627) and male gender (n = 3946) respectively.

	Female Patients NO (%)	Male Patients NO (%)	Female to Male Ratio
Non-serious	3167 (16.14%)	464 (11.76%)	6.83:1
Congenital anomaly	81 (0.41%)	69 (1.75%)	1.17:1
Percentage calculated based on the total number of reported cases for the female gender (n = 19627) and male gender (n = 3946) respectively.			

Table 3
Classification of the first 30 suspected ADEs at PT level

Female Patients	NO (%)	Male Patients	NO (%)
Drug ineffective	8892 (45.30%)	Drug ineffective	1609 (40.78%)
Rheumatoid arthritis	5052 (25.74%)	Rheumatoid arthritis	806 (20.43%)
Drug intolerance	3056 (15.57%)	Drug intolerance	557 (14.12%)
Pain	2348 (11.96%)	Joint swelling	450 (11.40%)
Joint swelling	2200 (11.21%)	Pain	392 (9.93%)
Arthralgia	2171 (11.06%)	Treatment failure	303 (7.68%)
Drug hypersensitivity	1993 (10.15%)	Arthralgia	302 (7.65%)
Nausea	1942 (9.89%)	Condition aggravated	269 (6.82%)
Fatigue	1775 (9.04%)	Contraindicated product Administered	259 (6.56%)
Treatment failure	1672 (8.52%)	Nausea	256 (6.49%)
Contraindicated product administered	1638 (8.35%)	Synovitis	228 (5.78%)
Rash	1573 (8.01%)	Off label use	227 (5.75%)
Condition aggravated	1519 (7.74%)	Drug hypersensitivity	215 (5.45%)
Synovitis	1279 (6.52%)	Therapeutic product effect decreased	196 (4.97%)
Abdominal discomfort	1264 (6.44%)	Loss of personal independence in Daily activities	193 (4.89%)
Therapeutic product effect decreased	1256 (6.40%)	Peripheral Swelling	186 (4.71%)
Diarrhoea	1229 (6.26%)	Therapeutic product effect incomplete	169 (4.28%)

Percentage calculated based on the total number of reported cases for the female gender (n = 19627) and male gender (n = 3946) respectively.

Female Patients	NO (%)	Male Patients	NO (%)
Off label use	1139 (5.80%)	Pain in extremity	153 (3.88%)
Alopecia	1110 (5.66%)	Fatigue	148 (3.75%)
Arthropathy	1062 (5.41%)	Renal failure	147 (3.73%)
Peripheral swelling	1040 (5.30%)	Pneumonia	142 (3.60%)
Therapeutic product effect incomplete	1035 (5.27%)	Rash	141 (3.57%)
Headache	1012 (5.16%)	Dyspnoea	138 (3.50%)
Vomiting	940 (4.79%)	Infection	137 (3.47%)
Pain in Extremity	889 (4.53%)	Diverticulitis	134 (3.40%)
Malaise	877 (4.47%)	Mobility decreased	132 (3.35%)
Swelling	819 (4.17%)	Headache	129 (3.27%)
Musculoskeletal Stiffness	798 (4.07%)	C-reactive protein increased	129 (3.27%)
Loss of personal independence in daily Activities	780 (3.97%)	Gastrointestinal disorder	128 (3.24%)
Infection	736 (3.75%)	Diarrhoea	128 (3.24%)
Percentage calculated based on the total number of reported cases for the female gender (n = 19627) and male gender (n = 3946) respectively.			

Disproportionality Analyses

Detect gender difference for specific drug-event combinations summarized at SOC level

The data on suspected ADEs classified by SOC showed some gender-based differences (Table 4). In the absolute number of reports, the ADEs number of female in each SOC was higher than that of male, but the disproportional outcome is different between male and female. Of the total 27 SOC, ROR analysis

show that the female patients were more likely to report these drug-event combinations in 10 different SOC, of which target ADEs from HCQ label involved 8 SOC, including eye disorders, musculoskeletal and connective tissue disorders, skin and subcutaneous tissue disorders, gastrointestinal disorders, immune system disorders, nervous system disorders, endocrine disorders, ear and labyrinth disorders. On the contrary, male patients were more susceptible to reporting these drug-event combinations in 11 different SOC, and 5 SOC involve target ADEs in HCQ label, including cardiac disorder, hepatobiliary disorders, renal and urinary disorders, psychiatric disorders, blood and lymphatic system disorders. No gender differences were observed in 6 SOC, except for general disorders and administration site conditions or metabolism and nutrition disorders, which also not involve target ADEs in HCQ label, including investigations, pregnancy, puerperium and perinatal conditions, reproductive system and breast disorders, product issues. Female showed endocrine disorders [ROR = 6.03; 95%CI (3.21; 11.31)] as the most significant signal of SOC whereas congenital, familial and genetic disorders [ROR = 0.28; 95%CI (0.22; 0.36)] was the most significant signal of SOC for male. However, there were few data on both, which may lead to data bias (Table 4).

Table 4
Gender difference for specific drug-event combinations summarized at SOC level

Systemic Organ Class (SOC)	Female/Male	ROR (95%CI)
General Disorders and Administration Site Conditions	13556/2476	1.01 (0.96; 1.06) *
Musculoskeletal and Connective Tissue Disorders	9276/1630	1.05 (1.00; 1.12) *
Gastrointestinal Disorders	5534/870	1.19 (1.10; 1.28) *
Injury, Poisoning and Procedural Complications	5283/912	1.07 (1.00; 1.15)
Investigations	4984/925	0.99 (0.92; 1.07)
Skin and Subcutaneous Tissue Disorders	4745/678	1.31 (1.21; 1.42) *
Infections and Infestations	4415/893	0.90 (0.84; 0.97)
Nervous System Disorders	3544/558	1.18 (1.08; 1.29) *
Immune System Disorders	2900/329	1.65 (1.47; 1.85) *
Respiratory, Thoracic and Mediastinal Disorders	2547/621	0.75 (0.68; 0.82)
Eye Disorders	2092/222	1.76 (1.53; 2.02) *
Psychiatric Disorders	1721/386	0.82 (0.73; 0.91) *
Social Circumstances	1362/293	0.85 (0.75; 0.97)
Cardiac Disorders	1232/306	0.74 (0.65; 0.84) *
Blood and Lymphatic System Disorders	1190/353	0.61 (0.54; 0.69) *
Vascular Disorders	1166/332	0.64 (0.57; 0.73)
Metabolism and Nutrition Disorders	1141/238	0.88 (0.77; 1.01) *
Surgical and Medical Procedures	1033/151	1.26 (1.06; 1.50)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1002/272	0.67 (0.59; 0.77)
Statistically significant difference between males and females highlighted in bold.		
* Target ADEs from HCQ label be approved by FDA which involved 15 different SOC.		

Systemic Organ Class (SOC)	Female/Male	ROR (95%CI)
Hepatobiliary Disorders	888/198	0.82 (0.71; 0.96) *
Renal and Urinary Disorders	743/320	0.42 (0.37; 0.48) *
Ear and Labyrinth Disorders	501/65	1.42 (1.10; 1.84) *
Pregnancy, Puerperium and Perinatal Conditions	332/63	0.97 (0.74; 1.27)
Endocrine Disorders	326/10	6.03 (3.21; 11.31) *
Reproductive System and Breast Disorders	187/23	1.50 (0.97; 2.31)
Product Issues	169/33	0.94 (0.65; 1.37)
Congenital, Familial and Genetic Disorders	163/107	0.28 (0.22; 0.36)
Statistically significant difference between males and females highlighted in bold.		
* Target ADEs from HCQ label be approved by FDA which involved 15 different SOC.		

Detect gender difference for specific drug-event combinations summarized at PT level

According to drug labels on the FDA website and the EUA health care provider fact sheets for HCQ safety profile, we focused our gender disproportional analysis in several ADEs highly related to HCQ. Further analysis conducted at PT level revealed some clinically significant signals of gender difference in drug-event combinations (Table 5). Disproportional algorithm showed that female taking HCQ were more susceptible to 12 PTs, including electrocardiogram Qt prolonged [ROR = 2.01; 95%CI (1.02; 3.96)], retinal toxicity [ROR = 3.48; 95%CI (1.71; 7.08)], macular degeneration [ROR = 2.78; 95%CI (1.01; 7.64)], photophobia [ROR = 2.99; 95%CI (1.09; 8.20)], vomiting [ROR = 2.95; 95%CI (2.24; 3.88)], fatigue [ROR = 2.04; 95%CI (1.72; 2.41)], musculoskeletal disorder [ROR = 8.65; 95%CI (3.5; 20.96)], muscle spasms [ROR = 2.16; 95%CI (1.17; 4.00)], hypersensitivity [ROR = 2.07; 95%CI (1.57; 2.74)], anaphylactic reaction [ROR = 7.52; 95%CI (3.35; 16.89)], dizziness [ROR = 2.22; 95%CI (1.63; 3.01)], alopecia [ROR = 2.02; 95%CI (1.64; 2.50)], while male were more tended to 11 PTs, including cardiac failure [ROR = 0.37; 95%CI (0.26; 0.53)], tremor [ROR = 0.22; 95%CI (0.15; 0.31)], photosensitivity reaction [ROR = 0.28; 95%CI (0.19; 0.41)], respiratory failure [ROR = 0.25; 95%CI (0.17; 0.38)], completed suicide [ROR = 0.30; 95%CI (0.21; 0.43)], pancytopenia [ROR = 0.39; 95%CI (0.28; 0.55)], white blood cell decreased [ROR = 0.22; 95%CI (0.17; 0.28)], haemoglobin decreased [ROR = 0.32; 95%CI (0.23; 0.44)], acute kidney injury [ROR = 0.36; 95%CI (0.25; 0.53)], renal failure [ROR = 0.09; 95%CI (0.07; 0.12)], renal disorder [ROR = 0.21; 95%CI (0.13; 0.32)].

Table 5
Gender difference for specific drug-event combinations at PT level

SOC/PT	Female/Male	ROR (95% CI)
Cardiac disorders		
Electrocardiogram Qt prolonged	107/9	2.01 (1.02; 3.96)
torsade de pointes	70/7	1.69 (0.78; 3.67)
Ventricular arrhythmias	20/1	3.37 (0.45; 25.13)
Cardiomyopathy	131/26	0.85 (0.56; 1.29)
Cardiac failure	94/43	0.37 (0.15; 0.89)
Eye disorders		
Visual impairment	400/36	1.88 (1.33; 2.64)
Eye disorder	312/40	1.32 (0.95; 1.83)
Vision blurred	163/18	1.53 (0.94; 2.49)
Retinal toxicity	165/8	3.48 (1.71; 7.08)
Photophobia	71/4	2.99 (1.09; 8.20)
Macular degeneration	66/4	2.78 (1.01; 7.64)
Retinopathy	139/15	1.56 (0.92; 2.66)
Visual field defect	93/18	0.87 (0.53; 1.44)
Maculopathy	87/12	1.22 (0.67; 2.24)
Visual acuity reduced	65/8	1.37 (0.66; 2.86)
Retinopathy	66/7	1.59 (0.73; 3.47)
Retinal degeneration	31/4	1.31 (0.46; 3.70)
Retinal disorder	66/7	1.59 (0.73; 3.47)
Blindness	54/9	1.01 (0.50; 2.05)
Detachment of retinal pigment epithelium	4/3	0.22 (0.05; 1.00)
Musculoskeletal and connective tissue disorders		
Musculoskeletal stiffness	798/96	1.40 (1.14; 1.74)
Musculoskeletal pain	419/53	1.33 (1.00; 1.78)
Musculoskeletal disorder	256/5	8.65 (3.57; 20.96)
Statistically significant difference between males and females highlighted in bold.		

SOC/PT	Female/Male	ROR (95% CI)
Muscle spasms	141/11	2.16 (1.17; 4.00)
Neuromyopathy	11/2	0.93 (0.21; 4.18)
Myopathy toxic	22/6	0.62 (0.25; 1.52)
Myopathy	85/9	1.59 (0.80; 3.17)
Musculoskeletal discomfort	41/12	0.58 (0.30; 1.10)
Muscle atrophy	30/3	1.69 (0.51; 5.53)
Respiratory, Thoracic and Mediastinal Disorders		
Respiratory failure	57/38	0.25 (0.17; 0.38)
Skin and subcutaneous tissue disorders		
Rash	1573/141	1.89 (1.59; 2.25)
Alopecia	1110/93	2.02 (1.64; 2.50)
Pruritus	443/55	1.36 (1.03; 1.80)
Pigmentation disorder	15/3	0.84 (0.24; 2.91)
Mucous membranes		
Hair colour changes	8/2	0.67 (0.14; 3.18)
Dermatitis bullous	22/5	0.74 (0.28; 1.96)
Erythema multiforme	60/16	0.63 (0.36; 1.10)
Stevens-Johnson syndrome	61/6	1.71 (0.74; 3.97)
Toxic epidermal necrolysis	60/3	3.37 (1.06; 10.76)
Drug reaction with eosinophilia and systemic symptoms	56/14	0.67 (0.38;1.21)
Dermatitis exfoliative	32/12	0.45 (0.23; 0.87)
Photosensitivity reaction	74/44	0.28 (0.19; 0.41)
Acute generalised exanthematous pustulosis	68/7	1.64 (0.75; 3.57)
Psoriasis	140/24	0.98 (0.64; 1.52)
Immune system disorders		
Hypersensitivity	662/54	2.07 (1.57; 2.74)
Anaphylactic reaction	267/6	7.52 (3.35; 16.89)
Statistically significant difference between males and females highlighted in bold.		

SOC/PT	Female/Male	ROR (95% CI)
Urticaria	30/78	0.73 (0.57; 0.94)
Angioedema	97/12	1.36 (0.75; 2.48)
Bronchospasm	25/1	4.22 (0.57; 31.12)
Renal and Urinary Disorders		
Acute kidney injury	86/40	0.36 (0.25; 0.53)
Renal Failure	78/147	0.09 (0.07; 0.12)
Renal disorder	43/35	0.21 (0.13; 0.32)
Hepatobiliary disorders		
Liver function tests abnormal	192/32	1.01 (0.70;1.47)
Acute hepatic failure	6/9	0.11 (0.04; 0.32)
Blood and lymphatic system disorders		
Pancytopenia	109/47	0.39 (0.28; 0.55)
White blood cell decreased	140/108	0.22 (0.17; 0.28)
Haemoglobin decreased	104/55	0.32 (0.23; 0.44)
Anaemia	96/45	0.73 (0.53; 1.02)
Aplastic anaemia	7/4	0.30 (0.09; 1.01)
Agranulocytosis	43/13	0.56 (0.30; 1.04)
Leukopenia	298/61	0.82 (0.62; 1.08)
Bone marrow failure	39/6	1.10 (0.46; 2.59)
Thrombocytopenia	153/48	0.54 (0.39; 0.74)
Ear and labyrinth disorders		
Vertigo	43/12	0.60 (0.32; 1.15)
Tinnitus	102/18	0.96 (0.58; 1.58)
Nystagmus	12/1	2.02 (0.26; 15.56)
Deafness neurosensory	55/1	9.28 (1.28; 67.05)
Deafness	145/22	1.11 (0.71; 1.74)
General disorders and administration site conditions		
Statistically significant difference between males and females highlighted in bold.		

SOC/PT	Female/Male	ROR (95% CI)
Fatigue	1775/148	2.04 (1.72; 2.41)
Metabolism and nutrition disorders		
Decreased appetite	266/25	1.80 (1.19; 2.71)
Hypoglycaemia	81/12	1.14 (0.62; 2.09)
Porphyria	1/1	0.17 (0.01; 2.70)
Weight decreased	476/58	1.39 (1.05; 1.82)
Nervous system disorders		
Dizziness	577/44	2.22 (1.63; 3.01)
Headache	102/129	1.33 (1.10; 1.59)
Seizure	92/17	0.91 (0.54; 1.53)
Ataxia	20/2	1.69 (0.39; 7.22)
Extrapyramidal disorder	10/0	-
Dystonia	3/0	-
Dyskinesia	4/0	-
Tremor	64/50	0.22 (0.15; 0.31)
Psychiatric disorders		
Completed suicide	79/45	0.30 (0.21; 0.43)
Suicidal behaviour	5/0	-
Affect lability	24/0	-
Nervousness	33/2	2.78 (0.67; 11.60)
Irritability	23/4	0.97 (0.34; 2.80)
Nightmare	18/0	-
Acute psychosis	4/7	0.10 (0.03; 0.33)
Statistically significant difference between males and females highlighted in bold.		

Discussion

Despite the obvious physical and physiological gender differences, gender differences in ADEs are lack of awareness rarely considered in clinical treatment. More specifically, gender differences in ADEs are still widely unknown and poor data is available in the literature in this topic. To the best of our knowledge, this

is the first comparative safety study on FAERS aiming at assessing gender differences for HCQ related ADEs. Overall, three main findings emerged: a) reports of ADEs are more likely to concern female than male regardless of SOC or PT level, especially the ADEs that are common, such as fatigue, alopecia, vomiting, malaise, dizziness, and so on; b) we found disproportionality signal for female in ocular, musculoskeletal, skin, gastrointestinal, ear, neurological, immune systems and endocrine systems at SOC level, for male in cardiac, hematologic, renal, liver and psychiatric; c) disproportionality analysis for female showed a higher reporting in electrocardiogram Qt prolonged, retinal toxicity, musculoskeletal disorder, muscle spasms, hypersensitivity, anaphylactic reaction, among others, while cardiac failure, completed suicidal, photosensitivity reaction, kidney injury include renal failure have been more commonly reported for male. To provide instructional advice on gender difference, we focused our analysis on label warning related ADEs of HCQ provided by FDA, as shown below.

Cardiotoxicity The cardiac effects induced by HCQ predominantly including conduction disorders and cardiomyopathy. The mechanism is poorly understood but likely involves direct lysosomal dysfunction via inhibition of lysosomal enzymes, leading to accumulation of metabolic products [8–9]. We found that conduction disorders associated with HCQ, especially QT interval prolongation, were more commonly reported in female, while cardiomyopathy – though rare – which may result in cardiac failure was more frequent in male.

Conduction disorders Conduction disorders complications from HCQ therapy are rare but clinically important events manifest as QT interval prolongation, torsade de pointes, ventricular arrhythmias, bundle branch block/atrio-ventricular block, ventricular tachycardia and ventricular fibrillation were reported in FAERS. Susceptibility to HCQ-induced QT interval prolongation was greatest for female in our study. This finding was confirmed by clinical observations and in vitro experimental data that female gender is an independent risk factor for drug-induced Long QT syndrome [10–12] which in females is influenced by other factors, including age, menstrual cycle, and hormone replacement therapy in previous studies [13]. The mechanism remains uncertain, the estrogen-mediated reduced repolarization reserve in female is believed to be responsible for their higher susceptibility to drug-induced Long QT syndrome [14, 15]. Medications that cause QT prolongation generally act by blocking *I_{Kr}*, a potassium channel protein that regulates an important rapid delayed repolarizing current in phase 3 of the cardiac action potential [14]. Underlying genetic defects of ion channels that may even be asymptomatic in normal conditions may be unmasked by QT prolonging drugs in female more frequently than in male [11]. Additionally, overdose of HCQ was more likely to concern female than male [116/7, ROR = 2.80, 95%CI (1.30; 6.00)], which may resulted in conduction disorders including QT prolongation.

The occurrence of drug-induced torsade de pointes (TdP), which is much more frequent in female. During AV block, longer QT interval and female gender strongly correlate with the risk of TdP [14]. Female gender increases the risk of TdP in the Long QT syndrome and it is assumed that this increased risk is due to their longer QT interval. However, each of these variables is an independent predictor of TdP [16]. There was a trend of female signal in TdP, but the gender difference was not statistically significant. The fact may be that few patients reported to suffered from abnormal conduction such as TdP and ventricular

arrhythmias owe to relatively unrecognized and many cases may go undiagnosed and serious underreported.

Cardiomyopathy Epidemiological studies showed that male sex is an important risk factor for developing cardiac failure [17], which consistent with the disproportionality signal for female of our study. Cardiac failure associated with HCQ can be the consequence of a number of cardiovascular conditions including cardiomyopathy, myocarditis [9]. The gender difference been confirmed in clinical studies that myocarditis is considered as a male predominant disease. For myocarditis and cardiomyopathy female gender is protective, in sharp contrast to its more adverse impact in more clearly defined autoimmune disorders such as lupus and rheumatoid arthritis [18]. And the better myocardial recovery in females than males was observed in murine models of myocarditis and in clinical studies of recent onset cardiomyopathy. The mechanism remains uncertain, but differences in immune function by gender almost certainly play an important role [18]. It is crudely noted in our results that cardiomyopathy associated with HCQ may be more probable with male compared with female even though the gender difference was not statistically significant.

Ocular Retinopathy, the most well-known complication of HCQ, may manifest as a spectrum of changes from asymptomatic and reversible pigment changes to visual loss persisting or progressing after drug discontinuation. HCQ affect lysosomal function of retinal pigment epithelium with an additional role of oxidative stress [19]. A retrospective case-control study involving 2361 people who had used HCQ continuously for at least 5 years indicates that the risk factors of HCQ retinopathy include high daily intake and with long durations of use or in the presence of kidney disease or concurrent tamoxifen therapy, excluding gender [20]. Here, interestingly, ocular toxicity appears to be stronger associated with the use of HCQ in female patients, both at the SOC and PT level. Considering that few male patients suffered from HCQ retinopathy especially macular degeneration, photophobia and so on owe to the epidemiology of autoimmune diseases which predominantly affect female and consequently to the gender distribution. We cannot conclude if female gender is a risk factor for retinal damage due to HCQ. We will continue to focus on the gender difference of retinal toxicity.

Musculoskeletal Our study observed a slightly higher frequency for female gender in musculoskeletal and connective tissue disorders at the SOC level. The most commonly reported musculoskeletal ADEs with HCQ were predominantly skeletal muscle myopathy and neuromyopathy, which usually leading to progressive weakness and atrophy of proximal muscle groups, depression of tendon reflexes and abnormal nerve conduction. Clinically, most of the symptomatic patients exhibited muscle weakness with proximal greater than distal distribution. At the PT level, signal main emerged as musculoskeletal disorder and muscle spasms for female. Despite the small number of cases, especially in male, these gender differences skim the significance: musculoskeletal disorder [ROR = 8.65, 95%CI (3.5;20.96)] muscle spasms [ROR = 2.16, 95%CI (1.17-4.00)]. Muscle and nerve biopsy are the gold standard for diagnosis of HCQ muscle myopathy. Curvilinear bodies – a rare finding on ultrastructural examination of muscle biopsy, are specific for HCQ-induced myopathy [21]. Female gender is one of the risk factors for development of curvilinear bodies [22] and myopathy [21] related to HCQ, which could

partially explain our finding. This is an occasionally and interesting finding of this study that respiratory failure maybe associated with proximal myopathy secondary to HCQ [23] was more often reported in male.

Skin In our study, female is at greater risk of anaphylactic reaction and hypersensitivity related HCQ than male, and this was proved by the conclusion female is a risk factor for allergic reactions to certain drugs. Additionally, in gender-based medicine, a particularly significant, emerged from several studies, is the higher risk of female developing dermatologic events (e.g., rash) than male [2, 12, 24–25]. This can be explained by the disproportionality signal in SOC “skin and subcutaneous tissue disorders” for female when viewing the skin disorders as a whole. Besides, we found a disproportionality signal for female in alopecia, whereas, for male, the ROR became significant in photosensitivity reaction, and there was no difference in the proportion of male or female in severe cutaneous drug reactions, which including Stevens–Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, dermatitis bullous, acute generalized exanthematous pustulosis and drug reactions with eosinophilia and systemic symptoms due to few data. Drug-induced photosensitivity reactions can be subdivided into photoallergy and phototoxicity, which clinically resemble contact dermatitis and sunburn, respectively [26, 26]. Interestingly, HCQ, often used for photosensitive diseases such as lupus erythematosus (up to 69% of patients with SLE have photosensitivity), can induce photoallergy [27]. Furthermore, we need to pay attention to skin hyperpigmentation which may serve as a marker for patients at risk for developing more severe side effects [27].

Gastrointestinal Our results come as no surprise to us that female gender tends to have a higher risk of gastrointestinal events (e.g., vomiting) in specific SOC and PT level. This corresponds to the clinical observation that gastrointestinal disorders, which are generally considered to be a dose-related or commonly occurring ADEs, occurred in a higher proportion of female than male [2]. Many of the pharmacokinetic differences, such as higher plasma drug levels in female and higher percentage of body fat in female (e.g., drug redistribution effect), may result in female patients experiencing more dose-related effects [12]. Additionally, this finding is coincidental with higher rates of drug utilization and exposure to a larger variety of drug classes among female patients [25]. **Others** HCQ – uncommonly recognized as a nephrotoxin, lysosomal accumulation of globotriaosylceramide leads to chronic kidney disease. Histologically, laminated podocyte inclusions known as zebra bodies are the hallmark finding [28]. A stronger association with renal insufficiency including renal failure were emerged in male following HCQ treatment and further researches are needed to confirm this.

Completed suicidal associated with HCQ appears to be more often in male patients. This was consistent with epidemiological study shows that females have higher rates of suicidal ideation and behaviour while completed suicides occur primarily among males [29].

Some studies continue to suggest female are more likely to develop DILI [30], but others suggest that the genders share a nearly equal risk [31]. Reports of HCQ in liver injury or liver failure still insufficient to draw firm conclusions in our study.

Fewer cases of SOC “endocrine disease” were reported, but the most significant difference between male and female due to disease interferes such as osteoporosis, resulting in skewed results. Hypoglycaemia related to HCQ, though not common, is an ADE of clinical special interest as it may be life-threatening, and there is no significant difference between male and female.

We acknowledge inherent limitations of our study: by definition, FAERS data cannot be used to calculate the incidence of an ADE, because of the under-reporting phenomenon, the lack of solid data on population exposure and the absence of certainty that the drug is actually responsible for the reported event [32]. ROR computing does not allow a quantification of the true risk of ADE for different gender, it only suggests a statistically significant disproportionality of specific drug-event pair of interest, which should be further investigated for signal validation [33]. In addition, various biases such as over-reporting, duplicates, missing data, the possibility effect of diseases and drug interaction on signal detect should be taken into account when interpreting the results obtained from spontaneous report analysis [34]. Despite these caveats, the ROR methodology is a well-established tool for identifying drug-event pairs reported more frequently between females and males, as it is likely that many of the limitations mentioned are equalized across different gender and over time [35]. In our analysis, four steps were taken to weaken for the limitations of disproportionality analysis of FAERS data: (1) Definite gender reports were used for analysis; (2) SOC analysis was performed to control for underestimation of HCQ-event pair significance due to variability in describing the same ADEs with different PTs; (3) filtered out the HCQ-event with occurrences less than 50 for two genders combinations; (4) $ROR \geq 2$ for female or $ROR \leq 0.5$ for male thresholds and $n \geq 3$ were selected to increase the certainty of recognition HCQ signals at PT level; (5) correlation of disproportionality results to data from published researches, where possible.

Conclusion

In conclusion, ADEs submitted to the FDA were reviewed to confirm whether differences exist in reported ADEs of HCQ for male and female and to clarify rank-order in terms of susceptibility. Despite the inherent limitations of the FAERS data, some of the results we obtained regarding the gender difference are in agreement with the results of previous studies, suggesting the usefulness of the FAERS database and the data mining method used herein. Greater caution should be taken when prescribing HCQ to female in electrocardiogram Qt prolonged, retinal toxicity, musculoskeletal disorder, hypersensitivity, anaphylactic reaction, while cardiac failure, renal failure, completed suicidal, photosensitivity reaction, to male, but these require further investigation to better define the risk. In summary, a heightened understanding of gender differences is critical for improving treatment strategies and clinical management that will lead to optimal care for both female and male with these potentially devastating. And such gender-based differences pharmacovigilance study could blaze new trails for further research in gene-gender effects.

Declarations

Acknowledgements

The Smart medicine Project Affiliated to the Education Committee of Chongqing Municipality (No. ZHXY2019022).

Competing Interests

The authors declare no potential conflicts of interests.

Author Contributions

All the authors were involved in the study. Study design: H.H.J., L.S. and Y.T.J. Extraction data: H.H.J. and L.S. Analysis and interpretation of data: H.H.J., L.S. and Y.T.J. All the authors took part in the discussions of the results and contributed to the manuscript.

Funding Information: The Smart medicine Project Affiliated to the Education Committee of Chongqing Municipality (No. ZHXY2019022)

Statements: The datasets generated and/or analysed during the current study are available in the [FDA Adverse Event Reporting System (FAERS) database] repository, [<http://openvigil.sourceforge.net>]

And all data generated or analysed during this study are included in this published article.

References

1. FDA, Plaquenil-hydroxychloroquine sulfatet ablets. Drug label (2020). <https://www.drugs.com/pro/plaquenil.html>. Accessed 19 April 2020.
2. Zopf Y, Rabe C, Neubert A, et al. Women encounter ADRs more often than do men [J]. Eur J Clin Pharmacol. 2008, 64 (10): 999–1004.
3. Harpaz R, DuMouchel W, LePendur P, et al. Performance of pharmacovigilance signal-detection algorithms for the FDA adverse event reporting system [J]. Clin Pharmacol Ther. 2013, 93 (6): 539–46.
4. Yue Y, Jun C, Dingcheng L, et al. Systematic analysis of adverse event reports for sex differences in adverse drug events [J]. Scientific Reports, 2016, 6(1), 249–55.
5. van Puijenbroek EP, Bate A, Leufkens HG, et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol Drug Saf. 2002;11 (1):3–10.
6. Understanding the epidemiology and progression of systemic lupus erythematosus [J]. Semin Arthritis Rheum. 2010, 39 (4): 257–68.
7. Rydberg DM, Mejr S, Loikas D, et al. Sex differences in spontaneous reports on adverse drug events for common antihypertensive drugs [J]. Eur J Clin Pharmacol. 2018, 74 (9): 1165–73.
8. Sabato LA, Mendes LA, Cox ZL. Restrictive Cardiomyopathy Associated With Long-Term Use of Hydroxychloroquine for Systemic Lupus Erythematosus [J]. J Pharm Pract. 2017, 30 (5): 571–5.

9. Yogasundaram H, Hung W, Paterson ID, et al. Chloroquine-induced cardiomyopathy: a reversible cause of heart failure [J]. *ESC Heart Fail.* 2018, 5 (3): 372–75.
10. Lu HR, Remeysen P, Somers K, et al. Female Gender is a Risk Factor for Drug-Induced Long QT and Cardiac Arrhythmias in an In Vivo Rabbit Model [J]. *J Cardiovasc Electrophysiol.* 2001, 12(5):538–45.
11. Kaab S, Pfeufer A, Hinterseer M, et al. Long QT syndrome. Why does sex matter? [J]. *Z Kardiol.* 2004, 93 (9): 641–5.
12. Anderson GD. Chapter 1 Gender Differences in Pharmacological Response [J]. *International Review of Neurobiology.* 2008, 83: 1–10.
13. Li G, Cheng G, Wu J, et al. Drug-induced long QT syndrome in women [J]. *Adv Ther.* 2013, 30 (9): 793–802.
14. Monitillo F, Leone M, Rizzo C, et al. Ventricular repolarization measures for arrhythmic risk stratification [J]. *World J Cardiol.* 2016, 8 (1): 57–73.
15. Vlachos K, Georgopoulos S, Efremidis M, et al. An update on risk factors for drug-induced arrhythmias [J]. *Expert Rev Clin Pharmacol.* 2016, 9 (1): 117–27.
16. Chorin E, Hochstadt A, Viskin S, et al. Female gender as independent risk factor of torsades de pointes during acquired atrioventricular block [J]. *Heart Rhythm.* 2017, 14 (1): 90–95.
17. Cleland JG, Swedberg K, Follath F, et al. The EuroHeart Failure survey programme—a survey on the quality of care among patients with heart failure in Europe Part 1: patient characteristics and diagnosis [J]. *European Heart Journal.* 2003, 24 (5): 442–63.
18. Fairweather D, Cooper LT, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy [J]. *Curr Probl Cardiol.* 2013, 38 (1): 7–46.
19. Yusuf IH, Sharma S, Luqmani R, et al. Hydroxychloroquine retinopathy [J]. *Eye (Lond).* 2017, 31 (6): 828–45.
20. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy [J]. *JAMA Ophthalmol.* 2014, 132 (12): 1453–60.
21. Kwon JB, Kleiner A, Ishida K, et al. Hydroxychloroquine-induced myopathy [J]. *J Clin Rheumatol.* 2010, 16 (1): 28–31.
22. Khoo T, Otto S, Smith C, et al. Curvilinear bodies are associated with adverse effects on muscle function but not with hydroxychloroquine dosing [J]. *Clin Rheumatol.* 2017, 36 (3): 689–93.
23. Siddiqui AK, Huberfeld SI, Weidenheim KM, et al. Hydroxychloroquine-Induced Toxic Myopathy Causing Respiratory Failure [J]. *Chest.* 2007, 131(2): 588–590.
24. Pistone G, Gurreri R, Alaimo R, et al. Gender differences in adverse drug reactions in dermatological patients in west Sicily: an epidemiological study [J]. *J Dermatolog Treat.* 2014, 25 (6): 510–2.
25. Rodenburg EM, StrickerL BH, Visser LE. Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands [J]. *Br J Clin Pharmacol.* 2011, 71 (1): 95–104.
26. Monteiro AF, Rato M, Martins C. Drug-induce photosensitivity: photoallergic and phototoxic reactions [J]. *Clin Dermatol.* 2016, 34 (5): 571–81.

27. Glatz M, Hofbauer GF. Phototoxic and Photoallergic Cutaneous Drug Reactions [J]. Chem Immunol Allergy. 2012, 97:167–79.
28. Sperati CJ, Rosenberg AZ. Hydroxychloroquine-induced mimic of renal Fabry disease [J]. Kidney Int. 2018, 94 (3): 634.
29. Mościcki EK. Gender differences in completed and attempted suicides [J]. Annals of Epidemiology 1994, 4 (2):152–8.
30. Sutti S, Tacke F. Liver inflammation and regeneration in drug-induced liver injury: sex matters! [J]. Clin Sci (Lond). 2018, 132 (5): 609–13.
31. Shapiro MA, Lewis JH. Causality assessment of drug-induced hepatotoxicity: promises and pitfalls [J]. Clin Liver Dis. 2007, 11 (3): 477–505, v.
32. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes- complementing spontaneous reporting systems [J]. Drug Saf. 2013, 36 (2): 75–81.
33. Raschi E, Moretti U, Salvo F, et al. Evolving Roles of Spontaneous Reporting Systems to Assess and Monitor Drug Safety [M]: Pharmacovigilance [Working Title]. 2018.
34. Palleria, C, Leporini, C, Chimirri, S, et al. (). Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two “challenging” case reports [J]. Pharmacol. Pharmacother. 2013, 4, S66- 72.
35. Cortes J, Mauro M, Steegmann JL, et al. Cardiovascular and pulmonary adverse events in patients treated with BCR-ABL inhibitors- data from the FDA adverse event reporting system [J]. Am J Hematol. 2015, 90 (4): E 66–72.

Figures

Figure 1

Age distribution. The real line stands for the total reports, whereas the dotted line and the long dashed line stand for female and male respectively.

Figure 2

Year distribution. The dotted line stands for the total reports, whereas the real line and the long dashed line stand for female and male respectively.