

Supplemental Material

Hydroxychloroquine Use and Risk of CKD in Patients with Rheumatoid Arthritis

Chia-Lin Wu,^{1,2,3,4,5} Chia-Chu Chang,^{1,2,3,5} Chew-Teng Kor,^{2,6} Tao-Hsiang Yang,^{2,3}

Ping-Fang Chiu,^{1,5} Der-Cherng Tarn,^{4,7,8} and Chih-Cheng Hsu^{9,10,11}

Author affiliations:

¹Division of Nephrology, Department of Internal Medicine, Changhua Christian Hospital,

Changhua, Taiwan; ²Internal Medicine Research Center, Department of Internal Medicine,

Changhua Christian Hospital, Changhua, Taiwan; ³Environmental and Precision Medicine

Laboratory, Department of Internal Medicine, Changhua Christian Hospital, Changhua,

Taiwan; ⁴Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan;

⁵Department of Medicine, School of Medicine, Chung-Shan Medical University, Taichung,

Taiwan; ⁶Graduate Institute of Statistics and Information Science, National Changhua

University of Education, Changhua, Taiwan; ⁷Department and Institute of Physiology,

National Yang-Ming University, Taipei, Taiwan; ⁸Division of Nephrology, Department of

Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; ⁹Institute of Population Health

Sciences, National Health Research Institutes, Zhunan, Taiwan; ¹⁰Department of Health

Services Administration, China Medical University, Taichung, Taiwan; and ¹¹Department of

Family Medicine, Min-Sheng General Hospital, Taoyuan, Taiwan

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Supplemental Table 1. ICD-9-CM and A codes used to identify rheumatoid arthritis, kidney outcomes, and comorbidities

Diseases	Corresponding ICD-9-CM codes	A codes
Rheumatoid arthritis	714.0	A430
Systemic lupus erythematosus	710.0	A431
Psoriasis	696.x	A429
Chronic kidney disease (lenient criterion)	016.00, 095.40, 189.00, 189.90, 223.00, 236.91, 250.40, 271.40, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.12, 404.92, 404.03, 404.13, 404.93, 440.10, 442.10, 447.30, 572.40, 580.00, 580.40, 580.80, 580.81, 580.89, 580.90, 581.00, 581.10, 581.20, 581.30, 581.80, 581.81, 581.89, 581.90, 582.00, 582.10, 582.20, 582.40, 582.80, 582.80, 582.89, 582.90, 583.00, 583.10, 583.20, 583.40, 583.60, 583.70, 583.80, 583.81, 583.89, 583.90, 584.00, 584.50, 584.60, 584.70, 584.80, 584.90, 585.00, 586.00, 587.00, 588.00, 588.10, 588.90, 591.00, 642.10, 642.20, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 794.40	A350
Chronic kidney disease (stringent criterion)	250.4, 274.1, 403, 404, 580, 581, 582, 583, 585, 586, 587	
Co-morbid diseases		
Hypertension	401.x–405.x	A269
Diabetes mellitus	250.x	A181
Hyperlipidemia	272.x	A189
Coronary artery disease	410.x–414.x	A279
Congestive heart failure	428.x	A289
Gout	274.x	A189
Stroke	430.x–438.x	A293
Chronic obstructive pulmonary disease	491.x, 492.x, 496.x	A325
Peripheral artery occlusive disease	443.x–444.x	A301
Arrhythmia	426.x-427.x, V45.0, V53.3	A281

ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification.

Supplemental Table 2. The propensity score model results of the probability of use of hydroxychloroquine

Parameter	Estimate	Odds Ratio	95% CI		<i>P</i> value
			Lower	Upper	
Age, per year	0.007	1.007	1.000	1.014	0.045
Male gender	0.079	1.082	0.890	1.315	0.43
Monthly Income, new Taiwan dollars	-0.034	0.966	0.916	1.019	0.21
Geographic location					
Northern Taiwan		1.000			
Central Taiwan	0.292	1.422	1.164	1.736	0.002
Southern Taiwan	-0.053	1.007	0.831	1.221	0.56
Eastern Taiwan and islands	-0.179	0.888	0.529	1.489	0.36
Clinic visit frequency, visits per year	0.005	1.005	0.999	1.011	0.11
Charlson's comorbidity index score	0.007	1.008	0.935	1.086	0.85
Hypertension	0.035	1.035	0.805	1.331	0.79
Hyperlipidemia	-0.072	0.931	0.722	1.200	0.58
Diabetes Mellitus	-0.577	0.562	0.340	0.929	0.03
Coronary artery disease	-0.141	0.868	0.617	1.222	0.42
Congestive heart failure	-0.514	0.598	0.322	1.112	0.10
Gout	-0.477	0.621	0.482	0.799	<0.001
Stroke	0.128	1.137	0.738	1.751	0.56
Chronic obstructive pulmonary disease	-0.284	0.753	0.565	1.002	0.05
Peripheral artery occlusive disease	0.310	1.363	0.608	3.058	0.45
Arrhythmia	-0.327	0.721	0.471	1.104	0.13
Anti-Diabetic drugs	0.583	1.792	1.003	3.202	0.049
Anti-hypertensive drugs	-0.024	0.977	0.745	1.281	0.87
Non-steroidal anti-inflammatory drugs	-0.187	0.830	0.636	1.082	0.17
Glucocorticoids	0.755	2.127	1.557	2.907	<0.001
Calcineurin Inhibitors	0.695	2.004	0.182	22.100	0.57
Tumor necrosis factor- α inhibitors	0.417	1.517	1.127	2.041	0.01
Other Immunosuppressants	0.075	1.077	0.650	1.787	0.77

CI, confidence interval.

Supplemental Table 3. Risk of incident chronic kidney disease in rheumatoid arthritis patients with exposure to hydroxychloroquine within 120 days and observation period beginning since 121st day after diagnosis of rheumatoid arthritis

	Events (n/N)	Incident rate ^a (95% CI)	cHR (95% CI)	<i>P</i> value	aHR ^{b,c} (95% CI)	<i>P</i> value
Cohorts						
Hydroxychloroquine non-users	114/1368	13.3 (10.8–15.7)	1.00	—	1.00	—
Hydroxychloroquine users	46/1230	9.9 (7.0–12.7)	0.68 (0.48–0.95)	0.03	0.65 (0.46–0.93)	0.02

aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval.

^aper 1000 person-years.

^bAdjusted for propensity scores.

^cAll-cause death was considered a competing risk.

Supplemental Table 4. Risk of incident chronic kidney disease in rheumatoid arthritis patients with exposure to hydroxychloroquine within 150 days and observation period beginning since 151st day after diagnosis of rheumatoid arthritis

	Events (n/N)	Incident rate ^a (95% CI)	cHR (95% CI)	<i>P</i> value	aHR ^{b,c} (95% CI)	<i>P</i> value
Cohorts						
Hydroxychloroquine non-users	109/1322	13.1 (10.6–15.6)	1.00	—	1.00	—
Hydroxychloroquine users	47/1258	10.0 (7.1–12.8)	0.70 (0.49–0.98)	0.04	0.68 (0.47–0.96)	0.03

aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval.

^aper 1000 person-years.

^bAdjusted for propensity scores.

^cAll-cause death was considered a competing risk.

Supplemental Table 5. Risk of incident chronic kidney disease in rheumatoid arthritis patients with exposure to hydroxychloroquine within 180 days and observation period beginning since 181st day after diagnosis of rheumatoid arthritis

	Events (n/N)	Incident rate ^a (95% CI)	cHR (95% CI)	<i>P</i> value	aHR ^{b,c} (95% CI)	<i>P</i> value
Cohorts						
Hydroxychloroquine non-users	107/1288	12.2 (9.9–14.5)	1.00	—	1.00	—
Hydroxychloroquine users	46/1271	8.6 (6.1–11.1)	0.68 (0.48–0.96)	0.03	0.66 (0.46–0.94)	0.02

aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval.

^aper 1000 person-years.

^bAdjusted for propensity scores.

^cAll-cause death was considered a competing risk.

Supplemental Table 6. Baseline characteristics of patients with rheumatoid arthritis before and after propensity score matching

Characteristics ^a	Before propensity score matching		After propensity score matching	
	Hydroxychloroquine non-users (n=1,407)	Hydroxychloroquine users (n=1,212)	Hydroxychloroquine non-users (n=593)	Hydroxychloroquine users (n=593)
Demographics				
Age, years	51 ± 14	52 ± 14	49 ± 11	49 ± 11
Male gender	342 (24%)	290 (24%)	77 (13%)	77 (13%)
Monthly income, new Taiwan dollars	18838 ± 15982	17689 ± 14610	17247 ± 12300	17920 ± 12355
Geographic location				
Northern Taiwan ^b	721 (51%)	554 (46%)	321 (54%)	304 (51%)
Central Taiwan ^b	277 (20%)	320 (26%)	104 (18%)	118 (20%)
Southern Taiwan	371 (26%)	311 (26%)	158 (27%)	157 (26%)
Eastern Taiwan and islands	38 (3%)	27 (2%)	10 (2%)	14 (2%)
Clinic visit frequency (visits per year) ^b	26 ± 16	27 ± 15	25 ± 14	25 ± 14
Comorbidities				
Charlson's comorbidity index score	1.2 ± 1.4	1.2 ± 1.4	0.9 ± 1.1	1.0 ± 1.3
Hypertension	305 (22%)	274 (23%)	109 (18%)	99 (17%)
Hyperlipidemia	183 (13%)	146 (12%)	66 (11%)	68 (11%)
Diabetes Mellitus	106 (8%)	81 (7%)	30 (5%)	29 (5%)
Coronary artery disease	107 (8%)	84 (7%)	33 (6%)	25 (4%)
Congestive heart failure	33 (2%)	20 (2%)	5 (0.8%)	3 (0.5%)
Gout ^b	214 (15%)	131 (11%)	48 (8%)	43 (7%)

Stroke	51 (4%)	53 (4%)	15 (3%)	20 (3%)
Chronic obstructive pulmonary disease	146 (10%)	111 (9%)	37 (6%)	42 (7%)
Peripheral artery occlusive disease	11 (0.8%)	15 (1%)	3 (0.5%)	2 (0.3%)
Arrhythmia	65 (5%)	41 (3%)	18 (3%)	14 (2%)
Long-term medications				
Anti-diabetic drugs	63 (4%)	64 (5%)	26 (4%)	22 (4%)
Anti-hypertensive drugs	244 (17%)	220 (18%)	76 (13%)	79 (13%)
Angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers	103 (7%)	94 (8%)	29 (5%)	30 (5%)
Diuretics	71 (5%)	65 (5%)	20 (3%)	21 (4%)
Non-steroidal anti-inflammatory drugs	160 (11%)	138 (11%)	44 (7%)	46 (8%)
Analgesic drugs other than non-steroidal anti-inflammatory drugs ^{c,d}	133 (9%)	137 (11%)	35 (6%)	56 (9%)
Glucocorticoids ^b	89 (6%)	149 (12%)	22 (4%)	13 (2%)
Calcineurin Inhibitors ^c	1 (0.1%)	3 (0.3%)	1 (0.2%)	0 (0%)
Tumor necrosis factor- α inhibitors ^b	86 (6%)	116 (10%)	34 (6%)	37 (6%)
Other immunosuppressants ^f	72 (5%)	66 (5%)	25 (4%)	19 (3%)
Cumulative dose of hydroxychloroquine within 90 days (g)	—	43.2 \pm 24.8	—	41.9 \pm 24.8
Propensity score ^b	0.45 \pm 0.09	0.48 \pm 0.1	0.55 \pm 0.06	0.55 \pm 0.06

SD, standard deviation.

^aVariables are expressed as Mean \pm SD or n (%).

^bStatistically significant between hydroxychloroquine user and hydroxychloroquine non-user cohorts before propensity score matching.

^cStatistically significant between hydroxychloroquine user and hydroxychloroquine non-user cohorts after propensity score matching.

^dInclude aspirin, cyclooxygenase-2 inhibitors and acetaminophen.

^eInclude ciclosporin and tacrolimus.

^fInclude methotrexate, azathioprine, sulfasalazine, and leflunomide.

Supplemental Table 7. Risk of incident chronic kidney disease in patients with rheumatoid arthritis after propensity score matching

	Events (n/N)	Incident rate ^a (95% CI)	cHR (95% CI)	<i>P</i> value	aHR ^{b,c} (95% CI)	<i>P</i> value
Cohorts						
Hydroxychloroquine non-users	41/593	10.2 (7.1–13.3)	1.00	—	1.00	—
Hydroxychloroquine users	15/593	6.0 (3.0–9.1)	0.55 (0.30–0.99)	0.045	0.54 (0.30–0.98)	0.04

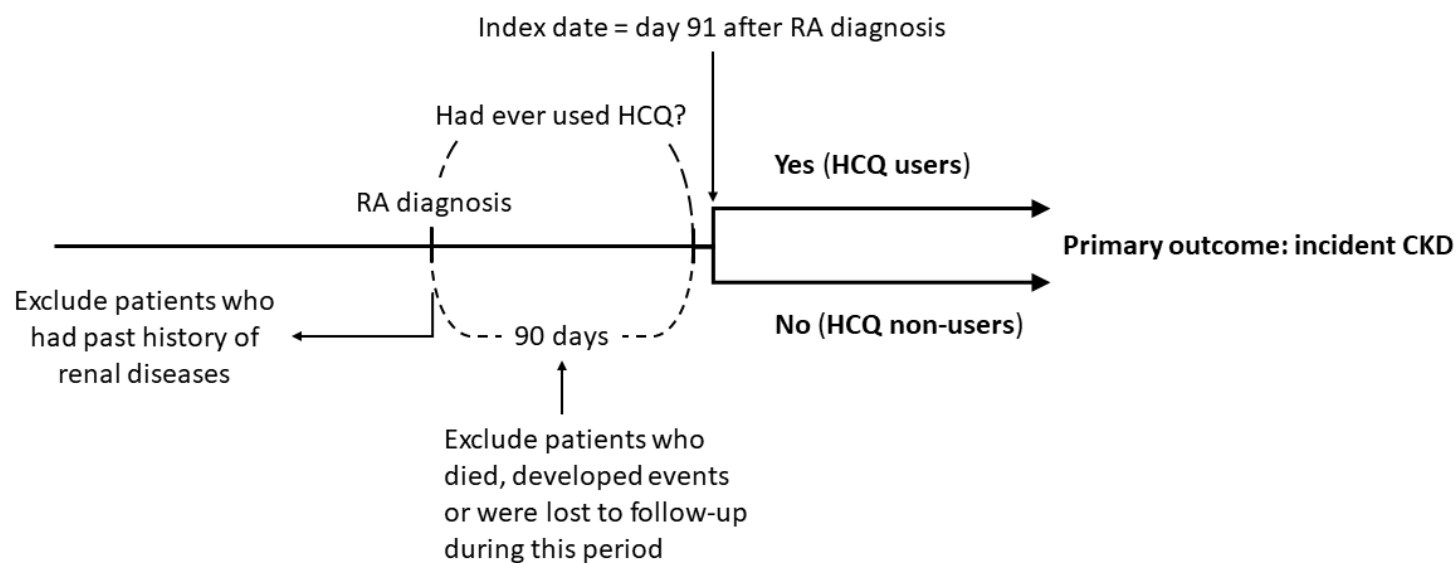
aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval.

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Supplemental Figure 1. Schematic diagram of study design. CKD, chronic kidney disease; HCQ, hydroxychloroquine; RA, rheumatoid arthritis.



Supplemental Figure 2. Association between duration of hydroxychloroquine (HCQ) exposure and risk of subsequent chronic kidney disease (CKD).

