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BRIEF COMMUNICATION

Hydroxychloroquine and maintenance immunosuppression use in kidney transplant recipients: Analysis of linked US registry and claims data

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Abstract

Hydroxychloroquine (HCQ) is an antimalarial drug with immunomodulatory effects used to treat systemic lupus erythematosus (SLE) and scleroderma. The antiviral effects of HCQ have raised attention in the context of the COVID-19 pandemic, although safety is controversial. We examined linkages of national transplant registry data with pharmaceutical claims and Medicare billing claims to study HCQ use among Medicare-insured kidney transplant recipients with SLE or scleroderma (2008–2017; N = 1820). We compared three groups based on immunosuppression regimen 7 months-to-1 year post transplant: (a) tacrolimus (Tac) + mycophenolic acid (MPA) + prednisone (Pred) (referent group, 77.7%); (b) Tac + MPA + Pred + HCQ (16.5%); or (c) other immunosuppression + HCQ (5.7%). Compared to the referent group, recipients treated with other immunosuppression + HCQ had a 2-fold increased risk of abnormal ECG or QT prolongation (18.9% vs. 10.7%; aHR, $_{1.12}1.96_{3.42}$, p = .02) and ventricular arrhythmias (15.2% vs. 11.4%; aHR, $_{1.00}1.81_{3.29}$, p = .05) in the >1-to-3 years post-transplant. Tac + MPA + Pred + HCQ was associated with increased risk of ventricular arrhythmias (13.5% vs. 11.4%; aHR, $_{1.02}1.54_{2.31}$, p = .04) and pancytopenia (35.9% vs. 31.4%; aHR, $_{1.03}1.31_{1.68}$, p = .03) compared to triple immunosuppression without HCQ. However, HCQ-containing regimens were not associated with an increased risk of death or graft failure. HCQ may be used safely in selected kidney transplant recipients in addition to their maintenance immunosuppression, although attention to arrhythmias is warranted.

KEYWORDS
hydroxychloroquine, immunosuppression, kidney transplantation, outcomes, pharmacy claims, registries, scleroderma, systemic lupus erythematosus

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TABLE 1 HCQ and immunosuppression use 7 months-to-1 year post transplant, according to baseline traits, among Medicare-insured kidney transplant recipients with kidney failure due to SLE or scleroderma (N = 1820)[a]

	Tac + MPA + Pred (n = 1415)	Tac + MPA + Pred + HCQ (n = 301)	Other[b] + HCQ (n = 104)	
Baseline characteristics	**n (%)**	**n (%)**	**n (%)**	***p*-value**
Induction				
Yes	1253 (78.0)	266 (16.6)	87 (5.4)	.33
No	162 (75.7)	35 (16.4)	17 (7.9)	Reference
Age, years				
18 to 30	322 (73.9)	89 (20.4)	25 (5.7)	.31
31 to 44	529 (76.2)	118 (17.0)	47 (6.8)	Reference
45 to 59	432 (81.8)	73 (13.8)	23 (4.4)	.05
≥60	132 (81.5)	21 (13.0)	9 (5.6)	.35
Sex				
Male	289 (87.6)	27 (8.2)	14 (4.2)	Reference
Female	1126 (75.6)	274 (18.4)	90 (6.0)	<.0001
Race				
White	368 (83.6)	53 (12.1)	19 (4.3)	Reference
African-American	656 (77.0)	148 (17.4)	48 (5.6)	.02
Hispanic	281 (73.8)	70 (18.4)	30 (7.9)	.002
Other[c]	110 (74.8)	30 (20.4)	7 (4.8)	.04
Body mass index, kg/m^2				
<18.5	82 (80.4)	16 (15.7)	4 (3.9)	.76
18.5 to <25	640 (78.1)	133 (16.2)	46 (5.6)	Reference
25 to <30	400 (76.6)	87 (16.7)	35 (6.7)	.69
≥30	271 (77.0)	62 (17.6)	19 (5.4)	.84
Duration of dialysis, months				
None (pre-emptive)	78 (78.8)	18 (18.2)	3 (3.0)	.38
>0 to 24	253 (76.9)	54 (16.4)	22 (6.7)	Reference
25 to 60	514 (76.2)	122 (18.1)	39 (5.8)	.72
>60	564 (79.6)	106 (15.0)	39 (5.5)	.59
Pretransplant PRA level, %				
<10	730 (75.9)	169 (17.6)	63 (6.6)	Reference
10 to 79	441 (79.9)	80 (14.5)	31 (5.6)	.20
≥80	242 (79.6)	52 (17.1)	10 (3.3)	.10
Previous transplant				
Yes	285 (85.3)	38 (11.4)	11 (3.3)	.001
No	1130 (76.0)	263 (17.7)	93 (6.3)	Reference
Donor type				
Living donor	367 (77.6)	71 (15.0)	35 (7.4)	.04
Deceased, KPDI < 20	271 (77.0)	59 (16.8)	22 (6.3)	.38
Deceased, KDPI 20 to 85	731 (78.1)	164 (17.5)	41 (4.4)	Reference
Deceased, KDPI > 85	46 (78.0)	7 (11.9)	6 (10.2)	.08
Transplant year				
2006 to 2011	757 (82.0)	120 (13.0)	46 (5.0)	Reference
2012 to 2016	658 (73.4)	181 (20.2)	58 (6.5)	<.0001

Abbreviations: HCQ, hydroxychloroquine; KDPI, kidney donor profile index; MPA, mycophenolic acid; PRA, panel reactive antibody; Pred, prednisone; SLE, systemic lupus erythematosus; Tac, tacrolimus.

[a]Data are presented as row percentages.

[b]Other maintenance immunosuppression included cyclosporine, azathioprine, and mammalian target of rapamycin inhibitors.

[c]Other race includes Asian, Native American, Pacific Islander, and multi-racial.

1 | INTRODUCTION

Hydroxychloroquine (HCQ) is an antimalarial drug with immunomodulatory effects that traditionally has been used to treat patients with systemic lupus erythematosus (SLE) and scleroderma. Previous studies have shown that HCQ is associated with increased survival,[1,2] decreased frequency of lupus flares[3,4] and damage accrual,[5] and lower risk of kidney failure if used prior to the onset of lupus nephritis.[4] For patients with scleroderma, HCQ appears to have beneficial effects on joint involvement.[6,7] As such, HCQ is considered an effective agent for management of SLE and scleroderma.

The potential antiviral and immunomodulatory properties of HCQ (a derivative of chloroquine) received global attention as a potential prophylaxis and/or treatment against the coronavirus disease 2019 (COVID-19).[8] However, a multinational registry analysis of 96 032 patients with COVID-19 reported that HCQ and/or chloroquine treatment resulted in an increased risk of in-hospital mortality and ventricular arrhythmias. Subsequently, this article was retracted from Lancet due to concerns about the validity of the data source and outcomes,[9] leading to ongoing uncertainty about the safety and tolerability of this medication.

Even less is known about HCQ use in the kidney transplant population,[10] particularly related to safety and potential drug interactions with maintenance immunosuppression. Transplant patients typically receive a combination of antirejection drugs, including tacrolimus (Tac), mycophenolic acid (MPA, which includes mycophenolate mofetil and mycophenolate sodium), and prednisone (Pred).[11–13] Recipients with SLE or scleroderma who have well-controlled symptoms while using HCQ may continue this agent post transplant in addition to their maintenance immunosuppression therapy. We conducted this retrospective study to better understand the safety and outcomes of immunosuppression and HCQ use in a national cohort of kidney transplant recipients with SLE and scleroderma. We examined a novel linkage of national transplant registry data with medication fill records from a large pharmaceutical claims clearinghouse to determine correlates of post transplant immunosuppression and HCQ use and associations with clinical complications, including patient and graft survival.

2 | METHODS

2.1 | Data sources, population, and exposure definitions

We conducted a retrospective cohort study using linked healthcare databases in the United States to study kidney-only transplant recipients with SLE or scleroderma (2008–2017). This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR system includes data on all donors, waitlist candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

A large US pharmaceutical claims data (PCD) warehouse from Symphony Health was used to obtain prescription drug fill records for the exposure medications, including immunosuppression and HCQ. The PCD comprises National Council for Prescription Drug Program (NCPDP) 5.1-format prescription claims aggregated from multiple sources including data clearinghouses, retail pharmacies, and prescription benefit managers for approximately 60% of US retail pharmacy transactions. After Institutional Review Board approvals, PCD records were linked with SRTR records for kidney recipients, as previously described.[14–16] HCQ and immunosuppression use were ascertained 7 months-to-1 year post transplant, a period chosen to reflect "early" medication use, but after the initial postoperative period of regimen adjustments. Medication regimens were categorized into three groups: (a) Tac + MPA + Pred (no HCQ: referent group); (b) Tac + MPA + Pred + HCQ; (c) other immunosuppression + HCQ. Other maintenance immunosuppression included cyclosporine, azathioprine, and mammalian target of rapamycin inhibitors. Recipient, donor, and transplant characteristics were defined by the OPTN Transplant Candidate Registration and Transplant Recipient Registration forms (Table 1).

2.2 | Outcomes ascertainment

Clinical complications were assessed using Medicare billing claims, which include diagnostic and procedure codes for patients with Medicare insurance using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM; through September 2015) and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10; starting October 2015) diagnosis codes on billing claims (Table S1).[17–19] Clinical complications including abnormal electrocardiogram (ECG), post transplant QT prolongation, ventricular arrhythmia, acute myocardial infarction, stroke/transient ischemic attack (TIA), pancytopenia, cytomegalovirus infection, BK virus infection, retinopathy, and myopathy were ascertained. Death was defined by transplant center reports to the registry and supplemented with the Social Security Death Master File. Graft failure was defined as the return to maintenance dialysis or re-transplant, as defined in SRTR registry records. All-cause graft failure included graft loss due to death.

2.3 | Statistical analyses

Distributions of medication regimen use (7 months-to-1 year post-transplant) according to baseline demographic and clinical traits were compared by the chi-square test. Outcomes were examined from >1-to-3 years post transplant, following the period of medication exposure classification and ending because Medicare medical care coverage expires at the third transplant anniversary in the absence of age > 65 years or disability, as per previous methods.[17]

At-risk time for all models was censored at the end of the assessment period, end of Medicare enrollment, or end of study (May 22, 2018).

Incidence of each post transplant event >1-to-3 years post transplant was estimated by the Kaplan–Meier method, with use of the log-rank test to assess the statistical significance of unadjusted differences. Propensity scores for the likelihood of HCQ use were estimated by logistic regression. Adjusted associations of medication regimen and clinical complications were quantified by multivariate Cox regression (adjusted hazard ratio with 95% upper and lower confidence limits, $_{LCL}aHR_{UCL}$), including adjustment for recipient, donor, and transplant characteristics listed in Table 1, and propensity for HCQ use. Impact of daily HCQ dosing of 200 vs. 400 mg was compared in secondary analysis. We also examined associations of the regimens of interest in the larger sample of kidney transplant recipients without restriction by cause of kidney failure as additional secondary analysis. Data management and analyses were performed with SAS for Windows software, version 9.4 (SAS Institute Inc).

3 | RESULTS

The sample included 1820 kidney-only transplant recipients with kidney failure due to SLE (97.6%) or scleroderma (2.4%) (Table 1). In the cohort, 77.7% received triple maintenance immunosuppression with Tac + MPA + Pred (referent group), 16.5% received triple immunosuppression and HCQ, and 5.7% received other immunosuppression and HCQ. Compared with the referent group, HCQ-containing regimens were more common in women, non-White recipients,

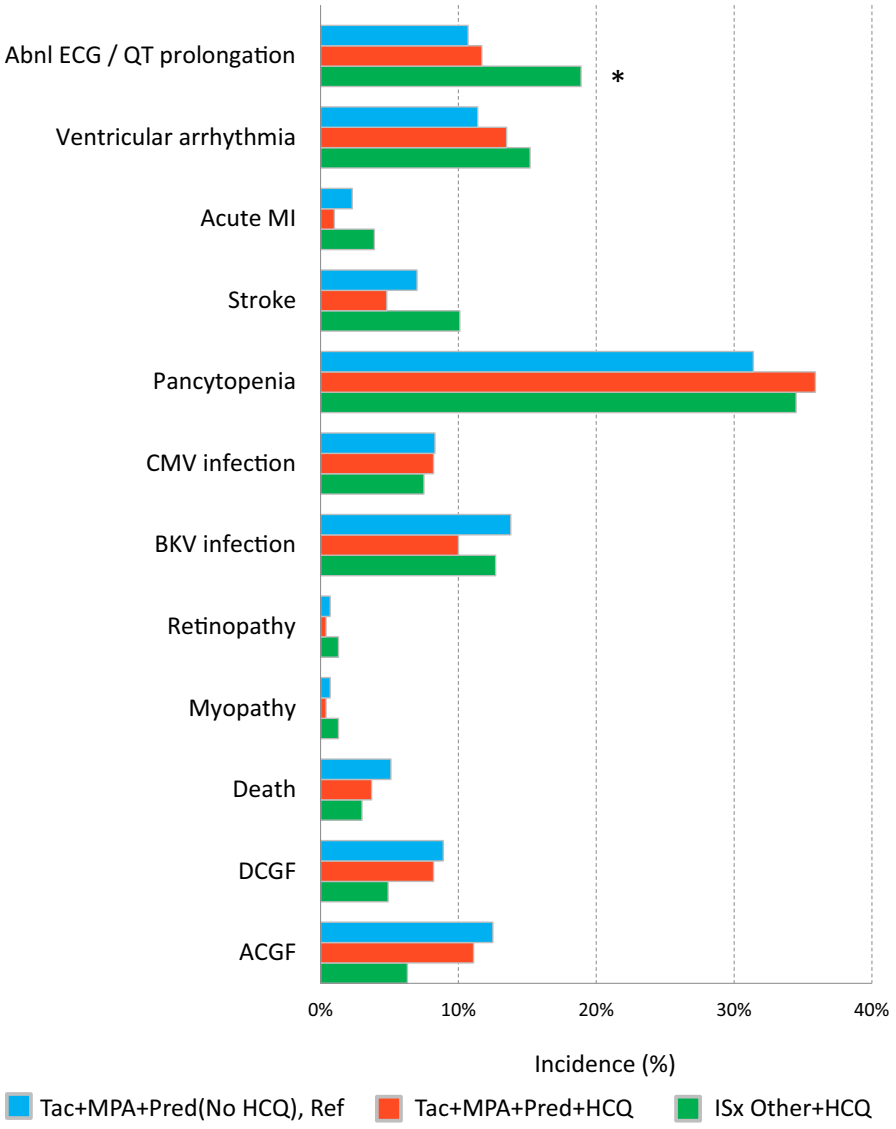

FIGURE 1 Incidence of clinical complications >1-to-3 years post transplant according to HCQ and immunosuppression regimen. Medication regimen defined 7 months-to-1 year post transplant. Abnl, abnormal; ACGF, all-cause graft failure; BKV, BK virus; CMV, cytomegalovirus; DCGF, death-censored graft failure; ECG, electrocardiogram; HCQ, hydroxychloroquine; ISx, immunosuppression; MI, myocardial infarction; MPA, mycophenolic acid; Pred, prednisone; Ref, referent; Tac, tacrolimus

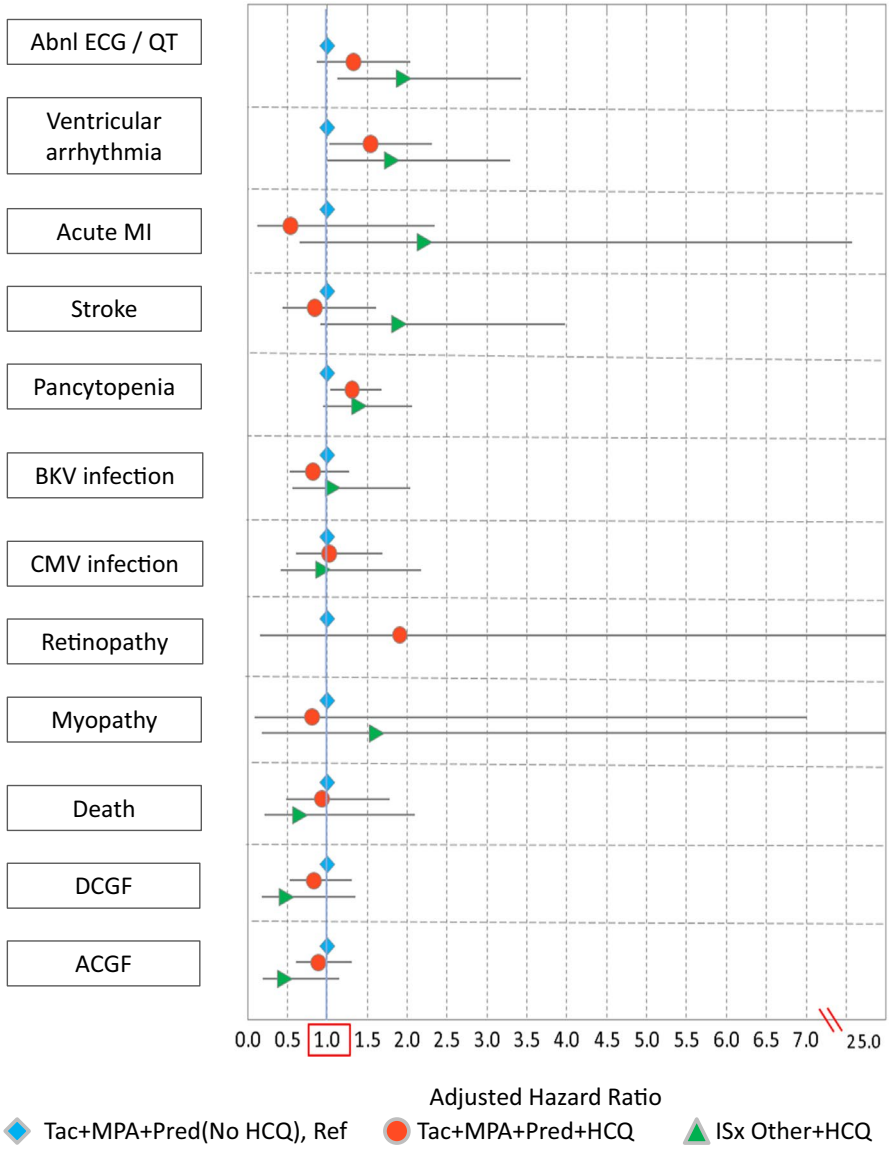

FIGURE 2 Adjusted association of HCQ and immunosuppression regimen with clinical complications >1-to-3 years post transplant. Medication regimen defined 7 months-to-1 year post transplant. Abnl, abnormal; ACGF, all-cause graft failure; BKV, BK virus; CMV, cytomegalovirus; DCGF, death-censored graft failure; ECG, electrocardiogram; HCQ, hydroxychloroquine; ISx, immunosuppression; MI, myocardial infarction; MPA, mycophenolic acid; Pred, prednisone; Ref, referent; Tac, tacrolimus

first-time recipients, and recipients who underwent transplant in the more recent era (2012–2016 vs. 2006–2011). Adjusted associations were similar in the propensity models (Table S2).

Compared with standard triple immunosuppression, the addition of HCQ did not result in a significant difference in the incidence or adjusted risk of an abnormal ECG or QT prolongation in the >1-to-3 years post transplant; however, the incidence (18.9% vs. 10.7%) (Figure 1) and risk (aHR, $_{1.12}1.96_{3.42}$) was higher in patients who received other immunosuppression and HCQ (Figure 2). After adjustment, transplant recipients treated with HCQ-containing regimens were at higher risk of ventricular arrhythmias in the >1-to-3 years post transplant (Tac + MPA + Pred + HCQ: 13.5% vs. 11.4%; aHR, $_{1.02}1.54_{2.31}$, p = .04; other immunosuppression + HCQ: 15.2% vs. 11.4%; aHR, $_{1.00}1.81_{3.29}$, p = .05). The risk of pancytopenia was higher in patients managed with Tac + MPA + Pred + HCQ compared to the referent group (35.9% vs. 31.4%; aHR, $_{1.03}1.31_{1.68}$, p = .03). We found no significant differences in the risk of the other clinical complications, including cytomegalovirus or BK virus infections, according to HCQ treatment. There was no difference among the three medication regimens with respect to death or graft failure (death-censored or all-cause) over >1-to-3 years post transplant. In secondary analysis, we did not observe any significant differences in outcomes based on HCQ daily dosing of 200 vs. 400 mg.

In secondary analysis among 38 549 kidney transplant recipients with linked pharmacy and Medicare data, without restricting cause of kidney failure to lupus or scleroderma, the proportion of the sample treated with Tac + MPA + Pred + HCQ (0.9%) and other

immunosuppression + HCQ (0.3%) was smaller. However, significant associations of HCQ-containing regimens with higher risk of abnormal ECG or QT prolongation, ventricular arrhythmias, and pancytopenia were observed, with patterns similar to the primary analyses (Figure S1).

4 | DISCUSSION

In this large national study of kidney transplant recipients with SLE and scleroderma, we found that the addition of HCQ to maintenance immunosuppression was associated with a 56% to 2-fold increased risk of ventricular arrhythmias in the >1-to-3 years post transplant. Compared with triple maintenance immunosuppression, the addition of HCQ was associated with a 32% increased risk of pancytopenia, and HCQ with other immunosuppression was associated with a 2-fold increased risk of an abnormal ECG or QT prolongation. However, HCQ-containing regimens were not associated with an increased risk of death or graft failure.

In the non-transplant population, HCQ appears to have protective effects on renal damage in patients with lupus nephritis.[20] The renal protective benefits of HCQ are related to its immunomodulatory and anti-inflammatory effects, including blocking toll-like receptor activation and decreasing auto-antibody formation.[21–24] In addition, one study found that the anti-inflammatory effects of HCQ attenuated renal ischemia/reperfusion injury in mice, which suggests possible additional benefits of continuing HCQ in the early posttransplant period.[25] To date, there is little guidance on use of HCQ in kidney transplant recipients with kidney failure due to SLE or scleroderma. Our study suggests that HCQ use with immunosuppression does not negatively affect patient death or graft survival in the short term.

HCQ-related retinopathy is well-described in the literature and can result in vision-threatening disease. Recently, cardiotoxicity associated with HCQ use has gained international attention given its increased use and safety concerns in the context of the COVID-19 pandemic.[9] In our study, conducted prior to the pandemic, we found an increased risk of ventricular arrhythmias associated with HCQ-containing regimens. Cardiotoxicity with HCQ use includes cardiomyopathies and conduction abnormalities resulting in ventricular arrhythmias.[26] Intracellular deposits on endomyocardial biopsy can help distinguish HCQ-related cardiomyopathy from other infiltrative or restrictive causes.[27] Long-term HCQ use can also result in QRS and QT prolongation similar to quinidine-like effect.[27] Kidney transplant recipients may be at particular risk due to the potential additive effects of immunosuppression on QT prolongation.[28] Discontinuation of HCQ can lead to cardiac recovery, but some studies have described patients who require a heart transplant or die from cardiotoxicity, suggesting irreversible damage.[26] While it is recommended that patients using HCQ receive regular eye examinations to prevent vision-threatening retinopathy, there are no guidelines for cardiotoxicity screening[26,27]; however, annual ECG and echocardiography have been proposed.[26,27]

Our study has a number of strengths, including the linkage of US transplant registry data with pharmaceutical prescription fills and Medicare claims data. This allowed us to study a large national sample of kidney transplant recipients with SLE and scleroderma to identify exposure to HCQ in addition to immunosuppression, and to assess associations with clinical outcomes. There are also limitations. First, our observations of the clinical outcomes associated with HCQ use among Medicare beneficiaries with SLE or scleroderma may not generalize to patients with other insurance coverage, or to those who receive HCQ for other indications including COVID-19, or to treatment at other time periods after transplant. HCQ use in our cohort varied based on certain socio-demographics and transplant-related characteristics; however, our outcome analyses adjusted for many of these factors. The significant risk relationships were also present in secondary analysis without restriction by cause of kidney failure. We relied on diagnostic billing codes to capture clinical outcomes, such as abnormal ECG, which have not been validated in the kidney transplant population. Lastly, given the retrospective nature of the study design, we can only describe associations, not causation. We cannot infer that screening for cardiotoxicity in recipients on HCQ will result in improved outcomes.

In summary, we report that in a cohort of 1820 kidney transplant recipients with SLE and scleroderma, HCQ use did not impact risk of death or graft failure, but was associated with increased risk of ECG abnormalities, ventricular arrhythmias, and pancytopenia. Further research is needed to characterize HCQ safety in the transplant population and to mitigate potential risks associated with concurrent immunosuppression.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

KLL and MAS participated in study design, acquisition of data and regulatory approvals, interpretation and writing of the paper. NNL and YC participated in study design, interpretation, and writing of the paper. HX participated in data analysis and manuscript preparation. TA, SHC, DA, DLS, MMD, BLK, GPH and DCB participated in study design, interpretation, and manuscript review/critical editing as part of our pharmacoepidemiologic consortium.

DATA AVAILABILITY STATEMENT

This study was approved by the Saint Louis University Institutional Review Board. Individual participant deidentified data will not be shared by the authors due to restrictions of Data Use Agreements. SRTR registry data can be obtained from the SRTR.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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