Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Seminars in Arthritis and Rheumatism 52 (2022) 151946

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Antimalarials exert a cardioprotective effect in lupus patients: Insights from the Spanish Society of Rheumatology Lupus Register (RELESSER) analysis of factors associated with heart failure

Iñigo Rúa-Figueroa[a,*], David Rúa-Figueroa[b], Natalia Pérez-Veiga[c], Ana M. Anzola[d], María Galindo-Izquierdo[e], Jaime Calvo-Alén[f], Antonio Fernández-Nebro[g], Clara Sangüesa[h], Raúl Menor-Almagro[i], Eva Tomero[j], Natividad del Val[k], Esther Uriarte-Isazelaya[l], Ricardo Blanco[m], José L. Andreu[n], Alina Boteanu[o], Javier Narváez[p], Tatiana Cobo[q], Cristina Bohórquez[r], Carlos Montilla[s], Esteban Salas[t], Francisco J. Toyos[u], José A. Bernal[v], Eva Salgado[w], Mercedes Freire[x], Antonio J. Mas[y], Lorena Expósito[z], José A. Hernández-Beriain[aa], Oihane Ibarguengoitia[bb], María L. Velloso-Feijoo[cc], Nuria Lozano-Rivas[dd], Gemma Bonilla[ee], Mireia Moreno[ff], Inmaculada Jiménez[gg], Víctor Quevedo-Vila[hh], Angela Pecondón[ii], Elena Aurrecoechea[jj], Elia Valls[kk], Coral Mouriño[ll], Tomás Vázquez-Rodríguez[mm], José M. Pego-Reigosa[nn]

[a] *Hospital Universitario de Gran Canaria Dr Negrin, Las Palmas GC, Spain*
[b] *Hospital Universitario de Gran Canaria Doctor Negrin, Las Palmas GC, Spain*
[c] *Galicia Sur Health Research Institute, Vigo, Spain*
[d] *Hospital General Universitario Gregorio Marañón, Madrid, Spain*
[e] *Instituto de Investigación Hospital 12 de Octubre, Madrid, Spain*
[f] *Hospital Universitario Araba, País Vasco, Spain*
[g] *Hospital Universitario de Málaga, Málaga, Spain*
[h] *Hospital Germán Trias i Pujol, Barcelona, Spain*
[i] *Hospital Jerez de la Frontera, Cádiz, Spain*
[j] *Hospital de la Princesa, Madrid, Spain*
[k] *Hospital de Navarra, Pamplona, Spain*
[l] *Hospital de Donostia, San Sebastián, Spain*
[m] *Hospital Universitario Marqués de Valdecilla, Santander, Spain*
[n] *Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain*
[o] *Hospital Ramón y Cajal, Madrid, Spain*
[p] *Hospital Universitari de Bellvitge, Barcelona, Spain*
[q] *Hospital Infanta Sofía, Madrid, Spain*
[r] *Hospital Universitario Príncipe de Asturias (Alcalá de Henares), Madrid, Spain*
[s] *Hospital Clínico de Salamanca, Salamanca, Spain*
[t] *Hospital Marina Baixa, Villajoyosa, Alicante, Spain*
[u] *Hospital Universitario Virgen Macarena, Sevilla, Spain*
[v] *Hospital General Universitario de Alicante, Alicante, Spain*
[w] *Complejo Hospitalario De Orense, Orense, Spain*
[x] *Hospital Juan Canalejo de la Coruña, A Coruña, Spain*
[y] *Hospital Son Llàtzer, Palma de Mallorca, Spain*
[z] *Hospital Universitario de Canarias, La Laguna (Tenerife), Spain*
[aa] *Hospital Universitario Insular de Gran Canaria, Gran Canaria, Spain*
[bb] *Hospital de Basurto, Bilbao, Spain*
[cc] *Hospital Virgen de Valme, Sevilla, Spain*
[dd] *Hospital Virgen de la Arrixaca, Murcia, Spain*
[ee] *Hospital Universitario La Paz, Madrid, Spain*
[ff] *Hospital de Sabadell, Barcelona, Spain*

[*] Corresponding author. Rheumatology Service, Hospital Universitario de Gran Canaria Doctor Negrin, 35020, Las Palmas GC, Spain.
E-mail addresses: iruafer@gobiernodecanarias.org (I. Rúa-Figueroa), david_ruilla@yahoo.es (D. Rúa-Figueroa), mgalindo@h12o.es (M. Galindo-Izquierdo), jaime.calvoalen@osakidetza.eus (J. Calvo-Alén), tomeroeva@yahoo.es (E. Tomero), esther.uriarteisacelaya@osakidetza.net (E. Uriarte-Isazelaya), rblanco@humv.es (R. Blanco), fjnarvaez@bellvitgehospital.cat (J. Narváez), mtcoboiba@yahoo.es (T. Cobo), crisbohorquez@yahoo.es (C. Bohórquez), estebansalas@msn.com (E. Salas), eva.salgado.perez@sergas.es (E. Salgado), mercedes.freire.gonzalez@sergas.es (M. Freire), antonio.juan@hsll.es (A.J. Mas), hernandezberiain@yahoo.es (J.A. Hernández-Beriain), gemabonilla@ser.es (G. Bonilla), elena.aurrecoechea@scsalud.es (E. Aurrecoechea), coral.mourino@iisgaliciasur.es (C. Mouriño), tomas.ramon.vazquez.rodriguez@sergas.es (T. Vázquez-Rodríguez), jose.maria.pego.reigosa@sergas.es (J.M. Pego-Reigosa).

https://doi.org/10.1016/j.semarthrit.2021.11.012

[gg] Hospital Universitario San Cecilio, Granada, Spain
[hh] Hospital Comarcal de Monforte, Lugo, Spain
[ii] Hospital Universitario Miguel Servet, Zaragoza, Spain
[jj] Hospital Sierrallana, Torrelavega, Spain
[kk] Hospital Universitario Doctor Peset, Valencia, Spain
[ll] Galicia Sur Health Research Institute, Vigo, Spain
[mm] Hospital Lucus Augusti, Lugo, Spain
[nn] Complexo Hospitalario Universitario de Vigo, Spain

ARTICLE INFO

Keywords:
Systemic lupus erythematosus
Chronic heart failure
Antimalarials

ABSTRACT

Background/objectives: Factors associated with chronic heart failure (CHF) in patients with systemic lupus erythematosus (SLE) have received little attention. Recent data on the use of hydroxychloroquine in the treatment of SARS-CoV-2 infection have cast doubt on its cardiac safety. The factors associated with CHF, including therapy with antimalarials, were analyzed in a large multicenter SLE cohort.
Methods: Cross-sectional study including all patients with SLE (ACR-1997 criteria) included in the Spanish Society of Rheumatology Lupus Register (RELESSER), based on historically gathered data. Patients with CHF prior to diagnosis of SLE were excluded. A multivariable analysis exploring factors associated with CHF was conducted.
Results: The study population comprised 117 patients with SLE (ACR-97 criteria) and CHF and 3,506 SLE controls. Ninety percent were women. Patients with CHF were older and presented greater SLE severity, organ damage, and mortality than those without CHF. The multivariable model revealed the factors associated with CHF to be ischemic heart disease (7.96 [4.01−15.48], $p < 0.0001$), cardiac arrhythmia (7.38 [4.00−13.42], $p < 0.0001$), pulmonary hypertension (3.71 [1.84−7.25], $p < 0.0002$), valvulopathy (6.33 [3.41−11.62], $p < 0.0001$), non-cardiovascular damage (1.29 [1.16−1.44], $p < 0.000$) and calcium/vitamin D treatment (5.29 [2.07−16.86], $p = 0.0015$). Female sex (0.46 [0.25−0.88], $p = 0.0147$) and antimalarials (0.28 [0.17−0.45], $p < 0.000$) proved to be protective factors.
Conclusions: Patients with SLE and CHF experience more severe SLE. Treatment with antimalarials appears to confer a cardioprotective effect.

Introduction

Cardiovascular disease (CVD) is a main cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE) [1,2]. The 2020 meta-analysis by Yazdany et al. [3] showed SLE to be associated with an increased risk of myocardial infarction (pooled relative risk, 2.99 [95% CI 2.34−3.82]). However, the prevalence and factors associated with congestive heart failure (CHF) in SLE patients have not been studied in sufficient depth [4,5].

Antimalarials are associated with a reduced risk of CVD in the vast majority of published observational studies [6−8]. However, data collected during the COVID-19 pandemic, including those reported in a randomized controlled trial (REMAP-CAP), suggest that hydroxychloroquine might carry a risk of cardiotoxicity, at least when used for treating SARS-CoV-2 infection [9−11]. Other studies, such as the RECOVERY trial, did not confirm cardiotoxicity in the setting of COVID-19 [12]. Reported cases of cardiotoxicity induced by antimalarials have consisted mainly of arrhythmias related to QTc interval prolongation, particularly when combined with other drugs and administered at higher doses than usual. However, concerns still remain regarding the cardiac safety of antimalarials prescribed for the usual indications. Additionally, several studies demonstrated that chronic exposure to antimalarials can induce, albeit rarely, so-called antimalarial-induced cardiomyopathy [13].

Due to the current lack of safety data from randomized controlled trials investigating long-term treatment with antimalarials for rheumatic diseases, large observational studies can serve as a crucial means of confirming the absence of cardiac events associated with hydroxychloroquine and other antimalarial drugs. Using the data recorded in a large multicenter SLE cohort drawn from the RELESSER register, we carried out an analysis not only to identify factors associated with CHF in patients with SLE, but also to gain insight into the cardiac safety of long-term therapy with hydroxychloroquine in this population.

Methods

All patients registered in the retrospective phase of the RELESSER register (RELESSER-TRANS) who met at least 4 of the 1997 criteria of the American College of Rheumatology (ACR) were considered for this study. The methodology, including definitions of variables and the main characteristics of the register, has been described elsewhere [14]. Patients with or without CHF were compared in terms of cumulative clinical characteristics, treatment at any time, severity of SLE (as estimated using the Katz index) [15], organ damage (modified Systemic Lupus International Collaborating Clinics [SLICC]/ACR Damage Index, i.e., excluding cardiovascular components [mSDI]), classic cardiovascular risk factors, and comorbidity (Charlson index). In contrast, activity was measured only at the last visit (SELENA-Systemic Lupus Erythematosus Disease Activity Index [SLEDAI]).

CHF was defined according to standard clinical and imaging criteria, as recorded in the clinical charts.

Dichotomous variables were compared using the Fisher exact test; numerical variables were compared using the Mann-Whitney test, since none of them fulfilled the assumption of normality.

A multivariable analysis was carried out to identify variables associated with CHF. A total of 35 variables, all of which were significant in the bivariate analysis, were ultimately included in the multivariable analysis. Up to 21 variables were automatically deleted and, while the remaining selection was used to build the model manually, an analysis of variance test was used to compare nested models. Multicollinearity was tested using the generalized variance inflation factor (GVIF) method [16].

Statistical significance was set at $p < 0.05$. All the analyses were carried out using R version 4.0.2.

Results

CHF was detected in 152 of the 3658 patients enrolled in the RELESSER registry. We excluded 17 patients whose diagnosis of CHF was made before that of SLE and an additional 18 patients whose medical records contained no reliable information regarding the date of onset of CHF. Finally, 117 patients (3% of the whole cohort) with SLE and CHF were included in the analysis. The mean age of patients with CHF at their last visit was higher than in controls without CHF (59.8 ± 18.2 *vs.* 46.2 ± 4.3 years), 90% were females and 93% were Caucasian).

Onset of CHF took place a median (IQR) of 9.4 years (4.2−18.3) following the diagnosis of SLE.

The results of the bivariate analysis, in which the eventual association with CHF was tested, are provided in Tables 1 and 2. In order to clarify the presentation of data, we segregated the potential confounding variables, i.e., those that are known to be associated with CHF in the general population (Table 2). Briefly, patients with CHF had more severe disease (Katz index, median [IQR], 4 [3−5] vs 2 [1−3]), organ damage (mSDI: 3 [2−4] vs 0 [0−1]), and greater degree of comorbidity (as measured using a modified Charlson index, excluding cardiovascular items, 4 [3−6] vs 1[1−3]). In addition, more patients with CHF died from cardiovascular causes (37.5% vs 6.7%) or any other cause (43.2% vs 4.7%) ($p < 0.0001$ for all comparisons). Likewise, patients with CHF were more often refractory to standard treatments (33.3% vs 24%, $p = 0.0377$) and were more frequently hospitalized for SLE-related causes (median 3 [1−5] vs 1 [0−2], $p < 0.0001$). The results of the multivariable analysis are shown in Table 3. GVIF values were less than 1.5 for all of the independent variables included in the model, thereby excluding collinearity.

Discussion

Despite the well-established high prevalence of CVD in SLE patients, little attention has been paid to risk factors associated with CHF. In this study, using historically gathered data, we identified

Table 1
Bivariate analysis of factors associated with chronic heart failure (CHF) (lupus-related characteristics).

Cumulative clinical characteristics and treatments	Entire cohort N/total* (%)**	Patients without CHF N/total* (%) **	Patients with CHF N/total* (%)**	*p*-value
Cutaneous manifestations	2,622/3623 (72.4)	2,540/3454 (73.5)	82/117 (70.1)	0.3963
Constitutional symptoms	687/3623 (19.0)	638/3425 (18.6)	49/116 (42.2)	<0.0001
Myositis	131/3509 (3.7)	124/3395 (3.7)	7/114 (6.1)	0.1994
Articular manifestations	2,760/3533 (78.1)	2,671/3416 (78.2)	89/117 (76.1)	0.5707
Pulmonary manifestations	223/3623 (6.2)	201/3455 (5.8)	22/117 (18.8)	<0.0001
Neuropsychiatric lupus	454/3623 (12.5)	414/3441 (12.0)	40/117 (34.2)	<0.0001
Glomerulonephritis	690/3623 (19.0)	655/3506 (18.7)	35/117 (29.9)	0.0038
Chronic kidney failure	186/3488 (5.3)	150/3372 (4.4)	36/116 (31.0)	<0.0001
Antiphospholipid syndrome	490/3546 (13.8)	460/3429 (13.4)	30/117 (25.6)	0.0005
Small vessel thrombosis	128/3481 (3.7)	112/3364 (3.3)	16/117 (13.7)	<0.0001
Vasculitis	317/3494 (9.1)	296/3379 (8.8)	21/115 (18.3)	0.0014
Raynaud syndrome	1167/3460 (33.7)	1122/3346 (33.5)	45/114 (39.5)	0.1913
Statins, any time	819/3257 (25.1)	746/3141 (23.8)	73/116 (62.9)	<0.0001
Calcium or vitamin D, any time	2,217/3293 (67.3)	2107/3177 (66.3)	110/116 (94.8)	<0.0001
Corticosteroids, any time	3,034/3410 (89.0)	2,920/3293 (88.7)	114/117 (97.4)	0.0013
Cyclophosphamide, any time	761/3384 (22.5)	723/3268 (22.1)	38/116 (32.8)	0.0091
Mycophenolate, any time	563/3323 (16.9)	540/3207 (16.8)	23/116 (19.8)	0.3796
Antimalarials, any time	2,830/3395 (83.4)	2768/3278 (84.4)	62/117 (53)	<0.0001
Time on antimalarials (months), mean (SD)	78.16 (78.4)	78.28 (78.6)	73.87 (70.9)	0.5199
Creatinine, mean (SD)	0.92 (1.16)	0.90 (1.14)	1.50 (1.33)	<0.0001
Anti-Ro antibodies	1,371/3473 (39.5)	1,326/3360 (39.5)	45/113 (39.8)	1
Anti-RNP antibodies	869/3455 (25.2)	837/3341 (25.1)	32/114 (28.1)	0.4446
Low complement	2,734/3510 (77.9)	2,632/3395 (77.5)	102/115 (88.7)	0.0040
Antiphospholipid antibodies	1,343/3623 (37.1)	1,292/3506 (36.9)	51/117 (43.6)	0.1449
Katz SI[#], median (IQR)	2 [1−3]	2 [1−3]	5 [3−5]	< 0.0001
mSDI[§], median (IQR)	0 (0−1)	0 (0−1)	3 [2−4]	< 0.0001

* "total" means number of patients with the value available.
** unless otherwise specified.
[#] Katz SI = Katz severity index.
[§] mSDI = modified SLICC/ACR damage index (i.e., without cardiovascular items).

Table 2
Bivariate analysis of factors associated with chronic heart failure (CHF) (confounding variables, i.e. variables commonly associated to CHF in general population).

	Total N/total* (%)**	Patients without CHF N/total* (%)**	Patients with CHF N/total* (%)**	*p*-value
Age at inclusion, mean (SD)	46.64 (14.71)	46.19 (14.36)	59.78 (18.24)	<0.0001
Hypertension	1031/3564 (28.9)	945/3447 (27.4)	86/117 (73.5)	<0.0001
Alcoholism	134/3283 (4.1)	126/3172 [4]	8/111 (7.2)	0.1345
Diabetes	171/3539 (4.8)	154/3424 (4.5)	17/115 (14.8)	<0.0001
Hyperlipidemia	1073/3451 (31.1)	999/3335 (30)	74/116 (63.8)	<0.0001
Ischemic heart disease	116/3570 (3.2)	88/3454 (2.5)	28/116 (24.1)	<0.0001
Myocarditis	23/3515 (0.7)	11/3398 (0.3)	12/117 (10.3)	<0.0001
Cardiac arrhythmia	139/3548 (3.9)	101/3432 (2.9)	38/116 (32.8)	<0.0001
Pulmonary embolism	119/3554 (3.3)	108/3437 (3.1)	11/117 (9.4)	0.0016
Pulmonary hypertension	104/3334 (3.1)	73/3218 (2.3)	31/116 (26.7)	<0.0001
Cardiac valvulopathy	114/3375 (3.4)	76/3260 (2.3)	38/115 (33)	<0.0001

* "total" means number of patients with the value available ** unless otherwise specified.

Table 3
Factors associated with congestive heart failure (multivariable analysis).

	Odds Ratio	95% CI	p-value
Calcium or vitamin D	5.29	2.07 - 16.86	0.0015
Antimalarials any time	0.28	0.17 - 0.45	<0.0001
Sex (female)	0.46	0.25 - 0.88	0.0147
Ischemic heart disease	7.96	4.01 - 15.48	<0.0001
Cardiac arrhythmia	7.38	4.00 - 13.42	<0.0001
Pulmonary hypertension	3.71	1.84 - 7.25	0.0002
Cardiac valvulopathy	6.33	3.41 - 11.62	<0.0001
Hospitalization (due to SLE)	3.74	1.81 - 8.65	0.0008
mSDI *	1.29	1.16 - 1.44	<0.0001

* mSDI = modified SLICC/ACR damage index (i.e., excluding cardiovascular items).

factors associated with CHF in a large multicenter and well-characterized, European lupus cohort. Consistent with findings reported elsewhere, the usual causes of CHF in the general population were all associated with CHF in SLE, namely, ischemic heart disease, arrhythmia, pulmonary hypertension, and valvulopathy. These cardiovascular conditions exhibit the strongest association with CHF in terms of the odds ratio. Additionally, patients with CHF had greater cumulative non-cardiovascular organ damage, were more frequently hospitalized owing to SLE, and died more often from both cardiovascular and non-cardiovascular causes, suggesting that they constitute a subset with more severe disease.

Notably, antimalarials conferred some cardio-protective effects in our analysis. These drugs are considered essential medications for treatment of SLE [17–20]. Although hydroxychloroquine and chloroquine are generally well-tolerated, they can have severe cardiologic adverse effects, including cardiomyopathy and conduction defects [13]. Furthermore, a recent survey from the United States Food and Drug Administration Adverse Event Reporting System indicated a relatively high risk of cardiomyopathy and myocardial disorders following exposure to hydroxychloroquine in older adults [21]. In contrast, the use of antimalarials was associated with a lower prevalence of CHF in our large multicenter retrospective SLE cohort, and, interestingly, this effect occurred independently of disease severity. Of note, this apparently cardioprotective effect was also documented independently of ischemic heart disease, suggesting that mechanisms other than antithrombotic effects could be involved, for example, better control of subclinical myocarditis or overall disease activity.

The protective effect of female sex is not surprising, given the well-known lower frequency of CHF among women in the general population [22].

An association between CHF and the use of calcium or vitamin D was found and confirmed in the multivariable analysis. A possible association between 25-hydroxyvitamin D and CVD in patients with SLE was previously suggested based on data from a large international inception cohort [23]. While the variable used in this study is not a direct measure of vitamin D status in the study patients, our results indicate that phosphate and calcium metabolism may have an impact on CVD in persons with SLE. One explanation for the positive association between CHF and vitamin D or calcium would be an underlying deficiency, probably related to corticosteroid treatment, which could necessitate supplements. Thus, we can hypothesize that vitamin D has a cardioprotective effect, consistent with findings for the general population [24,25]. However, a recent meta-analysis of studies carried out in the general population suggests that vitamin D supplementation does not confer cardiovascular protection [26]. Obviously, prospective and specifically designed studies would be required to test such a hypothesis in SLE.

Our study is subject to a series of limitations. First, as it is not population-based, the prevalence of CHF may be underestimated. In particular, one must take into account the fact that several patients with CHF were finally excluded, since we were unable to determine the time of onset of CHF. Moreover, bias inherent to the study's retrospective design, particularly under-reporting of explanatory or confounding variables, cannot be excluded. Given the cross-sectional nature of our study, it is not possible to talk about protective or deleterious factors; the variables found to be significant in the multivariable analysis are merely associations. Regarding the dependent variable, given that CHF is a highly relevant clinical event and easily diagnosed in daily clinical practice, it seems unlikely that it would go unnoticed and not be recorded. However, we cannot exclude underdiagnosis of ventricular disfunction. On the other hand, assessment of exposure to antimalarials was not robust, as it was based on a single categorial variable, namely the use of antimalarials at any time. On the other hand, the large number of patients included could minimize the impact of this definition-related limitation.

Conclusions

- Patients with SLE and CHF experience more severe SLE, with more pronounced cumulative damage.
- Treatment with antimalarials seems to confer some cardioprotective effects.

Key messages

- CHF is a late complication of SLE and is associated with high mortality.
- Patients with SLE and CHF experience more severe SLE, with more pronounced cumulative damage, higher overall SLE-related mortality, and greater refractoriness to SLE treatments.
- Treatment with antimalarials, as usually administered in patients with SLE, is not only safe for the heart, but might confer cardioprotective effects.

Data availability statement

Data are available at the Spanish Society of Rheumatology Research Unit under request, wherever legally and ethically possible.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest associated with this original article.

Ethical approval

The RELESSER register and studies derived therefrom have been approved by the Ethics Committee of Doctor Negrin Hospital (ID: RELES-SER-2009–01). All patients gave their informed consent for their data to be used in the study.

Funding statement

This work was supported by the Spanish Foundation of Rheumatology.

Acknowledgements

We are grateful to the entire group of RELESSER registry researchers. We also thank the Spanish Society of Rheumatology for support in the revision of the English translation.

References

[1] Liu Y, Kaplan MJ. Cardiovascular disease in systemic lupus erythematosus: an update. Curr Opin Rheumatol 2018;30:441–8.

[2] Schoenfeld SR, Kasturi S, Costenbader KH. The epidemiology of atherosclerotic cardiovascular disease among patients with SLE: a systematic review. Semin Arthritis Rheum 2013;43:77–95.
[3] Yazdany J, Poozley N, Langham J, Nicholson L, Langham S, Embleton N, et al. Systemic lupus erythematosus; stroke and myocardial infarction risk: a systematic review and meta-analysis. RMD Open 2020;6:e001247.
[4] Kim CH, Al-Kindi SG, Jandali B, Askari AD, Zacharias M, Oliveira GH. Incidence and risk of heart failure in systemic lupus erythematosus. Heart 2017;103:227–33.
[5] Yiu KH, Tse HF. Editorial commentary: heart failure in systemic lupus erythematosus: a problem to address. Trends Cardiovasc Med 2018;28:198–9.
[6] Fernández-Nebro A, Rúa-Figueroa Í, López-Longo FJ, Galindo-Izquierdo M, Calvo-Alén J, Olivé-Marqués A, et al. EAS-SER (Systemic diseases study group of spanish society of rheumatology). Cardiovascular events in systemic lupus erythematosus: a nationwide study in Spain From the RELESSER registry. Medicine (Baltimore) 2015;94:e1183.
[7] Haugaard JH, Dreyer L, Ottosen MB, Gislason G, Kofoed K, Egeberg A. Use of hydroxychloroquine and risk of major adverse cardiovascular events in patients with lupus erythematosus: a Danish nationwide cohort study. J Am Acad Dermatol 2020;12 S0190-9622(20)33163-7.
[8] Liu D, Li X, Zhang Y, et al. Chloroquine and hydroxychloroquine are associated with reduced cardiovascular risk: a systematic review and meta-analysis. Drug Des Devel Ther. 2018;12:1685–95.
[9] Bansal P, Goyal A, Cusick 4th A, Lahan S, Dhaliwal HS, Bhyan P, Bhattad PB, Aslam F, Ranka S, Dalia T, Chhabra L, Sanghavi D, Sonani B, Davis 3rd JM. Hydroxychloroquine: a comprehensive review and its controversial role in coronavirus disease 2019. Ann Med 2021;53:117–34.
[10] Tleyjeh IM, Kashour Z, AlDosary O, Riaz M, Tlayjeh H, Garbati MA, et al. The cardiac toxicity of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-regression analysis. Mayo Clin Proc Innov Qual Outcomes 2020 Nov 2.
[11] Arabi YM, Gordon AC, Derde LPG, et al. Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial [published online ahead of print, 2021 Jul 12]. Intensive Care Med 2021:1–20.
[12] RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med 2020;383:2030–40.
[13] Tselios K, Deeb M, Gladman DD, Harvey P, Urowitz MB. Antimalarial-induced cardiomyopathy: a systematic review of the literature. Lupus 2018;27:591–9.
[14] Rúa-Figueroa I, López-Longo FJ, Calvo-Alén J, et al. National registry of patients with systemic lupus erythematosus of the Spanish Society of Rheumatology: objectives and methodology. Reumatol Clin 2014;10:17–24.
[15] Katz JD, Senecal JL, Rivest C, Goulet JR, Rothfield N. A simple severity of disease index for systemic lupus erythematosus. Lupus 1993;2:119–23.
[16] Fox J, Monette G. Generalized collinearity diagnostics. JASA 1992;87:178–83.
[17] Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis 2020;79:713–23.
[18] Ruiz-Irastorza G. M Ramos-Casals, P Brito-Zeron, M A efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis 2010;69:20–8.
[19] Wallace DJ, Gudsoorkar VS, Weisman MH, Venuturupalli SR. New insights into mechanisms of therapeutic effects of antimalarial agents in SLE. Nat Rev Rheumatol 2012;8:522–33.
[20] Olsen NJ, Schleich MA, Karp DR. Multifaceted effects of hydroxychloroquine in human disease. Semin Arthritis Rheum 2013;43:264–72.
[21] Nishtala PS, Gill S, Chyou TY. Analysis of the US FDA adverse event reporting system to identify adverse cardiac events associated with hydroxychloroquine in older adults. Pharmacoepidemiol Drug Saf 2020;29:1689–95.
[22] Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Framingham Heart Study. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation 2002;106:3068–72.
[23] Lertratanakul A, Wu P, Dyer A, Urowitz M, Gladman D, Fortin P, et al. 25 hydroxyvitamin D and cardiovascular disease in patients with systemic lupus erythematosus: data from a large international inception cohort. Arthritis Care Res (Hoboken) 2014;66:1167–76.
[24] Bouillon R. Vitamin D and cardiovascular disorders. Osteoporos Int 2019;30:2167–81.
[25] Camici M, Galetta F, Franzoni F, Carpi A, Zangeneh F. Vitamin D and heart. Intern Emerg Med 2013;8(Suppl 1):S5–9.
[26] Barbarawi M, Kheiri B, Zayed Y, Barbarawi O, Dhillon H, Swaid B, Yelangi A, Sundus S, Bachuwa G, Alkotob ML, Manson JE. Vitamin D supplementation and cardiovascular disease risks in more than 83 000 individuals in 21 randomized clinical trials: a meta-analysis. JAMA Cardiol 2019;4:765–76.