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ORIGINAL ARTICLE

Predictors of hospitalization in patients with systemic lupus erythematosus: a 10-year cohort study

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Abstract

Introduction/objectives Recognising systemic lupus erythematosus (SLE) patients at higher risk for hospitalization, aiming at developing tailored management strategies, may help minimize admissions and improve long-term health outcomes. Our study aimed to identify predictors for hospitalization in patients with SLE.

Method Cohort study of SLE patients followed in a referral centre. All hospitalizations from study baseline up to 120 months were identified, and the primary indication for admission was categorized as follows: (1) SLE disease activity; (2); infection; and (3) other conditions. Demographic, clinical, and laboratory parameters at baseline were sought as predictors of hospitalization for (i) any cause, (ii) disease activity, and (iii) infection using survival analysis with Kaplan–Meier curves and log-rank tests. Potential predictors were further tested using multivariate Cox proportional hazards regression models.

Results We included 398 patients (median follow-up: 120 months). The incidence rate of hospitalization was 17.7 per 100 patient-years. The most frequent indications for hospitalization were SLE disease activity (29.4%) and infection (23.4%). In multivariate analysis, male gender, age > 50 years, antiphospholipid antibodies positivity (aPL), SLEDAI-2 K > 5, organ damage, and prednisone daily dose (PDN) predicted hospitalization for any cause. SLEDAI-2 K > 5, aPL, PDN, and IS medication predicted hospitalization for active SLE. Male gender, prior biopsy-proven lupus nephritis, aPL, organ damage, and ongoing treatment with high-risk IS predicted hospitalization for infection. Treatment with antimalarials was associated with a lower risk of hospitalization for any cause and for infection.

Conclusions Positive aPL identifies SLE patients presenting a higher risk of hospitalization, while medication with antimalarials was associated with a lower risk.

Key Points

- *Positive aPL is predictive of hospitalization for any medical condition, disease activity, and infection*
- *Organ damage is predictive of hospitalization for any condition and infection*
- *Antimalarials are predictive of a lower risk of hospitalization for any condition and infection*

Keywords Systemic lupus erythematosus · Hospitalizations · Infection · Disease activity · Predictors

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Introduction

The long-term survival of patients with systemic lupus erythematosus (SLE) improved over the last decades, following earlier diagnosis, improved management strategies, and novel treatment approaches [1]. Nevertheless, these patients have a wide gap in health outcomes compared to the general population, including a higher risk of hospitalization, with a significant proportion of patients with SLE being hospitalized during their disease course [1–4]. The requirement for hospitalizations identifies a subgroup of SLE patients

with worse health outcomes, including higher morbidity and mortality [4–9], while carrying high direct and indirect costs [10, 11]. Disease activity and infection are consistently reported as the leading causes of hospitalization in these patients [4–9, 12–17].

Previous studies assessed data collected from national and hospital registries, allowing an extensive portrayal of admission rates, length of stay, causes for admission, costs, and in-hospital mortality [4, 6, 12, 13, 15–18]. However, they lack individual patient-level clinical information and rely on physician-reported diagnoses of SLE at hospital discharge, which may be inaccurate. Conversely, studies in well-characterized unicentric SLE cohorts were performed to evaluate the incidence, causes, predictors of hospitalization, and predictors of increased length of stay on admission [5, 7, 8, 14, 19], although with smaller sample sizes and shorter follow-up periods. Accounting for the follow-up time until hospitalization with survival analysis may be more suitable to predict which patients have the highest risk for hospitalization, thus allowing risk stratification and its use to optimise patient-level management to reduce admissions and improve long-term health outcomes.

This study aims to identify clinical predictors of hospitalization in SLE patients for any reason and, specifically, for disease activity and infection.

Methods

Study design and population

This single-centre retrospective cohort study included adult SLE patients followed at a tertiary referral centre (CHUC Lupus Clinic) [20–22], which provides assistance to a wide geographical area, with more than 50,000 patients hospitalized yearly at this institution. Fulfilment of the revised 1997 American College of Rheumatology (ACR'97) [23] or the Systemic Lupus International Collaborating Clinics (SLICC) [24] classification criteria and compliance with regular follow-up (defined as at least two outpatient visits, no longer than 12 months apart, during the study period) were required for inclusion. This project adhered to the principles of the Declaration of Helsinki and has been approved by the Local Ethics Committee (protocol number CHUC04618). All patients provided written informed consent before inclusion.

Patient assessments and outcomes

The study baseline for each patient was set at their first scheduled outpatient visit during the study period (January 1, 2009, to December 31, 2020). The follow-up period was completed at their last clinical observation up to 120 months from baseline. The electronic database of the CHUC Lupus Clinic cohort and individual medical records from our hospital database were reviewed to characterize each patient at the study baseline and to identify all hospitalizations occurring in our hospital during the inclusion period.

Baseline characteristics assessed for each patient at study baseline included demographic features, SLE cumulative manifestations and immunological features, SLE disease activity, cumulative organ damage, and ongoing medication for SLE, including hydroxychloroquine (HCQ), immunosuppressants (IS), and prednisone (PDN). Positivity to antiphospholipid antibodies (aPL) was considered when medium-to-high levels of immunoglobulin G (IgG) or immunoglobulin M (IgM) anticardiolipin or anti-beta-2-glycoprotein I or positive lupus anticoagulant were measured on at least two occasions, at least 12 weeks apart. Antiphospholipid syndrome (APS) was defined according to classification criteria [25]. Disease activity was scored with the SLE Disease Activity Index 2000 (SLEDAI-2 K) [26] and organ damage with the SLICC/ACR-damage index (SDI) [27].

The primary causes for hospitalization were determined by review of the discharge summary record and categorized as follows: (1) SLE disease activity, (2) infection, or (3) other conditions. Only one primary cause for inpatient admission was considered for each hospitalization event. Hospitalizations for SLE disease activity were further classified according to the main organ manifestation motivating the inpatient admission. Hospitalizations for programmed intravenous administration of therapy or pregnancy, labour, or childbirth complications were excluded from the analysis. The co-primary outcomes of the study included time-to-first hospitalization, up to 120 months from baseline, for (i) any condition; (ii) SLE disease activity; and (iii) infection.

Statistical analysis

Descriptive statistics were performed, with continuous data presented as mean and standard deviation (SD) or median with interquartile range (IQR), as appropriate, and categorical variables presented using frequencies and absolute counts. Comparison of categorical variables among subgroups of patients was performed by applying chi-squared tests, adjusting the significance level according to the number of variables in multiple comparisons with the Bonferroni correction. The incidence rate of hospitalizations was calculated by dividing the number of hospitalizations by the number of patients and observation time at risk.

Survival analyses with Kaplan–Meier curves and log-rank test were applied to test for associations between potential univariate categorical predictors of each outcome. The set of

pre-specified candidate variables evaluated at study baseline included gender; age at SLE diagnosis (≤25 vs > 25 years old); age at baseline (≤50 vs > 50 years old); disease duration (≤2 vs > 2 years); SLE classification criteria (fulfilment of ACR'97 vs SLICC criteria alone); SLEDAI-2 K score (≤5 vs > 5); cumulative SLE manifestations (yes/no for each feature); cumulative organ damage (SDI = 0 vs ≥ 1); and ongoing medication with HCQ, IS, or PDN > 7.5 mg/day (yes/no for each class). Regarding time-to-first hospitalization for infection, IS were further categorized as low-risk (methotrexate, sulfasalazine, belimumab) or high-risk (azathioprine, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide, rituximab) [9].

In a second step, variables with $p < 0.1$ on the log-rank test for the outcome of interest were included in multivariate analysis applying Cox proportional hazards regression models (backward stepwise method, Wald-based) with estimation of hazard ratios (HR) and 95% confidence intervals (95%CI). Although the PDN daily dose was categorized (≤ 7.5 vs > 7.5 mg/day) according to the 2019 update of the EULAR recommendations for the management of SLE [28] for allowing univariate analysis, it was analysed as a continuous variable in the multivariable analysis. The proportional hazards assumption was verified with log-minus-log plots. Independent variables with $p < 0.05$ were considered significant. The analysis was performed using IBM SPSS Statistics, version 26.0.

Results

Study population

The baseline characteristics of the 398 patients included are described in Table 1.

Table 1 Baseline characteristics of the study population ($n = 398$)

Patient characteristics	
Female gender, *n* (%)	345 (86.7)
Caucasian ethnicity, *n* (%)	294 (98.7)
Age (years), mean ± SD	41.2 ± 15.1
Age at SLE diagnosis (years), mean ± SD	31.1 ± 14.4
SLICC only/ACR'97 classification criteria	100 (25.1%) /298 (74.9%)
Disease duration (years), median (IQR)	8.0 (3–5)
Cumulative disease manifestations	
Mucocutaneous, *n* (%)	234 (58.8)
Arthritis, *n* (%)	187 (47.0)
Serositis, *n* (%)	90 (22.6)
Nephritis, *n* (%)	115 (28.9)
Neuropsychiatric, *n* (%)	24 (6)
Haematological, *n* (%)	318 (79.9)
Haemolytic anaemia, n (%)	33 (8.3)
Leukopenia, *n* (%)	160 (42.5)
Thrombocytopenia, *n* (%)	91 (22.9)
Antiphospholipid antibodies, n (%)	126 (31.7)
Lupus anticoagulant	108 (27.2)
Anti-beta2-glicoprotein1 antibodies	49 (12.3)
Anticardiolipin antibodies	45 (11.3)
Single/double/triple positive	72 (57.1)/ 29(23.0)/ 25(19.8)
Secondary antiphospholipid syndrome, *n* (%)	30 (7.5)
SLEDAI-2 K	
Median (IQR)	3 (2–4)
Score > 5, *n* (%)	72 (18.1%)
Ongoing SLE medication	
Antimalarials*, *n* (%)	314 (78.9)
Immunosuppressants, *n* (%)	119 (29.9)
High-risk**, *n* (%)	111 (27.9%)
Prednisone, *n* (%)	230 (57.8)
> 7.5 mg/day, *n* (%)	70 (17.6)
SDI score≥1	113 (28.4)

N, absolute count; *SD*, standard deviation; *SDI*, Systemic Lupus Erythematosus Damage Index; *SLEDAI-2 K*, Systemic Lupus Erythematosus Disease Activity Index 2000

*Hydroxychloroquine ≤ 6.5 mg/kg/daily

**High-risk immunosuppressants: azathioprine, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide; rituximab

Table 2 Survival analysis of baseline predictors of hospitalization for any condition, SLE disease activity, and infection (multivariate Cox analysis)

Tested variables	Any condition (HR (95%CI), *p*-value)	SLE disease activity (HR (95%CI), *p*-value)	Infection (HR (95%CI), *p*-value)
Male gender	**HR = 1.60 (1.08–2.36), *p* = 0.020**	-	**HR = 2.33 (1.31–4.15), *p* = 0.004**
Age > 50 years	**HR = 1.62 (1.20–2.20), *p* = 0.002**	-	-
Age at SLE diagnosis (≤25 years)	-	-	-
Disease duration < 2 years (vs. > 2)	-	**HR = 1.63 (1.0–2.67), *p* = 0.050**	-
ACR'97 (vs SLICC only) criteria	-	HR = 1.74 (0.94–3.21), *p* = 0.080	-
Mucocutaneous lupus	-	-	-
Arthritis	-	-	-
Serositis	-	-	n.s
Biopsy-proven lupus nephritis	-	-	**HR = 1.70 (1.03–2.81), *p* = 0.040**
Neuropsychiatric lupus	-	n.s	n.s
Leukopenia	-	-	-
Thrombocytopenia	-	-	-
Haemolytic anaemia	-	n.s	-
Positive aPL	**HR = 1.56 (1.14–2.13), *p* = 0.006**	**HR = 1.84 (1.19–2.84), *p* = 0.006**	**HR = 2.56 (1.56–4.19), *p* < 0.001**
Secondary aPL syndrome	-	-	-
SLEDAI-2 K > 5	**HR = 1.06 (1.01–1.12), *p* = 0.030**	**HR = 1.98 (1.25–3.13), *p* = 0.004**	-
Organ damage (SDI ≥ 1)	**HR = 1.68 (1.24–2.29), *p* = 0.001**	HR = 1.50 (0.95–2.28), *p* = 0.080	**HR = 1.83 (1.13–2.97), *p* = 0.020**
Prednisone			
> 7.5 mg/day (vs. ≤ 7.5)	-	-	-
daily dose (mg)	**HR = 1.03 (1.01–1.04), *p* < 0.001**	**HR = 1.04 (1.02–1.05), p < 0.001**	-
Immunosuppressants	HR = 1.35 (0.99–1.85), *p* = 0.060	**HR = 1.84 (1.20–2.81), *p* = 0.005**	-
High-risk immunosuppressants	-	-	**HR = 1.93 (1.17–3.18), *p* = 0.010**
Antimalarials	**HR = 0.64 (0.46–0.90), *p* = 0.009**	n.s	**HR = 0.55 (0.33–0.91), *p* = 0.020**

ACR, American College of Rheumatology; *aPL*, antiphospholipid antibodies; *HR*, hazard ratio; *SDI*, SLICC damage index; *SLE*, systemic lupus erythematosus; *SLICC*, Systemic Lupus International Collaborating Clinics. *n.s.*, non-significant variables not included in the final model. Values with statistical significance are highlighted in bold

Incidence rate and causes for hospitalizations during follow-up

Over a median follow-up of 120 months (IQR = 57.7–120.0) and a total of 3018.6 patient-years, 615 hospitalizations were recorded. After excluding 35 admissions due to pregnancy, labour, or childbirth and 46 for programmed administration of parenteral medication, 534 hospitalizations were included in the analysis.

The incidence rate of hospitalizations was 17.7 per 100 patient-years of follow-up. The median follow-up time until the first admission was 27.2 months (IQR = 9.1–57.8). The most frequent causes for hospitalization were SLE disease activity (29.4%) and infections (23.4%). The exact causes for hospitalization are shown in Supplementary Table S1. Among causes for admission due to SLE disease activity, lupus nephritis was the most frequent (48.4%), followed by haematologic (19.1%) and neuropsychiatric (7.0%) involvement. Pneumonia (28.0%) and urosepsis (26.4%) were the most common infections motivating hospital admission. Almost one-half of the admissions (47.2%) were due to conditions other than SLE disease activity or infection, mainly for elective surgery (27.0%). Admissions potentially related to lupus complications or morbidity, including cardiovascular disease (11.9%), malignancy (7.5%), and renal transplant grafting procedure or complications (7.5%), were also observed. Of note, thrombosis, namely cardiovascular and cerebrovascular events, including myocardial infarction (7), ischaemic stroke (3), and pulmonary embolism (3), motivated 13 (2.4%) admissions.

Predictors of hospitalization for any condition

Of the 398 patients participating in the study, 184 (46.2%) were hospitalized for any condition at least once during follow-up. In Supplementary Table S2 and Table 2, results of univariate and multivariate survival analyses of potential risk factors for hospitalization are summarized. In univariate analysis, putative predictors ($p < 0.1$) at baseline included male gender, age over 50 years, moderate-to-high disease activity with SLEDAI-2 K > 5, ongoing treatment with PDN > 7.5 mg/day, IS medication, organ damage with SDI ≥ 1, and positive aPL. Patients receiving therapy with HCQ presented a lower risk. In the multivariate Cox regression analysis, independent predictors of hospitalization for any condition included (Table 2, Fig. 1) male gender, age > 50 years, aPL positivity, SLEDAI-2 K > 5, SDI ≥ 1, and PDN daily dose. Medication with HCQ was associated with a lower risk for the outcome.

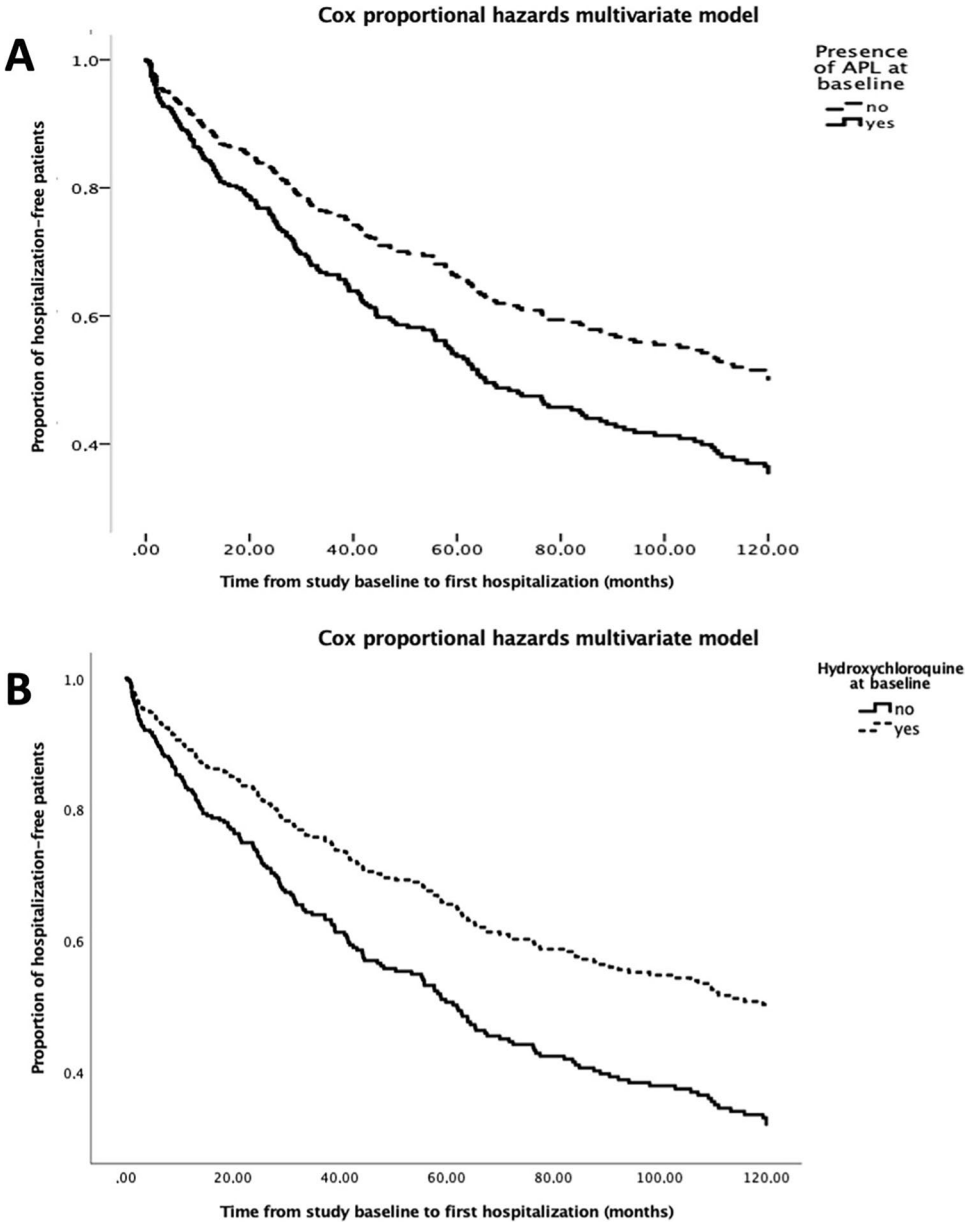

Fig. 1 Cox proportional hazards multivariate model for time-to-first hospitalization, according to aPL (**A**) and hydroxychloroquine (**B**) at baseline

Patients receiving HCQ at study baseline presented previous mucocutaneous lupus more frequently than those not treated with HCQ, without any other significant differences among these subgroups (Supplementary Table S3).

Predictors of hospitalization for SLE disease activity

Of the 398 patients, 94 (23.6%) were hospitalized for SLE disease activity at least once during the follow-up. In univariate analysis (Supplementary Table S2), putative predictors at baseline were: fulfilment of ACR'97 classification criteria; SLEDAI-2 K > 5; previous neuropsychiatric lupus; SDI ≥ 1; aPL positivity; ongoing treatment with PDN > 7.5 mg/day; and IS medication.

In multivariate analysis (Table 2), after adjusting for the other variables in the model, SLEDAI-2 K > 5, positive aPL, PDN daily dose, and IS medication (Table 3, Fig. 2) were confirmed independent predictors.

Predictors of hospitalization for infection

Regarding infections, 69 (17.3%) patients were hospitalized at least once for this cause. In univariate analysis, potential baseline predictors of hospitalization for infection included (Supplementary Table S2) male gender, prior biopsy-proven lupus nephritis, previous neuropsychiatric lupus, serositis, positive aPL, SDI ≥ 1,

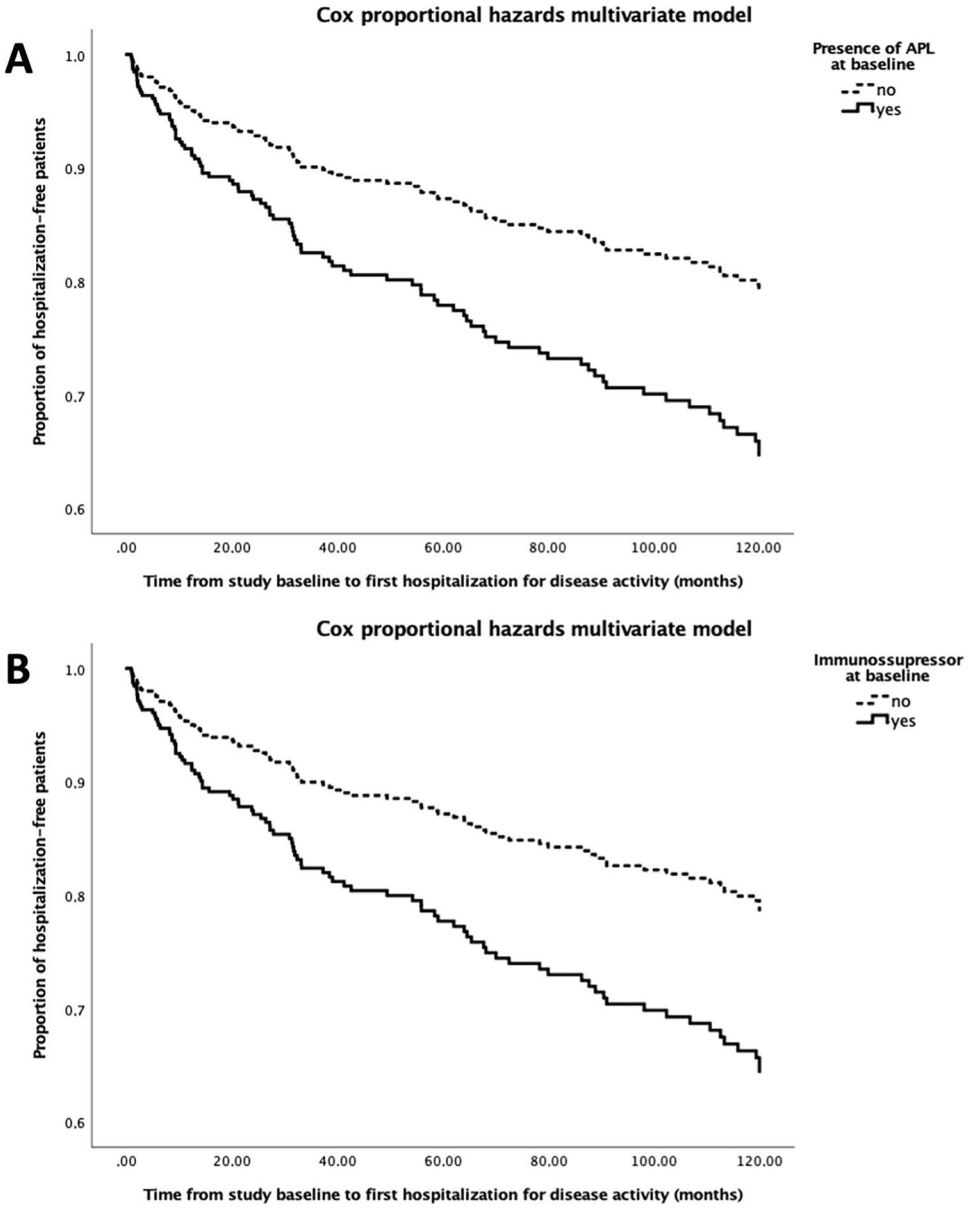

Fig. 2 Cox proportional hazards multivariate model for time-to-first hospitalization for SLE disease activity, according to aPL (**A**) and IS (**B**) at baseline

and ongoing treatment with high-risk IS. Patients receiving HCQ presented a lower risk.

In multivariate Cox regression analysis, male gender, prior biopsy-proven lupus nephritis, positive aPL, SDI ≥ 1, and ongoing treatment with high-risk IS were confirmed independent predictors. Medication with HCQ at baseline was associated with a lower risk for the outcome (Table 2, Fig. 3).

Discussion

In this cohort study, including 398 SLE patients over a median follow-up of 10 years, positive aPL and markers of severe SLE predicted hospitalization, whereas antimalarials were protective. Importantly, positive aPL was predictive of admissions for any condition, SLE disease activity, and infection, regardless of antiphospholipid syndrome criteria fulfilment. Among markers of severe SLE, patients with higher disease activity (SLEDA-2 K > 5), those requiring treatment with higher prednisone daily doses or those receiving IS for severe organ involvement presented an increased risk of hospitalization, as expected. Additionally, patients with lupus nephritis or treated with high-risk IS presented an increased risk of admission for infection. Irreversible organ damage (SDI ≥ 1) was predictive of hospitalization for any condition and infection. Conversely, treatment with antimalarials was associated with 36% and 45% lower risks of hospitalization for any condition and infection, respectively. However, standard-of-care (SOC) treatment with

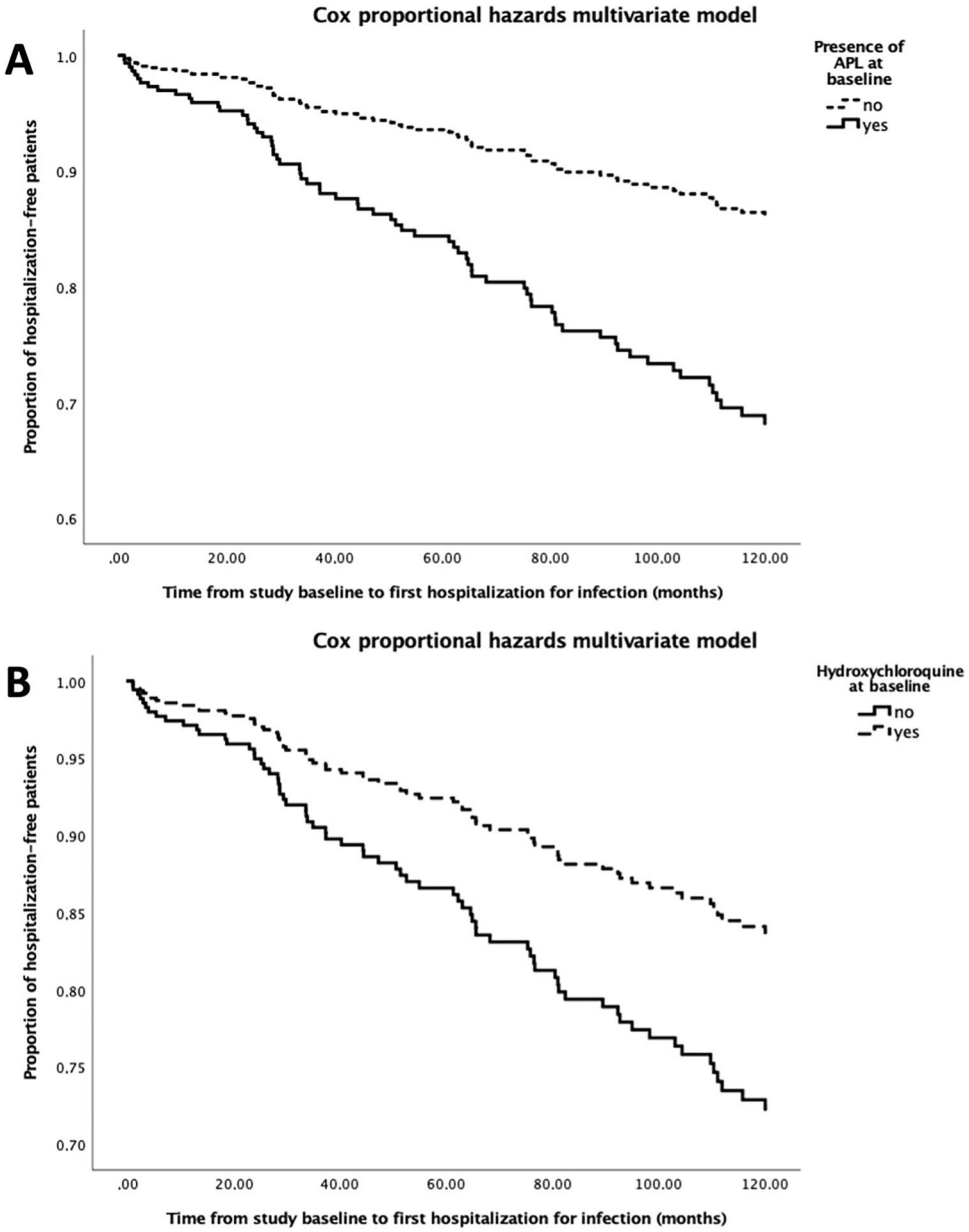

Fig. 3 Cox proportional hazards multivariate models for time-to-first hospitalization for infection, according to aPL (**A**) and hydroxychloroquine (**B**) at baseline

antimalarials or IS was insufficient to abrogate the higher risk of admission for disease activity of patients with severe SLE.

The incidence of hospitalizations was lower than reported in most cohort studies [5, 8, 14], which is in accordance with the study population, comprising primarily Caucasian European patients, with a less severe disease phenotype and inferior damage accrual compared to other ethnicities and geographical areas [29].

Disease activity and infection were the leading causes of hospitalization in SLE patients, as previously reported [3–9, 12–17]. Among hospitalizations for active disease, the primary organ involvements motivating the admission were similar to previous reports [3, 5, 6, 12–14, 16, 17, 19]. The most frequent infections leading to admission were also comparable to those of other studies [5, 16]. Notably, a considerable proportion of hospitalizations for other conditions were motivated by complications and morbidity potentially related to SLE and its medication, including cardiovascular disease, malignancy, renal transplantation, and osteoporotic fractures [5, 6, 8, 13, 14, 16, 17, 19].

Remarkably, positivity to aPL, regardless of antiphospholipid syndrome, was predictive of hospitalization for any condition, disease activity, and infection. Although APS has been associated with hospitalization in ICU and mortality [16], an association between aPL positivity and hospitalization has not been previously described. Prior studies suggest that secondary APS and positive aPL in SLE patients imply

a more severe disease phenotype regarding non-thrombotic and non-pregnancy-related manifestations, with higher damage accrual and mortality [30–33]. Since in our cohort few hospitalizations for thrombotic events were observed, with a lower frequency than previously reported [6, 16], and obstetric events were excluded, these causes do not explain the higher risk of admission associated with aPL. Hence, identifying aPL positivity as a predictor of hospitalizations suggests that aPL-related non-thrombotic phenomena may significantly impact health outcomes in SLE patients. Further research is warranted to assess whether these putative effects of aPL are relevant or a surrogate for an underlying variable that may be directly linked to hospitalizations.

Several predictors of hospitalization identified in this study were previously described in other cohort studies, including markers of severe SLE, namely high disease activity [5, 7, 19], daily prednisone dose [5, 7, 13, 16], and SDI, either as a categorical (SDI ≥ 1) [15] or continuous variable [7, 16]. While some studies found an association between shorter disease duration and hospitalization for disease activity [7, 13, 15, 16], in our cohort, disease duration (analysed either as a categorical or continuous variable) did not attain statistical significance after adjusting for confounders, probably because a prevalent cohort and not an inception cohort was analysed. The requirement for IS treatment is a marker of a more severe SLE subset and is associated with a higher risk of flares [21]. Thus, as expected, IS were found to predict hospitalizations for disease activity. Of note, we did not find an association between PDN and hospitalization for infection, which can probably be explained because a single baseline value and not the average corticosteroid dose along the follow-up time was considered.

The effect of antimalarials in reducing disease activity, preventing lupus flares, lowering damage accrual, and improving survival is well established [34–36]. Antimalarial use was also associated with reduced cardiovascular risk [37] and reduced infections [15, 16, 38, 39], in either the outpatient or inpatient settings. Our finding that antimalarials were associated with a lower risk of hospitalization for any condition is also consistent with previous evidence [15, 16]. Of note, we compared the subgroups of patients receiving HCQ or not receiving this medication, and there were no relevant differences regarding disease severity or other types of SLE drugs.

A significant strength of our study is that it is based on a large and well-characterized SLE cohort followed over 10 years in a referral lupus clinic. Detailed information regarding each hospitalization episode was available from the patients' clinical charts and electronic clinical files. Our centre is the primary provider of hospital healthcare for this population, making it unlikely that information regarding hospitalizations is missing. Furthermore, as these patients are enrolled in a SLE prospective cohort study of outcomes, baseline characteristics were systematically collected in the cohort database. Finally, survival analysis is the most appropriate methodologic approach in an open cohort study, where participants are enrolled and can be lost to follow-up over time. However, our study also has some limitations. Variables tested as predictors were set at baseline, although some may be time-varying. This option can facilitate the applicability of the study results in the clinical setting. However, it may have limited the accuracy of the risk estimates associated with SLEDAI-2 K and SLE medications. Secondly, the generalizability of our findings to different ethnic populations and other geographical settings should be carefully considered, especially bearing in mind that patients in this cohort mainly presented low disease activity at baseline.

In conclusion, we newly identified aPL as biomarkers that may be predictive of a higher risk of hospitalization, in addition to other clinical predictors that can be helpful to stratify SLE patients regarding the risk of hospitalizations. These can help clinicians adopt new and tailored management approaches to maintain patients under good control and prevent the need for admissions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06251-7.

Author contribution HA was involved in the bibliographic research, data collection, statistical analysis, interpretation of the data, and manuscript drafting. MR was involved in the data collection and manuscript review. ARP, ML, and JAP da Silva were involved in the manuscript review. LI was involved in the bibliographic research, conception, and design of the study, statistical analysis, interpretation of the data, and manuscript review. All the authors read and approved the final manuscript.

Data availability The data underlying this article will be shared at reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate This project was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Centro Hospitalar e Universitário de Coimbra (protocol number CHUC04618). All patients signed an informed consent form before the inclusion in this study.

Consent for publication Not applicable.

Disclosures None.

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