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ORIGINAL ARTICLE

Antimalarial treatment and minimizing prednisolone are associated with lower risk of infection in SLE: a 24-month prospective cohort study

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Abstract

Introduction/objectives Infections are a major cause of morbidity and death in systemic lupus erythematosus (SLE). Perfecting the understanding of contributors to infection burden in SLE is pivotal to improve management and outcomes. This study aims to identify clinical predictors of infection in SLE.

Method We conducted a prospective cohort study at a referral SLE clinic. Infections were identified at each visit and categorized as (a) any type, (b) serious, (c) non-serious, and (d) bacterial. Survival analysis followed by multivariate Cox regression with an estimation of hazard ratios (HR) with 95% confidence intervals (95%CI) was performed.

Results We included 259 patients during a mean follow-up of 23.3 ± 5.7 months. The incidence rate of infection of any type was 59.3 cases per 100 patient-years. Multivariate Cox models showed that (a) prednisolone ≥ 7.5 mg/day (HR = 1.95, 95%CI 1.26–3.03) and female gender (HR = 2.08, 95%CI 1.12–3.86) were associated with higher risk of infection of any type; (b) prednisolone ≥ 10 mg/day was associated with higher (HR = 4.32, 95%CI 1.39–13.40), and antimalarials with lower risk (HR = 0.18, 95%CI 0.06–0.51) of serious infection; (c) female gender (HR = 1.92, 95%CI 1.04–3.57) and prednisolone ≥ 7.5 mg/day (HR = 1.89, 95%CI 1.21–2.96) were associated with higher risk of non-serious infection; (d) antimalarials were associated with lower (HR = 0.49, 95%CI 0.26–0.93) and female gender (HR = 5.12; 95%CI 1.62–16.18) with higher risk of bacterial infection.

Conclusions The risk of infection was higher in females in this young, well-controlled, low-comorbidity SLE cohort. Antimalarials were associated with lower and prednisolone ≥ 7.5 mg with higher risk of infection.

Key Points
- *Lupus patients treated with prednisolone ≥ 7.5 mg/day were 89% more likely to present infections.*
- *Lupus patients receiving prednisolone ≥ 10 mg/day were four times more likely to present serious infections.*
- *Lupus patients receiving antimalarials were 82% less likely to present serious infections.*

Keywords Antimalarials · Corticosteroids · Infection · Systemic lupus erythematosus

Introduction

Infections are a major cause of morbimortality in patients with systemic lupus erythematosus (SLE), who have a higher risk of infection compared to the general population[1–5]. In the past decades, the leading cause of death of SLE patients has shifted from disease activity to comorbidities, as novel immunosuppressants and improved therapeutic strategies have become available, allowing better disease control [6–8]. Serious infections account for up to 37% of hospital admissions in SLE patients, and their incidence rate reaches 14 cases per 100 patient-years in

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some cohorts [9, 10]. Although most infections in SLE patients are non-serious, they can lead to increased morbidity, frequent use of antibiotics, and the need to modify SLE therapies [11]. Even non-serious infections constitute potential flare triggers [12, 13]. The spectrum of infectious diseases in SLE patients is broad, and both serious and non-serious events are most frequently represented by bacterial or viral infections of the respiratory and urinary tracts [14, 15].

Epidemiological knowledge and awareness of risk factors for infections are crucial for developing preventive strategies in SLE patients. In the last four decades, observational studies began to shed light on the influence of several clinical and demographic factors upon the risk of infection [16]. However, evaluation of non-serious infections has been scarce. Furthermore, most previous studies were conducted more than 10 years ago, and thus in the context of older SLE therapeutic approaches, including more aggressive immunosuppressant regimens and higher, long-duration glucocorticoid dosages, which might have a different impact on infectious risk [17–19]. Recent research has focused on serious infections, many being conducted exclusively in an inpatient setting or addressing specific infectious diseases [20, 21].

Better understanding of clinical risk factors contributing to the burden of infection in ambulatory SLE patients is needed to improve management and long-term outcomes. This is the aim of the current study.

Materials and methods

Study design and patients

This observational open cohort study enrolled patients prospectively evaluated at a referral lupus clinic, the Centro Hospitalar e Universitário de Coimbra (CHUC) Lupus Clinic [22, 23]. Fulfillment of classification criteria for SLE (revised 1997 American College of Rheumatology (ACR) and/or the Systemic Lupus International Collaborating Clinics (SLICC) criteria) was required for inclusion [24, 25]. The study baseline for each participant was at their first scheduled visit to the CHUC Lupus Clinic since January 2, 2017, and patients were followed up to 24 months until June 30, 2019. For inclusion, patients were required to have a regular follow-up, defined as at least two visits up to 6 months apart during the study period. All patients provided written informed consent, according to the Declaration of Helsinki. The Ethics Committee from CHUC approved this project (protocol number CHUC04618).

Primary and secondary outcomes

The primary outcome was the occurrence of infection (of any type) by physician diagnosis. Secondary outcomes were the occurrence of serious infection (defined as leading to death or requiring hospitalization or intravenous antibiotics), non-serious infection (defined as not fulfilling criteria for serious infection), and bacterial infection (of proven bacterial origin). At each assessment since study inclusion, infections occurring during the follow-up period, since the previous visit, were recorded. The diagnostic approach and classification of the infection outcome were ascertained by combining clinical, imaging, and laboratory findings, including bacterial isolates, response to antibiotics, and serologic results. Time since study baseline to the first event of each type of infection outcome, (i) any type, (ii) serious, (iii) non-serious, and (iv) bacterial, was determined for each patient. For each of these outcomes, patients were assessed for the study analyses up to the time of the first event or censored after 24 months of event-free follow-up.

Patients' assessments

Baseline patient characteristics and other potential risk factors for infection were assessed, including age; gender; age at SLE diagnosis; SLE disease duration; smoking status (yes/no (Y/N)); diabetes mellitus (Y/N); active cancer (Y/N); leukopenia (white blood cell count < 3000/μL) (Y/N); neutropenia (neutrophil count < 1000/ μL) (Y/N); lymphopenia (lymphocyte count < 1000/ μL) (Y/N); hypocomplementemia C3 and/or C4 (Y/N); anti-dsDNA positivity (Y/N); previous biopsy-proven lupus nephritis (Y/N); organ damage (defined as SLICC/ACR-damage index (SDI) ≥ 1) (Y/N); disease activity score (SLE Disease Activity 2000 (SLEDAI-2 K)); ongoing medications at baseline (antimalarials (Y/N), prednisolone daily dose, and other immunomodulators/immunosuppressants (any of the following: methotrexate, azathioprine, sulfasalazine, mycophenolate mofetil, calcineurin inhibitors, cyclophosphamide, belimumab or rituximab) (Y/N)).

Statistical analysis

Categorical variables were presented as absolute counts and frequencies. For continuous data, mean with standard deviation (SD) or median with interquartile range (IQR) was applied, as appropriate. Cumulative incidences and incidence rates were calculated for each infection outcome. Chi-square was performed, and odds ratios (OR) with 95% confidence intervals (95%CI) were calculated to compare

the risk of urinary tract infections (UTIs) between gender groups.

To identify potential clinical predictors for each of the infection outcomes, we used survival analysis. In a first step, we applied univariate analysis with Kaplan–Meier curves and log-rank tests. Tested variables at study baseline were gender; age ≥ 50 years (Y/N); active smoking (Y/N); diabetes mellitus (Y/N); previous biopsy-proven lupus nephritis (Y/N); leukopenia (Y/N); neutropenia (Y/N); lymphopenia (Y/N); hypocomplementemia (Y/N); positive anti-dsDNA (Y/N); SLEDAI-2 K ≥ 6 (Y/N); SDI ≥ 1 (Y/N); antimalarial use (Y/N); prednisolone dose (< 7.5 mg/day vs ≥ 7.5 mg/day (Y/N); < 10 mg/day vs ≥ 10 mg/day (Y/N)); other immunomodulators/immunosuppressants' use (Y/N). A subgroup analysis was conducted to test risk differences between patients receiving prednisolone between 1 and 5 mg/day and patients not receiving prednisolone. In a second step, the variables with $p < 0.1$ on log-rank tests were further evaluated applying multivariate Cox proportional hazards regression models (backward stepwise method, Wald-based) with an estimation of hazard ratios (HR) and 95%CI. We applied separate modelling for each of the infection outcomes, and independent variables with $p < 0.05$ in the Cox models were considered significant. The proportional hazard assumption was verified using log-minus-log plots. The analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY: IBM Corp.).

Results

We included 259 out of 272 SLE patients evaluated at the outpatient clinic during the study inclusion period (13 were excluded for not having regular follow-up). Patients' demographic, clinical, and laboratory characteristics at study baseline are described in Table 1.

During a mean follow-up time of 23.3 ± 5.7 months, 299 episodes of infection of any type were registered. Of all infectious episodes, 25 (8.36%) were serious, 274 (91.6%) were non-serious, and 169 (56.5%) were bacterial. The incidence rates of serious, non-serious, and bacterial infections were 4.96, 54.4, and 33.5 cases per 100 patient-years, respectively.

In total, 153 of the 259 patients (59.1%) experienced at least one episode of infection. Serious, non-serious, and bacterial infections were diagnosed in 17 (6.56%), 145 (55.9%), and 94 patients (36.3%), respectively. Most patients had only one episode (29.7%) or 2–4 episodes (27.0%) of infections of any type; only a minority had more than five infections during follow-up (2.32%).

Regarding the site of infections, for any type and non-serious infections, the upper respiratory tract was the most frequently affected (33.8% and 33.5% of the total, respectively), followed by the genitourinary tract (36.1% and 35.8%, respectively). Mucocutaneous and pulmonary/lower airway tract were the most frequent sites of serious infections (32.0% for each site). UTIs were the most common among bacterial infections (47.9%) (Table 2). Most infections of any type and serious infections were bacterial (56.5% and 76.0%, respectively). The non-serious infections were viral in 54.7% of cases (Table 3).

There was a statistically significant difference between genders in the development of UTIs of any type (OR = 4.32 (CI 95% 0.99–18.8); $p = 0.034$), non-serious (OR = 4.01 (CI 95%: 0.92–17.4); $p = 0.046$), and bacterial (OR = 4.32 (CI 95%: 0.99–18.7); $p = 0.034$), with females having a higher risk. This gender difference was not observed for serious infections.

The potential associations of infection of any type, identified in univariate analysis, were female gender ($p = 0.007$);

Table 1 Demographic, clinical, and laboratory characteristics of patients at baseline ($N = 259$)

Patients' characteristics	
Age, mean (SD), years	45.0 (14.3)
Age ≥ 50 years, %	10.0
Female gender, %	88.4
Caucasian, %	98.8
Age at SLE diagnosis, mean (SD), years	32.0 (13.3)
Time since SLE diagnosis, mean (SD), years	13.0 (8.9)
SLEDAI-2 K score, median (IQR)	2 (0–4)
Active disease (SLEDAI-2 K ≥ 6), %	5.4
Leukopenia, %	6.2
Neutropenia, %	1.9
Lymphopenia, %	17.8
Low C3 and/or C4, %	45.2
Anti-dsDNA positivity, %	37.8
History of lupus nephritis, %	40.9
SDI ≥ 1, %	18.1
Tobacco, current use, %	11.2
Diabetes mellitus, %	2.7
Active cancer, any, %	1.50
Drugs, % current users	
Antimalarials	92.3
Other immunomodulators/immunosuppressants[a]	39.4
Prednisolone ≥ 1–5 mg/day	21.6
Prednisolone ≥ 7.5 mg/day	11.2
Prednisolone ≥ 10 mg/day	6.9

SD, standard deviation; *SLE*, systemic lupus erythematosus; *SLEDAI-2 K*, Systemic Lupus Erythematosus Disease Activity Index 2000; *IQR*, interquartile range; *SDI*, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

[a]At least one of the following: methotrexate, sulfasalazine, azathioprine, mycophenolate mofetil, cyclosporin, cyclophosphamide, rituximab, belimumab

Table 2 Sites of infection in the study population ($N=259$) during follow-up

Location	Infections, *N* (%)			
	Any type	Serious	Non-serious	Bacterial
Upper respiratory tract	101 (33.8)	2 (8.0)	99 (36.1)	31 (18.3)
Genitourinary tract	100 (33.5)	2 (8.0)	98 (35.8)	81 (47.9)
Mucocutaneous	35 (11.7)	8 (32.0)	27 (9.9)	15 (8.9)
Pulmonary and lower airways	29 (9.7)	8 (32.0)	21 (7.7)	24 (14.2)
Nasopharyngeal, ears	21 (7.0)	1 (4.0)	20 (7.3)	15 (8.9)
Gastrointestinal tract	11 (3.7)	2 (8.0)	9 (3.3)	2 (1.2)
Osseous and articular	2 (0.7)	2 (8.0)	0 (0)	1 (0.6)
Central nervous system	0 (0)	0 (0)	0 (0)	0 (0)
Bacteraemia of unspecified focus	0 (0)	0 (0)	0 (0)	0 (0)
Total	299 (100)	25 (100)	274 (100)	169 (100)

Table 3 Etiology of infections in the study population ($N=259$) during follow-up

Etiological agent	Infections, *N* (%)		
	Any type	Serious	Non-serious
Bacterial	169 (56.5)	19 (76.0)	102 (37.2)
Viral	107 (35.8)	6 (24.0)	150 (54.7)
Fungal	22 (7.3)	0 (0)	22 (8.0)
Parasitic	1 (0.3)	0 (0)	1 (0.4)
Mycobacterial	0 (0)	0 (0)	0 (0)
Total	299 (100)	25 (100)	274 (100)

anti-dsDNA positivity ($p=0.052$); other immunomodulators/immunosuppressants ($p=0.083$); and prednisolone ≥ 7.5 mg/day ($p=0.001$). After multivariate Cox regression analysis, the significant predictors were prednisolone ≥ 7.5 mg/day (HR = 1.95, 95% CI 1.26–3.03; $p=0.010$) (Fig. 1a) and female gender (HR = 2.08, 95%CI 1.12–3.86; $p=0.052$).

For serious infection, univariate analysis identified potential predictors: leukopenia ($p=0.053$); lupus nephritis ($p=0.051$); prednisolone ≥ 10 mg/day ($p=0.010$); no treatment with antimalarials ($p<0.001$). After multivariate Cox regression analysis, a significant association persisted for prednisolone ≥ 10 mg/day (HR = 4.32, 95%CI 1.39–13.40; $p=0.011$) (Fig. 1b), while antimalarials were protective (HR = 0.18, 95%CI 0.06–0.51; $p<0.001$) (Fig. 2a).

For non-serious infectious, the potential predictors in univariate analysis were female gender ($p=0.016$); anti-dsDNA positivity ($p=0.018$); prednisolone ≥ 7.5 mg/day ($p=0.001$). After multivariate Cox regression analysis, significant associations persisted for female gender (HR = 1.92, 95%CI 1.04–3.57; $p<0.05$) and prednisolone ≥ 7.5 mg/day (HR = 1.89, 95%CI 1.21–2.96; $p=0.005$) (Fig. 3).

Regarding bacterial infections, female gender ($p=0.002$); diabetes mellitus ($p=0.058$); prednisolone ≥ 7.5 mg/day ($p=0.081$); and no treatment with antimalarials ($p=0.045$) were identified as potential predictors using univariate analysis. The multivariate Cox models confirmed a higher risk associated with female gender (HR = 5.12; 95%CI 1.62–16.18; $p=0.005$), while antimalarial treatment was protective (HR = 0.49, 95%CI 0.26–0.93; $p=0.03$) (Fig. 2b).

Univariate analysis (log-rank test) showed that patients receiving doses of prednisolone between 1 and 5 mg/day presented no differences in the risk of infections of any type ($p=0.315$), non-serious ($p=0.675$), or bacterial ($p=0.832$) when compared to patients not receiving prednisolone. For serious infections, as $p<0.1$ ($p=0.068$), we further analyzed it using Cox multivariate models with the other covariates with $p<0.1$. In the multivariate analysis, low-dose prednisolone (1–5 mg/day) was not a significant predictor ($p=0.241$) of serious infection.

Discussion

Our study showed that treatment with prednisolone ≥ 7.5 mg/day was associated with an 89% higher risk for any type of infection in patients with SLE and that those receiving a higher dose (≥ 10 mg/day) presented a fourfold higher risk for serious infections. Inversely, we found that patients treated with antimalarials were 82% less likely to present serious infections and had a 51% lower risk of bacterial infections. Female patients presented a higher risk for non-serious and bacterial infections, although not for serious infections.

Few previous studies have determined incidence rates per patient-years of exposure for serious and non-serious infections in SLE outpatient cohorts. In our prospective cohort study, we found an incidence of infections similar to the rate of 59 cases per 100 patient-years previously reported by Ginzler et al., who used a similar study design and method of data collection [9]. Our incidence rate of infections was, however, higher than the rate of 18.5 and 37.8 cases per patient-years found by Ng et al. and Paton

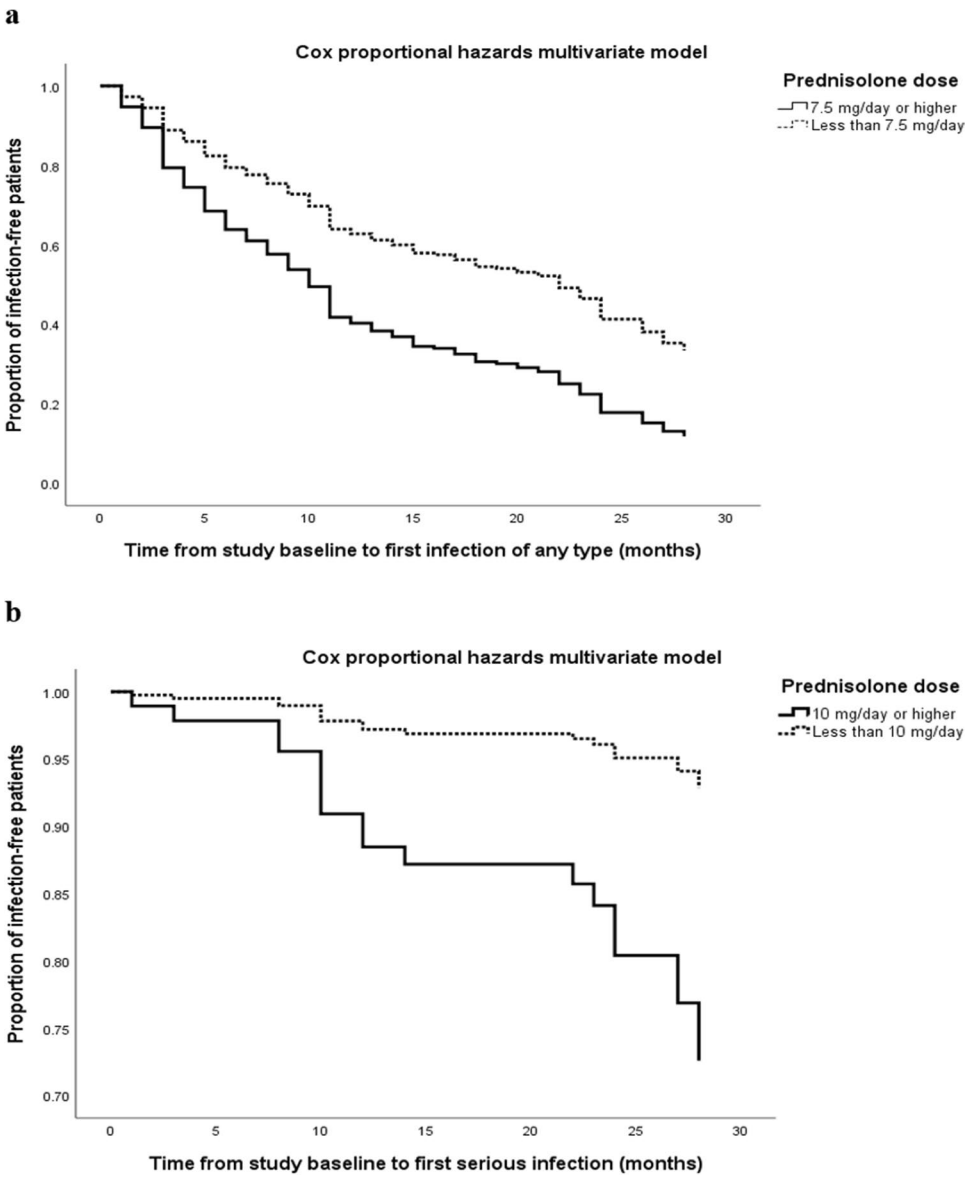

Fig. 1 Cox proportional hazards multivariate models for risk of any type of infection (**a**) and serious infection (**b**) according to daily prednisolone treatment status at study baseline

et al., respectively [10, 26]. These studies used a retrospective design, thus not including a systematic prospective recording of infection episodes, which could lead to apparent lower frequencies of infection. Conversely, our incidence of serious infections was lower than that in most previous studies, only comparable to the rate of 3.8 per 100 patient-years reported in a recent inception cohort study of retrospective design [20]. Most patients in our cohort presented low disease activity and received antimalarials, while only a minority were treated with ongoing prednisolone ≥ 7.5 mg/day; these factors probably contributed to the lower rate of serious infections. Bacterial and viral microorganisms were found to be the most prevalent cause for serious and non-serious infections, respectively, a finding consistent with previous reports [11, 14, 18].

Higher susceptibility to infection is a known consequence of glucocorticoid use [14, 20, 27]. Some studies have also evaluated the association of infection with different doses of glucocorticoids, including lower doses, and some have reported an apparent dose–effect [9, 19, 28]. However, to the best of our knowledge, this is the first study to independently assess the predictors of serious, non-serious, and bacterial infections. An important finding was the association of prednisolone cut-off values with infections of distinct severity. We found that prednisolone doses above 10 mg/day are associated with an increased risk of serious infections, a threshold that is higher than indicated by González-Echavarri et al. [27], similar to that reported by Rúa-Figueroa et al. (14), and lower than the 15 mg/day suggested by Pimentel-Quiroz et al. [14, 20]. We corroborated

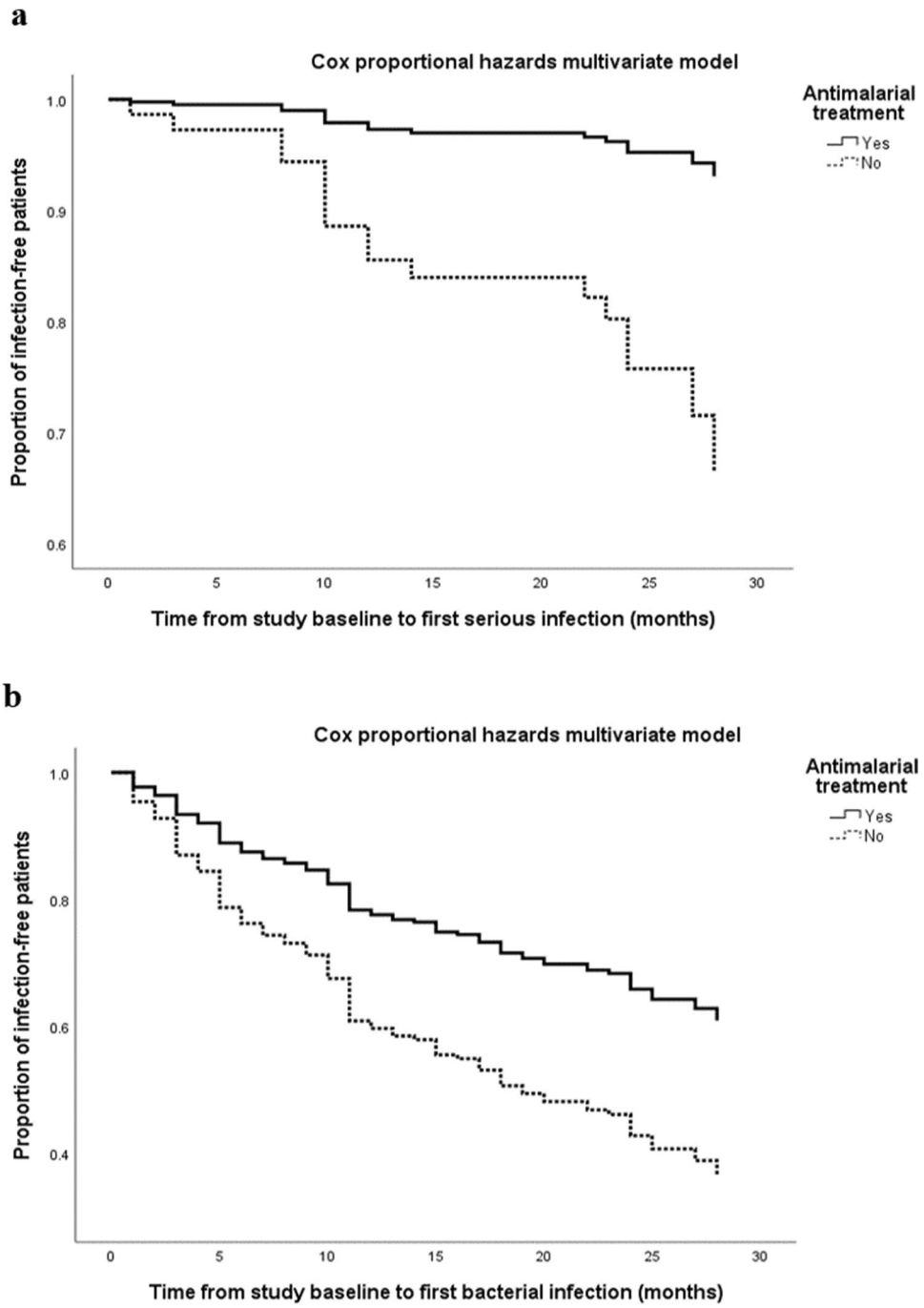

Fig. 2 Cox proportional hazards multivariate models for risk of serious infection (**a**) and bacterial infection (**b**) according to antimalarial treatment status at study baseline

the association of glucocorticoid treatment with the risk of serious and non-serious infections through separate predictor analyses for infections of different severity categories. We also concluded, through subgroup analysis, that patients taking prednisolone up to 5 mg/day were not more likely to present infections at any time point than those not treated with prednisolone.

Our real-life prospective data comes from a contemporaneous SLE cohort in which a treat-to-target strategy is adopted and an important management objective is the minimization of glucocorticoid treatment [29]. Our data supports this strategy by showing that prednisolone maintenance doses at or above 7.5 mg/day should be avoided whenever possible, taking into account the risk of infection.

Antimalarials have a broad range of antimicrobial properties, particularly by inhibiting the growth of intracellular agents [30, 31]. Its antibacterial effects have been demonstrated by in vitro experiments and murine models. Hydroxychloroquine has proved to be effective in the treatment of patients with chronic Q fever and Whipple's disease

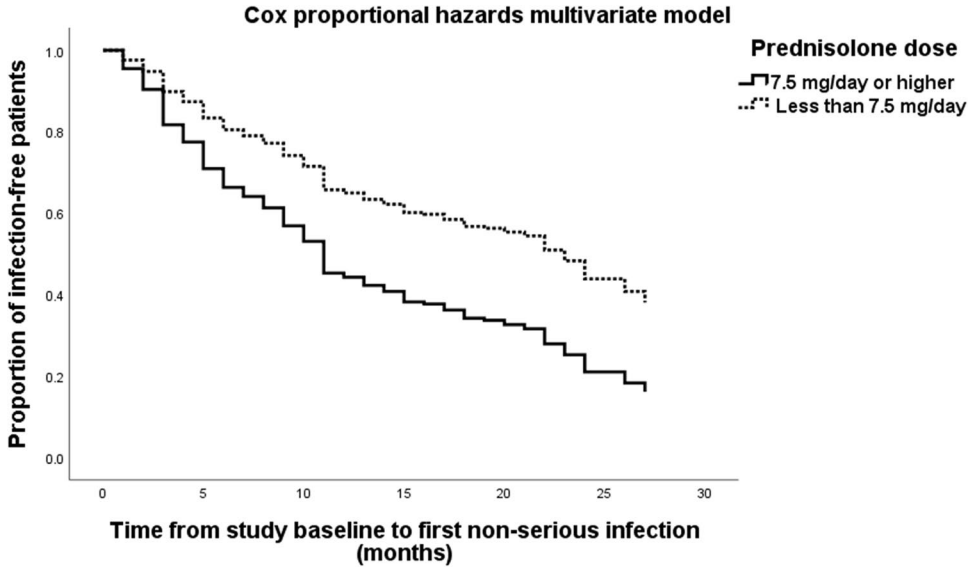

Fig. 3 Cox proportional hazards multivariate models for risk of non-serious infection according to daily prednisolone treatment status at study baseline

[30, 32]. Bacterial infections are among the most common infections in SLE, and we demonstrated, for the first time, that hydroxychloroquine treatment reduces the overall risk of bacterial infections independently of concurrent use of corticosteroids in a real-life clinical SLE outpatient setting. Our results confirm and strengthen the protective role of hydroxychloroquine for serious infections reported in other cohorts [20, 27, 33, 34].

We also found a difference between genders in the risk of infections, with females showing a higher risk of any type, non-serious, and bacterial infections. This might be explained by the higher proportion of female patients developing UTIs in these three infection subtypes. In fact, it is well known that UTIs are more frequent in adult females due to anatomic and perhaps sex hormone level differences [35, 36]. The severity of UTIs is usually higher in males [37], an effect that we have not observed, possibly due to the low number of patients with serious UTIs and the resulting low statistical power for that analysis. A few observational studies have addressed the role of gender on the risk of serious infections in SLE, and the available evidence suggests an increased risk of serious infections [8, 33] and hepatitis C [38] in males.

Although immunosuppressants have been generally associated with an increased infectious risk, results from different SLE cohort studies are conflicting, as several demonstrated no association between the use of these drugs and the risk of infection [11, 27, 34]. In this regard, a recent meta-analysis that included observational studies addressing the risk of infection in SLE confirmed a higher risk with the use of cyclophosphamide but not with other immunosuppressants commonly employed, such as methotrexate, azathioprine, mycophenolate mofetil, tacrolimus, or cyclosporin [39]. According to a treat-to-target strategy, achieving DORIS remission is compatible with persisting treatment with immunosuppressants [29, 40]. Our results support the treatment with the recommended doses of immunosuppressants, according to the best standard of care, as they were not associated with a higher risk of infections. In our cohort, the proportion of cyclophosphamide-treated patients was low and only low-dose treatment schemes were used. For these reasons, the risk of infection associated with this agent was probably minimized.

Our study, as all observational studies, is open to the risk of bias by indication. SLE activity and its related immune dysfunction have been associated with increased susceptibility to infection in SLE patients [41, 42]. Although this was not clearly demonstrated in other cohort studies [14, 39], the requirement for prednisolone treatment, for which we found an association with infection, can be a surrogate marker for disease severity. It should be recognized that in an observational study, even when multivariable analysis is used, the effects of disease severity and of medication on the risk of infection cannot be entirely untangled, and only large randomized controlled trials would entirely clarify the adverse effects of SLE therapies, including steroids [43]. However, we can infer that this is unlikely a major cause for concern in our study: we found no association between infection and SLEDAI-2 K or disease activity markers such as hypocomplementemia, leukopenia, lymphopenia, positive anti-dsDNA, or lupus nephritis. Additionally, patients in this cohort mainly presented with low disease activity, which not only limits the ability to identify an effect of high disease activity in the risk of infection but also reduces the potential influence of disease activity on the actual risk of infection. Another limitation of our study is that, despite that influenza and antipneumococcic vaccines are systematically recommended to the patients in this cohort, vaccination

status at baseline was not available and, therefore, while important, could not be considered for analysis [44, 45]. Our results are based on a mostly young, well-controlled, low comorbidity SLE cohort. Therefore, generalizability to SLE cohorts with poorly controlled disease activity, high rate of comorbidities, and use of aggressive immunosuppressive regimens should be applied with caution.

While non-serious infections might also lead to significant morbidity, health resource consumption, and disease flares, recent data informing its associated clinical factors is scarce. A strength of our study is that we have analyzed serious and non-serious infections and their predictors, providing up-to-date information on the prevalence, nature, and risk factors for infections based on a present-day cohort. For this purpose, we used a prospective study design with survival analysis that allows the investigation of the effect of several baseline clinical features on the risk of developing infections through time, overcoming the limitations of previous studies. Additionally, we have analyzed infections occurring in all organs and systems and have included a wide range of variables usually associated with a higher risk of infection, including comorbidities, damage, and disease activity markers.

Although not a substitute for a prospective randomized control trial, our study supports the need to minimize glucocorticoid treatment, while maintaining adequate control of SLE disease activity, given the increased risk of serious and non-serious infections. The systematic treatment with hydroxychloroquine is of utmost importance, given its protective effect against serious infections combined with the notable role in disease activity control and improvement of patients' long-term outcomes.

Author contribution AP was involved in the bibliographic research, data collection, statistical analysis, interpretation of the data, and manuscript drafting. ML was involved in the data collection and manuscript review. HA 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 datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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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