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Predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): a systematic review and meta-analysis.

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ABSTRACT

BACKGROUND. Cardiovascular disease represents an important cause of morbidity and mortality in patients with a diagnosis of systemic lupus erythematosus (SLE), due to a complex interplay between traditional risk factors and disregulation of autoimmunity, but uncertainty is still present about the most important predictors of cardiovascular events.

OBJECTIVES. Aim of our work is therefore to perform a collaborative systematic review on main predictors of cardiovascular events in SLE patients.

METHODS. PubMed, Cochrane was systematically searched for eligible studies on SLE and cardiovascular events between January 2008 and December 2012. Study features, patient characteristics, and incidence of stent thrombosis were abstracted and pooled, when appropriate, with random-effect methods (point estimate [95% confidence intervals]),and consistency of predictors was formally appraised.

RESULTS. A total of 17187 patients were included; of those, 93.1% were female, and the median age was of 39 years. After a median follow-up period of 8 years, cardiovascular events presented in 25.4%, including acute myocardial infarction (4.1%) and stroke (7.3%). The most important predictors may be divided in traditional risk factors, like male gender (OR 6.2, CI 95% 1.49 - 25), hyperlipaemia (OR 3.9, CI 95% 1.57 – 9.71), familiar history of cardiac disease (OR 3.6, CI 95% 1.15 – 11.32) and hypertension (OR 3.5, CI 95% 1.65 – 7.54),and SLE-related features, like the presence of auto-antibodies (OR 5.8 and 5.0, CI 95% 3.28 – 7.78) and neurological disorders (OR 5.2, CI 95% 2.0 – 13.9). A low correlation was shown for importance of organ damage and SLE activity (respectively

OR 1.4, CI 95% 1.09 – 4.44 and OR 1.2, CI 95% 1.2 – 1.2), as well as for the age at diagnosis (OR 1.1, CI 95% 1.07 – 1.17).

CONCLUSIONS. Cardiovascular events in SLE patients are caused by a multifactorial mechanism, including both traditional and disease-specific risk factors. A global valuation with an individual risk-stratification based on both these features is important to correctly manage these patients in order to reduce negative outcomes.

Keywords: systemic lupus erythematosus, cardiovascular events, predictors

INTRODUCTION

Systemic lupus erythematosus (SLE) represents a chronic autoimmune disorder displaying a wide spectrum of clinical manifestations, ranging from malar rash, arthralgias and characteristic plasma autoantibodies to life-threatening manifestations such as nephritis or thrombosis. In the past, renal and central nervous system involvement were the main causes of mortality. [1] [2] [3] but with the therapy improvement, especially steroid treatment, life expectancy extended, with a parallel increased cardiovascular mortality and morbidity.

Traditional risk factors (like diabetes, hypertension, hyperlipidemia and smoking addiction) are common in these young patients, probably as a side effect of immunosuppressant therapy; [4] [5] on the other side, from a pathological and clinical point of view, they do not completely explain the increased frequency and the early presentation of cardiovascular disease in this population. [6] [7] [8] Probably increased inflammatory response, as well as steroid therapy, may play a crucial role in atherogenesis. [9] [10] [11] [12] Several studies have been made to investigate this topic and to identify some predictors of the thrombosis burden, a crucial step to prevent undesirable outcomes. [13] [14] [15] [16]

However, the evidence of the increased cardiovascular disease incidence in the current era is fraught with conflicting data on risk and predictors, which remains difficult to overcome without a systematic approach. Therefore we aimed to perform a meta-analysis focusing on incidence and predictors of cardiovascular events in SLE patient.

METHODS

This work was conducted in keeping with current guidelines, including the recent Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses (QUOROM) statement, as well as recommendations from The Cochrane Collaboration and Meta-analysis Of Observational Studies in Epidemiology (MOOSE). [17] [18] [19] [20]

2.1. Search strategy

MEDLINE/PubMed was searched for pertinent articles published in English between January 2008 and December 2012 according to the following strategy, in keeping with established methods [21]and incorporating wild cards (identified by *): (systemic lupus erythematosus OR SLE) AND (((coronary OR arterial) AND (stent* OR ptca OR angioplasty OR cabg OR bypass AND (graft* OR surgery))) OR (myocardial infarction OR dissection OR thrombosis OR acute coronary syndrome)). We choose the time criteria because of the publication in 2008 of the guidelines of the Eular that deeply impacted on clinical practice.[22]

2.2. Study selection

Retrieved citations were first screened independently by two unblinded reviewers at the title and/or abstract level, with divergences resolved after consensus.

If potentially pertinent, they were then appraised as complete reports according to the following explicit selection criteria, which were piloted over the first 5 cases. Inclusion

criteria were (all had to be met for inclusion): (i) human studies, (ii) investigating patients with diagnosis of systemic lupus erythematosus, defined by American College of Rheumatology criteria [23] [24], with a thrombotic event, (iii) published between 2008 and 2012, (iv) reporting predictors of cardiovascular events obtained through univariable or multivariable analysis. Exclusion criteria were (any one alone was enough for exclusion):(i) non-human setting, (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients with SLE and cardiovascular events was selected, or if equal, the study with the largest number of overall patients).

2.3. Data extraction

The following data were independently abstracted by two unblinded reviewers on pre-specified electronic forms, which were piloted over the first 5 cases, with divergences resolved after consensus. In particular, authors, journal, year of publication, baseline, disease and therapy features, events and multivariate predictors (estimator, point summary estimate of risk, 95% confidence intervals).

End-points of interest for the present review were the incidence of cardiovascular events in SLE patients at the different time points as well as univariable and multivariable predictors of cardiovascular events. Given the exploratory yet comprehensive scope of this collaborative review, no explicit primary end-point was specified.

2.4. Internal validity and quality appraisal

The quality of included studies was independently appraised by two unblended reviewers on pre-specified electronic forms, which were piloted over the first 5 cases, with divergences resolved after consensus. Modifying the MOOSE item list in order to take into account the specific features of included studies, we separately abstracted and appraised study design, setting, data source, and statistical methods for univariable and multivariable analysis, as well as, in keeping with The Cochrane Collaboration approach, the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate, or high risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias).

2.5. Data analysis and synthesis

Continuous variables are reported as mean (standard deviation) or median (1st;3rd quartile). Categorical variables are expressed as n/N (%). Statistical pooling for incidence estimates was performed according to a random-effect model with genericinverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Conversely, risk estimates were not pooled from individual studies as this approach would have not been feasible and valid given the high risk for publication bias). We instead adopted Ross et al.'s approach [25], and appraised the prevalence of studies in which a given predictor was proven significantly and independently associated with the outcome of interest. Small study bias was appraised by graphical inspection of funnel plots. Using rates of event as dependent variable, a meta-regression was performed to test the effect of clinical features. Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and

based on the Cochran Q test, with I2 values of 25%,50%, and 75% representing, respectively, mild, moderate, and extensive statistical inconsistency.

RESULTS

3.1. Review profile and included studies

From a total of 2799, 32 studies were included (Figure 1); the median follow-up was of 8 years (1^{st} quartile 6.7 years; 3^{rd} quartile 8.8 years).

A total of 17187 patients were included; of those, 93.1% were female, and the median age was of 39 years. Hypertension was reported in 42.6% of the patients, dyslipidemia in 44% and almost 20% were active smokers (Table 1).

The median length of SLE diagnosis was 9 years, and most of the patients were in therapy with steroids (69.7%) and/or with other immunosuppressant (50.5%), and 36% with platelet inhibitors. Cardiovascular events presented in 25.4%, including acute myocardial infarction (4.1%) and stroke (7.3%) (Table 2).

3.2. Frequency and consistency of SLE predictors in cardiovascular events

Many candidate risk factors were considered in the included studies of our meta-analysis, some of them in common with the general population, some specific of SLE patients. The

most frequently and consistently reported predictors of cardiovascular events in SLE patients were male gender (OR 6.2, CI 95% 1.49 - 25), presence of plasmatic anti-cardiolipine antibodies (OR 5.8, CI 95% 2.22 – 15.5) and global anti-phospholipid antibodies (OR 5.0, CI 95% 3.28 – 7.78) and presence of neurological disorders (OR 5.2, CI 95% 2.0 – 13.9); dyslipidaemia (OR 3.9, CI 95% 1.57 – 9.71), familiar history of cardiac disease (OR 3.6, CI 95% 1.15 – 11.32), hypertension (OR 3.5, CI 95% 1.65 – 7.54), as well as azathioprine and steroid treatment also appeared significant predictors, even though less consistently. (Fig.2, Table 3)

A low correlation was shown for importance of organ damage and SLE activity (respectively OR 1.4, CI 95% 1.09 – 4.44 and OR 1.2, CI 95% 1.2 – 1.2), as well as for the age at diagnosis (OR 1.1, CI 95% 1.07 – 1.17). However, it must be emphasized that these are not pooled estimates but estimates from singles studies, and thus at high risk of small study effects and reporting bias. These results were confirmed at a subsequent meta-regression analysis.

3.3 Internal validity of the studies

The most important features of this study are summarized in Table 4. The design was more frequently retrospective (56%), with a multicenter setting in 46.8%; most of the studies were conducted in North America (40.6%) and Europe (37.5%).

DISCUSSION

Patients with systemic lupus erythematosus have an increased risk of cardiovascular events, especially a thrombotic event. To the best of our knowledge, this is the first systematic review focusing on incidence and predictors of cardiovascular events in SLE patients. In a total of 17187 patients from 32 studies, the incidence of cardiovascular events was almost 25%, and 4.5% of the patients had an acute myocardial infarction.

None of the 17 candidate predictors identified occurred in all the studies included, reflecting the complex pathophysiology of cardiovascular events in SLE and the limitations in its classification, and the ensuing challenges in conducting case–control or cohort studies capable of providing precise, accurate, and consistent statistical results. Nevertheless, analyzing some candidate predictors of cardiovascular events in this population, it emerged that they may be divided in two groups: traditional risk factors and features of SLE patients.

In the first group, male gender resulted to be one of the strongest predictor, but the weight of this feature should be carefully considered, remembering that the main part of SLE patients are women. An important role is also played by dyslipidemia, hypertension, familiar history of CAD (coronary artery disease) and smoking addiction. The prevalence of these risk factors in such young patients is unusual in the global population; the early onset of pathologies like hypertension and diabetes may be supposed to be related both to high inflammatory response due to the autoimmune disease, both to long-lasting pharmacological treatment with immunosuppressant, and especially steroids. The impact of cigarette smoking may be multifactorial: on one side, it may contribute to cardiovascular risk amplifying the classical atherogenic process. On the other hand, it may play a role on

some aspects of SLE evolution: smoking has been associated with progression of lupus nephritis to end-stage renal disease, it may reduce the response to immunosuppressant therapies, and, causing a low-grade systemic inflammatory response, it may worsen the progression of the disease. [26] [27]

In the second group, the highest correlation with cardiovascular events was shown by the presence of autoantibodies, like antiphospholipid antibodies, anticardiolipin and lupus anticoagulant, produced in thirty to forty percent of SLE patients. However, this risk factor doesn't fully explain the increased thrombosis risk in SLE, because literature data show that only 10% of "positive" patients experience a thrombotic event, and 40% of SLE thrombosis cases are autoantibodies negative. [28] [29]

A role in the increased risk of this population seemed to be associated with the therapy used to cure the autoimmune disease, both steroid and immune-suppressant. [30] Part of the effect of these treatments may be related to their impact on hypertension, dyslipidaemia and diabetes, well known side-effects of steroids, explaining on the other side the high prevalence of these comorbidities in this young population. [31] Furthermore, high dosages of glucocorticoids are associated with a higher disease activity, and therefore they are probably a proxy for this variable. Nevertheless, the activity and severity of the disease, expressed by some multi-variable scores like Systemic SLE Damage and SLEDAI2K, as well as disease duration, seemed instead to have a smaller impact on cardiovascular risk. This result appears in contradiction with the hypothesis of the increased atherogenesis due to inflammatory response in SLE, underlaying the multifactorial mechanism of cardiovascular disease in these patients.

Therefore, cardiovascular events in SLE patients cannot be systematically avoided just by addressing a single or a few risk factors, but only through a global appraisal and

management of each individual patient. To correctly manage these patients, it becomes fundamental to individually risk-stratify the patient, stressing the importance of acting on modifiable common risk factors like hypertension and dyslipidemia, and accurately searching for SLE-specific features.

Limits of this study

Our systematic meta-analysis have some limitations related to the nature of the primary studies. First, more than half of the included studies were case-control or cross-sectional studies rather than cohort studies, which did not have the same risk estimates.

Second, we did not perform a pooled analysis of risk predictors, because this would have been limited by substantial reporting bias.

Moreover, publication bias remains always a concern because the present review was based solely on published studies. Most predictors were appraised in only a subset of studies, limiting the precise quantitative estimation of their independent predictive role.

CONCLUSIONS

Systemic lupus erythematosus (SLE), an autoimmune disease with many presentations, is graved by an increased risk of cardiovascular events. Patients with this pathology, usually a young population, show a higher prevalence of common CAD risk

factors, unusual for the early age, and a wide spectrum of autoimmune-disease specific features related to coronary artery events.

A global evaluation with an individual risk-stratification based both on modifiable and SLE-specific risk factors of each patient is fundamental to correctly manage these patients in order to reduce negative outcomes.

REFERENCES

[1] Cervera R, Khamashta M A, Font J et al. Morbidity and mortality in systemic lupus erythematosus during a 5-years period: a multicenter prospective study of 1000 patients. *Medicine* 1999; 78:167-75

[2] Bernatsky S, Boivin JF, Joseph L et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2550–7.

[3] Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemiclupuserythematosus. *Arthritis Rheum* 2006;54(8):2550–7.

[4] Pirro M, Stingeni L, Vaudo G et al. Systemic inflammation and imbalance between endothelial injury and repair in patients with psoriasis are associated with preclinical atherosclerosis. *Eur J Prev Cardiol*. 2014 Jun 6.

[5] Awan Z, Genest J. Inflammation modulation and cardiovascular disease prevention. Eur J Prev Cardiol. 2014 Apr 7

[6] Mok CC, Tang SS, To CH, Petri M. Incidence and risk factors of thromboembolism in systemiclupuserythematosus: a comparison of three ethnic groups. *Arthritis Rheum* 2005;52(9):2774–82.

[7] Esdaile JM, Abrahamowicz M, Grodzicky T et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331–7.

[8] Boucelma M, Haddoum F, Chaudet H et al. Cardiovascular risk and lupus disease. *Int Angiol*. 2011 Feb;30(1):18-24.

[9] Shoenfield Y, Gerli R, Doria A et al. Accelerated atherosclerosis in autoimmune rheumatic diseases. *Circulation* 2005;112:3337-47

[10] Rhew EY, Ramsey-Goldman R Premature atherosclerosis disease in systemic lupus erythematosus: role of inflammatory mechanism. *Autoimmun Rev* 2006;5:101-5

[11] Salomon JE, Roman MJ. Subclinical atherosclerosis in rheumatoid disease arthritis and SLE. *Am J Med* 2008;121:S3-8

[12] Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum* 2000;43:1801–8.

[13] Bertoli AM, Vilá LM, Alarcón GS et al. Factors associated with arterial vascular events in PROFILE: a Multiethnic Lupus Cohort. *Lupus* 2009 Oct;18(11):958-65

[14] Burgos PI, McGwin G Jr, Reveille JD et al. Factors predictive of thrombotic events in LUMINA, a multi-ethnic cohort of SLE patients (LXXII).*Rheumatology (Oxford)*. 2010 Sep;49(9):1720-5

[15] Kaiser R, Cleveland CM, Criswell LA et al. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. *Ann Rheum Dis*. 2009 Feb;68(2):238-41.

[16] Nikpour M, Urowitz MB, Ibanez D et al. Importance of cumulative exposure to elevated cholesterol and blood pressure in development of atherosclerotic coronary artery disease in systemic lupus erythematosus: a prospective proof-of-concept cohort study. *Arthritis Res Ther.* 2011;13(5):R156.

[17] Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement .Quality of Reporting of Meta-analyses. *Lancet* 1999;354:1896–900.

[18] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.

[19] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12

[20] Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. *The Cochrane Collaboration*;2009. Available from www.cochrane-handbook.org.

[21] Wilczynski NL, Haynes RB; for the Hedges Team. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;2:23.

[22] BertsiasG, Ioannidis JP, Boletis J, Bombardieri S, Cervera R, Dostal C, Font J, Gilboe IM, Houssiau F, Huizinga T, Isenberg D, Kallenberg CG, Khamashta M, Piette JC, Schneider M, Smolen J, Sturfelt G, Tincani A, van Vollenhoven R, Gordon C, Boumpas DT; Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008 Feb;67(2):195-205

[23] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1997;40:1725.

[24] Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25:1271–1277.

[25] Ross JS, Mulvey GK, Stauffer B, et al. Statistical models and patient predictors of readmission for heart failure: a systematic review. *Arch Intern Med* 2008;168:1371–86.

[26] Ward MM, Studenski S. Clinical prognostic factors in lupus nephritis. The importance of hypertension and smoking. Arch Intern Med 1992;152(10):2082–8.

[27] Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EF. Systemic effects of smoking. Chest 2007;131(5):1557–66

[28] Lockshin MD. Update on antiphospholipid syndrome. *Bull NYU Hosp Jt Dis*. 2006; 64(1-2):57–9

[29] Afeltra A, Vadacca M, Conti L, Galluzzo S, Mitterhofer AP, Ferri GM, et al. Thrombosis in systemic lupus erythematosus: congenital and acquired risk factors. *Arthritis Rheum*. 2005; 53(3):452–9.

[30] Buckley T1, Morel-Kopp MC, Ward C et al. Inflammatory and thrombotic changes in early bereavement: a prospective evaluation. *Eur J Prev Cardiol*. 2012 Oct;19(5):1145-52.

[31] Cerrato E1, D'Ascenzo F, Biondi-Zoccai G, et al. Acute coronary syndrome in HIV patients: from pathophysiology to clinical practice. *Cardiovasc Diagn Ther.* 2012 Mar;2(1):50-5.