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CLINICAL MEASURES AND INDICES OF DISEASE ACTIVITY AND DAMAGE AS PREDICTORS OF MORBIDITY AND MORTALITY IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE): A SYSTEMATIC REVIEW OF THE LITERATURE

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10.1136/lupus-2016-000179.115

Background Despite validated clinical measures and indices of disease activity and damage, utilisation of these indices in clinical practice varies, as evidenced by a recent practice pattern survey of Canadian rheumatologists. In this review, we aimed to identify the impact of disease activity and damage on outcomes of mortality and damage to inform upcoming Canadian SLE recommendations utilising the GRADE (Grading of Recommendations Assessment, Development and Evaluation) method.

Materials and methods Following GRADE methodology to fill in evidence-to-decision tables to create recommendations for “minimal investigations needed to monitor SLE patients at baseline and subsequent visits”, a systematic review of the literature including all relevant articles from 1946 to November 2014 was performed searching Medline and Embase. The impact of disease activity and damage measured by commonly utilised indices of disease activity [eg SLEDAI-2K (SLE Disease Activity Index-2000), BILAG (British Isles Lupus Assessment Group), SLAM (SLE Activity Measure), ECLAM (European Consensus Lupus Activity Measurement)], Mexican SLEDAI, and damage [SDI [SLICC/ACR (Systemic Lupus International Collaborating Clinics/ACR Damage Index)] on mortality, damage, and disease flares was evaluated with meta-analyses performed when available. Study quality was assessed by the Newcastle Ottawa scale for observational studies.

Results A title screen of 2797 articles identified 771 papers for full paper review, 106 meeting inclusion criteria and 88 with extractable data. Fifty-five articles describing outcomes with disease activity indices (including BILAG, ECLAM, Mexican SLEDAI, SLEDAI-2K/SELENA-SLEDAI and SLAM) and twenty-four articles describing outcomes with damage based on SDI were identified. Mortality was associated with higher SLEDAI-2K in 6 observational studies [HR 1.14 (95% CI: 1.06,1.22)] and in 5 observational studies with higher SDI scores at baseline and/or immediately prior to death [HR 1.53 (95% CI: 1.28, 1.83)]. Higher SLAM scores were associated with increased risk of damage (SDI > 0) in 3 observational studies [OR 1.06 (95% CI: 1.04, 1.08)]. Mean total BILAG was associated with mortality in one observational study with HR of 1.15.

Conclusions Active lupus disease activity and presence of damage as represented by multiple clinical indices are associated with greater mortality and morbidity in lupus patients. Given the complexity of clinical assessments in SLE patients, the utilisation of validated measures for disease activity and damage is important and will serve to inform upcoming Canadian recommendations for the diagnosis and monitoring of SLE.

Acknowledgements This systematic literature review is being used by the Canadian SLE Working Group to inform future recommendations for the diagnosis and monitoring of SLE.

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ABSTRACT WITHDRAWN

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PHENOME-WIDE ASSOCIATION STUDIES IDENTIFY A NEW ASSOCIATION OF ATRIAL FIBRILLATION IN MALES WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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10.1136/lupus-2016-000179.116

Background Systemic lupus erythematosus (SLE) has a female to male ratio of 9:1. While SLE is more prevalent in females, males with SLE may have increased disease severity and mortality. Mechanisms for these worse outcomes are not fully known. We assessed differences in comorbidities in males vs. females by performing the first electronic health record (EHR)-based phenome-wide association studies (PheWAS) in SLE to compare ICD-9 code-based phenotypes in males versus females. PheWAS are a systematic and efficient approach to identify novel clinical associations within subgroups of patients.

Materials and Methods We used our validated algorithm of ≥ 4 counts of the SLE ICD-9 code (710.0) and ANA positive >1:160 while excluding dermatomyositis and systemic sclerosis ICD-9 codes to identify SLE cases in a de-identified EHR called the Synthetic Derivative (SD). The SD contains over 2.5 million subjects with clinical data collected over several decades with approximate even distribution of predominantly Caucasian males and females. Our algorithm has a positive predictive value (PPV) of 89%, sensitivity of 86%, and an internally validated PPV of 94%. PheWAS were performed in males vs. females adjusting for covariates in a logistic model and correcting for multiple testing using Bonferroni.

Results Using our validated algorithm, we identified 986 females and 111 males with SLE. Males and females with SLE were predominantly Caucasian (69% vs. 69%, $p = 0.32$) and had similar mean current age (52 ± 18 vs. 50 ± 17 , $p = 0.42$), age at first use of a SLE ICD-9 code (43 ± 18 vs. 40 ± 17 , $p = 0.08$), and years of follow-up in the EHR (8 ± 5 vs. 9 ± 5 , $p = 0.23$). Adjusting for race/ethnicity and current age, males were more likely to have cardiovascular ICD-9 codes vs. females including atrial fibrillation odds ratio (OR) = 4.50 (95% CI: 2.32 – 8.72), $p = 8.6 \times 10^{-6}$, other chronic ischaemic heart disease OR = 4.40 (2.24 – 8.64), $p = 1.7 \times 10^{-5}$, atrial fibrillation and flutter OR = 4.08 (2.12 – 7.83), $p = 2.4 \times 10^{-5}$ (Figure 1).

Conclusion We report the first association of atrial fibrillation in males with SLE. While there is a 5-fold increased risk of cardiovascular disease overall in SLE, the risk of atrial fibrillation, specifically in males, has not been identified. These findings demonstrate the ability of PheWAS to uncover novel phenotype associations within subgroups of a disease.