Research Paper

Coronary artery disease (CAD) risk factor analysis in an age-stratified hospital population with systemic lupus erythematosus (SLE)

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A B S T R A C T

Objectives: Patients with systemic lupus erythematosus (SLE) are at higher risk for coronary artery disease (CAD) particularly at a younger age. We sought to determine the effect of risk factors on the prevalence of CAD in age stratified hospitalized patients with SLE.

Methods: The National Inpatient Sample (NIS) was queried for hospitalized patients with SLE during the years 2010–2015, and a control group without SLE. The study sample was stratified by age, 18–35 years, 36–55 years, and adults >55 years. The effect of SLE and traditional Framingham risk factors on the prevalence of CAD were assessed. Dominance analysis allowed for ranking of CAD risk factors in each age group.

Results: A total 167,466 patients were matched to an equal number of controls. 88.8% were women, 48.5% Caucasian and 29% African-American. In lupus patients 18–35 years prevalent risk factors included hyperlipidemia, hypertension, hypercoagulability and CKD. Diabetes and depression ranked least important. In middle and older patients, traditional risk factors were dominant. In adults >55 years the prevalence of CAD appears higher in Caucasians whereas in young patients 18–35 years, African Americans are dominant.

Conclusion: CAD in the young adult patient with SLE is represented predominately by an African-American population and it is dominated by a hypercoagulable state and a less significant role for diabetes. In the lupus cohort over 55 years, which is predominantly Caucasian, SLE specific factors are less significant.

1. Introduction

The prevalence of atherosclerotic cardiovascular disease (CAD) is significant in patients with systemic lupus erythematosus (SLE), occurs in a younger age group, and is impacted by both traditional risk factors and the burden of immune mediated inflammation [1–5]. The pathogenesis of arterial wall injury in SLE is multifactorial related to the prevalence of renal disease and hypertension (HTN), antiphospholipid antibodies and thrombosis, treatment with corticosteroids, and the endothelial response to immune-complex mediated inflammation [6]. Traditional risk factors also contribute to the burden of vascular disease albeit, over many decades. While male sex is shown to be a risk factor for CAD, more females will develop atherosclerotic heart disease due to the epidemiology of the disease.

A recent long-term follow-up study by Tselios et al. covering the first 15 years following menopause observed differences over time in the importance of risk factors for a cardiovascular event [2]. For example, SLE was a powerful predictor in the first eight years of the study when the age ranged from 35 to 54 years. The authors noted that in the second half of the study when SLE activity had decreased, traditional Framingham risk factors, HTN, DM and HLD were more important. In fact, these authors suggest that the Framingham Risk Factor tool underestimates cardiovascular risk since it does not take into account systemic inflammation as well as long term organ damage which are strong predictors of all-cause mortality in agreement with other studies [7, 8].

Although strong recommendations can be made to recognize and manage the risk factors attendant to CAD in patients with SLE, the protean nature of the illness, chronicity and organ damage, and the insidious development of Framingham risk factors complicates the process. The primary objective of this observational study was to assess and contrast

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the prevalence of risk factors contributing to CAD in a large cohort of hospitalized lupus patients compared to matched controls. Specifically, we sought to determine the impact and ranking of individual risk factors on the diagnosis of CAD in defined age groups with SLE.

2. Patients and methods

2.1. Data source

This study was conducted using National Inpatient Sample (NIS) of the Health Care Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). NIS is a publicly available national registry that includes data from all community hospital discharges in the United States. The database represents a random selection of a 20% sample of all inpatient hospitalizations. Unique patient identifiers are not contained in the database. Since obtaining estimates of national or state level prevalence was not a primary study objective, we utilized unweighted data in compliance with regulatory guidelines outlined by HCUP. Full detail and structure were previously described [9, 10].

2.2. Study population

NIS data was queried for all patients diagnosed with systemic lupus erythematous during the years 2010–2015. Patients with SLE were identified using International Classification of Diseases, Ninth Revision (ICD-9) code 710.0. All patients with a diagnosis of SLE (primary and secondary) were included in the study. Patients who were diagnosed with any form of malignancy (primary solid tumor, metastatic lesion, or hematological malignancy), as well as patients diagnosed with autoimmune diseases other than SLE including discoid and drug induced lupus were excluded. The study sample was stratified according to age into young adults (18–35 years), middle aged (>35 ≤ 55 years) and older adults (>55 years). We used as controls a matched cohort of hospitalized patients from the NIS database without ICD-9 code 710.0. To reduce bias due to confounding, matching of demographic data was performed on age, sex, race, household income, insurance type, hospital teaching status and urban or rural location.

2.3. Covariates and study outcomes

Primary payers were classified into Medicare, Medicaid, private insurance, or self-pay. Household income was estimated based on the median income of the patient's ZIP code. Hospital classification into urban or rural was based on Core Based Statistical Area (CBSA) designated metropolitan or micropolitan. Hospitals were defined as a teaching institution if they had one or more ACGME approved residency programs or were a member of the Council of Teaching Hospitals (COTH).

Our primary objective was to assess the prevalence of CAD risk factors and their ranking among a hospitalized population of patients with SLE identified from the NIS data and compared to an equal number of hospitalized matched controls without SLE. Within the three age groups we assessed the prevalence and ranking of individual risk factors. We used Clinical Classification Software (CCS), a categorization scheme that groups the International Classification of Diseases, Ninth Revision (ICD-9) codes into mutually exclusive categories (Suppl. Table 2).

Traditional CAD risk factors were derived from prospective cohorts including the Framingham Heart Study and the Seven Countries Study and included diabetes mellitus, hypertension, hyperlipidemia, tobacco use and obesity [11, 12]. We also addressed known risk factors for CAD which are prevalent in SLE patients including a hypercoagulable state (primary and secondary) (ICD-9 codes 289.81, 289.82), lupus nephritis and depression [13, 14]. Corticosteroid therapy, immunosuppressive drugs and chronicity scores cannot be determined from the NIS data.

2.4. Statistical analysis

Patient demographics, socioeconomic status, comorbidities and hospital characteristics were compared between SLE patients and controls using the standardized mean difference (SMD) of effect size. Cohen recommends that a SMD value near 0.2, 0.5 and 0.8 correlate with a small, medium and large effect size respectively [15]. Results are given as SMD (95% CI). Multivariable conditional regression models were used to estimate adjusted odds ratios (AOR) (Suppl. Figure 2). Discrimination of aggregated risk factors to predict CAD was addressed with receiver-operator curves (ROC). The area under the curve ≥0.7 to <0.8 is considered as acceptable discrimination; ≥ 0.8 excellent discrimination.

General dominance statistic developed by Azen and Traxel (2009) was applied for ranking of risk factors [16]. General dominance statistics were derived by calculating the impact of each predictor on the overall model. The relative weight of each risk factor in explaining the risk for CAD was obtained. A bootstrap method in which a one thousand samples will be used to assess the robustness of the dominance relationships.

Variables had missing values in <1.0% of participants except for race which was missing in 5.3%. To test whether missing data could introduce bias into the study, we assumed that missing data on race was not random and accordingly, we obtained multivariate imputation by chained equations method estimated from sequential multivariable models with fully conditional specifications [17]. Since identical results were obtained, results without imputation are reported. Statistical analysis was performed using STATA 15 (Stata Corp.); the significance level was set at p ≤ 0.05.

3. Results

Between the years 2011–2015 we identified a total of 167,466 eligible SLE patients from the NIS database (Suppl. Figure. 1). Demographics and prevalence of risk factors for SLE and control populations are shown in (Suppl. Table 1). The mean age for the SLE population was 50.7 ± 17.2 years. The majority of patients were female (88.8%) and Caucasian (48.5%) followed by African-American (29.8%). For the entire population, the prevalence of CAD among SLE and controls was 17.2% and 14.5% respectively.

Table 1 summarizes the cardiovascular risk factors in the entire study population according to their age group. In reference to the control group, young patients with SLE had higher prevalence of chronic kidney disease (29.9% vs 5.1%; SMD = 0.7), hypertension (45.9% vs 13.2%; SMD = 0.8) and hypercoagulability (7.6% vs 0.5%; SMD = 0.4). As the population ages the difference in prevalence of these risk factors become less prominent.

Table 2 summarizes the cardiovascular risk factors among study population with CAD according to their age group. CKD and HTN are prevalent in both SLE and controls in all three age groups. Among young age group 18–35 years the prevalence of CAD is greater in African-American. As the population ages the prevalence of CAD increases in Caucasians and decrease in African-Americans. Hypercoagulability, a frequent comorbidity in SLE and prevalent in the young age group 18–35 years (SLE 18.7% vs control 3.0%; SMD = 0.4)), decreases with age. DM is less frequent in SLE vs controls in all age groups. This is most striking in young patients 18–35 years (SLE 13.8% vs control 47.4%; SMD = 0.9) but is also observed in middle age (SLE 33.6% vs control 55.4%; SMD = 0.4), and SLE patients >55 years (SLE 35.1% vs control 49.1% SMD = 0.3). Hyperlipidemia as a risk factor is less frequent in younger SLE patients with CAD than controls (SLE 21.6% vs control 37.2% SMD = 0.4) and remains lower in older age groups with a moderate effect size.

Ranking of risk factors according to their contribution for CAD are shown graphically in Fig. 1 in which ranking is graded based on dominance weight from one the highest to nine, the least dominant risk factor. HLD and HTN are dominant risk factors in all age groups, both SLE and non-lupus controls. Both depression and obesity are not considered important risk factors regardless of age. Other risk factors tend to

Table 1
Prevalence of risk factors stratified by age group.

	Age 18–35			Age 36–55			Age >55		
	Control n = 38,243	SLE n = 37,793	Std diff [95%CI]	Control n = 62,345	SLE n = 63,032	Std diff [95%CI]	Control n = 66,878	SLE n = 66,641	Std diff [95%CI]
Coronary artery disease	0.9	3.0	0.2 [0.1–0.2]	9.8	12.5	0.1 [0.1–0.1]	26.7	29.7	0.1 [0.1–0.1]
Hyperlipemia	2.8	6.6	0.2 [0.2–0.2]	20.7	18.8	0.0 [0.0–0.1]	41.9	34.8	0.1 [0.1–0.2]
Tobacco use	14.2	16.7	0.1 [0.1–0.1]	31.1	26.9	0.1 [0.1–0.1]	26.9	24.5	0.1 [0.1–0.1]
Hypercoagulability	0.5	7.6	0.4 [0.4–0.4]	0.7	6.3	0.3 [0.3–0.3]	0.4	3.2	0.2 [0.2–0.2]
Depression	7.0	12.6	0.2 [0.2–0.2]	15.9	17.8	0.1 [0.0–0.1]	15.8	17.5	0.0 [0.0–0.1]
Obesity	11.3	11.0	0.0 [0.0–0.0]	22.4	17.5	0.1 [0.1–0.1]	18.0	14.3	0.1 [0.1–0.1]
Diabetes mellitus	8.2	7.4	0.0 [0.0–0.0]	26.7	21.0	0.1 [0.1–0.1]	36.2	28.5	0.2 [0.2–0.2]
Hypertension	13.2	45.9	0.8 [0.8–0.8]	47.0	57.3	0.2 [0.2–0.2]	72.2	71.8	0.0 [0.0–0.0]
Chronic kidney disease	5.1	29.9	0.7 [0.7–0.7]	11.5	24.2	0.3 [0.3–0.4]	18.9	24.8	0.1 [0.1–0.2]

Data are presented as mean (SD) for continuous measures, and % for categorical measure.

discriminate between age groups. For example, hypercoagulability is dominant only in the young age group. By comparison, in young lupus patients DM typically an important Framingham risk factor, ranks low in the prediction model. Ranking of male sex increases with age becoming dominant in the older age group while the importance of CKD is greatest in the age group 18–35 years. Using dominance analysis in bootstrap samples, similar results were obtained (Supplement figure 3).

The discriminating ability of aggregate risk factors in predicting CAD was assessed by inspection of ROC (Fig. 2). The prediction model demonstrates acceptable discrimination in the SLE cohort 18–35 years of age (ROC 0.73), and 36–55 years (ROC 0.71) but fails to discriminate in the cohort >55 years (ROC 0.67). Overall, the discrimination ability of the prediction model was more robust in non-lupus controls compared to patients with SLE. This was most notable in controls 18–35 years (ROC 0.88)) and decreased with age >55 years (ROC 0.7).

4. Discussion

In a nationwide sample of hospitalized patients with SLE using the NIS database we investigated the impact of cardiovascular risk factors in predicting CAD in age stratified populations of SLE patients and matched control group. We found that CAD in the young adult patient with SLE is represented predominately by an African-American population and it is dominated by a hypercoagulable state and a less significant role for diabetes. In the lupus cohort over 55 years, which is predominantly Caucasian, SLE specific factors are less significant.

Two important risk factors noted in our study include hypercoagulability, a surrogate for the antiphospholipid syndrome, and kidney disease. These findings are consistent with published literature in which renal lupus and antiphospholipid syndrome are frequent corollaries of atherosclerosis, the metabolic syndrome and CAD [18–20]. In agreement with Scalzi et al. we found that with advancing age the prevalence of CAD in the Caucasian population increased by 2.5-fold while decreasing by a similar amount in African-Americans [22]. The present results including the ranking of risk factors and discriminating characteristics using ROC (Fig. 2) support the argument that SLE specific factors such as hypercoagulability and kidney disease in younger patients contribute to these age-related disparities. Traditional risk factors play a more dominant role in older populations.

In epidemiologic studies variability in the importance of individual risk factors for CAD among SLE populations is in part due to methodological design and inconsistency in patient and control group selection [3, 8, 21]. We sought to circumvent some of these issues by using single source SLE and exact-matching control groups. By dividing the populations into evenly matched age cohorts we could better assess the impact of individual and aggregate risk factors.

Among individual predictors of CAD, hyperlipidemia ranks as most important regardless of age in both SLE and controls (Fig. 1). Despite

Table 2
Age stratified risk factors in SLE and controls with CAD.

	Age 18–35			Age 36–55			Age >55		
	Control n = 331	SLE n = 1,141	Std diff [95% CI]	Control n = 6,118	SLE n = 7,903	Std diff [95% CI]	Control n = 17,838	SLE n = 19,799	Std diff [95% CI]
Race									
Caucasian	20.5%	25.6%	Ref	43.8%	44.7%	Ref	67.6%	69.0%	Ref
African-American	54.4%	51.4%	0.1 [0.0-0.3]	38.2%	35.5	0.1 [0.0-0.1]	20.5%	20.2%	0.0 [0.0-0.0]
Hispanic	15.1%	13.6%	0.2 [0.0-0.4]	9.3%	10.3%	0.0 [0.1-0.0]	7.4%	7.1%	0.0 [0.0-0.0]
Risk factors									
Hyperlipidemia	37.2	21.6	0.4 [0.2–0.5]	53.6	41.3	0.2 [0.2–0.3]	58.8	50.6	0.2 [0.1–0.2]
Tobacco use	29.9	27.4	0.1 [0.1–0.2]	44.8	36.8	0.2 [0.1–0.2]	31.8	28.6	0.1 [0.1–0.1]
Hypercoagulability	3.0	18.7	0.4 [0.3–0.6]	1.1	8.0	0.3 [0.3–0.4]	0.4	3.0	0.2 [0.2–0.2]
Depression	16.3	17.4	0.0 [0.1–0.2]	19.2	19.3	0.0 [0.0–0.0]	15.2	16.0	0.0 [0.0–0.0]
Obesity	29.0	18.1	0.3 [0.2–0.4]	28.7	21.3	0.2 [0.1–0.2]	18.9	14.4	0.1 [0.1–0.1]
Diabetes mellitus	47.4	13.8	0.9 [1.0–1.0]	54.4	33.6	0.4 [0.4–0.5]	49.1	35.1	0.3 [0.3–0.3]
Hypertension	70.4	69.8	0.0 [0.1–0.1]	79.8	75.6	0.1 [0.1–0.1]	84.6	80.2	0.1 [0.1–0.1]
Chronic kidney disease	42.9	49.2	0.1 [0.0–0.3]	27.9	32.9	0.1 [0.1–0.1]	29.4	31.8	0.1 [0.0–0.1]

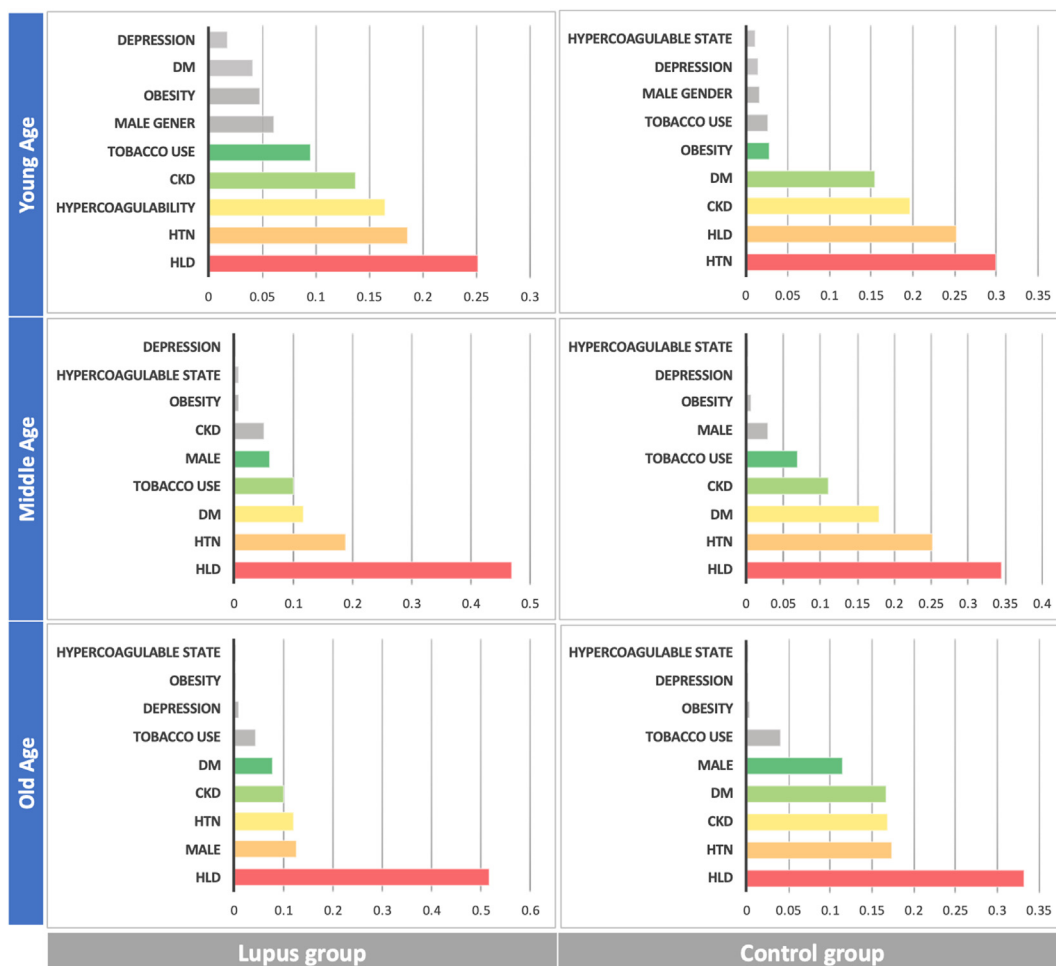Data are presented as mean (SD) for continuous measures, and % for categorical measure.

Fig. 1. Ranking of CAD risk factors based on dominance weight among the three age groups.

variations in study design and population sampling this observation is consistent throughout the literature on CAD in lupus [23,24]. Furthermore, there are ample explanations for deviant lipid values including autoantibodies to lipoprotein lipase and HDL, enhanced oxidation of LDL cholesterol and inflammatory cytokines which affect lipid metabolism. Corticosteroids and lupus nephritis also contribute to the comorbidity of dyslipidemia. While it has been suggested that lipid profiles be aggressively treated to target levels, lowering of cholesterol values has not always demonstrated a beneficial effect [25]. Explanations include inadequate surrogate markers for CAD, short duration of trials and small

sample size. Chan et al. has recently shown that a sub-fraction of SLE low-density lipoprotein cholesterol containing platelet activating factor and lysophosphatidylcholine promotes early vascular aging resulting in premature atherosclerosis [26]. An increase in a sub-fraction with enhanced potential for an inflammatory vascular event could explain why standard of care may not be effective.

Hypertension ranks second as a dominant risk factor in young and middle age lupus patients whereas male gender ranks second in importance in the age group >55 years, perhaps representing a permissive effect of estrogen in younger age lupus patients. It has also been
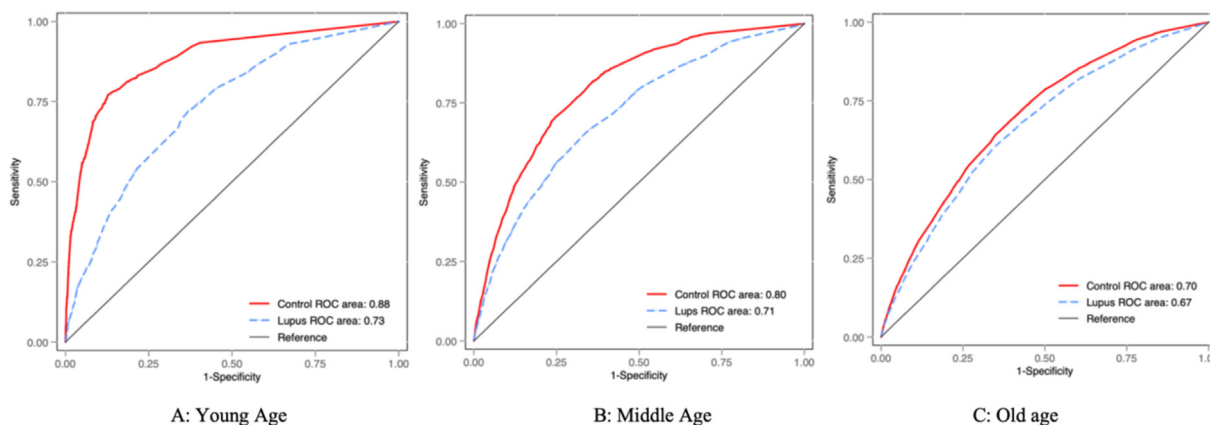

Fig. 2. Comparison of the predictive ability of CAD risk factors in the three age strata for SLE and controls. AUC = area under the receiver operating characteristics curve; A = 0.15, B = 0.09, C = 0.03.

suggested that cardiovascular risk calculators such as the Framingham Risk Score may be less sensitive in the lupus population, an observation consistent with the current data [7,27]. Using traditional calculation tools for CAD, diabetes mellitus would appear to be an important risk factor as seen in the control population regardless of age. However, a different model emerges in lupus in which the prevalence of diabetes is significantly less than in controls and in fact, appears to play a minimal role as a predictor of CAD in patients 18–35 years (Fig. 1). We speculate that hydroxychloroquine commonly used in SLE which has a favorable effect on glycemic control, may ameliorate the potential impact of diabetes mellitus in CAD [28–30]. The importance of this observation warrants further investigation.

Observational data in which we have explored risk profiles in a large lupus population have a number of limitations. Only categorical information is available based on the accuracy of inpatient ICD codes and which do not capture readmissions. Some conditions may not have formal validation of ICD codes. Factors such as family history, clinical, serologic and inflammatory markers of disease activity, medications including steroids and immunosuppressive drugs, and the extent of organ damage are not available in the NIS files. Lastly, the study is retrospective and prone to error more than prospective registries. The strength of this study lies in the large lupus population with an exact-matching control group available through the NIS.

In conclusion, CAD in the young adult patient with SLE is represented predominately by an African-American population and is related to both immunologic and inflammatory mechanisms in which kidney disease, hypercoagulability and hyperlipidemia play important roles. In the lupus cohort over 55 years, which is predominantly Caucasian, SLE specific factors are less significant. HLD and HTN are dominant in all age groups. DM is underrepresented in the entire SLE population. Prudence dictates attention to both investigation and management of traditional CAD risk factors while not losing sight of the underlying autoimmune process. Further analysis is planned to examine the impact of aggregated data on CAD outcome in SLE. The age spectrum of racial and sex distribution, lipid metabolism and the decreased prevalence of DM also warrant additional study.

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Declaration of competing interest

Authors have disclosed no conflicts of interest. Drs Levinson and Abugroun contributed equally to the manuscript. All authors had a role in writing the manuscript. All author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijchy.2020.100056.

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