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Sex Differences in Healthcare Utilization, End-stage Renal Disease and Mortality among Medicaid Beneficiaries with Incident Lupus Nephritis

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Abstract

Objective—While systemic lupus erythematosus (SLE) and lupus nephritis (LN) disproportionately affect females, prior studies suggest that males may experience poorer outcomes. We investigated sex differences in healthcare utilization, end-stage renal disease (ESRD) and mortality among patients with LN receiving Medicaid, public insurance for low-income individuals.

Methods—Within Medicaid Analytic eXtract (MAX) from 29 states (2000–2010), we used billing claims to identify individuals 5–65 years with incident LN (PPV 80%). MAX data were linked to the US Renal Data System to determine ESRD, and to Social Security Death Index files to determine death. We estimated adjusted incidence rate ratios (IRR) by sex for healthcare utilization using Poisson regression and used multivariable proportional hazards models to compare risks of ESRD and death by sex.

Results—Of 2750 patients with incident LN, 283 (10%) were male. Mean follow-up was 3.1 (SD 2.3). Mean age was 25 (SD 14) years among males; 30 (SD 14) among females (p<0.01). Males had fewer outpatient (IRR 0.88, 95% CI 0.80–0.97) and emergency department visits (IRR 0.75, 95% CI 0.63–0.90). The 5-year cumulative incidence of ESRD was 22.3% in males, 21.2% in females and of death, 9.4% in males, 9.8% in females. There were no sex differences in ESRD (HR 1.02, 95% CI 0.73–1.41, ref=females) or death (HR 0.81, 0.47–1.35).

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Conclusion—In this incident LN cohort, ESRD and mortality were extremely high overall, but not increased among males compared to females. In this vulnerable population, biologic and healthcare utilization differences by sex may not significantly affect outcomes.

Background

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease that disproportionately affects females; the prevalence is 6 to 9 times higher compared to males. (1, 2) Hypotheses for this female predominance include different environmental exposures, sex hormones, cell microchimerisms, and chromosome X dosage.(3) Prior studies suggest that while SLE is rare among males, their disease may be more severe and damage accrual greater.(4–6) Males with SLE have been shown to have more cytopenias, hemolytic anemia, cardiovascular disease and antiphospholipid antibodies, as well as more constitutional symptoms including fever and weight loss.(4, 6–8) In addition, a higher proportion of males may present with lupus nephritis (LN) at the time of SLE diagnosis, as well as during the disease course.(9, 10)

Few studies to date have examined differences in end-stage renal disease (ESRD) by sex. One study (N=93, 31 males), found no difference in end-stage renal disease (ESRD) or doubling of serum creatinine over approximately 40 months of follow-up, but did report that males experienced greater deterioration in renal function.(11) Another retrospective study of 121 patients, 17 male, found that males had an increased risk of chronic renal insufficiency compared to females.(12) Two larger studies have been performed. In a U.S.-based academic cohort of 1979 patients with incident SLE (8% male), there were 13 cases of ESRD among males and 85 among females (OR 2.3, 95% CI 1.2–4.5). A similarly increased risk was found in a Taiwanese cohort of 4130 SLE patients, 11% of whom were male (HR for ESRD 2.2, 95% CI 1.4–3.6 among men vs. women). Studies that have examined differences in mortality among SLE patients by sex have presented conflicting findings. One study including 408 SLE patients (69 males), demonstrated that mortality rates were higher among males, after adjusting for age, comorbidities and socioeconomic status (HR 1.55, 95% CI 1.02–2.35).(13) Another study however, that used standardized mortality ratios of deaths observed to expected, found higher mortality among females with SLE.(14)

To our knowledge, there are no incident LN cohort studies in diverse, non-academic center-based U.S. patient populations that have examined sex differences in ESRD or mortality. Similarly, while mortality is more than twice as high among patients with LN than SLE without LN, differences by sex are not well understood.(15) We aimed to study rates of ESRD and mortality in a diverse, nationwide cohort of incident LN patients enrolled in Medicaid, the U.S.-based public insurance covering >70 million low income individuals, to determine whether there were differences by sex. We hypothesized that rates of both ESRD and mortality would be higher among males. In addition, we aimed to examine healthcare utilization patterns among patients with LN prior to the development of ESRD. We hypothesized that healthcare utilization by males would be lower compared to females and potentially, that delays in care seeking would be related to ESRD, particularly in this vulnerable patient population.(16)

Methods

Cohort identification

We utilized the Medicaid Analytic eXtract (MAX) with billing claims from all Medicaid beneficiaries from the most populated 29 U.S. states from 2000–2010. We identified children and adults aged 5–65 years with ≥ 3 SLE claims and ≥ 2 LN claims using a validated ICD-9 code-based algorithm for LN (PPV 80%).(17) We required ≥ 24 months of continuous enrollment in Medicaid with no LN-related codes (ICD-9 codes for glomerulonephritis, renal failure or nephrotic syndrome) prior to the first LN code (index date) for inclusion as incident LN.(1)

Outcomes

End-stage renal disease (ESRD)—To assess incidence of ESRD, we merged MAX data with the U.S. Renal Data System (USRDS) from 2000–2010. USRDS is a national data system that integrates demographic and diagnosis data as well as dialysis claims for nearly all patients in the U.S. who receive renal replacement therapy (dialysis or transplantation). (18) In order for patients to be registered in the Centers for Medicare and Medicaid Services (CMS) ESRD database and to apply for Medicare eligibility, a renal provider must enroll the patient in USRDS and complete a Medical Evidence Report stating the primary cause of ESRD. Because most individuals in the U.S. with ESRD receive Medicare, Medicaid claims data alone do not allow for a comprehensive assessment of incident ESRD, requiring the linkage of these two databases to conduct our analyses. For our primary analysis, we included all cases of ESRD and for sensitivity analyses, we restricted our outcomes to exclude etiologies other than SLE nephritis and acute or chronic glomerulonephritis.

Mortality—Among ESRD patients enrolled in USRDS, a Death Notification Form must be completed by renal providers within 45 days of a death event and this is enforced by CMS. Therefore, for all patients in our cohort who developed ESRD, mortality was determined from USRDS. For incident LN patients enrolled in Medicaid who did not develop ESRD, death was determined using linked Social Security Death Index (SSDI) files. Cause of death was not available for this study for incident LN patients who died prior to ESRD.

Healthcare Utilization—We assessed healthcare utilization among all patients with incident LN using emergency department (ED) visits, outpatient visits and hospitalizations. In secondary analyses, we also examined these factors by sex specifically among those patients who developed ESRD, and among those who died, and restricting our cohort to adults only (≥ 18 years of age).

Covariates

We extracted all covariates during the 12-month period prior to and including the index date (date of first LN-related ICD-9 code). We assessed demographic factors including age, sex, race/ethnicity, geographic region, and ZIP code median household income from American Community Survey data (2006–2010) as a proxy for socioeconomic status (SES). We also examined medication use, specifically angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs), hydroxychloroquine, corticosteroids and

immunosuppressive medications (azathioprine, mycophenolate mofetil, methotrexate, leflunomide, cyclophosphamide, rituximab, tacrolimus, cyclosporine), as well as whether a renal biopsy was performed. We calculated the SLE-specific risk adjustment index, which has been shown to be a better predictor of inpatient mortality among patients with SLE than the Charlson comorbidity index.(19)

Statistical Methods

We compared baseline covariates between males and females using parametric and non-parametric tests. We used Cox proportional hazards models to compare the risk of death (HR, 95% CI) between males and females. We used Fine and Gray proportional hazards models to compare the risk of ESRD while accounting for the competing risk of death (subdistribution hazard ratio (sdHR), 95% CI).(20) A competing risk (here, death), is an event that precludes the possibility of observing the event of interest (ESRD). Censoring patients at time of death, rather than accounting for death as a competing risk, may violate the assumption of noninformative censoring as these individuals who died are likely different from those individuals who survived. Proportional hazards models were adjusted for age, race/ethnicity, calendar year of the index date, zip code-level median household income, and the SLE-specific risk adjustment index. We did not include the SLE-specific risk adjustment index in our analyses of the ESRD outcomes as it includes chronic kidney disease and may lie on the causal pathway. We examined immunosuppressive and corticosteroid use and renal biopsies following the index date as well however we adjusted for these factors only during the baseline period (183 days prior to and including the index date) and not after as we suspect that they lie on the causal pathway and may mediate and not confound the relationship between sex and adverse outcomes. A mediation analysis was not feasible given our sample size. We tested the proportional hazards assumption (sex multiplied by the natural log of time) and did not find violations in our models. We conducted additional sensitivity analyses to examine whether there were differences between the spacing between the first SLE code in our dataset and the first LN-related code by sex. We did not conduct this as a primary analysis given the limitation of including patients with prevalent SLE without knowledge of when their first-ever SLE code occurred. We used Poisson regression to calculate incidence rates (IR, 95% CI) and incidence rate ratios (IRR, 95% CI) of healthcare utilization (ED visits, outpatient visits and hospitalizations) in the cohort overall and then in secondary analyses among those who developed ESRD and among those who died. IRRs were adjusted for age, race/ethnicity, ZIP code median household income, SLE-specific risk adjustment index and calendar year of the index date.

All analyses were performed using SAS 9.3 (SAS Institute Inc. Cary, NC). We obtained Data Use Agreements for this study from both CMS and USRDS and data are presented according to Federal reporting standards (cell sizes <11 are suppressed). The Partners Human Research Committee at Brigham and Women's Hospital approved this study. All patient information was de-identified prior to our receipt of the data and therefore informed consent was not possible or required.

Results

We identified 2,467 females and 283 males with incident LN enrolled in Medicaid between 2000–2010. The mean ± SD age was 29.6 ± 13.9 among females, 24.7 ± 14.1 among males (p<0.01) and 37% of males were 12–17 years of age compared to 18% of females. (Table 1). The mean ± SD follow-up for both sexes was 3.1 ± 2.3 years. The cohort was racially and ethnically diverse and well-distributed geographically across the U.S. The ZIP code median household income was similar for both sexes. Baseline medication use (ACE-I/ARBs, hydroxychloroquine, immunosuppressives and corticosteroids) and renal biopsies in the 12 months prior to and including the index date, were similar for males and females. We also examined ACE-I/ARB, immunosuppressive medication and corticosteroid use and renal biopsies following the index date. Among patients who were followed until ESRD, a slightly higher percentage of males received immunosuppressive medications compared to females (64% vs. 58%), and received ACE-I/ARBs (76% vs. 66%). More females than males had renal biopsies (38% vs. 29%). There was minimal difference in corticosteroid use (79% among females vs. 80% among males). Among patients who were followed until death, 60% of females received immunosuppressives compared to 67% of males, 68% of females received ACE-I/ARBs compared to 77% of males, and 40% of females had a renal biopsy compared to 31% of males. Steroid use was comparable (80% among females vs. 81% among males).

Outcomes by Sex

In our incident LN cohort, we identified 394 cases of ESRD, 353 in females and 41 in males. The mean ± SD time to ESRD was 2.03 ± 1.8 years in females and 1.97 ± 1.8 years in males; the median time was 1.6 years in both groups. The primary cause of ESRD was LN for 295 patients, over 75% of both males and females (Supplemental Table 1), and other forms of nephritis comprised 10% of male cases and 5% of female cases. Hypertensive chronic kidney disease and diabetic nephropathy were the most common other etiologies. There were 190 deaths (174 among females, 16 in males). The mean ± SD time to death was 1.82 ± 1.9 years among females and 1.88 ± 1.5 years among males; the median time was 1.1 years for females and 1.8 years for males. Among patients with ESRD, 95 (86 females, 9 males) died following this diagnosis.

The yearly cumulative incidence of both ESRD and death was comparable for both sexes (Table 2). In the multivariable Fine and Gray proportional hazards model, adjusted for age, race/ethnicity, calendar year and median household income and accounting for the competing risk of death, there was no difference in ESRD comparing males to females (sdHR 1.05, 95% CI 0.76–1.45) (Table 3). We did observe an increased risk of ESRD among black patients compared to white (sdHR 1.37, 95% CI 1.02–1.84).

In the multivariable Cox proportional hazards model examining risk of death, after adjusting for age, race/ethnicity calendar year and median household income, we did not find a difference between males vs. females (HR 0.97, 95% CI 0.58–1.62). There was a non-statistically significant trend towards a reduced risk of death among males vs. females when the model was additionally adjusted by the SLE-specific risk adjustment index (HR 0.81, 95% CI 0.47–1.35). We observed an increased risk of death among older patients and a

reduced risk among Hispanic patients. We observed an increased risk of death among patients in the lowest median household income quartile (HR 1.56, 95% CI 1.02–2.36), however this risk was attenuated after adjusting for the SLE-specific risk adjustment index (HR 1.51, 95% CI 0.99–2.30). LN patients with higher SLE-specific risk adjustment indices had an increased risk of death (HR 1.14, 95% CI 1.10–1.19). In secondary analyses, we examined only those patients who developed ESRD attributed to LN by their attending nephrologist at the time of USRDS enrollment, and among those with diagnoses of LN or any other nephritis. We similarly did not find statistically significant differences in our adjusted models by sex for either ESRD or death. We did two additional sensitivity analysis examining both outcomes only among males and females who received immunosuppressives during the baseline period, and among those who had a renal biopsy and similarly found no differences by sex in either ESRD or death.

In additional sensitivity analyses, we examined time between first SLE code in our dataset and first LN-related code. We found that the median (IQR) time between first SLE code and first LN-related code was 62 (0, 503) days for females with 26% occurring on the same date, compared to 13 (0, 173) days for males with 38% on the same date. Among the females who developed ESRD, 27% had the first SLE code on the same date as the first LN code compared to 34% of the males. Among the females who died, 30% had the first codes on the same date compared to 19% of males. We conducted stratified analyses separating males and females with their first SLE and LN codes on the same day from those with any separation, and then also stratified on <30 days (vs. 30 days) and <60 days (vs. 60 days) and did not find any statistically significant differences in ESRD or death by sex.

Healthcare Utilization by Sex

After adjusting for age, sex, race/ethnicity, year, region, household income and SLE risk-adjustment index, males had lower rates of ED visits (IRR 0.75 95% CI 0.63–0.90) and outpatient visits (IRR 0.88, 95% CI 0.80–0.97) compared to females (Table 4). Rates of hospitalizations were also lower among males compared to females, but the IRR adjusted for age, race/ethnicity, year, median household income and SLE-specific risk adjustment index was not significantly different (IRR 0.85, 95% CI 0.71–1.02). In secondary analyses, we also examined utilization restricted to adults 18–65 years. We similarly found reduced incidence rates of outpatient visits among adult males compared to females (IRR 0.86, 95% CI 0.75–0.99) but no statistically significant difference in ED visits or hospitalizations.

In additional secondary analyses, examined utilization specifically among patients with LN who developed ESRD and among those who died in the period between the index date and the outcome of interest (Tables 5 and 6). We did not find statistically significant differences in ED visits, outpatient visits or hospitalizations by sex in either of these groups. However, among patients who developed ESRD and among patients who died, we did observe a trend towards greater hospitalizations and fewer ED visits prior to the outcomes among males compared to females.

Discussion

In this high-risk low-income population of Medicaid beneficiaries with incident LN, we observed extremely high rates of ESRD and mortality overall. Contrary to prior studies that suggested increased risk of adverse outcomes among males with SLE compared to females, in this cohort, rates of ESRD and mortality did not differ by sex. Healthcare utilization, and particularly ED visits and outpatient visits, was less frequent for males compared to females overall among patients with incident LN, but comparable among those patients who developed ESRD or who died.

Overall, compared to other cohorts, the cumulative incidence of ESRD and mortality was substantially higher among this population of Medicaid beneficiaries. In the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort, among patients with LN, the 10-year cumulative incidence of ESRD was 10.1% (95% CI 6.6–13.6), compared to the 5-year cumulative incidence in our cohort of 22.3% (95% CI 16.0–29.3) among males and 21.1% (95% CI 19.0–23.5) among females.(9) The SLICC 10-year cumulative incidence of death was 5.9% (95% CI 3.3–8.4) among patients with incident LN, compared to the 5-year cumulative incidence of 9.4% (95% CI 5.4–14.9) in males and 9.8 (95% CI 8.3–11.5) among females in our cohort.(9) There are several plausible explanations for the increased burden of adverse outcomes observed. The Medicaid population is a low-income population shown to have significant comorbidities and adverse SLE-related outcomes overall.(15, 21) In addition, the quality of care provided to Medicaid beneficiaries with LN has been shown to be suboptimal.(22) Patients with LN-related ESRD have been demonstrated to have poor post-ESRD care as well.(23) Care among Medicaid beneficiaries may be inconsistent given state-to-state differences in continuous enrollment policies and eligibility and within the Medicaid SLE population, medication adherence has been shown to be poor, and acute care utilization to be high.(24) In contrast, the SLICC network is comprised of academic medical centers and patients have been shown to receive standard of care treatments and sustained follow-up over the course of their 12-year follow-up period.(9) The racial/ethnic makeup of the two cohorts is also distinctly different with a significantly higher percentage of black individuals in our cohort, and lower percentage of both white and Hispanic individuals compared to SLICC, which may affect differences in quality of care received as well as outcomes.(23) In addition, the Medicaid population may be enriched with a more severe SLE phenotype as patients with more aggressive disease may lose their jobs, or be unable to work, and therefore be more likely to receive public health insurance.

Within a cohort of 344 incident SLE patients in Atlanta, Georgia, the 5-year cumulative incidence of ESRD was 5.2% overall, but only approximately one-third of these patients had early LN at the time of SLE diagnosis.(25) The proportion of ESRD was higher among blacks compared to whites (6.4% compared to 2.5%), and significantly higher than other SLE cohorts in Taiwan and Japan, in which it was approximately 3%.(26, 27) While it is challenging to compare these estimates to LN patients within Medicaid, our finding of ESRD burden was approximately four times higher than that of the Georgia cohort, which is more than what might be expected if only the third with LN had progressed. In the Georgia cohort, 79% of patients had ESRD attributed to SLE as reported by USRDS.(28) In our cohort, this proportion was similar.

In the current study, we found comparable rates of ESRD and mortality by sex. Findings from prior studies have varied; some demonstrated increased rates among males, and some like ours, found no significant differences by sex. Male sex was not associated with ESRD incidence in a study in the Georgia Lupus Registry.(25) In a Taiwanese SLE cohort, there was an increased risk of ESRD among males compared to females (HR 2.2, 95% CI 1.4–3.6).(26) In the Hopkins cohort, there was a doubled odds of renal biopsy, renal insufficiency and renal failure among males compared to females, adjusting for age, duration of SLE, ethnicity and smoking status.(4) In that cohort, male sex was also associated with two times greater risk of death.(29) In a U.S.-based inception cohort of approximately 400 patients, 17% male, in models adjusted for age, race, insurance status and area-level socioeconomic indicators, male sex was associated with increased risk of death.(13) It is challenging to compare findings across studies however, given the variation in patient populations by age, race/ethnicity and by academic vs. non-academic care setting, differences in inclusion of incident vs. prevalent SLE or LN cases, and sparse numbers of male SLE cases. While other studies suggest that outcomes may be poorer among males of non-White race/ethnicity, we lacked the power to substratify in order to investigate this question in our patient population.(4)

In keeping with prior studies, we found an increased risk of ESRD among black patients with LN overall compared to white.(25, 30) This has been attributed both to genetic factors (e.g. APOL1 G1 and G2 nephropathy alleles) as well as healthcare access and utilization factors.(23, 25, 31) We also found a decreased risk of death among Hispanic patients, which has been previously demonstrated in the Medicaid SLE population.(15) While we did not observe an association between lower ZIP code-level median household income and ESRD, we did see a relationship with mortality. LN patients living in the poorest areas did have an increased risk of death compared to those in the highest quartile. This finding is with the caveat that nearly all patients in this cohort would be classified as poor as this is part of the eligibility criteria for enrollment in Medicaid. This association between lower ZIP code median household income and death was attenuated after adjusting for SLE-related comorbidities. The relationship between area-level poverty and accrual of SLE-related damage resulting in adverse outcomes is in line with a prior study that similarly affirms the detrimental effects of poverty among patients with SLE.(32)

We originally hypothesized that an explanation for sex differences in outcomes seen in prior studies may in part be related to differences in healthcare utilization. In the general population, females have more regular contact with the healthcare system at younger ages because of pregnancy and increased preventive health measures (e.g. cervical and breast cancer screening) (33) and therefore SLE may be detected earlier and at a less severe state. Older male adolescents (age 16–20 years) have also been shown to have significantly fewer ambulatory care visits both compared to younger males and compared to females of the same age.(34) While we did not find differences in ESRD or mortality in our cohort, we did find that males overall had lower rates of ED visits and outpatient visits compared to females. When we restricted our cohort only to adults, we similarly found lower rates of outpatient care utilization among males compared to females. Further studies are needed to delineate whether this difference is related to behavioral differences or SLE disease manifestations and severity, and whether these patterns may contribute to variation in other

outcomes beyond ESRD and mortality. We did find that a greater percentage of males had their first SLE code in our dataset on the same date as their first LN-related code compared to females (38% vs. 26%). However, in stratified analyses, we did not observe differences in either ESRD or mortality by sex when we separately examined those with less versus more spacing between codes. Since this was an incident LN cohort within a prevalent SLE cohort, the interpretation of this sensitivity analysis is limited and further studies are needed to understand the relationship between duration of SLE at the time of LN and sex differences in outcomes.

There were limitations to our study. The use of claims data did not allow us to assess lab values or disease activity. Antiphospholipid antibody status is not available using ICD-9 codes, however we did not observe statistically significant differences in warfarin use by sex. Despite using a conservative definition for LN with high PPV, and requiring two years without codes to identify incident cases, there may have been some misclassification with prevalent LN. In this cohort, males were younger than females at LN onset and a smaller proportion were Black, which may have contributed to our non-significant differences in ESRD and mortality in males vs. females. However, in models fully adjusted for age, race/ethnicity, SES and the SLE risk-adjustment index, we still did not observe an increased risk of ESRD or death among the males. In addition, race/ethnicity may modify the relationship between sex and adverse outcomes however we lacked sufficient power to investigate this question in depth. While our cohort included more males than most studies to date, and unfortunately, adverse outcomes were not uncommon, we still may have been underpowered to detect differences by sex. In addition, while there were no significant differences in medication use or renal biopsy rates by sex prior to and including the index date, males received more immunosuppressive medications and ACE-I/ARBs following the index date, and underwent fewer renal biopsies. Immunosuppressive therapy and ACE-I/ARBs are contraindicated in pregnancy and thus are likely be more limited in use among women of reproductive age. Fewer biopsies among males may relate to lower rates of outpatient care utilization that we observed among males compared to females. However, from the data available, it is not possible to decipher whether the lower percentage of males who underwent renal biopsy was due to patient preference, lower quality of care for males compared to females, or more severe disease on presentation that was treated without biopsy. Given our sample size, and specifically, the small number of males receiving immunosuppressive medications who had the outcomes of interest, we were unable to do mediation analyses. We chose not to adjust for these factors in our proportional hazard models as we felt that they were likely to lie on the causal pathway. In addition, overall use of immunosuppressive medications and hydroxychloroquine, the standard-of-care treatments for patients with lupus nephritis, was low in this cohort. Previous work in the Medicaid population has affirmed this finding as well.(21, 22, 35) While we did conduct sensitivity analyses examining adverse outcomes restricted to patients who received immunosuppressive medications and did not find significant differences by sex, we cannot determine whether differences would be apparent if the entire cohort received standard-of-care regimens. We did demonstrate the ill effects of likely severe, poorly managed disease, and the reality that differences by sex may be less pronounced in this setting. Further studies

are needed to investigate the role of sex differences in care practices and medication use, and the direct impact of these factors on outcomes.

This study also had a number of strengths. We included a racially and ethnically diverse population of low-income high-risk individuals with a relatively large number of male SLE patients. Our Medicaid data were linked to USRDS, which captures nearly all ESRD cases in the U.S. While our findings may not be generalizable to all populations, we focused our study on a large, vulnerable and diverse patient population, shown in other studies to suffer from an excess burden of adverse outcomes, receiving care at both academic and non-academic centers.(21, 35, 36) With 10 years of data and a mean follow-up of approximately 3 years, we were able to capture high rates of ESRD and mortality in this population overall and demonstrate no statistically significant difference by sex. We cannot rule out the possibility of differences by sex among patients either with less severe disease and slower progression, or among patients who consistently receive timely, standard-of-care evaluation and treatment. However, the findings of this study are in line with prior work in the same vulnerable population and suggest the need for dedicated efforts to improve access to high quality care for these patients.

In this large, nationwide study of Medicaid beneficiaries with incident LN, we found extremely high rates of ESRD and mortality but no statistically significant differences by sex in these outcomes. While males had lower rates of emergency department and ambulatory care visits, we did not observe differences in these severe adverse outcomes. It is plausible that in this especially vulnerable population with overall poor access to high quality care, biologic differences may be less relevant in shaping adverse outcomes. This contrasts with academic-based cohort studies where most patients receive consistent, standard-of-care therapy. Ongoing studies with extended follow-up and increased numbers of male SLE patients are needed to further investigate the role of genetic and environmental factors, as well as healthcare quality and use in SLE-related outcomes by sex. The profoundly high rates of ESRD and mortality in this vulnerable population, and the increased risk of death seen among patients living in the poorest areas provide further evidence that heightened efforts are needed to improve care for these patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcon GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. Arthritis Rheum. 2013; 65(3):753–63. [PubMed: 23203603]

2. Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis Rheumatol. 2014; 66(2):369–78. [PubMed: 24504809]

3. Alonso-Perez E, Suarez-Gestal M, Calaza M, Blanco FJ, Suarez A, Santos MJ, et al. Lack of replication of higher genetic risk load in men than in women with systemic lupus erythematosus. Arthritis research & therapy. 2014; 16(3):R128. [PubMed: 24946689]

4. Tan TC, Fang H, Magder LS, Petri MA. Differences between male and female systemic lupus erythematosus in a multiethnic population. J Rheumatol. 2012; 39(4):759–69. [PubMed: 22382348]

5. Andrade RM, Alarcon GS, Fernandez M, Apte M, Vila LM, Reveille JD, et al. Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. Arthritis Rheum. 2007; 56(2):622–30. [PubMed: 17265497]

6. Crosslin KL, Wiginton KL. Sex differences in disease severity among patients with systemic lupus erythematosus. Gend Med. 2011; 8(6):365–71. [PubMed: 22153881]

7. Garcia MA, Marcos JC, Marcos AI, Pons-Estel BA, Wojdyla D, Arturi A, et al. Male systemic lupus erythematosus in a Latin-American inception cohort of 1214 patients. Lupus. 2005; 14(12):938–46. [PubMed: 16425573]

8. Molina JF, Drenkard C, Molina J, Cardiel MH, Uribe O, Anaya JM, et al. Systemic lupus erythematosus in males. A study of 107 Latin American patients. Medicine (Baltimore). 1996; 75(3):124–30. [PubMed: 8965681]

9. Hanly JG, O'Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. Rheumatology (Oxford). 2016; 55(2):252–62. [PubMed: 26342222]

10. Riveros Frutos A, Casas I, Rua-Figueroa I, Lopez-Longo FJ, Calvo-Alen J, Galindo M, et al. Systemic lupus erythematosus in Spanish males: a study of the Spanish Rheumatology Society Lupus Registry (RELESSER) cohort. Lupus. 2017; 26(7):698–706. [PubMed: 27799439]

11. Resende AL, Titan SM, Barros RT, Woronik V. Worse renal outcome of lupus nephritis in male patients: a case-control study. Lupus. 2011; 20(6):561–7. [PubMed: 21415256]

12. Hsu CY, Chiu WC, Yang TS, Chen CJ, Chen YC, Lai HM, et al. Age- and gender-related long-term renal outcome in patients with lupus nephritis. Lupus. 2011; 20(11):1135–41. [PubMed: 21719527]

13. Ward MM, Pyun E, Studenski S. Long-term survival in systemic lupus erythematosus. Patient characteristics associated with poorer outcomes. Arthritis Rheum. 1995; 38(2):274–83. [PubMed: 7848319]

14. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. Arthritis Rheum. 2006; 54(8):2550–7. [PubMed: 16868977]

15. Gomez-Puerta JA, Barbhaiya M, Guan H, Feldman CH, Alarcon GS, Costenbader KH. Racial/Ethnic variation in all-cause mortality among United States medicaid recipients with systemic lupus erythematosus: a Hispanic and asian paradox. Arthritis Rheumatol. 2015; 67(3):752–60. [PubMed: 25590668]

16. Ladwig KH, Marten-Mittag B, Formanek B, Dammann G. Gender differences of symptom reporting and medical health care utilization in the German population. European journal of epidemiology. 2000; 16(6):511–8. [PubMed: 11049093]

17. Chibnik LB, Massarotti EM, Costenbader KH. Identification and validation of lupus nephritis cases using administrative data. Lupus. 2010; 19(6):741–3. [PubMed: 20179167]

18. US Renal Data System (USRDS). Researcher's Guide to the USRDS Database. Bethesda, MD: 2010.

19. Ward MM. Development and testing of a systemic lupus-specific risk adjustment index for in-hospital mortality. J Rheumatol. 2000; 27(6):1408–13. [PubMed: 10852262]

20. Fine JP, Gray RG. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999; 94(446):496–509.

21. Feldman CH, Hiraki LT, Winkelmayer WC, Marty FM, Franklin JM, Kim SC, et al. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol. 2015; 67(6):1577–85. [PubMed: 25772621]

22. Yazdany J, Feldman CH, Liu J, Ward MM, Fischer MA, Costenbader KH. Quality of care for incident lupus nephritis among Medicaid beneficiaries in the United States. Arthritis Care Res (Hoboken). 2014; 66(4):617–24. [PubMed: 24124011]

23. Plantinga LC, Drenkard C, Patzer RE, Klein M, Kramer MR, Pastan S, et al. Sociodemographic and geographic predictors of quality of care in United States patients with end-stage renal disease due to lupus nephritis. Arthritis Rheumatol. 2015; 67(3):761–72. [PubMed: 25692867]

24. Feldman CH, Yazdany J, Guan H, Solomon DH, Costenbader KH. Medication Nonadherence Is Associated With Increased Subsequent Acute Care Utilization Among Medicaid Beneficiaries With Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2015; 67(12):1712–21. [PubMed: 26097166]

25. Plantinga L, Lim SS, Patzer R, McClellan W, Kramer M, Klein M, et al. Incidence of End-Stage Renal Disease Among Newly Diagnosed Systemic Lupus Erythematosus Patients: The Georgia Lupus Registry. Arthritis Care Res (Hoboken). 2016; 68(3):357–65. [PubMed: 26239749]

26. Lin WH, Guo CY, Wang WM, Yang DC, Kuo TH, Liu MF, et al. Incidence of progression from newly diagnosed systemic lupus erythematosus to end stage renal disease and all-cause mortality: a nationwide cohort study in Taiwan. Int J Rheum Dis. 2013; 16(6):747–53. [PubMed: 24382283]

27. Iseki K, Miyasato F, Oura T, Uehara H, Nishime K, Fukiyama K. An epidemiologic analysis of end-stage lupus nephritis. Am J Kidney Dis. 1994; 23(4):547–54. [PubMed: 8154491]

28. Plantinga LC, Drenkard C, Pastan SO, Lim SS. Attribution of cause of end-stage renal disease among patients with systemic lupus erythematosus: the Georgia Lupus Registry. Lupus Sci Med. 2016; 3(1):e000132. [PubMed: 26848398]

29. Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine (Baltimore). 2006; 85(3):147–56. [PubMed: 16721257]

30. Costenbader KH, Desai A, Alarcon GS, Hiraki LT, Shaykevich T, Brookhart MA, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. Arthritis Rheum. 2011; 63(6):1681–8. [PubMed: 21445962]

31. Freedman BI, Langefeld CD, Andringa KK, Croker JA, Williams AH, Garner NE, et al. End-stage renal disease in African Americans with lupus nephritis is associated with APOL1. Arthritis Rheumatol. 2014; 66(2):390–6. [PubMed: 24504811]

32. Yelin E, Trupin L, Yazdany J. A Prospective Study of the Impact of Current Poverty, History of Poverty, and Exiting Poverty on Accumulation of Disease Damage in Systemic Lupus Erythematosus. Arthritis Rheumatol. 2017; 69(8):1612–22. [PubMed: 28480630]

33. Vaidya V, Partha G, Karmakar M. Gender differences in utilization of preventive care services in the United States. J Womens Health (Larchmt). 2012; 21(2):140–5. [PubMed: 22081983]

34. Marcell AV, Klein JD, Fischer I, Allan MJ, Kokotailo PK. Male adolescent use of health care services: where are the boys? J Adolesc Health. 2002; 30(1):35–43. [PubMed: 11755799]

35. Barbhaiya M, Feldman CH, Guan H, Gomez-Puerta JA, Fischer MA, Solomon DH, et al. Race/Ethnicity and Cardiovascular Events Among Patients With Systemic Lupus Erythematosus. Arthritis Rheumatol. 2017; 69(9):1823–31. [PubMed: 28598016]

36. Gomez-Puerta JA, Feldman CH, Alarcon GS, Guan H, Winkelmayer WC, Costenbader KH. Racial and Ethnic Differences in Mortality and Cardiovascular Events Among Patients With End-Stage Renal Disease Due to Lupus Nephritis. Arthritis Care Res (Hoboken). 2015; 67(10):1453–62. [PubMed: 25624071]

Table 1

Baseline characteristics of incident lupus nephritis cohort by sex

Characteristics N=2750	Female N=2467	Male N=283	p-value
Age (years) at LN- mean ± SD	29.6 ± 13.9	24.7 ± 14.1	**<0.01**
Age group – N (%)			
5–11 years	129 (5.2)	24 (8.5)	
12–17 years	442 (17.9)	103 (36.8)	
18–34 years	1144 (46.4)	95 (33.6)	
35–50 years	492 (19.9)	39 (13.8)	
51–65 years	260 (10.5)	21 (7.4)	
Race/Ethnicity- N (%)			**<0.01**
Black	1351 (54.8)	124 (43.8)	
White	449 (18.2)	59 (20.9)	
Hispanic	460 (18.7)	73 (25.8)	
Asian	126 (5.1)	21 (7.4)	
AI/AN	32 (1.3)	NR	
Other	49 (2.0)	NR	
Region- N (%)			0.06
South	999 (40.5)	102 (36.0)	
Northeast	467 (18.9)	72 (25.4)	
Midwest	470 (19.1)	48 (17.0)	
West	531 (21.5)	61 (21.6)	
Zip code median household income-mean/10,000 ± SD	4.3 ± 1.6	4.4 ± 1.6	0.36
SLE risk adjustment index – mean ± SD	3.6 ± 2.9	3.8 ± 3.1	0.29
Hydroxychloroquine use – N (%)	1216 (49.3)	124 (43.8)	0.08
Corticosteroid use – N (%)	1778 (72.1)	197 (69.6)	0.38
Immunosuppressive use – N (%)	968 (39.2)	118 (41.7)	0.42
ACE-I/ARB use – N (%)	1180 (47.8)	149 (52.7)	0.12
Renal biopsy – N (%)	927 (37.6)	17 (41.3)	0.22

NR= not reported; cell sizes <11 suppressed per CMS regulations

Table 2

Cumulative incidence of ESRD and mortality by sex

Outcome	Year 1	Year 2	Year 3	Year 4	Year 5
ESRD[*]					
Males	7.1 (4.4–10.8)	9.6 (6.9–15.1)	15.9 (11.1–21.6)	18.3 (12.9–24.4)	22.3 (16.0–29.3)[#]
Females	5.9 (4.9–6.9)	10.4 (9.1–11.8)	13.9 (12.8–15.5)	17.8 (15.9–19.7)	21.2 (19.0–23.5)
Mortality					
Males	2.8 (1.3–5.5)	4.7 (2.3–8.2)	7.4 (4.2–12.0)	8.4 (4.8–13.4)	9.4 (5.4–14.9)[##]
Females	3.7 (3.0–4.7)	5.8 (4.8–6.8)	7.0 (5.9–8.3)	8.0 (6.8–9.4)	9.8 (8.3–11.5)

[*] ESRD analysis accounts for the competing risk of death

[#] 4.77 years,

[##] 4.5 years

Table 3

Comparative risks of ESRD and mortality by sex in multivariable adjusted models

Covariates	Model 1[*] HR (95% CI)	Model 2[**] HR (95% CI)	Model 3[+] HR (95% CI)
		Outcome: ESRD	
Sex (ref=female)			
Male	1.06 (0.76–1.46)	1.05 (0.76–1.45)	
Age	1.00 (0.99–1.00)	1.00 (0.99–1.00)	
Race (ref=white)			
Black	**1.35 (1.01–1.80)**	**1.37 (1.02–1.84)**	
Hispanic	0.97 (0.67–1.39)	0.97 (0.68–1.40)	
Asian	0.75 (0.42–1.35)	0.75 (0.42–1.35)	
AI/AN	1.85 (0.83–4.11)	1.86 (0.84–4.15)	
Median household income (ref=highest quartile)			
Quartile 1 (lowest)		1.09 (0.82–1.45)	
Quartile 2		0.93 (0.69–1.26)	
Quartile 3		1.04 (0.77–1.40)	
SLE risk adjustment index			
		Outcome: Mortality	
Sex (ref=female)			
Male	0.95 (0.57–1.59)	0.97 (0.58–1.62)	0.81 (0.47–1.35)
Age	**1.04 (1.03–1.05)**	**1.03 (1.02–1.04)**	**1.02 (1.01–1.03)**
Race (ref=white)			
Black	1.13 (0.78–1.63)	1.03 (0.71–1.50)	1.09 (0.74–1.60)
Hispanic	**0.50 (0.28–0.89)**	**0.47 (0.26–0.85)**	**0.50 (0.28–0.91)**
Asian	0.75 (0.33–1.67)	0.77 (0.34–1.74)	0.86 (0.38–1.94)
AI/AN	1.84 (0.66–5.16)	1.56 (0.55–4.41)	1.84 (0.65–5.24)
Median household income (ref=highest quartile)			
Quartile 1 (lowest)		**1.56 (1.02–2.36)**	1.51 (0.99–2.30)
Quartile 2		1.26 (0.82–1.93)	1.29 (0.84–1.98)
Quartile 3		1.03 (0.66–1.62)	1.07 (0.68–1.68)
SLE risk adjustment index			**1.14 (1.10–1.19)**

[*] Model 1 adjusted by age, race/ethnicity and calendar year of index date

[**] Model 2 adjusted by age, race/ethnicity, year and median household income (zip code-level) in quartiles

[+] Model 3 adjusted by age, race/ethnicity, year, median household income (zip code-level) and SLE-specific risk adjustment index [Not performed for ESRD as the risk adjustment index includes renal severity measures]

Bolded values indicate p<0.05, AI/AN=American Indian/Alaska Native
ESRD models account for the competing risk of death and hazard ratios (HR) represent subdistribution hazard ratios from Fine and Gray proportional hazard models

Table 4

Incidence rates (IR) and incidence rate ratios (IRR) for healthcare utilization among Medicaid beneficiaries with incident lupus nephritis by sex

	Females (N=2,467)			Males (N=283)			Male: Female
	Events	P–Y	IR* (95% CI)	Events	P–Y	IR (95% CI)	Adjusted IRR[+] (95% CI)
ED visits	18,772	6,929.3	270.9 (267.0–274.7)	1,518	790.7	192.0 (182.3–201.6)	**0.75 (0.63–0.90)**
Outpatient visits	68,433	6,929.3	987.6 (980.2–995.0)	6,994	790.7	884.5 (863.8–905.2)	**0.88 (0.80–0.97)**
Hospitalizations	5,468	6,929.3	78.9 (76.8–81.0)	522	790.7	66.0 (60.4–71.7)	0.85 (0.71–1.02)

*Incidence rates (IR) per 100 person-years (p–y) with 95% CIs starting at the index date of incident lupus nephritis diagnosis.

[+]Incidence rate ratios (IRR) adjusted for age, race/ethnicity, year, region, zip code median household income, and SLE-specific risk adjustment index

Table 5

Incidence rates (IR) and incidence rate ratios (IRR) for healthcare utilization among patients with incident LN prior to the development of ESRD, by sex

	Females (N=353)			Males (N=41)			Male: Female
	Events	P–Y	IR* (95% CI)	Events	P–Y	IR (95% CI)	Adjusted IRR+ (95% CI)
ED visits	2,382	766.5	310.8 (298.3–323.3)	175	85.5	204.7 (174.3–235.0)	0.72 (0.44–1.19)
Outpatient visits	6,092	766.5	794.8 (774.9–814.8)	712	85.5	832.9 (771.7 –894.0)	1.03 (0.78–1.36)
Hospitalizations	734	766.5	95.8 (88.8–102.7)	93	85.5	108.8 (86.7–130.9)	1.30 (0.89–1.92)

*
Incidence rates (IR) per 100 person-years (p–y) with 95% CIs starting at the index date of incident lupus nephritis diagnosis for those individuals who developed ESRD (N=394).

+
Incidence rate ratios (IRR) adjusted for age, race/ethnicity, year, region, zip code median household income, and SLE-specific risk adjustment index

Table 6

Incidence rates (IR) and incidence rate ratios (IRR) for healthcare utilization among patients with incident LN prior to death, by sex

	Females (N=174)			Males (N=16)			Male: Female
	Events	P–Y	IR* (95% CI)	Events	P–Y	IR (95% CI)	Adjusted IRR+ (95% CI)
ED visits	952	184.3	516.5 (483.7–549.3)	60	17.0	192.0 (182.3–201.6)	0.62 (0.28–1.39)
Outpatient visits	1,829	184.3	992.4 (946.9–1037.8)	134	17.0	789.7 (656.0–923.4)	0.74 (0.43–1.27)
Hospitalizations	254	184.3	137.8 (120.9–154.8)	44	17.0	259.3 (182.7–335.9)	1.90 (0.98–3.68)

*
Incidence rates (IR) per 100 person-years (p-y) with 95% CIs starting at the index date of incident lupus nephritis diagnosis for those individuals who died (N=190)

+
Incidence rate ratios (IRR) adjusted for age and race/ethnicity; additional covariates not included for model stability due to infrequent outcomes among males