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Chris Fan April 10, 2024

Varied Kidney Outcomes of Pediatric Lupus Nephritis Patients:

A Retrospective Cohort Study

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Abstract

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Background: Lupus nephritis (LN), the renal manifestation of systemic lupus erythematosus (SLE), carries significant morbidity and mortality. Early diagnosis and treatment are critical to prevent progressive kidney damage and improve long-term prognosis. There is evidence suggesting disparities in treatment response across different patient populations. This study investigates the association between race/ethnicity and remission status in pediatric LN patients.

Methods: This retrospective cohort study included 101 pediatric LN patients at Children's Healthcare of Atlanta (CHOA) with biopsy-proven LN diagnosed between 2010 and 2022. Patients were followed for at least 1 year after LN diagnosis. Associations between race/ethnicity and renal outcomes (complete remission, partial remission) were assessed using Kaplan-Meier curves, Cox proportional hazards, and accelerated failure time models.

Results: The study population was primarily non-Hispanic Black (52.5%) and female with a median age of 14.0 years at LN diagnosis. For adjusted models of complete remission, patients in the non-Hispanic White and Other subgroups were found to have statistically significantly greater likelihoods to achieve remission at 12 months after LN diagnosis and accelerated time to remission at 24 months after LN diagnosis. For adjusted models of partial remission, The Other subgroup was found to have a statistically significant greater likelihood to achieve remission at 12 months after LN diagnosis and accelerated time to remission at 24 months after LN diagnosis. The crude models for both complete and partial remission were insignificant for race/ethnicity alone.

Conclusion: Race/ethnicity, when adjusted by other variables, is statistically associated with short-term remission status, generally with Hispanic and non-Hispanic Blacks being less likely to achieve both complete and partial remission. Future studies should elucidate the role of social determinants of health on clinical outcomes and further analyze other predictors affecting renal survival within the pediatric LN population.

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Introduction

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with multisystem involvement, affecting millions of people globally. The etiology of the disease is not well understood, but has been described to involve genetic, epigenetic, hormonal, immunological, and environmental factors. SLE is ultimately characterized by a loss of self-tolerance, the ability to distinguish between self from foreign antigens, and is an autoantibody-driven clinical disease. The autoantibodies that appear as a hallmark of SLE disease activity exist in a wide spectrum and can recognize several cellular components, with a high prevalence of anti-nuclear antibodies (ANAs) among SLE patients [1]. Exogenous environmental variables including cigarette smoking, alcohol consumption, ultraviolet radiation, infections, and silica exposure are a few factors implicated in SLE pathogenesis [2].

It is diagnosed based on a combination of clinical and serological elements. Because the nature of SLE is wide-ranging, various classification criteria have been constructed for diagnostic, epidemiological, and research purposes. The golden standard for SLE criteria is the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria, which has built off on the high specificity of the 1997 ACR criteria and high sensitivity of the 2012 Systemic Lupus International Collaborating Centers (SLICC) criteria [3].

De novo presentation of SLE is largely heterogeneous as the convergence of various molecular pathways are implicated in disease activity and the degree of organ involvement can vary at

diagnosis. Patients can exhibit a broad range of clinical features which can range from mild symptoms to life-threatening conditions and treatment requires a multidisciplinary approach. Because there are many systemic manifestations that a patient with SLE can present with, diagnosis of SLE can be difficult because the clinical presentation can resemble many other diseases. This further necessitates the need for clinical in addition to laboratory criteria during patient workup to diagnose an individual with SLE [4].

Data from the Hopkins Lupus Cohort describes three major patterns of disease activity in SLE patients: chronically active, relapsing-remitting, and long quiescent [5,6]. A recent analysis of this patient cohort shows that the relapsing-remitting pattern is the most prevalent type, which results in unpredictable flares in disease activity spaced by periods of quiescence of varying intervals.

Lupus Nephritis (LN)

The renal involvement of SLE, lupus nephritis (LN), is defined as acute glomerulonephritis, and is characterized clinically by proteinuria, hematuria, hypertension and presence of acute kidney injury. The early diagnosis of renal involvement in SLE is critical, as it is a major cause of mortality and morbidity.

The pathogenesis of LN is complex and includes both extra- and intrarenal mechanisms. Extrarenal pathogenic mechanisms include secondary necrosis and incomplete chromatin digestion after apoptosis which both promote exposure of nuclear particles to the immune system, activation of antigen presenting cells and costimulation of immune cells by nuclear

antigens (as they resemble viral particles), and aberrant lymphocyte proliferation. Intrarenal pathogenic mechanisms include immune complex-mediated renal immunopathology (caused by both immune complex deposits and both activation of the complement cascade and depletion of complements), activation of toll-like receptors and interferon signaling, and chemokine-mediated recruitment of different leukocytes [7].

Clinical presentation does not always correlate with the severity of lupus nephritis, and sometimes can be "silent" with laboratory values within the reference range suggesting normal kidney function. Clinical findings also cannot predict the clinical development or prognosis of LN patients. Thus, renal biopsy is of paramount importance for confirmation of diagnosis, disease classification, and most importantly, therapeutic management and prognosis of LN. The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS), with revisions proposed in 2018, serves as the gold standard for the classification of glomerulonephritis in LN [3,4]. The ISN/RPS classification system proposes 6 LN classes and is summarized in **Table 1**.

Relapse in LN disease activity is referred to as a LN flare. These flare-ups in LN activity are particularly important to patient prognosis as they are often accompanied by progression in histological lesions, resulting in histological class transformation. Thus, LN flares, being deleterious to the kidney and precipitous of chronic kidney disease (CKD) and/or end stage renal disease (ESRD), are a major determinant of adverse outcomes in the disease course [8].

Lupus Nephritis Epidemiology

The global incidence of SLE is estimated to be 5.14 (1.4 to 15.13) per 100,000 person-years and the prevalence was estimated to be 43.7 (15.87 to 108.92) per 100,000 persons [9]. Childhood-onset SLE (cSLE) accounts for 10-20% of all SLE cases and has a reported global incidence of 0.3–0.9 per 100,000 person-years and prevalence of 1.9–25.7 per 100,000 children [10]. SLE preferentially affects non-Caucasian women during the childbearing ages between 15 to 44 years, suggesting hormonal influence in pathogenesis, with a female-to-male ratio of 9:1 [3].

Renal involvement typically develops early in the SLE disease course, generally within the first 6 to 36 months, but can also present with it at initial diagnosis [11]. LN occurs in 50–82% of children with SLE in comparison with 20–40% of adults [12]. Children with LN were also shown to have 7-23% risk for kidney failure at five years follow-up and 19-times higher mortality compared with age-matched healthy children [13]. Black and Hispanic patients tend to have more severe histopathology, higher serum creatinine, and more proteinuria compared to white patients at LN diagnosis [11]. Additionally, they have worse outcomes (e.g. lower likelihood to achieve remission, worse patient and renal survival) and are more likely than White patients to progress to ESRD [14,15].

Treatment of Lupus Nephritis

Treatment aims to preserve or improve kidney function in LN patients. Most treatment courses converge on incorporating three elements: reduction in protein excretion, stabilization/improvement in serum creatinine, and improvement of urinary sediment/cellular

cast. Complete clinical response (and partial clinical response to a degree because their kidney function is less protected) and the maintenance of remission are important to preserving long-term kidney function [16]. It is important to note that clinical response, as measured by laboratory tests, is not the same as histological remission, which can only be established by a repeat biopsy [17].

Treatment courses that physicians employ for LN treatment generally depend on the biopsy-proven classification of LN to determine the nature of renal involvement. Classes I and II LN represent purely mesangial disease and are generally mild forms of renal SLE involvement. Both classes have a good long-term prognosis and generally can be monitored without the need for targeted therapy at the kidney with treatment as dictated by other extrarenal manifestations of SLE [18,19]. Both pure and mixed forms (with class V) of classes III and IV will need treatment using immunosuppressants and glucocorticoids. Pure class V requires careful monitoring of proteinuria and can benefit from the use of immunosuppressants if indicated [20]. Class VI will usually need a form of renal replacement therapy (RRT), such as dialysis or transplantation, since more than 90% of the glomeruli have already been sclerosed [21].

Given that SLE is a prototypical example of a relapsing-remitting disease, treatment for LN flare is very similar to *de novo* LN treatment as there is a general agreement that there is no major difference in management between the two; the therapies that are used for *de novo* treatment can continue to be used for subsequent flares [20]. However, treatment options are not static and changes in the treatment course reflect the dynamic disease characteristics of SLE, meaning that a one-time diagnosis is not sufficient. As previously mentioned, some patients' LN classification

will change during an LN flare, as shown by a serial renal biopsy. Thus, the treatment course that was employed during their initial flare up may need an adjustment/reinforcement in pharmacotherapy to induce a renal response [22]. Furthermore, a study published in 2019 by Mejia-Vilet et al. found that immune gene expression could differ between subsequent disease flares which can influence treatment decisions, but the results have not yet found their application in clinical management [23].

Treatment for LN classes that have more severe renal involvement is generally subdivided into induction and maintenance therapy. Induction treatment is focused on eliciting a renal response by use of anti-inflammatory and immunosuppressive therapies to prevent progressive nephron loss. The inductive phase will normally average around six months, but can be as short as three months and as long as one year [17]. Once a renal response has been established after the inductive phase, maintenance treatment is done using less aggressive immunosuppressive for prolonged periods of time to prevent relapse.

The therapies that were examined in this study are described in brief below and summarized in **Table 2**.

Mycophenolate mofetil (MMF) is an immunosuppressive agent and pro-drug of mycophenolic acid (MPA), which inhibits inosine-5'-monophosphate dehydrogenase (IMPDH). IMPDH is the enzyme which catalyzes the conversion of inosine 5'-monophosphate into xanthosine 5'-monophosphate, the first step after the separation of the ATP and GTP *de novo* synthesis routes and a rate-limiting step for GTP synthesis [24]. The inhibitory effect that MPA has on

IMPDH preferentially inhibits *de novo* purine synthesis in B and T lymphocytes, which suppresses DNA synthesis and cell division, exerting an antiproliferative effect on early-stage autoimmune responses by the adaptive immune system [25]. MPA also inhibits mononuclear cell activity. Recruitment of such cells to sites of inflammation is reduced and the high nitrous oxide production mediated by inducible nitrous oxide synthase is inhibited in macrophages, which has a role in oxidative tissue damage [25,26]. MMF is delivered orally and can be used for inductive treatment at high doses and maintenance treatment at low doses (standard dose 1200 mg/m²/day, maximum 2000 mg/day; when poor response option to increase to maximum of 1800 mg/m²/day, maximum 3000 mg/day, but toxicity increases with higher dose) [27].

Rituximab (RTX) is an anti-CD20 monoclonal antibody. CD20 is a general B cell marker and is expressed on both normal and malignant B cells [28]. RTX induces cell death through various mechanisms once bound to CD20 positive cells. These mechanisms include antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, antibody-dependent phagocytosis, and other direct effects of RTX binding, which all effectively cause B cell depletion [29]. RTX is delivered through intravenous (IV) infusions and is used as an inductive treatment for refractory LN or non-response to other therapy (375 mg/m²/week up to four doses) [30]. The optimal dosing for use of RTX is unknown as it is not currently indicated nor approved by the FDA for use in SLE and has off-label uses with or without concurrent therapy with MMF or CYC.

Cyclophosphamide (CTX) is an alkylating agent derived from mustard gas. It is metabolized in the liver to its active form, phosphoramide mustard, which inhibits protein synthesis through

cross-linking guanine bases in DNA double-helix strands [31]. CTX has immunosuppressive effects and demonstrates selectivity for T cells, causing permanent modifications in their DNA strands and eventually leading to programmed cell death [32]. CTX is delivered through IV infusions and is used as an inductive treatment (500–750 mg/m²/pulse, if tolerated increase to 750 mg/m²/pulse, maximum dose 1000–1200 mg/pulse, 6 monthly pulses) [27].

Both prednisone (PRED) and methylprednisolone (MP) are commonly employed glucocorticoids in the treatment of LN. Glucocorticoids (GCs), being derived from cholesterol and lipophilic, are able to easily bypass the cell membrane and bind to the ubiquitous expressed glucocorticoid receptor (GR) [33]. PRED is a synthetic glucocorticoid derived from the steroid hormone cortisone. As a pro-drug, PRED is metabolized primarily in the liver by type 1 dehydrogenase into prednisolone [34]. Prednisolone then mediates the downstream glucocorticoid effects. MP is also a synthetic glucocorticoid, but unlike PRED, is not metabolized before it binds to GRs [35]. The effects of glucocorticoids are dose-dependent, with low doses providing anti-inflammatory effects primarily through genetic mechanisms and high doses providing immunosuppressive effects through both genetic and non-genetic mechanisms [36,37]. The classic genomic effects are mediated by the binding between glucocorticoids and the GR, resulting in a confirmation change of the receptor and translocation into the nucleus. The receptor can then bind DNA sequences directly at glucocorticoid response elements or interact with other transcription factors to influence protein expression [38]. The non-genomic immunosuppressive effects of high glucocorticoid doses are thought to arise from the complete saturation of GRs and occur as a rapid clinical response to drug delivery. One such proposed mechanism is that glucocorticoids are thought to intercalate in biological membranes, which produces an immunosuppressive effect

by reducing calcium and sodium cycling in immune cells [37]. PRED is commonly delivered orally as a low-dose, maintenance GC (0.3–0.5 mg/kg/day, reducing to ≤7.5 mg/day by 3–6 months), but can also be a high-dose, inductive GC (0.5-1 mg/kg/day tapered after a few weeks to lowest effective dose) [39,40]. MP is delivered through IV infusions as a high-dose, inductive GC (30 mg/kg/dose intravenous for three consecutive days, maximum 1000 mg/dose) [27]. Because it is delivered at a high dosage, MP is commonly used as a premedication prior to other therapy infusions to prevent infusion-related reactions.

Hydroxychloroquine (HCQ) is an antimalarial drug initially used for the treatment of *Plasmodium* infection, but has found other uses in autoimmune and infectious diseases [41]. Nirk et al. reports four sets of cellular functions: endolysosomal activities, cytokine signaling, NADPH oxidase signaling, and calcium mobilization from the endoplasmic reticulum [42]. HCQ differs from previously mentioned therapies because it is considered to have immunomodulatory rather than immunosuppressive effects. This is highlighted by the indirect modulation of CD154 expression on activated T cells by inhibition of the immune activation of different cell types which inhibits cytokine production [43]. The use of HCQ has been recommended for all patients in the absence of contraindications by several guidelines, such as the Kidney Disease: Improving Global Outcomes (KDIGO) and EULAR/European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), for the reported benefits of lowered flare rates, improve renal response rates, and lower risk for progression to ESRD and death [11,20,39]. HCQ is delivered orally as an immunomodulator recommended for all patients with SLE (<5 mg/kg/day) [44].

The chronic disease course of LN necessitates the extended use of immunosuppressants to lower the likelihood of relapse/flares. The long-term use of immunosuppressants has been associated with several side effects, given that they are not specifically targeted at mechanisms implicated in LN pathogenesis. Physicians must balance the toxicity of long-term immunosuppressive therapy with the preservation of kidney function. Perhaps most obvious is that the impairment of the immune system places the patient at high risk for infection, including the most common viral infections [45]**.** Glucocorticoids, which are a cornerstone of immunosuppressive therapy, can cause adrenal insufficiency by suppressing the hypothalamic-pituitary-adrenal axis and Cushing's syndrome (i.e. hypercortisolism), and when tapering them, glucocorticoid withdrawal syndrome may occur [46]. Lifetime CTX exposure is particularly important for children because cumulative dose has been associated with reproductive toxicity in both male and females and the chance of future malignancy increases after a total exposure of 36 g [20,47]. RTX can cause immediate adverse reactions during an infusion, and some patients can have more severe reactions that prevent its use [48].

Why Children?

Therapeutic options that are available to pediatric patients often lag behind those available to adults. This is largely in part because children are a unique patient population as they are still growing and rapidly changing, meaning they do not necessarily respond to therapies the same way fully-grown adults do. Even within the pediatric age range, there is vast diversity and heterogeneity from newborns to adolescents. Further efforts are still needed to optimize pediatric therapy formulations, dosing, and building up the literature to inform better clinical care for children.

Pediatric populations were significantly less likely to be involved in randomized controlled trials, systematic reviews, or studies of therapies when compared to adults, highlighting a difference when it comes to the quality of care, funding, and directions in research for pediatric patients [49]. Furthermore, among all pediatric specialties, pediatric nephrology has the lowest number of clinical trials published even though they are among the most costly to all payers, but are a small population, which provides little incentive for pharmaceutical companies to invest in treatment development or trials [50].

Additionally, adverse childhood experiences (ACEs) have entered the limelight as important determinants of adult disease and health outcomes. Individuals with a high burden of ACEs have an increased risk of developing chronic disease in early adulthood, and for those diagnosed with a chronic disease in early adulthood, they are disadvantaged compared to adults who do not develop chronic disease until their elderly years [51]. Children with chronic medical complications are especially vulnerable to caregiver neglect. This can be possibly attributed to the high burden of care which places additional pressure on parents [52]. Additionally, given the chronic remitting–relapsing course and multisystem involvement of SLE, children with the disease will have to face a lifetime of treatment as there is no cure. This also means that there is a high economic burden on the patient to pay for their immunosuppressive treatment, outpatient clinic visits, diagnostic labs, and hospitalization episodes. These costs can climb even higher for patients who progress to ESRD and need to pay for dialysis. More specifically to address patients with LN, both patients without SLE and those with SLE without LN had substantially lower direct costs than those with LN [53].

From a prognostic and life-course perspective, the renal involvement of SLE tends to get worse with each flare. Studies have shown a frequency of stage 5 CKD/kidney failure of up to 15% for pediatric cohorts with LN [54]. Even though there are therapy options for kidney failure like dialysis and kidney transplantation, their entire life becomes painted over by their medical condition and must navigate that in concurrence with the typical challenges that come with growing up and emerging adulthood. More studies are needed to predict flares with biomarkers other than the standard invasive percutaneous kidney biopsy to optimize LN therapy and reduce the risk of severe renal involvement.

Study Question

Are there differences in renal response to immunosuppressive treatment for lupus nephritis patients of varying race/ethnicity?

Study Aims

Primary Aim:

- Association of race and ethnicity with complete or partial renal remission of LN at 12 months after diagnosis of LN.

Secondary Aim:

- Association of race and ethnicity with complete or partial renal remission of LN at 24 and 60 months after diagnosis of LN.
- Association of immunosuppressive treatment course with complete or partial renal remission of LN at 12 and 24 months after diagnosis of LN.

- Association of renal histology on complete with partial renal remission of LN at 12 and 24 months after diagnosis of LN.
- Association of race, ethnicity, and renal histology with LN flares.
- Kidney function at 12, 24, and 60 months after diagnosis of LN.

Hypothesis

There will be a statistically significant difference between renal response towards treatment by individuals of varying race/ethnicity.

Patients and Methods

Study Population

The present study is a retrospective cohort study of 101 pediatric patients seen within the nephrology and rheumatology practices of Children's Healthcare of Atlanta (CHOA) with a biopsy-proven diagnosis of LN and disease onset at age ≤ 18 years, who presented between January 1, 2010 and December 31, 2022. The cutoff date for follow-up data abstraction was December 31, 2023. This study was approved by the CHOA Institutional Review Board (IRB) (STUDY00001429). The IRB waived the requirement for informed consent, parental permission and assent, and patient information/records were anonymized and de-identified prior to analysis.

A flowchart for patient selection is shown in **Figure 1**,

Measurements

All data was abstracted from the Epic electronic medical record system employed by CHOA. Patient age at time point, self-reported gender, and self-reported race/ethnicity were abstracted as demographic data. Height, weight, and treatment courses were abstracted as clinical data. Renal biopsy reports that included percentages of cellular crescents, interstitial fibrosis, and tubular atrophy, and LN class were abstracted as histological data. Laboratory data was used to collect time point values of ANA titer, anti-double stranded DNA (anti-dsDNA) titer, C3 & C4 complement assays, C-reactive protein (CRP) test, erythrocyte sedimentation rate (ESR), serum creatinine, serum albumin, white blood cell (WBC), hemoglobin, platelets, urine protein/creatinine ratio (UPCR), urine protein dipstick, and red blood cell (RBC) urine test. Reference ranges indicating a normal value for all laboratory variables are provided in **Table 3**.

Epic was used to identify patients with a diagnosis of lupus nephritis using ICD-10 code M32.14, and a chart review of those patients was conducted to confirm study eligibility. Patients were included if they were aged 0-18 years at diagnosis of LN, had a biopsy-proven diagnosis of LN at CHOA between 2010 and 2022 with follow-up for at least 1 year after diagnosis, and were treated using immunosuppressants. Patients were excluded if there was a history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C.

Study time points were at baseline and 12, 24, and 60 months after LN diagnosis/treatment initiation. The baseline time point was defined as the date on which LN treatment began, which aligned with the date of LN diagnosis. For patients who had a hospitalization for increased lupus activity, the date on which the LN diagnosis was made was baseline. Any outpatient nephrology

or rheumatology clinic visit within ±2 months of a study time point was abstracted for data collection. Labs were taken up to ±2 weeks from the selected date. Lab values for flares were taken at the time of initial presentation. Data from a particular time point interval was abstracted if height, serum creatinine, and UPCR were present to determine remission status. Patients were followed until they transitioned to adult care, progressed to ESRD/death, or were lost to follow-up.

Study data were collected and managed using REDCap electronic data capture tools hosted at CHOA. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [55,56].

Treatment Courses

This is a retrospective study, meaning treatment courses were not standardized and patients were not randomized to specific treatment courses. Patients received varying combinations of mycophenolate mofetil (MMF), rituximab (RTX), cyclophosphamide (CTX), prednisone (PRED), methylprednisolone (MP), and hydroxychloroquine (HCQ).

Statistical Methods

Descriptive statistical analysis was performed using frequencies and percentages for categorical variables, mean and standard deviation (SD) for normally distributed continuous variables, and

median and interquartile range (IQR) for non-normally distributed continuous variables. Categorical variables were examined using Pearson's chi-squared test, normally distributed continuous variables were examined using one-way linear model analysis of variance (ANOVA) test, and non-normally distributed continuous variables were examined using Kruskal–Wallis rank-sum test. Continuous variable normality was determined using a Shapiro-Wilk normality test.

Patients were stratified according to race/ethnicity, LN class, and treatment course. Race/ethnicity was stratified into four groups: 1) non-Hispanic Whites (NHWs), 2) non-Hispanic Blacks (NHBs), 3) Hispanics, and 4) Other (which included Asians, American Native/Alaska Native, and those who declined/had unknown race and were self-reported as non-Hispanic). LN class was stratified based on their biopsy-proven class diagnosis, with the mixed classes III+V and IV+V each being unique subgroups. Treatment course was stratified into three groups (listed as 'inductive therapy'/'maintenance therapy'): 1) GC+CYC/MMF, 2) GC+MMF/MMF, and 3) Other (which included all patients that were treated with RTX and other combinations outside the two previously listed).

Variables that had little variation and/or too few outcomes in subgroups defined by the variable of interest were excluded from the final analytic models. All patients except one (1.0%), due to type 1 diabetes mellitus, were seen to have had some form of high-dose GC during inductive treatment and low-dose GC during maintenance treatment. All patients except five (5.0%), due to contraindications (i.e.. ocular toxicity), non-compliance, or family preference, were treated using HCQ. Given the low variance in both therapies, they were excluded from analysis as a separate

subgrouping. Twenty-one patients (19.2%) were treated with RTX in concurrence with MP and either MMF or MMF for inductive treatment. Given that use of RTX was further stratified into subgroups by either PRED or MMF for maintenance treatment, the subgroups did not yield enough statistical power and were instead factored into the 'Other' stratification. Six patients (5.9%) were induced on only MP and were also factored into the 'Other' stratification. Out of the eight patients (7.3%) maintained on PRED alone who were already factored into the 'Other' stratification because they were induced on a RTX combination, one patient (1.0%) was induced on MMF and MP but was also factored into the 'Other' stratification due to lack of sample size.

Kaplan-Meier curves were used to estimate the probability of an event occurring over time. For curves estimating the probability to complete or partial remission, given that the curve was plotted over time and that each patient could have up to three time points to determine remissions status, each time point was logged as a separate event instance or was censored. For curves estimating the probability of time to a LN flare, each flare was logged as a separate instance of an event and all 12-, 24-, and 60-month time points were censored. Pairwise log rank comparisons were conducted to determine which subgroups had different survival distributions.

Cox proportional hazards models were used to determine associations with study outcomes using time-to event analyses. The proportional hazard (PH) assumption was checked using Schoenfeld residuals. The PH assumption is important to the model because it is a strong assumption that the relative hazard of an event is constant over time with different covariate or predictor levels. If a categorical covariate in a multivariate model did not meet the PH assumption, the data was stratified by that covariate. The focus of this model is the hazard of an event, defined as the

conditional probability that a single non-repeatable event will occur in a particular time interval, given that the person did not experience the event of interest before that time [57]. Hazard ratios (HR) and 95% confidence intervals (CI) were reported for crude (univariate) and adjusted (multivariate) models. A HR for a predictor that equals 1 means that the predictor does not affect survival. If the HR is less than 1, then the predictor is protective and associated with improved survival, and if the HR is greater than 1, then the predictor is associated with increased risk/decreased survival.

In the case where a univariate model failed to meet the PH assumption or a multivariate model was unable to be corrected after stratification, an accelerated failure time (AFT) model was used to conduct analysis. The AFT model looks at how a unit increase in an imputed covariate changes the survival time by a factor of the exponentiated coefficient. A positive coefficient results in an exponentiated coefficient greater than 1 and decelerates the time-to-event and increases the survival time. Conversely, a negative coefficient results in an exponentiated coefficient less than 1 accelerates the time-to-event and decreases the survival time. The data was fitted to the appropriate distribution based on a log-likelihood function.

Both hazard models and accelerated failure time models were adjusted for age, race/ethnicity, eGFR, UPCR, race/ethnicity, treatment course, and LN class.

Missing data for covariates were accounted for using a fully conditional specification multiple imputation (MI) method using the predictive mean matching method, which operates off a Markov chain Monte Carlo method when the pattern of missing data is arbitrary [58]. MI was

conducted so valid analysis of the data could be permissible in the presence of missing data and not to replace missing values. m=5 imputations with a maximum of 10 iterations were used for the MI models, and convergence and collinearity were assessed to determine model validity. The percentage of missing data at each time point was not greater than 10%.

All data was analyzed using R version 4.3.3 statistical software and the *mice*, *miceadds*, *survival*, *survminer*, and *eha* packages [59–65]. Statistical significance was set at $\alpha = 0.05$.

Operational Definitions

Lupus Nephritis

The ACR provides a case definition for Lupus Nephritis (LN) as persistent proteinuria > 0.5g per day or greater than 3+ by dipstick if quantitation was not performed, and/or cellular casts including red cell, hemoglobin, granular, tubular or mixed [66]. A review of the ACR criteria in 2012 recommended that a spot UPCR > 0.5 can be substituted for the 24-hour protein measurement, and “active urinary sediment” (>5 RBC/hpf, >5 WBC/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts. The ACR revisions also describe that a diagnosis of LN is valid if based on the opinion of a rheumatologist or nephrologist, but for the present study, a renal biopsy that demonstrates immune complex-mediated glomerulonephritis compatible with LN was necessary for patient inclusion [40].

Renal Biopsy and Histology

Classification of LN disease class was done through renal biopsy. The ISN/RPS classification of LN was used to evaluate biopsy samples to determine LN class [67,68].

Cellular crescents, as defined by the 2019 ISN/RPS revisions, refer to a lesion consisting of extracapillary hypercellularity, composed of a variable mixture of cells. 10% or more of the circumference of the Bowman's capsule should be involved (previously 25% or more in the 2003 guidelines) [67,68]. The percentage of cellular crescents observed in the biopsy refers to the number of glomeruli with crescents divided by the total number of glomeruli seen.

Interstitial fibrosis is a sign of kidney injury involving the infiltration of inflammatory cells, fibroblast activation and expansion, production and deposition of extracellular matrix components, and microvascular rarefaction [69]. Tubular atrophy is a general term describing patterns of chronic tubular injury with thickened kidney tubular basement membranes [70]. Both interstitial fibrosis and tubular atrophy (IFTA) percentages are quantified by the percentage of renal cortical area in the biopsy with the characteristics of either pattern.

Kidney Function

Kidney function was evaluated by a blood test known as the estimated glomerular filtration rate (eGFR) and is measured in units of mL/min/1.73 m^2 body surface area (BSA). The glomerular filtrate rate is a means to determine how well the kidneys are filtering, where a high eGFR estimates better kidney function. The "CKiD under 25 (U25)" set of eGFR equations were used to calculate these values using serum creatinine [71].

Induction and Maintenance Drug Dosage

Dosages and delivery routes for inductive and maintenance level therapies are summarized in **Table 2**.

Renal Response

Definitions of renal response to therapy in LN were adapted from the KDIGO 2024 Clinical Practice Guideline for the management of LN and listed below [20]:

Complete renal response:

- Reduction of proteinuria to <0.5 g/g measured as UPCR
- Stabilization or improvement in kidney function measured as eGFR (±10-15% of baseline)

Partial renal response:

- Reduction in proteinuria by at least 50% and <3 g/g measured as UPCR
- Stabilization or improvement in kidney function measured as eGFR (±10-15% of baseline)

No response:

- Failure to achieve a partial or complete response

Lupus Nephritis Flare/Relapse

Generally, the same clinical criteria that are employed to diagnose *de novo* LN are also used when diagnosing LN flares, given that a serial renal biopsy is absent.

The definition of a LN flare was adapted from the Consensus Document of the Spanish Group for the Study of Glomerular Diseases (GLOSEN) for the diagnosis and treatment of lupus nephritis and is as follows [72]:

A LN flare was defined by the presence of two or more of the following:

- Depressed C3 (<90 mg/dL) and/or C4 (<9 mg/dL) complement levels
- Recurrence or significant increase in hematuria (>15 RBC/hpf) with dysmorphic RBC and/or RBC casts
- Proteinuria as shown by ≥1 g/g UPCR
- Physician indication in patient medical record indicating impaired kidney function

Physician indication was used as a proxy for guidelines that specify a percent difference compared to baseline value, like a eGFR reduction ≥ 25% not attributable to other causes as noted in the GLOSEN consensus document [72]. This is because many of the patients included in this study presented with a flare during their initial diagnosis. Thus, if subsequent flares had comparable eGFR levels with the initial diagnosis, the flares could be dismissed from the analysis as a false negative. For the same reason, differentiation between a proteinuric and nephritic flare was also not distinguished because many of the definitions that distinguish the two reference a baseline value [73].

End Stage Renal Disease & Renal Replacement Therapy

End stage renal disease (ESRD) occurs when CKD reaches a final, permanent state. The 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury defines kidney failure/CKD stage 5 as a GFR < 15 mL/min/1.73 m^2 BSA, or requirement for renal replacement therapy (RRT) [74].

RRT can be either dialysis or preemptive kidney transplantation. Although some patients were seen to recover kidney function after an episode of acute kidney failure, the first instance of ESRD was recorded as an endpoint.

Results

Study Population Characteristics

The median age of the study population at LN diagnosis was 14.0 years (IQR: 12.0-16.0). The study population was predominantly female (80.2%) and non-Hispanic Black (52.5%) (**Table 4**). The two most represented LN classes were pure IV and IV + V at 36.6% and 23.8%, respectively. 29 patients are still being seen by the rheumatology and nephrology practices at CHOA and have not terminated their pediatric care. Among those who had their care terminated, the mean follow up time was 4.46 years (SD 2.15). 52 patients had a recorded transition of care to an adult practice, 16 patients were lost to follow up, 2 patients progressed to ESRD/RRT, and 2 patients progressed to death.

Race/Ethnicity on Remission Status

The study population at baseline consisted of 101 patients. Inflammatory markers (ANA, anti-dsDNA, C3 & C4 complement, CRP, ESR) markedly indicated active SLE activity, and eGFR, UPCR, urine protein dipstick, and urine RBC values all indicated active LN activity. Statistically significant baseline differences in race/ethnicity were found in age at diagnosis ($p=0.031$), cellular crescents ($p<0.001$), interstitial fibrosis ($p=0.034$), tubular atrophy ($p=0.020$), ESR ($p<0.001$), serum hemoglobin ($p=0.011$), serum platelets ($p=0.022$), urine protein dipstick (0.056), and urine RBC ($p<0.001$) (**Table 4**).

At 12 months after LN diagnosis, laboratory values generally became normal and were within reference values for the study population (n=81). The UPCR (0.320, IQR 0.179-0.790) remained high but the eGFR (99.1, IQR 88.7-112.2) was restored to normal kidney function range. All complete blood count labs (serum, WBC, hemoglobin, platelets) were significant at $p<0.001$. The ESR also remained significant at $p<0.001$, along with a significant anti-dsDNA at $p=0.018$ and urine RBC at $p<0.001$ (**Table 5**). At 24 months after LN diagnosis, both ESR and urine RBC continued to remain significant at $p<0.001$ and $p=0.008$, respectively (**Table 6**). Finally, at 60 months after LN diagnosis, only eGFR is significant at $p=0.013$ and has a normal mean (99.3, SD 34.7) (**Table 7**).

The crude HRs by race/ethnicity for complete remission at 12 months after diagnosis was insignificant for all subgroups but became significant in the adjusted HRs for the NHW ($p=0.049$) and Other ($p=0.023$) subgroups with a 30.9% and 22.8% chance of surviving the model compared to Hispanics. The NHB subgroup did not find significance at 12 months (**Table 8**).

The PH assumption was not met for the race/ethnicity variable 24 and 60 months after diagnosis for both complete and partial remission (**Figures 2, 3**). A multivariate AFT model was used and fitted to a log-normal distribution at both timepoints. At 24 months, the NHW and Other subgroups were found to have statistical significance again with a shorter survival time within the model that was 96.2% and 95.2% of what the Hispanic group survived for. These values were significant for NHW and Other at $p=0.006$ and $p=0.002$, respectively (**Table 9**). At 60 months,

only the NHB subgroup found significance at p=0.011 and had a survival probability that was 97.4% of Hispanics to complete remission (**Table 10**).

The crude HRs for race/ethnicity subgroups on partial remission at 12 months were not significant. Once adjusted, the Other subgroup found significance at p=0.009 and had a 13.2% chance of surviving compared to the Hispanic subgroup (**Table 11**). The Other subgroup remained significant in the AFT model at 24 months for partial remission at p=0.026 and had a survival probability that was 95.8% of the Hispanic subgroup (**Table 12**). At 60 months, the NHB subgroup found significance at p=0.005 and had a survival probability that was 97.3% of the Hispanic subgroup (**Table 13**).

The KM curves using race/ethnicity alone as a criterion for complete remission in **Figure 5** and for partial remission in **Figure 6** were both insignificant at p=0.5 and p=0.2, respectively.

LN Class on Remission Status

The crude HR model by LN class for complete remission at 12 months was insignificant for all class subgroups, but the mixed IV+V class became significant once adjusted at p=0.004 which showed that in comparison to class II, there is a 597.5% of surviving (**Table 14**). Like the race/ethnicity variable, the PH assumption was not met for the LN class variable 24 months after diagnosis for both complete and partial remission, so a multivariate AFT model was used and fitted to a log-normal distribution at that time point (**Figure 4**). At 24 months, classes III and IV were found to have statistically significant survival probabilities that were 95.1% and 94.3% of

class II's at p=0.013 and p<0.001, respectively. Additionally, class III+V was also found to be significant and had a survival time that was 105% of class II's at p=0.001 (**Table 15**).

The crude HRs for class IV+V for partial remission at 12 months was found to be significant at p=0.023 and had a survival time that was 289.4% of class II's. Once the model was adjusted, class IV+V continued to stay significant at p=0.014 with a higher survival probability that was 341.2% of class II's. All other classes were insignificant at 12 months (**Table 16**). The AFT model for partial remission did not show significance for any class at 24 months (**Table 17**).

The KM curves using LN class alone as a criterion for complete remission in **Figure 7** and for partial remission in **Figure 8** were both insignificant at p=0.4 and p=0.7, respectively.

Treatment Course on Remission Status

The crude HR model by treatment course for complete remission at 12 months was insignificant for all treatment subgroups, but the Other subgroup became significant once the model was adjusted at p=0.029 and showed a 34.3% chance of survival compared to the GC+CYC/MMF group (**Table 18**). At 24 months, the crude HR model was insignificant for all subgroups again, but once adjusted, the Other subgroup stayed significant at p<0.001 and showed a 12.3% chance of survival compared to the GC+CYC/MMF group. The GC+MMF/MMF treatment group also became significant at p=0.011 and showed a 16.8% chance of survival compared to the GC+CYC/MMF group (**Table 19**). The crude and adjusted HR models by treatment course for partial remission at both 12 and 24 months showed insignificance for all subgroups (**Tables 20, 21**).

The KM curves using treatment course alone as a criterion for complete remission in **Figure 9** and for partial remission in **Figure 10** were both insignificant at p>0.9 and p=0.3, respectively.

Incidence of complete and partial remission for the study population at each timepoint is summarized in **Table 22**.

LN Flares

31 patients (30.7%) in the study population experienced at least 1 LN flare and there was a total of 64 LN flare events. The median time to a flare after diagnosis of LN was 1.199 years (IQR 0.531-2.834), the median eGFR was 78.75 (IQR 52.50-100.99), and the median UPCR was 3.675 (IQR 1.397-6.082). In race/ethnicity subgroups, statistically significant differences were found in UPCR and urine RBC values with p=0.042 and p<0.001, respectively (**Table 23**). In LN class subgroups, statistically significant differences were found in urine RBC values with p<0.001 (**Table 24**). Lastly, in treatment course subgroups, statistically significant differences were found in the time to first flare, UPCR, and urine protein dipstick values with p=0.048, p=0.017, and p=0.019, respectively (**Table 25**).

The PH assumption failed for multivariate analysis, so an AFT model was used to determine the effect of covariates to accelerate or decelerate the survival time to a flare event. For race/ethnicity subgroups, the NHB subgroup was found to have a significant survival time that was 35.2% of Hispanics at p=0.001 (**Table 26**). For LN class subgroups, classes V and IV+V were found to have a significantly different survival time that was 1398.7% and 230.0% greater

than class II's at p=0.002 and p=0.012, respectively. The strikingly high time ratio shown by class V is likely due to the fact that there was only one individual in that group (**Table 27**). Lastly, for treatment course subgroups, GC+MMF/MMF was found to have a significant survival time that was 57.0% of the GC+CYC/MMF subgroup at p=0.044 (**Table 28**).

The KM curves using ethnicity/race, LN class, and treatment course as a criterion for LN flare in **Figures 11**, **12**, and **13** were found to have p values of p=0.085, p<0.001, and p=0.041, respectively. Once again, the low p value for the LN class subgrouping was likely due to the singular observation of a flare for class V, which in Figure 12 shows a markedly different KM curve.

Discussion

A total of 101 pediatric patients with biopsy-proven LN, from an urban tertiary medical center in the southeastern US, were included in this study. The mortality rate (2.0%) was relatively favorable when compared to other pediatric cohorts with rates of 2%, 5.66%,and 11.56% [75–77]. There appears to be an association of race/ethnicity where patients in the NHW and Other subgroups had a statistically significant increased likelihood of reaching complete remission in the short term (12 and 24 months) and the NHB subgroup had an increased likelihood of achieving complete remission in the long term (60 months). Additionally, patients, once again, in the Other subgroup had a statistically significant increased likelihood of reaching partial remission in the short term, and the NHB subgroup had an increased likelihood of achieving partial remission in the long term. This is consistent, in regards to short term outcomes, with findings that Black and Hispanic children with pediatric lupus have higher

morbidity and mortality than NHW children, but is slightly curious in that the Hispanic group did not show significant difference from the NHW and Hispanic subgroups at 60 months [78].

Class IV+V had a statistically significant protective effect in the survival model at 12 months after LN diagnosis for both complete and partial remission, meaning it had a higher probability of survival and clinically took longer to achieve remission. At 24 months, classes III and IV had a statistically significant harmful effect in the survival model and survived less time, meaning they clinically achieved complete remission in a shorter amount of time, and that III+V took longer to achieve complete remission because it had a protective effect. For partial remission at 12 months, class IV+V was found to also survive a significantly longer time in the model, thereby taking longer to achieve partial remission. There was no association between LN class and partial remission status at 24 months. The study findings seem to agree with conventional knowledge that the presence of class V LN (having a membranous component) is indicative of a worse prognosis and requires more aggressive treatment therapy.

Both the GC+MMF/MMF and Other subgroups had significantly lower survival in the complete remission model at both 12 and 24 months, meaning that it took a shorter amount of time to achieve complete remission. There was no apparent statistical difference between treatment courses in achieving partial remission at both 12 and 24 months. 19/28 (67.9%) of the patients in the Other subgroup had RTX as an add-on along with CYC/MMF in their inductive treatment, and interestingly, the results shown in this study seem to, in part, differ from the findings of the Lupus Nephritis Assessment with Rituximab (LUNAR) trial, which showed that RTX did not demonstrate statistically significant outcomes in combination with MMF and corticosteroids

versus just MMF and corticosteroids alone [79]. Additionally, the findings at 12 months showing significant difference between the GC+CYC/MMF and GC+MMF/MMF groups in regards to complete remission seem to differ from results found in the Aspreva Lupus Management Study (ALMS) study, which found no difference between MMF and CYC [80]. It is important to note, however, that the LUNAR trial and ALMS study were randomized controlled trials conducted in a primarily adult population, whereas the results presented in the present study were an observational review done in a pediatric population. The findings of the present study also differ from findings of a recent systematic review and meta-analysis published in 2020 that found MMF to precede CYC in complete remission independent of race [81].

In regard to flares, The NHB and GC+MMF/MMF subgroups had a significantly lower survival time and the IV+V subgroup had a significantly higher survival time, The findings of the NHB subgroup, again, concurs with data that they have worse outcomes compared to NHW patients. The findings of the GC+MMF/MMF and IV+V subgroups seem to differ from the literature and general clinical knowledge in that MMF should be more protective and the mixed V classes should experience worse outcomes.

The retrospective chart review design of this study allows for rare diseases like pediatric lupus nephritis to be studied based on historical data and identify trends or patterns that might not be readily available or apparent in prospective studies. Moreover, the results shown in this study also provide insights into current treatment patterns and resource utilization for current practices, having stratified the patient population by race/ethnicity, LN class, and treatment course. Given that this was a single-center study, variability in documentation practice was minimized. CHOA

also sees a diverse patient population, increasing the generalizability of the study findings due to identification of subgroup differences.

This study also has limitations that warrant consideration. First, data collection and interpretation were potentially influenced by variation in medical record documentation practices. This includes inconsistencies in how LN diagnoses were coded and how terms like "flare" were used during initial presentations. The medical records of some patients were further complicated due to the transition in medical record systems from ChartMaxx and Organ Transplant Tracking Record to Epic in 2015. The transition resulted in encounters prior to this change (i.e. clinic visits, labs, hospitalizations) appearing in the record, but sometimes not having any progress notes or recorded laboratory values associated with the encounter. The lack of data in some charts resulted in either patients being fully excluded from the study due to a lack of appreciable time points or only being able to partially collect data from a record, introducing bias in the estimation of parameters and reducing the overall statistical power. This was addressed by using a MI statistical model to account for the missing data and preserve statistical power, but the model is unable to recover the power that was lost from excluded patients/time points. Second, the study focused on analyzing discrete treatment episodes rather than longitudinal data, particularly by only looking at snapshots of patients at 12, 24, and 60 months after LN diagnosis. This approach may not fully capture the long-term course of the disease, particularly since patients are not followed for a full 60 months as they often transition to adult care. This restricted the ability to assess long-term study outcomes like progression to ESRD or mortality. The study time window also included the COVID-19 pandemic, where telemedicine encounters became a popular option for outpatient clinic visits. These clinic visits often were unable to be included

due to the lack of a height value or labs that were done weeks prior/after the visit that were outside the ±14-day window, so patients who had their care started right before/during the pandemic were underrepresented in the collected data. Certain time points were also excluded from analysis if they had a UPCR that was not calculated due to an analyte being above or below technical limits, biasing the data against those with particularly high or low UPCRs.

The study model itself has limitations. The models used in this study do not account for social determinants of health, which could influence treatment patterns and outcomes. This study provides much more descriptive analysis rather than inferences and does not provide reasoning to explain the observed associations between factors and clinical outcomes. Furthermore, the study did not consider concomitant medications or co-morbidities, which can alter a patient's treatment course given that SLE has multisystem involvement. The study design also resulted in a potential underrepresentation of Class 1 and 2 LN diagnoses, which generally do not need immunosuppressants in their treatment. The focus on treatment episodes requiring immunosuppressants likely excluded milder cases, which were also sometimes not biopsied and treated empirically. Similarly, Class 6 LN, typically presenting with severe renal dysfunction (i.e. ESRD) at disease onset, is also underrepresented due to the immediate need for RRT and has a generally short treatment course with immunosuppressants, if any. The stratification of patients can also introduce bias, but this was attempted to be controlled by comparing the baseline parameters. Inclusion of a patient required them to be compliant with medication and have good follow-up, creating a bias in the population whose data was abstracted. Lastly, the practice of percutaneous renal biopsy is not standardized in CHOA's nephrology clinical practice and tends to be more preferential depending on clinical presentation and level of comfort of the physician,

creating another selection bias for patients to be excluded due to lack of biopsy-proven LN diagnosis.

Statistical significance does not necessarily correspond with clinical significance. Likewise, statistical non-significance does not necessarily correspond with clinical non-significance. However, the observation of statistically significant results suggests that further research should be done to understand the underlying mechanisms at play that revealed those associations. Future studies should expand the time range of patients examined and time points included for analysis, both looking further into the past and also creating a prospective study to follow patients throughout their present care. This would allow for an increased sample size and also include various advancements in the treatment of LN that were not included in the present study, such as other biological agents apart from RTX and use of calcineurin inhibitors. As always, there is a need for pediatric populations to have more randomized controlled trials to discover better treatment options for children. Other factors at play beyond the three stratifications used in this study should be also considered. In particular, social determinants of health should be evaluated in concurrence with the study data to gain a thorough picture of the patient experience that is rooted in socioeconomic context. The multisystem interaction and interplay between physicians of different specialties working together as a care team to treat LN patients should also be considered in the future to contextualize renal involvement in the presence of other SLE manifestations.

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Abbreviations

ACE	Adverse Childhood Experience	ESR	Erythrocyte Sedimentation Rate
ACR	American College of Rheumatology	ESRD	End Stage Renal Disease
AFT	Accelerated Failure Time	EULAR	European League Against Rheumatism
ANA	Anti-Nuclear Antibody	GC	Glucocorticoid
ANOVA	Analysis of Variance	GLOSEN	Spanish Group for the Study of Glomerular Diseases
anti-dsDNA	Anti-Double Stranded DNA	GR	Glucocorticoid Receptor
ATP	Adenosine Triphosphate	GTP	Guanosine Triphosphate
BSA	Body Surface Area	HCQ	Hydroxychloroquine
CHOA	Children's Healthcare of Atlanta	HIV	Human Immunodeficiency Virus
CKD	Chronic Kidney Disease	HR	Hazard Ratio
CRP	C-Reactive Protein	ICD-10	International Classification of Diseases, Tenth Revision
cSLE	Childhood-Onset Systemic Lupus Erythematosus	IFTA	Interstitial Fibrosis and Tubular Atrophy
CTX	Cyclophosphamide	IMPDH	Inosine-5'-Monophosphate Dehydrogenase
DNA	Deoxyribonucleic Acid	IQR	Interquartile Range
eGFR	Estimated Glomerular Filtration Rate	IRB	Institutional Review Board
ERA-EDTA	European Renal Association-European Dialysis and Transplant Association	ISN	International Society of Nephrology

IV	Intravenous	SLICC	Systemic Lupus International Collaborating Centers
KDIGO	Kidney Disease: Improving Global Outcomes	UPCR	Urine Protein/Creatinine Ratio
LN	Lupus Nephritis	WBC	White Blood Cell
LUNAR	Lupus Nephritis Assessment With Rituximab		
MI	Multiple Imputation		
MMF	Mycophenolate Mofetil		
MP	Methylprednisolone		
MPA	Mycophenolic Acid		
NADPH	Nicotinamide Adenine Dinucleotide Phosphate		
NHB	Non-Hispanic Black		
NHW	Non-Hispanic White		
PH	Proportional Hazards		
PRED	Prednisone		
RBC	Red Blood Cell		
REDCap	Research Electronic Data Capture		
RPS	Renal Pathology Society		
RRT	Renal Replacement Therapy		
RTX	Rituximab		
SD	Standard Deviation		
SLE	Systemic Lupus Erythematosus		

Tables and Figures

Table 1. Summary of ISN/RPS Classification (2003) for Lupus Nephritis [67,68].

LN Class	Definition
Class I (Minimal mesangial LN)	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence.
Class II (Mesangial proliferative LN)	Purely mesangial hypercellularity (Four or more nuclei fully surrounded by matrix in the mesangial area not including the hilar region) of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.
Class III (Focal LN)	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.
Class IV (Diffuse LN)	Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class V (Membranous LN)*	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
Class VI (Advanced sclerotic LN)	≥90% of glomeruli globally sclerosed without residual activity

*Class V may occur in combination with class III or IV, in which case both will be diagnosed. Diffuse: A lesion involving most (≥50%) glomeruli, Focal: A lesion involving <50% of glomeruli, Global: A lesion involving more than half of the glomerular tuft, Segmental: A lesion involving less than half of the glomerular tuft (i.e., at least half of the glomerular tuft is spared)

Table 2. Summary of Therapies Examined in this Study.

Therapy	Class	Delivery Route	Dosage
Induction Therapy			
Mycophenolate Mofetil (MMF; CellCept®)	Immunosuppressive Agent	Oral	1800 mg/m²/day 3000 mg/day [2
Rituximab (RTX; Rituxan®)	Monoclonal Antibody	IV Infusion	375 mg/m²/week [30]
Cyclophosphamide (CTX; Cytoxan®)	Alkylating Agent	IV Infusion	500–750 mg/m²/ increase to 750 r maximum dose 1000–1200 mg/p pulses [27]
Methylprednisolone (MP; Solu-Medrol®)	Glucocorticoid	IV Infusion	30 mg/kg/dose i three consecutiv 1000 mg/dose [2
Maintenance Therapy			
Mycophenolate Mofetil (MMF; CellCept®)	Immunosuppressive Agent	Oral	1200 mg/m²/day 2000 mg/day [2
Prednisone (PRED; Deltasone®)	Glucocorticoid	Oral	0.5–1 mg/kg/day the minimal amo [27]
Immunomodulator			
Hydroxychloroquine (HCQ; Plaquenil®)	Antimalarial	Oral	<5 mg/kg/day [4

Table 3. Laboratory Reference Ranges for Study Variables.

Variable	Reference Range
Anti-Nuclear Antibody Titer	< 1:40
Anti-dsDNA Titer	< 1:10
C3 Complement	90 - 200 mg/dL
C4 Complement	12 - 51 mg/dL
C-Reactive Protein	< 1.0 mg/dL
Erythrocyte Sedimentation Rate	0 - 20 mm/hr
Estimated Glomerular Filtration Rate	≥ 90 mL/min/1.73 m2 BSA
Serum Albumin	3.7 - 5.5 g/dL
White Blood Cell Count	4.5 - 13.5 thou/μL
Hemoglobin Count	12.0 - 16.0 g/dL
Platelet Count	150 - 540 thou/μL
Urine Protein/Creatinine Ratio	< 0.2 g/g
Urine Protein Dipstick	< +1 (30 mg/dL)
Urine Red Blood Cell Count	0 - 5 #/hpf

Table 4. Characteristics of the Study Population at Baseline.

Variable	Total (n=101)	Hispanic (n=21)	NHB (n=53)	NHW (n=12)	Other (n=15)	P Value
Demographic Characteristics						
Age (Years) median (IQR)	14.0 (12.0-16.0)	13.0 (10.0-15.0)	15.0 (13.0-16.0)	14.0 (12.00-15.0)	14.0 (12.0-16.5)	0.031
Female n (%)	81 (80.2)	16 (76.2)	45 (84.9)	10 (83.3)	10 (66.7)	0.431
Pathological Characteristics						
LN Class n (%)						0.406
II	12 (11.9)	1 (4.8)	9 (17.0)	0	2 (13.3)	
III	7 (6.9)	2 (9.5)	3 (5.7)	1 (8.3)	1 (6.7)	
IV	37 (36.6)	11 (52.4)	14 (26.4)	7 (58.3)	5 (33.3)	
V	10 (9.9)	1 (4.8)	8 (15.1)	0	1 (6.7)	
III + V	11 (10.9)	3 (14.3)	7 (13.2)	0	1 (6.7)	
IV + V	24 (23.8)	3 (14.3)	12 (22.6)	4 (33.3)	5 (33.3)	
Cellular Crescents (%) median (IQR)	0 (0-13.3)	0 (0-4)	0 (0-17)	8 (0-17.5)	4 (0-23)	<0.001
Interstitial Fibrosis (%) median (IQR)	0 (0-10)	4 (0-10)	0 (0-10)	0 (0-5)	5 (0-17)	0.034
Tubular Atrophy (%) median (IQR)	0 (0-5)	0 (0-5)	0 (0-5)	0 (0-5)	5 (0-10)	0.020
Laboratory Characteristics						
ANA ≥1:80 n (%)	98 (97.0)	21 (100.0)	51 (96.2)	11 (91.7)	15 (100.0)	0.564
Anti-dsDNA ≥1:80 n (%)	82 (81.2)	19 (90.5)	39 (73.6)	12 (100.0)	12 (80.0)	0.553
Low C3 Complement n (%)	86 (85.1)	19 (90.5)	42 (79.3)	12 (100.0)	13 (86.67)	0.310
Low C4 Complement n (%)	71 (78.2)	17 (81.0)	38 (71.7)	12 (100.0)	12 (80.0)	0.200
Elevated C-Reactive Protein n (%)	42 (41.6)	10 (47.6)	24 (45.3)	3 (25.0)	5 (33.3)	0.839
ESR (mm/hr) median (IQR)	55 (52-125)	61 (28-118)	84 (61-112)	128 (81.8-140)	88 (86-138)	<0.001
eGFR (mL/min/1.73 m^2 BSA) mean (SD)	71.70 (33.29)	67.67 (35.87)	71.39 (31.60)	64.71 (25.82)	84.03 (40.19)	0.508
Serum Albumin (g/dL) mean (SD)	2.41 (0.72)	2.58 (0.59)	2.37 (0.74)	2.43 (0.92)	2.29 (0.66)	0.538
WBC (thou/µL) median (IQR)	4.87 (3.13-6.84)	4.91 (2.99-6.71)	5.09 (3.13-9.29)	4.75 (3.81-5.25)	4.58 (2.69-6.45)	0.062
Hemoglobin (g/dL) median (IQR)	10.5 (9.5-12.0)	10.7 (9.2-11.4)	10.4 (9.6-12.0)	10.1 (9.0-11.0)	11.8 (8.9-13.2)	0.011
Platelets (thou/µL) median (IQR)	241 (142-313)	238 (126-279)	253 (156-325)	218 (181-268)	227 (130-314)	0.022
UPCR (g/g) median (IQR)	2.26 (1.20-5.21)	2.17 (0.91-3.34)	1.93 (1.31-5.00)	3.30 (1.31-5.14)	3.11 (1.82-8.48)	0.100
Urine Protein Dipstick ≥100 mg/dL n (%)	88 (87.1)	15 (71.4)	48 (90.6)	10 (83.3)	15 (100.0)	0.056
Urine RBC (#/hpf) median (IQR)	15 (10-76)	15 (10-76)	12 (2-50)	43.5 (35-70)	24 (3-98)	<0.001

Table 5. Characteristics of the Study Population by Race/Ethnicity at 12 Months After LN Diagnosis.

Variable	Total (n=81)	Hispanic (n=15)	NHB (n=43)	NHW (n=11)	Other (n=12)	P Value
Demographic Characteristics						
Age (Years) median (IQR)	16.0 (14.0-17.0)	14.0 (12.0-17.0)	16.0 (14.0-17.0)	15.0 (13.0-16.0)	15.5 (13.8-18)	0.226
Female n (%)	66 (51.5)	12 (80.0)	37 (86.0)	9 (81.8)	8 (66.7)	0.501
Pathological Characteristics						
LN Class n (%)						0.341
II	11 (13.6)	1 (6.7)	8 (18.6)	0	2 (16.7)	
III	3 (3.7)	1 (6.7)	1 (2.3)	1 (9.1)	0	
IV	27 (33.3)	8 (53.3)	10 (23.3)	6 (54.5)	3 (25.0)	
V	9 (11.1)	1 (6.7)	7 (16.3)	0	1 (8.3)	
III + V	9 (11.1)	1 (6.7)	7 (16.3)	0	1 (8.3)	
IV + V	22 (27.2)	3 (20.0)	10 (23.3)	4 (36.4)	5 (41.7)	
Laboratory Characteristics						
Anti-dsDNA ≥1:80 n (%)	26 (32.1)	3 (20.0)	21 (48.8)	2 (18.2)	0	0.018
Low C3 Complement n (%)	11 (13.6)	1 (6.7)	6 (14.0)	3 (27.3)	1 (8.3)	0.522
Low C4 Complement n (%)	16 (19.8)	1 (6.7)	10 (23.3)	4 (36.4)	1 (8.3)	0.230
ESR (mm/hr) median (IQR)	18 (9-34)	17 (9.5-33)	25 (17.5-36)	7 (4-9.5)	9 (6-13)	<0.001
eGFR (mL/min/1.73 m^2 BSA) median (IQR)	99.1 (86.7-112.2)	109.7 (89.7-126.6)	97.4 (86.4-105.0)	101.5 (94.6-107.6)	91.8 (57.6-114.8)	0.246
Serum Albumin (g/dL) median (IQR)	3.80 (3.30-4.10)	3.90 (3.60-4.10)	3.50 (3.00-4.05)	3.80 (3.75-4.35)	4.40 (3.88-4.60)	0.002
WBC (thou/µL) median (IQR)	5.30 (4.04-7.12)	6.55 (5.10-10.10)	4.94 (3.80-6.70)	4.89 (3.25-7.40)	5.50 (3.60-6.76)	<0.001
Hemoglobin (g/dL) median (IQR)	12.3 (11.5-13.0)	12.5 (11.6-12.6)	11.9 (11.2-12.5)	12.3 (11.6-13.9)	12.6 (11.7-13.0)	<0.001
Platelets (thou/µL) median (IQR)	293 (240-335)	335 (295-370)	295 (245-334)	262 (208-321)	271 (236-294)	<0.001
UPCR (g/g) median (IQR)	0.320 (0.179-0.790)	0.340 (0.191-0.740)	0.330 (0.184-0.885)	0.200 (0.119-0.640)	0.395 (0.210-0.569)	0.639
Urine Protein Dipstick ≥100 mg/dL n (%)	29 (35.8)	4 (26.7)	21 (48.8)	2 (18.2)	2 (16.7)	0.068
Urine RBC (#/hpf) median (IQR)	2 (1-12)	3 (1-8)	2 (1-16)	3 (1-14)	1 (0-2)	<0.001

Table 6. Characteristics of the Study Population by Race/Ethnicity at 24 Months After Diagnosis.

Variable	Total (n=67)	Hispanic (n=15)	NHB (n=37)	NHW (n=9)	Other (n=6)	P Value
Demographic Characteristics						
Age (Years) median (IQR)	16.0 (14.0-18.0)	15.0 (14.0-17.0)	17.0 (15.0-18.0)	16.0 (14.0-17.0)	13.5 (12.2-17.8)	0.321
Female n (%)	54 (80.6)	12 (80.0)	32 (86.5)	7 (77.8)	3 (60.0)	0.216
Pathological Characteristics						
LN Class n (%)						0.441
II	6 (9.0)	0	5 (13.5)	0	1 (16.7)	
III	5 (7.5)	1 (6.7)	3 (8.1)	0	1 (16.7)	
IV	25 (37.3)	7 (46.7)	11 (29.7)	5 (55.6)	2 (33.3)	
V	7 (10.4)	1 (6.7)	6 (16.2)	0	0	
III + V	9 (13.4)	3 (20.0)	6 (16.2)	0	0	
IV + V	15 (22.4)	3 (20.0)	6 (16.2)	4 (44.4)	2 (33.3)	
Laboratory Characteristics						
Anti-dsDNA ≥1:80 n (%)	23 (34.3)	1 (6.7)	15 (40.5)	5 (55.6)	2 (33.3)	0.061
Low C3 Complement n (%)	17 (25.4)	2 (13.3)	10 (27.0)	4 (44.4)	1 (16.7)	0.363
Low C4 Complement n (%)	14 (20.9)	1 (6.7)	7 (18.9)	4 (44.4)	2 (33.3)	0.133
ESR (mm/hr) median (IQR)	14 (8-25	8 (5-26.5)	19 (11-30)	11 (5-14)	13 (10-41)	<0.001
eGFR (mL/min/1.73 m^2 BSA) median (IQR)	100.8 (81.1-109.4)	101.0 (84.5-112.0)	96.1 (80.2-106.4)	103.0 (82.7-110.0)	100.0 (71.0-107.3)	0.749
Serum Albumin (g/dL) median (IQR)	3.90 (3.60-4.20)	3.80 (3.55-4.30)	3.80 (3.40-4.10)	4.40 (3.70-4.50)	4.05 (4.00-4.25)	0.083
UPCR (g/g) median (IQR)	0.280 (0.134-0.551)	0.260 (0.155-0.589)	0.288 (0.100-0.540)	0.240 (0.150-0.940)	0.280 (0.198-0.295)	0.839
Urine Protein Dipstick ≥100 mg/dL n (%)	23 (34.3)	5 (33.3)	16 (43.2)	2 (22.2)	0	0.174
Urine RBC (#/hpf) median (IQR)	1 (0-6.5)	1 (1-6.5)	1 (0-6.5)	1 (1-3)	1 (0-1)	0.008

Table 7. Characteristics of the Study Population by Race/Ethnicity at 60 Months After Diagnosis.

Variable	Total (n=26)	Hispanic (n=6)	NHB (n=13)	NHW (n=2)	Other (n=5)	P Value
Demographic Characteristics						
Age (Years) mean (SD)	16.6 (2.2)	14.0 (2.0)	17.7 (1.7)	15.5 (0.7)	17.4 (1.1)	0.028
Female n (%)	21 (80.8)	3 (50.0)	12 (92.3)	2 (100.0)	4 (80.0)	0.154
Pathological Characteristics						
LN Class n (%)						0.602
II	2 (7.7)	1 (16.7)	1 (7.7)	0	0	
III	2 (7.7)	1 (16.7)	1 (7.7)	0	0	
IV	10 (38.5)	3 (50.0)	3 (23.1)	1 (50.0)	3 (60.0)	
V	4 (15.4)	0	4 (30.8)	0	0	
III + V	1 (3.8)	0	0	0	1 (20.0)	
IV + V	7 (26.9)	1 (16.7)	4 (30.8)	1 (50.0)	1 (20.02)	
Laboratory Characteristics						
eGFR (mL/min/1.73 m^2 BSA) mean (SD)	99.3 (34.7)	135.1 (33.8)	84.0 (29.2)	128.0 (10.3)	84.9 (13.7)	0.013
UPCR (g/g) median (IQR)	0.170 (0.113-0.453)	0.335 (0.107-0.810)	0.198 (0.137-0.370)	0.426 (0.275-0.578)	0.120 (0.111-0.137)	0.409
Urine Protein Dipstick ≥100 mg/dL n (%)	8 (30.8)	3 (50.0)	4 (30.8)	1 (50.0)	0	0.298

Table 8. Crude and Adjusted Hazard Ratios by Race/Ethnicity for Complete Remission 12 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Race/Ethnicity				
Hispanic	1.0 [Ref]	---	1.0 [Ref]	---
NHB	0.793 (0.354-1.777)	0.573	0.635 (0.231-1.744)	0.378
NHW	0.785 (0.280-2.20)	0.645	0.309 (0.096-0.993)	0.049
Other	0.649 (0.224-1.880)	0.426	0.228 (0.063-0.819)	0.023

*Adjusted for age, eGFR, UPCR, LN class, treatment course.

Table 9. Adjusted Accelerated Failure Time Model by Race/Ethnicity for Complete Remission 24 Months After Diagnosis.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
Race/Ethnicity*					
Hispanic	0 [Ref]	---	---	---	---
NHB	-0.016	0.048	0.984	-1.44	0.151
NHW	-0.038	0.011	0.962	-2.74	0.006
Other	-0.049	0.014	0.952	-3.06	0.002

*Adjusted for age, eGFR, UPCR, LN class, treatment course.

Table 10. Adjusted Accelerated Failure Time Model by Race/Ethnicity for Complete Remission 60 Months After Diagnosis.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
Race/Ethnicity*					
Hispanic	0 [Ref]	---	---	---	---
NHB	-0.027	0.010	0.974	-2.551	0.011
NHW	-0.025	0.013	0.975	-1.949	0.051
Other	-0.016	0.011	0.984	-1.413	0.158

*Adjusted for age, eGFR, UPCR, LN class, treatment course.

Table 11. Crude and Adjusted Hazard Ratios by Race/Ethnicity for Partial Remission 12 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Race/Ethnicity				
Hispanic	1.0 [Ref]	---	1.0 [Ref]	---
NHB	1.119 (0.513-2.441)	0.778	0.630 (0.211-1.8800	0.408
NHW	0.901 (0.339-2.396)	0.834	0.523 (0.153-1.788)	0.302
Other	0.953 (0.366-2.482)	0.992	0.132 (0.029-0.607)	0.009

*Adjusted for age, eGFR, UPCR, LN class, Treatment Course.

Table 12. Adjusted Accelerated Failure Time Model by Race/Ethnicity for Partial Remission 24 Months After Diagnosis.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
Race/Ethnicity*					
Hispanic	0 [Ref]	---	---	---	---
NHB	-0.015	0.058	0.985	-1.24	0.214
NHW	-0.011	0.012	0.989	-0.71	0.476
Other	-0.043	0.016	0.958	-2.22	0.026

*Adjusted for age, eGFR, UPCR, LN class, Treatment Course.

Table 13. Adjusted Accelerated Failure Time Model by Race/Ethnicity for Partial Remission 60 Months After Diagnosis.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
Race/Ethnicity*					
Hispanic	0 [Ref]	---	---	---	---
NHB	-0.027	0.010	0.973	-2.819	0.005
NHW	-0.018	0.009	0.982	-1.921	0.055
Other	-0.017	0.011	0.983	-1.609	0.108

*Adjusted for age, eGFR, UPCR, LN class, Treatment Course.

Table 14. Crude and Adjusted Hazard Ratios by LN Class for Complete Remission 12 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
LN Class				
II	1.0 [Ref]	---	1.0 [Ref]	---
III	0.875 (0.106-7.215)	0.901	0.894 (0.089-8.994)	0.924
IV	1.199 (0.500-2.874)	0.684	1.864 (0.562-6.189)	0.309
V	0.475 (0.122-1.845)	0.282	0.238 (0.047-1.207)	0.083
III + V	1.305 (0.436-3.905)	0.634	1.951 (0.543-7.018)	0.306
IV + V	1.911 (0.717-5.092)	0.195	5.975 (1.776-20.101)	0.004

*Adjusted for age, eGFR, UPCR, race/ethnicity, treatment course.

Table 15. Adjusted Accelerated Failure Time Model by LN Class for Complete Remission 24 Months After Diagnosis.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
LN Class					
II	0 [Ref]	---	---	---	---
III	-0.050	0.048	0.951	-2.49	0.013
IV	0.018	0.020	1.018	1.27	0.203
V	-0.058	0.014	0.943	-3.31	<0.001
III + V	0.049	0.018	1.050	3.19	0.001
IV + V	0.024	0.015	1.024	1.81	0.070

*Adjusted for age, eGFR, UPCR, race/ethnicity, treatment course.

Table 16. Crude and Adjusted Hazard Ratios by LN Class for Partial Remission 12 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
LN Class				
II	1.0 [Ref]	---	1.0 [Ref]	---
III	0.901 (0.110-7.410)	0.923	0.855 (0.100-7.301)	0.886
IV	1.451 (0.617-3.412)	0.393	1.486 (0.565-3.907)	0.422
V	0.782 (0.247-2.477)	0.676	0.719 (0.205-2.528)	0.607
III + V	1.534 (0.536-4.394)	0.425	1.585 (0.512-4.909)	0.424
IV + V	2.894 (1.159-7.225)	0.023	3.412 (1.286-9.051)	0.014

*Adjusted for age, eGFR, UPCR, race/ethnicity, treatment course.

Table 17. Adjusted Accelerated Failure Time Model by LN Class for Partial Remission 24 Months After Diagnosis.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
LN Class					
II	0 [Ref]	---	---	---	---
III	-0.037	0.023	0.964	-1.63	0.103
IV	0.004	0.018	1.004	0.24	0.814
V	-0.040	0.022	0.961	-1.82	0.068
III + V	0.025	0.019	1.026	1.32	0.188
IV + V	0.012	0.017	1.012	0.71	0.480

*Adjusted for age, eGFR, UPCR, race/ethnicity, treatment course.

Table 18. Crude and Adjusted Hazard Ratios by Treatment Course for Complete Remission 12 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Treatment Course				
GC+CYC/MMF	1.0 [Ref]	---	1.0 [Ref]	---
GC+MMF/MMF	0.801 (0.397-1.619)	0.537	0.899 (0.352-2.294)	0.823
Other	0.914 (0.455-1.835)	0.800	0.343 (0.131-0.894)	0.029

*Adjusted for age, eGFR, UPCR, race/ethnicity, LN class.

Table 19. Crude and Adjusted Hazard Ratios by Treatment Course for Complete Remission 24 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Treatment Course				
GC+CYC/MMF	1.0 [Ref]	---	1.0 [Ref]	---
GC+MMF/MMF	1.080 (0.552-2.282)	0.839	0.168 (0.043-0.663)	0.011
Other	1.044 (0.498-2.187)	0.909	0.123 (0.037-0.411)	<0.001

*Adjusted for age, eGFR, UPCR, race/ethnicity, LN Class.

Table 20. Crude and Adjusted Hazard Ratios by Treatment Course for Partial Remission 12 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Treatment Course				
GC+CYC/MMF	1.0 [Ref]	---	1.0 [Ref]	---
GC+MMF/MMF	0.620 (0.325-1.183)	0.147	0.844 (0.390-1.824)	0.666
Other	0.876 (0.482-1.591)	0.663	0.727 (0.378-1.400)	0.341

*Adjusted for age, eGFR, UPCR, race/ethnicity, LN Class.

Table 21. Crude and Adjusted Hazard Ratios by Treatment Course for Partial Remission 24 Months After Diagnosis.

	Crude (Univariate) Analysis		Adjusted (Multivariate) Analysis*	
Variable	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Treatment Course				
GC+CYC/MMF	1.0 [Ref]	---	1.0 [Ref]	---
GC+MMF/MMF	0.764 (0.391-1.492)	0.431	0.544 (0.231-1.281)	0.164
Other	0.768 (0.400-1.473)	0.427	0.566 (0.249-1.285)	0.174

*Adjusted for age, eGFR, UPCR, race/ethnicity, LN Class.

Table 22. Incidence of Complete and Partial Remission for Study Population at 12, 24, and 60 Months After Diagnosis.

	Complete Remission n (%)			**Partial Remission** n (%)		
Variable	**12m**	**24m**	**60m**	**12m**	**24m**	**60m**
Race/Ethnicity						
Hispanic	8 (53.3)	8 (53.3)	3 (50.0)	8 (53.3)	11 (73.3)	3 (50.0)
NHB	26 (60.5)	25 (67.6)	9 (69.2)	34 (79.1)	31 (83.8)	11 (84.6)
NHW	7 (63.6)	5 (55.6)	1 (50.0)	9 (81.8)	7 (77.8)	2 (100.0)
Other	6 (50.0)	5 (83.3)	4 (80.0)	9 (75.0)	5 (83.3)	4 (80.0)
LN Class						
II	7 (63.6)	6 (100.0)	1 (50.0)	7 (63.6)	6 (100.0)	1 (50.0)
III	1 (33.3)	2 (40.0)	1 (50.0)	1 (33.3)	3 (60.0)	2 (100.0)
IV	19 (70.4)	15 (60.0)	7 (70.0)	24 (88.9)	21 (84.0)	8 (80.0)
V	3 (33.3)	3 (42.9)	2 (50.0)	5 (55.6)	3 (42.9)	2 (50.0)
III + V	6 (66.7)	5 (55.6)	1 (100.0)	7 (77.8)	7 (77.8)	1 (100.0)
IV + V	11 (50.0)	12 (80.0)	5 (71.4)	16 (72.7)	14 (93.3)	6 (85.7)
Treatment Course						
GC+CYC/MMF	18 (52.9)	14 (56.0)	9 (60.0)	25 (73.5)	21 (84.0)	11 (73.3)
GC+MMF/MMF	14 (56.0)	14 (60.9)	5 (62.5)	15 (60.0)	16 (69.6)	6 (75.0)
Other	15 (68.2)	15 (78.9)	3 (100.0)	20 (90.9)	17 (89.5)	3 (100.0)

Table 23. Characteristics of the Study Population at LN Flares by Race/Ethnicity at LN Flares.

Variable	Total (n=64)	Hispanic (n=10)	NHB (n=44)	NHW (n=4)	Other (n=6)	P Value
Demographic Characteristics						
Age (Years) median (IQR)	17.0 (16.0-18.0)	17.0 (14.8-17.8)	18.0 (16.0-18.0)	16.5 (15.8-17.5)	15.0 (13.5-18.8)	0.519
Female n (%)	47 (73.4)	4 (40.0)	36 (81.8)	4 (100.0)	3 (50.0)	0.015
Time to First Flare (Years) median (IQR)	1.199 (0.531-2.834)	2.645 (1.865-4.040)	0.876 (0.526-1.821)	2.930 (2.570-3.290)	1.451 (0.729-2.285)	0.308
Laboratory Characteristics						
Low C3 Complement n (%)	57 (89.1)	9 (90.0)	39 (88.6)	4 (100.0)	5 (83.3)	0.867
Low C4 Complement n (%)	49 (76.6)	8 (80.0)	32 (72.7)	4 (100.0)	5 (83.3)	0.614
eGFR (mL/min/1.73 m^2 BSA) median (IQR)	78.75 (52.50-100.99)	74.74 (53.87-100.17)	79.98 (56.91-100.99)	80.53 (65.98-100.42)	77.54 (49.02-92.02)	0.978
UPCR (g/g) median (IQR)	3.675 (1.397-6.082)	5.140 (4.510-6.207)	2.065 (1.055-4.883)	2.820 (2.518-3.098)	6.410 (3.458-8.283)	0.042
Urine Protein Dipstick ≥100 mg/dL n (%)	58 (90.6)	10 (100.0)	38 (86.4)	4 (100.0)	6 (100.0)	0.390
Urine RBC (#/hpf) median (IQR)	20 (6-46)	26 (13-42)	19 (5-43)	3.25 (0-16.9)	24 (14-75)	<0.001

Table 24. Characteristics of the Study Population at LN Flares by LN Class.

Variable	Total (n=64)	II (n=12)	III (n=4)	IV (n=24)	V (n=1)	III+V (n=14)	IV+V (n=9)	P Value
Demographic Characteristics								
Age (Years) median (IQR)	17.0 (16.0-18.0)	16.0 (14.5-18.0)	16.0 (15.5-16.8)	17.0 (16.8-18.3)	18.0	18.0 (18.0-18.0)	16.0 (13.0-16.0)	0.033
Female n (%)	47 (73.4)	7 (58.3)	4 (100.0)	13 (54.2)	0	14 (100.0)	9 (100.0)	0.002
Time to First Flare median (IQR)	1.199 (0.531-2.834)	0.548 (0.311-1.076)	0.706 (0.571-2.600)	2.579 (1.427-3.381)	7.07	1.381 (1.009-1.887)	0.641 (0.493-1.022)	0.137
Laboratory Characteristics								
Low C3 Complement n (%)	57 (89.1)	12 (100.0)	3 (75.0)	21 (87.5)	1	12 (85.7)	8 (88.9)	0.751
Low C4 Complement n (%)	49 (76.6)	11 (91.7)	4 (100.0))	18 (75.0)	0	10 (71.4)	6 (66.7)	0.240
eGFR (mL/min/1.73 m^2 BSA) median (IQR)	78.75 (52.50-100.99)	100.02 (81.04-118.94)	74.93 (54.5-88.16)	74.74 (45.27-97.13)	17.89	68.06 (42.90-86.59)	84.02 (62.67-101.48)	0.067
UPCR (g/g) median (IQR)	3.675 (1.397-6.082)	2.228 (0.718-6.460)	2.305 (0.555-5.495)	4.065 (2.763-6.200)	10.13	1.765 (1.238-4.755)	2.860 (1.910-4.660)	0.384
Urine Protein Dipstick ≥100 mg/dL n (%)	58 (90.6)	9 (75.0)	3 (75.0)	24 (100.0)	1	13 (92.9)	8 (88.9)	0.199
Urine RBC (#/hpf) median (IQR)	20 (6-46)	8 (2-23.2)	5.5 (1-81)	24 (11.8-35.0)	6	30 (11-82)	54 (12-57)	<0.001

Table 25. Characteristics of the Study Population at LN Flares by Treatment Course.

Variable	Total (n=)	GC+CYC/MMF (n=24)	GC+MMF/MMF (n=21)	Other (n=19)	P Value
Demographic Characteristics					
Age (Years) median (IQR)	17.0 (16.0-18.0)	17.0 (15.0-18.0)	17.0 (16.0-18.0)	18.0 (16.5-18.5)	0.224
Female n (%)	47 (73.4)	15 (62.5)	17 (81.0)	15 (78.9)	0.305
Time to First Flare median (IQR)	1.199 (0.531-2.834)	2.341 (1.167-3.291)	0.531 (0.404-1.076)	1.274 (0.498-1.997)	0.048
Laboratory Characteristics					
Low C3 Complement n (%)	57 (89.1)	20 (83.3)	19 (90.5)	18 (94.7)	0.465
Low C4 Complement n (%)	49 (76.6)	16 (66.7)	18 (85.7)	15 (79.0)	0.296
eGFR (mL/min/1.73 m^2 BSA) median (IQR)	78.75 (52.50-100.99)	69.34 (45.27-97.13)	83.59 (63.70-99.22)	84.02 (58.39-103.30)	0.532
UPCR (g/g) median (IQR)	3.675 (1.397-6.082)	4.610 (2.763-6.945)	1.672 (0.680-4.030)	3.480 (1.665-6.030)	0.017
Urine Protein Dipstick ≥100 mg/dL n (%)	58 (90.6)	23 (95.8)	16 (76.2)	19 (100.0)	0.019
Urine RBC (#/hpf) median (IQR)	20 (6-46)	17 (3-38)	20 (10-57)	28 (11-41)	0.107

Table 26. Adjusted Accelerated Failure Time Model by Race/Ethnicity for LN Flare.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
Race/Ethnicity*					
Hispanic	0 [Ref]	---	---	---	---
NHB	-1.044	0.317	0.352	-3.29	0.001
NHW	-0.135	0.455	0.873	-0.30	0.766
Other	-0.486	0.377	0.615	-1.29	0.197

*Adjusted for age, eGFR, UPCR, LN class, treatment course.

Table 27. Adjusted Accelerated Failure Time Model by LN Class for LN Flare.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
LN Class					
II	0 [Ref]	---	---	---	---
III	0.634	0.429	1.885	1.48	0.139
IV	0.303	0.310	1.354	0.98	0.328
V	2.638	0.843	13.987	3.13	0.002
III + V	0.316	0.348	1.371	0.91	0.365
IV + V	0.833	0.333	2.300	2.51	0.012

*Adjusted for age, eGFR, UPCR, race/ethnicity, treatment course.

Table 28. Adjusted Accelerated Failure Time Model by Treatment Course for LN Flare.

Variable	Coefficient	Standard Error	Time Ratio	z	P Value
Race/Ethnicity*					
GC+CYC/MMF	0 [Ref]	---	---	---	---
GC+MMF/MMF	-0.563	0.279	0.570	-2.01	0.044
Other	0.008	0.280	1.008	0.03	0.979

*Adjusted for age, eGFR, UPCR, race/ethnicity, LN class.

Figure 1. Flowchart of Patient Selection.

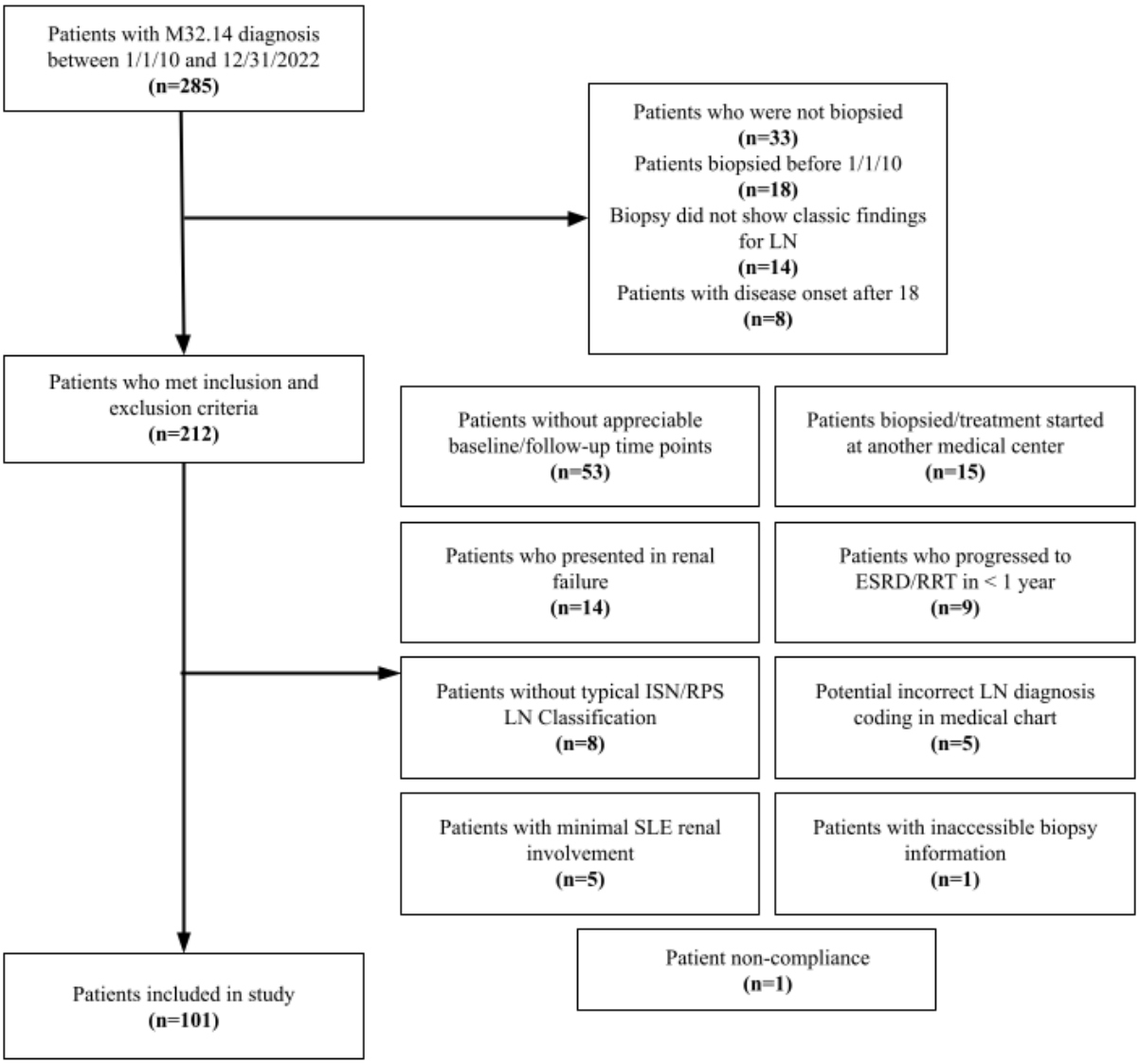
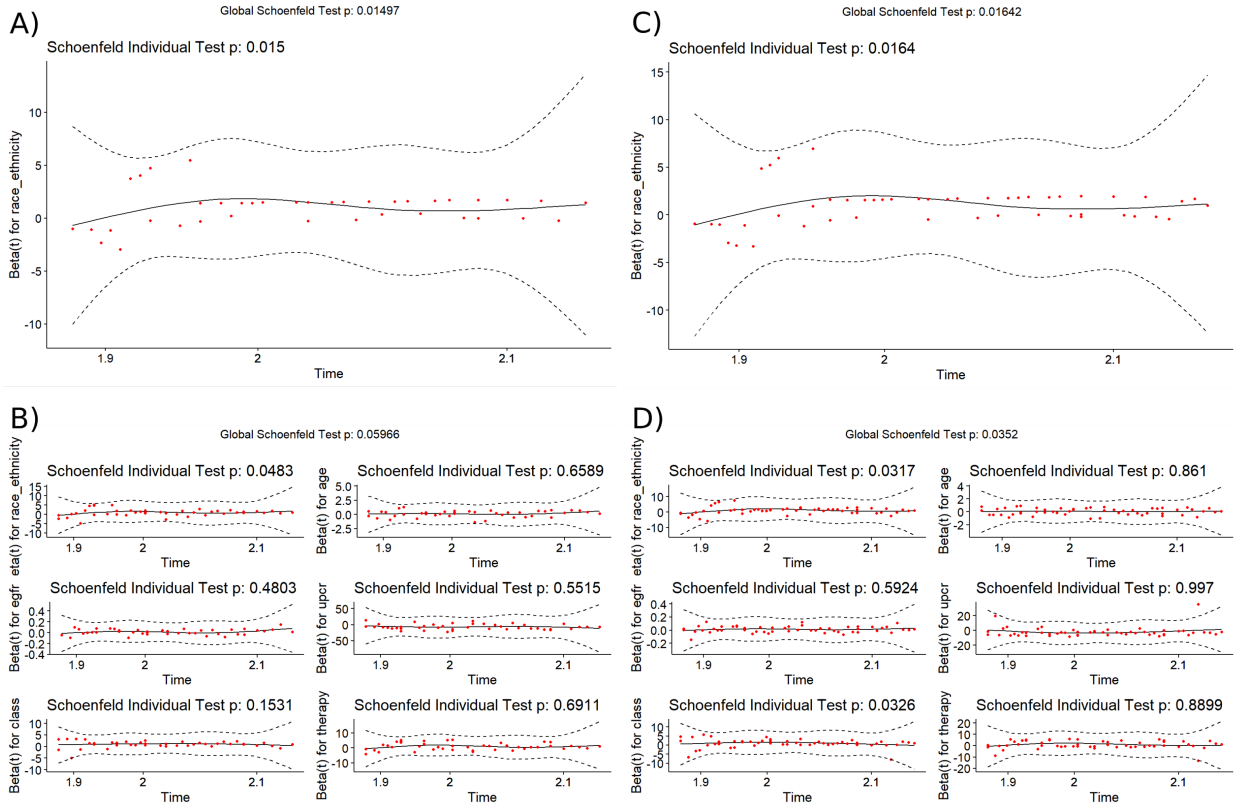
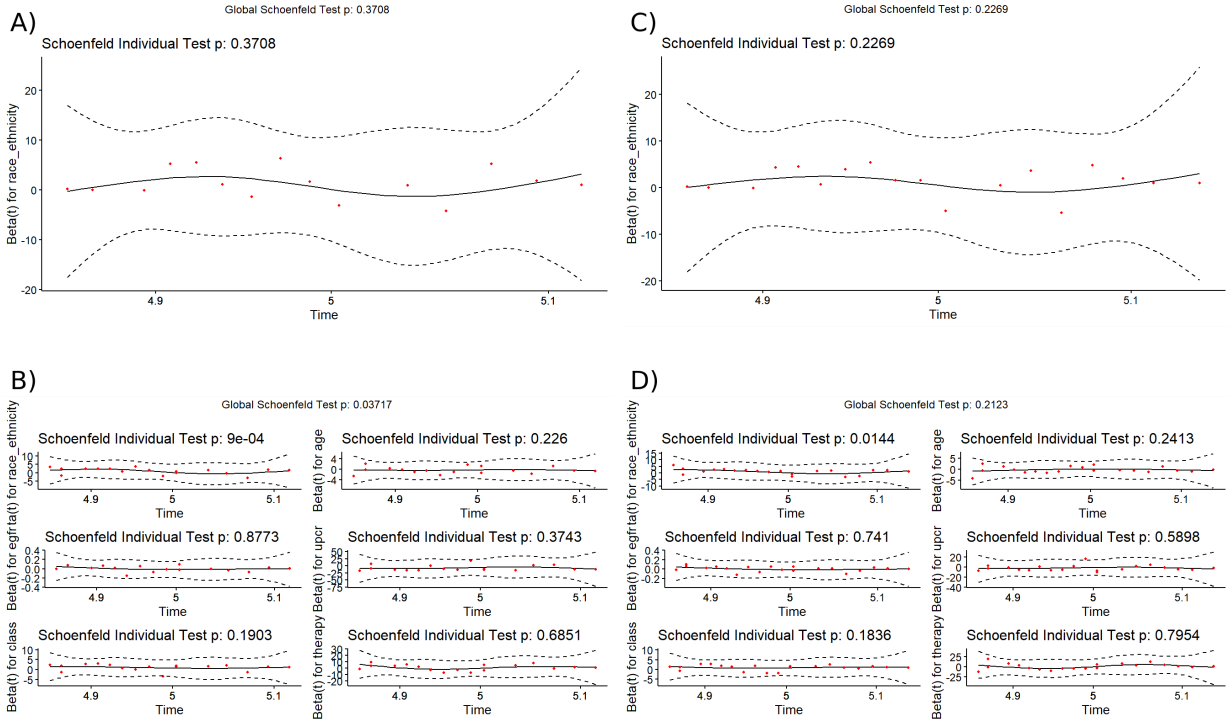


Figure 2. Plot of Schoenfeld Residuals against Time for Complete and Partial Remission by Race/Ethnicity at 24 Months After LN Diagnosis.



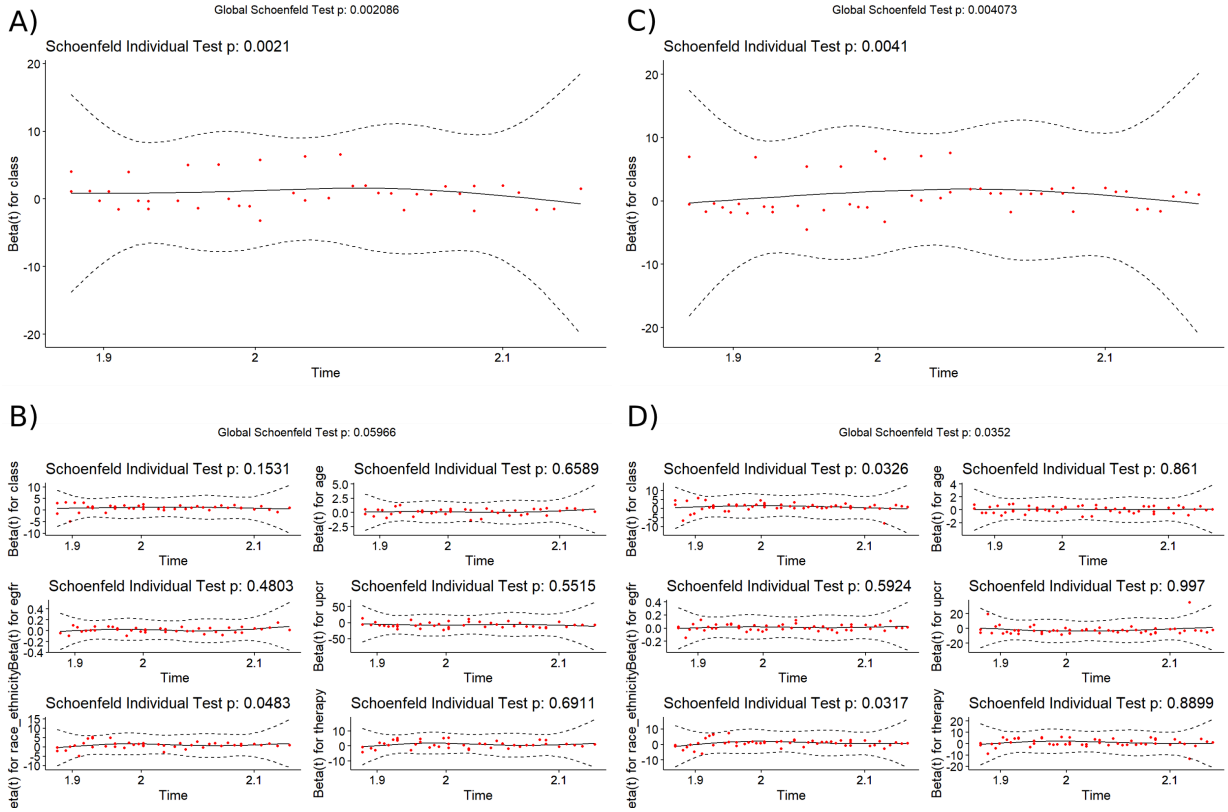
A) Schoenfeld residuals for univariate Cox model for complete remission by race/ethnicity.
B) Schoenfeld residuals for multivariate Cox model for complete remission by race/ethnicity
C) Schoenfeld residuals for univariate Cox model for partial remission by race/ethnicity.
D) Schoenfeld residuals for multivariate Cox model for partial remission by race/ethnicity.

Figure 3. Plot of Schoenfeld Residuals against Time for Complete and Partial Remission by Race/Ethnicity at 60 Months After LN Diagnosis.



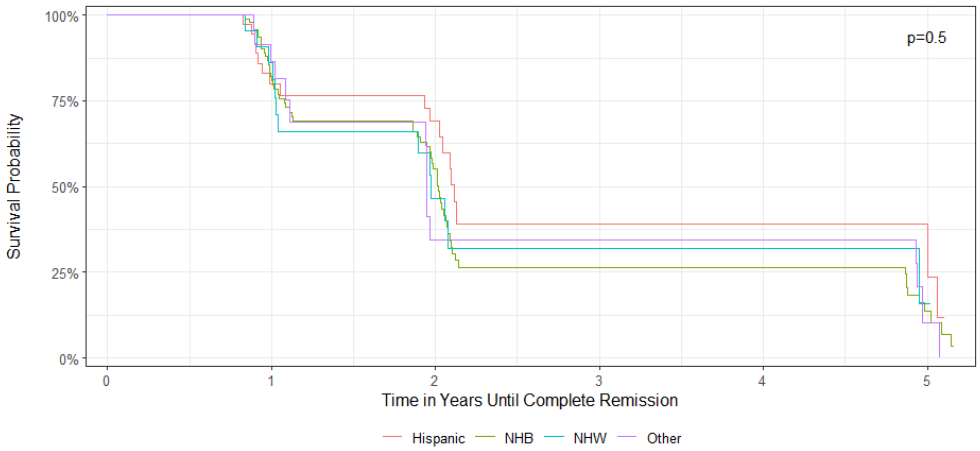
A) Schoenfeld residuals for univariate Cox model for complete remission by LN class.
B) Schoenfeld residuals for multivariate Cox model for complete remission by LN class.
C) Schoenfeld residuals for univariate Cox model for partial remission by LN class.
D) Schoenfeld residuals for multivariate Cox model for partial remission by LN class.

Figure 4. Plot of Schoenfeld Residuals against Time for Complete and Partial Remission by LN Class at 24 Months After LN Diagnosis.



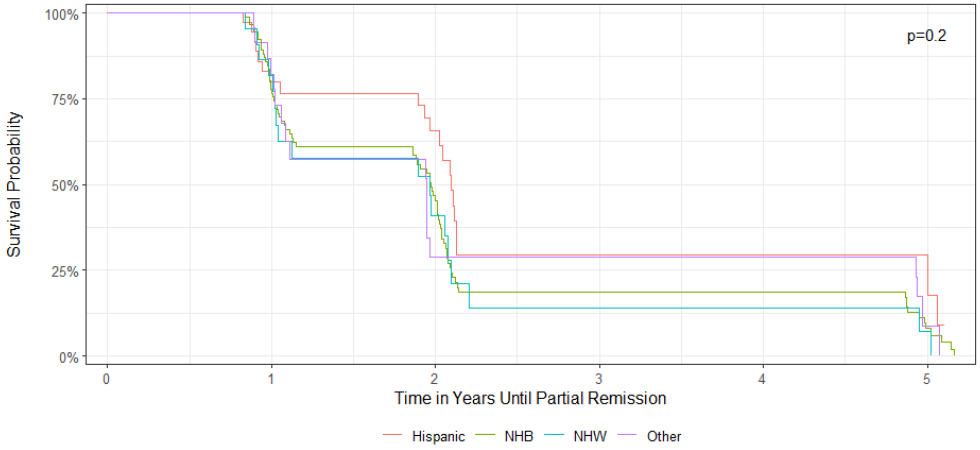
A) Schoenfeld residuals for univariate Cox model for complete remission by LN class.
B) Schoenfeld residuals for multivariate Cox model for complete remission by LN class.
C) Schoenfeld residuals for univariate Cox model for partial remission by LN class.
D) Schoenfeld residuals for multivariate Cox model for partial remission by LN class.

Figure 5. Kaplan-Meier Plot of Time to Complete Remission after LN Diagnosis by Race/Ethnicity.



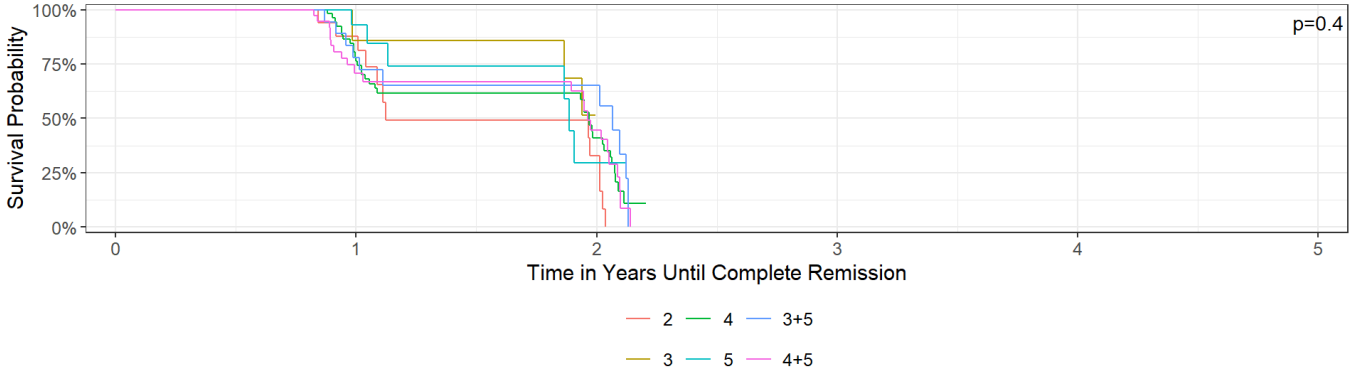
At Risk						
Hispanic	36	26	17	6	6	5
NHB	93	65	34	13	13	5
NHW	22	17	7	2	2	1
Other	23	18	5	5	5	1
Events						
Hispanic	0	7	10	16	16	16
NHB	0	17	35	51	51	57
NHW	0	3	10	12	12	13
Other	0	3	11	11	11	14

Figure 6. Kaplan-Meier Plot of Time to Partial Remission after LN Diagnosis by Race/Ethnicity.



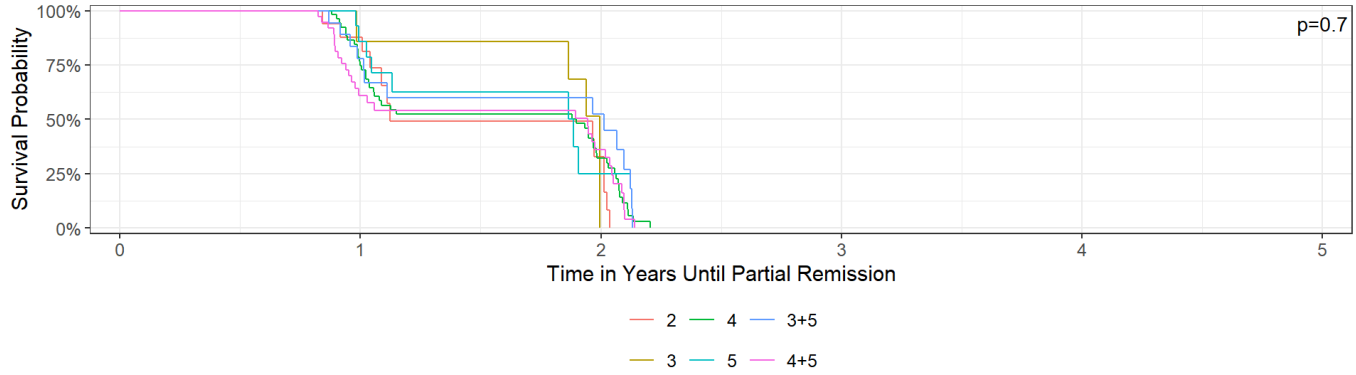
At Risk						
Hispanic	36	26	17	6	6	5
NHB	93	65	34	13	13	5
NHW	22	17	7	2	2	1
Other	23	18	5	5	5	1
Events						
Hispanic	0	7	11	19	19	19
NHB	0	21	46	65	65	72
NHW	0	4	12	16	16	17
Other	0	4	14	14	14	17

Figure 7. Kaplan-Meier Plot of Time to Complete Remission after LN Diagnosis by LN Class.



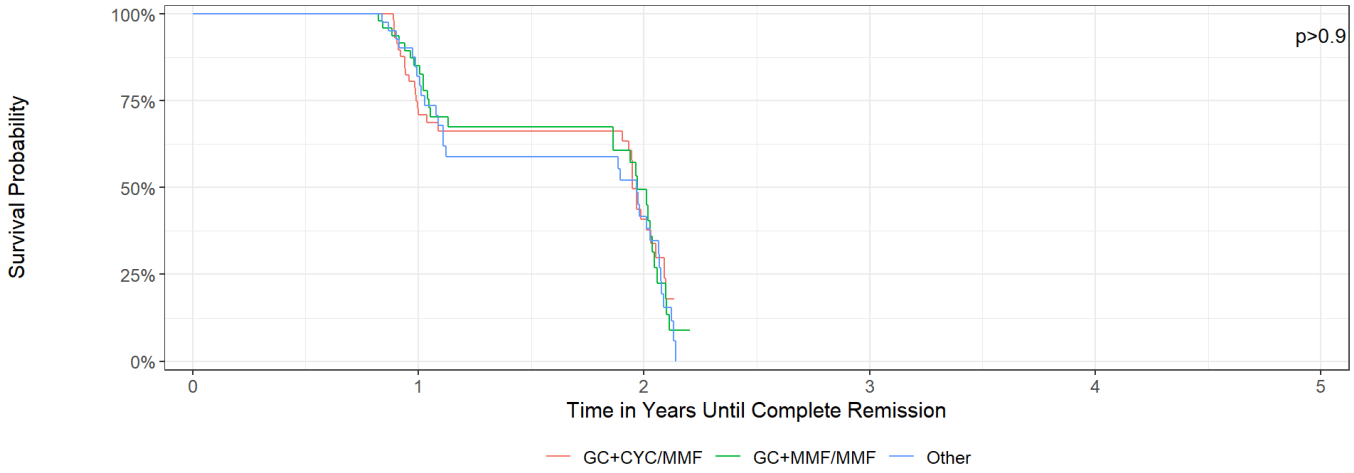
	At Risk					
2	17	13	4	0	0	0
3	8	6	0	0	0	0
4	52	37	14	0	0	0
5	16	12	2	0	0	0
3+5	18	14	7	0	0	0
4+5	37	18	10	0	0	0
	Events					
2	0	2	9	13	13	13
3	0	1	3	3	3	3
4	0	12	26	34	34	34
5	0	1	6	6	6	6
3+5	0	4	6	11	11	11
4+5	0	10	16	23	23	23

Figure 8. Kaplan-Meier Plot of Time to Partial Remission after Diagnosis by LN Class.



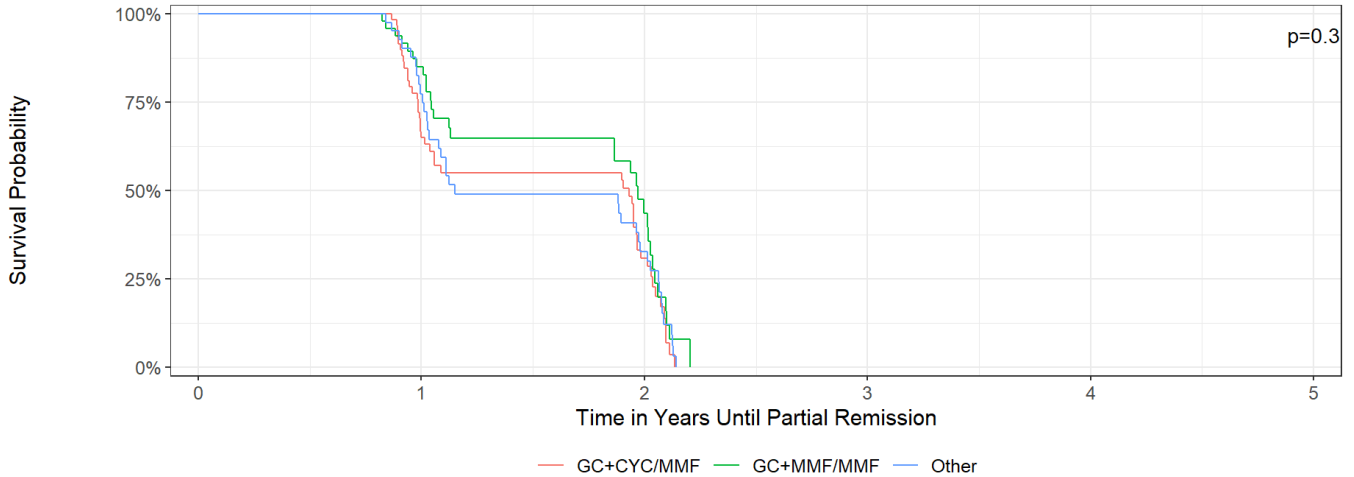
	At Risk					
2	17	13	4	0	0	0
3	8	6	0	0	0	0
4	52	37	14	0	0	0
5	16	12	2	0	0	0
3+5	18	14	7	0	0	0
4+5	37	18	10	0	0	0
	Events					
2	0	2	9	13	13	13
3	0	1	4	4	4	4
4	0	13	33	45	45	45
5	0	2	8	8	8	8
3+5	0	4	8	14	14	14
4+5	0	14	21	30	30	30

Figure 9. Kaplan-Meier Plot of Time to Complete Remission after LN Diagnosis by Treatment Course.



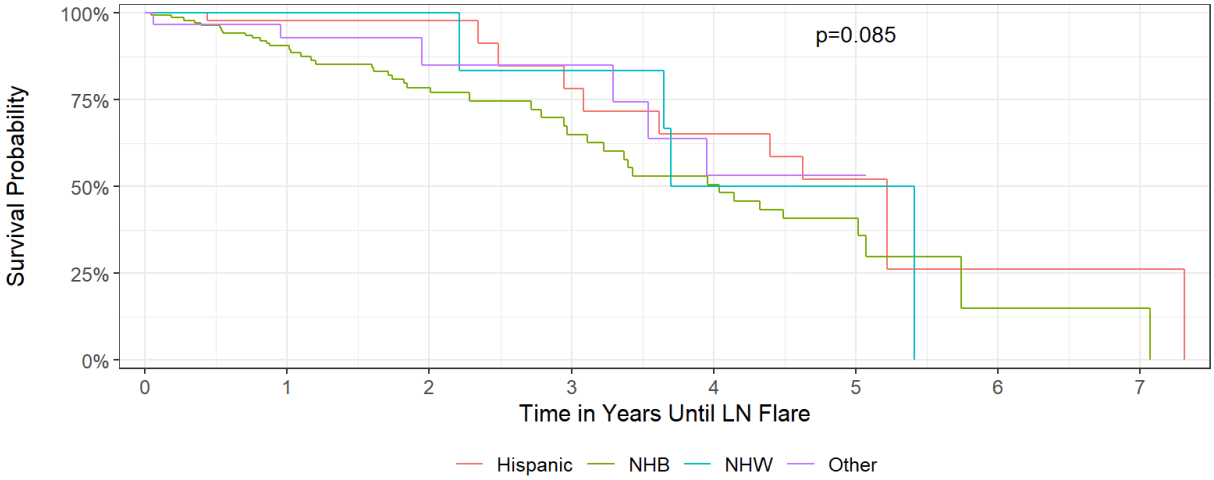
	At Risk					
GC+CYC/MMF	59	34	14	0	0	0
GC+MMF/MMF	48	36	11	0	0	0
Other	41	30	12	0	0	0
	Events					
GC+CYC/MMF	0	16	27	32	32	32
GC+MMF/MMF	0	7	19	28	28	28
Other	0	7	20	30	30	30

Figure 10. Kaplan-Meier Plot of Time to Partial Remission after Diagnosis by Treatment Course.



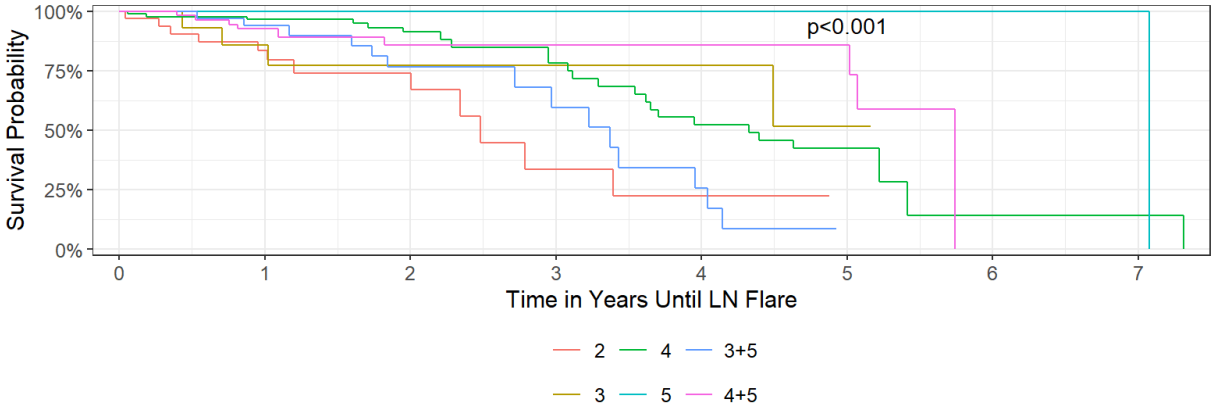
	At Risk					
GC+CYC/MMF	59	34	14	0	0	0
GC+MMF/MMF	48	36	11	0	0	0
Other	41	30	12	0	0	0
	Events					
GC+CYC/MMF	0	20	36	46	46	46
GC+MMF/MMF	0	7	21	31	31	31
Other	0	9	26	37	37	37

Figure 11. Kaplan-Meier Plot of Time to LN Flare after Diagnosis by Race/Ethnicity.



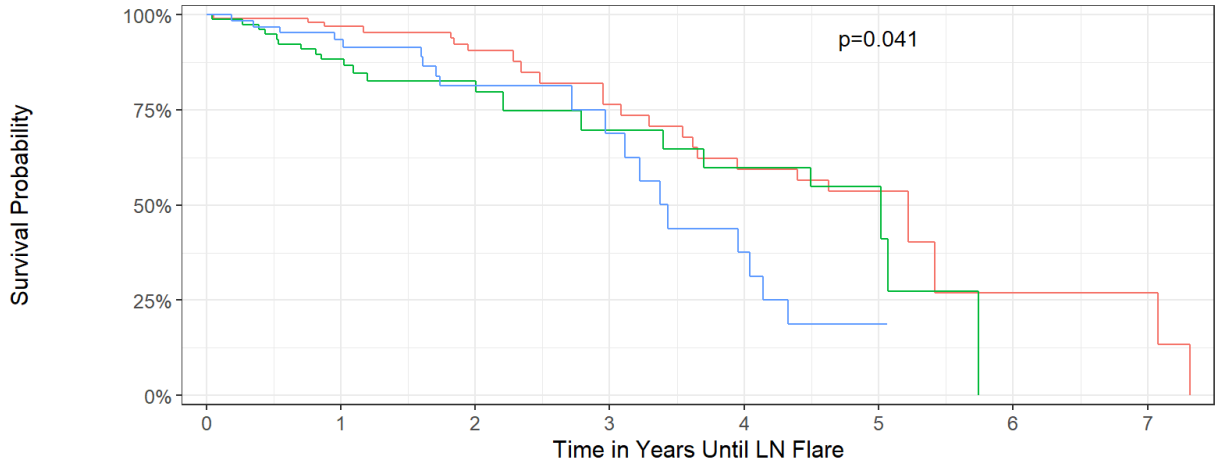
At Risk								
Hispanic	46	35	26	12	10	7	1	1
NHB	137	96	54	27	21	9	1	1
NHW	26	21	11	5	3	2	0	0
Other	29	22	8	8	5	1	0	0
Events								
Hispanic	0	1	1	4	6	8	9	9
NHB	0	13	24	30	36	40	43	43
NHW	0	0	0	1	3	3	4	4
Other	0	2	3	3	6	6	6	6

Figure 12. Kaplan-Meier Plot of Time to LN Flare after Diagnosis by LN Class.



At Risk								
2	31	22	11	3	2	0	0	0
3	14	10	3	3	3	2	0	0
4	86	68	42	24	16	7	1	1
5	21	17	7	5	5	3	1	1
3+5	33	27	16	7	3	0	0	0
4+5	53	30	20	10	10	7	0	0
Events								
2	0	5	7	11	12	12	12	12
3	0	2	3	3	3	4	4	4
4	0	3	6	10	18	21	23	23
5	0	0	0	0	0	0	0	0
3+5	0	2	6	8	12	14	14	14
4+5	0	4	6	6	6	6	9	9

Figure 13. Kaplan-Meier Plot of Time to LN Flare after Diagnosis by Treatment Course.



At Risk								
GC+CYC/MMF	98	70	46	27	21	11	2	2
GC+MMF/MMF	77	56	28	14	12	6	0	0
Other	63	48	25	11	6	2	0	0
Events								
GC+CYC/MMF	0	3	7	12	18	20	22	22
GC+MMF/MMF	0	9	12	15	17	18	21	21
Other	0	4	9	11	16	19	19	19