CARRA Analysis

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- Principle 1 : 20% to 75% of children with SLE will develop nephritis
- Principle 2: 82% of LN in cSLE develops within the first year of diagnosis and 92% within 2 years
- Principle 3: Membranous (class V) LN more often presents with nephrotic syndrome than proliferative LN (class III or IV)
    - Poor availability of data
    - UPC analysis based on available data
    - Frequency distribution of LN classes
- Principle 4: Short term renal outcomes are worse in blacks
    - GFR changes
    - Remission
    - Dialysis, transplant and ESRD
- Principle 5: Short term renal outcomes are worse in patients who present with GFR < 60mL/min/1.73 m2 and/or nephrotic-range proteinuria (> 1 protein/creatinine ratio)
    - GFR changes
    - Remission
    - Dialysis, transplant and ESRD
- Principle 6: Rituximab has been used as a steroid-sparing agent for induction in proliferative LN (LN vs no-LN, 3-4 vs 5)
    - Rituximab use by nephritis class
    - Is there differences in age/gender for people getting Rituximab
    - Differences in GFR by Rituximab use
    - Rituximab and concurrent medications
- Session information

Data version: The version of data we're using is from 2020-01-31 15:45.

Principle 1 : 20% to 75% of children with SLE will develop nephritis

From the data dictionary, this question is answered in the variable SLICC00

I have verified that this definition is compatible with the raw data when we use both WHO and ISNRPS criteria.

Note: Subject has lupus nephritis if any of WHO 2-6 or ISNRPS 2-6 are positive

Frequency of lupus nephritis

Lupus nephritis	N	Percent
Negative	440	65.2%
Positive	235	34.8%

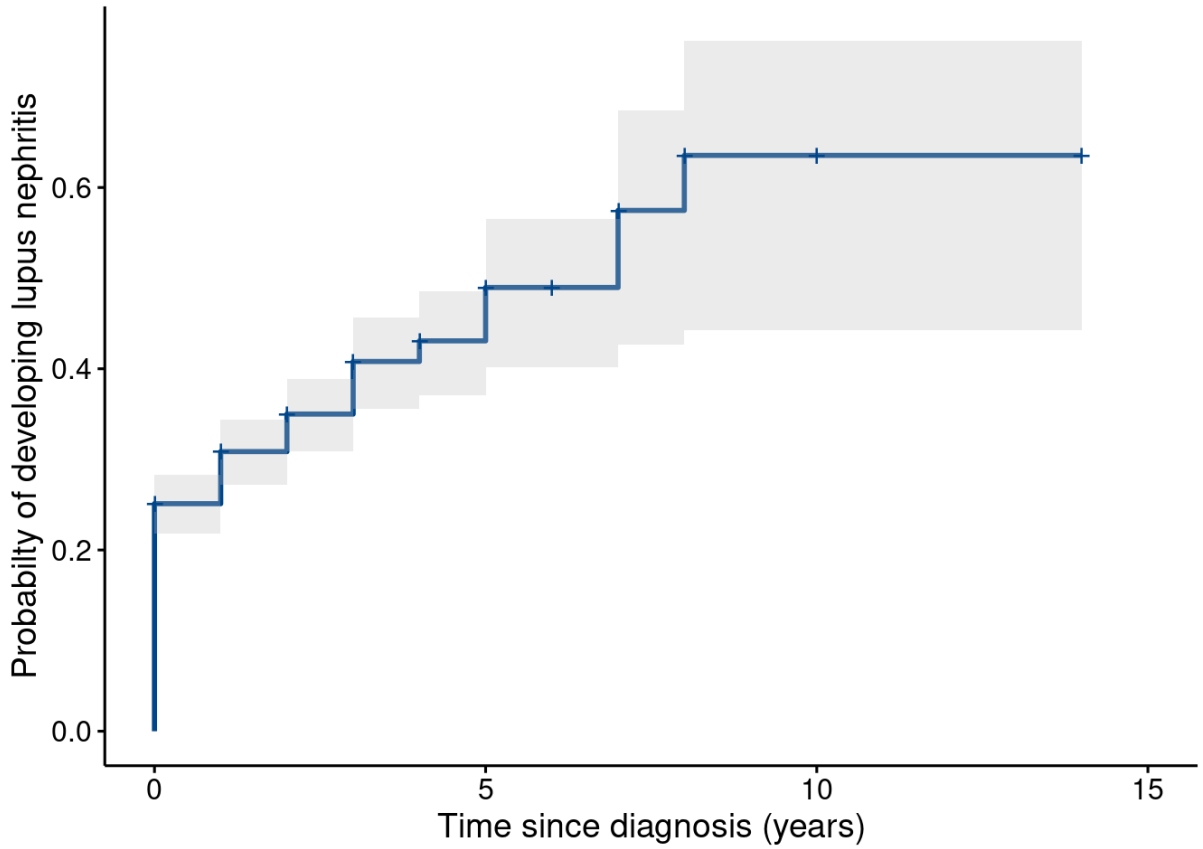
Principle 2: 82% of LN in cSLE develops within the first year of diagnosis and 92% within 2 years

We are going to look at actual date of SLE diagnosis and the date of biopsy. We'll restrict to individuals with LN. We'll also assume that biopsy dates prior to date of lupus diagnosis are aberrant and should be considered the same time as the diagnosis date.

A limitation of this analysis is that we only have year of diagnosis and year of biopsy, not the actual dates for identifiability reasons. So the differences in calendar years may represent periods longer than a year, depending on when the actual dates of the diagnosis and biopsy were.

Time from diagnosis to positive biopsy

Years	n	percent	Cumulative percent
0	173	73.6%	73.6%
1	31	13.2%	86.8%
2	13	5.5%	92.3%
3+	18	7.7%	100.0%
Total	235	•	•



> In this analysis there were 4 individuals who had a negative time between diagnosis and LN biopsy. I changed that time to 0, assuming that we're dealing with rounding error

Principle 3: Membranous (class V) LN more often presents with nephrotic syndrome than proliferative LN (class III or IV)

Definition of LN classes:

1. Class III = WHO-3 or ISNRPS-3
2. Class IV = WHO-4 or ISNRPS-4
3. Class V = WHO-5 or ISNRPS-5

Based on conversations (5/8/2020), we will create 3 mutually exclusive classes for LN for this analysis. These are

1. Class III/IV only
2. Class III/IV + V
3. Class V only

The definition of nephrotic syndrome is as follows:

1. The presence of nephrotic range proteinuria, which is a urine protein:creatinine ratio > 1mg/mg or if there is a 24 hour urine instead of a urine protein:creatinine ratio (different docs check it differently), it would be a 24 hour protein excretion greater than 3.5 g/24 hours.
2. Hypoalbuminemia (an albumin less than 3 g/dL)
3. On examination, documentation of edema

Poor availability of data

To evaluate this principle we need information on protein:creatinine ratios in urine, albumin levels and documentation of edema. First of all, it does not appear that **albumin was collected**, at least it is not available in the CARRA database.

Second, there is a serious lack of urine protein:creatinine ratios. See the separate report, which highlights the fact that only around 25-30% of subjects had urine protein:creatinine ratios available at any visit.

These two issues preclude us from looking at nephrotic syndrome as an outcome for any analysis.

UPC analysis based on available data

> In the following analysis, we took data from the first visit where LN was confirmed, which may be the baseline visit.
>
> There were 8 individuals who had different results in 2 biopsies; they were III/IV only in one and V only in another. I have placed them in the III/IV + V category

Discrete UPC outcome

	Class III/IV only (N=139)	Class III/IV + V (N=20)	Class V only (N=29)	Other (N=47)	Overall (N=235)
UPC in last 30 days					
< 0.5 mg/mg	30 (21.6%)	1 (5.0%)	4 (13.8%)	8 (17.0%)	43 (18.3%)
> = 0.5 mg/mg	39 (28.1%)	8 (40.0%)	8 (27.6%)	4 (8.5%)	59 (25.1%)
Missing	70 (50.4%)	11 (55.0%)	17 (58.6%)	35 (74.5%)	133 (56.6%)

Testing

If we take only the available data, we can do a bit of statistical testing.

Frequency distribution of UPC (discrete) by LN class using available data

	UPC in last 30 days			
LN class	**< 0.5 mg/mg**	**> = 0.5 mg/mg**	**Total**	**Test**
Class III/IV only	43.5% (30)	56.5% (39)	100.0% (69)	Fisher's test
Class III/IV + V	11.1% (1)	88.9% (8)	100.0% (9)	P-value = 0.08
Class V only	33.3% (4)	66.7% (8)	100.0% (12)	
Other	66.7% (8)	33.3% (4)	100.0% (12)	

Continuous UPC outcome

	Class III/IV only (N=139)	Class III/IV + V (N=20)	Class V only (N=29)	Other (N=47)	Overall (N=235)

	Class III/IV only (N=139)	Class III/IV + V (N=20)	Class V only (N=29)	Other (N=47)	Overall (N=235)
UPC ratio					
Mean (SD)	80.5 (351)	13.2 (20.1)	8.80 (19.4)	87.0 (168)	62.0 (278)
Median [Min, Max]	0.930 [0.0480, 2210]	5.90 [0.350, 60.0]	3.79 [0.160, 67.0]	0.420 [0.0400, 484]	1.41 [0.0400, 2210]
Missing	96 (69.1%)	11 (55.0%)	18 (62.1%)	38 (80.9%)	163 (69.4%)

We can also perform an ANOVA analysis using available data to see whether there are any differences in UPC ratio betwen the LN classes III/IV, III/IV + V, and V only. This gives a p-value of 0.68.

Frequency distribution of LN classes

As a descriptive analysis, we present the frequency distribution of LN classes in this dataset

Lupus nephritis frequency

LN	n	percent
No	440	65.2%
Yes	235	34.8%
Total	675	100.0%

Frequency distribution of LN classes

LN Class	n	percent
III/IV	138	73.0%
III/IV + V	22	11.6%
V only	29	15.3%
Total	189	100.0%

Principle 4: Short term renal outcomes are worse in blacks

Based on conversations, we will consider only LN patients and take their first visit with confirmed LN as the baseline time for the GFR change analysis. We will look at race, baseline GFR level, as well as LN classes, as stratifying variables

There are a total of 235 LN positive subjects in this study. Among these individuals, many are missing information on outcomes, or multiple visits post-diagnosis of LN. For example, if we look at availability of data by visit among people who are LN+, for the visits on or after their LN diagnosis, we get this picture:

Percent missing data by outcome and visit

visit	creat_status	eGFR	gfr_class	urine_rbc	transplant	dialysis	esrd	remission
Baseline	21.1	22.0	22.0	34.9	97.6	97.6	0.0	35.4
6 month	30.6	30.6	30.6	36.4	97.7	97.7	0.6	41.0
12 month	26.2	29.2	29.2	41.5	97.7	97.7	0.0	43.1

visit	creat_status	eGFR	gfr_class	urine_rbc	transplant	dialysis	esrd	remission
18 month	35.7	37.1	37.1	40.0	97.1	97.1	0.0	51.4
24 month	35.5	35.5	35.5	41.9	100.0	100.0	0.0	45.2
30 month	100.0	100.0	100.0	100.0	100.0	100.0	0.0	100.0
Unsch	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Also, 20 percent of LN+ subjects had only 1 available visit, so any change is not observable

Frequency of the number of visits per subject post LN diagnosis

Number of visits	Frequency	Percent
1	51	21.79
2	53	22.65
3	74	31.62
4	37	15.81
5	16	6.84
6	3	1.28
Total	234	100.00

> The information available for subject 597 showed that diagnosis was at an unscheduled visit, and where that visit was temporally between baseline, 6 month and 12 month visit was not available. So this subject was removed from the analysis since the number of visits post diagnosis could not be definitively computed for that subject.

GFR changes

Change in GFR stage among blacks

	Last			
First	Stage 1	Stage 2	Stage 3	Total
Stage 1	90.9% (40)	6.8% (3)	2.3% (1)	100.0% (44)
Stage 2	100.0% (1)	0.0% (0)	0.0% (0)	100.0% (1)
Stage 3	• 0.	• 0.	• 0.	100.0% (0)

Change in GFR stage among non-blacks

	Last

	Last			
First	Stage 1	Stage 2	Stage 3	Total
Stage 1	98.8% (81)	0.0% (0)	1.2% (1)	100.0% (82)
Stage 2	85.7% (6)	14.3% (1)	0.0% (0)	100.0% (7)
Stage 3	0.0% (0)	100.0% (1)	0.0% (0)	100.0% (1)

We can perform a permutation test to see if blacks do worse than non-blacks insofar as the chance of worsening GFR state if the initial GFR state was Stage 1 at time of LN diagnosis. Using 5000 permutations of black status, we find that the permutation test gives a p-value of 0.04, thus showing some evidence that blacks tend to worsen at a higher rate than non-blacks.

We can also look at the actual eGFR values to see if there is a difference in eGFR overall between the time of LN diagnosis and when they are last seen

	Black	Non-black	p	test
n	45	90		
egfr_change (median [IQR])	-0.73 [-11.60, 15.43]	3.19 [-8.25, 13.55]	0.316	nonnorm

This shows no evidence overall that eGFR changes from time of diagnosis. This is consistent with the previous result which shows that the vast majority of LN patients stay in the same eGFR stage after LN diagnosis.

Remission

We are defining remission by the following 2 criteria:

- Creatinine within normal range
- urine red blood cells<10/high powered field

At diagnosis, this can be assessed for 149 patients, which is 63.68% of all patients. Of those for whom remission state is observed, 68 or 45.64% entered the study in the remission state. Separating between blacks and non-blacks:

	remission		
black	No	Yes	NA_
No	67.9% (55)	67.6% (46)	68.2% (58)
Yes	32.1% (26)	32.4% (22)	31.8% (27)

We will now just look at individuals who were not in remission state at diagnosis

Of these individuals, 65.43% have at least one subsequent visit. We'll investigate these subjects for subsequent remission. The following table shows the frequency distribution of individuals who subsequently got to remission state at some point for blacks and non-blacks.

	remission	
black	No	Yes
No	76.3% (29)	46.7% (7)

	remission	
Yes	23.7% (9)	53.3% (8)

This is not statistically significant using Fisher's test

Dialysis, transplant and ESRD

All these outcomes are sparse in this data set, even on restricting to subjects who have been diagnosed with lupus nephritis

Frequency distribution for dialysis

dialysis	n	percent	valid_percent
Don't Know	3	0.48	21.43
No	8	1.28	57.14
Yes	3	0.48	21.43
NA	611	97.76	NA

Frequency distribution for transplant

transplant	n	percent	valid_percent
No	14	2.24	100
NA	611	97.76	NA

Frequency distribution for ESRD

esrd	n	percent	valid_percent
0	612	97.92	98.55
1	9	1.44	1.45
NA	4	0.64	NA

Principle 5: Short term renal outcomes are worse in patients who present with GFR < 60mL/min/1.73 m2 and/or nephrotic-range proteinuria (> 1 protein/creatinine ratio)

Distribution of GFR class at time of LN diagnosis

gfr_class	n	percent	valid_percent
Stage 1	167	71.37	92.78
Stage 2	11	4.70	6.11
Stage 3	2	0.85	1.11
NA	54	23.08	NA

We see that 93% of the available GFR classes are in Stage 1, and only 7% are worse than Stage 1.

GFR changes

Changes in GFR class between diagnosis time/baseline and last visit

	Last		
First	Stage 1	Stage 2	Stage 3
Stage 1	96.0% (121)	2.4% (3)	1.6% (2)
Stage 2	87.5% (7)	12.5% (1)	0.0% (0)
Stage 3	0.0% (0)	100.0% (1)	0.0% (0)

So, no one starting in Stage 2 or 3 gets worse, while 4% of people starting in Stage 1 do get worse.

A bit of statistics

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##      First     Stage 1 Stage 2+3
##    Stage 1 96.0% (121)  4.0% (5)
##  Stage 2+3 77.8%   (7) 22.2% (2)
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Remission

Chance of getting to remission by GFR class at LN diagnosis

	GFR class		
Ever in remission	Stage 1	Stage 2	Stage 3
No	66.7% (28)	87.5% (7)	100.0% (2)
Yes	33.3% (14)	12.5% (1)	0.0% (0)

A Fishers exact test gives a p-value of 0.4572083.

Dialysis, transplant and ESRD

As we saw earlier, we don't have sufficient information on these outcomes for this subset of subject who are LN-positive to assess how GFR stage at diagnosis is associated with them.

Principle 6: Rituximab has been used as a steroid-sparing agent for induction in proliferative LN (LN vs no-LN, 3-4 vs 5)

Rituximab use: IMMMED = 30 MEDCATON = 30

Rituximab use by nephritis class

Rituximab use between LN and non-LN subjects

	LN	
Rituximab	Neg	Pos

	LN	
No	88.0% (387)	75.7% (178)
Yes	12.0% (53)	24.3% (57)
Total	100.0% (440)	100.0% (235)

This is statistically significant, with the χ^2 test p-value being 6.8×10^{-5}.

Rituximab use by LN class

	Rituximab	
Class	No	Yes
III/IV	72.6% (106)	72.9% (35)
III/IV + V	10.3% (15)	12.5% (6)
V only	17.1% (25)	14.6% (7)
Total	100.0% (146)	100.0% (48)

This is not statistically significant (p-value = 0.8576421)

Is there differences in age/gender for people getting Rituximab

Rituximab use by age

ritux	Median age	IQR
No	14	4
Yes	14	3

This is not significant (Wilcoxon test p-value = 0.78)

Rituximab use by gender

Sex/Rituximab	No	Yes
Female	83.5%	82.4%
Male	16.5%	17.6%

This is not statistically significant (χ^2 test p-value = 0.8)

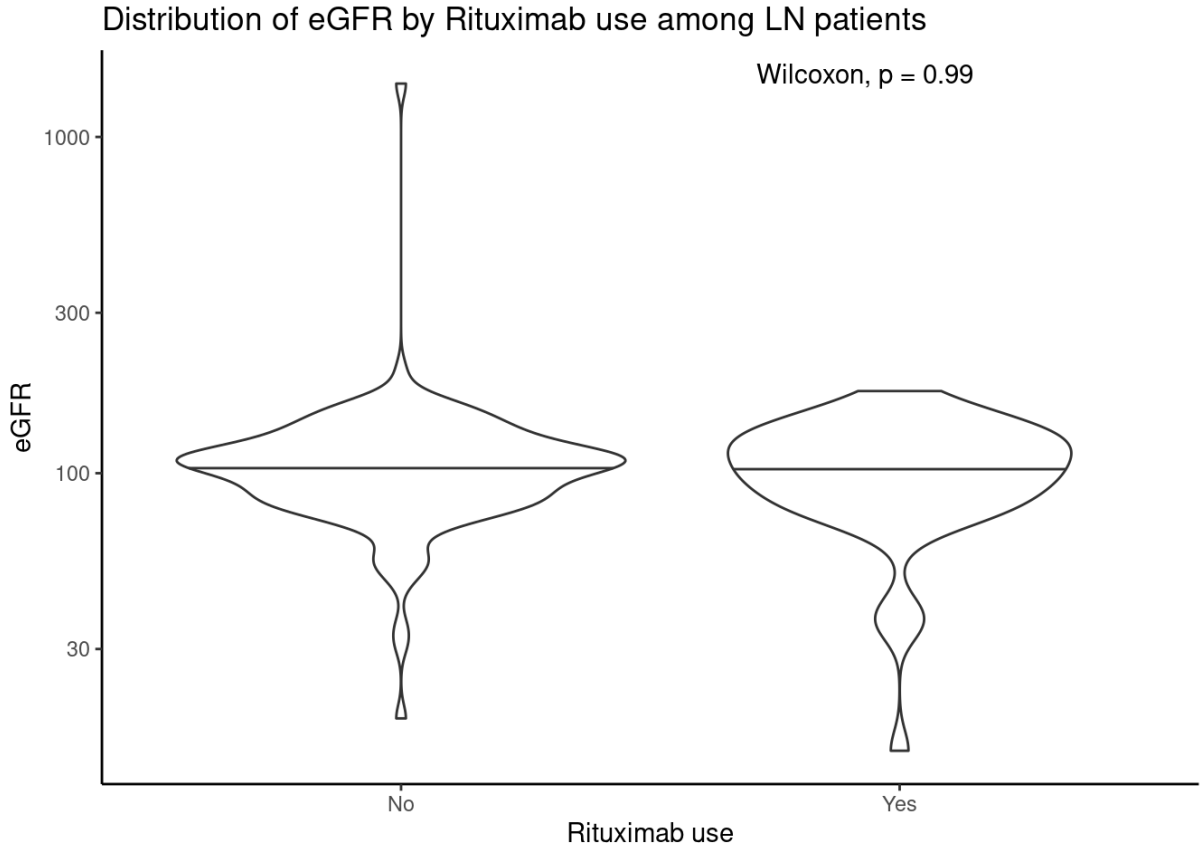
Differences in GFR by Rituximab use

We will look at LN+ patients and their GFR at time of diagnosis or at baseline, and compare the GFR levels for Rituximab users and non-users

GFR summaries by Rituximab use among LN patients; p-value

based on Wilcoxon test

Rituximab	N	Mean	Median	SD	IQR	P-value
No	132	114.46	106.53	120.13	36.59	0.99
Yes	48	103.57	102.02	33.75	45.47	



The violin plots have the medians marked. Hypothesis testing to test if the change in eGFR was the same in the two groups was performed using a Wilcoxon rank-sum test, with the two-sided alternative.

Rituximab and concurrent medications

Top 10 drugs among RTX users and corresponding proportions among non-RTX patients

Medication	No Ritux (N = 564)	With Ritux (N = 111)
Mycophenolate Mofetil (Cellcept)	38.12% (215)	68.47% (76)
Cyclophosphamide (Cytoxan)	7.09% (40)	60.36% (67)
Hydroxychloroquine (Plaquenil)	38.48% (217)	56.76% (63)
Immune Globulin (Ivig)	0.89% (5)	12.61% (14)
Tacrolimus Oral (Prograf)	1.95% (11)	12.61% (14)
Angiotensin Converting Enzyme Inhibitor	6.91% (39)	9.91% (11)

Medication	No Ritux (N = 564)	With Ritux (N = 111)
Azathioprine (Imuran)	6.74% (38)	9.91% (11)
Mycophenolic Acid (Mpa, Myfortic)	7.45% (42)	9.01% (10)
Aspirin (Asa)	2.66% (15)	8.11% (9)
Belimumab (Benlysta)	0% (0)	8.11% (9)

Top 10 drugs in difference of usage between RTX and non-RTX

Medication	No Ritux (N = 564)	With Ritux (N = 111)	Difference
Cyclophosphamide (Cytoxan)	7.09% (40)	60.36% (67)	53.27%
Mycophenolate Mofetil (Cellcept)	38.12% (215)	68.47% (76)	30.35%
Hydroxychloroquine (Plaquenil)	38.48% (217)	56.76% (63)	18.28%
Immune Globulin (Ivig)	0.89% (5)	12.61% (14)	11.73%
Tacrolimus Oral (Prograf)	1.95% (11)	12.61% (14)	10.66%
Belimumab (Benlysta)	0% (0)	8.11% (9)	8.11%
Aspirin (Asa)	2.66% (15)	8.11% (9)	5.45%
Diuretic	1.06% (6)	6.31% (7)	5.24%
Vitamin D	10.46% (59)	6.31% (7)	-4.15%
Ranitidine	1.24% (7)	4.5% (5)	3.26%

Session information

This analysis was done using R version 3.6.3 (2020-02-29) and the following packages

data.table (1.12.8); dplyr (1.0.0); forcats (0.5.0); fs (1.4.2); ggplot2 (3.3.2); glue (1.4.1); here (0.1); janitor (2.0.1); kableExtra (1.1.0); knitr (1.29); pacman (0.5.1); purrr (0.3.4); readr (1.3.1); readxl (1.3.1); stringr (1.4.0); tibble (3.0.3); tidyr (1.1.0); tidyverse (1.3.0); vroom (1.2.1)