CHAPTER 3

Secondary Glomerulonephritis

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3.1 Introduction

- This chapter reports the main secondary glomerulonephritis (GN) in adult (defined as age > 15) reported from the years 2005-2017.
- The commonest cause of secondary glomerulonephritis among patients who underwent renal biopsy was lupus nephritis (80.8%), followed by diabetic kidney disease (12.9%) and post-infectious GN (2.8%). *(Table 3.1)*
- The trend has been unchanged throughout 13 years of observation.
- Diabetic kidney is the main cause of end stage renal disease in Malaysia. However, the percentage of diabetic kidney disease reported to MRRB remained around 10-16% each year, as the diagnosis is usually made clinically. *(Table 3.1)*. The data is influenced by biopsy practices of the managing nephrologists.
- Other causes of secondary glomerulonephritis are relatively uncommon.
- From 2005-2017, only 45 cases of renal amyloidosis were reported; and 21 cases were identified with systemic vasculitis in renal biopsy. *(Table 3.1)*
- Some of the "rare" secondary GN may be under-diagnosed due to the limited availability of electron microscopy and the limited use of special staining.

3.2 Lupus Nephritis

3.2.1 Introduction

- Lupus Nephritis (LN) was the commonest form of biopsy-proven secondary GN in adults.
- The incidence was high, contributing to 34.6% of all native renal biopsies in Malaysia.
- In comparison to renal biopsy registry from other countries; Malaysia recorded the highest incidence - Spain (8.8%), Brazil (9.8%), Bahrain (15.7%), Australia (13.9%), Romania (7.4%), Korea (8.7%), China and Hong Kong (20.5%). [(1)]

3.2.2 Patient population and characteristics

- There was a total of 4824 biopsy-proven lupus nephritis reported from 1st January 2005 to 31st December 2017.

3.2.2.1 Age at time of biopsy

- LN affects young people with the median age at time of biopsy was 28.6 years old. *(Table 3.2.2.1(a))*
- The common age groups were 15-25 years old (37%) and 25-35 years old (32%). *(Figure 3.2.2.1)*
- The distribution of each age decade remained similar over the last 13-year observational period.

Table 3.2.2.1: Causes of secondary glomerulonephritis in adult, 2005-2017

Type of secondary GN	2005-2009 (n=1657)		2010-2014 (n=2796)		2015 (n=608)		2016 (n=608)		2017 (n=580)		Total (n=6249)	
	n	%	n	%	n	%	n	%	n	%	n	%
Lupus Nephritis	1414	85.3	2221	79.4	492	80.9	458	75.3	464	80.0	5049	80.8
Diabetic kidney disease	167	10.1	372	13.3	83	13.7	97	16.0	84	14.5	803	12.9
Post Infectious GN	32	1.9	93	3.3	10	1.6	21	3.5	17	2.9	173	2.8
Amyloidosis	9	0.5	20	0.7	5	0.8	9	1.5	2	0.3	45	0.7
Other infection	8	0.5	19	0.7	2	0.3	1	0.2	1	0.2	31	0.5
Systemic vasculitis	4	0.2	14	0.5	1	0.2	1	0.2	1	0.2	21	0.3
Henoch Schonlein Purpura	7	0.4	7	0.3	1	0.2	1	0.2	0	0	16	0.3
Multiple myeloma	8	0.5	4	0.1	3	0.5	0	0	0	0	15	0.2
Light / Heavy chain deposit disease	2	0.1	2	0.1	3	0.5	2	0.3	0	0	9	0.1
HUS / TTP	0	0	3	0.1	0	0	0	0	4	0.7	7	0.1
Malignancy	3	0.2	4	0.1	0	0.0	0	0	0	0	7	0.1
Anti GBM disease	0	0	3	0.1	2	0.3	0	0	2	0.3	7	0.1
Immunotactoid / fibrillary GN	0	0	1	0	0	0	2	0.3	0	0	3	0
Not Available	3	0.2	33	1.2	6	1.0	16	2.6	5	0.9	63	1.0

Table 3.2.2.1 (a): Age group at time of biopsy (years), 2005 –2017

Age group (years)	2005 (n=240)	2006 (n=275)	2007 (n=286)	2008 (n=312)	2009 (n=290)	2010 (n=311)	2011 (n=434)
Mean	30.48	30.89	29.83	30.54	29.19	30.36	30.75
Standard deviation	10.59	10.32	10.18	11.03	9.64	10.88	10.98
Median	29.00	29.64	27.5	28.37	27.68	27.86	27.93
Minimum	15.00	15.10	15.20	15.10	15.00	15.10	15.00
Maximum	70.40	59.40	67.50	65.40	62.80	78.90	72.10
Age group (years)	**2012 (n=437)**	**2013 (n=449)**	**2014 (n=478)**	**2015 (n=458)**	**2016 (n=405)**	**2017 (n=449)**	**Total (n=4824)**
Mean	30.32	30.62	31.03	31.00	31.94	31.24	30.70
Standard deviation	11.12	10.21	10.49	11.35	11.56	10.89	10.78
Median	27.53	28.47	29.63	29.18	29.68	29.55	28.6
Minimum	15.15	15.00	15.00	15.00	15.00	15.10	15.00
Maximum	72.40	64.10	63.90	77.70	69.20	70.10	78.90

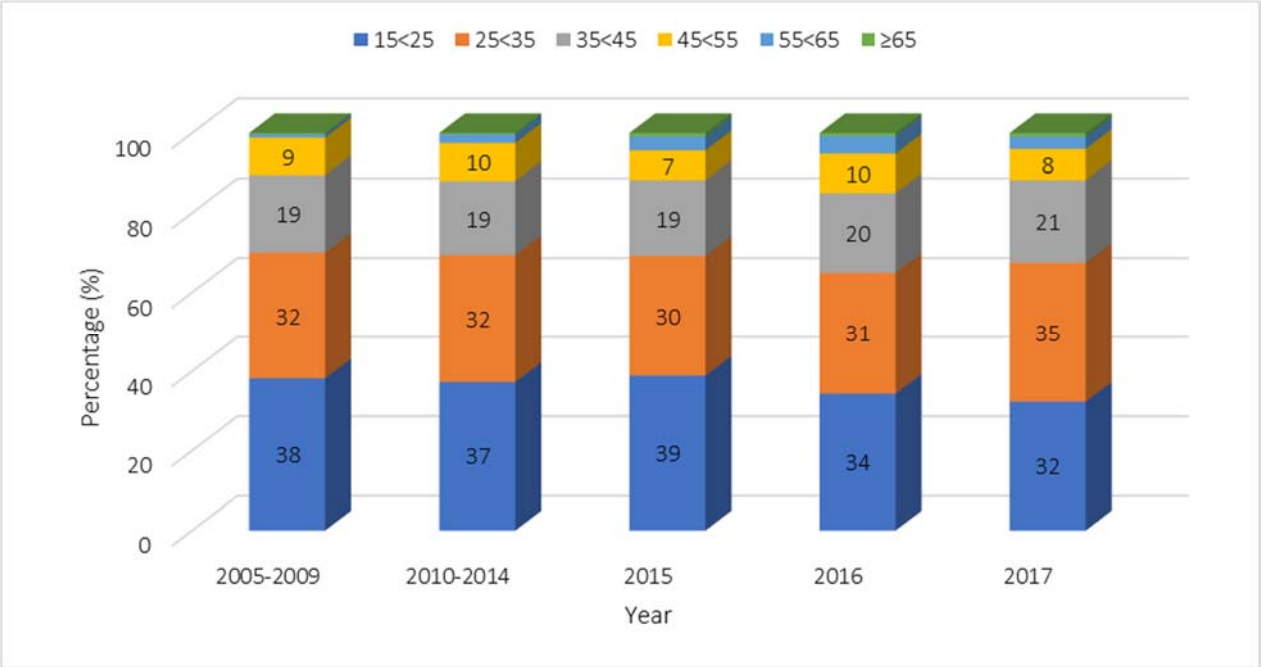


Figure 3.2.2.1: Age group at time of biopsy (years), 2005-2017

3.2.2.2: Gender distribution

- LN predominantly affects females in the child-bearing age group. In Malaysia, the female: male ratio was 9:1. *(Table & Figure 3.2.2.2(a))*
- The median age at the time of biopsy were 26.8 and 28.8 years in males and females, respectively. *(Figure 3.2.2.2 (b) and (c))*
- Our result was slightly different from the Japan renal biopsy registry, in which a "mountain-shaped" distribution with a peak at an age of between 30 and 39 years was observed for female patients. In men, a prominent peak was not present. [(1)]

Figure 3.2.2.2(a): Gender distribution, 2005-2017

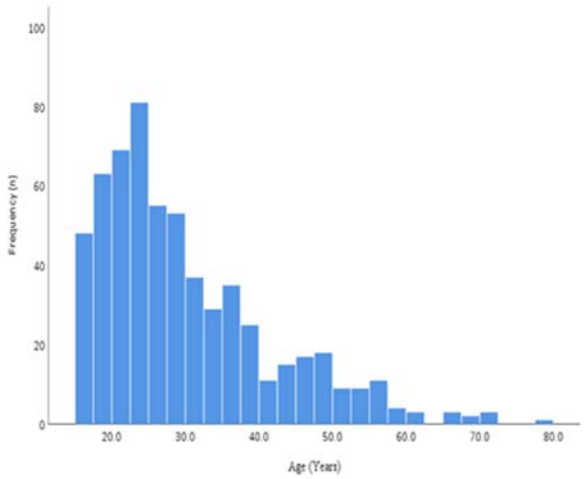


Figure 3.2.2.2 (b): Age distribution (Male), 2005-2017

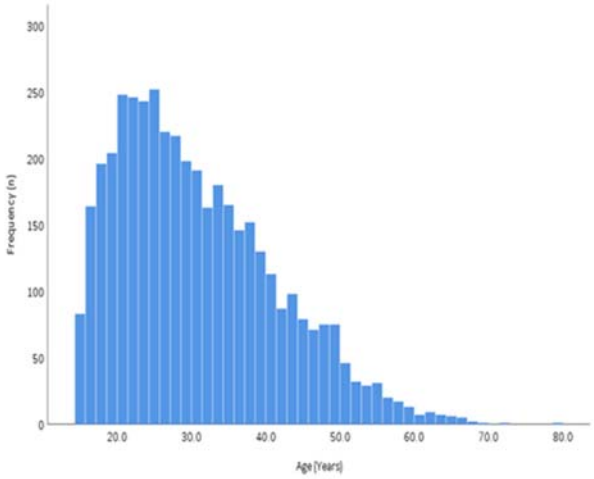


Figure 3.2.2.2 (c): Age distribution (Female), 2005 -2017

3.2.2.3 Ethnic prevalence

- The ethnic distribution followed the demographic composition of the country: Malays (60.8%), Chinese (25.7%) and Indians (4.2%) *(Figure 3.2.2.3)*
- There was no preponderance of LN in certain ethnic groups in the Malaysian population.

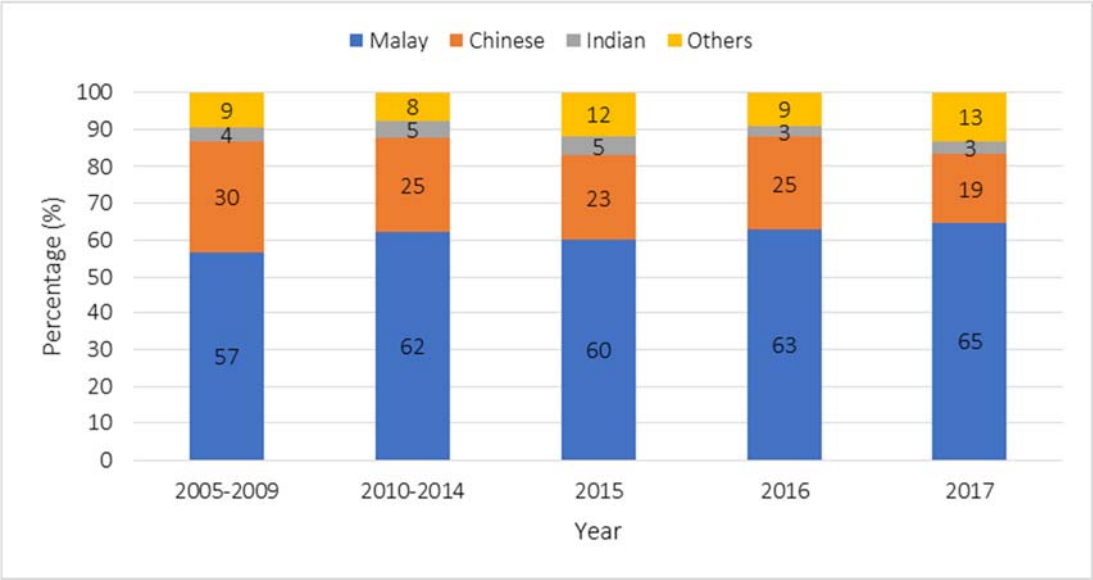


Figure 3.2.2.3: Ethnic distribution, 2005-2017

3.2.3 Clinical presentation

- Most of the patients (36.7%) were asymptomatic with urinary abnormalities at presentation. *(Figure 3.2.3)*
- Other clinical presentations include nephrotic syndrome (25.3%), nephritic-nephrotic syndrome (13.9%) and nephritic syndrome (8.6%).
- However, missing data was as high as 15.5%, which could mask the picture and make the data less accurate.
- At presentation, the prevalence of hypertension was 36.9%. *(Figure 3.2.3 (a))*
- Most of the patients had eGFR>90ml/min upon diagnosis, and 4.9% has eGFR<15 ml/min/1.73m^2. *(Table 3.2.3 (b))*

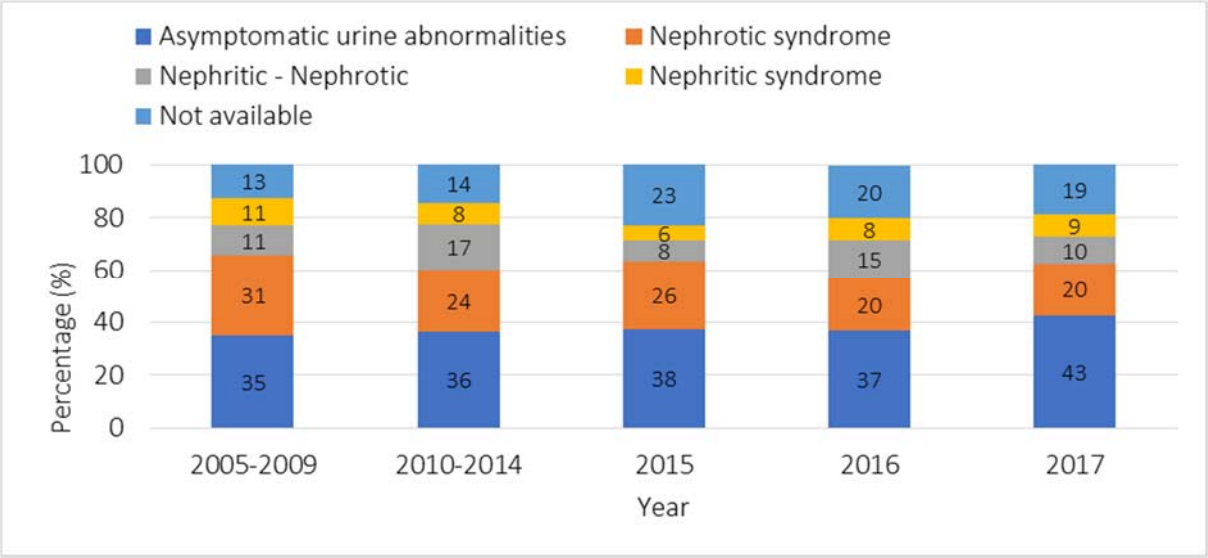


Figure 3.2.3: Clinical presentation by year, 2005-2017

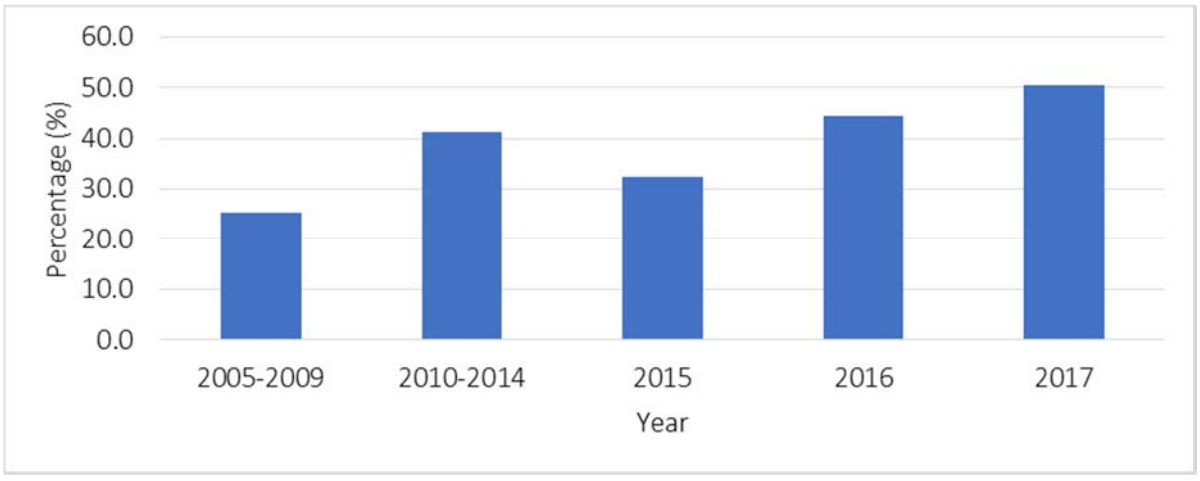


Figure 3.2.3 (a): Hypertension by year, 2005-2017

Table 3.2.3 (b): Renal function by year, 2005-2017

eGFR (mls/min/1.73m^2)	2005-2009 (n=1403)		2010-2014 (n=2109)		2015 (n=458)		2016 (n=405)		2017 (n=449)		Total (n=4824)	
	n	%	n	%	n	%	n	%	n	%	n	%
<15	78	5.6	98	4.6	11	2.4	19	4.7	28	6.2	234	4.9
15 to <30	119	8.5	149	7.1	31	6.8	33	8.1	28	6.2	360	7.5
30 to <60	281	20.0	345	16.4	62	13.5	63	15.6	62	13.8	813	16.9
60 to <90	343	24.4	471	22.3	84	18.3	75	18.5	80	17.8	1053	21.8
≥90	474	33.8	779	36.9	189	41.3	148	36.5	189	42.1	1779	36.9
Not available	108	7.7	267	12.7	81	17.7	67	16.5	62	13.8	585	12.1

**Total of 585 cases are missing on GFR, including 108 cases with GFR>200 (GFR range between 201 to 2463)*

3.2.3.1 Clinical Presentation by age

- Asymptomatic urinary abnormalities was the commonest manifestation of LN across all age groups. *(Figure 3.2.3.1(a))*
- The prevalence of hypertension among LN patients increased with age *(Figure 3.2.3.1(b))*. Relatively low prevalence of hypertension in those aged ≥65 years old may be explained by the significant number of missing data in this age group.
- The percentage of lupus nephritis patients with impaired renal function increased with age. For those above the age of 55, about 63.6% had eGFR of less than 60ml/min/1.73m^2. *(Table 3.2.3.1(c))*

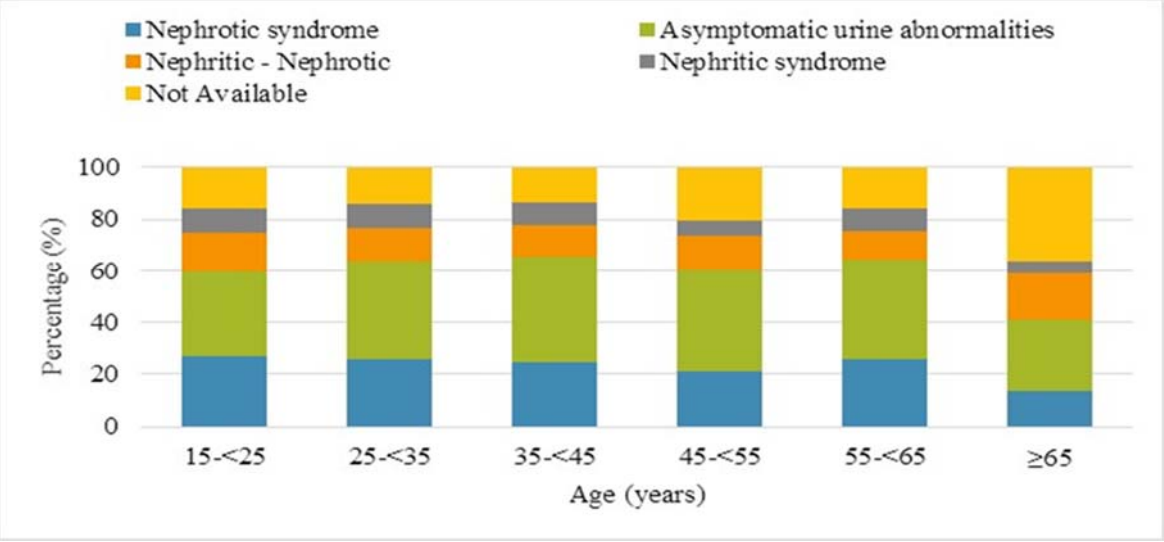


Figure 3.2.3.1(a): Clinical presentation by age group, 2005-2017

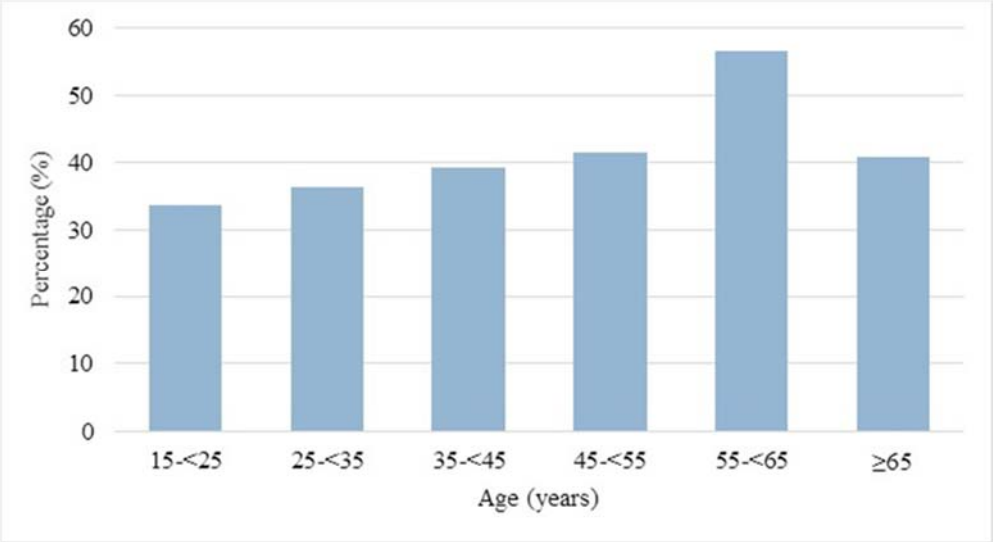


Figure 3.2.3.1(b): Hypertension by age group

Table 3.2.3.1(c): Renal function by age group, 2005-2017

eGFR (mls/min/1.73m^2)	15-<25 (n=1784)		25-<35 (n=1546)		35-<45 (n=924)		45-<55 (n=442)		55-<65 (n=106)		≥65 (n=22)		Total (n=4824)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<15	80	4.5	69	4.5	46	5.0	30	6.8	6	5.7	3	13.6	234	4.9
15-29	96	5.4	114	7.4	88	9.5	48	10.9	8	7.5	6	27.3	360	7.5
30-59	227	12.7	256	16.6	187	20.2	111	25.1	27	25.5	5	22.7	813	16.9
60-89	330	18.5	327	21.2	248	26.8	117	26.5	27	25.5	4	18.2	1053	21.8
≥90	811	45.5	616	39.8	239	25.9	88	19.9	23	21.7	2	9.1	1779	36.9
Not available	240	13.5	164	10.6	116	12.6	48	10.9	15	14.2	2	9.1	585	12.1

**Total of 585 cases are missing on GFR, including 108 cases with GFR>200 (GFR range between 201 to 2463)*

3.2.3.2 Clinical presentation by gender

- There were no differences in the clinical presentation between the two genders. *(Figure 3.2.3.2 (a))*
- At presentation, 40.3% of males versus 36.4% of the female patients had hypertension upon presentation. *(Figure 3.2.3.2 (b))*
- Renal function also did not differ much between the two groups. *(Table 3.2.3.2 (c))*

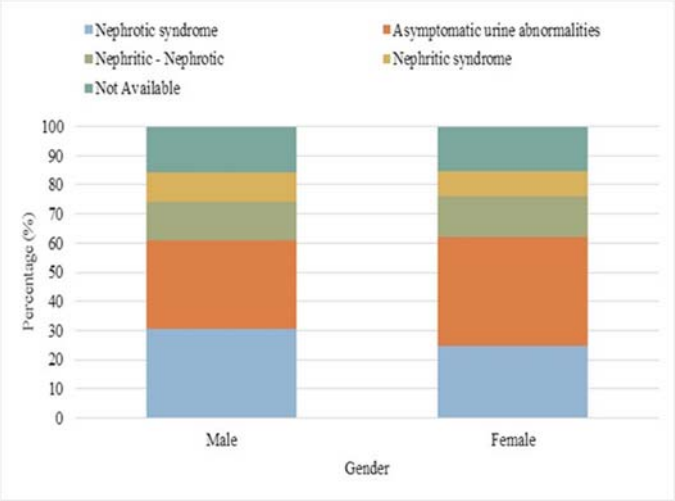


Figure 3.2.3.2 (a): Clinical presentation by gender, 2005-2017

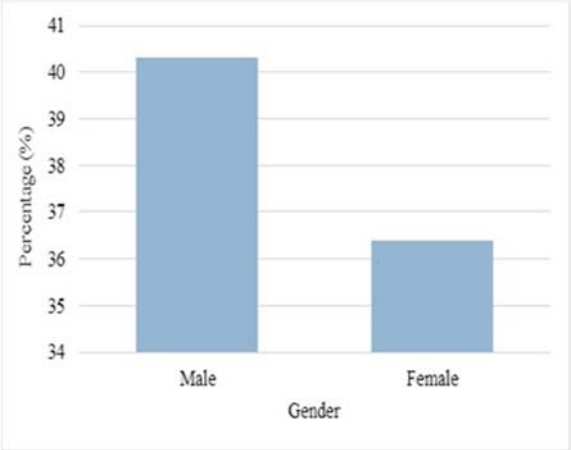


Figure 3.2.3.2(b): Hypertension by gender, 2005-2017

Table 3.2.3.2(c): Renal function by gender, 2005-2017

eGFR (mls/min/1.73m^2)	Male (n=601)		Female (n=4223)		Total (n=4824)	
	n	%	n	%	n	%
<15	30	5.0	204	4.8	234	4.9
15-29	53	8.8	307	7.3	360	7.5
30-59	98	16.3	715	16.9	813	16.9
60-89	122	20.3	931	22.0	1053	21.8
≥90	233	38.8	1546	36.6	1779	36.9
Not Available	65	10.8	520	12.3	585	12.1

**Total of 585 cases are missing on GFR, including 108 cases with GFR>200 (GFR range between 201 to 2463)*

3.2.4 Histopathological diagnosis

- Class IV /class IV+V LN was the predominant histopathological diagnosis, accounting for 54.3% of patients .This was followed by class III/ III+V (25.2%), class V/ II+V (10.4%).
- The trend remained unchanged during the 13 years observation period.
- About 0.9% of patients had advanced sclerosing lupus nephritis at the time of biopsy. *(Table 3.2.4)*

Table 3.2.4: Histopathological diagnosis in lupus nephritis by year, 2005-2017

Histopathological diagnosis	2005-2009 (n=1403)		2010-2014 (n=2109)		2015 (n=458)		2016 (n=405)		2017 (n=449)		Total (n=4824)	
	n	%	n	%	n	%	n	%	n	%	n	%
I	9	0.6	19	0.9	6	1.3	3	0.7	1	0.2	38	0.8
II	121	8.6	127	6.0	28	6.1	16	4.0	16	3.6	308	6.4
III & III+V	290	20.7	538	25.5	124	27.1	106	26.2	157	35.0	1215	25.2
IV & IV+V	802	57.2	1124	53.3	246	53.7	233	57.5	213	47.4	2618	54.3
V & II+V	144	10.3	230	10.9	43	9.4	34	8.4	49	10.9	500	10.4
VI	9	0.6	28	1.3	2	0.4	2	0.5	1	0.2	42	0.9
Others	9	0.6	2	0.1	1	0.2	0	0.0	1	0.2	13	0.3

** 90 cases are missing on lupus subclass*

3.2.4.1: Histopathological diagnosis by age

- The proportion of histopathological diagnoses was similar in all age groups.
- However, the frequency of Class V & II+V increased with age, with the prevalence of 7.9% in those with age 15-<25, as compared with 20% in those ≥65 years old. *(Table 3.2.4.1)*

Table 3.2.4.1: Histopathological diagnosis by age group in lupus nephritis, 2005-2017

Histopathological diagnosis	15-<25 (n=1752)		25-<35 (n=1519)		35-<45 (n=906)		45-<55 (n=433)		55-<65 (n=104)		≥65 (n=20)		Total (n=4734)	
	n	%	n	%	n	%	n	%	n	%	n	%		
I	19	1.1	8	0.5	5	0.6	3	0.7	2	1.9	1	5.0	38	0.8
II	122	7.0	95	6.3	51	5.6	34	7.9	6	5.8	0	0.0	308	6.5
III & III+V	395	22.5	422	27.8	248	27.4	112	25.9	33	31.7	5	25.0	1215	25.7
IV & IV+V	1060	60.5	820	54.0	470	51.9	208	48.0	50	48.1	10	50.0	2618	55.3
V & II+V	138	7.9	157	10.3	122	13.5	67	15.5	12	11.5	4	20.0	500	10.6
VI	13	0.7	14	0.9	8	0.9	6	1.4	1	1.0	0	0	42	0.9
Others	5	0.3	3	0.2	2	0.2	3	0.7	0	0	0	0	13	0.3

** 90 cases are missing on lupus subclass*

3.2.4.2 Histopathological diagnosis by gender

- Both male and female patients had similar pattern of histopathological diagnosis on renal biopsy. *(Table 3.2.4.2)*

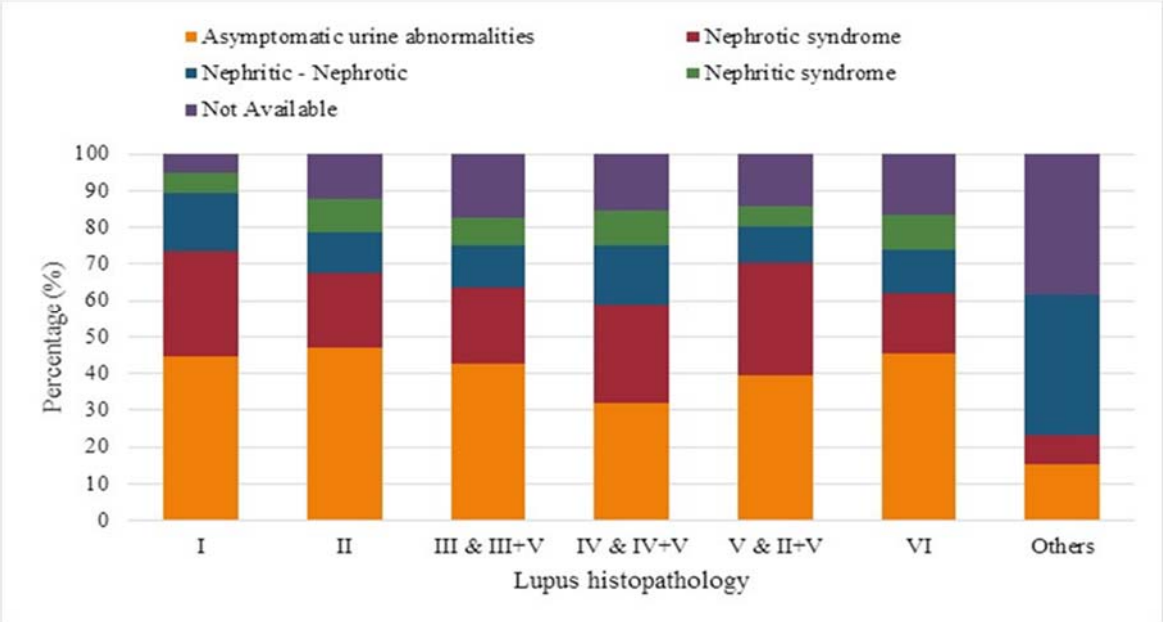
Table 3.2.4.2: Histopathological diagnosis by gender, 2005-2017

Histopathological diagnosis	Male (n=593)		Female (n=4141)		Total (n=4734)	
	n	%	n	%	n	%
I	5	0.8	33	0.8	38	0.8
II	35	5.9	273	6.6	308	6.5
III & III+V	157	26.5	1058	25.5	1215	25.7
IV & IV+V	315	53.1	2303	55.6	2618	55.3
V & II+V	76	12.8	424	10.2	500	10.6
VI	4	0.7	38	0.9	42	0.9
Others	1	0.2	12	0.3	13	0.3

** 90 cases are missing on lupus subclass*

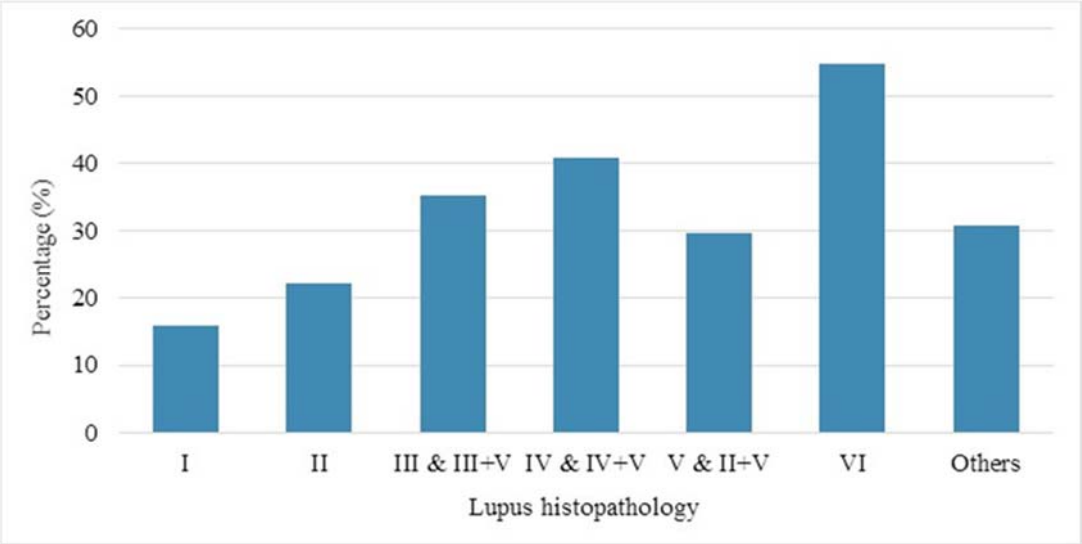
3.2.4.3 Clinical Presentation by histopathology

- Asymptomatic urine abnormalities was the commonest clinical presentation in patients with biopsy-proven LN, without any differences in sub-classes. *(Figure 3.2.5.3 (a))*
- Clinical presentation did not predict histopathological findings.
- Hypertension was most prevalent in Class VI LN (54.8%), followed by class IV/ IV+V (40.8%) and Class III/III+V (35.3%). *(Figure 3.2.4.3(b))*
- The prevalence of impaired kidney function correlated with histopathological findings. Impaired eGFR (<60ml/min/1.73m^2) occurred most frequently in Class VI LN (59.4%).
- Proliferative lupus nephritis, class IV/ IV+V and Class III/III+V was associated with impaired renal function in 39.0% and 17.4% of cases, respectively. *(Table and Figure 3.2.4.3(c))*



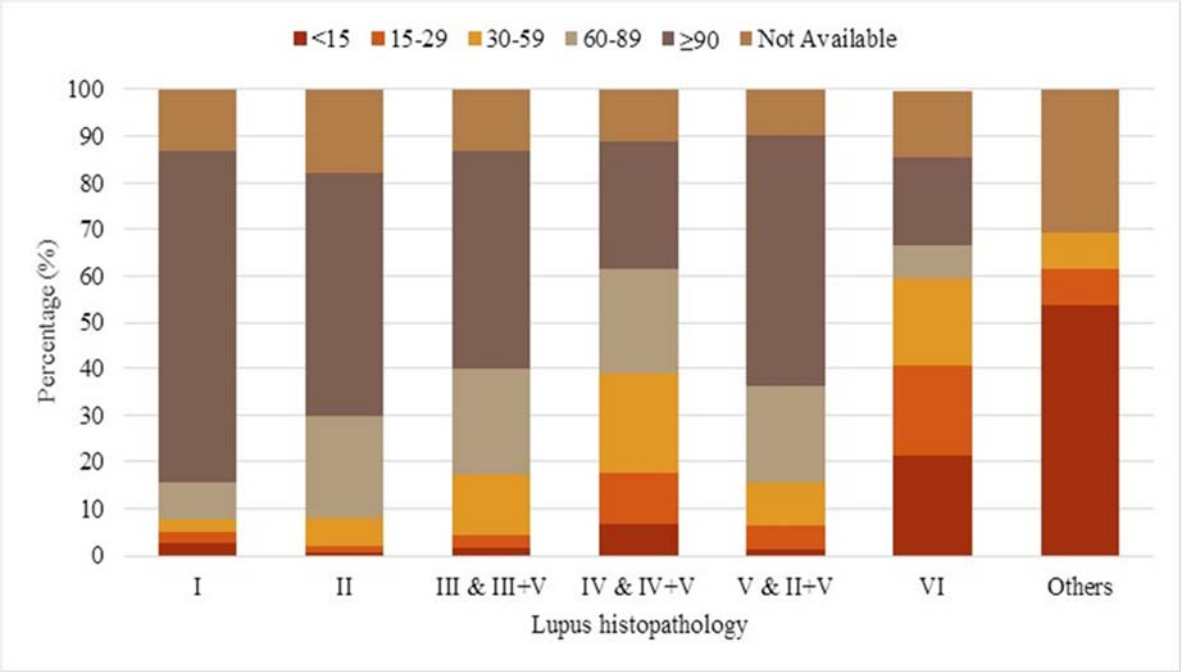
** 90 cases are missing on lupus subclass*

Figure 3. 2.4.3 (a): Clinical presentation by histopathology in lupus nephritis, 2005-2017



** 90 cases are missing on lupus subclass*

Figure 3.2.4.3 (b): Hypertension by histopathology in lupus nephritis, 2005-2017



** 90 cases are missing on lupus subclass*

*** 570 cases are missing on GFR, including 107 cases with GFR>200 (GFR range between 201 to 2463)*

Figure 3.2.4.3(c): Renal function by histopathology, 2005-2017

3.2.5: Extra-renal involvement

3.2.5.1: American College of Rheumatology (ACR) criteria in lupus nephritis.

- About 57.2% of patients with biopsy-proven LN did not fulfil the ACR criteria for SLE at presentations. Percentage of patients who had ≥4 ACR criteria seemed to decrease over the years. *(Table 3.2.5.1)*

Table 3.2.5.1: ACR criteria in lupus nephritis, 2005-2017

Number of ACR criteria	2005-2009 (n=1403)		2010-2014 (n=2109)		2015 (n=458)		2016 (n=405)		2017 (n=449)		Total (n=4824)	
	n	%	n	%	n	%	n	%	n	%	n	%
<4	439	31.3	935	44.3	250	54.6	193	47.7	246	54.8	2063	42.8
≥4	964	68.7	1174	55.7	208	45.4	212	52.3	203	45.2	2761	57.2

3.2.5.2: ACR criteria in lupus nephritis by age

- Only 27% of patients ≥65 years old satisfied ≥4 ACR criteria of SLE. The percentage seemed to decrease with age. *(Figure 3.2.5.2)*

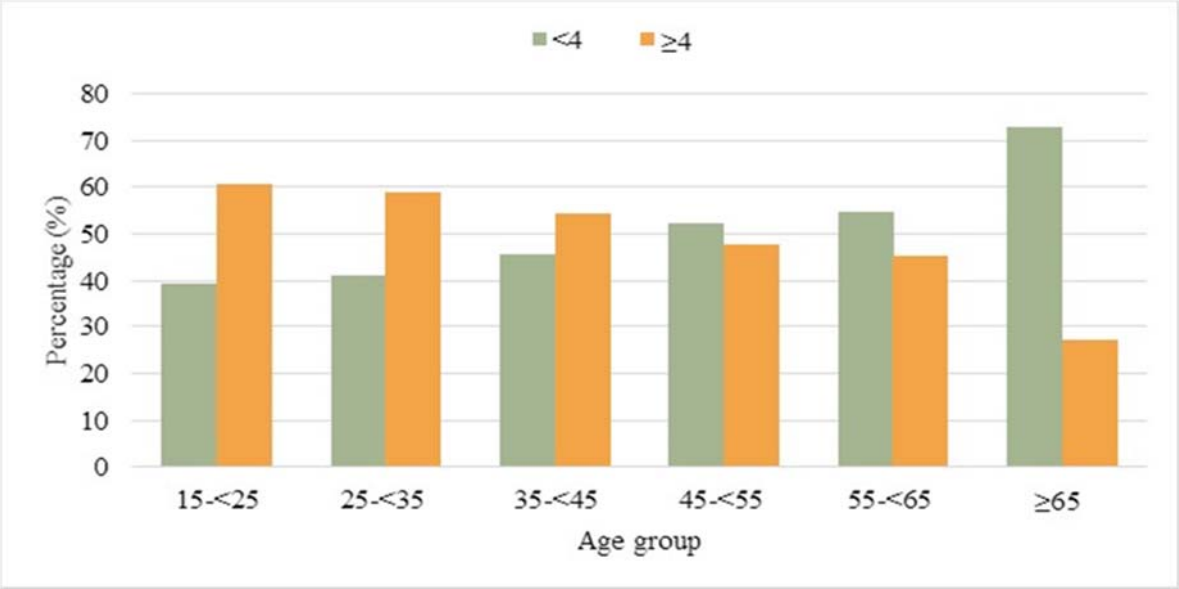


Figure 3.2.5.2: ACR criteria by age group, 2005-2017

3.2.5.3: ACR criteria by gender

- The percentage of patients who fulfilled the ACR criteria did not differ between the two genders. *(Figure 3.2.5.3)*

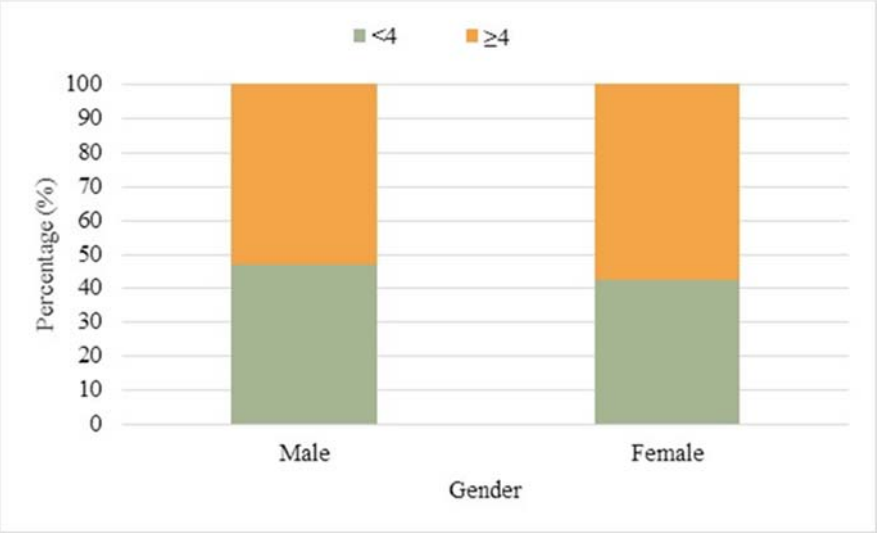
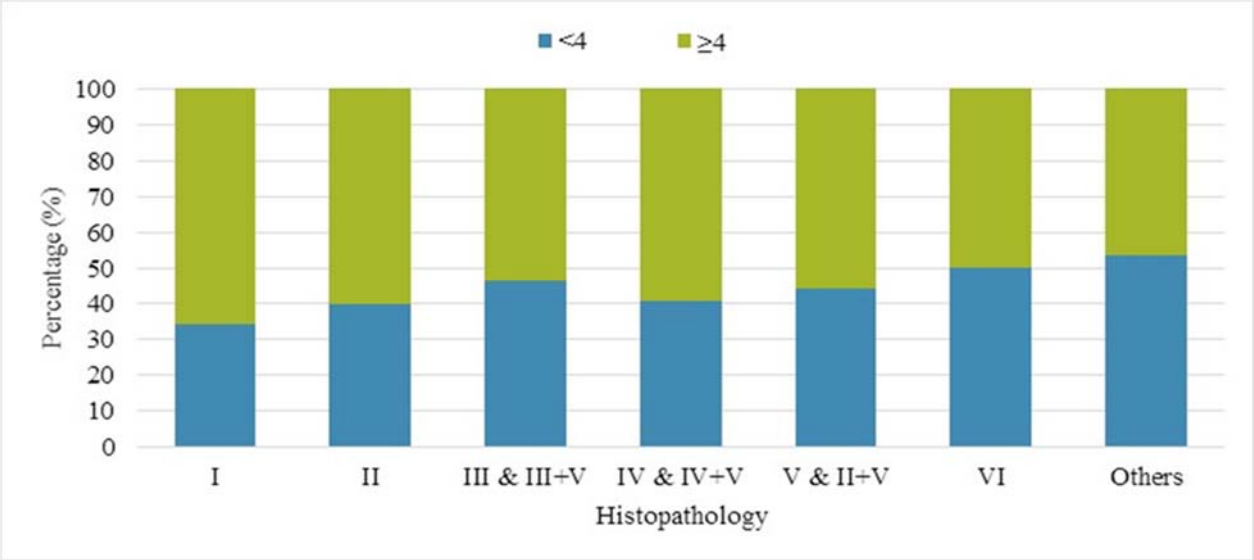


Figure 3.2.5.3: ACR criteria by gender, 2005-2017

3.2.5.4: ACR criteria by histopathological findings

- Histopathological diagnosis did not influence the proportion of number of ACR criteria. *(Figure 3.2.5.4)*



90 cases are missing on lupus subclass

Figure 3.2.5.4: ACR criteria by histopathology, 2005-2017

3.2.5.5: Extra-renal involvement

- Mucocutaneous involvement (45.4%) was the commonest extra-renal involvement followed by hematological involvement (34.5%) and arthritis (30.2%). *(Figure 3.2.5.5(a))*
- Both genders had similar pattern of extra-renal involvements but male patients seemed to have more cerebral lupus (11.4%) as compared to females (8.0%).
- Malar rash was the commonest mucocutaneous manifestation. *(Table 3.2.5.5(b))*

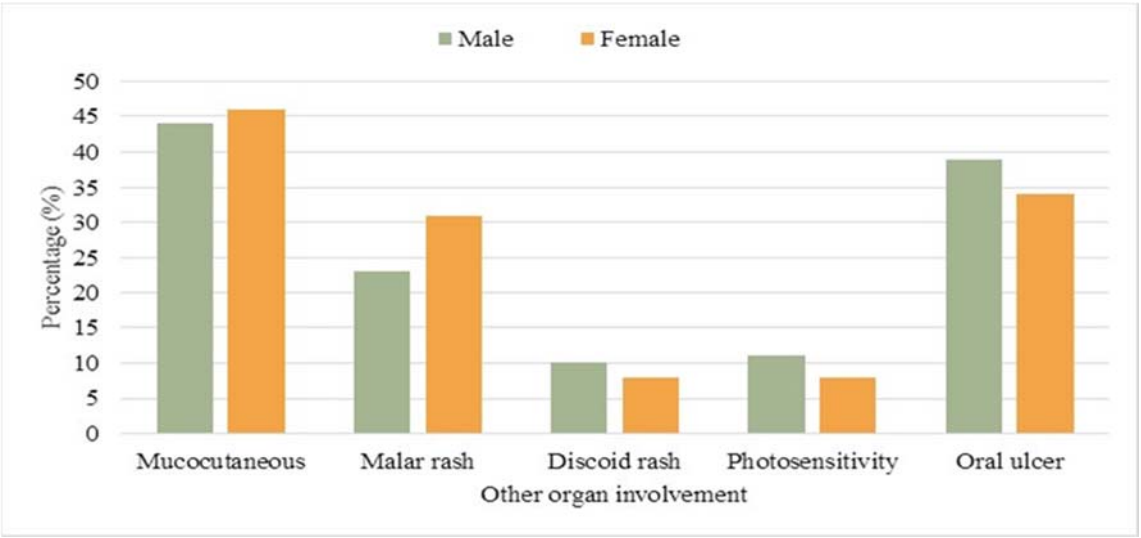


Figure 3.2.5.5 (a): Extra-renal involvement by gender, 2005-2017

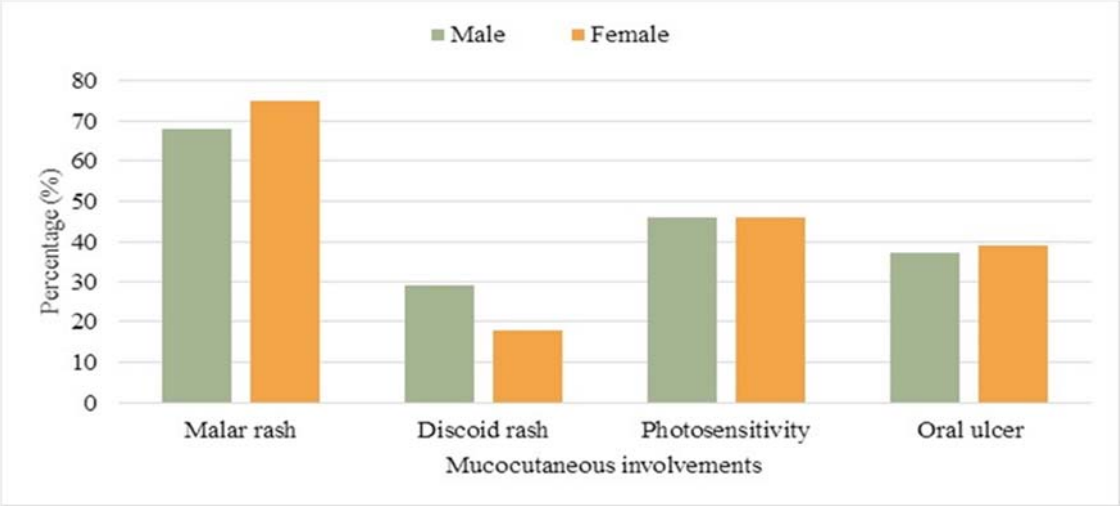


Figure 3.2.5.5(b): Mucocutaneous involvement by gender in lupus nephritis, 2005-2017

3.2.6: Survival in lupus nephritis

- To evaluate patient and renal survivals, data on the date of death and date of the onset of End Stage Renal Failure was obtained by data mapping based on the patient's new identity card (NRIC) from the National Registration Department and from Malaysian Dialysis and Transplant Registry.

3.2.6.1: Patient survival in lupus nephritis

- The patient survival was 94% and 85% at 1 year and 5 years from the time of renal biopsy, respectively *(Table and Figure 3.2.6.1)*. Our result was much lower than the reported data from Hong Kong, in which patient survival rates were 98.6% and 98.2%, at 5 and 10 years respectively. [2]

Table 3.2.6.1: Patients Survival estimates for death in lupus nephritis, 2005-2017

Interval (months)	Patient's survival		
	n	% survival	SE
0	4821	100	-
12	4044	94	0.004
24	3546	91	0.004
36	3057	89	0.005
48	2566	87	0.005
60	2138	85	0.006
72	1725	84	0.006

**Missing of 3 event cases (date event before date of biopsy)*

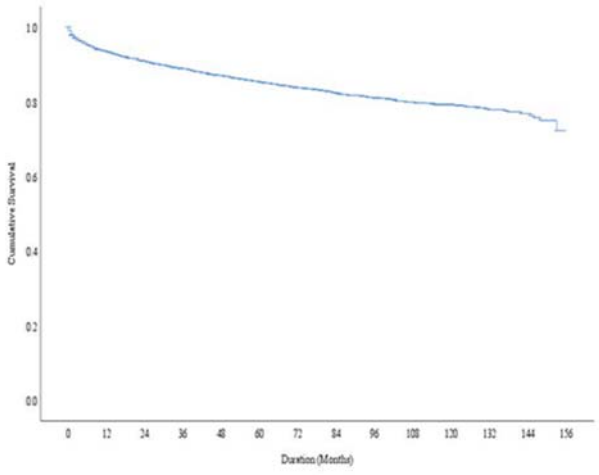


Figure 3.2.6.1: Patients Survival estimates for death in lupus nephritis, 2005-2017

3.2.6.2: Renal survival in lupus nephritis

- After censoring for death, the renal survival was 97% and 92% at 1 year and 5 years, respectively. *(Table and Figure 3.2.6.2)*. Comparatively, the death censored renal survival at Hong Kong were 99.5% and 98%, at 5 and 10 years respectively. [2]

Table 3.2.6.2: Death-censored Renal Survival estimates for lupus nephritis, 2005-2017

Interval (months)	Ronal survival		
	n	% survival	SE
0	4815	100	-
12	3912	97	0.003
24	3358	95	0.003
36	2844	94	0.004
48	2346	93	0.004
60	1922	92	0.005
72	1521	90	0.005

**Missing of 9 cases (7 event cases where the outcome date < date of 1st biopsy; and 2 event cases of the same date). (based on first biopsy date to the first ESRF outcome for adult patients with history of lupus nephritis, or as at 31st December 2017)*

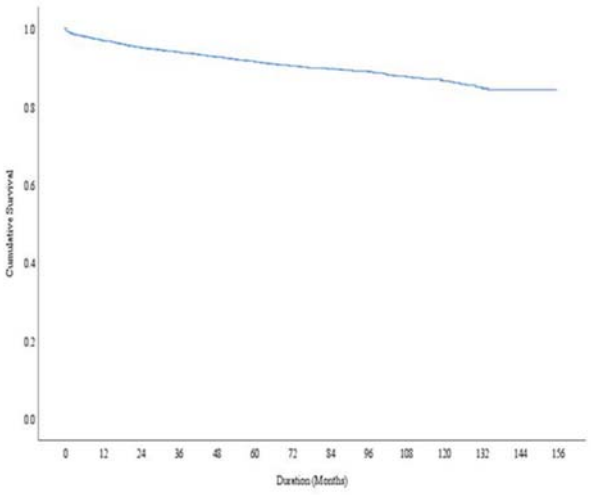


Figure 3.2.6.2: Death-censored Renal Survival estimates for lupus nephritis, 2005-2017

References:

1. *Fiorentino M, Bolignano D, Tesar V, Pisano A, Van Biesen W, D'Arrigo G, et al. Renal Biopsy in 2015-From Epidemiology to Evidence-Based Indications. Am J Nephrol. 2016. February 5;43(1):1–19].*
2. *Yap DY, Tang CS, Ma M. et al. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant 2012; 27: 3248–3254].*