

CHAPTER 3

SECONDARY GLOMERULONEPHRITIS

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3.1: Introduction

- Chapter 3 reports the main secondary glomerulonephritis (GN) in adults (defined as age > 15) from the years 2005 till 2020.
- The commonest cause of secondary glomerulonephritis among patients who underwent renal biopsy was lupus nephritis (79.9%), followed by diabetic kidney disease (13.6%) and post-infectious GN (2.9%). (Table 3.1)
- The percentage diabetic kidney disease reported to MRRB was not high although it's the leading cause of end stage kidney disease in Malaysia. The data showed an increasing trend of diabetic kidney disease being reported, from 10.1% in the initial years of registry to 22.1% in 2020. This could be due to the changing biopsy practices of the managing nephrologists or the evolving natural history of diabetic kidney disease.
- Other causes of secondary glomerulonephritis are uncommon and probably under-diagnosed due to limited availability of electron microscopy and special staining.
- From 2005 till 2020, only 60 cases of renal amyloidosis, 27 cases of systemic vasculitis and 20 cases of multiple myeloma were reported. This constitutes less than 1% of all biopsies performed (Table 3.1)

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% 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 6588 biopsy-proven lupus nephritis reported from 1st January 2005 to 31st December 2020. (Table 3.1)

3.2.2.1 Age at time of biopsy

- LN affects young people with the median age at time of biopsy was 28.7 years old. (Table 3.2.2.1)
- The common age groups were 15-25 years old (36.5%) and 25-35 years old (32.5%). (Figure 3.2.2.1)
- The distribution of each age decade remained similar over the last 16-year observational period.

Table 3.1: Causes of secondary glomerulonephritis in adult, 2005-2020

Type of secondary GN	2005-2009 (n=1657)		2010-2014 (n=2797)		2015-2019 (n=3130)		2020 (n=665)		Total (n=8249)	
	n	%	n	%	n	%	n	%	n	%
Lupus Nephritis	1414	85.3	2221	79.4	2474	79.0	479	72.0	6588	79.9
Diabetic nephropathy	167	10.1	373	13.3	433	13.8	147	22.1	1120	13.6
Post Infectious GN	32	1.9	93	3.3	98	3.1	13	2.0	236	2.9
Amyloidosis	9	0.5	20	0.7	23	0.7	8	1.2	60	0.7
Other infection	8	0.5	19	0.7	16	0.5	4	0.6	47	0.6
Systemic vasculitis	4	0.2	14	0.5	9	0.3	0	0	27	0.3
Henoch Schonlein Purpura	7	0.4	7	0.3	3	0.1	0	0	17	0.2
Multiple myeloma	8	0.5	4	0.1	7	0.2	1	0.2	20	0.2
Anti GBM disease	0	0	3	0.1	7	0.2	3	0.5	13	0.2
Light / Heavy chain deposit disease	2	0.1	2	0.1	6	0.2	1	0.2	11	0.1
HUS / TTP	0	0	3	0.1	5	0.2	2	0.3	10	0.1
Malignancy	3	0.2	4	0.1	1	0	0	0	8	0.1
Immunotactoid / fibrillary GN	0	0	1	0	2	0.1	1	0.2	4	0
Not Available	3	0.2	33	1.2	46	1.5	6	0.9	88	1.1

Table 3.2.2.1: Age group at time of biopsy (years), 2005-2020

Age group (years)	2005 (n=240)	2006 (n=275)	2007 (n=286)	2008 (n=312)	2009 (n=290)	2010 (n=311)	2011 (n=434)	2012 (n=447)	2013 (n=451)	2014 (n=478)	2015 (n=459)	2016 (n=409)	2017 (n=463)	2018 (n=538)	2019 (n=478)	2020 (n=476)	Total (n=6337)
Mean	30.48	30.89	29.83	30.54	29.19	30.36	30.75	30.32	30.56	31.03	30.99	31.96	31.16	31.39	32.26	30.47	30.85
SD	10.59	10.32	10.18	11.03	9.64	10.88	10.98	11.12	10.21	10.49	11.34	11.53	10.87	10.91	11.77	11.11	10.89
Median	29.00	29.64	27.5	28.37	27.68	27.86	27.93	27.53	28.45	29.63	29.16	29.73	29.37	29.23	30.50	27.50	28.65
Minimum	15.00	15.10	15.20	15.10	15.00	15.10	15.00	15.15	15.00	15.00	15.03	15.03	15.05	15.01	15.05	15.00	15.00
Maximum	70.40	59.40	67.50	65.40	62.80	78.90	72.10	72.40	64.10	63.90	77.65	69.18	70.14	70.48	69.42	76.19	78.87

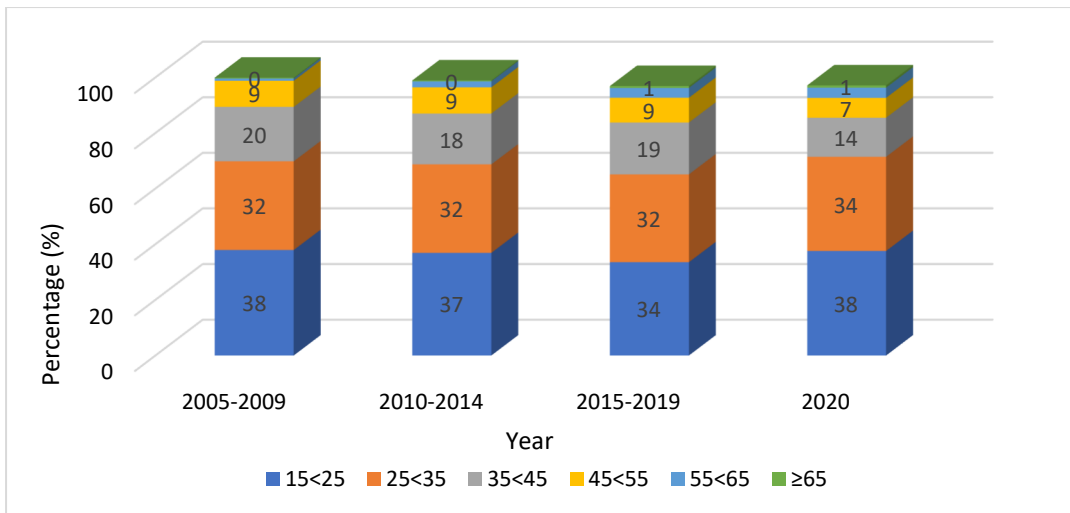


Figure 3.2.2.1: Age group at time of biopsy (years), 2005-2020

3.2.2.2: Gender distribution

- LN predominantly affects females in the child-bearing age group.
- The female: male ratio was 9:1. (Figure 3.2.2.2(a))
- The median age at the time of biopsy were 19.3 and 22.8 years in males and females, respectively. (Figure 3.2.2.2 (b) and (c))

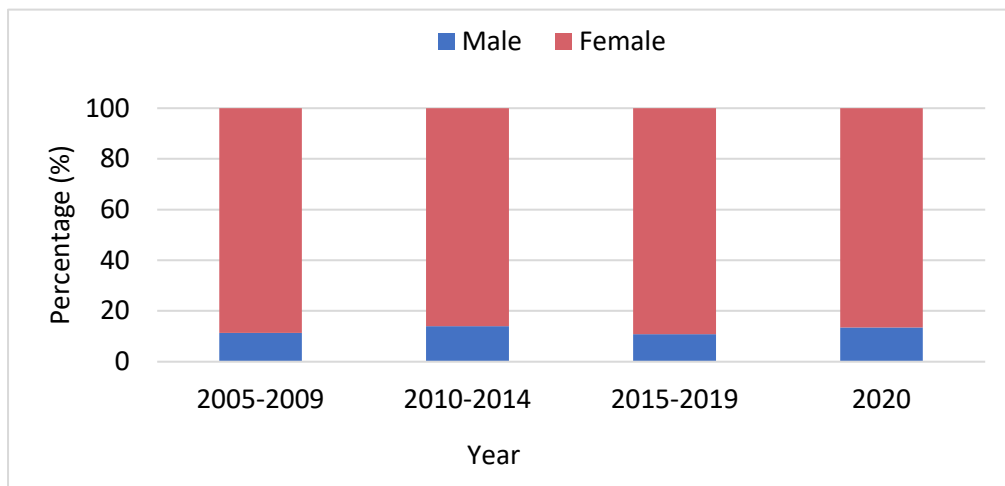


Figure 3.2.2.2(a): Gender distribution, 2005-2020

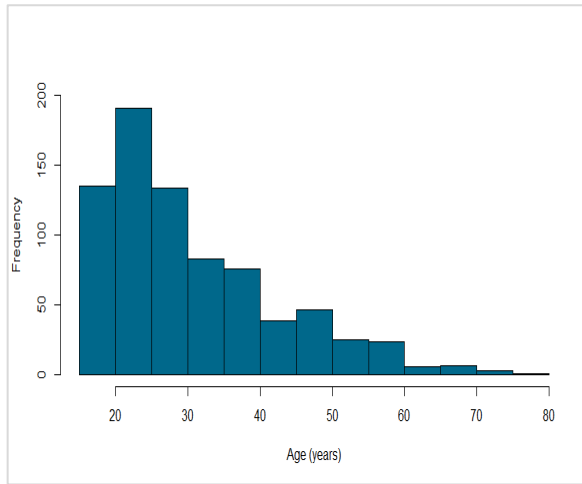


Figure 3.2.2.2(b): Age distribution (Male) , 2005-2020

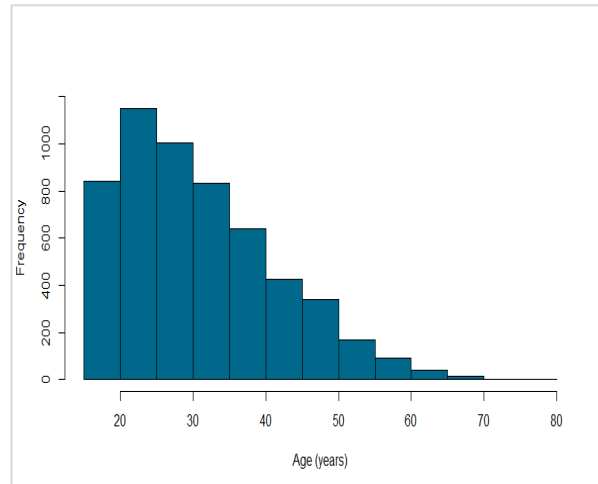


Figure 3.2.2.2(c): Age distribution (Female) , 2005-2020

3.2.2.3 Ethnic prevalence

- The ethnic distribution followed the demographic composition of the country: Malays (61.7%), Chinese (23.9%) and Indians (4.2%) (Figure 3.2.2.3)
- There was no preponderance of LN in certain ethnic groups in the Malaysian population.

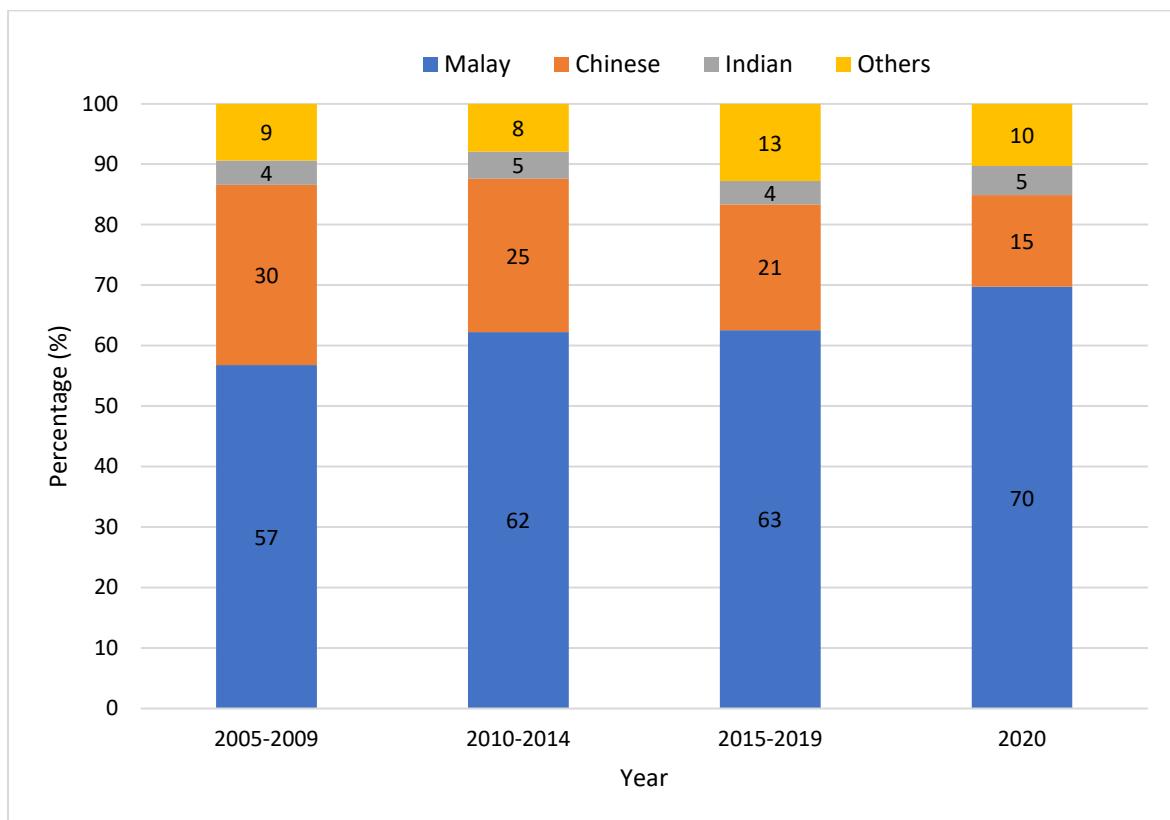


Figure 3.2.2.3: Ethnic distribution, 2005-2020

3.2.3: Clinical presentation

- Most of the patients (37.3%) were diagnosed with SLE and detected to have kidney involvement through screening (asymptomatic urinary abnormalities) at presentation, followed by nephrotic syndrome (25%). (Figure 3.2.3)
- Other clinical presentations include nephritic-nephrotic syndrome (13.9%) and nephritic syndrome (8.6%).
- Missing data was as high as 15.2%, potentially making the data less accurate.
- At presentation, the prevalence of hypertension was 37.1%. (Figure 3.2.3 (a))
- Most of the patients (38%) had eGFR>90ml/min upon diagnosis, and 4% has eGFR<15 ml/min/1.73m. (Table 3.2.3)

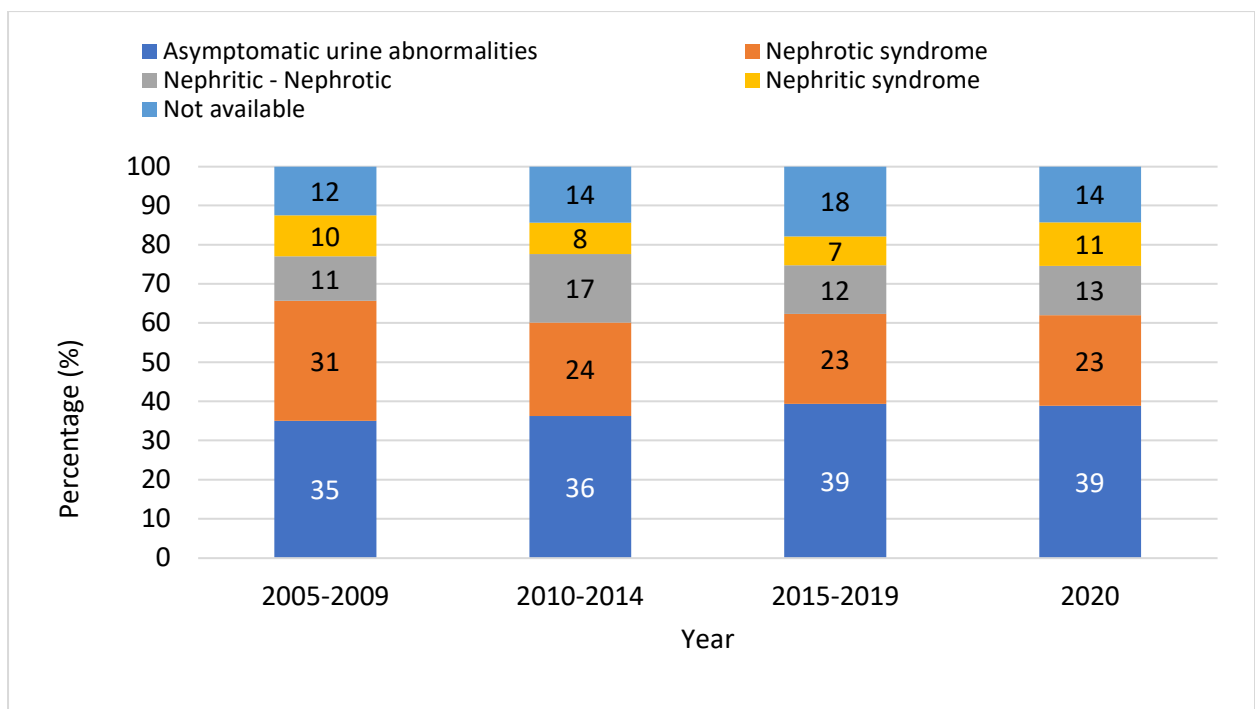


Figure 3.2.3: Clinical presentation by year, 2005-2020

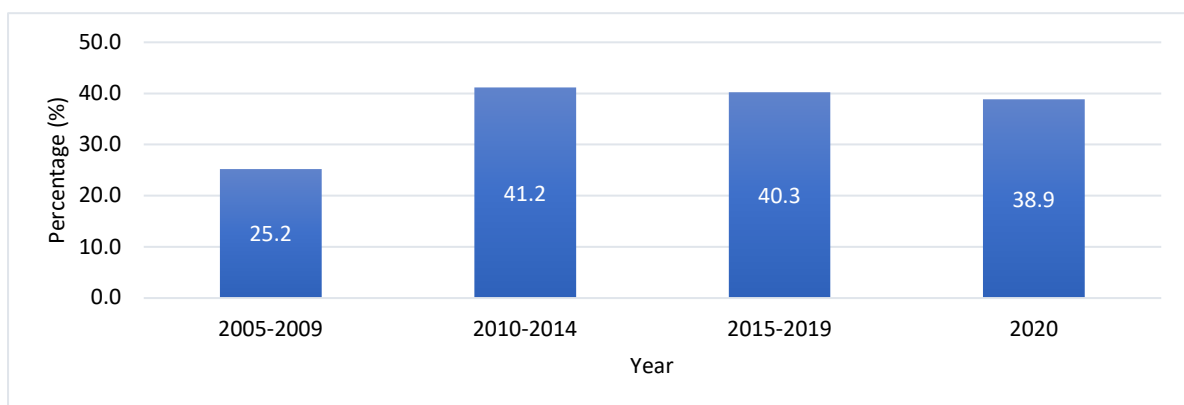


Figure 3.2.3(a): Hypertension by year, 2005-2020

Table 3.2.3: Renal function by year, 2005-2020

eGFR (ml/min/1.73m ²)	2005-2009 (n=1403)		2010-2014 (n=2111)		2015-2019 (n=2347)		2020 (n=476)		Total (n=6337)	
	n	%	n	%	n	%	n	%	n	%
<15	78	6	98	5	91	4	13	3	280	4
15 to <30	119	8	149	7	154	7	36	8	458	7
30 to <60	281	20	345	16	350	15	79	17	1055	17
60 to <90	343	24	471	22	445	19	87	18	1346	21
≥90	474	34	779	37	979	42	192	40	2424	38
Not available	108	8	269	13	328	14	69	14	774	12

*Total of 774 cases are missing on GFR, including 140 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 above the age of 65 years old may be explained by the significant number of missing data.
- The percentage of lupus nephritis patients with impaired renal function increased with age. For those aged ≥65, about 67.7% had eGFR of less than 60ml/min/1.73m, as compared to 21.3% in the group aged 15-<25. (Table 3.2.3.1)

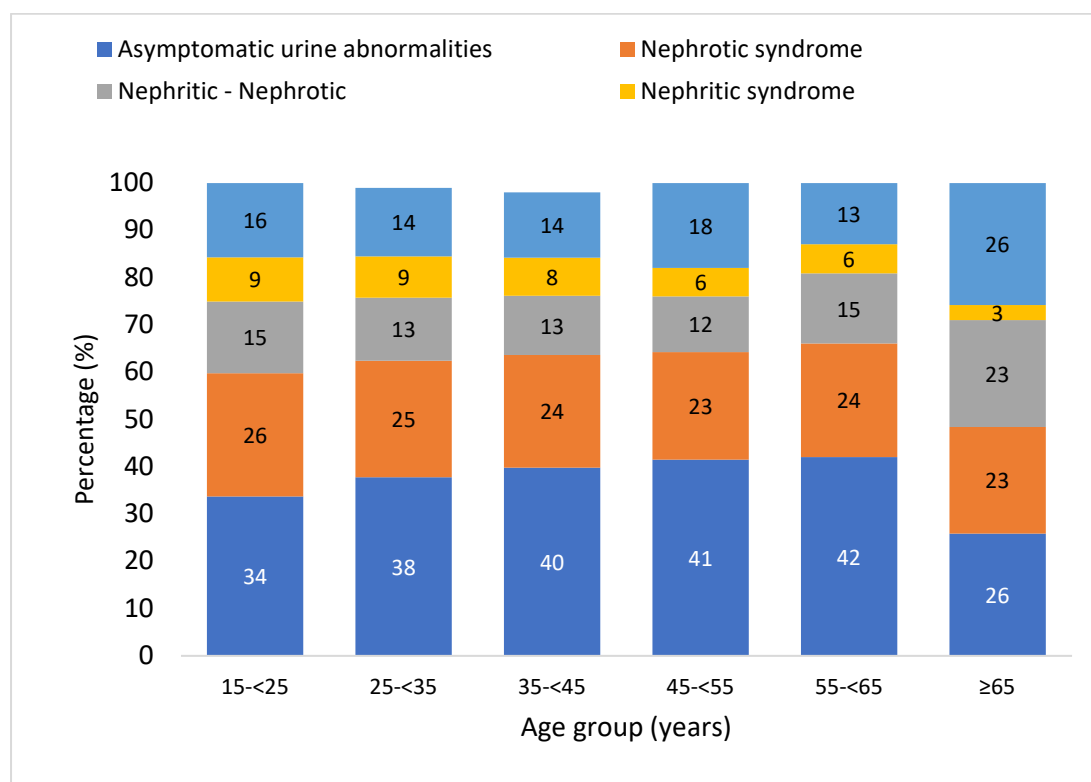


Figure 3.2.3.1(a): Clinical presentation by age group, 2005-2020

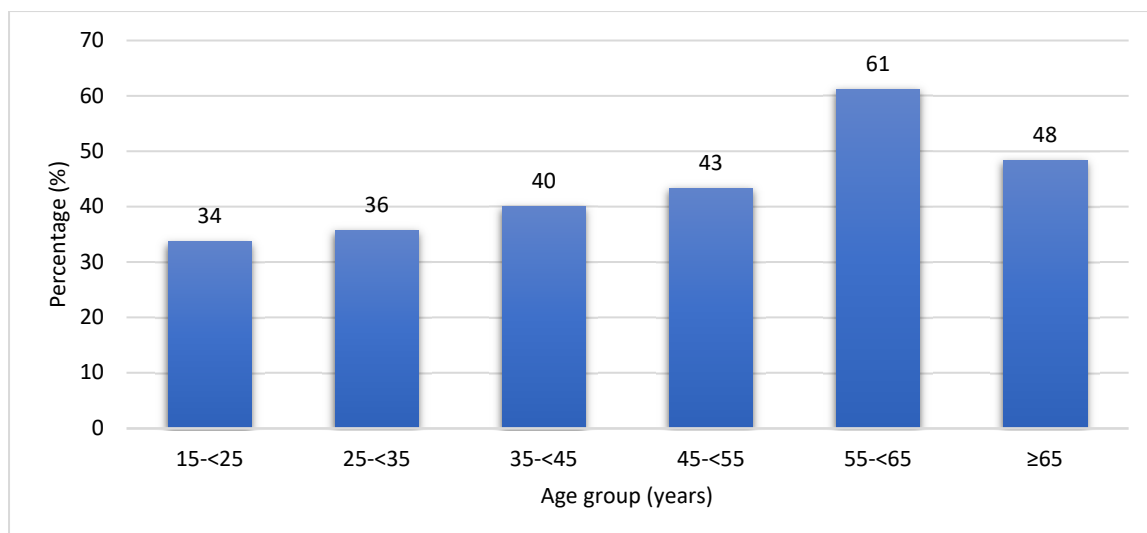


Figure 3.2.3.1(b): Hypertension by age group, 2005-2020

Table 3.2.3.1: Renal function by age group, 2005-2020

eGFR (ml/min/1.73m ²)	15-<25 (n=2315)		25-<35 (n=2058)		35-<45 (n=1187)		45-<55 (n=584)		55-<65 (n=162)		≥65 (n=31)		Total (n=6337)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
<15	94	4.1	80	3.9	56	4.7	37	6.3	9	5.6	4	12.9	280	4.4
15-29	123	5.3	151	7.3	107	9.0	56	9.6	13	8.0	8	25.8	458	7.2
30-59	284	12.3	328	15.9	247	20.8	143	24.5	44	27.2	9	29.0	1055	16.6
60-89	400	17.3	432	21.0	311	26.2	155	26.5	43	26.5	5	16.1	1346	21.2
≥90	1091	47.1	838	40.7	329	27.7	132	22.6	31	19.1	3	9.7	2424	38.3
Not Available	323	14.0	229	11.1	137	11.5	61	10.4	22	13.6	2	6.5	774	12.2

*Total of 774 cases are missing on GFR, including 140 cases with GFR>200 (GFR range between 201 to 2463)

3.2.3.2: Clinical presentation by gender

- 31.1% of the male patients as compared to 24.1% females presented with nephrotic syndrome. (Figure 3.2.3.1(a))
- At presentation, 41% males versus 37% females had hypertension. (Figure 3.2.3.2(b))
- Renal function did not differ much between the two genders. (Table 3.2.3.2 (c))

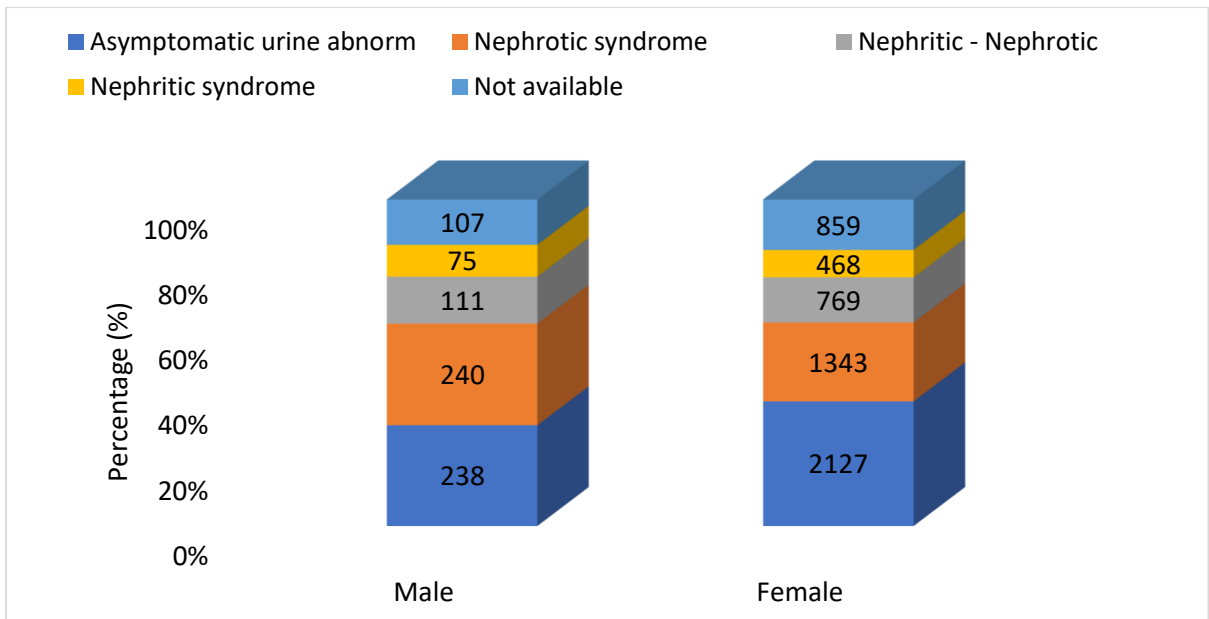


Figure 3.2.3.2(a): Clinical presentation by gender, 2005-2020

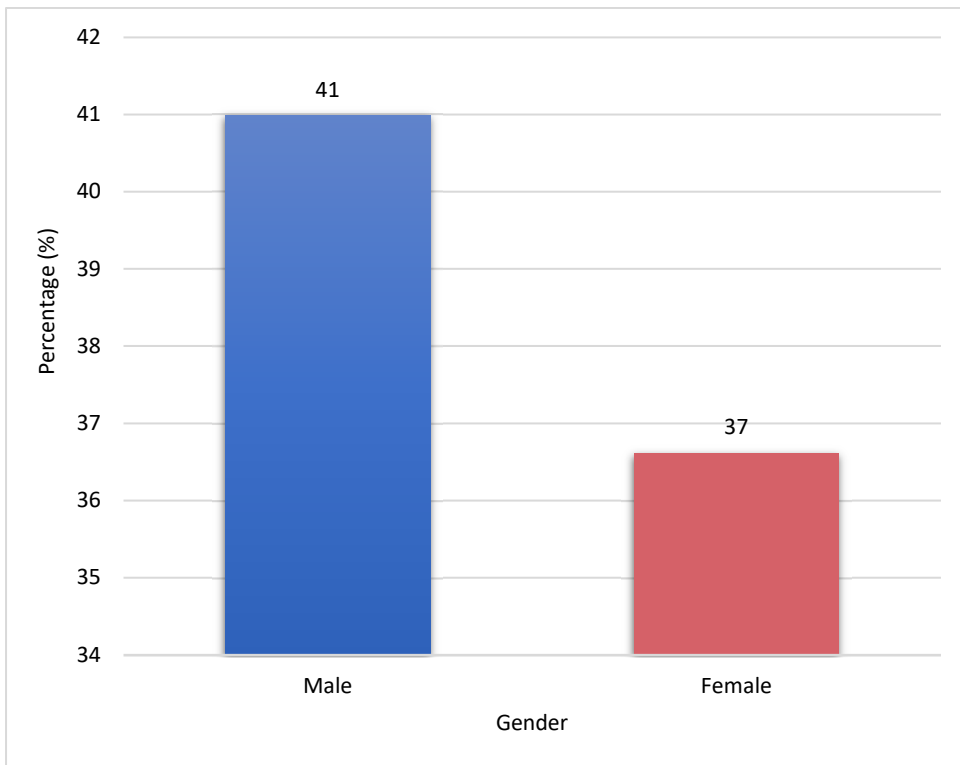


Figure 3.2.3.2(b): Hypertension by gender, 2005-2020

Table 3.2.3.2(c): Renal function by gender, 2005-2020

eGFR (ml/min/ 1.73m ²)	Male (n=771)		Female (n=5566)		Total (n=6337)	
	n	%	n	%	n	%
<15	36	4.7	244	4.4	280	4.4
15-29	72	9.3	386	6.9	458	7.2
30-59	131	17.0	924	16.6	1055	16.6
60-89	155	20.1	1191	21.4	1346	21.2
≥90	293	38.0	2131	38.3	2424	38.3
Not Available	84	10.9	690	12.4	774	12.2

3.2.4: Histopathological diagnosis

- Class IV /class IV+V LN was the predominant histopathological diagnosis, accounting for 52.6% of patients.
- This was followed by class III/ III+V (27.1%), and class V/ II+V (10.4%).
- The trend remained unchanged during the 16 years observation period.
- About 0.7% of patients had advanced sclerosing lupus nephritis (class VI) at the time of biopsy. (Table 3.2.4)

Table 3.2.4: Histopathological diagnosis in lupus nephritis by year, 2005-2020

Histopathological diagnosis	2005-2009 (n=1403)		2010-2014 (n=2111)		2015-2019 (n=2347)		2020 (n=476)		Total (n=6337)	
	n	%	n	%	n	%	n	%	n	%
I	9	0.6	19	0.9	20	0.9	4	0.8	52	0.8
II	121	8.6	127	6.0	114	4.9	26	5.5	388	6.1
III & III+V	290	20.7	538	25.5	742	31.6	148	31.1	1718	27.1
IV & IV+V	802	57.2	1126	53.3	1181	50.3	227	47.7	3336	52.6
V & II+V	144	10.3	230	10.9	228	9.7	57	12.0	659	10.4
VI	9	0.6	28	1.3	6	0.3	3	0.6	46	0.7
Others	9	0.6	2	0.1	3	0.1	0	0.0	14	0.2
Not available	19	1.4	41	1.9	53	2.3	11	2.3	124	2.0

3.2.4.1: Histopathological diagnosis by age

- The proportion of histopathological diagnoses was similar across all age groups.
- However, the frequency of Class IV & IV+V was highest (57.8%) in those with age 15-<25, as compared with 41.9% in those ≥65 years old. (Table 3.2.4.1)

Table 3.2.4.1: Histopathological diagnosis by age group in lupus nephritis, 2005-2020

Histopathological diagnosis	15-<25 (n=2315)		25-<35 (n=2058)		35-<45 (n=1187)		45-<55 (n=584)		55-<65 (n=162)		≥65 (n=31)		Total (n=6337)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
I	26	1.1	12	0.6	7	0.6	4	0.7	2	1.2	1	3.2	52	0.8
II	146	6.3	125	6.1	69	5.8	40	6.8	8	4.9	0	0.0	388	6.1
III & III+V	562	24.3	594	28.9	328	27.6	173	29.6	51	31.5	10	32.3	1718	27.1
IV & IV+V	1338	57.8	1062	51.6	597	50.3	252	43.1	74	45.7	13	41.9	3336	52.6
V & II+V	183	7.9	214	10.4	151	12.7	91	15.6	1	9.9	4	12.9	659	10.4
VI	16	0.7	15	0.7	8	0.7	6	1.0	1	0.6	0	0.0	46	0.7
Others	5	0.2	3	0.1	2	0.2	3	0.5	1	0.6	0	0.0	14	0.2
Not available	39	1.7	33	1.6	25	2.1	15	2.6	9	5.6	3	9.7	124	2.0

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, 2005-2020

Histopathological diagnosis	Male (n=711)		Female (n=5566)		Total (n=6337)	
	n	%	n	%	n	%
I	6	0.8	46	0.8	52	0.8
II	43	5.6	345	6.2	388	6.1
III & III+V	215	27.9	1503	27.0	1718	27.1
IV & IV+V	399	51.8	2937	52.8	3336	52.6
V & II+V	90	11.7	569	10.2	659	10.4
VI	4	0.5	42	0.8	46	0.7
Others	1	0.1	13	0.2	14	0.2
Not available	13	1.7	111	2.0	124	2.0

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 3.2.4.3 (a))
- Clinical presentation did not predict histopathological findings.
- Hypertension was most prevalent in Class VI LN (52.2%), followed by class IV/ IV+V (41.7%) and Class III/III+V (33.9%). (Figure 3.2.4.3(b))
- The prevalence of impaired kidney function also correlated with histopathological findings. Impaired eGFR (<60ml/min/1.73m²) occurred most frequently in Class VI LN (69.2%), followed by class IV/ IV+V (43.6%) and Class III/III+V (18.7%). (Figure 3.2.4.3(c))

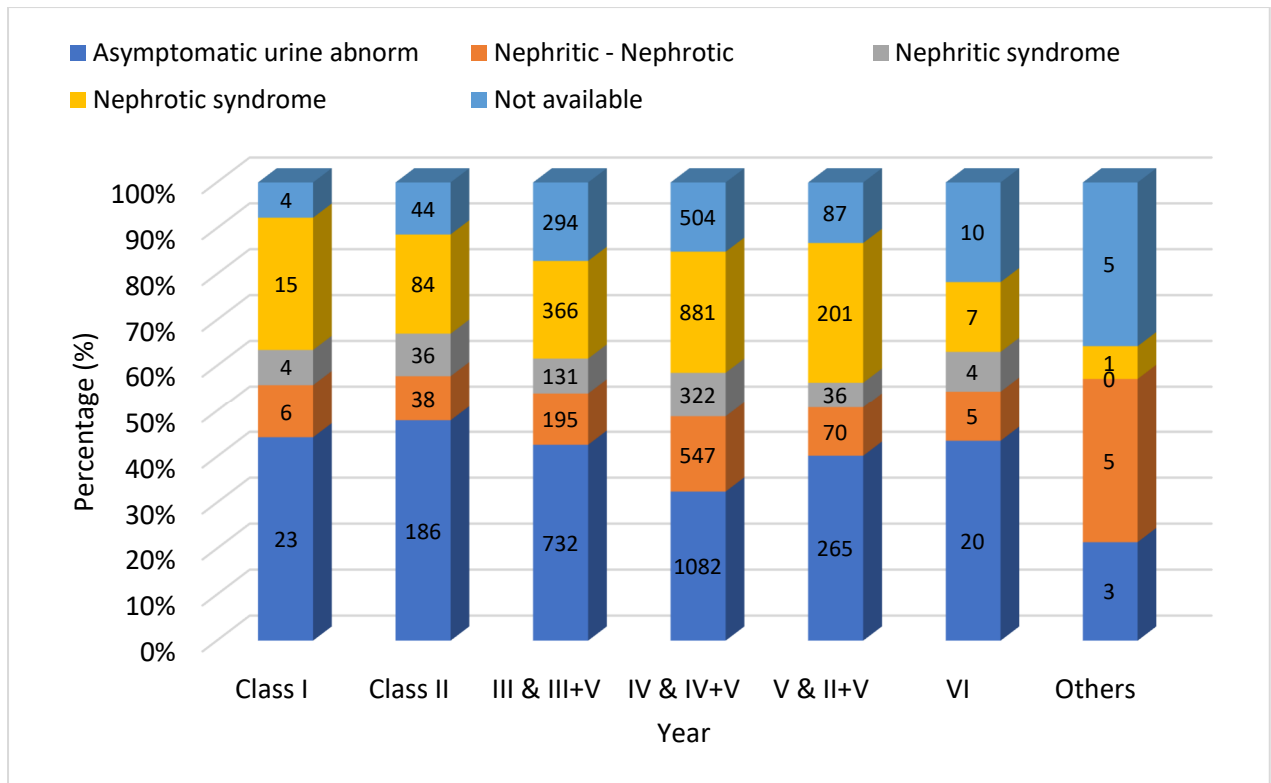


Figure 3.2.4.3(a): Clinical presentation by histopathology in lupus nephritis, 2005-2020

* 124 cases are missing on lupus subclass

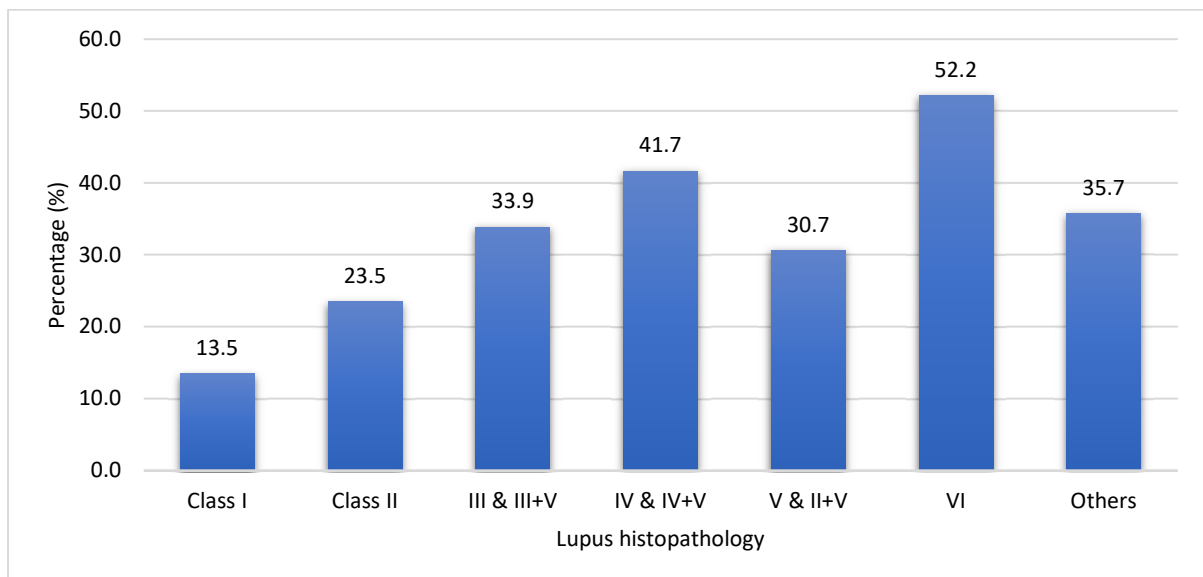


Figure 3.2.4.3(b): Hypertension by histopathology in lupus nephritis, 2005-2020

* 124 cases are missing on lupus subclass

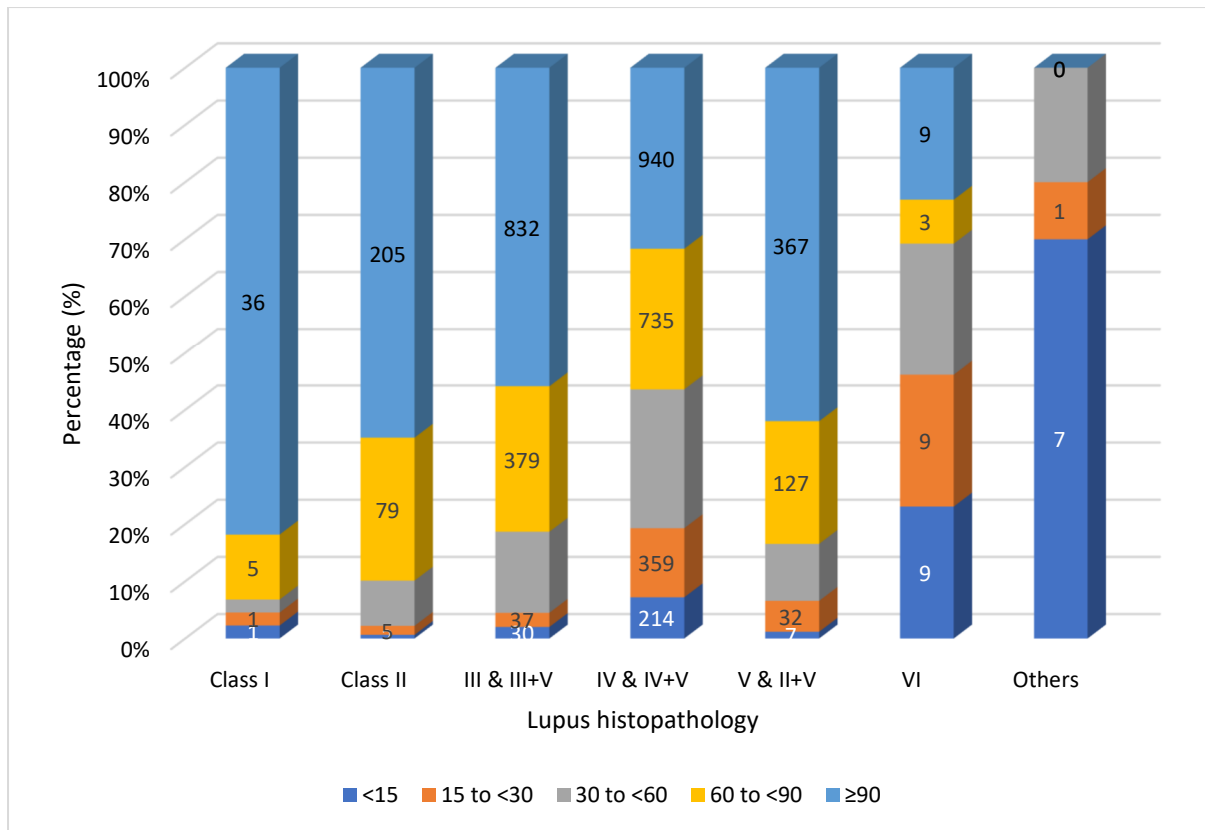


Figure 3.2.4.3(c): Renal function by histopathology, 2005-2020

* 124 cases are missing on lupus subclass

*Total of 774 cases are missing on GFR, including 140 cases with GFR>200 (GFR range between 201 to 2463)

3.2.5: Extra-renal involvement

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

- About 51.5% of patients with biopsy-proven LN fulfilled the ACR criteria for SLE at presentations. (Table 3.2.5.1)

Table 3.2.5.1: ARA criteria in lupus nephritis, 2005-2020

Number of ACR criteria	2005-2009 (n=1403)		2010-2014 (n=2111)		2015-2019 (n=2347)		2020 (n=476)		Total (n=6337)	
	n	%	n	%	n	%	n	%	n	%
<4	542	38.6	1011	47.9	1263	53.8	256	53.8	3072	48.5
≥4	861	61.4	1100	52.1	1084	46.2	220	46.2	3265	51.5

3.2.5.2: ACR criteria in lupus nephritis by age

- Only 19% of patients ≥65 years old satisfied ≥4 ACR criteria of SLE. The percentage seemed to decrease with age. (Figure 3.2.5.2)

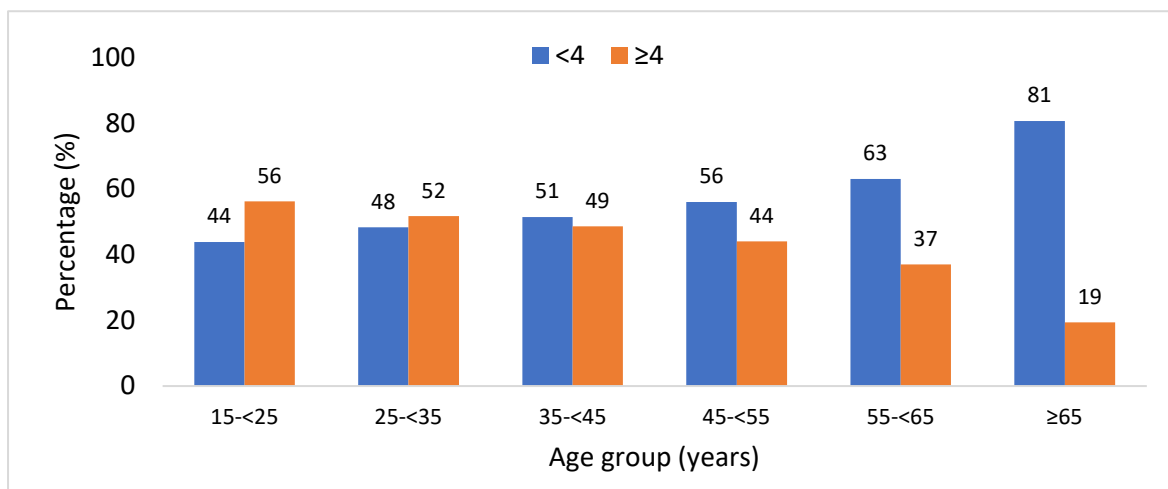
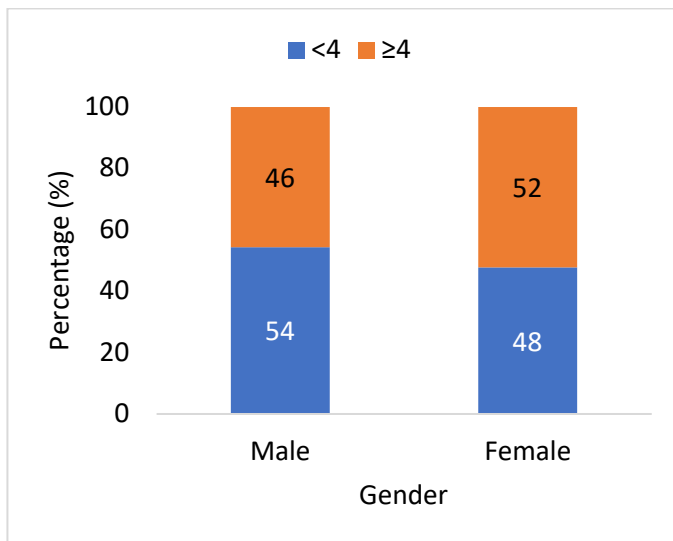


Figure 3.2.5.2: ACR criteria by age group, 2005-2020

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, 2005-2020

3.2.5.4: ACR criteria by histopathological findings

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

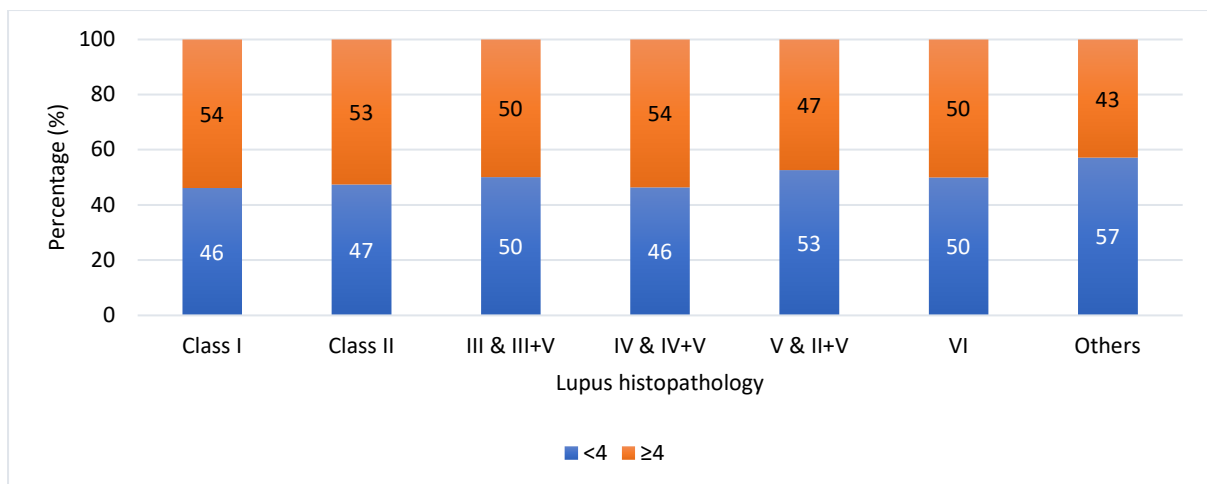


Figure 3.2.5.4: ACR criteria by histopathology, 2005-2020

* 124 cases are missing on lupus subclass

3.2.5.5: Extra-renal involvement

- Mucocutaneous involvement (81.5%) was the commonest extra-renal involvement followed by haematological involvement (36.2%) and arthritis (30.2%). (Figure 3.2.5.5(a))
- Both genders had similar pattern of extra-renal involvements.
- Malar rash was the commonest mucocutaneous manifestation. (Table 3.2.5.5(b))

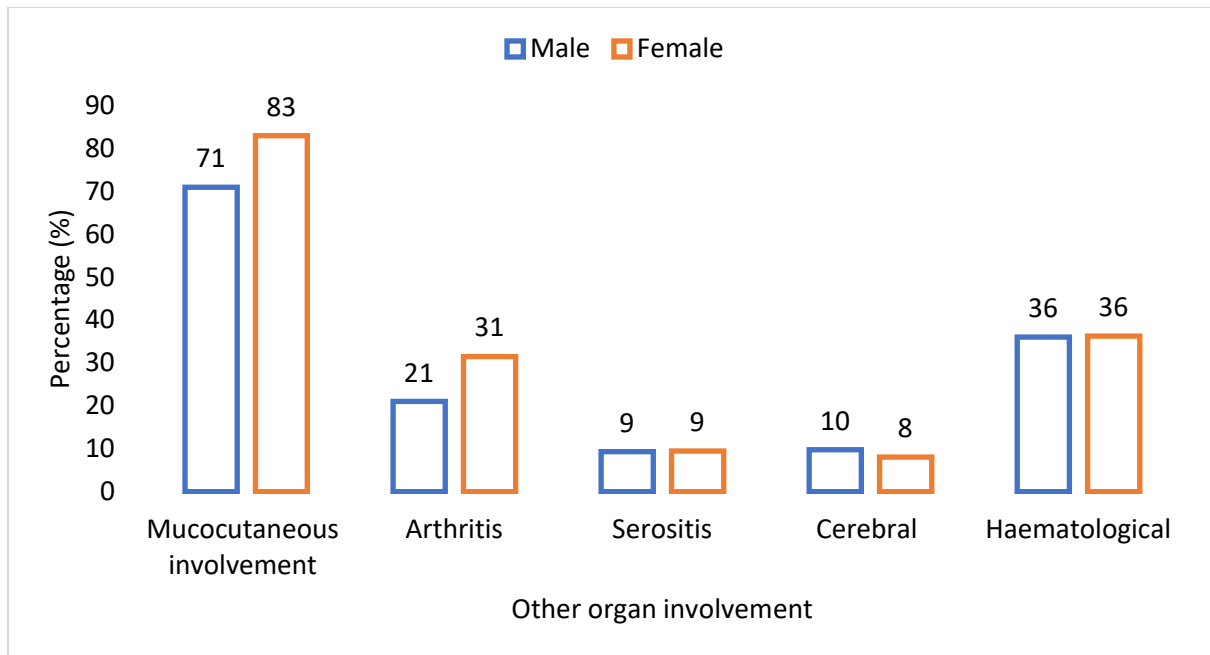


Figure 3.2.5.5(a): Extra-renal involvement by gender, 2005-2020

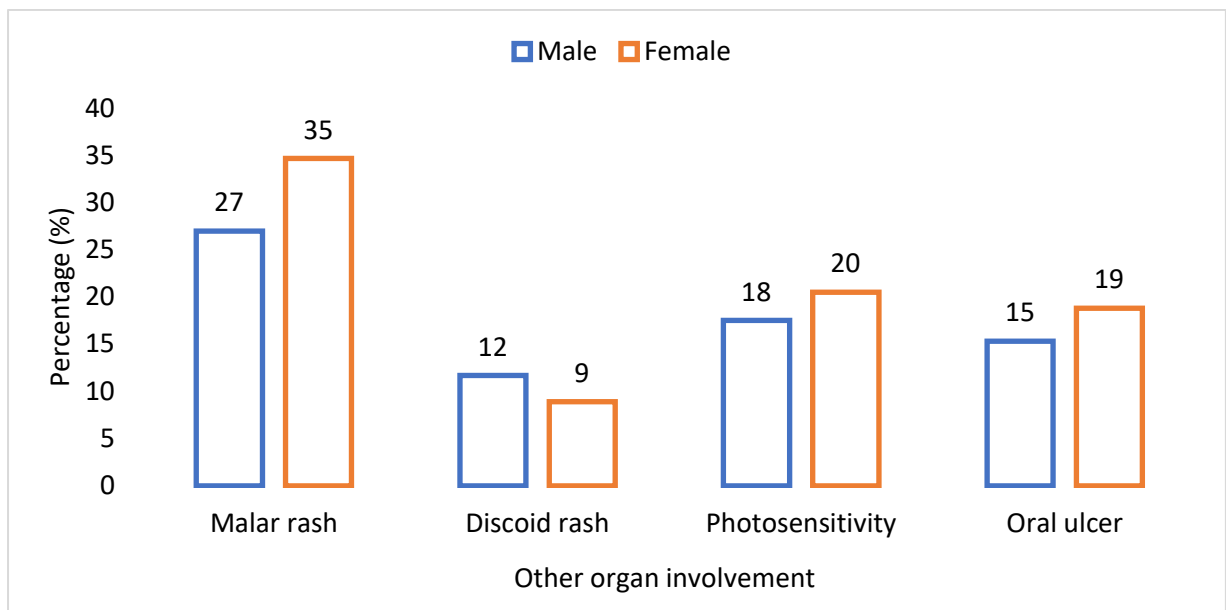


Figure 3.2.5.5(b): Mucocutaneous involvement by gender in lupus nephritis, 2005-2020

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 Kidney Disease was obtained by mapping the data on 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 84% 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, 2005-2020

Interval (months)	Patients with lupus nephritis		
	n	% Survival	SE
0	6337	100	-
12	5458	94	0.003
24	4831	91	0.004
36	4204	88	0.004
48	3682	86	0.005
60	3237	84	0.005

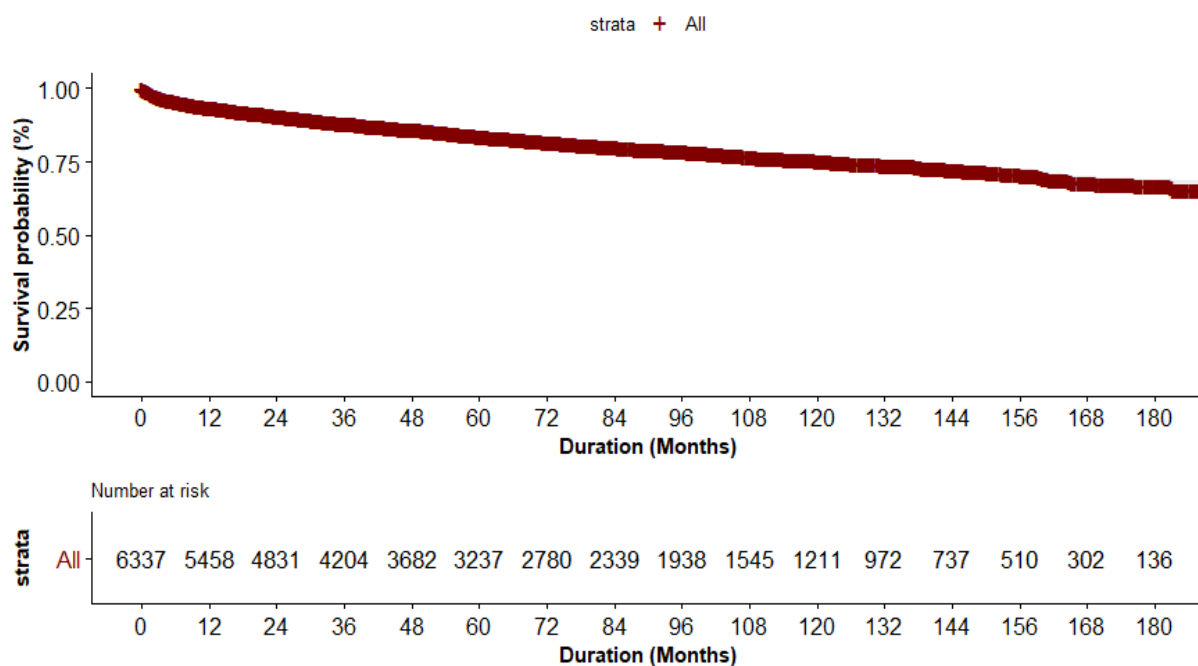


Figure 3.2.6.1: Patients Survival estimates for death in lupus nephritis, 2005-2020

3.2.6.2: Renal survival in lupus nephritis

- After censoring for death, the renal survival was 96% and 91% 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, 2005-2020

Interval (months)	Patients with lupus nephritis		
	n	% Survival	SE
0	6337	100	-
12	5273	96	0.002
24	4608	95	0.003
36	3962	93	0.003
48	3441	92	0.004
60	2998	91	0.004

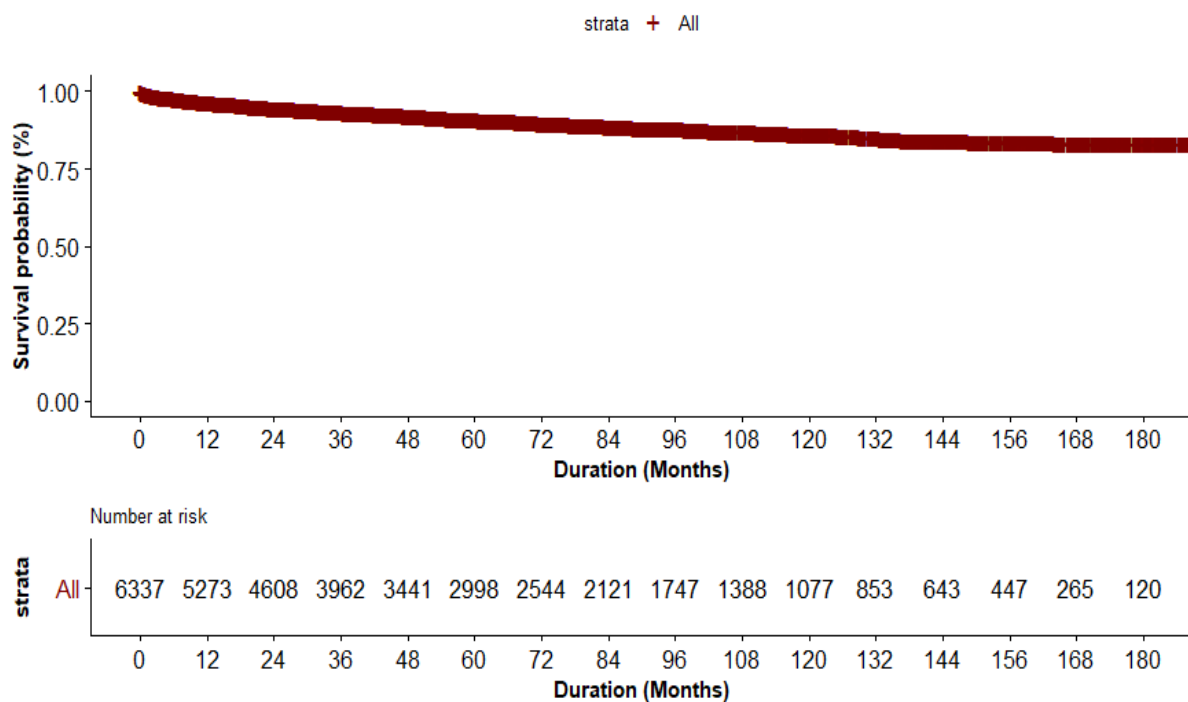


Figure 3.2.6.2 Death-censored Renal Survival estimates for lupus nephritis, 2005-2020

References:

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