ORIGINAL ARTICLE

Pattern of biopsy-proven renal disease in Sabah: A retrospective cross-sectional study over 3.5 years

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ABSTRACT

Objectives: To explore the epidemiological and histopathological patterns of glomerular diseases in Sabah.

Methods: A state-wide cross-sectional study was conducted. There were 336 native renal biopsies in 296 eligible patients from 1st January 2013 to 30th June 2016. All patients aged ≥12 years with sufficient sampling (≥8 glomeruli) for histopathological assessment were included. Graft kidney biopsies, protocol-based biopsies and patients with uncertain demographics were excluded. Demographics of patients, clinical data, laboratory parameters prior to biopsy, and histology findings of renal biopsies were collected from local unit database and recorded into a standardised data collection form. Descriptive statistical analyses were employed and factors associated with Lupus nephritis (LN) were explored using logistic regression.

Results: The mean age during biopsy was 34.53 years (Standard Deviation 0.759). Primary glomerulonephritis (PGN) accounted for 42.6% (126) of all native renal biopsies. The commonest cause of PGN was minimal change disease (38.9%, 49) followed by focal segmental glomerulosclerosis (33.3%, 42) and IgA nephropathy (14.3%, 18). LN is the leading cause for secondary glomerulonephritis (SGN) (87.2%, 136). Younger age (Odds Ratio, OR 0.978; 95% Confidence Interval, 95%CI 0.960, 0.996); female gender (OR 17.53; p<0.001); significant proteinuria (OR 132.0; p<0.001); creatinine level at biopsy (OR 11.26; p=0.004); positive antinuclear antibody (ANA) (OR 46.7; p<0.001); and ANA patterns (OR 8.038; p=0.018) were significant in predicting the odds of having LN.

Conclusion: This is the first epidemiology study of glomerular diseases in Sabah. The predominance of LN suggests lower threshold for renal biopsy in patients with suspected glomerular disorders. We have identified significant predictors for early detection and treatment of LN.

KEY WORDS:
kidney, biopsy, glomerulonephritis, lupus nephritis, histology, epidemiology

INTRODUCTION

Glomerular diseases have variable aetiology and clinical presentation.[1] Clues to the underlying pathology can be obtained from the clinical history, physical examination and laboratory findings of patients but rarely provide a conclusive diagnosis.[1] Therefore, a percutaneous renal biopsy is the cornerstone in the diagnostic workup for glomerular diseases as a means to guide the appropriate subsequent therapy having obtained the histopathological diagnosis.[1,2] Additionally, the findings in a renal biopsy carry much prognostic information, allowing clinicians to assess the disease activity and chronicity of renal damage.[3]

The Malaysian Society of Nephrology (MSN) maintains a Malaysian Registry of Renal Biopsy (MRRB) and compiles extensive data related to glomerular diseases nationwide.4 For Malaysia, biopsy-proven glomerulonephritis of various aetiology accounted for only 3% of incident dialysis patients in the year 2014.[4] However, data in the Malaysian Dialysis and Transplant Registry (MDTR) showed that unknown primary diseases accounted for 15% of incident dialysis-dependent chronic kidney disease.[5]

It is possible and in fact likely that a significant proportion of these were undiagnosed (and therefore untreated) chronic glomerulonephritis. The MRRB also audits the procedure of renal biopsy in terms of indication, sample adequacy and any resulting complications4. Based on the 5th Report of the MRRB, the commonest PGN in Malaysian adults were minimal change disease (32%) FSGS (29%) and IgA nephropathy (22%) while membranous glomerulonephritis constituted 9% of total PGN.[4]

LN was the commonest secondary glomerulonephritis (SGN) accounting for 80% followed by diabetic nephropathy at 11 percent.4 However, as a nationwide database, the findings in MRRB do not present its data by the individual participating centres or states. Therefore, to date we do not have sufficient data regarding the burden of glomerular disorders in the state of Sabah. We observed that LN seems to account for a significant number of glomerular disease among the population of Sabah but have never fully confirmed or put to test the aforementioned observation.

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Table I: Patients' characteristics (N=296)

Patients' characteristics	n	%
Gender		
Female	211	71.3
Male	85	28.7
Age, years (mean, SD)	34.53, SD 0.759	
Age groups (years)		
12-19	31	10.5
20-39	171	57.8
40-59	76	25.7
>60	18	6.1
Ethnicity		
Kadazandusun	111	37.5
Bajau	75	25.3
Chinese	34	11.5
Others	16	5.4
Brunei	12	4.1
Malay	9	3
Suluk	6	2
Rungus	5	1.7
Sungai	5	1.7
Bisaya	5	1.7
Data not available	5	1.7
Bugis	3	1
Iban	3	1
Murut	2	0.7
Indian	2	0.7
Indonesian	1	0.3
Kadayan	1	0.3
Jawa	1	0.3
Cycle of biopsy		
First biopsy	235	79.4
Second biopsy	59	19.9
Data Not Available	2	0.7

The aim of this study was to explore the epidemiological distribution of glomerular diseases in Sabah in terms of demography, clinical presentations of disease, laboratory parameters, indications for biopsy and final histopathological patterns. We also explored the relationship between prior serum antinuclear antibody (ANA) positivity, pattern and titre with LN

MATERIALS AND METHODS

Study design

This is a retrospective cross-sectional study conducted in a nephrology unit at the Queen Elizabeth Hospital, Sabah, a state tertiary healthcare centre from September to December 2016. The tertiary nephrology centre maintains electronic and hardcopy records of all patients who underwent kidney biopsies under the unit. In this study, we reviewed the clinical case note records and local electronic database to review existing clinical and biopsy records of patients'. Relevant information was extracted and recorded into standardized data collection form (hardcopy) by the researchers. Thereafter, data was transcribed into an electronic database (Excel) for compilation which later was used as master copy dataset for analysis in statistical packages.

Study population

The study population comprised of patients residing in Sabah who underwent kidney biopsies in the nephrology unit of the centre from 1st January 2013 to 30th June 2016. The inclusion criteria were all patients who underwent the renal biopsies within the selected time period; aged ≥12 years at the time of biopsy and has ≥8 glomeruli on biopsy samples. The exclusion criteria were renal transplant patients undergoing graft kidney biopsies and patients in whom demographic data was indeterminate, whose age was not available based on available identification documents.

Study variables

The age of each patient was calculated from the date of birth to the date of biopsy. The patient's ethnicity was recorded. The subject's clinical presentation was recorded and categorised into diabetic versus non-diabetic, and normotensive versus hypertensive. Patients with blood pressure >140/90mmHg at time of biopsy were categorised as hypertensive.

Laboratory parameters that were examined include the following:

1. Renal function as measured by serum creatinine (µmol/L) at the time of biopsy, and categorised into "Normal creatinine" (for normal range), "Abnormal serum creatinine" (>80µmol/L in female; >100µmol/L in male) not requiring dialysis and "Severely impaired" creatinine requiring dialysis.
2. Hepatitis B infection status (positivity as measured by HBsAg).
3. Hepatitis C infection status (positivity as measured by anti-HCV antibody).

Table II: Patients' laboratory parameters before biopsy procedure (N=296)

Laboratory parameters before biopsy	n	%
Diabetic status		
Not diabetic	278	93.9
Diabetic	18	6.1
Blood pressure (BP)		
Hypertensive (BP>140/90)	137	46.3
Normotensive (BP<140/90)	104	35.1
Data not available	55	18.6
Serum creatinine		
Normal	107	36.1
Abnormal(>80µmol/L in ladies, >100µmol/L in men)	147	49.7
Severely impaired	29	9.8
Data not available	13	4.4
ANA status		
Positive	140	47.3
Negative	128	43.2
Data not available	28	9.5
ANA pattern		
ANA negative	128	43.2
Homogenous	42	14.2
Speckled	48	16.2
Nucleolar	1	0.3
Mixed pattern	11	3.7
ANA positive, but pattern data is not available	38	12.8
ANA data not available	28	9.5
ANA titre		
Negative	128	43.2
1 in 40-160	14	4.7
1 in 320	14	4.7
1 in 640	21	7.1
1 in 1280 and above	56	18.9
Data not available	28	9.5
ANA positive but data not available	35	11.8
Hepatitis B status		
Negative	279	94.3
Positive	17	5.7
Hepatitis C status		
Negative	294	99.3
Positive	2	0.7
HIV serology (ELISA) status		
Negative	296	100
Positive	0	0

4. Human immunodeficiency virus (HIV) infection status (positivity as measured by ELISA).
5. Antinuclear antibody status (positive versus negative, ANA patterns and titres).

The final histopathological diagnosis was recorded as per the validated pathologist's report and any missing or untraceable data was categorized as 'Data not available'.

Statistical analysis

Descriptive statistical analysis was used to describe all the study variables. Factors associated with histopathological lupus diagnosis were explored using simple logistic regression. A value of $p<0.05$ is considered statistically significant. Likelihood ratio test was used for antinuclear antibody test performance. All data gathered was analysed using SPSS version 20.

RESULTS

Patients' characteristics

A total of 336 native renal biopsies were performed in 296 eligible patients. The overall mean age during biopsy was 34.53 years (Standard Deviation, SD 0.759). Majority were females (71.3%, 211), of Kadazans/Dusuns ethnicity (37.5%, 111) and those undergone only one renal biopsy procedure (79.4%, 235). Characteristics of patients are summarised in Table I.

Patients' laboratory parameters and histopathological findings

Prior to biopsy, 46.3% (137) of the patients presented with hypertension (BP>140/90mmHg) and 49.7% (147) were with abnormal serum creatinine (>80µmol/L in female, >100µmol/L in male). Majority of the renal biopsies were performed on non-diabetic patients (93.9%, 278). In all 47.3% (140) were found to have positive ANA. Among those with ANA positive, the majority were speckled pattern (16.2%, 48) followed by homogenous (14.2%, 42) pattern. Laboratory parameters of patient before biopsy is summarised in Table II.

Majority of the renal biopsies with positive ANA were in high titre. There were 18.9% (56) with ANA titre 1 in 1280 and above. Unfortunately, there were 9.5% of ANA status data (28) not available for analysis. We found that the majority of renal biopsies performed have negative Hep B Ag (94.3%,

Table III: Distribution of glomerulonephritis classification based on the main histopathological findings (N=296)

Classification of glomerulonephritis and histological types	n	%
Primary glomerulonephritis (n=126, 42.6%)		
Minimal change Ds	49	38.90
FSGS	42	33.30
IgA Nephropathy	18	14.30
Membranous Nephropathy	11	8.70
Membranoproliferative GN	2	1.60
Minor glomerular changes, inconclusive HPE diagnosis	2	1.60
Misc/Others	2	1.60
Secondary glomerulonephritis (n=156, 52.7%)		
Lupus Nephritis	136	87.20
Post infectious GN	9	5.80
Diabetic nephropathy	8	5.10
Misc/Others	3	1.90
Tubulointerstitial Disease (n=3, 1.0%)		
Interstitial Nephritis	3	100.0
Vascular nephropathy (n=1, 0.3%)		
Hypertensive nephropathy	1	100.0
Others (n=10, 3.4%)		
Advance/Global glomerulosclerosis,actual diagnosis not determined	8	80.0
Others	2	20.0

Table IV: Factors associated with histopathological lupus diagnosis (using simple logistic regression)

Variable	Odds Ratio	95%CI	p-valuea
Age (year)	0.978	0.960, 0.996	0.013
Age groups (years old)			0.008
12-19	7.500	1.469, 38.28	0.015
20-39	8.094	1.806, 36.284	0.006
40-59	6.140	1.318, 28.592	0.021
>60	1.00		
Gender			
Female	17.53	7.710, 39.856	<0.001
Male	1.00		
Prior clinical presentation			<0.001
Significant proteinuria	132.0	15.267, 1141.27	<0.001b
Proteinuria	1.750	0.209, 14.629	0.605b
Nephritic picture	1.833	0.145, 23.153	0.639b
Mixed nephritic & nephrotic	2.973	0.342, 25.154	0.342b
Unexplained AKI	1.00		
Creatinine at biopsy			0.004
Severely impaired	0.368	0.156, 0.866	0.022b
Abnormal creatinine	0.455	0.274, 0.756	0.002b
Normal creatinine	1.00		
ANA positivity			
Positive ANA	46.722	22.31, 97.848	<0.001
Negative ANA	1.00		
ANA patterns			0.018
Speckled	0.232	0.070, 0.767	0.017b
Nucleolar/ Mixed pattern	1.158	0.900, 11.454	0.900b
Homogenous	1.00		
ANA titre			
High titre	0.281	0.137, 1.784	0.299
Low titre	1.00		

a Likelihood Ratio (LR) test
b Wald test
95%CI – 95% Confidence Intervals

279). Only two biopsies were found to have positive hepatitis C antibody. During this study, we did not encounter any biopsy with positive HIV serology. (Table II).

More common than PGN, biopsy-confirmed SGN accounted for 52.7% (156) of all the renal diseases. PGN accounted for 42.6% (126) of all the renal diseases confirmed through biopsies (Table III).

The commonest histological diagnosis contributing to PGN is minimal change disease (38.9%, 49) followed by focal segmental glomerulosclerosis (FSGS) (33.3%, 42), IgA nephropathy (14.3%, 18) and membranous nephropathy (8.7%, 11) (Table III).

LN is the leading cause for SGN (87.2%, 136), followed by post-infectious GN (5.8%, 9), diabetic nephropathy (5.1%, 8) and others (1.9%, 3) (Table III).

Exploration of factors associated with histopathology LN diagnosis
We found that younger age (Odds Ratio, OR 0.978; 95% Confidence Interval, 95%CI 0.960, 0.996), and females (OR17.53; 95%CI 7.710, 39.856), significant proteinuria (OR132.0; 95%CI 15.267, 1141.27), creatinine level at biopsy (COR 1.26; p=0.004), positive ANA result (OR46.7; 95%CI 22.31, 97.848), and ANA patterns (OR 8.038; p=0.018) were found to be significant factors in predicting the odds of having LN diagnosis. (Table IV).

DISCUSSION

According to the MRRB, majority of the Malaysian patients with native renal biopsies were females (59.5%) compared to males (40.5%).[4] In Sabah, there are similar findings with majority of the patients being females (71.3%, 211). This was probably attributed to the higher number of females amongst patients diagnosed with LN. MRRB also listed that minimal change disease (32%) was the leading cause of PGN in Malaysian adults, followed by FSGS (29%) and IgA nephropathy (22%).[4] The commonest SGN in Malaysia was LN (80%).[4] In general, the spectrum of glomerular diseases from 2013 to 2016 in Sabah was similar to the finding in MRRB 2012.

According to ACR guidelines ANA is one of the qualifying immunologic criteria in systemic lupus erythematosus.[6,7] However, it was known that up to 5% of patients with SLE may be seronegative in clinical practice, thus its absence does not rule out the disease.[8] It was suggested that modern standard test may not be able detect autoantibodies which indeed contribute to the formation of immune complexes.[8,9] In our study, a histopathological diagnosis of LN was detected among 12 patients who tested negative for ANA. Thereafter, we interpreted that serum ANA test has 90.62% sensitivity and only 82.86% specificity in diagnosing LN. This was the first state-wide and robust review of epidemiological distribution and histopathological pattern of native kidney biopsies in Sabah. We have provided the description of glomerular disease burden in Sabah by exploring its demography, clinical presentations of disease, laboratory parameters, indications for biopsy and also quantifying its prevalence.

The outcome of our study represents the most recent clinical presentation and spectrum of glomerular disease in North Borneo. We also provided the odds of having LN and thus promoting early detection and prompt treatment to improve the outcome of renal involvement. This study showed a marked improvement in 5-year survival from 44 to 95% over the past 50 years when prompt diagnosis and treatment was given.[10]

However, our findings were limited by some of the detailed information such as blood pressure at time of biopsy, albumin, ANA pattern and titre that were not available, This could lead to an underestimation of the clinical presentation glomerular disease. Due to this cross-sectional study design, we were unable to measure the incidence of glomerular disease in Sabah. Also biopsies were not performed in all ESRF patients during the study period.

The MRRB classified the patient population studied merely into a four ethnic groups namely Malay, Chinese, Indian, Others.[4] Various national registries and studies have shown that the distribution of glomerular diseases vary with ethnicity as much as it does with age.[11-15] The state of Sabah differs very much from peninsular Malaysia in terms of population demographics and is composed of no less than 42 ethnic groups and 200 sub-ethnic groups.[16] Indeed, with a population so diverse it is reasonable to state that the data in MRRB may not be applicable to the North Borneo.

In general, the commonest biopsy-confirmed renal disease identified in this study was LN (45.9%, 136). LN is the leading cause for SGN (87.2%, 136). However, International Diabetes Federation (IDF) showed that the prevalence diabetes in Malaysia is above average when compared all regions in the world.[17] In all 61% of new dialysis patients in Malaysia had primary renal disease due to diabetes mellitus.[5] Therefore, diabetic nephropathy may likely be the commonest SGN rather than LN if the option of renal biopsy was offered to all diabetic patients with nephrotic range proteinuria. In our study, LN patients are predominantly females. Nonetheless, study showed that males have more commonly SLE that has renal involvement as compared to females.[18]

A previous study showed that significant predictors for LN were Hispanic (odds ratio, OR 2.71, p=0.04) and African-American ethnicities (OR 3.13, p=0.02), not married or living together (OR 3.45, p=0.0003), higher Systemic Lupus Activity Measure Index (SLAM) score (OR 1.11, p=0.007), anti-dsDNA (OR 3.14, p< 0.0001) and anti-RNP antibodies (OR 4.24, p<0.0001). In comparison, we have found that parameters predictive of LN are younger age, female gender, significant proteinuria, normal creatinine level at biopsy, positive ANA, and homogenous patterns.[20]

The predominance of SGN and LN in particular is important to justify a lower threshold for renal biopsy in patients with suspected glomerular disorders. We encourage early referrals and frequent follow up for SLE patients with predicted risk factors of developing LN. Further studies are needed to assess if seronegative LN responded to SLE pharmacotherapy or eventually seroconverted.

ANA-negative LN pose a significant challenge to prompt diagnosis and treatment. The finding of ANA-negative LN warrants further investigation to observe if these patients eventually develop extra renal SLE manifestations or responded to SLE pharmacotherapy. Our results emphasize the need for further study. If a patient is highly suspected of LN, he/she should be treated promptly and appropriately with close monitoring.

CONCLUSION

The causes of glomerular disorders in the population of Sabah are generally consistent with the national data on glomerular disorders available in the Malaysian MRRB. Diabetic nephropathy may likely be the commonest SGN rather than LN if the option of renal biopsy was offered to all diabetic patients with nephrotic range proteinuria. Parameters predictive of LN include younger age, female gender, significant proteinuria in renal-affecting systemic disease, creatinine level at biopsy, positive ANA result, and ANA patterns. ANA serology is regardless as a screening test for SLE. However, seronegative SLE may present in clinical practice and its absence doesn't rule out the disease. The predominance of LN is important to justify a lower threshold for renal biopsy in patients with suspected glomerular disorders.

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CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

ETHICAL APPROVAL

This study received ethical clearance from Medical Research Ethics Committee (MREC), Ministry of Health on the 9th August 2016. MREC reference number: (05) KKM/NIHSEC/P16-1214.

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