TIMING AND PREDICTIVE FACTORS TO DEVELOP CHRONIC KIDNEY DISEASE IN CHILDREN WITH IDIOPATHIC NEPHROTIC SYNDROME

BY:

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DISSERTATION SUBMITTED IN PARTIAL FULLFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF THE MASTER OF MEDICINE (PAEDIATRICS)

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CHAPTER I:
PRELIMINARIES

ACKNOWLEDGEMENT

Alhamdulillah. All praise to Allah SWT for blessing me with the passion, courage and strength to finish this dissertation. It was an ardous task, but a meaningful experience.

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Last but not least, my sincere appreciation to my family and friends for continuous support, unwavering sacrifice and understanding throughout the thesis preparation and my journey as post graduate master student in Paediatrics.

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Figure .1: Kaplan Meier plots for time to renal survival in children with SSNS and SRNS.

LIST OF ABBREVIATIONS AND NOMENCLATURE

AKI	: Acute kidney injury
CAPD	: Continuous ambulatory peritoneal dialysis
CKD	: Chronic kidney disease
ESRD	: End-stage renal disease
FRNS	: Frequent relapse nephrotic syndromes
FSGS	: Focal segmental glomerulosclerosis
INS	: Idiopathic nephrotic syndromes
KDIGO	: Kidney Disease Improving Global Outcomes
MCD	: Minimal change disease
MPGN	: Membranoproliferative glomerulonephritis
SDNS	: Steroid dependent nephrotic syndromes
SRNS	: Steroid resistant nephrotic syndromes
SSNS	: Steroid sensitive nephrotic syndromes

ABSTRAK

Pengenalan: Sindrom nefrotik idiopatik adalah jenis sindrom nefrotik yang paling lazim dikalangan kanak-kanak. Sebahagian besar pesakit akan pulih sepenuhnya. Walaubagaimanapun, sebahagian kecil akan mendapat masalah buah pinggang yang kronik. Kami menyiasat median jangkahayat buah pinggang dan faktor-faktor yang menyumbang kearah terjadinya masalah buah pinggang kronik dikalangan kanak-kanak ini.

Kaedah: Kaedah semakan rekod secara retrospektif digunakan untuk mendapatkan maklumat berkenaan ciri-ciri klinikal, biokemikal dan histologi bagi kanak-kanak yang menghidapi sindrom nefrotik idiopatik yang berusia 12 bulan sehingga 18 tahun ketika didiagnos, semenjak tahun 2001 sehingga 2016 di Hospital Universiti Sains Malaysia. Tempoh median jangkahayat buah pinggang sehingga terjadinya masalah buah pinggang kronik tahap III atau lebih ditentukan dengan menggunakan keluk analisa Kaplan-Meier. Cox regresi berbilang digunakan untuk mengenalpasti faktor terjadinya masalah buah pinggang kronik.

Keputusan: Sejumlah 112 subjek (lelaki = 71, perempuan = 41) dianalisa dan majority adalah sensitif kepada steroid. Sepuluh peratus mendapat masalah buah pinggang kronik Tempoh jangkahayat median buah pinggang bagi jenis sindrom nefrotik kerintangan steroid adalah 13 tahun. Fokal segmental glomerulosclerosis adalah jenis paling banyak dikalangan jenis kerintangan steroid. Faktor- faktor yang menyumbang kearah kejadian masalah buah pinggang kronik adalah jenis kerintangan steroid (HR: 23.8, 95%CI 2.8-200.9) dan darah tinggi pada permulaan (HR: 8.1, 95% CI 1.2-55.7).

Kesimpulan: Tempoh median jangkahayat buah pinggang adalah bersamaan dengan analisa yang lain. Jenis kerintangan steroid dan darah tinggi pada permulaan adalah faktor-faktor utama terjadinya masalah buah pinggang kronik dikalangan subjek kami.

Kata kunci: sindrom nefrotik idiopatik; kanak-kanak; masalah buah pinggan kronik; tempoh jangkahayat median buah pinggang; sindrom nefrotik kerintangan steroid

ABSTRACT

Introduction: Idiopathic nephrotic syndrome (INS) is the commonest type of nephrotic syndrome in children and majority has favourable outcomes. A small proportion of INS would progress to chronic kidney disease (CKD). We investigated the timing and predictive factors associated with progression of CKD in this children.

Methods: A retrospective record review was used to investigate the demographic variables, biochemical and histological changes in children with INS aged 12 months to 18 years old from 2001-2016 in Hospital Universiti Sains Malaysia (Hospital USM). The median renal survival time to progress to CKD III or higher was determined using survival curve analysis. Multiple cox regression was used to identify predictive factors related to outcomes to CKD.

Results: The total of subjects were 112 enrolled (male =71, female= 41) and majority was steroid sensitive type. Ten percents of INS progressed to CKD III or higher. The median renal survival time in steroid-resistance nephrotic syndromes (SRNS) was 13 years. Focal segmental glomerulosclerosis (FSGS) was predominant in SRNS type. The predictors to progression to CKD were steroid-resistance type (adjusted HR: 23.8, 95% CI 2.8- 200.9) and the presence of hypertension at presentation (adjusted HR: 8.1, 95% CI 1.2- 55.7).

Conclusion: The median renal survival time was comparable to other studies but SRNS type and the presence of hypertension at presentation were the main predictors to develop CKD in our population.

Key words: idiopathic nephrotic syndrome; children; chronic kidney disease; median survival time; steroid-resistance nephrotic syndrome

CHAPTER II:

THE TEXT

Section A: Introduction

1. INTRODUCTION

Idiopathic Nephrotic syndrome (INS) has been recognized as one of the most frequent glomerular disease in childhood with the worldwide incidence of 2-7/100 000 children below 16 years old, and the prevalence of 16/100 000[1]. Most children with INS had favourable outcomes as only small percentage progress to chronic kidney disease (CKD). Eighty to ninety percent of children with INS are steroid sensitive whereas the remaining 10-20% is steroid-resistance. Fifty to sixty percent of steroid resistance nephrotic syndrome (SRNS) progress to CKD[2] with median renal survival time 14 years, as compared to 28 years in steroid sensitive type[3]. The prevalence of CKD was approximately 3-10% [3-5] in other studies.

Apart from resistance to steroid therapy, there are other clinical, biochemical and histological changes that is associated with progression to CKD. In two separates cohort done in Taiwan[4] and Brazil[3], older age is a significant risk towards progression of CKD especially after the age 10 years old[2]. Presence of systemic hypertension and hypertensive encephalopathy[4], acute kidney injury (AKI)[6] and microscopic haematuria [3] were also a poor predictive factor in other studies. The histopathological findings of focal segmental glomeruloscerosis (FSGS) carries a poor prognostic as up to 64% will progress to ESRD[5].

Now researchers are looking at the genetic basis of INS to determine the renal outcomes. Genetic study were not available to all in our country, hence not a reliable method to determine the outcome of children with INS. Regional data were also insufficient. Previous study in Malaysia were looking at the histological findings of patient with renal disease[7] specifically adults in Kelantan[8] and children in Johor[9]. However none of them looking at the overall prevalence, long term outcome, and its correlation with CKD. The study was aim to provide the local data of children with INS

in Hospital Universiti Sains Malaysia (Hospital USM). We also would like to determine the median renal survival time and perhaps would be able to identify early those at the highest risk of progression to CKD, thus an early intervention could be done.

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Section B:

Study protocol

B (I): Documents submitted for ethical approval

RENAL SURVIVAL AND OUTCOMES OF CHILDREN AND ADOLESCENT WITH IDIOPATHIC NEPHROTIC SYNDROME IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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P-UM0052/13

THESIS PROPOSAL

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2017

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Dissertation Research Proposal

TITLE: Renal Survival and Outcome of children and adolescent with idiopathic nephrotic syndrome in Hospital Universiti Sains Malaysia

1. INTRODUCTION

1.1 Background and literature review

Nephrotic syndrome (NS) has been recognized as one of the most frequent glomerular disease in childhood with the worldwide incidence of 2-7/100 000 children below 16 years old, and the prevalence of 16/100 000 (Skrzypczyk, Panzyk-Tomaszewska et al, 2014). They are at risk of life threatening complications such as peritonitis, venous thrombosis and hypovolemic shock.

The overall renal survival in Taiwan was 97% at 5 years, and 95% at 10 years. (Chang, Tsai et al, 2012) which is comparable to another study done by Mendonca et al in Brazil. She predicted that 6% may progress to CKD by 5 years, and 8% by 10 years. The long term outcome of nephrotic syndrome is poorer in steroid resistant group compared to steroid sensitive group with median survival of 14 years in former groups, and 28 years in later group.

Risk factor towards progression to CKD among patient with NS

1.1.1. Age

Children who have NS at earlier age (beyond 1 year old) may have better outcome and lesser chance to developed CKD. In 2 separates cohort done in Taiwan and Brazil, older age is a significant risk towards progression of CKD (HR 1.15; 95% CI 1.12-1.21)(Chang, Tsai et al. 2012), (HR 1.25; 95% CI 1.15- 1.37) (Mendonça, Oliveira et al. 2015) especially after the age 10 years old (Mekahli, Liutkus et al, 2009). This could be attributed by the higher prevalence of minimal change disease (MCD) in younger children as compared to higher incidence of focal segmental glomeruslosclerosis (FSGS) in older child (Tavares, de Oliviera, 2013).

1.1.2. Gender

Male gender is more common affected by INS by 1.7- 1.9 but this does not predict the outcome of disease (Chang, Tsai et al, 2012), (Mendonca, Oliviera et al, 2015).

1.1.3. Hypertension

Presence of systemic hypertension and hypertensive encephalopathy among patient with NS increase the risk towards progression to CKD (Mendonca. Oliviera et al, 2015), (Chang, Tsai et al, 2012), (Fomina, Pavlenko et al, 2010). Hypertension in nephrotic syndrome occurs due to sodium and water retention secondary to activation of renin- angiotensin- aldosterone- system (RAAS) or intrinsic renal defect of sodium excretion (Ray, Rondon- Berrios et al, 2015).

1.1.4. Haematuria

Initial haematuria as a predictor towards to CKD in NS is not consistent. Mendonca et al found out that the presence of hematuria at presentation significantly increase the risk to develop CKD (HR 1.25; 95 % CI 2.5- 11.4) (Mendonca. Oliviera et al, 2015), while others was unable to find its significance (Chang, Tsai et al, 2012), (Mekahli, Liutkus et al, 2009), (Fomina, Pavlenko et al, 2010).

1.1.5. Acute kidney injury (AKI)

Initial AKI does significantly increase the risk of progression to CKD (Mekahli, Liutkus et al, 2009), (Fomina, Pavlenko et al, 2010), (Mendonca. Oliviera et al, 2015). However in other study done in Taiwan, the findings are contradictory as most causes of AKI are reversible (Chang, Tsai et al, 2012), such as hypovolemia, sepsis and thrombosis.

1.1.6. Focal segmental glomerulosclerosis (FSGS)

The histopathological findings of FSGS was significantly increased the risk for CKD (HR 6.12; 95% CI 2.50-14.9; $p < 0.001$) (Mendonca, Oliviera et al, 2015), as early as 3-5 years (Chang, Tsai et al. 2012), and later 35-64% will progress to ESRD by 10 year (Tavares, de Oliviera et al, 2013). The main pathogenesis is progressive sclerosis that occurs in glomeruli. These changes triggers an overexpression of vasoactive factors and cytokines, that will leads to further glomerular scarring and damages. Upon comparing children with SRNS, 58% of those with FSGS as opposed to only 4.9% of those with Minimal change disease (MCD) progress to ESRD. Persistent proteinuria is a poor prognostic factor among adults with FSGS (HR 11.45; 95% CI 3.11- 42.1) (Tang, Xu et

al, 2013), and worst among children (HR 23.2; 95% CI 5.43- 100.3) (Mendonca, Oliviera et al, 2015).

1.1.7. Steroid-resistant nephrotic syndrome (SRNS)

About half of the patient with SRNS is at risk of end-stage renal disease in 5 years if they did not achieve remission (KDIGO, 2012). with the risk of progression to end-stage renal disease (ESRD) is reaching up to 50% (Mekahli, Liutkus et al, 2009). The survival rate of SRNS at 5 years is 75%, at 10 years is 58% and at 15 years is 53%. (Mekahli, Liutkus et al, 2009).

1.2 Problem statement

Children and adolescence are commonly being diagnosed in our clinical practice with NS. There are many studies done looking at the long term outcome of NS but data in Malaysia, especially Kelantan is limited. Previous studies in Malaysia were looking at the histological findings of patient with renal disease (Prathap, Looi et al, 1983) specifically adults in Kelantan (Zainal, Riduan et al, 1995) and children in Johor (Khoo, Pee et al, 2004). However none of them looking at the overall prevalence, long term outcome, and its correlation with CKD. Recently in 2005 the National Kidney Foundation (NKF) had developed Malaysia Renal Registry Biopsy (MRRB) to aid in data collection of patient with renal disease in Malaysia. However it has limited data among children with NS. To date this will be the first retrospective record review looking at the demographic characteristics, clinical features, specific laboratory investigation and the outcomes of children and adolescence diagnosed with NS in Hospital USM.

1.2. Justification of the study

1.2.1. The study aim to provide the local data of children with nephrotic syndrome (NS) in HUSM.

1.2.2. To determine the renal survival for children and adolescence with NS in Hospital USM.

2. OBJECTIVE

2.1 General objective:

To study the renal outcomes and risk factors associated with shorter renal survival time and among children and adolescence with nephrotic syndrome in Hospital USM

2.2 Specific objectives

2.2.1 To estimate the renal survival time of children and adolescents with NS

2.2.2 To determine the associated risk factors (clinical and laboratory features) that may contribute to renal survival

2.2.3 To study the renal outcomes of children and adolescents with NS

2.3 Research questions

2.3.1 What are the baseline characteristics, clinical presentation and treatment response among children and adolescence with nephrotic syndrome in Hospital USM?

2.3.2 What is the renal survival time among children and adolescents with nephrotic syndrome in Hospital USM?

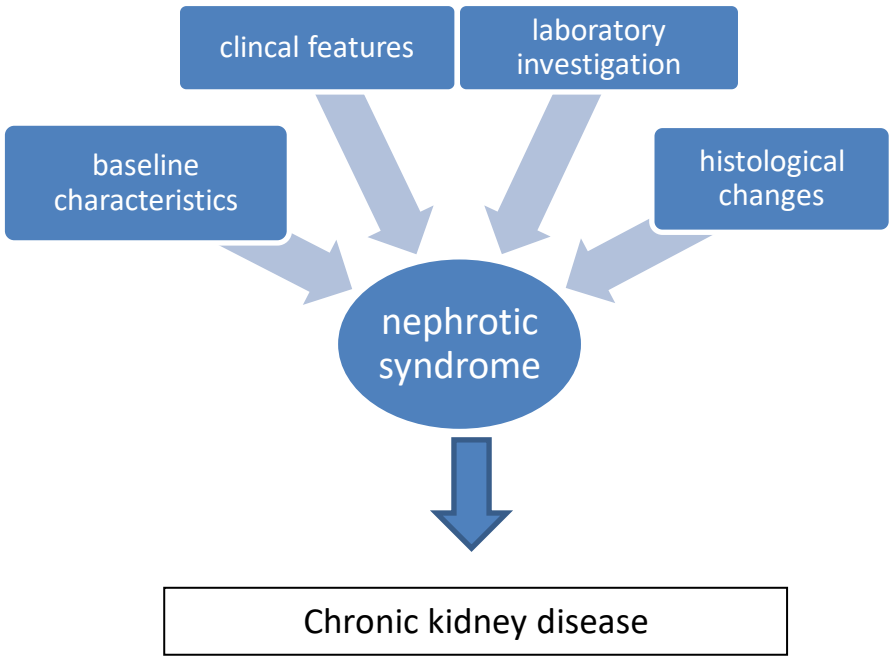
2.3.3 What are the risk factors of the renal survival time among children and adolescents with nephrotic syndrome in Hospital USM?

2.4 Research hypothesis

2.4.1 The renal survival time is comparable to other study

2.4.2 Presence of studied risk factors that will influence the renal survival time

2.5 Conceptual frameworks



3. METHODOLOGY

3.1 Study design:

The study is as retrospective record review study.

3.2 Study period:

This study will be conducted from October 2016- June 2017

3.3 Study location:

This study will done at paediatric nephrology clinic Hospital USM, Kubang Kerian

3.4 Reference population:

The reference population are children and adolescence patients diagnosed with NS in Malaysia

3.5 Source population:

The source population are children and adolescents patients diagnosed with NS in Kelantan

3.6 Sampling frame:

The sampling frames are children and adolescence patients diagnosed with NS in Hospital University Sains Malaysia

3.7 Study sample

The study samples are children and adolescence patients diagnosed with NS in Hospital University Sains Malaysia who fulfilled inclusion and exclusion criteria.

3.8 Study population

The study samples are children and adolescents patients diagnosed with NS in Hospital University Sains Malaysia who fulfilled inclusion and exclusion criteria, and consented to participate in study.

3.9 Inclusion and exclusion criteria

3.9.1 Inclusion criteria:

3.9.1.1 All children diagnosed with NS in paediatric clinic HUSM from 2000- 2015

3.9.1.2 Age 1 year to 18 years old

3.9.2 Exclusion criteria

3.9.2.1 Children with infantile & secondary nephrotic syndrome.

3.9.2.2 Those with missing or untraceable record

3.10 Sample size determination

The sample size is calculated based on associated risk factor towards renal survival time, using power sample (PS) software:

$\alpha = 0.05$; power = 0.8, m1 = 26 years (3)

A= 10 years; F = 5 years

3.10.1 Factor: steroid resistant nephrotic syndrome (SR NS)

R = 36.3; m = 2.1 (3)

N = 63 experimental + 132 control + 39 loss = 234

3.10.2 Factor: hematuria

R = 5.3; m1 = 2.4 (3)

N = 49 experimental + 118 control + 33 loss = 200

3.10.3 Factor: FSGS

R = 6.12; m = 1.6 (3)

N = 54 experimental + 86 control + 28 loss = 188

3.11 Sampling methods

No sampling method applied for the study. All children who fulfilled the inclusion and exclusion will be recruited as the calculated sample size required is more than the available sample size.

3.12 Research tool

Patient's case study record consisting of demographic data, diagnostic criteria of NS at the time of presentation, other clinical manifestations at the time of diagnosis, laboratory investigations at the time of diagnosis, renal biopsy details, medications given with their total duration as well as other management modalities such as dialysis.

3.13 Data collection

Patient with NS will be identified during sampling frame from admission book in 6s from and clinic referral form 2000-2015. A list of patients will be printed and sent to record office for folder tracing. Patient's record will be reviewed and only those who fulfilled inclusion and exclusion criteria will be included in the study.

All relevant data were obtained, included

3.13.1 Clinical & laboratory features at presentation, including the age, gender, race, presence of hypertension, presence of macroscopic or microscopic hematuria, and renal impairment

3.13.2 Current age, weight, height

3.13.3 Histological finding (if performed)

3.13.4 Steroid response e.g steroid sensitive and steroid resistant

3.14 Definition of operational terms

3.14.1 Nephrotic syndrome: is a clinical syndrome of oedema, proteinuria defined as urine protein: creatinine ratio (uPCR) ≥ 2000mg/g or 200mg/mmol or 300mg/dl or urine protein 3+ on dipstick, hypoalbuminemia define as serum albumin ≤ 2.5g/dL or ≤ 25g/L (10).

3.14.2 Steroid resistant NS: failure to achieve remission after 8 weeks of prednisolone 2mg/kg/day or 4 weeks of prednisolone 60mg/m^2/d followed by 1.5mg/kg/d or 40mg/m^2 alternate dose for 4 weeks (10).

3.14.3 **Steroid dependent NS**: > 2 consecutive relapse occurring during corticosteroid therapy or within 14 days of ceasing of therapy (10)

3.14.4 **Relapse**: uPCR ≥ 200mg/g or ≥ 200mg/mmol or ≥ 3+ urine protein on dipstick for 3 consecutive days (10)

3.14.5 **Remission**: uPCR < 200mg/g or < 20mg/mmol or < 1+ on dipstick for 3 consecutive days (10).

3.14.6 **Frequent relapse NS**: 2 or more relapse within 6 months of initial response; or 4 or more relapse in any 12-months period (10)

3.14.7 **Hypertension**: BP > 95th centile for age, weight & height for more than 3 consecutive reading. (11)

3.14.8 **Pre- hypertension**: BP 90th-95th centile for age, weight & height (11)

3.14.9 **Macroscopic hematuria**: presence of gross red blood cells (RBC) in urine (12)

3.14.10 **Microscopic hematuria**: presence of more than 2 rbc per high power field (hpf) (12)

3.14.11 **Chronic kidney disease**: abnormalities of kidney structure or function for more than 3 months with implication of health. Criteria of CKD: (13)

Criteria for CKD (either of the following present for >3 months)

Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 hours; ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a-G5)

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥ 90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	< 15	Kidney failure

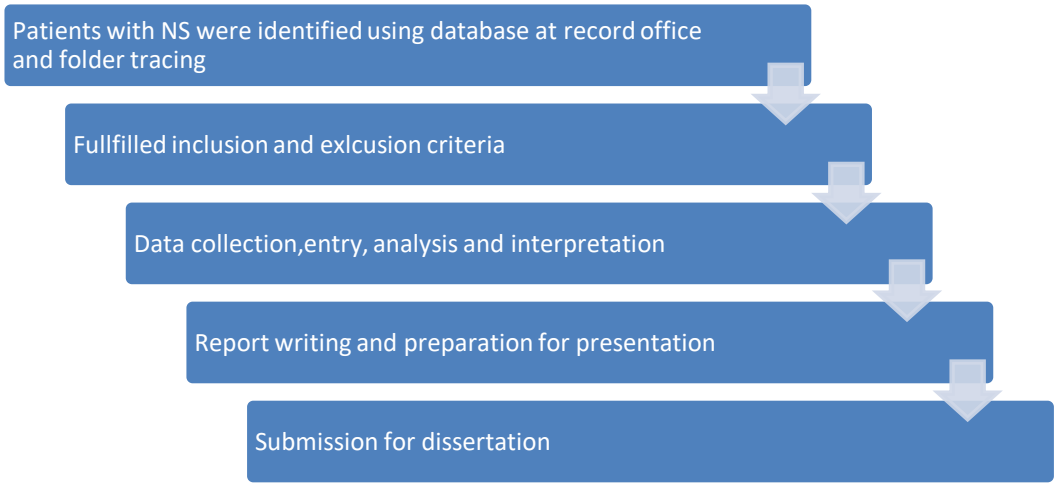
Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

**Estimated glomerular filtration rate (eGFR) < 60ml/mt is considered significant as at it is associated with complications such as altered drug excretion, impaired exocrine and metabolic function of kidney, as well as higher risk of cardiovascular disease & death (13)

eGFR will be calculated based on Schwartz formula: (13)

$$GFR = \frac{k \times height\ (cm)}{S.\ Creatinine\ (mg/dL)}$$

3.15 Study Flow chart



3.16 Intended statistical analysis

The data will be processed and analyzed using IBM SPSS Statistics version 20. Numerical data will be presented as mean and standard deviation (Mean, SD) 0r median and interquartile range (Median 25^{th}, 75^{th}) depending on distribution. The categorical data is expressed as number and percentage.

The endpoint is the occurrence of chronic kidney disease (CKD). Renal survival was measured from the date of diagnosis to the date of last estimated eGFR meeting criteria of CKD. Median survival time will be determined using Kaplan-Meir regression. Potential variables will be examined against the endpoint by univariate analysis using log rank test, and multivariate analysis with Cox proportional hazards. P value of less than 0.05 will be considered significant.

3.17 4.Ethical issue

This study will be conducted in concordance with Declaration of Helsinki and follows Malaysian Good Clinical Practice (GCP) Guidelines. Ethical clearance will be obtained from Research Ethics Committee. Personal information will be safeguarded to ensure confidentiality. The risk of to the safety or health of participants of the study is very minimal.

All forms are anonymous using code number and will be entered into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually. A separate list of names, registration number with code number will be kept by the researcher in a locked cabinet.

EXPECTED RESULTS

4.1 Descriptive statistics

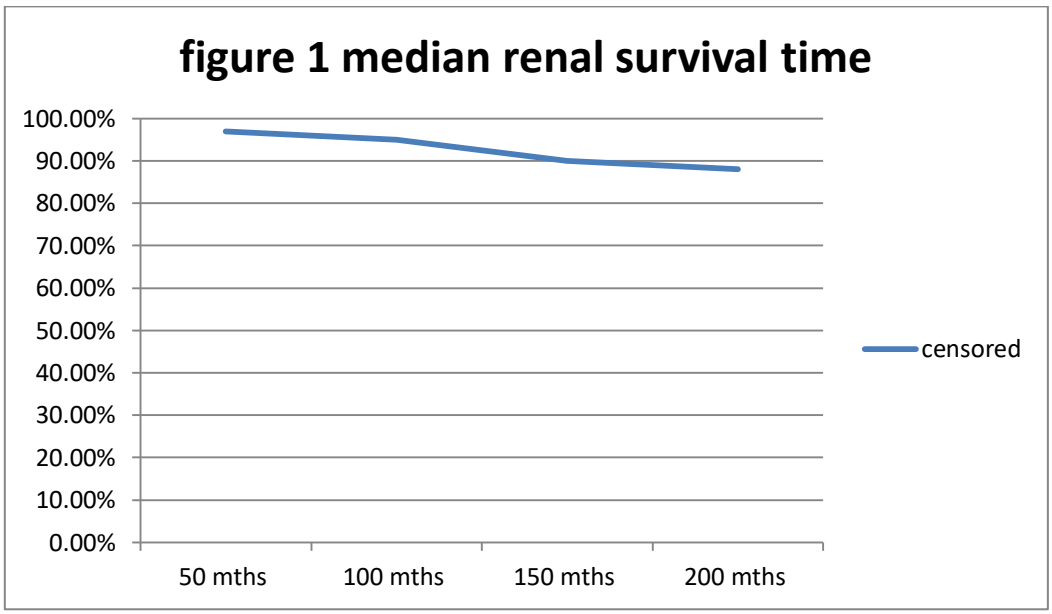


Fig. 2 Renal survival according to age at diagnosis

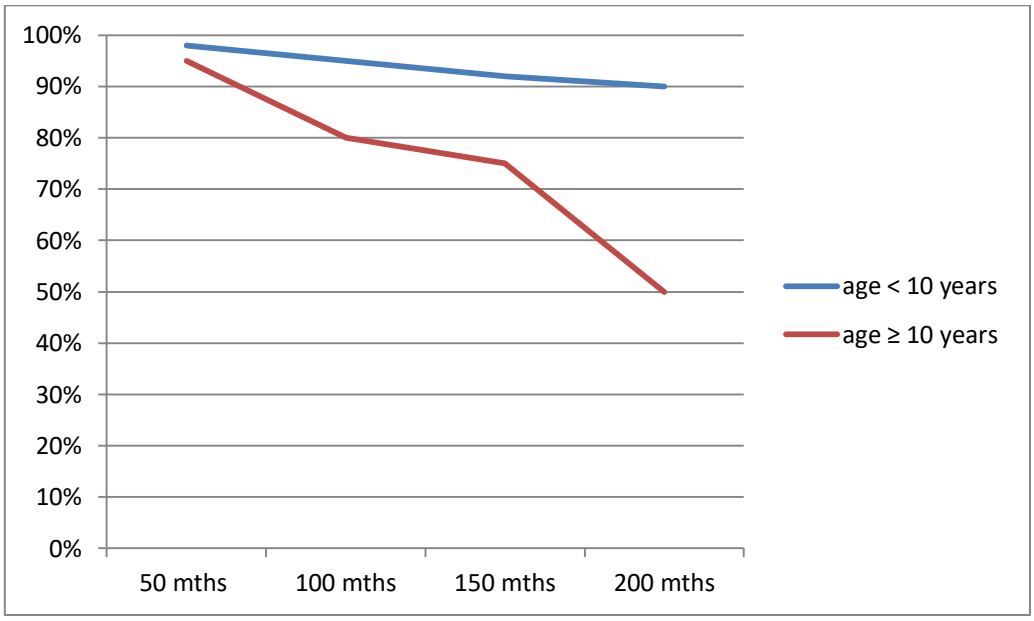


Fig. 3 Renal survival according to steroid response

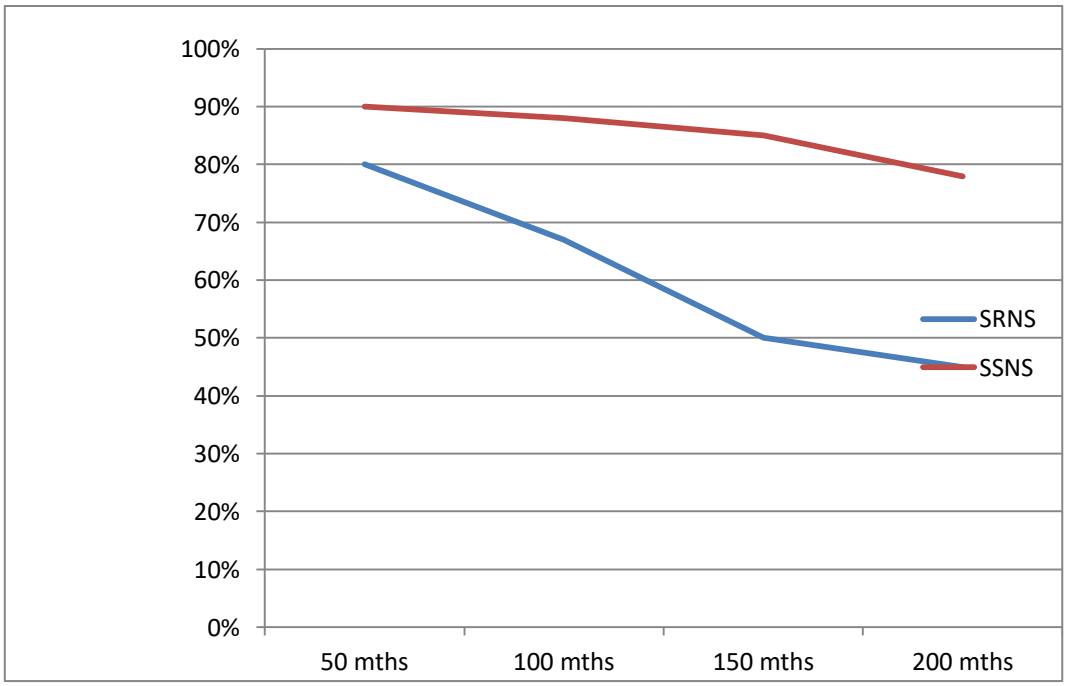
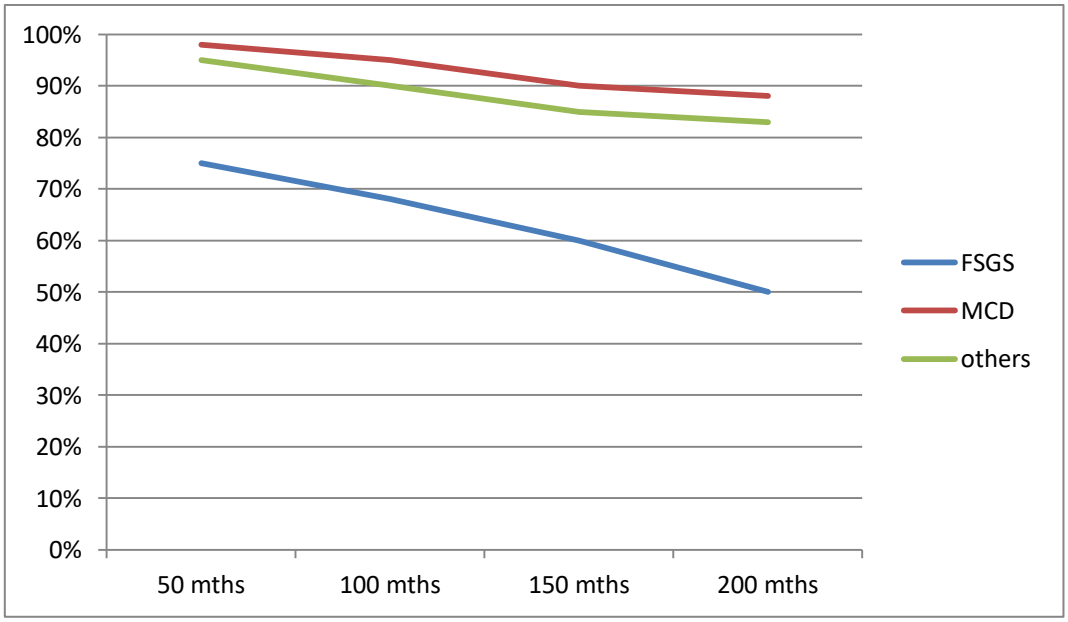


Fig. 4 Renal survival according to histological changes



4.2 Inferential statistics:

median survival time

		mean				median	
		95% CI				95% CI	
estimate	std error	lower bound	upper bound	estimate	std error	lower bound	upper bound

log rank test for categorical variables

age <10 years old and >

10 years old

	chi-square	df	sig.
log rank (Mantel-cox)			

hematuria (absence or presence)

	chi-square	df	sig.
log rank (Mantel-cox)			