RENAL OUTCOMES AND PREDICTORS IN SPINA BIFIDA CHILDREN: 10 YEARS REVIEW IN TWO TERTIARY HOSPITALS

DR. NUR FARHANA BINTI SODDRI

DISSERTATION SUBMITTED IN PARTIAL
FULFILLMENT OF THE REQUIREMENTS FOR
THE DEGREE OF MASTER OF MEDICINE
(PAEDIATRICS)

UNIVERSITI SAINS MALAYSIA
2022

CHAPTER I:

THE PRELIMINARIES

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ACKNOWLEDGEMENT

First and foremost, praises and thanks to Allah, the Almighty, for His showers of blessings until I manage to complete my research.

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LIST OF TABLES AND FIGURES

ABBREVIATIONS AND NOMENCLATURE

USM	: Universiti Sains Malaysia
HUSM	: Hospital Universiti Sains Malaysia
HSB	: Hospital Sultanah Bahiyah
SB	: Spina Bifida
eGFR	: Estimated Glomerular Filtration Rate
CKD	: Chronic Kidney Disease
CIC	: Clean Intermittent Catheterization
UTI	: Urinary Tract Infection
VUR	: Vesicoureteral Reflux
BPL	: Bipolar Length
US KUB	: Ultrasonography of Kidney, Ureter and Bladder
MCUG	: Micturating Cystourethrogram
DMSA	: Dimercaptosuccinic Acid
SPSS	: Statistical Package for Social Sciences

ABSTRAK

Pengenalan: Tujuan semakan rekod secara retrospektif ini adalah untuk mengkaji kesan jangka masa panjang fungsi ginjal dan mengenal pasti faktor-faktor kegagalan fungsi ginjal dikalangan pesakit yang menghidap penyakit spina bifida (SB).

Kaedah: Semakan rekod retrospektif selama 10 tahun telah dijalankan melibatkan pesakit kanak-kanak berumur sejak lahir sehingga 18 tahun, yang menghidap penyakit SB. Data asas termasuk jenis SB, aras kecacatan tulang belakang, kesan sampingan neurologi (inkontinasi pundi kencing, usus, keboleh upayaan bergerak), fungsi buah pinggang dan pengimejan (ultrasound, MCUG, DMSA) telah didokumenkan. Analisis deskriptif telah dilaksanakan untuk ciri-ciri sosio-demografi, analisis 'univariable' telah dijalankan untuk menyaring pembolehubah bebas, manakala analisis 'multiple logistic regression' digunakan untuk menentukan hubungan di antara factor-faktor utama penyebab ginjal berparut dan kegagalan buah pinggang yang kronik.

Keputusan: Sebanyak 60 orang pesakit yang menghidapi masalah SB, dengan purata umur diantara 11.8±3.8 tahun semasa pengumpulan data telah dipilih di dalam kajian ini. Kebanyakan mereka mengalami masalah tulang belakang dari aras Lumbar 5 dan ke bawah dan majoriti dikalangan mereka masing-masing mempunyai komplikasi inkontinasi pundi kencing dan usus (88.3% dan 93.3%). Walaupun sebahagian besar di kalangan pesakit menjalankan pembuangan air kencing secara aseptic menggunakan tiub kencing, sebanyak dua pertiga daripada mereka masih mengalami masalah jangkitan kuman pada air kencing. Satu pertiga daripada mereka telah mengalami masalah kebengkakan ginjal dan kebengkakan salur ureter yang dapat dikenal pasti semasa imbasan ultrasound dan separuh daripadanya mengalami masalah *vesicoureteral reflux*. Separuh daripada pesakit telah mengalami masalah

kegagalan buah pinggang. Masalah ginjal berparut adalah 8.3 kali lebih tinggi di kalangan perempuan berbanding lelaki (p=0.046). Pesakit yang berumur 13 tahun dan ke atas mempunyai kaitan yang ketara dengan CKD (p=0.038). Kebengkakan ginjal dan salur ureter dikenal pasti sebagai faktor penting untuk pesakit menghidapi masalah kegagalan fungsi ginjal.

Konklusi: Kebengkakan ginjal dan salur ureter adalah faktor-faktor masalah kegagalan fungsi ginjal dikalangann pesakit tiub neural yang dapat dikenal pasti melalui saringan imbasan ultrasound. Jantina perempuan telah dikenal pasti sebagai faktor utama untuk masalah ginjal berparut berbanding lelaki.

Kata kunci- Spina bifida, kebengkakan salur ureter, kebengkakan ginjal, ginjal berparut, kegagalan buah pinggang yang kronik

ABSTRACT

Introduction: Spina bifida (SB) is usually associated with mortality and long-term morbidities specifically renal complications. The purpose of this study is to determine the long-term renal outcomes and their predictors in SB children.

Materials and Methods: A 10-year retrospective record review was conducted involving pediatric patients who were diagnosed with SB. Baseline data including type of SB, level of spinal lesion, neurological sequalae (bladder, bowel incontinence, ability to walk), renal function and imaging findings (ultrasound, MCUG, DMSA) were documented. Descriptive analysis was performed for socio-demographic characteristics. Univariable analysis was conducted to screen independent variables. Multiple logistic regression analysis was used to determine the association between significant predictors for renal scarring and CKD.

Results: A total of sixty SB children with mean age 11.8±3.8 years during data collection were recruited. Most of the lesions were at L5 and below. Majority were complicated with urinary (88.3%) and bowel incontinence (93.3%). Despite majority performed CIC, almost two-third had symptomatic UTI. One-third of them had both hydroureter and hydronephrosis and fifty percent were shown to have vesicoureteric reflux. The odds for developing renal scarring were 8.3 times in female compared to male (p=0.046). Half of the cohort progressed into CKD. The presence of hydroureter and hydronephrosis on ultrasound were identified as the significant factor for development of CKD (OR 3.8; 95%CI 1.239, 11.385).

Conclusion: The presence of hydroureter and hydronephrosis were the predictors for development of CKD whereas female gender is associated with renal scarring.

Keywords – Spina bifida, hydroureter, hydronephrosis, renal scarring, chronic kidney disease

CHAPTER II: THE TEXT

2.1 Section A:

INTRODUCTION

INTRODUCTION

Spina bifida (SB) is a primary neurulation defect caused by the failure of fusion in the caudal region of the neural tube. Majority of the causes are unknown but it has been attributed to the chromosomal abnormalities, single gene disorders, and teratogenic exposures.[1] Inadequate periconceptional folic acid supplementation or dietary sources are also associated with an increased risk of spina bifida.[1,2] The annual incidence of SB in Oman before and after the supplementation and fortification of wheat flour with iron and folate showed 2.3 to 4.0 per 1,000 births between 1991 and 1996 reduce tremendously to 0.29 per 1,000 by 2006.[3]

In the United States, the prevalence of SB among children and adolescents was slightly higher which is around 0.31 cases per 1000 children, with the incidence being lower for males and non-Hispanic, black children.[4] In Malaysia, anencephaly (38.3%) is the most common type of neural tube defects, followed by spina bifida (29.8%) and encephalocoele (17.0%).[5] The prevalence of SB children (SB aperta only) in Malaysia was 0.11 per 1000 live births.[5]

Although SB is usually associated with mortality and long-term morbidities, the recent advancements in medical and surgical therapies have improved the short- and long-term survival of children with SB.[1] Urological consequences caused by a neurogenic bladder include urinary incontinence, recurrent urinary tract infections (UTI), vesicoureteric reflux (VUR), kidney damage, chronic renal failure, and death. [1,6,7] Renal scarring and chronic kidney disease (CKD) are more likely to occur as a result of secondary VUR causing neuropathic bladder. Clean intermittent catheterization (CIC) remains the mainstay in the management of neurogenic bladder among patients with SB.[6,8,9] The purpose of this study is to determine the long-term renal outcomes and identify their predictors in children with SB.

2.2 SECTION B:

STUDY PROTOCOL

2.2.1 DOCUMENTS SUBMITTED

FOR ETHICAL APPROVAL

DISSERTATION PROPOSAL

School of Medical Science
University Science Malaysia
Prepared in partial requirement fulfilment
For the Degree of Master of Medicine (Paediatric)
2018/2022

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Research title: Renal Outcomes and Predictors in Spina Bifida Children: 10 years Review in Two Tertiary Hospitals

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Kelantan

Introduction:

Spina bifida is congenital neural tube defects (NTDs) of the spinal cord that is caused by failure of process of folding and fusion of the embryonic neural plate.(1) Spina bifida can be divided into open and closed defects. Open spinal dysraphism (spina bifida aperta) occurs when the meninges and spinal cord are exposed whereas closed spinal dysraphism (spina bifida occulta) is when neural tissue is not exposed.

The prevalence of NTDs was 0.42 per 1000 live births, being highest among the indigenous people of Sarawak (1.09 per 1000 live births) and lowest among Malaysians of Chinese descent (0.09 per 1000 live births).(2) The most common type of NTDs was anencephaly (n = 54, 38.3%), followed by spina bifida/myelomeningocoele (n = 42, 29.8%), encephalocoele (n = 24, 17.0%) and miscellaneous types (n = 24, 17.0%).(2) In United States, the prevalence of spina bifida among children and adolescents0 to 19 years of age in the study regions was

3.1 cases per 10 000 in 2002.(3) Majority children born with open spina bifida have a neuropathic bladder which may result in urinary incontinence, urinary tract infections, vesicoureteric reflux, renal damage, chronic renal failure and death.(4, 5)

Problem statement & Study rationale

This study is the first study done in the east coast and northern region of Malaysia to determine the predictors for long term renal outcomes among spina bifida children. This study has larger sample size compared to a study done by Kanaheswari *et al.* It ascertain spina bifida children at highest risk of developing long term renal outcomes. Sims-Williams *et al* reported that 64% incidence of renal cortical scarring in spina bifida children in Uganda population. Whereas, Kanaheswari *et al.* stated that 33% of spina bifida children in a multidisciplinary Malaysian centre developed chronic kidney disease. Hence, knowing predictors associated with poor renal outcomes will provide huge input to clinician in particularly to focus and be more specific in the management of spina bifida and reduce these adverse renal outcomes.

Research Question(s)

1. What are the long term renal outcomes in spina bifida children?

2. What are the predictors for poor renal outcomes in spina bifida children?

Objectives

General: To determine the long term renal outcomes in spina bifida children and to identify the predictors for poor renal outcomes in spina bifida children

Specific:

1. To determine the incidence of renal cortical scarring and chronic kidney disease in spina bifida children

2. To identify the association between predictors and poor renal outcomes in spina bifida children

Research Hypothesis

1. There is significant association between predictors and chronic kidney disease in spina bifida children

2. There is significant association between predictors and renal scarring in spina bifida children

Literature review

Renal damage still constitutes the foremost reason for morbidity and mortality in spina bifida children. A pro-active follow-up programme with early conservative treatment showed a high rate of success in preventing renal damage.(6)

A local study done by Kanaheswari et al. determined the occurrence of renal cortical scarring and chronic kidney disease (CKD) in children with neurogenic bladder secondary to spina bifida (SB) managed at the Universiti Kebangsaan Malaysia Medical Centre and identified the clinical factors associated with these adverse outcomes. Fifty six patients were managed from 1997 and found out that sixteen patients developed renal scarring whereas six patients

developed CKD. Late referral (≥6 months of age), small kidneys at referral, dilating VUR and bladder trabeculation were significant independent factors associated with scarring.

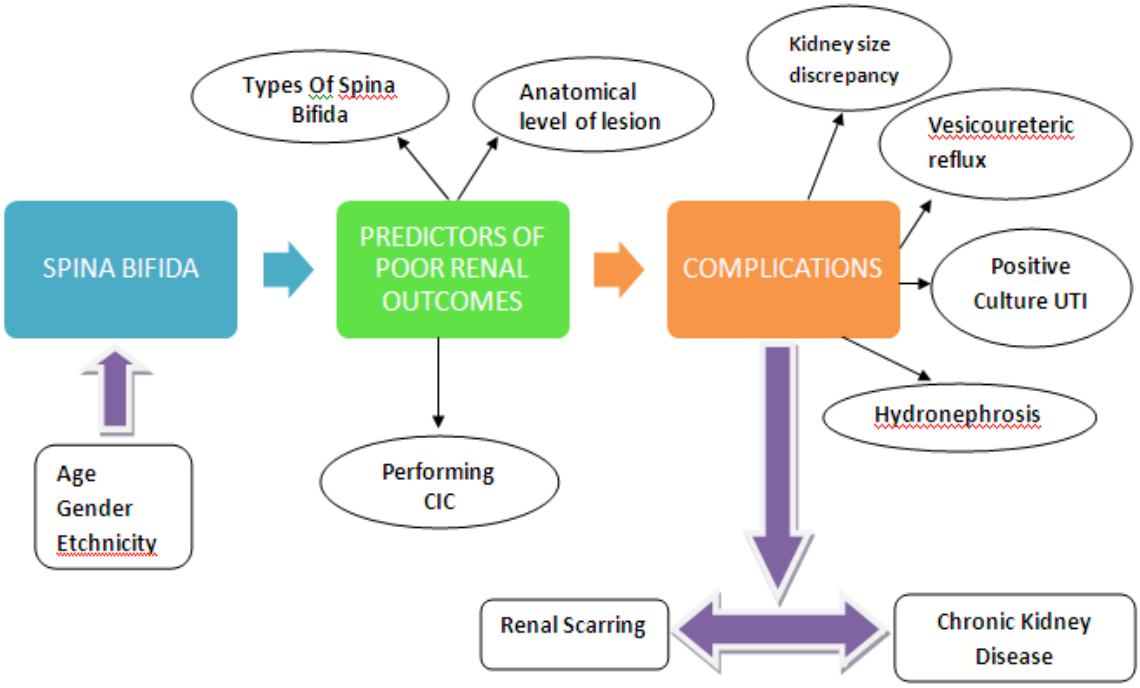
A cross sectional study done by Sims-Williams *et al* described the extent of renal disease in Ugandan children surviving at least ten years after spina bifida repair and to investigate risk factors for renal deterioration in this cohort. One child had elevated creatinine, hydronephrosis in 10 children (15%), scarring in 42 (64%), and >1cm size discrepancy in 28 (43%).

Early intervention to relieve urinary retention in children born with spina bifida is needed in preserving renal function and less incidence of vesicoureteric reflux and urinary tract infection. A retrospective study in 2009, done by Kari, Safdar *et al* investigated the urological complications in spina bifida children who were born and followed up. Patients were divided into Group A and Group B. Only 8 patients (group A) received clean intermittent catheterization (CIC), while the rest (group B) were either non-complaint or did not receive it. Twelve (36%) patients had evidence of renal scars (10 in one kidney and 2 had scars in both kidneys) and one patient progressed to chronic renal failure at 6 years of age (creatinine was 146 μmol/L).

A retrospective study by Johnston *et al.* described the neurourological problems seen at presentation of children with closed spinal defects who were referred to a specialist pediatric neurourology centre over 20 years. At the time of referral, 21 patients had normal ultrasonography of the renal tract, while 14 showed evidence of dilated upper renal tracts, six showed residual volume post micturition, six had thick walled bladders, two had a unilateral small kidney, and one patient had renal scars.

Another study by Wide, Gladh *et al*. showed outcome on renal function in children with neurogenic bladder dysfunction of a standardized follow-up programme. All children had a normal total renal function but 4 of the 41 had a detectable renal damage by renal scintigraphy (MAG3 or DMSA). Two of the children had a borderline GFR on Cr-EDTA-clearance, but in the normal range, while the remaining had normal laboratory results.

Conceptual framework



Methodology

Study Design

- Retrospective record review

Study Period

- Data collection from January 2005 until December 2014

Study Location

- Hospital USM, Kubang Kerian and Hospital Sultanah Bahiyah, Alor Setar

Study Population

Reference population – All paediatric patient with open or close spina bifida

Target population - Paediatric patients who was born in Hospital USM or Hospital Sultanah Bahiyah and those referred from other hospitals at varying ages (at birth until 18 years old). Participants not directly involved.

Subject criteria

Inclusion criteria:

The study will include all pediatric patients who are diagnosed with an occulta or aperta. Patient was born either in Hospital USM or Hospital Sultanah Bahiyah or those referred from other hospitals at varying ages at birth to 18 years old. These patients must be diagnosed between January 2005 and December 2014 and followed up in the respective centres until 2020.

All patients must have ultrasonography of kidney, ureter and bladder (US KUB) and micturating cystourethrogram (MCUG) examinations. Patients with evidence of neurogenic bladder may or may not underwent dimercaptosuccinic acid (DMSA) scans performed as clinically indicated. The first imaging results will be collected in this study.

Exclusion criteria:

Congenital malformation co-existing with spina bifida and patient with inadequate essential data. Essential data include the lack of record for ultrasound kidney findings, renal function during study period and lack of follow up record.

Sample size estimation

Objective 1*:* To determine the long term renal outcomes in spina bifida children with neurogenic bladder. The sample size was calculated using **single proportion formula** based on the study done by Kanaheswari *et al*.

$$n = \frac{Z^2 p(1-p)}{d^2}$$

n = min. required sample

Z = 1.96 (standard value of normal distribution when confidence interval at 95%)

d = precision = 5 %

p = proportion for chronic kidney disease and renal scarring

n = sample size

For renal scarring, p = 0.35, n =349, required sample size is 383 after consideration of 10% missing data.

For chronic kidney disease, p = 0.1, n = 138, required sample size is 152 after consideration of 10% missing data.

Thus, based on sample size calculation, precision $\pm$ 0.05 with 95% confidence interval, sample size required will be 383 after consideration of 10% missing data.

Objective 2: To study the association between predictors and poor renal outcomes in spina bifida children. The sample size was calculated using multiple logistic regression analysis based on the study done by Kanaheswari and Mohd Rizal, 2015.

$$n = \frac{10k}{p}$$

n = min. required sample

k = number of independent variables (predictors)

p = proportion

For renal scarring, p = 0.36, k = 9, n = 250, required sample size is 275 after consideration of 10% missing data.

For chronic kidney disease, p = 0.13, k = 9, n =692, required sample size is 760 after consideration of 10% missing data.

Thus, based on sample size calculation, sample size required will be 760 after consideration of 10% missing data.

Sampling method and subject recruitment

No sampling method is applied. All paediatric patients who was born in Hospital USM or Hospital Sultanah Bahiyah and those referred from other hospitals at varying ages (at birth until 18 years old) will be recruited.

Research Tool

Socio-demographic Porforma and medical Record

Demographic Data

Study	
Age	
Sex	
Race	
Total family income / month	
Weight	
Height	
Primary caregiver	

Study Details

Date of study	
Mobility	□ Able to walk (with or without aid) □ Unable to walk
Types of spina bifida	□ Open □ Close
Anatomical level of lesion	□ L2 and above □ L3-L4 □ L5 and below
Clean Intermittent Catheterisation	□ Yes □ No
Urinary Continence	□ Yes □ No
Bowel Continence	□ Yes □ No
Symptomatic culture positive UTI	□ None documented □ At least one

MCUG finding	□ Normal	□ Abnormal □ VUR grade I-II □ VUR grade III,IV,V □ Others
Renal function status at the point of study	Creatinine GFR	
USG KUB	Kidney BPL Renal involvement Hydronephrosis Hydroureter Renal scarring	☐ RK cm ☐ LK cm □ single ☐ bilateral □ absent ☐left ☐ right □ absent ☐ left ☐ right □ Yes ☐ No
DMSA	□ Done □ Type 1 □ Type 2 □ Type 3 □ Type 4 □ Not Done	

Operational definition

Renal scarring: Areas of focal renal cortical defect associated with defects in the renal outline based on DMSA scan.(9)

DMSA types were classified as type 1: no more than two scars, type 2: more than two scars with some normal parenchyma between them, type 3: generalized damage to the whole kidney and type 4: end stage "shrunken". (20)

Urinary tract infection: Presence of pure bacterial growth of single species more than 10^5 colony-forming units (cfu) per milliliter of urine.(10)

Chronic kidney disease: Renal function is based on glomerular filtration rate, using the creatinine based bedside Schwartz equation.(11)

$$eGFR\ (mL/min/1.73m^2) = k \times height(cm) / serum\ creatinine\ (\mu mol/L)$$

Stages of CKD		GFR
G1	Normal or High	>90
G2	Mildly decreased	60-89
G3a	Mildly to moderately decreased	45–59
G3b	Moderately to severely decreased	30–44
G4	Severely decrease	15–29
G5	Kidney failure	<15

Data collection

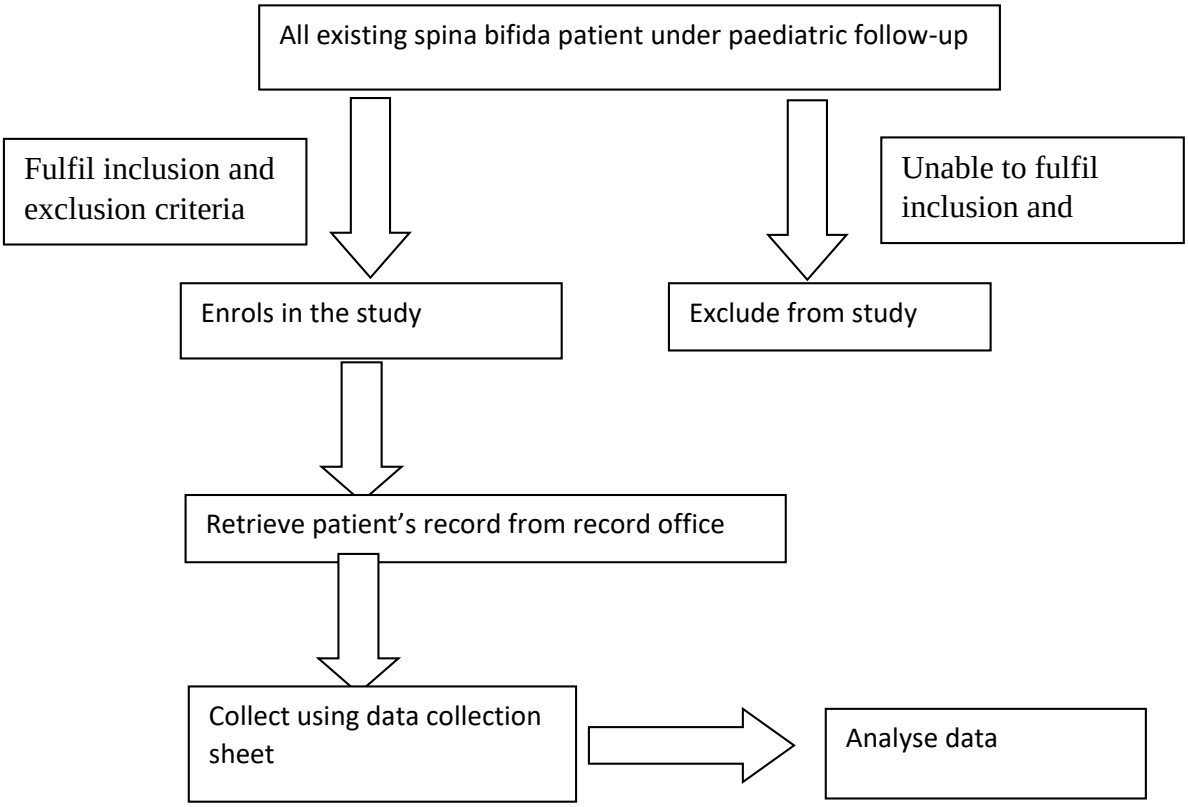
Retrospective record review were collected using a standardised proforma sheet involving all pediatric patients who were diagnosed with close or open spina bifida. Patients involved were either born in Hospital USM or Hospital Sultanah Bahiyah or those referred from other hospitals at varying ages and must be diagnosed in Hospital USM or Hospital Sultanah Bahiyah between January 2005 and December 2014 and under follow up in the respective centres until 2020.

Data collected include age at referral, gender, ethnicity, type of spina bifida lesion, size of spina bifida lesion, anatomical level of lesion, mobility, presence of ventriculoperitoneal shunt, bladder and bowel incontinence, date of initiation of clean intermittent catheterisation and previous symptomatic culture positive urinary tract infection.

All patients must have ultrasonography of kidney, ureter and bladder (US KUB) and micturating cystourethrogram (MCUG) examinations. Patients with evidence of neurogenic bladder may underwent dimercaptosuccinic acid (DMSA) scans performed as clinically indicated. The first imaging results will be collected in this study.

A latest blood samples taken to measure serum creatinine, and the Schwartz formula was applied to access renal function by using estimate glomerular filtration rate (GFR).

Study flowchart



Data analysis

Data will be entered and analysed using Statistical Package for Social Sciences (SPSS) version *22*. Descriptive analysis will be used to summarise the socio-demographic characteristics of subjects. Numerical data will be presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data will be presented as frequency (percentage).

Multiple logistic regression analysis will be used to determine the association between predictors (independent variables) and the presence of renal scarring and chronic kidney disease (dependent variable). Univariable analysis will be conducted first to screen the important independent variables. Predictors that is known clinically importance or significant on univariable analysis (*P*-value < 0.25) were then proceeded with forward stepwise logistic regression model to decide the predictive value (odds ratio) for renal scarring and chronic kidney disease.

Expected result(s)

Table 1: Socio-demographic and specific characteristics of the participants

Characteristics	n(%)
Mean age at assessment (months)	
Gender	
Male	
Female	
Ethnicity	
Malay	
Chinese	
Indian	
Others	
Primary caregiver	
Mother	
Father	
Grandparents	
Other	
Mobility	
Able to walk (with or without aids)	
Unable to walk	
Anatomical level of lesion	
L2 and above	
L3-L4	
L5 and below	
Types of Spina Bifida	
Open spina bifida	
Closed spina bifida	

Table 2: Clinical characteristics of the participants

Characteristics	n(%)
Currently performing clean intermittent catheterisation (CIC)	
Yes	
No	
Urinary Continence	
Dry	
Wet daytime	
Wet day and night	
Bowel Continence	
Yes	
No	
Previous symptomatic culture positive urinary tract infection (UTI)	
None documented	
Atleast one	
Renal scarring on Ultrasound scan	
Yes	
No	
Hydronephrosis on ultrasound scan	
Yes	
No	
Kidney size discrepancy on ultrasound scan	
Less than 1cm 21	
Greater than 1cm	
Vesicoureteric reflux	
None	
Grade I-II	
Grade III, IV, V	

Table 3: Clinical variables associated with renal scaring in patient with spina bifida

Independent variables (value label)	Scarring present (*n*)	*P*-value	Odds ratio	95% CI
Gender				
Male (0)				
Female (1)				
Age referred				
Before 6 months (0				
After 6 months (1)				
Kidney size discrepancy				
No (0)				
Yes (1)				
Vesicoureteric reflux				
None (0)				
Grade I-II (1)				
Grade III, IV, V (2)				
Currently performing CIC				
No (0)				
Yes (1)				
Symptomatic culture positive UTI				
No (0)				
Yes (1)				
Urinary Continence				
Dry (0)				
Wet daytime (1)				
Wet day and night (2)				
Bowel Continence				
Yes (0)				
No (1)				

Table 4: Predictors of chronic kidney disease

Variables associated with chronic kidney disease	P value	Odd ratio	95% CI
Gender			
Male (0)			
Female (1)			
Age referred			
Before 6 months (0			
After 6 months (1)			
Kidney size discrepancy			
No (0)			
Yes (1)			
Vesicoureteric reflux			
None (0)			
Grade I-II (1)			
Grade III, IV, V (2)			
Currently performing CIC			
No (0)			
Yes (1)			
Symptomatic culture positive UTI			
No (0)			
Yes (1)			
Urinary Continence			
Dry (0)			
Wet daytime (1)			
Wet day and night (2)			
Bowel Continence			
Yes (0)			
No (1)			

Gantt chart & milestone

Project activities		2020			2021								
Months	9	10	11	12	1	2	3	4	5	6	7	8	9
Research Activities													
Data collection													
Data Analysis/Interpretation													
Presentation/Submission													
Report Writing													
Thesis submission													

Budget proposal [If applicable]:

Not applicable

Ethical consideration(s) [if applicable]:

1. **Subject vulnerability**

a) The subject is a patient under my care as a doctor. However, the patient will be given full freedom to take part or not without affecting his/her medical condition management and care.

b) The subject is my subordinate in my entity of management. The data will be independent and will not be used for any achievement assessment and decision related to work.

2. **Declaration of absence of conflict of interest**

There is absence of conflict of interest between researcher and participants in this study

3. Privacy and confidentiality

Subject's name should be kept on a password-protected database and will be linked only with a study identification number for this research. The identification number instead of patient identifiers will be used on subject data sheets. All data will be entered into SPSS software that is password protected. On completion of this study, data in the computer will be copied to CDs and the data in the computer erased. CDs and any hardcopy data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The CDs and data will be destroyed after that period of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database.

4. Community sensitivities and benefits

This study will benefits the community in determining the importance of the clean intermittent catheterisation (CIC) in spina bifida children. There is minimal risk from the investigational product and study procedures. Study findings shall potentially greatly improve treatment outcomes. The expected benefit outweighs the minimal risk to subjects and thus this study should be supported.

5. Publication Policy

No personal information will be disclosed and subjects will not be identified when the findings of the survey are published

6. Honorarium and incentives

NIL

7. Collaborative study terms of reference

There is no authorship and IP between all researchers beforehand.

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