CLINICAL PROFILES AND OUTCOMES OF RENAL SCARRING IN CHILDREN UNDERWENT DIMERCAPTOSUCCINIC ACID RENAL SCAN IN A TERTIARY HOSPITAL

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

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CHAPTER 1:

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PRELIMINARIES

Acknowledgement

Firstly, thanks to GOD ALMIGHTY for his bestowed upon the strength and good health in order to complete this research. I would like to express my sincere gratitude to Dr Mohamad Ikram Ilias for his expertise, assistance, guidance and patience throughout the process of this thesis becomes a reality. I would like to thank Dr Syed Ejaz Shamim and Associate Professor Dr Azriani Berahim @ Ab. Rahman for their advice and contribution for this thesis. I am highly indebted to my fellow lecturers, colleagues, supporting staffs, friends and family for the encouragement and supports along the walks.

LIST OF TABLES AND FIGURES

LIST OF ABBREBIATION AND NOMENCLATURE

Hospital USM :	Hospital Universiti Sains Malaysia
HRPZII	Hospital Raja Perempuan Zainab II
DMSA	Dimercaptosuccinic Acid
UTI	Urinary tract infection
VUR	Vesico-ureteric reflux
CAKUT	Congenital abnormality of kidney and urinary tract
CKD	Chronic kidney disease

ABSTRACT

Title

Clinical Profiles and Outcomes of Renal scarring in Children Underwent Dimercaptosuccinic acid (DMSA) Renal scan in a Tertiary Hospital.

Background: DMSA renal scan is universally applied to detect renal scarring. It is a known cause for hypertension and proteinuria and may progressed into chronic kidney disease (CKD). We reviewed the proportion of renal scarring and looking at their risk factors and its outcomes in all children that were referred for DMSA renal scan at tertiary centre hospital.

Methodology: All records of children less than 18 years old that were referred for DMSA renal scan over ten years period were reviewed. Among children whose renal cortical defects were confirmed by DMSA scan, data of their risk factors and its outcome were collected manually.

Results: Out of 92 children referred for DMSA renal scan, forty-eight of them were shown to have renal scarring of which more than 50% of them had underlying vesico-ureteric reflux (VUR). More than half had recurrent urinary tract infections (UTIs) of non-*Escherichia coli* organisms. The most common complication was CKD, of which majority were stage 3 with median duration of one year after detection

of renal scarring. Six children (12.5%) developed hypertension with median age of 10.5 years and median duration of one year after diagnosis of renal scarring was demonstrated.

Conclusion: DMSA renal scan is recommended to be performed in children with VUR to detect scarring as its long term complications such as hypertension and CKD have been demonstrated to occur as early as one year after diagnosis. Hence, early diagnosis and treatment of the underlying problem is crucial.

Keywords: renal scarring, recurrent urinary tract infections, vesico-ureteric reflux, Dimercaptosuccinic acid renal scan, congenital abnormality of kidney and urinary tract, chronic kidney disease

ABSTRAK

Tajuk

Profil Klinikal dan Komplikasi Parut Buah Pinggang di Kalangan Kanak-Kanak yang Menjalani Imbasan 'Dimercaptosuccinic acid' (DMSA) di Pusat Rujukan Tertiari.

Latar belakang: Imbasan DMSA digunakan secara universal bagi mengesan parut buah pinggang. Parut buah pinggang merupakan faktor komplikasi seperti darah tinggi, peningkatan paras protein dalam air kencing seterusnya kegagalan buah pinggang. Kami mengkaji pengkadaran parut buah pinggang dan melihat faktor risiko serta komplikasinya terhadap kanak-kanak yang telah dirujuk untuk imbasan DMSA di hospital tertiari.

Kaedah: Ini merupakan kajian rentas yang melihat data klinikal bagi kanak-kanak yang menjalani imbasan DMSA dalam tempoh masa 10 tahun. Di kalangan kanak-kanak yang mengalami parut buah pinggang, siasatan susulan mengenai faktor risiko dan komplikasinya direkodkan secara manual.

Keputusan: Dari 92 jumlah kanak-kanak yang dirujuk untuk menjalani imbasan DMSA, empat puluh lapan daripada mereka dikesan menghidap parut buah pinggang di mana lebih dari 50% daripada mereka mengalami masalah refluks vesikoureter. Lebih separuh daripada mereka mengalami jangkitan saluran kencing berulang disebabkan organisma selain *Escherichia coli*. Komplikasi utama yang

berlaku adalah kegagalan buah pinggang di mana kebanyakan daripada mereka dikesan mengalami kegagalan buah pinggang tahap 3, dengan jangka masa setahun selepas parut buah pinggang dikenal pasti. Enam orang kanak-kanak (12.5%) menghidap darah tinggi pada median umur 10.5 tahun dengan median jangka masa setahun selepas parut buah pinggang dikesan.

Kesimpulan: Imbasan DMSA disyorkan di kalangan kanak-kanak yang mengalami masalah refluks vesikoureter bagi mengesan parut buah pinggang memandangkan komplikasi seperti darah tinggi dan kegagalan buah pinggang dikesan seawal setahun selepas parut buah pinggang dikenalpasti. Maka, pengesanan awal penyakit dan rawatan awal adalah penting.

Kata kunci: parut buah pinggang, jangkitan saluran kencing berulang, refluks vesikoureter, ketidaknormalan buah pinggang dan saluran kencing kongenital, kegagalan buah pinggang

CHAPTER II:

THE TEXT

2.1 Section A:

Introduction

Introduction

Renal scarring is an established cause for hypertension and proteinuria in which some may progress into chronic kidney disease (CKD). [1,2] Dimercaptosuccinic acid (DMSA) renal scan has been universally applied to detect renal scarring, either focal or global, by assessing uptake of the radioisotope and at the same time to determine the relative function of kidneys. [3,4]

Various risk factors for the development of renal scarring have been identified, such as male gender, increasing grade of vesicoureteral reflux (VUR), recurrent urinary tract infections (UTIs), and older onset of first diagnosis. [5,6] Congenital anomaly of kidney and urinary tract (CAKUT) which include VUR, horseshoe kidney, duplex kidney, or any obstruction over pelvi-ureteric or vesicoureteric junction can lead to further deterioration of renal function in children.[6]

Hypertension can be manifested 8 years after detection of renal scarring and affected approximately 30% of children with renal scars formation.[7] Nevertheless, there are limited studies on looking at the time taken to develop CKD after diagnosis of renal scarring in children.

A study by Kim et al revealed that 41% of children with acute pyelonephritis developed renal scarring on DMSA follow-up scans which were performed 6 months after the last UTIs.[1] The cohort demonstrated that children aged more than 12 months old had 5.8 times greater influence on renal cortical defects while high-grade VUR (grade IV onwards) had a 14.7 times higher incidence rate on renal scar formation. Similar findings were demonstrated by Park et al in which they found that the formation of renal scar was highly significant in infants with increasing severity of VUR.[7]

A meta-analysis by Shaikh et al in which 9 studies were included with a total number of 1,280 children concluded that children and adolescents with the combination of high fever (≥39°C) and abnormal renal ultrasonography, and recurrent UTIs of non-*Escherichia coli* organisms were at higher risk of developing renal cortical defects.[8]

This study aimed to determine the proportion of renal scarring and looking at their risk factors and outcomes in all children that were referred for DMSA renal scan at a tertiary centre hospital.

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)
2017/2021

CLINICAL PROFILES AND OUTCOMES OF RENAL SCARRING IN CHILDREN UNDERWENT DIMERCAPTOSUCCINIC ACID RENAL SCAN IN A TERTIARY HOSPITAL

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Hospital USM, Kubang Kerian, Kelantan
Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

Supervisor:
Dr Mohamad Ikram Ilias (Co-investigator)
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Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan

Research title: Clinical Profiles and Outcomes of Renal Scarring in Children Underwent Dimercaptosuccinic acid Renal Scan in a Tertiary Hospital

Principal investigator (MMC No.): Dr Nordiyana binti Azmi (MMC 48036)
Co-researchers : Dr Mohamad Ikram Bin Ilias (MMC 40439)
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Introduction

Renal scarring is an established cause for hypertension and proteinuria in which some may progress into chronic kidney disease (CKD). [1,2] Dimercaptosuccinic acid (DMSA) renal scan has been universally applied to detect renal scarring, either focal or global, by assessing uptake of the radioisotope and at the same time to determine the relative excretory function of kidneys. [3,4]

Various risk factors for the development of renal scarring have been identified, such as male gender, increasing grade of vesicoureteral reflux (VUR), recurrent urinary tract infections (UTI), and older onset of first diagnosis.[5,6] Congenital anomaly of kidney and urinary tract (CAKUT) which include VUR, horseshoe kidney, duplex kidney, or any obstruction over pelvi-ureteric or vesicoureteric junction can lead to further deterioration of renal function in children.[6]

Hypertension can be manifested up to 8 years from detection of renal scarring and affected approximately 30% of children with renal scars formation.[7] Nevertheless, there are limited studies on looking at the time taken to develop CKD after diagnosis of renal scarring in children.

The aim of this study was to determine the proportion of renal scarring and looking at their risk factors and its outcomes in all children that were referred for DMSA renal scan at tertiary centre hospital.

Problem statement & Study rationale

This research intended to provide local data looking for various causes, contributing factors and outcome of renal scarring. By analyzing the result, these findings may help for early identification of children at risk for renal scarring, therefore more aggressive follow up (eg antibiotic prophylaxis, imaging) may prevent renal scarring and its outcome.

Research Question(s)

1) What is the proportion of children with renal scarring?
2) What are the risk factors of renal scarring and its association with renal scarring in children?
3) What are the outcomes of renal scarring in children?
4) What are the association between risk factors with outcomes of renal scarring in children?

Objectives

General:

To determine the proportion, risk factors and outcome of renal scarring among children at tertiary centre, Kelantan

Specific:

1) To determine the proportion of renal scarring among children underwent DMSA renal scan in Kelantan

2) To determine association between risk factors and development of renal scarring

3) To describe the outcomes of renal scarring in children

4) To determine the association between risk factors and outcome of renal scarring

Literature review

A study by Kim et al regarding Prognostic Factors of renal Scarring on Follow Up DMSA Scan in Children with Acute Pyelonephritis was published in 2016. They recruited 59 participants admitted at Daegu Fatima Hospital for first febrile urinary tract infection from March 2008 to April 2015 and follow up was performed within 6 months after the last urinary tract infection with cortical defects were confirmed by using DMSA scans. The study revealed that 41% of children with acute pyelonephritis showed cortical defects on follow up DMSA scan. The cohort demonstrated that children aged more than 12 months old had 5.8 times higher incidence rate of renal scarring while high grade VUR (grade IV onwards) had 14.7 times greater influence on renal scar formation. Similar findings were demonstrated by Park et al in which they found the rate of renal scar formation was significantly higher in infants with increasing severity of VUR.

A meta-analysis by Shaikh et al in which 9 studies were included with total number of 1,280 children concluded that children and adolescents with an abnormal renal

ultrasonographic or with a combination of high fever (≥39°C), and etiological organism other than *Escherichia coli*, were at high risk for the development of renal scarring.

Another study regarding risk factors for renal scarring was done by Mei Ju Chen, Hong-Lin Cheng and Yuan Yow Chiou from National Cheng Kung Univeristy, Taiwan that was published in 2013. They conducted a study regarding Risk Factors for Renal Scarring and Deterioration of Renal Function in Primary Vesicoureteral Reflux Children. A total of 173 patients with primary vesicoureteral reflux (VUR) admitted to the National Cheng Kung University Hospital were recruited in 15 years period from 1994 to 2009 and retrospectively analysed. It was found that older age of VUR diagnosis (> 5 years) (p value < 0.049), higher grade of VUR (grade IV-V) (p value < 0.0001), more than 2 episodes of urinary tract infections (p value <0.039) were risk factors for renal scarring, whereas a younger age of VUR diagnosis (<1 year) (p value < 0.002), renal scarring (p value= 0.013) and acute pyelonephritis (p value = 0.0041) were risk factors for developing chronic kidney disease stage 2 or higher. The proportion of patients with hypertension was particularly high for those who had bilateral low (23.8%) and high (33.3%) grade VUR.

Another study conducted by Yeong Seo Park from University of Ulsan College of Medicine, Seoul, Korea regarding Renal Scar Formation after Urinary Tract infection in Children and the study was published in 2012. The study concludes that the rate of scar formation was significantly higher in infants with vesicoureteral reflux (39.4%) than in those without vesicoureteral reflux. (p value < 0.001). Severity of vesicoureteral reflux was significantly associated with the risk of permanent renal damage. 40% of children with VUR grade III, 70% of children with VUR grade IV and 55.6% children with VUR grade V had persistent renal scarring.

Research design

This was a cross-sectional study conducted in Hospital USM, Kubang Kerian which is a tertiary centre located at east coast peninsular Malaysia. All records of children less than 18 years old that were referred for DMSA renal scan beginning from the 1st January 2008 until 31st December 2019 were reviewed. The medical records retrieved were reviewed retrospectively and follow up records reviewed by using data collection sheet containing patient's information and determinants. Among children whose renal cortical defects were confirmed by DMSA scan, data of their risk factors and its outcome were collected.

Study area

Tertiary centre in Kelantan

1) Hospital Universiti Sains Malaysia Kubang Kerian

2) Hospital Raja Perempuan Zainab II, Kota Bharu

Study population

Reference population

Children diagnosed with renal scarring at tertiary centre in Kelantan

Source population / sampling pool

Children underwent DMSA renal scan at Hospital HUSM from 1st January 2008 – 31st December 2019

Subject criteria

Inclusion criteria

Children less than 18 years' old who has been under Hospital USM or Hospital Raja Perempuan Zainab II follow up

Exclusion criteria

1) Records with inadequate crucial data include missing data and lack of follow up records

2) Outcomes occur after end of study period

Sample size estimation

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

n = min. required sample

Z = value of standard normal distribution = 1.96

d = precision = 7%

p =

n =

<u>Sample Size Calculation for Objective Number 1:</u>

n = min. required sample

Z = value of standard normal distribution = 1.96

d = precision

p =

n =

Reference: Sample not calculated because no information or study regarding this objective available

Sample Size Calculation For Objective Number 2:

n = min. required sample

Z = value of standard normal distribution = 1.96

d = precision = 7%

p = 15.5%

Reference: Nader Shaikh et al (2014) Identification of Children and Adolescents at Risk for Renal Scarring After a First Urinary Tract Infections: A Meta-analysis with Individual Patient Data: JAMA Pediatric

n = 103

Considering 10% non-response, minimum required sample is 103 + 10 = 113

Sample Size Calculation for Objective Number 3:

n = min. required sample

Z = value of standard normal distribution = 1.96

d = precision = 5%

p = 10%

Reference: Young Seo Park (2012) Renal Scar Formation after Urinary Tract Infection in Children, Korean Pediatric Society

n = 139

Considering 10% non-response, minimum required sample is 139 + 14 = 153

Sample Size Calculation for Objective Number 4:

n = min. required sample

Z = value of standard normal distribution = 1.96

d = precision

p =

n =

Reference: Sample not calculated because no information or study regarding this objective available

Sampling method and subject recruitment

All eligible children that fulfilled inclusion criteria will be included and recruited in this study

Research tool

Data will be collected using sociodemographic porforma and medical record

Operational definition

i.Renal scarring: Presence of photopenia (decreased uptake of isotopes) detected on Dimercaptosuccinic acid renal scan (DMSA) with or without change of renal contour

(Identification of Children and Adolescents at Risk for Renal Scarring, Nader Shaikh, 2014)

ii.Urinary Tract Infections: Clinical features with bacteriuria and abnormal urine analysis. The diagnosis was confirmed by proven positive urine culture test of >105 cfu/ml.

(NICE.Urinary tract infection in under 16s Diagnosis and management. Natl Inst Heal Care Excell. 2007)

iii.Vesico-Ureteric Reflux: Retrograde passage of urine from bladder into ureter. Grading is based on MCUG scan.

(Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Mobius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol 1985)

iv. Hypertension**:** Hypertension is defined as systolic BP and/or diastolic BP that is greater than or equal to the 95th percentile for gender, age and height on three or more occasions

(National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics)

v. Chronic Kidney Disease**:** Abnormalities of kidney structure or function, present for more than 3 months. CKD is classified based on Cause, GFR category (G1-G5).

(KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014)

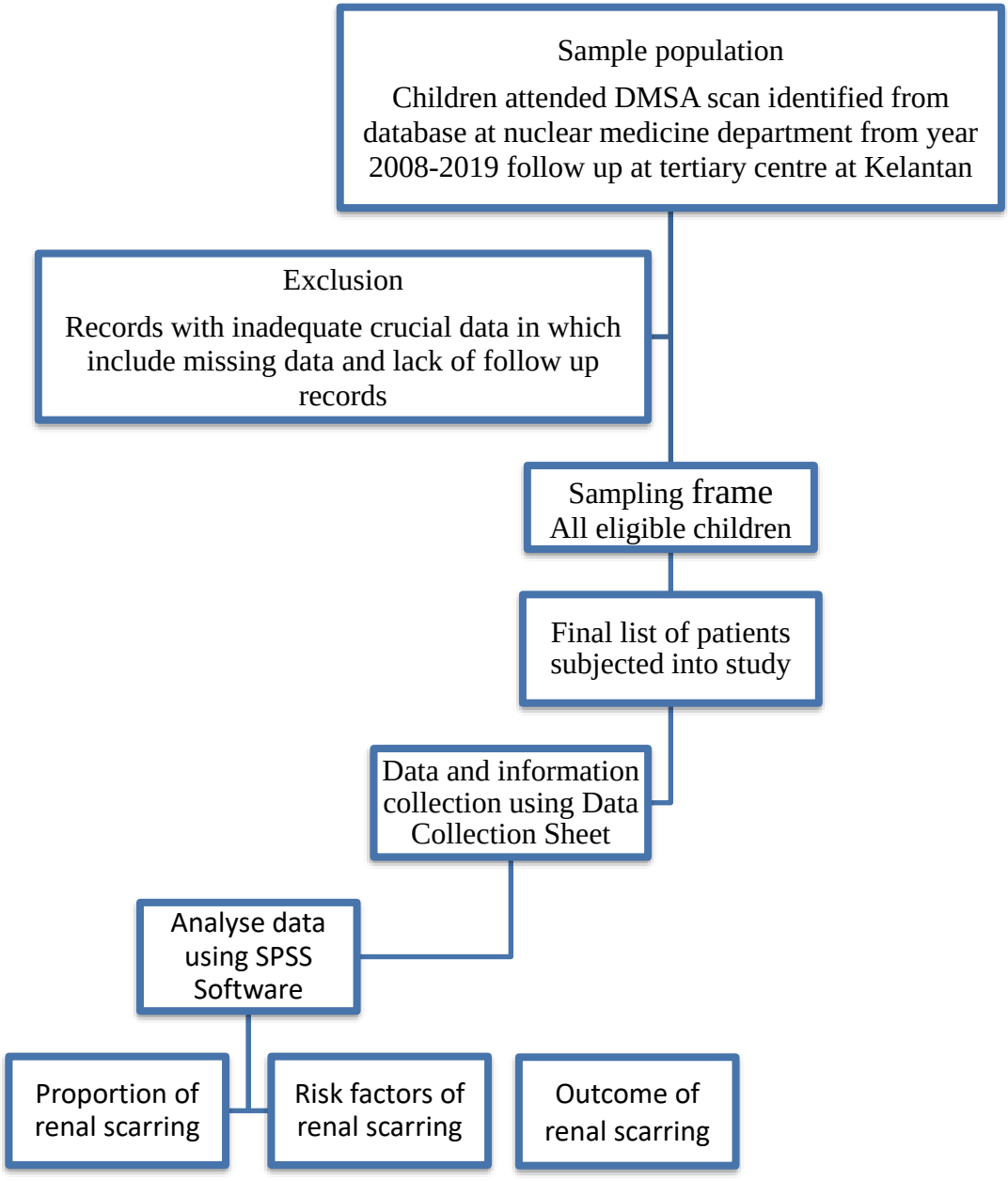
Data collection method

Patient will be identified from database at nuclear medicine department from 1st January 2008 until 31st December 2019**.** All children less than 18 years old that underwent DMSA renal scan in Hospital USM recruited and medical record of patients will be traced and reviewed from Hospital USM and Hospital Raja Perempuan Zainab II (HRPZII). Those who fulfilled inclusion will be included in the study. Patient's records were reviewed and only those who fulfilled inclusion criteria will be included in the study.

All relevant data were obtained, included:

- Baseline demographic characteristics: age, gender, weight, age detected with renal scars
- Baseline clinical examinations: weight, blood pressure
- Baseline laboratory findings: urine dipstick and renal function test
- Diagnosis of the underlying problems
- Findings of DMSA renal scans and outcomes of renal scarring

Study flowchart



Data analysis

Statistical analyses were performed using SPSS version 26. Numerical data were presented as mean ± standard deviation (SD) and median and interquartile range (IQR) for skewed data. Categorical variables were expressed as frequencies and percentages.

Comparison of categorical data was performed either using Pearson Chi-Square test or Fisher's exact test to determine the association between risk factors and the development of renal scarring and association between risk factors and outcome of renal scarring. A probability value (*P*-value) of less than 0.05 were reported as statistically significant.

Expected result(s)

Dummy tables

1) Demographic Details

Variables	Renal scarring *n* (%)
Age	Mean (SD)
Sex Male Female	
Race Malay Chinese Indian Others	

Table 2: Proportion of renal scarring

Renal Scarring	*n* (%)
• Renal scarring detected • Renal scarring not detected	

Table 3: Association between risk factors and development of renal scarring

Variable(s)	**Presence of renal scarring**		χ^2 **(df)**	***p*-value**
	Yes ***n (%)***	**No** ***n (%)***		
Recurrent UTI s - Yes - No				
Congenital anomaly of kidney and urinary tract (CAKUT) - VUR - Non-VUR				

Table 4: Outcomes of Renal Scarring

Outcome	*n* (%)
Proteinuria	
Hypertension	
Chronic Kidney Disease	

Table 5: Association between risk factors and outcomes of renal scarring

Variable(s)	**Proteinuria**			**Hypertension**			**CKD**		
	Yes ***n*** ***(%)***	**No** ***n*** ***(%)***	***p*-value**	**Yes** ***n (%)***	**No** ***n*** ***(%)***	***p*-value**	**Yes** ***n*** ***(%)***	**No** ***n*** ***(%)***	***p*-value**
Recurrent UTI s - Yes - No									
Congenital anomaly of kidney and urinary tract (CAKUT) - VUR - Non-VUR									

Gantt chart & milestone

Project activities	2018	2019		2020		
	Dec	Jan	Feb-Dec	Jan-Feb	March	April
Proposal Submission and Ethical application						
Data collection						
Data Analysis/Interpretation						
Report Writing						
Thesis submission						

Ethical consideration(s) [if applicable]:

1. **Subject vulnerability**

   Nil.

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

   There is no conflict of interest

3. **Privacy and confidentiality**

   All forms are anonymous 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.

4. **Community sensitivities and benefits**

   No part of this study may trigger social stigma. This study will benefit the community in the aspect of establishing the outcome of renal scarring in children.

5. **Honorarium and incentives**

   Nil.

6. **Risk and Benefit to Study Participants**

   The study procedures are all using retrospective data. Therefore, this study put on minimal risk to subject. This study does not present any direct benefit to the participants. However, this study will benefit the future treatment outcome of incoming patient.

7. Risk Benefit Assessment

There is very minimal risk from this study. Study findings shall potentially greatly improve treatment outcomes. The expected benefit outweighs the minimal risk and thus this study should be supported

8. Ethics of Study

Study will be conducted in compliance with ethical principles outlines in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

9. Informed Consent/Assent Process

Not applicable

10. Privacy and Confidentiality

Subjects' names will 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 the patients' identifiers will be used on subject data sheet. All data will be entered into a computer that is password-protected.

On completion of the study, data in the computer will be copied to CDs and the data in the computer will be 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. Subjects can write to the investigators to request access to study findings.

11. Publication Policy

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

12. Termination of Study

The investigator may decide to terminate the study at any time.

References

1. Lee J, Woo BW, Kim HS. Prognostic Factors of Renal Scarring on Follow-up DMSA Scan in Children with Acute Pyelonephritis. Child Kidney Dis. 2016;20(2):74–8.
2. NICE. (NICE) Urinary tract infection in under 16s Diagnosis and management. Natl Inst Heal Care Excell. 2007.
3. Bush NC, Keays M, Adams C, Mizener K, Pritzker K, Smith W, et al. Renal damage detected by DMSA, despite normal renal ultrasound, in children with febrile UTI. J Pediatr Urol. 2015.
4. Silva JMP, Diniz JSS, Lima EM, Pinheiro S V., Marino VP, Cardoso LSB, et al. Independent risk factors for renal damage in a series of primary vesicoureteral reflux: A multivariate analysis. Nephrology. 2009;14(2):198–204.
5. Ramayani OR, Ritarwan K, Eyanoer PC, Siregar R, Ramayati R. Renal survival analysis of CAKUT and outcomes in chronic kidney disease. Curr Pediatr Res. 2017.
6. Park YS. Renal scar formation after urinary tract infection in children. Korean J Pediatr. 2012;55(10):367–70.
7. Shaikh N, Craig JC, Rovers MM, Da Dalt L. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: A meta-analysis with individual patient data. JAMA Pediatr. 2014;168(10):893–900.
8. Bandari B, Sindgikar S, Kumar S, Vijaya M, Shankar R. Renal scarring following urinary tract infections in children. Sudan J Paediatr. 2019;19(1):25–30.
9. Kidney Disease Improving Global Outcomes. KDIGO Clinical practice guideline for glomerulonephritis. Kidnet Int Suppl. 2012.
10. Yen TC, Chen WP, Chang SL, Liu RS, Yeh SH, Lin CY. Technetium-99m-DMSA

renal SPECT in diagnosing and monitoring pediatric acute pyelonephritis. J Nucl Med. 1996.

11. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014.
12. Swerkersson S, Jodal U, Sixt R, Stokland E, Hansson S. Relationship Among Vesicoureteral Reflux, Urinary Tract Infection and Renal Damage in Children. J Urol. 2007;178(2):647–51.
13. Vachvanichsanong P, Dissaneewate P, Thongmak S, Lim A. Primary vesicoureteral reflux mediated renal scarring after urinary tract infection in Thai children. Nephrology. 2008;13(1):38–42.
14. Cara-Fuentes G, Gupta N, Garin EH. The RIVUR study: a review of its findings. Pediatr Nephrol. 2015.
15. Filho MZ, Calado AA, Barroso U, Amaro JL. Spontaneous resolution rates of vesicoureteral reflux in Brazilian children: A 30-year experience. Int Braz J Urol. 2007.

2.2.2 Ethical approval letter

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

2nd May 2019

Dr. Nordiyana Azmi
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JEPeM Code : USM/JEPeM/19010090
Protocol Title : The Proportion, Risk Factors and Outcome of Persistent Renal Scarring among Children in Kelantan.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM). Your study has been assigned study protocol code **USM/JEPeM/19010090**, which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **2nd May 2019** until **1st May 2020.**

Study Site: Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan.

The following researchers also involve in this study:

1. Dr. Mohamad Ikram Ilias
2. Dr. Syed Ejaz Shamim

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Patient Data Collection Form

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2019: Continuing Review Application Form.**
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2019: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2019: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2019.**

JEPeM
JAWATANKUASA ETIKA
PENYELIDIKAN MANUSIA

6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2019: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/a Kompleks Institut Kesihatan Negara
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Seksyen U13, Bandar Setia Alam,
40170 Shah Alam, Selangor.
Tel: 03-3362 8888/8205

Ref : KKM/NIHSEC/ P19-2815 (6)
Date: 06-January-2020

DR NORDIYANA BINTI AZMI
UNIVERSITI SAINS MALAYSIA HOSPITAL

Dear Sir/ Mdm,

ETHICS INITIAL APPROVAL: NMRR-19-3454-45925 (IIR)
THE PROPORTION, RISK FACTORS AND OUTCOME OF PERSISTENT RENAL SCARRING AMONG CHILDREN IN KELANTAN

This letter is made in reference to the above matter.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are to be taken to maintain data confidentiality. Permission from the District Health Officer / Hospital Administrator / Hospital Director and all relevant heads of departments / units where the study will be carried out must be obtained prior to the study. You are required to follow and comply with their decision and all other relevant regulations, including the Access to Biological and Benefit Sharing Act 2017.

3. The investigators and study sites involved in this study are:

HOSPITAL RAJA PEREMPUAN ZAINAB II
Dr Mohamad Ikram Ilias
Dr Nordiyana binti Azmi (Penyelidik Utama)
Dr Syed Ejaz Shamim

UNIVERSITI SAINS MALAYSIA HOSPITAL
Dr Mohamad Ikram Ilias
Dr Nordiyana binti Azmi (Penyelidik Utama)
Dr Syed Ejaz Shamim

4. The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:

1. Study Protocol_Version_2.0, dated 31-12-2019
2. Study Clinical Report Form (CRF) / Data Collection Form Version_1.0, dated 15-12-2019
3. Investigator's documents: Declaration of Conflict of Interest (COI), IA-HOD-IA, and CV:
   a) Dr Mohamad Ikram Ilias
   b) Dr Nordiyana binti Azmi (Penyelidik Utama)
   c) Dr Syed Ejaz Shamim

5. Please note that ethical approval is valid until **05-January-2021**. The following are to be reported upon receiving ethical approval. Required forms can be obtained from the Medical Research Ethics Committee (MREC) website (**http://www.nih.gov.my/mrec**).

i. **Continuing Review Form** has to be submitted to MREC within 2 month (60 days) prior to the expiry of ethical approval.

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ii. **Study Final Report** upon study completion to the MREC.
iii. Ethical approval is required in the case of **amendments / changes** to the **study documents/ study sites/ study team**. MREC reserves the right to withdraw ethical approval if changes to study documents are not completely declared

6. This study involves the following methods:

    i. **Retrospective**
    ii. **Secondary data**

7. Please take note that the reference number for this letter must be stated in all correspondence related to this study to facilitate the process.

Comments (if any): Nil

Project Sites:
HOSPITAL RAJA PEREMPUAN ZAINAB II
UNIVERSITI SAINS MALAYSIA HOSPITAL

Decision by Medical Research & Ethics
(√) Approved
( ) Disapproved

Date of Approval : 06-January-2020

s.k. HRRC Hospital Perempuan Zainab II, Kelantan

ZUZ/Approval2019/Mrecshare