

**CLINICAL PREDICTORS OF ACUTE KIDNEY
INJURY IN CHILDREN WITH ACUTE POST-
STREPTOCOCCAL GLOMERULONEPHRITIS:
A TERTIARY CENTRE EXPERIENCE**

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**Dissertation Submitted in Partial Fulfillment of the Requirement for the
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LIST OF ABBREVIATION AND NOMENCLATURE

HUSM	: Hospital Universiti Sains Malaysia
APSGN	: Acute post-streptococcal glomerulonephritis
GAS	: Group A beta-haemolytic streptococcus
AKI	: Acute Kidney Injury
ASOT	: Anti-Streptolysin O titre
DNAse	: Deoxyribonuclease
ULN	: Upper limit of normal
eGFR	: Estimated glomerular filtration rate
KDIGO	: Kidney Disease Improving Global Outcomes
IQR	: Interquartile range
SD	: Standard deviation
CI	: Confidence interval
SPSS	: Statistical Package for the Social Sciences

ABSTRAK

Acute post-streptococcal glomerulonephritis (APSGN) dalam kalangan kanak-kanak merupakan salah satu beban kesihatan utama dalam negara-negara membangun. Kecederaan buah pinggang akut merupakan komplikasi yang sering ditemui dalam kalangan kanak-kanak yang menghadapi APSGN.

Objektif: Untuk mengkaji kelaziman dan petunjuk-petunjuk klinikal kecederaan buah pinggang akut, dan masa median untuk penyembuhan kecederaan buah pinggang akut dalam kalangan kanak-kanak yang menghadapi APSGN.

Kaedah: Kami telah mengkaji semula nota-nota pesakit yang berumur antara 12 bulan ke 18 tahun yang menghadapi APSGN yang dimasukkan ke Hospital Universiti Sains Malaysia. Regresi logistik berganda telah digunakan untuk menganalisa petunjuk-petunjuk klinikal kecederaan buah pinggang akut seperti umur, jantina, etnik, hipertensi, hematuria kasar, dan positif ASOT. Analisa survival Kaplan-Meier digunakan untuk mengkaji masa median untuk penyembuhan kecederaan buah pinggang akut dalam kalangan kanak-kanak yang menghadapi APSGN.

Keputusan: Empat ratus kanak-kanak yang memenuhi kriteria telah dikenalpasti untuk dimasukkan ke dalam kajian ini, di mana kebanyakannya adalah kanak-kanak lelaki ($n = 262, 65.5\%$).

Kelaziman kes kecederaan buah pinggang akut adalah 21.7% ($n = 86$) (95% CI: 17.6-25.7). Kanak-kanak yang berusia lebih dari lima tahun ($p = 0.004$) dan mempunyai hematuria kasar ($p = 0.002$) merupakan petunjuk-petunjuk klinikal yang penting untuk mengenalpasti pesakit yang berisiko untuk mendapat kecederaan buah pinggang akut dalam kalangan kanak-kanak yang menghadapi APSGN. Masa median untuk penyembuhan kecederaan buah pinggang akut dalam kalangan kanak-kanak yang menghadapi APSGN adalah 18.9 (95% CI 15.3-20.7) hari.

Kesimpulan: Kanak-kanak yang berusia lebih dari lima tahun dan mempunyai hematuria kasar merupakan petunjuk-petunjuk klinikal yang penting untuk pembentukan kecederaan buah pinggang akut dalam kalangan kanak-kanak yang menghadapi APSGN.

Kata Kunci: Kecederaan buah pinggang akut, acute post streptococcal glomerulonephritis.

ABSTRACT

Acute post-streptococcal glomerulonephritis (APSGN) in paediatric population remains the major health burden to the health care system in developing countries. Acute kidney injury (AKI) is not an uncommon complication of APSGN. This study aimed to look at the prevalence and predictors of AKI, and the median time of AKI resolution among APSGN children.

Methods: An 11-year retrospective review of medical records of patients with APSGN aged between 12 months to 18 years old admitted at Hospital Universiti Sains Malaysia (Hospital USM) was performed. Multiple logistic regression analysis was used to identify predictors for AKI (age, gender, race, hypertension, gross haematuria and ASOT titre). Kaplan-Meier survival analysis was applied to study the median time of resolution of AKI among paediatric patients with APSGN.

Results: Four hundred children were included in the study with predominantly males ($n = 262$ (65.5%). The prevalence of AKI in the cohort was 21.7% ($n = 86$) (95% CI: 17.6-25.7). Children older than 5 years old and gross haematuria had been identified as significant predictors for AKI in APSGN ($p = 0.004$) and ($p = 0.002$), respectively. The median time of AKI resolution in APSGN patients is 18.9 (95% CI 15.3-20.7) days.

Conclusion: Children older than 5 years old and the presence of gross haematuria had been demonstrated to be significant risk factors towards the development of AKI in children with APSGN.

Keywords: acute kidney injury, acute post streptococcal glomerulonephritis.

CHAPTER II:

THE TEXT

2.1 SECTION A: INTRODUCTION

INTRODUCTION

Acute post-streptococcal glomerulonephritis (APSGN) is a well-recognized post-infectious auto-immune sequela of group A beta-haemolytic streptococcus (GAS).⁽¹⁾ Globally, the incidence of PSGN is still high, with an annual occurrence of APSGN is over 470,000 cases, with 97% occurring in underprivileged countries^(1,2) due to poor hygiene, overcrowding, and low socioeconomic background. The high prevalence of APSGN in developing countries, including Malaysia, poses a significant impact on the health care system,⁽³⁾ particularly those requiring dialysis and/or intensive care management or longer hospital stay as it is widely known APSGN is among the leading cause of severe AKI in children.^(4,5)

In general, APSGN among the paediatric age group has an excellent prognosis.^(6,7) Typically, the development of acute nephritic syndrome followed by preceding streptococcal pharyngitis within 1-2 weeks whereas 3-6 weeks in post-streptococcal skin infection.^(8,9,10) In children, AKI precipitated by APSGN alone is about 2.2%.⁽⁴⁾ It is estimated that only less than one per cent of these patients might end up with immediate mortality secondary to hyperkalaemia and pulmonary oedema.⁽¹¹⁾ The ability to identify children at risk of developing complicated APSGN, particularly severe AKI, will enable better resource allocation to closely monitor those at risk to achieve a better outcome.

The study aims to describe the epidemiology of paediatric patients with APSGN, including the local prevalence, risk factors and median time to resolution for AKI in children with APSGN.

To the best of our knowledge, there are limited studies on the risk factors of AKI and, particularly, its prevalence in children. In addition, our study also focused on median time for AKI resolution, which was not reported widely in many studies. Early recognition and timely treatment of children at risk of developing AKI can prevent morbidity and mortality, subsequently enhance effective and cost-efficient health care services by adequately planning for urgent or emergency care in these patients. In addition, by knowing the time for resolution of AKI it will enable us to better counsel parents and the patients on the expected time course of the illness.

2.2 SECTION B: STUDY PROTOCOL

2.2.1 DOCUMENT SUBMITTED FOR ETHICAL APPROVAL

Dissertation proposal



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Research title: Clinical Predictors of Acute Kidney Injury in Children with Acute Post-streptococcal Glomerulonephritis: A Tertiary Centre Experience

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Introduction

This study aimed to describe the demographic data and clinical characteristics of children who had been diagnosed as acute post-streptococcal glomerulonephritis (APSGN) complicated with acute kidney injury (AKI) admitted to Hospital Universiti Sains Malaysia. We will also be looking at the proportion of AKI and its median time taken for to achieve complete resolution.

In children, APSGN contributes approximately 80% of acute nephritic syndrome (ANS) cases (Ranjit Ranjan & Kamrul, 2014). There is a decreased incidence of APSGN seen in urban nations; nevertheless, the global burdens of this illness remain a major health problem in middle and low income countries (Mohamad Ikram, *et al.*, 2020). Annual occurrence of APSGN is over 470,000 cases, with 97% occurring in less developed countries (Steer, Danchin & Carapetis, 2007). In Malaysia, it is still an important public health problem.

In general, APSGN in paediatric age group has excellent prognosis. It is estimated that less than 1% of these patients end up with immediate mortality mainly attributed by hyperkalaemia and pulmonary oedema (Ranjit Ranjan & Kamrul, 2014). Acute GN is among the leading causes of AKI in children which account 6% of children with AKI, whereby AKI secondary to APSGN alone contributes 2.2% (Duzova, *et al.*, 2010).

In view of limited data on the predictors of AKI in APSGN worldwide and also the local data, we have looked the risk factors of AKI in atypical APSGN as children from this

group has higher incidence and more severe AKI compared to the typical APSGN patients. By considering these risk factors, we take into account of these predictors to determine whether they are as significant risks of AKI development in our local population of children with APSGN.

Problem statement & Study rationale

Blyth et al reported that PSGN is still a frequent cause of acute nephritis in children and the global burden of this illness persistently high, with global incidence estimation of 472, 000 cases per year with 77% contributed from low- and middle-income countries (Balasubramanian & Marks, 2017), despite a decrease in the incidence of post-streptococcal diseases in some populations. It is well known that children with APSGN who developed AKI have higher risk of morbidity and mortality. Hence, it is important for healthcare providers to identify who are at risk of complicated APSGN as it allows us to timely and promptly treat and avoid fatal complication during acute stage.

Nonetheless, there is paucity of data locally or globally on these clinical predictors of AKI in children with APSGN that might assist in recognizing APSGN patients who will develop AKI. Thus, this study intended to explore patients' profile, prevalence and risk factors of AKI in children with PSGN, and median time to resolution of AKI among this population (children with PSGN). Thus, early identification of patients who are at risk will help in improving the outcome and reducing the morbidity and mortality.

Research Question(s)

1. What are the characteristics of APSGN paediatric patients who are at risk of developing AKI?
2. What is the prevalence of AKI among paediatric patients with APSGN?

3. What are the risk factors for AKI among paediatric patients with APSGN?
4. What is the median time of AKI resolution among paediatric patients with APSGN?

Objective

General:

To examine the characteristics of APSGN paediatric patients, prevalence, risk factors and median time to resolution of AKI among these patients.

Specific:

1. To determine risk factors of AKI among paediatric patients with APSGN.
2. To estimate median time to resolution of AKI among paediatric patients with APSGN.

Literature review

According to Rodriguez-Iturbe, PSGN is one of the oldest recognized renal diseases. A reduction in the incidence of PSGN has been noted in the past 40 years in China and Singapore. In fact, in central Europe, nephritis has practically disappeared. However, PSGN remains a common disease in population with low- to middle-socioeconomic status nations. The global incidence estimation is 472, 000 cases per year with 77% contributed from low- and middle-income countries (Balasubramanian & Marks, 2017). Similarly, finding by Carapetis et al that it was estimated 470, 000 cases of PSGN occur annually. The clinical spectrum of APSGN varies from subclinical disease to rapidly progressive glomerulonephritis (RPGN) requiring acute dialysis. It is widely known that acute postinfectious glomerulonephritis is frequently the cause of severe acute renal failure necessitating dialysis and/or admission to paediatric intensive care unit (Duzova, et al, 2010).

Wong et al reported on the *Outcome of severe acute post-streptococcal glomerulonephritis in New Zealand children*: out of twenty-seven children in their study, seven (26%) children presented with rapid onset of anuric renal failure associated with severe uraemia and a clinical feature suggestive of rapidly progressive glomerulonephritis. These children required urgent dialysis because of severe electrolyte derangement and volume overload. This retrospective study concluded that this disease is still a major cause of acute renal failure and contributes in a significant burden to the health care systems particularly in the underprivileged world.

Gunasekaran et al conducted a prospective study regarding *Clinical Characteristics and Outcome of Post-Infectious Glomerulonephritis in Children in Southern India* and was published in 2015. They evaluated the clinical characteristics, complications, and outcome of post-infectious glomerulonephritis (PIGN). Among 83 children with acute nephritic syndrome, 72 (86.7%) had PIGN with PSGN as the most common aetiology [65 (90.3%)] among PIGN cases. They found that males had slightly higher preponderance of PSGN which accounts of 53.9% (n=35). PSGN occurred more commonly in children aged more than 5 years old [n=46, (70.8%)], with quite a significant number of patients developed hypertension [n=60 (92.3%)], and gross haematuria [n=40 (61.5%)]. However, there was minimal PSGN patients with positive ASOT (4.6%) in their study. This prospective study showed that gross haematuria was associated with AKI on univariate analysis [OR (95% CI) being 4.92 (0.99 – 24.29)] (p=0.036). Their study also revealed there was high prevalence of APSGN complications that often-required intensive care management; hypertensive emergency (21.5%) and AKI (23.1%). Hence, few significant clinical characteristics have been identified in children with PSGN including gender, age >5 years, hypertension, gross hypertension. Whereby, gross haematuria had a significant association with AKI, $p=0.036$. as

for the outcome, their findings were similar with previous study that AKI remained an essential outcome of PSGN.

Another study done by Blyth et al, published in 2007, entitled *Post-streptococcal glomerulonephritis in Sydney: A 16-year retrospective review* discovered that among thirty-seven subjects identified with PSGN during the study period, more subjects were male [n=24, (64.9%)], mean age was 8.1 ± 3.5 years, hypertension was 67.% (n=25), gross haematuria 75.7% (n=28), and ASOT positivity was 78.4% (n=29). Similar with study by Gunasekaran et al and any previous study, there is no study done that investigate on the significance of different races in development of PSGN or development AKI in PSGN. Regarding complications of PSGN, they reported thirty subjects developed renal failure (81.1%), with seven subjects (8.3%) requiring dialysis. Other complications include hypertensive encephalopathy (n=2, 5.6%), and fluid overload requiring respiratory support (n=2, 5.6%). Blyth et al study had almost similar findings with Gunasekaran et al study except their ASOT positivity was higher in which much parallel with our experience with local PSGN patients.

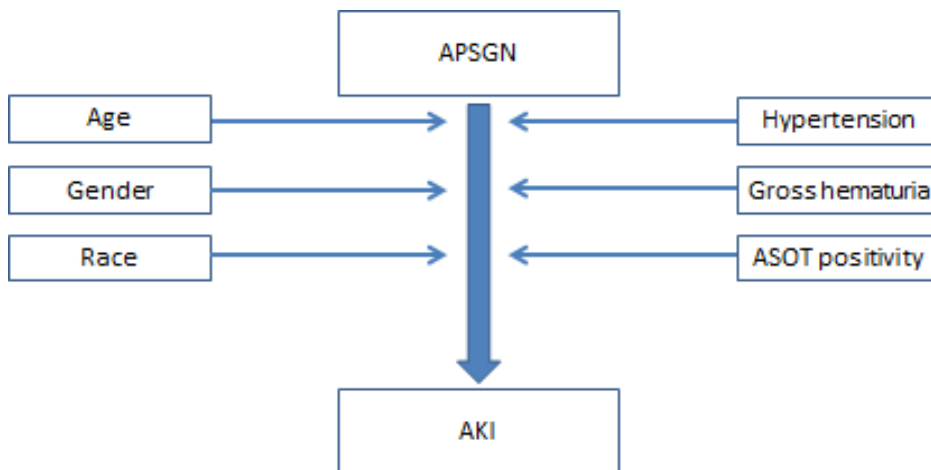
In view of paucity of data on predictors of AKI in children with PSGN, we also reviewed on article that described demographic data of patient with *atypical PSGN as these group of patients mainly develop AKI. Thus, by knowing the risk factors of atypical PSGN, we can consider those factors that contributed in AKI development in typical PSGN as well. An article by Takeno et al published in 2013, looking into the risk factors and outcome of atypical acute post-streptococcal glomerulonephritis in paediatrics. The demographics findings of their study showed most patients in the study were male (72%), age older than 7 years (77%), no significant differences in gender or age between the atypical and typical PSGN groups. Most common findings were hypertension and oedema (90.2%), followed by

gross haematuria (72.1%). Apart from that, atypical APSGN group had significantly more patients with marked elevation in anti-streptolysin O (ASO) titre ($p=0.025$), high urine specific gravity ($p<0.01$), haematuria ($p<0.031$) and pyuria ($p<0.046$).

*Atypical APSGN is defined by:

- severe proteinuria (nephrotic range proteinuria or a spot urine protein > 200mg/mmol)
- serum creatinine (Cr) > 176.8 μ mol/L)
- Oliguria (<0.5ml/kg/h) and/or azotaemia (serum BUN $\geq$ 20mg/dl convert to mmol/L) lasting more than 2 weeks
- Persistently low C3 level for more than 8 weeks.
- Hypertension or gross haematuria lasting more than 3 weeks
- Proteinuria ($\geq$ 1+ on a urine dipstick) lasting for more than 6 months
- Microscopic haematuria lasting for more than 1 year.

Conceptual framework



Research design

This research will be conducted as a cross sectional (retrospective) study to determine the patient characteristics, risk factor, and outcome of children with PSGN, whereas cohort (retrospective) study to determine median time to resolution of AKI among PSGN patients.

Study area

This study will be reviewing patient medical notes diagnosed with Acute Glomerulonephritis in Hospital Universiti Sains Malaysia from 2008 to 2018.

Study population

Reference population – All patients with AGN

Target population- Patients who were diagnosed with APSGN within study period in HUSM

Source population: AGN patients within study period in HUSM.

Sampling frame – The list of patients admitted to paediatrics ward HUSM within the study period

Subject criteria

Inclusion criteria - All patients <18 years old diagnosed as AGN admitted under paediatrics within the study period.

Exclusion criteria - Patients with AGN due to other causes (SLE, HSP etc) and patients with pre-existing hypertension.

Sample size estimation

For objective 1 (to describe the characteristics of patient with APSGN). No sample size was calculated as the objective only involves a description of study participants. For objective 4, no sample size was calculated as the objective only involves description of median survival time for resolution of AKI among patients with APSGN. Sample size was calculated for objective 2 and 3 as shown below.

For objective 2 (To determine the prevalence of paediatric patients with APSGN who developed AKI), the sample size was calculated using a sample size formula for estimation of a population's proportion as below.

$$n = \frac{Z^2 P(1-P)}{\Delta}$$

Where n is the calculated sample size, Z is the critical value corresponding to the level of confidence, Δ is the one-sided precision of estimation (margin of error) and P is the proportion of patients with the outcome of interest obtained. A previous study reported the prevalence of AKI among patients with APSGN of 23.1% (Gunasekaran, et al., 2015). To

estimate the population's prevalence to 95% level of confidence and 5% one-sided margin of error, the required sample size was 273 APSGN patients.

For objective 3 (To determine risk factors of AKI among paediatric patients with APSGN), the sample size was calculated using sample size calculation for comparison of two independent mean (for numerical variables) and two independent proportion (for categorical variables) for univariable analysis. All calculations were conducted in SPSS

Software, with type I error of 5%, Type II error of 20% (to obtained 80% power of study) and ratio (m) between non-AKI to AKI patients of 3. The summary of sample size calculations was tabulated in table below.

Sample size calculation for two independent means.

Variable	Standard deviation among patients without AKI	Reference	Estimated difference	Calculated sample size
Age	2.8 years	Gunasekaran, et al., 2015	2 years	84

Sample size calculation for two independent proportions.

Variable	Proportion of patients with exposure among those without AKI (P0)	Reference	Expected proportion of patients with exposure among those with outcome (AKI) (P1)	Ratio between non-exposed to exposed group	Calculated sample size
Gender (Males)	53.9%	Gunasekaran, et al., 2015	73.9%	3	240
Race (which race is higher risk?)	No information from previous study				
Gross haematuria	61.5%	Gunasekaran, et al., 2015	81.5%	3	216

(Yes)					
Hypertension (hypertensive emergency)	21.5%	Gunasekaran, et al., 2015	41.5%	3	212
ASOT Positivity	78.4%		98.4%	3	116

For multivariable analysis, the sample size was calculated using a method recommended by Peduzzi et al. (1996), in which sample size for a multivariable binary logistic regression analysis needs to take into account two factors; the number of predictors (k), and the probability of the event (p), using formula $n = 10k/p$. For a multivariable model with 6 predictors and a proportion of 23.1% (Gunasekaran, et al., 2015), the required sample size for the multivariable binary logistic model was 260 patients.

In conclusion, the largest sample size was obtained from the calculation for objective 4 (n=260 for multivariable analysis). After adding 10% missing data, the required sample size was 289 paediatric patients with APSGN.

Reference:

Gunasekaran, K., Krishnamurthy, S., Mahadevan, S., Harish, B. N. & Kumar, A. P. (2015) Clinical Characteristics and Outcome of Post-Infectious Glomerulonephritis in Children in Southern India: A Prospective Study. Indian J Pediatr, 82(10), 896–903.

PEDUZZI, P., CONCATO, J., KEMPER, E., HOLFORD, T. R. & FEINSTEIN, A. R. 1996. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol, 49, 1373-9.

Sampling method and subject recruitment

No sampling method will be used. We anticipate the number of APSGN patients in the 11 years period will be almost equal to the calculated sample size. Therefore, we will include all eligible patients in this study.

Research tool

Proforma forms: Demographic data, biochemical and immunological marker level, treatment given

Operational definition

TERM	DEFINITION										
Acute kidney injury (AKI)	- An absolute increase in serum creatinine by either >0.3 mg/dl (from upper range) or an increase of ≥50% from baseline or a glomerular filtration rate decrease ≥25% from baseline, or a reduction in urine output (<0.5ml/kg for >8 hours) - eGFR = $0.413 \times (\text{Height/Serum Creatinine})$ if height is expressed in centimetres (Modified Schwartz formula (2009)) (Duzova, <i>et al.</i>, 2010)										
Hypertension (1-18 years old)	TABLE 3 Updated Definitions of BP Categories and Stages <table> <tr> <th>For Children Aged 1–13 y</th><th>For Children Aged ≥13 y</th></tr> <tr> <td>Normal BP: <90th percentile</td><td>Normal BP: <120/<80 mm Hg</td></tr> <tr> <td>Elevated BP: ≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)</td><td>Elevated BP: 120/<80 to 129/<80 mm Hg</td></tr> <tr> <td>Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)</td><td>Stage 1 HTN: 130/80 to 139/89 mm Hg</td></tr> <tr> <td>Stage 2 HTN: ≥95th percentile + 12 mmHg, or ≥140/90 mm Hg (whichever is lower)</td><td>Stage 2 HTN: ≥140/90 mm Hg</td></tr> </table> Flynn JT, Kaelber DC, Baker-Smith CM, et al., and AAP Subcommittee on Screening and Management of High Blood Pressure in Children. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. <i>Pediatrics</i>. 2017;140(3):e20171904 (Flynn JT, Kaelber DC, Baker-Smith CM, et al. <i>Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics</i>. 2017;140(3):e20171904)	For Children Aged 1–13 y	For Children Aged ≥13 y	Normal BP: <90th percentile	Normal BP: <120/<80 mm Hg	Elevated BP: ≥90th percentile to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	Elevated BP: 120/<80 to 129/<80 mm Hg	Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg	Stage 2 HTN: ≥95th percentile + 12 mmHg, or ≥140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥140/90 mm Hg
For Children Aged 1–13 y	For Children Aged ≥13 y										
Normal BP: <90th percentile	Normal BP: <120/<80 mm Hg										
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Stage 1 HTN: ≥95th percentile to <95th percentile + 12 mmHg, or 130/80 to 139/89 mm Hg (whichever is lower)	Stage 1 HTN: 130/80 to 139/89 mm Hg										
Stage 2 HTN: ≥95th percentile + 12 mmHg, or ≥140/90 mm Hg (whichever is lower)	Stage 2 HTN: ≥140/90 mm Hg										
Haematuria	≥10red blood cells (RBC)/high powerfield (hpf) on a centrifuged urinary specimen (Meyers, 2004)										

Gross haematuria	≥100red blood cells(RBC)/high power field (hpf) on a centrifuged urinary specimen (Bergstein, Leiser & Andreoli, 2005)										
Nephrotic range proteinuria	≥ 2+ protein in urine, urine protein creatinine index (PCI) > 200mg/mmol (Gunasekaran, <i>et al.</i>, 2015)										
Residual renal injury at discharge	Abnormal creatinine for age, hypertension, albuminuria. <table border="1"> <thead> <tr> <th>Age</th><th>Normal serum creatinine level (μmol/L)</th></tr> </thead> <tbody> <tr> <td>Neonate</td><td>27 - 88 μmol/L</td></tr> <tr> <td>Infant</td><td>18 – 35 μmol/L</td></tr> <tr> <td>Child</td><td>27 – 62 μmol/L</td></tr> <tr> <td>Adolescent</td><td>44 – 88 μmol/L</td></tr> </tbody> </table> (Gunasekaran, <i>et al.</i>, 2015)	Age	Normal serum creatinine level (μmol/L)	Neonate	27 - 88 μmol/L	Infant	18 – 35 μmol/L	Child	27 – 62 μmol/L	Adolescent	44 – 88 μmol/L
Age	Normal serum creatinine level (μmol/L)										
Neonate	27 - 88 μmol/L										
Infant	18 – 35 μmol/L										
Child	27 – 62 μmol/L										
Adolescent	44 – 88 μmol/L										
Atypical APSGN	• severe proteinuria (nephrotic range proteinuria or a spot urine protein > 200mg/mmol) • serum creatinine (Cr) > 176.8μmol/L) • Oliguria (<0.5ml/kg/h) and/or azotaemia (serum BUN ≥ 20mg/dl convert to mmol/L) lasting more than 2 weeks • Persistently low C3 level for more than 8 weeks. • Hypertension or gross haematuria lasting more than 3 weeks • Proteinuria (≥1+ on a urine dipstick) lasting for more than 6 months • Microscopic haematuria lasting for more than 1 year. (Takeno, <i>et al.</i>, 2013)										
AKI resolution	Full recovery at discharge was defined as absence of oedema, hypertension, and normal renal function. (Arunagirinathan, <i>et al.</i>, 2015)										

Data collection method

The cohort of patients was identified from coded clinical data. At HUSM, the electronic database used is 'CodEx' or Coding Expert. This coding system followed the ICD-10 disease classification. For AGN, the code is N00.9 followed by the specific age group and sampling frame. All patients less than 18 years old diagnosed with AGN in HUSM from January 2008 to December 2018 were identified and included. Patients with AGN due to other causes (e.g. SLE, HSP etc) and patients with pre-existing hypertension will be excluded from the study. Medical records will be reviewed in all patients.

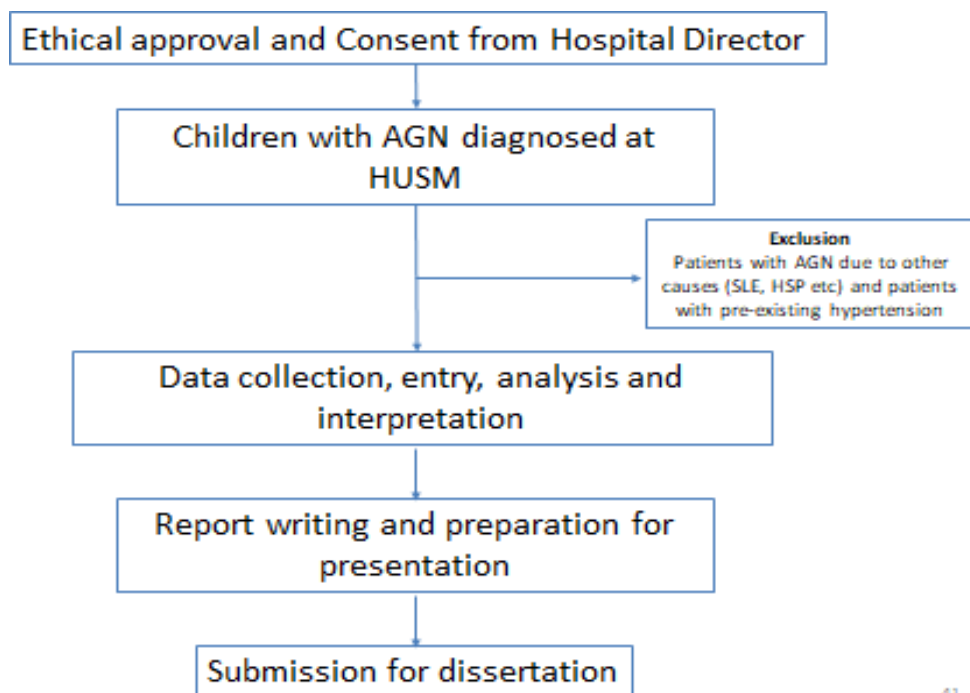
The list of patients was then printed and submitted to record unit for folder tracing. After tracing the medical record for each patient, a detailed review was done to ascertain the APSGN cases and ensure it had fulfilled the inclusion criteria.

All the relevant data were then entered anonymously using the code number in the separate pro forma. Information extracted from the medical record for each patient included the following:

- Epidemiological data: date of birth, hospital registration number, identity card number, date of presentation, age, weight, height, race, gender, month of presentation, place of residence, total household income.
- Clinical features and outcome: present of oedema, haematuria, proteinuria, urea level, serum creatinine level (the level were recorded during admission and at highest level) , serum albumin level, eGFR, complementary level on admission and follow up (C3, C4), ASO titre, ANA, and duration of haematuria. The usage of antihypertensive and number of patients underwent haemodialysis and its indication was also recorded.

Personal information will be safeguarded to ensure confidentiality. All forms are anonymous using code number and will be keyed into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the subjects individually. A separate list of names, registration numbers with code number will be kept by the researcher.

Study flowchart



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Data analysis

The analyses will be performed using the IBM SPSS Statistics for Windows Version 24.0. The data will be manually entered into the software before the cleaning process takes place.

After data has been entered, it will be explored, checked, and cleaned.

In this study, **descriptive statistics** will be employed for socio-demographic variables. The findings will be presented based on the types of data and their distribution.

Categorical data will be presented as frequencies and percentage while numerical data will be presented as means and standard deviations if normally distributed, and if not, as medians and interquartile ranges.

Kaplan-Meier survival analysis will be applied to estimate the median time of AKI development to resolution.

Simple logistic regression and multiple logistic regressions will be used to study the association between socio-demographics factor and AKI in children with APSGN. A level of significance of less than 0.05 ($p\text{-value} < 0.05$) will be considered as statistically significant.

JEPeM-USM review Panel and regulatory authorities may review the study data.

Expected results

Table 1 Clinical characteristics, biochemical and serological results of children with PSGN (n =)

Characteristics	n (%)	Mean (SD)
Age		
Gender		
Male		
Female		
Weight		
Height		
Race		
Malay		
Chinese		
Indian		
Others		
Month of presentation/diagnosis		
Duration of hospital stay		
Duration of haematuria		
Outcome at discharge		
Complete resolution		
Partial resolution		
Oedema		
Hypertension		
UFEME		
Haematuria		
Gross haematuria		
Proteinuria		
C3/C4		
Low		
Normal		
ANA		
+ve		
-ve		
ASOT		
+ve		
-ve		
Urea level		
Creatinine level		
Albumin level		
eGFR		
Anti-hypertensive agents		
1		
2		
Dialysis		
Yes		
No		

Table 2: Median time for resolution AKI among patients with APSGN

	Median time	95% Confidence interval of median time
Time for resolution of AKI		

Table 3: Univariate analysis (simple logistic regression analysis) to determine predictors for AKI among paediatric patients with APSGN

Variables	B	Crude OR	95% CI	<i>p</i> -value
Age				
Gender				
Race				
Gross haematuria				
Hypertension				
ASOT Positivity				
Peak serum creatinine				

Table 4: Multivariate analysis (multiple logistic regression analysis) to determine important predictors for AKI among paediatric patients with APSGN

Variables	B	Adjusted OR	95% CI	<i>p</i> -value
Age				
Gender				
Race				
Gross haematuria				
Hypertension				
ASOT Positivity				
Peak serum creatinine				

Gantt chart & milestone

Project Activities	2020											
	J	F	M	A	M	J	J	A	S	O	N	D
Research Activities												
Data Collection												
Data Analysis/Interpretation												
Presentation and Submission of Reports												
Writing of Report												
Project Completion												
Submission of Research Papers												

Research milestones activities

Project Activities	Tentative Date
Research Activities	1 st January 2020 – 29 th February 2020
Data Collection	Once approval obtained from JEPeM – 30 th June 2020)
Data Analysis/Interpretation	1 st July 2020 – 30 th September 2020
Presentation and Submission of Reports	1 st – 31 st October 2020
Writing of Report	1 st – 30 th November 2020
Project Completion	1 st – 31 December 2020
Submission of Research Papers	1 st – 31 December 2020

Ethical consideration(s) [if applicable]:**1. Subject vulnerability**

The participants are vulnerable as they are children, the consent to review clinical notes will be attained from the Hospital Director. All the information will be kept confidential by the researchers and will not be made publicly available.

2. Declaration of absence of conflict of interest

There is no conflict of interest in this study.

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

This study will benefit the community and health care providers in providing new knowledge and better health care to children with complicated APSGN as knowing the predictors of AKI in these patients will help us to promptly provide appropriate and aggressive treatment. Aside from that, this study might help in the consideration of giving vaccine against Group A streptococcus in near future that may curtail its occurrence, once it is available.

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