THE PREVALENCE AND ASSOCIATED FACTORS OF CLINICAL AND SUBCLINICAL RHEUMATIC HEART DISEASE AMONG RHEUMATIC HEART DISEASE CHILDREN ADMITTED IN HUSM.

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DECLARATION

This is to certify to the best of my knowledge, this dissertation is entirely the work of the candidate, Ahmad Rodzi bin Zainol.

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TABLE OF CONTENT

	Page
DECLARATION	ii
ACKNOWLEDGEMENTS	iii
TABLE OF CONTENT	iv
LIST OF ABBREVIATIONS	viii
LIST OF TABLES	x
LIST OF FIGURES	xi
ABSTRAK	xii
ABSTRACT	xiv

CHAPTER 1: INTRODUCTION

1.1	Overview Rheumatic Fever	1
1.2	History of Rheumatic Heart Disease	4
1.3	Epidemiology	5
1.4	Etiology and pathogenesis	8
1.5	Clinical Rheumatic Heart Disease	10
1.6	Subclinical Rheumatic Heart Disease	10
1.6	Echocardiography	11
1.7	WHO criteria to diagnose subclinical RHD	13
1.8	Reasons for this study	13

CHAPTER 2: OBJECTIVES

2.1	General objective	15
2.2	Specific objective	15
2.3	Study hypothesis	15

CHAPTER 3: METHODOLOGY

3.1	Study design and location	16
3.2	Study population	16
3.3	Inclusion criteria	17

3.4 exclusion criteria 17

3.5 Ethical consideration 17

3.6 Calculation of sample size and sampling method 18

3.7 Duration of study 19

3.8 Data collection 20

3.9 Statistical analysis 21

3.10 Operational definition 22

3.11 Study flow chart 26

CHAPTER 4: RESULTS

4.1 Introduction 27

4.2 Prevalence of clinical and subclinical RHD 27

4.3 Characteristic of children with RHD presented to HUSM 29

4.4 Associated factors with subclinical rheumatic heart disease 42

CHAPTER 5: DISCUSSION

5.1 Prevalence of rheumatic heart disease 48

5.2 Demographic characteristic of RHD patient 49

5.3 Clinical characteristic and investigation of RHD 52

5.4 Echocardiography and outcome 54

5.5 Prophylaxis 54

CHAPTER 6: LIMITATION AND CONCLUSION

6.1 Limitation 56

6.2 Conclusion 57

CHAPTER 7 :RECOMMENDATION AND FUTURE WORKS

7.0 Recommendation and future works 58

REFERENCES 59

APPENDIX

I : Data Collection Form 64

II: Jones Criteria(revised 1992) 66

III Ethical approval letter 67

LIST OF ABBREVIATIONS AND SYMBOLS

%	Percentage
<	Less than
>	More than
≤	Less or equal than
RHD	Rheumatic Heart Disease
RF	Rheumatic Fever
ARF	Acute Rheumatic Fever
CI	Confidence interval
CVS	Cardiovascular system
et al	And others (Latin: *et alii)*
HUSM	Hospital Universiti Sains Malaysia
IM	Intramuscular
IV	Intravascular
OR	Odds ratio
PPSP	Pusat Pengajian Sains Perubatan
PS	Power and Sample Size Software
SPSS	Statistical Package for Social Sciences
USM	Universiti Sains Malaysia
WHO	World Health Organization
LV	Left ventricular
MR	Mitral regurgitation

HIV	Human Immunodeficiency Virus
CHF	Congestive Heart Failure
MHC	Major Histocompatibility Complex
HLA	Human Leucocytes Antigen
CRP	C- Reactive Protein
ASOT	AntiStreptolysin O Titre
ESR	Erythrocytes Sedimentation Rate
GH	Growth Hormone
IGF	Insulin- Like Factor
RA	Rheumatoid Arthritis
USMKK	Universiti Sains Malaysia Kubang Kerian

LIST OF TABLE

Table 1: Clinical features and investigations in children presented to HUSM with rheumatic heart disease.

Table 2: Descriptive analysis for variables associated with subclinical rheumatic heart disease.

Table 3: Factors associated with subclinical rheumatic heart disease in comparison to clinical rheumatic heart disease in children presented to HUSM.

Table 4: Multivariate multiple logistic regression analysis for factors associated with subclinical rheumatic heart disease in comparison to clinical RHD.

LIST OF FIGURES

Figure 1 : Type of rheumatic heart disease presentation among children presented to HUSM with rheumatic heart disease.

Figure 2: Age distribution among children presented to HUSM with rheumatic heart disease.

Figure 3 : Gender distribution among children presented to HUSM with rheumatic heart disease.

Figure 4: Type of housing distribution among children presented to HUSM with rheumatic heart disease.

Figure 5 : Distribution of number of siblings among children presented to HUSM with rheumatic heart disease.

Figure 6: Household income distribution among families of children presented to HUSM with rheumatic heart disease.

Figure 7: Parental education among children presented to HUSM with rheumatic heart disease.

Figures 8: Type of valve involvement in children presented to HUSM with rheumatic heart disease.

Figure 9: Type of prophylaxis among children presented to HUSM with rheumatic heart disease.

Figure 10: Type of outcome in children presented to HUSM with rheumatic heart disease.

Figure 11 : Severity of valvular lesion in children presented to HUSM with rheumatic heart disease.

Figure 12: Outcome in children presented to HUSM with clinical and subclinical rheumatic heart disease.

ABSTRAK

PENGENALAN

Penyakit jantung rheumatik atau *rheumatik karditis* adalah antara penyakit jantung yang paling kerap dihidapi oleh kanak-kanak di seluruh dunia dan masih kekal menjadi antara masalah kesihatan yang utama di negara-negara membangun. Setakat ini, tiada data tempatan mengenai penyakit jantung rheumatik klinikal dan penyakit jantung rheumatik subklinikal.

OBJEKTIF:

Objektif utama kajian ini adalah untuk menentukan jumlah pesakit yang mengalami penyakit jantung rheumatik klinikal dan subklinikal serta mengkaji faktor-faktor yang berkaitan dengan penyakit jantung rheumatik klinikal dan penyakit jantung rheumatik subklinikal di kalangan kanak-kanak yang dirawat di Hospital Universiti Sains Malaysia.

KAEDAH :

Kajian ini dijalankan melalui kajian rekod retrospektif pesakit jantung rheumatik yang dirujuk atau dimasukkan ke Hospital Universiti Sains Malaysia dari tahun 2002 hingga 2014 yang memenuhi kriteria kajian.

KEPUTUSAN:

Terdapat 171 kes pesakit yang menghidap penyakit jantung rheumatik yang baru didiagnosa telah dimasukkan ke dalam kajian ini. Prevalens penyakit jantung rheumatik klinikal dan subklinikal adalah 86.5% dan 13.5% masing-masing. Purata umur sewaktu

diagnosa penyakit jantung rheumatik adalah 10.8 tahun dengan lelaki lebih ramai dari perempuan dengan kadar 1.1 kepada 1. Purata umur untuk penyakit jantung rheumatik subklinikal adalah 9 tahun dengan kebanyakannya perempuan. Semua pesakit yang menghidap penyakit jantung rheumatik yang terlibat dalam kajian ini berbangsa Melayu. Majoriti pesakit yang menghidap penyakit jantung rheumatik berasal dari kawasan luar bandar yang menyumbang sebanyak 60.2%. Pesakit dengan penyakit jantung rheumatik lebih ramai mempunyai adik-beradik yang lebih daripada 5 iaitu 52.6% berbanding dengan bilangan adik-beradik yang kurang atau sama dengan 5 iaitu sebanyak 47.4%. Pendapatan isi rumah yang rendah mempunyai prevalens yang tinggi bagi penyakit jantung rheumatik klinikal, iaitu 78.7% kes berbanding dengan 56.3% kes bagi penyakit subklinikal. Kebanyakan ibubapa berpendidikan sehingga ke peringkat pendidikan sekolah menengah iaitu sebanyak 76.4%. Secara statistik, didapati hanya faktor umur pesakit yang mempunyai kaitan yang signifikan dengan penyakit jantung rheumatik subklinikal berbanding penyakit jantung rheumatik klinikal.

KESIMPULAN

Prevalens penyakit jantung rheumatik subklinikal dalam kajian ini setara berbanding kajian-kajian lain. Peningkatan usia pesakit boleh menyebabkan kurang kemungkinan untuk mendapat penyakit jantung rheumatik subklinikal berbanding penyakit jantung rheumatik klinikal.

ABSTRACT

INTRODUCTION

Rheumatic heart disease or rheumatic carditis remains the leading cause of acquired heart disease in children worldwide and continues to be an important public health problem in developing countries. To date, there is no local data regarding the clinical and subclinical rheumatic heart disease.

OBJECTIVES:

The main objectives of this study is to determine the prevalence of clinical and subclinical rheumatic heart disease and to study the factors associated with both clinical and subclinical rheumatic heart disease in children presented to Hospital Universiti Sains Malaysia.

METHODS:

This study was conducted via retrospective record review of children with rheumatic heart disease who was referred or admitted to Hospital Universiti Sains Malaysia from 2002 to 2014 who meet all the study criteria.

RESULT

There were 171 newly diagnosed rheumatic heart disease patients included in this study. The prevalence of clinical rheumatic heart disease and subclinical rheumatic heart disease were 86.5% and 13.5% respectively. The mean age at diagnosis of rheumatic heart disease was 10.8 years old and predominantly male with ratio of 1.1 to 1. The mean age for subclinical rheumatic heart disease was 9 years old and predominantly

female. All patients of rheumatic heart disease involved in this study were Malay. Majority of the patients of rheumatic heart disease were from rural areas and it accounted for 60.2%. Patient with rheumatic heart disease mainly have siblings more than 5 which is 52.6%, as compared to number of siblings less or equal to 5 which comprised only 47.4%. The low household income group showed high prevalence of rheumatic heart disease, in which 78.7% of the cases of clinical rheumatic heart disease and comprised of 56.3% cases of subclinical. The majority of the parents were educated up to secondary school level, which was comprised of 76.4%. Age was the only significant factor which influenced subclinical RHD compare to clinical RHD.

CONCLUSION

The prevalence of subclinical rheumatic heart disease in this study was comparable to other studies. Increasing age was less likely to develop subclinical rheumatic heart disease compare to clinical RHD.

CHAPTER 1: INTRODUCTION

The prevalence and associated factors of clinical and subclinical rheumatic heart disease among rheumatic heart disease children in Kelantan.

1.1 Overview Rheumatic Fever

Rheumatic fever is an acute, non suppurative, immunologically mediated, multisystem inflammatory disease that occurs 10 days to 6 weeks after an episode of group A streptococcal pharyngitis (Kumar, 2010) in genetically susceptible hosts (Glenn G Fort, 2011) commonly appears in children between the ages of 5 and 15, with only 20% of first-time attacks occurring in adults (Kumar, 2007), and results from antibodies cross-reacting (Type II hypersensitivity) with tissues in the heart, joints, skin, and central nervous system at the level of B and T lymphocytes (Abul K. Abbas MBBS 2004). Acute rheumatic heart disease is a frequent manifestation during the active phase of RF and may progress over time to chronic rheumatic heart disease (RHD), of which most commonly mitral valve and less commonly aortic valve abnormalities are key manifestations (Kumar, 2010).

Diagnosis of rheumatic fever or rheumatic heart disease are based on the set of guidelines known as Jones criteria (revised 1992). This criteria consist of clinical and laboratory findings and categories into major and minor criteria. The clinical features of major manifestation:

1. carditis
2. polyarthritis
3. sydenham chorea
4. erythema marginatum

5. subcutaneous nodule.

The minor manifestations consist:

1. arthralgia
2. fever
3. raised erythrocytes sedimentation rate or C- reactive protein
4. prolonged PR interval on electrocardiogram.

In order to make the diagnosis, two major or one major and two minor manifestations must be present, plus evidence of antecedent group A streptococcus infection. The evidence of antecedent group A streptococcus infection includes raised or rising streptococcal antibody titre, positive throat swab culture or rapid antigen test for group A streptococcus. Chorea and indolent carditis do not require evidence of antecedent group A streptococcus infection. For the recurrence episodes of rheumatic fever, the requirement only one major or several minor manifestations, plus evidence of antecedent group A streptococcus infection (WHO, 2004) (Refer table in appendix II).

There are a number of hallmarks of acute carditis noted on physical examination of a patient with an initial episode of RF. There may be a prominent left ventricular (LV) impulse secondary to cardiac enlargement but not as localized as with chronic mitral regurgitation (MR). Because of recent onset, there is usually at most only mild LV dilation. Sinus tachycardia is common, but atrial fibrillation is rare. The first heart sound may vary from normal to diminished intensity, either because of MR, prolonged PR interval, or both. The second heart sound is normal or widely or variably split, depending on the degree of the MR. The pulmonary component of the second sound is accentuated with the presence of pulmonary hypertension caused by severe MR. Although classically the aortic second sound is diminished in chronic aortic insufficiency, in acute RF it is usually normal, even

with significant aortic regurgitation, because mobility of the aortic valve is not affected at the early phase. The soft, blowing, pansystolic murmur of MR is a hallmark of carditis in RF. The murmur is best heard at the apex and selectively conducted to the axilla and back; the latter suggests severe MR. A non-pansystolic murmur may occur when MR is mild, although it retains its high-frequency, soft, blowing character, which distinguishes it from the physiological murmurs seen in children. The apical diastolic murmur of Carey Coombs is often related to the severity of MR, but is also associated with flow disturbances caused by mitral valve deformity secondary to valvulitis, in addition to the increased flow in diastole. The murmur is typically mid-diastolic as opposed to the late diastolic accentuation seen with mitral stenosis. The aortic valve is involved in a minority of cases (up to 40 percent) and is associated with an early diastolic murmur of aortic regurgitation best heard along the base and left sternal border. Aortic insufficiency in the absence of MR is uncommon. A murmur of functional tricuspid regurgitation may occur in the setting of severe heart failure, pulmonary hypertension, and right ventricular dilation, with associated neck vein distention and other hallmarks of tricuspid insufficiency. Traditionally, the diagnosis has been made on the basis of auscultation of mitral or, less commonly, aortic insufficiency in the setting of heart failure, with cardiomegaly in the most severe cases. Severe MR is most commonly associated with the worst prognosis—acute and sometimes refractory and fatal heart failure. This subgroup is most likely to develop significant chronic RHD, with an incidence as high as 90 percent. There is a linear relationship between the severity of MR during the first episode of RF and subsequent RHD (WHO, 2004).

Because the valvulitis can be transient, repeated auscultation is appropriate. Whereas acute carditis may result in fulminant pulmonary oedema, in a significant percentage of patients the carditis is subclinical, setting the stage for scarring of the mitral or aortic valve apparatus with manifestations occurring years or decades later. Rheumatic tricuspid disease is uncommon, and pulmonic valve disease is rare. Although left ventricular dysfunction secondary to chronic valvulitis is thought to account for the majority of myocardial dysfunction seen, there is a characteristic regional wall motion abnormality seen in patients, primarily in the inferobasal segment of the heart adjacent to the mitral valve. The valvulitis typically involves the leaflets, but extends into the submitral apparatus in a significant percentage of cases. In the setting of LV dysfunction or pericarditis without valvular involvement, the consensus is that the pathology is unlikely to be secondary to RF. Because pericarditis alone is not diagnostic of rheumatic carditis, detection of an associated valvular lesion is important. Pericardial involvement is usually associated with significant valvulitis and may result in an effusion, but large effusions, chronic constriction, or tamponade are rare. Tachycardia and various arrhythmias are nonspecific findings. The use of endomyocardial biopsy for the diagnosis of rheumatic carditis has been explored but has not provided sufficient additional diagnostic information to warrant its use (WHO, 2004).

1.2 History of Rheumatic Heart Disease

Guillaume de Baillou (1538-1616), also known as Ballonius, first clearly distinguished acute arthritis from gout. Later on Thomas Sydenham (1624-1689) described chorea but failed to associate this entity with other manifestations of acute rheumatic fever (ARF). Raymond Vieussens (1641-1715) published pathologic descriptions of mitral

stenosis and aortic insufficiency. It remained, however, for William Charles Wells in 1812 to emphasize the association of rheumatism and carditis and to provide the first clear description of subcutaneous nodules. Jean-Baptiste Bouillard in 1836 and Walter B. Cheadle in 1889 published extensive studies of rheumatic arthritis and carditis that have come to be regarded as classic works in this field, and form the basis for modern clinical concepts of ARF. In 1880, J. K. Fowler pointed out the association between sore throat and rheumatic fever. In 1904, Ludwig Aschoff described the specific rheumatic lesion in the myocardium (Gerald L. Mandell, 2010).

1.3 Epidemiology

Group A streptococcus has a global mortality range after human immunodeficiency virus (HIV), tuberculosis, and malaria. It was comparable to pathogens causing hepatitis, *measles*, and *Haemophilus influenzae*. *Streptococcus pyogenes* is responsible for a spectrum of diseases, ranging from pharyngitis to glomerulonephritis, necrotizing fasciitis and toxic shock syndrome. However, suppurative pharyngitis is the only well-established prequel to acute RF. It was estimated in 2005 that approximately 15.6 millions people had RF or RHD, with sub-Saharan Africa and South Central Asia accounting for the majority of cases (John E. Bennett MD 2010).

There were estimated about 12 million individuals worldwide suffered from rheumatic fever and rheumatic heart disease in 1994, and at least 3 million required hospitalization for congestive heart failure (CHF). Majority of the patients with CHF required cardiac valve replacement surgery within 5–10 years. The mortality rate for RHD varied from 0.5 per 100 000 population in Denmark, to 8.2 per 100 000 population in

China. The estimated annual number of mortality from RHD for 2000 was 332,000 worldwide (WHO, 2004).

The prevalence of rheumatic heart disease up to 20 per cent of cardiology cases in Malaysia. The similar trend seen in other developing Asian countries. The reasons for this high prevalence in Malaysia are not immediately obvious but may be related to under treatment of streptococcal sore throats by medical practitioners. On the other hand, it may simply be due to the lack of patient awareness of the need to seek prompt medical attention for severe bacterial pharyngitis (Jamal F 1988). In Malaysia cardiovascular diseases rank number one cause of death since the beginning of the last decade. Among the cardiovascular diseases, coronary artery disease is the top killer. Systemic arterial hypertension comes next and valvular heart disease is the third killer of which rheumatic fever is the main cause. Of all new adult patients referred to the adult cardiac clinic in Hospital Universiti Sains Malaysia between 1991-1992, the commonest diagnosis made was rheumatic valvular heart disease (Ibrahim and Rahman, 1995).

From 1920 to 1950, acute rheumatic fever (ARF) was the leading cause of death in U.S. children and the most common cause of heart disease in individuals younger than age 40 years (John Marx, 2010). The incidence of ARF began to decline long before the introduction of antibiotics into clinical practice, decreasing from 250 to 100 patients/100,000 population from 1862 to 1962 in Denmark. The introduction of antibiotics in 1950 rapidly accelerated this decline, until by 1980 the incidence ranged from 0.23 to 1.88 patients/100,000, with disease occurring primarily in children and teenagers (Firestein *et al.*, 2012).

Only a few M serotypes (types 5, 14, 18, and 24) have been identified with outbreaks of ARF, suggesting that certain strains of group A streptococci may be more

“rheumatogenic” than others. In Trinidad, types 41 and 11 have been the most common strains isolated from the oropharynx of patients with ARF. Kaplan and colleagues isolated several M types from patients seen during an outbreak of ARF in Utah (Firestein *et al.*, 2012) However, some streptococcal strains capable of causing well-documented pharyngitis is generally capable of causing ARF (Gary S. Firestein, 2008).

The incidence of acute rheumatic fever is closely related to streptococcal pharyngitis. The peak age of incidence is 5 to 15 years, but the primary case of rheumatic fever also can occur in adults. Acute rheumatic fever is rarely occur in children younger than 4 years old. This fact has led some author to speculate that development of the disease required repetition of streptococcal infections. There is no obvious gender predilection has been observed, but certain manifestations, such as Sydenham's chorea and mitral stenosis, are more prone to develop in female patients (Goldman and Schafer, 2011).

Patients with a history of acute rheumatic fever and developed significant immunological response to streptococcal infection are susceptible to recurrent attacks of rheumatic fever. This is supported by the one long-term prospective study of patient with a history of rheumatic fever. The result showed that one of every five documented streptococcal infections gave rise to a recurrence of the disease. The risk of recurrence was more in patients with preexisting rheumatic heart disease and in those experiencing symptomatic throat infections, whereas the risk to develop recurrence attack were reduced with advancing age and with increasing interval since the most recent rheumatic attack (Goldman and Schafer, 2011).

Rheumatic fever occurs in majority area in the worlds and it occur in all races without any racial predisposition. In temperate climates area, acute rheumatic fever peaks in the winter and early spring. The major environmental factors that influence occurrence of

rheumatic fever were overcrowding, as in large households and military barracks. Interpersonal spread of group A streptococci were more favorable in overcrowding area and perhaps enhances streptococcal virulence by increase frequent of human passage (Goldman and Schafer, 2011).

Acute rheumatic fever is still common disease in developing countries such as the Middle East, the Indian, and Africa. The incidence of acute rheumatic fever is extremely high among indigenous populations such as the Maori of New Zealand and the Australian aborigines. This was contrasted to the incidence of acute rheumatic fever and the prevalence of rheumatic heart disease both in North America and in Western Europe during the 20th century where it showed the decline in number. Rates of fewer than 2 per 100,000 school children were common, especially in affluent suburbs. The higher incidence rates reported in blacks peoples compare to whites appear to be due to socioeconomic factor rather than to genetic influence (Lee Goldman, 2008).

1.4 Etiology and pathogenesis

Even though there is little evidence for the direct involvement of group A streptococci in the affected tissues of ARF patients, there is a lot of epidemiologic and immunologic evidence indirectly implicating group A streptococci in the initiation of the disease process:

(1) It is well known that outbreaks of ARF closely follow epidemics of either streptococcal sore throat or scarlet fever (Whitnack E. , 1980).

(2) The incidence of subsequent ARF were markedly reduce after adequate treatment of documented streptococcal pharyngitis (Denny *et al.*, 1950).

(3) Recurrence of disease in known patients with ARF were prevented by appropriate antimicrobial prophylaxis (Markowitz and Gerber, 1987).

(4) If one tests the sera of most ARF patients for three anti-streptococcal antibodies (streptolysin O, hyaluronidase, and streptokinase), most ARF patients (whether or not they recall an antecedent streptococcal sore throat) have elevated antibody titers to these antigens (Stollerman G H, 1956).

Group A streptococci falls into two main classes based on differences in the C repeat regions of the M protein. One class is associated with streptococcal pharyngeal infection, and the other is commonly associated with impetigo. The particular strain of streptococci may be crucial in initiating the disease process. The pharyngeal site of infection with its large repository of lymphoid tissue also may be important in the initiation of the abnormal humoral response by the host to the antigens cross-reactive with target organs. Finally, although impetigo strains do colonize the pharynx, they do not seem to elicit as strong an immunologic response to the M protein moiety as do the pharyngeal strains. This may prove to be an important factor, especially in light of the known cross-reactions between various streptococcal structures and mammalian proteins (Gary S. Firestein, 2008).

The development of acute rheumatic fever requires antecedent infection with the group A streptococcus at the upper respiratory tract. While cutaneous streptococcal infection, a precursor of post-streptococcal acute glomerulonephritis, has never been shown to cause rheumatic fever (Lee Goldman, 2008).

A study done by Ayoub and associates showed whites and black patient with rheumatic heart disease has an increase in frequency of HLA-DR4 and HLA-DR2 (Ayoub *et al.*, 1986). Other studies have implicated HLA-DR1 and HLA-DRW6 as susceptibility

factors in South African black patients with RHD (Maharaj *et al.*, 1987). More recently, Guilherme and associates have reported an increased frequency of HLA-DR7 and HLA-DW53 in RF patients in Brazil (Guilherme *et al.*, 1991).

Shin da Lee speculate that the long-term decrease in GH and IGF-I and increase in MMP-9 activity may be partially involved in the long-term pathogenesis of heart failure in RHD patient and it will be use as possible diagnostic markers in RHD for developing heart failure (Lee *et al.*, 2006).

Recent studies found nanobacteria-like materials in the effected valves of rheumatic heart patients, which plays a center role in the calcifications of these valves and result in dysfunctional valves (Hu *et al.*, 2010).

1.5 Clinical Rheumatic Heart Disease

Carditis is a single most important prognostic factor in rheumatic fever as valvulitis lead to permanent damage and the presence carditis in patient with rheumatic fever will determines the prophylactic strategy. The diagnosis of clinical rheumatic heart disease is based on the presence of significant cardiac murmur (suggestive of mitral and/ or aortic regurgitation), pericardial rub or an unexplained cardiomegaly with congestive heart failure.

1.6 Subclinical Rheumatic Heart Disease

Diagnosis of rheumatic heart disease or rheumatic carditis usually depends on detecting typical cardiac murmur (mitral murmurs and/ or aortic valvular regurgitation murmur). Two dimensional echo-doppler and colour flow Doppler echocardiography can detect silent, but significant mitral and aortic regurgitation in patient with acute rheumatic

fever. A new categories of rheumatic heart disease which is subclinical carditis or subclinical RHD has been proposed based on the presence of very mild silent but significant valvular regurgitation in patient with chorea and polyarthritis (Folger and Hajar, 1989).

Subclinical RHD is defined as features of RHD on echocardiography in the absence of symptoms and signs of heart valve disease. Patient with subclinical valvular regurgitation may develop an audible murmur in two week (Abernethy *et al.*, 1994), and may continue without audible murmur for 18 months to 5 year (Voss *et al.*, 2001). Echocardiogram is known to be more sensitive than auscultation for detection of pathologic valve disease. It proved by data from the study conducted by Marijon and associates where the comprehensive screening, including echocardiography in children might reveal a high prevalence of rheumatic heart disease (approximately 10 times) as compare to clinical screening (Marijon *et al.*, 2007).

A systemic review of studies on subclinical carditis also showed that approximately half of the patients diagnosed as subclinical RHD at time of ARF showed persistence or deterioration of their carditis in the following 2 year (Tubridy-Clark and Carapetis, 2007).

1.7 Echocardiography

Several studies have used echocardiography as a more sensitive tool than auscultation to detect valve pathology. Primarily mitral but occasional aortic insufficiency has been diagnosed in a minority of putative RF patients in whom characteristic murmurs were not heard, although this finding has not been uniform. Because echocardiographic-Doppler findings in the absence of auscultatable murmurs are not specific for rheumatic valvulitis, the use of echocardiography alone to justify a diagnosis of carditis for this major

Jones criteria is a subject of controversy. Despite the development of criteria to differentiate pathological from functional regurgitation, including posterior direction of the mitral jet, holosystolic flow, significant turbulence in the MR jet, and MR seen in orthogonal planes, in general the inclusion of patients with “silent carditis” or “echocarditis” has been thought to result in overdiagnosis. MR in particular is seen in other febrile illnesses. Longitudinal studies of patients with carditis by echoardiography but not physical examination may shed light on the long-term implications of “silent carditis” (WHO, 2004).

There is considerable inconsistency in the literature regarding the echocardiographic findings characteristic of acute rheumatic carditis. Mitral insufficiency is the most common finding, associated subsequently (but not acutely) with restricted leaflet motion rather than prolapse and with ventricular but not annular dilation. When chordal rupture occurs, however, both flail leaflets and prolapse are seen. Nodular lesions are seen in a significant minority (25 percent). Although it has been suggested that echocardiography may be helpful in settings such as concomitant pericarditis, in which auscultation may be difficult, MR is usually moderate or severe when pericarditis is secondary to RF and the murmur is detectable, despite a friction rub, which is frequently intermittent. Echocardiography is useful for confirming the findings on auscultation, excluding non-rheumatic causes (e.g., physiological murmurs or congenital heart disease), and sequential follow-up of valvular insufficiency, cardiac chamber size, pulmonary hypertension, valve thickening, and left ventricular systolic function (WHO, 2004).

1.8 WHO criteria to diagnose subclinical RHD with echocardiogram

- Excluding the non-rheumatic causes, such as congenital mitral valve cleft and/or anomalies, degenerative floppy mitral valve, bicuspid aortic valve; and acquired valvular diseases due to infective endocarditis, systemic disease and others.
- Silent, but significant, very mild (grade 0+) mitral and/or aortic valvular regurgitation. It is recommended that such significant mitral and/or aortic regurgitation be labelled as probable rheumatic heart disease (RHD) until proven otherwise (WHO, 2004).

1.8 Reasons for this study

From the above discussion and literature review, these are the reasons for pursuing the study on prevalence and associated factors of clinical and subclinical rheumatic heart disease among RHD children in Kelantan.

- This is the first study describing the subclinical RHD in Malaysia.
- To determine the ratio of subclinical RHD in our population.
- To determine the difference of the associated factors between subclinical and clinical RHD.
- This study may help to determine whether it is worth to do wide echo screening on population.

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CHAPTER 2

STUDY OBJECTIVES AND HYPOTHESIS

2.1 General Objectives

To describe the characteristics of children with clinical and subclinical rheumatic heart disease (RHD) presented to HUSM

2.2 Specific Objectives

i). To determine the prevalence of clinical and subclinical case among rheumatic heart
disease children.

ii) To compare the associated factors between clinical and subclinical cases in rheumatic heart disease children.

2.3 Study Hypothesis

i) Significant number of subclinical cases among RHD who presented to HUSM

ii) Significant associated factor between clinical and subclinical cases in rheumatic heart disease.

CHAPTER 3

METHODOLOGY

3.1 Study design and location

This study was designed as a retrospective study. It was retrospectively reviewed hospital record of children with rheumatic heart disease who referred or admitted to Hospital Universiti Sains Malaysia (HUSM) from 2002 to 2014. HUSM is a tertiary centre that received referrals from other hospitals in Kelantan. HUSM was the only referral centre for paediatric cardiology in Kelantan until 2010. Since then, Hospital Raja Perempuan Zainab II started to have similar subspecialty facilities.

3.2 Study population

The reference population was the pediatric rheumatic heart disease patient in Kelantan whereas the source population was the newly diagnosed rheumatic heart disease who were referred as outpatient or admitted to Hospital Universiti Sains Malaysia, Kubang Kerian Kelantan.

3.3 Inclusion criteria

All patient age from 3 year old to 18 year old at diagnosis and fulfilled Revised Jones Criteria 1992 with carditis at the time of diagnosis or incidental ECHO findings of rheumatic heart disease according to WHO echocardiography criteria (please refer appendix II for Revised Jones Criteria).

3.4 Exclusion criteria

The exclusion criteria were those with missing or untraceable case notes and patients who were diagnosed as acute rheumatic fever without carditis.

3.5 Ethical consideration

The ethical clearance was obtained from Ethical Committee of Pusat Pengajian Sains Perubatan (PPSP) Universiti Sains Malaysia (reference: USMKK/PPP/JEPeM[244.4(1.1). The medical records obtained remained confidential. No individual names were used and cases were coded accordingly.

3.6 Calculation of Sample Size and Sampling Method

Objective 1: To determine the prevalence of clinical and subclinical case among RHD children in Kelantan.

The sample size was calculated using single proportion sample size calculation.

Population proportion formula. Anticipated population proportion (p) = 10% (0.1) (Eloi Marijon et al, 2007), Z score as 1.96 (for 95% confidence level), absolute precision at 5% (0.05).Therefore, the calculated sample size is 152. Considering dropout rate of 20%, the total sample required, N is:

N = 152 + 20% drop out

= 167

Objective 2:

To compare the associated factors between clinical and subclinical cases in RHD children in Kelantan.

The calculated sample size using PS software are as follow:

(Arief Hermanu S, 2001)
5 % precision and estimated power 80%
Po = estimated exposed proportion among control
P1 = estimated exposed proportion among cases

The sample of calculation were as below:
Male gender:
Po = 0.45 P1 = 0.55
Calculated sample size (n = 391) for each group
Total sample size =782 + 78 (10 % drop out) = 860

3.7 Duration of Study

The study was conducted within two months (from March 2015 until May 2015).

3.8 Data Collection

RHD cases were identified by obtaining the list of patient with the list of patient with the diagnosis of RHD (both outpatient and inpatient) during simple frame from the record office using their electronic database. The electronic database used is Coding Expert. This coding system followed the ICD-10 disease classification. For RHD, we had enter the code followed by the specified age group and sampling frame.

The list of patient was than printed and submitted to record unit for folder tracing .After tracing the medical record for each patient, the detailed review was done to ascertain the RHD cases and ensure it had fulfilled the inclusion criteria. The duplication of patient was avoided by examination of name and date of birth for each patient. Each patient was given a code number.

All relevant data were then entered anonymously using the serial number in the preset proforma. (Appendix B). Information extracted from the medical record for each patient included the following:

- Demographic data: age, hospital registration number, telephone number, date of diagnosis, gender, race, address.
- Type of RHD (clinical or subclinical)
- Associated factors studied: Age, gender, housing area, household income, number of sibling and parental education.
- Clinical features (Modified Jones Criteria 1992, major and minor criteria)

- Echocardiography finding on diagnosis.
- Outcome including asymptomatic, on antifailure and surgery (valve replacement surgery).
- Type of prophylaxis (oral penicillin or IM benzathine penicillin)

3.9 Statistical Analysis

Statistical analysis was done using IBM Statistical Packages for Social Science (SPSS) software version 22.0 licenced to Hospital Universiti Sains Malaysia. All data collection forms were given serial numbers. Data were entered, checked for data entry errors, explored and cleaned. The alpha (α) of 0.05 was taken as the level of significant at 95% confidence interval.

Descriptive analyses were expressed as frequencies, means with standard deviation and percentages and presented as bar chart, pie chart, or line graphs as seen appropriate. Simple and multiple logistic regression analyses were used to identify the risk factors in this study which were significantly associated with subclinical rheumatic heart disease. Factors with a univariate p-value $\leq$ 0.25 were incorporated into a multivariate multiple logistic regression analysis using forward selection elimination. Multivariate odds ratios for risk factor were calculated. A p-value $\leq$ 0.05 was considered as statistically significant for all statistical analyses in this study.

3.10 Operational definition

Case definition of clinical and subclinical RHD

- **Clinical rheumatic heart disease: Patient fulfilled Jones criteria with evidence of carditis at the time of diagnosis.**
- **Subclinical rheumatic heart disease: Patients who do not fulfilled the Jones Criteria but ECHO findings shows evidence of RHD based on WHO Echo criteria for RHD.**

Carditis:

Evidence of carditis consist of presence of cardiomegaly with congestive cardiac failure, pericarditis, tachycardia out of proportion of fever, pathological or changing murmur.

Definition of positive result:

- CRP > 30 mg/L
- ASOT > 200unit/mL
- ESR > 30mm/h
- Positive throat swab culture :positive culture for group A streptococci
- Prolonged PR interval: prolonged PR interval if PR interval is more than 200 ms in duration.

Age:

- All patient aged 3 year old until 18 year old who fulfilled the inclusion and exclusion criteria would be included in the study.

Type of housing area:

- Definition of urban and rural area are based on definition by Jabatan Perangkaan Malaysia 2000 (Jabatan Perangkaan Malaysia, 2000)

Household income:

Definition of household income are according to the household income and basic amenities survey 2012 report, Jabatan Perangkaan Malaysia (Malaysia, 2012).

- Low income define as household income less than RM 3,000 per month.
- Middle income define as household income between than RM 3,000 to RM 5,000 per month.
- High income define as household income more than RM 5,000 per month.

Parental education:

- Parental education are categories as to primary (primary school), secondary (secondary school) and tertiary (college or university).

Echocardiogram:

- Echocardiogram finding at first diagnosis will be recorded. All echocardiogram were performed by cardiologist or echocardiographer at the cardiology unit, Hospital Universiti Sains Malaysia.

Echocardiography criteria for diagnosis for subclinical RHD

- Excluding the non -rheumatic causes, such as congenital mitral valve cleft and/or anomalies, degenerative floppy mitral valve, bicuspid aortic valve, and acquired valvular disease due to infective endocarditis, systemic disease and other.
- Criteria used to define subclinical RHD Based on Doppler characteristic of the valvular regurgitation and morphological criteria.
- Doppler criteria (**WHO criteria**) to diagnosed subclinical RHD; define by the association of the regurgitation jet > 1 cm in length, seen in at least 2 planes, a mosaic colour jet with a peak velocity > 2.5 m/s, persisting throughout systole and diastole.
- **Morphological criteria** :
  1) Leaflet morphology(typical marked thickening of the margin)
  2) Leaflet mobility (abnormal motion due to the posterior leaflet tip restriction)
  3) Subvalvular apparatus morphology (prominent thickening most often just below the valve, and shortening of chordal structures)
- Echo grading of valvular regurgitation:

  0: Nil, including physiological or trivial regurgitant jet <1.0 cm, narrow, small, of short duration, early systolic at mitral valve or early diastolic at aortic valve.

  0+: Very mild regurgitant jet, more than 1.0 cm, wider, localized immediately above or below the valve, throughout systole at the mitral valve or diastole at the aortic valve (clinically, no murmur audible).

  1+: Mild regurgitant jet.

  2+: Moderate regurgitant jet, longer and at a wider area.