DEPRESSIVE SYMPTOMS IN RHEUMATOID ARTHRITIS PATIENTS IN A GENERAL HOSPITAL SETTING IN KUCHING

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FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR
2019

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DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PSYCHOLOGICAL MEDICINE

FACULTY OF MEDICINE
UNIVERSITY OF MALAYA
KUALA LUMPUR
2019

CERTIFICATION

We hereby certify that the candidate, Dr. Joven Mailvaganam has carried out this research project, and to the best of our knowledge this dissertation is entirely his work.

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ORIGINAL LITERARY WORK DECLARATION

Name of Candidate: JOVEN MAILVAGANAM

Registration/Matric No: MGC 150003

Name of Degree: MASTER OF PSYCHOLOGICAL MEDICINE

Title of Project Paper/Research Report/Dissertation/Thesis ("this Work"):

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ABSTRACT

DEPRESSIVE SYMPTOMS IN RHEUMATOID ARTHRITIS PATIENTS IN A GENERAL HOSPITAL SETTING IN KUCHING

Introduction

Rheumatoid Arthritis is a common, chronic and debilitating autoimmune illness with long-term physical and psychological implications to sufferers. The comorbid diagnosis of depression is a well-known entity in patients with Rheumatoid Arthritis but remains unrecognized due to the lack of vigilance on the part of the clinician.

Objectives

This study was conducted to establish the prevalence of depression among patients with Rheumatoid Arthritis. We had also aimed to determine the association between socio-demographic profile and clinical parameters of Rheumatoid Arthritis patients with symptoms of depression. Next, we intended to understand the link between disease severity of Rheumatoid Arthritis and symptoms of depression. Finally, we evaluated the association between functional status in Rheumatoid Arthritis and the presence of depressive symptoms.

Methods

This is a hospital-based cross-sectional study on Rheumatoid Arthritis patients in Hospital Umum Sarawak. Convenience sampling was used in this study. Ethics approval was obtained from the Malaysian Ethics and Research Committee (MREC). Patients who consented to the enrolment into this study were given Hospital Anxiety and Depression Scale (HADS) Questionnaire and Health Assessment Questionnaire

(HAQ). Disease Severity of Rheumatoid Arthritis was evaluated and scored with the Disease Activity Score-28 (DAS-28). Socio-demographic and clinical data were also obtained. Patients who were diagnosed with depression based on HADS were further evaluated with MINI International Neuropsychiatric Inventory (MINI) to confirm diagnosis of Major Depressive Disorder and referred to the psychiatry clinic. The prevalence of depression and patients who reported depressive symptoms was determined. Univariate and multivariate analysis were done to determine the association between depressive symptoms and correlates.

Results

A total of 207 patients were recruited in this study. The prevalence of depression in Rheumatoid Arthritis was 1.5% (n=3). However, 38.7% (n=80) of patients reported having at least one symptom of depression. Apart from the status of cardiovascular disease (One-way ANOVA, p=0.032), other Rheumatoid Arthritis clinical parameters and medical comorbidities were not associated with depressive symptoms. Finally, socio-demographic data (such as age, sex, marital status, education level and employment) were not associated with symptoms of depression. Following multivariate analysis, functional status (based on HAQ score) in Rheumatoid Arthritis was found to be significantly associated with symptoms of depression (ANCOVA, $p<0.001$). Interestingly, disease severity (based on DAS-28 score) of Rheumatoid Arthritis was no longer associated with depressive symptoms (ANCOVA, p=0.697).

Conclusion

Although the prevalence of depression was low, more than a third of patients had some form of symptoms of depression. There was a significant association between functional status of Rheumatoid Arthritis patients towards symptoms of depression. However,

there was no association between Rheumatoid Arthritis disease severity and depressive symptoms. Therefore, the author recommends the routine screening for depression and a more rigorous approach to the improvement of functional status in Rheumatoid Arthritis patients to minimize the risk of depression. Finally, a larger population and prospective longitudinal study is also recommended in future research in the region.

ABSTRAK

GEJALA KEMURUNGAN DI KALANGAN PESAKIT RHEUMATOID ARTHRITIS DI HOSPITAL BESAR DI KUCHING

Pengenalan

Rheumatoid Arthritis adalah sejenis penyakit autoimun yang kronik dan melesukan. Penyakit ini mempunyai implikasi jangka panjang terhadap kesihatan fizikal dan mental. Kemurungan di kalangan pesakit Rheumatoid Arthritis adalah keadaan yang kerap berlaku namun sering dilepas pandang dan kurang dikesan oleh doktor yang merawat.

Objektif

Kajian ini bertujuan untuk mengenalpasti kelaziman penyakit kemurungan di kalangan pesakit Rheumatoid Arthritis. Kajian ini juga ingin memahami hubungkait faktor-faktor sosio-demografi dan klinikal dengan gejala kumurungan. Di samping itu, kajian ini bertujuan untuk memeriksa hubungkait antara tahap keterukan penyakit Rheumatoid Arthritis dengan gejala kemurungan. Selain itu, kajian ini turut bertujuan untuk mengenalpasti hubungkait antara tahap kebolehfungsian di kalangan pesakit Rheumatoid Arthritis dengan gejala kemurungan.

Kaedah

Kajian ini merupakan kajian keratin rentas yang dijalankan di kalangan pesakit Rheumatoid Arthritis di Hospital Umum Sarawak. Kaedah persampelan bukan rawak digunakan dalam kajian ini. Kelulusan etika diperolehi daripada Jawatankuasa Etika dan Penyelidikan Perubatan Malaysia. Pesakit yang menyertai kajian ini diberi soal selidik

untuk mengkaji tahap kemurungan, tahap kebolehfungsian dan keterukan penyakit Rheumatoid Arthritis. Data sosio-demografi dan faktor-faktor klinikal turut diambil. Pesakit yang disahkan mempunyai penyakit kemurungan dirujuk ke Klinik Psikiatri untuk rawatan lanjut. Kelaziman penyakit kemurungan dan pesakit yang mempunyai gejala kemurungan dikenalpasti. Analisis univariat dan multivariat dijalankan seterusnya untuk mengkaji hubungkait antara gejala kemurungan dengan faktor-faktor yang berkaitan.

Keputusan

Seramai 207 pesakit menyertai kajian ini. Kelaziman penyakit kemurungan hanya 1.3% (n=3). Manakala, 38.7% (n=80) pesakit dilaporkan mempunyai sekurang-kurangnya satu gejala kemurungan. Selain daripada status penyakit kardiovaskular (One-way ANOVA, p=0.032), faktor-faktor sosio-demografi dan klinikal yang lain tidak mempunyai kaitan dengan gejala kemurungan. Berdasarkan analisis multivariate, tahap kebolehfungsian (berdasarkan skor HAQ) didapati mempunyai kaitan ketara dengan gejala kemurungan (ANCOVA, $p<0.001$). Namun, tahap keterukan penyakit Rheumatoid Arthritis (skor DAS-28) didapati tidak mempunyai kaitan dengan gejala kemurungan (ANCOVA, p=0.697).

Kesimpulan

Walaupun kelaziman penyakit kemurungan didapati rendah, lebih daripada satu pertiga pesakit mengalami gejala kemurungan. Kajian ini mendapati bahawa tahap kebolehfungsian mempunyai kaitan ketara dengan gejala kemurungan. Namun, tiada kaitan ketara dilaporkan antara tahap keterukan penyakit Rheumatoid Arthritis dengan gejala kemurungan. Oleh sedemikian, penyelidik mencadangkan supaya pihak perawat menjalankan pemeriksaan rutin untuk kemurungan dan mengambil langkah-langkah

yang sewajarnya untuk memantapkan tahap kebolehfungsian pesakit Rheumatoid Arthritis. Akhirnya, kajian pada masa hadapan perlulah melibatkan populasi yang lebih besar dan menggunakan kaedah kajian prospektif longitudinal.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my gratitude to both my supervisors, Professor Dr. Ahmad Hatim Bin Sulaiman and Associate Professor Dr. Aili Hanim Binti Hashim for their continuous and unwavering support and guidance throughout the research.

Next, I would like to thank Dr. Teh Cheng Lay, an experienced Consultant Rheumatologist, who graciously supported and allowed me to conduct the study in her clinic in Hospital Umum Sarawak. Without her support, this thesis would not have materialized.

I would also like to thank Dr. Selvasingam Ratnasingam, the head of department of Psychiatry in Hospital Umum Sarawak, who graciously allowed me to take up as much time to perform my data collection and write up my dissertation between clinical duties. Your support and encouragement is much appreciated.

Next, I would like to thank the Rheumatology clinic staff for kindly assisting me in the data collection process despite their busy schedules.

To the participants, I humbly thank you for being a part of this study. Without them, this study would not have been possible.

Last but not least, to my loving wife, Dr. Tan Sue Lyn, I would like to thank her for her continuous support and encouragement in the process of completing this dissertation. To my mother, Madam Alice Chin Li Yee, your prayers have helped me through the struggle of completing this thesis. And to both my children, Paige and Josiah, I hope to be an inspiration to both of you in your future endeavors.

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LIST OF ABBREVIATIONS

CDC	Centre for Disease Control
CRP	C- Reactive Protein
DAS-28	Disease Activity Score-28
DMARDS	Disease Modifying Anti-rheumatic Drugs
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESR	Erythrocyte Sedimentation Rate
HADS	Hospital Anxiety and Depression Scale
HAQ	Health Assessment Questionnaire
HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
MI	Myocardial Infarction
MREC	Malaysian Research and Ethics Committee
NICE	National Institute for Health and Care Excellence
NMRR	National Medical Research Registry
RA	Rheumatoid Arthritis
SD	Standard Deviation

CHAPTER 1

INTRODUCTION

The consequences of Rheumatoid Arthritis are far reaching and have devastating effects on the afflicted individual's physical and psychological wellbeing. It is regarded as the most common form of autoimmune disease that prevails due to a combination of both genetic and environmental factors (Majithia & Geraci, 2007). The disease most typically affects the small joints of the hands, feet and cervical spine, although larger joints such as the shoulder and knee joints may also be damaged as the culminations of disease progression (McInnes & Schett, 2011). The long-term effects of synovitis, joint and skeletal damage lead to physical deformities that adversely influences the individual's ability to perform their desired routine activities of daily living such as dressing, bathing and walking (Majithia & Geraci, 2007). The outcome is a chronic and debilitating illness with life-altering consequences to both sufferers and their loved ones.

The gold standard for the diagnosis of Rheumatoid Arthritis is based on the criteria set by The American College of Rheumatology which takes into account clinical, serological and radiological factors of the disease (Arnett et al., 1988). Patients with Rheumatoid Arthritis should present with at least four criteria over six weeks, which includes; stiffness of the joints in the morning which last for at least 1 hour, swelling that involves three or more joints, arthritis involving hand joints, arthritis that involves both sides of the body, presence of Rheumatoid nodules, elevated serum Rheumatoid factor levels and radiographical changes of the hands.

Rheumatoid Arthritis typically progresses gradually and insidiously, however, some patients may experience rapid progression where symptoms develop over the course of

a few weeks (Harris Jr, 1990). In addition to the more common complaints of pain, swelling and stiffness of smaller joints, patients may experience fatigue and general malaise in the early stages of the disease (Carr et al., 2003).

According to Scott and Huskisson (1992), Rheumatoid Arthritis presents as a progressive disease in about 70% of affected individuals, whereby they experience episodes of flares and remissions as part of the protracted course of RA. A quarter of individuals experience a milder form of the disease characterized by prolonged intervals of remission. The remainder of patients with Rheumatoid Arthritis experiences a dire form of disease, which leads to joint destruction and possibly, permanent disability.

Chronic medical conditions such as Rheumatoid Arthritis were, by convention, approached with a predominantly biomedical focus with the emphasis on physical manifestation and pharmacological treatment (Reinseth & Arild Espnes, 2007). The traditional point of view was challenged by the likes of Eliot Friedson and Michael Bury, both esteemed medical sociologist, who emphasized the need to understand illnesses as the embodiment and lived experiences of sufferers (Barns, Svanholm, Kjellberg, Thyberg, & Falkmer, 2015). They proposed a view of the individual with Rheumatoid Arthritis as a meaningful participant (*embodiment*) who attributes the interpretation of their medical condition and its effects within the circumstances of their day to day lives (*lived experiences*) (Barns et al., 2015). Therefore, the psychological impact of the disease on the individual should not be neglected in the management of Rheumatoid Arthritis.

Studies have determined that the relationship between Rheumatoid Arthritis and depression were closely linked and remain a significant problem in this population with a prevalence that is two to three times more than in the general population (C. Dickens,

McGowan, Clark-Carter, & Creed, 2002; Margaretten, Julian, Katz, & Yelin, 2011). Furthermore, Sheehy, Murphy, and Barry (2006) reported that the negative impact of depression was more pronounced in patients with Rheumatoid Arthritis because it remained under-recognized with up to 50% of sufferers not receiving appropriate treatment for depression.

Moreover, depression in Rheumatoid Arthritis is linked to adverse health outcomes such as increased risk of cardiovascular risk factors and mortality due to myocardial infarction and increased work disability; resulting in increased public spending in health care (Margaretten, Julian, et al., 2011; Scherrer et al., 2009).

Research suggest that there is an association between disease activity and functional status in Rheumatoid Arthritis with depressive symptoms (T. O. Bruce, 2008; Margaretten et al., 2009). Although the nature of this relationship is unclear, there have been postulations about the role of a combination of biological, psychological or behavioral mechanisms (T. O. Bruce, 2008; Dowlati et al., 2010).

Thus far, there have been an abundance of research articles that attempt to understand the links between chronic illnesses such as Rheumatoid Arthritis and depression. However, these studies are mainly conducted in developed Western nations, which are set in predominantly urban settings (C. Dickens et al., 2002; Lok, Mok, Cheng, & Cheung, 2010; Matcham, Rayner, Steer, & Hotopf, 2013).

In Malaysia, the author had managed to only identify three other similar research articles that studied depression in Rheumatoid Arthritis (Chow, Guan, Chong, Nor, & Yeap, 2002; Ruhaila & Chong, 2018; Sulaiman, Zanyuin, Kheong, Bhojwani, & Seung, 2017). Between these studies, the prevalence of depression among Malaysians with Rheumatoid Arthritis was reported to be between 17.2% to 38.6%; although different screening tools for depression were utilized. Only Ruhaila and Chong (2018) and

Sulaiman et al. (2017) established the association between depression and various factors in Rheumatoid Arthritis.

It is also important to note that these studies were all conducted in Peninsular Malaysia, which has a number of distinctive demographical differences compared to Sarawak. This study esteems to look into the prevalence of Depression in RA patients in Kuching, Sarawak. Sarawak is located on the island of Borneo and is the largest state in Malaysia. The city of Kuching, which is the capital of Sarawak, is a melting pot of diverse population with more than 40 sub-ethnic groups. As such, Sarawak holds different demographic profiles from Peninsular Malaysia (Malaysia, 2011). The study would be conducted in Hospital Umum Sarawak, which is the sole Tertiary Referral Institution in the state and houses experts in the field of Rheumatology. Here, patients from as far as Miri converge for their routine assessments and treatments.

Additionally, the paucity of data studying the prevalence and important factors linked to depression in chronic illnesses in Sarawak provided the impetus for the conception of this study. The specific choice to look into the association between Depression and Rheumatoid Arthritis was because of the support provided by the Consultant Rheumatologist, Dr. Teh Cheng Lay, who expressed her concerns about the prevalence of depression among her patients with Rheumatoid Arthritis.

With that, the study aims to look into the links between depression and factors such as socio-demographics, disease severity, and functional well being of individuals with Rheumatoid Arthritis in Sarawak. The prevalence and the identification of important links of depression in this group of patients would aid policymakers in providing target intervention strategies that provide a more holistic and balanced approach to the management of patients with Rheumatoid Arthritis, hence improving long-term outcomes (Margaretten, Julian, et al., 2011; Scherrer et al., 2009).

Finally, results of this study would provide an important platform for local researchers and clinicians that may spearhead future research in the area and in other forms of chronic illnesses.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiology Of Rheumatoid Arthritis

Rheumatoid Arthritis affects between 0.5 to 1% of individuals worldwide. (Rudan et al., 2015; D. Symmons, 2002). Researchers from developed nations in North America and North Europe conducted much of the epidemiological studies regarding RA. The Centers for Disease Control and Prevention (2001) stated that the disease had become a leading cause of disability in the US, affecting almost 43 million adults. Helmick et al. (2008) and Lawrence et al. (2008) estimated the prevalence of the disease to be about 0.6%. These reports suggest Rheumatoid Arthritis and other rheumatic conditions would increase public health burden as the number of people affected will rise as the U.S. population ages (Centers for Disease Control and Prevention, 2001, 2002).

Similarly, in European countries, RA is considered a chronic and disabling disease. Researches have reported the prevalence of RA among the European countries varies between 0.2% and 1.1% (Carmona et al., 2002; Guillemin et al., 2005; Simonsson, Bergman, Jacobsson, Petersson, & Svensson, 1999; D. Symmons et al., 2002).

In contrast, there is inadequate information on the prevalence or incidence of Rheumatoid Arthritis in other parts of the world, including Malaysia. Rudan et al. (2015) in a systematic review analysis of RA in low and middle-income countries discovered the prevalence of Rheumatoid Arthritis in South East Asia was at about 0.40%. Woo, Wong, Wang, and Woo (1987) and (Lau et al., 1993) reported much lower rates compared to the Western studies.

Research indicated the variation in the prevalence among the different population groups might be due to factors such as environmental and genetic influences. Other factors such as variability in disease classifications, the age of onset, sample size and sampling methods may also contribute to the variation (Rudan et al., 2015). According to Kangesan (2012), the prevalence of Rheumatoid Arthritis varied between different ethnic groups; he demonstrated in his research that it was least seen among people of black African and Chinese descent. Interestingly, Ferucci and colleagues found in the United States that there is an increased prevalence of Rheumatoid Arthritis among North American Indians and Alaska Natives (E.D. Ferucci et al., 2008; E. D. Ferucci, Templin, & Lanier, 2005).

Epidemiological and clinical studies in western population, such as Creed (1990), C. Dickens and Creed (2001) and Sheehy et al. (2006) consistently disclosed a higher prevalence of depressive and anxiety disorders in patients with RA. The existence of psychiatric symptoms in RA patients increases their perception of pain, and disrupts their quality of life (Sheehy et al., 2006). Thus, many literatures have stressed significance of the link between Rheumatoid Arthritis and psychiatric illness.

2.2 Living With Rheumatoid Arthritis

Rheumatoid arthritis is a severely debilitating illness as affected experience chronic pain, and painful flare-ups from the disease. The functional deterioration may occur as the disease progresses which leads interpersonal stress and social isolation. This increases the risk of developing psychiatric symptoms such as anxiety and depression. Then there is the functional loss, social stress, and isolation as a consequence of the progression of the disease which consequently contribute to the development of psychiatric symptoms (C. Dickens et al., 2002; P.P. Katz & Yelin, 2001; Margaretten, Julian, et al., 2011; Zautra, Burleson, Matt, Roth, & Burrows, 1994).

Importantly, patients with Rheumatoid Arthritis are more likely to develop medical comorbidities compared to the general population (Dougados et al., 2014; Panoulas et al., 2007; Panoulas, Metsios, et al., 2008). Researchers have postulated that this may be due to effects of inflammatory mediators on the cardiovascular system, the adverse effects of some anti-rheumatic treatments and functional decline due to the effects of joint damage leading to reduced mobility (Panoulas et al., 2007; Rincon, Freeman, Haas, O'Leary, & Escalante, 2005; Rincon, Williams, Stern, Freeman, & Escalante, 2001).

2.2.1 Medical Comorbidities And Rheumatoid Arthritis

Rheumatoid Arthritis has been postulated to cause an increase in arterial stiffness, which subsequently, may lead to hypertension (Klocke, Cockcroft, Taylor, Hall, & Blake, 2003). The presence of high C-Reactive Protein (CRP) levels as a result of inflammation results in reduced nitric oxide production in endothelial cells, resulting in a cascade of events in the form of vessel constriction, elevated levels of endothelin-1, leucocyte adherence, platelet activation, oxidation and then eventually, thrombosis

(Devaraj, Xu, & Jialal, 2003; Verma et al., 2002). Additionally, CRP may also affect the renin-angiotensin system, which is an essential component in the pathophysiology of hypertension, by influencing the up-regulation of Angiotensin Type-1 receptors (C. H. Wang et al., 2003).

Interestingly, some studies have implicated the role of treatment used in Rheumatoid Arthritis as a contributing factor to hypertension. Various studies have found that the long-term use of oral glucocorticoids (prednisolone dose of 7.5mg) have been significantly associated with elevated blood pressures in both normotensive and hypertensive patients ((Panoulas, Douglas, et al., 2008; Panoulas, Metsios, et al., 2008). Although the mechanism of action is not precise, the role of glucocorticoids in hypertension is multifactorial. Studies have shown that endogenous plasma cortisol levels, implicated in hypertension, have been found to be elevated in subjects who were on regular, long-term oral glucocorticoids (Filipovsky et al., 1996; Litchfield et al., 1998). Furthermore, it may inhibit extra-neuronal uptake and catechol-O-methyltransferase and subsequently raise noradrenaline levels in the synaptic cleft (Kalsner, 1969). Glucocorticoids may also elevate the production of angiotensinogen from adipose tissue and inhibit prostaglandin production, which would lead to the retention of renal sodium and increase in the volume of blood (Panoulas, Metsios, et al., 2008; Rhen & Cidlowski, 2005).

Non-steroidal Anti-inflammatory Drugs (NSAIDs) and cyclooxygenase-II inhibitors (Coxibs) have also been implicated as a contributor to hypertension (Panoulas, Metsios, et al., 2008; White, 2007). The risk associated with these drugs is two-fold, as recent studies have shown that the elevation of blood pressure from NSAIDs was associated with a significantly increased risk of cerebrovascular accidents and ischemic heart disease (Collins et al., 1990). Concerning the mechanism of action, a

reduction in prostaglandin formation occurs as a result of blockade of both cyclooxygenase-1 (COX-1) and COX-2 enzymes by NSAIDs and Coxibs; this causes increases in sodium and elevated blood volumes (Armstrong & Malone, 2003).

Some DMARDs such as Leflunomide and Cyclosporin have been associated with hypertension (Panoulas, Metsios, et al., 2008). Studies have indicated that Leflunomide increases sympathetic drive and displaces both diclofenac or ibuprofen (both NSAIDs) from protein binding, which then increases the effect of NSAIDs on the distribution of renal blood flow and retention of sodium and water (Fox et al., 1999). Next, Cyclosporin is implicated as it causes a drop in levels of nitric oxide which affects vessel dilatation, systemic endothelin-related vasoconstriction, reduced glomerular filtration rate due to renal vessel and elevated levels of sodium in the vasculature (Taler, Textor, Canzanello, & Schwartz, 1999).

Next, studies conducted by Georgiadis et al. (2006) and Park et al. (1999) reported a higher prevalence of dyslipidemia among patients with Rheumatoid Arthritis. Both studies postulated that untreated patients in early stages of Rheumatoid Arthritis exhibited adverse lipid levels; elevated serum levels of Triglyceride and Total Cholesterol, Low Density Lipoprotein (LDL) with a reduction in levels of High Density Lipoprotein (HDL) (Georgiadis et al., 2006; Park et al., 1999). This data is very concerning because high levels of LDL, cholesterol and low levels of HDL cholesterol, typically seen in dyslipidemia, are risk factors for atherosclerosis, which is an essential component in the development of cardiovascular diseases (Manninen et al., 1988)

Of interest, these findings conflicted with data from another meta-analysis, which indicated that there was no difference in prevalence of dyslipidemia among patients with Rheumatoid Arthritis and controls (Boyer, Gourraud, Cantagrel, Davignon, & Constantin, 2011). Furthermore, the same analysis adds that patients with

RA had lower levels of High-Density Lipoproteins, Low-Density Lipoproteins, and Total Cholesterol compared to controls; which brings to question the role of chronic inflammation and its association with lower lipid levels (Boyer et al., 2011; Choy & Sattar, 2009).

The inflammatory process involved in Rheumatoid Arthritis has been found to be pro-atherogenic in nature (Sattar, McCarey, Capell, & McInnes, 2003). Atherogenesis is moderated by cytokines, such as Interleukin-6 (IL-6) and Tumor Necrosis Factor (TNF-α) as the result of systemic inflammation in RA. These inflammatory mediators act on adipose tissue (to increase free fatty acid release), the liver (to increase production of triglyceride and Free Fatty Acid) and on vascular endothelium (to decrease Lipoprotein lipase activity). This neutral lipid exchange results in lower HDL and higher LDL levels (Gonzalez-Gay, Gonzalez-Juanatey, & Martin, 2005; Sattar et al., 2003) Additionally, corticosteroids, which are commonly used in the treatment of RA, have also been implicated as being pro-atherogenic because of its association with dyslipidemia, although the effect of their long-term administration in RA is not yet completely understood (Boers et al., 2003).

Conversely, inflammation is linked to low cholesterol levels as a result of reduced lipid synthesis and increased clearance and consumption of cholesterol (Choy & Sattar, 2009; Liao et al., 2014). This fascinating finding is exhibited in observational studies that showed that Tocilizumab, (an IL-6 receptor blocker which is anti-inflammatory in nature) causes an elevation in lipid levels (Emery et al., 2008; Genovese et al., 2008).

The mechanisms behind this “lipid paradox” in Rheumatoid Arthritis are unclear. However, these contrasting results could be attributed to aspects such as sample

size, the type of study (prospective or cross-sectional), differences in stage of Rheumatoid Arthritis or variations in disease activity (Jagpal & Navarro-Millán, 2018).

A meta-analysis conducted by Boyer et al. (2011) revealed a higher prevalence of diabetes mellitus in Rheumatoid Arthritis patients. There appears to be an important link between glucose intolerance and the disease activity in Rheumatoid Arthritis, as defined by acute phase reactants of inflammation which mimics peripheral insulin resistance, as seen in type 2 diabetes mellitus (Gonzalez-Gay et al., 2005; Svenson, Pollare, Lithell, & Hallgren, 1988). The resulting chronic hyperglycemia causes increased production of TNF-α. Increased levels of TNF-α have harmful effects on insulin sensitivity in diabetes, by reducing the activity of Tyrosine Kinase activity on insulin receptors and blocking insulin-glucose-mediated uptake in skeletal muscles (Fukuzawa et al., 1999; Gonzalez-Gay et al., 2005). Additionally, observational studies have disclosed the benefits of medication that inhibit TNF-α on insulin resistance (Gonzalez-Gay et al., 2005; Gonzalez-Juanatey et al., 2004).

The association between corticosteroids and diabetes in Rheumatoid Arthritis is an interesting phenomenon. Instead of being diabetogenic, corticosteroids were found to improve peripheral insulin sensitivity among patients with Rheumatoid Arthritis (Gonzalez-Gay et al., 2005). Thus, the degree of inflammation, as reflected by disease severity, appeared to be associated with peripheral insulin sensitivity and subsequently, diabetes mellitus (Svenson et al., 1988).

Data from the Comorbidities in Rheumatoid Arthritis Study (COMORA), an international cross-sectional study, indicate that 6% of participants had co-morbid cardiovascular diseases (Dougados et al., 2014). Cardiovascular-related deaths among patients with Rheumatoid Arthritis have been found to be significantly higher, with a 50% additional risk than in individuals without Rheumatoid Arthritis (Avina-Zubieta et

al., 2008). Furthermore, cardiovascular diseases have been found to be the highest cause of mortality among patients with Rheumatoid Arthritis (Pincus et al., 1984; Prior, Symmons, Scott, Brown, & Hawkins, 1984; Rincon et al., 2001).

As discussed earlier, cardiovascular risk factors such as hypertension, diabetes mellitus, and dyslipidemia have been found to be higher in patients with Rheumatoid Arthritis (Gonzalez et al., 2008; Jagpal & Navarro-Millán, 2018; Rincon et al., 2005). Similar to individuals without Rheumatoid Arthritis, these risk factors may contribute to higher mortality rates from cardiovascular diseases (Rincon et al., 2005; Rincon et al., 2001). Additionally, the pro-atherogenic adverse effects of anti-rheumatic treatment, diminished functional status (which may result in physical inactivity and resulting obesity) and disease severity (systemic inflammatory process acting on the vascular endothelium) of Rheumatoid Arthritis are essential contributing factors to cardiovascular mortality (Manzi & Wasko, 2000; Rincon et al., 2001). As a result, the mortality rate due to cardiovascular disease is higher in patients with Rheumatoid Arthritis than the general population (Rincon et al., 2001).

2.3 Depression And Rheumatoid Arthritis

On a psychological level, depression is hallmarked by the presence of repetitive negative thinking which forms the cognitive framework for depression to act as a *response shift* (Beck, 1979). These negative thoughts could potentially lead patients to make decisions that do not best benefit their medical condition (Ehring & Watkins, 2008; Ruscio, Seitchik, Gentes, Jones, & Hallion, 2011).

Additionally, the physiological effects of depression may be the result of diminished natural endorphins, which are associated with the psychosomatic effects of depression such as avolition, lethargy, fatigue and pain (Fichna, Janecka, Costentin, & Do Rego, 2007; Hegadoren, O'Donnell, Lanius, Coupland, & Lacaze-Masmonteil, 2009; Rovner, Casten, & Leiby, 2012; Wrosch, Schulz, Miller, Lupien, & Dunne, 2007). These symptoms may limit individual's participation in day-to-day activities and result in deconditioning of the body and subsequent disability and worsening of functional status in Rheumatoid Arthritis.

The management of the chronic disease state is a significant challenge for numerous health care providers as depression is likely to emerge as a frequent setback for patients with Rheumatoid Arthritis. Moreover, depression is under-recognized because it may present in an insidious manner with no obvious clinical signs and catches the individual, their family and professional health care by surprise (Abdel-Nasser et al., 1998).

There is a voluminous commentary in the literature regarding the presence of depressive symptoms in patients with Rheumatoid Arthritis (C. Dickens & Creed, 2001; C. Dickens et al., 2002; Sheehy et al., 2006). Evers, Kraaimaat, Geenen, and Bijlsma (1997) reported that studies done in the 1980s found raised levels of psychiatric morbidities in the form of anxiety and depressive symptoms in about 20% of patients

with long-standing Rheumatoid Arthritis. This finding was slightly higher than a later study conducted by C. Dickens et al. (2002) who found 13% to 17% of patients with Rheumatoid Arthritis have major depressive disorders.

A prospective study conducted by F. Wolfe and Michaud (2009) indicated that patients had a cumulative risk for depression of 38.3% over nine years from the onset of Rheumatoid Arthritis. Additionally, Hyrich, Symmons, Watson, Silman, and BSRBR (2006), using data from the British Society for Rheumatology Biologics Register reported that at any one time, 19% of these patients were given a formal diagnosis of depression and required treatment. Overall, the prevalence of depression in patients with Rheumatoid Arthritis was found to be significantly higher at 16.8%, compared to 6.8% in the general population (C. Dickens et al., 2002; Kessler et al., 2003; Matcham et al., 2013).

The author is aware of three prior studies that investigated depression among patients with Rheumatoid Arthritis that were conducted in Malaysia. In 2002, the prototypical study in this field of interest in Malaysia reported prevalence for depression of 17.2% (n=16) (Chow et al., 2002). Another study in Ipoh reported that 38.6% (n=40) of participants has depression (Sulaiman et al., 2017). A more recent study in 2018 which was conducted in Hospital Melaka recorded a significantly higher prevalence of depression of 23.3% (n=44) (Ruhaila & Chong, 2018). The findings from all three studies were similar to the findings of other international papers in which the prevalence of depression in Rheumatoid Arthritis was demonstrably higher compared to individuals without the chronic illness. However, the author would like to point out that both these studies were conducted in Peninsular Malaysia and that were was no local data from East Malaysia.

The importance in identifying depression in Rheumatoid Arthritis should be repeatedly emphasized. Both the Centre for Disease Control (CDC) and the National Institute for Health and Care Excellence (NICE), from the United States and United Kingdom respectively, have recommended that clinicians be vigilant and mindful of the presence of depression in patients with chronic medical conditions. These guidelines highlight importance of routine screening to detect depression early among patients with chronic medical conditions. Newly diagnosed depressed patients should then be referred to psychiatric specialist services and treated promptly (Colton & Manderscheid, 2006; Pilling, Anderson, Goldberg, Meader, & Taylor, 2009). Despite these recommendations, depression among patients with Rheumatoid Arthritis was frequently missed and under-diagnosed in Rheumatology clinics (Colton & Manderscheid, 2006; Nicassio, 2008; Pilling et al., 2009). The under-recognition of depression may severely alter outcomes and progression of Rheumatoid Arthritis. Studies have indicated that the co-existence of Rheumatoid Arthritis and depression has a detrimental effect to adherence and response to anti-rheumatic treatment; thereby worsening disease activity (Di Matteo, Lepper, & Croghan, 2000; Nicassio, 2008).

Additionally, the burden of depression in Rheumatoid Arthritis is also observed in public healthcare. A study had found that the annual cost to treat a single patient with both depression and Rheumatoid Arthritis was approximately 7.2% more than it was to treat a Rheumatoid Arthritis patient without depression (Joyce, Smith, Khandker, Melin, & Singh, 2009).

Therefore, it is essential to establish how symptoms of depression are associated with Rheumatoid Arthritis in the local setting to bridge the gap between current medical practice and the present state of the content knowledge.

2.3.1 Socio-Demographical Correlates of Depression In Rheumatoid Arthritis

To date, there have still been differences in opinion between researchers on the significance of the contribution of socio-demographic factors towards the formation of psychological distress in patients with Rheumatoid Arthritis. A better understanding of the link between these factors may hold clinical relevance in the holistic management of patients with Rheumatoid Arthritis (F. Wolfe & Michaud, 2009).

In the absence of a chronic medical condition such as Rheumatoid Arthritis, there are a number of proposed mechanisms and predisposing factors that are linked to the formation of depression. Among these factors include past history of traumatic experiences, premorbid personality, coping skills, temperament, interpersonal relations, genetic factors such as family history of mental illness, and disruption of the hypothalamic pituitary adrenal axis. However, to date, there has been insufficient evidence to establish these factors as determinants and predictors of depression among patients with Rheumatoid Arthritis (Ehlert, Gaab, & Heinrichs, 2001; Kendler, Gardner, & Prescott, 1999; F. Wolfe & Michaud, 2009).

Among individuals who do not have Rheumatoid Arthritis, a low socioeconomic status which is determined by having low income, education level and unemployment have also been implicated with elevated risk of depression and other psychiatric morbidities (Lorant et al., 2003; Stringhini et al., 2010). Individuals who fall within the category of low socioeconomic status have a higher prevalence of depression due to the increased risk of stress exposure and undergoing adverse life events, having poorer coping skills and inadequate perceived social supports (Turner & Lloyd, 1999).

In patients that have Rheumatoid Arthritis, socioeconomic factors such as lower education level, unmarried status, lower income and a younger age have been significantly associated with depression, as they do in most chronic medical conditions

(F. Wolfe & Michaud, 2009). Other studies have proposed other aspects of demographics such as the female gender and an earlier age of onset of Rheumatoid Arthritis as factors that are strongly linked to depression (Pincus, Griffith, Pearce, & Isenberg, 1996; Wright et al., 1998).

Finally, researchers have had contrasting views of the association of ethnicity of patients with Rheumatoid Arthritis and depression. On one hand, studies have reported that Asian American patients with Rheumatoid Arthritis had lower prevalence of depression compared to their Hispanic and African American counterparts (Escalante, del Rincon, & Mulrow, 2000; Margaretten, Julian, et al., 2011). This finding may be the result of the effects of perception and stigma of mental illness, differences in language, help-seeking behavior and symptom recognition of depression, which may explain the differential findings between ethnicity. Conversely, it is also worth noting that Wolfe et al reported that there was no association between ethnicity and the formation of depression in Rheumatoid Arthritis (F. Wolfe & Michaud, 2009).

In summary, socio-demographic factors such as the female gender, a younger age group, an unmarried status and low socioeconomic status, which is reflected by unemployment, lower levels of education and lower income, have all been found to be associated with depression in Rheumatoid Arthritis. However, the link between ethnicity and depression remains unclear.

2.3.2 Depression And Functional Status In Rheumatoid Arthritis

Having Rheumatoid Arthritis is living with a chronic illness. The co-existence of depression poses an additional burden on the individual and their loved ones (Margaretten, Julian, et al., 2011; Sheehy et al., 2006).

Rheumatoid arthritis is associated with protracted pain, with consequences on the individual's capacity and performance (Margaretten, Barton, et al., 2011; F. Wolfe & Michaud, 2009). Its unpredictable and chronic course confronts the affected

individuals presenting them with an unexpected, and uncontrollable stressor (Evers et al., 1997; Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003). Physical disability and the resulting functional decline was found to predict the development of psychological distress, which may ultimately lead to depression in the later stages of Rheumatoid Arthritis (Gettings, 2010).

The prolonged course of illness and resulting debilitating state invariably burdens the individuals with Rheumatoid Arthritis. These afflicted individuals are faced with many functional limitations, which lead to absenteeism, work-related, and adaptive skills disabilities (C. Dickens et al., 2002; Majithia & Geraci, 2007; Sheehy et al., 2006; Sleath et al., 2006). Consequently, the effects of Rheumatoid Arthritis on function take a considerable toll on the ability to perform valued and treasured life activities, which lead to life-altering consequences to afflicted individuals and their caregivers (C. Dickens et al., 2002; Majithia & Geraci, 2007; Sheehy et al., 2006; Sleath et al., 2006).

In addition, depression increases the risk of work disability and the need for healthcare resources. In comparison to those without depression, Rheumatoid Arthritis patients who have depression had a 60% higher risk of experiencing some form of work disability (Lowe et al., 2004). In an eighteen year prospective study which involved 823 subjects, F. Wolfe and Hawley (1999) found that almost a quarter of participants experienced work disability six years after the onset of Rheumatoid Arthritis. In the same study, individuals who reported symptoms of depression and anxiety were noted to have a higher degree of work disability. Work disability was more likely to occur late in the course of Rheumatoid Arthritis and was a result of reduced mobility that led to diminished functioning. Consequently, Rheumatoid Arthritis patients with work disability described having lower family income. The loss of income adds additional

burdens and stress; further compounding the effects of Rheumatoid Arthritis on the functional and psychological well being of afflicted individuals.

Ultimately, these studies reveal the importance of diminished functional status and its significant association with the development of depressive symptoms. In this study, the author hopes to understand the links between these two variables in this special population of patients.

2.3.3 Depression And Disease Severity In Rheumatoid Arthritis

In the early stages of the disease, pain and fatigue, both of which are symptoms of inflammation and are used to evaluate disease severity, were reported to be the predictors for psychological distress in Rheumatoid Arthritis (Gettings, 2010). In another study, it was demonstrated that there were positive psychological effects of clinical remission among patients with moderate-to-severely active early Rheumatoid Arthritis; whereby there was a reduction of depressive and anxiety symptoms following a reduction in Rheumatoid Arthritis disease severity (Sinclair & Blackburn, 2008).

Zautra and Smith (2001) and Covic, Adamson, Spencer, and Howe (2003) also reported that Rheumatoid Arthritis patients that had depressive symptoms were more likely to report having more discomfort due to attenuated levels of pain. These patients also encountered more negative situations due to an increased sensitivity to perceived stress. Brown, Glass, and Park (2002) also demonstrated that depressed individuals with Rheumatoid Arthritis reported more pain and suggested, in his study, that the presence of depression mediated the pain–cognition relationship. Furthermore, studies have found that increased levels of pain, which reflects disease severity of Rheumatoid Arthritis, was a predictor of the formation of depressive symptoms as opposed to

previously suspected socio-demographic variables (Covic et al., 2009; C. Dickens & Creed, 2001; C. Dickens et al., 2002).

A prospective study involving 2400 participants from The National Rheumatoid Arthritis Registry, Fifield, Tennen, Reisine, and McQuillan (1998) discovered that a single episode of major depression, even if it occurred prior to the onset of Rheumatoid Arthritis, gravely affected the severity of the disease. Participants, who had recovered from an episode of major depression but still persistently had some symptoms of depression, reportedly complained of higher levels of joint pain. Thus, the presence of symptoms of depression, despite not fulfilling criteria for Major Depressive Disorder, appeared to also affect outcomes and the course of Rheumatoid Arthritis.

The reduction of depressive symptoms has been observed in interventional studies involving treatment such as short-term corticosteroid pulse treatment and a combination of Disease Modifying Anti-rheumatic Drugs (Methotrexate and Etanercept) (Jacobs et al., 2001; Kekow, Moots, Emery, et al., 2010). These studies have found that the amelioration of symptoms associated with Rheumatoid Arthritis such as pain, swelling and fatigue led to an improvement of depressive symptoms over time. Thus, this could also suggest a significant association between Rheumatoid Arthritis disease severity and symptoms of depression.

There have been a limited number of interesting studies that evaluated the associations between depression and non-adherence to anti-rheumatic treatment. Inferentially, the non-adherence to treatment would lead to worsening disease severity due to the elevation of systemic inflammatory mediators typically seen in Rheumatoid Arthritis. Data from these studies have yielded mixed results. One such study reported that patients who had symptoms of depression were more likely to discontinue DMARD treatment (Mattey, Dawes, Hassell, Brownfield, & Packham, 2010). Although, the same

study did not specify the reason for discontinuation; whether it was due to common factors related to non-adherence such as the adverse reaction of treatment or perhaps the lack of efficacy of the anti-rheumatic treatment in question. Conversely, other studies reported different observations and concluded that depression was not associated with adherence to DMARD treatment (Cho, Sung, Choi, & Bae, 2012; Wong & Mulherin, 2007).

Interestingly, limited studies have found that symptoms of depression could modulate outcomes by reducing the clinical response of anti-rheumatic treatment. One particular study found that persistence of depressive symptoms reduced short-term efficacy of anti-TNF treatment in Rheumatoid Arthritis despite not having any effects on the long-term results with anti-TNF therapy (measured by changes in DAS-28 score over repeated visits) (Hider, Tanveer, Brownfield, Mattey, & Packham, 2009). Another study demonstrated symptoms of depression influenced the effects of long-term DMARD treatment on Rheumatoid Arthritis disease activity (Kekow, Moots, Khandker, et al., 2010). However, the findings from both studies are restricted because they were conducted in specialized patient populations with limited consideration and adjustment for confounders.

The link between disease severity of Rheumatoid Arthritis and depression is not as clear-cut. Some studies have argued that there was no association between disease severity and depression in Rheumatoid Arthritis (Evers et al., 1997; Margaretten et al., 2009). Conversely, the author was able to identify more studies that established a significant association between disease severity and depression.

2.4 Summary

This information highlights the vulnerabilities and the difficulties that patients who live with Rheumatoid Arthritis have to endure. In summary, patients with Rheumatoid have a higher prevalence of medical comorbities. The prevalence of depression in patients with Rheumatoid Arthritis is high. Next, symptoms of depression are linked to increased disease severity of Rhuematoid Arthritis. Finally, the presence of depression has a significant effect on functional status and quality of life in Rheumatoid Arthritis.

CHAPTER 3

METHODOLOGY

3.1 Study Design

The proposed study will be a hospital-based, cross-sectional study to estimate the prevalence of depression in patients with Rheumatoid Arthritis and to determine its association with socio-demographical data, RA disease severity and functional status.

3.2 Study Subjects

The source population of this study will be patients diagnosed with Rheumatoid Arthritis who are attending their routine follow-up in the Rheumatology clinic.

3.3 Study Setting

The study will be conducted in the Rheumatology Clinic in Sarawak General Hospital, which serves as both a secondary and tertiary referral center. Clinics for patients with Rheumatoid Arthritis are scheduled from 2 pm to 5 pm every Tuesday to Thursday. Rheumatology physicians and medical officers from the Internal Medicine Department of Sarawak General Hospital run the clinics. The clinic is attended by an average of 120 patients with Rheumatoid Arthritis per month, with an estimated number of 500 patients in total.

3.4 Study Period

The proposed study will be conducted from 1st October 2018 to 30th November 2018. However, the author involved would consider concluding the proposed research should the desired sample size be met before the stipulated date of completion.

3.5 General Objectives

The main objective of this study is to determine the prevalence and associations of depressive symptoms in patients with Rheumatoid Arthritis.

3.5.1 Specific Objectives

- To establish the prevalence of Rheumatoid Arthritis patients with depression in Hospital Umum Sarawak, Kuching.
- To determine the associated factors (socio-demographic profiles, anti-rheumatic treatment, medical comorbidities) towards depressive symptoms.
- To understand the association between the severity of Rheumatoid Arthritis and symptoms of depression.
- To determine the association between the functional status of a patient with Rheumatoid Arthritis and depressive symptoms.

3.6 Research Hypothesis

- The prevalence of depression in Rheumatoid Arthritis patients in Hospital Umum Sarawak is high.
- There is a significant association between symptoms of depression and socio-demographic profile (age, gender, ethnicity, socioeconomic status), disease activity and functional status of Rheumatoid Arthritis patients in Hospital Umum Sarawak, Kuching.

3.7 Study Criteria

The criteria for enrolment into this study are listed below:

3.7.1 Inclusion Criteria

- Patients with a diagnosis of Rheumatoid Arthritis aged 18 years and above.
- Patients who are able to provide written informed consent are allowed to participate in the study.
- Patients with previously diagnosed Depression will be included.
- Proficient in either Malay or English language and able to participate during the assessments or interviews in English and Malay.

3.7.2 Exclusion Criteria

- Patients with significant medical or neurological conditions that can impair cognition (such as Epilepsy, Head Injury, and Cerebral Vascular Disease).
- Patients with Major Psychiatric Illness (Schizophrenia and Bipolar Disorder).
- Patients with underlying Major Neurocognitive Disorders (such as Dementia and Delirium).
- Patients with Neurodevelopmental Disorders (such as Autism Spectrum Disorder and Intellectual Disability) that may impair cognition.
- Patients who do not want to participate and are not able to cooperate during the interview.
- Patients who are not able to provide written consent.
- Patients who are not able to understand and converse in either Malay or English language.

3.8 Sample Size

The sample size for this study is determined using the manual sample size calculation formula for prevalence studies (Kish, 1965) as follows:

$$\mathbf{n= (Z1-\alpha)^2 [P (1-P)/ D^2]}$$

$Z_{\alpha/2} = Z_{0.95} = 1.96$ (for CI of 95%, Z= 1.96; normal distribution table)

P (Prevalence)= 17.2% = prevalence from previous Malaysian study conducted by Chow in 2001.

D (Absolute precision required) = 5% = 0.05

Hence,

$$\mathbf{n = 1.96^2 [0.172 (1-0.172)/ 0.05^2]}$$

$$= \underline{\mathbf{217}}$$

Sample Size required for this study is at least 217.

3.9 Study Procedure

Adult patients above the age of 18 years old with a diagnosis of Rheumatoid Arthritis attending the Rheumatology Clinic would be invited to participate in this study. Based on available information, there are approximately 500 patients with Rheumatoid Arthritis enrolled in the Rheumatology Clinic.

Prior to enrolment in the study, subjects will be carefully provided information regarding the proposed research with the aid of the attached Patient Information Sheet. Any concerns potential subjects have will be alleviated and addressed before obtaining written consent for participation. Confidentiality is strictly assured, and no names will be included in questionnaires; instead, a coding system will be used to identify subjects.

As part of the study, socio-demographic and clinical information will be obtained from subjects. Hospital Anxiety and Depression Scale (HADS) and the Health Assessment Questionnaire (HAQ) will be self-administered by subjects of the proposed study with the assistance of the author.

In the same setting, Rheumatology physicians will perform clinical assessments on subjects as part of Disease Activity Score (DAS-28); this is a routinely performed assessment for all patients attending the Rheumatology Clinic.

Subjects that score 8 or more in the depression sub-scale of HADS will then be evaluated by the investigator with experience in Psychiatry via Structured Clinical Interview with the use of MINI International Neuropsychiatric Inventory version 6.0.0 (Major Depressive Episode Sub-Scale) to establish a diagnosis of Depression based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR).

Should a subject be diagnosed with Depression, the investigator will refer the subject to the Psychiatry Specialist Clinic for further management.

This study does not intend to stratify the severity of Depression (mild, moderate or severe) in the target population. As such, all patients who are diagnosed with Depression, regardless of severity, will be referred to the Psychiatry Specialist Clinic for evaluation and management. The proposed study will only require one-off subject participation, and thus, there will be no follow-up of the subjects.

3.10 Study Measures

3.10.1 Socio-Demographic And Clinical Data Form

The socio-demographic form includes information such as age, ethnic group, marital status, employment status, and educational level. Clinical information regarding patient's age when they were first diagnosed with RA and treatment they are receiving were also included. Other information included in the form were common comorbid medical conditions, which may be potential confounders. The author will fill this form upon the signing of consent by participants.

3.10.2 Hospital Anxiety And Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) was chosen to assess depression in a bustling rheumatology clinic setting here in Hospital Umum Sarawak, Kuching. The questionnaire was first developed more than 30 years ago by Zigmond and Snaith to screen for anxiety and depression in a general medical population of patients (Zigmond & Snaith, 1983). The main decision to choose HADS was its simplicity and ease of use in the general clinical setting that involves patients with a wide range of literacy. Additionally, a questionnaire that could be completed fast was needed to prevent disruption in the clinic flow; patients would be seeing the Rheumatologist at the same time.

As opposed to another widely used questionnaire, Patient Health Questionnaire (PHQ9), HADS can assess both anxiety and depression, which commonly co-exist (McManus, Meltzer, Brugha, Bebbington, & Jenkins, 2009). Thus, the use of the questionnaire could be beneficial and continue to be a mainstay in the assessment of a patient with Rheumatoid Arthritis upon completion of the study because non-mental health professionals poorly recognize symptoms of anxiety.

A score of 8 or more for depression had a sensitivity of 0.83 and specificity of 0.79. Furthermore, HADS was reported to have good internal consistency for the depression (0.86) subscales (Olssøn, Mykletun, & Dahl, 2005).

Furthermore, HADS has been validated in numerous languages, including in the Malay language (Yahya & Othman, 2015). In the context of patients with Rheumatoid Arthritis, HADS was found to be valid for the assessment of depression among patients with Rheumatoid Arthritis (Covic et al., 2009).

3.10.3 MINI-International Neuropsychiatric Inventory (Ver. 6.0.0)

The MINI International Neuropsychiatric Inventory is a structured clinical interview, which was conceived to diagnose mental disorders based on the Diagnostic and Statistical Manual (DSM) diagnostic criteria. An interviewer without prior experience in psychiatry may administer this test due to the structured nature of the interview. A number of screening questions are included to aid in quickly excluding a diagnosis (Sheehan et al., 1998).

3.10.4 Disease Activity Score 28 Joints (DAS-28)

The Disease Activity Score (DAS-28) is a widely used tool in the field of rheumatology for the evaluation of disease severity of Rheumatoid Arthritis (Prevoo et al., 1995).. As part of the assessment, clinicians would perform a tender and swollen joint count (range 0-28). The Erythrocyte Sedimentation Rate (ESR) levels are also included in this assessment. Next, an optional general health assessment on a visual analog scale is done (range 0-100).

The level of disease activity can be interpreted as low (DAS-28 < 3.2), moderate (3.2 < DAS-28 < 5.1), or severe (DAS-28 > 5.1), while DAS-28 < 2.6 corresponds to being in remission. This tool is routinely used to evaluate the disease severity of all

patients with Rheumatoid Arthritis in the Rheumatology clinic in Hospital Umum Sarawak.

3.10.5 Health Assessment Questionnaire (HAQ)

First published in 1980, The Health Assessment Questionnaire (HAQ) was developed in Stanford University to effectively measured functional health status and quality of life in Rheumatoid Arthritis based on generic and patient-centered dimensions (B. Bruce & Fries, 2003). HAQ evaluates impediments to an individual's ability to perform daily tasks across eight domains over the past week. Twenty specific functions defined these eight domains of function in HAQ, which include activities such as dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, errands and chores. It is available and validated in the Malay language and more than sixty other languages (B. Bruce & Fries, 2003; Hussein, Mustafa, Quek, Hassanudin, & Shahid, 2008).

3.11 Study Flowchart

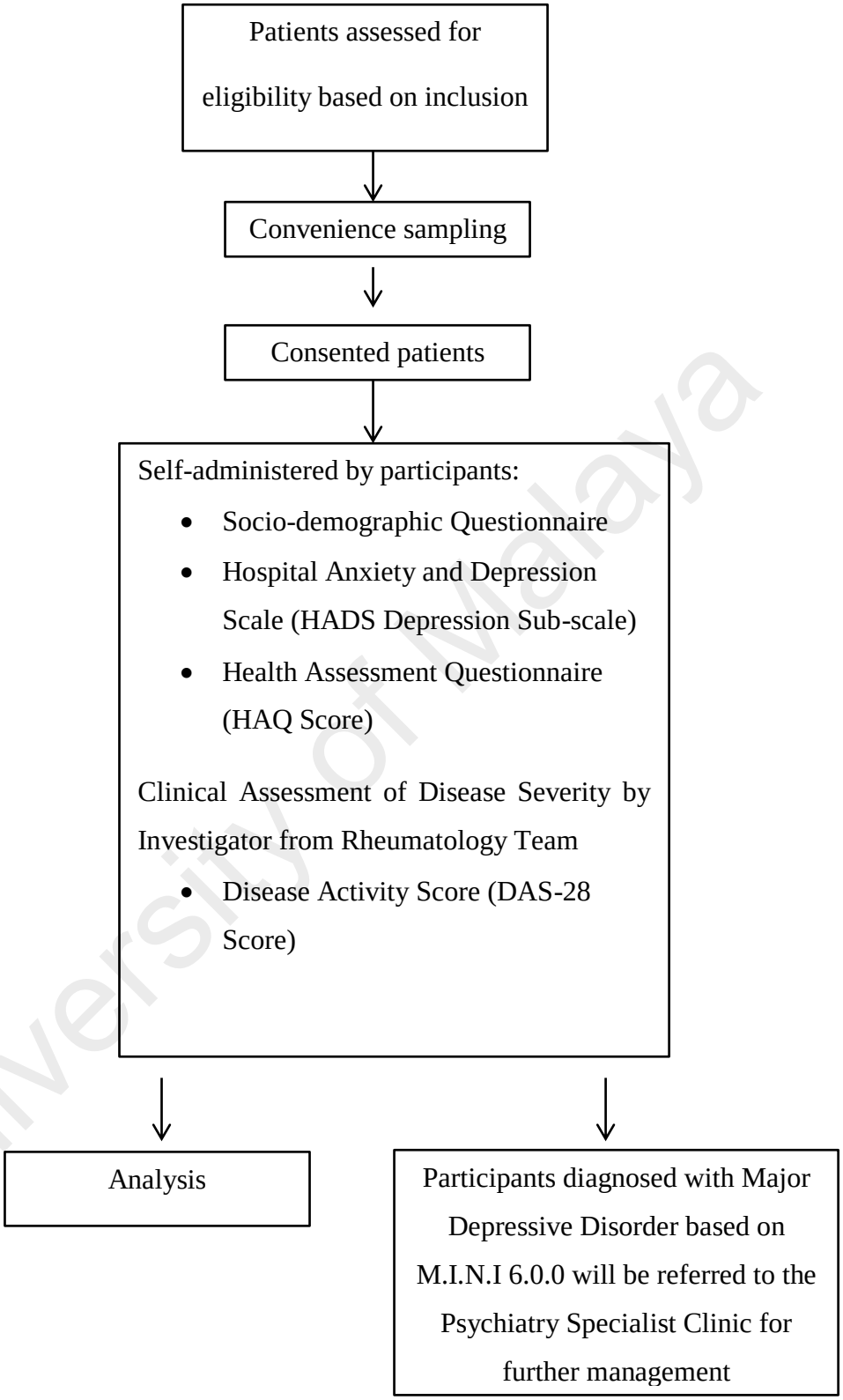

Figure 3.1 Flow chart of the research study

3.12 Study Variables

3.12.1 Independent Variables

- Socio-Demographic Factors- Age, Sex, Occupation, Education Level, Religion, Marital Status (Evaluated by self-generated Socio-Demographic Questionnaire)
- Functional Status and Quality of Life in Rheumatoid Arthritis (Measured by HAQ)
- Clinical Factors such as Disease Severity of Rheumatoid Arthritis (Measured by DAS-28), types of medication and onset of illness (included in Socio-Demographic Questionnaire).

3.12.2 Dependent Variable

- Symptoms of depression among Rheumatoid Arthritis patients (based on HADS score).

3.13 Data Analysis

The categorical variables were presented with frequency and percentage while the numerical variables were presented in mean with standard deviation (SD).

Univariate analysis such as using One-way ANOVA and Spearman's correlation test were conducted to determine the association between the potential factors and symptoms of depression (based on HADS score). Multivariate analysis using Analysis of Co-Variance (ANCOVA) was performed to determine whether or not the disease activity (DAS-28 score) and functional status (HAQ score) were associated with symptoms of depression (based on HADS score) after the potential confounder(s) is included in the model. All analyses were carried out using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

3.14 Ethical Considerations

The National Medical Research and Ethics Committee (MREC) of Ministry of Health (MOH), Malaysia via the National Medical Research Registry (NMRR) approved this research project. Written approval to conduct the study in Hospital Umum Sarawak was obtained from the Hospital Director and Head of Department of Internal Medicine.

All questionnaires administered in this study are in accordance with the ethical standards of the institutional and national research committee, and with the Declaration of Helsinki 1964, and its later amendments or comparable ethical standards.

Participation in this study was entirely voluntary. An informed consent was obtained from the voluntary respondents, and all responses will be ensured of confidentiality. Instead of respondent identifiers, each respondent was assigned an identification number, which was used on the subject data sheets. The participants were also given flyers containing the information on Depression and how to approach the nearest psychiatric clinic should they require any further assistance in the future. Additionally, participants who were diagnosed with Depression were referred to the Psychiatry Specialist Clinic for additional management.

All data were entered into a computer that is password protected. On completion of the study, data in the machine was copied to compact discs or other physical data storage mediums (such as USB Drives and Portable Hard Disks) while the data in the computer was erased for protection. All physical storage mediums containing patient and study data will be stored in a locked office in the investigator's department and maintained for a minimum of **three (3) years** following the completion of the study. After that period, the physical storage mediums will be destroyed. Subjects will not be allowed to view their personal information and study data, as the data will be consolidated into a database.

The data from the study was used to generate a report, which may be used for publication purposes. When writing up the dissertation and possible publication, all subjects will be acknowledged anonymously as patients with Rheumatoid Arthritis in Hospital Umum Sarawak, with no references to any names. Hence, the confidentiality of the participants will be protected.

3.15 Conflict Of Interest

The author declared that he has no conflict of interest. The author will not and did not receive any financial support for this study.

CHAPTER 4

RESULTS

4.1 Overview Of Subject Participation

A total of 255 patients were approached during the course of the data collection period from October 2018 to the end of November 2018. Of the total, forty-eight subjects (18.8%, n=48) attending the Rheumatology Clinic with Rheumatoid Arthritis were excluded from the study due to their refusal to be enrolled into the study and for fulfilling the exclusion criteria.

By the end of the data-collection period, a total of 207 participants were enrolled, which was ten short of the target of 217 subjects based on Kish's Sample Size Calculation for Prevalence Studies.

4.2 Socio-Demographic Characteristics Of Participants

The mean age of the 207 subjects enrolled into the study was 55.4 years (SD=11.7 years). The majority of participants were female (86%, n=176), which was about 5.6 times the total number of male participants.

Participants of Malay ethnicity made up the majority with 39.6% (n=82). This was followed by participants of Bumiputera Sarawak ethnicity (33.3%, n=69), Chinese ethnicity (26.6%, n=55) and finally, Indian ethnicity (0.5%, n=1).

The study enrolled a diverse group of individuals from various religions. Participants who were Christians (42%, n=87) and Muslim (39.1%, n=81) were the most common; followed by Buddhist (14%, n=29) while the remainder comprised of Hindu (0.5%, n=1), Atheist (2.4%, n=5) and unspecified religions (1.9%, n=4).

More than two thirds of subjects were married (75.8%, n=157) while another 16.4% (n=34) were single. The remainder consists of participants who were either divorced (3.9%, n=8) or widowed (3.9%, n=8).

A substantial portion of participants was educated up to secondary level (45.4%, n=94) while 29.5% (n=61) were educated up to primary level. The proportion of participants who received no formal education and tertiary education were equal at 12.6% (n=26) respectively.

In terms of employment, a significant proportion of subjects was unemployed (57.5%, n=119), followed by service (22.7%, n=47), professional (8.7%, n=18), sales (4.3%, n=9), clerical work (3.9%, n=8) and retired (2.9%, n-6). Table 4.1 summarizes the socio-demographic characteristics of the study subjects.

Table 4.1: Socio-demographic characteristics of participants

Profile	Mean	SD	n	%
Age	55.4	11.7		
Gender				
Male			31	14.0
Female			176	86.0
Race				
Malay			82	39.6
Chinese			55	26.6
Indian			1	0.5
Bumiputera Sarawak			69	33.3
Religion				
Islam			81	39.1
Christian			87	42.0
Others			4	1.9
Buddhist			29	14.0
Hindu			1	0.5
Atheist/None			5	2.4
Marital Status				
Single			34	16.4
Married			157	75.8
Divorced			8	3.9
Widowed			8	3.9
Education Level				
No Formal Education			26	12.6
Primary Education			61	29.5
Secondary Education			94	45.4
Tertiary Education			26	12.6
Employment				
Professional			18	8.7
Clerical			8	3.9
Sales			9	4.3
Service			47	22.7
Unemployed			119	57.5
Retired			6	2.9

4.3 Clinical Characteristics Of Participants

The participants sampled in the Rheumatology clinic had a mean age for diagnosis of Rheumatoid Arthritis at 48.1 years old (SD=12.0 years). The mean duration of illness of RA among the studied population was 7.3 years (SD=6.5 years).

Of the 207 subjects sampled, patients with duration of illness between 1 to 5 years and more than 10 years were the most common at 32.4% (n=67) and 30.9% (n=64) respectively. Participants with a duration of illness between 5 to 10 years made up 25.1% (n=52) of the population, while subjects with newly diagnosed RA (less than 1 year) made up 11.6% (n=24) of patients sampled.

In terms of treatment for Rheumatoid Arthritis, 55.6% (n=115) of all 207 subjects were on Non-Steroidal Anti-inflammatory Drugs (NSAIDs), 60.4% (n=125) were on Corticosteroids and finally, 91.8% (n=190) of subjects were on some form of Disease Modifying Anti-Rheumatic Drugs (DMARDs).

A modest majority of participants had some form of medical comordities (58%, n=120). Hypertension was the most common chronic medical condition with a prevalence of 41.1% (n=85) of the population. Dyslipidemia affected 16.9% (n=35) of the population while 10.1% (n=21) had diabetes mellitus. A small segment of the population had cardiovascular illness (2.9%, n=6). Lastly, 19.3% (n=40) of subjects sampled had other unspecified chronic illnesses. Table 4.2 summarizes the clinical characteristics of Rheumatoid Arthritis and medical comorbidities in the sampled population.

Table 4.2 Clinical characteristics of participants

	Mean	SD	n	%
Age of onset of RA (years)	48.1	12		
Duration of RA illness (years)	7.3	6.5		
Duration of illness (RA)				
less than 1 year			24	11.6
1 to 5 years			67	32.4
5 to 10 years			52	25.1
more than 10 years			64	30.9
RA Treatment (NSAIDs)				
Yes			115	55.6
No			92	44.4
RA Treatment (Corticosteroids)				
Yes			125	60.4
No			82	39.6
RA Treatment (DMARDs)				
Yes			190	91.8
No			17	8.2
Medical Comorbidities				
Yes			120	58
No			87	42
Diabetes Mellitus				
Yes			21	10.1
No			186	89.9
Hypertension				
Yes			85	41.1
No			122	58.9
Dyslipidemia				
Yes			35	16.9
No			172	83.1
Cardiovascular Disease				
Yes			6	2.9
No			201	97.1
Others				
Yes			40	19.3
No			167	80.7

From a psychiatric perspective, summarized in Table 4.3, only seven participants (3.4%) have a history of being diagnosed with clinical depression; of which only three (1.4%) were actively on some form of treatment for depression and under regular follow-up in a Psychiatry Clinic.

Table 4.3 Profiles of participants with existing depression

	n	%
History of Depression		
Yes	7	3.4
No	200	96.6
Current Treatment For Depression		
Yes	3	1.4
No	204	98.6
Antidepressants		
Yes	2	1
No	205	99
Psychotherapy		
Yes	1	0.5
No	205	99
Others		
Yes	1	0.5
No	206	99.5
Follow up in Psychiatry Clinic		
Yes	3	1.4
No	204	98.6

4.4 Findings From Depression Screening

All 207 participants were screened for depression with the Hospital Anxiety and Depression Scale (HADS), summarized below in Table 4.4. The mean score for HADS (Depression Sub-Scale) among the 207 participants was merely 0.7 (SD=1.6). A significant proportion of participants (61.4%, n=127) reported not having any symptoms of depression. The remaining 38.7% (n=80) of the 207 subjects reported at least one or more depressive symptom based on HADS.

Interestingly, only three patients (1.5%) recorded scores of eight or more in the HADS Depression Sub-Scale, which is the cut off point for depression.

All three patients were subsequently diagnosed with Major Depressive Disorder after being subjected to a structured clinical interview in the form of the MINI International Neuropsychiatric Interview (MINI) Version 6.0.0. None of the patients had history of self-harm, suicidal ideation or organized plans (based on MINI). They were all given early appointments to the Psychiatry outpatient clinic.

Table 4.4 HADS score (Depression sub-scale)

	Mean	SD	n	%
HADS Score	0.7	1.6		
HADS				
0			127	61.4
1			47	22.7
2			19	9.2
3			6	2.9
4			3	1.4
5			1	0.5
6			1	0.5
7			0	0.0
8			1	0.5
9			1	0.5
10			0	0.0
11			1	0.5
12			0	0.0
13			0	0.0
14			0	0.0
15			0	0.0
16			0	0.0
17			0	0.0
18			0	0.0
19			0	0.0
20			0	0.0
21			0	0.0

4.5 Functional Health Status And Quality Of Life In Rheumatoid Arthritis

Based on the Health Assessment Questionnaire (HAQ), summarized in Table 4.5, a significant majority of patients that were screened had no difficulties performing important daily tasks. The mean HAQ score (without factoring the inclusion of aids and devices) was 0.25 (SD=0.43).

In terms dressing and grooming, 14.5% (n=30) reported having some difficulty dressing themselves and 6.8% (n=14) complained of having some difficulty shampooing their hair.

Looking at tasks that involve arising, 14.5% (n=30) of subjects complained of having some difficulty standing up from a straight chair. 15.9% (n=33) had some difficulty getting in and out of bed.

A relatively sizeable portion of subjects had some difficulties in tasks that required the consumption of food. 12.6% (n=26) had some difficulty cutting their own meat with a knife, 9.7% (n=20) had some difficulty lifting a cup to mouth and 13.0% (n=27) had some difficulty opening a new milk carton.

About a fifth (20.3%, n=42) of participants complained of having some difficulty walking up five steps while 6.3% (n=13) were unable to perform this specific task. A total of 8.2% (n=17) of subjects were reported to have some difficulty walking on flat surfaces with 2.4% (n=5) stating that they were even unable to do this.

In terms of tasks required to ensure self-hygiene, 6.8% (n=14) of patients sampled had some difficulty washing and drying themselves, 5.3% (n=11) complained of having some difficulty having a tub bath while 12.1% (n=25) had some difficulty getting on and off the toilet.

Next, 15.5% (n=32) of participants had some difficulty reaching and carrying a five-pound object over the head while an additional 5.8% (n=12) were unable to

perform this task. Another 16.4% (n=34) of respondents had some difficulty bending down and reaching objects and 2.4% (n=5) were unable to do this.

Additionally, among tasks that involved gripping of the fingers, 10.1% (n=21) of subjects had some difficulty opening previously opened jars, 8.7% (n=18) had some difficulty turning a faucet while 5.3% (n=11) had some difficulty opening car doors.

Finally, with regards to day-to-day activities, a rather sizeable 10.6% (n=22) of patients were unable to perform chores such as vacuuming and yard work. While, 11.6% (n=24) of patients had some difficulty running errands and shopping and 9.2% (n=19) of patients complained of having some difficulty getting in and out of the car.

Table 4.5 Functional health status in Rheumatoid Arthritis (HAQ)

	Mean	SD	No Difficulty n (%)	Some Difficulty n (%)	Much Difficulty n (%)	Unable To Do n (%)
HAQ Score	0.25	0.43				
Dressing and grooming						
Dress yourself			174 (84.1)	30 (14.5)	2 (1.0)	1 (0.5)
Shampoo hair			191 (92.3)	14 (6.8)	1 (0.5)	1 (0.5)
Arising						
Stand up from straight chair			161 (77.8)	30(14.5)	13 (6.3)	3 (1.4)
Get in and out of bed			163 (78.7)	33 (15.9)	9 (4.3)	2 (1.0)
Eating						
Cut own meat			167 (80.7)	26 (12.6)	8 (3.9)	6 (2.9)
Lift cup to mouth			185 (89.4)	20 (9.7)	2 (1.0)	0 (0)
Open new milk carton			162 (78.3)	27 (13.0)	8 (3.9)	10 (4.8)
Walking						
Outdoors on flat ground			177 (85.5)	17 (8.2)	8 (3.9)	5 (2.4)
Climb up five steps			138 (66.7)	42 (20.3)	14 (6.8)	13 (6.3)
Hygiene						
Wash and dry body			192 (92.8)	14 (6.8)	0 (0)	1 (0.5)
Tub bath			193 (93.2)	11 (5.3)	2 (1.0)	1 (0.5)
Get on and off toilet			176 (85.0)	25 (12.1)	3 (1.4)	3 (1.4)
Reach						
Get 5lbs object over head			156 (75.4)	32 (15.5)	7 (3.4)	12 (5.8)
Bend down and reach object			161 (77.8)	34 (16.4)	7 (3.4)	5 (2.4)
Grip						
Open Car Door			193 (93.2)	11 (5.3)	1 (0.5)	2 (1.0)
Open Jars			179 (86.5)	21 (10.1)	2 (1.0)	5 (2.4)
Turn Faucet			184 (88.9)	18 (8.7)	3 (1.4)	1 (0.5)
Activities						
Errands and shop			164 (79.2)	24 (11.6)	9 (4.3)	10 (4.8)
Get in and out of car			176 (85.0)	19 (9.2)	8 (3.9)	4 (1.9)
Chores			149 (72.0)	29 (14.0)	7 (3.4)	22 (10.6)

4.6 Disease Severity Of Rheumatoid Arthritis

The mean score of the Disease Activity Score (DAS-28) was 3.0 (SD=1.1). The majority of patients were in remission (37.7%, n=78). This was followed by low disease activity (29.0%, n=60), moderate disease activity (27.5%, n=57) and severe (5.8%, n=12). The findings are listed below in Table 4.6 and depicted in Figure 4.1.

Table 4.6 Disease severity of Rheumatoid Arthritis (DAS-28

	Mean	SD	n	%
DAS-28 Score	3.0	1.1		
Severity				
Remission (<2.6)			78	37.7
Low Disease Activity (2.6-3.2)			60	29.0
Moderate Disease Activity (3.2-5.1)			57	27.5
Severe (>5.1)			12	5.8

4.7 Association Between Socio-Demographic Profile And Clinical Characteristics Towards HADS

There is no sufficient evidence to indicate that the demographics of subjects is associated with HADS. Treatment modalities for Rheumatoid Arthritis were not significantly associated with depressive symptoms. Out of all clinical parameters, only the status of Cardiovascular Disease is associated with depressive symptoms in HADS (p-value=0.032). This is detailed in Table 4.7 and Table 4.8.

Table 4.7 Analysis of association between socio-demographic profiles towards HADS

	Spearman's rho		One-way ANOVA	
	Correlation Coefficient	**p-value**	**Mean (SD)**	**p-value**
Age	-0.024	0.733		
Gender				0.784
Male			0.7 (1.0)	
Female			0.8 (1.5)	
Race				0.574
Malay			0.7 (1.5)	
Chinese			0.7 (1.1)	
Indian			2.0 (-)	
Bumiputera Sarawak			0.9 (1.7)	
Religion				0.778
Islam			0.7 (1.5)	
Christian			0.9 (1.6)	
Others			0.3 (0.5)	
Buddhist			0.7 (1.1)	
Hindu			2.0 (-)	
Atheist/None			0.4 (0.5)	
Marital Status				0.654
Single			0.7 (1.4)	
Married			0.7 (1.4)	
Divorced			1.4 (3.2)	
Widowed			0.6 (0.7)	
Education Level				0.318
No Formal Education			1.2 (1.6)	
Primary Education			0.6 (1.2)	
Secondary Education			0.8 (1.6)	
Tertiary Education			0.5 (1.1)	
Employment				0.537
Professional			0.3 (0.6)	
Clerical			0.6 (0.7)	
Sales			0.2 (0.4)	
Service			0.6 (1.5)	
Unemployed			0.9 (1.6)	
Retired			0.8 (1.6)	

Table 4.8 Analysis of association between clinical characteristics towards HADS

	Spearman's rho Correlation Coefficient	p-value	One-way ANOVA Mean (SD)	p-value
Age of onset of RA	-0.061	0.386		
RA Treatment (NSAIDs)				0.742
Yes			0.8 (1.4)	
No			0.7 (1.5)	
RA Treatment (Corticosteroids)				0.436
Yes			0.8 (1.5)	
No			0.6 (1.4)	
RA Treatment (DMARDs)				0.776
Yes			0.8 (1.5)	
No			0.6 (0.7)	
Medical Comorbidities				0.070
Yes			0.9 (1.8)	
No			0.5 (0.8)	
Diabetes Mellitus				0.568
Yes			0.6 (1.0)	
No			0.8 (1.5)	
Hypertension				0.345
Yes			0.9 (1.6)	
No			0.7 (1.3)	
Dyslipidemia				0.996
Yes			0.7 (1.5)	
No			0.7 (1.4)	
Cardiovascular Disease				**0.032***
Yes			2.0 (1.4)	
No			0.7 (1.4)	
Others				0.265
Yes			1.0 (1.8)	
No			0.7 (1.4)	

** Statistically significant (p <0.05)*

4.8 Association Between Functional Status (HAQ Score) And Depressive Symptoms (HADS Score)

Symptoms of depression do notably affect the functioning status of Rheumatoid Arthritis patients. Out of twenty parameters, eighteen were found to be statistically significant ($p<0.001$ until $p=0.007$). Among all the functioning status, only "Shampoo Hair" and "Turn Faucet" were not statistically significant. Table 4.9 depicts the associations.

Table 4.9 Analysis of association between HAQ and HADS

	One-way ANOVA				
	No Difficulty	**Some Difficulty**	**Much Difficulty**	**Unable To Do**	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**p-value**
Dressing and Grooming					
Dress Yourself	0.6 (1.2)	1.4 (2.2)	0.5 (0.7)	4.0 (0)	**0.007***
Shampoo Hair	0.7 (1.5)	0.9 (0.9)	1.0 (0)	4.0 (0)	0.159
Arising					
Stand Up From Straight Chair	0.5 (1.1)	1.3 (2.1)	1.9 (2.5)	2.0 (2.0)	**<0.001***
Get In and Out of Bed	0.5 (0.9)	1.6 (2.4)	2.2 (3.1)	1.0 (1.4)	**<0.001***
Eating					
Cut Own Meat	0.5 (1.0)	1.3 (2.0)	1.8 (2.1)	2.8 (4.3)	**<0.001***
Lift Full Cup To Mouth	0.6 (1.1)	2.1 (2.9)	3.0 (4.2)	0 (0)	**<0.001***
Open New Milk Carton	0.5 (0.8)	1.4 (2.0)	1.9 (2.7)	2.6 (3.6)	**<0.001***
Walking					
Walk Outdoors On Flat Ground	0.6 (1.1)	1.6 (2.6)	1.9 (2.6)	2.4 (2.6)	**<0.001***
Climb Up Five Steps	0.4 (0.7)	1.2 (1.7)	1.1 (0.9)	2.6 (3.6)	**<0.001***

Cont.

Hygiene					
Wash and Dry Body	0.6 (1.2)	1.9 (3.0)	0 (0)	4.0 (0)	**<0.001***
Tub Bath	0.7 (1.3)	2.0 (3.2)	0 (0)	4.0 (0)	**0.002***
Get On and Off Toilet	0.5 (1.0)	2.0 (3.0)	0.7 (1.2)	2.0 (2.0)	**<0.001***
Reach					
Get Five Pound Object	0.5 (1.1)	1.2 (1.6)	0.7 (1.1)	2.3 (3.3)	**<0.001***
Bend Down	0.5 (1.2)	1.5 (2.1)	0.6 (1.0)	2.6 (2.4)	**<0.001***
Grip					
Open Car Door	0.7 (1.4)	1.5 (1.6)	0 (0)	5.0 (1.4)	**<0.001***
Open Jars	0.7 (1.4)	0.7 (0.9)	3.5 (2.1)	2.8 (2.2)	**<0.001***
Turn Faucet	0.7 (1.4)	1.2 (1.8)	0.7 (1.2)	4.0 (0)	0.064
Activities					
Run Errands and Shop	0.5 (0.9)	1.1 (2.0)	2.1 (3.4)	2.1 (2.9)	**<0.001***
Get In and Out of Car	0.6 (1.3)	0.8 (1.1)	2.3 (2.7)	2.0 (2.8)	**0.005***
Chores	0.5 (0.7)	1.3 (2.0)	1.1 (1.2)	1.8 (3.0)	**<0.001***

**Statistically significant (p <0.05)*

4.9 Disease Activity (DAS-28 Score) And Functional Status (HAQ Score) Of Rheumatoid Arthritis Towards Depressive Symptoms (HADS)

Based on univariate analysis that was performed and out of the numerous variables, disease activity and functional status of Rheumatoid Arthritis (DAS-28 and HAQ Score respectively) were associated with depressive symptoms (HADS) (Spearman rank test, $p=0.005$ and $p<0.001$ respectively).

However, following multivariate analysis and the control for potential confounder in the form of cardiovascular disease (CVD) status, DAS-28 score was no longer significant (ANCOVA, $p=0.697$) but HAQ Score remained significant with $p<0.001$. Figure 4.2, Figure 4.3 and Table 4.10 highlights this.

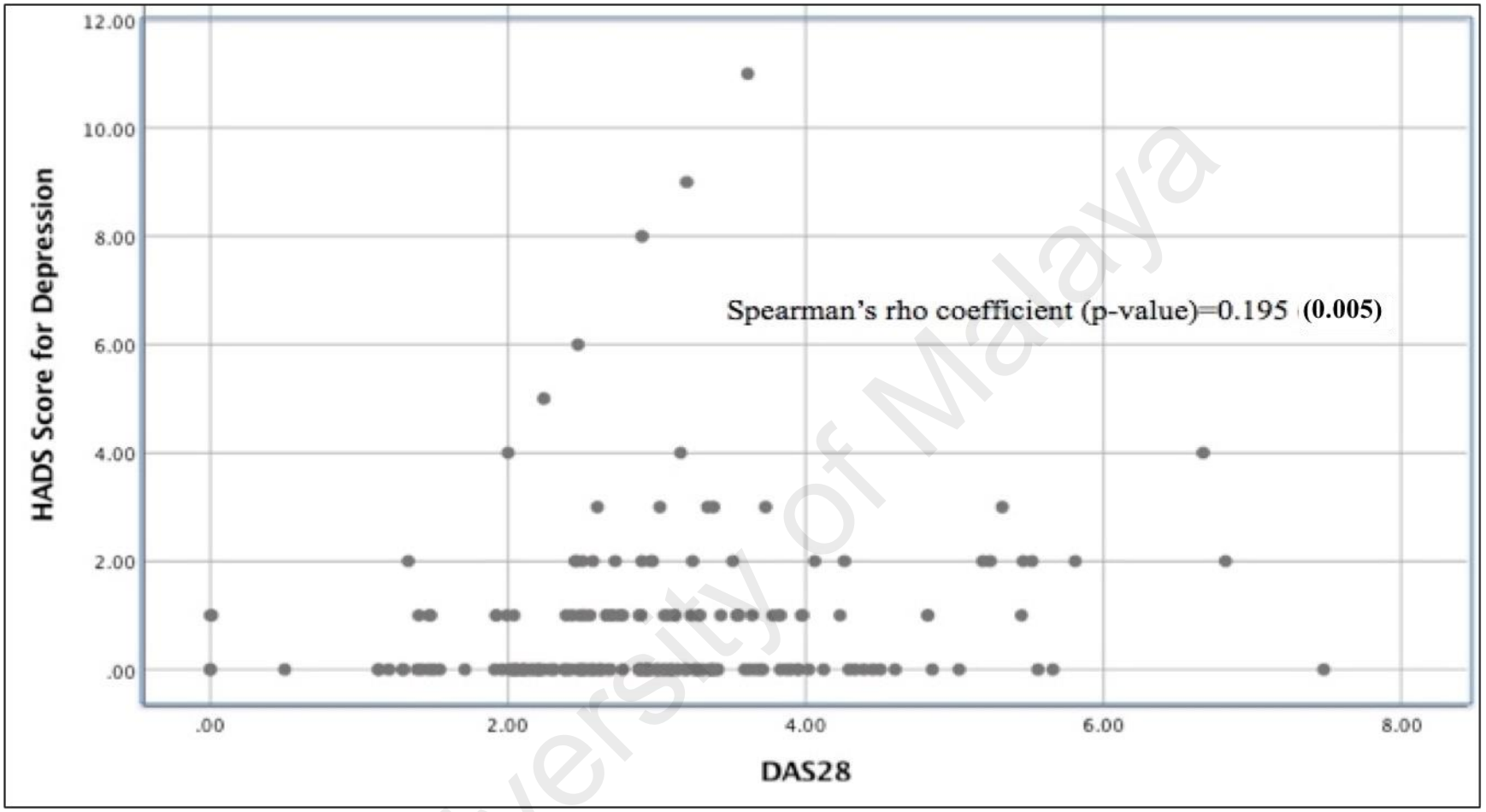

Figure 4.1: Scatter plot and correlation between DAS-28 and HADS score for depression among patients with RA

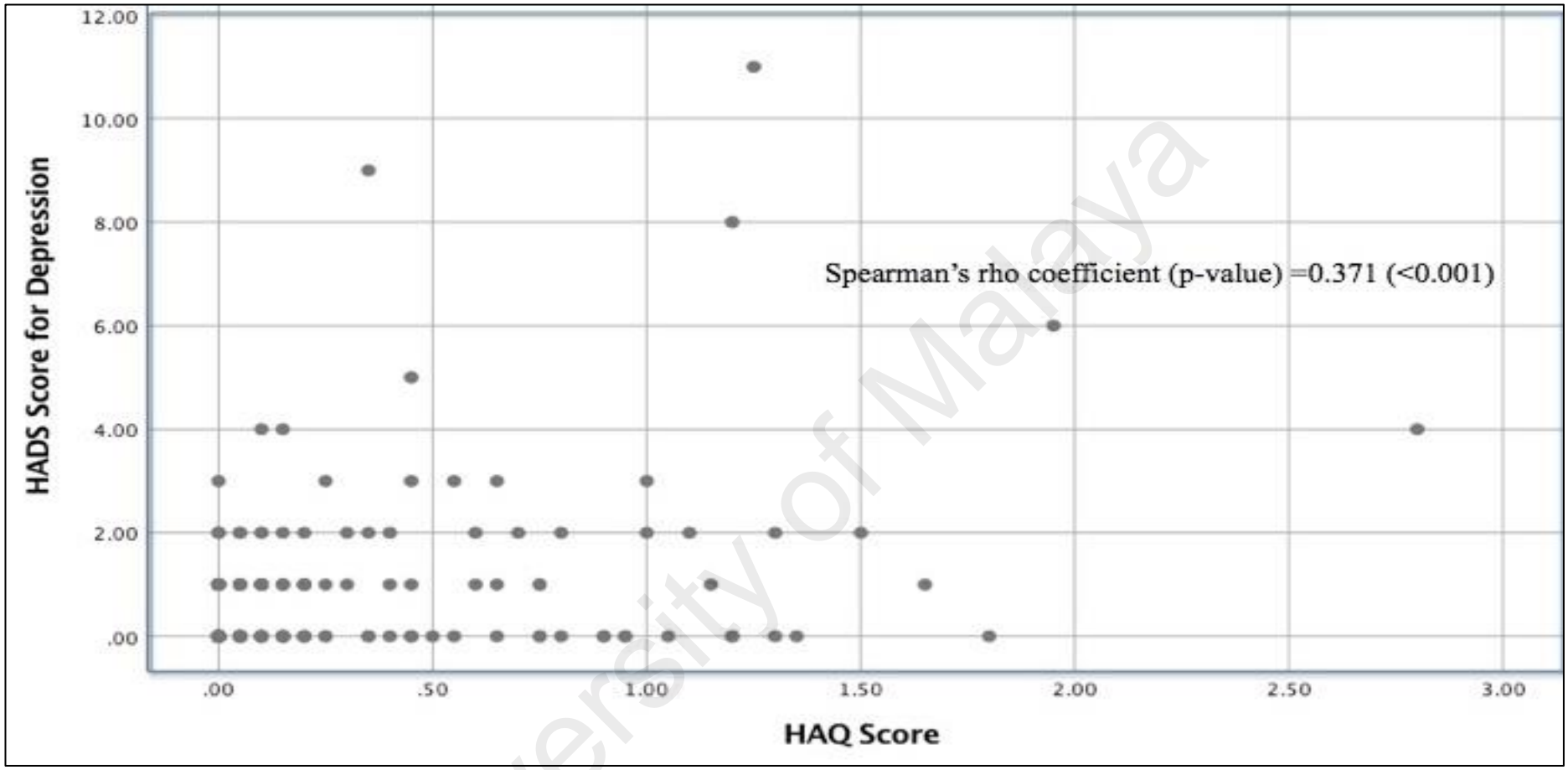

Figure 4.2: Scatter plot and correlation between HAQ Score and HADS score for depression among patients with RA

Table 4.10: Analysis of association between DAS-28 and HAQ score towards HADS score for depressive symptoms after controlled for status of cardiovascular disease (CVD)

Source	Type III Sum of Squares	df	Mean Square	F	p-value
Corrected Model	69.323a	3	23.108	12.743	<0.001
Intercept	6.636	1	6.636	3.659	0.057
CVD	1.912	1	1.912	1.054	0.306
DAS-28	0.276	1	0.276	0.152	0.697
HAQ Score	52.693	1	52.693	29.059	**<0.001***
Error	368.107	203	1.813		
Total	552	207			
Corrected Total	437.43	206			

a R Squared = 0.158 (Adjusted R Squared = 0.146)

**Statistically significant (p <0.05)*

CHAPTER 5

DISCUSSION

The study aimed to identify the prevalence of depression among Rheumatoid Arthritis patients in the Sarawak General Hospital. A significant number of studies regarding the matter have been conducted in the Western industrialized nations with a predominantly Caucasian group. The author aimed to ascertain if the findings were similar in the local setting. Additionally, the author aimed to identify probable associations of depression in a local setting with an emphasis on severity of the Rheumatoid Arthritis disease and functional status.

Overall, the study recruited 207 participants, with a mean age of 55.4 years (SD=11.7 years). In 11.6% (n=24) of subjects, Rheumatoid Arthritis was recently diagnosed with duration of illness of less than one year. A further 58.0% (n=120) of the subjects have at least one form of medical comorbidity.

In the study, 3.4% (n=7) of the participants have a pre-existing history of clinical depression. Three of the subjects with pre-existing depression were still actively managed by the psychiatric services.

Based on the HADS questionnaire, the prevalence of active clinical depression was low at 1.5% (n=3). However, 38.7% (n=80) of the subjects in the study reported having at least one depressive symptom. The remaining participants (61.4%, n=127) did not report having any depressive symptoms.

5.1 Prevalence Of Depression In Patients With Rheumatoid Arthritis

Only 3.4% (n=7) of participants were reported to have a pre-existing history of clinical depression. Less than half of that number (1.4%, n=3) was still actively managed for depression and on regular follow-up with psychiatry services.

The author screened all 207 participants for depression using the Hospital Anxiety and Depression Scale (HADS). The author took a score of eight or more on the HADS Depression Sub-scale as the cut-off score for clinical depression. Surprisingly, the mean score for HADS (Depression Sub-Scale) among the 207 participants was only 0.7 (SD=1.6). The study found that the prevalence of depression among the subjects with RA was only 1.5% (n=3).

The prevalence of depression in patients with Rheumatoid Arthritis was lower compared to previous studies conducted in Malaysia. In a study conducted in Hospital Melaka, Ruhaila and Chong (2018) recorded a higher prevalence of depression of 23.3% (n=44). Sulaiman et al. (2017) reported that 38.6% (n=40) of patients have depression in a Rheumatology and Pain clinic in Ipoh. Moreover, Chow et al. (2002) reported the prevalence of depression in 17.2% (n=16) of the subjects surveyed. Their finding was comparable to that observed by Matcham et al. (2013), in a widely cited meta-analysis study, who reported the overall prevalence of major depressive disorder among patients with RA was 16.8%.

It is worth noting that the three studies had smaller sample sizes and were conducted in Peninsular Malaysia. The areas are comparatively more urbanized compared to states in East Malaysia. Additionally, there did not appear to be any attempt to establish a diagnosis of Major Depressive Disorder based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) among the patients screened in the other local studies.

The Hospital Anxiety and Depression Scale (HADS) is one of the most widely used screening tools among studies listed in the review, with the use of a different threshold for depression (Matcham et al., 2013). The prevalence levels according to the HADS with limits of 8 and 11 were 34.2% and 14.8%, respectively (Matcham et al., 2013; Matcham et al., 2014). However, Matcham et al. (2013) noted that some of the individual studies listed in the meta-analysis reported a low prevalence of depression among patients with Rheumatoid Arthritis, ranging from 0.04% to 2.9%.

COMORA, a large international cross-sectional study, involving some 4586 patients from 17 different countries, reported that depression was the most commonly observed comorbidity among patients with Rheumatoid Arthritis (15%) (Dougados et al., 2014). However, it is worth noting that there were variations in the definition of "depression" among the participating centers. This study reported a wide range in the prevalence of depression; the participating center in Morocco reported a prevalence of 2% while a center in the United States had a prevalence of 33% (Dougados et al., 2014). In fairness, the authors have stated that factors such as variation in the degree of Rheumatoid Arthritis disease severity and variations in mental health literacy among patients from different cultural settings might lead to diverse interpretations of questions included in the questionnaire (Dougados et al., 2014).

In a prospective study, conducted in California, Margaretten et al. (2009) findings echoed the low prevalence of depression among the Rheumatoid Arthritis patients screened in Hospital Umum Sarawak. They reported that patients of Asian descent had lower depression scores (based on PHQ-9) compared to their Hispanic, African-American and Caucasian counterparts. Margaretten et al. (2009) postulated that the low prevalence of depression among Asians may be due to stigma and the perception of mental illness as a character weakness.

As a result of the low prevalence of depression in this study, the initial goal to evaluate the associations of depression had to be realigned to the evaluation of the associations of symptoms of depression in Rheumatoid Arthritis.

Several studies have shown that depressive symptoms, even in the absence of major depressive disorder, may contribute to the psychosocial dysfunction and the burden of suffering faced by Rheumatoid Arthritis patients (P. P. Katz & Yelin, 1993; Smarr et al., 2000). Although not ideal, this may help provide some valuable information into the care of individuals with Rheumatoid Arthritis.

As stated earlier, a low prevalence of depression was reported among patients with Rheumatoid Arthritis in Hospital Umum Sarawak. These findings were not comparable with the results of similar studies conducted among patients with Rheumatoid Arthritis in peninsular Malaysia and Western countries (Ruhaila & Chong, 2018). Patients with RA have a significantly higher level of depression than that of the general population (Geenen, Newman, Bossema, Vriezekolk, & Boelen, 2012; Matcham, Ali, Irving, Hotopf, & Chalder, 2016).

The first and possibly most notable observation would be the differences in setting between studies conducted in our center compared to Peninsular Malaysia and Western countries. The author had the opportunity to converse with many patients over the course of two months. For example, some patients from the Betong division have spoken about having to hike for hours on logging roads before taking another five-hour bus ride to reach Kuching. This makes attending a routine follow-up in Hospital Umum Sarawak both financially taxing and time-consuming. Unfortunately, the author did not gather data of the location of origin and distance from treating center in this study. However, it is important to note that a large number of patients who participated in this study originated from non-urban areas of Sarawak (Serian, Simunjan and Betong divisions).

The differences in urban and rural settings and its role in the prevalence of depression are well documented. Some studies have found that individuals in rural areas had a lower prevalence of depression compared to individuals in urban areas (Mueller, 1981; Romans, Cohen, & Forte, 2011; J. L. Wang, 2004). The increased risk of depression in urban areas may be explained by Leighton's "sociocultural disintegration hypothesis" which describes the breakdown in family and matrimonial relationships, diminished interaction with peers and elevated levels of hostility seen in the urban setting which disrupts psychological well-being (J. L. Wang, 2004).

Additionally, patients from rural areas had comparatively lower emotional stress associated with housing, vocation, marriage, children and the general sense of security which may contribute to the lower prevalence of mental illness (Marsella, 1998). The role of rural to urban migration, which has its own set of stressors, requires a degree of coping and resilience due to cultural adaptation to integrate and assimilate in the face of inevitable rejection, may have an impact on mental health (J. L. Wang, 2004).

In Malaysia, there appeared to be significant differences in the understanding and beliefs of depression between urban and rural populations. Two studies have been identified and conducted among both rural and urban Malay and Chinese groups (Loo & Furnham, 2012; Swami, Loo, & Furnham, 2010). Rural participants were more likely to link depression to an external locus of control and supernatural causes as opposed to urban participants who were more likely to connect depression to biological reasons (Swami et al., 2010). Furthermore, the rural participants were more likely to emphasize the role of religion in the treatment of depression compared to their urban counterparts (Swami et al., 2010). In other words, the low prevalence rates among individuals from rural areas, as seen here in this study, may be a result of under-reporting due to poorer mental health literacy which is associated with poor symptom recognition and reduced rates of help-seeking behavior (Swami et al., 2010).

The low prevalence of depression seen in this study could also be attributed to superior social support among patients from rural areas compared to their urban counterparts (J. L. Wang, 2004). This is supported by studies that have found that patients who have been diagnosed with Rheumatoid Arthritis that had higher perceived social support reported to exhibit less depression and pain compared to those with lower social support (Evers et al., 1997; Treharne, Kitas, Lyons, & Booth, 2005). However, it is worth noting that aspects of perceived social support were not evaluated in this study.

Conversely, it is also worth noting that more recent studies have reported that there was no significant difference in prevalence of depression between rural and urban populations (Peen, Schoevers, Beekman, & Dekker, 2010; Probst et al., 2006). Moreover, cultural beliefs of different ethnic groups have been implicated to differentially affect the prevalence of depression between rural and urban populations (Weaver, Himle, Taylor, Matusko, & Abelson, 2015).

Another possible explanation of the low prevalence could be the relatively small proportion of patients screened who were in the early stages of Rheumatoid Arthritis. Rheumatoid Arthritis patients in the early stages of the disease were reported to have a higher prevalence of depression compared to patients with chronic illness (Crotty et al., 1994; Isik, Koca, Ozturk, & Mermi, 2007; Smedstad, Vaglum, Moum, & Kvien, 1997).

Additionally, the significance between the association of perception of Rheumatoid Arthritis and depression, in the early stages of the disease, is apparent in patients who view their illness as serious had increased disability and prevalence of depression (Schiaffino, Shawaryn, & Blum, 1998; Sharpe, Sensky, & Allard, 2001). Sharpe et al. (2001) investigated 22 patients with early Rheumatoid Arthritis and found that factors such as a previous history of depression, the level of disability, pain, beliefs about the consequences of arthritis and their coping strategies significantly contributed to the development of depression.

5.1.1 Depressive Symptoms In Rheumatoid Arthritis

An interesting observation was made in this study; whereby 38.7% (n=80) of the subjects reported having depressive symptom while the remaining participants (61.4%, n=127) did not report having any depressive symptoms in this study. The presence of depressive symptoms may not be sufficient to diagnose clinical depression as they may have a cumulative score below the threshold established in HADS.

Thus far, there is a lack of data from literature that reported the prevalence of depressive symptoms in Rheumatoid Arthritis. P. P. Katz and Yelin (1993) reported that 17% of patients with Rheumatoid Arthritis had depressive symptoms, which was lower compared to this study.

Despite the lack of data, the symptoms of depression should not be disregarded because, even in the absence of major depressive disorder, it may contribute to the psychosocial dysfunction and the burden of suffering faced by Rheumatoid Arthritis patients (P. P. Katz & Yelin, 1993; Smarr et al., 2000).

5.2 Depressive Symptoms And Functional Status In Rheumatoid Arthritis

Increasing research and interest have focused on the health-related quality-of-life in patients with Rheumatoid Arthritis. Based on the raw Health Assessment Questionnaire (HAQ), the mean HAQ score for Rheumatoid Arthritis patients in Hospital Umum Sarawak was 0.25 (SD=0.43). The finding was significantly lower compared to the mean HAQ score of patients in Hospital Melaka (HAQ Score=1.00, SD=0.77) (Ruhaila & Chong, 2018). Furthermore, the mean score was lower compared to a population-based cohort of Rheumatoid Arthritis patients (Sokka, Kautiainen, Hannonen, & Pincus, 2006).

Based on univariate analysis, the functional status of Rheumatoid arthritis based on HAQ Score was associated with depressive symptoms, based on HADS (Spearman rank test, $p<0.001$). After multivariate analysis, the HAQ score remained significantly associated with depressive symptoms (ANCOVA, $p<0.001$) even after control of potential confounder (status of cardiovascular disease).

Therefore, it may be extrapolated that the physical disability as a result of Rheumatoid Arthritis, which is reflected by elevated HAQ scores, is a strong predictor of depressive symptoms. With this, it may be postulated that the low mean HAQ score was in line with the low prevalence of depressive symptoms (and clinical depression) among patients with Rheumatoid Arthritis in Hospital Umum Sarawak.

This finding was in line with numerous studies that have reported strong associations between physical disability or diminished functional status and depressive symptoms in Rheumatoid Arthritis (Abdel-Nasser et al., 1998; Imran et al., 2015; P. P. Katz & Yelin, 1993, 1995; Margaretten et al., 2009; Nakajima et al., 2006; Peck, Smith, Ward, & Milano, 1989; Ruhaila & Chong, 2018). Researchers found depression is significantly linked to the level of physical disability (Hider et al., 2009; F. Wolfe,

2000; F. Wolfe & Hawley, 1999). Interestingly, the comorbid depression increases both the work disability (Hider et al., 2009; Lowe et al., 2004).

Pincus et al. (1984) found disability affected close to 80% of the patients surveyed. The disability increased as the disease progressed or increased in severity. Lowe et al. (2004) surveyed 603 patients from the rheumatology outpatient clinic and found in close to half of the patients surveyed, the presence of psychiatric comorbidity increased the patients' work disability. The disability is substantial in patients with severe RA. From the study, Lowe et al. (2004) suggested that identifying the predictors of work disability may help target treatments aimed at improving the patients' overall and work functioning.

In an attempt to understand the strong association between disability or decline in function (reflected by HAQ Score) and depression in Rheumatoid Arthritis, the author considered Seligman's model of learned helplessness. Following exposure to an uncontrollable outcome, in this case, the functional decline and physical disability due to their Rheumatoid Arthritis state, an individual develops helplessness, or the belief that they are no longer in control of future outcomes despite still having some degree of control. This results in motivational, cognitive, and affective deficits, which consist of depressive symptoms (Seligman, 1975).

Moreover, Abramson, Seligman, and Teasdale's reformulated learned helplessness model highlights the role of interpretation of uncontrollable events and proposes that causal attributions mediate between the absence of control and the development of helplessness-related deficits and depression (Abramson, Seligman, & Teasdale, 1978). If a person is unable to produce a highly desirable outcome, in this case, disability or functional decline due to Rheumatoid Arthritis, they may start to question why this is happening to them. Subsequently, they may form a "causal

attribution for this loss of control over their lives due to the functional decline, which is sufficient to produce symptoms of depression" (Banks & Kerns, 1996).

Interestingly, these models for learned helplessness are similar to Beck's cognitive distortion model (Beck, 1979). Cognitive distortions that may be seen in individuals who experience disability such as those in Rheumatoid Arthritis include catastrophizing, overgeneralization, personalization and selective abstraction. The processing and interpretation of these cognitive distortions may cause negative emotions and maladaptive behaviors that may be seen in patients with functional declines, such as, to avoid walking or physiotherapy altogether due to fear of falling. There is sufficient evidence that these cognitive distortions may be seen in individuals with Rheumatoid Arthritis with diminished functional status (Smith, Christensen, Peck, & Ward, 1994; Smith, Peck, & Ward, 1990).

5.3 Depressive Symptoms And Disease Severity In Rheumatoid Arthritis

Researchers have proposed possible contributory factors contributing to depression among patients with Rheumatoid Arthritis. Matcham et al. (2014) proposed the factors include the individual's social context and the disease state of that person's RA.

In this study the mean score of the Disease Activity Score (DAS-28) was 3.0 (SD=1.1). The majority of the patients surveyed were in remission (37.7%, n=78). This was followed by 29.0% (n=60) with low disease activity state, 27.5% (n=57) with moderate disease activity state, and severe in 5.8% (n=12) of participants.

Clinicians often decide to start or stop treatment depending on their assessment regarding the patients' disease activity state (Van der Heijde et al., 1990). The relatively low mean of the DAS-28 score likely reflected the majority of participants who were in remission and had low disease activity. Only 12 patients (5.8%) were deemed to have severe Rheumatoid Arthritis.

A large proportion of patients in this study were on some form of the anti-rheumatic drug, which could explain the relatively low mean score of the DAS-28. Hence, the low mean score of the DAS-28 would reflect the positive effects of treatment for Rheumatoid Arthritis on reducing disease severity.

Similar studies from other countries that looked into the relationship of disease severity and depression, reported comparatively higher DAS-28 Scores as well (Attar, 2014; Hider et al., 2009; Kekow, Moots, Emery, et al., 2010; Margaretten et al., 2009; Matcham, Ali, et al., 2016).

Interestingly, in this study, multivariate analysis found that the disease severity of Rheumatoid Arthritis was not significantly associated with symptoms of depression, based on the HADS score (ANCOVA, p=0.697).

As in this study, there are a number of studies that support the notion that disease activity in Rheumatoid Arthritis did not significantly associate with presence of

depression (Berkanovic et al., 1996; Klaassen, Nyklíček, Traa, & de Nijs, 2012; Margaretten et al., 2009; Matcham, Ali, et al., 2016).

The inclusion of the study by Matcham, Ali, et al. (2016) is significant because this is the only known prospective study, to the author's knowledge. Due to its robustness, which implied causality, the study provides a valuable insight into the understanding of the prospective relationship between depression and the disease severity in Rheumatoid Arthritis. This negative association could suggest that the impact of depression is predominantly towards perceptions and behaviors of patients with Rheumatoid Arthritis as opposed to a disproportionate immune, although further evaluation is warranted to support this notion (Matcham, Ali, et al., 2016). Additionally, Rathbun, Reed, and Harrold (2012) observed that patient's negative cognitive perceptions effected their response tendency.

Conversely, in their study in Hospital Melaka, Ruhaila and Chong (2018) reported that subjects with a severe disease state, i.e., multiple swollen and painful joints were likely to be more depressed. This finding was also seen in another study conducted by Sulaiman et al. (2017) in Ipoh that reported that there was a significant association between depression and the presence of pain, which is a component in the assessment of disease severity.

Remarkably, Hider et al. (2009) found depressed subjects at baseline had higher DAS-28 scores than those who were not depressed. Hider et al. (2009) too discovered depressed patients had higher disease activity scores (DAS-28) at all time points, and the patients with persistent depression had smaller reductions in the DAS-28.

Interestingly, Kekow, Moots, Emery, et al. (2010) also found that patients who were depressed were less likely to maintain symptoms of depression if they achieve clinical remission compared with non-remitters. In another study, Kekow, Moots, Khandker, et al. (2010) added that patients who had early Rheumatoid Arthritis with

moderate-to-severe disease severity and experienced early clinical remission of Rheumatoid Arthritis reported having reduced symptoms of depression.

Matcham, Ali, et al. (2016) reported in a study of 379 patients with Rheumatoid Arthritis that increased joint tenderness, which corresponded with an increase in the DAS-28 score, was significantly associated with the presence of baseline depression. In the same study, Matcham, Ali, et al. (2016) discovered that the increase in DAS-28 scores was significantly linked to the persistence of depressive symptoms. In their second analysis of the same 379 patients, Matcham, Norton, Scott, Steer, and Hotopf (2016) found that persistent depressive symptoms were associated with increased DAS-28 scores, HAQ scores, and thus, reduced the chances of patients with Rheumatoid Arthritis from reaching clinical remission.

However, it should be noted that these studies had reported a higher prevalence of depression and a higher number of participants with higher disease severity compared to our research.

5.5 Limitations And Strengths Of The Study

It should be noted that this study has a number of limitations. First, this study is a cross-sectional study and does not denote a causal relationship between depressive symptoms and its associations in Rheumatoid Arthritis. There is a limit to the information that can be produced about the waxing and waning nature of Rheumatoid Arthritis and depressive symptoms over time. To establish causality, a longitudinal cohort study would be a more appropriate study design, whereby; items such as DAS-28 for disease severity, HAQ for functional status and HADS for depressive symptoms are accumulated throughout follow-up over weeks to months.

Next, this study utilized convenience sampling due to the limitations in financial costs, human resources and time. As this study was solely conducted in a general hospital setting, the use of non-random sampling techniques may cause sampling bias and hence, may not represent the general population of Rheumatoid Arthritis sufferers. For future studies, a combination of tertiary government hospital, community-based and private healthcare settings may be ideal.

Third, the author was unable to achieve the desired sample size. The smaller sample size limits the statistical power and the scope to control relevant covariates in the study and thus, reduces the ability to meaningfully evaluate the associations of depressive symptoms in patients with Rheumatoid Arthritis. The extremely low prevalence of depression (n=3) means that it was difficult to differentiate the true difference between the depressed and non-depressed participants (i.e., a type II error may have resulted).

This study's reliance on self-rated questionnaires, instead of a structured clinical interview, means that HADS score for depression and HAQ score for functional status could have been underestimated. As discussed earlier, the perception of illness and

stigma of mental illness may play a role and such may result in changes in understanding of the severity of disease or the reporting of disease among Rheumatoid Arthritis subjects. In the future, the use of structured clinical interviews such as MINI International Neuropsychiatric Inventory (MINI) can be used for all participants along with the inclusion of detailed socioeconomic data, global pain scoring and perceived social support to control for confounding factors.

Finally, this study relies on the presence of depressive symptoms based on HADS. Due to the very low prevalence of clinical depression in the screened population, the author was unable to properly analyze the associations of clinic depression. As a result, the author decided shift the focus on to the presence of depressive symptoms. It should be noted that several studies have shown that depressive symptoms, even in the absence of major depressive disorder, may contribute to the psychosocial dysfunction and the burden of suffering faced by Rheumatoid Arthritis patients (P. P. Katz & Yelin, 1993; Smarr et al., 2000).

Conversely, this study is the first of its kind to evaluate depression among patients with Rheumatoid Arthritis in East Malaysia. Only two other studies have been conducted in this area of interest, all of which were done in Peninsular Malaysia. Data from this study may provide valuable information in the holistic management of individuals suffering from Rheumatoid Arthritis in the state.

The evaluation of disease severity (with DAS-28) and functional status (with HAQ) in conjunction with depressive symptoms (with HADS) in Rheumatoid Arthritis has all been validated in both the English and Malay Language.

Finally, the use of convenience sampling and a cross-sectional study design means that data can be collected in a cost and time efficient manner. This study design can provide essential data such as the prevalence of depression and determine specific

associations of depression in Rheumatoid Arthritis.

CHAPTER 6

CONCLUSION AND RECOMMENDATION

Rheumatoid Arthritis is a chronic and debilitating inflammatory disease with far-reaching physical and psychological implications. Although the condition is treatable with modern anti-rheumatic treatment modalities, it remains incurable. This study reported a low prevalence of depression among patients with Rheumatoid Arthritis in Hospital Umum Sarawak. However, more than a third of patients reported some form of depressive symptoms. Symptoms of depression should not be disregarded because, even in the absence of a major depressive disorder, it may contribute to the psychosocial dysfunction and the burden of suffering faced by Rheumatoid Arthritis patients (P. P. Katz & Yelin, 1993; Smarr et al., 2000).

The study did not find any association between socio-demographic factors (age, sex, marital status and socioeconomic factors such as employment and education level) and depressive symptoms. There were no associations between depressive symptoms and treatment modalities in Rheumatoid Arthritis. Apart from cardiovascular disease, depressive symptoms were not associated with other forms of medical comorbidities.

Interestingly, the findings of this study suggest that depressive symptoms in Rheumatoid Arthritis may not be caused by the clinical manifestation of Rheumatoid Arthritis disease severity. Instead, this study finds that a decline in function and possible long-term disability due to Rheumatoid Arthritis which lead to a diminished ability to perform valued daily activities result in the development of symptoms of depression.

Despite the low prevalence of clinical depression among participants in this study, the author recommends the routine screening of depression among patients with Rheumatoid Arthritis with screening tools such as HADS. Rheumatoid arthritis patients

should be adequately treated with anti-rheumatic drugs to minimize the risk of permanent joint damage, which could lead to long-term loss of function and ability to perform valued tasks.

Clinicians should also be vigilant of depressive symptoms, which are associated with diminished function because this may progress to clinical depression. Thus, the author recommends the screening for depression of all Rheumatoid Arthritis patients who exhibit some form of functional decline based on the Health Assessment Questionnaire as part of the holistic management of Rheumatoid Arthritis. There may be a significant role for the implementation of rehabilitation management to reduce the risk of depression in this population.

For future research, a longitudinal cohort study with larger sample size, involving multiple centers in different geographical locations in Malaysia, may be useful to establish the relationship of depression and its associations in Rheumatoid Arthritis and would enable the calculation of relative risk and reduce the possibility of recall bias.

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