PREVALENCE OF PERIODONTITIS AND ITS IMPACT ON QUALITY OF LIFE AMONG SUBJECTS WITH RHEUMATOID ARTHRITIS.

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PREVALENCE OF PERIODONTITIS AND ITS IMPACT ON QUALITY OF LIFE AMONG SUBJECTS WITH RHEUMATOID ARTHRITIS.

ABSTRACT

Background and Objective(s): Traditional clinical measurement parameters alone cannot capture the extent of disease. Quality of life (QoL) measures provide understanding from the patient's perspective. There is a gap in the knowledge of the impact of periodontitis (PD) on QoL among rheumatoid arthritis (RA) subjects. This study aimed to determine the prevalence of PD in Malaysian RA patients and assess the impact on their health related QoL (HRQoL) and oral health related QoL (OHRQoL).

Materials and Methods: Subjects from periodontology and RA clinics were screened. Complete periodontal examination was then performed. Subjects were divided into 4 groups: RA(+)PD(+), RA(+)PD(-), RA(-)PD(+) and RA(-)PD(-). Questionnaire on sample characteristics and Malaysian versions of Oral Health Impact Profile (OHIP-14(M)) and Health Assessment Questionnaire (HAQ-DI)) were answered.

Results: Fifty percent of 108 screened RA subjects recorded BPE scores '3' or '4'. Prevalence of PD in 87 RA subjects who consented for periodontal examination was 33.3% (4.6% mild, 10.3% moderate, 18.4% severe PD). OHIP-14(M) severity score was highest in the RA(-)PD(+) group (17.23±10.36) but only significantly higher than RA(-)PD(-) group ($p < 0.05$). HAQ-DI scores of RA(+)PD(-) and RA(+)PD(+) groups were significantly higher ($p<0.05$) than the non-RA groups. Differences remained significant when age, gender, education level and brushing frequency were controlled. There was a weak negative correlation ($r = -0.269$, $p<0.05$) between the number of teeth and OHRQoL in the RA(+)PD(-) group but none from other periodontal parameters.

Conclusion: The prevalence of PD in RA subjects in this study was lower than that reported worldwide. Subjects with PD have significantly lower OHRQoL than subjects

without PD. Subjects with RA have significantly lower HRQoL compared to their healthy counterparts regardless of PD status.

Keywords: periodontitis, rheumatoid arthritis, quality of life

KELAZIMAN PENYAKIT PERIODONTITIS DAN IMPAK ATAS KUALITI HIDUP SUBJEK-SUBJEK RHEUMATOID ARTHRITIS.

ABSTRAK

Latar Belakang dan Objektif: Parameter pengukuran klinikal yang tradisional sahaja gagal menangkap gambar keseluruhan sesuatu penyakit. Pengukuran kualiti hidup (QoL) memberikan pemahaman dari perspektif pesakit. Terdapat jurang pengetahuan tentang kesan periodontitis (PD) pada QoL subjek-subjek rheumatoid arthritis (RA). Kajian ini bertujuan untuk menentukan kelaziman PD di antara pesakit RA di Malaysia dan menilai impak kepada kualiti hidup mereka dari segi kesihatan am (HRQoL) dan mulut (OHRQoL).

Bahan dan Kaedah: Subjek-subjek dari klinik Periodontologi dan klinik RA disaring dan diberikan pemeriksaan periodontik yang lengkap. Mereka dibahagikan kepada 4 kumpulan: RA(+)PD(+), RA(+)PD(-), RA(-)PD(+), dan RA(-)PD(-). Soal selidik mengenai ciri-ciri sampel dan instrumen QoL versi Malaysia – Oral Health Impact Profile (OHIP-14 (M)) dan Health Assessment Questionnaire (HAQ-DI)) telah dijawab.

Keputusan: Lima puluh peratus daripada 108 subjek RA mencatatkan skor BPE '3' atau '4'. Kelaziman PD dalam 87 subjek RA yang diperiksa dengan lebih lanjut adalah 33.3% (4.6% ringan, 10.3% sederhana, 18.4% PD parah). Skor OHIP-14 (M) tertinggi dicatat oleh kumpulan RA(-)PD(+) (17.23 ± 10.36) tetapi hanya lebih tinggi daripada kumpulan RA(-)PD(-) dalam segi statistik ($p < 0.05$). Skor HAQ-DI kumpulan RA(+)PD(-) dan RA(+)PD(+) lebih tinggi ($p < 0.05$) daripada kumpulan bukan RA. Perbezaan yang dilihat masih signifikan apabila umur, jantina, tahap pendidikan dan kekerapan memberus gigi dikawal. Terdapat korelasi negatif yang lemah ($r = -0.269$, $p < 0.05$) di antara bilangan gigi dan OHRQoL dalam kumpulan RA(+)PD(-) tetapi tiada daripada parameter periodontik yang lain.

Kesimpulan: Kelaziman PD di antara subjek RA dalam kajian ini lebih rendah daripada yang dilaporkan di seluruh dunia. Subjek dengan PD mempunyai OHRQoL yang lebih rendah daripada subjek tanpa PD. Subjek dengan RA mempunyai HRQoL yang lebih rendah berbanding dengan subjek yang sihat tanpa mengira status PD.

Kata kunci: periodontitis, rheumatoid arthritis, kualiti hidup

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A special mention goes to my pillars of support – my wife and my daughter. I would not have been able to do this without them. Their love for and faith in me were my main drive. This is for them.

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LIST OF SYMBOLS AND ABBREVIATIONS

A. actinomycetemcomitans	*Aggregatibacter actinomycetemcomitans*
AAP	American Academy of Periodontology
AAP-EFP	American Academy of Periodontology – European Federation of Periodontology
ACPA	Anti-citrullinated Protein Antibody
ACR/EULAR	American College of Rheumatology/ European League Against Rheumatism
AIMS2	Arthritis Impact Measurement Scale
BOP	Bleeding on Probing
BPE	Basic Periodontal Examination
BSP	British Society of Periodontology
CAL	Clinical Attachment Loss
CDC	Centers for Disease Control and Prevention
CDC-AAP	Centers for Disease Control and Prevention - American Academy of Periodontology
CEJ	Cemento-enamel Junction
CI	Confidence Interval
CPI	Community Periodontal Index
CPQ_{11-14}	Child Perceptions Questionnaire
CRP	C-Reactive Protein
DAS	Disease Activity Score
DIDL	Dental Impact on Daily Living
DIP	Dental Impact Profile
DM	Diabetes Mellitus
DQOL	Diabetes Quality of Life
ESR	Erythrocyte Sedimentation Rate
F. nucleatum	*Fusobacterium nucleatum*
FMBS	Full Mouth Bleeding Score
FMPS	Full Mouth Plaque Score
GCF	Gingival crevicular fluid
GOHAI	Geriatric (General) Oral Health Assessment Index
GR	Gingiva Recession
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HRQoL	Health Related Quality of Life
ICIDH	International Classification of Impairments, Disabilities and Handicaps
MREC	Medical Research Ethics Committee
NHANES I	First National Health and Nutrition Examination Survey
NHP	Nottingham Health Profile
NOHSA	National Oral Health Survey of Adults
OA	Osteoarthritis

OHIP	Oral Health Impact Profile
OHIP-14 (M)	Malaysian Version of OHIP-14
OHRQoL	Oral Health Related Quality of Life
OQoLQ	Orthognathic Quality of Life Questionnaire
OR	Odds Ratio
P. gingivalis	*Porphyromonas gingivalis*
P. intermedia	*Prevotella intermedia*
PAD	Peptidyl arginine deiminase
PD	Periodontitis
PDL	Periodontal Ligament
PIS	Patient Information Sheet
PPAD	*P. gingivalis* PAD
PPD	Probing Pocket Depth
QoL	Quality of Life
RA	Rheumatoid Arthritis
RA(-)PD(-)	Subjects without RA and PD
RA(-)PD(+)	Subjects without RA but with PD
RA(+)PD(-)	Subjects with RA but without PD
RA(+)PD(+)	Subjects with RA and PD
RAQoL	Rheumatoid Arthritis Quality of Life
RF	Rheumatoid Factor
SD	Standard Deviation
SF-36	Short Form Health Survey-36
SIP	Sickness Impact Profile
SLE	Systemic Lupus Erythematosus
SPSS	Statistical Package of Social Sciences
T. forsythia	*Tanarella forsythia*
T2DM	Type II Diabetes Mellitus
TNF-α	Tumour necrosis factor alpha
UMMC	University of Malaya Medical Centre
WHO	World Health Organisation
WHOQOL	World Health Organisation Quality of Life Assessment
B	Unstandardised Regression Coefficient
β	Standardised Regression Coefficient

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Periodontal disease, of which periodontitis (PD) is part of, has been identified by the World Health Organisation (WHO) to be a significant contributor to the global burden of oral disease and is reported to be the 6th most prevalent disease globally (Petersen & Ogawa, 2005; Tonetti, Jepsen, Jin, & Otomo-Corgel, 2017). On the other hand, rheumatoid arthritis (RA) has a significantly lower prevalence globally of 1% (Li et al., 2016; Pischon et al., 2008). Both of these diseases cause destruction, in PD to the periodontal apparatus, and in RA to the cartilage and underlying bone.

Both of these diseases have also been associated with other systemic conditions. PD has been associated with diabetes mellitus, cardiovascular disease, respiratory disease, obesity, osteoporosis and preterm and low birth weight among pregnant women (Hujoel, Drangsholt, Spiekerman, & DeRouen, 2000; Khader & Ta'ani, 2005; Offenbacher et al., 1996; Scannapieco & Ho, 2001; Soskolne & Klinger, 2001; Wactawski-Wende et al., 1996). RA on the other hand has been associated with Type I Diabetes Mellitus, cardiovascular diseases, pulmonary diseases, ocular diseases, neurological diseases among others (Eriksson, 2017). Both also share common risk factors such as smoking (Gerlag, Norris, & Tak, 2015; Ramseier, 2005; Tomar & Asma, 2000) and genetic factors such as the HLA-DRB1 SE alleles (Källberg et al., 2007; Katz, Goultschin, Benoliel, & Brautban, 1987). To date, an increasing number of studies have reported a positive association between PD and RA (Bartold, Marshall, & Haynes, 2005; De Pablo, Chapple, Buckley, & Dietrich, 2009; Detert, Pischon, Burmester, & Buttgereit, 2010; Fuggle, Smith, Kaul, & Sofat, 2016; Khantisopon et al., 2014; Mercado, Marshall, Klestov, & Bartold, 2001; Pischon et al., 2008; Potikuri et al., 2012; Tang et al., 2017).

While we as researchers and clinicians focus on the clinical manifestations of both PD and RA, however that which is more relevant to subjects with PD, RA or both these diseases are symptoms that are not measurable with a clinician's measurement parameter (D Locker, 1988; Tijhuis et al., 2001). Recognition of this shortfall has yielded in the development of numerous instruments to fill this gap of knowledge. These instruments measure patient-centred quality of life (QoL) and oral health related quality of life (OHRQoL) and contribute to ideal care management providence.

One of the most widely used instrument to measure OHRQoL in patients with PD is the Oral Health Impact Profile (OHIP) (Slade & Spencer, 1994) which has been adapted to many different languages and validated for use in different populations with cultural diversity. The most commonly used instrument for health related quality of life (HRQoL) in RA patients is the Health Assessment Questionnaire (HAQ) which was published by the Stanford Arthritis Center in 1981 (Fries, Spitz, Kraines, & Holman, 1980). These instruments best report the disease from a patient's perspective and measures how significantly it impacts their life (Al-Harthi, Cullinan, Leichter, & Thomson, 2013).

Current evidence points to the importance of the HRQoL and OHRQoL measurements in understanding the diseases and formulating patient-centred treatment strategies. There is currently no published study investigating the impact of PD on the HRQoL and OHRQoL among those suffering from RA. This study will explore this gap in knowledge in a Malaysian population.

1.2 AIM OF THE STUDY

The aim of this study is to determine the prevalence of PD in RA subjects and assess the impact on their quality of life.

1.3 OBJECTIVES OF THE STUDY

1. To determine the prevalence of PD in subjects with RA.
2. To compare the OHRQoL and HRQoL between 4 groups of subjects: subjects with RA and PD (**RA(+)PD(+)**), subjects with RA but without PD (**RA(+)PD(-)**), subjects without RA but has PD (**RA(-)PD(+)**) and subjects without both RA and PD (**RA(-)PD(-)**).
3. To assess the relationship between periodontal parameters (total number of teeth, plaque score, gingival bleeding, clinical attachment loss and probing depth) and OHRQoL.

CHAPTER 2: LITERATURE REVIEW

2.1 PERIODONTITIS (PD)

In humans, a healthy periodontium is made up of intact gingiva, periodontal ligament (PDL), cementum and alveolar bone. These tissues in tandem, protect the dentition from the daily microbial and mechanical challenges sustained (Lang & Lindhe, 2015; Rios, 2015). Despite its resilience, the integrity of the periodontium can be compromised by the chronic inflammatory responses characteristic to periodontitis (PD). Progressive inflammatory destruction of the gingiva, PDL and alveolar bone as well as the contamination of the cementum will eventually lead to significant tooth loss if not properly managed (Darveau, 2010; Tonetti et al., 2017; Wikesjö & Selvig, 1999).

2.1.1 CLASSIFICATION

Periodontal disease can range from a relatively benign, reversible form of gingivitis to a more severe chronic periodontitis and even the aggressive subtype (Armitage, 1999). The commonly used classification for periodontal disease is based on the American Academy of Periodontology (AAP) Classification (Armitage, 1999) which is shown in Table 2.1 below.

Table 2.1: American Academy of Periodontology (AAP) Classification of Periodontal Diseases and Conditions

Classification of Periodontal Diseases and Conditions
Gingival Diseases
Chronic Periodontitis
Aggressive Periodontitis
Periodontitis as a Manifestation of Systemic Disease
Necrotising Periodontal Diseases
Abscesses of the Periodontium
Periodontitis Associated with Endodontic Lesions
Developmental or Acquired Deformities and Conditions

Source: (Armitage, 1999)

Chronic PD is further divided into generalised and localised. The guidelines for determining the severity of PD is shown in Table 2.2 below.

Table 2.2: Periodontitis severity

	Mild PD	**Moderate PD**	**Severe PD**
Probing depths	>3 & <5mm	≥5 & <7mm	≥7mm
Bleeding on probing	Yes	Yes	Yes
Radiographic bone loss	≤ 15% of root length or 2-3mm	16-30% of root length or >3 & ≤5mm	>30% of root length or >5mm
Clinical attachment loss	1-2mm	3-4mm	≥5mm

Source: (Armitage, 1999)

A new classification was recently introduced in the joint American Academy of Periodontology – European Federation of Periodontology (AAP-EFP) Workshop in 2017 (G. Caton et al., 2018). A brief breakdown is as in Table 2.3.

Table 2.3: American Academy of Periodontology – European Federation of Periodontology (AAP-EFP) Classification of Periodontal and Peri-Implant Diseases and Conditions

Classification of Periodontal Diseases and Conditions	**Classification of Peri-Implant Diseases and Conditions**
Periodontal Health, Gingival Diseases and Conditions Periodontitis Other Conditions Affecting the Periodontium	Peri-Implant Health Peri-Implant Mucositis Peri-Implantitis Peri-Implant Soft and hard Tissues Deficiencies

Source: (G. Caton et al., 2018)

A standardised case definition is critical for surveillance of a disease or condition in population-based studies (Page & Eke, 2007). It is used to define whether an individual has the specific disease or health condition being investigated. A plethora of different definitions have been used prior to the Oral Health Division of the Centers for Disease Control and Prevention (CDC)'s collaboration with the American Academy of Periodontology (AAP) to formulate a standardised case definition for PD (Page & Eke, 2007). This version only defined "moderate" and "severe" PD and was later modified to include "mild" PD by Eke and colleagues (Eke et al., 2012). This widely used PD case definition in epidemiological studies is as described in Table 2.4.

Table 2.4: Centers for Disease Control and Prevention -American Academy of Periodontology (CDC-AAP) Case Definition

Periodontitis	Description
Mild	Subjects who had ≥ 2 interproximal sites with CAL ≥ 3 mm, and ≥2 interproximal sites with PD ≥ 4 mm (not on the same tooth) or one site with PD ≥ 5 mm.
Moderate	Subjects who had ≥ 2 interproximal sites with CAL ≥ 4 mm (not on the same tooth), or ≥ 2 interproximal sites with PD ≥ 5 mm (not on the same tooth).
Severe	Subjects who had ≥ 2 interproximal sites with CAL ≥ 6 mm (not on the same tooth) and ≥ 1 interproximal site with PD ≥ 5 mm.

Source: (Eke et al., 2012)

2.1.2 PREVALENCE

In most parts of the modern world, chronic diseases and injuries have been attributed to be the foremost health problems (Petersen, 2003). The World Health Organization (WHO) has identified that oral diseases constitute as major health problems (Petersen, 2003) and that periodontal disease (of which PD is a part of) is a significant contributor to the global burden of oral disease (Petersen & Ogawa, 2005). This reinforced the findings of a report out of Sweden in 1996 which stated that periodontal disease is one of the two major dental diseases with high worldwide prevalence (Papapanou, 1996). A 2002 report showed that periodontal disease affected an estimated 90% adults in the Western world (Borrell, Burt, Gillespie, Lynch, & Neighbors, 2002). Sheiham and colleagues in their 2002 systematic review emphasised their view that it was a general consensus that contrary to previous views, current epidemiological evidence suggests that periodontal disease is moderately prevalent globally while severe PD displays an even lower prevalence (Aubrey Sheiham & Netuveli, 2002).

Pertinent to note is that these rates vary from region to region across the globe. More recently, Tonetti et al. in 2017 reported that severe PD, the 6th most prevalent disease globally, affects 743 million people worldwide with an overall prevalence of 11.2% (Tonetti et al., 2017). It has also been reported that Asians in developing nations are "perhaps" more susceptible than their Caucasian counterparts (Corbet & Leung, 2011). This is substantiated further by the most recent National Oral Health Survey of Adults (NOHSA) in 2010 in Malaysia that reported the presence of PD in 48.5% of the Malaysian population of which 18.2% is of the severe form (Oral Health Division, 2012).

2.1.3 AETIOPATHOGENESIS

The current understanding is that PD initiates from dental biofilm accumulation (Tonetti et al., 2017). The biofilm, through modification of the environment and the host inflammatory response coupled by the individual's unique susceptibility profile, might become dysbiotic (Hajishengallis et al., 2011; Tonetti et al., 2017). Hence it initiates a disease process which causes inflammatory destruction of the supporting structures of the dentition (cementum, periodontal ligament and alveolar bone) and eventually significant tooth loss if not properly treated (Darveau, 2010; Hajishengallis et al., 2011; Kornman, 2008; Tonetti et al., 2017).

It is only as recent as half a decade ago that our understanding of the natural history of progression of PD in man hinged on the assumption that chronic oral hygiene neglect was the sole perpetrator of the disease (Kornman, 2008). The earliest modern-era model of pathogenesis of PD was an uncomplicated, linear model which attributed bacteria as the primary, direct factor initiating and leading to the progression of the disease (Kornman, Newman, Moore, & Singer, 1994). The knowledge paradigm during that time was shaped by 2 much-cited, classical human (Löe, Theilade, & Jensen, 1965)

and animal (Lindhe, Hamp, & Löe, 1973) experimental models out of Denmark and Sweden which demonstrated that bacteria in "oral debris" was critical in the formation of gingivitis and periodontitis respectively. This inevitably led to a breakthrough in management principles of PD and further studies on its bacterial causation. Certain specific bacteria type which were Gram negative, microaerophilic or anaerobic such as *Porphyromonas gingivalis (P. gingivalis)*, *Tanarella forsythia (T. forsythia)*, *Prevotella intermedia (P. intermedia)*, *Fusobacterium nucleatum (F. nucleatum)* and *Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans)* were identified as periodontal pathogens (Listgarten, 1988; Newman, 1984; Slots, 1979; Socransky, 1977).

In recent years, viruses such as herpes simplex virus, human cytomegalovirus and Epstein-Barr virus have been reported to be found in periodontitis samples (Kubar, Saygun, Özdemir, Yapar, & Slots, 2005; Slots, 2010). It is now recognized that these "oral debris" or dental plaque are in fact, microbes-harbouring biofilms, defined as "matrix-enclosed bacterial populations adherent to each other and/or to surfaces or interfaces"(Consterton, Lewandowski, Caldwell, Karber, & Lapin-Scott, 1995).

Socransky and Haffajee established that supragingival and subgingival bacteria exists in "complexes" or "communities" in their respective environments and certain complexes are more predisposed in periodontal conditions (Haffajee, Socransky, Patel, & Song, 2008; Socransky, Haffajee, Cugini, Smith, & Kent, 1998). It has been reported that these periodonto-pathogens present more in subjects with periodontitis as compared to their healthy counterparts (Griffen, Becker, Lyons, Moeschberger, & Leys, 1998; Van Winkelhoff, Loos, Van Der Reijden, & Van Der Velden, 2002). On the other hand, a study in 1993 reported a similar prevalence of *P. gingivalis* and *A. actinomycetemcomitans* in subjects with gingivitis and periodontitis (Wolff et al., 1993). The argument that periodontitis is not caused solely by pathogens was supported

also by Lamell and colleagues' report of the presence of *P. gingivalis* and *A. actinomycetemcomitans* in healthy subjects (prevalence of 36% and 48% respectively) and also in 20-days-old infants (Lamell, Griffen, McClellan, & Leys, 2000).

Concurrent with the paradigm shift in periodontal understanding, the protective and more crucially, destructive role of host immune-inflammatory response in health and disease (Nisengard, 1977; Page & Schroeder, 1976; Van Dyke, 1985), host susceptibility (Löe, Anerud, Boysen, & Morrison, 1986), environmental and genetic factors have yielded a more complex, non-linear model relevant to the current knowledge (Kornman, 2008). The current belief is that periodontal homeostasis is the dynamic balance between the periodontal microbiology and the host innate defence (Jin, 2011) and a shift in this equilibrium results in the manifestation of the disease. As it is not feasible to eliminate all the microflora, returning the microbe load to a threshold level which would in turn suppress the host immune-inflammatory response, represents the current management goal in periodontal therapy (Lang & Lindhe, 2015).

All these studies lend support to the hypothesis that host susceptibility may in fact possess a genetic background where genes which vary across populations and even within a single population may define the anti-microbial host response (Lang & Lindhe, 2015). Genetic variations in certain genes encoding the regular host immune responses were revealed to potentially have a deleterious effect. Hence, an individual's susceptibility may be governed not just by the oral microbiota, internal or external factors but also, their unique genetic constitution (Lang & Lindhe, 2015).

2.1.4 MODIFYING, RISK FACTORS AND ASSOCIATIONS WITH OTHER DISEASES AND CONDITIONS

It is the current understanding that certain environmental and modifying factors contribute in the pathogenesis of PD.

Diabetes mellitus (DM) and periodontal disease has been found to exhibit bi-directional relationship (Casarin et al., 2013; Mealey & Rose, 2008; Soskolne & Klinger, 2001) and patients with DM regardless of the type of DM are reported to have more severe periodontal disease (Papapanou, 1996; Ramseier, 2005; Verma & Bhat, 2004). On the other hand, the periodontal status of well-controlled diabetics are reported to be no different than that of their non-diabetic counterparts (Westfelt, Rylander, Biohmé, Jonasson, & Lindhe, 1996). The bi-directional relationship between periodontal disease and diabetes mellitus is now widely accepted and established.

Smoking is also identified as a major risk factor in the initiation and progression of periodontal disease in addition to limiting the effectiveness of therapy. Ramseier in 2005 identified cigarette smoking as the second most important risk factor in periodontal disease (Ramseier, 2005). A dose-response relationship has been reported in addition to the reports that smokers display higher prevalence, severity and extent of chronic periodontitis (Kinane & Chestnutt, 2000; Ramseier, 2005; Tomar & Asma, 2000). It is reported that a smoker's risk of periodontal attachment loss is greater by 2.5 to 3.5 times (Bergström, 1989). Any subsequent phases of periodontal therapy could be rendered less effective based on evidence from previous studies which reported less than favourable outcomes in non-surgical and surgical therapies (Feldman, Bravacos, & Rose, 1983; Grossi et al., 1996; Tonetti, Pini-Prato, & Cortellini, 1995). Encouragingly, a prospective study reported that periodontal health improvement is boosted by cessation of smoking (Bergström, Eliasson, & Dock, 2000).

Most chronic diseases share similar modifying and risk factors. To date, countless studies are being done to investigate possible associations between periodontal disease and many other altered systemic health conditions such as diabetes mellitus, cardiovascular disease, respiratory disease, osteoporosis, obesity, preterm and low birth weight in pregnant women among many others (Hujoel et al., 2000; Khader &

Ta'ani, 2005; Offenbacher et al., 1996; Scannapieco & Ho, 2001; Soskolne & Klinger, 2001; Wactawski-Wende et al., 1996). In the recently concluded 2017 World Workshop of Classification, Albandar and colleagues reported that there might be an association between PD and RA (Albandar, Susin, & Hughes, 2018).

2.2 RHEUMATOID ARTHRITIS (RA)

Rheumatoid arthritis (RA), coined by Sir Alfred Baring Garrod in 1859, is a complex autoimmune disorder with unclear aetiology characterized by an irreversible destruction of cartilage and underlying bone due to synovial joint inflammation and pannus formation (Choy, 2012).

2.2.1 CLASSIFICATION

RA is widely diagnosed using the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) 2010 criteria. The suspicion of RA is ascribed when a patient has a swelling of at least 1 joint that cannot be caused by another disease. Table 2.5 shows the classification criteria (score-based algorithm) for RA. Definite RA is diagnosed when a score of ≥6 out of 10 is reached. A tree algorithm adapted from Aletaha and co-workers summarises the ACR/EULAR criteria well as demonstrated in Figure 2.1 (Aletaha et al., 2010).

Table 2.5: Classification Criteria for RA

Classification Criteria	Item	Score
Joint involvement	1 large joint	0
	2-10 large joints	1
	1-3 small joints (with or without involvement of large joints)	2
	4-10 small joints (with or without involvement of large joints)	3
	>10 joints (at least 1 small joint)	5
Serology	Negative RF and Negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
Acute-phase reactants	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
Duration of symptoms	< 6weeks	0
	≥ 6 weeks	1

RF: rheumatoid Factor; ACPA: anti-citrullinated protein antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Source: (Aletaha et al., 2010)

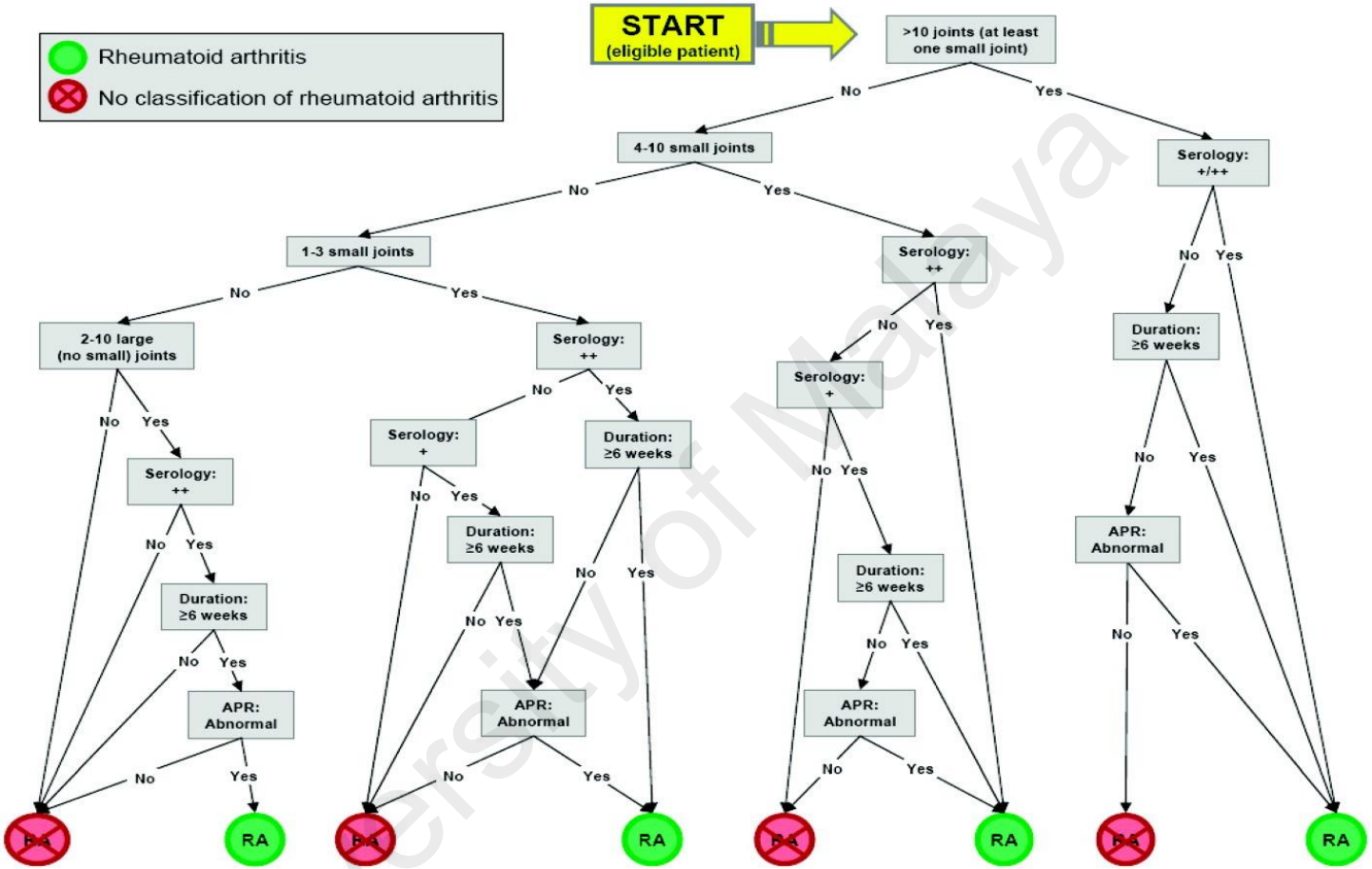

Figure 2.1: Tree Algorithm for American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) 2010 Diagnostic Criteria

APR: acute-phase response; Serology: +: low-positive for rheumatoid factor (RF) or anti–citrullinated protein antibody (ACPA); serology: ++: high-positive for RF or ACPA; serology: +/++ serology either + or ++.

Source: (Aletaha et al., 2010)

2.2.2 PREVALENCE

RA has a 1% prevalence globally, increases with age and is three times more likely to affect women (Li et al., 2016; Pischon et al., 2008). In Malaysia, the exact prevalence of this disease is unclear but is estimated to be around 0.5% (Hussein, Mustafa, Quek, Hassanudin, & Shahid, 2008). The disease course can be exhibited in two different patterns – a "relapsing-remitting" affecting 7-79% of RA patients or a "chronic-persistent" affecting 20-44% of RA patients. (Eriksson, 2017; Lindqvist, Saxne, Geborek, & Eberhardt, 2002).

2.2.3 AETIOPATHOGENESIS

RA is a progressive inflammatory autoimmune disease. Although its exact aetiology is still unknown, current literature suggests that it may be a combination of genetic, infectious, hormonal and environmental risk factors. This condition is characterized by synovial joint inflammation and hypertrophied synovium (pannus) formation which induces an irreversible destruction of the cartilage and underlying bone (Choy, 2012; Persson, 2012). This joint inflammation is associated with an increase in production of cytokines and proteases as a direct result of the increase in infiltration of inflammatory cells (typically T-cells, B-cells and macrophages) as well as the hyperplastic expansion of the synovial cells (McInnes & Schett, 2011).

Central to the RA pathogenesis is the overproduction of pro-inflammatory infiltrate like tumour necrosis factor alpha (TNF-α). This stimulates the production of collagenases by synovial chondrocytes and fibroblasts and also the differentiation of osteoclasts, leading to cartilage and bone destruction respectively (Bartok & Firestein, 2010; McInnes, Buckley, & Isaacs, 2016).

The two serological markers used frequently for the diagnosis of the disease are the rheumatoid factor (RF) and the anti-citrullinated protein antibody (ACPA). Presence

of these antibodies are linked to a more aggressive form of the disease and confer the term "sero-positivity" to approximately 70-80% of RA patients (El-Gabalawy, 2009). The RF was the first antibody associated with this disease and can be detected up to 5-15 years before the disease onset (Brink et al., 2016). RF however can be detected in a variety of other diseases too and has a lower level of specificity than ACPA. Nevertheless, it is still used in the classification criteria of RA (Aletaha et al., 2010).

ACPA on the other hand was first described in 1964 and was only recognized as a diagnostic criterion for RA in 2010 (Aletaha et al., 2010). It is shown that ACPA can be detected 10-15 years prior to disease onset (Leech & Bartold, 2015) and has a specificity level of 95-98% (Avouac, Gossec, & Dougados, 2006). It is theorized that ACPA-positive and ACPA-negative subsets may command different pathogenic pathways (Klareskog, Rönnelid, Lundberg, Padyukov, & Alfredsson, 2008).

2.2.4 MODIFYING, RISK FACTORS AND ASSOCIATION WITH OTHER DISEASES

An established association has already been made between RA with smoking (Hutchinson & Moots, 2001) and genetic polymorphisms (HLA-DRB1) (Källberg et al., 2007). This chronic inflammatory condition has also been associated with other systemic complications which include type I Diabetes Mellitus, cardiovascular diseases, pulmonary diseases, ocular diseases, neurological diseases among others (Eriksson, 2017). In addition to all these, there is an increase in interest in the plausible association with periodontal disease as these two conditions share many similar features (Albandar et al., 2018; Persson, 2012).

2.3 PD-RA ASSOCIATION

PD and RA are both chronic inflammatory diseases that can lead to permanent disability resulting from host mediated pathogenesis, have multifactorial aetiologies, and are to a large part, incompletely understood. However, they do share similar risk factors (such as smoking), tissue and bone destruction pathways, disease progression and immunogenetics hence justifying a plausible inter-relation. Cigarette smoking is a well-established risk factor in both PD and RA with reports of an increase in disease severity in a dose dependent relationship (Gerlag et al., 2015; Ramseier, 2005; Tomar & Asma, 2000). From a genetic standpoint, the HLA-DRB1 SE alleles which have been established as a genetic risk factor for RA has also been implicated as a risk factor in PD (Källberg et al., 2007; Katz et al., 1987).

In addition to shared risk factors, antibodies associated with RA such as ACPA and RF have also been detected in patients with PD (Rosenstein, Greenwald, Kushner, & Weissmann, 2004). Lappin and colleagues in 2013 reported higher serum ACPA levels in patients with periodontitis compared to their healthy counterparts (Lappin et al., 2013). Inflamed periodontal tissues have also been reported to contain an increased level of cittrulinated proteins (Harvey et al., 2013). Furthermore, ACPA has also been detected in the saliva and gingival crevicular fluid (GCF) of RA patients (Harvey et al., 2013). Similar to this, the presence of RF has also been demonstrated in the gingiva, subgingival biofilm and serum of patients suffering from PD (Rosenstein et al., 2004).

2.3.1 MICROORGANISMS STUDIES

The "bacterial link" between PD and RA was first hypothesised in 2004 where *P.gingivalis* was implicated to be involved in the pathogenic connection through the process of citrullination (Rosenstein et al., 2004). *P. gingivalis,* a common periodontal pathogen, has been reported to be the sole peptidyl arginine deiminase (PAD) expressing micro-organism (McGraw, Potempa, Farley, & Travis, 1999). PAD initiates

the conversion of arginine into citrulline. Accumulation of PAD have been hypothesized to break the immune tolerance to endogenous citrullinated peptides of genetically susceptible individuals and development of anti citrullinated peptide antibody (ACPA) implicated in the development of RA (Bright, Proudman, Rosenstein, & Bartold, 2015; Rosenstein et al., 2004). The PAD expressed by *P. gingivalis*, termed *P. gingivalis* PAD (PPAD) is reported to be equivalent to the PAD1-4 and PAD6 enzymes in mammals (Rosenstein et al., 2004) which are capable of initiating citrullination of mammalian proteins.

2.3.2 EPIDEMIOLOGICAL STUDIES

From epidemiological standpoint, there is an increasing number of studies concluding that there is a considerable positive association between these two diseases. While the relationship is unlikely to be causal, most of these studies have reported that PD is more severe and common in patients with established RA (Bartold et al., 2005; De Pablo et al., 2009; Detert et al., 2010; Khantisopon et al., 2014; Mercado et al., 2001; Pischon et al., 2008; Potikuri et al., 2012).

In the Americas, De Pablo et al., in a study including 103 RA cases and 4358 controls, reported more missing teeth in RA patients (De Pablo et al., 2009). They concluded that there may be an association between RA and tooth loss and PD. Mercado et al found that while there was no difference between plaque and bleeding indices between the RA group and controls, there were more missing teeth and deeper probing depths in the RA subjects (Mercado et al., 2001). In an American study of 32 subjects newly diagnosed with RA, a high prevalence of PD was reported (Scher et al., 2012). In a much larger scale study of the American population, Demmer and colleagues in 2011 used the epidemiological data collected during the First National Health and Nutrition Examination Survey (NHANES I) and reported a positive yet

weak association between poor periodontal status, tooth loss and RA in 9702 subjects (males and females) (Demmer, Molitor, Jacobs, & Michalowicz, 2011). In contrast, Arkema and colleagues who studied 292 American women with incident RA from an 81132-subjects pool reported no association between severe periodontitis and RA (Arkema, Karlson, & Costenbader, 2010). However, this conclusion however was drawn by "diagnosing" the subjects as having severe PD through an estimated history of tooth loss and/or periodontal surgery.

In Europe, a prospective study in a Finnish population reported poorer periodontal parameters in early untreated RA and chronic active RA compared to their non-RA counterparts (Äyräväinen et al., 2017). In studies comparing PD association with RA and non-inflammatory arthritis (oasteoarthritis – OA), many reports demonstrated that PD is more common in ACPA-positive RA and RA compared to OA subjects (Coburn et al., 2015; Dissick et al., 2010). Fuggle et al. in their 2016 systematic review and meta-analysis however reported that the risk of BOP is increased in OA compared to RA and there is no significant difference in prevalence of PD between both groups (Fuggle et al., 2016). A very recent study of a London population in 2018 reported similar PD prevalence in 83 patients with RA and 122 patients with SLE (Orlandi et al., 2018). Conversely, a study in Sweden of 6682 subjects (2470 RA cases and 3942 matched controls) concluded that there was no evidence of an increased prevalence of PD in patients with established RA despite verifying that smoking is a significant risk factor (Eriksson et al., 2016). A limitation of this study was that they used records of patients that were screened for dental treatment in dental clinics and there was no data on periodontal parameters.

In Asia, in a cross-sectional study from India, Potikuri and colleagues in 2012 reported that the odds for PD was 4.28 times higher in non-smoking RA patients compared to the healthy controls (Potikuri et al., 2012). The same population also

demonstrated that the ACPA titres were high when periodontitis was present along with RA (Potikuri et al., 2012). A Taiwanese study with the largest sample size to date – 13,779 RA cases and 137,790 controls demonstrated a weak and limited association between PD and RA (Chen et al., 2013). However, the measurement for PD was questionable as this study categorized a patient as having PD based only on the individual's history of periodontitis-related dental visit.

Looking at epidemiological studies in the Southeast Asian region, a pilot study in Malaysia concluded that an association between PD and RA could not be significantly proven. The same study however admitted that data collected was limited – 16 RA cases and 16 controls (Suhaimi, Kamaruzaman, Taib, Mohamad, & Ghazali, 2016). Similarly, an Indonesian study in 2013 with a larger sample size of 75 RA patients and 75 matched controls reported that the severity and prevalence of periodontitis was similar in RA patients and their healthy counterparts (Susanto et al., 2013). The authors did however report that the RA patients had a significantly lower surface area of healthy pocket epithelium and a higher tendency to a higher inflammatory state as noted by the higher CRP levels reported (Susanto et al., 2013). In contrast, a 2014 study from Thailand with 196 RA cases concluded a high prevalence of moderate to severe PD in patients with RA (Khantisopon et al., 2014) at 42% and 57% respectively. This study also reported that there was no significant association between RA parameters such as Disease Activity Index (DAS) and the Thai Health Assessment Questionnaire (HAQ) with the periodontal conditions (Khantisopon et al., 2014).

The most current studies with the highest level of evidence – systematic reviews and meta-analyses have reported a significant association between RA and PD. Fuggle and colleagues in their 2016 systematic review and meta-analysis of 21 papers reported significantly increases of the risk of periodontitis, mean probing depth, risk of bleeding on probing (BOP) and absolute clinical attachment loss (CAL) in RA patients compared

to healthy controls (Fuggle et al., 2016). In a more recent systematic review and meta-analysis of eight publications, Tang and colleagues demonstrated that when comparing RA subjects to healthy controls, the odds ratio (OR) for PD was 4.68 (Tang et al., 2017). They also reported an OR for PD of 1.28 when comparing RA and non-RA subjects. The conclusion was that RA is significantly associated with overall risk of periodontitis (Tang et al., 2017).

It is very obvious that there is conflicting data which may be attributed to variations in sample sizes, classifications used for PD and RA, evaluation of disease status, selection bias and study design. What was clear is that larger scale studies with larger sample sizes are needed to draw more pertinent conclusions. A breakthrough like the 12,000 cases and 16,000 controls Rheumatoid Arthritis GWAS with the identification of 46 risk genes (Eyre et al., 2012) is promising if utilized ideally to search for an association. Chapple and colleagues in their recent post workshop publication summarized the current understanding well – that while current literature indicates that there is an increased prevalence of periodontitis in RA patients, the certainty of this association is at best, still low (Chapple et al., 2017).

2.4 QUALITY OF LIFE (QoL)

The last half a decade has seen the introduction of new nomenclature such as "quality of life (QoL)" and "health-related quality of life (HRQoL)" in the field of medicine (research and clinical) regarding various health conditions and the management therapies directed at these conditions (Gill & Feinstein, 1994). There is a growing recognition that a true picture cannot be captured using traditional clinical measurement parameters alone but should be ideally supplemented by the individual's point of view to give a more holistic representation (Fitzpatrick, Davey, Buxton, &

Jones, 1998). This emphasis on QoL shows that the betterment of life holds just as much importance as the prolonging of it and rendering it disease-free (Guyatt & Cook, 1994). It is also clear that from a patient or subject's perspective, QoL is a crucial determinant with regards to how we seek for care, compliance to treatment regimens and also the post-operative satisfaction (Leplege & Hunt, 1997).

2.4.1 HEALTH RELATED QUALITY OF LIFE (HRQoL) INSTRUMENTS

Many instruments have been created and used to measure the HRQoL. Modifications are still being made to "successful" instruments to make them more relevant to each study population through cross cultural adaptation and other methods. Karnofsky was probably the pioneer in this field with his scale to measure the QoL of patients (Zhan, 1992). These HRQoL instruments can be divided into generic or specific instruments. The former being an instrument to gauge the general well-being of the patient, while the latter being more specific to the disease being investigated.

Common generic instruments used across all continents are the Nottingham Health Profile (NHP) (Hunt, McKenna, McEwen, Williams, & Papp, 1981), the Sickness Impact Profile (SIP) (Bergner, Bobbitt, Carter, & Gilson, 1981), Short Form Health Survey-36 (SF-36) (Ware Jr & Sherbourne, 1992), the World Health Organisation Quality of Life Assessment (WHOQOL) (Group, 1995) and the Health Assessment Questionnaire (HAQ) (Fries et al., 1980).

Disease specific HRQoL instruments have also been introduced like the Diabetes-39 (Boyer & Earp, 1997) and Diabetes Quality of Life (DQOL) (Watkins & Connell, 2004) for diabetes mellitus; the cardiovascular specific health-related questionnaire CD-HRQoL for cardiovascular disease (Lee, Tahk, Shin, Lee, & Song, 2007); the Functional Assessment of Cancer Therapy – Lung for lung cancer (Cella et al., 1995); and the Arthritis Impact Measurement Scale (AIMS2) (Meenan, Mason,

Anderson, Guccione, & Kazis, 1992), its predecessor – AIMS (Meenan, Gertman, & Mason, 1980).

2.4.2 HEALTH ASSESSMENT QUESTIONNAIRE (HAQ) INSTRUMENT

The Health Assessment Questionnaire (HAQ) which was published by the Stanford Arthritis Center in 1981 (Fries et al., 1980) is arguably the most widely used instrument to measure the QoL of various diseases. The HAQ centers on 5 dimensions, namely, 'disability', 'pain', 'medication effects', 'costs of care' and 'mortality' (Fries et al., 1980). The HAQ is widely known now to be available as a "Full HAQ" which assesses all of these 5 dimensions or the "Short/ 2-page HAQ" which measures only the 'disability' dimension (HAQ-DI). The HAQ-DI has now been cross-culturally adapted and translated into more than 60 different languages and dialects (Bruce & Fries, 2005). Hussein et al validated the Malay version of the HAQ (Malay-HAQ) in 2008 for use among the Malay-speaking RA population in Malaysia (Hussein et al., 2008).

The "Full HAQ" has been used to study multiple diseases and in a myriad of different populations (the disabled, aging, HIV/AIDS patients) (Bruce & Fries, 2005). HAQ-DI on the other hand has been widely used among RA, osteoarthritis, psoriatic arthritis and systemic erythematosus lupus patients (Bruce & Fries, 2005). It can be administered in 5 minutes and scored within a minute which renders it a favourable instrument in population studies.

2.4.3 HRQoL OF PATIENTS WITH RA

Among the current instruments used to measure HRQoL in patients with RA are generic instruments like Nottingham Health Profile (NHP) (Hunt et al., 1981), the Sickness Impact Profile (SIP) (Bergner et al., 1981) or Short Form Health Survey-36 (SF-36) (Ware Jr & Sherbourne, 1992), while more disease-specific ones like the

comprehensive Arthritis Impact Measurement Scale (AIMS2) (Meenan et al., 1992), AIMS (Meenan et al., 1980) or the Rheumatoid Arthritis Quality of Life (RAQoL) developed by Whalley et al.(Whalley, Mckenna, De Jong, & Van der Heijde, 1997). Although there is no consensus on the best measure for QoL of patients with RA to date, the most widely used instrument to measure the QoL of patients with RA is now the Health Assessment Questionnaire (HAQ) (Fries et al., 1980), or specifically, the shortened version – HAQ-DI or "Short HAQ".

It is recognized that RA has a deteriorating effect on not just the physical, but also psychological and social functioning aspects of life (Tijhuis et al., 2001). Tijhuis et al also demonstrated that females experienced worse QoL than males (Tijhuis et al., 2001). Multiple studies using different instruments demonstrated that the detrimental effect of RA extends to moods and emotions, social life, hobbies, everyday tasks, physical contact and fatigue (Ahlmen, Bengtsson, Sullivan, & Bjelle, 1990; Tijhuis et al., 2001; Whalley et al., 1997). A recent systematic review and meta-analysis by Matcham and colleagues in 2014 corroborated this. In their report of 31 publications with a total of 22,335 RA patients, it was revealed that RA has a substantial impact on the health related QOL of the patients involved (Matcham et al., 2014).

2.4.4 ORAL HEALTH RELATED QUALITY OF LIFE (OHRQoL) INSTRUMENTS

Similar to their medical counterparts, dental researchers have also started adopting the oral health-related quality of life (OHRQoL) measures in substantiating the literature regarding oral conditions and their management therapies. Prior to this widely accepted terminology, this measure was originally referred to as "socio-dental indicators" or "measures of oral health status" or "social impacts of oral disease" (David Locker & Allen, 2007). Slade in 1997 defined OHRQoL broadly as "a broad conception of health, encompassing the traditional definition of health, as well as an individual's

subjective impact of health on well-being and functioning in everyday life (Slade, 1997b)".

Various instruments have been introduced to measure OHRQoL. Most of these instruments are based on WHO's 1980 International Classification of Impairments, Disabilities and Handicaps (ICIDH) (Badley, 1987), which Locker subsequently adapted for use in Dentistry in 1988 (D Locker, 1988). Among the first instruments are the Oral Health and the Sickness Impact Profile in 1989 (Reisine, Fertig, Weber, & Leder, 1989), the General Oral Health Assessment Index (GOHAI) in 1990 (Atchison & Dolan, 1990), the Dental Impact Profile (DIP) in 1993 (Strauss & Hunt, 1993) and The DELTA in 1996 (Kressin, SPIRO III, Bossé, Garcia, & Kazis, 1996).

A non-exhaustive list of OHRQoL instruments used in oral health research over the years is compiled in Table 2.6.

Table 2.6: OHRQoL instruments used in oral health research.

Instrument	Number of Items	Year Introduced	Reference
Oral Health and the Sickness Impact Profile (-SIP)	73	1989	(Reisine et al., 1989)
Geriatric (General) Oral Health Assessment Index (GOHAI)	12	1990	(Atchison & Dolan, 1990)
Dental Impact Profile (DIP)	25	1993	(Strauss & Hunt, 1993)
Psychosocial Impact Score	42	1994	(David Locker & Miller, 1994)
Oral Health Impact Profile (OHIP-49)	49	1994	(Slade & Spencer, 1994)
The DELTA	6	1996	(Kressin et al., 1996)
Dental Impact on Daily Living (DIDL)	36	1996	(Leao & Sheiham, 1996)
Oral Health Impact Profile (OHIP-14)	14	1997	(Slade, 1997a)
Orthognathic Quality of Life Questionnaire (OQoLQ)	22	2000	(Cunningham, Gilthorpe, & Hunt, 2000)
Oral Health Impact Profile (OHIP-EDENT)	20	2002	(F. Allen & Locker, 2002)
Oral Health Impact Profile (OHIP-Aesthetic)	14	2007	(Wong, Cheung, & McGrath, 2007)

2.4.5 ORAL HEALTH IMPACT PROFILE (OHIP) INSTRUMENT

One of the more sophisticated measures (Saub, Locker, & Allison, 2005) was the original Oral Health Impact Profile (OHIP-49) that was developed in 1994 (Slade & Spencer, 1994). It was developed based on the perceived functional and psychological impacts of oral diseases in a conceptual framework (Slade & Spencer, 1994). This instrument has 49 questions which fall under seven dimensions or subscales, namely 'functional limitation', 'physical pain', 'psychological discomfort', 'physical disability', 'psychological disability', 'social disability' and 'handicap'. The instrument is widely used globally and has been translated into many languages like German, Spanish, Chinese, Malay, Thai among others for relevance in the respective population. In the Malaysian setting, Saub and colleagues successfully introduced the Malaysian OHIP (L-

OHIP(M)) which has 45 items as compared to the original OHIP-49 of 49 items (Saub et al., 2005).

A shorter version (OHIP-14) was created in 1997 for the ease of use (Slade, 1997a). Its psychometric qualities have been confirmed in many studies (David Locker & Allen, 2002). Locker and Allen justified the use of these shorter measures for various reasons such as less-responsiveness with length, administrative costs and others (David Locker & Allen, 2002). In Malaysia, the OHIP-49 was shortened, translated and adapted for the Malaysian population by performing a thorough cross-cultural adaptation process and coined as the OHIP-14 (M) in 2005 (Saub et al., 2005).

The relevance of the OHIP questionnaire in oral health research is unquestionable but recently, current literature has shown that when comparing the OHIP tool to others (GOHAI or DIP), there are certain domains in which the OHIP tool has shown to not be as sensitive. Hence, many researchers and academicians have sought to modify the OHIP instrument so that it would be more specific and relevant to the study population. Allen and Locker in 2002 modified the OHIP-49 using an item impact reduction method to create the OHIP-EDENT for measurement of the OHRQoL in edentulous adults (F. Allen & Locker, 2002). Similarly, Wong and colleagues have also modified the OHIP questionnaire to produce an OHIP-aesthetic for dental aesthetic procedures especially teeth whitening (Wong et al., 2007). A similar modification is yet to be made for periodontitis and its management.

2.4.6 OHRQoL OF PATIENTS WITH PD

Documentation of the severity and presence of PD is usually done clinically using parameters such as probing pocket depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP). However, this does not account for other symptoms like persistent bad breath, bleeding while brushing and loosening of affected teeth (Ng

& Leung, 2006), which adversely impact a patient's QoL and is relevant to them (D Locker, 1988). A consensus maintains that OHRQoL is best reported from a patient's perspective as it is subjective, although there is no universal agreement on the definition of OHRQoL (Al-Harthi et al., 2013).

Until recent years, the impact of PD on quality of life has been overlooked, probably as fewer symptoms are experienced during the initial stages of the disease (Thomson, 2011). In what was the earliest study of this sort, Needleman et al, using the UK oral health-related quality of life measure (OHQoL-UK©) on 205 patients in a private periodontal clinic, demonstrated that OHRQoL can be directly affected by PD (Needleman, McGrath, Floyd, & Biddle, 2004). This was followed by Ng and Leung from Hong Kong with a group of 727 participants who reported on the significant impact of PD on functional limitation, physical pain and disability (Ng & Leung, 2006). Lawrence et al, with a study of a birth cohort of 924 subjects born in New Zealand also corroborated this when they found that PD has a significant impact on the prevalence and severity of OHRQoL (Lawrence, Thomson, Broadbent, & Poulton, 2008). More recently, utilising the Chinese version of OHIP-14, He and colleagues studied a sample population of 480 Chinese adults in the Chongqing municipality in 2018 and reported that chronic periodontitis was associated with poorer OHRQoL in Chinese adults (He, Wei, Wang, & Ji, 2018). A similar result was reported in a Malaysian study of 130 subjects (65 severe PD and 65 healthy controls) (Sulaiman et al., 2019). Using the OHIP-14(M), the authors reported that the OHRQoL of subjects with severe PD was significantly impacted especially in the functional limitation and psychological discomfort dimensions.

In contrast, a study from Australia in 2008 of 603 subjects from Greek and Italian background reported that there was no direct association between PD status and OHIP score (Mariño, Schofield, Wright, Calache, & Minichiello, 2008). A similar study

performed in 2018 on older participants (804 subjects with ages above 70 years) using the OHIP-14 questionnaire also did not show an association between periodontitis with poor OHRQoL. However, it did show a significant association between the number of teeth and poor OHRQoL (Kato, Abrahamsson, Wide, & Hakeberg, 2018). A study in Germany which assessed 309 patients on supportive periodontal therapy (SPT) reported that there was no significant difference between the OHIP-14 scores for periodontal and prosthetic status (Sonnenschein, Betzler, Kohnen, Krisam, & Kim, 2018). However, they did report that good compliance with SPT intervals seems to contribute to a better OHRQoL compared to irregular attendance.

This instrument and others similar to it have proven to be vital in better understanding the disparity and consequences between PD patients and their healthy counterparts beyond just clinical parameters. Conflicts in data can be attributed to small sample sizes and also the lack of standardization of OHRQoL instruments.

2.4.7 OHRQoL OF PATIENTS WITH PD WITH OTHER SYSTEMIC DISEASES AND CONDITIONS

While the PD-RA association is still being debated on, the association of periodontal disease with conditions such as diabetes mellitus, cardiovascular disease, respiratory disease, osteoporosis and preterm and low birth weight among pregnant women have already been established (Hujoel et al., 2000; Khader & Ta'ani, 2005; Offenbacher et al., 1996; Scannapieco & Ho, 2001; Soskolne & Klinger, 2001; Wactawski-Wende et al., 1996).

A recent UK study in 2015 using OHIP-49 concluded that type II Diabetes Mellitus (T2DM) does not significantly impact the overall OHRQoL of patients with PD compared to its controls without T2DM (Irani, Wassall, & Preshaw, 2015). The author attributed this to the burden of this chronic disease. Similarly, a study in Iran reported no significant co-relation between OHRQoL and PD in patients with T2DM

(Kakoei, Navabi, Aghaabbasi, & Hashemipour, 2016). This corroborated the findings of a couple of studies earlier which declared that diabetes mellitus does not have a significant impact on OHRQoL (Sadeghi, Taleghani, & Farhadi, 2014; Sandberg & Wikblad, 2003).

On the other hand, using the Chinese version OHIP-14S, Chen et al concluded that DM subjects had more missing teeth and those with greater clinical attachment loss (CAL) demonstrated inferior OHRQoL in the psychological disability subscale than their controls (Chen, Ng, Siu, Leung, & Corbet, 2013). A Brazilian study using OHIP-14 to measure the OHRQoL of patients with T2DM in relation to different PD Classifications (AAP, Beck, Machtei, Lopez, Albandar, Tonetti, Community Periodontal Index) demonstrated significant impacts on different aspects of QoL for each different classification (de Pinho, Borges, de Abreu, & Vargas, 2012).

PD has also been reported to be a significant risk factor for preterm and low birth weight among pregnant women (Khader & Ta'ani, 2005; Offenbacher et al., 1996). PD is also considered one of the more prevalent diseases among pregnant women. (Khader & Ta'ani, 2005). Lu et al reported no significance of OHRQoL and the periodontal status of pregnant women in all 3 trimesters in Shanghai, China (Lu, Xu, Wong, Wei, & Feng, 2015). However, a recent Indian study however claimed that pregnant women had poorer periodontal health and OHRQoL than their non-pregnant counterparts (Geevarghese, Baskaradoss, & Sarma, 2017).

2.4.8 OHRQoL OF PATIENTS WITH RA

There are no current published studies about the OHRQoL of patients with PD and RA however there are a few studies that described the OHRQoL of RA patients. A cross sectional study in Toulouse, France used the Health Assessment Questionnaire (HAQ) and General Oral Health Assessment Index (GOHAI) on 73 RA patients and

reported that the OHRQoL of these patients were low (Blaizot et al., 2013). This study however did not compare the results against a group of healthy controls.

Ahola and colleagues in 2015 used the OHIP-14 questionnaire on 995 participants (564 rheumatic diseases patients and 431 controls) from the Finnish Rheumatism Association. They concluded that patients with rheumatic diseases reported significantly more oral discomfort and reduced oral health related quality of life (Ahola et al., 2015). It has to be noted that in of the diseased group, only 282 of the patients had RA while the rest that made up the group were suffering from other rheumatic conditions such as fibromyalgia, unspecified poly or oligoarthritis, unspecified connective tissue disease or ankylosing spondylitis whereas the control group was made up of patients with osteoarthritis (OA) or rheumatic fever (Ahola et al., 2015).

Muhlberg and colleagues in their study of a German population (103 RA subjects, 104 controls) using the German version of the OHIP-14 (OHIP-G14) in 2017 reported that there was no significant difference in periodontitis status between both groups. However, there was significantly higher BOP values in RA patients and the OHRQoL was significantly worse in the RA group compared to their healthy counterparts (Mühlberg et al., 2017).

Since there are currently no reported studies on the impact of PD on the HRQoL and OHRQoL among those suffering from RA, it is imperative that studies are performed to explore this gap in knowledge.

CHAPTER 3: MATERIALS AND METHODS

This study was conducted in two phases: Phase 1 and Phase 2. Phase 1 of the study was designed to study the prevalence of PD in RA patients. The ethical approval for this phase of the study was obtained from the Medical Research Ethics Committee (MREC), University of Malaya Medical Centre (UMMC) (Reference number: MRECID.NO: 2017510-5227) (Appendix A). Phase 2 of the study was conducted to evaluate the impact of PD and RA on the HRQoL and OHRQoL of the subjects. The ethical approval for this phase of the study was obtained from the Medical Ethics Committee, Faculty of Dentistry, University of Malaya (Reference number: DF RD1707/0029(L)) (Appendix B).

3.1 PHASE 1

3.1.1 STUDY DESIGN

Phase 1 of the study was a cross-sectional study of subjects with RA regardless of their periodontal status. The subjects recruited were then subdivided into those with RA and PD (**RA(+)PD(+)**) and subjects with RA but without PD (**RA(+)PD(-)**). After screening and collection of all periodontal parameters, all subjects who had been screened were provided necessary periodontal management or referral to the relevant departments for necessary dental care.

3.1.2 SUBJECT RECRUITMENT

3.1.2.1 SAMPLING FRAME

The target population for Phase 1 of this study was patients with RA. The sampling frame used was the list of patients diagnosed with RA based on the 2010 classification by the American College of Rheumatology and European League Against

Rheumatism (ACR-EULAR) (Aletaha et al., 2010) obtained from the Rheumatology Clinic in the University of Malaya Medical Centre (UMMC).

3.1.2.2 SAMPLING DESIGN

All patients who fulfilled inclusion and exclusion criteria were recruited provided that they voluntarily consented to participate in this study.

Inclusion Criteria

1. All patients who fulfilled the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) 2010 criteria for the classification of RA (Aletaha et al., 2010) within 1 year of diagnosis.
2. Had at least 8 teeth excluding third molars.

Exclusion Criteria

1. Patients who were on antibiotic use during the previous 4 months before study.
2. Patients who received periodontal treatment 4 months before study.
3. Patients who had any concurrent systemic or debilitating conditions such as diabetes mellitus or other autoimmune diseases.
4. Patients who were pregnant.
5. Patients who refused to give informed consent.

3.1.2.3 SAMPLE SIZE

A target of 100 subjects undergoing treatment for RA at the RA clinic in UMMC was set. Convenience sampling was carried out over a period of 14 months (November 2017- December 2018).

3.1.3 MEASUREMENTS

Questionnaires and clinical examinations were used to collect data.

3.1.3.1 QUESTIONNAIRES

The questionnaire used (Appendix C) was divided into three sections as described below:

- The first section consisted of questions pertaining to social demographics, oral health related habits, medical history and dental history.
- The second section of this questionnaire was the modified Oral Health Impact Profile (OHIP-14) which has been validated to be used in Malaysia (Saub et al., 2005). This bi-lingual instrument has both English and Malay language translations. Subjects were required to report on the frequency of experiencing negative impacts over a 1-year period affecting seven domains such as functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability and handicap.
- The third section of this questionnaire was the modified Stanford Health Assessment Questionnaire Disability Index (HAQ) (Fries et al., 1980) which has also been translated into the Malay language and validated for use in Malaysia (Hussein et al., 2008). This instrument is also bi-lingual with both English and Malay language translations. Subjects were required to report disability over the last 1-week period on this 20-question questionnaire.

3.1.3.2 CLINICAL EXAMINATION
RHEUMATOID ARTHRITIS (RA)

The records of subjects who participated in the study was obtained from the patient software registry of the University of Malaya Medical Centre (UMMC). These records include duration of RA diagnosis and current medications.

PERIODONTITIS (PD)

All subjects were screened for PD by 3 calibrated and trained examiners using a WHO periodontal probe (Hu Friedy®, Chicago, IL, USA) at 20g force. Measurement is based on the guidelines by the updated Basic Periodontal Examination (BPE) index by the British Society of Periodontology (BSP) in 2016. The scoring codes are as below in Table 3.1:

Table 3.1: Basic Periodontal Examination (BPE) Scoring

Scores	Description
0	No pockets >3.5 mm, no calculus/overhangs, no bleeding after probing (black band completely visible)
1	No pockets >3.5 mm, no calculus/overhangs, but bleeding after probing (black band completely visible)
2	No pockets >3.5 mm, but supra- or subgingival calculus/overhangs (black band completely visible)
3	Probing depth 3.5-5.5 mm (black band partially visible, indicating pocket of 4-5 mm)
4	Probing depth >5.5 mm (black band entirely within the pocket, indicating pocket of 6 mm or more)
*	Furcation involvement
X	Excluded sextant

Source: (BSP, 2016)

All subjects were then subjected to a full periodontal charting, plaque score and bleeding on probing (BOP) measurement if they consented to have all these extra measurements taken. A UNC 15 periodontal probe (Hu Friedy®, Chicago, IL, USA) was used by the 3 same examiners at a constant force of 20g to measure the pocket probing depth (PPD) and gingival recession (GR) on 6 sites (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual/palatal, mid-lingual/palatal, disto-lingual/palatal) on each tooth.

- PPD was measured as the distance between the gingival margin to the base of the periodontal pocket.
- GR was measured as the distance between cemento-enamel junction (CEJ) and the free gingival margin. A positive value was given when the margin was below the CEJ and a negative value was given when the margin lied above the CEJ.
- Clinical attachment loss (CAL) was calculated as the sum of the PPD and GR.
- Dental plaque was measured as present or absent on 4 sites (mesio-buccal, mid-buccal, disto-buccal and lingual/ palatal) of each tooth using the Visible Plaque Index (Ainamo & Bay, 1975) and recorded as Full Mouth Plaque Score (FMPS) which was calculated as a percentage score of total of number of sites with plaque present over the total number of sites studied.

  Bleeding on probing (BOP) was recorded using the Gingival Bleeding Index (Ainamo & Bay, 1975) which is also a dichotomous measure (yes/no) within 10 seconds of probing at 6 sites per tooth. BOP was reported as Full Mouth Bleeding Score (FMBS), a percentage score of total of number of sites with BOP over the total number of sites studied.

This population's PD status was classified according to the CDC-AAP case definitions (Eke et al., 2012). The detailed explanation is as below in Table 3.2:

Table 3.2: Centers for Disease Control and Prevention -American Academy of Periodontology (CDC-AAP) Case Definition

Periodontitis	Description
Mild	Subjects who had ≥ 2 interproximal sites with CAL ≥ 3 mm, and ≥2 interproximal sites with PD ≥ 4 mm (not on the same tooth) or one site with PD ≥ 5 mm.
Moderate	Subjects who had ≥ 2 interproximal sites with CAL ≥ 4 mm (not on the same tooth), or ≥ 2 interproximal sites with PD ≥ 5 mm (not on the same tooth).
Severe	Subjects who had ≥ 2 interproximal sites with CAL ≥ 6 mm (not on the same tooth) and ≥ 1 interproximal site with PD ≥ 5 mm.

Source: (Eke et al., 2012)

3.1.4 PRE-TEST OF THE QUESTIONNAIRE

A pretest of the questionnaire which consists of social demographics, oral health related habits, medical history, dental history, OHIP-14(M) (Saub et al., 2005) and the Malaysian version HAQ-DI (Hussein et al., 2008) was performed on 10 subjects from the Faculty of Dentistry, University of Malaya in August 2017 prior to subject recruitment for validation. No modification to the questionnaire was required.

3.1.5 STANDARDISATION OF THE EXAMINERS

Standardisation was done to ensure the reliability of the results obtained. All 3 examiners underwent both intra-examiner and inter-examiner standardisations for PPD and GR scores on 2 neutral subjects who volunteered for this exercise in August 2017. The intra-examiner standardisation was performed on different clinical sessions (morning/afternoon) while the inter-examiner standardisation was done against a senior supervisor in the Periodontology discipline in the University of Malaya's Faculty of Dentistry.

A Kappa score of more than 0.75 was obtained by all 3 examiners for both intra-examiner and inter-examiner standardisations and were considered "reproducible" and "standardised".

3.1.6 DATA COLLECTION

Each potential subject was contacted via a phone call and invited to participate in the study after a brief explanation of the study was given in their preferred language of communication (Malay or English languages). Participants were screened in the Postgraduate Periodontology Clinic, Faculty of Dentistry of the University of Malaya. Subjects were classified as not contactable if their recorded contact numbers were no longer in service, wrong or if they did not answer after 3 attempts of contacting had been made.

Subjects who presented at the Postgraduate Periodontology Clinic, Faculty of Dentistry, University of Malaya were given patient information sheets (PIS), available in both the English and Malay languages (Appendices D and E). Subjects who consented for this study provided written informed consent (Appendices F and G) in either English or Malay language and were then assigned an identification number.

They were then administered the questionnaire by the calibrated examiners, whereby section 1 was administered by the examiner whereas sections 2 and 3 (the OHIP-14(M) (Saub et al., 2005) and the Malaysian version HAQ-DI (Hussein et al., 2008)) was self-administered to the best of their abilities. After completion of the questionnaire, clinical examination was performed to record the total number of teeth present and BPE. FMPS (Visible Plaque Index (Ainamo & Bay, 1975)), FMBS (Gingival Bleeding Index (Ainamo & Bay, 1975)), GR and PPD was then recorded for subjects who consented. Clinical attachment loss (CAL) scores were obtained by the summation of the gingiva recession (GR) scores and the pocket probing depth (PPD).

The subject recruitment and the data collection procedures are summarised in Figure 3.1 and Figure 3.2 respectively below.

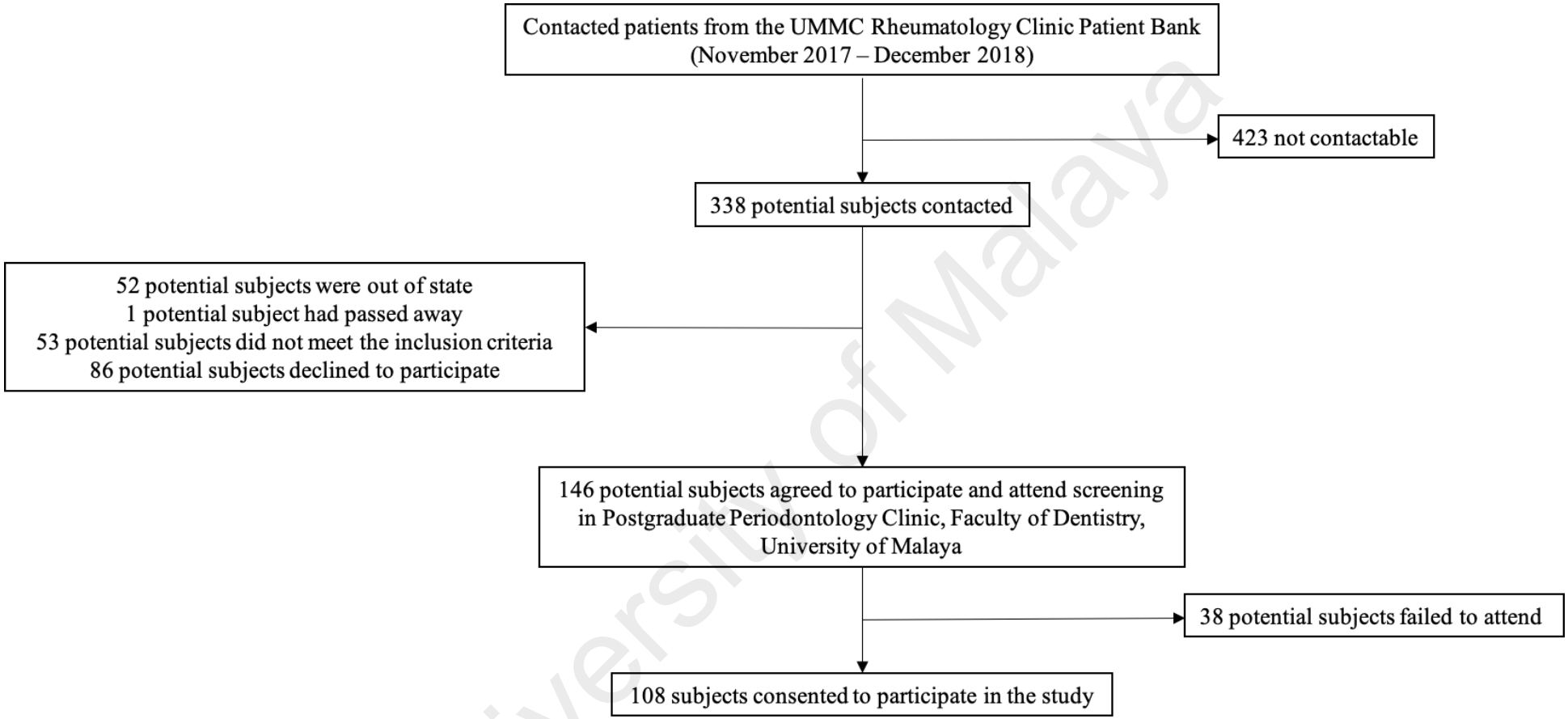

Figure 3.1: Flowchart of subject recruitment in Phase 1

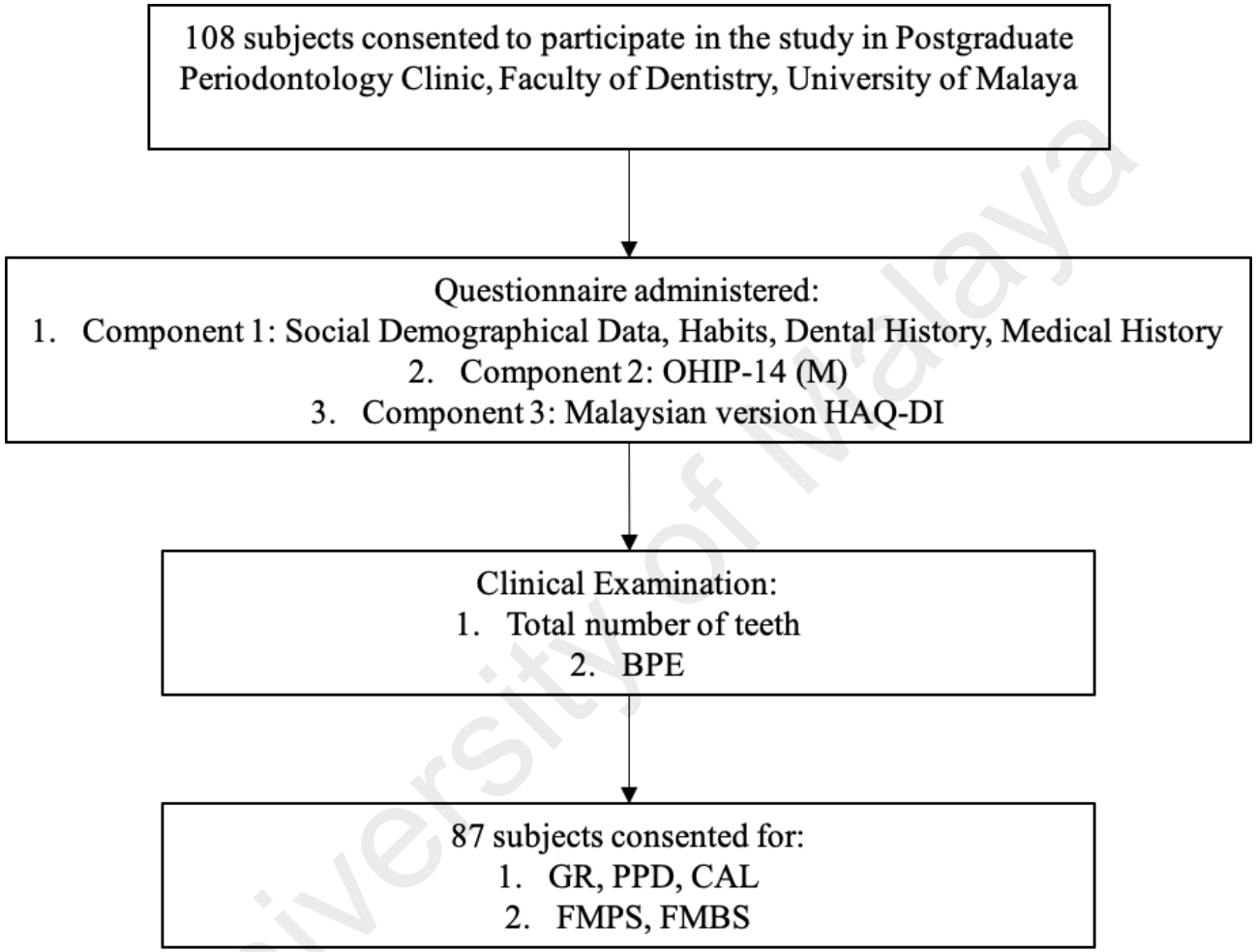

Figure 3.2: Flowchart of data collection in Phase 1

3.1.7 DATA MANAGEMENT AND ANALYSIS

RA subjects were categorised according to their BPE scores. Subjects who consented to further investigations were further classified into having no, mild, moderate or severe PD. The prevalence score of PD in RA subjects was calculated. The categorical and continuous data to compare differences between groups of participants was analysed by using Pearson Chi Square-test and Anova or Kruskal-Wallis tests respectively. Data analysis was performed using the Statistical Package of Social Sciences (SPSS) (SPSS, Chicago, IL, USA) version 23.0.

3.2 PHASE 2

3.2.1 STUDY DESIGN

Phase 2 was a comparative cross-sectional study of subjects with RA and those without RA regardless of their periodontal status. They were subdivided into subjects with RA and PD (**RA(+)PD(+)**), subjects with RA but without PD (**RA(+)PD(-)**), subjects without RA but has PD (**RA(-)PD(+)**) and subjects without both RA and PD (**RA(-)PD(-)**). All subjects who have been screened were provided necessary periodontal management or referral to the relevant departments for necessary dental care.

3.2.2 SUBJECT RECRUITMENT

3.2.2.1 SAMPLING FRAME

The samples for the RA group (disease group) were recruited from Phase 1 of the study. Subjects for the control group (without RA but with or without PD) were recruited from the Primary Care Unit, Faculty of Dentistry, University of Malaya. RA is diagnosed based on the 2010 classification by the American College of Rheumatology and European League Against Rheumatism (ACR-EULAR) (Aletaha et al., 2010) and presence, absence and extent of PD was determined using the CDC-AAP case definitions (Eke et al., 2012).

3.2.2.2 SAMPLING DESIGN

Purposive sampling was used to select the sample.

i) Diseased Group (RA Subjects: RA(+)PD(+) & RA(+)PD(-) groups)

All subjects with RA recruited in Phase 1 who fulfilled the inclusion and exclusion criteria were included in the Phase 2 of the study. The subjects were divided into two groups based on the presence or absence of PD.

Inclusion Criteria

1. All patients who fulfilled the American College of Rheumatology/ European League Against Rheumatism (ACR/EULAR) 2010 criteria for the classification of RA (Aletaha et al., 2010) within 1 year of follow up.
2. Had at least 8 teeth excluding third molars.

Exclusion Criteria

1. Patients who were on antibiotic use during the previous 4 months before study.
2. Patients who received periodontal treatment 4 months before study.
3. Patients who had any concurrent systemic or debilitating conditions such as diabetes mellitus or other autoimmune diseases.
4. Patients who were pregnant.

ii) Control Group (non-RA Subjects: RA(-)PD(+) & RA(-)PD(-) groups)

All subjects without RA were recruited from the Primary Care Unit, Faculty of Dentistry, University of Malaya. The subjects were divided into two groups based on the presence or absence of PD.

Inclusion Criteria

1. Sought dental treatment at the Primary Care Unit, Faculty of Dentistry, University of Malaya.
2. Had at least 8 teeth excluding third molars.

Exclusion Criteria

1. Patients with diagnosed or self-reported RA.
2. Patients who received periodontal treatment 4 months before study.
3. Patients who were on antibiotic use during the previous 4 months before study.
4. Patients who had any concurrent systemic or debilitating conditions such as diabetes mellitus or other autoimmune diseases.

5. Patients who were pregnant.

3.2.2.3 SAMPLE SIZE

Sample size was calculated using a study by Mulhberg and colleagues in 2017 as reference (Mühlberg et al., 2017). The mean (M) and standard deviation (SD) values for the German version OHIP-14 scores both RA and non-RA groups were M:7.7, SD:9.6 and M:1.6, SD:3.0 respectively. The sample size for this phase of study was calculated to be 35 subjects for all 4 groups using the PS sample size calculation software.

3.2.3 MEASUREMENTS

The questionnaires and clinical examination used in this phase were the same as in Phase 1.

3.2.4 DATA COLLECTION

Data collection for the diseased group (**RA(+)PD(+) & RA(+)PD(-))** was performed as described in Phase 1. Subject recruitment for the control group (**RA(-)PD(+) & RA(-)PD(-))** was performed in the Primary Care Unit, Faculty of Dentistry, University of Malaya. Potential subjects were approached while they were waiting for their turn for dental treatment at the waiting area. Potential subjects who were interested were screened based on the inclusion and exclusion criteria and were also given the patient information sheets (PIS), available in both the English and Malay languages. Subjects who consented for this study signed a written consent form and were then assigned an identification number. The same data collection method as in Phase 1 was used. Subject recruitment and data collection for the non RA group (RA(-)PD(+) and RA(-)PD(-)) during Phase 2 is summarised as in Figure 3.3 below.

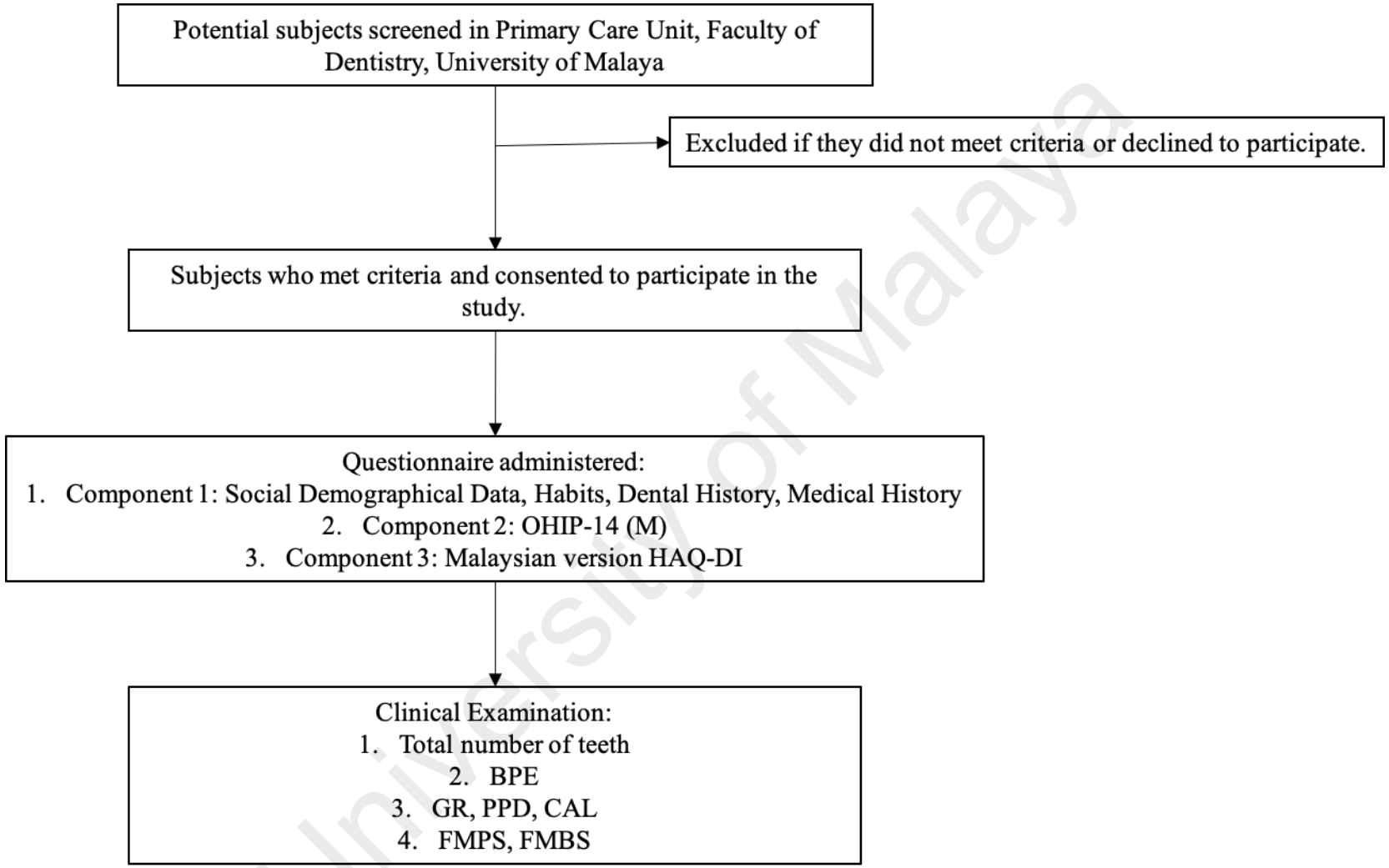

Figure 3.3: Flowchart of subject recruitment and data collection in Phase 2

3.2.5 DATA MANAGEMENT AND ANALYSIS

Clinical attachment loss (CAL) scores were obtained by the summation of the gingiva recession (GR) scores and the pocket probing depth (PPD). Two parameters of OHIP-14 (M) were computed - the prevalence and severity of impacts. The prevalence was defined as percentage of people reporting one or more items 'quite often' or 'very often'. This reflected the proportion of the population who experienced very frequent impacts associated with their oral condition. The severity of impacts was the sum of the ordinal responses on the 5-point Likert scale for all 14 questions whereby the higher the score, the poorer the OHRQoL of the subject. A "tick" for "never" was attributed a score of "0"; "seldom" = "1"; "sometimes" = "2"; "quite often" = "3"; and "very often" = "4". If more than 20% of the items were coded missing, then the participant was excluded from further analysis. Otherwise, the values were imputed using the mean of that particular item. Similar procedures were done for items with "don't know" response. Hence possible scores ranged from 0-56. The Cronbach alpha value for OHIP-14 (M) was 0.95.

On the other hand, for the HAQ-DI, a score of "0" was attributed to "without any difficulty"; "1" for "with some disability"; "2" for "with much disability"; and "3" for "unable to do". Severity scores were subsequently calculated by choosing the greatest score (0-3) from each part within the eight categories. These 8 highest scores for their respective categories were then averaged out to get a final mean which has 25 possible values from 0 to 3. The higher the score, the greater the disability and hence, the poorer the HRQoL of the RA subject.

Data analysis was performed using the Statistical Package of Social Sciences (SPSS) (SPSS, Chicago, IL, USA) Version 23.0. The categorical and continuous data to compare differences between groups of participants was analysed by using Pearson Chi Square-test and Anova or Kruskal-Wallis tests respectively. Multiple linear regression

analysis was performed to analyse the relationship between age, gender, education level and brushing frequency with the OHRQoL of subjects. Correlation between clinical parameters and OHIP-14 (M) score were explored through two-tailed Pearson's correlation coefficient.

CHAPTER 4: RESULTS

4.1 PHASE 1

4.1.1 SAMPLE CHARACTERISTICS OF ALL RA SUBJECTS

The total number of potential RA subjects in the patient bank was 761. Only 338 of these subjects were contactable of which only 146 subjects who fit the inclusion criteria agreed to attend screening at the Postgraduate Periodontology Clinic, Faculty of Dentistry of the University of Malaya. Only 108 of these subjects kept the appointment. The sample characteristics of all 108 RA subjects screened are represented in Table 4.1. The mean age of these subjects is 55.2±10.3 years old and there are made up of 93 (86.1%) females and 15 males (13.9%). A majority of the RA subjects were of Chinese descent (55.6%) followed by Malay and Indian descent at 25% and 18.5% respectively. There was one subject (0.9%) of Punjabi descent. A big majority of the RA subjects had secondary or tertiary education (45.4% and 47.2% respectively). The majority of these subjects (83.4%) fell into the monthly household income bracket of RM2000-9999. A large proportion of these subjects (95.3%) were non-smokers.

Table 4.1: Sample characteristics of all **RA** subjects (N=108).

Sample Characteristics	**RA Subjects** (N=108)
Gender, n(%)	
Male	15(13.9)
Female	93(86.1)
Age group, n(%)	
Below 30	1(0.9)
30-44	19(17.6)
45 and above	88(81.5)
Mean Age (**Mean±SD)**	**55.2±10.3**
Ethnicity, n(%)	
Malay	27(25.0)
Chinese	60(55.6)
Indian	20(18.5)
Others	1(0.9)
Education, n(%)	
Primary	8(7.4)
Secondary	49(45.4)
Tertiary	51(47.2)
Monthly Household Income (in Malaysian Ringgit), n(%)	
<1999	15(13.9)
2000-4999	45(41.7)
5000-9999	45(41.7)
>10000	3(2.7)
Duration of RA diagnoses, n(%)	
1-5 years	31(28.7)
6-10 years	37(34.3)
>10 years	40(37.0)
Smoking, n(%)	
Current smoker	3(2.8)
Former smoker	2(1.9)
Non smoker	103(95.3)
Oral Hygiene Practices: n(%)	
Brushing frequency	
≥ 2x/day	97(89.8)
≤1x/day	11(10.2)
Interdental cleaning	
Yes	55(50.9)
No	52(48.1)
Mouth rinsing	
Yes	59(54.6)
No	48(44.4)

RA: Rheumatoid arthritis

4.1.2 BPE SCORES OF ALL RA SUBJECTS

None of the 108 RA subjects presented with score '0'. Fifty percent of these subjects (54 subjects) presented with a BPE score of '3' or '4'. The detailed breakdown of the number of RA subjects presenting with each BPE score is captured in Figure 4.1.

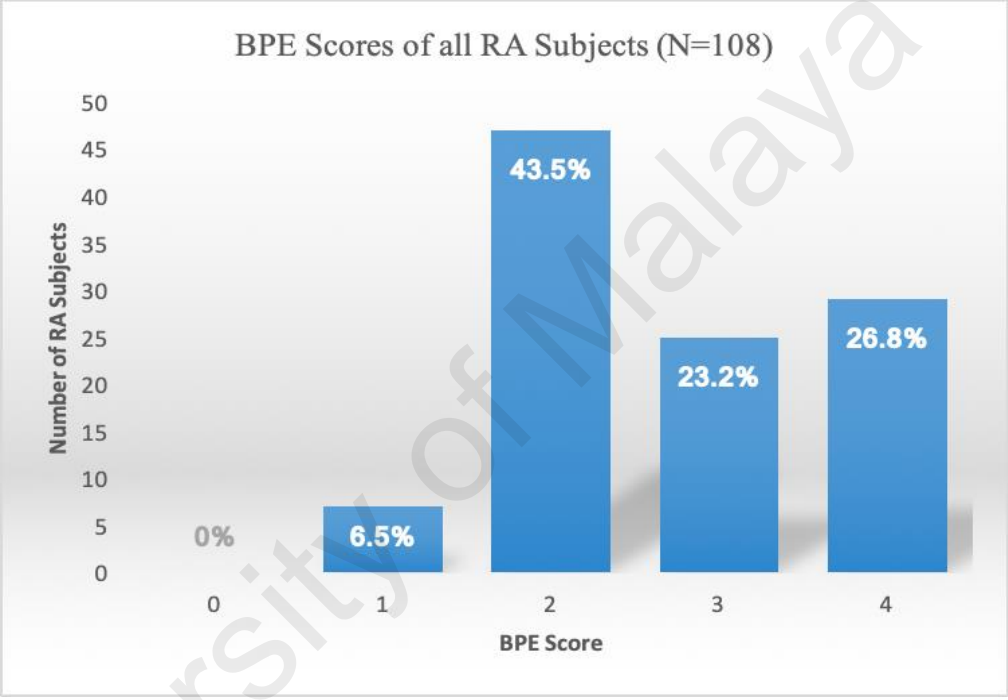

Figure 4.1: BPE Scores of all RA subjects (N=108).

4.1.3 PERIODONTAL STATUS OF RA SUBJECTS

Twenty-one of these RA subjects only consented for BPE screening and not full mouth periodontal charting. Hence, only 87 of these subjects contributed a complete set of data. Table 4.2 shows the periodontal status of the 87 RA subjects who consented to complete periodontal charting. Twenty-nine subjects (33.3%) presented with PD. The prevalence of mild, moderate and severe PD was 4.6%, 10.3% and 18.4% of the recruited RA subject population respectively. The distribution of the periodontal status of these RA subjects is also represented in Figure 4.2.

Table 4.2: Periodontal status of RA subjects (N=87)* based on the CDC-AAP case definition (Eke et al., 2012).

Periodontal Status	**RA Subjects** (N=87) n(%)
No periodontitis	58(66.7)
Mild periodontitis	4(4.6)
Moderate periodontitis	9(10.3)
Severe periodontitis	16(18.4)

RA: Rheumatoid arthritis
**(Only 87 subjects of the 108 RA subjects who underwent BPE screening consented to complete periodontal charting)*

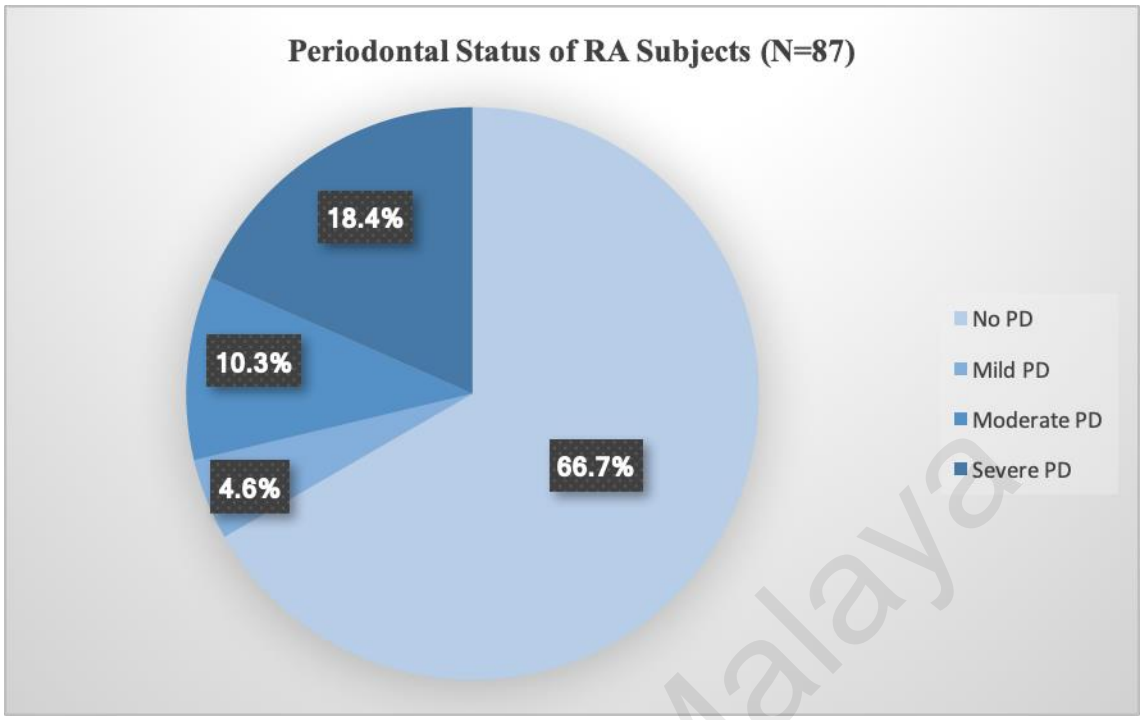

Figure 4.2: Periodontal status of RA subjects (N=87) based on the CDC-AAP case definition (Eke et al., 2012).

4.2 PHASE 2

4.2.1 SAMPLE CHARACTERISTICS OF ALL GROUPS.

All 87 RA subjects from Phase 1 were included in this phase of study. Another 100 non-RA subjects were recruited from the Primary Care Unit, Faculty of Dentistry of the University of Malaya. The sample characteristics of all 4 groups of subjects are demonstrated in Table 4.3. There were 29 subjects in the RA(+)PD(+) group and 58, 43 and 57 subjects in the RA(+)PD(-), RA(-)PD(+) and RA(-)PD(-) groups respectively. Most of the subjects recruited were females at 75.9%, 89.7%, 53.5% and 64.9% for RA(+)PD(+), RA(+)PD(-), RA(-)PD(+) and RA(-)PD(-) groups respectively. The RA(+)PD(+) group had the highest mean age at 55±9.3 whereas the RA(-)PD(-) group had the lowest mean age at 32.1±12.8. The majority of the subjects in all 4 groups had education up to the secondary and tertiary level. There was significant difference ($p<0.01$) between groups in terms of gender, mean age and education level. Subjects with Chinese descent made up the largest majority of all groups (44.2%-56.9%) except in the RA(-)PD(+) group which had a larger Malay race proportion at 47.4%. A large majority of the subjects in all groups never smoked (83.7% - 100%).

Table 4.3: Sample characteristics of subjects of all groups.

Sample Characteristics	**RA(+)PD(+)**, (n=29)	**RA(+)PD(-)** (n=58)	**RA(-)PD(+)** (n=43)	**RA(-)PD(-)** (n=57)	p-value[a]
Gender, n(%)					
Male	7(24.1)	6(10.3)	20(46.5)	20(35.1)	<0.01*
Female	22(75.9)	52(89.7)	23(53.5)	37(64.9)	
Age group, n(%)					
Below 30	0(0)	1(1.7)	13(30.2)	30(52.6)	<0.01*
30-44	5(17.2)	11(19.0)	15(34.9)	18(31.6)	
45 and above	24(82.8)	46(79.3)	15(34.9)	9(15.8)	
Mean Age (Mean±SD)	**55.0±9.3**	**54.7±10.6**	**40.±15.0**	**32.1±12.8**	**<0.01[b]***
Ethnicity, n(%)					
Malay	9(31.0)	13(22.4)	18(41.9)	27(47.4)	0.191
Chinese	13(44.8)	33(56.9)	19(44.2)	20(35.1)	
Indian	6(20.7)	12(20.7)	5(11.6)	8(14.0)	
Others	1(3.5)	0(0)	1(2.3)	2(3.5)	
Education, n(%)					
Primary	1(3.4)	3(5.2)	0(0)	0(0)	<0.01*
Secondary	20(69.0)	23(39.7)	14(32.6)	8(14.0)	
Tertiary	8(27.6)	32(55.2)	29(67.4)	49(86.0)	
Monthly Household Income (in Malaysian Ringgit)					
<1999	5(17.2)	9(15.5)	12(27.9)	15(26.3)	0.561
2000-4999	9(31.0)	26(44.8)	20(46.5)	24(42.1)	
5000-9999	14(48.3)	21(36.2)	10(23.3)	17(29.8)	
>10000	1(3.4)	2(3.4)	1(2.3)	1(1.8)	
Smoking, n(%)					
Current smoker	2(6.9)	0(0)	4(9.3)	5(8.8)	0.078
Former smoker	2(6.9)	0(0)	3(7.0)	1(1.8)	
Non smoker	25(86.2)	58(100)	36(83.7)	51(89.5)	
Oral Hygiene Practices: n(%)					
Brushing frequency					
≥ 2x/day	28(96.6)	49(84.5)	42(97.7)	54(94.7)	0.043*
≤1x/day	1(3.4)	9(15.5)	1(2.3)	3(5.3)	
Interdental cleaning					
Yes	10(34.5)	29(50.0)	23(53.5)	30(42.6)	0.382
No	19(65.5)	29(50.0)	20(46.5)	27(47.4)	
Mouth rinsing					
Yes	16(45.2)	31(53.4)	21(48.9)	31(54.4)	0.852
No	13(44.8)	27(46.6)	22(51.1)	26(45.6)	
Mean duration of RA diagnosis (Mean±SD)	**9.72±9.30**	**10.67±9.24**	**-**	**-**	**0.916**

RA: Rheumatoid arthritis**; PD:** Periodontitis**; RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; **a**: Pearson Chi-Square Test; **b**: Kruskal-Wallis Test; *****: Significant difference observed between groups at p<0.05

4.2.2 CLINICAL PERIODONTAL PARAMETERS FOR ALL GROUPS

The clinical periodontal parameters recorded for each group are shown in Table 4.4. The subjects in the RA(-)PD(-) groups had significantly more ($p<0.05$) teeth than the RA(+)PD(+) and RA(+)PD(-) groups. Both groups of subjects without PD showed significantly lower ($p<0.05$) PPD, CAL and FMBS scores than their counterparts in groups with PD. The FMPS scores of both groups with PD were significantly higher ($p<0.05$) than the RA(-)PD(-) group. There was no difference in all periodontal parameters between RA(+)PD(+) and RA(-)PD(+) group.

Table 4.4: Clinical periodontal parameters of subjects of all groups.

Clinical Periodontal Parameters	**RA(+)PD(+)** (n=29)	**RA(+)PD(-)** (n=58)	**RA(-)PD(+)** (n=43)	**RA(-)PD(-)** (n=57)	*p*-value
Number of teeth (mean±SD)	24.10±5.96$_{z}$	25.33±5.09$_{y}$	27.63±4.50	28.81±2.39$_{zy}$	**<0.01$_{b}$***
PPD (mean±SD)	2.93±0.67$_{zy}$	1.95±0.29$_{zx}$	3.29±0.83$_{xw}$	2.19±0.99$_{yw}$	**<0.01$_{b}$***
CAL (mean±SD)	3.61±1.09$_{zy}$	0.72±0.23$_{zx}$	4.36±3.12$_{xw}$	0.65±0.19$_{yw}$	**<0.01$_{b}$***
FMPS in % (mean±SD)	51.25±29.13$_{z}$	40.90±27.10$_{y}$	54.84±26.89$_{yx}$	29.90±23.43$_{zx}$	**<0.01$_{a}$***
FMBS in % (mean±SD)	28.13±21.61$_{zy}$	7.51±7.67$_{zx}$	30.50±22.95$_{xw}$	9.25±11.43$_{yw}$	**<0.01$_{b}$***

RA: Rheumatoid arthritis**; PD:** Periodontitis**; RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; **PPD**: Probing pocket depth; **CAL**: Clinical attachment loss; **FMPS**: Full mouth plaque score; **FMBS**: Full mouth bleeding score; **a**: One-way Anova Test;
b: Kruskal-Wallis Test; *****: Statistically significant between 2 or more groups at $p<0.05$; **w**, **x**, **y**, **z**: Statistically significant difference between 2 groups at $p<0.05$ (Tukey HSD & Dunnet T3)

4.2.3 PREVALENCE AND SEVERITY IMPACTS OF THE OHRQoL FOR ALL GROUPS

Table 4.5 shows the prevalence and severity impacts of the OHRQoL of all 4 groups of subjects. On a subject level, the highest prevalence of impact on the OHRQoL was reported to be 69.8% in the RA(-)(PD)(+) group followed by the RA(-)PD(-), RA(+)PD(-) and RA(+)PD(+) groups at 65.1%, 62.1% and 58.6% respectively. This however was not statistically significantly different ($p>0.05$).

The dimension of 'psychological discomfort' was reported to be most frequently impacted by all the 4 groups of subjects (36.8% - 55.8% of subjects in each group). On the other hand, no subjects from the RA(+)PD(+) group and only 1 subject from each of the other 3 groups (1.7% - 2.3%) reported that the dimension of 'social disability' was impacted 'quite often' or 'very often'.

On the item level, 'discomfort due to food stuck' was the most frequently reported by all 4 groups of subjects (33.3% - 51.1%) while 'avoid going out' was only reported by 1 subject (1.7%) from the RA(+)PD(-) group and none from the other 3 groups. The differences between groups were however not significant ($p>0.05$).

The severity of OHIP-14 (M) scores was the highest in the RA(-)PD(+) group, at 17.23±10.36 but was only significantly higher than the RA(-)PD(-) group (12.14±9.59). The RA(+)PD(-) group reported higher severity OHIP-14 (M) scores than the RA(+)PD(+) group (13.23±7.89 vs 11.72±7.18) but the difference was not significant ($p>0.05$).

The severity of impacts on the dimensions of 'physical pain', 'psychological discomfort', 'psychological disability' and 'social disability' were not significant between the 4 groups. However, there were significant differences ($p<0.05$) between groups in the dimensions of 'functional limitation', 'physical disability' and 'handicap'. The severity scores of the RA(-)PD(-) group was significantly lower ($p<0.05$) from both

of the groups with PD – RA(+)PD(+) and RA(-)PD(+) in the dimension of ‘functional limitation’. On the other hand, the RA(-)PD(+) group showed significantly higher ($P<0.05$) severity scores in the dimension of ‘physical disability’ compared to the RA(+)PD(+) and RA(+)PD(-) groups. In the dimension of ‘handicap’, the RA(+)PD(+) group reported a significantly lower ($p<0.05$) severity score when compared to the RA(+)PD(-) and RA(-)(PD(+) groups.

Table 4.5: The prevalence and severity of impacts by dimensions, items and overall **OHIP-14 (M)** scores between all groups.

Dimensions and items	OHIP-14 (M) Scores									
	Prevalence: n(%)				p-value[a]	Severity: mean±SD				p-value
	RA(+)PD(+), (n=29)	**RA(+)PD(-)** (n=58)	**RA(-)PD(+)** (n=43)	**RA(-)PD(-)** (n=57)		**RA(+)PD(+)**, (n=29)	**RA(+)PD(-)** (n=58)	**RA(-)PD(+)** (n=43)	**RA(-)PD(-)** (n=57)	
Functional limitation	**9(31.3)**	**8(13.8)**	**12(27.9)**	**10(17.5)**	**0.213**	**2.93±1.91z**	**2.07±1.80**	**3.00±2.26y**	**1.77±1.71zy**	**0.003b***
Difficulty in chewing	4(13.8)	5(8.6)	9(20.9)	2(3.5)		1.45±1.27	1.09±1.08	1.47±1.37	0.82±0.95	
Bad breath	6(20.7)	4(6.9)	9(20.9)	8(14.0)		1.48±1.35	0.98±1.12	1.53±1.20	0.95±1.23	
Physical pain	**4(13.8)**	**12(20.7)**	**12(27.9)**	**9(15.8)**	**0.238**	**2.21±1.40**	**2.47±1.82**	**2.70±1.75**	**2.18±1.67**	**0.431b**
Discomfort eating	3(10.3)	10(17.2)	10(23.3)	4(7.0)		1.07±1.16	1.33±1.32	1.56±1.26	0.95±1.04	
Oral ulcer	1(3.4)	5(8.6)	3(7.0)	7(12.3)		1.14±0.92	1.14±1.07	1.14±0.99	1.23±1.00	
Psychological discomfort	**13(44.8)**	**32(55.2)**	**24(55.8)**	**21(36.8)**	**0.213**	**3.10±1.74**	**3.36±1.87**	**3.86±2.13**	**3.04±2.01**	**0.187b**
Discomfort due to food stuck	12(41.4)	29(50.0)	22(51.1)	19(33.3)		2.31±1.28	2.41±1.16	2.30±1.10	1.86±1.03	
Felt shy	1(3.4)	8(13.8)	9(20.9)	9(15.8)		0.79±0.90	0.95±1.23	1.56±1.35	1.18±1.30	
Physical disability	**4(13.8)**	**13(22.4)**	**13(30.2)**	**10(17.5)**	**0.238**	**1.45±1.74z**	**1.67±2.07y**	**2.67±1.97zy**	**1.77±1.75**	**0.023b***
Avoid eating food	2(6.9)	11(19.0)	11(25.6)	4(7.0)		0.97±1.02	1.16±1.30	1.67±1.25	0.88±1.04	
Avoid smiling	2(6.9)	5(8.6)	4(9.3)	8(14.0)		0.48±1.02	0.52±1.06	1.00+1.25	0.89±1.09	
Psychological disability	**1(3.4)**	**2(3.4)**	**5(11.6)**	**6(10.5)**	**0.213**	**0.76±1.24**	**1.12±1.46**	**1.84±2.06**	**1.53±1.96**	**0.085c**
Disturbed sleep	0(0)	1(1.7)	2(4.7)	4(7.0)		0.24±0.58	0.47±0.75	0.84±1.07	0.65±1.01	
Disturbed concentration	1(3.4)	2(3.4)	5(11.6)	5(8.8)		0.52±0.83	0.66±0.95	1.00±1.18	0.88±1.09	
Social disability	**0(0)**	**1(1.7)**	**1(2.3)**	**1(1.8)**	**0.261**	**0.41±0.91**	**0.53±1.17**	**0.98±1.50**	**0.53±1.05**	**0.313c**
Avoid going out	0(0)	1(1.7)	0(0)	0(0)		0.10±0.41	0.22±0.62	0.30±0.67	0.18±0.47	
Daily activities disturbed	0(0)	1(1.7)	1(2.3)	1(1.8)		0.31±0.66	0.31±0.65	0.67±0.99	0.35±0.67	
Handicap	**1(3.4)**	**8(13.8)**	**11(25.6)**	**6(10.5)**	**0.213**	**0.86±1.06zy**	**1.84±1.99z**	**2.19±1.89y**	**1.33±1.62**	**0.012c***
Spending money	1(3.4)	6(10.3)	5(11.6)	2(3.5)		0.45±0.74	1.26±1.22	1.02±1.14	0.58±0.91	
Less confident	0(0)	5(8.6)	7(16.3)	5(8.8)		0.41±0.73	0.59±1.03	1.16±1.34	0.75±1.02	
OHIP-14 (M)	**17(58.6)**	**36(62.1)**	**30(69.8)**	**28(65.1)**	**0.213**	**11.72±7.18**	**13.23±7.89**	**17.23±10.36z**	**12.14±9.59z**	**0.020b***

OHIP-14 (M): Oral Health Impact Profile Shortened Malaysian Version; **RA:** Rheumatoid arthritis**; PD:** Periodontitis**; RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD;
a: Pearson Chi-Square Test; **b**: One-way Anova Test; **c**: Kruskal-Wallis Test; *****: Statistically significant difference between two of more groups at p<0.05;
z, **y**: Statistically significant difference between two groups at p<0.05 (Tukey HSD)

4.2.4 RELATIONSHIP BETWEEN RAPD STATUS, AGE, GENDER, EDUCATION LEVEL AND BRUSHING FREQUENCY WITH TOTAL OHRQOL SCORES

It was previously shown in Table 4.3 that there was a significant difference in the age, gender, education level ($p<0.01$) and brushing frequency ($p<0.5$) between the 4 groups of subjects. A multiple linear regression analysis was performed to see how the OHRQoL scores could be accounted for among all the subjects (N=187) when these 4 variables were controlled.

In combination, RAPD status, age, gender, education level and brushing frequency accounted for a non-significant 0.6% of the variability in the OHRQoL scores (R_2=0.064, adjusted R_2=-0.021, $F(8,178)=1.511$, p=0.156). Table 4.6 shows that individually, age, gender, education level and brushing frequency had no significant relationship to the OHRQoL of all subjects ($p>0.05$). The OHRQoL score of the RA(-)PD(+) group remained significantly higher ($p=0.01$) than the RA(-)PD(-) group when all the mentioned sample characteristics were controlled.

Table 4.6: Relationship between RAPD status, age, gender, education level and brushing frequency with OHRQoL (OHIP-14(M)) scores.

Variable	B (95% CI)$_a$	β_a	*p*-value
RAPD Status			
RA(+)PD(+)	-1.09 (-6.01, 3.83)	-0.04	0.66
RA(+)PD(-)	0.61 (-3.64, 4.86)	0.03	0.78
RA(-)PD(+)	4.91 (1.16, 8.67)	0.23	**0.01***
Mean Age	0.01 (-0.10, 0.12)	0.02	0.82
Gender			
Female	0.99 (-2.06, 4.03)	0.05	0.52
Education Level			
Tertiary	4.34 (-4.99, 13.68)	0.23	0.36
Secondary	5.05 (-4.22, 14.32)	0.27	0.28
Brushing Frequency			
≥2x a day	1.65 (-3.47, 6.78)	0.05	0.53

RAPD: Rheumatoid arthritis and periodontitis; **RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; B**:** Unstandardised regression coefficients; β: Standardised regression coefficients; CI: confidence interval *****: Statistically significant difference at $p<0.05$; **a**: Multiple linear regression analysis

Dummy variables excluded: RA(-)PD(-) Group, Male gender, Brushing frequency ≤ 1x a day, Primary level education

4.2.5 REGRESSION ANALYSES OF RAPD STATUS, AGE, GENDER, EDUCATION LEVEL AND BRUSHING FREQUENCY SCORES WITH OHRQOL SCORES OF VARIOUS DIMENSIONS

Multiple linear regression analyses were also performed to see whether the differences observed between subject groups in the various OHIP-14 (M) dimensions remained significant after controlling for age, gender, education level and brushing frequency. Table 4.5 indicates the dimensions of interests – "functional limitation", "physical disability" and "handicap".

In the dimension of "functional limitation", Table 4.7 shows that after controlling the selected 4 sample characteristics, the difference between OHRQoL scores for the RA(-)PD(-) and RA(+)PD(+) groups were no longer significant ($p>0.05$). However, the score for the RA(-)PD(-) was still significantly lower ($p=0.01$) than the RA(-)PD(+) group.

On the other hand, the higher OHRQoL score seen in the dimension of "physical disability" for the RA(-)PD(+) group remained significantly higher ($p<0.05$) than both the RA groups – RA(+)PD(+) ($p=0.01$) and RA(+)PD(-) ($p=0.02$) groups even after controlling the 4 sample characteristics. Table 4.8 shows this analysis in detail.

The similar result was seen in the dimension of "handicap". The OHRQoL score of the RA(+)PD(+) group remained significantly lower than that of the RA(+)PD(-) ($p=0.01$) and RA(-)PD(+) ($p<0.01$) groups after controlling for age, gender, education level and brushing frequency. This is captured in Table 4.9.

Table 4.7: Regression analysis for OHIP-14(M) dimension of "functional limitation".

Variable	B (95% CI)a	βa	*p*-value
RAPD Status			
RA(+)PD(+)	0.77 (-0.27, 1.8)	0.14	0.15
RA(+)PD(-)	-0.2 (-0.92, 0.88)	-0.01	0.97
RA(-)PD(+)	1.08 (0.29, 1.88)	0.23	**0.01***
Mean Age	0.02 (-0.01, 0.41)	0.14	0.14
Gender			
Female	0.17 (-0.47, 0.82)	0.04	0.59
Education Level			
Tertiary	1.11 (-0.86, 3.08)	0.27	0.27
Secondary	1.12 (-0.84, 3.07)	0.27	0.26
Brushing Frequency			
≥2x a day	0.62 (-0.46, 1.70)	0.08	0.26

RAPD: Rheumatoid arthritis and periodontitis; **RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; B**:** Unstandardised regression coefficients; β: Standardised regression coefficients; CI: confidence interval *****: Statistically significant difference at p<0.05; **a**: Multiple linear regression analysis
Dummy variables excluded: RA(-)PD(-) Group, Male gender, Brushing frequency ≤ 1x a day, Primary level education

Table 4.8: Regression analysis for OHIP-14(M) dimension of "physical disability".

Variable	B (95% CI)a	βa	*p*-value
RAPD Status			
RA(+)PD(+)	-1.44 (-2.43, -0.45)	-0.27	**0.01***
RA(+)PD(-)	-1.02 (-1.90, -0.14)	-0.24	**0.02***
RA(-)PD(-)	-0.74 (-1.54, 0.05)	-0.18	0.07
Mean Age	0.01 (-0.02, 0.30)	0.04	0.67
Gender			
Female	-0.13 (-0.78, 0.52)	-0.03	0.69
Education Level			
Tertiary	0.37 (-1.61, 2.35)	0.09	0.71
Secondary	0.89 (-1.08, 2.86)	0.22	0.37
Brushing Frequency			
≥2x a day	0.18 (-0.91, 1.27)	0.02	0.75

RAPD: Rheumatoid arthritis and periodontitis; **RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; B**:** Unstandardised regression coefficients; β: Standardised regression coefficients; CI: confidence interval *****: Statistically significant difference at p<0.05; **a**: Multiple linear regression analysis
Dummy variables excluded: RA(-)PD(+) Group, Male gender, Brushing frequency ≤ 1x a day, Primary level education

Table 4.9: Regression analysis for OHIP-14(M) dimension of "handicap".

Variable	B (95% CI)[a]	β[a]	*p*-value
RAPD Status			
RA(+)PD(-)	1.12 (0.31, 1.94)	0.29	**0.01***
RA(-)PD(+)	1.58 (0.67, 2.48)	0.37	**<0.01***
RA(-)PD(-)	0.88 (-0.07, 1.83)	0.23	0.07
Mean Age	0.01 (-0.01, 0.30)	0.10	0.32
Gender			
Female	0.07 (-0.52, 0.66)	0.20	0.81
Education Level			
Tertiary	0.75 (-1.05, 2.56)	0.20	0.41
Secondary	1.06 (-0.73, 2.86)	0.28	0.24
Brushing Frequency			
≥2x a day	0.36 (-0.63, 1.35)	0.50	0.47

RAPD: Rheumatoid arthritis and periodontitis; **RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; B**:** Unstandardised regression coefficients; β: Standardised regression coefficients; CI: confidence interval *****: Statistically significant difference at $p<0.05$; **a**: Multiple linear regression analysis

Dummy variables excluded: RA(+)PD(+) Group, Male gender, Brushing frequency ≤ 1x a day, Primary level education

4.2.6 SEVERITY OF IMPACTS OF THE HRQoL SCORES FOR ALL GROUPS

The HAQ-DI scores are shown in Table 4.10. On the subject level, the severity HAQ-DI score was highest in the RA(+)PD(-) group at 0.85±0.83 followed by the RA(+)PD(+), RA(-)PD(+) and RA(-)PD(-) groups with scores of 0.54±0.49, 0.09±0.15 and 0.08±0.19 respectively. The scores of the RA(+)PD(-) and RA(+)PD(+) groups were significantly higher ($p<0.05$) than the non-RA groups but not significantly different from each other ($p>0.05$).

Likewise, on the disability category level, the HAQ-DI scores for both RA groups did not differ significantly ($p>0.05$) between each other but were respectively significantly higher ($p<0.05$) than both the non-RA groups in all disability categories except 'hygiene'. The HAQ-DI score for the RA(-)PD(-) group in the 'hygiene' disability category was significantly lower than that of the RA(+)PD(-) group but not the RA(+)PD(+) group.

Table 4.10: The severity of impacts by dimensions and overall HAQ-DI scores between all groups.

Disability Categories	HAQ-DI Scores				
	Severity: (mean ±SD)				
	RA(+)PD(+), (n=29)	**RA(+)PD(-)** (n=58)	**RA(-)PD(+)** (n=43)	**RA(-)PD(-)** (n=57)	*p*-value[c]
Dressing and grooming	0.48±0.57$_{zy}$	0.64±0.85$_{xw}$	0.12±0.39$_{zx}$	0.04±0.19$_{yw}$	**<0.01***
Arising	048±0.51$_{zy}$	0.69±0.80$_{xw}$	0.09±0.29$_{zx}$	0.07±0.26$_{yw}$	**<0.01***
Eating	0.59±0.63$_{zy}$	1.02±1.03$_{xw}$	0.12±0.32$_{zx}$	0.04±0.19$_{yw}$	**<0.01***
Walking	0.48±0.57$_{zy}$	0.83±0.92$_{xw}$	0.09±0.29$_{zx}$	0.09±0.29$_{yw}$	**<0.01***
Hygiene	0.38±0.62$_{z}$	0.72±0.85$_{yx}$	0.02±0.15$_{zy}$	0.11±0.31$_{x}$	**<0.01***
Reach	0.69±0.76$_{zy}$	0.98±1.16$_{xw}$	0.16±0.53$_{zx}$	0.11±0.31$_{yw}$	**<0.01***
Grip	0.62±0.68$_{zy}$	0.98±1.64$_{xw}$	0.05±0.21$_{zx}$	0.11±0.31$_{yw}$	**<0.01***
Daily activities	0.62±0.78$_{zy}$	0.95±1.08$_{xw}$	0.09±0.29$_{zx}$	0.09±0.29$_{yw}$	**<0.01***
HAQ-DI	**0.54±0.49$_{zy}$**	**0.85±0.83$_{xw}$**	**0.09±0.15$_{zx}$**	**0.08±0.19$_{yw}$**	**<0.01***

HAQ-DI: Health Assessment Questionnaire Disability Index; **RA:** Rheumatoid arthritis**;** **PD:** Periodontitis**;** **RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD
a: Kruskal-Wallis Test; *****: Statistically significant difference between 2 or more groups at p<0.05;
w, **x**, **y**, **z**: Statistically significant difference between 2 groups at p<0.05 (Dunnet T3)

4.2.7 RELATIONSHIP BETWEEN RAPD STATUS, AGE, GENDER, EDUCATION LEVEL AND BRUSHING FREQUENCY WITH TOTAL HRQOL SCORES

Two multiple linear regression analyses were performed to see how the HRQoL scores can be accounted for among all the subjects (N=187) when age, gender, education level ($p<0.01$) and brushing frequency ($p<0.48$) were controlled.

The RA(-)PD(-) group was used as the reference group in the first analysis. Table 4.11 shows that when age, gender, education level and brushing frequency were controlled, the HRQoL score of the RA(+)PD(-) group remained significantly higher ($p<0.01$) than the RA(-)PD(-) group but the HRQoL score of the RA(+)PD(+) was no longer significantly higher ($p>0.05$).

The second analysis was performed using the RA(-)PD(+) group as the reference group. Table 4.12 shows that the HRQoL scores of both the RA groups - RA(+)PD(+) ($p=0.02$) and RA(+)PD(-) ($p<0.01$) groups remained significantly higher than that of the RA(-)PD(+) group when the 4 sample characteristics were controlled.

Table 4.11: Regression analysis for HAQ-DI scores (RA(-)PD(-) as reference).

Variable	B (95% CI)a	βa	*p*-value
RAPD Status			
RA(+)PD(+)	0.25 (-0.02, 0.53)	1.80	0.07
RA(+)PD(-)	0.62 (0.38, 0.86)	0.46	**<0.01***
RA(-)PD(+)	-0.06 (-0.27, 0.15)	-0.04	0.60
Mean Age	0.01 (-0.01, 0.01)	0.10	0.22
Gender			
Female	-0.01 (-0.18, 0.17)	-0.01	0.95
Education Level			
Tertiary	-0.49 (-1.01, 0.40)	-0.38	0.07
Secondary	-0.29 (-0.81, 0.23)	-0.23	0.27
Brushing Frequency			
≥2x a day	0.04 (-0.25, 0.33)	0.02	0.77

RAPD: Rheumatoid arthritis and periodontitis; **RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; B**:** Unstandardised regression coefficients; β: Standardised regression coefficients; CI: confidence interval *****: Statistically significant difference at p<0.05; **a**: Multiple linear regression analysis
Dummy variables excluded: RA(-)PD(-) Group, Male gender, Brushing frequency ≤ 1x a day, Primary level education

Table 4.12: Regression analysis for HAQ-DI scores (RA(-)PD(+) as reference).

Variable	B (95% CI)a	βa	*p*-value
RAPD Status			
RA(+)PD(+)	0.31 (0.05, 0.57)	0.18	**0.02***
RA(+)PD(-)	0.67 (0.44, 0.91)	0.51	**<0.01***
RA(-)PD(-)	0.06 (-0.15, 0.27)	0.04	0.60
Mean Age	0.01 (-0.01, 0.01)	0.10	0.22
Gender			
Female	-0.01 (-0.18, 1.67)	-0.01	0.95
Education Level			
Tertiary	-0.49(-1.01, 0.04)	-0.38	0.07
Secondary	-0.29 (-0.81, 0.23)	-0.23	0.27
Brushing Frequency			
≥2x a day	1.65 (-0.25, 0.33)	0.05	0.53

RAPD: Rheumatoid arthritis and periodontitis; **RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; B**:** Unstandardised regression coefficients; β: Standardised regression coefficients; CI: confidence interval *****: Statistically significant difference at p<0.05; **a**: Multiple linear regression analysis
Dummy variables excluded: RA(-)PD(+) Group, Male gender, Brushing frequency ≤ 1x a day, Primary level education

4.2.8 CORRELATION BETWEEN PERIODONTAL PARAMETERS AND THE OHRQoL OF ALL GROUPS

The correlation between periodontal parameters (mean number of remaining teeth, PPD, CAL, FMPS and FMBS) and duration of RA diagnosis with the OHRQoL of all subjects was studied using the Pearson Correlation Test. Table 4.13 shows the correlation results for each of the 4 groups of subjects.

There is a significant weak negative correlation ($r = -0.269$, $p<0.05$) between the mean remaining number of teeth and OHRQoL in the RA(+)PD(-) group. This is also demonstrated in the scatter plot below (Figure 4.3). There is however no significant difference between this parameter and the OHRQoL in the remaining 3 groups of subjects.

No significant correlation was found between the other clinical periodontal parameters – PPD, CAL, FMPS and FMBS and the duration of RA diagnosis with the OHIP-14 (M) severity scores of subjects in all 4 groups.

Table 4.13: Correlation between periodontal and RA parameters with severity of **OHIP-14 (M)** of all groups.

	Mean OHIP-14 (M) Severity Scores							
	RA(+)PD(+), (n=29)		**RA(+)PD(-)** (n=58)		**RA(-)PD(+)** (n=43)		**RA(-)PD(-)** (n=57)	
	r value[a]	*p*-value[a]	r value[a]	*p*-value[a]	r value[a]	*p*-value[a]	r value[a]	*p*-value[a]
Mean Number of Teeth	0.139	0.471	-0.269*	0.041	-0.002	0.989	-0.075	0.578
Mean PPD	0.186	0.334	0.072	0.593	0.223	0.151	0.048	0.724
Mean CAL	0.034	0.863	0.185	0.164	-0.011	0.944	0.075	0.578
Mean FMPS	-0.104	0.592	0.163	0.222	-0.168	0.282	0.021	0.874
Mean FMBS	0.130	0.501	0.038	0.779	0.127	0.418	-0.060	0.658
Mean duration of RA diagnosis	-0.003	0.989	0.250	0.058	-	-	-	-

RA: Rheumatoid arthritis**; PD:** Periodontitis**; RA(+)PD(+)**: subjects with RA and PD; **RA(+)PD(-)**: subjects with RA but without PD; **RA(-)PD(+)**: subjects without RA but has PD; **RA(-)PD(-):** subjects without both RA and PD; **PPD**: Probing pocket depth; **CAL**: Clinical attachment loss; **FMPS**: Full mouth plaque score; **FMBS**: Full mouth bleeding score**; a**: Pearson's Correlation Coefficient Test; *****: Correlation is significant at the 0.05 level (2-tailed)

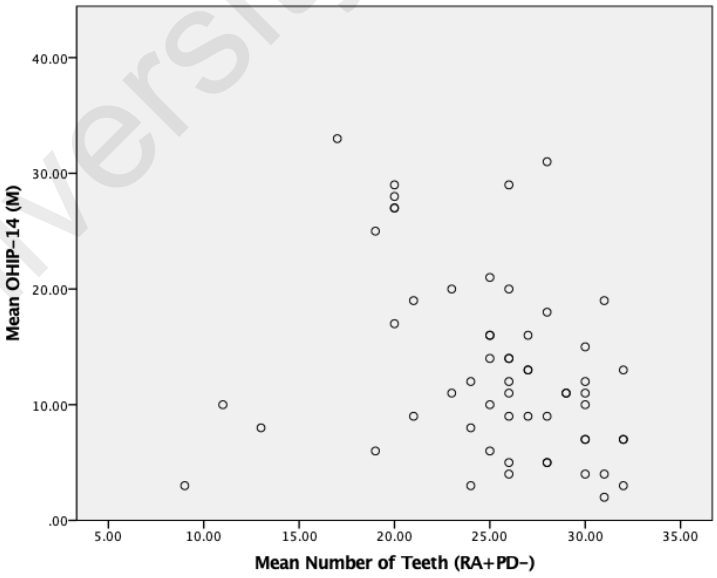

Figure 4.3: Correlation between mean number of teeth with the severity of **OHIP-14 (M)** scores in the **RA(+)PD(-)** group.

CHAPTER 5: DISCUSSION

5.1 STUDY DESIGN AND METHODS

5.1.1 NOVEL STUDY

The plausible association between PD and RA has been studied globally with many reports of a weak to considerable positive association (Bartold et al., 2005; Detert et al., 2010). The wealth of research literature regarding the PD-RA association coming from the Americas and Europe is immense (Äyräväinen et al., 2017; De Pablo et al., 2009; Demmer et al., 2011; Dissick et al., 2010; Eriksson et al., 2016; Mercado et al., 2001; Orlandi et al., 2018; Scher et al., 2012). Studies on this issue in the Southeast-Asian populations have however been limited to one study each from Indonesia (Susanto et al., 2013) and Thailand (Khantisopon et al., 2014) as well as a pilot study with a very small sample size of a Malaysian subpopulation (Suhaimi et al., 2016).

QoL (both HRQoL and OHRQoL) measurements ideally supplements traditional clinical parameters to give a more holistic representation of the disease from a patient's perspective (Al-Harthi et al., 2013; Fitzpatrick et al., 1998). Since Needleman et al.'s study on the OHRQoL of periodontal patients (Needleman et al., 2004), there have been many other similar studies (Abdullah et al., 2018; He et al., 2018; Kato et al., 2018; Lawrence et al., 2008; Mariño et al., 2008; Ng & Leung, 2006; Sulaiman et al., 2019) and even some looking at the OHRQoL of RA patients (Ahola et al., 2015; Blaizot et al., 2013; Mühlberg et al., 2017).

Nevertheless, there is currently no published study comparing the impact of PD in particular on the OHRQoL of RA patients. This is a novel study attempting to explore both of these gaps in knowledge by determining the prevalence of PD in a Malaysian RA subpopulation and assessing the impacts on their QoL (HRQoL and OHRQoL).

5.1.2 SCREENING AND PERIODONTAL PARAMETERS RECORDING

This study utilised the BPE for initial assessment of all recruited subjects and then proceeded with a complete periodontal examination (PPD, GR, FMPS and FMBS) of those who consented to it.

Many epidemiological studies adopt the Community Periodontal Index (CPI) for screening(Baelum, Fejerskov, Manji, & Wanzala, 1993). The disadvantage of the CPI is that it underestimates the disease prevalence in a population (Baelum et al., 1993; Beltrán-Aguilar, Eke, Thornton-Evans, & Petersen, 2012). The British Society of Periodontology modified the CPI for use in private and public settings to form the BPE (Smales, Mosedale, & Floyd, 1987) which examined all teeth and not just index teeth like the CPI.

The BPE gives an extra advantage of speed in screening. However, it has been reported that BPE might give an overestimation or underestimation of the disease prevalence when measuring cumulative attachment loss or in populations of lower susceptibility respectively (Beck & Löe, 1993; Carlos, Wolfe, & Kingman, 1986; Eaton, Duffy, Griffiths, Gilthorpe, & Johnson, 2001).

On the other hand, a complete periodontal examination optimally captures the disease paradigm and is now adopted by many studies despite being a more time-consuming process (Baelum & Scheutz, 2002; Savage, Eaton, Moles, & Needleman, 2009). We adopted both assessment techniques as we wanted to also include potential subjects who might be deterred from participating in the study if the duration for data collection was too long. This method of assessment was different from studies in the neighbouring populations which used full periodontal examinations only (Potikuri et al., 2012; Susanto et al., 2013) and a combination of periodontal examination and Community Periodontal Index (CPI) scores (Khantisopon et al., 2014).

5.1.3 PERIODONTITIS CASE DEFINITION

Many different case definitions have been used in periodontology epidemiology studies. The CDC-AAP case definition (Eke et al., 2012) was used in this study, similar to the Indonesian and Thai studies (Khantisopon et al., 2014; Susanto et al., 2013). On the other hand, other studies have utilised radiographic bone loss analysis alone (Mercado et al., 2001) or along with BOP and tooth mobility (Dissick et al., 2010), history of periodontal therapy (H.-H. Chen et al., 2013) or even self-reporting by subjects (Orlandi et al., 2018).

The CDC-AAP case definition utilises both PPD and CAL to accurately define cases of PD as in takes current (PPD) and cumulative (CAL) damage into consideration, rendering it arguably more optimal than the afore-mentioned methods of case definitions (Beltrán-Aguilar et al., 2012). Taking only the 4 interproximal sites into account (excluding the mid-facial and mid-lingual sites) reflects true disease more accurately as these excluded sites commonly have recessions caused by non-PD origins such as traumatic tooth-brushing (Eke et al., 2012). Hence we decided that this was the most ideal case definition to be used in our epidemiological study.

5.1.4 INCLUSION AND EXCLUSION CRITERIA

This study adopted strict inclusion criteria. Potential subjects who were pregnant, who underwent periodontal therapy within the previous 4 months, who had consumed any types of antibiotics over the prior 4 months, who had concurrent debilitating systemic conditions (Diabetes Mellitus or other autoimmune disorders) and had lesser than 8 teeth (excluding third molars) were excluded from the study. These criteria were similar to that of Mercado and colleagues in 2001 (Mercado et al., 2001).

This study chose 4 months as the threshold period criterion following periodontal therapy for inclusion as a subject. Haffajee et al described that it took 3

months for re-formation of perio-pathogenic microbial complexes (Haffajee et al., 2008). Using a 4-months threshold allows more time for the re-establishment of these disarrayed perio-pathogenic microbial complexes and can better capture a subject's periodontal status.

This study also chose a 4-month threshold duration following antibiotic therapy. It has been shown that certain antibiotics target and suppress certain perio-pathogenic bacteria for a period of 10 days (*Eikenella corrodens*) to 3 months (*Porphyromonas gingivalis*) (Ehmke, Moter, Beikler, Milian, & Flemmig, 2005). Certain periodontal therapy-specific antibiotic regimes might even suppress *Aggregatibacter actinomycetemcomitans* for 18 months (adjunct to periodontal therapy) (Ehmke et al., 2005). A 4-month threshold was set regardless on the type of antibiotics taken by the subject to better present a more accurate periodontal profile. This strict criterion included all types of antibiotics and not just PD specific ones as most of the Malaysian population are unaware of the name of the antibiotics they take.

Subjects who had concurrent diseases like diabetes mellitus (DM) or other autoimmune disorders were excluded. The two-way relationship between DM and PD has long been established (Grossi & Genco, 1998). Controlling this gave the investigators a better picture of the plausible association between PD and RA, independent of the proven association with DM. In addition, the burden of disease felt by the subject who have concurrent autoimmune conditions might be reflected in the self-reported QoL assessments. Excluding it allowed a better reflection of the impacts of RA solely on the individual.

This present study only included subjects with 8 or more teeth (excluding third molars). Dissick et al's criterion for remaining number of teeth in dentate potential subjects was at least 4, with no mention of third molars (Dissick et al., 2010). Having a remaining number of 20-21 teeth had been traditionally associated to functional

adequacy and better OHRQoL (A Sheiham et al., 2001; Steele et al., 2004). As tooth loss is most prevalently caused by dental caries or periodontal disease (Petersen, 2003), choosing 8 as a threshold number prevents over- or under-estimation of the PD prevalence and also plausible effects on the QoL.

5.1.5 REPRODUCIBILITY OF EXAMINERS

All 3 examiners in this study underwent both intra-examiner and inter-examiner alignment and standardisation exercises. The reproducibility of data collected was ensured as all 3 examiners obtained a Kappa score of more than 0.75 in both exercises. Ramfjord discussed on the importance of "reliability" among examiners in periodontal research as early as in 1967 (Ramfjord, 1967). Undoubtedly, the reproducibility of data collected by many examiners or even a single examiner is the backbone of any high quality research (Hefti & Preshaw, 2012). This ensures that the data collected in this study is comparable and reproducible despite being collected by 3 different examiners.

5.1.6 SAMPLE SIZE CALCULATION

Sample size calculation was performed for Phase 2 but not Phase 1 of this study. Similar to this study, a few studies on the prevalence of PD in RA subjects did not adopt a sample size calculation (Dissick et al., 2010; Khantisopon et al., 2014; Susanto et al., 2013). Within the time and logistics limitations, we set a target of 100 RA subjects instead for Phase 1 as RA has a low prevalence. Recruiting 100 subjects was realistically achievable and represented a large-enough sample.

The required sample size of 35 per group for Phase 2 was exceeded in all groups except the RA(+)PD(+) group where only 29 subjects were successfully recruited. However, this number would be different as 21 of the RA subjects who were screened

with BPE did not consent for further periodontal examination. A majority of these subjects scored '3' and '4' in the BPE.

5.1.7 MATCHING OF SAMPLE CHARACTERISTICS

This study was a cross sectional study. Non-RA subjects were not matched to the RA subjects by age, gender and other sample characteristics. This was different from a few other studies who matched their healthy controls to the test (RA) subjects (Mercado et al., 2001; Potikuri et al., 2012; Susanto et al., 2013). We were unable to get matched samples due to time and logistics limitation. Nevertheless, we controlled the differences seen between groups in age, gender, education level and brushing frequency during data analyses, using regression analyses. This would still allow meaningful interpretation of this present study's results.

5.2 BPE AND COMPLETE PERIODONTAL EXAMINATION RESULTS

5.2.1 PREVALENCE OF PD IN RA SUBJECTS USING BPE SCORES

This study reported a 50% prevalence of BPE scores of '3' and '4'. There are no other comparable studies which also use the BPE tool. Comparison with studies using CPI might be valid since the BPE is a modification of the CPI (Smales et al., 1987). Kantisopon et al described a prevalence of 92.7% of CPI scores of '3' and '4' in the Thai population (Khantisopon et al., 2014). This figure is much higher than that seen in the present study. However, when compared to the most recent (2010) National Oral Health Survey of Adults (NOHSA) in Malaysia, the figures are more comparable. NOHSA 2010 reported a 48.5% prevalence of CPI scores of '3' and '4' (Oral Health Division, 2012). The BPE scores of '3' and '4' cumulatively of this Malaysian RA

subpopulation closely resembles the CPI scores of '3' and '4' of the Malaysian population in general.

5.2.2 PREVALENCE OF PD IN RA SUBJECTS

The prevalence of PD in 87 RA subjects in this study was 33.3% (4.6%, 10.3% and 18.4% for mild PD, moderate PD and severe PD respectively). This figures are much lower than other studies (Mercado et al., 2001; Susanto et al., 2013) which reported the prevalence of PD in RA subjects of > 50%. Kantisopon et al reported an even higher prevalence of PD in their RA subjects - > 95% (Khantisopon et al., 2014).

Our findings might be different from that of Mercado and colleagues as they used radiographic analysis of bone level changes to diagnose cases of periodontitis (Mercado et al., 2001). It has been suggested that the estimation of the CAL via this method could differ significantly to clinical measurements (Åkesson, Håkansson, & Rohlin, 1992).

Although Kantisopon et al reported a much higher prevalence than the current study, they disclosed that 64% of their subjects had undergone periodontal therapy. Unlike the present study, they did not set a threshold duration post-periodontal therapy for recruitment of these subjects. They only reported that none of the recruited subjects were on periodontal care during the study period.

Another reason why our findings might differ might be due to the different subject recruitment method (telephone call vs face-to-face) applied in our study compared to that of the Indonesian and Thai studies (Khantisopon et al., 2014; Susanto et al., 2013). There can be potential non-response and volunteer bias with subject recruitments made via telephone call (Sedgwick, 2015). As many as 53 subjects did not meet the inclusion criteria which included at least 8 teeth remaining excluding third

molars. Many claimed early loss of teeth but were not screened as we adhered to this inclusion criterion.

Furthermore, another 86 subjects declined to participate for a host of reasons, many among them claimed they were "shy about their teeth and gums". We infer that there might be non-response bias with these non-responders. In contrast, a large number of subjects who volunteered to participate in the study verbalised that they would like to have a specific dental problem checked during the screening. This would contribute to volunteer bias. We feel that the non-response and volunteer bias caused our findings to poorly reflect the RA subpopulation we are studying and might have underestimated the true prevalence of the disease.

The prevalence of severe PD in the current study's RA subpopulation was 18.4%. This is similar to the prevalence of severe PD in 18.2% of the Malaysian population (Oral Health Division, 2012). This indicates that the prevalence of severe PD in this RA subpopulation is similar to that of the Malaysian population. Susanto et al, and Eriksson et al, also reported similar prevalence between their RA and non-RA subpopulations (Eriksson et al., 2016; Susanto et al., 2013), albeit in all forms of periodontitis and not just the severe form.

5.3 PERIODONTAL PARAMETERS BETWEEN GROUPS

In this study, periodontal parameters such as PPD, CAL, FMPS and FMBS were significantly different ($p<0.01$) between PD groups and non-PD groups regardless of their RA status. No significant difference was detected when comparing RA and non-RA subjects with similar PD status (RA(+)PD(+) vs RA(-)PD(+) groups; and RA(+)PD(-) vs RA(-)PD(-) groups). This corresponds to the findings of studies by Javed et al and Attarbashi et al (Attarbashi Moghaddam, Dehghan, Ghasemi, & Rashidi Maybodi, 2016; Javed et al., 2016). The authors of these studies also reported no

significant differences in the periodontal parameters between PD patients with and without RA (Javed et al., 2016) and between RA and non-RA patients whose PD status are unknown prior to screening (Attarbashi Moghaddam et al., 2016). It appears from these data together with the data from the context of our study which suggests that the role RA plays in affecting the signs (periodontal parameters) seen in subjects is limited. The periodontal parameters recorded appear to be possibly a reflection of the presence and intensity of PD solely. It is however crucial to note that response and volunteer bias might contribute to this.

This present study also reported a significantly lesser ($p<0.01$) number of remaining teeth in the RA subjects compared to the group of subjects without RA and PD (RA(-)PD(-) group). This finding is consistent to that of a number of studies (De Pablo et al., 2009; Mercado et al., 2001; Susanto et al., 2013). De Pablo et al, in a study including 103 RA cases and 4358 controls, reported more missing teeth in RA patients compared to the controls (De Pablo et al., 2009). Likewise, Mercado et al found more missing teeth in RA subjects compared to controls (Mercado et al., 2001). Similar to our study, these authors also reported that there was no difference between plaque and bleeding indices between the RA group and controls (Mercado et al., 2001). In the neighbouring Indonesian population, Susanto et al also reported a significant lesser number of remaining teeth in RA subjects compared to the controls (Susanto et al., 2013).

5.4 OHRQoL OF ALL SUBJECTS

In this study, the severity of OHIP-14 (M) scores of the RA(-)PD(+) group was higher than that of the RA(+)PD(-) group and RA(+)PD(+) groups but was not significant ($p>0.05$). This is different from the findings of 2 studies which reported poorer OHRQoL in the RA subjects compared to their counterparts (Ahola et al., 2015;

Mühlberg et al., 2017). Both studies used modified OHIP-14 questionnaires adapted to their respective cultures, just as in our study. However, the control group in the study by Ahola et al was made up of subjects with osteoarthritis (OA) and rheumatic fever; and in Mühlberg et al's study, matched healthy controls were recruited from a private dental practice. The present study's control group (non-RA) however consisted of subjects who were all seeking dental treatment. On the other hand, 82% of the health control subjects did not have a dental complaint during the recruitment and screening session in Mühlberg et al's study. Our systemically healthy control group are also not comparable with that of Ahola et al's study. This could explain why the PD subjects within the present study's non-RA group exhibit clinically poorer OHRQoL than their RA counterparts.

When comparing both non-RA groups in this study, the OHIP-14 (M) scores was significantly higher in the RA(-)PD(+) group than the RA(-)PD(-) group. This is consistent with many studies which reported poorer OHRQoL in PD subjects compared to their healthy counterparts (Bernabé & Marcenes, 2010; Durham et al., 2013; Lawrence et al., 2008; Ng & Leung, 2006). Other concerns such as dental caries, orthodontic malocclusions, endodontic conditions among others would also affect the OHRQoL of the subjects. However, within the limits of this study, the OHIP-14(M) appears to be sufficiently specific to report on the difference in OHRQoL between subjects with and without PD.

This study showed that there were significant differences ($p<0.05$) between groups in the dimensions of 'functional limitation' and 'physical disability'. The RA(-)PD(+) group showed significantly higher ($p<0.05$) severity scores in the dimension of 'physical disability' compared to the RA(+)PD(+) and RA(+)PD(-) group. There are currently no studies that report on this among RA subjects. However, a similar report is

seen in Ng & Leung's study (Ng & Leung, 2006) when comparing periodontal subjects and their healthy counterparts.

Our study also reported that the severity scores of the RA(-)PD(-) group was significantly lower ($p<0.05$) from both of the groups with PD in the dimension of 'functional limitation'. This corroborates with the similar findings of Ng & Leung (Ng & Leung, 2006) who reported higher severity impacts on the dimension of 'functional limitation' in the PD group. This is probably due to the fact that the absence of PD in the RA(-)PD(-) group allows them to chew well and also not experience the impacts of bad breath as much as the groups with PD.

The OHRQoL of the RA(-)PD(+) group in this study was higher than that of the RA(+)PD(+) group. Although not statistically significant ($p>0.05$), it is clinically relevant to the subjects individually. A possible explanation is that these 2 groups of PD patients have different motivations when first encountered. The non-RA subjects were recruited from the Primary Care Unit while the RA subjects were recruited over the telephone and invited for a screening. Similar to Needleman et al's study, this group of non-RA subjects represent a group which sought specialist periodontal care or were referred for it (Needleman et al., 2004) whereas all 29 RA subjects who were diagnosed with PD were not aware of their oral and periodontal condition prior to the screening visit. The self-awareness of an undiagnosed or untreated PD condition might result in the self-reporting of poorer OHRQoL among the RA(-)PD(+) group. Similarly, this might also explain why this group of subjects demonstrated the highest prevalence of 'quite often' and 'very often' reporting in all dimensions of the OHIP-14 (M) compared to the other 3 groups.

In this study, the OHRQoL of both the RA groups were not significantly different ($p>0.05$) despite the differences in their periodontal status. In fact, as mentioned before, their OHRQoL was better than that of the subjects without RA but

suffering from PD. There is no literature currently which compares the impact of PD on the OHRQoL of RA subjects hence we are not able to draw any comparisons at this point of time. However, similar findings have been reported in studies comparing the impact of PD on subjects with other systemic diseases. In their 2015 study in the UK, Irani et al concluded that the OHRQoL of subjects with Type II Diabetes Mellitus (T2DM) was not significantly different regardless of their PD status. However, it was lower than that of the subjects with PD but without T2DM (Irani et al., 2015). As in the case with T2DM, the lack of impact of RA on the OHRQoL might be due to the burden of the chronic nature of RA on the individual, hence minimising the impact on the oral health related dimensions within the OHIP-14(M).

5.5 SAMPLE CHARACTERISTICS AND THE OHRQOL

This study showed significant differences in the age, gender, education level and brushing frequency of subjects between groups. When controlled and analysed, all these sample characteristics showed no significant relationship with the OHRQoL of subjects.

This study's finding regarding age and OHRQoL corresponds to that of a pilot study performed on a similar Malaysian subpopulation (Abdullah et al., 2018). On the other hand, some studies have reported increasing age resulted in a decrease in the OHRQoL scores (better OHRQoL) (da Silva Araújo, Gusmão, Batista, & Cimões, 2010; Steele et al., 2004). Similarly McGrath and Bedi demonstrated that OHRQoL seems to be negatively impacted with increasing age (McGrath & Bedi, 2002). Mulhberg et al found no correlation between age and OHRQoL in their non-RA group but reported a significant low impact on the OHRQoL of their RA subjects who were more than 60 years of age (Mühlberg et al., 2017).

The present study reported no significant relationship between gender and OHRQoL. This is similar to the findings of a pilot study in Malaysia and an early Hong

Kong study (Abdullah et al., 2018; Ng & Leung, 2006). It has been reported that gender impacts the OHRQoL differently due to different "lifecourse influences" experienced by males and females (Mason, Pearce, Walls, Parker, & Steele, 2006). Nevertheless, we do not see this in our study population and that of the Hong Kong study. This is probably because of the cultural diversity with the population studied by Mason and colleagues.

Ng & Leung reported that education level has a significant negative correlation to OHRQoL scores (Ng & Leung, 2006). Our study however does not show any significant relationship between education level and OHRQoL. Ng & Leung's finding was supported also by a Brazilian and UK study (Piovesan, Antunes, Guedes, & Ardenghi, 2010; Tsakos et al., 2009). Piovesan et al reported on how the education levels of mothers affected their child's OHRQoL while Tsakos et al reported on how education level affected the OHRQoL of an older age Greek population in London. Our findings might defer as this study's population demographics is different from these studies. Additionally, different OHRQoL instruments were used – the Brazilian version of Child Perceptions Questionnaire (CPQ_{11-14}) (Piovesan et al., 2010) and the Geriatric Oral Health Assessment Index (GOHAI) (Tsakos et al., 2009). This makes it harder to draw concrete conclusions from the comparison of results.

5.6 HRQoL OF ALL SUBJECTS

In this study, the HRQoL scores of the RA groups - RA(+)PD(+) and RA(+)PD(-) groups were significantly higher ($p<0.01$) than that of the non-RA groups - RA(-)PD(+) and RA(-)PD(-) groups. This indicates that the RA subjects have significantly poorer HRQoL compared to their non-RA counterparts. The finding is in agreement with that reported by both Haroon et al and Husted et al (Haroon, Aggarwal, Lawrence, Agarwal, & Misra, 2007; Husted, Gladman, Farewell, & Cook, 2001) that

RA subjects have poorer HRQoL than their healthy counterparts. The World Health Organisation Quality of Life Assessment, Short form (WHOQOL-BREF) and HAQ were used by Haroon and colleagues, whereas Husted et al used the Medical Outcomes Study 36-item short form survey (SF-36) and the HAQ. Similarly, Matcham and colleagues also reported that RA has a substantial impact on the HRQoL.

Our study is the first to compare the impact of PD on the HRQoL of RA and non-RA patients using the HAQ. There was no significant difference in the HRQoL between the RA groups. We can infer from the results obtained that the effect of PD on the overall HRQoL of an RA subject or even a non-RA subject was not fully captured by the HAQ-DI instrument.

We performed 2 regression linear analyses to control for the age, gender, education level and brushing frequency differences observed between all 4 groups. The RA(-)PD(-) and RA(-)PD(+) groups were each used in turn as the reference group in each analysis. Results from both these analyses showed that upon controlling these variables, the HRQoL of the RA(+)PD(+) group was no longer significantly higher than the RA(-)PD(-) group ($p=0.07$).

This might be because of the subjects in the RA(-)PD(-) group are not true "healthy controls" with an absence of all ailments. This present study's exclusion criterion of systemic and debilitating diseases (DM and other autoimmune diseases) does not include a blanket of all diseases. Hence, it is possible that the HAQ-DI scores reported by some in the RA(-)PD(-) group might reflect a disease or health condition that they are currently having.

While the p value of 0.07 indicates no statistical significance, the HAQ-DI scores of the RA(+)PD(+) group (0.54 ± 0.49) is clinically higher than that of the RA(-)PD(-) group (0.08 ± 0.19). The actual values of the HAQ-DI scores indicate that the

HRQoL impact is still clinically higher and relevant in the RA(+)PD(+) group than the RA(-)PD(-) group.

The HAQ-DI is a specific instrument for the measurement of rheumatic diseases hence it is suitable for use among the RA subjects, however it might not be sufficient to detect the synergism of impacts by PD and RA on the HRQoL of subjects. Future studies with a more focused design to investigate this are needed to give a clearer conclusion.

5.7 PERIODONTAL PARAMETERS AND THE OHRQOL

In this current study, we found that periodontal parameters (PPD, CAL, FMPS and FMBS) were all not significantly related to the OHRQoL of all 4 groups of subjects studied. There is no study in the literature which reports on correlation between these 4 periodontal parameters and the OHRQoL of RA patients. Mulhberg et al recorded these parameters but did not report on their correlation with the OHRQoL of the RA subjects they studied. There was no correlation seen between periodontal parameters and OHRQoL in subjects who are suffering from other severe chronic diseases such as ankylosing spondylitis, on chronic haemodialysis and after kidney transplant (Gerhard Schmalz et al., 2018; G Schmalz et al., 2016).

There is however more available literature on this in periodontal OHRQoL research. Our findings did not match that of a few other studies. Needleman et al and Durham et al both reported that the number of pockets ≥ 5mm significantly correlated with poorer OHRQoL scores (Durham et al., 2013; Needleman et al., 2004). Ng & Leung reported that subjects with CAL > 3mm presented with significantly poorer OHRQoL on all dimensions except the social disability and handicap subscales (Ng & Leung, 2006).

This study reported a significant weak negative correlation between the remaining number of teeth and OHRQoL scores in the RA(+)PD(-) group. No significant correlation was however seen in the other 3 groups of subjects. Ng & Leung also reported a significant negative correlation between number of remaining teeth and the OHRQoL of their subjects (PD vs controls) (Ng & Leung, 2006). Blaizot et al reported that poorer OHRQoL was reported by RA patients with lesser number of teeth (Blaizot et al., 2013). The adverse correlation between tooth loss and OHRQoL has also been established by a number of other studies (P. F. Allen & McMillan, 1999; Gerritsen, Allen, Witter, Bronkhorst, & Creugers, 2010; Steele et al., 2004). Interestingly, Steele et al, when comparing the national samples of UK and Australia suggested that the effect of tooth loss on the OHRQoL might not be 'monotonic' (Steele et al., 2004). They suggested that there might be a 'plateau' in which further tooth loss might not correlate to more adverse OHRQoL.

5.8 STRENGTHS AND LIMITATIONS

5.8.1 STRENGTHS OF THE STUDY

This study is the first study of both prevalence of PD in RA patients and the impact on their quality of life in the Malaysian population. The findings gave a better insight on the association between diseases and the impacts on the QoL of those suffering from it. Although the prevalence of RA subjects in Malaysia is low compared to the prevalence of PD, the implications of PD in these group of RA patients are immense. Hence, understanding the nature of association and patient-centered outcomes is crucial.

Our study design included a sufficiently large sample size compared to certain studies (Attarbashi Moghaddam et al., 2016; Pischon et al., 2008) and comparable to other studies (Khantisopon et al., 2014; Susanto et al., 2013). Another strength of this

study is that we included control groups for both RA and PD cases. This enabled meaningful comparisons to be made. Additionally, the present study's strict inclusion criteria enabled the collection of a higher quality pool of subjects who better reflect their populations.

5.8.2 LIMITATIONS OF THE STUDY

There are a few limitations in both phases of this study. The population studied were those who sought treatment. The RA subjects recruited were patients who were on follow up with the Rheumatology clinic in UMMC while the non-RA patients where patients at the Primary Care Unit who attended for a particular dental concern. How accurately these subpopulations reflect the general population their groupings are meant to reflect is arguable. However, within the limits of the study, we feel that they are justifiable.

Another limitation is that there was heterogeneity among the RA subjects with regards to the medications and current disease activity. It is unclear how the medications taken might affect their OHRQoL.

Due to time limit constraints, we were unable to perform the Disease Activity Scoring -28 (DAS 28) scoring for every RA subject we screened. RA disease parameters (CRP and ESR) that we retrieved from the UMMC database was incomplete or outdated for some of the subjects and thus was not used as they did not allow meaningful analysis to be performed.

We also detected volunteering hesitance through both phone and face-to-face recruitment procedures. This inevitably contributed to response and volunteer bias.

Despite these limitations, we feel that this cross-sectional study enabled meaningful conclusions to be drawn.

5.9 CLINICAL RELEVANCE

This study, being the first of its kind in Malaysia, gave us a better insight about the patient-centered outcomes reported by patients suffering from PD, RA or both diseases. This extra paradigm of knowledge enables clinicians to better empathise and customise management strategies to not just manage the disease but also address the dimensions of needs.

CHAPTER 6: CONCLUSIONS AND FUTURE RECOMMENDATIONS

6.1 CONCLUSIONS

Within the limits of this study, the following conclusions can be drawn:

1. Prevalence of PD in RA subjects in this Malaysian subpopulation is 33.3% which is comparably lower than that reported globally. The prevalence of these subjects suffering from the severe form of PD is comparable to that which was reported during the NOHSA 2010 (18.4% vs 18.2%).
2. Subjects with PD have significantly poorer OHRQoL than subjects without PD.
3. Subjects with RA have significantly poorer HRQoL than subjects without RA regardless of their PD status.
4. Age, gender, education level, brushing frequency, PPD, CAL, FMPS, FMBS did not have any significant correlation with OHRQoL scores. The total number of remaining teeth had a significant weak negative correlation with OHRQoL scores in the RA(+)PD(-) group.

6.2 FUTURE RECOMMENDATIONS

In view of the limitations of this study, we recommend that future studies could investigate the DAS of RA subjects to get a clearer picture of their present disease status, recruit true "healthy controls" to give a more meaningful comparison and also include more centers (hospitals and RA support groups) in Malaysia to better capture the general RA population in Malaysia.

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