

EVALUATION OF ANXIETY AND DEPRESSION, AND THEIR
ASSOCIATED FACTORS IN HYPERTHYROID PATIENTS
UNDERGOING RADIOACTIVE IODINE THERAPY:
A CROSS-SECTIONAL STUDY

by

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DECLARATION

I hereby declare that this research was sent to Universiti Sains Malaysia (USM) for the degree of Master of Medicine in Nuclear Medicine. It has not been sent to other universities. With that, this research can be used for consultation and photocopied as reference.

Sincerely,

DR. PIRIATHARISINI GOPINATHAN

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TABLE OF CONTENT

DECLARATION	I
ACKNOWLEDGEMENT	II
TABLE OF CONTENT	III
LIST OF TABLES	VII
ABBREVIATIONS	VIII
ABSTRAK	X
ABSTRACT	XII
RESEARCH BACKGROUND	1
1.0 Introduction.....	1
LITERATURE REVIEW	3
2.0 Hyperthyroidism.....	3
2.0.1 Definition, Epidemiology and Risk Factors of Hyperthyroidism.....	3
2.0.2 Aetiology.....	4
2.0.3 Signs and Symptoms.....	4
2.0.4 Diagnosis of Hyperthyroidism.....	5
2.0.5 Treatment.....	6
2.0.5.1 Overview of Treatment.....	6
2.0.5.2 Medical Therapy.....	6

2.0.5.3	Surgical Treatment	7
2.0.5.4	Radioactive Iodine Therapy	7
2.1	Overview of Anxiety and Depression Among Radioactive Iodine Therapy Patients	8
2.2	Causes of Fear, Anxiety and Depression in Radioactive Iodine Therapy Patients	10
2.3	Sociodemographic Factors and Its Association With Anxiety and Depression	11
2.4	Aetiology and Biochemical Factors and Its Association With Anxiety and Depression	12
2.5	Instrument to Evaluate Anxiety and Depression	13
RATIONALE/BENEFIT OF THE STUDY		15
3.0	Aim	15
3.1	Objective:	16
3.1.1	General Objective	16
3.1.2	Specific Objectives:	16
3.2	Hypothesis	16
MATERIALS AND METHODS		17
4.1	Study Design, Location and Recruitment Time frame	17
4.2	Study Sample	17
4.3	Inclusion and Exclusion Criteria	17
4.3.1	Inclusion criteria:	17
4.3.2	Exclusion Criteria:	18

4.4	Sample Size Calculation.....	18
4.5	Sampling Method	19
4.6	Research Tool.....	19
4.7	Scoring.....	20
4.8	Data Collection and Procedure.....	20
4.9	Data Analysis.....	21
4.10	Study Outcome	22
4.11	Ethics and Disclosure	22
4.12	Study Flow Chart.....	23
	RESULTS.....	24
5.1	Socio Demographic Data of Subjects Undergoing RAI therapy	24
5.2	Level of Anxiety and Depression in Hyperthyroid Participants Subjected to RAI Therapy	28
5.3	Factors Associated with Anxiety by Univariate Binary Logistic Regression Model.....	30
5.4	Factor Associated of Anxiety by Multivariate Binary Logistic Regression Model	34
5.5	Factors Associated with Depression by Univariate Binary Logistic Regression Model.....	37
5.6	Factor Associated with Depression by Multivariate Binary Logistic Regression Model	41
	DISCUSSION	44
6.1	Demographics and Clinical Data.....	44
6.2	Level of Anxiety and Depression In RAI Therapy Subjects.....	48

6.3 Factors Associated with Anxiety and Depression Among Hyperthyroid Subjects Undergoing RAI therapy 50

CONCLUSION.....	58
RECOMMENDATIONS.....	59
CLINICAL IMPLICATION.....	60
REFERENCES.....	61
APPENDICES.....	70
Appendix A1: Hospital Anxiety and Depression Scale (HADS questionnaire) (English).....	70
Appendix B1: Sociodemographic Data (English).....	74
Appendix C: Clinical Data Collection Sheet.....	76
Appendix D: Medical Research and Ethics Committee (MREC Approval Letter).....	77
Appendix E: USM/JEPEN Approval Letter.....	80
Appendix F: Treatment Charges at Malaysian Hospital.....	83
Appendix G: RAI Therapy Workflow at Nuclear Medicine Department, Hospital Pulau Pinang.....	92
Appendix H1: Patient Information Sheet (English).....	95
Appendix H2: Patient Information Sheet (Malay).....	101

LIST OF TABLES

Table 1	Sociodemographic characteristic of patients
Table 2	Level of anxiety and depression among hyperthyroid subjects referred for RAI therapy
Table 3	Factors associated with anxiety by univariate binary logistic regression model
Table 4	Factors associated with anxiety by multivariate binary logistic regression model
Table 5	Factors associated with depression by univariate binary logistic regression model
Table 6	Factors associated with depression by multivariate binary logistic regression model

ABBREVIATIONS

ESR	Erythrocytes sedimentation rate
GD	Graves' Disease
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale-Depression subscale
I 131	Iodine-131
I 123	Iodine-123
JEPeM	Jawatankuasa Etika Penyelidikan Manusia
MeV	Megaelectron volt
mCi	millicurie
mm	Millimeter
MREC	Medical Research Ethics Committee
RAI therapy	Radioiodine therapy
RAIU	Radioactive iodine uptake
RM	Ringgit Malaysia
ROC	Receiving operating curve
SOP	Standard Operating Procedure

TA	Toxic Adenoma
T3	Triiodothyronine
T4	Thyroxine
TMNG	Toxic Multinodular Goiter
TRAb	Thyrotropin Receptor Antibody
TSH	Thyroid Stimulating Hormone
^{99m}Tc	^{99m}Tc pertechnetate

ABSTRAK

Tajuk: Penilaian Tahap Kegelisahan dan Kemurungan Serta Faktor-Faktor Yang Berhubungkait Dikalangan Pesakit Yang Menjalani Terapi Radioaktif Iodin.

Pendahuluan: Terapi radioaktif iodin adalah satu daripada terapi perubatan yang digunakan untuk merawat hipertiroid. Namun, sorotan kajian mendapati bahawa pesakit yang menjalani terapi radioaktif iodin mengalami kemurungan dan kegelisahan yang ketara. Walaupun faktor-faktor seperti kurang tahap pemahaman, ketakutan terhadap prosedur dan kesan sampingan telah dilaporkan sebagai punca kepada tekanan emosi, perkaitan antara faktor sosioekonomi, biokimia, etiologi dan faktor rawatan masih belum dinilai dengan sempurna.

Objektif: Tujuan kajian ini adalah untuk menilai tahap kegelisahan dan kemurungan subjek serta memberi penegasan terhadap faktor-faktor sosioekonomi, biokimia, etiologi dan kaedah rawatan pesakit semasa menjalani rawatan radioaktif iodin.

Kaedah: Subjek-subjek hipertiroid yang dirujuk dari pusat kesihatan untuk terapi radioaktif dipilih sebagai sampel kajian. Setelah menghadiri penilaian klinikal dan kaunseling oleh pakar perubatan nuklear, subjek perlu mengisi borang sosio-demografi serta borang soal selidik Skala Keresahan dan Kemurungan Hospital sebelum menjalani terapi radioaktif iodin. Semua data sosio-ekonomi serta klinikal berserta skor kegelisahan dan kemurungan telah dicatatkan.

Keputusan: Seramai 123 subjek direkrut untuk kajian ini dan majoriti subjek adalah wanita, berbangsa Melayu dan beragama Islam. Manakala umur min adalah 43.9 tahun. Tahap pendidikan adalah rendah dengan pendapatan min adalah RM2303.88. Kebanyakan subjek adalah dari negeri Kedah, sudah berkahwin, didiagnos menghidapi penyakit Grave's, tidak mempunyai masalah kesihatan lain dan secara biokimia berada dalam keadaan hipertiroid. Secara keseluruhan, kesemua subjek menerima rawatan radioaktif iodin pada kali pertama dengan dos kumulatif sebanyak 15mCi. Sebanyak 40.7% subjek berada pada tahap gelisah serta 21.1% subjek pula mengalami kemurungan semasa menjalani rawatan radioaktif iodin. Kajian juga mendapati bahawa, tahap pendidikan (adjusted odds

ratio, 0.291; 95% confidence: 0.128, 0.659; $p = 0.003$) dan status perkahwinan (adjusted odds ratio, 0.363; 95% confidence: 0.146, 0.904; $p = 0.029$) adalah berhubungkait dengan kegelisahan. Tahap pendidikan (adjusted odds ratio, 0.23; 95% confidence: 0.071, 0.740; $p = 0.014$) dan status perkahwinan (adjusted odds ratio, 0.159; 95% confidence: 0.032, 0.803; $p = 0.026$) juga didapati berhubungkait dengan kemurungan secara signifikan.

Kesimpulan: Didapati subjek yang menjalani rawatan radioaktif iodine mengalami tahap kegelisahan yang signifikan dan tahap kemurungan yang rendah semasa terapi tersebut. Subjek dengan tahap pendidikan yang rendah dan bujang didapati mengalami gangguan emosi yang lebih ketara apabila dibandingkan dengan subjek yang mempunyai tahap pendidikan yang tinggi serta sudah berumahtangga.

Kata Kunci: Hipertiroid, Terapi Radioaktif Iodin, Kegelisahan dan Kemurungan, Faktor-faktor berhubungkait

ABSTRACT

Title: Evaluation of Anxiety and Depression, and Associated Factors in Patients Undergoing radioactive iodine therapy.

Introduction: Radioactive iodine therapy (RAI therapy) is increasingly utilized for the treatment of hyperthyroidism. However, a significant level of anxiety and depression have been documented in patients undergoing RAI therapy. Although factors like poor understanding of the affliction, procedural fear and reported side effects of the therapy can precipitate an emotional distress, the association between socioeconomic, biochemical, etiological, treatment factors and anxiety and depression remain poorly evaluated.

Objective: The aim of this study was to evaluate the levels of anxiety and depression that subjects manifested while undergoing RAI therapy and to address the knowledge gap that exist on the association between socioeconomic, biochemical, etiological, treatment factors and anxiety and depression while undergoing RAI therapy.

Methods: Hyperthyroid subjects referred for RAI therapy were recruited as participants in the study. Self-administered sociodemographic and Hospital Anxiety and Depression Scale (HADS) questionnaire were administered to subjects after clinical assessment and counselling by Nuclear Medicine Physicians, prior to RAI therapy. Socioeconomic and clinical data as well as anxiety and depression scores were recorded.

Results: A total of 123 subjects were recruited, the majority of them female, of mean age of 43.9 years, of Malay ethnicity and from the Islamic faith. The majority of them hailed from the state of Kedah, were married, had acquired lower education, were employed with mean income of RM2303.88 and were diagnosed with Graves' disease with no other comorbidity and biochemically were in hyperthyroid state. The majority of them receiving RAI therapy for the first time and were given a fixed cumulative dose of 15mCi. 40.7% of subjects in this cohort displayed anxiety and 21.1% were depressed while undergoing RAI therapy. Study also showed that education level (adjusted odds ratio, 0.291; 95%

confidence: 0.128, 0.659; $p = 0.003$) and marital status (adjusted odds ratio, 0.363; 95% confidence: 0.146, 0.904; $p = 0.029$) were associated with anxiety. Education level (adjusted odds ratio, 0.23; 95% confidence: 0.071, 0.740; $p = 0.014$) and marital status (adjusted odds ratio, 0.159; 95% confidence: 0.032, 0.803; $p = 0.026$) were also associated with depression.

Conclusion: A significant level of anxiety and a fairly lower-level depression were experienced by subjects during RAI therapy. Subjects with lower education and who were single were more likely to experience psychological distress compared to those with a higher level of education and married individuals.

Keywords: Hyperthyroidism, RAI therapy, Anxiety and Depression, Associated Factors.

CHAPTER 1

RESEARCH BACKGROUND

1.0 Introduction

Hyperthyroidism is a clinical condition of excess thyroid hormone due to a hyperactive thyroid gland (De Leo *et al.*, 2016). It is a common endocrine disease with world-wide prevalence of 0.2 to 0.3% (Muñoz-Ortiz *et al.*, 2020 ; Taylor *et al.*, 2018). Its prevalence is recorded higher in Malaysia at 3.4% as compared to countries like United States, Europe and Australia (Shahar *et al.*, 2015). A good treatment outcome can be achieved either by medical, surgical or radioiodine therapy (RAI therapy) (Ross, 2011). The usage of RAI therapy is steadily increasing over the last few decades owing to its high cure rate. Although it has a high safety profile with minimal side effects, a significant level of anxiety and depression attends its therapeutic usage (Rosenthal, 2006; Sundaresh *et al.*, 2017). It is estimated that as high as 40 to 80% of patients experience significant anxiety and depression while undergoing this therapy (Domènech *et al.*, 2010 ; Zdanowska *et al.*, 2010). Factors like poor understanding about the therapy, procedural fear and worrisome side effects are the common concerns cited in the literatures (Rosenthal, 2006 ; Domènech *et al.*, 2010 ; Zdanowska *et al.*, 2010). What causes poor understanding, fear and undue worried about the therapy is a question that remained unanswered. There could also be compounding socio-demographic factors to reckon with, such as age, gender, ethnicity, religion, education, employment, income, marital status and comorbidity. Several researchers have noted that the emotion of hyperthyroid patients is largely influenced by thyroid function level, the etiology of hyperthyroidism, the number of RAI therapy and possibly cumulative dose (Placidi *et al.*, 1998; Bové *et al.*, 2014b; von Müller *et al.*, 2014). However, the correlations are still unclear, and the data are scarce. This has prompted the present study to evaluate the relative influences of social, biochemical, etiology and therapy factors on anxiety and depression that patients face when undergoing

RAI therapy. Understanding these relationships could facilitate Nuclear Medicine physicians to tailor the treatment approach according to patient's socioeconomic, biochemical, etiological and therapy circumstances. This will result in the reduction of unnecessary emotional distress, ensure good treatment outcome and compliances as well as to deliver treatment of the highest quality.

CHAPTER 2

LITERATURE REVIEW

2.0 Hyperthyroidism

2.0.1 Definition, Epidemiology and Risk Factors of Hyperthyroidism

Hyperthyroidism is a clinical state that results from excessive production and secretion of thyroid hormone by an overactive thyroid gland (Ross *et al.*, 2016). Depending on its biochemical values, hyperthyroidism can be classified as overt or subclinical. One is said to have overt hyperthyroidism when the serum thyrotropin (TSH) is subnormal with elevated serum triiodothyronine (T3) and/or tetraiodothyronine/thyroxine (T4) and in a subclinical state when the serum TSH is low but with a normal range of T3 and T4 (Ross *et al.*, 2016). Those with a normal thyroid function are referred to as euthyroid (Cappola *et al.*, 2015).

Hyperthyroidism is a common endocrine disorder encountered in all parts of the world. The prevalence in the United States is 1.2% whereas the prevalence in Malaysia is reported to be higher at 3.4% (Ross *et al.*, 2016 ; Shahar *et al.*, 2015). Although it can affect any age group, the usual age of presentation is 20 to 50 years old (Sanjeeva *et al.*, 2015). It has female preponderance in the ratio of 4:1 to male (Vanderpump, 2011). Living in geographically iodine deficient areas, smoking, alcohol consumption, stress, the presence of autoimmune and syndromic conditions as well as exposure to therapeutic drugs increase the risk of hyperthyroidism (Taylor *et al.*, 2018).

2.0.2 Aetiology

Graves's disease (GD) is the most common aetiology of hyperthyroidism followed by toxic multinodular goiter (TMNG), adenoma (TA) and thyroiditis (Taylor *et al.*, 2018). GD accounts for 70-80% and it is an autoimmune disease. Due to the thyrotropin receptor antibodies' (TRAb) activity against the TSH receptors, the thyroid gland undergoes stimulations to synthesize and produce excessive thyroid hormones (Abraham and Acharya, 2010). TMNG and TA account for 5% each (Ziessman and O'Malley, 2013). The nodules in the thyroid gland make excessive thyroid hormone without responding to signal to keep thyroid hormones in balance. It is believed to be caused by somatic or the germline mutation (Ross *et al.*, 2016). A less common cause is the thyroiditis. Hyperthyroidism is characterized by an inflammatory process of thyroid tissue and is commonly precipitated by respiratory tract infection and drugs like lithium, cytokine, tyrosine kinase inhibitor therapy or amiodarone (Taous and Islam, 2010 ; Ross *et al.*, 2016).

2.0.3 Signs and Symptoms

Hyperthyroidism can present with a wide range of symptoms. Loss of weight, palpitation, breathlessness, tremors, lethargy, heat intolerance, excessive sweating, increased bowel movement, anxiety, nervousness, muscle weakness, oligo or amenorrhea and loss of libido are the usual complains (Vaidya and Pearce, 2014). A multiplicity of signs is associated with hyperthyroidism. These include weight loss, tachycardia, atrial fibrillation, fine tremor, skin erythema, sweaty palms and palmar erythema, onycholysis, prominent eyes and eyelid retraction, muscle weakness, systolic hypertension, thyroid bruit and cardiac failure (Vaidya and Pearce, 2014). These signs and symptoms are more pronounced in younger patients and those with larger goiter (Ross *et al.*, 2016). Older patients tend to display fewer symptoms (Boelaert *et al.*, 2010).

Hyperthyroidism can also manifest as thyrotoxic periodic paralysis and rarely as thyroid storm. Thyrotoxic periodic paralysis is a combination of hyperthyroidism, acute muscle weakness and hypokalemia, commonly seen in Asian men (Taylor *et al.*, 2018). The thyroid storm reflects an extreme state of hyperthyroidism. It is a life-threatening condition that presents with tachycardiac, fever, agitation, altered mental state, features of cardiac failure and deranged liver function (Akamizu *et al.*, 2012).

2.0.4 Diagnosis of Hyperthyroidism

The diagnosis of overt hyperthyroidism is confirmatory when serum TSH is subnormal accompanied by an increase in serum free T₄, T₃ or both and subclinical when the serum TSH is low with a normal range of serum free T₄ and T₃ (Ross *et al.*, 2016). Once the diagnosis is made, patients should undergo a comprehensive history, physical examination, other biochemical besides thyroid function test and imaging evaluations to identify the underlying etiology. Occasionally, clinical history and physical examination alone can provide clues to determine the cause (Bartalena *et al.*, 2016).

GD can be easily recognized by the presence of ophthalmopathy, dermopathy and acropachy (Bartalena *et al.*, 2016). In the absence of these hallmark features, antibodies to TSH receptor (TRAb), radioactive iodine uptake (RAIU) or ultrasonography maybe helpful (Ross *et al.*, 2016). In TMNG and TA, a combination laboratory diagnosis and radionuclide imaging with Iodine 123 (¹²³I) or ^{99m}Tc pertechnetate (^{99m}Tc) are confirmatory (Ross *et al.*, 2016).

Subacute thyroiditis is easily diagnosed based on the clinical history and physical examination. Patients often give a history of upper respiratory tract infection with a clinically tender thyroid gland (Ziessman and O'Malley, 2013). In addition, the use of inflammatory markers such as erythrocytes sedimentation rate (ESR) and C reactive protein maybe helpful (Vaidya and Pearce, 2014). It is confirmatory when RAIU shows no uptake (Ziessman and O'Malley, 2013). Patients with painless

thyroiditis often have personal or family history of autoimmune thyroid disease and have measurable anti-thyroid peroxidase antibodies (Taous and Islam, 2010). Occasionally, thyroglobulin can be used as diagnostic test in both painful and painless thyroiditis (Taous and Islam, 2010).

2.0.5 Treatment

2.0.5.1 Overview of Treatment

The choice of treatment depends on etiology, severity, size of the goiter, age, comorbid conditions and treatment desires (Reid and Wheeler, 2005). The goal is to correct the hypermetabolic state with lesser side effects and minimal incidence of hypothyroidism (Reid and Wheeler, 2005). Currently, there is no general consensus on which treatment modalities yield the best outcome (Sztal-Mazer *et al.*, 2012). Treatment decision should be based on patients-physician discussion, benefits, potential side effects, cost and drawbacks (Brito *et al.*, 2015). The treatment options available for hyperthyroidism are the thionamide drugs, thyroidectomy or radioiodine therapy (Allahabadia *et al.*, 2001). Symptomatic hyperthyroidism is best controlled with beta adrenergic blockers such as propranolol (Ross *et al.*, 2016).

2.0.5.2 Medical Therapy

Thionamide drugs such as methimazole, carbimazole and propylthiouracil block the organification process of thyroid hormone synthesis (Reid and Wheeler, 2005). Thus, it reduce the circulating level of thyroid hormone (Ziessman and O'Malley, 2013). Methimazole and carbimazole are recommended in GD. Propylthiouracil is preferred in pregnant women as methimazole and carbimazole increases the risk of congenital abnormalities (Reid and Wheeler, 2005). The advantage of thionamide is that it favors remission when used for long term (Reid and Wheeler, 2005; Vaidya and Pearce, 2014).

Thereby avoiding unnecessary surgery, life long-long thyroid hormone replacement and exposure to radiation by RAI therapy (Ross *et al.*, 2016). According to Allahabadia *et al.*, (2000), women over 40 years, small thyroid size, mild hyperthyroxinaemia, triiodothyronine thyrotoxicosis, a low titer of TSH receptor antibodies and those without extrathyroidal manifestation are the best candidates to have successful outcomes (Allahabadia *et al.*, 2000). However, relapse can occur in those who are smokers, have large goiter and raised thyroid stimulating antibody levels at the end of therapy (Nedrebo *et al.*, 2002). Side effects like pruritis, agranulocytosis, arthralgia are seen in a small percentage of patients (Vaidya and Pearce, 2014).

2.0.5.3 Surgical Treatment

Near or total thyroidectomy is highly effective in controlling hyperthyroidism in GD, TMNG and TA (Ríos *et al.*, 2005 ; Genovese *et al.*, 2013). It has the highest success and lowest relapse rate compared to other modalities (Ross *et al.*, 2016). Those with large goiters, recurrent disease, active Graves' ophthalmopathy, poorly controlled hyperthyroidism in pregnancy and uncontrolled hyperthyroidism despite with high doses of thionamide can benefit from surgery (Abraham and Acharya, 2010). Surgical complications include hypoparathyroidism and recurrent laryngeal nerve injury (Ross *et al.*, 2016).

2.0.5.4 Radioactive Iodine Therapy

RAI therapy (^{131}I) was first used in 1941 to treat hyperthyroidism (Silberstein, 2012). ^{131}I is a beta emitter. It has a maximum energy of 0.61 MeV, an average energy of 0.192 MeV and a range in tissue of 0.8 mm (Mumtaz *et al.*, 2009). It has a physical half-life of 8 days (Mumtaz *et al.*, 2009). The beta emission causes damage to the thyroid's DNA (Vaidya and Pearce, 2014). Hence, continuous radiation to thyroid cells results in extensive local destruction over a period of 6 to 18 weeks (Abraham

and Acharya, 2010). As a result, a gradual reduction in the thyroid volume is observed with subsequent control of hyperthyroidism (Mumtaz *et al.*, 2009).

RAI therapy is indicated in GD, TMNG, TA and non-toxic multinodular goiter (Silberstein *et al.*, 2012). It is absolutely contraindicated in pregnancy, breast feeding and uncontrolled hyperthyroidism (Silberstein *et al.*, 2012). It is ingested orally and gets rapidly concentrated into the thyroid via a sodium iodide transporter. It undergoes organification similarly to iodine (Ziessman and O'Malley, 2013). The goal of RAI therapy is to control hyperthyroidism by rendering patients euthyroid or hypothyroid (Silberstein *et al.*, 2012). This can be achieved either by administering fixed activity or calculation based activity (Ross *et al.*, 2016). Patient's preparation is vital to increase the efficacy of the therapy. Medication and contrast agents that might interfere with RAI therapy need to be withheld for the intended period of time (Silberstein *et al.*, 2012). Issues like low diet iodine, radiation precaution, resuming medication, the timing of pregnancy, therapy complications and follow up need to be discussed beforehand (Silberstein *et al.*, 2012). A written and verbal information are mandatory before therapy (Silberstein *et al.*, 2012). Various studies agreed that RAI therapy yields a good outcome with lower relapse and recurrence rate compared to thionamide drugs (McCready, 2017 ; Bakos *et al.*, 2013). The success rate is even higher when treated with a larger radioiodine dose (Sztal-Mazer *et al.*, 2012). It is cost effective and became the treatment of choice in countries like the United States and Brazil (Bakos *et al.*, 2013 ; Ross *et al.*, 2016).

2.1 Overview of Anxiety and Depression Among Radioactive Iodine Therapy Patients

Approximately 40 to 80% of patients undergoing RAI therapy tend to exhibit anxiety and depression (Domènech *et al.*, 2010 ; Zdanowska *et al.*, 2010 ; Bové *et al.*, 2014b). This proportion is comparable with other therapies such as chemotherapy and radiotherapy (Neilson *et al.*, 2013). Although hyperthyroidism is a benign disorder and RAI therapy has an exceptionally high success rate on curing it with relatively lower side effects as compared to chemotherapy and radiotherapy, a

significant level of fear, anxiety and depression has been documented (Rosenthal, 2006). Treatment related anxiety and depression are common and may present with varying levels of severity.

According to the Diagnostic and Statistical Manual of Mental Disorder (DSM-5), generalised anxiety disorder is characterized by uncontrolled worry, feeling on edge, poor concentration, restlessness, irritability, impaired social or occupational functioning, fatigue, muscle tension, and difficulty in sleeping. Depression on the other hand is characterized by persistent low mood, loss of interest, difficulty in concentrating, sleep disturbances and fatigue (Tolentino and Schmidt, 2018). In more severe form, it can manifest functional impairment and suicidal ideation (Tolentino and Schmidt, 2018). These negative emotions can cause various health implications such as refusal of treatment, non-compliance to medication and follow up, and poorer health outcomes and quality of life. In addition, anxiety and depression may lead to maladaptive attitudes and health pattern behaviour. Moreover, anxiety can independently exacerbate other medical conditions such as obesity, diabetes, asthma, hypertension, arthritis, ulcer, physical pain, back/neck problem, cardiovascular, neurodegenerative and autoimmune disease (Scott *et al.*, 2007 ; Niles *et al.*, 2015). Depression if left unaddressed, may lead to many other medical problems such as cardiovascular disease, stroke and migraine (Roose *et al.*, 2001; Bruti *et al.*, 2012 ; Simon *et al.*, 2002). Anxiety and depression can coexist and when they do, the outcome is even more severe (Wittchen *et al.*, 2002). On a bigger scale, not only does emotional distress place a burden on patients, but also on society, work productivity and the economic due to increased health costs and hospitalization (Tyrer and Baldwin, 2006 ; McLaughlin, 2011). Early identification allows early intervention through various methods such as counselling, pharmacotherapy, psychotherapy, psychosocial intervention, physical or electro-convulsive therapy (Guan, 2014 ; Hoge *et al.*, 2012 ; Khaiyom *et al.*, 2019).

2.2 Causes of Fear, Anxiety and Depression in Radioactive Iodine Therapy Patients

Historically, the fear of radioactivity set in with the atomic bombs dropped at Hiroshima and Nagasaki, Japan towards the end of World War II (Rosenthal, 2006). Although there has been no nuclear warfare since then, the fear of radioactive compounds remains entrenched in the minds of people, exacerbated by such nuclear plant disasters as at Three Mile Island, Pennsylvania in 1979, Chernobyl, Ukraine in 1986 and Fukushima, Japan in 2011. In a long term follow up study of people living in these vicinities, it has been noted that many among them suffer from anxiety, depression, post-traumatic stress disorder, poor health and medically unexplained symptoms (Bromet, 2014). Media highlights of people in affected areas suffering from hair loss, birth defects and death have contributed much to the ingrained fear in the general public of all radioactive compounds (Rosenthal, 2006). With this fear in their mind, patients naturally nurse some anxiety the moment they step into a Nuclear Medicine Department and indeed, this fear has also be substantiated in a study (Barbus *et al.*, 2018 ; Domènech *et al.*, 2010).

Apart from that, the treatment procedure itself creates a fearful situation for patients. As part of the radiation protocol, patients are required to self-isolate for a few days. For some, isolation creates fear (von Müller *et al.*, 2014). Those with large goitre, high pre-treatment T4 level, male gender with age younger than 40 years old, TMNG, pre-treatment with carbimazole and propylthiouracil may require more than one RAI therapy to achieve euthyroid or hypothyroid state (Yau *et al.*, 2009 ; Allahabadia *et al.*, 2000 ; Körber *et al.*, 2001 ; Hancock *et al.*, 1997). Despite previous RAI therapy, the intensity of fear did not reduce for subsequent treatment (von Müller *et al.*, 2014). This clearly points to the fact that regardless of the number of times the patients undergoes RAI therapy, the procedure appears to be uncomfortable.

Another reason for patients not favouring radioactive based therapy is due to fear of radioactive contamination. After RAI ingestion, it is excreted via bodily fluid such as urine, sweat, saliva, blood from wound, epistaxis, menstruation, vomitus and nasal mucus (Sisson *et al.*, 2011). Therefore, contamination is high likely to take place during self-handling and since this contamination is not visible

to the eye, patients perceive it as intimidating (Freudenberg *et al.*, 2009). Besides threat to themselves, many expressed their concern of radiation exposure to their loved ones. (Domènech *et al.*, 2010). Furthermore, the consequences of RAI therapy like hypothyroidism, prolong requirement of thyroid hormone replacement therapy, and other side effects dissuade patients from opting for this therapy (Rosenthal, 2006). Inaccuracy in the information about RAI projected on many internet sites is another reason for anxiety and depression (Rosenthal, 2006). These sites misuse the term radiation therapy for radiotherapy. This information is highly misleading to those who seek extra information.

Besides patient's related factors, what appears to be more surprising is the poor understanding of ionizing and non-ionizing radiation among medical students and doctors. This is evident in a study conducted at Pakistan, whereby students failed to appreciate dosage levels in diagnostic procedures from the total spectral energy content present in gamma rays (Mubeen *et al.*, 2008). Reportedly, even physician tend to misjudge the radiation dose exposure from a diagnostic tool to patients (Freudenberg and Beyer, 2011). Moreover, consultants were found to score lower regarding knowledge about radiation as compared to junior doctors (Freudenberg and Beyer, 2011). These findings are worrisome because lack of knowledge among medical students and physician leads to misinformation being imparted to patients regarding nuclear medicine based therapy. The discordant in information delivered to patient was apparent in a cross-sectional study conducted by (Domènech *et al.*, 2010).

2.3 Sociodemographic Factors and Its Association With Anxiety and Depression

Literature citations in the past have identified culturally embedded fear of nuclear substances, fear of Nuclear Medicine surroundings, procedural fear, fear of contamination, misinformation by physicians and the internet as causative factors to anxiety and depression. An interesting finding reported by Zdanowska *et al.*, (2010) is that despite verbal and written explanations about the therapy, patients generally claim that the information to them is complicated and incomprehensible or irrelevant (Zdanowska *et al.*, 2010). This poses the question of whether literacy is a factor that needs to be

considered, as the level of understanding of the nature of the disease, treatment required, the outcome and side effects may significantly vary among patients, impacting their behavioural changes.

Besides education, other factors like age, gender, ethnicity, religion, income, employment, marital status and comorbidity are known to exert impacting roles in patient's anxiety and depression in other treatment modalities. For example, in a cross-sectional study involving breast cancer patients undergoing chemotherapy, education, residential status and income were found to influence anxiety and depression (Mukherjee *et al.*, 2018). In another study involving 522 internal medicine and surgical patients, sociodemographic factors such as age, sex, marital education, employment, socioeconomic status were found to significantly affect anxiety and depression (Yüksel and Bahadır-Yılmaz, 2020).

Growing body of research has highlighted that good socio-demographics are the driving factors for good health outcomes, both at the personal and national levels. The consensus based on previous observational studies is that those with lower education, lower income, without a job, without religion or spiritual belief, as well as those who are single, female gender and with comorbidity are found to have a higher level of anxiety and depression (Wittchen *et al.*, 1994 ; Coryell *et al.*, 1986 ; Hoge *et al.*, 2012 ; Hackney and Sanders, 2003; Nurasikin *et al.*, 2013). However, from the RAI therapy point of view, these factors are still debatable. Due to limited data, the association of sociodemographic, biochemical, the aetiology of hyperthyroidism and therapy factors remain unclear. Investigating these predictive factors helps to identify vulnerable patients so that they can be targeted for early intervention.

2.4 Aetiology and Biochemical Factors and Its Association With Anxiety and Depression

Besides RAI therapy and sociodemographic factors, the aetiology of thyroid disease and abnormal thyroid function are also associated with anxiety and depression in various literatures. Bové *et al.*, (2014b) found that patients with underlying GD were more anxious and depressed as compared to other patients with chronic thyroid disease and the general population (Bové *et al.*, 2014a). Anxiety

in GD was found to be linked to TRAb, stressful life events and an abnormal thyroid function level (Ghanem *et al.*, 2010 ; Fukao *et al.*, 2020). Anxiety and depression in hyperthyroidism were also found to be closely tied to an abnormal thyroid function (Geffken *et al.*, 1998; Placidi *et al.*, 1998 ; Patronellia *et al.*, 1998). Hendrick *et al.*, (1998) found that even the slightest change in thyroid level resulted in mood changes (Hendrick *et al.*, 1998). With adequate treatment, the reversal of symptoms was observed (Bauer and Whybrow, 2001). However, some authors completely oppose the idea that thyroid function is responsible for anxiety and depression. A large cross-sectional study involving 30 589 patients in Norway, found that there were no differences in the frequency of anxiety and depression between thyroid function abnormalities and healthy control (Engum *et al.*, 2002). These findings were similar to studies by Lee *et al.*, (2003) and (Saidi *et al.*, 2018) that showed that thyroid function has no relationship with anxiety and depression (Lee *et al.*, 2003 ; Saidi *et al.*, 2018). In contrast to the findings of Bauer and Whybrow, (2001), Bunevicius *et al.*, (2005) reported that despite normalization of thyroid function, psychiatric and somatic complaint still persists (Bunevicius *et al.*, 2005). Therefore, abnormal thyroid function levels alone cannot be held accountable for the anxiety and depression in hyperthyroidism.

2.5 Instrument to Evaluate Anxiety and Depression

There are several tools available to measure anxiety and depression and one of them is Hospital Anxiety and Depression scale (HADS). HADS is observed to successfully facilitate the measurement of anxiety and depression levels in the non-psychiatric department. HADS was developed by Zigmond and Snaith in 1983. It is a self-administered screening tool consisting of two subscales, anxiety subscale (HADS-A) and depression subscale (HADS-D). It was designed with special attention given to psychological symptoms of neurosis only (Herrmann, 1997). Therefore, the physical symptoms that could be possibly caused by medical symptoms are excluded which makes it suitable to be used in a hyperthyroid patient. Also, it is designed as to exclude major psychiatric symptoms which are not commonly seen in a nonpsychiatric clinic setting (Bjelland *et al.*, 2002). The advantage of HADS questionnaire lies in its simplicity, speed and user-friendly nature (Stern, 2014). Few people ever have

difficulty in completing it (Stern, 2014). HADS is translated and validated into various languages and has been applied in various settings, including general practice and community settings (Snaith, 2003). It is one of the recommended tools for the diagnosis of anxiety and depression by the National Institute for Health and Care Excellence (NICE). HADS is available in the Malay language (Yahya and Othman, 2015). In term of scoring, HADS-A and HADS-D consists of seven questions each and they are scored separately. Each question is scored 0-3 depending on severity experienced, Zigmond and Snaith, (1983) advocated a cut off between eight to ten for mild, eleven to fourteen for moderate and fifteen to twenty-one for severe cases (Zigmond and Snaith, 1983). A score of 7 and below is considered as non-cases. Generally, a score of 8 and above is used for case studies. It has a sensitivity of 90% and a specificity of 86.2% for anxiety and sensitivity of 93.2% and specificity of 90.8% for depression for a cut off score of eight/nine (Yahya and Othman, 2015). HADS takes only two to five minutes to be completed by patients (Snaith, 2003). Since it is a score based, it is easily evaluated by physicians and other health care workers.

CHAPTER THREE

RATIONALE/BENEFIT OF THE STUDY

This study is conducted to determine the level of anxiety and depression as well as which factors are associated with anxiety and depression among hyperthyroid participants subjected to RAI therapy. By acknowledging the level, its severity and associated factors, it will give insights to patients emotion, and how this factors can be used as a platform to modify RAI treatment approach. With modifications suited to sociodemographic background, aetiology, biochemical and therapy factors, it will minimize emotional distress, increase comfort and patients become more receptive to RAI therapy.

3.0 Aim

This study aims to address the lack of scientific knowledge on the level of anxiety and depression as well as to determine the key factors that underpin anxiety and depression among hyperthyroid subjects undergoing RAI therapy; these include socio-demographic, biochemical, etiology of hyperthyroidism and RAI therapy related factors.

3.1 Objective:

3.1.1 General Objective

The objective of this study is to determine the level of anxiety and depression among hyperthyroid patients who were subjected to RAI therapy and to analyze the underpinning factors.

3.1.2 Specific Objectives:

1. To describe sociodemographic of patients undergoing radioactive iodine therapy
2. To determine the level of anxiety and depression in hyperthyroid patients subjected to radioiodine therapy
3. To determine the association between sociodemographic, biochemical, etiology, RAI therapy related factors and anxiety and depression among hyperthyroid patients subjected to RAI therapy.

3.2 Hypothesis

Alternate hypothesis:

- Patients subjected to radioiodine therapy suffer from anxiety and depression

Null hypothesis:

- Patients subjected to radioiodine therapy do not suffer from anxiety and depression.

CHAPTER FOUR

MATERIALS AND METHODS

4.1 Study Design, Location and Recruitment Time frame

A cross sectional study was carried out in the Department of Nuclear Medicine, Hospital Pulau Pinang from May 2019 to May 2020.

4.2 Study Sample

This study was conducted in all consented adult subjects with underlying hyperthyroidism referred to the Department of Nuclear Medicine, Hospital Pulau Pinang for RAI therapy based on inclusion and exclusion criteria noted below.

4.3 Inclusion and Exclusion Criteria

4.3.1 Inclusion criteria:

- Above 18 years old
- Hyperthyroid patients who were referred for radioiodine therapy

4.3.2 Exclusion Criteria:

- Unable to read and understand Malay and English
- Patients with cognitive impairment
- Underlying psychiatry disorder
- Underlying cancer

4.4 Sample Size Calculation

The sample size calculation is based on (Domènech *et al.*, 2010). The sample size calculation is as follow:

1) Sample size is calculated based on the following formula for objectives I and II

$$\begin{aligned} & (z/\Delta)^2 p(1-p) \\ &= (1.96/0.1)^2 (0.47) (1-0.47) \\ &= 384.16 \times 0.2491 \\ &= 96 \text{ patients} \\ &= 96 + 28^* \\ &= 124 \end{aligned}$$

$z = 1.96$
$\Delta = 0.1$
$p = 0.47$

2) Objective III was calculated based on studies by Domènech *et al.*, (2010).

The number of patients required was 45. By taking 30% dropouts, the total number of patients were 59.

- Based on the objectives, the highest sample size number was 124.

4.5 Sampling Method

Convenient sampling method was used for this study.

4.6 Research Tool

The Hospital Anxiety and Depression Scale (HADS) (Appendix A) was used to measure the level of anxiety and depression in this study. This scale comprises of an anxiety subscale (HADS-A) and a depression subscale (HADS-D). It can discriminate somatic from psychiatric symptoms, making it suitable to be used in hyperthyroidism. It has Cronbach's alpha of 0.68 to 0.93 (mean 0.83) for HADS-A and 0.67 to 0.90 (mean 0.82) for HAD-D (Bjelland *et al.*, 2002).

There were two sections of questions given to patients. The first set consists of HAD-A and HAD-D whereas the second set of questions consist of sociodemographic details (Appendix B). The sociodemographic characteristics included were subjects' age, gender, ethnicity, religion, education level, employment status, household income, marital status and residence.

4.7 Scoring

Each domain of the HADS questionnaire consists of 7 items. Each item scores 0-3 depending on the severity of anxiety and depression. The total score for each subscale ranges from 0-21. The score of 7 and less was considered as non-cases and scores of 8 and above were considered as cases. It is further categorized as mild, moderate and severe based on the number of scores. A score of 8-10 is considered as mild, 11-14 as moderate and more than 15 as severe cases.

4.8 Data Collection and Procedure

Patients with underlying hyperthyroidism, referred for RAI therapy were given an appointment as well as written instruction regarding the therapy beforehand. On the day of RAI therapy, the patient's general condition was assessed by the doctor in charge. Details about their disease, RAI therapy benefits, side effects and issues concerning patients were addressed. This procedure is in line with standard operating procedure (SOP) of the Nuclear Medicine Department, Hospital Pulau Pinang.

During this appointment, patients were screened for eligibility to participate in this study. Those who fulfilled the inclusion and exclusion criteria and consented to participate were recruited. Based on the preferred language (Malay/English language), they were required to complete the HADS questionnaire (Appendix A1 and A2) and the sociodemographic details (Appendix B1 and B2).

Additional information regarding comorbidity, etiology, biochemical values, number of RAI therapy and cumulative dose were collected in separate data sheets by the principal investigator (Appendix C). This information was extracted from the subject's case file. Upon completion of the questionnaire and demographic data, RAI therapy was be given. Subjects who refused to participate, withdrawn, provided incomplete answers or withheld data were excluded from the study. Of 124 subjected recruited, one subject was excluded because of incomplete answers given. The subjects' recruitment and data collections were done before RAI therapy administration to limit radiation exposure to the investigator and staffs.

4.9 Data Analysis

Statistical Package for Social Science Inc, Chicago Illinois (SPSS) version 24 was used for data entry, exploration, cleaning and statistical analysis. Descriptive statistics were performed for each variable, with continuous variables represented as mean and standard deviation and categorical variables as frequencies and percentage.

Simple logistic regression was performed on each independent variable to determine the association between anxiety and depression. The variables which were statistically significant at the level of $p < 0.25$ or deemed clinically significant were included in the multiple logistic regression analysis. Forward, backward and stepwise elimination strategies were used so that the final model contained only the most significant variables. The selection of the best fit model was used based on the rule of parsimony. Model of fitness for assumption check was done. In multiple logistic regression analysis, variables were considered to be significant at the level $p < 0.05$. Interpretation and presentation of the final model done.

4.10 Study Outcome

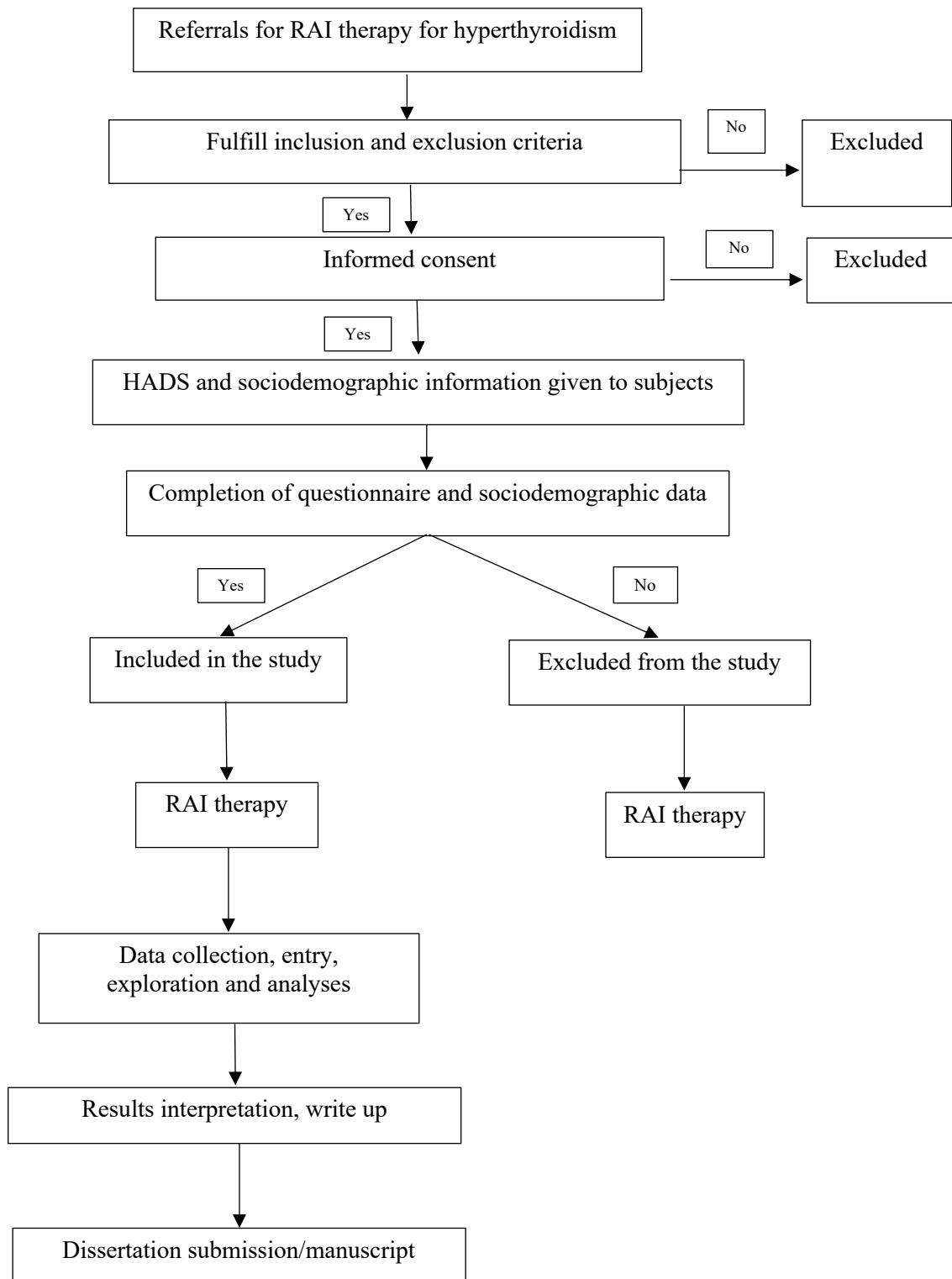
The study outcome is to estimate the level of anxiety and depression as well as to improve the treatment approach based on the significant factors associated with anxiety and depression.

4.11 Ethics and Disclosure

This research procedures were in accordance with ethical standards of the Helsinki Declaration of 1964, revised in 2013 (World Medical Association, 2013) and Malaysian Guideline for Good Clinical Practice ((National Committee for Clinical Research 2011). This study was approved by Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia and registered with National Medical Research Registry (NMRR ID: NMRR-19-530-47103 (IIR) (Appendix D). It is also approved by the Jawatankuasa Etika Penyelidikan Malaysia (JEPeM) of Universiti Sains Malaysia. (USM/JEPeM/19040234) (Appendix E). Written informed consent was obtained from all subjects prior to the initiation of the study. The confidentiality and privacy of the patients were strictly maintained. Information and data collected were kept confidential. The author had no conflicts of interest to disclose, which may influence the impartiality of this study.

Subjects that were found to have mild anxiety and depression were referred for counselling whereas subjects with moderate and severe anxiety and depression were referred to the psychiatric department for further evaluation and care.

4.12 Study Flow Chart



CHAPTER FIVE

RESULTS

5.1 Socio Demographic Data of Subjects Undergoing RAI therapy

Table 1: Socio- demographic and clinical characteristic of subjects

Characteristics	n (%)	Mean (SD)
Gender		
Male	39 (31.7)	
Female	84 (68.3)	
Age (years)		43.85 (13.81)
Ethnicity		
Malay	99 (80.5)	
Non-Malay	24 (19.5)	
Religion		
Islam	99 (80.5)	
Non-Islam	24 (19.5)	
