ASSESSMENT OF RISK FACTORS AND IDENTIFICATION OF POTENTIAL BIOMARKERS ASSOCIATED WITH BREAST CANCER-RELATED LYMPHEDEMA IN MALAYSIAN BREAST CANCER SURVIVORS

By

KHAIRUNNISA' BINTI MD YUSOF

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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This thesis is dedicated to my beloved mother, Fatimah Abdullah and father, Md Yusof Arsad who have shown me that education is a lifelong journey, knowledge is the key to success, and wisdom is the reward of life experience.

Abstract of thesis presented to the Senate of Universiti Putra in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chair : Professor Rozita Rosli, PhD
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Survival rates for breast cancer have been increasing over the years due to early detection and improved treatment. However, these cancer survivors faced several challenges following cancer treatment including breast cancer-related lymphedema (BCRL). BCRL is characterized by fluid retention and abnormal swelling in one or both arms that arises after obstruction of lymphatic vessels resulting from surgery insults or radiotherapy. The aim of this study was to identify risk factors and potential biomarkers associated with BCRL in the Malaysian breast cancer population. A set of questionnaires comprising demographic and medical history, quality of life assessment, and upper quadrant function were self-administered by 173 female breast cancer survivors. Anthropometry, arm circumference measurement, and ultrasound examination of the arms were performed on all participants before they were divided into either (1) lymphedema group (BCRL), based on self-reporting diagnosis and arm circumference difference of ≥1.5cm between the affected and unaffected arms or the (2) non-lymphedema group (non-BCRL). For laboratory analysis, a total of 6mL of whole blood was collected and processed to obtain the serum. Experimental analysis including small RNA-sequencing, quantitative polymerase chain reaction (qPCR), and detection of adipokines levels was performed on all serum samples. One hundred and sixty women were eligible for the study and 33 of them (20.5%) were classified into the lymphedema group. Those with multiple breast cancer surgeries on the same site of the breast, had ≥10 lymph nodes excised, higher body mass index (≥25 kg/m2), higher waist-to-hip ratio (>0.9), hypertension, and received fewer rehabilitation treatment (<2 types of treatment) were associated with increased odds of lymphedema by two to five-fold. Diabetes mellitus was found to have a significant association with the development of early-onset lymphedema within the lymphedema group ($p<0.05$). The analysis of arm circumference difference revealed the highest difference in the forearm when compared to the other measured sites. Analysis of the

ultrasound images of lymphedema patients showed skin and subcutaneous thickness of the forearm were higher in the affected arms accompanied by accumulation of fat with a lattice-like structure when compared to the unaffected arms. MicroRNA profiling results demonstrated that miR-199a-3p and miR-151a-3p were downregulated in the early-onset lymphedema group when compared to the late-onset and non-lymphedema group ($p<0.05$). Findings from the pathway analysis showed the involvement of metabolic syndrome (MetS) pathways including sphingolipid, phospholipase D, adrenergic signalling in cardiomyocytes and cGMP-PKG signalling in the lymphedema group. One of the analysed adipokines, leptin concentration was significantly higher in the lymphedema group and correlated with BMI, fat percentage, and hypertension. The adiponectin/leptin ratio was lower in the lymphedema group ($p<0.05$) and negatively correlated with blood pressure and waist-to-hip ratio ($p<0.05$). Taken together, findings between the modifiable and molecular factors in the present study revealed a strong association between BCRL with MetS in the study population. This study has characterised risk factors and potential biomarkers of BCRL and this has provided a better understanding of the condition that may lead to the development of a screening tool and molecular-based therapies for lymphedema.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENILAIAN FAKTOR RISIKO DAN PENGENALPASTIAN PENANDA BIOLOGI BERKAITAN DENGAN LIMFEDEMA-KANSER PAYUDARA DALAM KALANGAN PEMANDIRI KANSER PAYUDARA DI MALAYSIA

Oleh

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Kadar kemandirian kanser payudara telah meningkat berikutan pengesanan awal dan rawatan kanser yang lebih baik. Walaubagaimanapun, pemandiri kanser payudara ini menghadapi beberapa masalah selepas rawatan kanser seperti limfedema-kanser payudara. Limfedema-kanser payudara boleh didefinisikan sebagai pengumpulan cecair dan pembengkakan abnormal pada satu atau kedua belah lengan yang disebabkan oleh kerosakan pada salur limfa, berpunca dari pembedahan atau rawatan radioterapi. Kajian yang dijalankan ini bertujuan untuk mengenalpasti faktor risiko dan penanda biologi berkaitan dengan limfedema-kanser payudara dalam kalangan pemandiri kanser payudara di Malaysia. Borang soal selidik yang mengandungi demografik dan sejarah perubatan, penilaian kualiti kehidupan, dan fungsi kuadran atas telah diisi oleh seramai 173 pemandiri kanser payudara wanita. Pengukuran antropometri, ukurlilit lengan, dan pemeriksaan ultrabunyi ke atas lengan turut dijalankan ke atas kesemua peserta sebelum dibahagikan kepada kumpulan (1) limfedema berdasarkan laporan diagnosis dan perbezaan ukurlilit ≥1.5cm di antara lengan yang bengkak (limfedema) dan (2) bukan limfedema. Bagi tujuan analisis di dalam makmal, sejumlah 6mL darah telah diambil dan kemudian diproses untuk mendapatkan serum darah. Eksperimen seperti penjujukan-RNA kecil, asai pengesahan mikroRNA (qPCR), dan pengenalpastian aras adipokin telah dijalankan ke atas kesemua sampel serum. Seramai 160 orang peserta layak menyertai kajian ini dan seramai 33 orang (20.5%) dikelaskan dalam kumpulan limfedema. Pembedahan berganda atau berulang di tempat sama, pembuangan >10 kelenjar nodus limfa, mempunyai indeks jisim tubuh yang tinggi (≥25 kg/m2), nisbah pinggang-pinggul >0.9, hipertensi, serta menerima <2 rawatan rehabilitasi selepas pembedahan (<2 jenis rawatan) mempunyai kebarangkalian mendapat limfedema sebanyak dua hingga lima kali ganda. Diabetes mellitus juga dikatakan mempunyai perkaitan secara signifikan dengan masa mula-awal limfedema dalam kalangan kumpulan limfedema (<0.05). Analisis ukurlilit lengan menunjukkan lengan bawah mempunyai perbezaan ukurlilit yang paling tinggi jika dibandingkan dengan titik atau tempat pengukuran lain lengan. Analisis imej ultrabunyi ke atas kumpulan limfedema menunjukkan ketebalan kulit dan

subkutaneus di bahagian lengan bawah lebih tinggi di bahagian lengan yang bengkak, disertai dengan pengumpulan lemak (berstruktur seperti rotan) jika dibandingkan dengan lengan yang tidak bengkak. Profil mikroRNA menunjukkan regulasi menurun miR-199a-3p dan miR-151a-3p dalam kumpulan masa mula-awal berbanding dengan kumpulan masa mula-lewat dan bukan limfedema ($p<0.05$). Analysis tapak jalan menunjukkan penglibatan tapakjalan sindrom metabolik seperti sfingolipid, fosfolipase D, isyarat adrenergik dalam sel kardio, serta isyarat cGMP-PKG dalam kumpulan limfedema. Kepekatan leptin (sejenis adipokin) dilaporkan tinggi secara signifikan dalam kumpulan limfedema dan berkait rapat dengan indeks jisim tubuh, peratusan lemak, serta hipertensi. Nisbah adiponektin/leptin dilaporkan rendah di dalam kumpulan limfedema ($p<0.05$) dan tidak berkadar terus dengan tekanan darah dan nisbah pinggang-pinggul ($p<0.05$). Kesimpulannya, dapatan kajian mengenai faktor boleh ubah dan faktor molekul di dalam kajian ini menunjukkan perkaitan signifikan di antara limfedema-kanser payudara dan sindrom metabolik. Kajian ini telah mengenalpasti faktor risiko dan penanda biologi berkaitan dengan limfedema serta dapat meningkatkan kefahaman mengenai limfedema, seterusnya dapat membatu dalam perkembangan alat saringan dan perubatan berasaskan molekul untuk limfedema.

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In the name of Allah, the Most Gracious and the Most Merciful.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

3'-UTR	3-untranslated region
ALND	Axillary lymph nodes dissection
BCRL	Breast cancer-related lymphedema
BCS	Breast conserving surgery
BMI	Body mass index
BP	Biological process
BRCA1/2	Breast cancer type 1/2
CC	Cellular components
CD	Circumference difference
cDNA	Complementary DNA
CDT	Complete decongestive therapy
DAMP	Danger-associated molecular patterns
DASH	Disabilities of the Arm, Shoulder, and Hand
DCIS	Ductal carcinoma in situ
ECM	Extracellular matrix
ELISA	Enzyme-linked immunosorbent assay
EndMT	Endothelial mesenchymal transformation
EORTC QLQ BR-23	European Organization for Research and Treatment of Cancer QOL Questionnaire
ER	Estrogen receptor
EWB	Emotional well-being
FACT-B	Functional Analysis of Cancer Therapy – Breast
FACT-G	Functional Analysis of Cancer Therapy – General
FC	Fold change
FDR	False discovery rate

FOXC2	Forkhead box protein C2
Foxp3	Forkhead box P3
FWB	Functional well-being
GO	Gene ontology
HER2	Human epidermal growth factor receptor
HGF	Hepatocyte growth factor
HR	Hazard ratio
ICC	Intraclass coefficient
IFN-γ	Interferon-gamma
IGF1	Insulin like growth factor 1
IL	Interleukins
iNOS	Inducible nitric-oxide synthase
IQR	Interquartile range
ISL	International Society of Lymphedema
KEGG	Kyoto Encyclopedia of Genes and Genomes
LCIS	Lobular carcinoma in situ
LCP2	Lymphocyte cytosolic protein 2
LEC	Lymphatic endothelial cells
LTB_4	Leukotriene B4
LYVE-1	Lymphatic vessel endothelial hyaluronan receptor 1
MAPK	Mitogen activated protein kinase
MetS	Metabolic syndrome
MF	Molecular function
MicroRNA	MiRNA
MicroRNA-seq	MiRNA-sequencing

MLD	Manual lymphatic drainage
NCRM	National Cancer Registry of Malaysia
NFATc1	Nuclear factor activated-T cell 1
NFKB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NRP2	Neuropilin-2
OR	Odd ratio
PDPN	Podoplanin
PECAM-1	Platelet endothelial cell adhesion molecule-1
PHQ-9	Patient health questionnaire
PHQ-ADS	PHQ- Anxiety, expression, and stress
PR	Progesterone receptors
PROX-1	Prospero-homeobox-1
PWB	Physical well-being
QoL	Quality of life
qPCR	Quantitative polymerase chain reaction
RORC	Related orphan receptor gamma
SD	Standard deviation
SLNB	Sentinel lymph nodes biopsy
SNP	Single nucleotides polymorphism
SOCS7	Suppress cytokine signalling-7
SOX-18	SRY-related HMG-box 18
STAT3	Signal transducer and activator of transcription 3
SWB	Social well-being
SYK	Protein tyrosine kinase
TGF-β1	Transforming growth factor beta-1

Th	T helper cell
TLR	Toll-like receptor
TNBC	Triple negative breast cancer
TNF-α	Tumor necrosis factor alpha
Tregs	Regulator T cell
VANGL2	Vang-like 2
VCAM-1	Vascular cell adhesion molecule 1
VEGF-C	Vascular endothelial growth factor C
VEGFR/FLT4	Vascular endothelial growth factor receptor
WHO	World health organization
WHR	Waist to hip ratio
WHtR	Waist-to height ratio

CHAPTER 1

INTRODUCTION

Breast cancer is the second most common cancer diagnosed worldwide with an estimated of 2.26 million new cases in 2020, and it is more prevalent in less developed countries such as Middle Africa and Eastern Asia compared to European countries[1]. In Malaysia, the National Cancer Registry (2018) reported breast cancer (32.1%) as the leading cancer in female Malaysian residents, followed by colorectal (16.3%) and cervical cancer (7.7%). However, breast cancer has the highest 5-year relative survival rate among all cancers in females with 66.8% after corpus uteri cancer (70.6%) and thyroid cancer (82.3%) in Malaysia[2].

The number of breast cancer survivors has increased every year due to early detection, improved treatments, and multi-disciplinary rehabilitation methods. However, the improved treatments also come with various late side effects such as arm lymphedema, menopausal symptoms, or infertility[3, 4]. Breast cancer-related lymphedema (BCRL) is one of the major side effects following cancer treatment or surgery. BCRL is characterized by progressive swelling of the arm due to obstruction or blockage of the lymphatic vessels resulting from surgery insults or irradiation therapy[5, 6]. The chronic accumulation of the lymph fluid leads to the pathological conditions of BCRL including inflammation, immune system dysfunction, and fibrosis[7]. Consequently, it results in the formation of an orange texture of the skin (*peau de orange*), disfiguration of the arms, heaviness or tightness, pain, physical dysfunction, and decreased quality of life for breast cancer survivors[3, 8, 9].

BCRL was reported to develop in 10-50% of women who underwent axillary lymph node dissection (ALND) and 5-20% of women who underwent sentinel lymph node biopsy (SLNB)[10, 11]. On the other hand, lymphedema also was reported to develop in patients with an increased number of lymph nodes removed[10, 12], or those who received taxane-based chemotherapy[13, 14], or regional radiotherapy[12, 15, 16]. Besides treatment-related modalities, mounting evidence has demonstrated the association of patient-related risk factors of BCRL including obesity[17, 18], hypertension[19, 20], and low physical activity[21, 22]. Due to various conditions that contribute to the development of BCRL, a continuous search of the mechanisms, reasons, and risk factors that are involved in the condition are warranted to facilitate better management and treatment of BCRL in the future.

In the past years, several lines of evidence have revealed a genetic association with the development of BCRL. Genotyping and protein expression studies showed that several candidate genes were identified to be involved in lymphatic and angiogenesis pathways associated with BCRL, namely, forkhead box protein C2 (*FOXC2)*, nuclear factor kappa-light-chain-enhancer of activated B cells (*NFKB),* vascular endothelial growth factor C (*VEGF-C)*, vascular endothelial growth factor receptor (*VEGFR/FLT4*), vascular cell adhesion molecule 1 (*VCAM-1)*, neuropilin-2 (*NRP2)*, protein tyrosine kinase (*SYK)*, and lymphocyte cytosolic protein 2 (*LCP2),* interleukins (*IL-6, IL-10*)[23-26] and transforming growth factor beta-1 (TGF-β1)[27-29]. This suggests that cytokines and inflammatory

factors may play a role in the pathological features of secondary lymphedema following breast cancer treatment.

Although the identification of these novel genes has uncovered an association between BCRL and lymphatic candidate genes, extensive investigations are warranted to further elucidate additional molecular pathways involved in BCRL. One of the approaches to uncover the molecular markers is through the use of biological fluids that contain molecular signatures related to a certain pathophysiological condition as it is stable across individuals of the same species. Serum, one of the types of body fluid is commonly used in biomarker detection studies due to a higher concentration of metabolites as compared to plasma[30, 31]. It contains a ribonuclease enzyme that induces the breakdown of high molecule proteins or peptides, hence increasing the sensitivity of analyses aimed at detecting small molecules, such as circulating microRNAs (miRNA)[30]. MiRNAs are non-coding RNAs that are involved in a variety of cellular functions[32]. Due to their stability within vesicles, miRNAs have been widely studied as potential biomarkers in various diseases such as Parkinson's disease and cardiovascular disease[33, 34]. To the best of our knowledge, characterisation of miRNAs in relation to BCRL development is limited.

As a circulating carrier of exogenous and endogenous liquid in the blood, the serum also contains adipokines; the circulating cell-signalling molecules or factors produced by adipose tissue to regulate energy and lipid metabolism in normal physiological functions and pathological conditions including inflammation, apoptosis, organogenesis, and cell differentiation[35, 36]. A fluctuation of the adipokines reflecting the current biological states in a human body and the dysregulation of adipokines is directly associated with insulin sensitivity, abdominal obesity, and an individuals' lipid profile[36, 37]. A previous study reported that increased levels of adipokines; interleukin-6 (IL-6) and leptin were observed in the serum of obese-lymphedema patients, reflecting the expansion of adipose tissue of the affected limbs[38]. Moreover, Fu and co-workers (2021) implicated that cytokine levels (IL-1α, IL-6, IL-8, and tumor necrosis factor alpha, TNF-α) in serum may serve as a biomarker to predict the risk of arm lymphedema symptoms in their recent study[39].

Due to various conditions that contribute to the development of BCRL, the identification of risk factors for BCRL in a specific population may aid in the development of a standardized screening method for early detection and improve management of the condition so that it is tailored to the affected individual. The risk factors for developing BCRL in Malaysia are unknown and this study is the first to address this condition among Malaysian breast cancer survivors. Furthermore, it should be noted that physical disturbance is the most common unmet need after psychological distress, in Malaysian breast cancer survivors throughout cancer treatment and survivorship, which has been shown to hamper their quality of life (QoL)[40]. Recent studies have shown poor body weight management and dietary behaviour among Malaysian breast cancer survivors, suggesting most of them remained obese due to lack of health consciousness and guidance from health care professionals in a long-term survivorship care[41, 42]. Cumulatively, these findings imply that Malaysian breast cancer survivors are challenged with various factors throughout their survivorship.

Additionally, several molecular signatures of secondary lymphedema in breast cancer survivors have been identified[29, 43], but the inconsistent findings between studies represent a challenge for personalized treatment for BCRL. Therefore, the continuous identification of molecular factors attributed to BCRL may impart new knowledge on the mechanisms underlying lymphedema, hence enticing the development of a diagnostic tool for early detection or new molecular-based therapies for this incurable lymphatic disease.

1.1 Objective

1.1.1 General objective

To identify risk factors and molecular biomarkers associated with breast cancer-related lymphedema in Malaysian female breast cancer survivors.

1.1.2 Specific objectives:

i. To validate the Malay version of *Functional Analysis of Cancer Therapy – Breast* (FACT-B) in the Malaysian breast cancer population.
ii. To evaluate quality of life, risk factors, and skin ultrasound presentation associated with BCRL.
iii. To identify serum circulating miRNAs and adipokines as molecular biomarkers related to BCRL.

1.2 Hypothesis

i. Significant risk factors of BCRL can be identified between BCRL and non-BCRL groups of Malaysian breast cancer survivors.
ii. Molecular biomarkers associated with BCRL can be determined from the blood serum of breast cancer survivors.

1.3 Thesis outline

An extensive description on the risk factors and screening method of BCRL, as well as pathogenesis of BCRL are described in Chapter 2. The Malay version of the FACT-B is validated and discussed in Chapter 3. The assessment of quality of life, potential risk factors, and skin structure presentation are detailed, presented, and discussed in Chapter 4. Chapter 5 comprises the analysis and discussion of molecular factors in the serum of breast cancer survivors including miRNAs profiling, detection of adipokines levels, as well as analysis on the signalling pathways associated with BCRL. Finally, a general summary, limitations of the study, and future recommendations are described in Chapter 6.

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