IMPACT OF TRADITIONAL PROGNOSTIC FACTOR AND CHEMOTHERAPY SCHEDULE MODIFICATION ON BREAST CANCER PATIENTS: A 5 YEAR RETROSPECTIVE STUDY IN A DISTRICT SPECIALIST HOSPITAL IN THE STATE OF PERAK

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by

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LIST OF SYMBOLS

-	Negative
+	Positive
χ^2	Chi-square
Exp (β)	Exponentiation of B coefficient
*	Multiply
%	Percentage
I	One
II	Two
III	Three
IV	Four

LIST OF ABBREVIATIONS

A	Adriamycin (Doxorubicin)
AC	Adriamycin (Doxorubicin), Cyclophosphamide
ACT	Adjuvant chemotherapy
ADL	Activities of daily living
AHR	Adjusted hazard ratio
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASR	Age-standardised incidence rate
BHT	Bedhead ticket
C	Cyclophosphamide
CDC	Centers for Disease Control and prevention
CI	Confidence interval
CMF	Cyclophosphamide, methotrexate, and fluorouracil
COX Ph	Cox Proportional Hazard
CRC	Clinical Research Centre
DNA	Deoxyribonucleic acid
E	Epirubicin
EBCTCG	Early breast cancer trialists' collaborative category
EC	Epirubicin, Cyclophosphamide
EORTCSTBS	European Organisation for Research and treatment of Cancer Soft Tissue and Bone Sarcoma Category
ER	Estrogen receptor
F	5-Fluorouracil
FDA	Food and Drug Administration

FEC	Fluorouracil, Epirubicin, Cyclophosphamide
FPC	Finite Population Correction Factor
GLOBOCAN	Global Cancer Observatory
HER2	Human epidermal growth factor receptor 2
HKL	Hospital Kuala Lumpur
HR	Hazard Risk
HSM	Hospital Seri Manjung
ICD	International Classification of Diseases
ID	Identification
IHC	immunohistochemistry
IQR	Interquartile range
JPN	Jabatan Pendaftaran Negara
KKM	Kementerian Kesihatan Malaysia
KM	Kaplan-Meier
LML	Log-Minus-Log
MBC	Metastatic Breast Cancer
MERC	Medical Ethical Review Committee
NCR	Malaysian Cancer Registry
MOH	Ministry of health
Mykad	Malaysia national identification number
MySCan	Malaysian Study on Cancer Survival
N	Number
NACT	Neoadjuvant chemotherapy
NCR	National Cancer Registry
NIHSEC	National Institute of Health Sectary

NMRR	National Medical Research Registry
NRD	National registry department of Malaysia
NSABP	National Surgical Adjuvant Breast and Bowel Project
NUS	National Universiti Hospital, Singapore
OS	Overall survival
P-P plot	Probability-probability plot
PCT	Palliative Chemotherapy
PR	Progesterone Receptor
RCT	Randomised clinical trials
RR	Relative risk
SD	Standard deviation
SEER	Surveillance Epidemiology and End Results Program
Sig	Significance
SPP	System Pengurusan Pesakit
SPSS	Statistical package for social science
T_COV	Time-dependent covariate
TAX	Taxane
TNBC	Triple negative breast cancer
TNM	Tumour, Lymph Node, Metastatic
UK	United Kingdom
UMMC	Universiti Malaya Medical Centre
USA	United States of America
VIF	Variance Inflation Factor

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PENGARUH FAKTOR PROGNOSTIK TRADISIONAL DAN PENGUBAHSUAIAN JADUAL KEMOTERAPI TERHADAP PESAKIT KANSER PAYUDARA: KAJIAN RETROSPEKTIF 5 TAHUN DI HOSPITAL PAKAR DAERAH DI NEGERI PERAK

ABSTRAK

Pengubahsuaian jadual kemoterapi kerap dilakukan dalam praktik klinikal akibat komplikasi rawatan atau di atas permintaan pesakit. Beberapa kajian klinikal telah membuktikan kesan negatif prognostik kelewatan dos terhadap kadar kelangsungan hidup. Kajian ini bertujuan untuk mengkaji kelaziman dan faktor penyumbang kepada pengubahsuaian jadual kemoterapi. Kajian ini juga bertujuan untuk mengkaji kesan pengubahsuaian jadual terhadap kelangsungan keseluruhan hidup pesakit barah payudara. Kajian kohort retrospektif ini dilakukan di kalangan pesakit barah payudara yang menerima kemoterapi dari 2013 hingga 2017 dan diikuti hingga 31 Dis 2018. Rekod perubatan pesakit barah telah dikaji semula. Kriteria inklusi yang terlibat adalah pesakit wanita berusia lebih dari lapan belas tahun, karsinoma primer payudara, menerima rejim kemoterapi yang mengandungi anthracycline atau Taxane dan menyelesaikan lebih dari dua kitaran kemoterapi. Pesakit dikategorikan dalam tiga kumpulan tanpa pengubahsuaian jadual, dengan pengubahsuaian jadual dan jadual tidak lengkap. Penganggar Kaplan-Meier digunakan untuk menguji perbezaan kelangsungan hidup dalam pengaturan univariat dan model regresi Cox digunakan dalam pengaturan multivariate.Ukuran hasil utama kajiaan ini ialah kelaziman, kadar kelangsungan hidup keseluruhan dan nisbah bahaya ketiga-tiga kumpulan rawatan in. Di antara 171 pesakit yang menerima kemoterapi, 28 (16.4%) tidak mempunyai pengubahsuaian jadual, 118 (69.0%) mengalami pengubahsuaian

jadual dan 25 orang yang lain (14.6%) mempunyai jadual yang tidak lengkap dengan kelangsungan keseluruhan hidup masing-masing 75.0%, 59.3% dan 52.0%. Pesakit yang lengkap menjalani kemoterapi dengan pengubahsuaian jadual mempunyai 2.34 kali peningkatan risiko kematian berbanding pesakit yang tidak mempunyai pengubahsuaian jadual (AHR 2.34; 95% CI, 1.03-5.32; p = .043). Kesimpulannya, ketidakpatuhan terhadap jadual kemoterapi adalah perkara biasa dalam praktik klinikal kerana komplikasi rawatan, faktor sosial dan pentadbiran fasiliti. Pesakit yang mengalami pengubahsuaian jadual dan jadual yang tidak lengkap mengalami kelangsungan keseluruhan hidup yang rendah. Oleh itu, kelewatan antara kitaran harus dikurangkan seboleh mungkin untuk mencapai manfaat kemoterapi maksimum.

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ABSTRACT

Chemotherapy schedule modifications are done in clinical practice due to treatment complications or the patients preference. Multiple clinical studies have established the negative prognostic impact of dose delay on survival rates. This study aims to investigate the prevalence and reason for chemotherapy schedule modification with the impact of schedule modification on the Overall Survival (OS) of the breast cancer patient. This retrospective cohort study was done among breast cancer patients receiving chemotherapy from 2013 to 2017 and was followed until 31 Dec 2018. Medical records of patients with cancer were reviewed. Inclusion criteria involved the female patients over eighteen years old, primary carcinoma of the breast, received Anthracycline or Taxane based chemotherapy regimen and completed more than two cycles of chemotherapy. Patients were categorised into three categories of no schedule modification, with schedule modification, and incomplete schedule. The Kaplan-Meier were used to test for survival differences in the univariate setting, and the Cox regression model was used in the multivariate setting. This study aims to measure the prevalence, OS rates, and Hazard Risk (HR) of these three treatment categories. Among 171 patients receiving chemotherapy, 28 (16.4%) had no schedule modification, 118 (69.0%) had schedule modification, and the remaining 25 (14.6%) had an incomplete schedule with OS of 75.0%, 59.3%, and 52.0%, respectively.

Patients who completed chemotherapy with schedule modification had 2.34 times increased HR compared to patients with no schedule modification (HR=2.34; 95% CI, 1.03-5.32; p=.043). Nonconformity to chemotherapy schedules are common in clinical practice due to treatment complication, patients social and facility administrative factor. Patients with schedule modification and incomplete schedules have reduced OS. Thus, the length of delays between cycles should be reduced whenever possible to achieve the maximal chemotherapeutics benefit.

CHAPTER 1

INTRODUCTION

1.1 Introduction to Cancer

Cancer [other common names; "neoplasm "or "tumour"] is an umbrella term used to defined uncontrolled cell growth (Kaiser, 2021). From a histological standpoint, the characteristics of each cancer differ by the tissue in which cancer originates. The types of cancer could be grouped into six major categories:

a. Carcinoma: Neoplasm of epithelial origin developed in the skin or the tissues of organs.
b. Sarcoma: Neoplasm of supportive and connective tissues such as bones, muscles, cartilage, and blood vessels.
c. Myeloma: Neoplasm of plasma cells, which produced antibodies.
d. Leukaemia: Neoplasm originating from the bone marrow, which creates blood cells.
e. Lymphoma: Neoplasm of the immune system develops in the glands or nodes of the lymphatic system.
f. Mixed Types: Combination of neoplasm from different categories.

In early 2000, Biologists Douglas Hanahan and Robert Weinberg proposed six common traits that could explain the complexity of neoplasm, known as "six hallmarks of cancer" (Hanahan & Weinberg, 2000). Their paper defines the characteristics of a malignant tumour. They include:

a. Self-sufficiency in growth signals: Defects in homeostasis which regulate cell growth and division.

b. Insensitivity to anti-growth signals: Resistance for anti-growth signal.
c. Evading programmed cell death: Inherent coping mechanism to evade programmed cell death.
d. Unlimited replicative potential: Capable of a limitless number of cell divisions.
e. Sustained angiogenesis: Self-promotion of blood vessel construction.
f. Tissue invasion and metastasis: Ability to invade neighbouring tissues and metastases to distant organs.

A decade later, the same research group proposed two new hallmarks titled "Hallmarks of cancer the next generation." (Hanahan & Weinberg, 2011)

a. Emerging Hallmarks:
    i. Unregulated metabolism: Cells with atypical metabolic pathways.
    ii. Evading the immune system: Loss of cytokine immune system.
b. Enabling Characteristics:
    i. Genomic variability: Neoplasm with multiple chromosomal abnormalities, which accumulates with disease progression.
    ii. Inflammation: Prolonged local inflammation producing unique microenvironment for the development of cancer.

Essentially, the propagation of cancer cells is due to uncontrolled proliferation with homeostasis defects. This defect confers cancer cell advantage for survival and proliferation in the unique tumour microenvironment with the potential to metastasis to the distant organ, which could be life-threatening due to the disruption of normal tissues and organs function (Varga & Greten, 2017).

1.2 Prevalence of breast cancer

Breast cancer is a common disease as one in eight women has a lifetime risk of developing breast cancer and is the leading cause of female mortality (DeSantis et al., 2017; Bray et al., 2018). Global Cancer Observatory (GLOBOCAN) estimated that about 25% of all new cancers diagnosed are of breast cancer origin, and the global incidence is projected to reach 3.2 million by 2050 (DeSantis et al., 2017).

Nearly 24.7% of all breast cancer cases were diagnosed in the Asia-Pacific region, with the higher proportion seen in China, Japan, and Indonesia (Ghoncheh et al., 2016). In 2012 alone, 277,054 new breast cancer cases comprising 107,545 cases in Southeast Asia and 223,899 cases in south-central Asia were diagnosed (Cancer, 2012). Current epidemiology evidence suggests that during 1988–2013, the highest prevalence of breast cancer incidence was observed among Southeast Asia women (Momenimovahed & Salehiniya, 2019)

Among new breast cancer cases and mortality, the Asian population had the highest proportion of [new cancer cases (48.4%); Mortality (57.3%)], followed by Europe (23.4%; 20.3%) and by America (21%; 14.4%). In contrast to other regions, the shares of cancer deaths in Asia are higher than those of incidence. The mortality-to-incidence rate ratio in Asia was between 0.23 and 0.48, indicating lower survival than North America's 0.16 (Kim et al., 2015). The overall survival (OS) rate of Malaysian breast cancer patients is at 66.8%, which is lower than neighbouring Asian countries such 70% achieved by Singapore (Ho et al., 2020) and ≥80 % survival achieved by Korea (91.2%) (Park et al., 2017), Japan (88.1%) (Jung et al., 2009) and China (82%) (Sankaranarayanan et al., 2010).

The low OS among Malaysian patients are worrying as the Malaysian government provides universal health care coverage for cancer diagnosis and treatment. Malaysia's healthcare system is highly accessible, with access to either government-funded or self-funded health care systems. The delivery of health services in government facilities is publicly funded for Malaysian citizens, with minimal charges for certain services (Petrilli, 2007). The accessibility of treatment is an essential factor in cancer survival as 80% of cancer patients will require surgical intervention (Sullivan et al., 2015), followed by 50%-67.1% of patients who will receive chemotherapy treatment (Yahaya e al., 2015; Nies et al., 2018). The Ministry of Health has at least 61 hospitals (6 institutes, 14 state hospitals, 21 major specialist hospitals, and 20 minor specialist hospitals), with 92% of urban and 69% of rural populations having access to health facilities (Organization, 2012).

1.3 Rationale and significance of this study

Traditional prognostic factors such as age, ethnicity, tumour stage, molecular subtypes, treatment modality, and chemotherapy regimen on breast cancer patients survival have been extensively studied. Regional-based studies on prognostic factors are important to healthcare providers as they reflect the local population's actual HR. However, there is a limited number of such studies among Malaysian breast cancer patients.

The impact of traditional prognostic factors has been extensively studied and accepted as a clinically significant prognostic factor. Recently, there has been increased interest in treatment-related prognostic factors such as chemotherapy regimen and chemotherapy schedule in impacting OS. While chemotherapy regimen

has been widely investigated, treatment-related factor such as chemotherapy schedule modification in clinical practice is often neglected. The chemotherapy schedule is often modified due to medical and non-medical reasons in clinical practice, contributing to delays in the completion chemotherapy regimen. Studies have shown that prolonged schedule modification carries the risk of suboptimal outcomes among cancer patients receiving chemotherapy (Nagel et al., 2012; Liutkauskiene et al., 2018).

The clinical practice of chemotherapy schedule modification and the survival outcome of patients among those who received chemotherapy with varying schedules in Malaysia is currently unknown. This study aims to identify the prevalence and reason for chemotherapy schedule modification. This study will also investigate the OS and HR of chemotherapy schedule modification adjusted for traditional prognostic factors.

The finding of this research could explain the impact of the chemotherapy schedule and provide information for clinicians to reduce the incidence of rescheduling. The outcome of this study could subsequently initiate clinical practice to monitor the chemotherapy schedule to improve compliance to the chemotherapy regimen.

1.4 Research study aims and objectives

This study aims to evaluate the impact of traditional prognostic factors such as age, ethnicity, tumour stage, molecular subtypes, treatment modality, chemotherapy regimen, and covariates of interest in this study which is the reason for disruption and chemotherapy schedule modification on OS and the HR of the breast cancer patient. The following objective was used to achieve the main objective:

a. To determine the association of age, ethnicity, tumour stage, molecular subtypes, treatment modality, type of chemotherapy and reason for the disruption between chemotherapy schedule modification category.

b. To determine the overall survival and mean survival between age, ethnicity, tumour stage, molecular subtypes, treatment modality, type of chemotherapy, reason for the disruption, and chemotherapy schedule modification category.

c. To determine the crude hazard risk and adjusted hazard risk for age, ethnicity, tumour stage, molecular subtypes, treatment modality, type of chemotherapy, the reason for the disruption, and chemotherapy schedule modification category.

1.5 Thesis overview.

This thesis consists of six chapters. Chapter 1 describes the study rationale, significance, aims, and objectives. Chapter 2 reviews the history of breast cancer, studies on breast cancer prognostics in Malaysia, evaluation of prognostic factors including age, ethnicity, tumour stage, molecular subtypes, treatment modality, type

of chemotherapy, the reason for the disruption, and chemotherapy schedule modification. Chapter 3 describes the methodology of this study, including research design, study setting, research population, sampling strategy and sample size, data collection procedure, classification of covariates, statistical analysis, and ethical consideration. Chapter 4 presents the result of descriptive analysis of patients demographic and study covariates. Next, the survival distribution and crude HR of respective covariates are presented. Finally, the result of adjusted HR and model adequacy is presented. Chapter 5 discuss the study finds according to patients demographics and study covariates. Chapter 6 draws the study conclusion and provides recommendations for policymakers, healthcare professionals, and future research.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Breast cancer is a leading cause of female mortality and accounts for up to 5% death risk among women every year (Lan, Laohasiriwong, and Stewart, 2013). Prior studies among Malaysian breast cancer patients have postulated that cancer survival may be associate with multiple well known traditional prognostic factors such as age, ethnicity, cancer stage, treatment modality, and molecular subtype (Bellon et al., 2000; Abdullah & Yip, 2003; Chong et al., 2010; Subramaniam et al., 2015; Kong et al., 2017).

2.2 History of breast cancer throughout the ages

The earliest evidence of breast cancer could be traced back to a 4,200 BC old Egyptian mummy (Granada, 2017). The first recorded evidence of breast cancer could be traced to The Edwin Smith Surgical Papyrus, dating back to 3,000–2,500 BC, where the disease was described as "cool to touch, bulging and spread all over the breast" (Breasted, 1930). During ancient Greece in 400 B.C, Hippocrates' the father of Western Medicine, hypothesised the cause of cancer as a humoral disease (Lucretius, 1959).

The first recorded treatment for breast cancer was surgical modality in the 1st century AD, where Leonidas, a native Greek doctor of Alexandria, provided a detailed approach of incision and cautery (Ariel & Clearly, 1987). His surgical method

of wide margin excision was the first detailed description of mastectomy, which became the contemporary surgical practice for the coming centuries (Lewison, 1953).

However, until the late 15th century, the emergence of religious philosophies preferred faith healing and miracles over surgery. Early scholars such as Avicenna and Albucasis preserved medicine through translations, thus saved Greek medical knowledge (Cooper, 1941).

During the 14th century, caustic pastes were used to shrink the tumour before surgery which is the predecessor of the modern age of chemotherapy (Cooper, 1941). During the same period, Henri de Mondeville and Guy de Chauliac introduced surgical equipments for removing breast tumours. By the 17th century, Francois de la Boe Sylvius hypothesised that the accumulation of lymphatic fluid aided cancer development in the lymph vessel. During the same era, Surgeon John Hunter theorised lymph as the cause of breast cancer and established the initial concept of staging (Evans, 2007), while French doctor Henri Le Dran proposed surgical removal of the tumour with regional lymph nodes could treat breast cancer. This ideology shaped the creation of radical mastectomy or extensive removal of the breast. However, up to the 19th century, surgical approaches were limited as anaesthesia was not yet developed for surgical procedures (Brown & Fee, 2006).

From the 19th century onwards, advancements in technology have propelled significant improvements in understanding cancer cells' disease and cellular nature (Brown & Fee, 2006). The development of cytotoxic agents was ongoing as well, with nitrogen mustards (Gilman & Philips, 1946), antifolates (Heidelberger et al., 1957)

among the first neoplastic agents used for systemic treatments for cancer (Goodman et al., 1984).

In 1975, Gianni Bonadonna presented the first study on the efficacy of chemotherapy treatment in reducing the risk of breast cancer recurrence after surgery (Italian Multicentre Breast Study et al., 1988). This finding propelled the use of chemotherapy as an adjuvant (ACT) treatment modality. Since then, chemotherapy has become a mainstay treatment modality along with surgical intervention.

2.3 Breast Cancer in Malaysia

Neoplasm of the breast is the most common cancer of the primary organ diagnosed among Malaysian females. The lifetime risk of developing cancer is 1 in 22 for Chinese, 1 in 24 for Indian, and 1 in 35 for Malay (National Cancer Registry, 2018). The latest National Cancer Registry (NCR) reported that 64,275 cancer mortality was reported over five years from 2007-2011 (National Cancer Registry, 2018). Regionally, Malaysia has a breast cancer mortality rate of 18 per 100,000 while Singapore and Thailand with 15 and 11 per 100,000 populations, respectively (Cancer, 2012). On the bright side, 2018 NCR reported a reduction in breast cancer death rate to 11.82% compared to 16.8% as reported in NCR 2011 (Azizah et al., 2016; National Cancer Registry, 2018). Although there was a reduction in breast cancer mortality rate, the mortality rate is still higher when compared to the Asian average of 6.05% (Mubarik et al., 2020).

The NCR reported that 18,343 new breast cancer were diagnosed from 2007 to 2011, accounting for 17.8% of total cancer cases (Azizah et al., 2016), while for the

year 2018 alone, it is estimated that 7593 new breast cancer cases were reported (Asia Globocan, 2019). With the ageing of Malaysian female population, the incidence rate of breast cancer among older people is expected to increase (Shin et al., 2012). Identifying risk factors that reduce survival outcomes for breast cancer is important in implementing targeted interventional programs to improve breast cancer delivery for breast patients.

2.4 Studies on breast cancer prognostic factor in Malaysia.

2.4.1 Early institutional-based cancer report.

The first study of breast cancer survivorship in Malaysia was reported in 1996 among 205 patients seen in UMMC (University Malaya Medical Centre) between January 1992 and November 1994 (Yip, 1996). As the national cancer registry was not established during that period, this study was significant as it provided baseline observation of breast cancer patients in Malaysia. This study reported that the median age at presentation was 48 years, much younger than those 60 - 65 years reported in Western women. About 55.6% of the women presented with early breast cancer (stage 0 to II), and 34.2% presented with advanced stage (stage III and IV), while the remaining 10.2% had missing data. Most of the patients were non-Malay ethnics (79%), and the rest came from the Malay ethic (21%). The study author postulated that the advanced stage at presentation could be due to a strong belief in traditional medicine. This study was influential in establishing age, breast cancer stage, and ethnicity as an important prognostic parameters.

In 2004, a study comparing the presentation of new breast cancer cases between Hospital Kuala Lumpur (HKL) and UMMC was published (Hisham & Yip,

2004). Between 1998 and 2001, 774 and 752 patients were diagnosed with breast cancers in HKL and UMMC. The mean age between both the facilities was 50 years. This study confirms that Malaysian women present with breast cancer at a younger age than the western population. This study also observed that most patients (30-60%) presented at an advanced stage. The authors concluded that although Malaysian women develop breast cancer at a younger age, the advanced stage at diagnosis is contributed by the delayed presentation to treatment facilities.

2.4.2 National and institutional Cancer Registry-based report

Ministry of Health (MOH) initiated its population-based cancer registry in 1993. The pilot registry was started in Penang with regional population-based cancer registries to cover the northern region (Azizah et al., 2016). Following the successful establishment of the Penang cancer registry, other regional registries were established in Sarawak, Kelantan, Pahang, Johor, and Sabah. Since 2007, all states in Malaysia have set up their population-based registries, headed by the National Cancer Registry (NCR) in the Ministry of Health under the Non-Communicable Disease Sector, Disease Control Division.

2.4.2(a) Penang Cancer registry

One of the early cancer regional registries was Penang Cancer Registry, established in 1994 (Zarihah et al., 2003). The finding of the registry comprising of patients diagnosed from 1994 to 1998 and was published in 2003. The information from the registry was limited as it only reported the proportion of staging at diagnosis. 15.8% of patients were diagnosed with stage I, 46.9% for stage II, 22.2% for stage III, and 15.5% for stage IV.

2.4.2(b) Universiti Malaya Medical Centre cancer registry

UMMC has maintained a facility-based registry since 1993 (Yip et al., 2006). This registry was the first to report that OS breast cancer patients in Malaysia were 58% in the 1990s. This registry also reported that the Malay ethnic had the poorest OS rate of 45.9%, followed by Indians ethnic with an OS rate of 57.1% and Chinese ethnic with the highest OS rate of 63.2%. This report reported that the OS decreases with increasing stage where stage I had 81.7% OS, stage II with 72.4% OS, stage III with 39.9% OS, and stage IV with 12.9% OS. This report concluded that the survival was poorer among Malay ethnic groups as they tend to present at an advanced stage compared with non-Malay ethnics women.

2.4.2(c) Kelantan State breast cancer registry

A study based on the Kelantan state breast cancer registry was published in 2018 (Nordin et al., 2018). The mean age among 549 patients was 50.4 years and comprised of 85.8% of Malay and 14.2% non-Malay ethnics. As for the breast cancer stage, 29.7% presented at stage I, 29.3% at stage II, 16.4% at stage III, and 24.6% at stage IV. The OS rate was 67.5% for stage I, 79.5% for stage II, and decreased to 41.1% for stage III and 12.6% for stage IV. This study found that ethnicity was a significant prognostic factor by which Malay had HR increased by 2.5 times compared to non-Malay (HR 2.52; 95% CI 1.54 to 4.13, $p<0.001$). When compared to stage I, stage III, and stage IV, patients had HR increased by 2.3 times (HR 2.31; 95% CI 1.57 to 3.39, $p<.001$) and 6.2 times (HR 6.20; 95% CI 4.45 to 6.65, $p<0.001$) respectively. Besides, surgery was a significant factor ($p<0.001$) as HR was increased by two times for patients without surgery than patients who received surgical intervention. However,

the result of this study was limited by the low proportion of non-Malay ethnic and the absence of other prognostic factors such as molecular subtype, treatment modality and chemotherapy.

2.4.2(d) Universiti Malaya Medical Centre and National Universiti of Singapore breast cancer database

UMMC, Malaysia, and National Universiti Hospital, Singapore (NUS) reported a collaborative study comprising 4058 breast cancer patients diagnosed between 1990 and 2007 (Yip, 1996). The study population consisted of 84% non-Malay ethnics and 16% Malays ethnic. This study reported OS of 82.5% in early-stage and 30.2% in later stages. The median survival times were 164 months for stage II, 53 months for stage III, and 17 months for stage IV breast cancer. This study was unique as it was a comparative study between two neighbouring countries with similar ethnic compositions. However, this study does suffer from limitations such as heterogeneous socioeconomic populations as Malaysia is an upper-middle-income while Singapore is a high-income nation. The data was collected from two study facilities, a tertiary academic centre, and may not reflect the cancer treatment practice in the government hospital. This study highlights that the late stage at diagnosis remains a shortfall to healthcare in this region.

2.4.2(e) Malaysian National Cancer registry

Malaysia National Cancer Registry (NCR) was launched in 2002, initiating population-based cancer surveillance in Malaysia (Lim et al., 2003). By 2003, 3738 new breast cancer cases were registered, providing an Age-Standardised-Rate (ASR) of 46.2 per 100,000 women. The ASR among the Chinese ethnic was highest, with

59.7 per 100,000, followed by the Indian ethnic at 55.8 per 100,000, and the Malay ethnic had the lowest ASR of 33.9 per 100,000. The mean age at diagnosis was 50 years old with an ethnicity breakdown of 48 years in Malays, 51 years in Chinese, and 52 years in Indians. About 50% of the cases were below 50 years, where the highest proportion (30%) were among the 40 to 49 year age category. During this period, the pathological features of the diseases were not recorded in the registry; hence the stage at diagnosis is not available.

The latest study of NCR was published in 2013 (Abdullah et al., 2013). This study observed that majority of the patients diagnosed with cancer were of Malay ethnic (53.8%), and the remaining were non-Malay ethnics (46.2%), with a mean age of presentation at 50.6 years old. The median survival time was 68.1 months, with an OS rate of 49%. This study also observed Indian ethnic (54%) had a higher OS compared to Chinese ethnic (49%) and Malay ethnic (45%). However, this study did not adjust the impact of other covariates such as cancer stage, hormone receptors, and treatment variable as the registry does not capture such data. This study concluded that the OS rate of Malaysian breast cancer patients was lower than survival rates in developed nations.

2.4.2(f) Malaysian Study on Cancer Survival

Malaysian Study on Cancer Survival (MySCan) is the latest national cancer report of population-based data from 15 state cancer registries (Azizah et al., 2016). This report provides an analysis of those who were diagnosed from 1 Jan 2007 until 31 Dec 2011. The latest nationwide OS for female breast was at 66.8%. The current report has evaluated the cancer stage and reported that stage IV had an unadjusted HR

increase by 7.52 times (HR 7.52; 95% CI 6.83 to 8.28) compared to stage I. However, the latest report could not evaluate the impact of other covariates such as tumour histopathology and treatment variable as the registry does not capture such data.

The review of the above reports and studies from the local database and registry has identified important prognostic factors relevant to the Malaysian population, such as age, ethnicity, tumour stage, molecular subtypes, and treatment modality. Additional covariate such as chemotherapy regimen, reason for the disruption, and chemotherapy schedule modification was evaluated as a novel prognostic factor to add value to the current study.

2.5 Breast cancer prognostic factors

Breast cancer is a heterogeneous disease with disparities in prognosis (Polyak, 2011). Breast cancer prognosis is defined as death or disease progression which develops over an observed length of time, based on demographic and disease profiles (Moons et al., 2009). The breast cancer prognostic factors are important as they project the disease trajectory over time. Prognostic factors help clinicians select appropriate treatment modalities by balancing treatments with their related side effects and financial costs. Besides, the prognosis factor helps policymakers monitor the efficacy of health care delivery and develop future public health programs.

2.5.1 Age

Breast cancer incidence and death rates are known to increase with age (Kresovich et al., 2019). The estimated risk of developing breast cancer before 49 years of age is 1 in 53, and this risk rises to 1 in 43 for 50–59 age category, 1 in 23 for 60–

69 age category, and to 1 in 15 for women aged ≥70 years old (Russell et al., 2000). Although age increases the risk of developing breast cancer, a higher survival rate was observed. The survival rate for patients < 40 years old are 84.5%, 89.4% for patients between 40-49 years old, 90.9% for patients between 50-59 years old are and 90.8% for patients between 60-69 years old before dropping to 73% for patient ≥ 70 years old (Siegel et al., 2012). In Malaysia, breast cancer patients present around 50 years old (Azizah et al., 2016), which is younger when compared with 60 to 75 years old for western counterparts (Stapleton et al., 2018). The latest MySCan reported that the current OS for breast cancer patients 15 to 50 years is 65.9%, while those 50 years and above were at 67.9% (Azizah et al., 2016). The breast cancer disease burden is expected to increase in the near future due to increased ageing.

2.5.2 Ethnic

Ethnicity has been an influential traditional prognosis factor due to variations in tumour genomic, comorbidities and socioeconomic status (Gathani et al., 2014). Epidemiologic data suggest ethnic disparities have persisted even when accounted for advancement in breast cancer treatment and detection (Yedjou et al., 2017). For example, a better prognosis was observed among eastern Asian origin while South Asian origin tend to experience poorer outcomes (Seiler et al., 2017). While the average lifetime risk for developing breast cancer for the Malaysian population is 1 in 30 women, the ethnicity disparities are profound as the lifetime risk is 1 in 22 for Chinese, 1 in 24 for Indian, and 1 in 35 for Malay (Azizah et al., 2016). While Malay women have the lowest incidence of breast cancer, they have a poorer prognosis than their Chinese and Indian counterparts (Nordin et al., 2018).

2.5.3 Tumour stage

The tumour stage at the time of diagnosis is one of the most important prognostic factors. In 1959, the American Joint Committee on Cancer (AJCC) established a uniform cancer staging system, known as TNM classification (Cserni, et al., 2018). TNM stages breast cancer based on tumour size (T), lymph node involvement (N), and evidence of metastasis (M). The T, N, and M groupings correspond with the disease stage where "T" with the number from 0 to 4 is used to describe the primary tumour's size in centimetres (cm). Higher T numbers correspond to a larger tumour. "N" with the number from 0 to 3 indicates s regional lymph node involvement. N1 indicates the involvement of 1 to 3 axillary lymph nodes, while N2 indicates the involvement of 4 to 9 axillary lymph nodes, and N3 indicates the involvement of 10 or more axillary lymph nodes. The "M" with the number 0 or 1 indicates whether cancer has spread to other parts of the body.

Breast cancers were staged from stage 0 through stage IV, with an increasing number indicating disease spread. Generally, early stage breast cancer has a favourable prognosis in comparison with late-stage diagnosis.

Stage 0 is considered a pre-cancerous condition that requires close observation but not treatment (Institute, 2017).

Stage I is the first stage of invasive breast cancer. In stage I, the tumour could measure up to 2 cm with no lymph node involvement and is considered to have a good prognosis with an OS rate of more than 99% (Institute, 2017).

Stage II breast cancer is also known as invasive breast cancer. In this stage, the tumour measures between 2 cm to 5 cm or has limited spread to the regional lymph nodes. Stage II breast cancer indicates a slightly more advanced form of the disease. The OS rate for women with non-metastatic invasive breast cancer is 91-93% (Institute, 2017).

Stage III breast cancer, also known as locally advanced breast cancer, is an advanced form of the disease with a tumour larger than 5 cm in diameter and extensive lymph nodes involvement but with no evidence of spreading to distant sites. The OS rate for patients with non-metastatic invasive breast cancer is 72% (Institute, 2017).

Stage IV breast cancer, also known as metastatic breast cancer (MBC), has spread beyond the primary tumour to a distant site. The OS rate for stage IV is only 22% (Institute, 2017).

2.5.4 Molecular subtypes

For the past 30 years, hormone receptor has been widely used to aid therapeutic decision-making (Goldhirsch et al., 2011). The identification of hormone receptors is made by immunohistochemistry (IHC) and gene expression profiling. A tumour may have the expression of Estrogen receptor (ER), progesterone receptor (PR), and Human epidermal growth factor receptor 2 (HER2). A tumour with overexpression of receptor will be labelled positive (+), while a tumour with normal expression will be labelled negative (-).

Breast cancer is uncommon before 20 years old; however, the incidence gradually increases with age (Shoemaker et al., 2018). The pathogenesis of breast cancer is closely related to the age-dependent reproductive hormones produced by the ovaries (Momenimovahed & Salehiniya, 2019). The result of a case-control study reported that younger age during menarche increases the risk of breast cancer by two times (OR 2.83; 95% CI 1.02 to 7.86) while the age of menopause over 50 years is associated with an increased incidence of breast cancer (OR 2.43; 95% CI 1.2 to 4.9) (Thakur et al., 2017).

The expression of molecular subtypes among western and Asian populations markedly different from Western populations have greater proportions of hormone receptor-positive tumours (Bray et al., 2012). The largest analysis of breast cancer receptors released in April 2018 showed different survival rates between hormone receptor-positive and negative hormone patients (Li et al., 2020). Patients with single receptor-positive such as ER+PR- (HR 1.27; 95% CI 1.24 to 1.29) and ER-PR+ (HR 1.07; 95% CI 1.03 to 1.11) tumours had better survival outcomes than patients with the ER-PR-. However, this study did not include HER2 status, and the result was not adjusted for other prognostic factors.

Recent studies have classified breast cancer IHC results according to the St. Gallen Consensus 2011. Tumour subtypes are categorised as Luminal A (ER+ and/or PR+, HER2-), Luminal B (ER+ and/or PR+, HER2+), HER2-overexpression (ER-,PR-,HER2+) or triple-negative breast cancers [TNBC (ER-,PR-,HER2-)] which provides a better correlation with prognosis, treatment and survival outcome (Goldhirsch et al., 2011; Kumar et al., 2015). A registry-based study among 21,384 breast cancer patients

reported that females < 50 years old were more likely to have HER2-positive and TNBC tumours, while females above 70 years old commonly had luminal A-like tumours.

An observation among 1034 Sarawak breast cancer patients reported a prevalence of 48% for Luminal A, 12% for Luminal B, 29% for TNBC, and 11% for HER2-overexpression molecular subtypes, respectively. 37% of the native Sarawak population had TNBC, while HER2-overexpression was prevalent among the Malay ethnic (29%) (Devi et al., 2012). Similarly, another observation among 3012 women with invasive breast cancer diagnosed between 2003 and 2016 in the Department of Radiotherapy, Sarawak General Hospital reported a prevalence of 34% for Luminal A followed by 33% for Luminal B, 13% for HER2-overexpression and 20% for TNBC, respectively (Abubakar et al., 2018).

Women with TNBC molecular subtype have an increased risk of death (HR 4.39; 95% CI 3.79 to 5.08) when adjusted for age, cancer stage, and treatment modalities (Johansson et al., 2019). Worryingly, the Asian population are known to have a higher proportion of receptor-negative subtypes (Howlader et al., 2014; Li et al., 2020).

Although there are a few reports on molecular subtypes of breast cancer in Malaysia, the studies are primarily descriptive. Thus, the impact of molecular subtypes among the Malaysian population have yet to be extensively investigated.

2.5.5 Treatment modality

Once the patients are diagnosed with breast cancer, the spread of the disease determines if adjuvant chemotherapy (ACT), neoadjuvant chemotherapy (NACT), or palliative chemotherapy (PCT) treatment modality is indicated.

2.5.5(a) Adjuvant chemotherapy modality

Adjuvant chemotherapy (ACT) refers to the administration of chemotherapy following surgical removal of the primary tumour to eradicate microscopic foci or inhibit micrometastases. The use of ACT is responsible for reducing global breast cancer mortality. The 20-year follow-up of The Early Breast Cancer Trialists' Collaborative Category (EBCTCG) meta-analysis published in 2012 reported ACT chemotherapy decreased breast cancer mortality from 36% to 29 % (HR 0.79; 95% CI 0.72 to 0.85) when adjusted for nodal status, tumour size or grade and ER status (Category, 2012).

2.5.5(b) Neoadjuvant chemotherapy modality

Neoadjuvant chemotherapy (NACT) refers to the administration of chemotherapy before surgical therapy. NACT is generally used to render inoperable breast cancer resectable, decrease axillary lymph node dissection, and evaluate tumour response to chemotherapy (Deo et al., 2003). The safety and survival outcomes of NACT have been studied in several randomised trials (Fisher et al., 1998; Broët et al., 1999; Van Der Hage, 2001). The National Surgical ACT Breast and Bowel Project (NSABP) Protocol B-18 study reported comparable OS between ACT and NACT modality over 16 years of follow-up (Rastogi et al., 2008). Similarly, the NACT modality has been reported to reduce progression towards axillary metastases in node-

negative women and avoided axillary dissection (Mamtani et al., 2016). In addition, meta-analysis has indicated no difference in OS benefit between the ACT and NACT modality categories (HR 1.03; 95% CI 0.94 to 1.13, p=.51) (Chen et al., 2018).

Despite the benefit of NACT, a higher risk of local recurrences and a decrease in OS was reported for NACT (Asselain et al., 2018). While the available evidence indicates s similar OS rates between NACT and ACT for operable breast cancer, the OS among inoperable breast cancer remains questionable.

2.5.5(c) Palliative treatment modality

Palliative chemotherapy (PCT) is a non-curative treatment for metastatic disease to improve patients' quality of life and prolong survival (Neugut & Prigerson, 2017). Among all newly diagnosed breast cancer, between 5% and 10% of patients will present with MBC. Even when diagnosed with early-stage disease, the disease can progress to metastatic disease (Mariotto et al., 2017; Thrift-Perry et al., 2018). The overall survival of patients with MBC is still poor, with a mean survival of 36.6 months (Gobbini et al., 2018) and only about 20%-24% surviving up to 5 years (Chamberlain et al., 2017). A meta-analysis of 11 randomised trials evaluating chemotherapy in patients with MBC has reported that PCT increased OS by approximately three months (HR 0.91; 95% CI 0.84 to 0.99) (Gennari et al., 2011).

Despite ongoing research, MBC generally remains incurable. Therefore, the main treatment goal among patients receiving PCT is prolonging survival and symptom palliation with improved quality of life.

2.5.6 Chemotherapy Regimen

The addition of chemotherapies following surgical modalities has globally declined breast cancer mortality rates (Munoz et al., 2014). In 1958, NSABP B-01 conducted the first randomised trial evaluating ACT modality in breast cancer patients (Bernard Fisher et al., 1968). The study results showed that chemotherapy significantly decreased the recurrence rate of women with positive axillary lymph nodes. In 1975, the Istituto Nazionale Tumori in Milan, Italy, presented the first report on the efficacy of antimetabolite chemotherapy regimen as the ACT for breast cancer steering into the modern age of chemotherapy regimens clinical practice (Bonadonna et al.,1976). The clinical benefit of the chemotherapy persistent over 28.5 years follow-up study with a reduction in relative risk of death (RR 0.79; 95% CI 0.63 to 0.98, P = 0.04) (Bonadonna et al., 2005). Latest trials have established the clinical benefit of chemotherapy both in premenopausal and post-menopausal women (Giuliano et al., 2019; Pagani et al., 2020).

2.5.6(a) Anthracyclines based

Anthracycline has been the backbone cytotoxic agent for breast cancer treatment in the past 50 years (McGowan et al., 2017). Anthracycline is derivatives from gram-positive Streptomyces, and the pharmacotherapeutic effect is exerted through intercalation of Deoxyribonucleic acid (DNA), cross-linking of DNA to proteins, and generation of free radicals (Munro, Cameron, & Bartlett, 2010). The anthracycline-based regimen consists of either doxorubicin, Daunorubicin, Epirubicin (a stereoisomer of doxorubicin), or Idarubicin.