SURVIVAL ANALYSIS OF PREGNANCY ASSOCIATED BREAST CANCER IN KELANTAN: A HOSPITAL-BASED RETROSPECTIVE COHORT STUDY

SYED SANA ABRAR

UNIVERSITI SAINS MALAYSIA

2023

SURVIVAL ANALYSIS OF PREGNANCY ASSOCIATED BREAST CANCER IN KELANTAN: A HOSPITAL-BASED RETROSPECTIVE COHORT STUDY

by

SYED SANA ABRAR

Thesis submitted in fulfilment of the requirements
for the Degree of
Master of Science

July 2023

ACKNOWLEDGEMENTS

This thesis would not have been possible without the support of several people who helped me immensely throughout the process. I am sincerely grateful to each person who has helped me in my postgraduate journey. I would like to express my sincerest gratitude to Professor Dr Norsa'adah Bachok, my main supervisor. Her continuous guidance and support have helped me enormously during the preparation of this dissertation. Her guidance has helped me achieve the completion of this research project and I am incredibly thankful to her. I would like to thank Dr Maya Mazuwin Binti Yahya and Dr Junaidi Awg Isa, my co-supervisors for spending their valuable time to review my work and giving advice that led to the completion of my thesis. I would like to thank Dr Professor Abdul Razak Sulaiman, the Dean of School of Medical Sciences, Universiti Sains Malaysia, IPS staff and postgraduate office staff for giving their technical support to me. I am thankful to the Ethical Committee of School of Medical Sciences, Universiti Sains Malaysia for allowing me to conduct my research in Hospital USM. I am grateful to the Ministry of Health and National Medical Research Register (NMRR) for allowing me to collect data at HRPZ II. I would like to thank the staff at the Record Unit Department USM who helped me during the entire process of data collection. I am sincerely grateful to the Institute of Postgraduate Office (IPS) for their financial support. I would like to thank my parents, whose love and guidance are with me in whatever I pursue. I truly appreciate my family's encouragement and support that assisted me to overcome difficulties during my study. Thank you very much!

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF ABBREVIATIONS

APGAR	Appearance, Pulse, Grimace, Activity and Respiration
ACOG	American College of Obstetricians and Gynaecologists
BC	Breast Cancer
BRCA1	Breast Cancer 1 Gene
BRCA2	Breast Cancer 2 Gene
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DFS	Disease Free Survival
ER	Estrogen Receptor
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
LRR	Locoregional Recurrence
NICU	Neonatal Intensive Care Unit
Non-PABC	Non- Pregnancy Associated Breast Cancer
OR	Odds Ratio
OS	Overall Survival
PABC	Pregnancy Associated Breast Cancer
PR	Progesterone Receptor
WHO	World Health Organization

ANALISIS KEMANDIRIAN KANSER PAYUDARA BERKAITAN KEHAMILAN DI KELANTAN: KAJIAN KOHOT RETROSPEKTIF BERASASKAN HOSPITAL

ABSTRAK

Menurut Pertubuhan Kesihatan Sedunia, 2.3 juta wanita telah didiagnosis dengan kanser payudara pada tahun 2020, dan kira-kira 685,000 kematian telah direkodkan di seluruh dunia. Bilangan pesakit kanser payudara di Malaysia meningkat pada kadar yang membimbangkan, dengan hampir separuh daripada semua pesakit kanser payudara berumur kurang dari 50 tahun. Kanser payudara yang berkembang semasa mengandung atau dalam tempoh 12-24 bulan selepas bersalin dikenali sebagai kanser payudara berkaitan kehamilan (KPBK). Pesakit KPBK mungkin mempunyai keputusan klinikal dan kelangsungan hidup bebas penyakit yang buruk. Penyelidikan yang meneroka kelangsungan hidup dalam kalangan pesakit kanser payudara adalah terhad, terutamanya di negara Asia. Objektif kajian ini adalah untuk membandingkan kadar kemandirian keseluruhan dalam pesakit KPBK dan bukan KPBK dan mengenal pasti sama ada kehamilan adalah faktor prognostik untuk kelangsungan hidup dalam kalangan pesakit KPBK. Reka bentuk kajian adalah kohot retrospektif. Dua kohot wanita kanser payudara, satu kohot hamil dan satu lagi kohot tidak hamil, telah diikuti untuk hasil kelangsungan hidup. Data pesakit dari pangkalan data Universiti Sains Malaysia dan Hospital Raja Perempuan Zainab II dari 1 Januari 2001 hingga 31 Disember 2020 telah disemak, dan maklumat yang berkaitan telah diambil dan

direkodkan dalam borang pengumpulan data. Semua wanita kanser payudara yang hamil yang memenuhi kriteria kemasukan telah dipilih untuk penyertaan, dan telah dipadankan dengan wanita kanser payudara yang tidak hamil dengan umur dan tahun diagnosis. Dua nisbah kumpulan kawalan telah dipilih. Fungsi kelangsungan hidup keseluruhan bagi kedua-dua kumpulan pesakit dianalisis mengikut kaedah Kaplan-Meier dan dibandingkan menggunakan kaedah peringkat log Mantel-Cox. Faktor prognostik dianalisis dengan menggunakan regresi bahaya berkadar Cox. Sebanyak 35 pesakit dalam kumpulan KPBK telah dianalisis dan dipadankan dengan 35 pesakit bukan KPBK dalam kumpulan nisbah 1:1 dan 70 pesakit bukan KPBK dalam kumpulan nisbah 1:2. Masa kelangsungan hidup median dalam kumpulan KPBK ialah 40.32 bulan (95% julat keyakinan (JK), 0.00-94.18), 26.29 bulan dalam kumpulan bukan KPBK padanan 1:1 (95% JK 22.45-30.13; p=0.080) dan 43.59 bulan dalam kumpulan 1:2 kumpulan bukan KPBK ialah (95% JK, 0.00-89.92; p=0.941). Kemandirian 5 tahun dalam KPBK, bukan KPBK (1:1) dan bukan KPBK (1:2) masing-masing ialah 47.54%, 25.69% dan 45.11%. Perbezaan kadar kelangsungan hidup antara kumpulan adalah tidak bererti; p=0.080 untuk kumpulan 1:1 dan p=0.941 untuk kumpulan 1:2. Kehamilan didapati sebagai bukan faktor prognosis yang bebas; nisbah bahaya terselaras (NBT) = 0.56, 95% JK: 0.30, 1.03, p=0.063 untuk kumpulan 1:1 dan NBT = 0.72, 95% JK (0.39, 1.28), p=0.266 untuk kumpulan 1:2. Penemuan menunjukkan bahawa wanita yang didiagnosis dengan KPBK tidak mempunyai perbezaan dalam kadar kelangsungan hidup yang bererti berbanding wanita bukan KPBK. Kehamilan adalah bukan faktor prognostik bebas untuk kelangsungan hidup kanser payudara. Maklumat ini berguna apabila wanita diberi kaunseling dan menyokong pilihan untuk memulakan rawatan dengan meneruskan kehamilan. Walau

bagaimanapun, disebabkan saiz sampel yang kecil dan kajian yang berkuasa rendah, hasil kajjan ini harus ditafsirkan dengan berhati-hati.

Kata kunci: Kanser payudara, Kehamilan, Kanser payudara berkaitan kehamilan, Kelangsungan hidup

SURVIVAL ANALYSIS OF PREGNANCY-ASSOCIATED BREAST CANCER IN KELANTAN: A HOSPITAL-BASED RETROSPECTIVE COHORT STUDY

ABSTRACT

According to the World Health Organization, breast cancer was diagnosed in 2.3 million women in 2020, and approximately 6,85,000 deaths were recorded worldwide. The number of breast cancer patients in Malaysia is increasing at an alarming rate, with almost half of all breast cancer patients aged < 50 years. Breast cancer that develops during pregnancy or within 12-24 months of delivery is known as pregnancy-associated breast cancer (PABC). PABC patients may have poor clinical results and survival. Research exploring survival outcomes in pregnant breast cancer patients is limited, especially in Asian countries. The objective of this study was to compare the survival probability in PABC and non-PABC patients and identify if pregnancy is an independent prognostic factor in PABC. The study design was retrospective cohort. Two cohorts of breast cancer women, one pregnant cohort and another non-pregnant cohort, were followed for the survival outcome. Patients' data from the Universiti Sains Malaysia (USM) and Hospital Raja Perempuan Zainab (HRPZ) II database from 1st January 2001 until 31st December 2020 was reviewed, and relevant information was extracted and recorded in a data collection form. The survival of the two groups of patients were analysed following the Kaplan-Meier

method and compared using the Mantel-Cox log-rank method. Prognostic factors were analysed using Cox proportional hazard regression. A total of 35 patients in the PABC group were analysed and matched with 35 non-PABC patients in the 1:1 group and 70 non-PABC patients in the 1:2 group on the basis of age and year of diagnosis. The median (IQR) follow-up times were 30.93 (42.20), 25.17 (29.55), and 36.57 (58.25) months for the PABC, non-PABC (1:1), and non-PABC (1:2) groups, respectively. The median survival time in the PABC group was 40.32 months (95% confidence interval (CI), 0.00-94.18), 26.29 months in the 1:1 matched non-PABC group (95% CI 22.45-30.13; p=0.080) and 43.59 months in the 1:2 matched non-PABC group was (95% CI, 0.00-89.92; p=0.941). The 5-year survival of PABC, non-PABC (1:1), and non-PABC (1:2) was 47.54%, 25.69%, and 45.11%, respectively. There were no significant differences between groups; p=0.080 for 1:1 group and p=0.941 for 1:2 group. Pregnancy was not found to be an independent significant prognostic factor; adjusted hazard ratio (AHR) 0.56, 95% CI: 0.30, 1.03, p=0.063 for the 1:1 group and AHR 0.72, 95% CI (0.39, 1.28), p=0.266 for 1:2 group. The findings show that women diagnosed with PABC had non-significant difference of overall survival compared to non-PABC. Pregnancy is not an independent prognostic factor for the survival of breast cancer. This information may be useful when women with breast cancer are counselled and supports the option of beginning treatment with pregnancy continuation. However, due to the small sample size and low power of the study, the outcomes should be interpreted with caution.

Keywords: Breast cancer, Pregnancy, PABC, Survival, Prognosis.

CHAPTER 1

INTRODUCTION

1.1 Background of the study

1.1.1 Overview of Breast Cancer

One of the most common cancer among women in Malaysia, breast cancer is a condition in which cells in the breast proliferate uncontrollably. There are various types of breast cancer based on the type of breast cells that become malignant (Htay, *et al.*, 2021). It comprises for 25% of all cancers in female across the globe and 18.2% of all deaths related to cancer in both males and females. Over 1.5 million women are diagnosed with breast cancer across the globe every year (Stewart & Wild, 2014). Breast cancer is mainly associated with formation of a thick tissue or a lump in the woman's or man's breast. The stages of breast cancer ranges from early, curable to metastatic cancer (Breast Cancer, CDC, 2020). Several treatments including hormonal therapies have been developed over the years for treating this condition. Screening and other preventative strategies have the likelihood to lower the burden of breast cancer caused by late diagnosis. (Htay, *et al.*, 2021). In recent decade, scientists and clinicians have made huge progress in the understanding of this disease.

1.1.2 Incidence of Breast Cancer Worldwide

According to the World Health Organization, breast cancer was diagnosed in 2.3 million women in 2020, and approximately 6,85,000 deaths were recorded worldwide. A total of 7.8 million women living with breast cancer were documented by the end of 2020. These statistics from around the globe have made breast cancer as the most common form of cancer known to have affected patients in the last five years (WHO, 2021). Women in Asia have a lower incidence of breast cancer than their counterparts in the west across all age groups, according to current data. Around 25% of all breast cancers were detected in the Asia-Pacific region (approximately 404,000 cases), with China (46%) leading the way. South Korea and Japan have the highest rates in East Asia. In Southeast Asia, Singapore has the highest rate with 65 cases per 100,000. (Bhatia, 2016).

1.1.3 Breast Cancer in Malaysia

The number of breast cancer patients in Malaysia is increasing at an alarming rate. It is the most common malignancy affecting Malaysian women. One in every 19 women in Malaysia is at risk of developing breast cancer. In 2003, one-third of all the cases were diagnosed between the ages of 40 to 49. Almost half of all the breast cancer patients is under the age of 50 (Lee *et al.*, 2019). The incidence has increased drastically for patients above 30 years of age. The age group of 50-59 has the highest age-specific incidence. This scenario remains constant across different ethnicities including Malays, Indians, and Chinese. With an ASR of 46.4 per 100,000 population, women with Chinese ethnicity had the highest incidence. Indian women were next

with 38.1 per 100,000 population followed by Malay women with 30.0 per 100,000 population (Ministry of Health Malaysia, 2019b).

A 2006 study evaluated the risk factors of breast cancer in Kelantan. The control individuals were matched in terms of age (under 5 years) and ethnicity. The researchers interviewed 147 patients with primary breast cancers. Infiltrative ductal carcinoma was the most prevalent histological type (73%). 60% of breast cancers are presented at stage III or IV. In terms of family history, univariate analysis revealed significant differences between the two groups (p=0.0018). Statistical differences were also observed between cases and controls in terms of regular use of oral contraceptives (p=0.02) and history of bilateral oophorectomy (p=0.025). In multivariate analysis, women with positive family history had 4.3 times the odds of having the disease than women without a family history. Women who used OCs on a regular basis had 2.5 times the risk of developing breast cancer than those who did not use OCs regularly. This study confirmed that breast cancer in Kelantan is caused by identical risk factors as those found in Western populations (Norsa'adah *et al.*, 2005).

A recent study evaluated survival and prognostic factors in breast cancer women across different age groups. The study was conducted in Penang and involved 2,166 patients diagnosed with breast cancer between 2010 and 2014. The life table method was used to compute overall and relative survival rates. Kaplan-Meier method and the log-rank test were used for further analysis. The overall survival rate in Penang was 72.9% with a mean survival time of 92.5 months. The 5-year survival rate was 75.2%. The 5-year breast cancer-specific survival rates in different age groups were

as follows - 74.9% in the young, 77.8% in the middle-aged, and 71.4% in the elderly. The mean survival time across these age groups was 95.7 months in the young, 97.5 months in the middle-aged, and 91.2 months in the elderly. The survival rates differed significantly by age, with the elderly group having the lowest survival rate (p=0.003). (Tan *et al*., 2021).

1.1.4 Gestational Cancer

Cancer diagnosed during pregnancy or the first year after delivery is referred to as gestational cancer (Ji *et al*., 2013). Common malignancies during pregnancy are breast, melanoma, and cervical cancers. Cervical and breast cancers constitute 50% of pregnancy-associated cancers. Haematological cancers, including leukaemia and lymphoma, accounting for 25% of all occurrences of prenatal cancer. Cancer of the ovary, colon, and thyroid is less prevalent (Allouch *et al.*, 2020).

1.1.5 Pregnancy Associated Breast Cancer (PABC)

Breast cancer that develops during or within a year or two year after pregnancy is known as PABC or pregnancy associated breast cancer, and it poses a diagnostic and treatment challenge (Johansson *et al*., 2018). PABC is also known as “gestational breast cancer”.

PABC is extremely uncommon, with breast cancer complicating 0.2 percent to 3.8 percent of pregnancies and roughly 10% of patients with breast cancer (<40 years) getting the condition while being pregnant. However, the frequency of PABC is predicted to rise as maternal age at the time of pregnancy continues to rise, from 26.0 years in 1982 to 27.4 years in 2002. As a result, the most effective diagnostic and treatment procedures are essential (Beadle *et al.*, 2009)

Accounting for approximately 3,500 new cases per year, breast cancer can be found in one out of every 3,000-10,000 women during pregnancy in the United States. The reason can be a delay in pregnancy (>30 years) and higher levels of breast cancer identification in young women (Moreira *et al.*, 2010).

1.1.6 Various definitions of PABC

It can be defined as breast cancer diagnosed during pregnancy or in the first year following delivery (Keyser *et al*., 2012), or 24 months after delivery (Gooch *et al*., 2019), or as cancers diagnosed within five years of a woman's last childbirth (Callihan *et al*., 2013).

The number of years after birth that breast cancer can be identified using this criterion has varied from 0.5 to 5 years, and even longer in some cases. The definition of PABC varies, which could lead to different conclusions about the relationship between pregnancy, postpartum, and breast cancer. To further define the elevated risk

provided by a postpartum diagnosis, Shao et. al (2020) proposed expanding the definition of PABC to encompass patients diagnosed up to 6 years after giving birth.

1.2 Problem statement/Originality of research

First reported in 1954, researchers suggested a link between pregnancy and the unfavourable progression of breast cancer. The reports show that among pregnant women with breast cancer, <20% survived for more than five years (Moreira *et al.*, 2010). Plenty of research has supported this pessimistic outlook for PABC patients. It has been found over the years that pregnancy may lead to poor outcomes for breast cancer patients (Rodriguez *et al*., 2008; Stensheim *et al*., 2009; Ali *et al*., 2012; Nagatsuma *et al*., 2013; Choi *et al*., 2019). Advanced cancer stages, aggressive tumours, overexpression of HER-2, and negative ER and PR status can potentially contribute to the poor survival in PABC cases. These factors, in addition to a delayed diagnosis and delivery, may also have a negative impact on survival outcomes (Genin et al., 2012). However, there is a lot of debate in the literature regarding the impact of pregnancy on breast cancer prognosis. Although certain studies have shown a relationship between breast cancer and pregnancy, the amount of research in Asian countries is scarce.

1.3 Justification of the Study

The motivation for this study was to conduct research that specifically focused on pregnancy-associated breast cancer in the Malaysian population. There have been conflicting outcomes for PABC patients in different settings. This study is necessary

as more understanding is needed of the behaviour and outcome of PABC in the Asian population, where the research on PABC is limited.

One of the important benefits of this study is that it will outline the trend in PABC outcomes in Malaysia, preparing clinicians with treatment plans and providing information to help them understand any possible complications that may arise during the process.

With the growing incidence of breast cancer in Malaysia, further research on PABC will also enable an understanding of the feasibility of treatment options for women diagnosed with breast cancer during pregnancy. Through this study, the aim is to encourage researchers in low- and middle-income countries to conduct thorough research on PABC, as the number of cases tends to increase.

Thus, this study can serve as a foundation for future research in Malaysia and encourage better healthcare services for PABC patients.

1.4 Research questions

1. Is the survival probability in PABC patients significantly different compared to non-PABC in Kelantan?

2. Is the median survival time significantly different between PABC and non-PABC in Kelantan?

3. Is pregnancy a significant independent prognostic factor for survival in PABC in Kelantan?

1.5 General objective

The general objective was to determine the survival outcomes and prognostic factors of pregnancy-associated breast cancer in Kelantan, Malaysia.

1.5.1 Specific Objectives

1. To compare the survival probabilities between patients with PABC and non-PABC in Kelantan.
2. To compare median survival time between PABC and non-PABC in Kelantan.
3. To determine whether pregnancy is a prognostic factor for survival in PABC in Kelantan.

1.6 Research hypotheses

1. PABC women have significantly lower survival probabilities than non-PABC women.
2. PABC women have significantly shorter median survival time than non-PABC
3. Pregnancy is a significant prognostic factor for survival in PABC women.

CHAPTER 2

LITERATURE REVIEW

2.1 Literature search strategy

Literature search methodologies included phrase searching, keyword searches with Boolean operators, and citation searches. The following phrases were used in phrase searching:

1. “Breast cancer” AND “pregnancy”
2. “Pregnancy-associated breast cancer”
3. “survival” AND “PABC”
4. “outcome” AND “pregnancy-associated breast cancer”.
5. “prognosis” AND “pregnancy associated breast cancer”.

For citation search, author’s name and title of article were used to search for the citation. Search engines used were PubMed, Science Direct, and Google scholar. Most studies were from developed countries, including the United States of America, Canada, and European nations like Sweden, Italy and France. Research from low- and middle-income countries were limited. Review of the obtained publish literature is presented below.

2.2 Pathophysiology and Risk Factors for PABC development

The pathophysiological aspects of PABC are being studied intensively. The most prevalent histological type is invasive ductal carcinoma. When compared to the general breast cancer patient population, the expression of estrogen (ER) and/or progesterone (PR) receptors is frequently reduced in PABC. Ishida *et al*., (1992) conducted a case-control study with data from 18 Japanese institutions. The study included 192 women with breast cancer diagnosed during pregnancy or breastfeeding. The ER-positive rate in pregnant and lactating women was 44%, which was lower than in the control group. Pregnant individuals had considerably lower ER-positive than the control group ($p<0.05$). PR positive was likewise low in both pregnant and lactating women, at 29% ($p<0.01$). Many other studies have also reported similar Er and PR-related findings (Rodriguez *et al.*, 2008; Strasser-Weippl *et al.*, 2015; Kim *et al.*, 2017).

One of the most well-known risk factors is a family history of the disease. A collaborative reanalysis of familial breast cancer evaluated 58209 breast cancer women and 101986 controls. In all, 12.9% breast cancer and 7.3% controls reported that one or more first-degree relatives had breast cancer. One affected relative affected 12% of women with breast cancer, while two or more affected 1%. Having one affected first-degree relative increased the risk by 1.8 times. For women aged 35 years, the risk increased by 2.9 times (Collaborative group on hormonal factors in breast cancer, 2001). This may partially explain the observed relationship between family history and PABC.

PABC patients (diagnosed 2 years following parturition) were more likely to carry BRCA1-2 mutations than non-PABC mothers and nulliparous women (Paris *et al*., 2021). A matched case-control study of 1,260 women with two breast cancer gene (BRCA1 and BRCA2) mutations found that high parity (≥2) was linked with an increased risk of breast cancer (Cullinane *et al*., 2005).

According to several studies, the greatest risk factor is advanced age. A study of 1,248 Slovenian women reported the age at first pregnancy to be linked to an increased risk of breast cancer among parous women (after 25 years) (Robertson *et al.*, 1997). Breastfeeding has been found to protect against breast cancer. Furthermore, it has been shown in several studies to have a protective effect for basal-like tumours. It also appears to lower luminal A tumours risk after a delayed first delivery (Paris *et al*., 2021). According to a meta-analysis, more than 12 months of breastfeeding can lower the risk of BC by 26% (Chowdhury *et al*., 2015). Another meta-analysis involving over 50,000 breast cancer and 100,000 breast cancer-free women found that breastfeeding reduced the lifetime risk of breast cancer by 4.3% for every year (p<0.0001) (Collaborative Group on Hormonal Factors in Breast Cancer, 2002).

2.3 Incidence of PABC

PABC is a rare condition with limited research from low- and middle-income countries. Around 4% of women under the age of 45 are diagnosed with breast cancer during pregnancy or during the first year after giving birth (Anderson *et al.*, 2009;

Eibye *et al.*, 2013; Johansson *et al.*, 2018). The age distribution of PABC coincides with the age profiles of breast cancer and pregnancy, thus, people in the 30-34 age group constitute maximum number of cases (Anderson *et al.*, 2009).

Several population-based studies have reported the incidence rate of PABC. The incidence of the disease varies greatly between populations and calendar years. PABC incidence rates diagnosed during pregnancy (3.0-7.7%) and during the first year after delivery (13.8-32.2%) have been reported to vary from 17.5-39.9 per 100,000 births (Johansson *et al.*, 2020). A population-based study conducted in Lombardo, Italy, reported PABC incidence to be 39.9 per 100,000 pregnancies (Parazzini *et al*., 2017). Another Danish study recorded 17.5 PABC cases per 100,000 pregnancies (Eibye *et al*., 2013) while, a Swedish study reported PABC incidence as 32.4 per 100,000 pregnancies (Anderson *et al*., 2015).

2.4 Nulliparous women and PABC women

Breast cancer in pregnant women is comparable to that in nulliparous women; around 75%-90% of tumours are invasive ductal carcinomas of no specific kind (Ishida *et al.*, 1992; Middleton *et al.*, 2003; Keyser *et al.*, 2012; Callihan *et al.*, 2013). Nagatsuma *et al*. (2013) investigated 526 premenopausal women between the ages of 20 and 44 diagnosed with primary invasive breast cancer between 2000-2007. Women survived for a substantially shorter time than nulliparous women (log-rank test; $p<0.001$). After controlling for tumour features, the hazard ratio for death in women

who gave birth during the previous two years was 2.19 (95% CI, 1.05-4.56; *p*=0.036) higher than in nulliparous women.

Callihan *et al*. (2013) conducted a retrospective study of ≤45-year-old women with breast cancer at the University of Colorado Hospital and The Shaw Cancer Center in Edwards, CO, between 1981 and 2011 to investigate clinicopathologic characteristics and the risk of distant recurrence and death. Breast cancer cases were categorised according to time of diagnosis: nulliparous, pregnant, <5 years postpartum, >5—<10 years postpartum, and ≥10 years postpartum. Their findings show that breast cancer identified within five years of delivery had a 2.7 times higher mortality risk than nulliparous cases.

Patients with PABC are less likely to have invasive lobular carcinoma or other histological types. Previous research has connected postpartum time to an increased chance of developing more aggressive, high-grade with a high nuclear grade and poorly differentiated tumours. PABC has also been linked to lymphovascular invasion, lymph node involvement, and greater tumour size. Compared to nulliparous women, women with PABC reportedly have worse clinical results and disease-free survival, as well as a higher mortality rate in several other studies (Henderson *et al*., 1982; Sullivan *et al*., 2013; Genin *et al*., 2014; Johanson *et al*., 2018). Management of PABC can be difficult and may require proper considerations of the possible risks that can cause harm to the foetus.

2.5 Outcomes in pregnancy-associated breast cancer

There is a lot of debate in the literature about the association of pregnancy with breast cancer prognosis (Dimitrakakis *et al.*, 2013). According to some research, women with PABC had a worse outcome than non-pregnant breast cancer patients while few studies have reported similar survival in both pregnant and non-pregnant breast cancer cohorts.

Mathelin *et al*. (2008) conducted a prospective study with 40 PABC and 61 matched non-pregnant breast cancer patients. Non-pregnant patients outlived PABC in terms of overall survival (OS) (p=0.0001) and disease-free survival (DFS) (p=0.015). Furthermore, pregnant individuals had a worse outcome than post-partum patients (p=0.017). They concluded that pregnancy and the post-partum period increase the aggressiveness of breast cancer, with pregnancy being the most harmful.

Beadle *et al*. (2009) conducted a study to compare distant metastases (DM), locoregional recurrence (LRR), and OS in young PABC and non-PABC patients. The data for 652 patients aged ≤35 years was evaluated retrospectively. One hundred and four breast cancers were linked to pregnancy, comprising both occurring during pregnancy (51) and occurring within a year of delivery (53). Alive patients had a median follow-up of 114 months. When compared to patients without PABC, patients with PABC had more advanced T classification, N classification, and stage group (all p<0.04). There were no statistically significant differences in 10-year rates of LRR (p=0.47). No significant difference was observed in OS (64.6% vs 64.8%; p=0.60).

In a matched controlled study, 32 women with PABC were identified between 1995 and 2007. Data were collected on diagnosis and management. Data related to delivery, foetal and maternal outcomes were also analysed. The PABC and controls were matched based on age (during diagnosis), size of the tumour, and stage of breast cancer. Histological findings in both groups were similar. Estrogen-negative tumours were more prevalent in PABC. OS in patients from both groups was similar (p=0.449). Breast cancer patients diagnosed within a year of parturition had a shorter time to recurrence than controls or gestational cancer patients (p=0.017) (Halaska *et al.*, 2009).

Researchers at two centres in Brazil, undertook a retrospective, paired case-control study. There were 87 PABC patients and 252 control individuals in the research. Using univariate and multivariate analyses, the effect of different covariables (primary tumour size, tumour histology, grade of malignancy, metastasis, interval between first symptoms and diagnosis, axillary lymph node involvement and hormone receptor status) and pregnancy on OS was investigated. The median OS for PABC patients was 30.1 months (95 % CI: 19.4-40.9 months) compared to the control group (53.1 months; 95% CI: 35.1-71.0 months) (p=0.005). Independent factors that significantly influenced disease prognosis were tumour size, malignancy grade, distant metastasis, and pregnancy. Pregnancy was found to be an independent predictive factor in the study. PABC patients had a worse OS rate than non-pregnant patients (Moreira *et al.*, 2010).

In another study, two authors conducted a literature search that was not limited by time or language. In this meta-analysis, 30 papers were considered (3,628 cases and 37,100 non-PABC controls). PABC women had a significantly greater risk of death than controls. The same results were obtained when the study was limited to multivariate analysis. Those diagnosed postpartum had poorer outcome than those with a diagnosis during pregnancy. PABC was also linked to a significantly increased risk of relapse in DFS analysis. Their findings demonstrate that PABC is linked to a poor prognosis, especially in women diagnosed soon after giving birth. This suggests that the pregnant breast microenvironment may have an impact on the biology and, as a result, the prognosis of these cancers (Azim *et al.*, 2012).

Another researcher developed a matched case-case study, which matched 39 PABC cases with premenopausal breast cancer patients based on age, stage, and diagnosis year. The researchers used univariate and multivariate survival analyses, adjusting for stage, grade, oestrogen receptor status, and age at diagnosis. In terms of OS, univariate analysis revealed that non-PABC cases had a longer OS than PABC cases. As a result, a higher stage predicted a shorter life expectancy. Pregnancy was found to be a poor predictive factor for breast cancer in the study (Dimitrakakis *et al.*, 2013).

In a retrospective cohort study, researchers investigated the association of pregnancy on DFS in women with breast cancer history by the ER status. They recruited 333 patients who became pregnant any time after breast cancer and matched them (1:3) with 874 nonpregnant patients with breast cancer on the basis of age, ER, adjuvant

therapy, and year of diagnosis. There was no difference in DFS between the two groups in ER-positive ((Hazard ratio) HR = 0.91; 95% CI, 0.67 to 1.24, *p*=0.55). Similarly, no difference was observed in ER-negative (HR = 0.75; 95% CI, 0.51 to 1.08) cohort (*p*=0.12). The pregnant group, on the other hand, had a better OS with a HR of 0.72 (*p*=0.03). The pregnancy outcome and the interval between pregnancies were not shown to influence the probability of recurrence. (Azim *et al.*, 2013).

A multicentric registry of patients with breast cancer detected during pregnancy generated prospectively and retrospectively between 2003 and 2011 was compared to patients without related pregnancies, with a 45-year age restriction. They wanted to know how patients with breast cancer detected during pregnancy performed. Patients having a postpartum diagnosis were not included in the study. The main analysis used Cox proportional hazards regression to predict DFS and OS based on exposure (pregnant or not), age, grade, and stage. Clinical data included hormone receptor status (ER/PR), HER2 (human epidermal growth factor 2) status and histology. Treatment-related data included type of chemotherapy, trastuzumab use, radiation, and hormonal therapy. There were 447 women with breast cancer detected during pregnancy in the registry. Most patients were from Germany and Belgium, and of all recruited, only 311 were suitable for analysis. There were 865 women in the non-pregnant group. The pregnant group had a median age of 33 years, whereas the non-pregnant patients had a median age of 41 years. The average period of follow-up was 61 months. Pregnancy had a HR of 1.34 (95 % CI: 0.93 to 1.91) for DFS. The HR with respect to OS was 1.19 (95 % CI: 0.73 to 1.93). The results suggest that patients diagnosed during pregnancy have a similar OS to non-pregnant patients (Amant *et al.*, 2013).

A descriptive study conducted at the Cancer Centre of the Pontificia Universidad Católica de Chile, Santiago, Chile, identified 17 patients with invasive PABC between 1999 to 2013. They compared the findings of PABC to those of a cohort of patients with non-pregnancy-related breast cancer (similar age range) treated at the institution during the same period. he median age in the PABC group was 35 years (range: 29– 42 years). Women with PABC had a greater rate of total mastectomy (78.6% versus 40.5%, p=0.02). The estimated OS (75.5% versus 80.5%, p=0.043) was higher in the non-PABC group. Disease-specific survival rates were 83.9% for PABC and 75.5% for unrelated pregnancy breast cancer (p=0.37) (Sanchez *et al*., 2014).

A meta-analysis (including 54 papers) was conducted by a group of researchers in 2020 to understand the prognosis of PABC. They also investigated the dose-response interaction in order to give quantitative evidence for the definition of PABC. They systematically searched for observational studies on the prognosis of PABC published up to June 1, 2019, in PubMed, Embase, and the Cochrane Library and calculated summary-adjusted HRs and 95% confidence intervals for them. Subgroup analyses were conducted depending on the time of diagnosis, the PABC definition, the geographic location, the year of publication, and the HR estimation process. OS, DFS, and cause-specific survival (CSS) were all linked with poor prognosis, with pooled HRs (95% CI) of 1.45 (1.30–1.63), 1.39 (1.25–1.54), and 1.40 (1.17– 1.68), respectively. Non-PABC patients were the comparable reference group. According to subgroup analysis, different definitions of PABC resulted in different outcomes. The dosage response analysis revealed a nonlinear relationship (p<0.001) between the period from the last delivery to the diagnosis of breast cancer and the HR of overall

mortality. Women with PABC diagnosed at 12 months following last delivery had a mortality rate over 60% higher than nulliparous women (HR = 1.59, 95% CI, 1.30–1.82). The rate of mortality was not statistically different at 70 months following the last delivery (HR = 1.14, 95 % CI, 0.99–1.25). To account for the increasing risk, the criteria of PABC should be expanded to encompass patients diagnosed up to about 6 years following the last delivery. According to this meta-analysis, PABC is linked to a poor prognosis (Shao *et al.*, 2020).

2.6 Maternal and Foetal outcome in PABC patients

Cardonick *et al*. (2010) prospectively evaluated 130 women with breast cancer to monitor the disease and perinatal and neonatal outcomes. On follow-up, 103 had primary breast cancer during pregnancy and 8 had a recurrence. Chemotherapy was administered during pregnancy in 104 cases. Three patients miscarried within one month of their first-trimester surgery. The 7% miscarriage rate is not higher than the overall population. A total of 116 infants were delivered by vaginal delivery (64.6%) and caesarean section (31.8%). For four infants, the method of delivery was not known. Low birth weight was reported in three infants, and two had premature-associated complications.

To identify PABC patients, researchers searched the clinical databases of Dana-Farber Center. A retrospective record review was used to gather sociodemographic, breast cancer-related, and treatment data. Pregnancy, maternal and foetal outcomes related information was also collected and analysed. There were 74

patients found, the majority of whom had early-stage breast cancer. During pregnancy, the majority (73.5%) had surgical resection, with 32% having rapid reconstruction. During pregnancy, nearly half (48.6%) patients got anthracycline-based chemotherapy. Nearly a quarter of them were on a dose-dense regimen, with 8.3% also receiving paclitaxel. Over half of the babies were born preterm (37 weeks), with the majority of them scheduled for more maternal cancer treatment. All the new-borns had normal Apgar scores. Almost 90% had birth weights above the 10th percentile. The foetal malformation rate (4.4%) was comparable to the expected population rate (Meisel *et al.*, 2013).

Shechter *et al.* (2018) used the 1999-2012 Healthcare Cost and Utilization Project—Nationwide Inpatient Sample (HCUP-NIS) from the United States to conduct a population-based cohort analysis. The effect of PABC on new-born outcomes was investigated using logistic regression models that were adjusted for maternal baseline factors. Between 1999 and 2012, there were 11, 846,300 deliveries. With 772 instances of PABC diagnosis, the overall incidence was 6.5 cases per 100 000 pregnancies. There was a higher risk of preterm delivery (OR 4.84, 95% CI: 4.055.79) and preterm premature rupture of membranes in pregnancies complicated by breast cancer (OR 1.79, 95% CI: 1.06-3.05). There were no links found between PABC and complications like, intrauterine growth restriction, congenital abnormalities, or foetal death.

In another study, researchers analysed 13 PABC and 66,265 non-PABC patients. PABC patients had a lower mean gestational age at delivery, as well as

increased rates of induction of labour and preterm. The average maternal age upon diagnosis and the gestational age were 34 years and 35 weeks respectively. Diagnosis during the second trimester was most common. PABC patients had a higher rate of induction of labour and caesarean section, and less spontaneous birth ($p< 0.001$). Two patients had their pregnancies terminated. In the non-PABC group, 90.8% of patients delivered after 37 weeks, whereas only 45.4% of PABC delivered after 37 weeks ($p< 0.001$) (Gomez-Hidalgo *et al.*, 2019).

2.7 Pregnancy-associated Breast Cancer (PABC) in Asia

Although Asia has a lower incidence of breast cancer than North America, Western Europe, and Oceania, rates have been rising fast in recent decades. Breast cancer cases in Asian countries now account for 40% of all cases diagnosed globally, and breast cancer mortality has similarly risen among Asian women (Kim et al., 2015). With an average rate of 29.1, breast cancer incidence rates in Asian countries are projected to be one-fourth to one-third of those in historically high-risk countries (Ferlay et al., 2015). More than 600,000 new breast cancer cases were reported in Asia in 2012, making breast cancer the most frequent cancer among Asian women, accounting for 21.2% of all cancer cases in women (Fan et al., 2015).

India, followed by Pakistan, has the highest incidence rates of breast cancer from southern Asia (Ghoncheh et al., 2015), while Japan and South Korea lead from eastern Asia (Fan et al., 2009). Lebanon has the highest ASIR (Age Standardized

Incidence Rate) of 78.7 from West Asia (Roshandel et al., 2014), and Singapore has recorded most cases from south-eastern Asia (Seow et al., 1996).

The age at diagnosis in Asian countries is lower than in high-income countries, with a study detecting 15.5% of cases of breast cancer under the age of 40 in Korean women (Lee et al., 2019), another reporting the average age to be 41.8 years in Bangladesh (Hossain et al., 2014), and the median age of breast cancer diagnosis to be 44 years in Jordan (Abu-Salem, 2002), 45 years in Saudi Arabia (Elkum et al., 2007) and 48-50 years in China (Fan et al., 2009).

Compared to European nations, breast cancer-associated mortality is much higher in Asian countries, with a mortality rate of 231.0 vs. 131.3 (Dhakal et al., 2022). Death from breast cancer accounted for an estimated 231,013 women in Asia in 2012, accounting for 7% of all deaths and 40.8% of cancer deaths, ranking second to lung cancer in women (Fan et al., 2015). On the other hand, the mortality-to-incidence ratios in Asia are substantially greater than in Western countries. Most Asian countries are low- and middle-income countries (LMICs), where breast cancer occurs at a younger age and a later stage, and patients are more likely to die from the disease than in Western countries (Fan et al., 2015).

PABC poses a significant challenge in diagnosis and treatment with limited research from Asian countries. A systematic literature review and narrative synthesis was carried out to identify survival and pregnancy outcomes for PABC patients in Asia. Search engines used were Medline, PubMed, Cochrane Library. The reference

lists of the included English language articles for studies conducted between January 2010 to August 2022 was also searched. The search terms were: pregnancy-associated breast cancer, breast cancer and pregnancy, survival in PABC, prognosis of PABC and pregnancy outcome of PABC patients.

Articles on breast cancer and pregnancy from Asian countries were collected. A total of 11 studies were included after the final screening. The following data were extracted from the included studies by one author and verified by another author: country, date, Study design, patient recruitment period, number of PABC patients, time at diagnosis, the median age at diagnosis, family history, survival outcomes measured (5-year survival rate, disease free survival, event free survival, local recurrence, HR & 95% CI).

Most (72.7%) of the articles were published between 2018-2021 with three of them published on or before 2015 (Nagatsuma *et al.*, 2013; Yang *et al.*, 2014; Strasser-Weippl *et al.*, 2015). Chuang *et al.* (2018) reported data from 2430 PABC patients, presenting one of the largest sample sizes. The smallest series presented 26 PABC patients from a medical centre in northern Taiwan (Yang *et al.*, 2014). Seven studies were based on the case-control study design while four followed the retrospective cohort methodology.

The eleven studies included were from 6 countries: China (4), South Korea (2), Taiwan (2), Japan (1), India (1), and Saudi Arabia (1). More than half of the studies were single-centred with only two reporting data from National databases and one

presenting data from multiple centres in China (Bae *et al.*, 2018; Chuang *et al.*, 2018; Jin *et al.*, 2021). Four studies did not mention whether the PABC patients were diagnosed at antepartum or postpartum (Strasser-Weippl *et al.*, 2015; Bae *et al.*, 2018; Suleman *et al.*, 2019; Han *et al.*, 2020). Of the remaining, 262 cases were diagnosed during pregnancy while 2662 cases were diagnosed after birth. Five studies reported on the exact survival rate observed in PABC patients, while the rest mentioned details related to prognosis and DFS with only three reporting on pregnancy outcomes (Nagatsuma *et al.*, 2013; Yang *et al.*, 2014; Chuang *et al.*, 2018; Suleman *et al.*, 2019; Choi *et al.*, 2019; Jin *et al.*, 2021; Zhang *et al.*, 2021; Bajpai *et al.*, 2021).

In the majority of studies, the survival rate was found to be lower in PABC than their non-pregnant counterparts. The survival rate of PABC group was lower in five studies (Nagatsuma *et al.*, 2013; Yang *et al.*, 2014; Chuang *et al.*, 2018; Choi *et al.*, 2019; Suleman *et al.*, 2019). A study from Japan observed that young breast cancer patients who had just given birth had tumours with more aggressive characteristics and poorer prognoses than individuals who had given birth less recently or were nulliparous. The 5-year survival rate for PABC women with <2 years of pregnancy was observed to be comparatively very low (64.3% v/s 90.6%) than non-PABC women (Nagatsuma *et al.*, 2013).

A retrospective study conducted in a tertiary setting in Saudi Arabia from January to December 2014 reported on a total of 110 PABC patients and 114 non-pregnant patients. Patients in the PABC group were much younger (median age- 34 years, 20 to 45 years) compared to the non-PABC group, in which the median age was