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Breast cancer treatment modalities, treatment delays, and survival in Brunei Darussalam

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Abstract

Introduction Breast cancer remains a leading cause of cancer-related mortality globally. This study aims to examine the demographic variables and effects of different treatment modalities and treatment delays on overall and relative survival rates of breast cancer patients in Brunei Darussalam.

Methods This retrospective study analysed data from the Brunei Darussalam Cancer Registry on breast cancer cases diagnosed and treated between 2013 and 2022. Statistical analyses included descriptive statistics to characterise the study population, Kaplan-Meier estimates to compare survival curves of different groups, Log rank tests to determine significant differences in survival rates among groups, and Cox Proportional Hazard (PH) models to estimate hazard ratios (HRs) and identify predictors of survival outcomes. Overall survival (OS) and relative survival (RS) rates were calculated.

Results Out of the 431 women treated for breast cancer, the majority were diagnosed at the regional stage (45.7%), with 39.0% at the localised stage. Over half (55.4%) of the diagnoses occurred in women aged 40 to 59, while about a quarter (25.5%) were in the 60–69 age group. Surgery was the most common first-line treatment modality (55.9%), with a median time to treatment of 37 days, followed by chemotherapy (30.6%). More than half of the patients (62.9%) were treated within 60 days of diagnosis. Treatment varied by age and cancer stage, with younger patients more likely to undergo surgery and older patients more likely to receive chemotherapy or hormonal therapy. Survival rates were high for patients receiving only surgery (5-year RS: 98.7%, OS: 92.3%), and significant survival differences were found for cancer stage and treatment delay, with a HR of 2.5 for delays over 60 days. Multivariate analysis showed that patients with distant stage cancer had a significantly higher risk of death (HR = 15.3) compared to localised stage.

Conclusion This study highlights the impact of treatment modalities and delays on breast cancer survival in Brunei Darussalam, emphasising the need for timely treatment to improve survival rates. Our findings suggest that ensuring breast cancer treatment initiation within two months post-diagnosis may enhance patient outcomes, supporting potential policy targets for timely access to care.

Keywords Breast cancer, Treatment delays, Treatment modalities, Cancer mortality, Survival rates, Brunei Darussalam, Surgery, Cox proportional hazards model

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Introduction

Cancer is the leading cause of mortality globally, with approximately 9.3 million deaths annually [1]. In 2022, there were an estimated 20 million new cancer cases were reported globally, and 9.7 million deaths. Breast cancer alone constituted 2.3 million cases (11.6%) and 670,000 deaths (6.9%) [2]. It is estimated that 1 in 27 women is diagnosed with breast cancer, and 1 in 48 women dies from it [3]. In 2020, breast cancer accounted for 15.5% of all cancer-related fatalities globally [4].

In Brunei Darussalam, cancer is also the leading cause of death, accounting for 19% of all mortalities, with breast cancer ranking as the second deadliest across all gender and age categories [5, 6]. Brunei Darussalam is a small nation with a population of about 450,500, comprising of 52.8% males and 47.2% females, with ethnicities consist of Malay (76.8%), Chinese (9.6%), and Others (13.6%). These residents are spread across four districts: Brunei-Muara (72.4%), Belait (14.9%), Tutong (10.6%), and Temburong (2.1%) [7]. Medical services in Brunei Darussalam are provided free of charge to its citizens and permanent residents, as part of the universal health coverage commitment by the government [8].

Cancer treatments in Brunei Darussalam follows international management guidelines and include surgery, radiotherapy, chemotherapy, hormonal therapy, and others such as immunotherapy and target therapy. Treatment plans are developed by multidisciplinary teams, including oncologists and surgeons, based on cancer stage, pathology findings, and patient's conditions. Surgery procedures such as lumpectomy (partial mastectomy) and mastectomy are commonly carried out in combination with other neoadjuvant and adjuvant therapies including chemotherapy, radiotherapy and hormonal therapy [9].

Despite the availability of treatments, delays in the initiation of these treatments can significantly impact patient outcomes. Treatment delays, defined as the time from diagnosis to the start of treatment exceeding the recommended timeframe, have been associated with poorer survival rates in breast cancer patients [10]. Factors contributing to these delays can include sociocultural factors, patient health-seeking behaviours, financial and logistic challenges within healthcare facilities [11, 12]. Although previous studies in Brunei Darussalam have examined survival rates among breast cancer patients in Brunei Darussalam [11, 13], a notable gap remains regarding how specific treatment modalities and treatment delays interact to influence survival outcomes. This gap is especially important in a setting where financial barriers to treatment are minimal under universal health coverage, yet other factors might still lead to delayed treatment initiation.

This study aims to address this gap by comparing demographic variables among breast cancer patients who have received treatment modalities such as surgery, chemotherapy, radiotherapy, hormonal therapy, and to investigate the effects of various treatment modalities and potential treatment delays influence overall and relative survival rates of breast cancer patients in Brunei Darussalam.

Materials and methods

Study design and data source

This retrospective study used data from a population-based cancer registry, the Brunei Darussalam Cancer Registry (BDCR) from the Ministry of Health, focusing on patients diagnosed with breast cancer and received treatment in Brunei Darussalam between 1 January 2013 and 31 December 2022 (10-year study period). The follow-up period extended until 31 May 2023.

Variables and classification

Demographic and clinical variables included ethnicity (Malay, Chinese, or Others), district (Brunei-Muara, Belait, Tutong or Temburong), cancer stage (Localised, Regional, Distant, and Unknown), treatment types (Surgery, Chemotherapy, Radiotherapy, Hormonal therapy, Others), histology (Ductal carcinoma, Medullary, Mucinous, Lobular, Tubular, Papillary, Others), delay in treatment groups (≤60, > 60, unknown) alongside patient demographics such as date of birth, age of diagnosis (<40, 40–49, 50–59, 60–69, > 70), date of incidence, and date of death.

Cancer stage is categorised according to the Surveillance, Epidemiology, and End Results Program (SEER) classifications, with stages defined as follows: localised (SEER Summary Stage 1), regional (SEER Summary Stages 2 to 5), distant (SEER Summary Stage 7), and unknown (SEER Summary Stage 9) [14]. The SEER program serves as a comprehensive source of information on cancer incidence and survival in the United States.

Histology, examination of the microscopic structure of cancerous tissues classified cases into several categories: ductal carcinoma (codes 8500, 8501, 8503, 8504), medullary carcinoma (codes 8510, 8513, 8514), mucinous carcinoma (code 8480), lobular carcinoma (codes 8520, 8521, 8522, 8523, 8524), tubular carcinoma (code 8211), and papillary carcinoma (code 8050) [15, 16]. Cases not fitting these classifications were grouped as 'Others'.

First-line treatment type refers to the treatment chosen by the oncologist as the primary intervention, based on the patients' specific circumstances. Treatment delay is measured by the duration from the diagnosis of breast cancer to the start of the first treatment. Delay groups were categorised as ≤60 days, > 60 days [11, 17], and unknown. The 'unknown' category is used when

treatment has been administered, but the date of treatment is unavailable. Adjuvant treatment refers to the use of additional therapies following first-line treatment to reduce the risk of recurrence [18].

Study population

The study included only citizens and permanent residents of Brunei Darussalam who have been diagnosed and treated with breast cancer. Observations of males and in-situ cases (a total of 22) were excluded from the analysis.

Statistical analysis

Descriptive statistics, including counts and median, were used to summarise the demographic and clinical characteristics of the study population. The Kaplan-Meier method was used to compare the survival curves of different groups, such as types of first-line treatment, and treatment delays. The Log-rank test was used to assess whether there is a significant difference in survival rates among these groups.

To further examine the association between various covariates such as demographic factors, treatment type, and delay status, and the hazard of death, we used the Cox Proportional Hazards (Cox PH) regression in both univariate and multivariable analyses. These models were used to estimate the hazard rate of death and its confidence interval. The Cox PH model assumes that hazard ratios for the covariates remain constant over time, known as the proportional hazards assumption. Mathematically, for a given time t, the hazard function $h(t)$ is modelled as:

$$h(t) = h_0(t) \exp\left(\sum_{i=1}^{k} \beta_i X_i\right)$$

where $h_0(t)$ is the baseline hazard function, and $X_1, X_2, \ldots, X_k$ are the covariates of interest with corresponding coefficients $\beta_1, \beta_2, \ldots, \beta_k$. The exponentiated coefficients $\exp(\beta)$ represent the hazard ratios, indicating the relative change in the hazard of death associated with a one-unit increase in the covariate or the presence of a categorical factor, after adjusting for other variables in the model.

We tested the proportional hazards assumption using scaled Schoenfeld's residuals for each model and visually examined plots of these scaled Schoenfeld's residuals. The results of these diagnostic checks did not indicate any violations of the proportional hazards assumption. The Kruskal-Wallis test was used to find the difference between several independent groups. The Chi-squared test was used to evaluate the association between categorical variables, and for small sample sizes with less than five data points per group, the Fisher Exact test was used.

Overall survival rate was defined as the proportion of individuals within the study who survived, irrespective of the cause of death. Relative survival rate was calculated as the ratio of observed survivors within breast cancer patients to the expected number of survivors within a cancer-free population. This metric evaluates survival among breast patients who died from the cancer rather than from other causes. To compute the relative survival rates, the life table of Brunei Darussalam and Ederer II method [19] were used. Overall survival was analysed using the Kaplan-Meier method. A p-value less than 0.05 was considered to be statistically significant. All analyses were conducted using R software (version 4.3.1) [20].

Ethical approval

This study adhered to ethical principles and guidelines and received approval from the Medical and Health Research Ethics Committee of the Ministry of Health, Brunei Darussalam [Ref: MHREC/MOH/2022/1(1)]. This approval ensures that the research was conducted in accordance with ethical standards, safeguarding participant rights, privacy, and data confidentiality. Furthermore, ethical considerations were observed at all stages of the study, and the researchers ensured that the data collected was used only for the intended research objectives. Informed consent was not required for this study, as the data used were de-identified and there was no direct contact with participants. The waiver of consent was approved by the Medical and Health Research Ethics Committee, in compliance with national regulations.

Results

In examining the demographic characteristics of 431 women who were diagnosed with breast cancer and received treatment, the regional stage was the most common (45.7%), followed by localised stage (39.0%) (Table 1). The age distribution indicates a higher incidence among women aged 40 to 59, who accounted for over half of the diagnoses (55.4%). The data also show a higher proportion of breast cancer diagnoses and treatment among Chinese women (18.3%) compared to their representation in the population (9.6%). Geographically, majority of the cases were reported in the Brunei-Muara district (61.3%), while the Temburong district recorded the least (2.6%). Histologically, ductal carcinoma was the predominant histological type (75.2%). Among the women treated for breast cancer, surgery was the most frequently chosen first-line treatment (55.9%), followed by chemotherapy (30.6%). More than half of the patients (62.9%) were treated within the first 60 days after diagnosis.

Table 2 presents the demographics and characteristics of the types of first-line treatment. The median age at diagnosis varied by treatment type, with surgery and

Table 1 Demographics characteristics as variables for 431 women diagnosed and treated with breast cancer

Variables			
Median age at diagnosis in years (IQR)		**55.2 (46.4–63.2)**	
		n	**%**
Stage	Localised	168	39.0
	Regional	197	45.7
	Distant	45	10.4
	Unknown	21	4.9
Age at diagnosis	< 40	38	8.8
	40 to 49	122	28.3
	50 to 59	117	27.1
	60 to 69	110	25.5
	> 70	44	10.2
Ethnicity	Malay	331	76.8
	Chinese	79	18.3
	Others	21	4.9
District	Brunei-Muara	264	61.3
	Belait	84	19.5
	Tutong	57	13.2
	Temburong	11	2.6
	Unknown	15	3.5
Histology	Ductal	324	75.2
	Medullary	8	1.9
	Mucinous	14	3.2
	Lobular	36	8.4
	Tubular	3	0.7
	Papillary	5	1.2
	Others	41	9.5
First-line treatment	Surgery	241	55.9
	Chemotherapy	132	30.6
	Radiotherapy	5	1.2
	Hormonal therapy	40	9.3
	Others	13	3.0
Delay in treatment	≤ 60	271	62.9
	> 60	150	34.8
	Unknown	10	2.3

chemotherapy patients averaging around 53.3 to 55.1 years. However, patients who underwent radiotherapy and hormonal therapy were older, with median ages of 64.2 and 65.4 years, respectively. The median time from diagnosis to first-line treatment for surgery was 37 days (IQR: 24–56), and 37 days (IQR: 27–66) for chemotherapy. Radiotherapy had a median time of 29 days (IQR 14–70), while hormonal therapy had the shortest median time of 25.5 days (IQR:17–50.5).

Most patients who underwent surgery as a first-line treatment were diagnosed at localised or regional stages (92.6%). For chemotherapy, the majority of the patients were diagnosed in the regional stage (53.8%). Only 5 patients underwent radiotherapy, most of whom were diagnosed at regional and distant stages (80.0%). Hormonal therapy was provided to the majority of patients diagnosed at localised and regional stages (62.5%).

The age distribution of patients receiving different treatments varied, with those under 50 being least likely to receive radiotherapy as first-line treatment. Surgery was the most common treatment modalities among those aged 40–69 age range (78.9%), whereas chemotherapy was more common among 50–59 age group (35.6%). Hormonal therapy was mainly received by those in the 60–69 (42.5%). Histologically, ductal carcinoma was the most common type across all treatments, especially in radiotherapy (80.0%), chemotherapy (81.1%), and surgery (73.4%) groups. Majority of the patients received their treatment within 60 days of diagnosis, especially for surgery (71.4%) and hormonal therapy (70.0%). Fisher's Exact Test revealed a significant association between treatment and cancer stage ($p < 0.001$), age at diagnosis ($p < 0.001$), ethnicity ($p = 0.011$), and delay in treatment ($p < 0.001$)

Figure 1 shows the overall survival curves of the types of first-line treatment, stratified by cancer stage. Patients with localised stage breast cancer consistently demonstrate the highest survival rates across all first-line treatment types. In contrast, patients with distant stage breast cancer had poorer survival, especially those who received surgery, chemotherapy, and hormonal therapy, where the survival rates decrease over time. Radiotherapy had relatively consistent survival outcomes across different stages. Although survival trends differed across stages, Cox proportional hazards and log-rank tests showed no statistically significant differences in survival across different first-line treatments within each cancer stage ($p > 0.05$).

Table 3 presents the survival rates and patient distributions by first-line and adjuvant treatments. The majority of patients (47.7%) underwent surgery alone, with a 5-year relative survival rate (RS) of 98.7% (95% CI: 93.9, 100.0) and an overall survival rate (OS) of 92.3% (95% CI: 82.6, 96.7). When surgery was combined with chemotherapy (22.8%), patients had an RS of 94.1% (95% CI: 83.8, 100.0) and an OS of 90.4% (95% CI: 72.2, 96.9). Smaller groups of patients received first-line surgery in combination with radiotherapy (6.2%) or hormonal therapy (12.5%), both of which had RS and OS rates at 100.0%. Combinations involving two or more adjuvant treatments, such as surgery + chemotherapy + radiotherapy (5.4%) had an RS of 92.0% (95% CI: 77.0, 100.0) and an OS of 90.9% (95% CI: 50.8, 98.7). On the other hand, the combination of surgery, chemotherapy, and hormonal therapy (1.7%) had an RS and OS of 0.0%, although this should be interpreted with caution due to the small sample size ($n = 4$). Other combinations such as surgery + radiotherapy + hormonal therapy (2.9%), as well as,

Table 2 Demographics characteristics for first-line treatment of 431 women diagnosed

Variables		First-line treatment					*p*-value [a]
		Surgery	Chemotherapy	Radiotherapy	Hormonal therapy	Others	
Median age at diagnosis in years (IQR)		55.1 (45.1–63.9)	53.3 (45.8–59.7)	64.2 (60.0–69.9)	65.4 (55.0–69.8)	56.1 (47.6–63.3)	
Median time to first-line treatment in days (IQR)		37 (24–56)	37 (27–66)	29 (14–70)	25.5 (17–50.5)	66 (63–75)	
		n (%)					
Stage	Localised	118 (49.0)	36 (27.3)	0 (0.0)	13 (32.5)	1 (7.7)	**< 0.001**
	Regional	105 (43.6)	71 (53.8)	2 (40.0)	12 (30.0)	7 (53.8)	
	Distant	9 (3.7)	21 (15.9)	2 (40.0)	10 (25.0)	3 (23.1)	
	Unknown	9 (3.7)	4 (3.0)	1 (20.0)	5 (12.5)	2 (15.4)	
Age at diagnosis	< 40	22 (9.1)	15 (11.4)	0 (0.0)	1 (2.5)	0 (0.0)	**< 0.001**
	40 to 49	71 (29.5)	38 (28.8)	0 (0.0)	8 (20.0)	5 (38.5)	
	50 to 59	60 (24.9)	47 (35.6)	2 (40.0)	4 (10.0)	4 (30.8)	
	60 to 69	59 (24.5)	29 (22.0)	2 (40.0)	17 (42.5)	3 (23.1)	
	> 70	29 (12.0)	3 (2.3)	1 (20.0)	10 (25.0)	1 (7.7)	
Ethnicity	Malay	176 (73.0)	114 (86.4)	3 (60.0)	26 (65.0)	12 (92.3)	**0.011**
	Chinese	52 (21.6)	14 (10.6)	2 (40.0)	11 (27.5)	0 (0.0)	
	Others	13 (5.4)	4 (3.0)	0 (0.0)	3 (7.5)	1 (7.7)	
District	Brunei-Muara	148 (61.4)	82 (62.1)	4 (80.0)	23 (57.5)	7 (53.8)	0.964
	Belait	48 (19.9)	24 (18.2)	1 (20.0)	8 (20.0)	3 (23.1)	
	Tutong	30 (12.4)	20 (15.2)	0 (0.0)	5 (12.5)	2 (15.4)	
	Temburong	6 (2.5)	2 (1.5)	0 (0.0)	2 (5.0)	1 (7.7)	
	Unknown	9 (3.7)	4 (3.0)	0 (0.0)	2 (5.0)	0 (0.0)	
Histology	Ductal	177 (73.4)	107 (81.1)	4 (80.0)	26 (65.0)	10 (76.9)	0.075
	Medullary	5 (2.1)	2 (1.5)	0 (0.0)	1 (2.5)	0 (0.0)	
	Mucinous	8 (3.3)	4 (3.0)	0 (0.0)	2 (5.0)	0 (0.0)	
	Lobular	18 (7.5)	7 (5.3)	0 (0.0)	10 (25.0)	1 (7.7)	
	Tubular	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Papillary	3 (1.2)	0 (0.0)	0 (0.0)	1 (2.5)	1 (7.7)	
	Others	27 (11.2)	12 (9.1)	1 (20.0)	0 (0.0)	1 (7.7)	
Delay in treatment	≤ 60	172 (71.4)	68 (51.5)	3 (60.0)	28 (70.0)	0 (0.0)	**< 0.001**
	> 60	65 (27.0)	61 (46.2)	2 (40.0)	9 (22.5)	13 (100.0)	
	Unknown	4 (1.7)	3 (2.3)	0 (0.0)	3 (7.5)	0 (0.0)	

[a]p-value from the Fishers Exact test

surgery + chemotherapy + radiotherapy + hormonal therapy (0.8%), had RS and OS of 100.0% for both. There is a statistically significant difference in survival outcomes among patients receiving different types of adjuvant treatment following surgery as the first-line treatment $(p < 0.001)$.

Patients treated with chemotherapy alone (68.9%) had 5-year RS of 85.0% (95% CI: 73.1, 98.9) and an OS of 82.0% (95% CI: 65.0, 91.2). Combining chemotherapy with other treatments was associated with higher survival rates: patients who received chemotherapy with surgery (16.7%), radiotherapy (0.8%), or hormonal therapy (1.5%), had RS and OS rates of 100.0% in each case. However, the combination of chemotherapy + surgery + radiotherapy (3.0%) had lower survival rates, with an RS of 53.8% (95% CI: 23.8, 100.0) and an OS of 50.0% (95% CI: 5.8, 84.5).

Radiotherapy was used as a first-line treatment in a very small group of patients ($n = 5$). Despite the limited sample size, radiotherapy, whether used alone or in combination with other therapies, generally resulted in excellent outcomes, with RS and OS rates of 100.0% in most cases. However, the small number of patients treated with radiotherapy requires careful interpretation of these results.

Patients who received hormonal therapy alone (45.0%) had an RS of 90.5% (95% CI: 76.8, 100.0) and an OS of 88.5% (95% CI: 61.4, 97.0). These survival rates were higher when hormonal therapy was combined with surgery (27.5%) or chemotherapy (2.5%), each reaching 100.0% for both RS and OS. In cases where two adjuvant treatments were added to hormonal therapy, the RS and OS were 100.0%, except for the single patient (2.5%) who received surgery and radiotherapy, whose RS was 4.3% (95% CI: 0.6, 30.5) and OS of 0.0%. Patients who received all four treatments (5.0%) also achieved 100.0% RS and OS when hormonal therapy was the first-line treatment.

The log-rank analysis revealed a significant difference in survival between cancer stages ($p < 0.001$) and delays

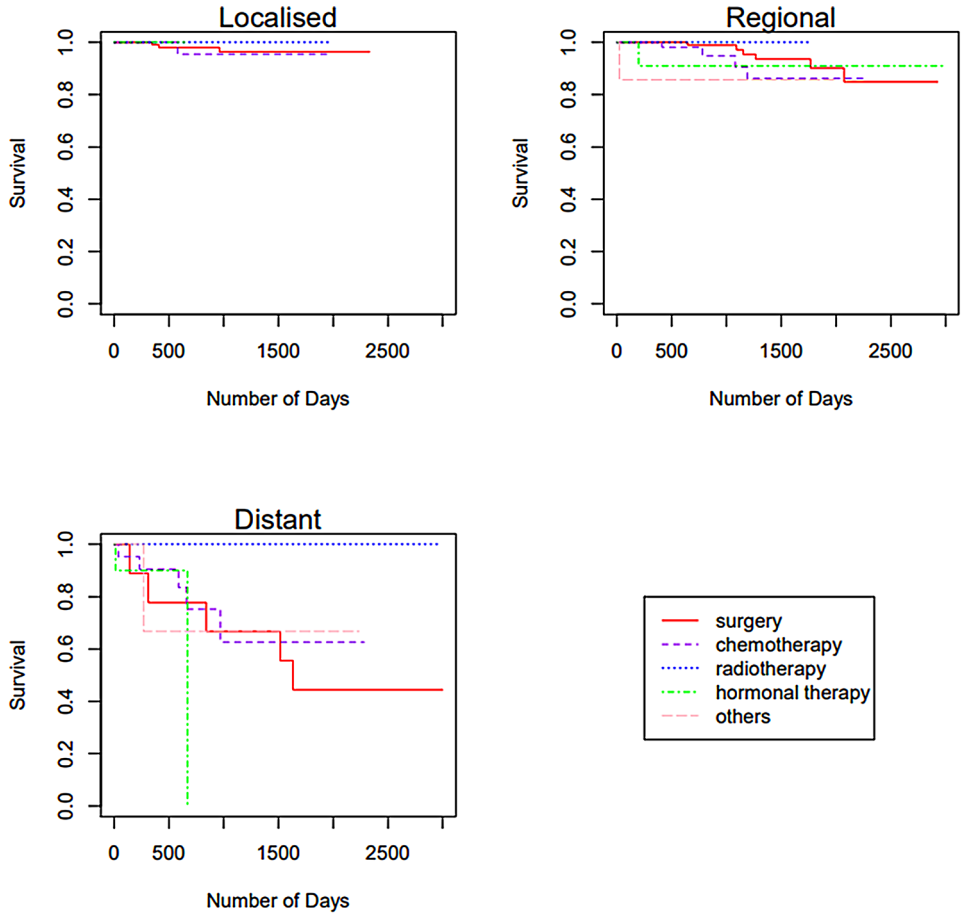

Fig. 1 Overall survival rate of first-line treatment stratified by cancer stage

in treatment ($p = 0.020$) (Table 4). In the univariate Cox proportional hazards analysis, using the localised stage as the reference, the distant stage showed a significant difference ($p < 0.001$) with a hazard ratio (HR) of 13.6. Compared to delays of less than 60 days, a delay of more than 60 days was associated with an increased HR of 2.5 ($p = 0.012$). Furthermore, compared to surgery as the reference, the others category showed a significant difference ($p = 0.018$) with HR of 4.5. In the multivariate Cox proportional hazard analysis, after adjusting for all other variables, the distant stage remained significant compared to the localised stage (HR = 15.3; $p < 0.001$). However, the association between delays in treatment exceeding 60 days and survival outcomes was no longer statistically significant ($p = 0.358$).

The median age at diagnosis was slightly lower for the delay group of less than 60 days after diagnosis (group 1) at 55.1 years (IQR: 45.8–63.2), compared to 56.1 years (IQR: 46.4–63.4) for the group with delays of more than 60 days (group 2), although both groups showed a broad age distribution (Table 5). The median delay time to first treatment for all patients was 37 days (IQR: 23–56). A larger proportion of group 1 patients were diagnosed at regional (45.4%) or localised (42.8%) stages, while group 2 had a higher percentage of patients with distant stage (16.0%) compared to group 1. Age distribution among group 1 was spread across the 40 to 49 years old (28.8%), 50 to 59 years old and 60 to 69 years old (25.8% each), with the majority of patients in group 2 aged 50 to 59 years (29.3%). Histology showed varied distributions, with ductal carcinoma being the most common type in both groups (76.4% in group 1 and 73.3% in group 2).

The log-rank test showed significant differences in survival outcomes between the two delay groups in several subgroups. Patients aged 50 to 59 at diagnosis had a highly significant difference in survival ($p = 0.005$) between the two delay groups, as did patients with ductal histology ($p < 0.001$). Additionally, there was a significant difference for patients living in the Brunei-Muara district ($p = 0.03$). A borderline significant difference in survival was observed for patients with localised cancer stage ($p = 0.05$). However, the analysis of ethnicity did not show statistically significant differences between the groups with delays of less than 60 days and more than 60 days ($p > 0.05$).

Table 3 Survival rates and patient distributions by first-line treatment and adjuvant treatments ($n=431$)

					5-year SR	
Variables		**n**	**%**	**p-value** [a]	**RS (95% CI)**	**OS (95% CI)**
Surgery	Surgery only	115	47.7	**0.001**	98.7 (93.9, 100.0)	92.3 (82.6, 96.7)
	Surgery + Chemotherapy	55	22.8		94.1 (83.8, 100.0)	90.4 (72.2, 96.9)
	Surgery + Radiotherapy	15	6.2		100.0	100.0
	Surgery + Hormonal Therapy	30	12.5		100.0	100.0
	Surgery + Chemotherapy + Radiotherapy	13	5.4		92.0 (77.0, 100.0)	90.9 (50.8, 98.7)
	Surgery + Chemotherapy + Hormonal Therapy	4	1.7		0.0	0.0
	Surgery + Radiotherapy + Hormonal Therapy	7	2.9		100.0	100.0
	Surgery + Chemotherapy + Radiotherapy + Hormonal Therapy	2	0.8		100.0	100.0
Chemotherapy	Chemotherapy only	91	68.9	0.300	85.0 (73.1, 98.9)	82.0 (65.0, 91.2)
	Chemotherapy + Surgery	22	16.7		100.0	100.0
	Chemotherapy + Radiotherapy	1	0.8		100.0	100.0
	Chemotherapy + Hormonal Therapy	2	1.5		100.0	100.0
	Chemotherapy + Other	5	3.8		100.0	100.0
	Chemotherapy + Surgery + Radiotherapy	4	3.0		53.8 (23.8, 100.0)	50.0 (5.8, 84.5)
	Chemotherapy + Surgery + Hormonal Therapy	5	3.8		100.0	100.0
	Chemotherapy + Surgery + Other	2	1.5		100.0	100.0
Radiotherapy	Radiotherapy only	1	20.0	-	100.0	100.0
	Radiotherapy + Chemotherapy	1	20.0		100.0	100.0
	Radiotherapy + Chemotherapy + Hormonal Therapy	1	20.0		100.0	100.0
	Radiotherapy + Chemotherapy + Other	2	40.0		100.0	100.0
Hormonal Therapy	Hormonal Therapy only	18	45.0	0.400	90.5 (76.8, 100.0)	88.5 (61.4, 97.0)
	Hormonal Therapy + Surgery	11	27.5		100.0	100.0
	Hormonal Therapy + Chemotherapy	1	2.5		100.0	100.0
	Hormonal Therapy + Other	3	7.5		100.0	100.0
	Hormonal Therapy + Surgery + Chemotherapy	1	2.5		100.0	100.0
	Hormonal Therapy + Surgery + Radiotherapy	1	2.5		4.3 (0.6, 30.5)	0.0
	Hormonal Therapy + Chemotherapy + Radiotherapy	2	5.0		100.0	100.0
	Hormonal Therapy + Radiotherapy + Other	1	2.5		100.0	100.0
	Hormonal Therapy + Radiotherapy + Chemotherapy + Surgery	2	5.0		100.0	100.0

[a]p-value from the log-rank test; SR: Survival rate; RS: Relative survival rate; OS: Overall survival rate; CI: Confidence interval

Figure 2 presents the relative survival (RS) and overall survival (OS) rates according to treatment delays for 431 women diagnosed and treated for breast cancer. Among those with a treatment delay of less than 60 days after diagnosis, the 1-year RS was 99.6% with an OS of 98.4%, decreasing to 96.8% (RS) and 91.7% (OS) at 5-year. In contrast, patients treated more than 60 days after diagnosis had a 1-year RS of 97.4% and an OS of 96.6%, which declined to 83.8% (RS) and 81.5% (OS) at 5 years.

Discussion

Our study provides a comprehensive analysis of the demographic and clinical characteristics of 431 women diagnosed and treated for breast cancer in Brunei Darussalam from 2013 to 2022. The most common stage at diagnosis was regional (45.7%), followed by localised (39.0%), indicating a need for enhanced early detection efforts to reduce the number of cases diagnosed at more advanced stages. The age distribution showed a higher incidence among women aged 40 to 59, consistent with findings from studies in Canada [21], Singapore [22], and Malaysia [23]. This trend highlights the importance of targeted screening programs for middle-aged women, aligning with the US Preventive Services Task Force's recommendation to begin screening in their forties [24].

Breast cancer incidence was highest in the Brunei-Muara district and among Malay women, reflecting Brunei's population distribution, where 76.8% are Malay, 9.6% are Chinese and 13.6% are of other ethnicities [7]. Ductal carcinoma was the most common histological type (75.2%), consistent with global data where ductal carcinoma represents about 80% of all breast cancer cases [25], and comparable prevalence was observed regionally: 72.1% in Singapore [26], 77.1% in Penang [27], and 89.3% in Kuala Lumpur [28]. Surgical intervention was the most common treatment in our study, followed by chemotherapy. A majority of patients (62.9%) received treatment within 60 days of diagnosis.

Our study found significant differences in the distribution of cancer stages among the different first-line treatment types, indicating that the modality of first-line treatment is significantly associated with the stage of

Table 4 Univariate and multivariate Cox proportional hazard and log-rank test analyses for factors affecting survival outcomes in breast cancer patients

Variables		Cox Proportional Hazard				Log-rank test	
		Univariate		Multivariate		Chi-squared test	p-value [b]
		HR	p-value [a]	HR	p-value [a]		
Stage	Localised					41.8	**< 0.001**
	Regional	2.3	0.144	2.3	0.166		
	Distant	13.6	**< 0.001**	15.3	**< 0.001**		
	Unknown	3.2	0.184	1.8	0.541		
Age at diagnosis	< 40					4	0.400
	40 to 49	8.4×10^{7}	0.997	1.8×10^{8}	0.998		
	50 to 59	7.5×10^{7}	0.997	1.4×10^{8}	0.998		
	60 to 69	6.2×10^{7}	0.997	1.7×10^{8}	0.998		
	> 70	1.1×10^{8}	0.997	1.5×10^{8}	0.998		
Ethnicity	Malay					4.3	0.100
	Chinese	1.9	0.110	1.7	0.274		
	Others	4.2×10^{-8}	0.997	4.7×10^{-9}	0.998		
District	Brunei-Muara					2	0.700
	Belait	1.8	0.175	1.3	0.563		
	Tutong	1.3	0.606	0.6	0.483		
	Temburong	1.5	0.672	2.7	0.378		
	Unknown	1.1	0.915	0.3	0.338		
Histology	Ductal					2.7	0.800
	Medullary	3.6×10^{-8}	0.997	3.7×10^{-9}	0.998		
	Mucinous	1.0	0.986	3.6	0.235		
	Lobular	0.4	0.360	0.3	0.225		
	Tubular	3.6×10^{-8}	0.999	8.7×10^{-10}	1.000		
	Papillary	3.6×10^{-8}	0.998	6.9×10^{-10}	1.000		
	Others	1.2	0.753	0.8	0.729		
First-line treatment	Surgery					8.1	0.090
	Chemotherapy	1.9	0.115	1.4	0.490		
	Radiotherapy	1.1×10^{-7}	0.997	1.2×10^{-9}	0.999		
	Hormonal therapy	1.9	0.331	1.9	0.347		
	Others	4.5	**0.018**	1.9	0.427		
Delay in treatment	≤ 60					7.9	**0.020**
	> 60	2.5	**0.012**	1.5	0.358		
	Unknown	1.5×10^{-7}	0.996	2.8×10^{-9}	0.999		

[a]p-value from the CoxPH test; [b]p-value from the log-rank test

cancer at diagnosis. According to our data, patients with localised stage cancer were more likely to undergo surgery, while those with regional stage cancer were more likely to receive chemotherapy. Most localised stages are treated with surgery, followed by radiotherapy or endocrine therapy for five years to eliminate any remaining cancer cells [29]. Regional stages are often treated using chemotherapy, endocrine therapy, or immunotherapy before surgery, and advanced stages with distant metastasis focus on relieving symptoms, which may involve palliative care [30]. However, treatment decisions can vary; for example, patients with localised cancer may receive chemotherapy in cases such as triple-negative or HER-2 positive breast cancers, while some patients with regional cancer may undergo surgery depending on tumour characteristics and other clinical considerations. Treatment decisions are complex and depend on various factors, including tumour characteristics, patient health status, and preferences. This highlights the importance of a multidisciplinary team approach in deciding the first-line treatment to ensure the most appropriate and personalised care for each patient.

We also observed a significant difference in age group distribution among various first-line treatment types. Younger patients (< 50 years) were more likely to receive surgery as the first-line treatment, whereas older patients (> 60 years) were more likely to receive radiotherapy or hormonal therapy, which are less invasive and commonly indicated as an adjuvant treatment to improve the quality of life of breast cancer patients. This aligns

Table 5 Demographics characteristics of patients by time to first treatment delay groups ($\leq$ 60 days vs $>$ 60 days)

Variables		Time to first treatment, in days		*p*-value [a]
		$\leq$ 60	$>$ 60	
Median age at diagnosis in years (IQR)		55.1 (45.8–63.2)	56.1 (46.4–63.4)	
Median delay time in days (IQR)		30 (19–42)	97 (77–158)	
		n (%)		
Stage	Localised	116 (42.8)	50 (33.3)	**0.050**
	Regional	123 (45.4)	67 (44.7)	0.900
	Distant	20 (7.4)	24 (16.0)	0.700
	Unknown	12 (4.4)	9 (6.0)	0.500
Age at diagnosis	< 40	26 (9.6)	12 (8.0)	-
	40 to 49	78 (28.8)	41 (27.3)	0.600
	50 to 59	70 (25.8)	44 (29.3)	**0.005**
	60 to 69	70 (25.8)	38 (25.3)	0.900
	> 70	27 (10.0)	15 (10.0)	0.700
Ethnicity	Malay	208 (76.8)	115 (76.7)	0.090
	Chinese	50 (18.5)	27 (18.0)	0.100
	Others	13 (4.8)	8 (5.3)	-
District	Brunei-Muara	169 (62.4)	88 (58.7)	**0.030**
	Belait	52 (19.2)	30 (20.0)	1.000
	Tutong	35 (12.9)	21 (14.0)	0.900
	Temburong	6 (2.2)	5 (3.3)	0.300
	Unknown	9 (3.3)	6 (4.0)	0.200
Histology	Ductal	207 (76.4)	110 (73.3)	**< 0.001**
	Medullary	6 (2.2)	2 (1.3)	-
	Mucinous	10 (3.7)	4 (2.7)	1.000
	Lobular	17 (6.3)	16 (10.7)	0.400
	Tubular	2 (0.7)	1 (0.7)	-
	Papillary	3 (1.1)	2 (1.3)	-
	Others	26 (9.6)	15 (10.0)	0.500

[a]p-value from the Log-rank test

with a study finding that younger patients tend to opt for more surgical interventions, while older patients prioritise minimally invasive treatments [31]. However, it is essential to emphasise that treatment decisions are individualised, with older patients also undergoing surgery when deemed appropriate by a multidisciplinary team approach.

In our study, Malay women were more likely to undergo surgery and chemotherapy as their first-line treatment, while Chinese women had a higher likelihood of receiving radiotherapy and hormonal therapy. Our findings align with a previous study that identified variations in breast cancer treatment patterns among ethnicities in Southeast Asia. Specifically, the study found that Malay women were more likely to receive mastectomies compared to Chinese and Indian women [32]. It is also reported that Malay women were more likely to undergo chemotherapy, while Chinese and Indian women were more likely to undergo hormonal therapy, consistent with our results. A local study indicated that Malay women had higher BRCA2 mutation, which may contribute to an increased risk of early onset of breast cancer [33]. Additionally, the majority of breast cancer patients in Brunei are hormone receptor positive, with 64% being human epidermal growth factor receptor 2 (HER2) positive [34]. Although HER-2positive cases typically require chemotherapy combined with anti-HER2 targeted therapy such as Herceptin and Pertuzumab, our study's preference for hormonal therapy among older patients may reflect other factors influencing treatment decisions, such as hormone receptor status or the presence of comorbidities.

Significant differences were also observed in treatment types among patients with varying delays in treatment groups. The majority of the patients in our study received their treatment within 60 days of diagnosis, especially for surgery (71.4%) and hormonal therapy (70.0%). The relatively short time intervals in receiving these treatments likely contributed to better management of the disease. The median time to first treatment from diagnosis for surgery was 37 days, consistent with the 30-day time interval for surgery reported by Abdel-Razeq [35]. These time intervals could be influenced by several factors, including preparation for procedures, the availability of operating rooms and surgeons, patient-related factors like comorbidities, and socioeconomic barriers [36]. Additionally, the COVID-19 pandemic has further contributed to delays in surgical treatment due to the need for reallocating resources, implementing additional safety protocols, and managing reduced operating room capacity. The median time interval for chemotherapy in our study was also 37 days, which contrasts with a reported median time of 74 days in another study [35], highlighting potential delays in chemotherapy initiation. Studies from other regions have shown varying median delays to treatment: 21 days in Malaysia [37], 120 days in Indonesia [38], 14 days in Korea [39], 72.3 days in Brazil [40], and 37 days in Denver [41]. Delays in treatment exceeding critical thresholds: 90 days for surgery, 120 days for chemotherapy, and 365 days for radiotherapy are associated with a measurable impact on outcomes [42]. Therefore, minimising treatment delays is crucial for improving patient outcomes and ensuring timely, effective care.

Our study found that patients diagnosed and treated at the localised stage consistently had higher survival rates across all treatment types compared to those diagnosed at the distant stage. Early diagnosis plays a crucial role in improving outcomes, as it often leads to the diagnosis at early stage. At the localised stage, surgical intervention can be particularly effective, as it often results in minimal residual disease and a reduced risk of recurrence [43]. However, distant stage cancer is more challenging to treat due to its spread and potential resistance to therapies, including mechanisms such as drug inactivation, active

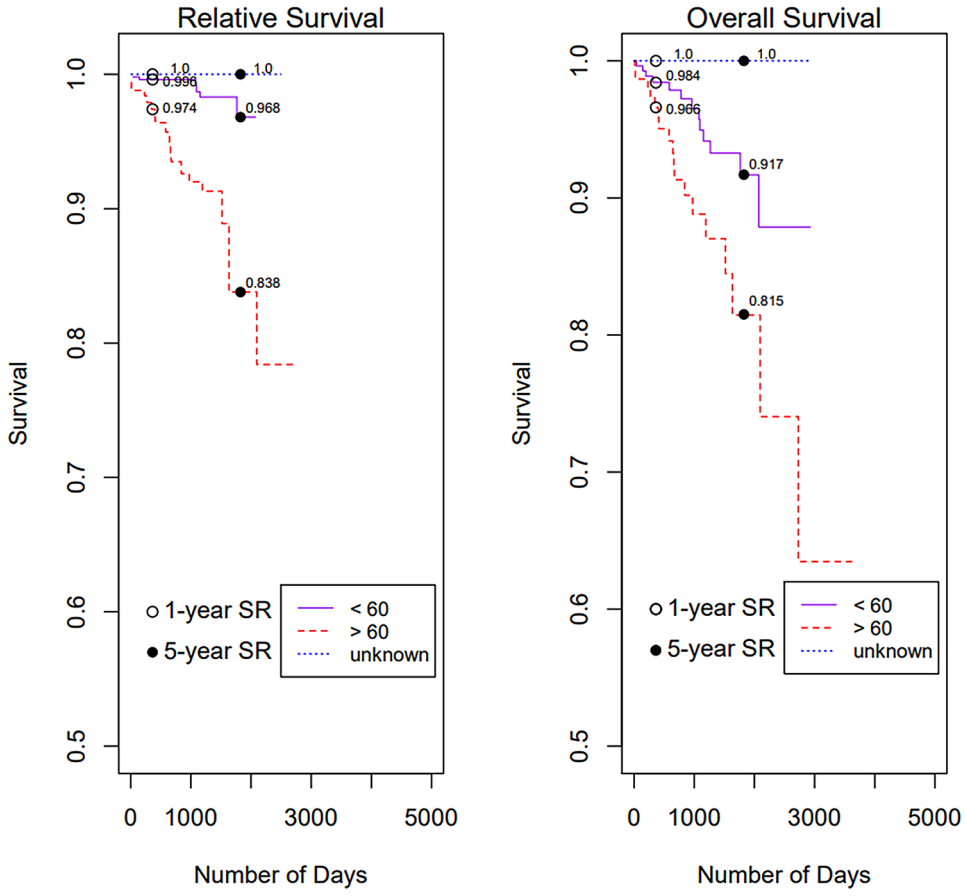

Fig. 2 Relative and overall survival curves of delay groups from time of diagnosis to the time of first treatment

removal of drug cells, repair of drug-induced DNA damage, and inherent heterogeneity of the cancer [44]. When stratified by cancer stage, we found no significant differences across different treatment modalities, suggesting that within each stage, treatment choices may not necessarily lead to varying survival outcomes. This observation is consistent with findings that treatment decisions are often guided by factors such as tumour subtype, cancer stage, and patient preferences, rather than the expectation of different survival benefits [45].

Despite our small sample size, multi-modal approaches have been found to be particularly beneficial for patients who can tolerate additional treatments. In our study, patients treated with chemotherapy alone had the lowest survival rates (RS: 85.0% and OS: 82.0%). However, when chemotherapy was combined with surgery, radiotherapy, or hormonal therapy, survival outcomes improved significantly. These findings support existing evidence that multi-modal approaches may be beneficial in improving patient outcomes, emphasising the need for personalised treatment strategies [46]. Recent advancements, such as the use of CDK4/6 inhibitors in combination with hormonal therapy, have further enhanced outcomes in high-risk, hormone receptor-positive breast cancer patients, particularly in the adjuvant setting [47]. Adapting treatment strategies to the specific characteristics of each tumour can greatly improve treatment effectiveness and patient survival. Patients receiving multiple adjuvant treatments tend to show better survival rates. Adjuvant treatments targets different aspects of the cancer biology, making it more challenging for cancer cells to develop resistance and reduce risk of recurrence in the later years [48]. Additionally, combining treatments can effectively eliminate any remaining cancer cells after primary treatment, reducing the likelihood of cancer spreading to other parts of the body [49].

The findings from this study demonstrate the significant impact of cancer stage on survival outcomes in breast cancer patients. The log-rank test shows a statistically significant difference in survival between different cancer stages, and the univariate and multivariate Cox proportional hazard analyses showed that patients with distant stage cancer had a higher risk of death compared to those with localised stage cancer. This is consistent with findings, where it was reported that patients with distant stage cancer in the Netherlands had a 2.49 times higher risk of death compared to those with localised stage cancer [50]. Similarly, a study on older women

in the United States with distant stage cancer had a 2.96 times higher risk of death [51]. These results align with the well-established understanding that advanced cancer stages are associated with poorer prognoses due to factors such as increased tumour burden and higher metastatic potential [52, 53].

Our investigation also explored treatment delays, revealing that the longer delays were associated with higher risks for breast cancer patients. Patients who received their treatment within 60 days of diagnosis had significantly better survival outcomes compared to those with delays over 60 days, who had a 2.5 times higher risk of death. This is consistent with findings that delayed treatment for advanced stage breast cancer significantly worsens survival outcomes, increasing the risk of mortality by 1.85 times [54]. Similarly, delays of more than three months have been associated with significantly lower survival rates, with an odds ratio for death of 1.47. These findings highlight the importance of timely intervention, as evidenced by mandates in countries like Brazil, where treatment waiting times are not to exceed 60 days after diagnosis [17]. A systematic review found that for breast cancer, each four-week delay in treatment is associated with a 6–8% increase in the risk of death, and a delay of three months could raise the risk of death by approximately 25% [10]. However, after adjusting for potential confounding factors in our multivariate Cox proportional hazards analysis, treatment delays were no longer a significant predictor of survival. These findings suggest that while prompt treatment is generally beneficial, its impact on survival may be less evident when considering the combined effect of various clinical and demographic factors.

In our study, most patients with localised and regional stages received treatment within 60 days, with 42.8% of localised stage and 45.4% of regional stage patients beginning treatment in this timeframe. In contrast, patients with advanced stage were more likely to experience delays, with 66.7% receiving treatment after 60 days. This may be due to factors such as patient-specific issues like comorbidities, logistic challenges, or personal decision-making. Tumour heterogeneity, where tumours grow in different parts of the body and have distinct biological characteristics, can lead to drug resistance and require personalized cancer treatment [55, 56]. Our findings also indicated that younger patients (under 50 years) were more likely to receive treatment before 60 days, while older patients (over 50 years) were more likely to experience longer delays, potentially due to challenges such as scheduling appointments, fear, and comorbidities, leading to longer delays [57].

Our study shows a significant relationship between treatment delays and survival outcomes in breast cancer patients. Those treated within 60 days had a 5-year survival rate of 96.8% (RS) and 91.7% (OS), showing a better prognosis compared to those who receive treatment after 60 days (RS: 83.8% and OS: 81.5%). This finding is consistent with previous research, which showed that breast cancer patients receiving treatment within 3 months had a higher 5-year survival rate of 52%, whereas those treated after 3 months had a lower survival of 40% [58]. Furthermore, a study in Vancouver, Canada, found that breast cancer patients treated within 60 days had a 5-year relative survival rate of 70%, whereas those who received treatment after 60 days had a significantly lower 5-year relative survival rate of 57% [59]. These findings reinforce the association between timely treatment and improved survival outcomes, as observed in our cohort.

This study has certain limitations that should be recognised. First, its retrospective design, which relies on existing records, may introduce inherent biases such as incomplete and inaccurate data. For instance, our analysis of treatment delays was based on a limited data subset, restricting our ability to conduct a more comprehensive analysis and highlighting the need for further research into factors such as treatment abandonment or completion. Selection bias may also arise if certain patient populations are underrepresented in the available records. Additionally, the lack of a formal control group prevents direct comparisons and limits our capacity to attribute observed differences in outcomes specifically to the interventions studied.

Our study did not capture data on the clinical rationale behind first-line treatment choices, including whether patients receiving radiotherapy were inoperable, unfit for surgery, or had declined surgery. Additionally, data on radiation-induced angiosarcoma (RIAS), a rare but aggressive histotype associated with prior radiotherapy, was unavailable. Given its poor prognosis and diagnostic challenges [60], future research with long-term follow-up and detailed histopathological data may help assess the prevalence and management of RIAS in our setting. Treatment decisions are influenced by multiple factors, including tumour characteristics, comorbidities, and patient preferences, which should be explored in future studies. Furthermore, information on the time from presentation to diagnosis and on treatment completion rates was unavailable, even though these factors are known to significantly influence the survival outcomes of breast cancer patients [11]. Nevertheless, high universal health coverage in Brunei Darussalam likely minimises treatment abandonment due to financial constraints, as the cost of treatment is covered by the government.

While the Brunei Darussalam Healthcare Information and Management System (Bru-HIMS) has significantly improved data accuracy and completeness of disease surveillance by transitioning from manual to digital records [13, 61], our study's reliance on historical data means

that rapid advancements in breast cancer treatments and changes in clinical practice guidelines over time are not fully accounted for, potentially influencing the observed effectiveness of different treatment strategies [62]. Despite these limitations, the findings offer valuable insights into the landscape of breast cancer treatment and survival in Brunei Darussalam, providing an important foundation for future research. Further investigations with prospective designs and control groups, along with more comprehensive data, could help refine our understanding of breast cancer outcomes and inform strategies to improve patient care.

In conclusion, this study provides insights into the relationship between treatment modalities, treatment delay, and breast cancer survival outcomes in Brunei Darussalam. Our findings suggest that timely treatment may be beneficial for improving survival outcomes. These results may help inform policy discussions on ensuring timely access to treatment, such as setting a potential target for initiating breast cancer treatment within 2 months post-diagnosis. The observed disparities in survival outcomes between early and delayed treatment suggest the importance of increased awareness, early diagnosis, and prompt treatment. These findings contribute to a deeper understanding of breast cancer survival outcomes, highlighting the need for future research to explore causal mechanisms and intervention strategies to improve patient outcomes.

Abbreviations

BDCR	Brunei Darussalam Cancer Registry
Bru-HIMS	Brunei Darussalam Healthcare Information and Management System
CI	Confidence Interval
DEPS	Department of Economics Planning and Statistics
MHREC	Medical and Health Research Ethics Committee
NCD	Noncommunicable Disease
OS	Overall Survival
RS	Relative Survival
SEER	Surveillance, Epidemiology, and End Results Program
WHO	World Health Organisation

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Author contributions

AWY and EL designed the research; AWY and EL analysed the data; SKO for data corroboration; AWY and EL wrote the paper; and AWY, EL, SKO and ZM critically revised the manuscript for important intellectual content.

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Data availability

The data that supports the findings of this study are available from Ministry of Health Brunei Darussalam but restrictions apply to the availability of these data, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of the Ministry of Health Brunei Darussalam.

Declarations

Ethical approval

This study adhered to ethical principles and guidelines and received approval from the Medical and Health Research Ethics Committee of the Ministry of Health, Brunei Darussalam [Ref: MHREC/MOH/2022/1(1)]. This approval ensures that the research was conducted in accordance with ethical standards, safeguarding participant rights, privacy, and data confidentiality. Furthermore, ethical considerations were observed at all stages of the study, and the researchers ensured that the data collected was used only for the intended research objectives. Informed consent was not required for this study, as the data used were de-identified and there was no direct contact with participants. The waiver of consent was approved by the Medical and Health Research Ethics Committee, in compliance with national regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. World Health Organization. World health statistics 2023: monitoring health for the SDGs, Sustainable Development Goals. Geneva, Switzerland. 2023. Licence: CC BY-NC-SA 3.0 IGO. Available from https://www.who.int/publications/i/item/9789240074323. Accessed 02 June 2024.
2. World Health Organization. Global cancer burden growing, amidst mounting need for services. Geneva, Switzerland. 2024. Available from https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services. Accessed 02 June 2024.
3. World Health Organization. Breast cancer. Geneva, Switzerland. 2024. Available from https://www.who.int/news-room/fact-sheets/detail/breast-cancer. Accessed 02 June 2024.
4. Lei S, Zheng R, Zhang S, Wang S, Chen R, Sun K, et al. Global patterns of breast cancer incidence and mortality: A population-based cancer registry data analysis from 2000 to 2020. Cancer Commun. 2021;41(11):1183–94. https://doi.org/10.1002/cac2.12207.
5. World Health Organization. Country Fact Sheet. Public Health Data at a Glance. Brunei Darussalam. 2020. Available from https://www.who.int/docs/default-source/wpro---documents/countries/brunei-darussalam/fact-sheet-brunei-darussalam.pdf?sfvrsn=b91eddf4_5. Accessed 02 June 2024.
6. Noncommunicable Disease Prevention Unit, Ministry of Health. Brunei Darussalam Cancer Registry Report 2002–2021. Brunei Darussalam. 2022. Available from. https://www.moh.gov.bn/Shared%20Documents/DOWNLOADS/BDCR%202002-2021%20vMay2023.pdf Accessed 05 June 2024.
7. Department of Economics Planning and Statistics, Ministry of Finance. Report of the Population Estimates. 2023. Available from https://deps.mofe.gov.bn/SitePages/Population.aspx. Accessed 02 June 2024.
8. Leong E, Ong SK, Jali F, Naing L, Incidence. Mortality and survival analysis of epithelial ovarian Cancer in Brunei Darussalam. Asian Pac J Cancer Prev APJCP. 2022;23(4):1415–23. https://doi.org/10.31557/APJCP.2022.23.4.1415.
9. Mutebi M, Anderson BO, Duggan C, Adebamowo C, Agarwal G, Ali Z, et al. Breast cancer treatment: A phased approach to implementation. Am Cancer Soc. 2020;126(10):2365–78. https://doi.org/10.1002/cncr.32910.
10. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371. https://doi.org/10.1136/bmj.m4087.
11. Ong SK, Haruyama R, Yip CH, Ngan TT, Li J, Lai D. Feasibility of monitoring global breast Cancer initiative framework key performance indicators in 21 Asian National Cancer centers alliance member countries. EClinicalMedicine. 2024;67:102365. https://doi.org/10.1016/j.eclinm.2023.102365.
12. Pawlicki M, Michalczyk A. Studies of the causes of treatment delay of cancer patients. Contemp Oncol. 2005;9(5):191–5.

13. Leong E, Madli F, Ong SK. Five-year survival rate of breast cancer patients in Brunei Darussalam. Brunei Int Med J. 2019;15:73–81.
14. Ruhl JL, Callaghan C, Schussler NSS. 2018: General Coding Instructions. Bethesda, MD. National Cancer Institute. 2023. https://seer.cancer.gov/tools/ssm/SSM-2018-GENERAL-INSTRUCTIONS.pdf
15. Nascimento RG, Otoni KM. Histological and molecular classification of breast cancer: what do we know? Mastology. 2020;30:1–8. https://doi.org/10.29289/25945394202020200024.
16. Sinn HP, Kreipe H. A brief overview of the WHO classification of breast tumors, focusing on issues and updates from the 3rd edition. Krager. 2013; 8(2), 149–154. https://doi.org/10.1159/000350774
17. Ferreira NAS, Schoueri JHM, Sorpreson ICE, Adami F, dos Santos Figueiredo FW. Waiting time between breast cancer diagnosis and treatment in Brazilian women: an analysis of cases from 1998 to 2012. Int J Environ Res Public Health. 2020;17(11):4030. https://doi.org/10.3390/ijerph17114030.
18. Chew HK. Adjuvant therapy for breast cancer: who should get what? West J Med. 2001;174(4):284. https://doi.org/10.1136/ewjm.174.4.284.
19. Ederer F, Heise H. Instructions to IBM 650 programmers in processing survival computations. Methodological note no. 10. Bethesda, MD: End Results Evaluation Section, National Cancer Institute; 1959.
20. R Foundation for Statistical Computing. R: A Language and Environment for Statistical Computation. Vienna, Austria. 2023. Available from https://www.R-project.org/. Accessed 02 June 2024.
21. Ugnat AM, Xie L, Morriss J, Semenciw R, Mao Y. Survival of women with breast cancer in Ottawa, Canada: variation with age, stage, histology, grade and treatment. Br J Cancer. 2004;90(6):1138–43. https://doi.org/10.1038/sj.bjc.6601662.
22. Jara-Lazaro AR, Thilagaratnam S, Tan PH. Breast cancer in Singapore: some perspectives. Breast Cancer. 2010;17:23–8. https://doi.org/10.1007/s12282-009-0155-3.
23. Hisham AN, Yip CH. Overview of breast cancer in Malaysian women: a problem with late diagnosis. Asian J Surg. 2004;27(2):130–3. https://doi.org/10.1016/S1015-9584(09)60326-2.
24. Preventive Services Task Force US. Screening for breast cancer: U.S. Preventive services task force recommendation statement. Ann Intern Med. 2009;151(10):716–26. https://doi.org/10.7326/0003-4819-151-10-200911170-00008.
25. Feng Y, Spezia M, Huang S, Yuan C, Zeng Z, Zhang L, et al. Breast cancer development and progression: risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes Dis. 2018;5(2):77–106. https://doi.org/10.1016/j.gendis.2018.05.001.
26. Teo SY, Chuwa E, Latha S, Lew YL, Tan YY. Young breast cancer in a specialised breast unit in Singapore: clinical, radiological and pathological factors. Annual Acad Med Singap. 2014;43(2):79–85. https://annals.edu.sg/pdf/43VolNo2Feb2014/MemberOnly/V43N2p79.pdf.
27. Tan KF, Adam F, Hussin H, Mujar NMM. A comparison of breast cancer survival across different age groups: a multicentric database study in Penang. Malaysia Epidemiol Health. 2021;43. https://doi.org/10.4178/epih.e2021038.
28. Norsa'adah B, Rampal KG, Rahmah MA, Naing NN, Biswal BM. Diagnosis delay of breast cancer and its associated factors in Malaysian women. BMC Cancer. 2011;11:141. https://doi.org/10.1186/1471-2407-11-141.
29. Trayes KP, Cokenakes SE. Breast cancer treatment. Am Family Phys. 2021;104(2):171–8. https://www.aafp.org/pubs/afp/issues/2021/0800/p171.html#stage-0--dcis--noninvasive-breast-cancer.
30. Maughan KL, Lutterbie MA, Ham PS. Treatment of breast cancer. Am Fam Physician. 2010;81(11):1339–46. https://www.aafp.org/pubs/afp/issues/2010/0601/p1339.pdf
31. Sio TT, Chang K, Jayakrishnan R, Wu D, Politi M, Malacarne D, et al. Patient age is related to decision-making, treatment selection, and perceived quality of life in breast cancer survivors. World J Surg Oncol. 2014;12(230):1–8. https://doi.org/10.1186/1477-7819-12-230.
32. Bhoo-Pathy N, Hartman M, Yip CH, Saxena N, Taib NA, Lim SE, et al. Ethnic differences in survival after breast cancer in South East Asia. PLoS ONE. 2012;7(2):e30995. https://doi.org/10.1371/journal.pone.0030995.
33. Abdullah N, Mohamed N. Influence of cultural practices on breast cancer risks, stage at presentation and outcome in a multiethnic developing country. Oncol Lett. 2021;22(5):1–9. https://doi.org/10.3892/ol.2021.13067.
34. Kang FR, Telisinghe PU, bin Abdallah S, Ramasamy R. Breast cancer in Brunei Darussalam– Differential community distribution and an analysis of common molecular tumour markers. Brunei Darussalam J Health. 2007;2:23–30.
35. Abdel-Razeq H, Mansour A, Edaily S, Dayyat A. Delays in initiating Anti-Cancer therapy for Early-Stage breast cancer– How slow can we go?? J Clin Med. 2023;12(13):4502. https://doi.org/10.3390/jcm12134502.
36. Tjoe JA, Heslin K, Moreno ACP, Thomas S, Kram JJ. Factors associated with breast cancer surgery delay within a coordinated multihospital community health system: when does surgical delay impact outcome? Clin Breast Cancer. 2022;22(1):e91–100. https://doi.org/10.1016/j.clbc.2021.04.012.
37. Mohd Mujar NM, Dahlui M, Emran NA, Hadi IA, Yan YW, Arulanantham S, et al. Breast cancer care timeliness framework: a quality framework for cancer control. JCO Global Oncol. 2022;8:e2100250. https://doi.org/10.1200/GO.21.00250.
38. Gondhowiardjo S, Hartanto S, Wirawan S, Jayalie VF, Astiti IAP, Panigoro SS, et al. Treatment delay of cancer patients in Indonesia: A reflection from a National referral hospital. Med J Indonesia. 2021;30(2):129–37. https://doi.org/10.13181/mji.oa.204296.
39. Lee YJ, Jeong JH, Jung J, Yoo TK, Lee SB, Kim J, et al. Waiting time for breast Cancer treatment in Korea: A nationwide cohort study. Study J Breast Cancer. 2023;26(4):334. https://doi.org/10.4048/jbc.2023.26.e26.
40. Lopes TCR, Gravena AAF, de Oliveira Demitto M, Borghesan DHP, DellAgnolo CM, Brischiliari SCR, et al. Delay in diagnosis and treatment of breast cancer among women attending a reference service in Brazil. Asian Pac J Cancer Prev. 2017;18(11):3017–23. https://doi.org/10.22034/APJCP.2017.18.11.3017.
41. Jaiswal K, Hull M, Furniss AL, Doyla R, Gayou N, Bayliss E. Delays in diagnosis and treatment of breast cancer: a safety-net population profile. J Natl Compr Canc Netw. 2018;16(12):1451–7. https://doi.org/10.6004/jnccn.2018.7067.
42. Bleicher RJ. Timing and delays in breast cancer evaluation and treatment. Annuals Surg Oncol. 2018;25:2829–38. https://doi.org/10.1245/s10434-018-6615-2.
43. Benson JR, Jatoi I, Keisch M, Esteva FJ, Makris A, Jordan VC. Early breast cancer. Lancet. 2009;373(9673):1463–79. https://doi.org/10.1126/science.aay9040.
44. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, et al. Drug resistance in cancer: an overview. Cancers. 2014;6(3):1769–92. https://doi.org/10.3390/cancers6031769.
45. Waks AG, Winer EP. Breast cancer treatment: a review. JAMA. 2019;321(3):288–300. https://doi.org/10.1001/jama.2018.19323.
46. Kocarnik JM, Compton K, Dean FE, Fu W, Gaw BL, Harvey JD, et al. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the global burden of disease study 2019. Jama Oncol. 2022;8(3):420–44. https://doi.org/10.1001/jamaoncol.2021.6987.
47. Slamon DJ, Stroyakovskiy D, Yardley DA, Huang CS, Fasching PA, Crown J, et al. Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2-early breast cancer: primary results from the phase III NATALEE trial. J Clin Oncol. 2023;41:27. https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA500.
48. Mokhtari RB, Homayouni TS, Baluch N, Morgatskaya E, Kummr S, Das B, et al. Combination therapy in combating cancer. Oncotarget. 2017;8(23):38022. https://doi.org/10.18632/oncotarget.16723.
49. Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: current status, drug candidates associated risks and progress in targeted therapeutics. Genes Dis. 2023;10(4):1367–401. https://doi.org/10.1016/j.gendis.2022.02.007.
50. Saadatmand S, Bretveld R, Siesling S, Tilanus-Linthorst MM. Influence of tumour stage at breast cancer detection on survival in modern times: population based study in 173 797 patients. BMJ. 2015;251. https://doi.org/10.1136/bmj.h4901.
51. Nagar H, Yan W, Christos P, Chao KC, Nori D, Ravi A. Older patients with early-stage breast cancer: adjuvant radiation therapy and predictive factors for cancer-related death. Am J Clin Oncol. 2017;40(3):300–5. https://doi.org/10.1097/COC.0000000000000144.
52. Park M, Kim D, Ko S, Kim A, Mo K, Yoon H. Breast cancer metastasis: mechanisms and therapeutic implications. Int J Mol Sci. 2022;23(12):6806. https://doi.org/10.3390/ijms23126806.
53. Yang SX, Hewitt SM, Yu J. Locoregional tumor burden and risk of mortality in metastatic breast cancer. NPJ Precision Oncol. 2022;6(1):22. https://doi.org/10.1038/s41698-022-00265-9.
54. Caplan L. Delay in breast cancer: implications for stage at diagnosis and survival. Front Public Health. 2014;2:87. https://doi.org/10.3389/fpubh.2014.00087.
55. Meric-Bernstam F, Mills GB. Overcoming implementation challenges of personalized cancer therapy. Nat Reviews Clin Oncol. 2012;9(9):542–8. https://doi.org/10.1038/nrclinonc.2012.127.

56. Sala E, Mema E, Himoto Y, Veeraraghavan H, Brenton JD, Snyder A. Unravelling tumour heterogeneity using next-generation imaging: radiomics, radiogenomics, and habitat imaging. Clin Radiol. 2017;72(1):3–10. https://doi.org/10.1016/j.crad.2016.09.013.
57. Arndt V, Stürmer T, Stegmaier X, Ziegler H, Dhom G, Brenner H. Patient delay and stage of diagnosis among breast cancer patients in Germany– a population based study. Br J Cancer. 2002;86(7):1034–40. https://doi.org/10.1038/sj.bjc.6600209.
58. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet. 1999;353(9159):1119–26. https://doi.org/10.1016/S0140-6736(99)02143-1.
59. Elwood JM, Moorehead WP. Delay in diagnosis and long-term survival in breast cancer. BMJ. 1980;280(6227):1291–4. https://doi.org/10.1136/bmj.280.6227.1291.
60. Strazzanti A, Trovato C, Gangi S, Marletta D, Milazzotto R, Spatola C. A single institution study experience of secondary breast angiosarcoma after breast conserving treatment: multidisciplinary management. Int J Cancer Clin Res. 2019;6114. https://doi.org/10.23937/2378-3419/1410114.
61. Mwalim MK, Leong E, Ong SK, Mohamad Z. Non-Hodgkin lymphoma incidence, mortality, and survival trends in Brunei Darussalam from 2011 to 2020. BMC Cancer. 2024;24(1):994. https://doi.org/10.1186/s12885-024-12725-5.
62. Tran KB, Lang JJ, Compton K, Xu R, Acheson AR, Henrikson HJ, et al. The global burden of cancer attributable to risk factors, 2010-19: a systematic analysis for the global burden of disease study 2019. Lancet. 2022;500(10352):563–91. https://doi.org/10.1016/S0140-6736(22)01438-6.

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