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FIVE-YEAR SURVIVAL RATE OF BREAST CANCER PATIENTS IN BRUNEI DARUSSALAM.

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ABSTRACT

Introduction: Breast cancer is the most common cancer and leading cause of cancer deaths among women worldwide. In Brunei Darussalam, breast cancer has the highest incidence rate among women. This study presents the survival rate of women diagnosed with breast cancer in Brunei Darussalam and explores the association between survival and demographic or clinical characteristics. **Methods:** This is a retrospective study of breast cancer diagnosed from 2007 to 2017 among women in Brunei Darussalam. Cancer data was retrieved from population based cancer registry. Kaplan-Meier survival analysis and Log rank test were applied to estimate the survival rates and the association between survival and important patients' characteristics. Hazard ratios were derived using Cox Proportional Hazard model. **Results:** The survival rates of breast cancer patients at 1, 3 and 5 years were 89.5%, 79.2% and 72.0% respectively. The 5-year survival rates for cancer stages were 92.2% for localized, 76.9% for regional, and 21.4% for distant metastasis. Ethnicity, cancer stages and cancer stages-morphology interaction were significant independent predictors for breast cancer survival in Brunei Darussalam. **Conclusion:** The survival rate of women diagnosed with breast cancer in Brunei Darussalam and its significant predictors are similar to those reported from other developed countries. Further studies on predictors such as health seeking behaviours and impact of different cancer treatment will provide further insight in improving survival rates of breast cancer through early cancer detection programmes and strengthening of the healthcare service delivery.

Keywords: Breast cancer; Brunei Darussalam; Death; Hazard rate; Proportional Hazards model; Survival rate.

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Keywords: Breast cancer; Brunei Darussalam; Death; Hazard rate; Proportional Hazards model; Survival rate.

INTRODUCTION

The World Health Organization has reported cancer as the second leading cause of deaths globally.¹ In 2018, it was estimated that there

were 18.1 million new cancer cases and 9.6 million cancer deaths.¹ Globally, cancer accounts for 1 in 6 deaths.¹ The most common cancer and leading cause of deaths among women worldwide is breast cancer. An estimate of 2,088,849 new cases and 626,679 deaths were reported for breast cancer alone in 2018.²

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According to GLOBOCAN 2018, breast cancer incidence rates far exceed those for other cancers in both developed and developing countries.³ Breast cancer incidence rates are highest in Australia/New Zealand, Northern Europe, Western Europe, Southern Europe, and Northern America. However, breast cancer mortality rates show less variability, with the highest mortality estimated in Melanesia, where Fiji has the highest mortality rates worldwide.² There is variation in survival rates of breast cancer worldwide which are influenced by various factors. Information about survival rates could help medical professionals and policy makers to strengthen further preventive measures in order to improve the prognosis of breast cancer patients.

Brunei Darussalam is a Southeast Asia nation with an estimated population of 421 300 people, of which 66% consists of the Malays, 10% are Chinese and 24% includes other ethnicity.⁴ It has 4 districts with 69% of the population resides in the Brunei-Muara, 12% in Tutong, 17% in Belait and 3% in Temburong district. The leading cause of deaths in Brunei Darussalam is from cancer, which accounts for about 19% of the total mortalities in the country followed by heart diseases (15%).⁵ Brunei Darussalam has relatively higher breast cancer incidence rates compared to its neighbouring countries.⁶

To date, only a few studies have documented the rising trend and lifetime risk of breast cancer in Brunei Darussalam.^{7,8} Currently there is no information available on survival of breast cancer patients in Brunei Darussalam. This study aims to estimate the survival rate of women diagnosed with breast cancer in Brunei Darussalam and to identify significant prognostic factors.

METHODS

Patient Population

This is a retrospective study examining all

breast cancer cases registered in the Brunei National Cancer Registry (BNCR) from 2007 to 2017 (11-year period). All female patients (citizens and permanent residents) diagnosed locally or abroad with breast cancers, registered with BNCR, were eligible to be included in the study. Breast cancers among men and temporary residents and in-situ carcinomas were excluded from the study.

Data Collection

De-identified data were retrieved from population based BNCR which captured cancer diagnosis and death reported in the health services and national death registry. Data collected included clinical demographic data, clinico-pathological information of the cancer patients and dates of last follow up or death which was tabulated in Excel proforma spreadsheet for analysis.

The covariates included for analysis were age at diagnosis, district (Brunei-Muara, Tutong, Belait, Temburong), ethnicity (Malay, Chinese, Others), location of tumour (lateral, medial, central, overlapping, others), morphology (ductal, lobular, others), and cancer stage (localized, regional and distant metastasis). Brunei Darussalam cancer registry classified the cancer cases according to staging system provided by SEER (Surveillance, Epidemiology and End Results program) which has 7 cancer stages.⁹ In this study, tumor stages were grouped using a staging system developed by the SEER program which classifies breast cancer cases into in situ, localized (SEER stage 1), regional (SEER Stages 2-5), and distant metastasis (SEER Stages 6-7).⁹

Statistical Analysis

Data were analysed using R Statistical software package. Kaplan-Meier survival analysis was used to compute the cumulative survival curves for patients with breast cancer. Patients who are still alive or lost to follow-up by the end of the study period were right censored from the analysis. Log-rank test was

used to compare the differences in survival distributions among groups. Cox proportional hazard model was used to derive the regression coefficients and to determine independent prognostic covariates which affect the survival rate of breast cancer patients. Covariate with p-value of less than 0.05 is considered as statistically significant.

Ethical Approval

Ethical approval for this study was obtained from PAPRSB Institute of Health Science Research and Ethics Committee (IHSREC) and the Medical and Health Research Ethics committee of Ministry of Health (MHREC), Brunei Darussalam [Ref: UBD/PAPRSBIHSREC/2018/149, dated 21st January 2019].

RESULTS

A total of 917 female breast cancer cases

were retrieved from BNCR but only 821 female patients with breast cancer malignancies were included in the study. The mean age at diagnosis was 52 ± 11.8 years. About 13% were diagnosed below the age of 40 years and can be classified as young breast cancer patients (Table 1). Majority of the cases were from the Brunei-Muara district (70.6%) and of Malay ethnicity (72.8%). More than a third of patients were diagnosed at localized stage but majority (43.6%) were diagnosed at regional stage and only 18.2% had distant metastases at time of diagnosis. Ductal carcinoma was the most common morphological type (73.3%).

Survival Analysis

Out of a total of 917 cases, there were 205 (25.0%) deaths recorded in the National death registry from breast cancer during the study period. The remaining 616 (75.0%) cases were right censored by the end of the

Table 1: Distribution of breast cancer cases by selected demographic and clinico-pathological characteristics.

Variables		Percentage of cases (%)	Percentage of deaths (%)	5-year survival rate (%)	Log-rank test
Age	< 40	13.3	10.8	81.8	$p = 0.003$
	40 – 49	29.7	22.9	77.2	
	50 – 59	33.8	39.0	67.8	
	60 – 69	15.2	15.6	68.8	
	≥ 70	8.0	11.7	57.9	
District of residence	Brunei Muara	70.6	68.3	74.7	$p = 0.415$
	Tutong	11.6	10.6	77.2	
	Belait	16.4	20.0	65.1	
	Temburong	1.4	1.1	72.7	
Ethnicity	Malay	72.8	78.5	70.4	$p = 0.091$
	Chinese	19.2	17.1	72.9	
	Other	8.0	4.4	85.2	
Cancer Stage	Localized	38.2	12.8	92.2	$p < 0.001$
	Regional	43.6	37.2	76.9	
	Distant metastasis	18.2	50.0	21.4	
Location of tumour	Lateral	9.4	4.4	66.3	$p = 0.310$
	Medial	4.6	1.5	84.9	
	Central	1.2	0.0	-	
	Overlapping	2.7	1.0	86.9	
	Others	82.1	93.2	71.0	
Morphology	Ductal carcinoma	73.3	69.3	70.9	$p = 0.347$
	Lobular carcinoma	4.4	3.9	79.1	
	Others	22.3	26.8	72.5	

study period. The overall Kaplan Meier survival rates of breast cancer patients at 1, 3 and 5 years were 89.5%, 79.2% and 72.0% respectively (Figure 1). Breast cancer patients residing in Tutong district have the highest 5-year survival rate at 77.2% followed by Brunei-Muara (74.7%), Temburong (72.7%) and Belait (65.1%). Moreover, Malay patients have lower 5-year survival rate compared to other ethnic groups. The 5-year survival rates for cancer stages in this study were 92.2% for localized stage, 76.9% for regional stage, and 21.4% for those with distant metastasis. Patient with lobular carcinoma (79.1%) has the highest 5-year survival rate compared to patients with ductal carcinoma or other morphology with 70.9% and 72.5% respectively. Using Log rank test, the differences in survival rates between patients from different age groups (Figure 2, $p=0.003$) and cancer stages (Figure 3, $p<0.001$) were statistically significant (Table 1).

Age at diagnosis, ethnicity, district of residence, site of cancers and morphology have significant impact on survival within stage ($p < 0.0001$) shown in Table 2. For distant metastasis, breast cancer patient with ductal carcinoma has the lowest 5-year

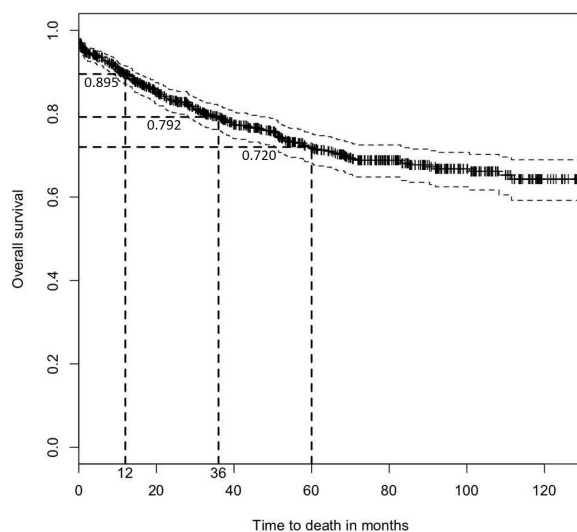


Figure 1: Kaplan Meier Overall Survival curve with 95% confidence interval among breast cancer patients.

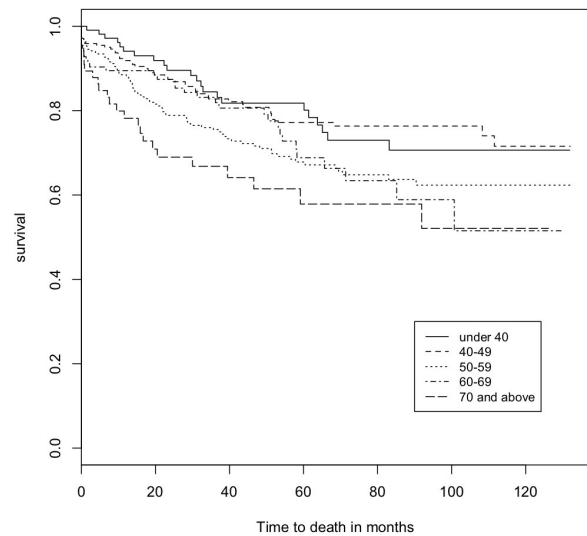


Figure 2: Kaplan Meier Survival Estimates by age group of breast cancer patients.

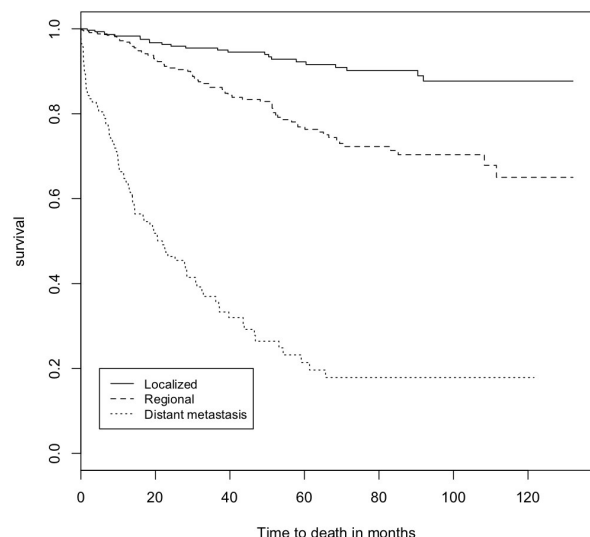


Figure 3: Kaplan Meier Survival Estimates by cancer stages of breast cancer patients.

survival rate as compared to other morphological groups (16.9%). Patient with localized stage has the highest 5-year survival rate among all the morphological groups compared to patients with regional or distant metastasis. The discrepancies in survival rate between ductal carcinoma and other morphological groups were small for localized and regional stage and much larger for distant metastasis. The observed survival advantage of other ethnicities is also seen within localized, regional and distant metastasis stages. Compared to

Table 2: Five-year survival rate of female breast cancer patients by cancer stage and significance associations with age at diagnosis, district of residence, ethnicity, location of tumour and morphology.

Variables		Cancer Stage						p
		Localised		Regional		Distant Metastases		
		%	5-yr SR (%)	%	5-yr SR (%)	%	5-yr SR (%)	
Age at Diagnosis (yrs)	< 40	5.2	94.3	6.6	75.8	1.7	55.0	<0.0001
	40 – 49	11.8	94.6	13.3	81.4	4.9	29.2	
	50 – 59	13.3	89.0	13.9	74.7	6.6	15.0	
	60 – 69	6.0	91.3	5.8	75.5	2.9	11.2	
	>70	1.9	92.9	4.0	71.6	2.0	11.7	
District of residence	Brunei-Muara	28.4	92.7	30.8	74.9	11.2	24.3	<0.0001
	Tutong	3.3	93.8	6.0	83.0	2.4	26.5	
	Belait	6.3	86.5	5.9	82.3	4.3	15.1	
	Temburong	0.5	100.0	0.5	-	0.4	66.7	
Ethnicity	Malay	26.9	90.6	32.7	76.1	14.1	20.1	<0.0001
	Chinese	8.1	94.7	7.9	75.6	2.6	-	
	Others	3.3	100.0	2.9	89.1	1.5	69.8	
Location of tumour	Lateral	3.5	63.8	4.7	94.0	1.5	-	<0.0001
	Medial	1.8	75.0	2.7	94.1	0.4	-	
	Central	0.4	100.0	0.8	-	0.1	-	
	Overlapping	0.6	-	1.3	100.0	0.9	-	
	Others	32.0	93.0	34.1	76.0	15.2	19.4	
Morphology	Ductal	26.3	90.0	34.0	77.2	1.9	16.9	<0.0001
	Lobular	1.9	100.0	2.0	73.4	0.6	40.0	
	Others	10.0	95.8	7.5	76.3	2.8	35.8	

SR = Survival rate

Malay patients with breast cancer, Chinese patients have higher 5-year survival rate (90.6% vs 94.7% respectively) at localized stage but slightly lower survival rate at regional stage (76.1% vs 75.6%). For patients with distant metastasis, majority is Malay women with 14.1% cases and also having the lowest 5-year survival rate (20.1%) compared to other ethnicities. Patients diagnosed at ages 40-49 years with localized stage experienced the best survival rate of 94.6% while patients aged 60-69 years diagnosed with distant metastasis has the lowest survival rate of 11.2%.

The significant prognostic factors from the best fitted Cox proportional hazard model were ethnicity, stage and interaction between stage and morphology (Table 3). No violations of proportional hazard assumptions were observed. Based on this model, the hazard of death of a breast cancer patient with

other ethnicity is 0.28 times lower as compared to a Malay female breast cancer patient [HR = 0.28, 95% C.I.: 0.11 - 0.70, $p=0.0062$]. However, there is no significant difference between Malay and Chinese breast cancer patients (HR=0.81, 95% CI: 0.53-1.25, $p=0.3330$). Age at diagnosis, district, location of tumour and morphology were not statistically significant in survival of women diagnosed with breast cancer ($p > 0.05$).

However, this study found that there was a significant interaction between stage and morphology at all levels with hazard ratios more than 1.0 as shown in Table 4. This means that each variable (stage) depends on the level of the other (morphology). From Table 4, the hazard of death for a breast cancer patient with distant metastasis and other morphology is 16.71 times higher as compared to a breast cancer patient at localized stage with ductal carcinoma, [HR = 16.71,

Table 3: Results of Cox Proportional Hazard model

Variables		coef	Exp(coef)	95% C.I.	p-value
Ethnicity	Malay	0	1		
	Chinese	-0.209	0.812	(0.532, 1.251)	0.3330
	Other	-1.267	0.282	(0.114, 0.697)	0.0062
Cancer Stage*	Localized	0	1		
	Regional	0.698	2.010	(1.179, 3.427)	0.0103
	Distant metastasis	2.661	14.310	(8.565, 23.918)	< 0.0001
Morphology*	Ductal carcinoma	0	1		
	Lobular carcinoma	-15.540	1.786x10 ⁻⁷	(0.000, ∞)	0.9936
	Others	-0.856	0.425	(0.145, 1.251)	0.1203

Reference level: Cancer Stage (Localized), Ethnicity (Malay) and Histopathology (Ductal). C.I. = Confidence Interval. For **Stage*Morphology interaction**, please see table 4.

95% C.I.: 8.17 – 34.17]. The hazard of death for a patient with distant metastasis and lobular carcinoma is 11.03 times higher as compared to a patient at localized stage with ductal carcinoma [HR = 11.03, 95% C.I.: 7.47 – 16.30]. In addition, comparing with patients at localized stage with ductal carcinoma, the hazards of death are 3.01 times higher [HR = 3.01, 95% C.I.: 1.55 – 5.86] for a patient at regional stage with other morphology and 2.97 times higher [HR = 2.97, 95% C.I.: 2.11 – 4.18] for a patient at regional stage with lobular carcinoma.

DISCUSSION

The overall survival rates of breast cancer patients among Bruneian females at 1, 3 and 5 years were 89.5%, 79.2% and 72.0% respectively. Studies from other Asian countries have reported similar 5-year overall survival rates among breast cancer patients of 79.7% in Singapore (2011-2015), 49.0% in Malaysia (2000-2005), 58.8% in China (1972-2011) and 69.5% in Iran (2000-2005).^{10,11,12,13} Patients diagnosed with localized stage have much higher survival rate at 5 years (92.2%) than those with regional stage and distant metastasis with 76.9% and 21.4% respectively. Our findings are comparable to the survival statistics provided by SEER (Surveillance, Epidemiology and End Results program) from National Cancer Institute, which are 100% for cancer in situ, localized

stage 93%, regional stage 72% and distant metastasis stage 22%.¹⁴

This study shows that ethnicity has an influence on the survival of breast cancer. The 5-year survival rate for breast cancer survivors among Chinese in Brunei Darussalam were higher compared to their Malay counterpart. Similar findings were reported from studies in Southeast Asian countries.^{15,16} A variety of factors have been assessed to explain the ethnic disparities in breast cancer survival including genetics predisposition and lifestyle factors such as body weight. About 30% of Bruneian women were found to have obesity with BMI ≥ 30kg/m².¹⁷ Obesity was found to be more common in Malay women and Indian women compared to Chinese women.^{18,19} The role of BMI and obesity in influencing survival may possibly be due to masking effect for early detection of breast lumps by adipose tissue and hence patients may present in more advance stage. This is

Table 4: Hazard ratio with 95% C.I. for the interaction term Stage and Morphology when compared to a breast cancer patient at localized stage with ductal carcinoma.

Variables (Stage*Morphology)	HR	95% C.I.
Regional*Lobular	2.968	(2.108-4.179)
Distant metastasis*Lobular	11.034	(7.471-16.295)
Regional*Others	3.010	(1.546-5.859)
Distant metastasis*Others	16.710	(8.172-34.168)

Reference level: Localized*Ductal. HR=Hazard ratio, C.I. = Confidence Interval.

supported by a study which reported that Malay female breast cancer patients tended to present at more advanced stage of breast cancer and hence have lower survival rate than patients of other ethnicity.²⁰ Another explanation for the differences in survival could be due to ethnic differences in cultural or religious belief system and socio-economic status which have an influence on health seeking behaviour and accessing effective treatments, as well as tolerability and response to treatment.¹⁵ This study however did not explore the association of ethnicity with health seeking behavior and socioeconomic statuses.

The result shows that there is a statistical significant interaction between morphology and stage in breast cancer survival. In this study, the expected hazard of death was found to be higher in a female breast cancer patient with distant metastasis than a patient with regional or localized stage, which is to be expected. This is consistent with the 5-year survival rates calculated in which the survival rate of breast cancer patients with distant metastasis is more than three times lower than that of patient with regional stage. Additionally, there were a higher number of deaths of patients with distant metastasis compared to that of patients with localized and regional stage. Several studies indicated that stage is a significant predictor for death in breast cancer patients.^{10,21,22}

Our finding is also consistent with several studies where morphology is found to have significant association with survival in breast cancer patients.^{23,24,25} However, based on Cox proportional hazard analysis, morphology was no longer a significant predictor but our analysis using stage*morphology interaction term did further increase the hazard ratios for death when comparing localized*ductal interaction term with the various other interaction terms. In this study, lobular carcinoma is found to have a slightly higher 5

-year survival rates compared to ductal carcinoma (although this was not significant), consistent with other studies.²⁶ One study from Canada found that lobular carcinoma has a better prognosis than ductal carcinoma for separate or combined stages.²³ Another study found that patients with ductal carcinoma or tumors of other designations have higher survival for localized stage as compared to regional stage, consistent with our findings.²⁷ It should be highlighted that age at diagnosis is found to have no significant association with survival in female breast cancer patients, consistent with other studies.^{28,29}

This study is the first to assess the survival rates of breast cancer patients in Brunei Darussalam and to establish the association between cancer survival and age at diagnosis, district, ethnicity, location of tumour, morphology and stage. Some limitations identified in this study were the lack of clinical data on cancer treatment in the BNCR and problem of missing data, which are commonly seen in all retrospective studies. In addition, due to heavy censoring in the dataset, results from this study might be biased and the estimates are slightly higher than the actual values. While it is expected that there would be certain degree of data inaccuracies in any population based cancer registry, the adoption of electronic medical record system by the Brunei Darussalam healthcare services in 2013 would have enhance the accuracy, timeliness and completeness of cancer registry.

CONCLUSION

This study indicated that the survival rates of patients diagnosed with breast cancer in Brunei Darussalam as well as the predictor variables for survival are comparable and similar to those reported from other developed countries. Future studies on predictors such as health seeking behaviours and impact of different cancer treatment will provide further insight in improving survival rates of breast

cancer through early cancer detection programme and strengthening of the healthcare service delivery.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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