Clinicopathology Profiles and Outcome of Breast Cancer in Indonesian National Health Insurance Patients

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Abstract**: Background:** Breast cancer is the most prevalent cancer in women and one of Indonesia's leading causes of death. Cancer has various clinical courses, molecular variations, and outcomes, which are not well understood and presented in the Indonesian context. This study aimed to determine breast cancer clinicopathology and the association to the treatment outcome or event of recurrence in Indonesia.
Methods: In this cohort study, we followed up 418 breast cancer patients from three major hospitals in West Sumatra Province of Indonesia with stage I-IV who had definitive treatment in 2017-2018. Demographic data, cancer stage, and different histopathology examination results were collected from the medical records. We followed up with the patients for two years in 2019-2020 to assess the cancer survival outcome. Bivariate analysis was conducted to determine the association between the histopathology profiles and cancer survival outcomes. Multivariate analysis with logistic regression was also performed to see the dominant factor.
Results: The cases were mostly age >50 years (54.1%), cancer stage IIIB (34.0%), lymphovascular invasion (LVI) negative (77.8%), estrogen receptor (ER) positive (56.9%), progesterone receptor (PR) positive (57.9%), HER2 negative (55.5%), and molecular subtype Luminal B (49.5%). Two years survival was 85.2% or with a recurrent rate of 14.8%. There was no association between age, LVI, PR, and HER2+ and cancer survival. By contrast, there was a significant statistical association to ER (p=0.002), cancer stage (p=0.040), molecular subtype (0.001), in which the survival was higher in luminal A subtype (93.8%), cancer stage-I (100.0%), and ER Positive (89.9%). Multivariate analysis also showed the cancer stage was the dominant factor for survival.
Conclusion: The study revealed that the association of clinicopathology and molecular markers to cancer survival varied, in which the lower cancer stage, luminal A subtype, and ER-positive are most likely to have a better outcome. A further multi-center study is necessary to evaluate in Indonesian nationwide outcomes.

Keywords*: Breast cancer; histopathology; outcome; recurrence*

1. Introduction

Breast cancer is one of the most prevalent cancers in women and one of the leading causes of death globally [1-3]. The incidence was likely to increase as more new cases of younger patients.4 The cancer is also the most prevalent in women in Indonesia, as World Health Organization (WHO) recorded that cancer is about 30.8% of all cancer in women and 16.6% in men and women. Moreover, second to lung cancer, the disease is also the most common cancer-related mortality cause among women in the country [5].

Breast cancer has various clinical courses, molecular variations, and outcomes [6]. The cancers can be classified into a molecular subtypes, including luminal A, luminal B, HER2+, and triple-negative (TN). Clinical courses, patterns of metastasis, and outcome

and prognosis may also vary among these subgroups [7]. The recurrence mostly happens during the first five years after treatment among all subtypes. However, late recurrence may also occur in the luminal subtype with HER2 negative and progesterone receptor-positive [8]. The recurrence may increase in cancer with high staging and HER2 positive, and inverse with the ER and PR status [9].

Overall, the disease survival or recurrence may associate with the cancer clinicopathology features and treatment, such as cancer subtype, HER2 expression, hormonal receptor expression, providing chemotherapy, and hormone therapy [10]. The existing publications on breast cancer recurrence were limited and heterogeneous [11]. The increasing invasive cancer tended to have a higher risk of recurrence [12]. Lafourcade et al. also reported that low breast cancer survival was associated with high grade of the tumor, large size, and negative estrogen and progesterone receptors [13]. However, the result may vary among studies [10,14] because the risk of recurrence is related to the clinicopathology stage and molecular and genetic [12].

To our knowledge, there is no adequate report to evaluate the histopathology profile of breast cancer in Indonesia and the association to survival or recurrence. Due to variation reports of the outcome and the possibility of cancer recurrence, we need to examine it in the Indonesian context. This study to determine breast cancer clinicopathology of cancer, including cancer staging, lymphovascular invasion (LVI) status, molecular subtype, estrogen receptor (ER), progesterone receptor (PR), and HER2 expression and the association to disease-free survival of breast cancer in the country to have better understanding clinicopathology and treatment prognosis of the disease.

2. Materials and Methods

2.1. Study design and research sample

This research was quantitative research with a prospective cross-sectional design. The study subjects were breast cancer patients who underwent surgery and other definitive treatment in 2017-2018. The initial clinicopathology data was collected during the cancer treatment recorded in the medical record.

The follow-up has been conducted with two years of the treatment to assess the outcome or event of recurrence of the disease. The two years of follow-up were very feasible to be undertaken due to the relatively short period. Within two years after treatment, breast cancer is more likely to have an initial recurrence.

The study subjects were collected from three hospitals in Padang City, West Sumatera Province of Indonesia, which were M Djamil General Hospital, YARSI Hospital, and Ropanasuri Surgical Hospital, which had final or definitive treatment for breast cancer. Within two years of follow-up, 418 cases were eligible for the study with completed clinicopathology data. All patients in the study were funded under the national health insurance scheme for their treatment.

2.2. Operational definitions

The variables of this study included age, cancer stage, lymphovascular invasion (LVI) status, ER expression, PR Expression, HER2 status, and molecular subtype as independent variables. All those variables were measured in categorical data.

The dependent variable was survival outcome status with the category survive and recurrence. The recurrence was measured by any signs in clinical examination, which clinician expert performed within two years of follow up. The recurrence was included local or regional and distant recurrence. Local recurrence was the cancer was back in the same place it first started. While regional recurrence means the cancer was back in the lymph nodes near the area it first started, distant recurrence means the cancer was back and growing in another part of the body, such as the lungs, liver, bone, or brain. Cancer survival means no local or regional signs of recurrence and distance during the follow-up.

2.3. Data collection technique and Analysis

The clinicopathology data, including age, LVI status, ER, PR, HER2, and molecular subtype, were collected during the patients' treatment by the clinicians who were also part of the research team. The data was written and available in the medical record. The clinicians and the researchers followed up on the patient's condition within two years. The followed-up mainly focuses on any recurrence signs, either local or regional, and distance.

Univariate, bivariate, and multivariate analyses were performed to answer the research questions and draw a conclusion. Univariate analysis was to see the proportion of cases in each pathology profile and the outcome within two years. Bivariate analysis by conducting chi-square with correction and Fisher exact test was done to examine the association of clinicopathology to the outcome. Later logistic regression was performed to determine the dominant factor associated with the survival outcome.

3. Results

The study found that the breast cancer cases were more in women with age > 50 years old (54.1%) and in stage IIIB (34.0%). The clinicopathology profiles showed that the cases were mostly LVI negative (77.8%), expression of ER-positive (56.9%), PR positive (57.9%), and HER2 negative (55.5%). Meanwhile, the molecular subtype of the cancer was majority luminal B (49.5%) (Table 1).

Table 1. Characteristic and Histopathology Profile

Variables		f (n=418)	%
Age	< 50	192	45.9
	≥ 50	226	54.1
Stage	I	8	1.9
	II		
	▪ IIA	96	23.0
	▪ IIB	82	19.6
	III		
	▪ IIIA	62	14.8
	▪ IIIB	142	34.0
	▪ IIIC	3	0.7
	IV	25	6.0
Lymphovascular Invassion	Negative	325	77.8
	Positive	93	22.2
Estrogen Receptor	Negative	180	43.1
	Positive	238	56.9
Progesterone Receptor	Negative	176	42.1
	Positive	242	57.9
HER2	Negative	232	55.5
	Positive	186	44.5
subtype	Luminal A	80	19.1
	Luminal B	207	49.5
	HER2-Enriched Non-Luminal	85	20.3
	Triple-Negative	46	11.0

Breast cancer has been survived for 85.2% within two years of follow-up, with a recurrent rate of 14.8%. Out of 62 cases of recurrence, the majority of them (87.1%) were distant recurrence (Table 2). The distant recurrence was mainly in the lung and liver, which was 33.3% and 31.3% respectively (Table 3).

Table 2. Treatment Outcome

Outcome		f	%
Disease-Free Survival (n=418)	Survive	356	85.2
	Recurrence	62	14.8
Recurrence (n=62)	Local & Regional	8	12.9
	Distance	54	87.1

Table 3. Location of Distant Recurrence

Location	f (n=54)	%
Lung	18	33.3
Liver	17	31.5
Bone	12	22.2
Neck and supraclavicula	4	7.4
Brain	5	9.3
Mediastinum	3	5.6
Lumbal	3	5.6
Distant lymph node	1	1.9

Table 4 shows that the breast cancer survival within two years were comparable between age <50 (82.3%) and >50 years old (87.6%) (p=0.132), LVI status negative (84,9%) and positive (86.0%) (p=0.870), and HER2 negative (84.9%) and positive (85.5%) (p=0.891). The cancer survival was slightly

higher in PR positive (88.0%) than PR negative (81.3%). However, the difference was not statistically significant (p=0.069).

The breast cancer survival outcome was higher in ER expression positive (89.9%) than ER-negative (78.9%) (p=0.002). The cancer survival outcome was also better in low staging, namely 100%, 92.1%), 82.1%, and 56.0% in stages I, II, III, and IV, respectively (p=0.040). Based on the molecular subtype, the cancer survival is higher in luminal A (93.8%) than in another subtype, which was statistically significant (p=0.001). Among all subtypes, the lowest outcome survival within two years was triple-negative breast cancer (TNBC) (Table 4).

Table 4. Factors of Disease-Free Survival Outcome

Variables		Survive f (%)	Recurrent f (%)	*p*	OR (CI)
Age	< 50	158 (82.3%)	34 (17.7%)	0.132	n/a
	≥50	198 (87.6%)	28 (12.4%)		
Lymphovascular Invasion	Negative	276 (84.9%)	49 (15.1%)	0.870	n/a
	Positive	80 (86.0%)	13 (14.0%)		
Estrogen Receptor	Negative	142 (78.9%)	38 (21.1%)	0.002*	0,419 (0,241-0,729)
	Positive	214 (89.9%)	24 (10.1%)		
Progesterone Receptor	Negative	143 (81.3%)	33 (18.8%)	0.069	n/a
	Positive	213 (88.0%)	29 (12.0%)		
HER2	Negative	197 (84.9%)	35 (15.1%)	0.891	n/a
	Positive	159 (85.5%)	27 (14.5%)		
Stages	I	8 (100.0%)	0 (0.0%)	0,040*	n/a
	II (A-B)	164 (92.1%)	14 (7.9%)		
	III (A-C)	170 (82.1%)	37 (17.9%)		
	IV	14 (56.0%)	11 (44.0%)		
subtype	Luminal A	75 (93.8%)	5 (6.3%)	0.001*	n/a
	Luminal B	178 (86.0%)	29 (14.0%)		
	HER2+ Non-Luminal	67 (78.8%)	18 (21.2%)		
	Triple-Negative	36 (78.3%)	10 (21.7%)		

Regression multivariate analysis shows that only staging factor significantly associated with the cancer survival outcome, which was free from local or distant recurrence (p=0.001) with OR=3.088 (Exp[B]=1.895-5.032). This finding implied that cancer with lower staging tended to have better survival outcomes. Overall, from all factors that have been studied as independent variables to the outcome, they had a role in the outcome 14.1% (R-square) (table 5).

Table 5. Multivariate Analysis of Breast Cancer Treatment Outcome

Variables	B	*p*	Exp-B (CI)	R-Square
Age	-.357	0.217	0.700 (0.397-1.233)	0.141
Estrogen Receptor	-.695	0.080	0.499 (0.229-1.087)	
Progesterone Receptors	.084	0.851	1.088 (0.453-2.611)	
subtype	.120	0.528	1.127 (0.777-1.636)	
Stages	1.128	0.001	3.088-(1.895-5.032)*	

4. Discussion

The clinicopathology profiles showed that the cases were mostly LVI negative (77.8%), expression of ER (56.9%), and PR positive (57.9%). The finding was similar to other studies, which was reported a higher proportion of expression of ER and PR [15-17]. Hosseini et al. reported that ER protein expression in breast cancer was 53% [16], and Sofi et al. reported that ER and PR positive in breast cancer was 66.3% and 63.4% respectively [17]. The hormonal receptor expression in breast cancer benefits hormonal therapy in breast cancer cases. Breast cancer with ER and PR expression positive had higher sensitivity to hormonal therapy [18,19]. However, due to the variation of expression of the markers, individual consideration is needed [20, 21].

The HER2 positive was found in 44.5% of the cases. This study indicated that target therapy or anti HER2 might benefit breast cancer treatment specifically for the positive expression and suitable subtype. Target therapy improved the outcome and survival of cancer [22]. However, individual case consideration, drug selection, and adequate treatment follow-up are needed [23, 24].

This study discovered that most molecular subtypes were luminal B (49.5%). This study was similar to a previous study by Paramitha et al. [25], which found that luminal B was the most common subtype (42.39%) and different from other studies, which reported luminal A as the most common subtype [26, 27]. The luminal B subtype can be differentiated into luminal B-like HER2 negative and luminal B-like HER positive by considering ER, HER2, PR, and Ki-67 expression [28]. Specific treatment for luminal B subtype must be regarded as other marker examinations for the individual case.

Cancer has been survived for 85.2% within two years of follow-up, with a recurrence rate of 14.8%. In our finding, the survival outcome of breast cancer was slightly better than the meta-analysis study by Salvo et al. [14], which reported that the recurrence was 17.2% on average. Another study by Abdulwassi et al. also mentioned that the DFS within five years was 57% (recurrence rate= 43%) [29]. With the possibility of early recurrence, clinical follow-up after treatment is needed to assess any signs and symptoms of the recurrence. Optimal follow-up may detect the recurrence in the early stage.

The breast cancer survival within two years were comparable between age <50 (82.3%) and >50 years old (87.6%) (p=0.132), LVI status negative (84,9%) and positive (86.0%) (p=0.870), and HER2 negative (84.9%) and positive (85.5%) (p=0.891). Similar to another study, the LVI status may associate with poor grades but not outcome therapy. The association of LVI to survival might vary among genetic and races [30].

The Association of HER2 to survival outcome in our study was inconsistent with other studies, which is needed more investigation, such as different therapeutic regimens of the individual case and age group. As other studies suggested, the outcome of the targeted therapy on HER2 positive in older patients is lower than in the younger group [31]. Some cases might be resistant to the anti-HER2 therapy [24, 32]. The treatment effect might vary among the patients due to the sensitivity to anti-HER2 therapy such as trastuzumab, which is also related to host individual immunity [33]. The variation outcome on HER2 positive might also relate to the molecular subtype. The cancer survival is higher in luminal A (93.8%) and luminal B (86.0%), HER2 nonluminal (78.8%) respectively, and triple-negative breast cancer (TNBC) as the lowest (p=0.001), which was similar to another study [34]. This finding implied that not all HER2 positive have better outcomes.

The cancer survival was slightly higher in PR positive despite not being statistically significant. The breast cancer survival outcome was also higher in ER expression positive (p=0.002) and low staging (p=0.040). In other words, breast cancer tended to have a higher risk of recurrence in higher stages and inverse to ER and PR positive. Better ER/ PR positive outcomes might be related to the sensitivity to hormonal treatment.19 Some finding of this study was consistent with the meta-analysis

study, where the risk of recurrence in cancer staging was positive (RR=1.82 [95%CI=1.44-2.31]), inverse to ER-positive (RR=0.60 [CI=0.39-0.91]), and PR (RR=0.65 [CI=0.48-0.88]).9 The variation of outcome was evidence that the therapeutic outcome is also influenced by the individual case that needs to be considered for the treatment [20, 21].

Regression multivariate analysis shows that only staging factor significantly associated with the cancer survival outcome (p=0.001) with OR=3.088 (Exp-B=1.895-5.032). This finding implied that cancer with lower staging tended to have better survival outcomes. Overall, from all factors that have been studied as independent variables to the outcome, they had a role in the outcome 14.1% (R-square). The finding was consistent with the previous study that the increased cancer stage and more invasive had a higher risk of recurrence [12]. The finding implies that breast cancer's initial diagnosis and treatment are necessary to increase disease survival. Preventing the recurrence by early diagnosis and treatment is very beneficial because it tends to be more severe with the distant location when the recurrence occurred. In this study, we found the breast cancer cases were distributed almost equal between young (<50 yo) and pre-menopause age (>50 yo). This implies that the risk of breast cancer has to oversee from a young age, which affects health financing. The cases were also first diagnosed in relatively in a higher stage, which was predominantly above stage-II. This finding indicated the consequences of higher risk recurrence followed by the increasing health financing burden.

In conclusion, the survival outcome within two years after treatment varied among clinicopathology and molecular profiles. Lower cancer stage, luminal A subtype, and ER-positive are most likely to have better outcomes. Molecular marker expression may increase breast cancer cases, which became a consideration for hormonal and target therapy for the individual case.

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Disclosure

The authors declare no conflict of interest.

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