RESEARCH ARTICLE

Prognostic Value of Clinicopathological Factors for Indonesian Breast Carcinomas of Different Molecular Subtypes

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Abstract

Background: Breast carcinoma (BC) is a heterogeneous disease due to its different molecular profiles i.e. luminal (luminal A and luminal B) and non-luminal (HER2 positive and triple negative) subtypes. Prognostic value of clinicopathological factors of Indonesian BC of different molecular subtypes has never been reported previously. This study aims to elaborate prognostic impacts on Indonesian BCs focusing on separate molecular subtypes. Methods: A hundred and fifty cases of invasive BC, stage I-IIIA, in Sardjito Hospital, Indonesia, were stained using anti ER, PR, HER2 and Ki-67 antibodies. Survival and prognostic values were statistically analyzed. **Results:** Compared to the luminal subtypes, the non-luminal subtypes demonstrated higher proportions of intermediate-to-high grade, stage IIIA, positive lymph node infiltration and mortality. The triple negative subtype was typically intermediate-to-high grade, stage IIIA and with a high relative death risk. Luminal A lesions were characteristically low grade, stage I-II and less likely to cause death. **Conclusion:** In non-luminal BC, staging and lymph node metastasis are independent prognostic factors for survival in HER2 positive and triple negative subtypes, respectively. In luminal BC, clinicopathological factors demonstrated no influence on survival. This study suggests that staging and lymph node metastasis are correlated with survival in non-luminal Indonesian BCs.

Keywords: Indonesian breast carcinoma- molecular subtypes- clinicopathological factors- prognostic value- survival

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Introduction

Breast carcinoma (BC) is the most common cancer and the leading cause of cancer-related death among women worldwide. The most frequent histological type of BC is invasive ductal carcinoma, non-specific type (NST). Several clinicopathological factors that influence the treatment and prognosis of BC are age, tumor grade, tumor size, lymph node metastasis, hormonal receptor status, HER2 status and cell proliferation status (Tavassoli and Devilee, 2003; Hoda et al., 2009).

Breast carcinoma is a heterogenous disease that has different prognosis and response to therapy, despite of the similarities in histological type, tumor grading and staging. It is believed that different clinical behaviors of BC are due to different molecular characteristics. Therefore, tracing of specific mammary epithelial cells is important to definitely identify cells of origin in different tumor types (Rouzier et al., 2005; Visvader, 2009). Normal breast ducts are lined by two distinct differentiated cell types, luminal cells lining the apical surface of the duct and myoepithelial cells that reside within the basal layer. Therefore, BC can be categorized into subtypes that are consistent with derivation from the normal basal and luminal mammary epithelial cells (Jones et al., 2004; Huper and Marks, 2007).

Gene expression studies have identified several BC subtypes. These include two main subtypes of Estrogen Receptor (ER) positive cancers (Luminal A and Luminal B) and ER negative cancers (Triple Negative and HER2 positive). These subtypes are markedly different in prognosis and therapeutic choices. Genes that differentiate these subtypes are called the intrinsic genes and made up of several clusters of gene relating to ER, PR (Progesteron Receptor), HER2 expression, proliferation and cluster of basal genes (Marchiò and Reis-Filho, 2008).

Sixty percent of BC cases are Luminal subtype. The Luminal subtype of BC tends to have a better prognosis compared with the Non-Luminal subtype since the Luminal subtype is hormone receptor-positive. Therefore, it is more sensitive to hormonal therapy approach. Luminal cancer consists of Luminal A and Luminal B subtypes. Characteristics of Luminal A subtype cancers are ER positive, PR positive/ negative, HER2 negative, and low Ki-67 index. Luminal A subtype is associated with good prognostic factors, low relapse and high survival

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rate. Meanwhile Luminal B subtype cancers, has high cell proliferation rate, tends to occur among young age, has higher grade and big-size tumor. The prognosis of Luminal B subtype is relatively worse in comparison to Luminal A subtype (Kao et al., 2009; Onitilo et al., 2009).

Non-Luminal BC consists of HER2 positive and Triple Negative subtypes. These subtypes have a fairly poor prognosis and are more prone to early and frequent recurrence and metastasis. Prognosis of HER2 positive subtype is better compared with Triple Negative subtype since it can be treated with Trastuzumab/ Herceptin. Meanwhile for Triple Negative subtype, chemotherapy is the only best choice of treatment (Sorlie et al., 2003; Chanrion et al., 2007; Campbell et al., 2011).

The correlation of clinicopathological factors and molecular subtypes of breast carcinoma remains unclear and several studies showed controversial results (Goldhirsch et al., 2005; Rouzier et al., 2005; Onitilo et al., 2009; Goldhirsch et al., 2011). Thus, further exploration to obtain more precise prognosis and therapy approach is indeed necessary. This study was performed in order to define prognostic value of clinicopathological factors of Indonesian BC in different molecular subtypes

Materials and Methods

The design of this study was a prospective cohort study. No follow-up or reverse back intervention was done in this research. Subjects used in this study were 150 paraffin-embedded tissues of invasive duct carcinoma of the breast (NST), stage I-IIIA, from Sardjito General Hospital, Yogyakarta, Indonesia. Clinical and histopathologic information was retrieved from medical record. Individual patient's information was unpublished. The study was approved by the Research Ethics Committee of Faculty of Medicine, Universitas Gadjah Mada.

Samples taken from biopsy containing small focus of tumor were excluded from this study. Hematoxyllin Eosin (HE) slides were examined to classify cancer morphology into low, moderate and high grade tumor based on WHO criteria. Cancer staging was determined with the TNM system (Tavassoli and Devilee, 2003).

Criterias for favourable prognostic factors of BC were: age > 50 years old, size ≤ 2 cm in, no lymph node metastasis, low grade tumor and Luminal subtype. Meanwhile, criterias for unfavourable prognostic factors were: age ≤ 50 years old, size > 2 cm in, positive lymph node metastasis, moderate - high grade tumor and Non-Luminal subtype. Adjuvant chemotherapy was determined by the type of adjuvant chemotherapy given to the patients after surgery, and was grouped into Anthracycline-based and Taxane-based. Survival was determined from the follow-up of patients from January 1st, 2008 – June 30, 2013. The follow up was carried out to collect survival information, which was determined in weeks.

Samples were stained immunohistochemically using monoclonal antobody anti ER (Biocare, 6F 11, dilution 1:50), PR (Biocare, PGR 636, dilution 1:50), HER2 (Biocare, cb 11, dilution 1:100) and Ki-67 (Abcam ab 16667, dilution 1:100) to classify breast carcinoma into Luminal (Luminal A and Luminal B) and Non-Luminal (HER2 positive and Triple Negative) subtypes. DAB chromogen and counter stain Hematoxyllin Mayer were used in this study.

Expression of ER, PR, HER2 and Ki-67 were detemined under light microscopy by two independent observers. Samples are considered ER, PR positive if > 1% of tumor cells show positive nuclear staining (Hammond et al., 2010). Samples are HER positive if > 30 % of tumor cells show positivity membrane staining (Wolff et al., 2007). Ki-67 expression is considered high if ≥ 14% of tumor cells show positive nuclear staining (Kim et al., 2012).

Bivariate analysis was used to identify correlation between each prognostic clinicopathological factor for survival in several molecular subtypes of BC. Survival analysis was performed using product limit of Kaplan Meier. Comparison between favourable and unfavourable prognosis was analyzed using Log-rank test with significance level <0.05. Multivariate analysis was conducted to determine prognostic value. To control other prognostic value, analysis of Proportional Hazards (Cox) Regression was performed.

Results

Demographic and clinical characteristics of this study (Table 1) demonstrated that mean of patients age was 52.61± 10.65 (31-81 y.o), proportion of post menopausal patients was 59.3%, and mean of tumor size was 4.82±2.65 (1-15 cm). Table 2 showed that Luminal A subtype tends to occur in older women and small sized cancer. Luminal A subtype showed the highest number of cancers with negative lymph node metastasis, low grade tumor, early stage and alive patients compare to other molecular

Table 1. Demographic and Clinical Characteristic of Indonesian Breast Carcinoma

	Characteristics	Number (%)
Age	≤ 50 yo	61 (40.7%)
	>50 yo	89 (59.3%)
Size	>2cm	127 (84.7%)
	≤ 2cm	23 (15.3%)
Grading	Moderate - high	124 (82.6%)
	Low	26 (17.4%)
Staging	IIIA	39 (26.0%)
	I-II	111 (74.0%)
Lymph node	Positive	92 (61.3%)
	Negative	58 (38.7%)
Molecular subtypes	Luminal A	54 (36.0%)
	Luminal B	27 (18.0%)
	HER2 positive	25 (16.7%)
	Triple negative	44 (29.3%)
Survival	Death	42 (28.0%)
	Alive	108 (72.0%)
Treatment	Antracycline	69(46.0%)
	Taxane	81(54.0%)

Table 2. Characteristic of Breast Carcinoma Based on Molecular Subtypes

Prognostic factors and survival		Luminal A	Luminal B	HER2 positive	Triple negative
Age (mean)		54.38± 1.01	52.33±1.07	50.80± 1.02	51.62± 1.15
Size (mean)		4.11± 2.03	4.77± 2.47	5.08±3.05	5.57±3.02
Lymph node status	Positive	27 (29.3)	17 (18.5)	18 (19.6)	30 (32.6)
	Negative	27 (46.6)	10 (17.2)	7 (12.1)	14 (24.1)
Grading	Moderate-high	35 (28)	26 (20.8)	22 (17.6)	42 (33.6)
	Low	19 (70)	1 (4)	3 (12)	2 (8)
Staging	IIIA	6 (15.4)	6 (15.4)	10 (25.6)	17 (43.6)
	I-II	48 (43.2)	21 (18.9)	15 (13.5)	27 924.3)
Survival	Death	4 (9.5)	10 (23.8)	10 (19)	20 (47.6)
	Alive	50 (46.3)	17 (15.7)	17 (15.7)	24 (22.2)

Table 3. Survival Analysis of Breast Carcinoma in Different Molecular Subtypes

Subtypes	Survival		Relative Risk	p
	Death (%)	Alive (%)	(95% CI)	
Non Luminal	28 (40.6)	41 (59.4)	RR= 3.27 (1.54 - 6.92)	0.001
Luminal	14 (17.3)	67 (82.7)		

subtypes. Breast carcinoma subtype with the youngest mean of age was HER2 positive subtype, while biggest mean of tumor size was Triple Negative subtype. Relative death risk of Non-Luminal subtype was 3.2 higher than Luminal subtype. By using Luminal A subtype as a standard, Luminal B, Triple Negative and HER subtype patients have a relative death rate 7.3; 10.4; and 5.8 times higher respectively (Table 3 and 4). In Luminal subtype, clinicopathological factors and treatment did not influence patient`s survival (Table 5), therefore multivariate analysis was not performed.

In Non-Luminal subtype breast carcinoma, stage and lymph node status were independent prognostic factors for survival (Table 6). Table 7 showed that staging was an independent prognostic factor for survival in HER2 positive BCs, after being adjusted with age. Table 8 showed that lymph node status was an independent prognostic factor for survival in Triple Negative subtype,

Table 4. Survival Analysis of Breast Carcinoma in Different Molecular Subtypes

Subtypes	Survival		Relative Risk	p
	Death (%)	Alive (%)	(95% CI)	
Luminal A	4 (7.4)	50 (92.6)		
Luminal B	10 (37.0)	17 (63.0)	RR=7.35 (2.04 - 26.53)	0.002
HER2 positive	8 (32.0)	17 (68.0)	RR=5.88 (1.57 - 22.03)	0.008
Triple negative	20 (45.4)	24 (54.6)	RR=10.42 (3.21 - 33.86)	0.000

Table 5. Clinicopathologic Factors Analysis of Luminal Subtype for Survival

Prognostic factors		Survival		p	Relative Risk
		Death (%)	Alive (%)		95% CI
Age	≤ 50 y.o	5 (17.9)	23 (82.1)	0,57	1.06 (0.32-3.54)
	>50 y.o	9 (17.0)	44 (83)		
Size	>2cm	10 (15.4)	55 (84.6)	0.28	0.54 (0.15-2.04)
	≤2cm	4 (25.0)	12 (75.0)		
Grading	Moderate – high	12 (19.7)	49 (80.3)	0,26	2.21 (0.45-10.82)
	Low	2 (10.0)	19 (90.0)		
Staging	III A	3 (25.0)	9 (75.0)	0.34	1.76 (0.42 -7.54)
	I-II	11 (15.9)	58 (84.1)		
Lymph node status	Positive	9 (20.5)	35 (79.5)	0,31	1.65 (0.49-5.43)
	Negative	5 (13.5)	32 (86.5)		
Treatment	Antracycline	7 (18.9)	30 (81.1)	0.47	1.23 (0.38-3.09)
	Taxane	7 (15.9)	37 (84.1)		

Table 6. Independent Prognostic Factors Analysis of Non-Luminal Subtype for Survival

Prognostic factors		Survival		p	Unadjusted	Adjusted
		Death (%)	Alive (%)		HR (95% CI)	HR (95% CI)
Staging	IIIA	17 (63.0)	10(37.0)	0.003	4.79 (1.69-13.58)	0.43(0.19-0.96)
	I-II	11 (26.2)	31(73.8)			
Lymph node status	positive	25 (52.1)	23(47.9)	0.003	6.53 (1.69-25.03)	0.28(0.08-0.96)
	negative	3 (14.3)	18(85.7)			

Table 7. Independent Prognostic Factor Analysis of HER2 Positive Subtype for Survival

Prognostic factors		Survival		p	Unadjusted	Adjusted
		Death (%)	Alive (%)		HR (95% CI)	HR (95% CI)
Age	≤ 50 y.o	5 (45.5)	6 (54.5)	0.19	3.06 (0,54-17,46)	0.42 (0.09-1.78)
	>50 y.o	3 (21.4)	11(78.6)			
Staging	IIIA	6 (60.0)	4 (40.0)	0.02	9.75 (1.38-68.79)	0.17 (0.03-0.84)
	I-II	2 (13.3)	13 (86.7)			

Table 8. Independent Prognostic Factors Analysis of Triple-Negative Subtype for Survival

Prognostic factors		Survival		p	Unadjusted	Adjusted
		Death (%)	Alive (%)		(HR 95% CI)	(HR 95% CI)
Age	≤ 50	7 (31.8)	15 (68.2)	0.065	0.32 (0.09-1.12)	2.21(0.87-5.55)
	> 50	13 (59.1)	9 (40.9)			
Staging	IIIA	11 (64.7)	3 (35.3)	0.042	3.67 (1.02-13.14)	0.74 (0.29-1.86)
	I-II	9 (33.3)	18 (66.7)			
Lymph node status	Positive	18 (60)	12 (40)	0.05	9.0 (1.7-47.6)	0.15 (0.14-0.65)
	Negative	2 (14.3)	12 (85.7)			

after being adjusted with age and stage.

Discussion

This present study found that Luminal A is the most common subtype of Indonesian breast carcinoma, followed by Triple Negative, Luminal B and HER2 positive subtypes, respectively (Table 1). Our results are parallel with other studies from Asia and Eropa (Raica et al., 2011; Chuthapisith et al., 2012; Galukande et al., 2014; Widodo et al., 2014). However, it is not similar with previous report in African-American women in which Triple Negative was the most frequent subtype (Carey et al., 2006; Foulkes et al., 2010). High frequency of Triple Negative subtype in Africa was influenced by many factors such as population and age differences, case-ascertainment method, genetic profile, life-style risk factor and mammography screening access. Biological factors, such as low penetrance of genetic variants might influence this discrepancy. Genetic factors seem to play an important role in the incidence and heterogeneity of BC accross different races and etnicities (Brewster et al., 2014).

Compared to other BC subtypes, Luminal A subtype in this study tends to be diagnosed in older patients, smaller tumor size, negative lymph node infiltration, early stage, low grade, and longer survival (Table 2). These results suported previous study that luminal A subtype was associated with favorable prognostic factors (Onitilo et al., 2009; Su et al., 2011; Yanagawa et al., 2012; Widodo et al., 2014; Liao et al., 2015).

Non-Luminal BC subtype has higher relative mortality risk compared to Luminal BC, and the highest one was Triple Negative subtype (Table 3 and 4). Non-Luminal BC derived from myo-epithelial and basal cells of mammary gland which are very active but prone to dysregulation during the cell cycle. Non-Luminal subtype commonly carries genetic abnormailty, such as p-53 mutation, HER2 amplification, BRCA-1 dysfunction, genomic instability and high cell proliferation. This carcinoma tends to occur at young ages as well as large sized and high grade tumor (Huper and Marks, 2007; Allison, 2012; Yanagawa et al., 2012).

In this study, clinicopathological factors are not independent predictor factor for survival in Luminal BC subtype (Table 5). Mortality of BC is influenced by many factors, among which is the stage of cancer at initial diagnosis. In this study, 84.2% of Luminal subtypes was found in early stage patients with number of death was 17.3 % (14 patients). According to Zaha et al., (2010) (Zaha et al., 2010), 5 year survival rate of early stage BC was 88%. High survival rate of Luminal subtype is due to a good response of anti hormonal therapy. During the first 4 years after therapy, Luminal subtype carcinoma can be dormant and become more aggressive in 10 to 15 years after complete therapy. It is likely due to the molecular alteration, where hormon receptor positive status becomes negative (Kennecke et al., 2010).

In this study, independent predictor factors of Non-Luminal subtype BC for survival were lymph node status (HR=0.28; 95% CI=0.08-0.96) and stage (HR=0.43; 95% CI= 0.19-0.96) (Table 5). Stage was independent prognostic factor for survival in HER2 positive subtype (Table7) and lymph node metastasis was independent prognostic factor for survival in Triple Negative subtype (Table 8). These results supported by previous study by Panopoulos et al., (2009) (Panopoulos et al., 2009) showing that stage and lymph node metastasis were aggressive indicators in Non-Luminal subtype BCs.

Non luminal subtype is hormone receptor-negative carcinoma with high proliferation rate and rapid growth, so that for tumor development, it requires a lot of nutrients (Carey et al., 2006; Campbell et al., 2011). Compared to normal cells, energy in cancer cells is produced through substrate level phosphorylation. The energy demand is obtained from aerobic glycolysis and oxydative phosphorilation. Although the energy from aerobic glycolysis is less effective than the energy from oxydative phosphorilation, it allows the cells to remain alive and resistant to therapy under hypoxic conditions (Demetrius et al., 2010). Hypoxia increases chance of tumor cells for migration and metastasis, as well as alter some inflammatory mediators such as IL-8. Il-8 that play a role in Epithelial Mesenchymal Trasition (EMT) therefore promoting tumor resistance to standard therapy (Waugh and Wilson, 2008; Voss et al., 2011).

Non-luminal BC subtype tends to metastasize to the visceral organs (Raica et al., 2011; Jaime Jans et al., 2014). Visceral metastasis occurs through the lymph vessels, blood vessels or afferent lymph vessels and eventually forming colonies on distant sites of the primer tumor. Distant metastasis has organo-specific manner, tumor cells in the lymph vessels can only alive and growth in a specific organ. Lymph node metastasis also facilitates the occurence of distant metastasis (Hirakawa et al., 2007; Ran et al., 2010).

This study suggests that stage and lymph node metastasis are correlated with survival in Non-Luminal subtype of Indonesian BC. Stage is correlated with survival in HER2 positive BC, while lymph node metastasis is correlated with survival in Triple Negative BC. In Luminal subtype BC, clinicopathological factors are unsignificantly correlated with survival.

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