RESEARCH ARTICLE

Editorial Process: Submission:04/27/2018 Acceptance:08/04/2019

Luminal B is the Most Common Intrinsic Molecular Subtypes of Invasive Ductal Breast Carcinoma Patients in East Kalimantan, Indonesia

Swandari Paramita[1,2]*, Eko Nugroho Raharjo[3], Maria Niasari[3], Fieska Azizah[4], Nur Ahlina Hanifah[4]

Abstract

Objective: Breast carcinoma has no longer been considered as a single and standalone disease. Its subtypes have been known to vary in terms of risk factors, natural histories, and responses to therapies. In particular, intrinsic molecular subtypes based on St. Gallen International Expert Consensus 2013 have classified breast carcinoma into luminal A, luminal B, *HER2*+, and triple-negative, depending on the expression of *ER*, *PgR*, *HER2*, and *Ki-67*. Research on intrinsic molecular subtypes of breast carcinoma in Indonesia, however, are rarely conducted, which then triggers the intention to conduct this study. **Methods:** In this work, a retrospective study was conducted on 92 formalin-fixed paraffin-embedded samples of invasive ductal breast carcinoma patients. These samples were from patients at Abdul Wahab Sjahranie County General Hospital Samarinda, East Kalimantan, Indonesia, in 2016. Next, immunohistochemical staining using *anti-ER*, *PgR*, *HER2*, and *Ki-67* antibodies was applied to classify intrinsic molecular subtypes. Then, an association between clinical and immunohistochemical factors with intrinsic molecular subtypes of breast carcinoma were analyzed using Chi-square test. **Results:** Looking at results of the retrospective study, luminal B was discovered as the most common intrinsic molecular subtypes of breast carcinoma (42.39%) in East Kalimantan, Indonesia. The next ranks of breast carcinoma subtypes in the region included *HER2*+ (39.13%), triple-negative (10.87%), and luminal A (7.61%). In fact, there was a significant association between age ($p = 0.019$) with intrinsic molecular subtypes of breast carcinoma. **Conclusion:** The study found luminal B as the most common intrinsic molecular subtypes of Indonesian breast carcinoma in the region under investigation. In the future, the higher positivity rate of luminal B in breast carcinoma patients compared to prior studies would require further investigations.

Keywords: Luminal B- intrinsic molecular subtypes- breast carcinoma

Asian Pac J Cancer Prev, **20 (8)**, 2247-2252

Introduction

Currently, breast carcinoma has been recognized as the world's most commonly occuring cancer type. It has been estimated to cause deaths of over 500,000 women annually all around the world. Besides, estimated 1.7 million cases of breast carcinoma are diagnosed every year (DeSantis et al., 2014). In fact, almost a quarter of breast carcinoma are diagnosed in Asia-Pacific regions, in which Indonesia is in third place. Among globally estimated 500,000 deaths of females annually, about 22% deaths occur throughout the Asia-Pacific region. Ranking third in the region, Indonesia accounted for 17% of breast carcinoma deaths in second place after China. Breast carcinoma has also estimated to account for 9% of cancer-related deaths among females in the Asia-Pacific, ranking fourth behind lung, liver, and stomach cancers (Youlden et al., 2014).

In current advances, breast carcinoma has been posited a heterogeneous disease. In other words, it has no longer been considered as a single and standalone one. Breast carcinoma subtypes can be determined by applying immunohistochemistry methods. These subtypes have been known to vary in terms of risk factors, natural histories, and responses to therapies (Goldhirsch et al., 2011). In 2013, St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer has determined a classification of intrinsic molecular subtypes of breast carcinoma based of their clinicopathologic surrogate definitions. The classification includes luminal A, luminal B, *HER2*+, and triple-negative (Goldhirsch et al., 2013).

In general, each subtypes group is characterized as having different prognosis and response to therapy (Tao et al., 2015). Luminal A particularly has a smaller tumor

*[1]Department of Community Medicine, [4]Medical Doctor Program,Faculty of Medicine, [2]Research Center of MCTrops, Mulawarman University, [3]Department of Pathological Anatomy, Abdul Wahab Sjahranie General County Hospital, Samarinda, East Kalimantan, Indonesia. *For Correspondence: s.paramita@fk.unmul.ac.id*

size, the best prognosis and the lowest recurrence rate than other subtypes. Technically, it is characterized by higher levels of *ER* and lower levels of the proliferation-related genes, including *Ki-67*. In practices, recommendations for luminal A are mainly based on endocrine therapy (Prat et al., 2013). Furthermore, Luminal B has an aggressive phenotype and worse prognosis compared to luminal A. It is characterized by higher levels of growth factor receptor such as *HER2*, which activates signaling pathways (Yan et al., 2015). In details, *HER2+* subtypes have a poor prognosis, and characterized by high proliferation rates. Therapy for luminal B subtype includes the uses of *anti-HER2* such as Trastuzumab. In terms of recommended therapies, luminal B delivers its best responses to neoadjuvant chemotherapy (Asif et al., 2016). Moreover, the triple-negative subtype has been recognized to show the most aggressive behavior with the worst outcome. This subtype is not responding well to either endocrine or adjuvant chemotherapy. Requiring a specific-targeted therapy, chemotherapy is hence stated as the only choice of treatment. Then, these subtypes have been actively studied by various researchers (Keam et al., 2011).

In the literature, prior studies on intrinsic molecular subtypes of breast carcinoma in Indonesia have been focusing on *ER*, *PgR*, *HER2*, and *Ki-67* markers. They are, however, largely produce different results (Prihantono et al., 2017a, 2017b; Rahmawati et al., 2018; Widodo et al., 2017, 2014).

Materials and Methods

Patients

A retrospective study was performed at Abdul Wahab Sjahranie County General Hospital, Samarinda, East Kalimantan, Indonesia, involving samples from patients between January-December 2016. An ethical clearance was obtained from the Ethical Review Committee of the Faculty of Medicine, Mulawarman University, Samarinda, Indonesia (49/KEPK-FK/VI/2017) before conducting the study. In addition to ER, PgR and HER2 status and *Ki67* index, clinical information used in this included ages at diagnosis, tumor sizes, and histological grades. After data gathering, there were 92 cases during the period under investigation. These cases had formalin-fixed paraffin-embedded blocks available for immunohistochemical staining.

Immunohistochemical

In this study, immunohistochemical staining method was performed on formalin-fixed paraffin-embedded blocks. Technically, a section of blocks was stained with primary antibodies for *ER*, *PgR*, *HER2*, and *Ki-67* (all from Leica Biosystem, Newcastle, UK). An automated immunohistochemical staining was conducted and assessed in Leica BOND MAX (Leica Biosystem, Newcastle, UK). Tumors with ≥ 1% positively nuclear-stained cells were considered positive for both ER and PgR expression (Hammond et al., 2010). Besides, HER2 positive was scored if the staining occured for > 10% of tumor cells (Wolff et al., 2013). Then, tumors containing ≥ 14% of nuclear *Ki-67* expression was considered as having a high *Ki-67* rate (Cheang et al., 2009).

Definition of intrinsic molecular subtypes

According to the 2013 St. Gallen Consensus, samples could be distinguished based on their *ER*, *PgR*, *HER2*, and *Ki-67* expressions. Technically speaking, samples were stated as luminal A (*ER+*, *PgR+*, *HER2-*, and *Ki-67* low), luminal B (*ER+*, *PgR+*, any *HER2*, and any *Ki-67*), *HER2+ (ER-*, *PgR-*, and *HER2* over-expressed) or triple negative (*ER-*, *PgR-*, and *HER2-*) (Goldhirsch et al., 2013).

Statistical analysis

In this study, a chi-square test was employed to examine the association of breast carcinoma intrinsic molecular subtypes with clinical and immunohistochemical factors. The test applied values of $p < 0.05$ as considerably significant. All statistical analyses were performed in PSPPIRE 1.0.1 software.

Results

Characteristics of patients

A total of 92 cases of breast carcinoma were included in this study with the following clinical information. First, the mean of patient's age was 48.29 years old (ranged between 23-83 years old), while the mean of tumor size was 5 cm (ranged between 1-17 cm). Besides, the majority of patient's histological grade was in the third group (68.48%). After the immunohistochemical staining process, the *ER*, *PgR*, and *HER2* positive expressions were

Table 1. Clinical and Immunohistochemical Characteristics of Patients

Characteristics		
Age (years)	Mean ± SD	48.29 ± 10.7
	Min – Max	23 – 83
Tumor size (cm)	Mean ± SD	5.00 ± 3.1
	Min – Max	1 – 17
Histological Grade	1	5 (5.43%)
	2	24 (29.09%)
	3	63 (68.48%)
Molecular Subtypes	Luminal A	7 (7.61%)
	Luminal B	39 (42.39%)
	HER2+	36 (39.13%)
	Triple negative	10 (10.87%)
ER	Negative	46 (50%)
	Positive	46 (50%)
PgR	Negative	47 (51.09%)
	Positive	45 (48.91%)
HER2	Negative	39 (42.39%)
	Positive	53 (57.61%)
Ki-67	<14 %	15 (16.30%)
	14-30 %	18 (19.67%)
	>30 %	59 (64.13%)

Table 2. Association between Clinical and Immunohistochemical Factors with Intrinsic Molecular Subtypes

Characteristics		All cases	Luminal A	Luminal B	HER2+	Triple negative	P value
		n (%)	n (%)	n (%)	n (%)	n (%)	
Age	≤ 35 ys	6 (6.5)	1 (14.3)	4 (10.3)	1 (2.8)	0 (0)	0.019†
	> 35 ys	86 (93.5)	6 (85.7)	35 (89.7)	35 (97.2)	10 (100)	
Size	≤ 2 cm	19 (20.7)	2 (28.6)	8 (20.5)	7 (19.4)	2 (20)	0.978
	> 2 cm	73 (79.3)	5 (71.4)	31 (79.5)	29 (80.6)	8 (80)	
Grade	1,2	29 (31.5)	3 (42.9)	13 (33.3)	7 (19.4)	6 (60)	0.091
	3	63 (68.5)	4 (57.1)	26 (66.7)	29 (80.6)	4 (40)	
ER	Negative	46 (50)	0 (0)	0 (0)	36 (100)	10 (100)	0.000†
	Positive	46 (50)	7 (100)	39 (100)	0 (0)	0 (0)	
PgR	Negative	48 (52.2)	0 (0)	3 (7.7)	36 (100)	9 (90)	0.000†
	Positive	44 (47.8)	7 (100)	36 (92.3)	0 (0)	1 (10)	
HER2	Negative	39 (42.4)	7 (100)	22 (56.4)	0 (0)	10 (100)	0.000†
	Positve	53 (57.6)	0 (0)	17 (43.6)	36 (100)	0 (0)	
Ki-67	Low	15 (16.3)	7 (100)	1 (2.6)	4 (11.1)	3 (30)	0.000†
	High	77 (83.7)	0 (0)	38 (97.4)	32 (88.9)	7 (70)	

†Chi-square, p value < 0.05

discovered to be 50%, 48.91%, and 57.61%, respectively. In particular, the majority of *Ki-67* expressions were in the high group (64.13%). Among observed samples, luminal B comprised the most common intrinsic molecular subtypes in the population (42.39%), which was then followed by *HER2+* (39.13%), luminal A (10.87%), and triple-negative (7.61%). Table 1 presents the characteristics of observed patients with breast carcinoma.

Association between clinical and immunohistochemical factors with intrinsic molecular subtypes

Looking at the chi-square test, a significant result (p = 0.019) was revealed for the association of between age with intrinsic molecular subtypes of breast carcinoma. In this study, luminal B was discovered as the most commonly occuring subtypes in patients aged ≤ 35 years, while *HER2+* was most common subtypes in older patients. Table 2 exhibits the association between clinical and immunohistochemical factors with intrinsic molecular subtypes of breast carcinoma.

Discussion

This research had evaluated the distribution of intrinsic molecular subtypes of breast carcinoma and studied their association and correlation with clinical and immunohistochemical factors. In this study, samples under investigation included 92 breast carcinoma patients. The mean age of these samples was 48.29 years old (ranged between 23-83 years old), which was in fact similar to prior study in Makassar, Indonesia, with 46 years old as the average age at diagnosis (Prihantono et al., 2017a). Besides, studies in Malaysia and Indonesia indicated breast carcinoma to present at a younger age for Indonesian women compared to Malaysian women. Ethnical and genetic differences might highlight these results (Ng et al., 2011).

Furthermore, the mean of tumor size in this study was 5 cm (ranged between 1-17 cm). In fact, similar results were discovered by other studies in Indonesia. It confirmed a behavior among breast carcinoma patients in Indonesia, who, in most cases, reported their health condition when their tumor had already become larger in size (Widodo et al., 2017). On the other hand, the majority of patient's histological grade in this research was in the high group (68.48%). Different results were revealed by other studies in Indonesia, in which moderate differentiation was the most common grade compared to high and low group. In practices, histological grading was the predictive and prognostic factor of breast carcinoma (Rahmawati et al., 2018; Widodo et al., 2014).

Furthermore, positive *ER*, *PgR*, and *HER2* expression were discovered at 50%, 48.91%, and 76.09%, respectively. It was parallel with the high frequency of positive *HER2* expressions (56.6%) found in prior study conducted in Makassar, Indonesia (Prihantono et al., 2017b). Besides, the majority of *Ki-67* expressions were in the high group (83.7%), which was similar to previous results of the study in Makassar with *Ki-67* positive index at about 54.2% (Prihantono et al., 2017a).

Next, this study discovered luminal B to comprise the most commonly occuring intrinsic molecular subtypes among observed population (42.39%). After luminal B, the following ranks were *HER2+* (39.13%), luminal A (6.52%), and triple-negative (4.36%). The result was particularly similar to other studies that focused on cases in Southeast Asia regions. Prior research in Vietnam, for example, revealed a relatively high percentage of luminal B subtype (56.5%) (Thang et al., 2015). In another research, the mean percentage of luminal B patients discovered in Myanmar was 46.2%, which was considerably higher than other subtypes (San et al., 2017). Results in Southeast Asia regions were also similar to studies conducted on breast carcinoma cases in other Asia regions. Outside Asia, e.g. in Morocco, luminal B was also discovered as the most frequently occuring molecular subtype of breast cancer

(Fatemi et al., 2012).

In terms of clinical information, this study revealed a significant association between patients' age with intrinsic molecular subtypes of breast carcinoma. Apparently, luminal B was the most common subtype in patients aged ≤ 35 years, while *HER2*+ was the most common subtype in older patients. Results as such indicated younger patients to generally have the worst prognosis. Similar results were discovered by a previous study conducted in Turkey, in which older age was found to act as a risk factor for *HER2*+ overexpressing subtype. Compared to other subtypes, luminal B cases were more likely to occur on patients with younger age at diagnosis (Turkoz et al., 2013).

However, of this study differed from previous reports in other provinces in Indonesia, which found luminal A as the most frequently occuring subtype (Rahmawati et al., 2018; Widodo et al., 2017, 2014). Also, it was different from prior research in Malaysia and Indonesia, which showed tumors suffered by Indonesian women to more likely be *HER2*+ compared to Malaysian women (Ng et al., 2011). The higher HER2 positivity rate in Indonesia has been previously reported about 64.2% (Aryandono et al., 2006).

According to the 2013 St. Gallen Consensus, luminal B could be further distinguished by looking at *ER*, *PgR*, *HER2*, and *Ki-67* expressions. The classification of luminal B included luminal *B-like HER2-* (*ER+*, *HER2-*, and at least one of *Ki-67* high or *PgR-*) and luminal B-like *HER2+* (*ER+*, any *PgR*, *HER2* over-expressed, and any Ki-67) (Goldhirsch et al., 2013). Practically, estrogen and progesterone receptors (*ER* and *PgR*) and *HER2* had been stated as having critical influences on the management of breast cancer. Estrogen had particularly been posited as an important mitogen exerting its activity by being bound to its estrogen receptor (*ER*), which found in almost 80% of breast cancer cases (Azizun-Nisa et al., 2008). Meanwhile, PgR had been recognized as a surrogate marker of a functional *ER*, which would be valuable in predicting the behavior of breast carcinoma. It had been discovered in almost 70% invasive breast carcinomas with a higher positivity in postmenopausal women. The presence of hormone receptors (*ER* and *PgR*) in the tumor tissues were then stated as being well correlated with expected responses to chemotherapy (Shaikh et al., 2016).

Furthermore, *HER2* had been recognized as a proto-oncogene located on chromosome 17q. Besides, it encoded a 185 kDa transmembrane phosphoglycoprotein with tyrosine kinase activity, which had mainly been found at the cell surface of tumor cells. It is amplified and *HER2* overexpressed in almost 25% of invasive breast carcinoma with associated poor prognosis (Tan et al., 2009). Another research in Mexico found *HER2* marker to considerably be associated with a number of pregnancies (Cindy et al., 2015). Meanwhile, prior research in Malaysia discovered women with *HER2+* tumors to significantly and more likely be parous than those with luminal A tumors (Devi et al., 2012). Then, a previous work conducted in East Kalimantan, Indonesia, had also associated risk factors of other cancer types with a number of pregnancies (Paramita et al., 2010).

In general, the limitation of this study included additional focuses on other factors such as genetic background, while ethnical and risk factors were also not evaluated. Further investigations of those factors would hence be necessary. Theoretically speaking, extensive distributions of intrinsic molecular subtypes among worldwide population suggested the critical role of human races or ethnicities in distinguishing breast carcinoma subtypes.

As the conclusion, this study discovered the frequency of intrinsic molecular subtypes of breast carcinoma to vary among different human populations. In particular, the current work had confirmed luminal B as the most commonly occuring intrinsic molecular subtypes of breast carcinoma in East Kalimantan, Indonesia. In terms of clinical information, age was found to be associated with intrinsic molecular subtypes of breast carcinoma. Therefore, the higher luminal B positivity rates in Indonesian patients would require a further study. Findings of this study highlighted an urgent need for a set of comprehensive breast carcinoma awareness programs particularly in East Kalimantan, Indonesia. It should particularly be designed to encourage women to be aware of their breast carcinoma-related health conditions at earlier stages.

Acknowledgments

Acknowledgments to the Faculty of Medicine, Mulawarman University, Samarinda, Indonesia, for financing this research, as part of the implementation of Research Grant of Mulawarman University year of 2017. All procedures followed were following the ethical standards from the Ethical Review Committee of the Faculty of Medicine, Mulawarman University, Samarinda, Indonesia. The authors declare that they have no competing interests.

Funding Statement

This research was funding by Research Grant of Mulawarman University, Samarinda, Indonesia.

Statement conflict of Interest

The authors do not have any conflicts of interest to declare.

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