Original Article

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The Impact of Subtype Distribution in Inflammatory Breast Cancer Outcome

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ABSTRACT

Objective: Inflammatory breast cancer (IBC) has an unfavourable prognosis despite the advances made in the treatment of breast cancer. Our study aimed to define immunohistochemistry-based surrogate subtype distribution to determine whether the breast cancer subtype accompanied survival outcome differences in IBC.

Materials and Methods: Medical records of female breast cancer patients with non-metastatic inflammatory breast cancer admitted to our clinic between March 2000 and December 2015 were retrospectively reviewed. Patient demographics, clinical and pathological feature of the primary tumour, adjuvant treatment options and survival data were analysed. Intrinsic breast cancer subtypes were defined according to ER, PR, HER-2 and ki-67 status.

Results: We identified 129 non-metastatic inflammatory breast cancer patients. Median follow-up was 73 months. 10 (7.7%) were luminal A-like, 67 (51.9%) were luminal B-like, 37 (28.6%) were HER-2 positive, and 15 (11.6%) were triple negative (TNBC) by immunohistochemistry. There were no statistically significant differences between subtypes in terms of histological type, grade, tumour size and lymph node status. Median disease-free survival was 47 months (95% confidence interval [CI] 29.2-82.6) and median overall survival was 75 months (95% CI 64.7-90.8). Triple negative breast cancer showed poorer outcome than other subgroups. Presence of TNBC disease was associated with poorer outcome compared to luminal A (HR: 0.19, 95% CI 0.04-0.92, p: 0.039), luminal B (HR: 0.34, 95% CI 0.15-0.74, p: 0.007) and HER-2 positive subgroups (HR: 0.40, 95% CI 0.17-0.94, p:0.037). Luminal A patients had a trend to have a better overall survival which did not reach to a statistical significant difference.

Conclusion: Our study put forth that IBC have a poor prognosis irrespective of breast cancer surrogate subtype distribution. Luminal A, the most frequent subtype of breast cancer was the least common in our IBC patient group. TNBC had the worst outcome when compared to other breast cancer subtypes.

Keywords: Inflammatory breast cancer, breast cancer subtypes, survival

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Introduction

Inflammatory breast cancer (IBC) is a rare and aggressive form of breast cancer with poor prognosis. Although the incidence has been reported 1–5%, IBC is responsible of 7% of all breast cancer related deaths (1).

Inflammatory breast cancer is defined by international guidelines as a clinicopathological entity. Rapid onset of breast erythema and oedema (*peau d'orange*) involving at least one third of breast skin with or without an underlying mass are the major components of the disease, any pathological type of breast cancer might present as IBC (2). Pathological diagnosis of invasive carcinoma is essential because several infectious conditions of the breast may mimic IBC. Skin biopsy demonstrating dermal lymphatic invasion is the hallmark of the disease however it is not essential for the diagnosis. The majority of IBC patients present with axillary node involvement or metastatic disease at initial diagnosis (3)

In breast cancer tumour stage and histology, nodal involvement, visceral disease and peritumoural lymphovascular invasion are regarded as prognostic features to predict outcomes (4-6). Besides tumour pathologic characteristics, tissue markers of hormone receptors (HR) and human epidermal growth factor receptor (HER-2) overexpression or gene expression studies identify several distinct breast cancer

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subtypes: Luminal A, Luminal B, HER-2 positive and basal like subgroups with diverse prognosis and treatment choices.

Despite well-known aggressive behaviour, recent data could not identify any specific signature of IBC that can predict treatment response or survival income. Although the majority of IBCs are HR negative and HER-2 (+) with high proliferative index, there is not enough data in the literature that determine the IBC outcome according to HR and HER-2 status (7, 8).

In this study, we aimed to define IHC based surrogate subtypes to determine whether breast cancer subtype distribution accompany survival outcome differences in IBC.

Materials and Methods

Patient selection and data collection

We retrospectively analysed medical data of female non-metastatic IBC patients admitted to our clinic between March 2000 and December 2015. Patients with incomplete immunohistochemical (IHC) data to define subtype were excluded. Primary tumour clinical and pathological feature, Patient demographics, clinical and pathological characteristics of the primary tumour, adjuvant treatment types and survival data were collected.

For patients who referred to our clinic by surgeons after surgery with IBC diagnosis, we reviewed the pathology reports to find dermal lymphatic invasion by tumour cells as we could not be certain about their IBC diagnosis without pathology. These patients received adjuvant chemotherapy. Patients who came to clinic prior to surgery, the diagnosis was done clinically and pathologically. These patients received neo-adjuvant treatment.

Ethical committee approval and informed consent was not taken due to retrospective design of the study. This study was conducted in accordance with the ethical standards of responsible committee on human experimentation and Helsinki Declaration.

Definition of molecular subtypes

Surrogate definitions qualified by 2013 St Gallen International Consensus Conference and European Society of Medical Oncology guidelines were used to determine intrinsic breast cancer subtypes (9, 10). Patient population was divided into four subtypes based on oestrogen receptor (ER), progesterone receptor (PR), HER-2, and ki-67 expression; Luminal A-like (ER positive, HER-2 negative, ki-67 low and PR high), Luminal-B like (ER positive, HER-2 negative and either ki-67 high or PR low OR ER positive, HER-2 positive with any ki-67 and PR value), HER-2 positive (HER-2 positive, ER and PR negative), triple negative (ER, PR and HER-2 negative). Suggested threshold value for PR and high ki-67 were 20%.

Statistical analyses

Categorical data were calculated as count and percent, and continuous data were defined as median and range. Chi-square and Kruskal-Wallis tests were used to compare categorical and continuous data among patient subgroups. Survival durations were estimated with Kaplan-Meier method, to compare the survival durations of patient subgroups log-rank test was performed. Disease-free survival (DFS) was defined as the interval between diagnosis of IBC and date of recurrence or death from any cause. Overall survival (OS) was measured from diagnosis to death from any cause. The possible factors identified with univariate analyses were further included in the Cox regression analysis, to determine independent predictors of DFS. All *p*-values reported were two-sided and a *p*-value of less than 0.05 was considered significant. Statistical analyses were performed using the Stata software (STATA version 14, Stata Corp LP, Texas, USA).

Results

Clinicopathological features

Medical records of breast cancer patients admitted to our clinic between March 2000 and December 2015 were reviewed, patients with metastatic disease and incomplete IHC data were excluded. One hundred and twenty-nine patients were included in the analysis.

The median age at diagnosis was 49.1 years (range: 28.8-78.4) and median follow-up was 73 months. Invasive ductal carcinoma was the most common histology (74.4%); 3.1% of the patients had invasive lobular carcinoma, 11.6% had mixed lobular and ductal histology and 10.9% of the patients had other histologic types including micropapillary carcinoma and apocrine carcinoma. The tumours were frequently grade III (53.4%) and 46.6% were grade I-II. Axillary lymph node status was N0 in 7.7%, N1 in 19.3%, N2 in 37.9% and N3 in 31.7% of the patients. ER was positive in 51.9% and HER-2 was positive in 48% of the patients. Clinical and pathological characteristics of the patient population according to surrogate subtypes are summarized in table 1. Of the 129 IBC patients; 10 (7.7%) were luminal A-like, 67 (51.9%) were luminal B-like, 37 (28.6%) were HER-2 positive, and 15 (11.6%) were triple negative (TNBC). HER-2 was positive in 37.3% of luminal B patients. There were no statistically significant differences in histological type, tumour grade, tumour size and lymph node status between subtypes. Median ki-67 expression was 15 in luminal A, 25 in luminal B, 27.5 in HER-2 positive and 30 in TNBC subtypes. Chemotherapy regimens were similar among patient subgroups. (Neo) adjuvant chemotherapy was administered to 123 patients (95.3%) and anthracycline-taxane combinations were preferred in 79.8% of the cases. Four patients' file had missing data about chemotherapy. One patient rejected to receive chemotherapy and still alive without disease progression. One patient had routine follow-up in Surgery Clinic without any chemotherapy. 59.5% of HER-2 positive subgroup and 28.4% of luminal B patients received trastuzumab in (neo) adjuvant setting.

Survival Outcomes

At a median follow-up of 73 months (range: 1-297 months), 65 DFS events and 61 deaths were observed. Median DFS was 47 months (95% confidence interval [CI] 29.2-82.6) and median OS was 75 months (95% CI 64.7-90.8) (Figure 1). Two and five-year DFS were 68% and 47%, respectively. Two and five-year OS were 91% and 63%, respectively. Survival data are summarized in Table 2.

Median DFS was 83.6 months in luminal A (95% CI 13.4-NE), 56.4 months (95% CI 34.3-99.7) in luminal B, 37 months (95% CI 8.5-20) in HER-2 positive, and 18.6 months (95% CI 6.7-NE) in TNBC patients (p=0.10). Five-year DFS was 89%, 49%, 40%, and 30% in luminal A, luminal B, HER-2 positive and TNBC. Median OS was not reached in luminal A, 89.7 months (95% CI 58–121) in luminal B, 74 months (95% CI 32–80) in HER-2 positive, and 52 months (95% CI 10.2–70.9) in TNBC patients (p=0.08). Five-year OS was 86%, 64%, 64%, and 46% in luminal A, luminal B, HER-2 positive and TNBC subtypes, respectively.

In univariate Cox regression analysis, advanced lymph node stage (N2/N3 vs N0/N1), larger tumour size (>5cm vs ≤5cm) were significant-

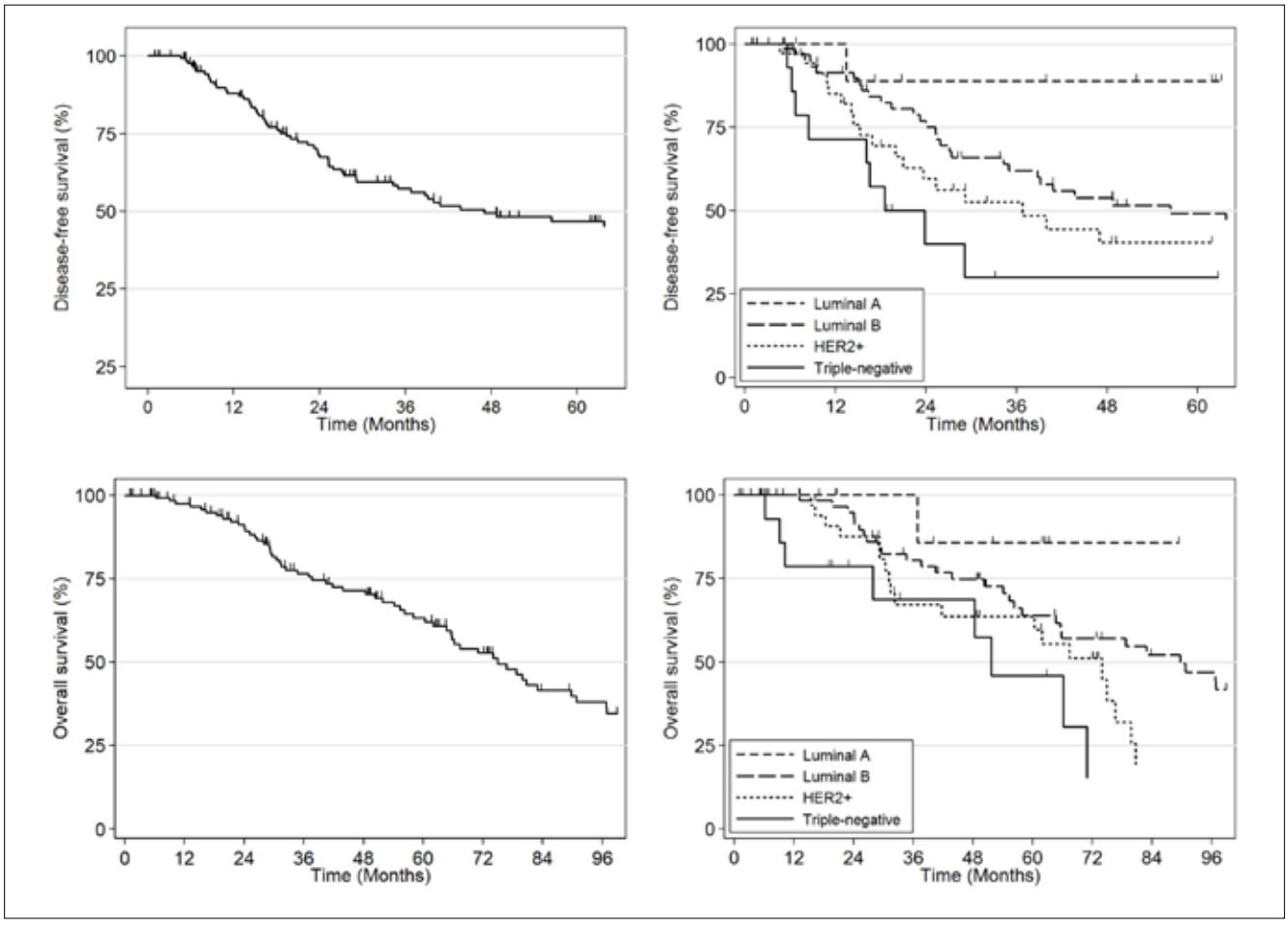

Figure 1. Disease free and overall survival curves in breast cancer subgroups
OS log rank: p: 0.08 DFS logrank: 0.1

ly associated with worse DFS, whereas age, ER expression, HER-2 expression, and Ki-67 level were not associated with DFS (Table 3). In univariate Cox regression analysis, luminal A subtype had significantly better DFS compared to TNBC (HR: 0.20, 95% CI 0.04-0.93, p: 0.04). Tumour subtype, age, lymph node stage and tumour size were included in the multivariate Cox regression analyses. Presence of TNBC disease was associated with poorer outcome compared to luminal A (HR: 0.19, 95% CI 0.04-0.92, p: 0.039), luminal B (HR: 0.34, 95% CI 0.15-0.74, p: 0.007) and HER-2 positive subgroups (HR: 0.40, 95% CI 0.17-0.94, p: 0.037) (Table 4).

Recurrence patterns

Sixty-five patients developed recurrences during follow-up. First metastatic site was locoregional in 6 (4.7%), bone in 24 (18.6%), visceral in 45 (34.9%) patients (Table 3). Lung (14.7%) and liver (15.5%) were the most common visceral sites. Central nervous system was the first metastatic site in 9 (7%) cases. Thirty (23.2%) patients had single, 32 (24.8%) patients had more than one metastatic site. Metastatic sites were not different among surrogate subtypes. The local relapse rate was not different among patient groups who had received adjuvant or neo-adjuvant chemotherapy.

Discussion and Conclusion

Inflammatory breast cancer is an infrequent cancer type. American Joint Committee on Cancer (AJCC) defines inflammatory carcinoma as T4d, irrespective of nodal and visceral involvement, is staged at least as IIIB; stage IIIC with nodal and stage IV at metastatic disease. Compared with other types of breast cancer, IBC tends to be diagnosed at younger ages.

Inflammatory breast cancer is a unique entity with aggressive characteristic features and worse outcomes (1). In a retrospective analysis consisted of 1071 locally advanced breast cancer (LABC) patients, Cristofanilli et al. (11) revealed IBC had 1.6 times the risk of recurrence and 1.4 times risk of death compared with LABC. A study that did a direct comparison of survival among women with inflammatory and non-inflammatory stage III breast cancer revealed that IBC patients had 43% increase risk of death when compared to non-IBC patients (12).

The distinct features of the disease and failure of standard therapeutic options gave rise to genome wide approaches in IBC however specific molecular features have not been defined (13, 14). There is not a surrogate marker to predict therapy response or survival (3).The multidisciplinary multimodal therapy consisting of neo-adjuvant systemic therapy followed by surgery and postmastectomy radiation has been shown to improve outcomes, however this approach is underutilized (15, 16). Despite the advances in adjuvant treatment of breast cancer, there is not a new therapeutic option for IBC patients yet. Gonzalez-Angulo et al. (17) reviewed the IBC patient data in MD Anderson Cancer Center and revealed that prognosis of IBC did not show a significant improvement in the last 30 years with DFS duration of 2.3 years and median OS of 4.2 years.

Table 1. Clinical and pathological characteristics*

	Luminal A (n=10)		Luminal B (n=67)		HER2-positive (Non-luminal) (n=37)		Triple-negative (n=15)		p
Median age (IQR)	48.8	(34.5-72.5)	46.6	(29.8-69.1)	52.4	(28.8-78.)	45.3	(30.4-76.7)	0.28
Histology									
Ductal	6	(60.0)	50	(74.6)	29	(78.4)	11	(73.3)	0.84
Lobular	1	(10.0)	2	(3.0)	1	(2.7)	0	(0.0)	
Mixed ductal and lobular	1	(10.0)	8	(11.9)	3	(8.1)	3	(20.0)	
Other**	2	(20.0)	6	(9.0)	4	(10.8)	1	(6.7)	
Tumour size									
≤5cm	7	(70.0)	41	(64.1)	25	(67.6)	11	(73.3)	0.91
>5cm	3	(30.0)	23	(35.9)	12	(32.4)	4	(26.7)	
Unknown	0	(0.0)	3	(4.5)	0	(0.0)	0	(0.0)	
Lymph node status									
N0	0	(0.0%)	6	(9.0%)	3	(8.1%)	1	(6.7%)	0.061
N1	6	(60.0%)	10	(14.9%)	5	(13.5%)	4	(26.7%)	
N2	3	(30.0%)	26	(38.8%)	12	(32.4%)	8	(53.3%)	
N3	1	(10.0%)	23	(34.3%)	15	(40.5%)	2	(13.3%)	
Unknown	0	(0.0%)	2	(3.0%)	2	(5.4%)	0	(0.0%)	
Grade									
Grade 1/2	3	(30.0)	19	(38.0)	10	(31.3)	6	(40.0)	0.88
Grade 3	7	(70.0)	31	(62.0)	22	(68.8)	9	(60.0)	
Unknown	0	(0.0)	17	(25.4)	5	(13.5)	0	(0.0)	
ER									
Negative	0	(0.0)	10	(14.9)	37	(100.0)	15	(100.0)	<0.001
Positive	10	(100.0)	57	(85.1)	0	(0.0)	0	(0.0)	
HER2									
Negative	10	(100.0)	42	(62.7)	0	(0.0)	15	(100.0)	<0.001
Positive	0	(0.0)	25	(37.3)	37	(100.0)	0	(0.0)	
Ki67									
<20%	10	(100.0)	15	(27.3)	6	(20.0)	2	(16.7)	<0.001
≥20	0	(0.0)	40	(72.7)	24	(80.0)	10	(83.3)	
Unknown	0	(0.0)	12	(17.9)	7	(18.9)	3	(20.0)	
Chemotherapy									
A	3	(30.0)	4	(6.0)	4	(10.8)	1	(6.7)	0.003
T	0	(0.0)	2	(3.0)	7	(18.9)	0	(0.0)	
A+T	6	(60.0)	60	(89.6)	23	(62.2)	14	(93.3)	

*Date are reported as number (%) or median (IQR)
**Other histological types include invasive micropapillary carcinoma and apocrine carcinoma
A: anthracycline; ER: oestrogen receptor; PR: progesterone receptor; T: taxane

In LABC, pathological complete response rate (pCR) following neo-adjuvant chemotherapy has emerged as the most common surrogate endpoint. The breast cancer subtypes demonstrate diverse pCR, HER-2 positive and TNBC patients had favourable response to neo-adjuvant chemotherapy (18). The breast cancer subtypes were defined in IBC patients also in several studies to evaluate if IHC based surrogate subtypes will have an additive prognostic feature on these patients.

Table 2. Disease-free and overall survival

	Luminal A (n=10)	Luminal B (n=67)	HER2 positive (n=37)	Triple-negative (n=15)	All (n=129)
Disease-free survival					
No. of events	2 (20%)	35 (52.2%)	19 (51.4%)	9 (60%)	65 (50.4%)
Median DFS, months	83.6	56.4	37	18.6	47
(95% CI)	(13.4-NE)	(34.3-99.7)	(8.5-20)	(6.7-NE)	(29.2-82.6)
2-year DFS,%	89	77	59	40	68
(95% CI)	(43-98)	(64-86)	(41-74)	(14-65)	(59-76)
5-year DFS,%	89	49	40	30	47
(95% CI)	(43-98)	(35-62)	(23-58)	(8-56)	(37-56)
Overall survival					
No. of events	1 (10%)	32 (47.8%)	20 (54.1%)	8 (53.3%)	61 (47.3%)
Median OS, months	NE	89.7	74	52	75
(95% CI)	-	(58-121)	(32-80)	(10.2-70.9)	(64.7-90.8)
2-year OS,%	100	95	87	79	91
(95% CI)	-	(85-98)	(70-95)	(47-92)	(84-95)
5-year OS,%	86	64	64	46	63
(95% CI)	(33-98)	(49-75)	(44-78)	(15-72)	(53-72)

DFS: disease-free survival; NE: not estimable; OS: overall survival

Table 3. Sites of first recurrence

	Luminal A (n=10)		Luminal B (n=67)		HER2-positive (n=37)		Triple-negative (n=15)		All (n=129)	
Bone	1	(10.0%)	16	(23.9%)	3	(8.1%)	4	(26.7%)	24	(18.6%)
Liver	2	(20.0%)	10	(14.9%)	7	(18.9%)	1	(6.7%)	20	(15.5%)
Lungs	0	(0.0%)	7	(10.4%)	9	(24.3%)	3	(20.0%)	19	(14.7%)
Brain	0	(0.0%)	8	(11.9%)	0	(0.0%)	1	(6.7%)	9	(7.0%)
Locoregional	0	(0.0%)	3	(4.5%)	2	(5.4%)	1	(6.7%)	6	(4.7%)

CNS: central nervous system

Masuda et al. (19) defined subtypes of IBC by HR and HER-2 status and evaluated the outcome of IBC patients after neo-adjuvant chemotherapy. Five hundred twenty seven stage III IBC patients received neo-adjuvant chemotherapy and definitive surgery in this study. Patient group separated to 4 subtypes: HR +/HER-2 +, HR+/HER-2 -, HR-/HER-2+, HR-/HER-2-. The pCR was found 15% in whole group with median follow- up of 38.4 months. pCR was found as a highly prognostic factor except HR+/HER-2+ group. In this study, unlike BC studies, HR positive disease was not found to have a favourable prognosis irrespective of HER-2 status. The pCR rates were found lower in HR+/HER-2 negative subgroup. TNBC had the worst survival rate. In a recent population based study from the SEER program also demonstrated that TNBC subtype had poorer OS and breast cancer specific mortality than other sub-types (20). The largest study in the literature with HR and HER-2 data was derived from a retrospective NCCN multi institution review with 478 non-metastatic IBC patients. In this study, patients were classified as HR positive, HER-2 enriched or TNBC. The data did not analyse ki 67 status so HER-2 positive patients could not be defined as Luminal B or HER-2 positive. This study clearly put forth the poor prognosis of IBC, 10-year survival of stage III patients who received aggressive multimodality treatment was found less than 50%. The median follow-up and survival were 30 and 66 months respectively. In the study, TNBC were more likely to develop metastatic disease than other types but as the study's primary objective was to characterize recurrence patterns and outcomes, the data lack comparative features of HR, HER-2 and TNBC subgroups (20, 21).

In our study, the patient groups were defined as 2013 St Gallen International Consensus to four groups: luminal A-like, luminal B-like, HER-2 positive and TNBC. Median age was found 49.1 years in our patient population. This is slightly younger than general breast can-

Table 4. Univariate and multivariate analysis for disease-free survival

		HR	95% CI	p
Univariate analysis				
Subtypes	Luminal A	0.20	0.04-0.93	0.040
	Luminal B	0.49	0.24-1.04	0.062
	HER-2-positive	0.25	0.28-1.37	0.239
	Triple-negative	Ref.		
Age	Continuous	1.01	0.99-1.03	0.26
Lymph nodes	N2/N3 vs N0/N1	1.97	1.03-3.78	0.042
Tumour size	>5cm vs ≤5cm	1.82	1.11-2.99	0.018
ER	Negative vs positive	1.51	0.93-2.46	0.10
HER-2	Positive vs negative	1.48	0.89-2.36	0.14
Ki-67	≥20 vs <20	1.14	0.63-2.07	0.66
Multivariate analysis				
Subtypes	Luminal A	0.19	0.04-0.92	0.039
	Luminal B	0.34	0.15-0.74	0.007
	HER-2-positive	0.40	0.17-0.94	0.037
	Triple-negative	Ref.		
Age	continuous	1.03	1.00-1.05	0.022
Lymph nodes	N2/N3 vs N0/N1	1.94	0.97-3.89	0.061
Tumour size	>5cm vs ≤5cm	2.10	1.23-3.60	0.006

CI: confidence interval; ER: oestrogen receptor; HR: hazard ratio; Ref: reference

cer population in Turkey which was reported as median 51 years by analysis of 13240 patients (22). Most of the patients (51.9%) were in the luminal B group. Luminal A subtype, which is the most frequent subtype in non-IBC and reported as 62% of all breast cancers in Turkey, was the least common group in our study (7.7%)(22). IBC There were any difference in histologic grade and lymph node status between subgroups. Fifty-five patients received neo-adjuvant (42.6%) and 74 (57.4%) patients received adjuvant treatment with similar protocols. Nearly half of our patient group received neo-adjuvant treatment although neo-adjuvant chemotherapy is a better option for these patients. Our patient data was collected starting from year 2000. Hence, in that period, neo-adjuvant chemotherapy as well as trastuzumab did not constitute the standard of care in Turkey. As a reference centre, we also saw patients who should ideally get chemotherapy initially however admitted to our clinic after surgery, so all these patients had to have adjuvant chemotherapy. In our patient population prognosis was poor; only 63% of the patients were alive at five years. The median OS and DFS were similar to a recent NCCN multi institution analysis (21). There were any significant OS and DFS difference between subgroups in Kaplan Meier survival analysis. 50.4% of our patients developed recurrence during follow-up. Among them, the most frequent site of first recurrence were bone (18.6%) and liver (15.5%), whereas CNS metastasis constitute 7% of metastatic disease which is diverse from a previous study with 21% CNS involvement (21).

Our study put forth that luminal A, which is the most favourable breast cancer subtype, was less common in IBC disease. These patients had a trend to have a better overall survival which did not reach to a statistical significant difference. However, the lymph node involvement was found 92.3% in luminal A patients that is discordant with luminal disease feature. TNBC subtype showed worse prognosis compared with luminal and HER-2 subtype. Our findings were similar with three previous studies that also reported the TNBC with the worst survival rate (19-21).

Until future molecular studies clarify the enigma of the disease character, IBC should be regarded as poor prognostic disease irrespective of subtype distribution and the best therapeutic strategy should be developed for these patients.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Informed consent was not received due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

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