



Prognostic Role of Lymphovascular Invasion and Lymph Node Status among Breast Cancer Subtypes

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Context: Breast cancer subtype (BCS) and lymphovascular invasion (LVI) have both been independently demonstrated as prognostic factors. **Aims:** The objective of this investigation was to evaluate the prognostic power of LVI among BCSs. **Settings and Design:** From an institutional database, 2017 women with a histopathologically confirmed the diagnosis of breast cancer treated between January 2006 and December 2014 were consecutively selected. **Subjects and Methods:** Information recorded for each patient included age at diagnosis, year of diagnosis, and date of death or last contact. Total incidences of recurrence or death from breast cancer were ascertained from follow-up lasting until 31 June 2013. Institutional review board approval was obtained through our institution's human investigations committee. **Statistical Analysis Used:** Univariate and multivariate survival analysis were performed using the Kaplan–Meier analysis and Cox proportional hazards model with a stepwise backward elimination to derive a final model of variables with a significant independent relationship with overall survival (OS) and recurrent-free survival (RFS). All statistical analyses were two-sided with significance defined as $P < 0.05$. **Results:** For the entire cohort, the median follow-up OS period was 43.2 months. Tumor size, LVI, lymph node status, and treatment factors (operation type, chemotherapy, and hormone therapy) differed among subtypes with respect to OS and RFS. The highest incidence of LVI positivity (26.4% vs. 26.9%, respectively) and lymph node involvement (39.7% vs. 36.4%, respectively) occurred in the luminal B and luminal HER2 subtypes. There were significant differences in the OS and RFS rates according the LVI among the BCS. On multivariate analysis, there were significant differences in OS according to the status of lymph node-negative and LVI-positive in the luminal HER2 subtype, as well as lymph node-positive and LVI-positive in the triple negative (TN) subtype. There were also significant differences in RFS according to the status of lymph node-negative and LVI-positive in the luminal A subgroup. **Conclusions:** LVI in BCS was an important prognostic factor for OS and RFS. LVI and lymph node status were important prognostic factor for OS and RFS among BCSs. There were significant differences in OS according to the lymph node-negative and LVI-positive in the distribution of luminal HER2, the lymph node-positive, and LVI-positive in the distribution of TN. There were also significant differences in the RFS according to the lymph node-negative and LVI-positive in the luminal A.

Key words: Breast cancer subtypes, lymphovascular invasion, lymph node status, overall survival, recurrence-free survival

INTRODUCTION

Gene expression profiling has established that breast cancer comprises a group of biologically distinct diseases.^{1,2} According

to St Gallen International Breast Cancer Conference (2011), breast cancer subtypes (BCS) are classified as luminal A; luminal

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B; luminal human epidermal growth factor receptor 2 (HER2); HER2; and triple negative (TN).^{3,4} Significant differences have been observed in response to treatment and survival outcome among these BCS.⁵⁻⁸ Therefore, accurate prognosis depends on multiple variables. The prognostic values of these variables are independent of other clinicopathological variables, such as patient age, lymph node status, histologic grade, tumor size, estrogen receptor (ER) status, and systemic therapy. The prognostic significance of lymphovascular invasion (LVI) in breast cancer was described more than four decades ago.⁹ Since then, several independent studies have investigated the prognostic significance of LVI in breast cancer. The 2007 St Gallen guidelines subsequently concluded that only extensive LVI should be used as an adverse prognostic factor.¹⁰ However, these guideline definitions are still relatively vague and require more evidence. Several authors have underscored a strong relation between LVI and lymph node status of patients with breast cancer¹¹⁻¹⁴ and were also recently reported to be a strong predictor of breast cancer survival.¹⁵⁻¹⁷ LVI is a part of risk assessment and delivers significant prognostic information, although with limited predictive value.¹⁸⁻²⁰ Although BCS and LVI have both been independently demonstrated as prognostic factors, there is a paucity of data describing the relationship between the two. Consequently, the primary objective of this investigation was to evaluate the prognostic power of LVI among BCS. The secondary objective was to investigate whether there is an association with LVI and lymph node status among BCS with regard to the overall survival (OS) and recurrence-free survival (RFS) rates.

SUBJECTS AND METHODS

Study population

From an institutional database, 2017 women were consecutively selected from patients with confirmed histopathological diagnosis with breast cancer treated between January 2006 and December 2011. Information recorded for each patient included age at diagnosis, year of diagnosis, and date of death or last contact. Total incidences of recurrence or death from breast cancer were ascertained from follow-up lasting until 31 June 2013. Institutional review board approval was obtained through our institution's human investigations committee. Patients were treated with either mastectomy or breast-conserving surgery. After completion of surgery, endocrine therapy, and local radiotherapy or adjuvant systemic treatments were administered as indicated based on the international recommendations.²¹

Eligibility criteria

Tumor characteristics included tumor size (<2 cm, 2–5 cm, >5 cm); lymph node status (negative or positive);

LVI (negative or positive); and treatment factors include radiotherapy, type of surgery, chemotherapy, or endocrine therapy.²²⁻²⁴ In this study, LVI was defined as the presence of carcinoma cells within a definite endothelial-lined space based on the CUMC standard pathological definition. To detect lymphatic and vascular channels more precisely, the immunohistochemical stain of CD31 was performed to highlight the endothelial cells. The St Gallen International Breast Cancer Conference (2011) identified the following BCS. If Ki-67 is not available, some alternative measure of proliferation, such as histological grade (G), may be used in making this distinction.^{3,25,26} Therefore, in our study, grading was used to capture proliferation activity as described earlier: luminal A (ER + and/or progesterone receptor (PR) +, HER2–, and G1/2), luminal B (ER + and/or PR+, HER2–, and G3), luminal HER2+ (ER + and/or PR+, HER2+, and any grade), HER2-type (ER–, PR–, and HER2+), and TN (ER–, PR–, and HER2–). ER/PR positivity was determined by immunohistochemistry analysis of the number of positively stained nuclei 1+, 1%. Tumors were considered as HER2+ when cells presented strong membrane staining (3+). Tumors exhibiting 0 or 1+ staining for HER2 protein overexpression were considered to be HER2–. In cases of equivocal membrane staining (score 2+) for HER2, fluorescence *in situ* hybridization was used to evaluate gene amplification.^{27,28}

Statistical analysis

Interrelationships between variables were assessed using contingency table analysis with the Chi-square test for trend as appropriate. Univariate and multivariate survival analyses were performed using the Kaplan–Meier analysis and Cox proportional hazards model with a stepwise backward elimination to derive a final model of variables with a significant independent relationship with OS and RFS. All statistical analyses were two-sided with significance defined as $P < 0.05$. All statistical analysis was performed using the SPSS Software version 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinicopathological characteristics

The clinicopathological BCS characteristics among the 2017 patients included in this study are shown in Table 1 (the total number of cases and controls do not correspond because of missing data). For the entire cohort, the median follow-up OS period was 42.7 months. The luminal A/B consisted of 1290 patients (64%), the luminal HER2 consisted of 499 patients (24.7%), the HER2 consisted of 119 patients (5.9%), and the TN consisted of 109 patients (5.4%). These features differed among subtypes with respect to tumor

LVI play an important factor among BCS

Table 1: Clinicopathological characteristics of all patients in breast cancer subtypes ($n=2017$)

Variable	Luminal A (%)	Luminal B (%)	Luminal HER2 (%)	HER2 (%)	TN (%)	<i>P</i>
Number of case	833 (41.3)	457 (22.7)	499 (24.7)	119 (5.9)	109 (5.4)	
Age						
≤0.3	415 (49.8)	217 (47.5)	234 (46.9)	48 (40.3)	49 (45.0)	0.338
>50	418 (50.2)	240 (52.5)	265 (53.1)	71 (59.7)	60 (55.0)	
Tumor size (cm)						
≤0	516 (64.7)	206 (46.3)	245 (53.6)	59 (53.6)	37 (37.0)	<0.001*
>2-5	253 (31.7)	201 (45.2)	186 (40.7)	40 (36.4)	51 (51.0)	
>5	29 (3.6)	38 (8.5)	26 (5.7)	11 (10.0)	12 (12.0)	
Lymphovascular invasion						
Negative	600 (89.4)	270 (73.6)	337 (82.2)	76 (73.1)	68 (77.3)	<0.001*
Positive	71 (10.6)	97 (26.4)	73 (17.8)	28 (26.9)	20 (22.7)	
Lymph node status						
Negative	541 (77.0)	238 (60.3)	320 (76.6)	68 (63.6)	62 (66.0)	<0.001*
Positive	162 (23.0)	157 (39.7)	98 (23.4)	39 (36.4)	32 (34.0)	
Operation type						
No	89 (10.9)	42 (9.5)	47 (9.6)	7 (6.1)	7 (6.7)	0.011*
Breast conservation surgery	278 (34.8)	134 (30.4)	162 (33.2)	28 (24.6)	34 (32.7)	
Modified radical mastectomy	435 (54.4)	265 (60.1)	279 (57.2)	79 (69.3)	63 (60.6)	
Radiotherapy						
No	323 (40.0)	201 (45.3)	200 (40.6)	50 (43.9)	53 (51.0)	0.125
Yes	484 (60.0)	243 (54.7)	293 (59.4)	64 (56.1)	51 (49.0)	
Chemotherapy						
No	183 (22.7)	93 (20.9)	149 (30.2)	44 (38.6)	39 (37.5)	<0.001*
Yes	622 (77.3)	351 (79.1)	344 (69.8)	70 (61.4)	65 (62.5)	
Endocrine therapy						
No	160 (20.1)	117 (26.7)	141 (28.7)	107 (93.9)	90 (86.5)	<0.001*
Yes	638 (79.9)	322 (73.3)	350 (71.3)	7 (6.1)	14 (13.5)	
Overall survival						
Live	780 (93.6)	393 (86.0)	445 (89.2)	109 (92.4)	93 (85.3)	<0.001*
Dead	53 (6.4)	64 (14.0)	54 (10.8)	9 (7.6)	16 (14.7)	
Recurrence-free survival						
Live	719 (95.1)	368 (88.5)	405 (90.8)	90 (84.9)	83 (83.0)	<0.001*
Dead	37 (4.9)	48 (11.5)	41 (9.2)	16 (15.1)	17 (17.0)	

*Statistically significant. The total number of cases and controls does not correspond because of missing data, *P* value from two-sided Chi-square test.
HER2=Human epidermal growth factor receptor 2; TN=Triple negative

size, LVI, lymph node status, treatment factor (operation type, received chemotherapy, and hormone therapy), OS, and RFS. The luminal A had smaller tumor size (64.7%) more than other subtypes, less to presence of LVI, and lymph node involvement (10.6% vs. 23.0%, respectively). Highest incidence of LVI positivity (26.4% vs. 26.9%, respectively) and lymph node involvement (39.7% vs. 36.4%, respectively) occurred in the luminal B and luminal HER2 subtypes. The TN was more likely to have a larger tumor size (12.0%) more than

other subtypes. With regard to treatment, most patients (90.1%) underwent surgery, of which 32.6% underwent surgery for breast conservation and 57.5% as modified radical mastectomy. In addition, 57.8% received radiotherapy, 74.1% received chemotherapy, and 68.4% received endocrine therapy.

Survival outcomes

Of the 2,017 patients with breast cancer in the BCS group, highest OS, and RFS rate were observed in luminal A (93.6%

vs. 95.1%, respectively) and lowest OS and RFS rate were observed in TN (85.3% vs. 83.0%, respectively) [Table 1]. There were significant differences in the OS and RFS rates according to the LVI among the BCS [Figures 1 and 2]. There were significant differences in OS according to the LVI in the distribution of luminal A ($P = 0.002$), luminal B ($P = 0.024$), luminal HER2 ($P < 0.001$), and TN ($P = 0.033$) subtypes. There were also significant differences in the RFS in the luminal B, luminal HER2, and HER2 subtypes ($P = 0.004$, <0.001 , and 0.024 , respectively). On cox proportional hazards model, after controlling for age and tumor sizes was independently associated with LVI among BCS [Table 2]. There were significant differences in OS according to the LVI in the distribution of luminal A ($P = 0.021$), and luminal HER2 ($P < 0.001$). There were also significant differences in the RFS in the luminal HER2 ($P = 0.002$). The luminal B and TN subtype, however, did not reach statistical significance in OS. The luminal B and HER2 subtype, however, did not reach statistical significance in RFS. Therefore, we inferred that there were stronger links among age and tumor size than LVI in the luminal B, HER2, and TN subtypes according to the OS and RFS. On multivariate analysis, after controlling for age and tumor sizes was

independently associated with LVI and lymph node status among BCS [Table 3]. There were significant differences in OS according to the lymph node-negative and LVI-positive in the distribution of luminal HER2 ($P = 0.021$ [odds ratio [OR], 1.248; 95% confidence interval [CI], 1.304–1.506]), the lymph node-positive and LVI-positive in the distribution of TN ($P = 0.048$ [OR, 1.336; 95% [CI], 1.003–1.781]). There were also significant differences in the RFS according to the lymph node-negative and LVI-positive in the luminal A ($P = 0.030$ [OR, 1.182; 95% [CI], 1.016–1.373]).

DISCUSSION

Previous well-designed studies have analyzed the prognostic factors in patients with invasive breast cancer. Lymph node involvement, age, high histological grade, and large tumor size were significantly associated with a poor survival outcome among BCS.^{5,25} In our series, a significant association with tumor size ($P < 0.001$), OS ($P < 0.001$), and RFS ($P < 0.001$) among BCS, in which TN subtype were associated with a larger tumor size, poor OS, and RFS survival outcome which is in accordance with previous studies.^{25,29,30} Previous studies have also shown

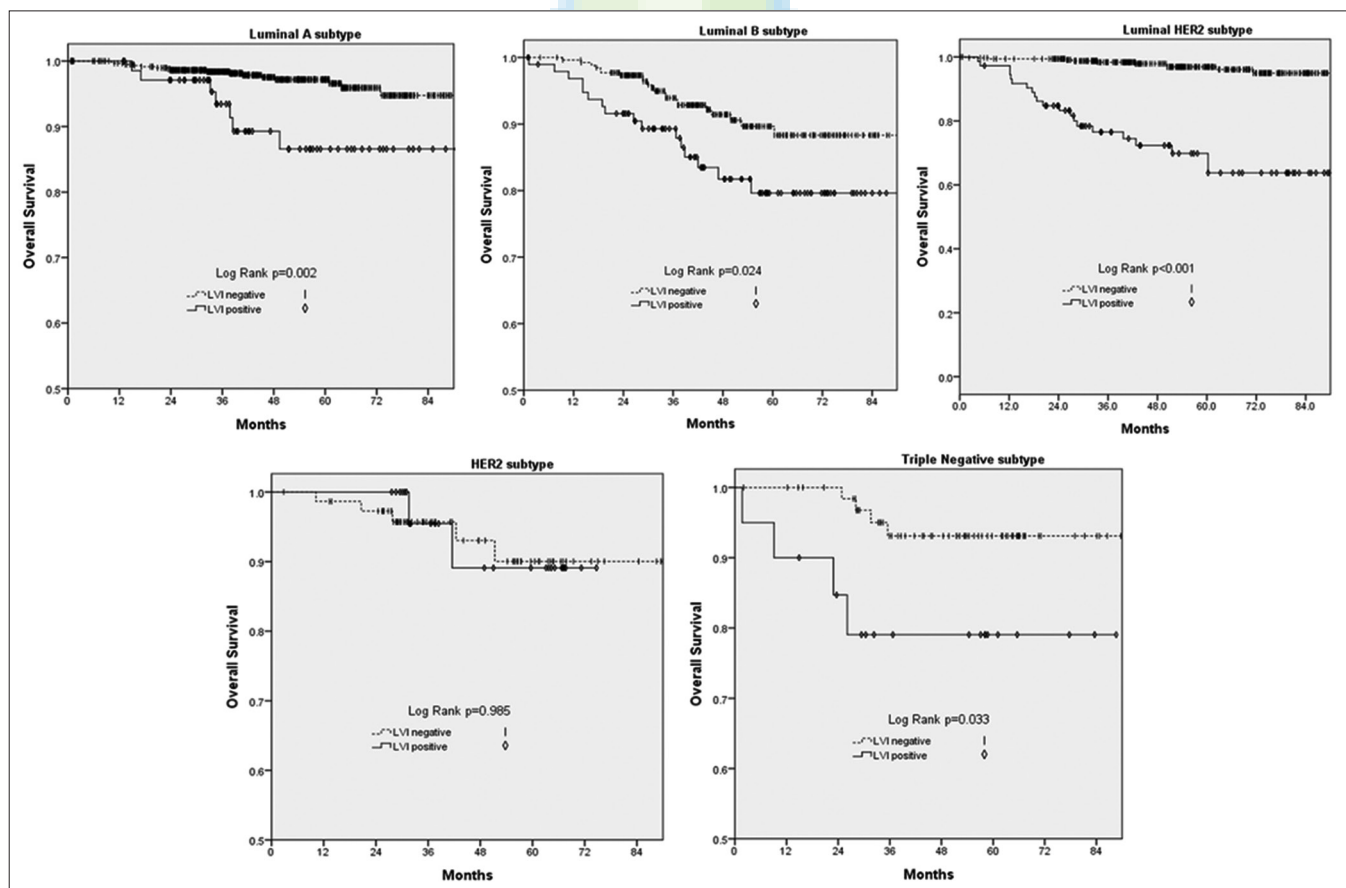


Figure 1: Overall survival according lymphovascular invasion in breast cancer subtypes

LVI play an important factor among BCS

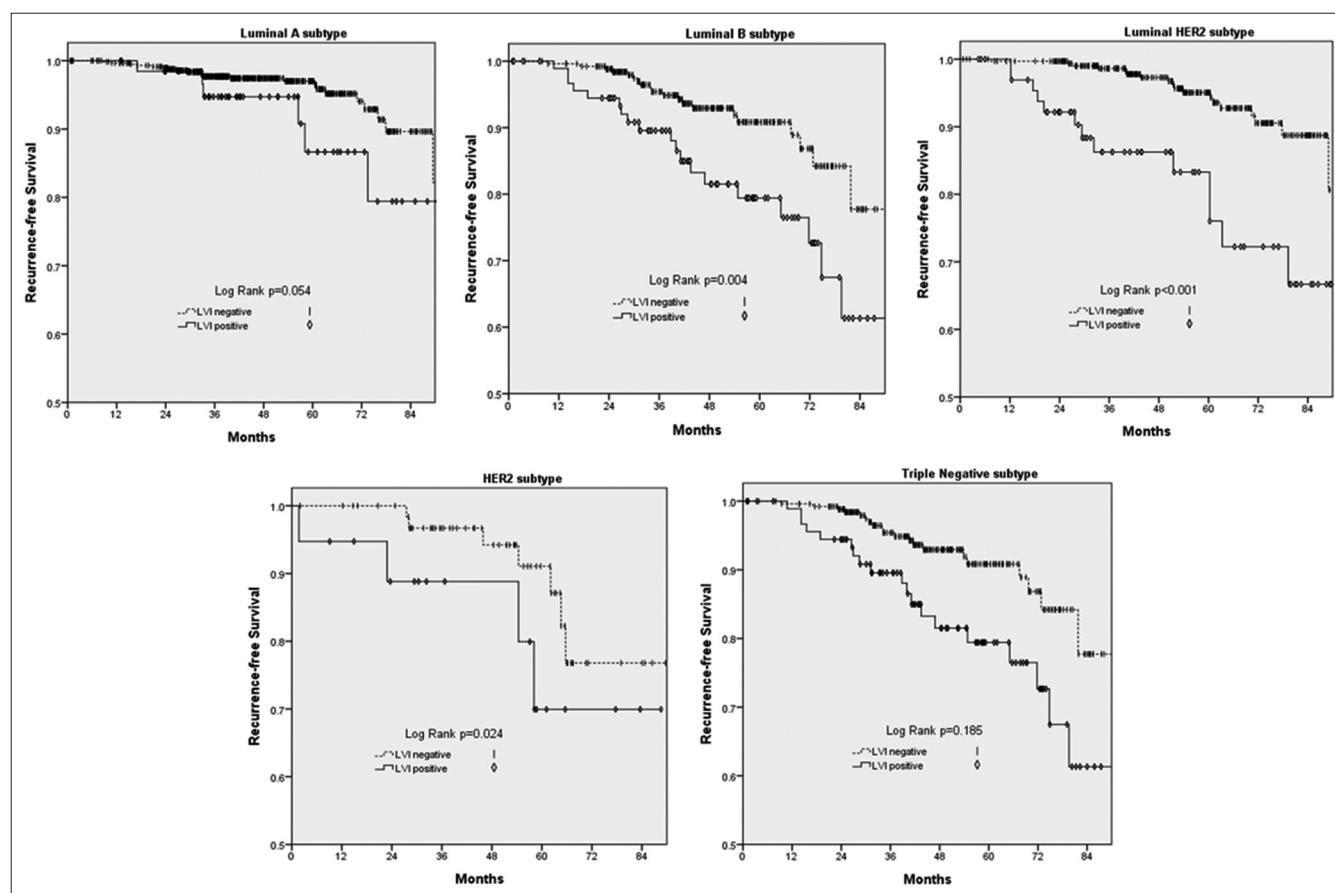


Figure 2: Recurrence-free survival according lymphovascular invasion in breast cancer subtypes

that LVI is an independent poor prognostic factor in patients with breast cancer. LVI, means cancer cells within lymphovascular channels, is a crucial step in the invasion-metastasis cascade. LVI, when identified morphologically in the peritumoural area, is an indicator of metastatic potential and is strongly associated with poor prognosis in many solid tumors, including breast cancer.^{15-17,31} In the present study, we also found a significant association between LVI and BCS ($P < 0.001$) [Table 1]. Highest incidence of LVI positivity occurred in the luminal B and HER2 subtypes. In survival outcome, there were significant differences in luminal A, luminal B, luminal HER2 and TN subtype between LVI with OS. Regarding RFS, there were significant differences in luminal B, luminal HER2, and HER2 subtype with LVI. Even adjusting the age and tumor size for OS and RFS by multivariate Cox proportional hazard analysis, a statistically significant difference remained among the luminal A and luminal HER2 subtypes. Based on our data, we observed a higher relationship with age and tumor size for luminal B, HER2, and TN.

According to our research data, even adjusting the age and tumor size for OS and RFS in lymph node-negative breast cancer

patients by multivariate Cox proportional hazard analysis, a statistically significant difference remained among the luminal HER2 with OS ($P = 0.034$; hazard ratio [HR]: 5.948; 95% CI, 1.148–30.809) and TN subtypes with RFS ($P = 0.034$; HR: 13.495; 95% CI, 1.215–149.886). Rakha *et al.*³¹ reported that LVI provides independent prognostic information for ER-negative and TN subtype in lymph node-negative breast cancer patients was similar our finding. Ragage *et al.* reported that LVI is an independent prognostic factor in lymph node-positive breast cancer. According to our research data, even adjusting the age and tumor size for OS and RFS in lymph node-positive breast cancer patients by multivariate Cox proportional hazard analysis, a statistically significant difference remained among the luminal A with OS ($P = 0.029$; HR: 4.505; 95% CI, 1.163–17.454) Song *et al.* reported that LVI provides independent prognostic information for hormone receptor in lymph node-positive breast cancer patients was similar to our finding.¹² This is an important finding, as OS and RFS rates can be accurately measured among BCS groups according to lymph node status and LVI.

Strengths of our study are the performance of ER, PR, HER2 and LVI testing in a single pathology laboratory.

Table 2: The survival outcome according to breast cancer subtype and lymphovascular invasion

	Luminal A	Luminal B	Luminal HER2	HER2	TN
Overall survival					
Number of LVI negative (%)	584 (97.3)	249 (92.2)	327 (97.0)	70 (93.3)	64 (94.1)
Number of LVI positive (%)	64 (90.1)	81 (83.5)	52 (71.2)	26 (92.9)	16 (80.0)
<i>P</i>	0.007*	0.019*	<0.001*	0.932	0.075
Recurrence-free survival					
Number of LVI negative (%)	565 (96.1)	245 (92.3)	305 (93.8)	68 (91.9)	60 (89.6)
Number of LVI positive (%)	59 (89.4)	74 (78.7)	55 (80.9)	18 (72.0)	15 (78.9)
<i>P</i>	0.024*	0.001*	0.001*	0.018*	0.250

*Statistically significant. The total number of cases and controls does not correspond because of missing data, *P* value from two-sided Chi-square test.

LVI=Lymphovascular invasion; HER2=Human epidermal growth factor receptor 2; TN=Triple negative

Table 3: The survival outcome according to lymph node status and lymphovascular invasion among breast cancer subtypes

	<i>P</i> /HR (95% CI)				
	Luminal A	Luminal B	Luminal HER2	HER2	TN
OS					
Lymph node-negative					
LVI-negative	1	1	1	1	1
LVI-positive	0.982/0.252 (0.000-3.870)	0.986/0.232 (0.000-1.178)	0.021*/1.248 (1.304-1.506)	0.868/1.028 (0.741-1.426)	1.000/0.822 (0.000-E)
Lymph node-positive					
LVI-negative	1	1	1	1	1
LVI-positive	0.096/1.154 (0.975-1.367)	0.609/0.942 (0.751-1.183)	0.183/1.122 (0.947-1.330)	0.659/1.061 (0.817-1.378)	0.048*/1.336 (1.003-1.781)
RFS					
Lymph node-negative					
LVI-negative	1	1	1	1	1
LVI-positive	0.030*/1.182 (1.016-1.373)	0.674/1.021 (0.928-1.1227)	0.260/1.071 (0.951-1.206)	0.419/0.898 (0.692-1.166)	0.149/0.821 (0.628-1.073)
Lymph node-positive					
LVI-negative	1	1	1	1	1
LVI-positive	0.634/0.968 (0.845-1.108)	0.104/1.121 (0.977-1.287)	0.971/0.988 (0.882-1.128)	0.174/1.137 (0.945-1.369)	0.921/1.016 (0.741-1.393)

*Statistically significant. The model is adjusted for age and tumor size. HR=Hazard ratio; CI=Confidence interval; LVI=Lymphovascular invasion; HER2=Human epidermal growth factor receptor 2; TN=Triple negative; OS=Overall survival; RFS=Recurrence-free survival

However, there are several potential limitations to this study. First, the data used in this study are retrospective. Second, the small sample sizes may have influenced the statistical calculations. However, despite the small numbers, to the best of our knowledge, the current study represents one of the largest series in the literature to date. There were studies discussed about the relationship between LVI and individually BCS, but no literature talked about the prognostic value of LVI and all BCSs. Nonetheless, a number of other studies on the prognostic value of LVI between BCS in more contemporary cohorts have similarly reported that

LVI is adequate to predict treatment outcomes in patients with various BCS.

CONCLUSIONS

We found that the LVI and lymph node status were an important prognostic factor for OS and RFS among BCSs. There were significant differences in OS according to the lymph node-negative and LVI-positive in the distribution of luminal HER2, the lymph node-positive, and LVI-positive in the distribution of TN. There were also significant differences

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in the RFS according to the Lymph node-negative and LVI-positive in the luminal A.

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Conflicts of interest

There are no conflicts of interest.

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