Original Article

Potential prognostic value of the lymph node ratio and its correlation with circulating sex hormone concentration in pathological T1/2 breast cancer patients: a retrospective study

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Background: The lymph node ratio (LNR) is an additional informative factor complementing anatomic TNM staging in breast cancer patients. The aim of this study was to evaluate the role of LNR in the cancer-specific and overall survival (OS) in a cohort of pT1/2 breast cancer patients and examine its correlation with circulating sex hormone concentrations in postmenopausal cases of the cohort from eastern China islands.

Methods: Clinical and pathological characteristics, preoperational sex hormone and tumor markers concentrations, and breast cancer-specific survival (BCSS) and OS were analyzed retrospectively in 732 pathological T1/2 breast cancer patients.

Results: The LNR was calculated, and the cut-off value was defined as 0.042 by receiver operative characteristic (ROC) curve according to the patient's mortalities. Patients with LNR ≥0.042 exhibited worse BCSS and OS than others (P<0.001) in pT1/2 breast cancer. Among patients with non-triple negative breast cancer (TNBC) and TNBC subtypes, the LNR ≥0.042 group also exhibited worse BCSS and OS than the LNR <0.042 group (P=0.003, 0.001, and P=0.032, 0.001, respectively). In univariate analysis, unfavorable BCSS and OS were both related with LNR ≥0.042 (P=0.001, <0.001). However multivariate analysis demonstrated TNBC subtypes were independent predictor for BCSS and OS [hazard ratio (HR) =1.449, 95% CI: 1.097–1.914, P=0.009; HR =1.365, 95% CI: 1.093–1.705, P=0.006, respectively]. Notably, Pearson or spearman correlation analysis revealed follicle-stimulating hormone (FSH) and, luteinizing hormone (LH) levels were significantly negatively associated with the LNR (P=0.007, 0.011, respectively) in postmenopausal cases, whereas CA153, CA125 and CEA were positively correlated with it (P<0.001, <0.001, 0.001, respectively) in all cases.

Conclusions: Among pT1/2 breast cancer patients from eastern China islands, the LNR is a predictive prognosis factor; a higher LNR seems to correlate with a worse survival outcome both overall and in the subgroups. Strikingly, the current results reveal that serum FSH and LH level inversely associated with axillary node invasion in postmenopausal cases, whereas tumor markers directly related with it. The LNR is

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an informative factor complementing TNM staging.

Keywords: Pathological T1/2 breast cancer; lymph node ratio; sex hormone concentration; survival; prognosis

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Introduction

Breast Cancer (BC) is a common cancer with a high morbidity and mortality rates. The mortality rate associated with breast cancer is the fifth highest mortality amongst different cancers worldwide. The GLOBOCAN 2020 by the International Agency for Research on Cancer estimates 2.3 million new cases and 685,000 deaths from the disease in 2020 (1). Despite the application of mammographic screening and promoting the early diagnosis of breast cancer with small sized tumors, increasing tumor size has a less liner correlation with possibility of metastasis (2). Moreover, lymph node involvement is a leading cause of death in breast cancer patients regardless of tumor size but correlates with lymph node numbers (3,4). In recent years, several studies have found the lymph node ratio (LNR) has an equal or better effect on predicting the prognosis of breast cancer patients than pathological lymph node staging, and is an independent predictor of breast cancer specific survival (5-8). In addition, the number of metastatic lymph nodes is different according to the different surgical procedure and dissected axillary lymph nodes, thus, the LNR is defined as metastatic lymph nodes (positive lymph nodes) divided by the total number of resected lymph nodes is more accurate than lymph node status alone (9,10). However, the predictive LNR status in the small sized tumors (less than 50 mm) is still unclear. Although a proportion of the analysis of the prognosis effect of the LNR was evaluated by the Surveillance, Epidemiology, and End Results (SEER) data or the National Cancer Database (NCDB), there has been less focus on data from a single institution especially from the archipelago of China. Moreover, the resected number of lymph node will be different in each hospital, thus the validation of the cut-off value for LNR in different hospital will also be essential for the more accurate evaluation of the prognostic value of LNR.

Furthermore, sex steroid hormones, especially estrogen, contribute to the development and progression of breast cancer, by combining to the estrogen receptor (ER) and triggering the ER signaling pathways (11). Androgen may exert both proliferative and anti-proliferative effect in mammary glands by converting to estrogens or acting as an estrogen antagonist (12). However, although circulating sex hormones associate with breast cancer risk, the potential prognostic value has still yielded inconsistent findings (13,14). Nevertheless, the correlation of pre-operational circulating sex hormones with the LNR is still unclear, additionally, postmenopausal women exhibit more stable hormone level, thus, the current study sought to reveal the relationship of these factors with the LNR to better understand the role of sex hormones in the postmenopausal patients with BC.

The Zhoushan archipelago is in eastern China and is composed of more than one thousand islands in which inhabitants have different dietary habits (15). The analysis of cases from archipelago will be a complement to the results from mainland. To better understand the prognostic state of breast cancer with tumor sizes less than 50 mm in these patients, we analyzed the potential risk factors, especially the LNR and its correlation with circulating sex hormone concentration in pathological T1/2 breast cancer patients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2039/rc).

Methods

Patients

A retrospective study was undertaken, in which a total of 732 patients with pathological T1–T2 (pT1–2) breast cancer who accepted surgical resection in the Department of Mammary Gland Disease at the Zhoushan hospital from January 2010 to December 2020 were enrolled retrospectively. Of these, 297 (40.6%) were pT1and 435 (59.4%) were pT2 breast cancer patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Committee of Zhoushan Hospital (No. 2022052) and informed consent was waived for this retrospective analysis.

Data collection

The data of patients were collected from the electronic medical records of Zhoushan Hospital, Zhejiang Province. The demographic characteristics of patients included age, sex, menopause, family history of cancer, personal history of cancer, and other specifications including the pathological tumor size, pathological type, lymph node status, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2), Ki-67 index, serum hormone levels, including estrogen, progesterone, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and serum carbohydrate antigen 153 (CA153), CA125, carcinoma embryonic antigen (CEA) as well as breast surgery procedural details were collected. Pathology was determined according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system (16). The LNR was determined by the ratio of metastatic axillary lymph node (ALN) number to total number of ALN, and the cut-off of the LNR was evaluated by receive operator characteristic (ROC) curve. The exclusion criteria for patients were: (I) pathological tumor size more than 5.0 cm; (II) distant metastasis at the time of diagnosis; (III) personal history of breast cancer; (IV) lost to follow-up; (V) patients died within 30 days post-surgery.

Laboratory detection

Two pathologists determine the expression level of ER, PR, HER2, and Ki-67 which were assessed by immunohistochemical analysis. ER/PR positive cells more than 1% were determined as positive. HER2 negative and weakly positive (+) was determined as negative and strong positive (+++) was confirmed as positive. For positive (++) cases, further fluorescence *in situ* hybridization was used to define HER2 expression. Preoperational serum level of estrogen, progesterone, prolactin, FSH, LH, testosterone, and CA153, CA125, CEA of 732 patients with breast cancer were detected by Cobas e602 automated chemiluminescence analyzer (Roche, German).

Follow-up and deaths ascertainment

Disease progression information was obtained from the follow-up, medical records, or the imaging and clinical examination. The outpatient follow-up was performed by calls or from the motility data base from Zhoushan Center of Disease Control and Prevention. The time of follow-up from the date of surgical resection until the time of death, or the last date of follow up in October, 2021, defined overall survival (OS). Breast cancer specific survival (BCSS) was assessed as those with death caused by breast cancer.

Statistical analysis

GraphPad Prism 5.0 (GraphPad Software Inc., San Diego, CA), MedCalc Statistical Software version 15.8 (MedCalc Software bvba, Ostend, Belgium) and SPSS 17.0 (SPSS Institute, Chicago, IL, USA) were used to analyze the data. Descriptive variables were examined based on the QQ plot and Kolmogorov-Smirnov test to identify normal distribution and presented as median and interquartile range (IQR) or mean value ± standard deviation (SD), then Mann-Whitney U test or unpaired *t*-test were performed to analyze the differences of the categories. Pearson's chi-squared test or Fisher's exact test (T <1 or n<40) was conducted for the comparison of continuous variables. Correlation between the LNR and serum hormone levels and tumor markers was analyzed by Pearson or Spearman correlated test, and BCSS and OS were evaluated by Kaplan-Meier survival curves and log-rank test. Multivariate Cox's proportional hazards regression model was used to identify prognostic factors with univariate analysis P≤0.05. All statistical tests were two-sided, with P value ≤0.05 considered as statistically significant.

Results

Demographic and clinicopathologic features of pathological T1/2 breast cancer patients

Demographic and clinic-pathologic characteristics are listed in *Table 1* for the 732 breast cancer patients with a maximum pathological diameter of 50 mm or less. The LNR was calculated, and the cut-off value was defined by ROC curve according to the death of OS, and we defined 0.042 as the cut-off value at the maximum Youden index of 0.3807 with 0.713 of area under the ROC curve (AUC), 70.6% sensitivity, and 67.5% specificity (*Figure 1*). Patients were then divided into two groups based on the LNR value and the difference between both groups was analyzed. Of these, the LNR ≥0.042 group were more likely to associated with older age (P=0.017), larger tumor size (P<0.001), N stage (P<0.001), pathological type of IDC (P<0.001), Ki67 ≥14% (P=0.003), subtype (P=0.031), pathological stage (P<0.001), and cause of death (P<0.001). All other demographic and clinical

Table 1 Demographic and clinicopathologic features of pathological T1/2 breast cancer patients stratified by LNR according to the Youden index

Characteristics	Total	LNR <0.042	LNR ≥0.042	P
Age (years), mean ± SD [range]	56.3±10.7 [26–84]	55.6±10.7 [28–84]	57.6±10.6 [26–77]	0.017*
Sex, n (%)				0.499
Male	5 (0.7)	4 (0.8)	1 (0.4)	
Female	727 (99.3)	477 (99.2)	250 (99.6)	
Family history of cancer, n (%)				0.737
No	587 (80.2)	203 (67.7)	384 (88.9)	
Yes	145 (19.8)	97 (32.3)	48 (11.1)	
Personal history of cancer, n (%)				0.575
No	683 (93.3)	447 (92.9)	236 (94.0)	
Yes	49 (6.7)	34 (7.1)	15 (6.0)	
Menopause, n (%)				0.658
No	53 (10.0)	32 (9.5)	21 (10.7)	
Yes	479 (90.0)	304 (90.5)	175 (89.3)	
Tumor size, n (%)	2.66±1.2	2.53±1.2	2.90±1.2	<0.001*
T1	297 (40.6)	217 (45.1)	80 (31.9)	0.001*
T2	435 (59.4)	264 (54.9)	171 (68.1)	
Histological grade, n (%)				<0.019*
I	25 (4.8)	21 (6.7)	4 (2.0)	
II	251 (48.4)	157 (49.8)	94 (46.1)	
III	243 (46.8)	137 (43.5)	106 (51.9)	
N stage, n (%)				<0.001*
N0	469 (64.1)	469 (97.5)	0	
N1	169 (23.1)	12 (2.5)	157 (62.6)	
N2	56 (7.6)	0	56 (22.3)	
N3	38 (5.2)	0	38 (15.1)	
Pathological type, n (%)				<0.001*
Ductal carcinoma *in situ*	46 (6.3)	46 (9.6)	0	
IDC	624 (85.2)	384 (79.8)	240 (95.6)	
ILC	18 (2.5)	12 (2.5)	6 (2.4)	
Others	44 (6.0)	39 (8.1)	5 (2.0)	
ER status, n (%)				0.213
Positive	471 (65.5)	301 (63.9)	170 (68.5)	
Negative	248 (34.5)	170 (36.1)	78 (31.5)	
PR status, n (%)				0.295
Positive	407 (56.6)	260 (55.2)	147 (59.3)	
Negative	312 (43.4)	211 (44.8)	101 (40.7)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total	LNR <0.042	LNR ≥0.042	P
HER2 status, n (%)				0.867
Positive	284 (39.5)	149 (34.3)	99 (34.9)	
Negative	435 (60.5)	286 (65.7)	185 (65.1)	
Ki67, n (%)				0.003*
<14%	238 (35.1)	173 (39.1)	65 (27.5)	
≥14%	441 (64.9)	270 (60.9)	171 (72.5)	
Subtype, n (%)				0.031*
Luminal A	155 (21.5)	112 (23.8)	43 (17.4)	
Luminal B	335 (46.6)	201 (42.7)	134 (54.0)	
HER2	102 (14.2)	70 (14.9)	32 (12.9)	
TNBC	127 (17.7)	88 (18.7)	39 (15.7)	
Pathological stage, n (%)				<0.001*
I and IIA	529 (72.3)	470 (97.7)	59 (23.5)	
IIB and III	203 (27.7)	11 (2.3)	192 (76.5)	
Cause of death, n (%)				<0.001*
Alive	698 (95.4)	471 (98.0)	227 (90.4)	
Breast cancer	20 (2.7)	5 (1.0)	15 (6.0)	
Other	14 (1.9)	5 (1.0)	9 (3.6)	

*, P<0.05. LNR, lymph node ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; TNBC, triple negative breast cancer.

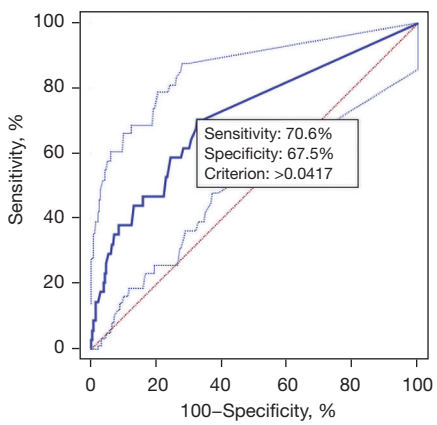

Figure 1 ROC curve for the definition of cut-off value of LNR according to the 34 deaths and 698 cases alive in 732 pT1/2 breast cancer patients (P<0.001). ROC, receiver operative characteristic; LNR, lymph node ratio.

characteristics were comparable between two groups (*Table 1*).

Correlation of LNR with preoperational serum hormone concentration and tumor markers

We then analyzed correlation of the LNR with the preoperational serum hormone in postmenopausal patients, and CA153, CA125, and CEA levels in whole cohort. Among postmenopausal T1/2 patients, FSH and LH levels were significantly lower in patients with LNR ≥0.042 than in patients with LNR <0.042 (P=0.001, 0.006, respectively; *Table 2*), whereas CA153 and CEA levels were obviously higher in patients with ≥0.042 than in the LNR <0.042 group (P<0.001, 0.002, respectively; *Table 2*). Preoperational serum estradiol progesterone, prolactin, and testosterone in postmenopausal patients and CA125 concentrations in all

Table 2 Correlation of LNR with preoperational serum hormone concentration in postmenopausal patients and tumor markers in whole pathological T1/2 breast cancer patients

Characteristics	LNR <0.042		LNR ≥0.042		P
	n	Mean ± SD/median (IQR)	n	Mean ± SD/median (IQR)	
Estradiol (pmol/L)	286	90.2±138.0	165	97.2±165.8	0.630[a]
Progesterone (nmol/L)	286	1.8±3.2	163	1.9±4.5	0.818[a]
Prolactin (mIU/L)	286	166.0±248.3	165	152.1±159.8	0.520[a]
FSH (mIU/L)	285	68.6 (56.4–87.2)	165	62.2 (44.8–78.7)	0.001*[b]
LH (mIU/L)	286	27.2 (20.1–34.4)	164	24.2 (16.7–31.6)	0.006*[b]
Testosterone (nmol/L)	286	1.1±1.0	164	1.0±0.9	0.124[a]
CA153 (U/mL)	359	8.9 (6.6–12.8)	192	10.3 (7.7–16.8)	<0.001*[b]
CA125 (U/mL)	359	14.6±14.0	192	17.7±33.0	0.126[a]
CEA (ng/mL)	359	1.6 (1.1–2.4)	193	1.9 (1.3–2.9)	0.002*[b]

*, P<0.05 by [a], *t*-test, [b], Mann-Whitney U test. LNR, lymph node ratio; FSH, follicle-stimulating hormone; LH, luteinizing hormone; CA153, carbohydrate antigen 153; CA125, carbohydrate antigen 125; CEA, carcinoma embryonic antigen; SD, standard deviation; IQR, interquartile range.

Table 3 Correlation of LNR with serum hormone concentration in postmenopausal patients and tumor markers in whole T1/2 breast cancer patients

Characteristics	r	P
Estradiol	−0.022	0.640[a]
Progesterone	−0.003	0.950[a]
Prolactin	−0.059	0.210[a]
FSH	−0.128	0.007*[b]
LH	−0.120	0.011*[b]
Testosterone	−0.051	0.285[a]
CA153	0.206	<0.001*[b]
CA125	0.165	<0.001*[a]
CEA	0.145	0.001*[b]

*, P<0.05 by [a], *Pearson* test, [b], *Spearman* test. LNR, lymph node ratio; FSH, follicle-stimulating hormone; LH, luteinizing hormone; CA153, carbohydrate antigen 153; CA125, carbohydrate antigen 125; CEA, carcinoma embryonic antigen.

patients were comparable between the two cohorts (*Table 2*). Spearman correlation analysis revealed FSH and LH levels were significantly negatively associated with the LNR (P=0.007, 0.011, respectively; *Table 3*, *Figure 2*), whereas CA153, CA125 and CEA were positively correlated with it (P<0.001, <0.001, 0.001, respectively; *Table 3*, *Figure 2*). Estradiol, progesterone, prolactin, and testosterone level had no obvious correlation with the LNR (*Table 3*, *Figure 2*).

BCSS and OS for pathological T1/2 breast cancer

The mean follow-up time was 67±38 months with a range of 3–144 months. Patients with an LNR ≥0.042 exhibited worse BCSS and OS than others (P<0.001, <0.001, respectively; *Figure 3*) in pT1/2 breast cancer. To further explore the predicted prognosis of the LNR, we further analyzed the subgroup survival according to the LNR status. Among patients with pT1 breast cancer, the LNR ≥0.042 group showed significantly worse OS than the LNR <0.042 group whereas BCSS was comparable between the two groups (P=0.039, 0.885, respectively; *Figure 4*). The LNR ≥0.042 group were also observed to have worse BCSS and OS in patients with pT2 breast cancer (P=0.001, 0.001, respectively; *Figure 4*). In addition, among patients with non TNBC and TNBC subtypes, the LNR ≥0.042 group also exhibited worse BCSS and OS than the LNR <0.042 group (P=0.003, 0.001, and P=0.032, 0.001, respectively; *Figure 5*).

Univariate and multivariate analysis for pathological T1/2 breast cancer

We used a ROC curve to define the cut-off value of circulating sex hormone concentration in postmenopausal patients and tumor markers for BCSS and OS, and the cut-off values are listed in *Table 4*. As the cut-off of Ki67 at 30%

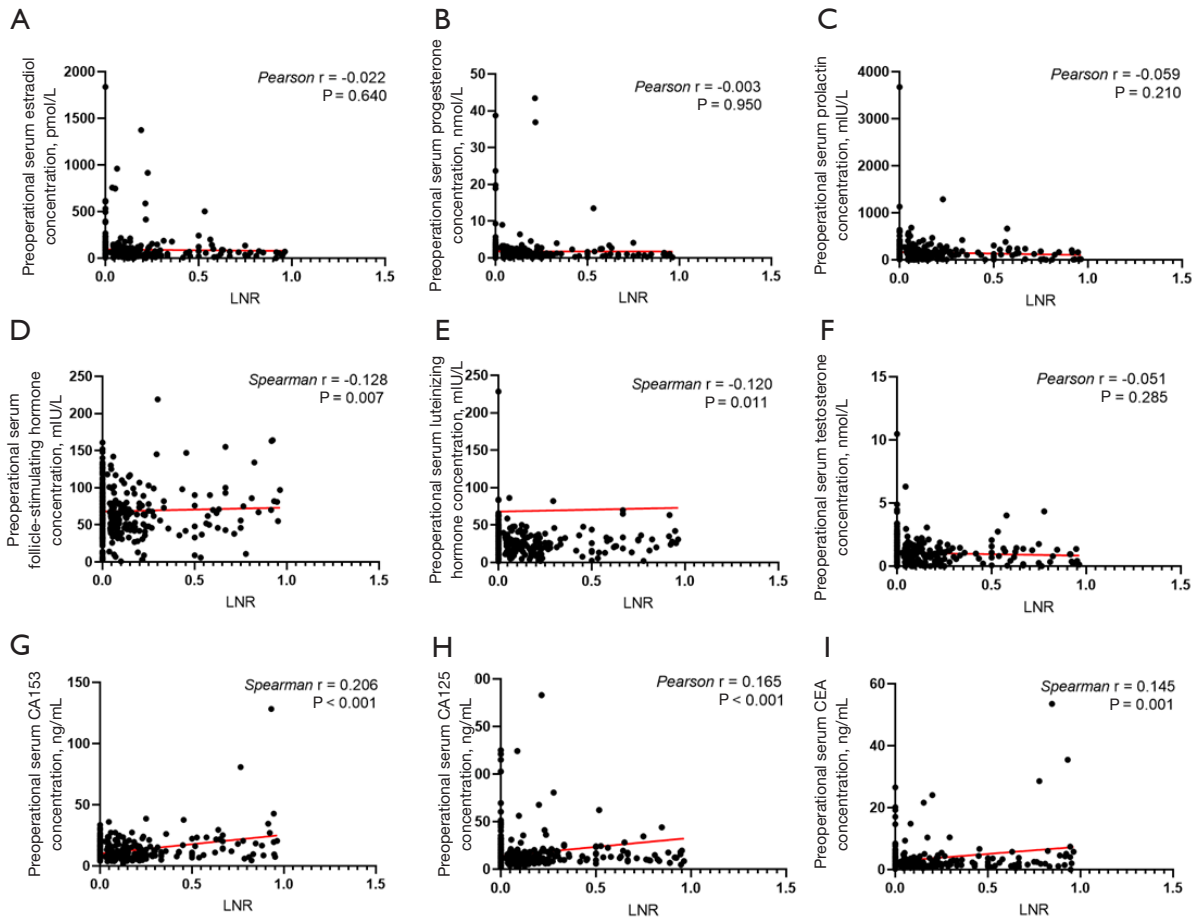

Figure 2 Pearson and Spearman correlated test for the relationship analysis between LNR and preoperational sex hormone concentration in postmenopausal patients and tumor markers in whole pT1/2 breast cancer patients. (A) Correlation between LNR and estradiol level, (B) progesterone level, (C) prolactin level, (D) FSH level, (E) LH level, (F) testosterone level, (G) CA153 level, (H) CA125 level, (I) CEA level. LNR, lymph node ratio; FSH, follicle-stimulating hormone; LH, luteinizing hormone; CA153, carbohydrate antigen 153; CA125, carbohydrate antigen 125; CEA, carcinoma embryonic antigen.

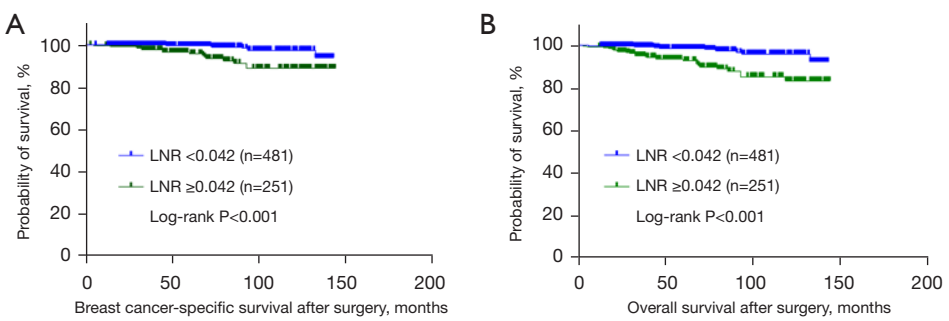

Figure 3 Kaplan-Meier curves after surgery in 732 pT1/2 breast cancer patients. (A) Breast cancer-specific survival and (B) overall survival stratified by LNR levels with a cut-off of 0.042. LNR, lymph node ratio.

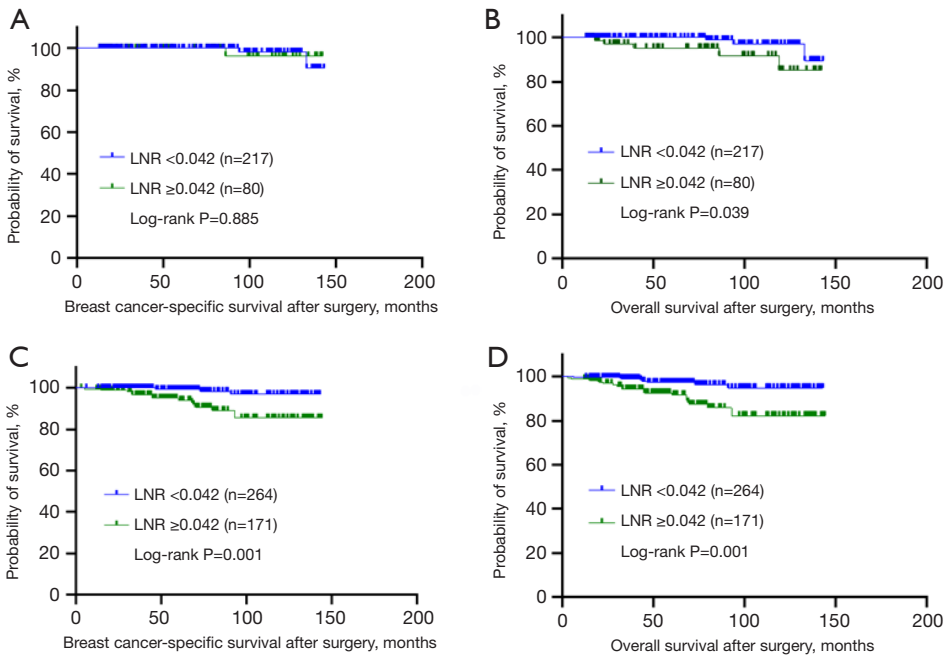

Figure 4 Kaplan-Meier curves after surgery in 297 pT1 and 435 pT2 breast cancer patients. (A) Breast cancer-specific survival and (B) overall survival stratified by LNR levels with a cut-off of 0.042 in pT1 cases. (C) Breast cancer-specific survival and (D) overall survival stratified by LNR levels with a cut-off of 0.042 in pT2 cases. LNR, lymph node ratio.

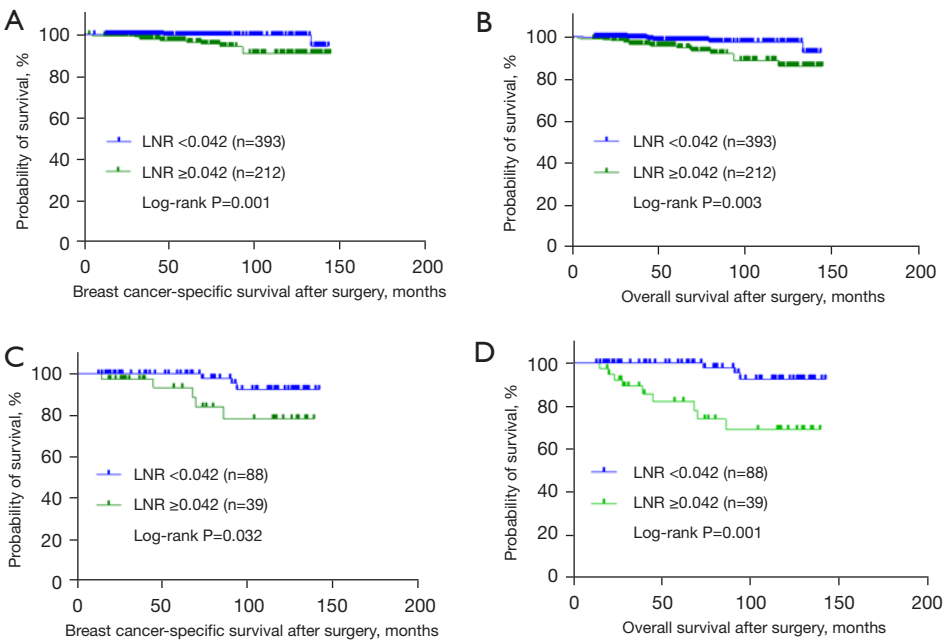

Figure 5 Kaplan-Meier curves after surgery in 605 non-TNBC and 127 TNBC breast cancer patients. (A) Breast cancer-specific survival and (B) overall survival stratified by LNR levels with a cut-off of 0.042 in non-TNBC cases. (C) Breast cancer-specific survival and (D) overall survival stratified by LNR levels with a cut-off of 0.042 in TNBC cases. TNBC, triple negative breast cancer; LNR, lymph node ratio.

Table 4 Cut-off values of ROC curve of preoperational serum hormone concentration in postmenopausal patients and tumor markers in whole cohort for identifying the survival of patients with breast cancer

Characteristics	AUC	Youden index	Cut-off	Sensitivity	Specificity	P
Estradiol	0.588	0.2097	≤43	57.1	63.8	0.1032
Progesterone	0.650	0.3067	≤0.65	55.6	75.1	0.0115*
Prolactin	0.551	0.2704	≤16.19	46.4	80.6	0.4437
FSH	0.529	0.1515	≤56	46.4	68.7	0.6189
LH	0.533	0.1489	≤29.96	77.8	37.1	0.5742
Testosterone	0.606	0.2632	≤0.42	53.6	72.8	0.0897
CA153	0.542	0.1457	≤9.9	66.7	47.9	0.4762
CA125	0.554	0.1812	≤10.7	63.0	55.2	0.3788
CEA	0.572	0.1960	>1.57	74.1	45.5	0.2720
LNR	0.713	0.3807	>0.0417	70.6	67.5	<0.0001*

*, P<0.05. ROC, receiver operative characteristic; AUC, area under the ROC curve; LNR, lymph node ratio; FSH, follicle-stimulating hormone; LH, luteinizing hormone; CA153, carbohydrate antigen 153; CA125, carbohydrate antigen 125; CEA, carcinoma embryonic antigen.

had significant predictive potential for survival outcome, this was used for analysis (17). The results of univariate and multivariate Cox proportional regression analysis for BCSS and OS are summarized in *Table 5*. In univariate analysis, an unfavorable BCSS was related to older age (P=0.015), pT2 stage (P=0.028), Ki67 >30% (P=0.031), TNBC subtype (P=0.043), N2 and N3 stage (P<0.001), LNR ≥0.042 (P=0.001), and advanced pathological stage (P<0.001). An unfavorable OS was associated with older age (P=0.003), personal history of cancer (P=0.002), pT2 stage (P=0.048), Ki67 >30% (P=0.032), TNBC subtype (P=0.031), N2 and N3 stage (P<0.001), LNR ≥0.042 (P<0.001), progesterone level >0.65 pmol/L (P=0.013) and advanced pathological stage (P<0.001). Multivariate analysis demonstrated age more than 55 years (HR =4.281, 95% CI: 1.353–13.545, P=0.013), TNBC subtype (HR =1.449, 95% CI: 1.097–1.914, P=0.009), and lymph node metastasis (HR =4.720, 95% CI: 1.358–16.398, P=0.015) were independent predictors of reduced BCSS (*Figure 6A*), while for OS in T1/2 breast cancer patients, a personal history of cancer (HR =7.235, 95% CI: 2.623–19.956, P<0.001) and TNBC subtype (HR =1.364, 95% CI: 1.094–1.699, P=0.006) were independent predictors (*Figure 6B*).

Discussion

We surveyed the prognostic value of the lymph node ratio in a cohort of 732 pT1/2 breast cancer patients with surgical resection from the eastern China islands. We firstly identified a cut-off value of the LNR according to the mortality of the cohort and found that a higher LNR was associated with advanced tumor progression. Extended BCSS and OS were observed in the group with an LNR less than 0.042, as well as that in the subgroup of pT1 and pT2, non-TNBC, and TNBC subgroups. In particular, we demonstrated correlation of the LNR with preoperational sex hormone concentration in postmenopausal cases, and revealed that FSH and LH levels were significantly negatively associated with the LNR, whereas CA153 and CEA were positively correlated with it in whole cohort.

While pN status was a crucial factor for anatomic TNM staging for the prediction of metastasis and prognosis of breast cancer patients, recent studies suggest the LNR is more accurate than pN status by reducing the variability of lymph node dissection and the standardization may be set up in the near future (6,10,18). We identified the cut-off value of the LNR as 0.042 based on our cohort, which was lower than that be reported in other studies, and may be because a greater percentage of our patients had early-stage disease, and there were different patient sources between institutions (19,20). Furthermore, we firstly focused on all stage patients with or without lymph node metastasis. Our results showed a higher LNR obviously correlated with older age, larger tumor size, N stage, pathological type of IDC, Ki67 ≥14%, subtype, and pathological stage, which is

Table 5 Univariate and multivariate analysis results of breast cancer-specific survival and overall survival in patients with T1/2 breast cancer

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Breast cancer-specific survival						
Age (<55 *vs.* ≥55 years)	3.498	1.270–9.631	0.015*	4.281	1.353–13.545	0.013*
Family history of cancer (no *vs.* yes)	1.753	0.838–3.669	0.136			
Personal history of cancer (no *vs.* yes)	2.120	0.491–9.150	0.314			
Tumour size (pT1 *vs.* pT2)	3.959	1.160–13.516	0.028*	4.199	0.794–22.207	0.091
Histological grade (I and II *vs.* III)	0.794	0.282–2.234	0.662			
Pathological type (ductal carcinoma in situ *vs.* IDC, ILC and others)	0.216	0.001–33.409	0.551			
ER status (negative *vs.* positive)	0.664	0.275–1.602	0.362			
PR status (negative *vs.* positive)	0.542	0.221–1.330	0.181			
HER2 status (negative *vs.* positive)	0.553	0.182–1.676	0.295			
Ki67 (≤30% *vs.* >30%)	2.895	1.101–7.610	0.031*	1.348	0.464–3.913	0.583
Subtype (Luminal A, B and HER2 *vs.* TNBC)	1.261	1.008–1.579	0.043*	1.449	1.097–1.914	0.009*
Lymph node metastasis (N0, N1 *vs.* N2, N3)	8.785	3.627–21.274	<0.001*	4.720	1.359–16.398	0.015*
LNR (<0.042 *vs.* ≥0.042)	5.253	1.909–14.458	0.001*	1.740	0.119–25.556	0.686
Progesterone (≤0.65 *vs.* >0.65 pmol/L)	0.474	0.191–1.174	0.107			
Pathological stage (stage I and IIA *vs.* IIB and III)	2.776	1.673–4.606	<0.001*	1.313	0.321–5.361	0.705
Overall survival						
Age (<55 *vs.* ≥55 years)	3.241	1.465–6.733	0.003*	2.275	0.966–5.360	0.060
Family history of cancer (no *vs.* yes)	1.753	0.838–3.669	0.136			
Personal history of cancer (no *vs.* yes)	3.912	1.618–9.461	0.002*	7.235	2.623–19.956	<0.001*
Tumour size (pT1 *vs.* pT2)	2.224	1.006–4.914	0.048*	1.743	0.588–5.167	0.316
Histological grade (I and II *vs.* III)	0.832	0.368–1.878	0.658			
Pathological type (ductal carcinoma in situ *vs.* IDC, ILC and others)	0.215	0.005–8.878	0.418			
ER status (negative *vs.* positive)	0.799	0.405–1.578	0.518			
PR status (negative *vs.* positive)	0.706	0.360–1.387	0.312			
HER2 status (negative *vs.* positive)	0.838	0.397–1.773	0.645			
Ki67 (≤30% *vs.* >30%)	2.224	1.073–4.609	0.032*	1.247	0.537–2.893	0.607
Subtype (Luminal A, B and HER2 *vs.* TNBC)	1.214	1.018–1.449	0.031*	1.364	1.094–1.699	0.006*
Lymph node metastasis (N0, N1 *vs.* N2, N3)	4.925	2.483–9.768	<0.001*	1.956	0.769–4.979	0.159
LNR (<0.042 *vs.* ≥0.042)	4.268	2.041–8.928	<0.001*	2.114	0.382–11.687	0.391
Progesterone (≤0.65 *vs*. >0.65 pmol/L)	0.418	0.210–0.832	0.013*	0.652	0.292–1.455	0.296
Pathological stage (stage I and IIA *vs.* IIB and III)	2.311	1.613–3.310	<0.001*	1.419	0.570–3.537	0.452

*, P<0.05. HR, hazard ratio; CI, confidence interval; LNR, lymph node ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; TNBC, triple negative breast cancer.

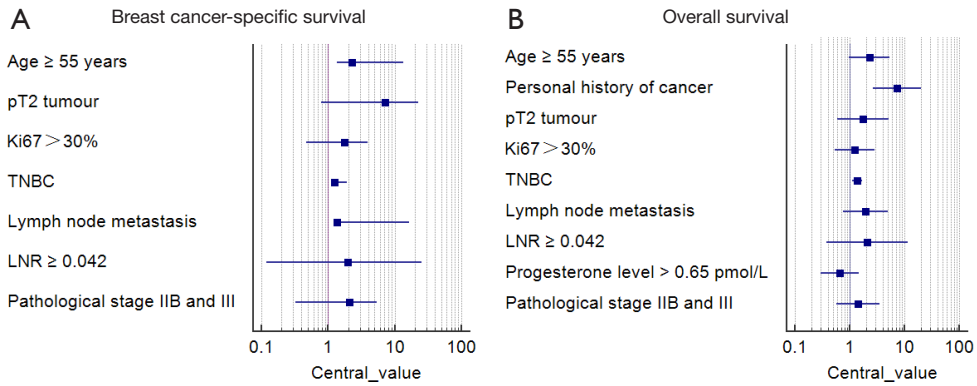

Figure 6 Forest plot for the multivariate analysis of pT1/2 breast cancer patients. (A) Breast cancer-specific survival and (B) overall survival. LNR, lymph node ratio.

consistent with previous studies (20,21). Moreover, in line with other studies, our results showed the LNR presented as a superior predictor in the survival outcome of pT1/2 breast cancer regardless of BCSS or OS (19,22,23). Breast cancer is considered a heterogeneous neoplasm, and different molecular subtypes are associated with distinct lymph node metastasis. In some molecular subtypes, the increased risk is observed in the lymph node involvement group (24,25). Liao and colleagues demonstrated pNs have no association with breast cancer whereas the LNR had a higher ratio and worse survival outcome in molecular subgroups (20). In our cohorts, a lower LNR exhibited extended BCSS and OS regardless of TNBC and non-TNBC grouping. Additionally, patients with an LNR above the threshold had worse OS than patients below the threshold, but this did not relate significantly with BCSS in pT1 patients. Larger cohort studies are required to verify the results.

Ultimately, univariate analysis demonstrated unfavorable BCSS and OS were related with the LNR above the cut-off value in T1/2 breast cancer patients, which is a result similar to that obtained by Vinh-Hung (18,26). However, in multivariate analysis, only the TNBC subtype was an independent predictor of reduced BCSS and OS, which may be because of a different case source and the number of early-stage patients in our cohort (7,10).

Notably, we first evaluated correlation of the LNR with preoperational sex hormone and tumor marker levels. Postmenopausal women have relatively stable sex hormone level, thus they were enrolled in the analysis of the correlation between LNR and sex hormone in the study. Our cohort revealed the LNR had a significant negative association with FSH and LH level in postmenopausal cases, whereas a positive correlation with the CA153, CA125, and CEA levels was seen in whole cohort. Previous study had revealed that patients operated on luteal phase of the menstrual cycle had a better prognosis than that operated on other phased, high LH concentration might play unopposed estrogens role in BC patients (27). Moreover, unlike BC patients with higher serum estradiol level had worse prognosis, preoperational FSH was not a useful predictor for the prognosis in pre- and postmenopausal BC patients (28,29). Furthermore, Lourdes and colleagues reported that FSH and LH had an inverse trend with the correlation with lymph node invasion, and FSH was related negatively with CEA in postmenopausal BC patients (30). Consistently, our results also revealed a negative relationship between LNR and serum level of FSH and LH in postmenopausal patients, BC patients might have complex endocrine environment in the progression, further study should be conducted to validate the function of sex hormone in BC development.

Our survey has several limitations, including its retrospective nature, lack of randomization, inclusion of lymph node negative patients, patients from single institution in the eastern China islands, the deficiency of treatment status of patients, and small sample size, any of which may have brought about inevitable and selective bias.

In conclusion, our study demonstrates that among pT1/2 breast cancer patients from the eastern China islands, the LNR is a predictive prognosis factor, and a higher LNR correlates with a worse survival outcome in whole group or subgroups. Strikingly, the current results reveal that serum FSH and LH level inversely related with axillary node invasion in postmenopausal cases, whereas tumor markers directly associated with it. The LNR is an informative

factor complementing TNM staging.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2039/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2039/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Review Committee of Zhoushan Hospital (No. 2022052) and informed consent was waived for this retrospective analysis.

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