

Neutrophil-to-lymphocyte ratio, obesity, and breast cancer risk in Chinese population

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Abstract

Breast cancer (BC), obesity, and metabolic syndrome (MetS) shared a common mechanism of dysregulated metabolism and inflammatory response in disease initiation. Neutrophil-to-lymphocyte ratio (NLR) is associated with adverse survival of BC patients. The aim of this study is to identify risk effect between NLR and BC in Chinese population with or without obesity and MetS. BC and age-matched breast benign disease (BBD) patients were retrospectively analyzed from Comprehensive Breast Health Center, Shanghai Ruijin Hospital. MetS was defined using AHA/NHLBI criteria. Individuals were classified into very low (0–1.30), low (1.31–1.67), intermediate (1.68–2.20), and high (>2.20) NLR subsets by each NLR quartile. In all, 1540 BC and 1540 BBD patients were included. Univariate and multivariate analysis found that NLR (OR: 1.27, 95% CI: 1.16–1.39, $P < .001$) and obesity (OR: 1.19, 95% CI: 1.00–1.42, $P = .046$) but not MetS ($P = .060$) were significantly associated with increased BC risk. Intermediate or high NLR substantially increased BC risk compared to very low NLR group (OR: 1.57, 95% CI: 1.29–1.92, $P < .001$; OR: 1.84, 95% CI: 1.50–2.25, $P < .001$; respectively) in whole population. Subgroup analysis found that the impact of higher NLR on BC risk was more obvious in patients without obesity (intermediate NLR, OR: 1.72, 95% CI: 1.37–2.16, $P < .001$; high NLR, OR: 1.92, 95% CI: 1.53–2.41, $P < .001$) or without MetS (intermediate NLR, OR: 1.70, 95% CI: 1.35–2.14, $P < .001$; high NLR, OR: 1.98, 95% CI: 1.57–2.51, $P < .001$). Higher preoperative NLR was found in BC patients compared with BBD patients. Intermediate to high NLR level substantially increased BC risk, which was more relevant for those without obesity or MetS.

Abbreviations: AHA/NHLBI = American Heart Association/National Heart, Lung, and Blood Institute, BBD = breast benign disease, BC = breast cancer, BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, ER = estrogen receptor, HER2 = human epidermal growth factor receptor-2, HR = hazard ratio, IDF = International Diabetes Federation, MetS = metabolic syndrome, NLR = neutrophil-to-lymphocyte ratio, OR = odds ratio, PR = progesterone receptor, RR = risk ratio.

Keywords: body mass index, breast cancer, metabolic syndrome, neutrophil-to-lymphocyte ratio, risk

1. Introduction

Breast cancer (BC) is the most common malignancy among women with an estimated 1.67 million newly diagnosed cancer cases in 2012, accounting for a quarter of all cancers.^[1,2] During the past decade, BC incidence in China has been increasing rapidly with more than twice the rate of global growth.^[3] Various independent variables have been identified for BC initiation, including lifestyle factors like pregnancy and breastfeeding

history, menstrual history, alcohol consumption, lack of physical exercise, and being obese.

Obesity is a common BC risk factor that has been broadly accepted.^[4–9] A meta-analysis including 282,137 incident cases found a relative risk of 1.16 (95% confidence interval [CI]: 1.01–1.32, $P = .009$) for premenopausal BC in Asia-Pacific women and a relative risk of 1.12 (95% CI: 1.08–1.16, $P < .001$) for postmenopausal BC with every 5 kg/m² increase in BMI.^[5] Meanwhile, metabolic syndrome (MetS), a group of pathophysi-

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ological disturbances and metabolic risk factors featuring central obesity, insulin resistance, dyslipidemia, and elevated blood pressure, has also been recognized for its increasing risk of BC. A recent meta-analysis confirmed a statistically significant increase of 47% BC risk for adult females with MetS (risk ratio [RR]: 1.47, 95% CI: 1.15–1.87, $P < .002$), demonstrating a modest positive association between MetS and BC.^[10] Moreover, MetS has also shown to be associated with worse disease outcome in BC patients.^[11] Among several potential pathways underlying between obesity, MetS, and BC, dysregulated systemic metabolism and inflammatory response play decisive roles. It is therefore of interest to develop the application of hematological parameters of systemic inflammatory response, for example, preoperative C-reactive protein (CRP) level, neutrophils, and lymphocytes, for their diagnostic and prognostic value.^[12,13] Compared to absolute counts of leukocytes, which could be altered facing different physiological or pathological conditions, neutrophil-to-lymphocyte ratio (NLR) showed superiority for its relative stability,^[12,14] and has been increasingly recognized for its prognostic value.^[15,16]

Previous studies found that higher NLR was related with more advanced or aggressive disease regarding tumor stage, nodal stage, and metastasis.^[13,17,18] Furthermore, we previously reported that higher NLR was associated with an adverse survival in BC patients,^[19] which is consistent with other studies.^[12,14,15,18,20] These works have proposed that cytokines and chemokines secreted by both tumor cells and leucocytes would accelerate tumor progression.^[21] Nevertheless, there is currently limited evidence reporting the risk factor of NLR on BC development. The correlation of NLR, obesity, and MetS has not been fully elucidated yet. Hence, in this study, we aimed to evaluate the role of NLR on BC development and to analyze the association between NLR and obesity or MetS for BC risk.

2. Materials and methods

2.1. Patient population

We retrospectively analyzed patients who underwent surgical procedure from December 2012 to January 2016 in Comprehensive Breast Health Center, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. Patients who met the following criteria were enrolled in the BC subgroup: female gender, BC proven by open excision biopsy or core needle biopsy, and complete clinical and follow-up data. The exclusion criteria included patients treated with neo-adjuvant therapy, de novo stage IV BC or inflammatory BC, and neutrophil count at diagnosis $>10 \times 10^9 \text{ L}^{-1}$. Those who received surgery during the same period of time for pathologically proven breast benign disease (BBD) were matched 1:1 by patient age as control group. Clinical details for patients with BC or BBD were achieved from Shanghai Jiao Tong University Breast Cancer Database (SJTU-BCDB) and Ruijin Hospital inpatient medical records. This approach was approved by the independent Ethical Committees of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine.

2.2. Clinical and laboratory data

Patient preoperative peripheral hematological parameters and C-reaction protein (CRP) level were collected by nurses and analyzed using XN-series blood analyzer (Sysmex Corporation,

Chuo-ku, Kobe, Hyogo, Japan) in the Department of Clinical Laboratory, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. Malignant and benign tumor diagnoses were performed in the Department of Pathology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

2.3. Definition of metabolic syndrome

The MetS was defined in accordance with the current guidelines, revised in 2005 by the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI). We chose the AHA/NHLBI criteria over the other widely used International Diabetes Federation (IDF) definition, since the former diagnosed 4% more people with MetS in the Chinese population, as shown in a previous study.^[22] Body mass index (BMI) was employed to evaluate central obesity with a cut-off value of no less than 25.0 kg/m^2 , according to the Chinese Medical Association criteria for MetS.^[23] The criteria for clinical diagnosis of MetS adjusted to the study population are shown in Supplementary Table S1, <http://links.lww.com/MD/C366>.

2.4. Statistical analysis

NLR was calculated by dividing absolute neutrophil count by number of lymphocytes. Different cut-off values were applied to classify NLR, including the median value of 1.67 for bipartition, as well as the first, second, and third quartiles of 1.30, 1.67, and 2.20 for quadripartition. χ^2 test or Fisher exact test were applied for descriptive characteristics of categorical variables. Baseline clinicopathologic features were compared using multinomial logistic regression analysis between BC and BBD subgroups. Subgroup analyses for risk factors were conducted using stratified Mantel-Haenszel test to estimate odds ratio (OR) with 95% CI among subsets. IBM SPSS statistics software version 23 (SPSS, Inc, Chicago, IL) was used for data analysis. Two-sided P values $< .05$ were considered significant.

3. Results

3.1. Patients baseline characteristics

In all, 1540 BC patients and matched 1540 BBD patients were enrolled in this study with a mean age of 50.75 ± 10.36 years (range 24–87 years). Among them, 33.90%, 10.00%, and 27.11% individuals were diagnosed with hypertension, hyperglycemia and hyperlipidemia, respectively. A total of 22.05% patients were obese, and 26.36% met the criteria of MetS. The mean NLR of all population was 1.84 ± 0.82 . The first, second, and third quartiles of NLR classified individuals into very low (0–1.30), low (1.31–1.67), intermediate (1.68–2.20), and high (>2.20) NLR subsets.

In univariate analysis, obesity was more frequent in BC patients than the BBD group (23.83% vs 20.26%, $P = .017$; Table 1). Three hundred and eighty-three patients (24.87%) in the BC group and 429 (27.86%) patients in the BBD group were diagnosed with MetS according to AHA/NHLBI criteria ($P = .060$). Compared with the BBD group, BC patients had a higher absolute neutrophil count ($3.36 \pm 1.19 \times 10^9 \text{ L}^{-1}$ vs $3.18 \pm 1.10 \times 10^9 \text{ L}^{-1}$, $P < .001$), lower lymphocyte count ($1.87 \pm 0.55 \times 10^9 \text{ L}^{-1}$ vs $1.92 \pm 0.56 \times 10^9 \text{ L}^{-1}$, $P = .009$), and a subsequent higher NLR (1.92 ± 0.81 vs 1.76 ± 0.82 , $P < .001$;

Table 1). Besides, surgical history of BBD was also different between the BC and BBD subgroups ($P < .001$). Multinomial logistic regression found NLR was much higher in the BC group compared with patients in the BBD group (OR: 1.27, 95% CI: 1.16–1.39, $P < .001$; Supplementary Table S2, <http://links.lww.com/MD/C366>). In addition, surgical history of BBD was an independent protective factor for BC (OR: 0.65, 95% CI: 0.53–0.78, $P < .001$), while obesity significantly increased BC risk (OR: 1.19, 95% CI: 1.00–1.42, $P = .046$). No significant difference was observed regarding other components of MetS including hypertension, hyperglycemia, or hyperlipidemia ($P > .05$; Table 1).

3.2. NLR and BC risk stratified by menopausal status

Overall, intermediate (1.68–2.20) and high (> 2.20) NLR significantly increased BC risk compared with very low (0–1.30) NLR group (OR: 1.57, 95% CI: 1.29–1.92, $P < .001$; OR: 1.84, 95% CI: 1.50–2.25, $P < .001$; respectively, Table 2). The mean NLR was 1.72 ± 0.76 for postmenopausal women, and 1.93 ± 0.85 for pre/perimenopausal women ($P < .001$). As shown in Table 2, the effect of intermediate to high NLR on increasing BC risk remained robust in both postmenopausal (OR: 1.62, 95% CI: 1.22–2.16, $P = .001$; OR: 1.59, 95% CI: 1.17–2.17, $P = .003$; respectively) and pre/perimenopausal population (OR: 1.61, 95% CI: 1.21–2.14, $P = .001$; OR: 2.13, 95% CI: 1.61–2.81, $P < .001$; respectively).

3.3. Association between NLR and BC risk stratified by obesity status

NLR was similarly distributed in patients with different BMI statuses ($P = .957$; Table 3). BC risk in patients with BMI < 25.0 kg/m² were more influenced by higher NLR, with an OR of 1.72 for intermediate NLR group (95% CI: 1.37–2.16, $P < .001$; Table 3; Fig. 1A) and an OR of 1.92 for high NLR group (95% CI: 1.53–2.41, $P < .001$). In contrast, the impact of higher NLR on BC risk was not statistically significant in patients with BMI ≥ 25.0 kg/m² ($P > .05$). Subgroup analysis stratified by BMI status was also conducted to show the influence of bipartite NLR on BC risk (Fig. 2). Higher NLR level was related with increased BC risk among overall population, which was more obvious in the nonobese group ($P < .001$), but not in the obese patients ($P = .182$, Supplementary Table S3, <http://links.lww.com/MD/C366>).

3.4. Association between NLR and BC risk stratified by MetS

No difference of NLR distribution was observed across different MetS statuses ($P = .541$; Table 4). In patients without MetS, intermediate NLR caused a 70.00% BC risk increase compared with very low NLR group (95% CI: 1.35–2.14, $P < .001$; Table 4; Fig. 1B). Meanwhile, high NLR almost doubled BC risk with an OR of 1.98 (95% CI: 1.57–2.51, $P < .001$). However, in patients with MetS, NLR level was no longer associated with increased BC risk ($P > .05$). Using bipartite NLR classification (NLR ≤ 1.67 vs NLR > 1.67), we also found that MetS status might influence the association between NLR level and BC risk (Fig. 2). Higher NLR level increased BC risk in patients without MetS ($P < .001$), but not in those with MetS ($P = .071$, Supplementary Table S3, <http://links.lww.com/MD/C366>).

Table 1

Patients characteristics and factors associated with breast cancer.

Characteristics	Whole population	BBD No., %	BC No., %	P value
Cases (no.)	3080	1540	1540	
Age, y	50.75 ± 10.36	50.75 ± 10.36	50.75 ± 10.36	1.000
Menstrual status				.232
Postmenopausal	1385	676 (43.90)	709 (46.04)	
Peri/premenopausal	1695	864 (56.10)	831 (43.96)	
Age of menarche, y				.949
≤ 12	263	129 (8.38)	134 (8.70)	
13–16	2398	1201 (77.99)	1197 (77.73)	
> 16	419	210 (13.64)	209 (13.57)	
History of pregnancy				.069
No	222	126 (8.12)	96 (6.23)	
Yes	2857	1414 (91.82)	1443 (93.70)	
NA	1	0 (0.00)	1 (0.06)	
History of breast feeding				.144
No	442	203 (13.18)	239 (15.52)	
Yes	2621	1327 (86.17)	1294 (84.03)	
NA	17	10 (0.65)	7 (0.45)	
Family history of BC				.947
No	2837	1419 (92.14)	1418 (92.08)	
Yes	243	121 (7.86)	122 (7.92)	
Surgical history of BBD				$< .001$
No	2574	1241 (80.58)	1333 (86.56)	
Yes	506	299 (19.42)	207 (13.44)	
Hypertension				.493
No	2036	1009 (65.52)	1027 (66.69)	
Yes	1044	531 (34.48)	513 (33.31)	
Hyperglycemia				.471
No	2772	1380 (89.61)	1392 (90.39)	
Yes	308	160 (10.39)	148 (9.61)	
Hyperlipidemia				.715
No	2245	1118 (72.60)	1127 (73.18)	
Yes	835	422 (27.40)	413 (26.82)	
Body mass index	22.99 ± 3.13	22.90 ± 3.15	23.08 ± 3.10	.120
Obesity			0.017	
No	2401	1228 (79.74)	1173 (76.17)	
Yes	679	312 (20.26)	367 (23.83)	
Metabolic syndrome				.060
No	2268	1157 (75.13)	1111 (72.14)	
Yes	812	383 (24.87)	429 (27.86)	
NLR	1.84 ± 0.82	1.76 ± 0.82	1.92 ± 0.81	$< .001$
NLR bipartition				$< .001$
≤ 1.67	1542	855 (55.52)	687 (44.61)	
> 1.67	1538	685 (44.48)	853 (55.39)	
NLR quadripartition				$< .001$
0–1.30	782	451 (29.29)	331 (21.49)	
1.31–1.67	760	404 (26.23)	356 (23.12)	
1.68–2.20	775	360 (23.38)	415 (6.95)	
> 2.20	763	325 (21.10)	438 (28.44)	

BBD = breast benign disease, BC = breast cancer, NA = not available, NLR = neutrophil to lymphocyte ratio.

4. Discussion

To our knowledge, the present study, enrolling a total of 3080 patients, is the largest study to evaluate the association between NLR and BC risk, and to explore its relationship with obesity and MetS in Chinese population. In this study, we found that higher preoperative NLR was associated with increased BC risk in the overall population, regardless of menopausal status. The risk-carrying effect of NLR was more evident in individuals with BMI < 25.0 kg/m², as well as in those without MetS.

Table 2**Risk of NLR on breast cancer stratified by menopausal status.**

NLR level	All					Postmenopausal					Pre/perimenopausal				
	BC n=1540	BBD n=1540	P	OR	95% CI	BC n=709	BBD n=676	P	OR	95% CI	BC n=831	BBD n=864	P	OR	95% CI
0–1.30	331	451		1.0		192	236		1.0		139	215		1.0	
1.31–1.67	356	404	.075	1.20	0.98–1.47	178	181	.186	1.21	0.91–1.60	178	223	.155	1.24	0.92–1.65
1.68–2.20	415	360	<.001	1.57	1.29–1.92	190	144	.001	1.62	1.22–2.16	225	216	.001	1.61	1.21–2.14
>2.20	438	325	<.001	1.84	1.50–2.25	149	115	.003	1.59	1.17–2.17	289	210	<.001	2.13	1.61–2.81

BBD = breast benign disease, BC = breast cancer, BMI = body mass index, CI = confidence interval, NLR = neutrophil to lymphocyte ratio, OR = odds ratio.

Table 3**Risk of NLR on breast cancer stratified by BMI.**

NLR level	All					BMI <25.0 kg/m ²					BMI ≥25.0 kg/m ²				
	BC n=1540	BBD n=1540	P	OR	95% CI	BC n=1173	BBD n=1228	P	OR	95% CI	BC n=367	BBD n=312	P	OR	95% CI
0–1.30	331	451		1.0		255	376		1.0		76	75		1.0	
1.31–1.67	356	404	.075	1.20	0.98–1.47	272	327	.077	1.23	0.98–1.54	84	77	.745	1.08	0.69–1.68
1.68–2.20	415	360	<.001	1.57	1.29–1.92	316	271	<.001	1.72	1.37–2.16	99	89	.670	1.10	0.72–1.69
>2.20	438	325	<.001	1.84	1.50–2.25	330	254	<.001	1.92	1.53–2.41	108	71	.069	1.50	0.97–2.33

BBD = breast benign disease, BC = breast cancer, BMI = body mass index, CI = confidence interval, NLR = neutrophil to lymphocyte ratio, OR = odds ratio.

Various modifiable lifestyle risk factors have been identified for BC initiation in previous studies. Obesity, defined as having a BMI ≥ 25 kg/m² for Chinese population,^[2,3] is known to affect BC risk and survival.^[4–9] Meanwhile, studies on MetS, another potential risk factor with an increasing prevalence worldwide, produced inconsistent results, especially in Asians.^[24–28] In the present study, we found a much higher NLR in pre/perimenopausal women, compared with postmenopausal women (1.93 ± 0.85 vs 1.72 ± 0.76 , $P < .001$). Similar conclusion was drawn in a study of Chen et al that women < 50 years old had significantly higher NLR than women of 51 to 70 years of age.^[29] Despite this different distribution, the impact of NLR on BC risk is consistent regardless of menopausal status. In addition, we showed that BMI ≥ 25 kg/m² at diagnosis is an independent risk factor for BC in Chinese population. MetS occurs slightly more frequently in BC patients compared with BBD carriers, but this difference is not statistically significant ($P = .060$). The effect of obesity for BC risk may be realized through numbers of overlapping pathways, altering adiposity-related host factors that result in high circulating insulin/insulin-like growth factor I, chronic inflammation, high serum leptin concentration, and low adiponectin. Furthermore, obesity has potential impact in clinical management of BC patients with regard to chemotherapy dosing decision, surgical treatment, and related comorbidities.^[30,31]

Previous studies have confirmed the role of inflammation in the initiation, promotion, and progression of BC.^[11–13] It is therefore of interest to establish the role of hematological parameters for systemic inflammatory response. NLR is an ideal factor to evaluate the balance between the innate and adaptive immunity. There is much evidence for the prognostic value of NLR, stating that higher preoperative NLR was associated with an adverse survival outcome in BC patients.^[12,14,15,18–20] A recent meta-analysis found that NLR greater than the cut-off value was associated with worse disease-free survival (hazard ratio [HR]: 1.74, 95% CI: 1.47–2.07, $P < .001$) and overall survival (HR: 2.56, 95% CI: 1.96–3.35, $P < .001$), either in early-stage BC setting or metastatic setting.^[15] On the other hand, the association between NLR and BC risk has not been completely

understood. In our study, we found that NLR was significantly higher in the BC group compared with the BBD group, and patients with NLR > 1.67 were related to a substantial increase risk factor for BC. Our finding was consistent with that of Ozyalvacli et al^[18] and Okuturlar et al,^[32] indicating NLR as an independent risk factor for BC development. Potential mechanism of the association between NLR and BC remained under-elucidated. Queen et al found that when cocultured with BC cells, neutrophils were stimulated to produce oncostatin M, a pleiotropic cytokine of interleukin-6 family, which promoted tumor progression by inducing vascular endothelial growth factor expression and enhancing metastasis.^[33] In addition, neutrophil-derived leukotrienes were shown to aid the colonization of distant tissue by selectively expanding highly tumorigenic BC cells.^[34] Meanwhile, it has been broadly accepted that lymphocytes play a role in antitumor activity in the adaptive immune system. Lymphocytopenia was established as independent prognostic factor for BC patient survival in both early and metastatic BC settings.^[35,36] Therefore, BC patient prognosis could be influenced by either peripheral neutrophils or lymphocytes counts, and these studies revealed the potential ability of NLR to reflect situations of different immune and inflammatory pathways.

Chronic systematic inflammation was also a critical mechanism underlying pathophysiology of obesity^[37,38] and MetS.^[39,40] Obesity and MetS produce a long-term low-grade activation of the immune system that affects metabolic homeostasis over time. In previous studies, NLR was found to be associated with the presence and severity of MetS in Turkish population,^[41] and to increase linearly with increasing number of MetS components (P for trend $< .001$) in Asian Indians.^[42] However, in this study, we found that NLR was similarly distributed in patients obese or nonobese, with or without MetS; but the effect of NLR on BC risk varied across different BMI or MetS statuses. In nonobese patients or those without MetS, NLR may be a better indicator for systematic inflammation caused by carcinogenesis, mostly due to the effect of neutrophils in creating a microenvironment conducive for tumor development. In contrast, NLR was not a good indicator for inflammatory status

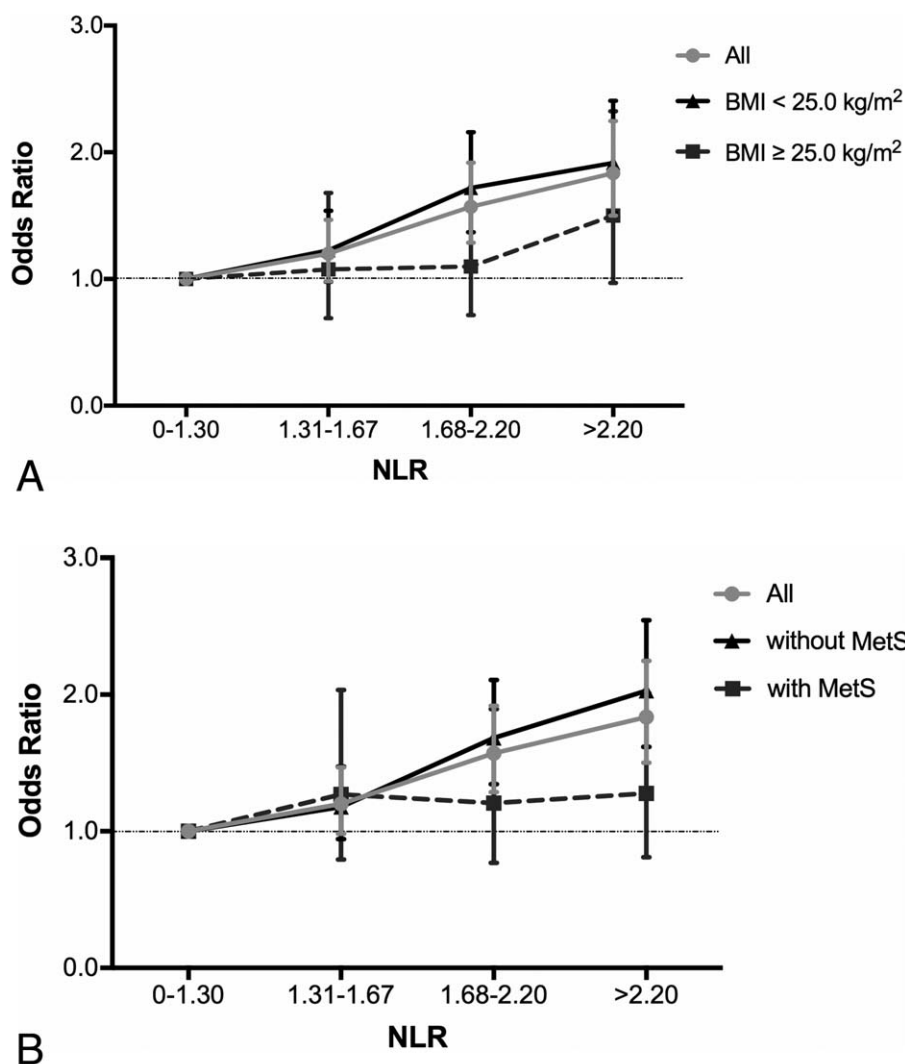


Figure 1. Association between NLR and odds ratio of BC by BMI status and MetS status: (A) Association between NLR and odds ratio of BC by BMI status. Overall odds ratios of different NLR ranges between BC versus BBD subgroups are shown as gray dots, which are then stratified into BMI < 25.0 kg/m² (black triangles) and BMI ≥ 25.0 kg/m² (black squares). I-shaped bars represent 95% CIs. Higher NLR levels are significantly associated with increasing BC risk in all population and in patients with BMI < 25.0 kg/m² ($P < .001$), but not in patients with BMI ≥ 25.0 kg/m² ($P > .05$). (B) Association between NLR and odds ratio of BC by MetS status. Overall odds ratios of different NLR ranges between BC versus BBD subgroups are shown as gray dots, which are then stratified into subgroup without MetS (black triangles) and with MetS (black squares). Higher NLR levels are significantly associated with increasing BC risk in all population and in patients without MetS ($P < .001$), but not in patients with MetS ($P > .05$). BBD=breast benign disease, BC=breast cancer, BMI=body mass index, MetS=metabolic syndrome, NLR=Neutrophil-to-lymphocyte ratio.

in patients with obesity and MetS, possibly because neutrophils and lymphocytes increased simultaneously with obesity degree and severity of MetS, thus the increase of NLR was not significant.^[43] Besides, it is hypothesized that other inflammatory factors and cytokines may also play important roles in intermediating the relationship between NLR and BC. In our study, additional test concerning CRP, an inflammation-related parameter, was conducted to assess its potential interaction between NLR, obesity, MetS, and BC. We found the distribution of CRP was similar between BC (N=708) and BBD (N=700) groups (0.28 ± 0.02 , 0.26 ± 0.01 for BC and BBD, respectively; $P = .220$; Supplementary Figure S1A, <http://links.lww.com/MD/C366>). Furthermore, CRP level was significantly lower in BBD group compared with BC group in patients with lower NLR (0.30 ± 0.03 , 0.24 ± 0.01 for BC and BBD, respectively; $P = .031$), but not in patients with higher NLR (0.26 ± 0.01 , 0.30 ± 0.02 for

BC and BBD, respectively; $P = .178$). Both obesity and MetS were found to have no interaction with CRP on BC risk (Supplementary Figure S1B, S1C, <http://links.lww.com/MD/C366>). Further studies are needed to evaluate other potential inflammation-related factors in consideration for assessing the causal relationship between NLR and BC.

There are several potential limitations in this study. First, we retrospectively included patients into this age-matched cohort study, so there might be a selection bias. In addition, waist circumference and waist-hip ratio were usually applied in previous studies to define MetS, but it was demonstrated that BMI ≥ 25.0 kg/m² could also be used as surrogate to reflect central obesity, especially in Chinese population.^[23] Moreover, due to the limited data about clinical and hematological factors from normal individuals, the control group in our study was BBD patients instead of normal individuals, thus our findings need to

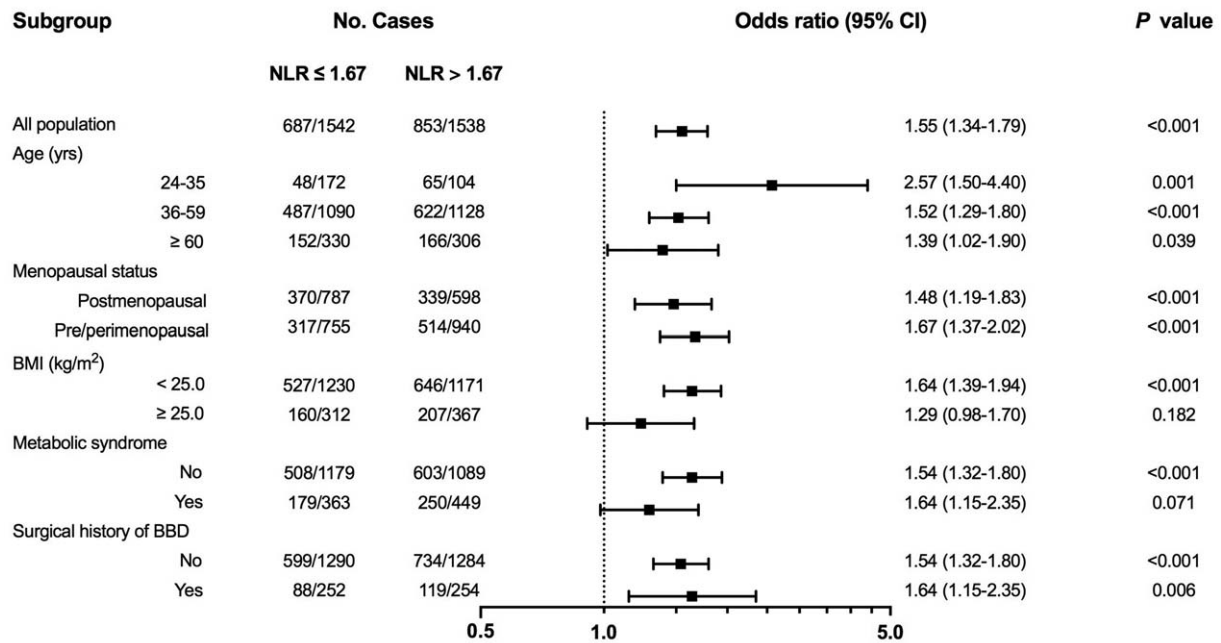


Figure 2. Subgroup analysis of NLR effect on BC risk. Prespecified subgroup analyses for risk factors were conducted to estimate OR with 95% CI among subgroups with the use of 2-sided P values. Higher preoperative NLR was an independent risk factor in all subgroups except for obese patients and MetS patients. BC=breast cancer, CI=confidence interval, MetS=metabolic syndrome, NLR=Neutrophil-to-lymphocyte ratio, OR=odds ratio.

Table 4
Risk of NLR on BC development stratified by metabolic syndrome.

NLR level	All					Without MetS					With MetS				
	BC n=1540	BBD n=1540	P	OR	95% CI	BC n=1111	BBD n=1157	P	OR	95% CI	BC n=429	BBD n=383	P	OR	95% CI
0-1.30	331	451		1.0		247	365		1.0		84	86		1.0	
1.31-1.67	356	404	.075	1.20	0.98-1.47	261	306	.050	1.26	1.00-1.59	95	98	.971	0.992	0.66-1.50
1.68-2.20	415	360	<.001	1.57	1.29-1.92	293	255	<.001	1.70	1.35-2.14	122	105	.393	1.19	0.80-1.77
>2.20	438	325	<.001	1.84	1.50-2.25	310	231	<.001	1.98	1.57-2.51	128	94	.105	1.39	0.93-2.08

BBD=breast benign disease, BC=breast cancer, CI=confidence interval, MetS=metabolic syndrome, NLR=neutrophil to lymphocyte ratio, OR=odds ratio.

be further explored and validated in independent normal individuals.

5. Conclusions

In conclusion, preoperative NLR was much higher in BC patients compared with BBD carriers. NLR was an independent risk factor for BC, regardless of menopausal status. Intermediate-to-high NLR level was associated with increased BC risk for the overall population, especially in nonobese or MetS-free patients. Future studies should be performed with additional normal patients to evaluate the relationship and interaction between NLR, obese, MetS, and BC risk in Chinese population.

Author contributions

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