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The combination of platelet count and lymphocyte to monocyte ratio is a prognostic factor in patients with resected breast cancer

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Abstract

Many inflammation indicators have been reported to be related with patient outcomes in various cancers. Previous studies have evaluated the combination of platelet (PLT) and lymphocyte to monocyte ratio (COP-LMR) as a systemic inflammatory marker for prognostication in lung cancer, yet its prognostic role among breast cancer patients remains unclear.

In the present study, a total of 409 breast cancer patients with surgical resection were retrospectively investigated. The receiver operating characteristic (ROC) curve was used to choose the optimal cut-off value of PLT and lymphocyte to monocyte ratio (LMR). Patients were classified into 3 groups according to the score of COP-LMR, and its relationship with various clinicopathological factors and breast cancer prognosis were further evaluated.

The ROC curve analysis showed that COP-LMR had a higher area under the ROC curve for the prediction of 5-year disease-free survival and overall survival than PLT or LMR alone. Multivariable analysis showed that an elevated COP-LMR was an independent predictor of poor disease-free survival ($P = .032$) and overall survival ($P = .005$). Subgroup analysis revealed that COP-LMR was still significantly associated with prognosis in both luminal A and luminal B subtypes.

Preoperative COP-LMR is a potential prognostic factor in breast cancer patients who underwent surgery.

Abbreviations: AUC = area under the ROC curve, COP-LMR = the combination of platelet count and lymphocyte-to-monocyte ratio, DFS = disease-free survival, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, LMR = lymphocyte-to-monocyte ratio, OS = overall survival, PLT = platelet, PR = progesterone receptor, ROC = receiver operating characteristic, TNBC = triple negative breast cancer.

Keywords: breast cancer, the combination of platelet count and lymphocyte-to-monocyte ratio, prognosis

1. Introduction

Breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death among females worldwide.[1] Despite the great improvement in cancer treatment, surgery based comprehensive therapeutic modality is still the fundamental and optimal strategy for early stage breast cancer patients.[2] However, tumor cells have the nature to disseminate from original sites and lodge to other tissues or organs at an early point,[3] which makes the outcome still unsatisfactory as an appreciable proportion of patients ultimately develop local recurrences or distant metastases after resection. Though the St. Gallen Consensus has for years endeavored to tailor breast cancer treatment and provided practical recommendations according to its clinical and biological subsets,[2] it is still essential to identify reliable biomarkers for prognosis prediction and treatment selection.

Tumor-promoting inflammation is an enabling characteristic for malignant cells,[3] as inflammation not just mirrors host responses to tumor cells but also contributes to the acquisition of core hallmarks for malignant cells. Cumulating evidence suggests that these inflammatory responses have paradoxical effects of fostering cancer development and neoplastic progression besides its endeavor to eradicate tumor cells.[4] Cancer-related inflammation consists of both immune response in situ and systemic reactions that manifest as the paraneoplastic symptoms observed by clinicians. Unlike local immune response, systemic inflammation is detectable and could be measured by peripheral blood based biomarkers such as circulating cytokines, small inflammatory proteins or acute-phase proteins, white blood cell counts including its subpopulations and platelet (PLT) counts.[4] These markers are readily available, avoiding the tests complexities and additional financial costs, and have been suggested to provide prognostic value in various malignancies including breast cancer.[5] However, anticancer drugs or carcinogens might have direct or indirect influences on these parameters,[6] which sets stringent requirements to those included patients in turn.

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Compared with single biomarkers, combinations of these parameters with convince predictability had been supposed to be of elevated prognostic values.[7–12] A combination of PLT count and lymphocyte to monocyte ratio, short as PLT and lymphocyte to monocyte ratio (COP-LMR), had been recently identified as a novel prognosis predictor in lung cancer.[13,14] However, its role in breast cancer was still undetermined. Yet we aimed to evaluate the prognostic significance of COP-LMR in breast cancer patients who received curative resection.

2. Material and methods

2.1. Patients and data collection

A total of 409 breast cancer patients who underwent surgery and received standard subsequent treatment in West China Hospital of Sichuan University from 2010 to 2011 were consecutively selected.

Inclusion criteria:

(1) female patients;
(2) histological validation of primary breast cancer;
(3) patients received en bloc resection of primary tumors;
(4) Patients with sufficient detailed clinicopathological information.

Exclusion criteria:

(1) patients with metastasis before surgery or secondary malignancies;
(2) patients who received chemotherapy before surgery;
(3) patients with inflammatory diseases, infections, autoimmune diseases or immunodeficiency diseases, or other diseases affects blood components (such as hematologic diseases, liver disfunction, chronic kidney diseases . . .);
(4) Patients receiving medicines that have unclear influences on blood cells.

Clinicopathological data including age, tumor stage according to *AJCC Cancer Staging Manual 7th ed*, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 status were evaluated for all enrolled patients. From laboratory data, white blood cell count, hemoglobin, PLT, red blood cell count, monocyte count, neutrophil cell count, and lymphocyte count were assessed.

Patients were followed up and examined approximately every 3 months after operation for 3 years, every 6 months for the next 5 years, and annually thereafter. The follow-up investigation included physical exam, laboratory test, gynecological examination and radiological assessments. The disease-free survival (DFS) was defined as the time from the diagnosis to the disease relapse, death, or last follow-up, and the overall survival (OS) was the time duration from the date of diagnosis to the date of death or last follow-up, whichever occurred first. The follow-up deadline was July 2018. This study was approved by the Research Ethics Committee of West China Hospital of Sichuan University.

2.2. Pathology methods and molecular subtypes

ER, PR, HER2, and Ki67 status were tested by immunohistochemical staining and the following antibodies were applied: monoclonal ER antibody (clone SP1; Ventana, Tucson, AZ), monoclonal PR (clone 1E2; Ventana), Ki-67 (clone 30–9; Ventana), and HER2 (clone 4B5; Roche, Sandhofer, Mannheim, Germany). The cut-off value for positive ER or PR was ≥1% of immunoreactive tumor cell nuclei, and for Ki-67 was ≥14%. The immunohistochemical staining for HER2 was scored as 0, 1+, 2+, or 3+; and 0 or 1+ was defined as HER2 negative, whereas 3+ was reported as positive. Fluorescence in situ hybridization was performed to explicate the HER2 gene amplification status in case of a 2+ score. Molecular subtypes were classified according to the St. Gallen expert consensus of 2011.[15]

2.3. Determination of the cut-off value and the categorization by COP-LMR

Lymphocyte-to-monocyte (LMR) was constructed as the ratio of absolute peripheral lymphocyte count to the absolute peripheral monocyte count. The receiver operating characteristic (ROC) curve analysis was used to analysis the sensitivity and specificity of LMR, PLT, and COP-LMR for the 5-year survival, and the Youden index was calculated to choose the optimal cutoff value. In accordance with previous studies, patients with both elevated PLT and low LMR were assigned a COP-LMR score of 2, and those with either or none of the parameters were scored 1 or 0, respectively (Table 1).[14,16]

2.4. Statistical analysis

The association between clinicopathological factors and COP-LMR was analyzed using 1-way analysis of variance. The DFS and OS survival curves were estimated by the Kaplan–Meier log-rank survival analysis. Variables which were calculated to be statistically significant in univariate analysis were next assessed in a backward stepwise multivariable Cox proportion analysis. The hazard ratios and corresponding 95% confidence intervals were reported. All the statistical analyses were performed using the SPSS (version 20.0) software package (SPSS Inc., Chicago, IL). A 2-side P value $< .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 409 female breast cancer patients with a median age of 46 years were enrolled in this study. All included patients had pathologically confirmed breast cancer and received surgical treatment as well as subsequent therapies if necessary, in West China Hospital. According to the St. Gallen recommendations,[15] patients were classified into different molecular subtypes and 109 (26.7%) cases were defined as luminal A, 213 (52.1%) cases luminal B, 44 (10.8%) cases HER2-enriched, 43 (10.5%) cases triple negative breast cancer (TNBC), respectively. All the patients were categorized into 3 groups according to their COP-LMR score, with 191,181, and 37 patients assigned to COP-LMR 0, 1, and 2, respectively.

Table 1

The calculation of the combination of platelet count and lymphocyte-to-monocyte ratio (COP-LMR) based on the categories of platelet and LMR determined by their cutoff values.

	Low platelet	High platelet
Low LMR	1	2
High LMR	0	1

COP-LMR = the combination of platelet count and lymphocyte-to-monocyte ratio, LMR = lymphocyte-to-monocyte ratio.

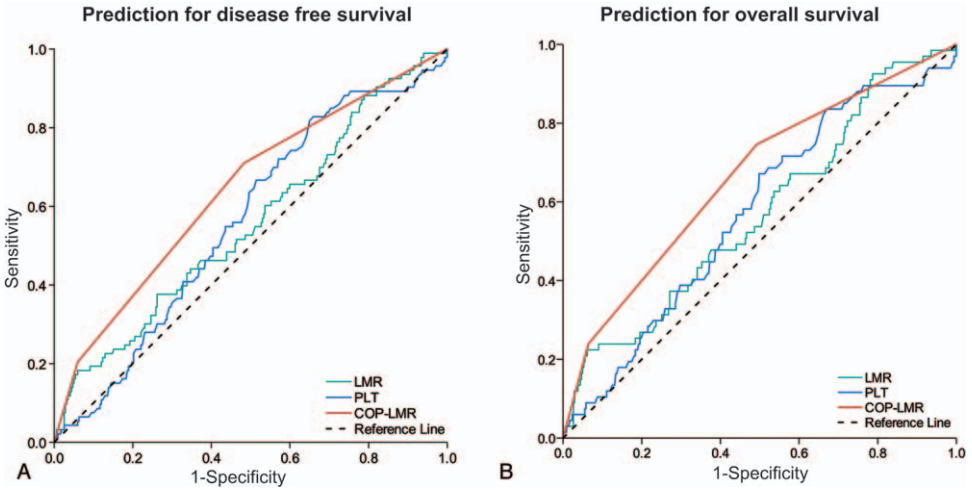

Figure 1. The ROC curves of LMR, PLT, and COP-LMR for predicting DFS (A) and OS (B). COP-LMR = the combination of platelet count and lymphocyte-to-monocyte ratio, DFS = disease-free survival, LMR = lymphocyte-to-monocyte, PLT =platelet, ROC = receiver operating characteristic.

3.2. ROC analysis for the prediction of survival

The results of ROC analysis showed that the optimal cut-off values of LMR and PLT were 221 and 3.96. The prognostic accuracies of LMR, PLT, and COP-LMR were explored using the area under the ROC curve (AUC) of the ROC curve for predicting the 5-year DFS and OS (Fig. 1A-1B). And AUC of LMR, PLT, and COP-LMR for DFS were 0.556, 0.562, and 0.642, respectively, while the AUCs of LMR, PLT, and COP-LMR for OS were 0.570, 0.571, and 0.662, respectively. Thus, the COP-LMR was the strongest factor for predicting the DFS and OS of included patients.

3.3. Relationship between COP-LMR and clinicopathological and laboratory parameters

The associations between COP-LMR and clinicopathological characteristics and laboratory parameters are presented in Table 2. The results indicated that COP-LMR was associated with Ki-67 status ($P = .011$), the absolute PLT count ($P < .001$), the monocyte count ($P < .001$), and the lymphocyte count ($P < .001$). All of those were the components of COP-LMR except for Ki-67 status.

3.4. Relationship between COP-LMR and survival

After a median follow-up of 60.7 months, tumor relapse occurred in 93 cases, among which 67 cases died. Figure 2 showed the Kaplan–Meier curves of DFS and OS. The results indicated that COP-LMR was a poor prognostic factor for both DFS and OS and patients in the third group (COP-LMR 2) were predicted to suffer the poorest DFS and OS ($P < .001$).

Based on univariate analysis, COP-LMR, Ki-67 status, pathological T stage (pT stage) and lymphnodes stage (pN stage), and PLT count were significantly associated with DFS, while COP-LMR, pT stage, pN stage, and PLT count were significantly associated with OS (Table 3). As shown in Table 4, in multivariate analysis, COP-LMR ($P = .032$), Ki-67 status ($P = .044$), tumor grade ($P = .001$), and lymph nodes post-surgery ($P = .003$) were independent predictors of DFS, whereas COP-LMR ($P = .005$), tumor grade ($P = .001$), and lymph nodes post-surgery ($P = .002$) were correlated with OS.

Subgroup analysis by subtype of breast cancer revealed that an elevated COP-LMR was significantly associated with poor prognosis in both luminal A and luminal B subtypes. However, COP-LMR was not an independent prognostic factor for survival in HER2-positive breast cancer patients or TNBC patients (Fig. 3).

4. Discussion

It has been widely reported that inflammation is critical in tumor growth, invasion, and metastasis. Many inflammation indicators, including PLT, LMR, neutrophilocyte-to-lymphocyte ratio, neutrophilocyte-to-lymphocyte ratio, PLT-to-lymphocyte ratio, are prognostic factors for the long term outcomes in several malignancies.[7–12] In the present study, we initially assessed the prognostic value of COP-LMR in resected breast cancer patients. According to the ROC curve, COP-LMR was more accurate in prognosis prediction compared with previously reported prognostic scoring systems, PLT or LMR. Moreover, we found that COP-LMR score obtained before surgery is an independent prognosis predictor for early breast cancer patients, and higher COP-LMR score indicates shorter DFS and OS.

Numerous studies have shown the significance of PLT in a wide range of pathophysiological events. The complex reciprocal interactions between PLTs and cancer cells not only contribute to the numerical and functional abnormalities of PLTs, which presents as paraneoplastic syndromes in cancer patients including thrombocytosis and coagulopathy, thrombosis for instance, but also play a pivotal role in almost the full spectrum of tumor progression, dissemination and angiogenesis.[17–23] Being a wandering reservoir of abundant cytokines and growth factors, PLT could stimulate tumor growth by secreting various dynamic granules. And its extensive membrane receptors mediated PLT-cancer cell-aggregation and its subsequent interactions could promote immune evasion and tumor progression.[24] Holmes etal. reported that breast cancer and its treatment influence the PLT phenotype by increasing the secretion of pro-angiogenic proteins, including vascular endothelial growth factor , thrombospondin-1, and transforming growth factor beta 1, following PLT activation, modulating the efficiency of PLT protein release.[25] As it was proved the other way around, Gu et al demonstrated that pretreatment elevated PLT count was

Table 2

Association of the combination of platelet count and lymphocyte-to-monocyte ratio (COP-LMR) with the clinicopathological and laboratory parameters of breast cancer patients.

	COP-LMR=0	COP-LMR=1	COP-LMR=2	*P*
Total	191	181	37	
Age no. (%)				.715
≤60	164 (85.9%)	160 (88.4%)	33 (89.2%)	
>60	27 (14.1%)	21 (11.6%)	4 (10.8%)	
ER no. (%)				.057
+	127 (66.5%)	111 (61.5%)	17 (45.9%)	
−	64 (33.5%)	70 (38.7%)	20 (54.1%)	
PR no. (%)				.079
+	115 (60.2%)	101 (59.1%)	15 (40.5%)	
−	76 (39.8%)	70 (40.9%)	22 (59.5%)	
HER2 no. (%)				.166
+	48 (25.1%)	55 (30.4%)	14 (39.5%)	
−	143 (74.9%)	126 (69.6%)	23 (60.5%)	
Ki-67 status no. (%)				.011
≥14%	116 (60.7%)	133 (73.5%)	29 (78.4%)	
<14%	75 (39.3%)	48 (26.5%)	8 (21.6%)	
pT Stage no. (%)				.329
1	66 (34.7%)	47 (26.0%)	12 (32.4%)	
2	97 (51.1%)	107 (59.1%)	22 (59.5%)	
3	27 (14.2%)	27 (14.9%)	3 (8.1%)	
pN Stage no. (%)				.720
0	84 (44.0%)	86 (47.5%)	19 (51.4%)	
1	60 (31.4%)	46 (25.4%)	11 (29.7%)	
2	27 (14.1%)	23 (12.7%)	4 (10.8%)	
3	20 (10.5%)	26 (14.4%)	3 (8.1%)	
Molecular subtype no. (%)				.960
Luminal A	52 (27.2%)	48 (26.5%)	9 (24.3%)	
Luminal B	99 (51.8%)	96 (53.0%)	18 (48.6%)	
HER2-enriched	21 (11.0%)	19 (10.5%)	4 (10.8%)	
TNBC	19 (9.9%)	18 (19.9%)	6 (16.2%)	
White blood cell count ($\times 10^9$/L)	7.64 ± 6.40	6.33 ± 6.11	6.52 ± 2.47	.832
Hemoglobin (g/dL)	128.75 ± 13.16	127.82 ± 12.70	126.55 ± 14.96	.592
Red blood cell count ($\times 10^9$/L)	4.32 ± 0.50	4.375 ± 0.49	4.46 ± 0.42	.293
Platelet ($\times 10^9$/L)	148.89 ± 41.11	206.53 ± 63.70	230.86 ± 47.29	<.001
Monocyte count ($\times 10^9$/L)	0.26 ± 0.11	0.31 ± 0.12	0.39 ± 0.16	<.001
Neutrophilocyte count ($\times 10^9$/L)	3.38 ± 1.42	4.56 ± 1.20	4.31 ± 2.38	.362
Lymphocyte count ($\times 10^9$/L)	0.26 ± 0.10	0.32 ± 0.11	0.40 ± 0.15	<.001

ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, PR = progesterone receptor, TNBC = triple negative breast cancer.

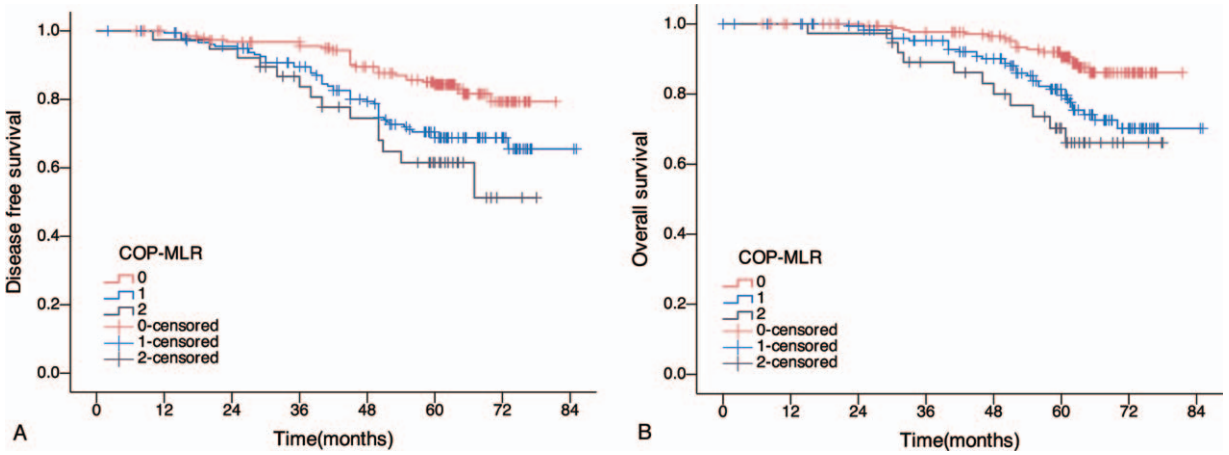

Figure 2. Kaplan–Meier survival analyses of the correlation between COP-LMR and survival among breast cancer patients: DFS (A) and OS (B). COP-LMR = the combination of platelet count and lymphocyte-to-monocyte ratio, DFS = disease-free survival, OS = overall survival.

Table 3

Results of the analysis of the prognostic factors for disease-free survival.

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
COP-LMR (0, 1, 2)	1.755 (1.306–2.357)	.001	1.498 (1.036–2.166)	.032
Patient age (>60 vs ≤60)	0.931 (0.496–1.750)	.825		
ER (positive vs negative)	1.286 (0.767–2.155)	.340		
PR (positive vs negative)	1.048 (0.674–1.632)	.834		
HER2 (positive vs negative)	0.955 (0.581–1.571)	.857		
Ki-67 status (≥14% vs <14%)	1.853 (1.126–3.050)	.015	1.695 (1.015–2.832)	.044
pT Stage (T_1-T_3)	1.365 (1.142–1.633)	.001	1.779 (1.267–2.498)	.001
pN Stage (N_0-N_3)	1.428 (1.146–1.779)	.001	1.337 (1.102–1.622)	.003
Molecular subtype (Luminal A, luminal B, HER2-enriched, TNBC.)	0.944 (0.752–1.185)	.619		
White blood cell count ($\times10^9$/L) (≥7.8 vs <7.8)	0.653 (0.240–1.778)	.404		
Hemoglobin (g/dL) (<130.5 vs ≥130.5)	0.696 (0.463–1.047)	.082		
Red blood cell count ($\times10^9$/L) (≤4.3 vs >4.3)	0.932 (0.616–1.413)	.742		
Platelet ($\times10^9$/L) (≥300 vs <300)	1.807 (1.198–2.726)	.005	1.121 (0.678–1.852)	.657
Monocyte count ($\times10^9$/L) (≤0.6 vs >0.6)	2.463 (0.897–6.763)	.080		
Neutrophilocyte count ($\times10^9$/L) (≤6.3 vs >6.3)	0.579 (0.212–1.579)	.286		
Lymphocyte count ($\times10^9$/L) (≥1.1 vs <1.1)	1.042 (0.607–1.791)	.881		

CI = confidence interval, COP-LMR = the combination of platelet count and lymphocyte-to-monocyte ratio, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, PR = progesterone receptor, TNBC = triple negative breast cancer.

associated with HER2 over-expression and prognosis in breast cancer patients.[5]

The immune response of the host to cancer is lymphocyte dependent, and high level of tumor-associated macrophage, derived from monocyte, is significantly related with tumor invasiveness and outcomes.[26] Calculated from these 2 parameters, LMR could reflect systemic inflammation status efficiently. And it was corroborated to be a prognostic marker in many malignancies, including hepatocellular cancer, endometrial cancer, breast cancer, and gastrointestinal cancer. A meta-analysis showed that LMR was significantly associated with tumor invasion depth and tumor size, and high LMR predicted better OS, DFS, and cancer-specific survival in colorectal cancer.[27] Hu et al found that low pretreatment LMR was associated with advanced clinicopathological features and poor prognosis in patients with pancreatic cancer.[28] Accordingly, several publications validated the prognostic value of LMR in breast cancer, and a meta-analysis demonstrated that low LMR was significantly associated with poor OS in breast cancer patients.[8,29–32]

Given the significance of both PLT and LMR in prognosis prediction among cancer patients, COP-LMR, the combination of these 3 parameters might integrate the accuracy of each component in condition assessment. Lim et al found that COP-LMR could be used to predict the survival of advanced NSCLC patients and it was superior to PLT or LMR.[14] Similarly, Liu et al demonstrated the likewise role of COP-LMR in early stage NSCLC patients who underwent surgery.[13]

Table 4

Results of the analysis of the prognostic factors for overall survival.

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
COP-LMR (0, 1, 2)	1.899 (1.346–2.679)	.001	1.812 (1.346–2.679)	.005
Patient age (>60 vs ≤60)	0.750 (0.343–1.638)	.470		
ER (positive vs negative)	1.255 (0.699–2.255)	.447		
PR (positive vs negative)	0.892 (0.547–1.456)	.649		
HER2 (positive vs negative)	1.343 (0.798–2.260)	.266		
Ki-67 status (≥14% vs <14%)	1.740 (0.993–3.050)	.053	1.515 (0.851–2.695)	.158
pT Stage (T_1-T_3)	1.316 (1.071–1.618)	.009	1.896 (1.284–2.799)	.001
pN Stage (N_0-N_3)	1.481 (1.161–1.890)	.002	1.413 (1.138–1.756)	.002
Molecular subtype (luminal A, luminal B, HER2-enriched, TNBC.)	0.959 (0.741–1.242)	.751		
White blood cell count ($\times10^9$/L) (≥7.8 vs <7.8)	0.434 (0.106–1.772)	.245		
Hemoglobin (g/dL) (<130.5 vs ≥130.5)	0.812 (0.501–1.315)	.397		
Red blood cell count ($\times10^9$/L) (≤4.3 vs >4.3)	0.949 (0.579–1.556)	.837		
Platelet ($\times10^9$/L) (≥300 vs <300)	1.861 (1.144–3.028)	.012	1.154 (0.664–2.004)	.612
Monocyte count ($\times10^9$/L) (≤0.6 vs >0.6)	1.974 (0.724–5.385)	.184		
Neutrophilocyte count ($\times10^9$/L) (≤6.3 vs >6.3)	0.384 (0.094–1.572)	.183		
Lymphocyte count ($\times10^9$/L) (≥1.1 vs <1.1)	0.982 (0.527–1.829)	.954		

CI = confidence interval, COP-LMR = the combination of platelet count and lymphocyte-to-monocyte ratio, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, PR = progesterone receptor, TNBC = triple negative breast cancer.

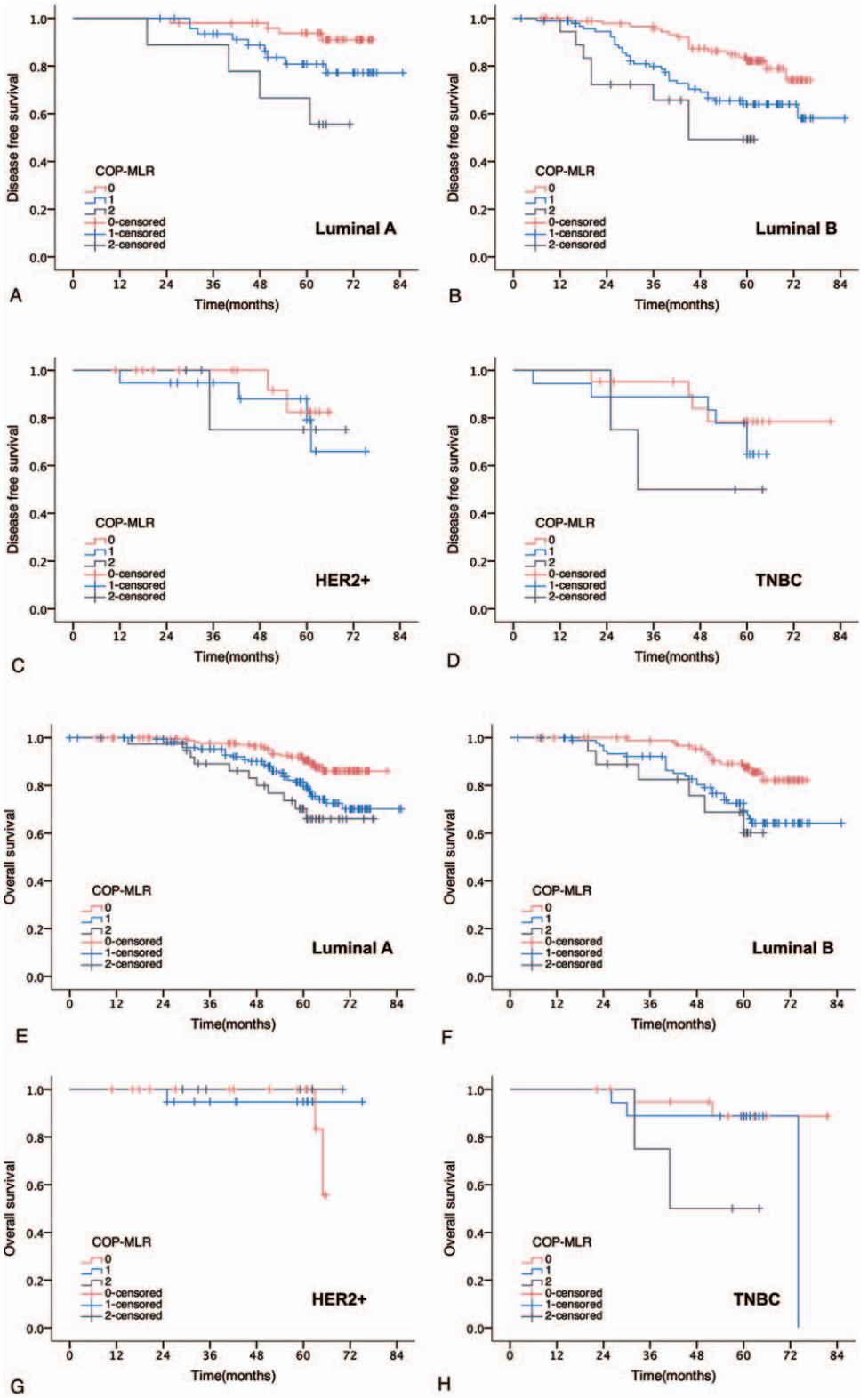

Figure 3. Kaplan–Meier survival analyses of DFS (A-D) and OS (E-H), according to COP-LMR among patients in molecular subgroups. DFS = disease-free survival, LMR = lymphocyte-to-monocyte, OS = overall survival.

Our findings showed that preoperative COP-LMR was negatively associated with long-term survival of breast cancer patients who received en bloc resection. Subgroup analysis also revealed that COP-LMR was an independent prognostic factor for luminal breast cancer, but not for patients with HER2-positive breast cancer or TNBC. A possible reason might be the

sample size, as there were less than 50 patients in each of these 2 subgroups and it became even smaller in an individual COP-LMR subgroup. And due to the retrospective nature of this research, some undetectable cofounding factors might also enlarge the influence of sample size. Limitations brought by the research nature could not be concealed, and it should be cautious to expand our conclusion to other populations of breast cancer patients if taking the geographic effects into consideration. But after all, we firstly evaluated the clinical value of COP-LMR in breast cancer patients and got some reliable results as mentioned above. More large-sized prospective researches are also needed to confirm its role in prognosis prediction in malignancies besides breast cancer.

5. Conclusion

In summary, this study showed that a higher preoperative COP-LMR score indicated a poorer prognosis in breast cancer patients who underwent curative resection. COP-LMR could be a simple but useful novel prognostic factor for therapeutic decision making.

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Visualization: Yunfu Deng.
Writing – original draft: Qinghua Zhou.
Writing – review & editing: Qinghua Zhou.

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