

Research Article

The Prognostic Value of Lymphocyte-to-Monocyte Ratio and Nutritional Index for Ovarian Cancer Patients with Normal CA125 Level

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Abstract

Background: Ovarian Cancer (OC) cases with low CA-125 concentration during routine physical examination testing are troublesome and raise false negative findings ratio. The aim of this analysis was to determine whether the Lymphocyte-To-Monocyte Ratio (LMR) and the Nutritional Index (NI) of OC patients with normal CA-125 levels had a predictive role.

Methods: This retrospective study enrolled a total of 102 OC-diagnosed patients who underwent primary cytoreductive surgery and adjuvant platinum-based chemotherapy from 2010 to 2019. Using Receiver Operating Characteristic Curves (ROC) for survival analysis, optimum cut-off values for NI and LMR were calculated. The Kaplan-Meier (KM) curve and Cox regression determined the prognostic value for Overall Survival (OS) and Progression-Free Survival (PFS).

Results: The results showed that the optimal cutoff values were 47.5 and 4.25, respectively, for NI and LMR. NI was shown to be significantly correlated with FIGO stage, Grade, the involvement of malignant ascites, and platinum response, and LMR with FIGO stage, lymph node metastasis, malignant ascites, and platinum response when the population was separated using optimized cut-off. The 5-year OS and PFS were greatly enhanced by a high NI (≥ 47.5). A low LMR (< 4.25) was associated significantly with poor 5-year PFS and OS. Both NI and LMR were independent prognosticators for the 5-year OS in multivariate analysis.

Conclusions: In CA125-normal ovarian cancer cases, elevated NI and LMR are positive prognosticators.

Keywords: Ovarian cancer, Lymphocyte-To-Monocyte Ratio (LMR), Nutritional Index (NI), Prognosis; CA125

Introduction

One of the leading causes of cancer-related mortality in women, Ovarian Cancer (OC) accounts for 295,000 new cancer cases and 185,000 deaths worldwide annually. Among malignant gynecological tumors, the OC mortality rate is the largest, which severely endangers the health of women [1]. CA-125 is the gold standard tumor marker and has thoroughly been studied in OC [2]. For OC screening and clinical evaluation help, thirty-five kilounits/L is the cut off value of serum CA125 concentration [3]. However, during the clinical examination for OC screening, not all OC patients show perfect testing outcomes. Around 20% of women with OC have serum CA125 concentrations smaller than 35 kilounits/L [4]. Elevated false negative findings are obtained during OC screening due to these low CA125 concentration cases, which do not facilitate early diagnosis of OC.

Inflammation increases the risk and development of cancer, including initiation, promotion, malignant conversion, invasion,

and metastasis [5-7]. It is considered to play an important role in tumorigenesis. Recent studies have shown a negative prognostic value of higher neutrophil-to-lymphocyte ratio and lower Lymphocyte-To-Monocyte Ratio (LMR) in OC patients, suggesting that low LMR is an independent survival prognostic factor in OC patients [8]. However, the predictive role of LMR in ovarian cancer with low CA125 concentration has not been explored.

Nutritional impairment has also been shown to have a detrimental effect on clinical outcomes [9]. At the time of diagnosis, patients with OC are also subject to starvation because of inadequate nutritional consumption due to cancer-related discomfort or psychiatric issues [10]. The prognostic Nutritional Index (NI), measured as mentioned above, could be particularly useful since both inflammation and nutritional status may serve as a surrogate marker [11]. To demonstrate the connection between postoperative complications and prognosis in patients with esophageal carcinoma [12], this index was originally examined. In this study, a low NI was seen as a poor survival predictor.

However, the predictive role of NI in ovarian cancer with low CA125 concentration has not been explored.

Based on these observations, it seems urgent to determine a way to prevent false negative results due to low CA125 concentration. The objective of this research was to determine the effects of NI and LMR on OC patients with low CA125 concentration.

Materials and Methods

Patient population

The research approved by Ethics Committee of Soochow University retrospectively enrolled a total of 102 OC patients who underwent primary debulking and adjuvant paclitaxel and carboplatin chemotherapy in university hospitals between January 2010 and January 2019. Due to potential influences on laboratory test outcomes, patients with any inflammatory disorder were omitted. No neoadjuvant chemotherapy was given to the patient. Histological diagnosis were based on WHO guidelines, and an expert pathologist examined all microscope slides. Information collection of absolute lymphocyte, monocyte counts, and albumin tests using a peripheral blood sample were performed within one week prior to treatment. Clinical variables of concern, including clinicopathological attributes, such as such as, age, FIGO stage, Grade, LN metastasis, malignant ascites, CA125 level, residual mass, Histopathology types, and platinum response were collected and evaluated, as shown in Table 1.

By dividing the baseline total peripheral lymphocyte count (cells/mm³) by the absolute peripheral monocyte count (cells/mm³), the LMR was computed. The NI was measured as follows: 10* serum albumin baseline (g/dL) + 0.005* absolute lymphocyte baseline count (cells/mm³).

Statistical Analysis

The R software x64 (version 4.0) was used to analyze the results. To evaluate variations between proportions, the Chi-square test was used, and Kaplan-Meier analysis using the log-rank test obtained the OS and PFS curves. In evaluating hazard ratios (HR) and multivariate analysis, Cox regression analysis was used. The P-values presented are two-sided, and statistical significance was considered at P<0.05.

Results

Study Population Characteristics

The normal concentration of CA125 was described in our study as patients with a concentration equal to or below 35 U/ml. The following optimal cut-off values were identified: 4.25 for LMR (AUC = 0.748, P < 0.001) and 47.5 for PNI (AUC = 0.755, P < 0.001), as shown in Figure 1. Therefore, patients with LMR > 4.25 were referred to High-LMR and patients with NI > 47.5 were referred to High-NI. Among those 102 patients, the median age was 53 years. As previously stated, in our patients, early stage disease was more frequent than advanced disease, 60 patients had stage I to II, and 42 had stage III to IV disease.

Table 1: Clinical and pathologic characteristics according to NI or LMR in 102 patients.

Variable		All Case	NI		p value	LMR		p value
			<47.5	≥47.5		< 4.25	≥4.25	
Age	<50	51	14	37	0.774	34	17	0.635
	≥50	51	15	36		31	20	
FIGO stage	I/II	60	24	36	0.005*	33	27	0.025*
	III/IV	42	5	37		32	10	
Grade	G1/G2	58	25	33	0.003*	12	46	0.531
	G3	44	4	40		14	30	
Histopathology	Serous	76	55	30	0.634	50	26	0.642
	Others	28	14	8		16	12	
LN metastasis	No	80	26	54	0.377	50	30	0.031*
	Yes	22	5	17		18	4	
Malignant ascites	No	67	24	43	0.046*	35	32	0.011*
	Yes	35	5	30		30	5	
Residual mass	<1 cm	81	26	55	0.255	51	30	0.147
	≥1 cm	21	3	18		15	6	
Platinum response	Sensitive	80	28	52	0.008*	48	32	0.033*
	Resistant	22	3	19		17	5	

Note: FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node.

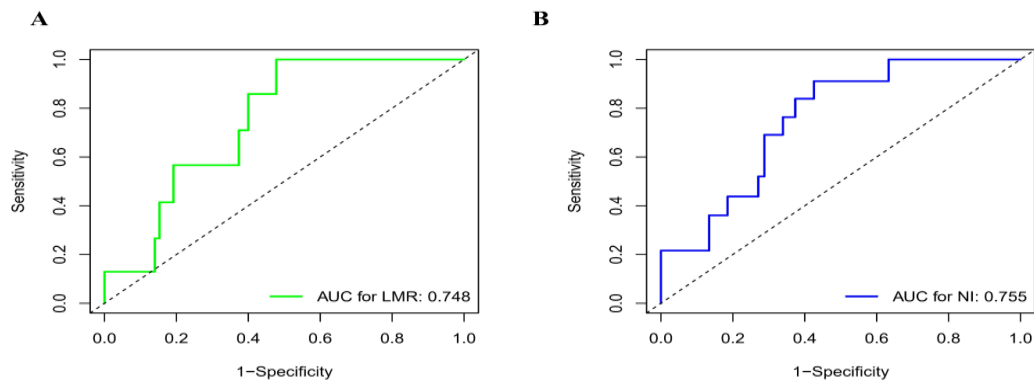


Figure 1: Receiver operating characteristic curves. Receiver operating characteristic curves for predicting the survival outcome. (A) Lymphocyte to Monocyte Ratio (LMR) (B) Nutritional Index (NI).

The histopathological type (76 patients) is mostly serous epithelial carcinoma. Eighty-one patients were optimally debulked with less than one cm of residual disease at primary surgery. Almost all patients are sensitive to platinum (Table 1).

Relations between NI, LMR and Clinical Features

The Chi-square test was used to evaluate the association between the levels of NI, LMR and clinical characteristics (Table 1), including Age, FIGO stage, Grade, Histopathology, LN metastasis, Malignant ascites, Residual mass, and Platinum response. NI was shown to be significantly correlated with FIGO stage ($P = 0.005$), Grade ($P = 0.003$), malignant ascites ($P = 0.046$), and platinum response ($P = 0.008$), and LMR with FIGO stage ($P = 0.025$), lymph node metastasis ($P = 0.031$), malignant ascites ($P = 0.011$), and platinum response ($P = 0.033$) when the population was separated using optimized cut-off.

KM analysis found that patients in the low NI group had worse PFS ($P = 0.023$) and OS ($P = 0.046$) selected for this research than patients in the high NI group. In terms of PFS ($P = 0.003$) and OS ($P < 0.016$), patients in the high LMR group had greater treatment outcomes than those in the low LMR group, as shown in Figure 2.

Prognostic Values of NI and MLR

Univariate analyses showed that interactions with FIGO stage ($P < 0.001$), Grade ($P < 0.001$), LN metastasis ($P = 0.002$), malignant ascites ($P = 0.003$), histopathology ($P = 0.004$), residual mass ($P = 0.005$), platinum reaction ($P = 0.009$), NI ($P = 0.043$) and LMR ($P = 0.004$) were identified in the findings obtained for PFS. Multiple cox regression analysis was used to analyze the association between survival outcomes and clinical features found in univariate analysis. A FIGO level (III-IV stage) (4.022 (1.754-9.322), $P=0.001$), grade III

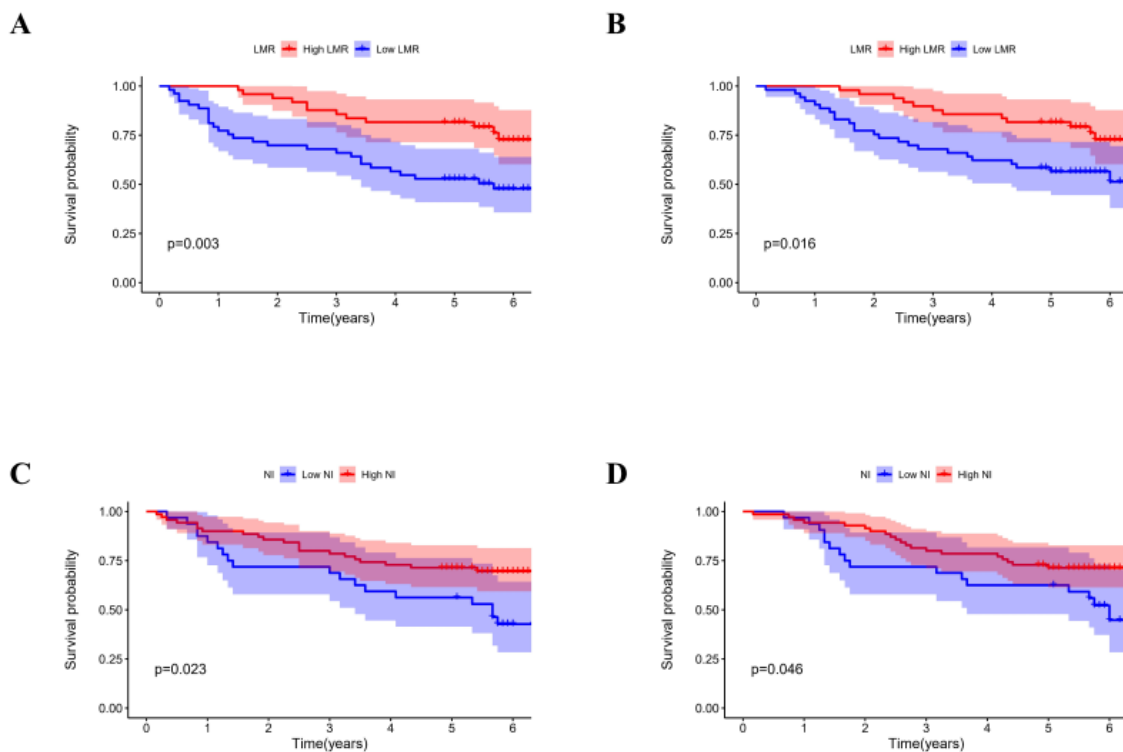


Figure 2: Kaplan-Meier survival curves. Kaplan-Meier survival curves by different level of LMR and NI. (A) LMR for Overall survival. (B) LMR for Progression-free survival. (C) NI for Overall survival. (D) NI for Progression-free survival.

(2.640 (1.333-5.229), P=0.005), residual mass ≥ 1 cm (2.540 (1.074-5.929), P=0.005) and immune platinum reaction (3.575 (2.672-6.752), P = 0.009), a low LMR (2.640 (2.364-5.731), P = 0.005) and a low NI (1.367 (0.243-2.254), P = 0.019), as shown in Table 2.

Likewise, univariate analysis showed important relationships between the following factors and OS: FIGO stage (P < 0.001), Grade (P < 0.001), LN metastasis (P = 0.033), histopathology (P = 0.014), residual mass (P = 0.007), platinum reaction (P = 0.001), NI (P = 0.034) and LMR (P = 0.001). However, COX multivariate analysis showed only the following were independent poor prognostic factor of OS, FIGO level (III-IV stage) (6.172 (2.315-10.112), P=0.003), grade III (3.640 (2.371-6.551), P=0.015), residual mass ≥ 1 cm (3.230 (2.099-4.872), P=0.035) and immune platinum reaction (6.533 (3.232-7.992), P = 0.001), a low LMR (3.540 (2.724-6.133), P = 0.002) and a low NI (1.667(0.349-3.692), P = 0.014), as shown in Table 3.

Discussion

For women with OC, the high fatality risk is largely attributed to a lack of early diagnosis. There is no diagnosis for certain women until the late stage, so early diagnosis of OC is urgent. The main method used for ovarian cancer screening during physical examination is

actually the concentration of serum CA125 monitoring. Furthermore, CA125 concentration can also be used to evaluate longevity following surgery in women who have been diagnosed with OC. Unfortunately, not all women with OC show high concentration of CA125. The low concentration of preoperative CA125 in OC patients was 20% [13], according to a retrospective study. It indicated that certain patients were preoperative CA125-normal OC patients and that there was a lack of effective serum biomarkers to determine the prognosis.

LMR was elevated in epithelial ovarian cancer in pretreatment and showed prognostic importance after following treatment. Immune Complexes (ICs) are formed against the antigen by the antigen and antibody, and free ICs circulating are Circulating Immune Complexes (CICs) [14]. Any medium-sized CICs, however, cannot be washed and stay in the circulatory system. Inflammatory reaction, which is a central mechanism for immune-complex diseases, could be triggered by these CICs. Daniel demonstrated the presence of CICs affecting CA125 in 2010, and proposed that CA125 CICs offer a reason for ovarian cancer with normal CA125 level [15]. LMR should be a good predictor of ovarian cancer based on both of these results.

A low PNI demonstrated a decrease in serum albumin and/or a low lymphocyte absolute count. Serum albumin is an essential component

Table 2: Univariate and multivariate analyses of PFS of patients according to clinicopathological characteristics including LMR and NI.

Variable	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (≥ 50 vs. <50)	1.544 (0.832-2.774)	0.123		
FIGO stage (III/IV vs. I/II)	8.337 (3.874-14.665)	< 0.001	4.022 (1.754-9.322)	0.001*
Grade (III vs. I/II)	6.367 (2.575-10.254)	< 0.001	2.640 (1.333-5.229)	0.005*
Histopathology (Others vs. Serous)	4.723 (3.687-7.263)	0.004	1.224 (0.875-3.354)	0.479
LN metastasis (Yes vs. No)	2.633 (1.377-5.357)	0.002	1.239 (0.994-2.995)	0.632
Malignant ascites (Yes vs. No)	3.627 (1.756-6.233)	0.018	0.994(0.383-3.411)	0.255
Residual mass (≥ 1 cm vs. <1 cm)	4.540 (1.383-5.929)	0.015	2.540 (1.074-5.929)	0.005*
Platinum response (Resistant vs. Sensitive)	10.367 (7.575-12.254)	0.009	3.575 (2.672-6.752)	0.009*
LMR (<4.25 vs. ≥ 4.25)	3.066 (1.432-6.229)	0.004	2.640 (2.364-5.731)	0.005*
NI (≥ 47.5 vs. <47.5)	1.795 (1.575-4.254)	0.043	1.367 (0.243-2.254)	0.019*

Note: HRs was obtained from Cox s proportional hazard model. HR, hazard ratio; CI, confidence interval; NI, neutrophil lymphocyte ratio; LMR, lymphocyte monocyte ratio; FIGO, The International Federation of Gynecology and Obstetrics; LN, lymph node.

Table 3: Univariate and multivariate analyses of OS of patients according to clinicopathological characteristics including LMR and NI.

Variable	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (≥ 50 vs. <50)	1.454 (0.730-2.668)	0.313		
FIGO stage (III/IV vs. I/II)	9.127 (3.765-20.175)	< 0.001	6.172 (2.315-10.112)	0.003*
Grade (III vs. I/II)	7.367 (3.723-12.557)	< 0.001	3.640 (2.371-6.551)	0.015*
Histopathology (Others vs. Serous)	3.436 (2.227-8.923)	0.014	2.367 (1.445-3.674)	0.331
LN metastasis (Yes vs. No)	1.783 (1.267-4.349)	0.033	1.211 (0.749-1.995)	0.362
Malignant ascites (Yes vs. No)	4.007 (1.366-5.273)	0.147		
Residual mass (≥ 1 cm vs. <1 cm)	4.880 (2.367-6.429)	0.007	3.230 (2.099-4.872)	0.035*
Platinum response (Resistant vs. Sensitive)	9.237 (6.945-10.322)	0.001	6.533 (3.232-7.992)	0.001*
LMR (<4.25 vs. ≥ 4.25)	6.014 (2.397-7.379)	0.001	3.540 (2.724-6.133)	0.002*
NI (≥ 47.5 vs. <47.5)	1.993 (1.235-5.641)	0.033	1.667(0.349-3.692)	0.014*

Note: HRs was obtained from Cox s proportional hazard model. HR, hazard ratio; CI, confidence interval; NI, neutrophil lymphocyte ratio; LMR, lymphocyte monocyte ratio; FIGO, The International Federation of Gynecology and Obstetrics; LN, lymph node.

in the nutritional status and inflammatory response of the host [16]. It is often considered that the absolute lymphocyte count is a significant participant in inhibiting cancer growth by initiating a cytotoxic immune response [17]. It has been documented that low immune-nutritional status is associated with an immunosuppressed disorder that offers a favorable micro-environment for tumor relapse. That may be the reason why the bad results may be caused by this immunosuppressed syndrome in low-NI patients. Important advancement in research on immune control points in tumor immunity has made it possible to elucidate the molecular mechanism underlying the immunological resistance of tumor growth. The relation between peripheral inflammatory biomarkers and immunotherapy treatment effects appears to be uncertain. These biomarkers could serve in the future as a helpful indicator of immunotherapy in the treatment of OC.

Taken together, this current literature has demonstrated that a severely compromised immune system may be affected by starvation and lymphocytopenia. The NI cutoff value reported in previous studies was 40-60 for other cancer forms [18-20]. In our study, patients with NI < 47.5 had dramatically decreased survival when multivariate regression was corrected for other prognostic factors. Furthermore, our findings have shown that low LMR is a predictor of poor prognosis in OC patients with average levels of CA125. According to the multivariate study, patients with LMR < 4.25 had a substantial decrease in OS and PFS. Moreover, since the LMR and NI are very quickly collected, the cost-effectiveness is in line with the criteria of regular screening markers.

Any of the present study's limitations merit attention. First, we were unable to thoroughly validate the prognostic value of LMR and NI due to the retrospective aspect of the analysis. Second, LMR is a non-specific inflammation marker, and while we omitted patients with any inflammatory disorder, the existence of other unrecognized systemic inflammatory disorders could have impaired laboratory findings. The strength of our research is that it is the first attempt to evaluate the prognostic importance of LMR and NI in OC patients with normal CA125 level.

Conclusion

In summary, our current study showed that patients with higher pretreatment LMR (≥ 4.25) showed significantly better survival than those with lower LMR (<4.25); Patients with higher NI (≥ 47.5) revealed pretreatment LMR and NI were also an independent prognostic factor that predicts OS and PFS.

Declarations

Ethics Approval and Consent to Participate

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 protocol was approved by the Hospital Ethics Committee of the Second Affiliated Hospital of Soochow University.

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