Preoperative Monocyte-to-Lymphocyte Ratio in Peripheral Blood Predicts Stages, Metastasis, and Histological Grades in Patients with Ovarian Cancer[1,2]

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Abstract

PURPOSE: The monocyte-to-lymphocyte ratio (MLR) has been shown to be associated with the prognosis of various solid tumors. This study sought to evaluate the important value of the MLR in ovarian cancer patients. *METHODS:* A total of 133 ovarian cancer patients and 43 normal controls were retrospectively reviewed. The patients' demographics were analyzed along with clinical and pathologic data. The counts of peripheral neutrophils, lymphocytes, monocytes, and platelets were collected and used to calculate the MLR, neutrophil-to-lymphocyte ratio (NLR). and platelet-to-lymphocyte ratio (PLR). The optimal cutoff value of the MLR was determined by using receiver operating characteristic curve analysis. We compared the MLR, NLR, and PLR between ovarian cancer and normal control patients and among patients with different stages and different grades, as well as between patients with lymph node metastasis and non–lymph node metastasis. We then investigated the value of the MLR in predicting the stage, grade, and lymph node positivity by using logistic regression. The impact of the MLR on overall survival (OS) was calculated by Kaplan-Meier method and compared by log-rank test. *RESULTS:* Statistically significant differences in the MLR were observed between ovarian cancer patients and normal controls. However, no difference was found for the NLR and PLR. Highly significant differences in the MLR were found among patients with different stages (stage I-II and stage III-IV), grades (G1 and >G1), and lymph node metastasis status. The MLR was a significant and independent risk factor for lymph node metastasis, as determined by logistic regression. The optimal cutoff value of the MLR was 0.23. We also classified the data according to tumor markers (CA125, CA199, HE4, AFP, and CEA) and conventional coagulation parameters (International Normalized Ratio [INR] and fibrinogen). Highly significant differences in CA125, CA199, HE4, INR, fibrinogen levels, and lactate dehydrogenase were found between the low-MLR group (MLR ≤ 0.23) and the high-MLR group (MLR > 0.23). Correspondingly, dramatic differences were observed between the two groups in OS. *CONCLUSION:* Our results show that the peripheral blood MLR before surgery could be a significant predictor of advanced stages, advanced pathologic grades, and positive lymphatic metastasis in ovarian cancer patients.

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Introduction

Ovarian cancer is the most lethal gynecologic cancer and one of the most important causes of cancer-related deaths in women worldwide [1]. Fewer than half of patients survive for more than 5 years after diagnosis. More than 75% of patients are diagnosed at an advanced stage after menopause because early-stage disease is usually asymptomatic, and the symptoms of late-stage disease are nonspecific [2]. Given the poor prognosis of ovarian cancer, a method for accurately predicting the prognosis of patients with ovarian cancer after curative surgical resection is necessary to improve patient survival [3,4].

Owing to increasing evidence regarding the role of inflammation in cancer biology, a systemic inflammatory response has been found to have prognostic significance in a variety of cancers. Kawata et al. have reported that lymphocyte infiltration around the tumor is associated with a better prognosis in HCC [5], whereas the presence of neutrophils in the tumor stroma is associated with a poor prognosis [6]. Likewise, the neutrophil-to-lymphocyte ratio (NLR), a predictor of inflammatory status, has been shown to be an effective prognostic marker for many solid tumors [7–13]. In addition to neutrophils and lymphocytes, monocytes are another important type of leucocyte. Studies have shown that monocytes are an independent prognostic factor, and a higher number of monocytes predict a poor prognosis, similar to the role of neutrophils in predicting prognosis. The monocyte-to-lymphocyte ratio (MLR), i.e., the monocyte count divided by the lymphocyte count, has recently been shown to be a much more efficient prognostic predictor in many solid tumors.

The purpose of this study was to evaluate the MLR's interindividual differences and its diagnostic efficiency, feasibility, and predictive value for patients with ovarian cancer.

Materials and Methods

This retrospective analysis was conducted by using the clinical data obtained from ovarian cancer patients who underwent surgical resection at the Department of Obstetrics and Gynecology, Shanghai General Hospital, Shanghai Jiaotong University School of Medicine, between January 2011 and March 2016. The study was reviewed and approved by the Institutional Review Board and the Research Ethics Committee of Shanghai First People's Hospital. All participants gave informed consent to participate in the study.

The cases of 133 ovarian cancer patients and 43 normal controls were retrospectively reviewed. The clinical stage of ovarian cancer was determined according to the International Federation of Gynecology and Obstetrics (FIGO) stage. The selection criteria for patients were as follows: 1) ovarian cancer confirmed by pathology; 2) no preoperative treatments, such as radiotherapy or neoadjuvant chemotherapy; 3) no coexisting cancers or prior cancers within the previous 5 years; 4) complete clinical, laboratory, imaging, and follow-up data; 5) no evidence of sepsis [7]; 6) no autoimmune disease or treatment with steroids; and 7) no hematological disorders or treatment that could result in an elevated MLR or NLR, for example, the administration of hematopoietic agents, such as granulocyte colony-stimulating factor, within 1 month before surgery. Routine blood tests, routine coagulation tests, and measurements of tumor markers (CA125, CA199, HE4, AFP, and CEA) were performed on the day before surgery. The normal controls are the healthy women aged 35 to 60 years. The MLR, NLR, and platelet-to-lymphocyte ratio (PLR) were defined as the ratio of the absolute peripheral blood monocyte and lymphocyte counts, absolute neutrophil and lymphocyte counts, and absolute platelet and lymphocyte counts, respectively.

Data, including information on patient demographics, were collected for analysis. The clinicopathologic variables, including age, FIGO stage, histologic grade, lymph node metastasis, and CA-125 levels, were obtained retrospectively from patient medical records. Each cytoreduction was principally aimed at maximal tumor resection without a visible residual tumor. If technically achievable, all visible cancer was resected to achieve optimal tumor debulking, leaving a residual tumor with a maximal diameter of ≤1 cm [40].

We determined the optimized MLR cutoff values for predicting survival outcomes using receiver operating characteristic (ROC) curve analysis, and the best MLR cutoff value for diagnosis was 0.23. Patients were grouped according to the results of the ROC curve

Table 1. The Clinical Baseline Characteristics of Ovarian Patients

Variable	No. of Patients (%)
Age (years, mean ± SD)	53.27 ± 13.57 (20-82)
Histological type, n (%)	133 (100%)
Serous	87 (65.41%)
Mucinous	14 (10.53%)
Endometrioid	10 (7.52%)
Clear cell	5 (3.76%)
Others	17 (12.78%)
Differentiation, n (%)	133 (100%)
G1	24 (18.04%)
G2	52 (39.10%)
G3	57 (42.86%)
Stage, n (%)	133 (100%)
I	37 (27.82%)
II	27 (20.30%)
III	65 (48.87%)
IV	4 (3.01%)
Lymphatic metastasis, n (%)	133 (100%)
Negative	111 (83.46%)
Positive	22 (16.54%)
Optimal debulking, n (%)	133 (100%)
No	6 (4.51%)
Yes	127 (95.49%)

Others: including immature teratoma (three cases), granulosa cell tumor (three cases), endodermal sinus tumor (three cases), undifferentiated tumor (three cases), carcinoid tumor (three case), squamous cell carcinoma (two case).

Table 2. Clinical and Test Characteristics of Ovarian Cancer Population

| Variable	Mean ± SD
CA-125 (U/ml)	1092.36 ± 94.53
CA-199(U/ml)	72.89 ± 16.27
AFP (ng/ml)	16.95 ± 4.49
CEA(ng/ml)	8.29 ± 2.70
HE4 (pmol/l)	455.57 ± 39.47
WBC (10^9/l)	6.59 ± 3.20
N (%)	67.63 ± 11.59
L (%)	24.37 ± 10.04
M (%)	6.04 ± 2.55
Hemoglobin (g/l)	119.87 ± 17.94
Platelet (10^9/l)	279.57 ± 112.24
Ln NLR	1.07 ± 0.59
Ln MLR	-1.45 ± 0.52
Ln PLR	5.22 ± 0.57
D-Dimer (mg/l)	2.43 ± 1.01
PT (s)	11.69 ± 1.39
INR	0.99 ± 0.09
APTT (s)	27.03 ± 4.00
TT (s)	18.43 ± 2.69
Fibrinogen, FIG (mg/l)	3.49 ± 1.06
LDH (U/l)	196.64 ± 88.8

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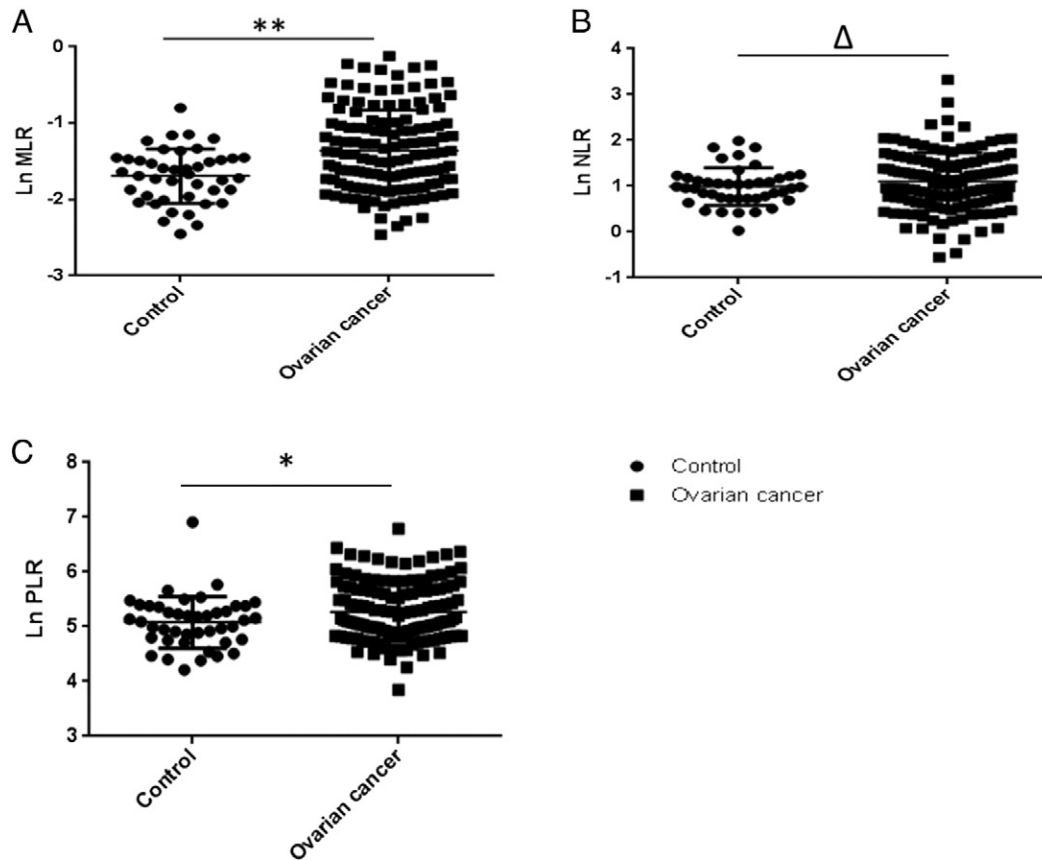
Figure 1. High MLR in ovarian cancer patients.(A, B, and C) The Ln MLR, Ln NLR, and Ln PLR between the control group and the ovarian cancer group, respectively. **$P = .0003$; *$P = .039$; $^\Delta P > .05$.

analysis, as follows: MLR-low (MLR ≤ 0.23) and MLR-high (MLR > 0.23). Differences in cancer- and host-related risk factors, including age, FIGO stage, histologic grade, optimal debulking (OD), serum CA-125 levels and overall survival (OS), between the MLR-low and MLR-high groups were analyzed.

Statistical Analysis

All statistical analyses were performed with SPSS version 19.0 software (Chicago, IL). After logarithmic transformations of the MLR, NLR, and PLR, the log-transformed data were close to a normal distribution. Therefore, we used the log-transformed data for statistical analysis. t tests and one-way analysis of variance (ANOVA) were used to analyze the data of two independent groups or three and four groups, respectively. To account for their effects on the relationships between the MLR and the stages, histological types, grades, lymphatic metastasis, and OD, all variables were included in a binary logistic regression analysis. The OS was assessed using the Kaplan-Meier method and compared by log-rank test. A P value of < .05 was considered to be statistically significant.

Results

The Clinical Baseline Characteristics of Ovarian Cancer Patients

The baseline characteristics of the patients are displayed in Table 1. Serous adenocarcinoma was the most common subtype (65.41%), and histological grade 3 was the most frequent grade (42.86%) in our cohort. In total, 37 (27.82%), 27 (20.30%), 65 (48.87%), and 4 (3.01%) patients had stage I, II, III, and IV disease, respectively.

Additionally, 22 (16.54%) patients had lymphatic metastasis. OD was performed in 127 (95.49%) patients.

The Hematological Baseline Characteristics of Ovarian Cancer Patients

The median neutrophil, monocyte, and platelet counts were $67.63 \times 10^9/l$, $6.04 \times 10^9/l$, and $24.37 \times 10^9/l$, respectively. The NLR, MLR, and PLR were 3.73, 0.30, and 225.96, respectively. The values for the coagulation system factor, D-dimer, prothrombin time (PT), International Normalized Ratio (INR), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen were 2.43, 11.69, 0.99, 27.03, 18.43, and 3.49, respectively. (Table 2). The median serum levels of the tumor markers CA125, CA199, AFP, CEA, and HE4 were 1092.36 U/ml, 72.89 U/ml, 16.95 U/ml, 8.29 U/ml, and 455.57 U/ml, respectively.

MLR, NLR, and PLR between Ovarian Cancer Patients and Controls

When we compared the MLR and PLR between ovarian cancer patients and controls, significant differences were observed ($P = .0003$ and $P = .046$). However, no differences in the NLR were found between ovarian cancer patients and normal controls ($P = .304$) (Figure 1).

MLR as an independent Predictor of Ovarian Cancer and Is Positively Correlated with CA125

Given that the MLR was different between the control group and ovarian cancer group, we sought to determine whether the MLR could be a predictor of ovarian cancer. In the binary logistic

Table 3. Independent Predictors of Ovarian Cancer in the Binary Logistic Regression Analysis

	β	P	OR	95% CI (OR)
MLR	2.14	.00	8.50	2.65-27.71
NLR	−1.49	.02	0.23	0.07-0.79
PLR	0.689	.20	1.92	0.70-5.64

All analyzed data were Ln (original data) transformed from the original data and tested with binary logistic regression.

regression, the MLR was identified as an independent predictor or risk factor of ovarian cancer [odds ratio (OR) = 8.50, 95% confidence interval (CI) = 2.65-27.71] (Table 3).

Then, we examined the ROC curve of the MLR in distinguishing the control from ovarian cancer patients. In the ROC analysis, the area under the curve is 0.68 (95% CI, 0.59-0.76). A cutoff of 0.23 was identified to reach a sensitivity of 50% and a specificity of 90% from this study cohort (Figure 2).

Because CA125 is an important maker of ovarian cancer, we next investigated the relationship with MLR by Spearman's rank correlation analysis using original data of MLR and CA125. There was a significant positive correlation between MLR and CA125 (r = 0.46, P = .00).

The Differences in the MLR across Stages, Histological Types, Grades, Lymphatic Metastasis, and OD

Next, we investigated differences in the MLR with respect to histological types, grades, stages, lymphatic metastasis, and OD. As shown in Figure 3, significant differences were found for categorical variables including FIGO stages (P < .0001), histological grades (P = .0076), and lymphatic metastasis (P = .0004), but not including histological types (P = .4034) and OD (P = .1056).

The MLR was an independent risk factor for advanced stages, lymphatic metastasis, and advanced pathological grades in ovarian cancer patients.

Because the MLR was significantly different among patients with different FIGO stages, lymphatic metastasis, and tumor pathological grades, we further investigated the association between the MLR with

the stages, lymphatic metastasis, and grades by using binary logistic regression. As shown in Table 4, the MLR was significantly associated with stages, lymphatic metastasis, and grades. All of the three β values and OR values were >1, indicating that the MLR was a significant independent risk factor for advanced stages, lymphatic metastasis, and advanced grades.

Initially, we assessed differences in the MLR in three pathologic grades by using one-way ANOVA. We found that the MLR was significantly different between G1 and G2 and between G1 and G3. However, no significant differences were observed between G2 and G3. Therefore, we merged the data of G2 and G3 into one group, the ">G1" group, and reanalyzed the data with the results shown in Figure 3B. Furthermore, logistic regression was performed and showed that the grade is associated with MLR (P = .01, β = 1.32, OR = 3.72).

Differences in the Baseline Characteristics between the MLR-Low and MLR-High Groups

The optimal cutoff value of the MLR was 0.23 (Figure 2). The MLR-low and MLR-high groups included 64 (48.12%) and 69 (51.88%) patients, respectively. To evaluate the relevance of the MLR, we assessed differences in the baseline characteristics of the patients according to the different MLR categories. Significant differences between the MLR-low and MLR-high groups were found for the following continuous variables: serum CA125 levels (P = .000), serum CA199 levels (P = .033), HE4 levels (P = .005), percentage of neutrophils (P = .000), percentage of lymphocytes (P = .000), percentage of monocytes (P = .000), NLR (P = .000), MLR (P = .000), PLR (P = .000), INR (P = .000), fibrinogen (P = .000), and lactate dehydrogenase (P = .016) (Table 5).

MLR Predicted OS in 124 Patients with Ovarian Cancer

After a median follow-up of 23.617 months (range, 0.767-69.4 months), there were 6 patients who died in the MLR-low group, and there were 14 patients who died in the MLR-high group. The total missed follow-up rate was 6.767%. Based on Kaplan-Meier analysis, high MLR was significantly associated with a lower OS rate and higher mortality in ovarian cancer (P = .037) (Figure 4).

Discussion

Ovarian cancer is the most lethal gynecologic cancer and is one of the major causes of cancer-related death in women worldwide. The high mortality is partly due to difficulties in early diagnosis and the development of metastases. Given this cancer's poor prognosis, methods for accurately predicting risk factors that affect cancer severity and early diagnosis are required to improve patient survival rates.

In recent years, several prognostic indicators derived from peripheral blood, such as the MLR, NLR, and PLR, have been widely investigated as useful prognostic markers in cancers. Despite inconsistent results, these markers have been reported to have significant diagnostic and prognostic value in a wide variety of cancers. The MLR has been suggested to be associated with survival in patients with malignant lymphomas and many solid tumors, such as head and neck, breast [14], lung, esophageal, gastric, colorectal [15,16], pancreatic, bladder [6], and cervical cancers [5]. A high MLR was associated with poor OS in previous reports, and the MLR can be considered to be a potential surrogate biomarker in various cancers. Although the mechanisms of the association between a higher MLR and a poorer prognosis have not been fully clarified, the MLR may reflect the balance between the favorable role of lymphocytes and the unfavorable effect of monocytes with respect to cancer progression.
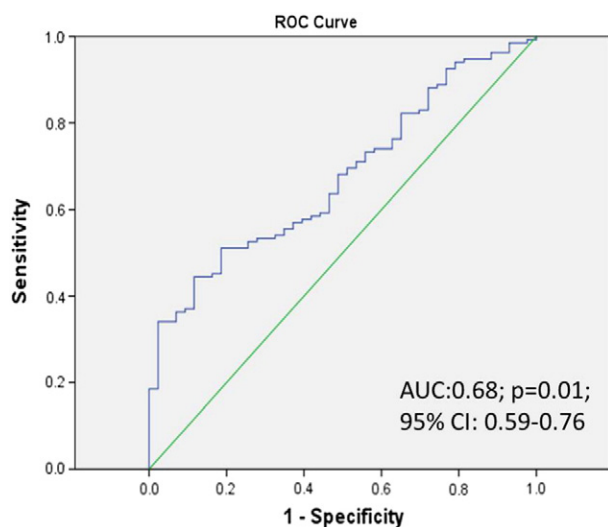

Figure 2. Diagnostic accuracy of the MLR for the prediction of ovarian cancer.*ROC analysis of the control group MLR and the ovarian cancer group MLR.AUC, area under curve.

In this study, the MLR was significantly higher in the ovarian cancer group than in the control group. The higher MLR indicated lower lymphocyte or higher monocyte levels in the peripheral blood of ovarian cancer patients. Lymphocytes play important roles in the defense against cancer cells by inducing cytotoxic cell death and suppressing tumor cell proliferation and migration. Many types of lymphocytes, such as T cells, dendritic cells, monocytes, and macrophages, have been shown to infiltrate ovarian cancer [17–23]. It is well accepted that tumor-infiltrating lymphocytes establish a defense barrier against cancer dissemination. Therefore, decreased lymphocyte counts in the blood and tumor stroma lead to a downregulation of the immune response against tumors [5]. Moreover, a decreased lymphocyte count in the blood has been identified as an independent prognostic factor for OS in various cancers. Additionally, the pretreatment number of peripheral blood monocytes has been shown to be correlated with poor prognosis in patients with various types of cancers. After recruitment into tumor tissue, monocytes differentiate into tumor-associated macrophages (TAMs) [22]. Evidence from clinical and experimental studies has indicated that TAMs promote solid-tumor progression and metastasis, and monocytes in the peripheral blood may reflect the formation or presence of TAMs, which are a prominent component of the mononuclear leukocyte population of solid tumors and display an ambivalent relationship with tumors. TAMs are educated by the tumor microenvironment, and they facilitate angiogenesis, matrix breakdown, and tumor-cell motility, all of which are elements of the metastatic process. During an inflammatory response, macrophages also produce many compounds, ranging from mutagenic oxygen and nitrogen radicals to angiogenic factors that can contribute to cancer initiation and promotion. As such, monocytes/TAMs can promote solid-tumor progression and metastasis [24–26]. Furthermore, ovarian cancer also has the ability to escape the immune system because pathological interactions between cancer cells and host immune cells in the tumor microenvironment create an immuno-suppressive network that promotes tumor growth and protects the tumor from the immune system [24,25]. Therefore, we speculated that the higher MLR of ovarian cancer patients may indicate increased monocyte differentiation and infiltration of TAMs, which are involved in ovarian cancer cell immune escape, thereby stimulating ovarian cancer progression and metastasis. However, this possibility requires further study.

Our results also showed, via logistic regression, that a higher MLR was observed in patients with a higher stage and grade, as well as those with positive lymphatic metastasis, and is therefore an independent
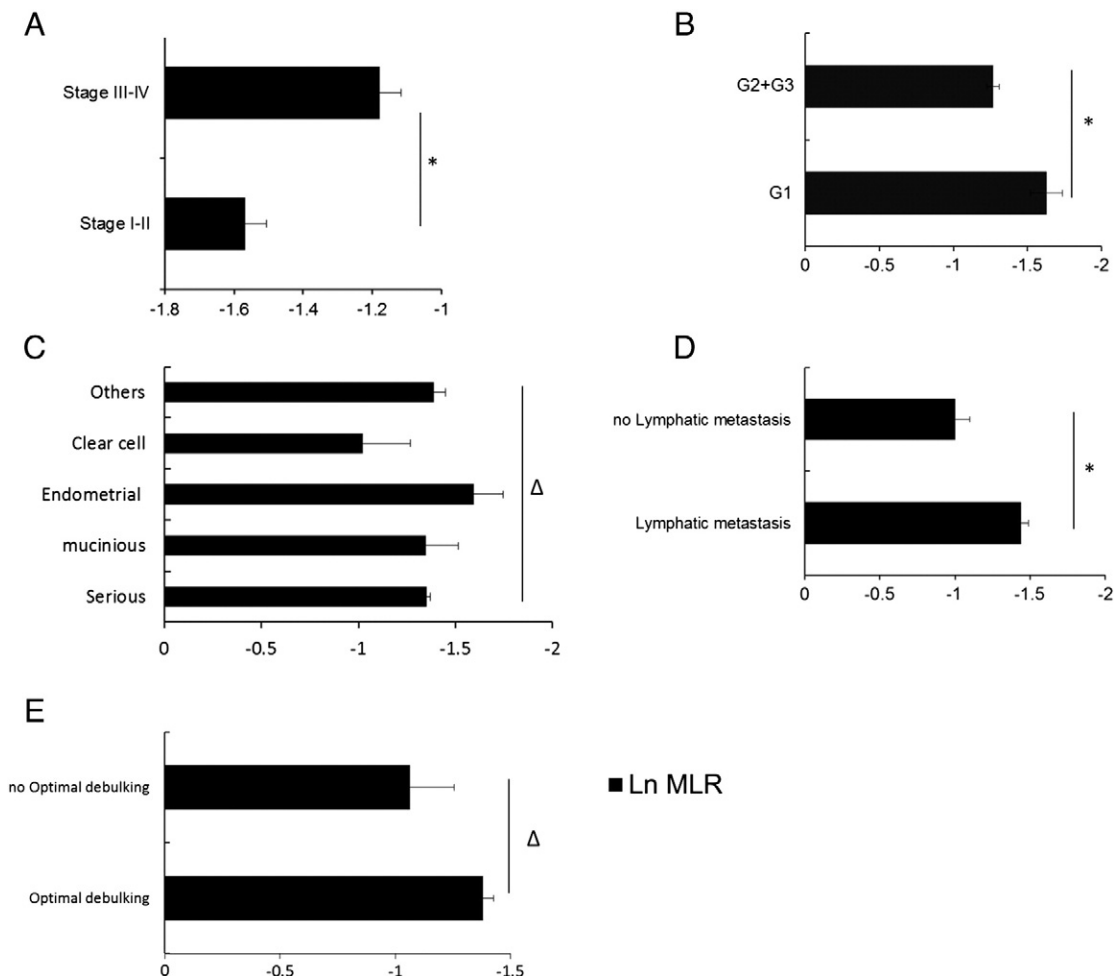

Figure 3. Differences in the MLR among various stages, histological types, pathologic grades, lymphatic metastasis, and OD.(A) *P < .0001(*t* test); (B) *P = .0076 (*t* test); (C) *P* = .4034, one-way ANOVA; (D) *P* = .0004 (*t* test); (E) *P* = .1056; one-way ANOVA.

Table 4. Logistic Regression Estimates (β Coefficients and 95% CI) of the Association between MLR and Stages, Lymphatic Metastasis, and Histological Grades

	β	P	OR	95% CI (OR)
Stages	1.15	.002	3.15	1.55-6.44
Lymphatic metastasis	1.55	.000	4.70	1.880-11.74
Histological grades	1.32	.01	3.72	1.36-10.17

All analyzed data were Ln (original data) transformed from the original data and tested with binary logistic regression. As in Figure 2, the stages were classified as stage I-II and stage III-IV, and β = 1.15 > 1, OR = 3.15 > 1, indicating that the MLR was a significant independent risk factor for advanced stage in ovarian cancer patients. Similarly, the MLR was also a significantly important predictor for lymphatic metastasis (β = 1.55 > 1, OR = 4.70 > 1). The pathology grades were divided into two groups, G1 and >G1 (G2 + G3), and tested with binary logistic regression. Because β = 1.32 > 1 and OR = 3.72 > 1, the MLR was also shown to be a significant independent risk factor of higher pathology grades.
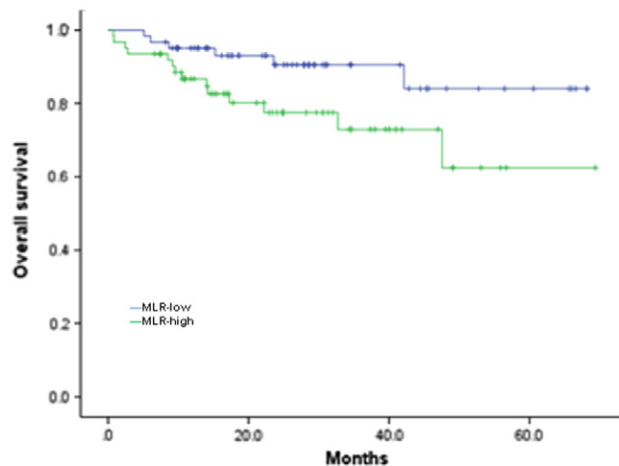

Figure 4. Kaplan-Meier survival curves for OS in patients with ovarian cancer.Significant differences were found between MLR-low and MLR-high groups ($P = .037$).

risk factor for advanced stage, advanced pathologic grade, and positive lymphatic metastasis. In most studies, the cutoff values for the MLR were determined by ROC curve analysis. Our cutoff point of MLR between normal and ovarian cancer was 0.23, also determined by ROC curve analysis. In the present study, significant differences were observed in the CA125, CA199, HE4, INR, fibrinogen levels, and lactate dehydrogenase between the MLR-low (≤0.23) and MLR-high (>0.23) groups ($P < .0001$). CA125 and CA199 are antibodies that are considered to be ovarian cancer biomarkers, and malignant cancer patients have hypercoagulation conditions with higher fibrinogen levels. The association of MLR with cancer survival has been reported for several cancers, such as bladder cancer, endometrial cancer, and hepatocellular carcinoma [27–29]; however, it was rarely reported in ovarian cancer. Our result revealed that lower MLR levels were associated with favorable OS of ovarian cancer ($P = .037$). These results were in accordance with other researches.

Unexpectedly, we found that the MLR was significantly associated with coagulation conditions. It is well known that the hemostatic components and the cancer biology are interconnected in multiple ways. The hemostatic factors play a role in tumor progression. Cancer cells are able to activate the coagulation system, release procoagulant

factor, microparticles that directly activate the coagulation cascade. Our results suggested a close relationship between immune regulation and hemostatic system, which may be involved in tumor progression. But it needed further research.

From these data, we conclude that the MLR is involved in immune escape and may reflect the immune regulation status of ovarian cancer. When the MLR is increased, more monocytes/TAMs are recruited and educated, more CA125 and CA199 are produced, and increased coagulation is established, thus supporting an important role of the MLR in ovarian cancer.

The strength of the current study is that it is the first attempt to evaluate the predictive value of the MLR in ovarian cancer patients. Moreover, the value of the MLR was evaluated together with previously validated biomarkers, namely, the NLR and PLR. Some limitations were present in this study, including its retrospective nature and the inclusion of a relatively small number of patients. Another limitation is that the MLR is a nonspecific marker of inflammation, and the results may be affected by the presence of other systemic diseases. Additional large-scale and standard investigations should be conducted to apply this convenient, simple, and inexpensive prognostic factor for risk stratification.

Conclusion

This study was the first attempt to assess the predictive value of the MLR in ovarian cancer patients. In this study, we found that an elevated MLR reflected patient immune conditions and was a strong risk factor for advanced ovarian cancer stages, pathologic grades, lymphatic metastasis, and OS rate. Therefore, the MLR may be clinically reliable and useful for the accurate prediction of ovarian cancer initiation and subsequently for patient prognosis.

Table 5. Clinical and Hematologic Characteristics of Ovarian Cancer Patients, according to the Cutoff Value of the MLR

Variable	MLR-Low (≤0.23)		MLR-High (>0.23)		P Value
	n	Mean ± SD	n	Mean ± SD	
Age (years)	64	49.81 ± 13.83	69	56.00 ± 12.60	.008
CA-125 (U/ml)	64	604.25 ± 1200.30	69	1557.93 ± 1790.81	.001
CA-199 (U/ml)	64	32.37 ± 84.37	69	113.41 ± 379.59	.108
AFP (ng/ml)	64	31.25 ± 171.52	69	2.87 ± 2.58	.205
CEA (ng/ml)	64	3.45 ± 10.23	69	13.21 ± 50.99	.151
HE4 (pmol/l)	38	240.84 ± 315.98	32	710.56 ± 867.76	.006
WBC (10^9/l)	64	5.99 ± 2.06	69	7.14 ± 3.96	.039
N (%)	64	62.57 ± 10.44	69	72.33 ± 10.79	.000
L (%)	64	30.53 ± 8.66	69	18.65 ± 7.73	.000
M (%)	64	4.93 ± 1.35	69	7.06 ± 2.97	.000
Hemoglobin (g/l)	64	124.42 ± 15.49	69	115.65 ± 19.33	.005
Platelet (10^9/l)	64	246.34 ± 89.99	69	310.39 ± 123.54	.001
D-Dimer (mg/l)	64	0.93 ± 0.82	69	3.70 ± 2.24	.001
PT (s)	64	11.54 ± 0.83	69	11.83 ± 1.78	.232
INR	64	0.97 ± 0.07	69	1.00 ± 0.11	.018
APTT (s)	64	26.51 ± 4.14	69	27.51 ± 3.86	.152
TT (s)	64	18.61 ± 2.28	69	18.25 ± 3.06	.445
Fibrinogen, FIG (mg/l)	64	3.08 ± 0.78	69	3.88 ± 1.16	.000
LDH (U/l)	64	180.60 ± 84.10	69	216.80 ± 84.88	.016

HE4 was detected after 2013.

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