Preoperative Lymphocyte-to-monocyte Ratio and CA125 Level as Risk Factors for Advanced Ovarian Cancer

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Research

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Abstract

Background: Detailed descriptions of the relationship between lymphocyte-to-monocyte ratio alone and combined with CA125 (COLC) and advanced stage of ovarian cancer (OC) have been lacking to date. This study is to analyze the relationship between LMR, CA125 and COLC and advanced stage of OC.

Methods: A retrospective clinicopathologic review was performed. The receiver-operating characteristic (ROC) curves of LMR, CA125, and COLC staging OC were constructed. Furthermore, a binary logistic regression model was used to assay the independent risk factors.

Results: A total of 225 patients with OC were identified in this cohort. Eighty-five patients with OC were diagnosed at an early stage, and 140 OC patients were diagnosed at an advanced stage. The median of LMR at the early stage was higher than the advanced stage (4.39 vs. 2.78), and the median of CA125 was lower than the advanced stage (80 U/mL vs. 251.25 U/mL). Multivariate logistic regression indicated that LMR (OR=0.314, 95% confidence interval [CI]: 0.143–0.687, P=0.004) and CA125 (OR=4.045, 95%CI: 1.883–8.692, P<0.001) were associated with OC staging. Furthermore, the area under the curve of COLC was higher than that of LMR (0.779 vs. 0.732) or CA125 (0.779 vs. 0.708) in staging OC. The specificity of COLC was higher than that of LMR (87.11% vs. 70.61%) or CA125 (87.11% vs. 61.21%) in staging OC.

Conclusions: LMR alone or in combination with CA125 might be associated with OC staging. Besides, as a predictive factor, COLC may have high specificity in staging OC.

Background

Ovarian cancer (OC) is the third most common gynecologic malignancy with high mortality [1]. Owing to the tissue and anatomical characteristics [2], a number of patients are diagnosed with advanced disease (FIGO III–IV, version 2014), by which time it is difficult to achieve optimal debulking surgery (ODS). Preoperative staging of OC is beneficial in terms of the choice of treatment. However, the effective index that can accurately reflect the preoperative stage of OC patients is not clear.

The lymphocyte-to-monocyte ratio (LMR) represents the lymphocyte levels divided by the monocyte levels in OC. The LMR has recently been evaluated for its magnitude of survival in various solid cancers [3–5]. However, few studies have evaluated the magnitude of LMR on OC staging. Cancer antigen 125 (CA125) is a mucin-type glycoprotein, produced by the *MUC16* gene, associated with the cellular membrane [6]. Previous studies have shown that CA125 was associated with the prognosis of OC [7]. However, the relationship between CA125 and OC staging is still not completely understood and shows inconsistent findings.

Thus, we assessed the magnitude of LMR alone and in combination with CA125 (COLC) to attempt to identify preoperative factors to stage OC.

Methods

Patients

In this retrospective study, data of 225 patients with OC diagnosed in the affiliated Nanchong Central Hospital of North Sichuan Medical College from January 2008 to May 2020 were collected. The inclusion criteria were as follows: (1)all patients underwent primitive surgery under the chief physician; (2) pathological diagnosis was used as the gold standard for assessing the stage of OC, and the pathology reports were obtained after evaluation and issuing by two senior pathologists; (3) the complete blood count and serum CA125 values were collected before initiation of anti-tumor therapy; (4) sufficient data could be extracted for the fourfold Table.

The exclusion criteria were as follows: patients who had received anti-tumor therapy such as radiotherapy and chemotherapy before the operation, and those that had complications due to other malignant tumors except OC.

Samples And Marker Assays

Preoperative blood samples collected in appropriate collection tubes were transported to the hospital clinical laboratory center at room temperature to determine whole blood cell count and CA125 level. Samples were retrieved and serum CA125 concentrations were measured by two-step immunoassay for the quantitative determination with flexible assay protocols [8]. All biomarkers were assayed in a central laboratory within 3 days before surgery, and the lab personnel were blinded to the clinical data.

Data analysis

Clinical variables such as age; BMI; FIGO stage; histological type and grade; malignant ascites; lymph node metastases; and clinical characteristics (white blood cell, lymphocyte, and monocyte count and serum CA125 levels) within 3 days before surgery were retrospectively analyzed. The LMR was calculated based on the ratio of peripheral blood lymphocyte count to monocyte count [4]. If the patient had several preoperative test results of blood parameters, the most recent results before surgery were selected for analysis.

Descriptive statistics were used to show the baseline characteristics of participants in this study. Chi square test and binary logistic regression were used to analyze the relationship between clinicopathological features and OC staging. Areas under the receiver operating characteristic curves (ROCs; MedCalc Software bvba [ver. 15.2.1], Ostend, Belgium) were used to assess LMR, CA125, and COLC. The optimal cut-off values were determined according to ROC. BMI was categorized as > 24 or ≤ 24 [9]. Age was classified as ≥ 50 or < 50 (years) [7]; white blood cell as > 6.4 or ≤ 6.4 [4]. The definition of COLC was based on the Glasgow prognostic score (GPS) (Table 5). Statistical analyses were performed using SPSS software (ver. 20.0; IBM Corp, Armonk, NY, USA). A two-sided P value of < 0.05 was considered to indicate statistical significance.

Table 5
Prediction scores of LMR, CA125 and COLC in ovarian cancer.

	Score
LMR	
≤ 3.67	1
> 3.67	0
CA125 (U/mL)	
≤ 95.7	0
> 95.7	1
COLC	
LMR > 3.67 and CA125 < 95.7U/mL	0
LMR > 3.67 and CA125 > 95.7U/mL	1
LMR ≤ 3.67 and CA125 ≤ 95.7U/mL	2
LMR ≤ 3.67 and CA125 > 95.7U/mL	3
LMR, lymphocyte/monocyte ratio; CA125, cancer antigen 125; COLC, combination of LMR and CA125.	

Results

Patient characteristics

A total of 225 patients with OC met the inclusion criteria. Eighty-five patients with OC were diagnosed at an early stage (FIGO I–II), and 140 OC patients were diagnosed at an advanced stage. The majority histologic subtype and grade of patients with OC were serous and G3, respectively. The median (range) of LMR and CA125 were 3.53 (0.47–18.00) and 161 (1.8–5672.6) U/mL. The baseline characteristics of all patients with OC are shown in Table 1.

Table 1
Clinical characteristics of patients with ovarian cancer.

Variable	Median (range)
Age	50(18–89)
BMI (kg/m2)	22.86(16.53–29.79)
Histologic subtype (n(%))	
Serous	156(69.33)
Endometrioid	25(11.11)
Transitional cell	20(8.89)
Clear cell	12(5.33)
Mucinous	11(4.90)
Other	1(0.44)
FIGO Stage (n(%))	
	62(27.56)
	39(17.33)
	109(48.44)
	15(6.67)
Histological grade (n(%))	
G1	42(18.66)
G2	48(21.33)
G3	135(60.00)
Malignant ascites (n(%))	
Yes	134(59.56)
No	91(40.44)
lymph node metastases (n(%))	
Yes	86(38.22)
No	139(61.78)
White blood cell*10^9	7.25(3.29–16.52)

BMI, body mass index; FIGO, Federation of Gynecologists and Obstetricians; LMR, lymphocyte/monocyte ratio; CA125, cancer antigen 125.

Variable	Median (range)
Lymphocyte*10^9	1.27(0.29–2.80)
Monocyte*10^9	0.39(0.05–1.64)
LMR	3.53(0.47-18.00)
CA125 (U/mL)	161(1.8-5672.6)
BMI, body mass index; FIGO, Federation of Gynecologists and Obstetricians; LMR, lymphocyte/monocyte ratio; CA125, cancer antigen 125.	

Roc Curves Of The Lmr And Ca125

The ROC curve of LMR staging OC is shown in Fig. 1a. The optimal cut-off value of LMR was 3.67, and the sensitivity and specificity were 70.17% and 70.61%, respectively. Patients with OC were divided into two groups based on this cut-off value (LMR > 3.67, n = 101, 44.89%; LMR ≤ 3.67, n = 124, 55.11%).

The ROC curve of CA125 staging OC is shown in Fig. 1b. The optimal cut-off value of CA125 was 95.7 U/mL. The sensitivity and specificity were 80.01% and 61.21%, respectively. OC patients were divided into two groups based on this cut-off value (CA125 > 95.70 U/mL, n = 145, 64.44%; CA125 ≤ 95.70 U/mL, n = 80, 35.56%).

Clinical Characteristics Of Oc Between Early And Advanced Stage

Clinicopathological features between early and advanced stage of OC were compared by chi-square test. The median of LMR in early stage cancer was higher than that in advanced stage cancer (4.39 vs. 2.78), and the median of CA125 was lower in the early than advanced stage of cancer (80 U/mL vs. 251.25 U/mL). Results showed that BMI ≥ 24, histologic serous and G1, malignant ascites (+), lymph node metastases (+), LMR ≤ 3.67, CA125 > 95.7 U/mL were all associated with advanced stage of OC (P < 0.05) (Table 2).

Table 2 Clinical characteristics of ovarian cancer between early stage and advanced stage.

Variable	Early stage (n= 85)		Avanced stage (n=140)		X^2	P value
	n (%)	Middle (Rang)	n (%)	Middle (Rang)		
Age (years)					0.414	0.520
50	43 (50.59)	43 (18 49)	77 (55.0)	43 (23 49)		
≥50	42 (49.41)	58 (50 89	63 (45.0)	60 (50 80		
BMI (kg/m2)					4.703	0.03
24	39 (45.89)	20.96 (17.05 23.81)	85 (60.71)	25.57 (24.01 29.79)		
≥24	46 (65.12)	24.79 (24.01 29.78)	55 (39.29)	20.89(16.53 23.81)		
Histologic subtype (n(%))						
Serous	43 (50.59)		108 (77.14)		16.897	<0.001
Non-serous	42 (49.41)		34 (22.86)			
Histological grade (n(%))						
G1	59 (69.41)		123 (54.67)		16.897	0.001
G2/G3	26 (30.59)		17 (45.33)			
Malignant ascites (n(%))					51.533	<0.001
Yes	25 (29.41)		109 (77.86)			
No	60 (70.59)		31 (22.14)			
lymph node metastases (n(%))					40.497	<0.001
Yes	10 (11.76)		76 (33.78)			
No	75 (88.23)		31 (66.22)			
White blood					0.213	0.644

cell*10^9						
⩽6.40	28	5.48 (3.62⩽ 6.35)	42 (60.71)	5.35(3.29⩽ 6.39)		
≥6.40	57	7.72 (6.42⩽ 16.52)	98 (39.29)	8.63(6.43⩽ 16.23)		
LMR					36.470	<0.001
≤3.67	25 (11.76)	2.43 (0.85⩽ 3.64)	99 (33.78)	2.15 (0.47⩽ 3.67)		
>3.67	60 (88.23)	4.93 (3.69⩽ 18.0)	41 (66.22)	4.93 (3.70⩽ 11.6)		
CA125 (U/mL)					39.13	<0.001
≤95.7	52	34.65 (2.2⩽ 95.7)	28	22.4 (1.8⩽ 74.7)		
>95.7	33	342.5 (98⩽ 1401)	112	423.5 (95.8⩽ 5672.6)		

BMI, body mass index; LMR, lymphocyte/monocyte ratio; CA125, cancer antigen 125.

Association of clinicopathological factors of OC patients at the early and advanced stage were analyzed by using univariate and multivariate binary logistic regression analyses. In univariate analyses, histological subtype and grade, malignant ascites, lymph node metastases (+), LMR ≤ 3.67, and CA125 > 95.7 U/mL were all associated with advanced stage in patients with OC ($P < 0.05$) (Table 3). In the multivariate logistic regression, malignant ascites (OR = 3.917, 95%CI: 1.560–9.833, $P = 0.004$); lymph node metastases (OR = 5.338, 95%CI: 2.356–12.093, $P < 0.001$); LMR (OR = 0.314, 95%CI: 0.143–0.687, $P = 0.004$); and CA125 (OR = 4.045, 95%CI: 1.883–8.692, $P < 0.001$) were associated with advanced stage (Table 3). Multivariate logistic regression for presence or absence of malignant ascites among matched samples is shown in Table 4. The results showed that both LMR and CA125 were associated with advanced stage of OC ($P < 0.05$) (Table 4).

Table 3 Binary logistic regression analysis of ovarian cancer staging.

Varies		Univariate			Multivariate	
	OR	95%CI	P	OR	95%CI	P
Age(age) (>50 vs. ≤50)	1.014	(0.591-1.738)	0.961	0.730	(0.339-1.571)	0.422
BMI (kg/m2) (≥24 vs.<24)	1.002	(0.421-2.386)	0.996	0.803	(0.377-1.710)	0.569
Histological subtype (serous vs. others)	3.188	(1.606-6.329)	0.001	2.120	(0.980-4.585)	0.056
Histological grade (G2-G3 vs. G1)	0.829	(0.482-1.423)	0.496	1.275	(0.488-3.335)	0.620
Malignant ascites (yes vs no)	8.439	(4.567-15.591)	<0.001	3.917	(1.560-9.833)	0.004
Lymph node metastases (yes vs no)	8.906	(4.254-18.646)	<0.001	5.338	(2.356-12.093)	<0.001
White blood cell(*10^9) (>6.4 vs. ≤6.4)	0.755	(0.314-1.817)	0.530	0.597	(0.262-1.359)	0.219
LMR (>3.67 vs. ≤3.67)	5.795	(3.207-10.473)	<0.001	0.314	(0.143-0.687)	0.004
CA125(U/mL) (≤95.7 vs.>95.7)	6.303	(3.454-11.502)	<0.001	4.045	(1.883-8.692)	<0.001

BMI, body mass index; LMR, lymphocyte/monocyte ratio; CA125, cancer antigen 125.

Table 4 Multivariate logistic regression analysis for presence or absence of malignant ascites of ovarian cancer among matched samples

Varies	Malignant ascites (+)			Malignant ascites (-)		
	OR	95%CI	P	OR	95%CI	P
Age(age) (>50 vs. ≤50)	0.512	(0.152–1.723)	0.280	1.219	(0.412–3.609)	0.721
BMI (kg/m2) (≥24 vs.<24)	0.986	(0.314–3.099)	0.981	0.623	(0.213–1.827)	0.389
Histological subtype (serous vs. others)	2.595	(0.750–8.974)	0.132	2.067	(0.732–5.838)	0.170
Histological grade (G2-G3 vs. G1)	2.755	(0.637–11.922)	0.175	0.484	(0.127–1.850)	0.289
Lymph node metastases (yes vs no)	4.344	(1.104–17.088)	0.036	2.916	(0.705–12.061)	0.140
White blood cell(*10^9) (>6.4 vs. ≤6.4)	0.406	(0.089–1.853)	0.244	0.682	(0.234–1.988)	0.483
LMR (>3.67 vs. ≤3.67)	0.254	(0.076–0.849)	0.026	0.299	(0.093–0.962)	0.043
CA125(U/mL) (≤95.7 vs.>95.7)	3.824	(1.163–12.570)	0.027	4.317	(1.436–12.977)	0.009

BMI, body mass index; LMR, lymphocyte/monocyte ratio; CA125, cancer antigen 125; +, presence of malignant ascites; -, absence of malignant ascites.

The usefulness of COLC in staging OC

As shown above, both LMR and CA125 were biomarkers to stage OC. However, whether COLC had the same efficacy needed further investigation. The definition of COLC was as per the GPS (Table 5). The ROC curve of COLC in staging OC was constructed (Fig. 1c). The capacities of LMR, CA125, and COLC in staging OC patients were compared by ROC curves. The result showed that the sensitivity and specificity of COLC were 64.41% and 87.11%, respectively, and the AUC of COLC was 0.779 (95%CI: 0.719–0.831, P < 0.001; Fig. 1c), which was higher than that of LMR (87.11% vs. 70.61%; Fig. 1a, 1c) or CA125 (87.11% vs. 61.21%, Fig. 1b, 1c).

Discussion

In this study, we attempted to determine preoperative indicators to stage OC to help attain ODS, reduce surgical complications and economic burden, and better evaluate the prognosis of OC patients. Multivariate logistic regression analysis showed that LMR was significantly associated with stage of OC (Table 3): the lower the LMR, the higher the stage, and the worse the prognosis, which was consistent with the conclusion of previous research [10]. Our study also showed that serum CA125 was associated with stage of OC (Table 3); however, the specificity was lower than LMR (Figs. 1a, 1b). To better analyze the factors associated with OC staging, we recommended COLC to improve the accuracy, which achieved a higher AUC and specificity than LMR or CA125, indicating that COLC might have a higher specificity associated with OC staging.

Our study also showed that ascites was associated with stage of OC (Table 3), one probable mechanisms is that constitutive expression of STAT3 in malignant ascites plays a role in ovarian tumor progression and metastasis[11]. Besides, Matt et al (2019) showed that ascites might be associated with CA125 by regulating MUC16 expression at a posttranscriptional level through an Akt-dependent pathway, accordingly, we matched samples with presence or absence of malignant ascites, and the results showed that both LMR and CA125 were significantly associated with OC staging for presence or absence of malignant ascites (Table 4).

LMR and CA125 are calculated directly or computed from blood and can be easily measured, in addition to being practical and inexpensive metrics. At present, several studies have been conducted with respect to the application of LMR and CA125 in OC. LMR and CA125 could likely serve as clinically useful indicators of metastasis and survival in OC patients [4, 7, 12]. CA125 also was reported as a risk factor in the diagnosis of OC [6]. However, few studies have been conducted with respect to the magnitude of LMR an CA125 on staging OC. Our study preliminarily showed that LMR, CA125, and COLC might be risk factors for OC staging.

The mechanisms underlying the capacity of LMR in OC have not yet been elaborated. We tried to explain the possible mechanisms. First, the association between lymphocytes and malignancies has been well established. Tumor infiltrating lymphocytes in OC can prevent cancer cells from spreading and metastasis by establishing a defense barrier [13]. The decrease of peripheral blood lymphocyte count may lead to weak and insufficient tumor immune response, thereby promoting tumor progression and metastasis [14] and resulting in rapid disease progression and late surgical pathological stage in OC patients. Second, inflammation can make monocytes migrate from the bone marrow into peripheral blood [15]. After being recruited into tumor tissue, monocytes can differentiate into tumor-associated macrophages (TAMs) [16]. TAMs can not only play an immunosuppressive role in a variety of tumor microenvironments, including OC, but can also promote tumor cell infiltration, growth and neovascularization, and metastasis [17, 18]. Therefore, to an extent, peripheral blood mononuclear cell counts can reflect the formation or existence of TAMs. Besides, the LMR often represents the relative decrease of lymphocyte count and (or) the relative increase of monocyte count, which can reflect the balance of anti-tumor immunity and pro-tumor inflammatory response [12]: low-level LMR often represents the dominant role of pro-tumor inflammatory response, indicating a high level of malignancy

and rapid progress in OC. Further, in this case, the possibility of advanced stage OC that is difficult to treat with relatively poor prognosis is higher; on the contrary, high-level LMR indicates that the anti-tumor immune system of patients with OC is more active, indicating that the disease progression of OC is slow, with the possibility of early stage OC and relatively better prognosis.

Rising and falling levels of serum CA125 correlate with the progression and regression of high-grade serous ovarian carcinomas [19], making CA125 a possible factor for OC staging. However, some researchers have also suggested that because of its low specificity and the observed increased levels in different physiological situations, CA125 is not considered as a very good differentiating biomarker for ovarian tumors [6]. Therefore, we recommended the combination of CA125 and LMR (COLC) to stage OC. Our results showed that the AUC and specificity of COLC were higher than those of LMR or CA125 to stage OC (Fig. 1), implying that COLC might improve the accuracy in staging OC and provide guidelines for selection of treatment. As a new biomarker, COLC might play a role in immune surveillance and provide novel approaches and strategies for treatment of OC.

To our knowledge, this is the first study to evaluate the relationship among LMR, CA125, COLC, and stage of OC. However, our study also has some limitations. Firstly, the retrospective design meant that we cannot conclusively state that LMR, CA125, and COLC are risk factors for advanced stage of OC. However, our study provides a potential clinical strategy for staging advanced OC. Secondly, the potential bias in testing serum CA125 and peripheral blood level cannot be completely eliminated. Nonetheless, we believe that the influence of LMR and CA125 level on the risk of advanced stage of OC will be of interest to clinicians to improve the accuracy in preoperative staging and make clinical strategies. Moreover, LMR is an inflammatory marker that could be affected by autoimmune status and other diseases; hence, we allowed a 30-min interval for blood collection to exclude any possible treatment or drug interference in the results.

Conclusions

LMR alone and in combination with preoperative CA125 might be used as independent risk factors for staging OC and may provide a new direction for making clinical decisions for OC.

Declarations

Ethics approval and consent to participate

Our study was approved by the Ethics Committee of the affiliated Nanchong Central Hospital of North Sichuan Medical College. Informed consent could not be obtained from every patient given the retrospective study design. Therefore, we posted a notice about our study design and contact information at a public location in Nanchong Central Hospital of North Sichuan Medical College.

Consent for publication

Not applicable, as all results presented in this manuscript were aggregated.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author Contributions

HH and JL conceived and designed the study. YT and FT analyzed the data. DL, LD, and MZ contributed materials and analysis tools. BS prepared fiFigs and Tables. YTcontributed to the writing of the manuscript, FX revised the manuscript.. All authors have reviewed the manuscript.

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References

1. Jin C, Yang M, Han X, Chu H, Zhang Y, Lu M, et al. Evaluation of the value of preoperative CYFRA21-1 in the diagnosis and prognosis of epithelial ovarian cancer in conjunction with CA125. Journal of ovarian research. 2019;12(1):114.
2. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018;68(4):284–96.
3. Abe S, Kawai K, Nozawa H, Hata K, Kiyomatsu T, Morikawa T, et al. LMR predicts outcome in patients after preoperative chemoradiotherapy for stage II-III rectal cancer. J Surg Res. 2018;222:122–31.
4. Eo WK, Kwon S, Koh SB, Kim MJ, Ji YI, Lee JY, et al. The Lymphocyte-Monocyte Ratio Predicts Patient Survival and Aggressiveness of Endometrial Cancer. J Cancer. 2016;7(5):538–45.
5. Kumarasamy C, Sabarimurugan S, Madurantakam RM, Lakhotiya K, Samiappan S, Baxi S, et al. Prognostic significance of blood inflammatory biomarkers NLR, PLR, and LMR in cancer-A protocol

for systematic review and meta-analysis. Medicine. 2019;98(24):e14834.
6. Dochez V, Caillon H, Vaucel E, Dimet J, Winer N, Ducarme G. Biomarkers and algorithms for diagnosis of ovarian cancer: CA125, HE4, RMI and ROMA, a review. Journal of ovarian research. 2019;12(1):28.
7. Yuan Q, Song J, Yang W, Wang H, Huo Q, Yang J, et al. The effect of CA125 on metastasis of ovarian cancer: old marker new function. Oncotarget. 2017;8(30):50015–22.
8. Harter P, Sehouli J, Lorusso D, Reuss A, Vergote I, Marth C, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. N Engl J Med. 2019;380(9):822–32.
9. Yang PK, Chou CH, Chang CH, Chen SU, Ho HN, Chen MJ. Changes in peripheral mitochondrial DNA copy number in metformin-treated women with polycystic ovary syndrome: a longitudinal study. Reproductive biology: RB&E. 2020;18(1):p. 69.
10. Gong J, Jiang H, Shu C, Hu MQ, Huang Y, Liu Q, et al. Prognostic value of lymphocyte-to-monocyte ratio in ovarian cancer: a meta-analysis. Journal of ovarian research. 2019;12(1):51.
11. Saini U, Naidu S, ElNaggar AC, Bid HK, Wallbillich JJ, Bixel K, et al. Elevated STAT3 expression in ovarian cancer ascites promotes invasion and metastasis: a potential therapeutic target. Oncogene. 2017;36(2):168–81.
12. Tang Y, Hu HQ, Tang FX, Lin D, Shen R, Deng L, et al. Combined Preoperative LMR and CA125 for Prognostic Assessment of Ovarian Cancer. J Cancer. 2020;11(11):3165–71.
13. Li J, Wang J, Chen R, Bai Y, Lu X. The prognostic value of tumor-infiltrating T lymphocytes in ovarian cancer. Oncotarget. 2017;8(9):15621–31.
14. Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev. 2018;32:1267–84.
15. Etzerodt A, Tsalkitzi K, Maniecki M, Damsky W, Delfini M, Baudoin E, et al. Specific targeting of CD163 TAMs mobilizes inflammatory monocytes and promotes T cell-mediated tumor regression. The Journal of experimental medicine. 2019;216(10):2394–411.
16. Szebeni GJ, Vizler C, Kitajka K, Puskas LG. Inflammation and Cancer: Extra- and Intracellular Determinants of Tumor-Associated Macrophages as Tumor Promoters. Mediators Inflamm. 2017;2017:9294018.
17. Zhu Q, Wu X, Wang X. Differential distribution of tumor-associated macrophages and Treg/Th17 cells in the progression of malignant and benign epithelial ovarian tumors. Oncol Lett. 2017;13(1):159–66.
18. Yin M, Li X, Tan S, Zhou HJ, Ji W, Bellone S, et al. Tumor-associated macrophages drive spheroid formation during early transcoelomic metastasis of ovarian cancer. J Clin Investig. 2016;126(11):4157–73.
19. Matte I, Garde-Granger P, Bessette P, Piché A. Ascites from ovarian cancer patients stimulates MUC16 mucin expression and secretion in human peritoneal mesothelial cells through an Akt-dependent pathway. BMC Cancer. 2019;19(1):406.

Figures

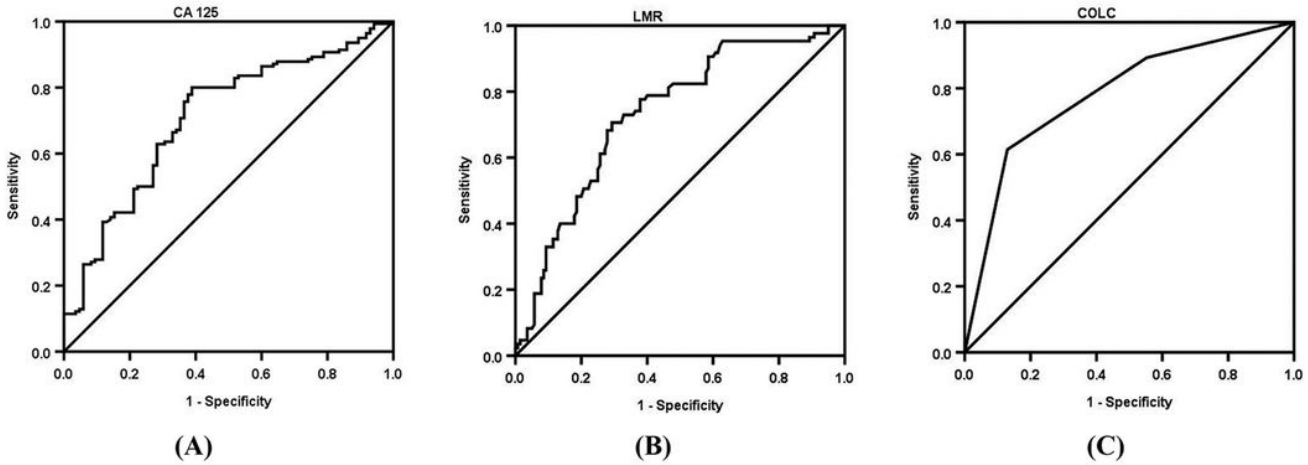

Figure 1

a. The ROC curve of LMR staging OC b. The ROC curve of CA125 staging OC c. The ROC curve of COLC in staging OC was constructed