Prognostic value of preoperative lymphocyte-monocyte ratio in patients with ovarian clear cell carcinoma

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Introduction

The factors known to influence treatment outcomes in ovarian clear cell carcinoma (OCCC) are FIGO stage, LN status, and the presence of endometriosis and residual tumor after primary cytoreductive surgery. However, most of these prognostic biomarkers are limited to intraoperative surgical findings and postoperative pathological features, and thus, clinically useful preoperative prognostic factors that accurately predict chemotherapeutic response and prognosis are needed to improve survival rates in OCCC.

Accumulating evidence indicates inflammation is a hallmark of cancer, and that tumor-associated inflammatory microenvironments facilitate tumor growth and metastasis. Several inflammatory response-related biomarkers in peripheral blood, such as, neutrophil-to-lymphocyte ratio (NLR), platelet-to- lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have been widely investigated as potentially useful prognostic markers in different cancers.

The prognostic and predictive values of several preoperative hematologic parameters have been investigated in epithelial ovarian cancer (EOC). Of these potentially useful parameter, a low LMR has been shown to be significantly associated with clinicopathological characteristics, indicative of poor prognosis and disease aggressiveness in patients with several solid tumor types. However, few studies have evaluated the prognostic significance of markers of systemic inflammatory response (SIR) in terms of predicting survival in OCCC. Therefore, we undertook the present study to investigate the prognostic values of preoperative SIR markers in OCCC.

Materials and Methods

A total of 109 patients diagnosed with OCCC that underwent primary cytoreductive surgery and adjuvant platinum-based chemotherapy from 2009 to 2012 were enrolled in this retrospective study. SIR markers were calculated from complete blood cell counts determined before surgery. Receiver operating characteristic (ROC) curve analysis was used to determine optimal cut-off values for neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR). Prognostic significances with respect to overall survival (OS) and progression-free survival (PFS) were determined by Kaplan–Meier curve and multivariate Cox regression analysis.

Results

1. Patient characteristics

Median age of the 109 study subjects was 50 years (range 24–77 years). As previously reported, early stage disease was more common than advanced disease in our patients; 64 (58.7 %) had disease stage I to II, and 45 (41.3%) had disease stage III to IV. Twenty-four patients (22.0 %) were endometriosis- associated. Eighty-five patients (78.0%) were optimally debulked at primary surgery with less than 1 cm of residual disease and all had platinum- sensitive disease.

2. Relations between SIR markers and clinicopathologic characteristics

Characteristics	NLR-low (<2.3) No. (%)	NLR-high (≥2.3) No. (%)	P	LMR-low (<4.2) No. (%)	LMR-high (≥4.2) No. (%)	P	PLR-low (<123.6) No. (%)	PLR-high (≥123.6) No. (%)	P
Age (yr)			0.786			0.638			0.453
<50	16 (48.5)	39 (51.3)		36 (52.2)	19 (47.5)		10 (58.8)	45 (48.9)	
≥50	17 (51.5)	37 (48.7)		33 (47.8)	21 (52.5)		7 (41.2)	47 (51.1)	
FIGO stage			0.005			0.026			0.585
I/II	26 (78.8)	38 (50.0)		35 (50.7)	29 (72.5)		11 (64.7)	53 (57.6)	
III/IV	7 (21.2)	38 (50.0)		34 (49.3)	11 (27.5)		6 (35.3)	39 (42.4)	
LN metastasis			0.316			0.031			0.094
No	28 (84.8)	58 (76.3)		50 (72.5)	36 (90.0)		16 (94.1)	70 (76.1)	
Yes	5 (15.2)	18 (23.7)		19 (27.5)	4 (10.0)		1 (5.9)	22 (23.9)	
Malignant ascites			0.047			0.013			0.608
No	26 (78.8)	45 (59.2)		39 (56.5)	32 (80.0)		12 (70.6)	59 (64.1)	
Yes	7 (21.2)	31 (40.8)		30 (43.5)	8 (20.0)		5 (29.4)	33 (35.9)	
Endometriosis			0.712			0.634			0.267
No	25 (13.8)	60 (23.1)		55 (79.7)	30 (75.0)		15 (88.2)	70 (76.1)	
Yes	8 (86.2)	16 (76.9)		14 (20.3)	10 (25.0)		2 (11.8)	22 (23.9)	
CA-125 (Unit/mL)			0.269			0.113			0.173
<88.2	19 (57.6)	35 (46.1)		29 (42.0)	25 (62.5)		11 (64.7)	43 (46.7)	
≥88.2	14 (42.4)	41 (53.9)		40 (58.0)	15 (37.5)		6 (35.3)	49 (53.3)	
Residual mass			0.254			0.178			0.150
<1 cm	28 (84.8)	57 (75.0)		51 (73.9)	34 (85.0)		11 (64.7)	74 (80.4)	
≥1 cm	5 (15.2)	19 (25.0)		18 (26.1)	6 (15.0)		6 (35.3)	18 (19.6)	
Platinum response			0.008			0.021			0.870
Sensitive	31 (93.9)	54 (71.1)		49 (71.0)	36 (90.0)		13 (76.5)	72 (78.3)	
Resistant	2 (6.1)	22 (28.9)		20 (29.0)	4 (10.0)		4 (23.5)	20 (21.7)	

Table 1.

Clinical and pathologic characteristics according to NLR, LMR or PLR in 109 patients with ovarian clear cell carcinoma

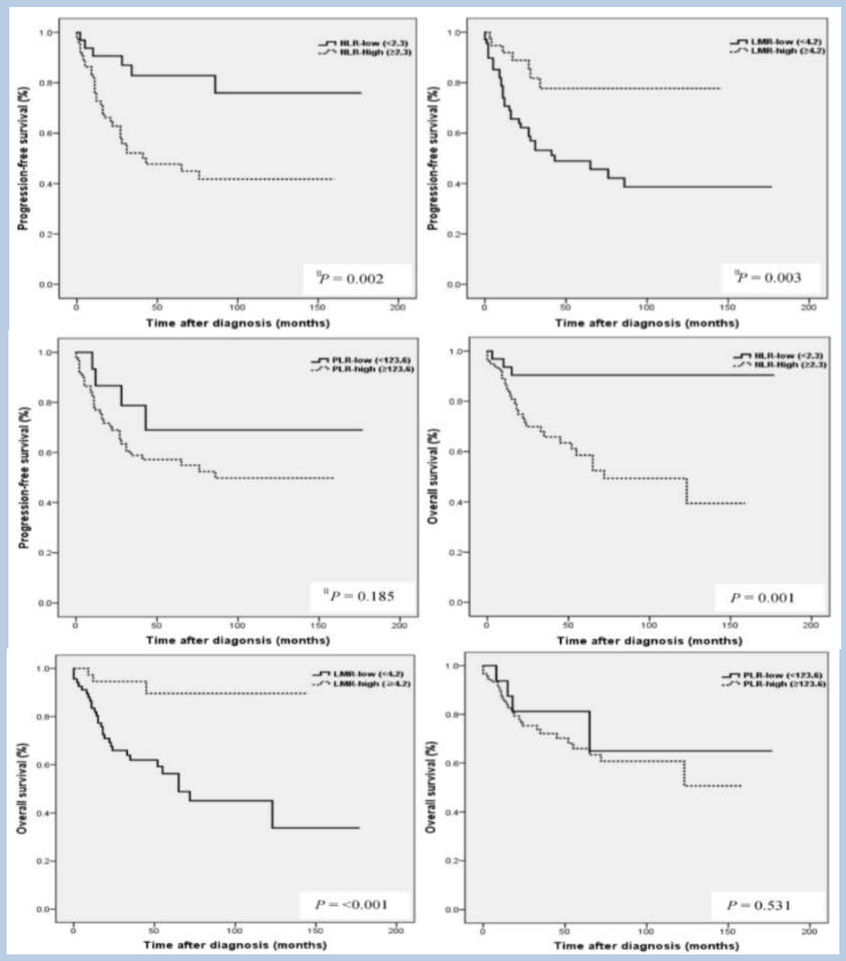

Figure 2.

Results of progression-free survival (PFS) and overall survival (OS) analysis with respect to NLR, LMR, and PLR in 109 patients with ovarian clear cell carcinoma.

3. Relationships between cancer- and host-related characteristics and prognosis

Characteristics	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Age (yr) (≥50 vs. <50)	1.561 (0842-20896)	0.158		
FIGO stage (III/IV vs. I/II)	8.239 (3.994-16.995)	< 0.001	4.027 (1.756-9.233)	0.001
LN metastasis (Yes vs. No)	2.640 (1.333-5.229)	0.005	1.367 (0.575-3.254)	0.479
Malignant ascites (Yes vs. No)	3.604 (1.929-6.733)	0.003	0.992 (0.283-3.477)	0.990
Endometriosis (No vs. Yes)	4.232 (1.307-13.697)	0.018	2.685 (0.968-5.667)	0.155
CA-125 (Unit/mL) (≥88.2 vs. <88.2)	3.567 (1.838-8.924)	0.005	1.769 (0.659-4.746)	0.257
Residual mass (≥1 cm vs. <1 cm)	4.577 (2.392-8.757)	< 0.001	2.540 (1.084-5.948)	0.032
Platinum response (Resistant vs. Sensitive)	10.105 (5.227-19.535)	< 0.001	3.595 (1.458-8.861)	0.005
NLR (≥2.3 vs. <2.3)	3.495 (1.466-8.331)	0.005	1.810 (0.714-4.587)	0.211
LMR (<4.2 vs. ≥4.2)	3.065 (1.416-6.634)	0.004	1.251 (0.689-3.716)	0.427
PLR (≥123.6 vs. <123.6)	1.974 (0.703-5.539)	0.197		

Table 2.

Relationship of cancer- and host-related characteristics with progression-free survival (PFS) in 109 patients with ovarian clear cell carcinoma

Characteristics	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Age (yr) (≥50 vs. <50)	1.451 (0.730-2.885)	0.287		
FIGO stage (III/IV vs. I/II)	9.330 (3.823-22.766)	< 0.001	5.587 (1.951-15.999)	0.001
LN metastasis (Yes vs. No)	2.928 (1.416-6.056)	0.004	1.073 (0.439-2.619)	0.878
Malignant ascites (Yes vs. No)	4.095 (2.006-8.358)	< 0.001	1.223 (0.479-3.126)	0.674
Endometriosis (No vs. Yes)	4.827 (1.155-20.178)	0.039	2.115 (0.669-6.935)	0.263
CA-125 (Unit/mL) (≥88.2 vs. <88.2)	3.732 (1.674-8.319)	0.001	1.720 (0.587-4.8866)	0.578
Residual mass (≥1 cm vs. <1 cm)	4.847 (2.361-9.952)	< 0.001	3.408 (1.434-8.099)	0.011
Platinum response (Resistant vs. Sensitive)	8.403 (4.044-17.459)	< 0.001	3.167 (1.023-7.086)	0.031
NLR (≥2.3 vs. <2.3)	5.071 (1.546-16.633)	0.007	2.145 (0.529-8.700)	0.285
LMR (<4.2 vs. ≥4.2)	6.603 (2.015-21.646)	0.001	2.655 (0.889-8.926)	0.038
PLR (≥123.6 vs. <123.6)	1.393 (0.490-3.962)	0.535		

Table 3.

Relationship of cancer- and host-related characteristics with overall survival (OS) in 109 patients with ovarian clear cell carcinoma

Discussion

EOC is the most lethal gynecologic cancer and a major cause of cancer-related death in women [1]. This high mortality is mainly due to difficulties associated with early diagnosis, the development of resistance to chemotherapeutic agents, and recurrence. OCCC often has a poorer prognosis than high grade serous carcinoma mainly because of its resistance to standard chemotherapy regimens. Known prognostic factors in OCCC include age, FIGO stage, LN status, the presence of endometriosis, and residual tumor after primary cytoreductive surgery. However, the abilities of these conventional intraoperative and postoperative factors to predict survival are inadequate. To date, few reliable preoperative biomarkers have been identified that can predict the prognosis in OCCC.

Accumulating evidence suggests SIR is a key determinant of outcome in patients with cancer, and several authors have suggested reported hematological markers of SIR, such as, NLR, PLR, and LMR, might serve as independent prognostic

In a previous study, in which we assessed the prognostic markers of survival. c value of LMR in a cohort of 234 EOC patients that underwent primary debulking surgery and adjuvant chemotherapy, we found a high LMR was strongly correlated with age, serum CA-125 level, FIGO stage and malignant ascites, and that 5-year PFS and OS rates were better for those with a high LMR. In addition, LMR was found to predict the outcome of primary surgical cytoreduction in EOC patients, and LMR, age, CA125 level, and WBC count were found to be reliable predictors of suboptimal cytoreduction. Although the prognostic value of SIR has been established in EOC, its value in OCCC has not been well studied, and few studies have compared the prognostic values of SIR, NLR, and PLR in OCCC, but the prognostic value of LMR has yet to be evaluated in OCCC.

In the present study, a high NLR was significantly associated with advanced FIGO stage (III to IV), presence of malignant ascites, and platinum resistance. In addition, survival analysis showed that high NLR was associated with poorer PFS and OS than low NLR. However, although univariate analysis showed NLR was significantly associated with PFS and OS, these relations were not supported by multivariate analysis. No significant correlation was found between PLR level and age, FIGO stage, LN metastasis, malignant ascites, the presence of endometriosis, CA-125 level, residual mass, or platinum response, and survival analysis showed that a high PLR was not significantly associated with poorer PFS or OS. A high LMR was significantly associated with early FIGO stage (I to II), no LN metastasis, no malignant ascites, and higher platinum response in OCCC. Kaplan-Meier analysis supported these positive relations as it show patients in the high LMR group had significantly higher PFS and OS than patients in low LMR group. These findings suggest that a high LMR caused by increased levels of peripheral lymphocytes, increases immune surveillance and response to adjuvant chemotherapy, and thus improves PFS and OS. Furthermore, univariate analysis showed LMR was significantly and positively associated with PFS and OS, and multivariate analysis showed that a high LMR independently predicted better OS, but not better PFS.

The strength of our study is that it represents a first attempt to evaluate the prognostic value of LMR in OCCC. Recent studies on SIR markers in OCCC did not include LMR as a potential prognostic marker. OCCC has been well demonstrated to be associated with chronic inflammation. Kato et al. reported that plasma cell rich inflammatory stroma and cancer cells were responsible for inducing inflammation and stimulating plasma cell differentiation in a paracrine manner in OCCC. Moreover, a large number of patients with OCCC despite its rarity were included.

Conclusion

This is the first study to assess the prognostic value of LMR in patients with OCCC, and it shows a high LMR is associated with better survival, and suggests LMR might be an independent prognostic factor of survival. Thus, our findings indicate preoperative SIR measurements might provide a straightforward, convenient means of identifying OCCC patients with a poor prognosis.