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Prognostic value of lymphocyte-to-monocyte ratio in ovarian cancer
A meta-analysis

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Abstract

Background: Lymphocyte-to-monocyte ratio (LMR) was recently proposed as a prognostic factor of ovarian cancer. However, prognostic value of the LMR in ovarian cancer remains inconclusive. The study aimed to assess prognostic value of the LMR in ovarian cancer.

Methods: Seven common databases were comprehensively searched for relevant studies. The analyses were performed for overall survival (OS), progression-free survival (PFS) and clinical parameters. The hazard ratio (HR) and 95% confidence interval (CI) were used to analyze OS and PFS.

Results: A total of 2343 patients with ovarian cancer were included in this meta-analysis. The results showed that a low LMR predicted shorter OS (HR = 1.81, 95% CI = 1.38–2.37, $P < .01$) and PFS (HR = 1.65, 95% CI = 1.46–1.85, $P < .01$) when compared to a high LMR in ovarian cancer. Besides, a low LMR was significantly associated with advanced clinical stage ($P < .01$), earlier lymph node metastasis ($P = .01$), higher carbohydrate antigen-125 levels ($P < .01$), larger residual tumor ($P < .01$) and worse chemosensitivity ($P < .01$) when compared to a high LMR in ovarian cancer.

Conclusion: Low LMR was associated with unfavorable survival in patients with ovarian cancer. LMR could serve as a prognostic biomarker of ovarian cancer.

Abbreviations: CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, LMR = lymphocyte-to-monocyte ratio, NLR = neutrophil-to-lymphocyte ratio, NOS = Newcastle–Ottawa scale, OS = overall survival, PFS = progression-free survival.

Keywords: clinical parameters, lymphocyte-to-monocyte ratio, meta-analysis, ovarian cancer, overall survival, progression-free survival

1. Introduction

Ovarian cancer remains the most lethal gynecologic malignancy and the leading cause of cancer-related deaths in women.[1,2] There are 22,440 estimated new cases and 14,080 estimated deaths for ovarian cancer in 2017.[1] Although the cytoreductive surgery

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followed by platinum-based adjuvant chemotherapy prolongs the survival of patients with ovarian cancer, prognosis of most cases remains disappointing.[3,4] Given the poor prognosis, identification of optimal biomarkers to predict prognosis of ovarian cancer attracts a growing number of researchers' attention.[5]

Inflammation has been proved to be associated with carcinogenesis and disease progression, and inflammation in tumor microenvironment can be reflected by a systemic inflammatory response.[6] Increasing evidence has shown that peripheral blood cells and relevant ratios are related to cancer prognosis, such as platelet-to-lymphocyte ratio[7] and neutrophil-to-lymphocyte ratio.[8,9] Similarly, absolute lymphocyte counts and monocyte counts have also been proved to be associated with prognosis of cancer.[10,11] Recently, a growing number of publications demonstrated that lymphocyte-to-monocyte ratio (LMR) was an independent prognostic factor for several types of cancer, such as colorectal cancer,[12] gastric cancer,[13] breast cancer,[14] and lung cancer.[15] Although many studies have explored clinical significance of the LMR in predicting prognosis of ovarian cancer, consensus has not been reached due to the inconsistent results of different studies.[16–22] Therefore, the aim of this meta-analysis was to explore prognostic significance of the LMR in ovarian cancer.

2. Materials and methods

2.1. Literature search

Seven common databases were comprehensively searched until July 21, 2018, including Scopus, PubMed, Web of Science,

Embase, Cochrane Library, China National Knowledge Infrastructure, and Wanfang Database. The following keywords were used: ("lymphocyte-to-monocyte ratio" OR "monocyte-to-lymphocyte ratio" OR "LMR" OR "MLR") AND ("ovarian cancer" OR "ovarian tumor" OR "ovarian neoplasm"). The references of retrieved studies were also checked to avoid missing relevant studies.

2.2. Inclusion criterion and exclusion criterion

Studies meeting the following criteria were eligible:

(1) patients diagnosed as ovarian cancer by pathological examination;
(2) focusing on prognostic value of the LMR in ovarian cancer;
(3) patients divided into 2 groups (high LMR group vs low LMR group);
(4) reporting overall survival (OS), progression-free survival (PFS), or clinical parameters;
(5) having sufficient data.

The following studies were ineligible for this meta-analysis: reviews, letters, case reports, cell experiments, animal experiments, studies with duplicated patients, or studies without sufficient data. The study eligibility was independently assessed by 2 authors. Any disagreement was resolved by discussing with the third author.

2.3. Data extraction and quality assessment

The following items were extracted: the first author, the publication year, countries, the number of patients, histology, clinical stage, treatment, cut-off values, outcomes, analysis models of OS, and information for quality assessment. For prognostic items (eg, OS and PFS), hazard ratio (HR) and 95% confidence interval (CI) were directly obtained from the included studies. Besides, for the studies without HR or corresponding 95% CI, HR and 95% CI would be extracted from survival curves as described by Tierney et al[23] The quality of the included studies was evaluated using Newcastle–Ottawa scale (NOS).[24] Data extraction and quality assessment were completed by 2 authors independently. Any disagreement was resolved by discussing with the third author.

2.4. Statistical analysis

All analyses were performed with Review Manager 5.3 and Stata 12.0 for Windows. For prognostic variables (eg, OS and PFS), HR and corresponding 95% CI were used to detect the overall effects. While for clinicopathological parameters (eg, clinical stage and lymph node metastasis), odds ratio and corresponding 95% CI were used. Inter-study heterogeneity was evaluated by Chi-square test and I^2 statistic. The $I^2 \leq 50\%$ showed there was no obvious heterogeneity among studies, hence, a fixed-effect model should be used. Or else, a random-effect model should be applied because of the obvious heterogeneity. Funnel plot was generated to assess the publication bias. Especially, the Begg test and Egger test were also performed to detect the publication bias for the meta-analysis of OS. Sensitivity analyses were conducted to check stability of the results. Galbraith plot was generated to explore the source of heterogeneity.

3. Results

3.1. The literature search and selection

As shown in Figure 1, a total of 191 papers were initially identified from electronic database search. After removal of duplicated papers, there were 84 papers left for further evaluation. Seventy papers were directly excluded by reading titles or abstracts. For the 14 remained papers, full-texts were carefully read and 7 papers were removed for following reasons: 4 papers irrelevant to this topic and 3 papers enrolled duplicated patients. Ultimately, 7 studies were included in this meta-analysis.[16–22]

3.2. Characteristics of the included studies

Characteristics of the included studies were listed in Table 1. Seven studies, containing 2343 patients, were analyzed in this paper.[16–22] The LMR was calculated using the lymphocyte count and monocyte count from routine blood test before treatment in all studies. There were 1240 patients in low LMR group and 1103 patients in high LMR group. Besides, 5 studies were conducted in China,[18–22] 1 study was performed in USA,[17] and 1 study was conducted in Korea.[17] Moreover, 6 studies reported histology of ovarian cancer[17–22] and all studies reported clinical stage of ovarian cancer based on the International Federation of Gynecology and Obstetrics (FIGO).[16–22] All patients received cytoreductive surgery with or without chemotherapy.[16–22] With regard to cut-off values, all studies provided cut-off values of the LMR, ranging from 2.22 to 4.35.[16–22] Regarding to outcomes, clinical parameters were reported by 5 studies,[16,18,19,21,22] PFS by 3 studies[16,21,22] and OS by 7 studies.[16–22] Furthermore, OS was assessed with multivariate analysis and univariate analysis in 6 studies[16–19,21,22] and 1 study,[20] respectively. The main adjusted factors in the multivariate analysis of OS are listed in Table 2, such as age, FIGO stage, lymph node metastasis, and so on. For quality assessment, NOS was equal to or greater than 6 in all studies, indicating that all studies had relatively high quality.[16–22]

3.3. Association between the LMR and OS

Seven studies reported OS, which were included into the meta-analysis for the association between the LMR and OS[16–22] (Fig. 2). As shown in Figure 2a, the random-effect model was used because of obvious heterogeneity ($I^2 = 78\%$), and the results showed a low LMR was significantly associated with shorter OS compared to a high LMR (HR = 1.81, 95% CI = 1.38–2.37, $P < .01$). The sensitivity analysis indicated that the pooled results would not be altered by excluding any studies (Fig. 2b). There was no obvious publication bias among the included studies based on the funnel plot (Fig. 2c), Begg test and Egger test (Supplementary Fig. 1, http://links.lww.com/MD/D29). Furthermore, Galbraith plot was generated to explore the source of heterogeneity, and the results showed Tang 2017,[18] Wang 2016,[19] and Li 2017[17] were the main sources of heterogeneity (Supplementary Fig. 2, http://links.lww.com/MD/D29). The results confirmed the unfavorable prognostic role of the low LMR in ovarian cancer after removal of the 3 studies (Supplementary Fig. 3, http://links.lww.com/MD/D29).

The subgroup analyses for the association between LMR and OS were also conducted based on the following categories:
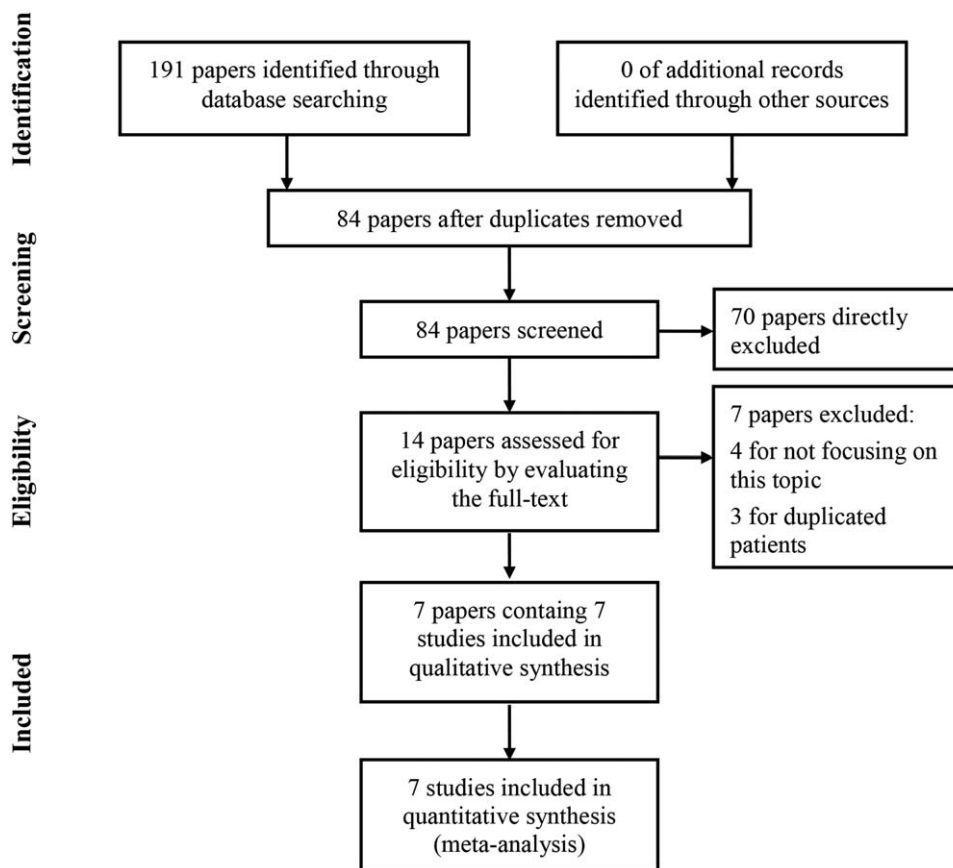
Figure 1. The flow chart of literature search and selection.

analysis models (multivariate analysis vs univariate analysis), countries (China vs other countries), sample size (<300 *versus* ≥300), cut-off values (<3.90 vs ≥3.90), and NOS (<8 vs ≥8) (Table 3). Significant relationship between the LMR and OS was observed in the majority subgroup analyses (P < .05) except for subgroup analyses of other countries (P = .34).

Subgroup analyses were also performed based on the adjusted factors in the multivariate analysis of OS (Table 4). There was obvious relationship between the LMR and OS in most subgroup analyses (P < .05) except for the subgroup analysis of adjusted carbohydrate antigen-125 (CA-125) (P = .24).

3.4. Association between the LMR and PFS

Three studies analyzed PFS and were included into this meta-analysis for association between the LMR and PFS (Fig. 3).[16,21,22] The fixed-effect model was employed for tiny heterogeneity ($I^2 = 5\%$), and the results showed that a low LMR predicted shorter PFS when compared to a high LMR (HR = 1.65, 95% CI = 1.46–1.85, P < .01) (Fig. 3a). There was no distinct publication bias among the included studies (Fig. 3b).

3.5. Association between the LMR and clinical parameters

As shown in Table 5, the LMR was obviously related to several clinical parameters, including FIGO stage (P < .01), lymph node

Table 1
The characteristics of included studies.

Study	Country	Patients (n)		Total	Histology (n) (serous/nonserous)	Treatment	FIGO stage (n) (I + II/III + IV)	Cut-off value	Outcomes	Analysis model	NOS
		Low LMR	High LMR								
Kwon 2018[16]	Korea	69	40	109	NA	CS + CT	64/45	4.20	CP, PFS, OS	M	8
Li 2017[17]	USA	259	352	611	529/125	CS	121/533	2.22	OS	M	7
Tang 2017[18]	China	128	86	214	146/68	CS + CT	99/115	3.85	CP, OS	M	7
Wang 2016[19]	China	153	87	240	214/26	CS + CT	59/181	3.95	CP, OS	M	7
Xiang 2017[20]	China	69	64	133	87/46	CS	64/69	4.35	OS	U	6
Yang 2017[21]	China	222	142	364	206/158	CS + CT	52/312	3.84	CP, PFS, OS	M	8
Zhu 2017[22]	China	340	332	672	484/188	CS + CT	0/672	3.45	CP, PFS, OS	M	8

CP = clinical parameter, CS = cytoreductive surgery, CT = chemotherapy, FIGO = International Federation of Gynecology and Obstetrics, LMR = lymphocyte-monocyte ratio, M = multivariate analysis, NA = not available, NOS = Newcastle–Ottawa scale, OS = overall survival, PFS = progression-free survival, U = univariate analysis.

Table 2

The main adjusted factors in the multivariate analysis of OS.

	Age	FIGO stage	LNM	Malignant ascites	CA-125	Residual tumor	Chemosensitivity	Differentiation grade	NLR	PLR
Kwon 2018[16]	√	√	√	√	√	√	√		√	√
Li 2017[17]	√	√				√		√	√	√
Tang 2017[18]	√	√		√	√				√	√
Wang 2016[19]	√	√			√			√		
Yang 2017[21]	√	√	√	√	√			√		
Zhu 2017[22]	√	√			√	√	√	√		

CA-125 = carbohydrate antigen-125, FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, NLR = neutrophil-to-lymphocyte ratio, OS = overall survival, PLR = platelet-to-lymphocyte ratio.

metastasis (P = .01), CA-125 (P < .01), residual tumor (P < .01), and chemosensitivity (P < .01). However, there was no significant association between the LMR and other clinical parameters, including age (P = .22), histology (P = .71), and histologic grade (P = .45). There was no obvious publication bias among the included studies (Fig. 4).

4. Discussion

To our knowledge, this is the first study to evaluate prognostic significance of the LMR in ovarian cancer. Our findings showed that a low LMR predicted shorter OS and PFS when compared to a high LMR in ovarian cancer. Besides, a low LMR was distinctly related to advanced FIGO stage, earlier lymph node metastasis, higher CA-125 levels, larger residual tumor, and worse chemosensitivity when compared to a high LMR. Therefore, the LMR might be a promising prognostic factor of ovarian cancer.

Subgroup analyses were also conducted for OS, and significant relationship between the LMR and OS was detected in the majority subgroup analyses. However, subgroup analyses demonstrated that the LMR was not significantly associated with OS in other countries except for China. It should be noted that only 2 studies were included into the analysis, and hence that conclusion might be affected by the small sample size. Therefore, more studies should be implemented to evaluate prognostic significance of the LMR in ovarian cancer in other countries.
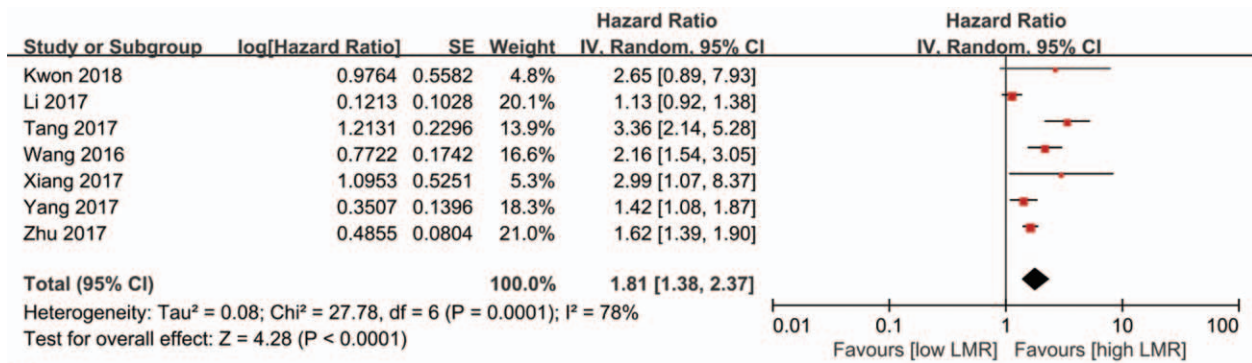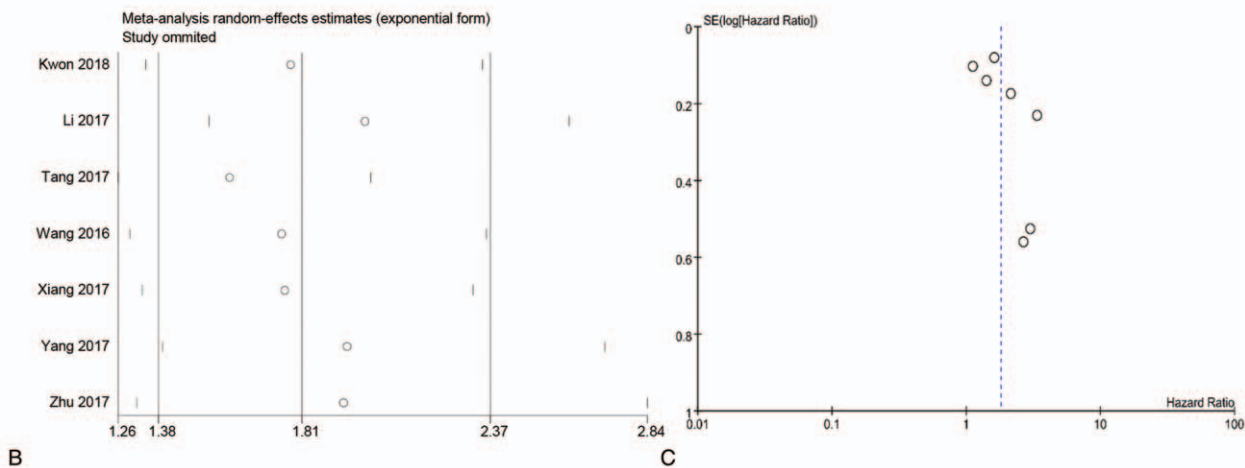
Figure 2. The meta-analysis for association between the LMR and OS (a, forest plot; b, sensitivity analysis; c, funnel plot). LMR = lymphocyte-to-monocyte ratio, OS = overall survival.

Table 3

The subgroup analyses for the association between LMR and OS.

Subgroups	Included studies (n)	HR 95% CI	P	I² (%)	Model
Analysis model					
Multivariate	6	1.76 [1.33,2.32]	<.01*	81	Random
Univariate	1	2.99 [1.07, 8.37]	.04*	NA	Fixed
Country					
China	5	1.97 [1.49, 2.61]	<.01*	71	Random
Other countries	2	1.45 [0.68, 3.12]	.34	56	Random
Sample size					
<300	4	2.57 [1.99, 3.32]	<.01*	0	Fixed
≥300	3	1.38 [1.09, 1.75]	<.01*	74	Random
Cut-off value					
<3.90	4	1.63 [1.19, 2.25]	<.01*	86	Random
≥3.90	3	2.27 [1.66, 3.09]	<.01*	0	Fixed
NOS					
<8	4	2.10 [1.17, 3.77]	.01*	89	Random
≥8	3	1.58 [1.38, 1.81]	<.01*	0	Fixed

CI = confidence interval, HR = hazard ratio, LMR = lymphocyte-monocyte ratio, NA = not available; NOS = Newcastle-Ottawa Scale, OS = overall survival.
* The association between LMR and OS was significant when P < .05.

Although a great number of publications have explored prognostic significance of the LMR in ovarian cancer, the underlying mechanism remains unclear.[16–22] The systematic inflammation status has been proved to be associated with progression and metastasis of ovarian cancer.[25,26] Plenty of studies have observed prognostic significance of tumor infiltrating immune cells in a variety of solid tumors.[14,16,27,28] The low LMR represented low lymphocyte or high monocyte levels in ovarian cancer. Lymphocytes can migrate into the tumor microenvironment and evolve into tumor-infiltrating lymphocytes.[29,30] CD4+ and CD8+ T lymphocytes play an important role in antitumor immune reaction through inducing cytotoxic cell death and inhibiting tumor cell proliferation and migration.[31,32] Moreover, several studies have demonstrated that lymphocytes prevent development of ovarian cancer.[27,33] Therefore, the decreased lymphocyte counts in blood and tumor stoma result in a weakened antitumor immune response.[32] On the other hand, numerous studies show that monocytes produce various cytokines, for instance, interleukin-6 and interleukin-10, which contribute to poor prognosis of cancer.[34,35] Furthermore, monocytes may promote the proliferation, angiogenesis, and metastatic potential of tumor cells by differentiating into tumor-associated macrophages (TAMs).[36,37] TAMs can facilitate angiogenesis, matrix breakdown, and tumor-cell motility, and then promote metastatic processes.[38,39] Besides, TAMs also produce many compounds to promote tumorigenesis, invasion, and metastasis of tumors, such as mutagenic oxygen and nitrogen radicals to angiogenic factors.[38] Monocytes/TAMs can promote solid-tumor progression and metastasis.[40,41] The aforementioned mechanisms may explain the unfavorable role of a low LMR in ovarian cancer. However, further studies should be conducted to investigate the exact mechanism.

Table 4

The subgroup analyses for the association between LMR and OS based on adjusted factors in multivariate analysis.

Adjusted factors	Included studies (n)	HR 95% CI	P	I² (%)	Random
LNM					
Yes	2	1.47 [1.13, 1.92]	<.01*	15	Fixed
No	4	1.83 [1.27, 2.64]	<.01*	88	Random
Malignant ascites					
Yes	3	2.23 [1.13, 4.41]	.02*	81	Random
No	3	1.55 [1.12, 2.15]	<.01*	85	Random
CA-125					
Yes	1	1.13 [0.92, 1.38]	.24	NA	Fixed
No	5	1.95 [1.48, 2.58]	<.01*	70	Random
Residual tumor					
Yes	3	1.44 [1.02, 2.02]	.04*	78	Random
No	3	2.12 [1.32, 3.41]	<.01*	82	Random
Chemosensitivity					
Yes	2	1.64 [1.40, 1.92]	<.01*	0	Fixed
No	4	1.79 [1.17, 2.74]	<.01*	88	Random
Histologic grade					
Yes	4	1.51 [1.19, 1.92]	<.01*	77	Random
No	2	3.25 [2.14, 4.93]	<.01*	0	Fixed

CA-125 = carbohydrate antigen-125, CI = confidence interval, HR = hazard ratio, LNM = lymph node metastasis, OS = overall survival.
* The association between LMR and OS was significant when P < .05.
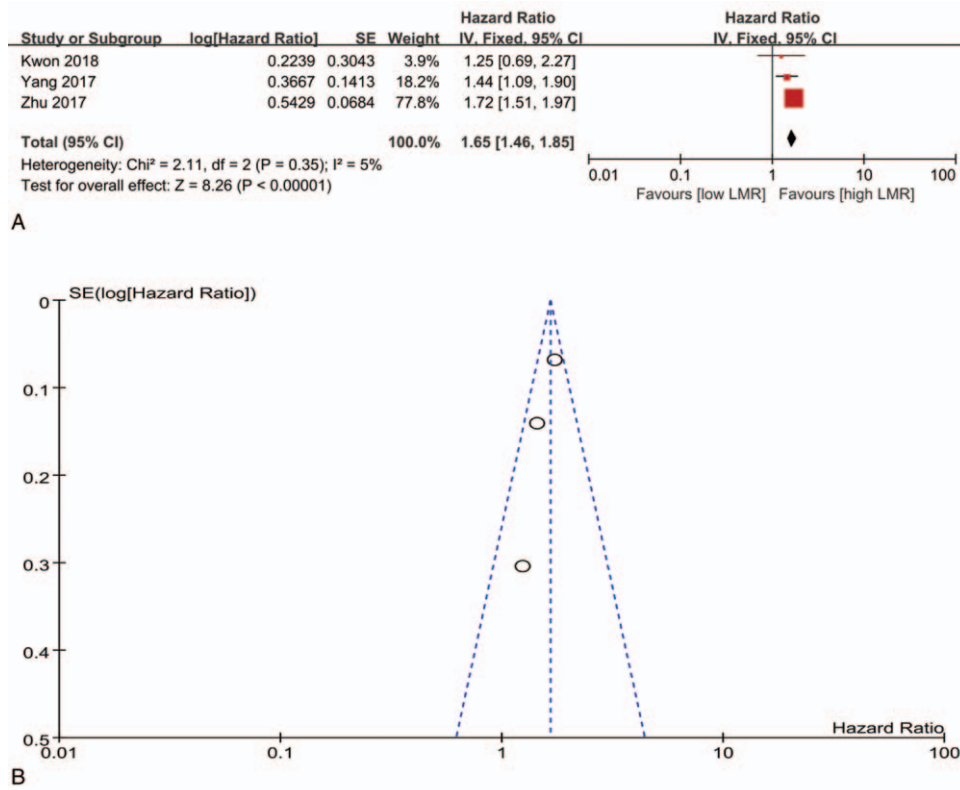
Figure 3. The meta-analysis for association between the LMR and PFS (a, forest plot; b, funnel plot). LMR = lymphocyte-to-monocyte ratio, PFS = progression-free survival.

To our knowledge, this is the first study to detect prognostic significance of the LMR in ovarian cancer. A total of 2343 patients were analyzed in our study, and the relatively large sample size could provide a more convincing conclusion. Moreover, subgroup analyses for OS were conducted in this study, which offered comprehensive results on prognostic significance of the LMR in ovarian cancer.

Several limitations should be considered when interpreting our results. First, the cut-off value for the LMR was not unified in our meta-analysis, which might affect the final conclusions. To lower the influence, we performed subgroup analyses based on the cut-off values and confirmed significant relationship between the LMR and OS. More studies should be carried to identify the optimal cut-off value of the LMR in future. Second,

the heterogeneity in several analyses was moderate and even evident. As a result, a random-effect model was used, which might influence accuracy of the results. However, it should be noted that significant correlation between the LMR and OS was still observed after excluding 3 studies to eliminate the heterogeneity. Third, the sample size for the meta-analyses of specific clinical parameters was relatively small, which failed to provide strong evidence. Fourth, all the enrolled patients received cytoreductive surgery with or without chemotherapy, and patients receiving other treatment modalities were not analyzed in this meta-analysis. Fifth, most included studies were conducted in China. As a result, caution should be taken when the conclusion was applied to the population in other countries.

Table 5

The meta-analysis for the association between LMR and clinical parameters.

Variables	Included studies (n)	Patients (n)	OR 95% CI	P	I^2 (%)	Model
Age (old vs young)	5	1599	1.14 [0.93, 1.39]	.22	16	Fixed
Histology (serous vs nonserous)	4	1490	1.04 [0.83, 1.32]	.71	0	Fixed
Histologic grade (poor vs well)	3	1276	1.20 [0.75, 1.93]	.45	62	Random
FIGO stage (III/IV vs I/II)	4	927	3.02 [2.20, 4.15]	<.01*	0	Fixed
LNM (yes vs no)	2	473	1.70 [1.13, 2.54]	.01*	41	Fixed
CA-125 (high vs low)	3	1021	2.53 [1.89, 3.39]	<.01*	37	Fixed
Residual tumor (>1 cm vs ≤1 cm)	2	781	3.49 [2.46, 4.94]	<.01*	23	Fixed
Chemosensitivity (no vs yes)	2	781	1.86 [1.36, 2.53]	<.01*	33	Fixed

CA-125 = carbohydrate antigen-125, CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, LMR = lymphocyte-monocyte ratio, LNM = lymph node metastasis, OR = odds ratio.
* The association between LMR and clinical parameters was significant when P < .05.
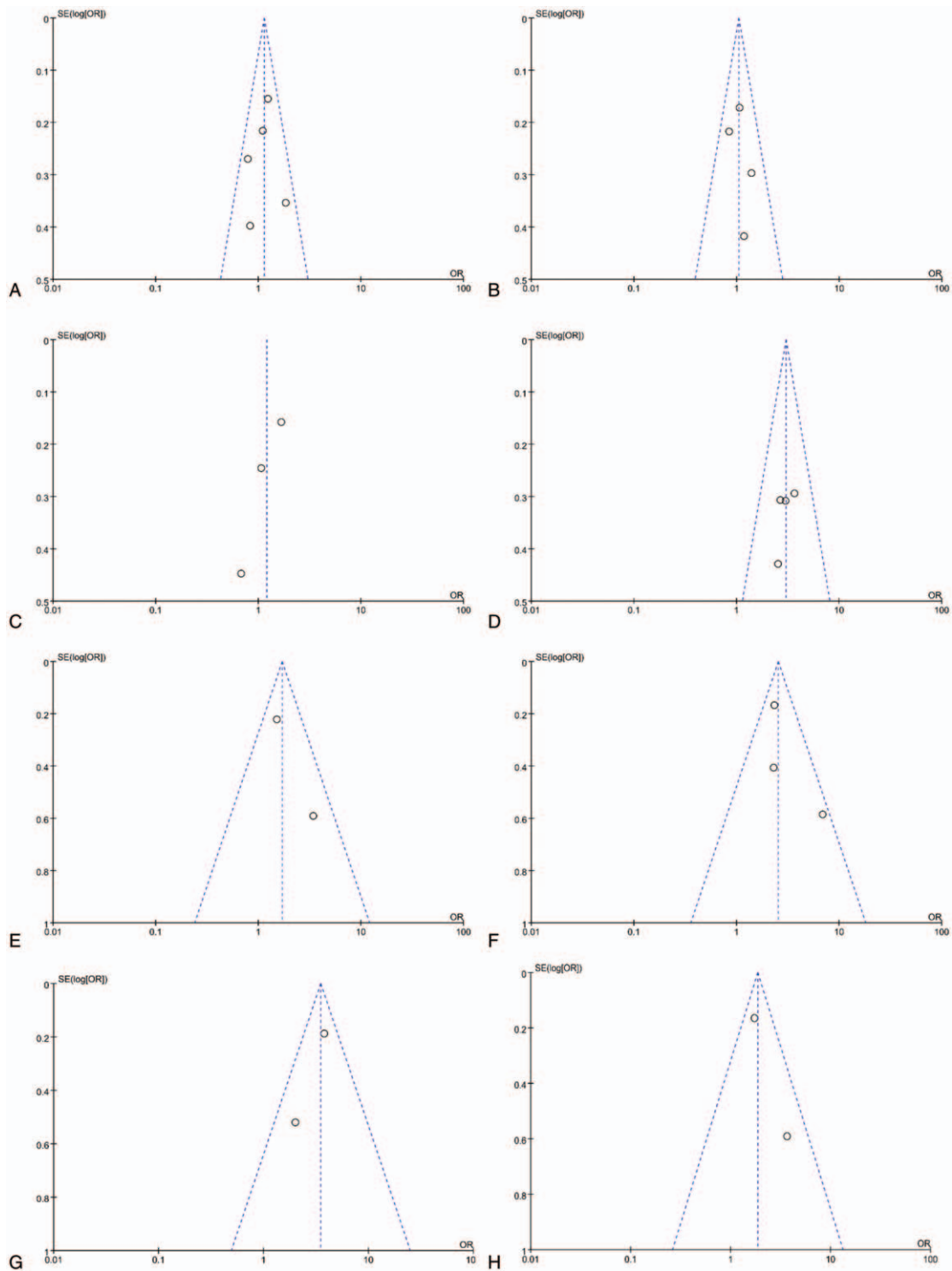
Figure 4. The funnel plots for association between the LMR and clinical parameters (a, age; b, histology; c, histologic grade; d, FIGO stage; e, lymph node metastasis; f, CA-125; g, residual tumor; h, chemosensitivity). CA-125 = carbohydrate antigen-125, FIGO = International Federation of Gynecology and Obstetrics, LMR = lymphocyte-to-monocyte ratio.

5. Conclusion

The LMR was closely associated with OS, PFS, FIGO stage, lymph node metastasis, CA-125, residual tumor, and chemo-sensitivity in ovarian cancer. Therefore, LMR could serve as a novel prognostic factor of ovarian cancer, especially in China.

Author contributions

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