Systematic Review and Meta-Analysis

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High L1CAM expression predicts poor prognosis of patients with endometrial cancer

A systematic review and meta-analysis

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Abstract

Backgroud: Previous studies have reported that the levels of L1 cell adhesion molecule (L1CAM) indicate poor prognosis of patients with various solid tumors. However, the prognostic significance of L1CAM in endometrial cancer has remained controversial. Herein, we conducted a systematic review and meta-analysis to evaluate the prognostic value of L1CAM in endometrial cancer.

Methods: All studies related to the association between L1CAM expression and clinical characteristics of endometrial cancer were identified by searching the PubMed, MEDLINE, EMBASE, and Web of Science databases. Primary outcomes of the meta-analysis were the hazard ratios (HRs) for overall survival (OS) and disease-free survival (DFS). Secondary outcomes were odds ratios (ORs) for clinicopathological characteristics. Publication bias and sensitivity analysis were conducted to ensure reliability of the results.

Results: Overall, 17 studies encompassing 7146 patients were eligible for the meta-analysis. Results showed L1CAM overexpression to be significantly associated with decreased overall survival (HR = 2.87, 95% CI; 1.81–4.55, $P < .001$) and disease-free survival (HR = 3.32, 95% CI; 1.99–5.55, $P < .001$) in patients with endometrial cancer. High L1CAM expression was also related to adverse clinicopathological characteristics.

Conclusion: This systematic review demonstrated that high L1CAM expression is correlated with poor survival outcomes and adverse clinicopathological parameters in patients with endometrial cancer.

Abbreviations: DFS = disease-free survival, HRs = hazard ratios, IHC = immunohistochemistry, L1CAM = L1 cell adhesion molecule, LVSI = lymphovascular space invasion, ORs = odds ratios, OS = overall survival.

Keywords: disease-free survival, endometrial cancer, L1CAM, meta-analysis, overall survival, prognosis

1. Introduction

Endometrial cancer is among the most common gynecologic malignancies worldwide, with increasing incidence every year.[1] Generally, the prognosis of women with endometrial cancer depends on whether the cancer is endometrioid or non-endometrioid. Endometrioid endometrial cancer is estrogen-dependent and characterized by a series of genetic mutations in mismatch repair genes or PTEN tumor suppressor genes.[2] The endometrium in endometrioid endometrial cancer shows endometrioid hyperplasia, and patients usually experience favorable outcomes. The histological and pathogenetic features of non-endometrioid endometrial cancer are considerably different from those of endometrioid endometrial cancer. Non-endometrioid endometrial cancer is characterized by estrogen-independent endometrial atrophy, and patients often show poorer prognosis.[3] However, the histological type, despite being a vital assessment parameter for endometrial cancer, does not precisely predict the outcomes in all situations. Of the patients with documented endometrioid endometrial cancer, 20% show prognosis similar to that in patients with non-endometrioid endometrial cancer.[4] Moreover, some endometrial cancers present mixed histological characteristics.[5] Thus, more effective biomarkers are required to predict the prognosis of women with endometrial cancer.

L1 cell adhesion molecule (L1CAM) is a 200 to 220-kDa membrane glycoprotein often detected in various solid malignancies.[6] Previous studies have indicated L1CAM to play an essential role in the process of epithelial-to-mesenchymal transition in tumor cells, thereby enhancing cellular migration.[7] Endometrial cancer with high L1CAM expression is evidenced to be more aggressive and associated with poor prognosis.[8] However, other studies have demonstrated high L1CAM

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All data generated or analyzed during this study are included in this published article and its supplementary information files.

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expression to predict poor outcomes, though only in patients with endometrioid endometrial cancer, and not in those with non-endometrioid endometrial cancer.[6]

Numerous studies have been conducted till date, using various detection methods, to investigate the association between L1CAM expression and prognosis of endometrial cancer at different stages [as defined by the International Federation of Gynecology and Obstetrics (FIGO)] and with different histological types.[9] However, the number of patients fully evaluated in most studies has been low. Thus, findings obtained there from may not be conclusive, and hence, the prognostic value of L1CAM expression in endometrial cancer remains unclear.[10] Here, we performed a meta-analysis to comprehensively evaluate the prognostic value of L1CAM expression in endometrial cancer. The association between L1CAM expression and clinicopathologic characteristics was determined to provide better insights to base treatment decisions on.

2. Methods

As this was a systematic review and meta-analysis, and our data are from published literature, ethical approval was not necessary for the study.

2.1. Search strategy

The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] Studies listed in PubMed, MEDLINE, EMBASE, and Web of Science were retrieved using the following search strategy: (((((“Endometrial Neoplasms”[Mesh]) OR ((((((((((Endometrial Neoplasm) OR Endometrial Carcinoma) OR Endometrial Carcinomas) OR Endometrial Cancer) OR Endometrial Cancers) OR Endometrium Cancer) OR Cancer of the Endometrium) OR Carcinoma of Endometrium) OR Endometrium Carcinoma) OR Endometrium Carcinomas) OR Cancer of Endometrium) OR Endometrium Cancers))) AND ((“Neural Cell Adhesion Molecule L1”[Mesh]) OR ((((((((((NILE Glycoprotein) OR Nerve Growth Factor-Inducible Large External Glycoprotein) OR CALL Protein) OR CamL1 Gene Product) OR Neural Adhesion Molecule L1) OR L1 Cell Adhesion Molecule) OR L1CAM) OR NILE Protein) OR Cell Adhesion Molecule L1) OR Cell Surface Glycoprotein L1) OR NGF-Inducible Glycoprotein) OR F11 Glycoprotein)))) AND ((“Prognosis”[Mesh]) AND ((((prognosis) OR prognostic) OR survival) OR mortality)). In addition, references for relevant meta-analyses and a clinical trial-registration website (http://www.clinicaltrials.gov) were searched to widen the scope of the meta-analysis.

2.2. Eligibility criteria

The inclusion criteria were as follows: studies on women with endometrial cancer, confirmed by pathological examination; studies on quantitative data of hazard ratios (HRs) for overall survival (OS) and disease-free survival (DFS), and odds ratios (ORs) for clinicopathological characteristics; and studies in which the detection techniques and cut-off values for L1CAM expression were provided.

2.3. Exclusion criteria

The exclusion criteria were as follows: case reports, reviews, letters, and other studies without sufficient data; non-English articles; and single-arm or multiple-arm studies.

2.4. Data extraction and quality assessment

The following baseline information was obtained from the included studies: the last name of authors, year of publication, country, sample size, age, FIGO stage, tumor grade, histologic category of the tumor, cut-off value, detection method, follow-up time, and primary outcome. The evaluated endpoints were OS and DFS. Association between L1CAM expression and clinicopathological characteristics of endometrial cancer was analyzed, including histology, grade, myometrial invasion, lymphovascular space invasion (LVSI), and lymph node status. Two investigators evaluated the data independently, and any inconsistency was resolved by discussion or by presentation of the information to a third investigator.

2.5. Statistical analysis

Stata statistical software version 15.0 (StataCorp, College Station, TX) was used for all statistical analyses of the included studies. The HRs for OS and DFS, and ORs for clinicopathologic characteristics, of all included studies, were pooled. Effect sizes were presented as 95% confidence intervals (95% CIs). Heterogeneity across trials was measured by the X^2-based Q test and I^2 statistics. When a $P < .10$ for the Q test or an $I^2 > 50\%$ indicated statistically significant heterogeneity across the studies, the effect sizes were measured using a random-effect model; otherwise, a fixed-effect model was used. We conducted sensitivity analysis and subgroup analysis to validate stability of the pooled effect sizes and explore the possible origins of heterogeneity. All P values were 2-sided, and $P < .05$ was considered statistically significant. We also generated a Begg funnel plot to detect potential publication bias.[12]

3. Results

3.1. Characteristics of eligible studies

The PRISMA flow diagram in Figure 1 illustrates the selection process. Through a preliminary database search, we identified 160 relevant studies. Thereafter, we removed the duplicate studies, and screened the remaining 112 studies. We read the abstracts of the studies and excluded 67 of them based on the inclusion criteria described in Section 2.2. The remaining studies were further examined by reviewing the full text; 28 studies, including conference abstracts, meta-analysis, reviews, and studies without available data, were excluded. Seventeen observational retrospective studies were finally included in this meta-analysis. The deadline for the study was January 2019. Baseline information of the eligible studies is summarized in Table 1.[2,8,10,13–26]

3.2. Prognostic value of L1CAM expression in OS

Nine studies reported the HRs for OS. The pooled results indicated high L1CAM expression to be associated with decreased OS in patients with endometrial cancer (HR 2.87, 95% CI 1.81–4.55, $P < .001$; Fig. 2). A subgroup analysis was conducted to investigate the origin of high heterogeneity ($I^2 = 82.6\%$, $P = .478$). We observed a significant relationship between high L1CAM expression and decreased OS in the following subgroups: the detection method (immunohistochemistry vs others), cut-off value (10% vs others), and FIGO stage (I–III vs I–IV). However, in subgroup analysis based on study region and

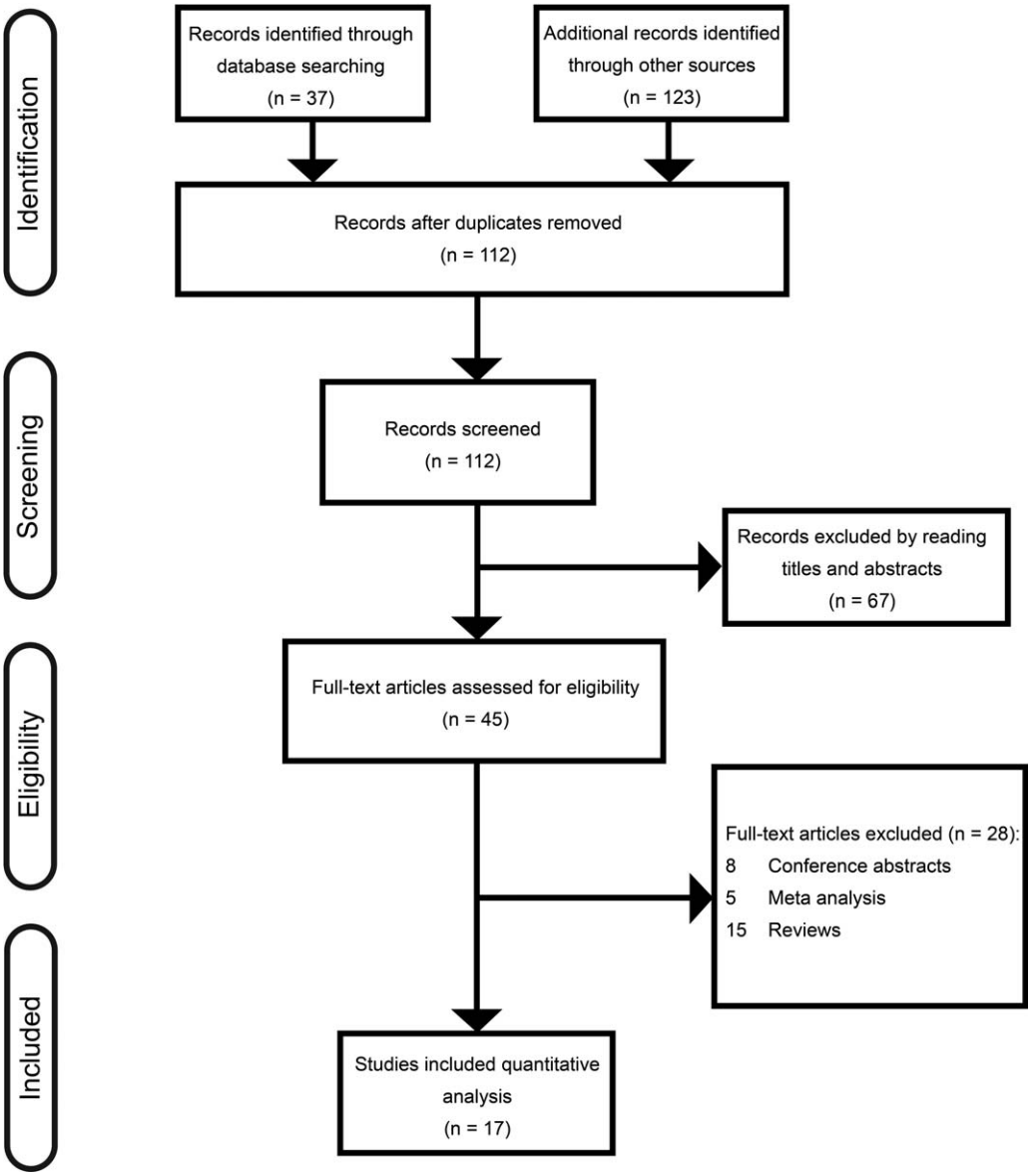

Figure 1. The PRISMA flow diagram.

sample size, significant results were observed in European group (HR 2.43, 95% CI 1.97–2.99, $P < .001$) and in sample size ≥200 group (HR 3.07, 95% CI 1.77–5.34, $P < .001$), although not so in the non-European (HR 3.83, 95% CI 0.84–17.42, $P = .082$) and sample size < 200 groups (HR 2.29, 95% CI 0.91–5.78, $P = .080$; Table 2).

3.3. Prognostic value of L1CAM expression in DFS

Eight studies reported the HRs for DFS. The pooled results indicated high L1CAM expression was associated with decreased DFS in patients with endometrial cancer (HR 3.32, 95% CI 1.99–5.55, $P < .001$; Fig. 2). Subgroup analysis was conducted to investigate the origins of high heterogeneity ($I^2 = 83.5\%$, $P = .545$). We observed a significant relationship between high L1CAM expression and decreased DFS in the following subgroups: study region (European vs non-European), sample size (< 200 vs≥ 200), detection method (immunohistochemistry vs others), cut-off value (10% vs others), and FIGO stage (I–III vs I–IV; Table 3).

3.4. Association between L1CAM expression and clinicopathological characteristics in women with endometrial cancer

Fifteen studies reported dichotomous data for clinicopathological characteristics. A high L1CAM expression was positively associated with disease grade (OR = 3.57, 95% CI 2.05–5.14, $P < .001$), myometrial invasion (OR = 1.50, 95% CI 1.12–1.87, $P < .001$), LVSI (OR = 2.48, 95% CI 1.40–4.38, $P = .002$), and lymph node status (OR = 3.99, 95% CI 1.76–5.77, $P < .001$). However, high L1CAM expression was negatively associated with endometrioid endometrial cancer (OR = 0.04, 95% CI 0.03–0.05, $P < .001$; Table 4).

Table 1

Basic features of the included studies.

Study (country)	Study design	FIGO stage	Tumor grade	Tumor type	Detection method	Cut-off value	Follow-up time, mo (median and range)	Patient numbers	Age, yr)
van der Putten et al[13] (Europe)	Retrospective	I–IV	1–3	Endometrioid/non-endometrioid	IHC	10%	70 (3–210)	293	64 (32–94)
de Freitas et al[14] (Brazil)	Retrospective	I–III	1–3	Endometrioid	IHC	10%	NA	47	61 (37–88)
Fadare et al[15] (USA)	Retrospective	I–IV	NA	Clear cell	Microarray	50%	31 (1–104)	49	NA
Pasanen et al[16] (Finland)	Retrospective	I–IV	1–3	All	IHC	10%	NA	241	67.3
Corrado et al[2] (Italy)	Retrospective	I–IV	1–3	Adenocarcinoma	IHC	20%	NA	113	67 (40–88)
van der Putten et al[10] (Europe)	Retrospective	I–IV	1–3	Endometrioid/non-endometrioid	IHC	10%	64 (1–210)	1199	63 (32–93)
Tangen et al[17] (Norway)	Retrospective	I–IV	1–3	ALL	L1CAM index	4	NA	795	NA
KLAT et al[8] (Czech Republic)	Retrospective	IA–IB	1–3	Endometrioid	IHC	10%	NA	312	63.4 (27–89)
Bosse et al[18] (Netherlands)	Retrospective	IB–IIA	1–3	Endometrioid/non-endometrioid	IHC	10%	NA	865	68.1 (41–90)
Geels et al[19] (Netherlands)	Retrospective	I–IV	1–3	Endometrioid/non-endometrioid	IHC	10%	57 (0–148)	103	63 (24–86)
Zeimet et al[20] (Austria)	Retrospective	I	1–3	Endometrioid	IHC	10%	63.6	1021	64 (34–96)
Van Gool et al[21] (Netherlands)	Retrospective	I–IV	1–3	ALL	IHC	10%	NA	116	66.3 (21–85)
Smogeli et al[22] (Norway)	Retrospective	I	1–3	Endometrioid/serous/ clear cell	IHC	10%	57.6 (1.2–105.6)	450	66.8 (39–91)
Pasanen et al[23] (Finland)	Retrospective	I–IV	1–3	ALL	IHC	10%	51 (1–98)	805	67.3
Abdel Azim et al[24] (Austria)	Retrospective	I–II	1–3	Adenocarcinoma	IHC	10%	114 (2.4–218.4)	142	66 (42–86)
Notaro et al[25] (Germany)	Retrospective	I–III	1–3	ALL	IHC	10%	NA	50	NA
Dellinger et al[26] (USA)	Retrospective	I–IV	1–3	ALL	TCGA	5.37	23 (0–192)	545	64 (31–90)

FIGO = International Federation of Gynecology and Obstetrics, IHC = immunohistochemistry, NA = not applicable, TCGA = The Cancer Genome Atlas.

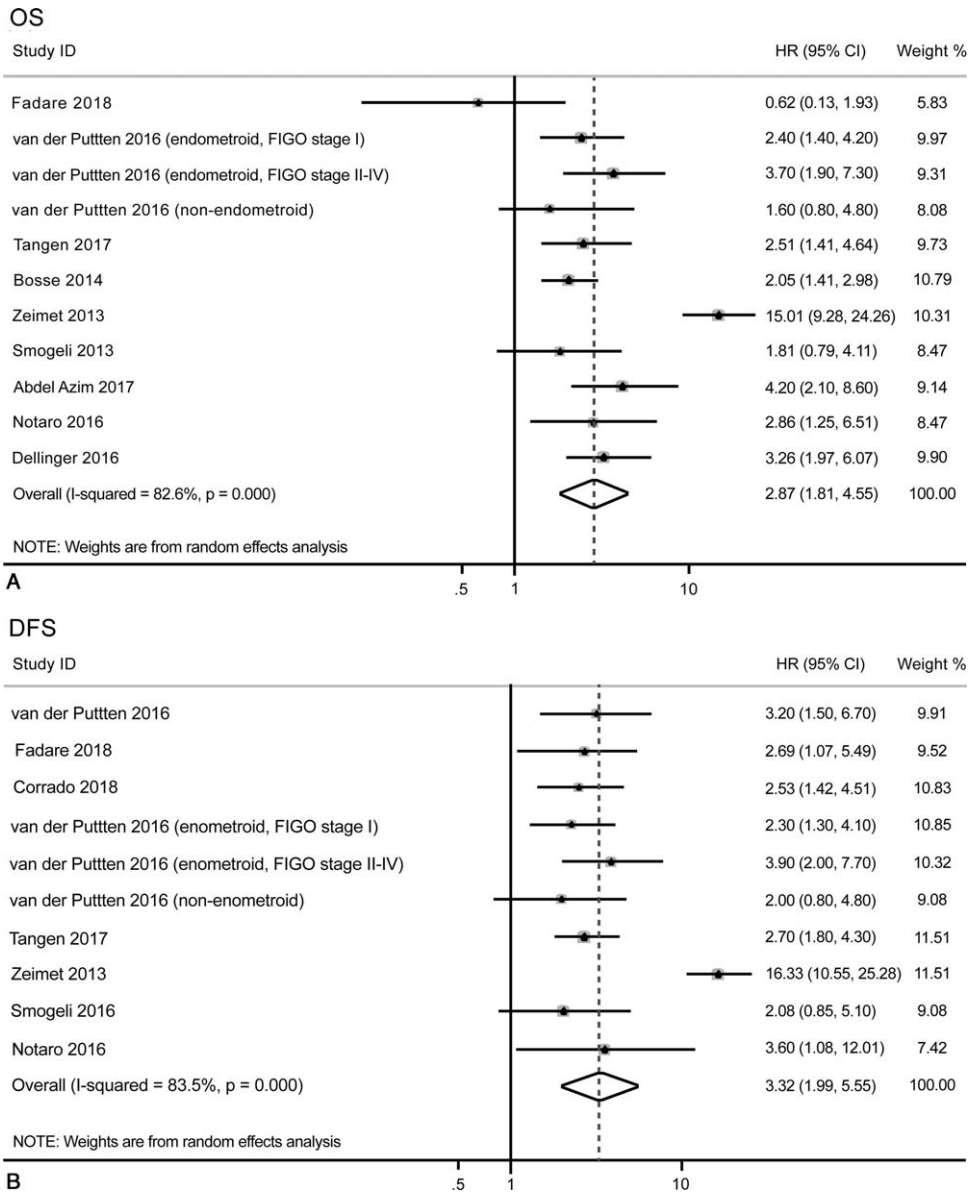

Figure 2. Forest plot to evaluate the association between L1CAM and overall survival, and between L1CAM and disease-free survival.

Table 2

Summary of subgroup analysis in overall survival.

Group	Subgroup	Observation	Patients	Pooled OS			I^2 (%)	Ph
				HR (95% CI)	Z	P		
Study region	European	6	3904	2.43 (1.97–2.99)	8.3	<.001	0	0.682
	Non-European	3	1212	3.83 (0.84–17.42)	1.74	.082	91.5	<0.001
Sample size	<200	3	241	2.29 (0.91–5.78)	1.75	.08	86.3	<0.001
	≥200	6	4875	3.07 (1.77–5.34)	3.98	<.001	67.1	0.048
Detection method	IHC	6	3727	2.18 (1.11–4.31)	3.91	<.001	59.6	0.084
	Others	3	1389	3.22 (1.79–5.78)	2.25	.024	86.2	<0.001
Cut-off value	10%	6	3727	2.18 (1.11–4.31)	3.91	<.001	59.6	0.084
	Others	3	1389	3.22 (1.79–5.78)	2.25	.024	86.2	<0.001
FIGO stage	I–III	5	2528	3.73 (1.53–9.12)	2.89	.004	91.2	<0.001
	I–IV	4	2588	2.47 (1.76–3.47)	5.21	<.001	30.7	0.205

Random-effects model was used when *P*-value for heterogeneity test < .1; otherwise, the fixed-effects model was used.
CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, IHC = immunohistochemistry, *P* = *P*-value for statistical significance based on *Z* test, PFS = progression-free survival, Ph = *P*-value for heterogeneity based on Q test.

Table 3

Summary of subgroup analysis in disease-free survival.

Group	Subgroup	Observation	Patients	Pooled DFS			I^2 (%)	Ph
				HR (95% CI)	Z	P		
Study region	European	6	2900	2.69 (2.13–3.39)	8.34	<.001	0	0.914
	Non-European	2	1070	6.86 (1.17–40.12)	2.14	.033	83.5	<0.001
Sample size	<200	3	212	3.50 (1.78–6.90)	4.43	<.001	88.2	<0.001
	≥200	5	3758	2.70 (1.74–4.19)	3.63	<.001	83.5	<0.001
Detection method	IHC	6	3126	2.70 (1.84–3.96)	3.78	<.001	0	0.994
	Others	2	844	3.49 (1.82–6.66)	5.06	<.001	85.9	<0.001
Cut-off value	10%	5	3013	2.65 (1.92–3.64)	3.45	.001	0	0.984
	Others	3	957	3.65 (1.75–7.62)	5.96	.001	86.7	<0.001
FIGO-stage	I–III	3	1521	5.22 (1.21–22.63)	2.21	.027	89.7	<0.001
	I–IV	5	2449	2.71 (2.14,3.43)	8.29	<.001	0	0.908

Random-effects model was used when *P*-value for heterogeneity test < .1; otherwise, the fixed-effects model was used.
CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, HR = hazard ratio, IHC = immunohistochemistry, *P* = *P*-value for statistical significance based on *Z* test, PFS = progression-free survival, Ph = *P*-value for heterogeneity based on Q test.

3.5. Publication bias and sensitivity analysis

We conducted a sensitivity analysis by sequentially omitting each study from the analysis. Results showed that the study by Zeimet et al[20] led to the statistical heterogeneity in the primary outcomes (OS and DFS; Fig. 3). When this study was omitted, the pooled results showed high L1CAM expression to be associated with decreased OS (HR 2.46, 95% CI 2.02–3.00, $P < .001$) and DFS (HR 2.69, 95% CI 2.15–3.37, $P < .001$) in patients with endometrial cancer. Moreover, heterogeneity in the remaining studies was significantly reduced and could be evaluated using a fixed model, resulting in $I^2 = 18.6\%$ and $P = .272$ for OS and $I^2 = 0.0\%$ and $P = .954$ for DFS. We also generated a Begg funnel plot and performed Egger test to investigate potential publication bias in the meta-analysis. Symmetry in the funnel plot was observed for both OS ($P = .436$ for Begg test and $P = .400$ for Egger test) and DFS ($P = .721$ for Begg test and $P = .214$ for Egger test).

4. Discussion

L1CAM, a member of the immunoglobulin superfamily, promotes cell migration by interacting with the epithelial-to-mesenchymal transition and Wnt signaling.[27,28] Till date, numerous studies have investigated the role of L1CAM

Table 4

The association between L1CAM expression and clinicopathological characteristics of endometrial cancer.

Clinicopathological characteristics	Observation	Model	Pooled OR			I^2 (%)	Ph
			OR (95% CI)	Z	P		
Histology (endometrioid vs non-endometrioid)	11	Fixed	0.04 (0.03–0.05)	7.61	<.001	40.1	0.082
Grade (3 vs 1–2)	14	Random	3.57 (2.05–5.14)	4.56	<.001	86.8	<0.001
Myometrial invasion (≥50% vs <50%)	13	Random	1.50 (1.12–1.87)	7.77	<.001	60.3	0.247
LVSI (yes vs no)	9	Random	2.48 (1.40–4.38)	3.12	.002	76.2	0.507
Lymph node status (positive vs negative)	6	Fixed	3.99 (1.76–5.77)	7.36	<.001	0	<0.001

Random-effects model was used when *P*-value for heterogeneity test < .1; otherwise, the fixed-effects model was used.
CI = confidence interval, LVSI = lymphovascular space invasion, OR = odds ratio, *P* = *P*-value for statistical significance based on the *Z* test, Ph = *P*-value for heterogeneity based on Q test.

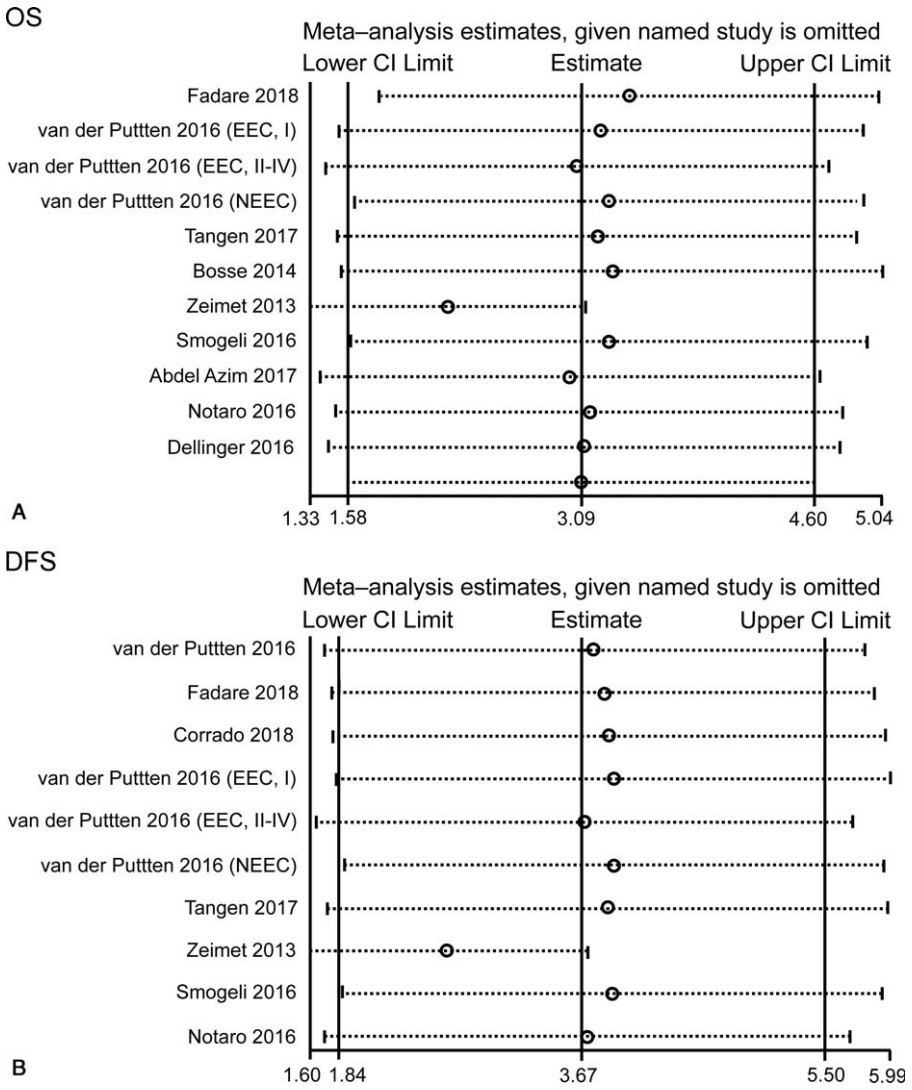

Figure 3. The leave-one-out sensitive analysis plot for publication bias of overall survival and disease-free survival.

expression in different types of tumors. High L1CAM expression has been found to be associated with poor prognosis in patients with ovarian cancer, neuroendocrine cancer, colorectal cancer, and liver cancer.[9] However, the prognostic value of high L1CAM expression in endometrial cancer remains controversial. Our meta-analysis included all published studies investigating the prognostic value of L1CAM expression in women with endometrial cancer. We found that high L1CAM expression was significantly associated with decreased OS and DFS in patients with endometrial cancer. Subgroup analysis revealed that high L1CAM expression predicted decreased DFS independent of study region (European vs non-European), sample size ($<$ 200 vs $\geq$200), detection method (immunohistochemistry vs others), cut-off value (10% vs others), and FIGO stage (I–III vs I–IV). High L1CAM expression also indicated decreased OS, independent of the detection method, cut-off value, and FIGO stage. However, decreased OS was not observed in the non-European group and in groups with sample size $<$ 200, even if they had high L1CAM expression.

We also explored the relationship between high L1CAM expression and clinicopathological characteristics in patients with endometrial cancer. Results showed that L1CAM overexpression was positively associated with disease grade, myometrial invasion, LVSI, and lymph node status, and negatively associated with endometrioid endometrial cancer. Among the clinicopathological factors, myometrial invasion and LVSI were important histological markers for predicting prognosis of women with endometrial cancer; however, these cannot be determined preoperatively.[16,29] L1CAM, as a molecular marker, offers advantages over traditional markers, as its expression is significantly associated with various factors, and can be easily determined using preoperative biopsy samples. Moreover, the inclusion of lymphadenectomy during surgery for endometrial cancer has been widely evaluated,[30] but recent randomized clinical trials have shown that lymphadenectomy provides no survival benefit and increases the rates of complications in patients without lymph node metastases.[31,32] Our results indicated L1CAM to be a good biomarker for identifying patients with lymphatic metastases, thereby avoiding unnecessary lymphadenectomy.

Significant heterogeneity was observed in the endpoint of OS and DFS in our meta-analysis. Sensitivity analysis suggested that

this heterogeneity was caused by inclusion of the study by Zeimet et al. After omitting this outlier study, heterogeneity across the remaining studies was significantly reduced and could be evaluated using the fixed model. Zeimet et al[20] had evaluated a patient population with FIGO stage I endometrioid endometrial cancer. Better outcomes in the study (HR 15.01, 95% CI 9.28–24.26 for OS and HR 16.33, 95% CI 10.55–25.28 for DFS) indicated L1CAM expression to be the most sensitive prognostic factor in this subgroup of women with endometrial cancer. As L1CAM signaling is initiated during the early stages of endometrioid endometrial cancer development, subgroups with high LICAM levels develop more aggressive diseases, despite having relatively favorable prognoses.[33]

There were some limitations to our meta-analysis. First, follow-up duration, which is an important factor for both OS and DFS analyses, was not included in some of the studies, thereby possibly affecting the results of both OS and DFS. Second, the sample size of our meta-analysis was limited. Although we had identified 160 relevant studies through a preliminary database search, only 17 were eventually included after screening, 9 (5116 patients) for OS analysis and 8 (3970 patients) for DFS analysis. Had the sample size been bigger, the conclusion would have been more persuasive. Third, all the included studies were retrospective, which may have caused selection bias. Additional prospective studies or randomized clinical trials would be required to support our conclusions.[34] Fourth, although we attempted to include the most persuasive evidence of L1CAM expression in the prognosis of endometrial cancer and exclude disturbances by various risk factors, our analysis was not based on individual patient-level data, and we did not assess the equivalent distribution of numerous variables related to baseline characteristics of patients, such as age, race, histological types of malignancies, surgery, and adjuvant treatment, between the high-expression and low-expression groups.[35]

In conclusion, this systematic review demonstrates that high L1CAM expression correlates with poor survival outcomes and adverse clinicopathological parameters in patients with endometrial cancer. Therefore, L1CAM expression could be a potential prognosis predictor for women with endometrial cancer.

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Author contributions

Conceptualization: Min Guo.
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Formal analysis: Min Guo, Han Gong, Dan Nie.
Investigation: Min Guo.
Methodology: Min Guo.
Writing – original draft: Min Guo, Han Gong.
Writing – review & editing: Zhengyu Li.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] Corrado G, Laquintana V, Loria R, et al. Endometrial cancer prognosis correlates with the expression of L1CAM and miR34a biomarkers. J Exp Clin Cancer Res 2018;37:139.
[3] Amant F, Mirza MR, Koskas M, et al. Cancer of the corpus uteri. Int J Gynaecol Obstet 2018;143:37–50.
[4] Geels YP, Pijnenborg JM, van den Berg-van Erp SH, et al. Endometrioid endometrial carcinoma with atrophic endometrium and poor prognosis. Obstet Gynecol 2012;120:1124–31.
[5] Engelsen IB, Akslen LA, Salvesen HB. Biologic markers in endometrial cancer treatment. APMIS 2009;117:693–707.
[6] Soovares P, Pasanen A, Butzow R, et al. L1CAM expression associates with poor outcome in endometrioid, but not in clear cell ovarian carcinoma. Gynecol Oncol 2017;146:615–22.
[7] Versluis M, Plat A, de Bruyn M, et al. L1CAM expression in uterine carcinosarcoma is limited to the epithelial component and may be involved in epithelial-mesenchymal transition. Virchows Archiv 2018;473:591–8.
[8] Klat J, Mladenka A, Dvorackova J, et al. L1CAM as a negative prognostic factor in endometrioid endometrial adenocarcinoma FIGO stage IA-IB. Anticancer Res 2019;39:421–4.
[9] Hua T, Liu S, Xin X, et al. Prognostic significance of L1 cell adhesion molecule in cancer patients: a systematic review and meta-analysis. Oncotarget 2016;7:85196–207.
[10] van der Putten LJ, Visser NC, van de Vijver K, et al. L1CAM expression in endometrial carcinomas: an ENITEC collaboration study. Br J Cancer 2016;115:716–24.
[11] Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015;350:g7647.
[12] Guo XX, Wu HL, Shi HY, et al. The efficacy and safety of olaparib in the treatment of cancers: a meta-analysis of randomized controlled trials. Cancer Manag Res 2018;10:2553–62.
[13] van der Putten LJM, Visser NCM, van de Vijver K, et al. Added value of estrogen receptor, progesterone receptor, and L1 cell adhesion molecule expression to histology-based endometrial carcinoma recurrence prediction models: an ENITEC Collaboration study. Int J Gynecol Cancer 2018;28:514–23.
[14] de Freitas D, Aguiar FN, Anton C, et al. L1 cell adhesion molecule (L1CAM) expression in endometrioid endometrial carcinomas: a possible pre-operative surrogate of lymph vascular space invasion. PLoS One 2018;13:e0209294.
[15] Fadare O, Roma AA, Desouki MM, et al. The significance of L1CAM expression in clear cell carcinoma of the endometrium. Histopathology 2018;72:532–8.
[16] Pasanen A, Loukovaara M, Tuomi T, et al. Preoperative risk stratification of endometrial carcinoma: L1CAM as a biomarker. Int J Gynecol Cancer 2017;27:1318–24.
[17] Tangen IL, Kopperud RK, Visser NC, et al. Expression of L1CAM in curettage or high L1CAM level in preoperative blood samples predicts lymph node metastases and poor outcome in endometrial cancer patients. Br J Cancer 2017;117:840–7.
[18] Bosse T, Nout RA, Stelloo E, et al. L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: pooled PORTEC trial results. Eur J Cancer 2014;50:2602–10.
[19] Geels YP, Pijnenborg JM, Gordon BB, et al. L1CAM expression is related to non-endometrioid histology, and prognostic for poor outcome in endometrioid endometrial carcinoma. Pathol Oncol Res 2016;22:863–8.
[20] Zeimet AG, Reimer D, Huszar M, et al. L1CAM in early-stage type I endometrial cancer: results of a large multicenter evaluation. J Natl Cancer Inst 2013;105:1142–50.
[21] Van Gool IC, Stelloo E, Nout RA, et al. Prognostic significance of L1CAM expression and its association with mutant p53 expression in high-risk endometrial cancer. Mod Pathol 2016;29:174–81.
[22] Smogeli E, Davidson B, Cvancarova M, et al. L1CAM as a prognostic marker in stage I endometrial cancer: a validation study. BMC Cancer 2016;16:596.
[23] Pasanen A, Tuomi T, Isola J, et al. L1 cell adhesion molecule as a predictor of disease-specific survival and patterns of relapse in endometrial cancer. Int J Gynecol Cancer 2016;26:1465–71.
[24] Abdel Azim S, Sprung S, Mutz-Dehbalaie I, et al. L1CAM and HER2 expression in early endometrioid uterine cancer. Int J Gynecol Pathol 2017;36:356–63.
[25] Notaro S, Reimer D, Duggan-Peer M, et al. Evaluating L1CAM expression in human endometrial cancer using qRT-PCR. Oncotarget 2016;7:40221–32.
[26] Dellinger TH, Smith DD, Ouyang C, et al. L1CAM is an independent predictor of poor survival in endometrial cancer: an analysis of The Cancer Genome Atlas (TCGA). Gynecol Oncol 2016;141:336–40.

[27] Kubelt C, Hattermann K, Sebens S, et al. Epithelial-to-mesenchymal transition in paired human primary and recurrent glioblastomas. Int J Oncol 2015;46:2515–25.
[28] Raveh S, Gavert N, Ben-Ze'ev A. L1 cell adhesion molecule (L1CAM) in invasive tumors. Cancer Lett 2009;282:137–45.
[29] Morice P, Leary A, Creutzberg C, et al. Endometrial cancer. Lancet 2016;387:1094–108.
[30] Wright JD, Barrena Medel NI, Sehouli J, et al. Contemporary management of endometrial cancer. Lancet 2012;379:1352–60.
[31] Frost JA, Webster KE, Bryant A, et al. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev 2017;10:Cd007585.
[32] Fossati N, Willemse PM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. Eur Urol 2017;72:84–109.
[33] Pfeifer M, Schirmer U, Geismann C, et al. L1CAM expression in endometrial carcinomas is regulated by usage of two different promoter regions. BMC Mol Biol 2010;11:64.
[34] Nie D, Yang E, Li Z. Pretreatment thrombocytosis predict poor prognosis in patients with endometrial carcinoma: a systematic review and meta-analysis. BMC Cancer 2019;19:73.
[35] Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient-level data. J Clin Oncol 2018;36:1981–90.