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ORIGINAL ARTICLE

Follow-up Study on the Association between LAG-3 and Clinicopathological Features/Prognosis in Ovarian Cancer Patients

Li Zuo [1], Yue Tan [1], Qiao-Ling Xu [1], Xiao-Li Li [1], Dong-Bing Zhang [2]

[1] *Department of Oncology, Minhang Branch of Fudan University Shanghai Cancer Center, Shanghai City, China*
[2] *Department of Oncology Surgery, Minhang Branch of Fudan University Shanghai Cancer Center, Shanghai City, China*

ABSTRACT

Background: **Ovarian cancer (OC) is a highly lethal gynecologic malignancy lacking reliable prognostic biomarkers. This study investigated the association between serum lymphocyte-activation gene 3 (LAG-3), a novel immune checkpoint molecule, and clinicopathological features/prognosis in OC patients.**
Methods: **Serum LAG-3 levels were retrospectively analyzed in 226 OC patients. The optimal cutoff value for mortality prediction (2.10 ng/mL) was determined by receiver operating characteristic curve analysis. Patients were stratified into high (≥ 2.10 ng/mL) and low (< 2.10 ng/mL) LAG-3 groups. Survival differences were assessed using Kaplan-Meier analysis with log-rank test. Univariate and multivariate Cox regression identified independent prognostic factors, and a nomogram was constructed.**
Results: **Patients with high LAG-3 had significantly shorter overall survival (OS; log-rank $p < 0.01$). Multivariate analysis confirmed LAG-3 (hazard ratio [HR] = 1.48, $p = 0.01$), tumor size (HR = 1.37, $p < 0.01$), and International Federation of Gynecology and Obstetrics (FIGO) stage (HR = 3.09, $p < 0.01$) as independent prognostic factors. The nomogram predicted 1-, 2-, and 3-year OS with areas under the curve of 0.76, 0.76, and 0.79, demonstrating good differentiating ability.**
Conclusions: **Elevated serum LAG-3 correlates with poor OC prognosis and serves as an independent biomarker. The LAG-3-based nomogram integrating tumor size and FIGO stage provides clinical utility for risk stratification and immunotherapy guidance.**
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Correspondence:
Dong-Bing Zhang
Department of Oncology Surgery
Minhang Branch of
Fudan University Shanghai Cancer Center
No. 106 Ruili Road, Minhang District
Shanghai City, 200240
China
Email: DR.zhangdb@outlook.com

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KEYWORDS

LAG-3, ovarian cancer, poor prognosis, immune checkpoint, nomogram

INTRODUCTION

Ovarian cancer (OC) is the leading cause of gynecological cancer mortality worldwide, with over 70% of cases diagnosed at advanced stages (III or IV) [1]. Early symptoms are nonspecific and often mimic urogenital, gastrointestinal, or gynecological disorders. Current treatments primarily involve tumor resection, radiotherapy, and chemotherapy, but the absence of targeted therapies leads to drug resistance and severe side effects [2]. The 5-year relative survival rate remains at 49.7% (2012 - 2018 data) [3], and reliable prognostic biomark-

ers are still lacking. There is an urgent need to identify biomarkers for prognosis prediction and develop practical models to guide personalized treatment strategies and improve outcomes.

In the tumor microenvironment (TME), cluster of differentiation 8 positive (CD8+) T-cell infiltration correlates with survival in OC patients [4,5]. Although CD8+ T cells are traditionally associated with favorable prognosis, their effector functions are often suppressed by inhibitory immune checkpoints [6]. Lymphocyte-activation gene 3 (LAG-3), a key co-inhibitory receptor, has emerged as a novel immune checkpoint [7]. Recently, LAG-3 has gained attention due to its frequent expression on tumor-infiltrating lymphocytes (TILs) in OC [8], making it a promising immunotherapeutic target. LAG-3 is expressed on activated CD4+ and CD8+ T cells, negatively regulating T-cell expansion by inhibiting T-cell receptor (TCR)-induced calcium flux and modulating memory T-cell pools [9]. Studies suggest that LAG-3 critically impairs the effector function of programmed cell death protein 1 (PD-1) + CD8+ T cells in ovarian tumors [10]. In high-grade serous ovarian carcinoma (HGSOC), which shows poor response to current immunotherapies, elevated circulating LAG-3 levels correlate with clinical outcomes, suggesting its potential as a noninvasive prognostic marker [11]. Additionally, LAG-3 overexpression in ovarian clear cell carcinoma is associated with reduced overall and progression-free survival [12]. These findings collectively implicate LAG-3 in OC progression, though its impact on overall survival (OS) remains controversial.

This study systematically analyzed clinical data to elucidate the relationship between serum LAG-3 levels, clinicopathological features, and prognosis in OC patients. The results may identify LAG-3 as a novel biomarker for immunotherapy and provide a theoretical basis for designing LAG-3-targeted clinical trials.

MATERIALS AND METHODS

Study subjects

A retrospective cohort of 226 OC patients treated between January 2022 and February 2024 was enrolled. Inclusion criteria were as follows: 1) Patients with histopathologically confirmed OC (via biopsy or postoperative examination); 2) patients meeting the diagnostic criteria of the Guidelines for Laparoscopic Diagnosis and Treatment of Ovarian Cancer (2023 Edition); 3) patients undergoing primary surgical resection without prior radiotherapy, chemotherapy, or hormonal therapy; 4) patients with normal comprehension and completed follow-up; 5) patients classified as International Federation of Gynecology and Obstetrics (FIGO) stages I - IV; and 6) patients with primary OC and no history of OC-related surgery, chemotherapy, or radiotherapy. Exclusion criteria were the following: 1) Patients with metastatic tumors to the ovary or concurrent malignancies in other organs; 2) patients with severe infectious diseases or immune dysfunction; 3) patients with severe cardiopulmonary, hepatic, or renal disorders; 4) patients who were pregnant or lactating; and 5) patients with incomplete clinical or follow-up data. This study was approved by the Medical Ethics Committee of Minhang Branch of Fudan University Shanghai Cancer Center, and written informed consent was obtained from all patients.

All patients were diagnosed via radiological imaging (computed tomography, positron emission tomography, magnetic resonance imaging, or combined modalities), independently verified by two gynecologic oncologists.

Methods

General data and biochemical parameter analysis

Demographic data, including age, body mass index (BMI), menopausal status, and comorbidities (e.g., hypertension, diabetes), were collected. Clinicopathological characteristics of OC patients, including menopausal status, histological type, and FIGO stage, were recorded.

Fasting venous blood (5 mL) was drawn from all patients at admission and centrifuged (3,500 rpm, 10 minutes) to isolate serum. Serum albumin (ALB) was measured using a fully automated chemiluminescence immunoanalyzer (Roche e601 and Autolumi APIUS2000). CA-125 levels were quantified by electrochemiluminescence immunoassay. Serum creatinine was analyzed using a BS-800 automatic biochemical analyzer (Mindray Bio-Medical Electronics, Shenzhen, China).

LAG-3 detection by enzyme-linked immunosorbent assay (ELISA)

Blood samples collected at enrollment were placed in serum separation tubes and maintained at room temperature for 2 hours or at 4℃ overnight, followed by centrifugation at 1,000 x g for 20 minutes to separate the supernatant. The supernatant was aliquoted into Eppendorf tubes and stored at -20℃ with precautions taken to avoid repeated freeze-thaw cycles. The ELISA procedure involved sequential loading of test reagents into coated microwells, incubation in a humidified chamber at 37℃ for 60 minutes. After six washes, TMB substrate was added to produce a blue color, which turned yellow after acidification. The optical density at 450 nm was measured and showed a positive correlation with LAG-3 concentration.

Follow-up protocol and outcome assessment

All OC patients received standardized postoperative treatment (chemoradiotherapy or targeted therapy) based on pathological type, clinical stage, and physical condition. Follow-up was conducted via telephone consultation, outpatient visits, and hospital readmission, with quarterly evaluations for the first 2 years and semi-annual evaluations thereafter. Patients were considered lost to follow-up after 3 consecutive failed contact attempts (7 excluded cases). Among 226 patients, follow-up duration ranged from 1 to 3 years, with data cen-

sored on January 31, 2025.
Recurrence was defined as radiologically or clinically confirmed tumor progression (new lesions/size increase with symptoms), verified by ≥ 1 criterion: 1) clinical manifestations of progression, 2) CA-125 elevation ≥ 2 x upper normal limit, or 3) RECIST v1.1-defined radiological evidence. OS was calculated from surgery to death from any cause.

Statistical analysis
Statistical analyses were performed using Statistical Package for the Social Sciences 26.0. Quantitative data were assessed for normality with the Shapiro-Wilk test and homogeneity of variance with Levene's test. Normally distributed variables were expressed as mean ± standard deviation and compared using Student's *t*-tests, while non-normally distributed data were presented as median (interquartile range, IQR) and analyzed with the Wilcoxon rank-sum test. Categorical variables were reported as numbers (percentages) and compared by χ^2 tests. Univariate analysis identified statistically significant variables ($p < 0.05$), which were subsequently included in multivariate Cox regression to determine independent risk factors ($p < 0.05$), with hazard ratios (HRs) calculated. Kaplan-Meier survival curves and log-rank tests evaluated the association between LAG-3 expression and prognosis. The multivariate Cox regression adjusted for potential confounders, and forest plots were generated using GraphPad Prism 10.0.2 (Graph Pad Software, USA). A nomogram prediction model was constructed using R 4.2.1. Individual variable scores were summed to obtain a total score, from which the estimated probability of OS was derived by projecting a vertical line. Predictive performance was evaluated by receiver operating characteristic (ROC) curve analysis, yielding the area under the curve (AUC), 95% confidence intervals (CI), sensitivity, specificity, and the optimal cutoff value for LAG-3. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Determination of LAG-3 cutoff value for prognostic stratification in OC
The cohort of 226 patients was stratified by overall survival (OS) outcomes into survivors (n = 160) and non-survivors (n = 66). ROC curve analysis established 2.10 ng/mL as the optimal serum LAG-3 cutoff for mortality prediction (Figure 1, Table 1), demonstrating 87.88% sensitivity and 57.50% specificity, with an AUC of 0.77 (95% CI: 0.71 - 0.83; $p < 0.001$). Comparative analysis revealed significantly higher LAG-3 levels in non-survivors compared to survivors (Figure 2).

Prognostic impact of LAG-3 in OC patients
Patients were stratified into two groups based on the predefined LAG-3 cutoff: LAG-3 < 2.10 ng/mL (n = 100) and LAG-3 ≥ 2.10 ng/mL (n = 126). The mean follow-up duration was 19.80 months (range: 1 - 3 years), during which 8 endpoint events occurred in the LAG-3 < 2.10 group and 58 in the LAG-3 ≥ 2.10 group. The LAG-3 < 2.10 group exhibited significantly higher OS rates (log-rank $p < 0.01$, Figure 3). Baseline clinicopathological characteristics are summarized in Table 2. No significant differences were observed in age (mean: 46.36 ± 4.45 vs. 45.95 ± 4.25 years for LAG-3 < 2.10 vs. ≤ 1.745 groups, $p > 0.05$), BMI, medical history, or laboratory parameters (ALB, creatinine; all $p > 0.05$). However, the LAG-3 < 2.10 group demonstrated significantly smaller tumor diameters ($p = 0.04$) and lower proportions of serous histologic type ($p = 0.03$) and fewer advanced FIGO stages (III - IV, $p = 0.03$) compared to the LAG-3 ≤ 1.745 group.

Univariate and multivariate cox regression analysis of prognostic factors in OC
Univariate Cox analysis (Table 3) identified elevated LAG-3 (HR = 1.69, $p < 0.01$), larger tumor diameter (HR = 1.69, $p < 0.01$), postmenopausal status (HR = 2.24, $p = 0.01$), serous histologic type (HR = 2.28, $p = 0.01$), and advanced FIGO stage (HR = 4.55, $p < 0.01$) as significant risk factors for poor prognosis. Multivariate Cox regression, adjusted for clinical confounders, confirmed LAG-3 (HR = 1.48, $p = 0.01$), tumor diameter (HR = 1.37, $p < 0.01$), and FIGO stage (HR = 3.09, $p < 0.01$) as independent predictors of OS (Figure 4).

Development and validation of a nomogram prediction model
The nomogram incorporated prognostic factors identified by univariate Cox regression - LAG-3, tumor diameter, histologic type, menopausal status, and FIGO stage - with a final predictive model integrating LAG-3, tumor diameter, and FIGO stage (Figure 5A). The model demonstrated progressively lower 1-, 2-, and 3-year OS rates in patients with elevated LAG-3 levels (≥ 2.10 ng/mL), larger tumor diameters, and advanced FIGO stages (III - IV). Receiver operating characteristic (ROC) curve analysis yielded AUC values of 0.76 (1-year), 0.76 (2-year), and 0.79 (3-year) (Figure 5B), confirming robust discriminative capacity.

DISCUSSION

Systematic analysis of 226 OC patients established 2.10 ng/mL as the prognostic cutoff for serum LAG-3, with elevated levels showing significant correlation with advanced FIGO stage, serous histology, and poor prognosis. These results validate LAG-3 as both a prognostic biomarker and potential immunotherapeutic target, extending prior clinical evidence through long-term survival analysis.
As an emerging immune checkpoint, LAG-3 regulates immune homeostasis through co-expression with PD-1 on TILs, inducing T-cell dysfunction. While its synergistic mechanisms with PD-1 require further elucida-

Table 1. ROC curve analysis of LAG-3 levels.

Indices	Cutoff	Sensitivity (%)	Specificity (%)	p-value
LAG-3 (ng/mL)	2.10	87.88%	57.50%	< 0.001

ROC: curve analysis of LAG-3 in OC patients ($p < 0.05$).
LAG-3: lymphocyte activation gene-3, ROC: receiver operating characteristic.

Table 2. Comparison of baseline clinical characteristics between the two patient groups.

Characteristics	LAG-3 < 2.10 group (n = 100)	LAG-3 ≥ 2.10 group (n = 126)	p-value
Age (years)	46.01 ± 4.16	46.36 ± 4.54	0.55
BMI (kg/m^2)	22.59 ± 0.71	22.50 ± 0.67	0.31
Smoking history	9 (9.00)	11 (8.73)	0.94
Hypertension	5 (5.00)	17 (13.49)	0.03
Diabetes	17 (17.00)	13 (10.32)	0.14
Ascites	14 (14.00)	14 (11.11)	0.51
Tumor diameter	3.00 ± 1.03	3.33 ± 1.32	0.03
Menopausal status			
Premenopausal	94 (94.00)	110 (87.30)	0.09
Postmenopausal	6 (6.00)	16 (12.70)	
Histologic types			
Non-Serous	91 (91.00)	106 (84.13)	0.13
Serous	9 (9.00)	20 (15.87)	
Histologic grade			
Well and moderate differerentiation	90 (90.00)	104 (82.54)	0.11
Poor differerentiation	10 (10.00)	22 (17.46)	
FIGO stage			
I - II	94 (94.00)	101 (80.16)	0.00
III - IV	6 (6.00)	25 (19.84)	
Scr (μmol/L)	45.73 (42.30, 49.24)	45.11 (41.65, 49.08)	0.54
ALB (g/L)	50.04 ± 4.68	50.12 ± 4.26	0.89
Serum CA-125 (U/mL)	221.16 (195.25, 251.59)	220.90 (188.86, 252.33)	0.87

*** Values represent median (interquartile range). $p < 0.05$ was considered statistically significant.**
LAG-3: lymphocyte activation gene-3, BMI: body mass index, FIGO: Federation of International of Gynecologists and Obstetricians, Scr: serum creatinine, ALB: serum albumin, CA-125: carbohydrate antigen 125.

tion, tumor antigen-driven LAG-3 overexpression demonstrates a consistent inverse correlation with patient survival. This aligns with findings by HE et al. in non-adenocarcinoma NSCLC [13] and QUE et al. in soft tissue sarcoma [13], where LAG-3 expression predicted advanced disease and poorer outcomes. This study confirmed higher LAG-3 levels in deceased versus surviving OC patients ($p < 0.05$), with ROC-derived cutoff values (2.10 ng/mL) and Kaplan-Meier analysis (log-rank $p < 0.01$) reinforcing its prognostic value. LAG-3 binds peptide-MHC class II, inhibiting TCR signaling via phosphatase recruitment [14,15]. Its blockade reverses T-cell suppression and reduces Treg activity. Recent evidence suggests LAG-3 disrupts TCR-Lck interaction by lowering synaptic pH, further impairing TCR transduction [16].

Univariate Cox analysis revealed that elevated LAG-3 levels (HR = 1.69) demonstrated comparable risk effects to established prognostic factors including larger tumor diameter, advanced FIGO stage, and serous histologic type. Notably, subgroup analysis showed differential prognostic value of LAG-3 across histological

Table 3. Univariate COX regression analysis of prognostic factors affecting patient survival.

Indices	HR	95% CI	p-value
Age	1.01	0.96 - 1.07	0.60
BMI	1.11	0.78 - 1.58	0.55
Smoking history	1.66	0.82 - 3.37	0.16
Hypertension	1.17	0.56 - 2.45	0.68
Diabetes	1.44	0.74 - 2.84	0.29
Ascites	1.19	0.59 - 2.41	0.62
Tumor diameter	1.70	1.40 - 2.06	< 0.01
Menopausal status	2.21	1.24 - 3.96	0.01
Histologic types	2.27	1.27 - 4.03	0.01
Histologic grade	1.49	0.82 - 2.70	0.19
FIGO stage	4.60	2.80 - 7.56	< 0.01
Scr	1.01	0.97 - 1.05	0.54
ALB	1.02	0.96 - 1.07	0.53
Serum CA-125	1.00	1.00 - 1.01	0.25
LAG-3	1.69	1.32 - 2.16	< 0.01

LAG-3: lymphocyte activation gene-3, BMI: body mass index, FIGO: Federation of International of Gynecologists and Obstetricians, Scr: serum creatinine, ALB: serum albumin, CA-125: carbohydrate antigen 125, HR: hazard ratio, CI: confidence interval. p < 0.05.

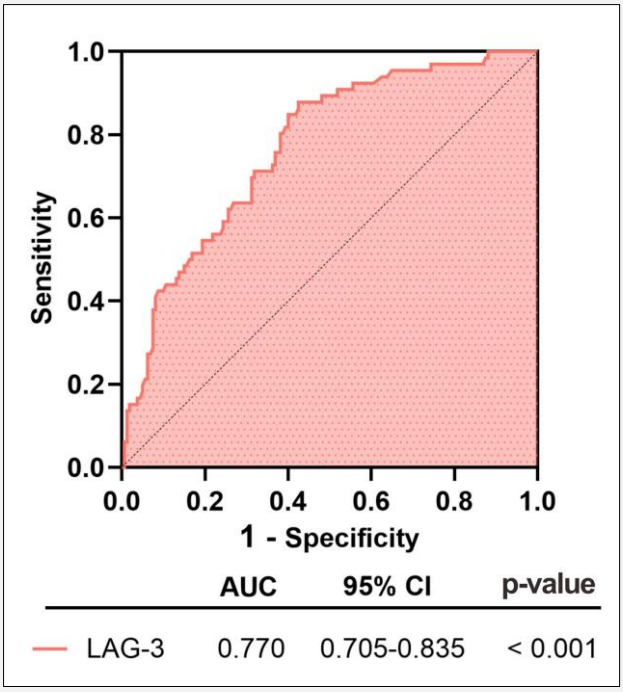

Figure 1. ROC curve analysis of LAG-3 for predicting OC prognosis (p < 0.05).

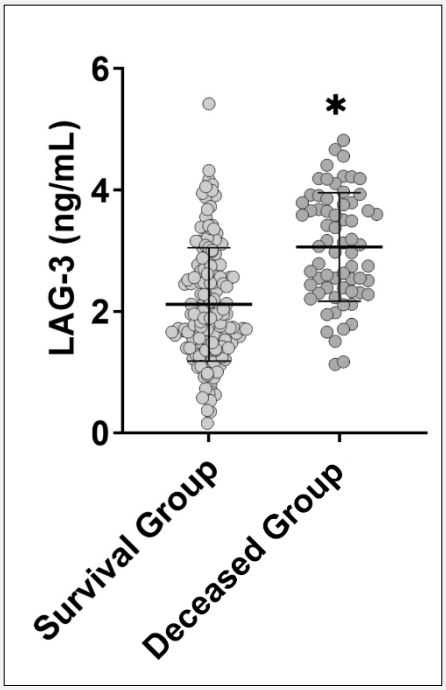

Figure 2. Comparison of serum LAG-3 levels between survival and deceased groups ($p < 0.05$).

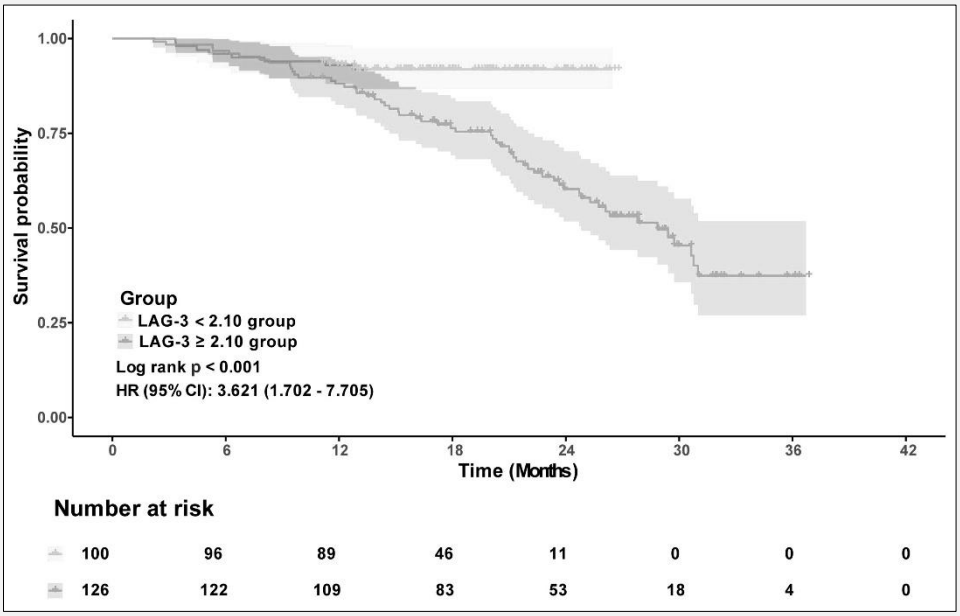

Figure 3. Kaplan-Meier survival analysis of OC patients stratified by LAG-3 expression levels ($p < 0.05$).

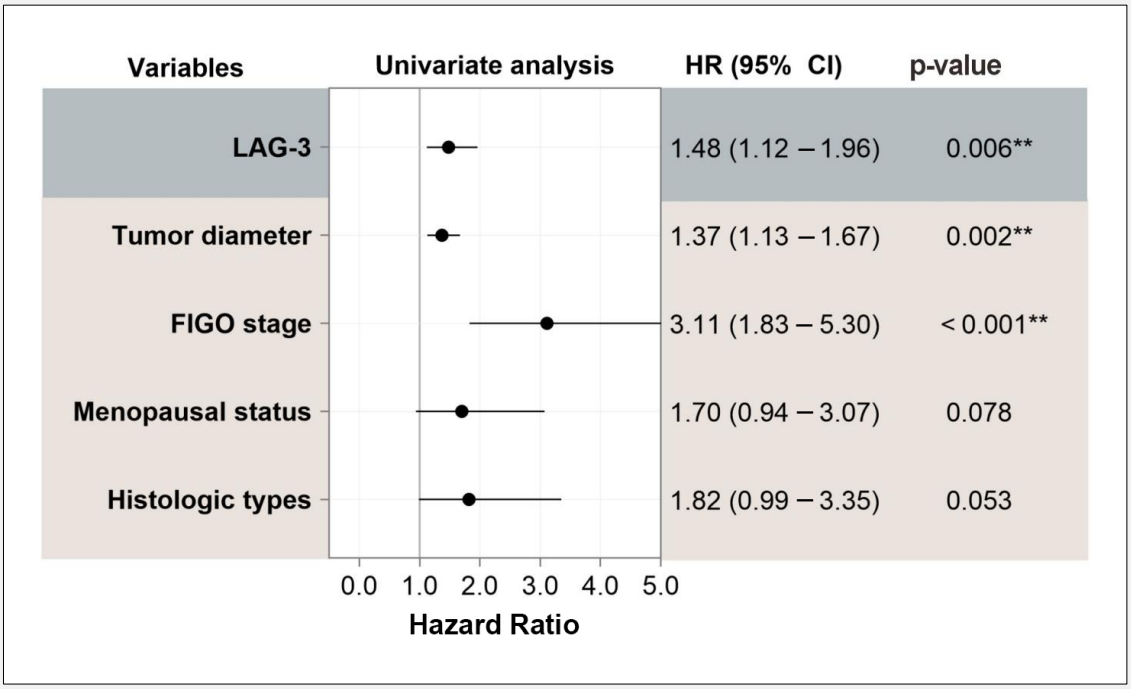

Figure 4. Forest plot of multivariate Cox regression analysis identifying independent prognostic factors for OC survival (p < 0.01).**

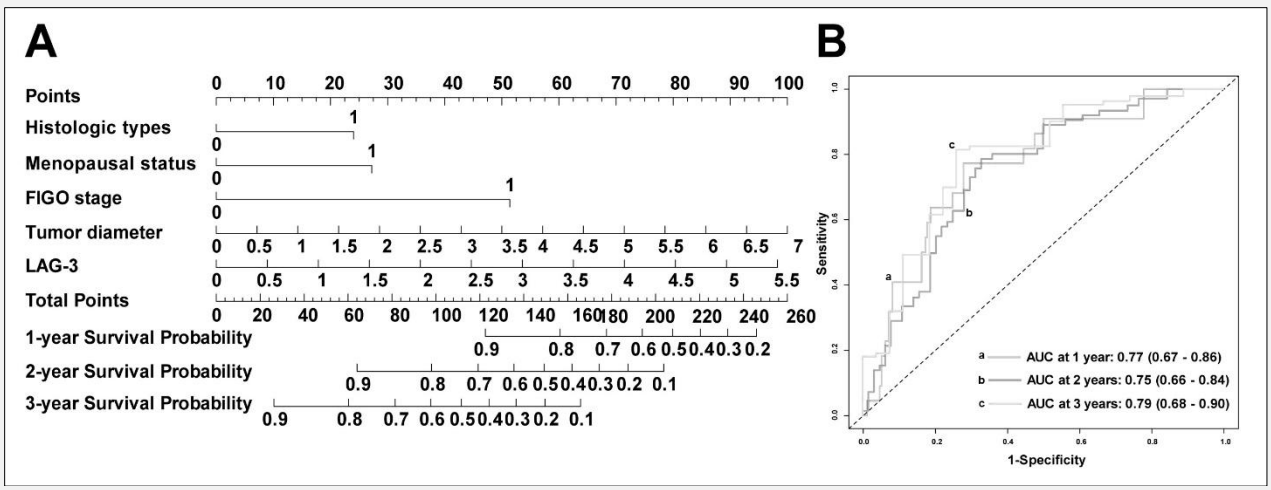

Figure 5. Clinical prognostic prediction model for OC patients (p < 0.05).

A: Nomogram integrating LAG-3, tumor diameter, and FIGO stage for survival prediction, B: ROC curves demonstrating the predictive accuracy of the model for 1-, 2-, and 3-year survival.

types, with a significantly higher prevalence in serous carcinomas ($p = 0.03$, Table 2), potentially attributable to their distinct immune microenvironment. Multivariate Cox regression, after adjusting for confounding factors, identified LAG-3 (HR = 1.48), tumor diameter (HR = 1.37), and FIGO stage (HR = 3.09) as independent predictors of poor prognosis [17]. The constructed nomogram, which integrated these three parameters into a visual scoring system, demonstrated consistent predictive accuracy for 1-, 2-, and 3-year OS (AUC: 0.76, 0.76, and 0.79, respectively).

Current immunotherapeutic research in OC has primarily focused on PD-1, PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Preclinical studies using murine models have demonstrated synergistic inhibition of CD8+ T-cell effector function by LAG-3 and PD-1, suggesting potential therapeutic benefit from combined blockade strategies [3]. Three major classes of LAG-3-targeting agents are under clinical investigation: 1) inhibitory monoclonal antibodies; 2) bispecific antibodies against LAG-3/PD-1(PD-L1) or LAG-3/CTLA-4; and 3) other modalities including soluble LAG-3 fusion proteins, depleting antibodies, and antagonists/agonists [18]. However, clinical trial data remain pending, necessitating further validation of therapeutic efficacy and safety.

This study has several limitations. First, its single-center retrospective design and limited sample size may introduce bias in the LAG-3 cutoff value and patient selection. Second, subjective assessment of clinicopathological staging and potential inaccuracies in follow-up data could affect the results. The retrospective nature and small sample size may also limit the robustness of the conclusions. Additionally, the lack of dynamic LAG-3 monitoring hinders comprehensive evaluation of its fluctuations during treatment. Future multi-center, large-scale prospective studies are needed to validate these findings. Further exploration of LAG-3's role in the TME via multi-omics approaches and clinical trials testing LAG-3-targeted therapies, especially in combination with other treatments, is warranted. Standardization of LAG-3 detection methods is also critical.

In conclusion, the combined prognostic model incorporating LAG-3, tumor diameter, and FIGO stage demonstrates significant predictive value for patient outcomes, potentially serving as a clinical reference for risk stratification in OC management.

Availability of Data and Materials:

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

Ethical Approval Statement:

The present study was approved by the Ethics Committee of Minhang Branch of Fudan University Shanghai Cancer Center, and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki and its later amendments or comparable ethical standards.

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Declaration of Interest:

The authors have no conflicts of interest to declare.

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