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Development and external validation of a multivariable nomogram predicting cancer specific survival in patients with serous ovarian carcinoma using SEER and TCGA cohorts

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Abstract

Purpose

Serous ovarian carcinoma is the most lethal gynecologic malignancy. Existing prognostic nomograms frequently lack independent external molecular validation. The present study aimed to develop and externally validate a parsimonious five-variable Cox nomogram predicting cancer-specific survival (CSS) in serous ovarian carcinoma using national population-based registries.

Methods

Patients diagnosed with primary serous ovarian carcinoma (2000–2022) were retrieved from the SEER database and allocated (7:3 ratio) to training (n = 34,402) and internal validation (n = 14,744) cohorts. The Cancer Genome Atlas Ovarian Serous Cystadenocarcinoma (TCGA-OV, n = 583) cohort served as an independent external validation set. Predictors were selected via ten-fold cross-validated LASSO-Cox regression. Discrimination, calibration, decision curve analysis (DCA), and Kaplan-Meier risk stratification were appraised across all cohorts.

Results

Five routine clinical variables were retained: age group, race, laterality, histologic grade, and summary stage. Distant stage (HR = 6.45, 95% CI: 5.62–7.42) and age ≥ 80 years (HR = 3.17, 95% CI: 2.99–3.35) were the strongest mortality determinants. The nomogram yielded a C-index of 0.6700 in the training cohort, 0.6690 in the internal validation cohort, and 0.6081 in the external TCGA-OV cohort. Five-year calibration curves demonstrated close agreement between predicted and observed survival. DCA verified net clinical benefit across 0.05–0.45 threshold probabilities, and risk stratification significantly segregated patients into high- and low-risk subgroups across all cohorts (all log-rank $P < 0.001$).

Conclusion

A practical five-variable Cox nomogram was established and externally validated to accurately estimate 1-, 3-, and 5-year CSS in serous ovarian carcinoma, providing a standardized tool for individualized post-treatment surveillance.

Clinical Highlights

- This study develops and externally validates a simple 5-variable nomogram based on routinely documented clinicopathologic features, providing reliable 1-, 3-, and 5-year cancer-specific survival predictions for serous ovarian carcinoma without requiring costly molecular testing.

- The model facilitates personalized risk stratification across distinct healthcare settings, assisting gynecologists in identifying high-risk patients who warrant closer surveillance and individualized therapeutic counseling.

Introduction

Ovarian cancer remains the most lethal gynecologic malignancy worldwide, characterized by high recurrence rates and dismal long-term clinical outcomes [1]. Epithelial ovarian carcinoma encompasses several biologically and clinically distinct histologic subtypes, among which serous ovarian carcinoma accounts for approximately 70% of all cases and represents the predominant cause of ovarian cancer mortality [2]. Due to the insidious, asymptomatic nature of early-stage disease and the absence of effective population-level screening modalities, over 70% of women with serous ovarian carcinoma present with regional invasion or extensive distant intra-abdominal dissemination at the time of initial diagnosis [3]. High-grade serous tumors are characterized by rapid cellular proliferation and early peritoneal seeding [4]. Standard front-line management consists of comprehensive cytoreductive surgery accompanied by platinum- and taxane-based systemic chemotherapy [5]. However, even among individuals presenting with identical clinical stages who undergo standard-of-care cytoreduction, substantial heterogeneity in post-therapeutic survival outcomes persists, highlighting the inadequacy of conventional staging systems in capturing individualized prognostic risk [6].

The International Federation of Gynecology and Obstetrics (FIGO) staging classification and the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) framework represent the standard framework for clinical decision-making and trial design [7]. Nonetheless, these anatomical classification systems fail to integrate essential host characteristics and tumor-intrinsic biological parameters, such as patient chronological age, racial disparities, tumor laterality, and differentiation grade [8]. Nomograms, which are pictorial mathematical models calculating continuous individualized probability estimators via multivariable regression, have gained widespread clinical acceptance across oncology disciplines [9]. By synthesizing diverse independent prognostic indicators onto a unified numerical scale, nomograms provide tailored survival estimations that consistently outperform traditional single-variable staging systems [10].

Despite the growing literature on prognostic models for ovarian cancer, several critical methodological gaps remain unresolved. Several authors have proposed nomograms for overall and disease-specific survival in ovarian cancer subsets [11]. However, previous models frequently incorporated non-standardized socioeconomic metrics or hospital-specific laboratory parameters that cannot be uniformly collected across independent treatment centers or community medical practices [12]. In addition, the majority of existing nomograms were derived from single-center cohorts or evaluated solely through internal split-sample validation without testing in an independent population. To the best of our knowledge, no large-scale study has developed a parsimonious nomogram specifically targeting serous ovarian carcinoma and rigorously validated its discriminative capacity on a completely independent

molecular cohort, such as The Cancer Genome Atlas Ovarian Serous Cystadenocarcinoma (TCGA-OV) project.

To bridge these clinical and methodological gaps, the present study used the national population-based Surveillance, Epidemiology, and End Results (SEER) registry to assemble a multi-decade cohort of 49,146 patients with serous ovarian carcinoma. Least absolute shrinkage and selection operator (LASSO) penalized regression was applied to identify five accessible clinicopathologic predictors and construct a Cox proportional hazards nomogram estimating 1-, 3-, and 5-year cancer-specific survival (CSS). The transportability and discrimination of the model were validated not only in an internal split-sample cohort of 14,744 patients, but also in an independent external cohort of 583 patients from TCGA-OV. This study provides a standardized, readily applicable tool for personalized risk assessment and follow-up guidance in clinical practice.

Methods

Study design and data sources

The present retrospective investigation was designed in compliance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement. Primary population-level training and internal validation data were obtained from the National Cancer Institute's SEER registry (covering 18 population-based registries from 2000 through 2022) [13]. The SEER program routinely collects demographic, clinicopathologic, first-course therapeutic, and vital status data, covering approximately 28% of the United States population. Independent external validation data were retrieved from TCGA-OV public repository through the Genomic Data Commons (GDC) portal, which contains comprehensive clinical and follow-up information for primary serous ovarian cystadenocarcinoma. Because both SEER and TCGA databases contain fully de-identified, publicly accessible health data, this study was deemed exempt from institutional review board oversight by our institution, and individual patient informed consent was waived.

Variable selection and data harmonization

Cases with histologically confirmed primary serous ovarian carcinoma were identified using International Classification of Diseases for Oncology, Third Edition (ICD-O-3) morphology codes: 8441/3 (serous cystadenocarcinoma, NOS), 8442/3 (serous cystadenoma, borderline malignancy), 8460/3 (papillary serous cystadenocarcinoma), 8461/3 (serous surface papillary carcinoma), and 8462/3 (serous papillary cystic neoplasm of borderline malignancy). The cohort selection criteria are illustrated in Fig. 1. Among 126,106 ovarian cancer entries registered between 2000 and 2022, 52,744 patients had confirmed serous histology. Patients diagnosed solely through death certificate or autopsy (n = 26), those with missing or zero survival months (n = 1,806), and those with missing marital status (n = 1,766) were excluded, resulting in a definitive analytic cohort of 49,146 patients.

To ensure seamless external application, clinical variables were systematically mapped and harmonized between the SEER and TCGA-OV registries: 1. *Age at diagnosis*: categorized into five ordinal strata (< 50, 50–59, 60–69, 70–79, and ≥ 80 years). 2. *Race*: categorized as White, Black, and Other (including Asian, Pacific Islander, and American Indian/Alaska Native). 3. *Laterality*: classified as Unilateral, Bilateral, or Unknown. 4. *Histologic differentiation grade*: classified as G1 (well-differentiated), G2 (moderately differentiated), G3 (poorly differentiated), G4 (undifferentiated), and Unknown. 5. *Summary stage*: categorized into Localized (tumor confined strictly to the ovaries), Regional (direct extension or regional lymph node spread), Distant (extra-abdominal metastases or peritoneal implants beyond pelvis), and Unknown. In TCGA-OV, FIGO stage designations were harmonized to SEER summary stages: FIGO Stage IA–IC was mapped to Localized, Stage IIA–IIC to Regional, and Stage IIIA–IV to Distant.

Patients with unrecorded or unstaged categories were preserved as distinct “Unknown” categories rather than being discarded, thereby preventing potential selection bias and reflecting real-world clinical decision-making.

Study endpoints and definitions

The primary study endpoint was cancer-specific survival (CSS), defined as the time interval in months from initial diagnosis until death attributed specifically to serous ovarian carcinoma. In SEER, cause-specific mortality was determined using the SEER cause-specific death classification variable; deaths due to other causes or individuals alive at last follow-up were censored. In the TCGA-OV cohort, survival was calculated from diagnosis to death or last clinical contact, converted from days to months by dividing by 30.5. The secondary endpoint was overall survival (OS), defined as time to death from any cause.

Nomogram development and model construction

Eligible SEER patients (n = 49,146) were randomly allocated at a 7:3 ratio using a fixed random seed (2026) to generate a training cohort (n = 34,402) for model derivation and an internal validation cohort (n = 14,744) for model verification. Feature selection was conducted within the training cohort using the least absolute shrinkage and selection operator (LASSO) method with the Cox proportional hazards regression model [14]. Ten-fold cross-validation with the concordance index as the objective metric was implemented to determine the optimal penalty parameter (lambda). To balance model parsimony and predictive capacity, the lambda.1se rule (the most regularized model within one standard error of the minimum cross-validation error) was selected as the penalty threshold.

The clinicopathologic variables with non-zero coefficients at lambda.1se were subsequently incorporated into a multivariable Cox proportional hazards regression model. Proportional hazards assumptions were verified using Schoenfeld residual tests. Estimated regression beta coefficients were

transformed to calculate the relative contribution of each variable, establishing a prognostic nomogram predicting 1-, 3-, and 5-year CSS probabilities via the rms and nomogramEx packages in R.

Model validation, discrimination, and clinical utility

Model validation was carried out in three distinct patient populations: the training cohort (n = 34,402), the internal validation cohort (n = 14,744), and the external validation cohort (TCGA-OV, n = 583). Discriminative capacity was measured using Harrell's concordance index (C-index) and its 95% confidence interval derived from 100 bootstrap resamplings [15]. Calibration was assessed by plotting the nomogram-predicted 5-year CSS probability against the observed Kaplan-Meier survival proportion across sample-weighted quintiles.

Clinical net benefit and decision utility were appraised through decision curve analysis (DCA), which quantifies the net benefit across a continuum of clinical threshold probabilities compared with default "treat-all" or "treat-none" strategies [16]. Individual risk scores were computed for every patient by summing the points assigned to their prognostic variables in the nomogram. Patients within each cohort were dichotomized into low-risk and high-risk groups according to the median risk score of the training cohort. Kaplan-Meier survival curves were generated and compared using the two-sided log-rank test [17]. Survival outcomes were monitored over extended follow-up to evaluate durable risk discrimination [18]. Multivariable regression and nomogram formatting were aligned with established clinical modeling standards [19]. Stratified subgroup analyses across age (< 65 vs. ≥65 years) and stage (early vs. late) along with interaction terms were conducted to assess the stability of the model across clinical subsets.

All statistical analyses were executed using R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Two-sided P values < 0.05 were considered statistically significant.

Results

Baseline characteristics of the study cohorts

A total of 49,146 eligible serous ovarian carcinoma patients from the SEER database and 583 patients from the TCGA-OV cohort were included in the final analysis (Fig. 1). The baseline demographic and clinical features across the training (n = 34,402), internal validation (n = 14,744), and external validation (n = 583) cohorts are summarized in Table 1.

In the SEER training cohort, the majority of patients were aged 60–69 years (28.9%, n = 9,930), followed by 50–59 years (23.4%, n = 8,059) and 70–79 years (22.5%, n = 7,750). White patients constituted 84.5% (n = 29,057), Black patients comprised 7.1% (n = 2,427), and other racial backgrounds represented 8.5% (n = 2,918). Bilateral ovarian tumor involvement was present in 48.8% (n = 16,789) and unilateral disease in 40.6% (n = 13,964). With respect to histologic differentiation, G3 and G4 tumors accounted for 31.9% (n = 10,981) and 18.1% (n = 6,213), respectively, while 38.6% (n = 13,277) had unclassified grade.

Advanced disease was predominant, with 65.5% (n = 22,526) presenting with distant metastases and 13.2% (n = 4,526) with regional disease.

The distribution of clinicopathologic variables between the SEER training and internal validation cohorts demonstrated excellent balance across all categories (Table 1). In contrast, the external TCGA-OV cohort displayed an enrichment for high-grade and advanced-stage disease: 84.8% of patients (n = 492) presented with G3 differentiation and 91.4% (n = 533) presented with distant stage disease, reflecting the tertiary referral pattern and molecular sampling criteria of the TCGA research network.

Table 1
Baseline clinicopathologic characteristics of patients across training, internal validation, and external validation cohorts.

Variable	Category	Training (SEER, n = 34,402)	Internal validation (SEER, n = 14,744)	External validation (TCGA-OV, n = 583)
Age, years	< 50	5,153 (15.0%)	2,218 (15.0%)	117 (20.1%)
	50–59	8,059 (23.4%)	3,452 (23.4%)	187 (32.1%)
	60–69	9,930 (28.9%)	4,222 (28.6%)	142 (24.4%)
	70–79	7,750 (22.5%)	3,417 (23.2%)	111 (19.0%)
	≥ 80	3,510 (10.2%)	1,435 (9.7%)	26 (4.5%)
Race	White	29,057 (84.5%)	12,432 (84.3%)	498 (85.4%)
	Black	2,427 (7.1%)	1,110 (7.5%)	34 (5.8%)
	Other	2,918 (8.5%)	1,202 (8.2%)	51 (8.7%)
Hispanic ethnicity	No	29,961 (87.1%)	12,903 (87.5%)	—
	Yes	4,441 (12.9%)	1,841 (12.5%)	—
Marital status	Married	19,042 (55.4%)	8,080 (54.8%)	—
	Single	5,774 (16.8%)	2,409 (16.3%)	—
	Divorced	3,787 (11.0%)	1,683 (11.4%)	—
	Separated	333 (1.0%)	140 (0.9%)	—
	Widowed	5,466 (15.9%)	2,432 (16.5%)	—
Laterality	Unilateral	13,964 (40.6%)	6,015 (40.8%)	152 (26.1%)
	Bilateral	16,789 (48.8%)	7,125 (48.3%)	400 (68.6%)
	Unknown	3,649 (10.6%)	1,604 (10.9%)	31 (5.3%)
Histologic grade	G1	946 (2.7%)	420 (2.8%)	6 (1.0%)
	G2	2,985 (8.7%)	1,225 (8.3%)	69 (11.9%)
	G3	10,981 (31.9%)	4,618 (31.3%)	492 (84.8%)
	G4	6,213 (18.1%)	2,693 (18.3%)	1 (0.2%)
	Unknown	13,277 (38.6%)	5,788 (39.3%)	15 (2.6%)

Note: Categorical variables are presented as counts and percentages [n (%)]. Localized, Regional, and Distant stages reflect harmonized SEER summary and FIGO/AJCC staging systems. —: Not available in the TCGA-OV dataset.

Variable	Category	Training (SEER, n = 34,402)	Internal validation (SEER, n = 14,744)	External validation (TCGA-OV, n = 583)
Summary stage	Localized	1,540 (4.5%)	691 (4.7%)	16 (2.7%)
	Regional	4,526 (13.2%)	1,849 (12.5%)	30 (5.1%)
	Distant	22,526 (65.5%)	9,704 (65.8%)	533 (91.4%)
	Unknown	5,810 (16.9%)	2,500 (17.0%)	4 (0.7%)

Note: Categorical variables are presented as counts and percentages [n (%)]. Localized, Regional, and Distant stages reflect harmonized SEER summary and FIGO/AJCC staging systems. —: Not available in the TCGA-OV dataset.

Identification of independent prognostic factors via Cox-LASSO regression

To eliminate multi-collinearity and identify the most robust prognostic determinants, all harmonized clinicopathologic features were subjected to LASSO penalized Cox regression in the training cohort (**Supplementary Fig. S1a**). Ten-fold cross-validation confirmed that all five candidate variables—age group, race, laterality, histologic grade, and summary stage—retained non-zero regression coefficients at the optimal regularization threshold (lambda.1se = 0.0038, **Supplementary Fig. S1b**).

The multivariable Cox proportional hazards regression model was fitted with these five variables (**Table 2** and **Supplementary Fig. S2**). All five factors demonstrated significant independent associations with cancer-specific survival (all $P < 0.001$). Distant stage was identified as the single strongest negative prognostic factor (HR = 6.45, 95% CI: 5.62–7.42, $P < 0.001$ vs. Localized stage), followed by Regional stage (HR = 2.47, 95% CI: 2.13–2.86, $P < 0.001$) and Unknown stage (HR = 5.81, 95% CI: 5.04–6.69, $P < 0.001$). Advanced age was strongly associated with elevated mortality: compared to patients aged < 50 years, hazard ratios escalated progressively from 1.27 (95% CI: 1.21–1.34) for ages 50–59 years, 1.51 (95% CI: 1.44–1.59) for ages 60–69 years, 1.98 (95% CI: 1.88–2.08) for ages 70–79 years, to 3.17 (95% CI: 2.99–3.35) for those aged ≥ 80 years (all $P < 0.001$).

With regard to histologic grade, poorly differentiated and undifferentiated tumors conferred a more than twofold increased risk of cancer-specific death relative to well-differentiated (G1) lesions (G2: HR = 1.95, 95% CI: 1.73–2.19; G3: HR = 2.26, 95% CI: 2.03–2.52; G4: HR = 2.16, 95% CI: 1.94–2.42; Unknown: HR = 2.23, 95% CI: 2.00–2.50; all $P < 0.001$). Bilateral ovarian tumors exhibited worse survival compared to unilateral disease (HR = 1.24, 95% CI: 1.20–1.28, $P < 0.001$). In addition, racial disparities were observed: Black patients experienced significantly inferior survival compared to White patients (HR = 1.26, 95% CI: 1.20–1.33, $P < 0.001$), whereas other racial groups showed a modestly reduced hazard of death (HR = 0.90, 95% CI: 0.85–0.95, $P < 0.001$).

Table 2 Multivariable Cox proportional hazards regression analysis of prognostic factors for cancer-specific survival in the training cohort (n = 34,402).

Variable	Category	Hazard Ratio (95% CI); P-value
Age, years	<50	1.00 (Reference)
	50–59	1.27 (1.21–1.34); P < 0.001
	60–69	1.51 (1.44–1.59); P < 0.001
	70–79	1.98 (1.88–2.08); P < 0.001
	≥80	3.17 (2.99–3.35); P < 0.001
Race	White	1.00 (Reference)
	Black	1.26 (1.20–1.33); P < 0.001
	Other	0.90 (0.85–0.95); P < 0.001
Laterality	Unilateral	1.00 (Reference)
	Bilateral	1.24 (1.20–1.28); P < 0.001
	Unknown	1.95 (1.86–2.04); P < 0.001
Histologic grade	G1	1.00 (Reference)
	G2	1.95 (1.73–2.19); P < 0.001
	G3	2.26 (2.03–2.52); P < 0.001
	G4	2.16 (1.94–2.42); P < 0.001
	Unknown	2.23 (2.00–2.50); P < 0.001
Summary stage	Localized	1.00 (Reference)
	Regional	2.47 (2.13–2.86); P < 0.001
	Distant	6.45 (5.62–7.42); P < 0.001
	Unknown	5.81 (5.04–6.69); P < 0.001

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, standard error. Reference categories: Age <50 years; Race White; Laterality Unilateral; Histologic grade G1; Summary stage Localized.

Construction and visualization of the prognostic nomogram

The five independent prognostic factors were integrated to construct the prognostic nomogram predicting 1-, 3-, and 5-year CSS in patients with serous ovarian carcinoma (**Fig. 2**). Each level of the prognostic variables was mapped to a point score on the top scale (0 to 100 points). Summary stage

demonstrated the widest point range (Distant stage assigned 100 points), followed by age group (age ≥80 assigned 63 points), histologic grade (G3 assigned 44 points), laterality (Bilateral assigned 13 points), and race (Black assigned 14 points). The sum of the points across the five variables was projected onto the bottom axes to estimate individualized 1-, 3-, and 5-year survival probabilities.

Internal and external validation of model calibration and discrimination

The discriminative capacity of the nomogram across the three cohorts is shown in **Supplementary Table S1** and **Supplementary Fig. S3**. The model achieved a C-index of 0.6700 (95% bootstrap CI: 0.664–0.676) in the training cohort and an almost identical C-index of 0.6690 (95% bootstrap CI: 0.660–0.678) in the internal validation cohort. When applied directly to the completely independent TCGA-OV external validation cohort, the nomogram maintained a solid discriminative performance, yielding a C-index of 0.6081 (95% bootstrap CI: 0.564–0.652).

Five-year calibration curves for the nomogram in the training, internal validation, and external validation cohorts are depicted in **Fig. 3a–c**. In both the training and internal validation cohorts, the calibration points closely aligned with the 45-degree ideal reference line across all sample quintiles, indicating excellent agreement between model-predicted probabilities and observed 5-year survival proportions. In the external TCGA-OV cohort, despite the severe clinical shift toward advanced disease, the calibration curve demonstrated satisfactory concordance without marked systematic over- or under-estimation.

Clinical utility and risk-stratification capability across cohorts

Decision curve analysis evaluated the net clinical benefit of the nomogram in the training cohort (**Fig. 4d**). The decision curve for the five-variable nomogram was superior to both the “treat-all” and “treat-none” strategies across the threshold probability range of 0.05 to 0.45, demonstrating strong clinical applicability for guiding post-treatment surveillance and adjuvant management.

Using the median risk score derived from the training cohort (cutoff = 3.13), patients in each cohort were classified into low-risk and high-risk groups. Kaplan-Meier survival curves demonstrated dramatic survival divergence between the two strata (**Fig. 4a–c**). In the training cohort, low-risk patients exhibited substantially superior CSS compared to high-risk patients (5-year CSS: ~55% vs. ~22%, log-rank $P < 0.001$; **Fig. 4a**). A virtually indistinguishable survival separation was verified in the internal validation cohort (log-rank $P < 0.001$; **Fig. 4b**). In the external TCGA-OV validation cohort, the nomogram-defined risk classification successfully stratified patients into distinct prognostic trajectories (log-rank $P < 0.001$; **Fig. 4c**), with the low-risk subgroup maintaining a prolonged median survival compared with the high-risk subgroup.

Subgroup consistency and sensitivity analyses

To evaluate the stability and potential effect modification of the five prognostic factors, stratified Cox-LASSO regression was conducted across four clinical subgroups defined by age (<65 vs. ≥65 years) and summary stage (Early vs. Late; **Supplementary Fig. S4a**). The regression coefficients for stage, histologic grade, and laterality remained consistent across all strata. Formal interaction testing revealed no significant qualitative interaction between stage and age subsets (all P for interaction > 0.05; **Supplementary Fig. S4b**), verifying that the prognostic effect of each variable was stable across diverse clinical presentations.

Discussion

In the present population-based study, a comprehensive yet parsimonious five-variable prognostic nomogram for serous ovarian carcinoma was constructed and externally validated based on 49,146 patients from the SEER registry and 583 patients from the TCGA-OV cohort. To the best of our knowledge, this represents one of the largest studies specifically dedicated to serous ovarian carcinoma that couples a multi-decade national population registry with independent external molecular cohort validation. The nomogram incorporates five universally accessible clinicopathologic variables: chronological age, race, tumor laterality, histologic grade, and summary stage. The model demonstrated robust discrimination (C-index 0.6700 in training, 0.6690 in internal validation, and 0.6081 in external validation), excellent 5-year calibration, clear decision-curve net benefit, and decisive Kaplan-Meier survival stratification across both internal and external cohorts.

Comparing our findings with previous ovarian cancer nomograms underscores the distinct strengths and clinical relevance of our model. In 2022, Huang et al. established a nomogram for high-grade serous ovarian cancer based on 3,788 SEER patients who received cytoreductive surgery and systemic chemotherapy, reporting a C-index of 0.66–0.68 [20]. While their discriminative performance was comparable to ours, their study was restricted to an internal split-sample validation without any independent external cohort, leaving its generalizability untested. Similarly, Chen and Guo developed a SEER-based nomogram for serous ovarian cystadenocarcinoma that also lacked external validation [21]. More recently, Zhao et al. formulated a socioeconomic-clinical nomogram predicting 10-year survival in epithelial ovarian cancer [22]; however, their model incorporated complex socioeconomic variables that vary substantially across national health systems and cannot be readily exported to non-US institutions. Although Zheng et al. incorporated an external validation cohort, their study investigated non-serous epithelial ovarian cancers and evaluated only 56 external patients [23]. The present study overcomes these historical limitations by assembling a cohort more than ten times larger than that of Huang et al., avoiding non-standardized socioeconomic metrics, and confirming predictive stability in an independent external cohort of 583 patients from TCGA-OV.

From a clinical translation perspective, the five-variable nomogram developed in the present study offers direct clinical applicability. Predictive models designed for real-world deployment must balance statistical rigor with clinical feasibility [24]. First, all five variables are routinely recorded at the time of initial diagnosis and surgical staging in every oncology clinic, requiring neither expensive next-generation

sequencing nor centralized laboratory testing. Second, the visual nomogram interface allows clinicians and patients to rapidly calculate a cumulative score and visualize individualized 1-, 3-, and 5-year survival probabilities, transforming abstract multivariable hazard ratios into tangible prognostic estimates. Third, as demonstrated by DCA findings, application of the nomogram provides meaningful net benefit across threshold probabilities of 5% to 45%. This capability can directly assist multidisciplinary tumor boards in identifying high-risk patients who warrant intensified radiographic surveillance, early maintenance therapy considerations, or clinical trial referrals.

The biological and clinical significance of the five predictors identified in our model aligns closely with established oncologic mechanisms. Summary stage emerged as the single most powerful prognostic determinant in our model, with distant dissemination conferring a hazard ratio of 6.45. Metastatic dissemination to peritoneal and distant organ sites introduces marked metabolic and vascular disruption, severely constraining long-term survival [25]. Once extra-pelvic or parenchymal metastasis occurs, complete macroscopic cytoreduction becomes considerably more challenging to achieve, which directly impairs therapeutic responsiveness and long-term disease control.

Patient chronological age was the second most dominant predictor in our model, demonstrating a steep dose-response trajectory where patients aged ≥80 years experienced a more than threefold higher risk of cancer-specific death compared to those aged <50 years. This phenomenon reflects several intersecting biological and clinical factors: age-related immunosenescence, diminished physiological bone marrow and renal reserve, a higher burden of cardiovascular and metabolic comorbidities, and consequently a decreased tolerance to aggressive platinum-based polychemotherapy or radical upper abdominal surgical procedures [26]. Histologic grade G3/G4 also conferred an HR of over 2.1 relative to G1 lesions. High-grade serous carcinomas are biologically distinct from low-grade counterparts, characterized by near-universal *TP53* mutations, extensive copy-number alterations, genomic instability, and defects in homologous recombination DNA repair, which dictate an aggressive initial growth rate and frequent emergence of chemoresistance. Tumor laterality also provided independent prognostic information, with bilateral involvement reflecting increased tumor burden and synchronous multifocality. In addition, the survival disadvantage observed among Black patients corroborates documented racial disparities in ovarian cancer care, likely stemming from systemic inequities in timely access to subspecialty gynecologic oncologists, adherence to NCCN guideline-concordant surgical cytoreduction, and post-recurrence clinical trial enrollment. Independent external validation across multicenter populations remains essential for confirming that these clinical associations retain discriminative utility beyond their training environments [27].

Several limitations of the present study should be acknowledged. First, as a retrospective observational study based on registry data, selection and reporting biases are inherently unavoidable. Observational registry analyses often lack detailed therapeutic exposure variables that may act as residual confounders [28]. Key surgical details, such as the completeness of cytoreduction (R0 vs. R1/R2 residual disease), intraoperative ascites volume, and specific regimens or cycles of adjuvant chemotherapy (e.g., dose-dense paclitaxel, intraperitoneal regimens), were not captured in the SEER registry. Second,

emerging targeted therapeutics, particularly poly(ADP-ribose) polymerase (PARP) inhibitors and bevacizumab maintenance therapies, have profoundly reshaped survival outcomes in homologous recombination-deficient and platinum-sensitive recurrent serous ovarian cancer over the past decade. Combining standard clinical variables with machine learning or molecular markers could further refine future iterations of these risk models [29]. Because SEER and TCGA do not systematically record targeted maintenance therapy exposure, our model reflects baseline survival probabilities that may slightly underestimate outcomes in modern cohorts receiving universal PARP inhibitor maintenance. Third, while external validation in TCGA-OV confirmed significant discriminative ability (C-index 0.6081) and clear risk stratification, the C-index was modestly lower than that achieved in the SEER internal cohorts (0.6690–0.6700). Heterogeneity in patient baseline risk profiles across independent cohorts is known to influence discrimination metrics [30]. In TCGA-OV, 91.4% of patients presented with distant stage disease and 84.8% had grade 3 histology. Because stage and grade demonstrated reduced variance within TCGA-OV, the model's discriminative power was inevitably attenuated, underscoring the necessity of recalibrating prognostic tools when deploying them across specialized tertiary research registries.

In conclusion, although serous ovarian carcinoma remains a therapeutic challenge with substantial prognostic heterogeneity, the present study established and externally validated a clinically intuitive five-variable Cox nomogram that accurately estimates 1-, 3-, and 5-year cancer-specific survival. Grounded in a cohort of 49,146 SEER cases and verified in an independent molecular cohort of 583 TCGA-OV patients, this study carries several notable clinical implications: First, it provides an accessible, standardized evidence-based instrument requiring only routine clinicopathologic parameters, thereby eliminating barriers associated with expensive or specialized profiling. Second, the rigorous external validation in a distinct molecular cohort confirms that the model retains generalizability and risk-stratifying power despite marked shifts in disease severity. Third, the clear risk stratification and decision-curve net benefit offer direct guidance for post-treatment surveillance planning and clinical decision-making. Additional prospective multicenter studies should investigate the integration of molecular markers to further refine individualized risk prediction in serous ovarian carcinoma.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Qin Tan and Yuqi Zhou contributed equally to this work and share first authorship. Author contributions according to journal taxonomy are specified as follows: - **Q Tan**: Protocol/project development, Data analysis, Manuscript writing/editing - **Y Zhou**: Data collection or management, Data analysis, Manuscript writing/editing - **T Han**: Data analysis, Manuscript writing/editing - **Y Wang**: Protocol/project development, Manuscript writing/editing, Other (funding acquisition) - **Z Sun**: Protocol/project development, Manuscript writing/editing, Other (study supervision)

All authors commented on previous versions of the manuscript, and read and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are publicly available in the following de-identified repositories: 1. Surveillance, Epidemiology, and End Results (SEER) program: De-identified population-based records for patients diagnosed with primary serous ovarian carcinoma between 2000 and 2022 were retrieved from the National Cancer Institute (NCI) SEER Research Plus Data (17 Registries, November 2024 submission). Access can be requested through the SEER Data Access portal at https://seer.cancer.gov/data/access.html using SEER*Stat software. 2. The Cancer Genome Atlas (TCGA) repository: Molecular and clinical data for the external validation cohort were obtained from the TCGA Ovarian Serous Cystadenocarcinoma project (Project ID: TCGA-OV; dbGaP study accession: phs000178) hosted on the NCI Genomic Data Commons (GDC) Data Portal at https://portal.gdc.cancer.gov/projects/TCGA-OV and accessible via cBioPortal for Cancer Genomics (Study ID: ov_tcga, https://www.cbioportal.org/study/summary?id=ov_tcga).

All analytical code, data extraction dictionaries, and derived summary tables are available from the corresponding author upon reasonable request.

Ethics approval

This is an observational study using publicly accessible, fully de-identified registry databases (SEER and TCGA). In accordance with national regulations and institutional policies, institutional review board approval was confirmed not to be required.

Consent to participate

Not applicable. Patient informed consent was waived by the database curators due to the retrospective nature and anonymous public availability of the data.

Consent to publish

Not applicable. The manuscript contains no individual personal data, identifying details, or images.

Use of artificial intelligence

The authors declare that no artificial intelligence (AI) or generative AI-assisted technologies were used in the conception, data collection, statistical modeling, analysis, drafting, or critical editing of this manuscript.

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Figures

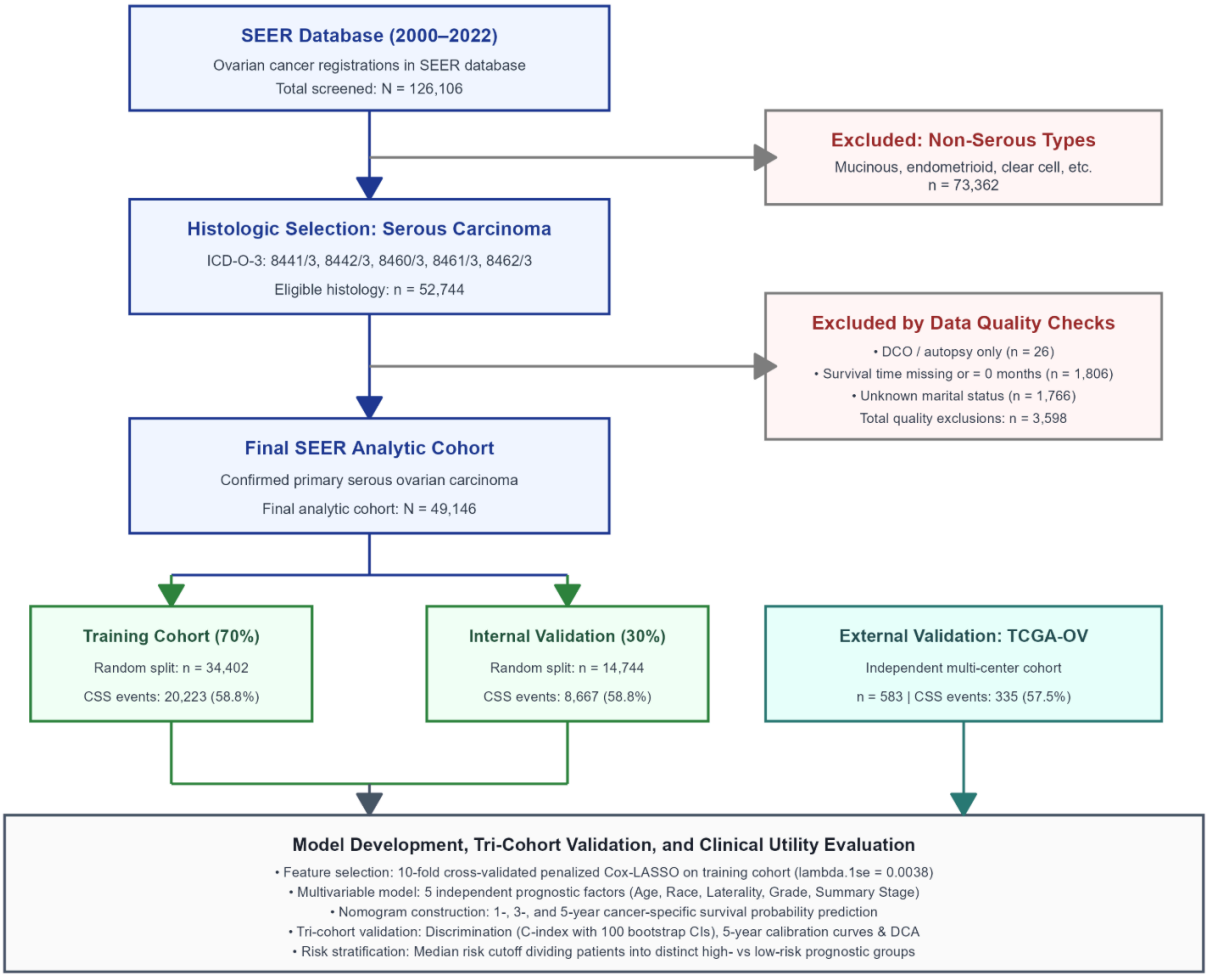


Figure 1

Flowchart of study design and patient selection. A total of 126,106 ovarian cancer entries registered in the SEER database (2000–2022) were screened. Following the exclusion of non-serous histology, autopsy/death-certificate-only cases, missing survival time, and missing marital status, 49,146 patients were identified and randomly split (7:3 ratio) into a training cohort (n = 34,402) and an internal validation cohort (n = 14,744). An independent cohort of 583 patients from the TCGA-OV project served as the external validation cohort

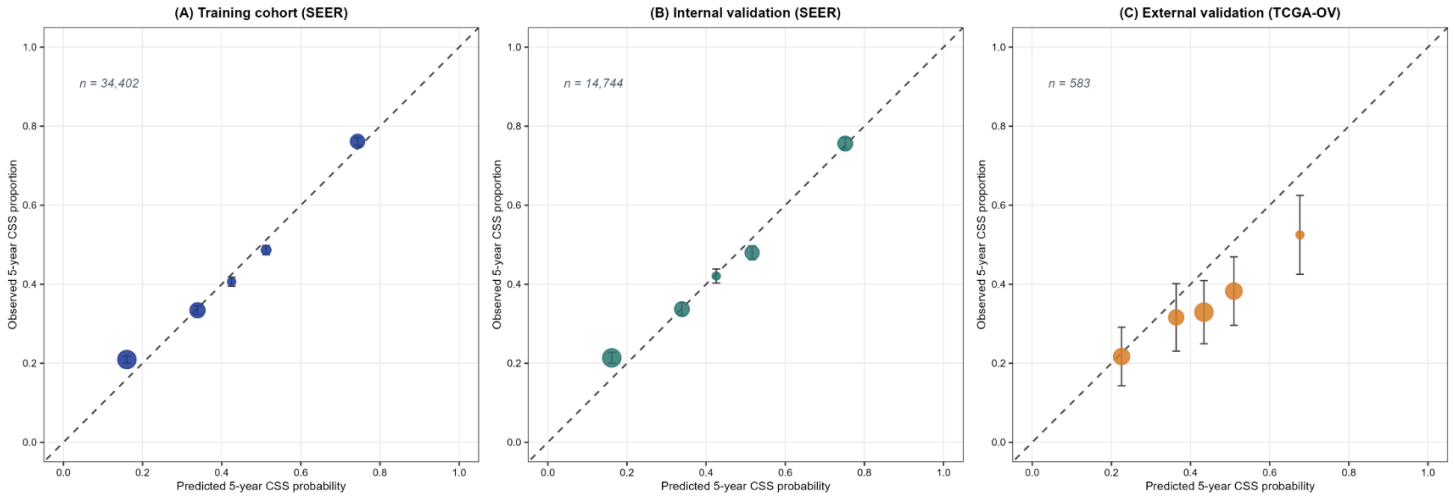


Figure 3

Calibration curves of the 5-variable nomogram for 5-year cancer-specific survival prediction across cohorts. a Training cohort (SEER, n = 34,402); b Internal validation cohort (SEER, n = 14,744); c External validation cohort (TCGA-OV, n = 583). Nomogram-predicted 5-year survival probability is plotted on the x-axis and observed Kaplan-Meier survival proportion on the y-axis. The 45-degree diagonal dashed line represents ideal calibration

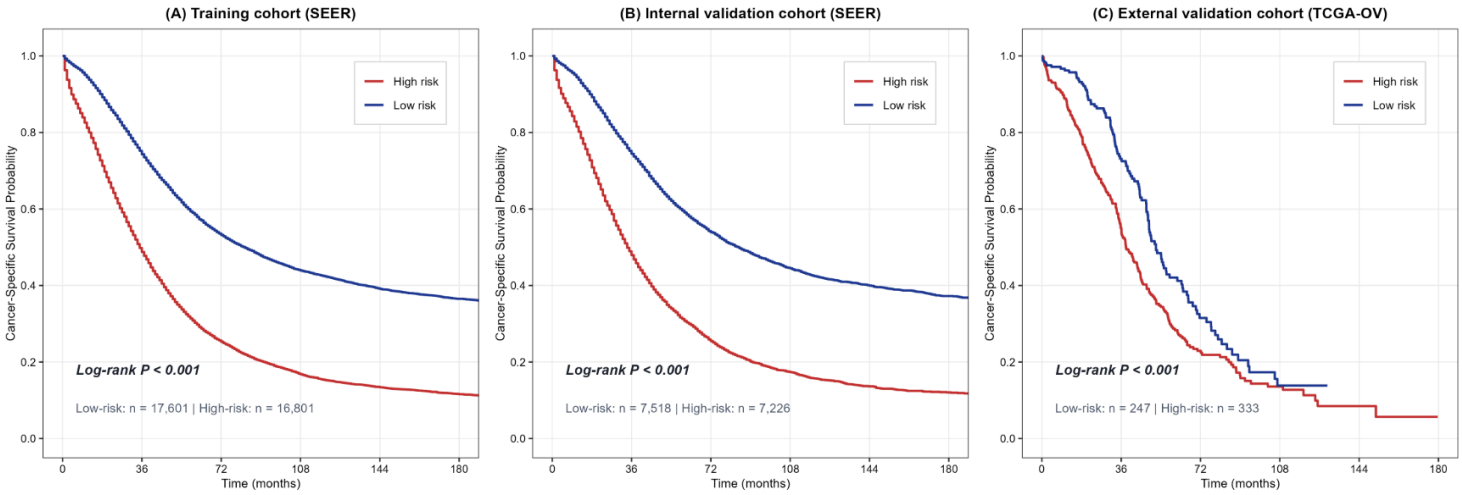


Figure 4

Decision curve analysis and risk stratification for cancer-specific survival. a–c Kaplan-Meier survival curves for cancer-specific survival stratified by median nomogram risk score across the training (a), internal validation (b), and external TCGA-OV validation (c) cohorts; d Decision curve analysis evaluating the net clinical benefit of the nomogram in the training cohort across threshold probabilities

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