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Clinical calculator redefines prognosis for high-risk early-stage ovarian cancers and potential to guide treatment in the adjuvant setting

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HIGHLIGHTS

- Risk calculator redefines prognosis in early stage high risk epithelial ovarian cancer.
- Cohort of patients identified by the calculator may not benefit from adjuvant treatment.
- A simplified calculator of age, stage, histology, and grade is also predictive of treatment benefit.

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ABSTRACT

Objective. To determine the utility of a clinical calculator to redefine prognosis and need for chemotherapy among patients with early-stage high-risk epithelial ovarian cancer.

Methods. Data were abstracted for stage I-II, high-risk ovarian cancer from the National Cancer Database from years 2005 to 2015. Based on demographic, pathologic, surgical, and laboratory characteristics, a clinical score was developed using Cox regression. Propensity score weighting was used to adjust for differences between patients who did and did not receive chemotherapy.

Results. Of 8188 patients with early-stage high-risk ovarian cancer, 6915 (84%) did and 1273 (16%) did not receive chemotherapy. A clinical calculator was created utilizing age, stage, histology, grade, tumor size, number of pelvic and paraaortic lymph nodes examined, the presence of malignant ascites, and CA125. The calculator divided patients into low, moderate, and high-risk groups with 5-year OS (overall survival) of 92%, 82%, and 66%, and 10-year OS of 85%, 67%, and 44%, respectively. Chemotherapy improved 5-year OS and 10-year OS in the high-risk group (56% to 73%; $p < 0.001$, 34% to 48%; $p < 0.001$). The moderate risk group had improved 5-year OS (80% to 85%; $p = 0.01$) but not 10-year OS (66% to 66%; $p = 0.13$). Chemotherapy did not improve 5-year or 10-year OS in low-risk patients (93% to 92%, $p = 1.0$, 86% to 84%, $p = 0.99$).

Conclusions. The prognosis among high-risk early-stage ovarian cancer patients is heterogeneous. This calculator may aid in patient-centered counseling regarding potential treatment benefits.

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1. Introduction

Epithelial ovarian cancer continues to be the one of the most lethal gynecologic malignancies in the United States [1]. Although the majority of these cancers are diagnosed at an advanced stage, approximately 30% of patients are diagnosed with stage I or II disease [2]. These early-stage patients have an improved prognosis compared to those diagnosed at an advanced stage but 10 to 30% of these patients will still die from their disease [2].

Traditionally, these early-stage patients have been defined as either high or low-risk based on a combination of stage, grade, and histology. For patients with low-risk disease, defined as stage IA, IB, grade 1 or 2

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disease, and non-clear cell histology, there is not currently a recommendation for adjuvant treatment [3]. However, treatment with chemotherapy is recommended for patients with high-risk disease [3].

Interestingly, prior research by Chan et al. has shown that there is heterogeneity in high-risk patient survival based on differences in patient age, tumor substage, tumor grade, and presence of malignant ascites [4]. These authors developed a risk score which separated patients into low, moderate, or high-risk. However, they were unable to evaluate if treatment improved the prognosis of patients within these separate risk categories [4].

The present study sought to examine if regression or machine learning algorithms could improve on prognostication of patients with high-risk early-stage epithelial ovarian cancer, as well as assist in redefining which patients may or may not benefit from adjuvant chemotherapy. This was performed using the National Cancer Database (NCDB) to examine over 8000 patients with early-stage high-risk epithelial ovarian cancer.

2. Methods

2.1. Data extraction and exclusion criteria

We performed a retrospective observational cohort study utilizing the NCDB to analyze treatment-based outcomes in patients with high-risk early-stage epithelial ovarian cancer. High-risk ovarian cancer was defined as stage I or II, grade 3; stage IC or stage II of any grade, stage I-II clear cell carcinoma or carcinosarcoma. The NCDB is a nationwide registry developed by the American Cancer Society and the Commission on Cancer® of the American College of Surgeons [5]. It captures 70–80% of all newly diagnosed cancers in the United States annually from more than 1500 Commission on Cancer® affiliated hospitals [5]. This study utilized only de-identified data from the NCDB and was exempt from Institutional Review Board approval.

Patients diagnosed with early-stage high-risk ovarian cancer between the years 2005 and 2015 were included for analysis. Patients were omitted if they had non-epithelial histology, if it was unknown whether they received or did not receive chemotherapy, if patients died prior to receiving chemotherapy, if the patient declined chemotherapy or was recommended to receive it and did not, if chemotherapy was contraindicated due to a comorbid medical condition, if they had a prior history of another malignancy, if they did not undergo surgical staging, if they were less than 18 years of age, if they were treated palliatively, or if they had low-risk early-stage ovarian cancer. A surgical staging was defined as having surgery at the primary site recorded within the NCDB and a pelvic and or paraaortic lymph node dissection. Low risk ovarian cancer was defined as having stage IA or IB disease, in combination with low or moderate grade. This resulted in a total of 8188 patients for analysis **Supplementary Fig. 1**.

2.2. Demographic and clinical characteristics

The demographic and clinical characteristics evaluated included age, race, type of hospital (community or academic), treatment center volume, location of treatment center, insurance, education, income, year of diagnosis, stage, histology, grade, lymphovascular invasion (LVSI), tumor size (cm), number of lymph nodes examined, presence of malignant ascites, CA125, and adjuvant treatment. A high-volume center (≥20 cases/year) was defined in accordance with prior publications using the NCDB to analyze ovarian cancer patients [6]. As defined by the NCDB, CA-125 was categorized as negative, elevated, or unknown. The numerical value of CA-125 was not available. Utilization of chemotherapy was defined as having received adjuvant chemotherapy at any facility. This was deciphered using the "RX_SUMM_CHEMO" column. Specifically, patients considered to have been treated were those with documented receipt of multi-agent or single-agent chemotherapy. Patients who did not receive chemotherapy included only those who were not recommended to receive chemotherapy by their physician which is encoded as "none" in the NCDB. Those who declined treatment despite being recommended to receive chemotherapy (n = 320) were held out as a separate dataset to further test the robustness of the model. The number of cycles and type of chemotherapy were not recorded within the NCDB.

2.3. Statistical analysis

Survival distributions were evaluated using the Kaplan-Meier method to estimate unadjusted survival. Overall survival was defined as the date of diagnosis to date of death (all-cause mortality) or the date of last clinical encounter (alive at last contact). Survival data were risk stratified and compared by receipt of adjuvant chemotherapy utilizing log-rank testing methods. Weights from propensity score matching were used when analyzing the effect of chemotherapy to control for statistical differences in baseline characteristics between those who did and did not receive chemotherapy.

Cox regression models were used to evaluate the relationship between demographic, clinical, and treatment variables with overall survival expressed as the hazard ratio (HR), 95% confidence interval (95% CI) and P-value. All P-values were two sided and a value of <0.05 were considered statistically significant. All statistical analyses were performed using R Studio version 1.1.383 (R Studio, Boston, Massachusetts).

2.4. Prognostic score and determination of chemotherapy benefit

A predictive algorithm was generated using age in combination with surgical and pathologic characteristics input into multivariate Cox regression, penalized Cox regression, random survival forest, gradient boosting, and extreme gradient boosting algorithms. Age, surgical, and pathologic characteristics were chosen because they are recorded in most clinical trials. Social determinants of health were not included in the model because their inclusion could potentiate biases these populations already experience. If any of the included variables in the model were missing, it was coded as unknown.

The data was partitioned into a training set and a test set. Of note, each training and test set also underwent propensity score matching. This was because it could not be assumed that using the same propensity scores from the entire dataset would result in balancing of characteristics of the training and test sets. Parameters included in propensity score matching were age, comorbidities, facility type, treatment center volume, treatment center location, insurance status, income, living in a rural, urban, or metro area, level of education, year of diagnosis, stage, histology, grade, lymphovascular invasion, tumor size, number of lymph nodes excised, presence of malignant ascites, and CA125. The models were initially evaluated using the concordance index in the training and test set. The concordance index is similar to area under the curve for the receiver operator characteristic except for censored data [7]. A value of 0.5 would mean the algorithm is the equivalent to guessing prognosis, while a value of 1 would indicate perfect prediction of prognosis. Using 50% of patients in the training set and 50% in the test set, multivariate Cox regression had comparable concordance indices to other models **Supplementary Table 1**. To aide in interpretability of the Cox model and to remove factors that did not improve performance, fast backward elimination was performed followed by creation of a nomogram.

Risk groups were then created in the following fashion. After the model had scored all patients with a linear predictor (lp) in the training set, patients were divided into each 10th percentile based on their respective lp score. Each 10th percentile was used as this would give a visual representation of how prognosis changed with increasing lp values across the entire training set. Using this information, in combination with plotting the hazard ratio as function of the interaction of the continuous linear predictor value and treatment, two cutoff values

were chosen to generate three risk groupings: low, moderate, and high-risk. The low-risk cutoff value was chosen based on a balance of where the interaction plot showed not treating resulted in a higher risk of death and that the Kaplan-Meier curves showed excellent prognosis (5-year survival rates of over 90%). The high-risk cutoff was chosen where the risk of not treating began to increase exponentially on the interaction plot. These risk groups were then assessed in the test set. A second validation of the model's survival predictions was then performed in patients who were recommended treatment but declined it ($n = 320$). This was performed using a calibration curve.

The benefit of chemotherapy was assessed using previously described methods [7,8]. The three risk groups were compared in patients who did and did not receive chemotherapy using Cox proportional hazards and Kaplan-Meier analysis. The interaction between patient score and chemotherapy was explored using the likelihood ratio test to assess if there was a significant interaction between risk score value and chemotherapy survival benefit. The significance of the interaction was assessed using the lp value as a continuous value and using the patients grouped into either the low risk group or a combined moderate and high risk group. The moderate and high-risk groups were placed together because both had a 5 year survival benefit with chemotherapy while the low-risk group did not.

2.5. Creation of a simplified calculator

Notably, prior clinical trials in early-stage ovarian cancer have not included all variables available in the NCDB [9,10,11,12]. However, all trials do include patient age, stage, tumor histology, and tumor grade. Therefore, a calculator only consisting of patient age, stage, tumor histology, and grade was generated using the same steps described above to see if it would still be predictive of treatment benefit, and thus applicable to prior clinical trials.

2.6. Creation of a web app

R Shiny apps® was used to create a web-based application to allow the created nomogram to be easily accessed and utilized by clinicians [13]. To ensure its reliability, the lp value for 10 patients included in this paper were cross checked with the results from the app online to ensure the same lp value and risk grouping were produced by the app as in this manuscript (results not shown).

3. Results

Of 8188 high-risk early-stage ovarian cancer patients, the median age was 57, 87% were white. Of these patients, 41% had stage IC disease, 41% had serous histology, and 67% had high grade cancers. The median tumor size was 10.7 cm and the median number of combined pelvic and paraaortic nodes removed was 13. Malignant ascites was present in 48% of patients and 62% of patients had an elevated CA125. Most patients (82%) received treatment with multiagent chemotherapy Table 1. Patient characteristics associated with worse 5-year overall are also summarized in Table 1. Demographic factors associated with worse prognosis are further summarized in **Supplementary Table 2**.

Those who did not receive chemotherapy were more likely to be older, have lower substage, lower grade, less lymph nodes removed, or negative CA125 Table 2. After propensity score weighting, there were no longer differences between all measured demographic, surgical and pathologic characteristics Table 2. The prior mentioned variables were also balanced in the training and test set, except for CA125 elevation in the training set **Supplementary Table 3**.

3.1. Risk calculator creation: cox regression

Multivariate cox regression was performed initially using age, stage, histology, grade, tumor size, presence of malignant ascites, LVSI, number of lymph nodes examined, and CA125. Fast backward elimination removed LVSI as part of the calculator. This resulted in the final scoring system predictive of patient prognosis Fig. 1. This model had a concordance index of 0.698 in the training set and 0.697 in the testing set.

Next, patients in the training set were divided into respective risk groups. This was done first by examining a plot of the hazard ratio as a function of the lp value in those who were treated and not treated with chemotherapy, respectively **Supplementary Fig. 2A**. Second, Kaplan-Meier curves were constructed dividing patients into each 10th percentile based on their respective lp score **Supplementary Fig. 2B**. Based on this, low-risk patients were defined as having a lp value of less than or equal to −0.3 or a score of 149 points. The second cutoff point was chosen at an lp value of 0.57 or a score of 183 points because at this point the risk of not treating began to increase exponentially on the interaction plot. This resulted in three separate risk groups: low (score ≤ 149 or lp value ≤ −0.3), moderate (149 < score ≤ 183, −0.3 < lp ≤ 0.57), and high (score > 183, lp > 0.57) Fig. 2**A**. The moderate risk group had 2.39 times increased risk of death (95%CI 1.96–2.92, $p < 0.001$) and the high-risk group had an HR of 5.70 (95%CI 4.66–6.98, $p < 0.001$) compared to the low-risk group. These risk groupings remained predictive in the test set Fig. 2**B**. A summary of the demographic, surgical, and pathologic characteristics of the individual risk groups is shown in **Supplementary Table 4**. A validation of the survival predictions was performed among those who declined treatment ($n = 320$). These patients were not part of the training or test set. The calibration curve showed that the model's survival predictions were correlated with actual patient survival among those who declined treatment **Supplementary Fig. 3**.

When examining the entire data set as a whole, patients in the low-risk group had a 5-year overall survival (OS) and 10-year OS of 92% and 85%, compared to 82% and 67% for the moderate-risk group, and 66% and 44% for the high-risk group. After defining prognostic groups, chemotherapy was then assessed for whether it improved survival in the low, moderate, or high-risk group, respectively.

3.2. Assessing chemotherapy benefit

Not treating with chemotherapy was associated with worse patient survival when considering the full cohort of propensity matched ovarian cancer patients (HR 1.5, 95%CI 1.37–1.64, $p < 0.001$). However, when exploring the relationship of between chemotherapy and survival within the low, moderate, and high-risk groups, the survival benefit was not ubiquitous. In the low-risk group, chemotherapy was not associated with a 5-year OS benefit (HR 1.0, 95%CI 0.66–1.51, $p = 1.0$). The moderate (HR 0.74, 95%CI 0.58–0.93, $p = 0.01$) and high risk (HR 0.46, 95%CI 0.40–0.54, $p < 0.001$) groups had improved 5-year OS when treated with chemotherapy Fig. 3. At 10 years, low risk patients continued to not benefit from chemotherapy (HR 1.0, 95%CI 0.70–1.42, $p = 0.99$). The moderate risk group no longer benefitted from chemotherapy at 10 years (HR 0.85, 95%CI 0.70–1.05, $p = 0.13$). Those who had received chemotherapy in the high-risk group continued to have improved survival at 10 years (HR 0.52, 95%CI 0.42–0.65, $p < 0.001$) Fig. 3.

In the low-risk group, the percent 5- and 10-year survival in untreated patients was 93% and 86% compared to 92% and 84% in those who were treated with chemotherapy. In the moderate risk group there was a 5% increase in 5-year OS (80% untreated to 85% treated) but a 0% increase in 10-year OS (66% untreated *vs* 66% treated). The high-risk group saw a 17% improvement in 5-year OS (56% untreated to 73% treated) and a 14% increase in 10-year OS (34% untreated to 48% treated).

The relationship of the interaction between risk score and benefit from treatment was formally assessed statistically using the likelihood ratio test. Increasing values of the lp score had an extremely significant association with improved outcomes with treatment ($p_{train} < 0.001$, $p_{test} < 0.001$, $p_{dataset} < 0.001$). However, because the lp score was not

Table 1
Summary of demographic, surgical pathologic, and treatment information for all patients. 5 year and 10-year overall survival were compared. P-values are for 10-year overall survival differences.

Characteristics		High risk patients (n = 8188)	Percent 5-year overall survival	Percent 10-year overall survival	p-value
Age (median [IQR])		57.00 [50.00, 65.00]			
	< 57		87%	76%	< 0.001
	≥ 57		81%	60%	
Race					
	White	7154 (87)	84%	67%	0.052
	Black	413 (5)	81%	69%	
	Other	621 (8)	86%	75%	
CDCC Total					
	0	6814 (83)	85%	70%	< 0.001
	1	1134 (14)	81%	59%	
	2	184 (2)	66%	51%	
	≥ 3	56 (1)	78%	27%	
Stage					
	1A	1622 (20)	88%	73%	< 0.001
	1B	190 (2)	85%	63%	
	1C	3352 (41)	87%	73%	
	2	3024 (37)	79%	59%	
Histology					
	Serous	3349 (41)	83%	61%	< 0.001
	Endometroid	2024 (25)	90%	76%	
	Clear Cell	1853 (23)	83%	74%	
	Mucinous	755 (9)	84%	71%	
	Carcinosarcoma	207 (3)	56%	40%	
Grade					
	High/Undifferentiated	5490 (67)	82%	64%	< 0.001
	Moderate	1682 (21)	86%	73%	
	Low	1016 (12)	92%	81%	
LVSI					
	Not present/Unknown	7789 (95)	84%	76%	0.006
	Present	399 (5)	79%	66%	
Tumor Size (median [IQR]) cm		10.60 [6.50, 15.00]			
	< 10.7		85%	69%	0.03
	≥ 10.7		83%	67%	
Pelvic and Paraaortic Nodes Examined		13.00 [6.00, 21.00]			
	< 13		82%	64%	< 0.001
	≥ 13		87%	71%	
Malignant Ascites					
	No	3155 (39)	87%	79%*	< 0.001
	Unknown	1086 (13)	83%	72%*	
	Yes	3947 (48)	82%	74%*	
CA125					
	Elevated	5072 (62)	84%	67%	0.09
	Negative	1486 (18)	85%	71%	
	Unknown	1630 (20)	83%	68%	
Chemotherapy					
	Multiagent chemotherapy	6745 (82)	85%	68%	< 0.001
	None	1273 (16)	80%	67%	
	Single-agent chemotherapy	170 (2)	78%	55%	

IQR: Interquartile Range; CDCC: Charlson/Deyo Comorbidity Score
* indicates that 7.5-year overall survival was used instead as there was not adequate follow up to 10 years in patients with the particular clinical characteristic.

used as a continuous variable and instead was used to bin patients into multiple risk groups, the low-risk group was compared to the combined moderate and high-risk groups to determine if this dichotomized cut off would also yield a significant interaction. Indeed, this also resulted in an interaction in the training, test, and entire dataset ($p_{train} = 0.002$, $p_{test} = 0.03$, $p_{dataset} = 0.00002$). This statistically proves that using the cutoff of a lp value of −0.3 or score of 149 correctly identifies those who would or would not benefit from chemotherapy rather than it being from chance alone.

3.3. Risk calculator simplification

A calculator only consisting of patient age, stage, tumor histology and grade was generated to see if it would still be predictive of treatment benefit, and thus applicable to prior clinical trials Supplementary Fig. 4 [9,10,11,12]. This new calculator had a concordance index of 0.687 in the training set and 0.692 in the testing set. Using the same process as described previously, the calculator was able to divide patients into low, moderate, and high-risk groups **Supplementary Fig. 5**. Furthermore, the calculator still had a significant interaction between both continuous lp value and treatment benefit ($p_{train} < 0.001$, $p_{test} < 0.001$, $p_{dataset} < 0.001$). When considering patients grouped as low *versus* moderate/high risk there was a significant interaction with risk group and treatment benefit in both the training set and the entire dataset ($p_{train} = 0.002$, $p_{test} = 0.94$, $p_{dataset} = 0.008$). In the test set only the highest risk group had a significant interaction with treatment benefit ($p_{test} = 0.05$).

4. Discussion

To determine the need for adjuvant chemotherapy, early-stage ovarian cancer has traditionally been split into high or low risk groups.

Table 2
Summary of demographic, surgical pathologic, and treatment information for all patients and their association with receipt of treatment.

Characteristics		No Chemotherapy (n = 1273)	Chemotherapy (n = 6915)	p-value	p-value after PSM
Age (median [IQR])		58.00 [50.00, 69.00]	57.00 [50.00, 65.00]	0.001	0.99
Race					0.98
	White	1066 (84)	6088 (88)		
	Black	82 (6)	331 (5)	< 0.001	
	Other	125 (10)	496 (7)		
CDCC Total					0.79
	0	1036 (81)	5778 (84)		
	1	190 (15)	944 (14)	0.17	
	2	35 (3)	149 (2)		
	≥ 3	12 (1)	44 (1)		
Facility Type					0.79
	Academic/Research Program	433 (34)	3054 (44)		
	Community Cancer Program	52 (4)	212 (3)		
	Comprehensive Community Cancer Program	504 (40)	2254 (33)	< 0.001	
	Integrated Network Cancer Program	190 (15)	991 (14)		
	Unknown	94 (7)	404 (6)		
Center Volume					0.194
	High	543 (43)	3585 (52)		
	Moderate	558 (44)	2632 (38)	< 0.001	
	Low	172 (14)	698 (10)		
Facility Location					0.25
	East North Central	176 (14)	1263 (18)		
	East South Central	91 (7)	369 (5)		
	Middle Atlantic	147 (12)	1010 (15)		
	Mountain	68 (5)	356 (5)		
	New England	40 (3)	418 (6)	< 0.001	
	Pacific	179 (14)	817 (12)		
	South Atlantic	267 (21)	1271 (18)		
	West North Central	59 (5)	669 (10)		
	West South Central	152 (12)	338 (5)		
	Unknown	94 (7)	404 (6)		
Insurance Type					0.94
	Private Insurance	739 (58)	4412 (64)		
	Medicare	396 (31)	1723 (25)	< 0.001	
	Medicaid	50 (4)	356 (5)		
	Other	88 (7)	424 (6)		
Income					0.88
	< $38,000	203 (16)	779 (11)		
	$38,000–$47,999	261 (21)	1521 (22)		
	$48,000–$62,999	339 (27)	1959 (28)	< 0.001	
	≥ $63,000	467 (37)	2644 (38)		
	Unknown	3 (0)	12 (0)		
Living Area					0.49
	Metro	1100 (86)	5878 (85)		
	Rural	21 (2)	98 (1)	0.25	
	Urban	152 (12)	939 (14)		
Rate of no high school diploma					0.29
	< 7.0%	326 (26)	2152 (31)		
	13.0–20.9%	328 (26)	1533 (22)		
	7.0–12.9%	402 (32)	2380 (34)	< 0.001	
	≥ 21.0%	215 (17)	839 (12)		
	Unknown	2 (0)	11 (0)		
Year of diagnosis					0.87
	2006	158 (12)	484 (7)		
	2007	113 (9)	501 (7)		
	2008	131 (10)	546 (8)		
	2009	133 (10)	558 (8)		
	2010	129 (10)	647 (9)	< 0.001	
	2011	130 (10)	717 (10)		
	2012	128 (10)	780 (11)		
	2013	105 (8)	839 (12)		
	2014	123 (10)	866 (13)		
	2015	123 (10)	987 (14)		
Stage					0.45
	1A	313 (25)	1309 (19)		
	1B	41 (3)	149 (2)	< 0.001	
	1C	594 (47)	2758 (40)		
	2	325 (26)	2699 (39)		
Histology					0.91
	Serous	479 (38)	2870 (42)		
	Endometroid	326 (26)	1698 (25)	< 0.001	
	Clear Cell	252 (20)	1601 (23)		

(continued on next page)

Table 2 (*continued*)

Characteristics		No Chemotherapy (n = 1273)	Chemotherapy (n = 6915)	p-value	p-value after PSM
	Mucinous	194 (15)	561 (8)		
	Carcinosarcoma	22 (2)	185 (3)		
Grade					0.44
	High/Undifferentiated	748 (59)	4742 (69)		
	Moderate	284 (22)	1398 (20)	< 0.001	
	Low	241 (19)	775 (11)		
LVSI					1
	Not present/Unknown	1228 (96)	6561 (95)	0.02	
	Present	45 (4)	354 (5)		
Tumor Size (median [IQR]) cm		11.00 [6.00, 15.50]	10.50 [6.50, 15.00]	0.33	1
Pelvic and Paraaortic Nodes Examined		11.00 [5.00, 19.00]	13.00 [7.00, 21.00]	< 0.001	0.41
Malignant Ascites					0.46
	No	457 (36)	2698 (39.0)		
	Unknown	131 (10)	955 (14)	< 0.001	
	Yes	685 (54)	3262 (47)		
CA125					0.1
	Elevated	672 (53)	4400 (64)		
	Negative	199 (16)	1287 (19)	< 0.001	
	Unknown	402 (31)	1228 (18)		
Chemotherapy					NA
	Multiagent chemotherapy	0 (0.0)	6745 (97.6)		
	None	1273 (100.0)	0 (0.0)	< 0.001	
	Single-agent chemotherapy	0 (0.0)	170 (2.4)		

IQR: Interquartile Range; CDCC: Charlson/Deyo Comorbidity Score.

Our data indicates that patients traditionally categorized as high-risk have very heterogeneous prognosis with some patients having a percent 5-year OS as high as 92% or as low as 66%. Furthermore, our data indicates that not all patients with high-risk early-stage ovarian cancer benefit from adjuvant chemotherapy.

Four sentinel trials, Young et al., ACTION, ICON1, and GOG157, examined the use of chemotherapy in patients with early-stage ovarian cancer [9,10,11,12]. The original article by Young et al. demonstrated that patients with high-risk ovarian cancer benefit from receiving chemotherapy [9]. In the ACTION trial, patients who

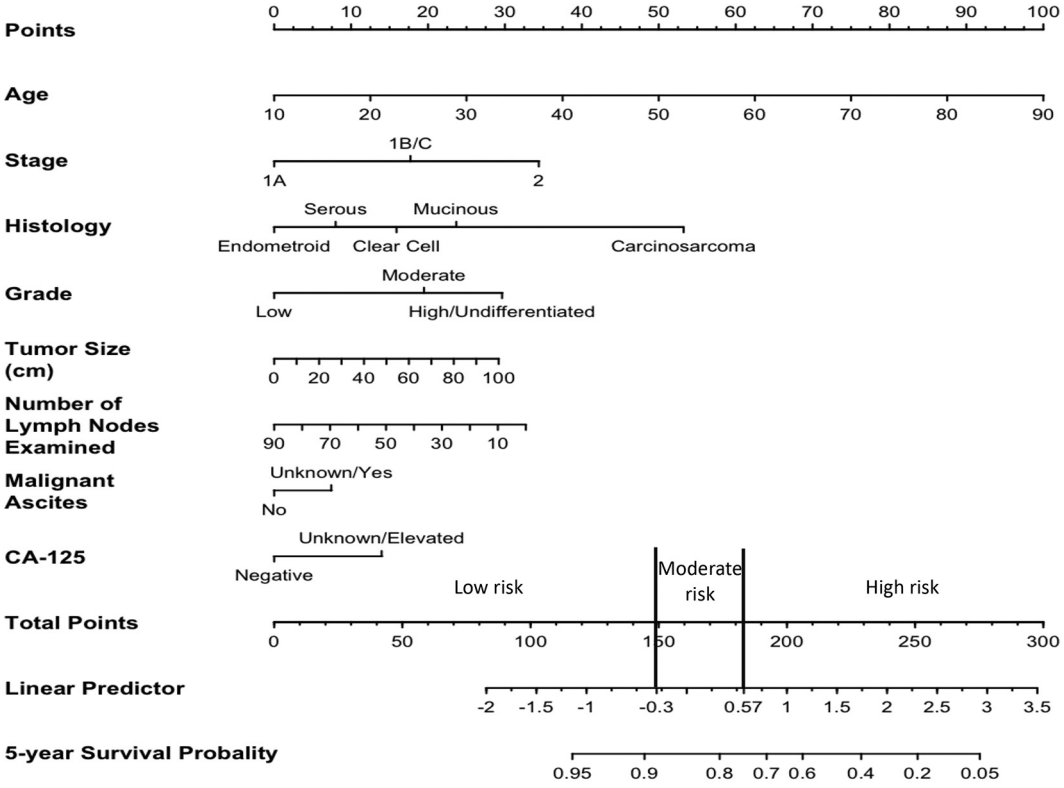
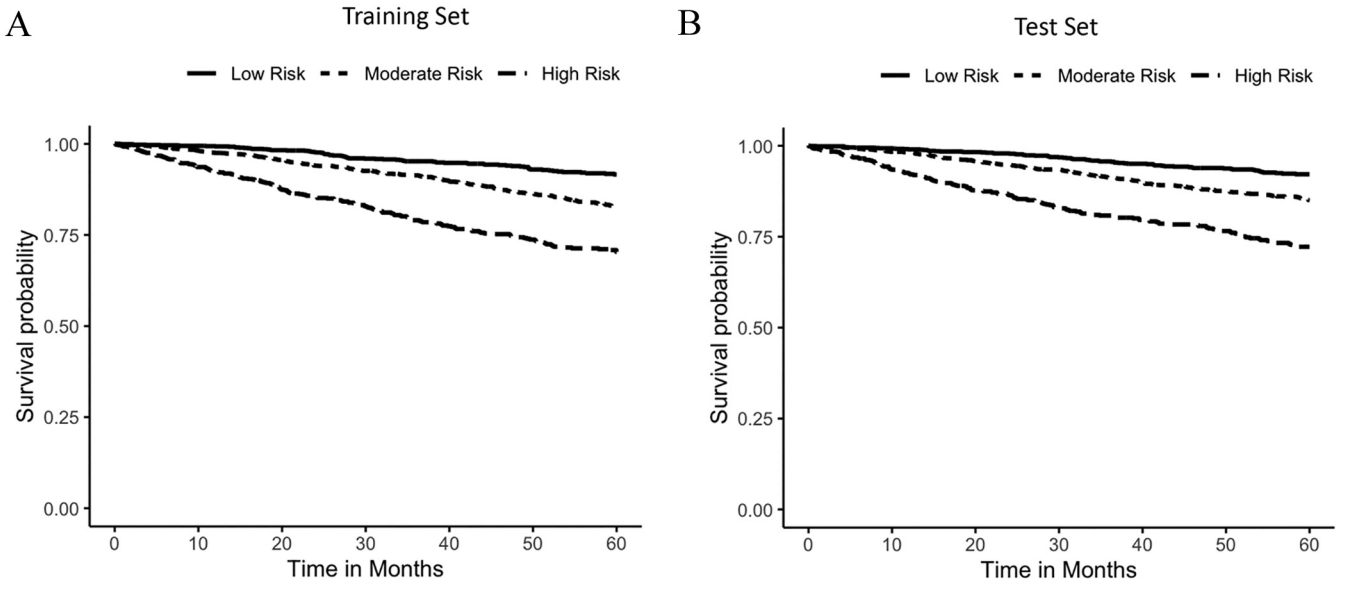


Fig. 1. Nomogram for predicting 5-year overall survival of women with high-risk early stage epithelial ovarian cancer. Instructions: Locate the patient's age on the age axis then draw a straight line up to the points axis to determine how many points the patient receives for her age. Repeat this process for each of the other factors, each time drawing a straight line to the points axis. Sum the points for each factor, and then locate where they fall on the total points axis. Draw a straight line down from the total points axis, to the probability of 5-year survival axis. If a patient's score is less than or equal to 149 points, they are considered low risk and may not benefit from chemotherapy. If their score falls between 149 points and 183 points, they are considered moderate risk and may benefit from chemotherapy. If their score is greater than or equal to 183, they fall into the high-risk group and also may benefit from chemotherapy. Once this has been determined continue to draw the line down to the survival probability axis to determine the probability of 5-year survival. Tumor size is measured in centimeters (cm). The cut-off for an elevated CA125 is not reported within the National Cancer Database.



Risk Group	Hazard ratio (95% Confidence Interval)	P - value
Low	*Ref*	*Ref*
Moderate	2.39 (1.96 – 2.92)	< 0.001
High	5.70 (4.66 – 6.98)	< 0.001

Risk Group	Hazard ratio (95% Confidence Interval)	P - value
Low	*Ref*	*Ref*
Moderate	2.14 (1.75 – 2.61)	< 0.001
High	5.69 (4.65 – 6.95)	< 0.001

Fig. 2. (A) Kaplan-Meier survival curves for low, moderate, high risk scores as determined by Cox Regression for training set (n = 4094) and (B) for the test set (n = 4094).

underwent complete surgical staging had no benefit from chemotherapy [10]. While those in the ICON1 trial, where complete surgical staging with a lymphadenectomy was not required, chemotherapy was beneficial [12]. However, when the ACTION and ICON1 trials were analyzed together, chemotherapy was beneficial [14]. Based on these prior trials, chemotherapy has been recommended for patients with high-risk early-stage ovarian cancer [3].

After the ACTION and ICON1 trials, GOG157 was performed to examine if treatment duration impacted survival for those with high-risk early-stage ovarian cancer. In this study there was no difference in survival if patients received 3 or 6 cycles of chemotherapy [11]. However, Chan et al., in a secondary analysis of GOG 157, showed that these patients have varying prognosis [4]. Unfortunately, because all patients in GOG157 received chemotherapy, they were unable to

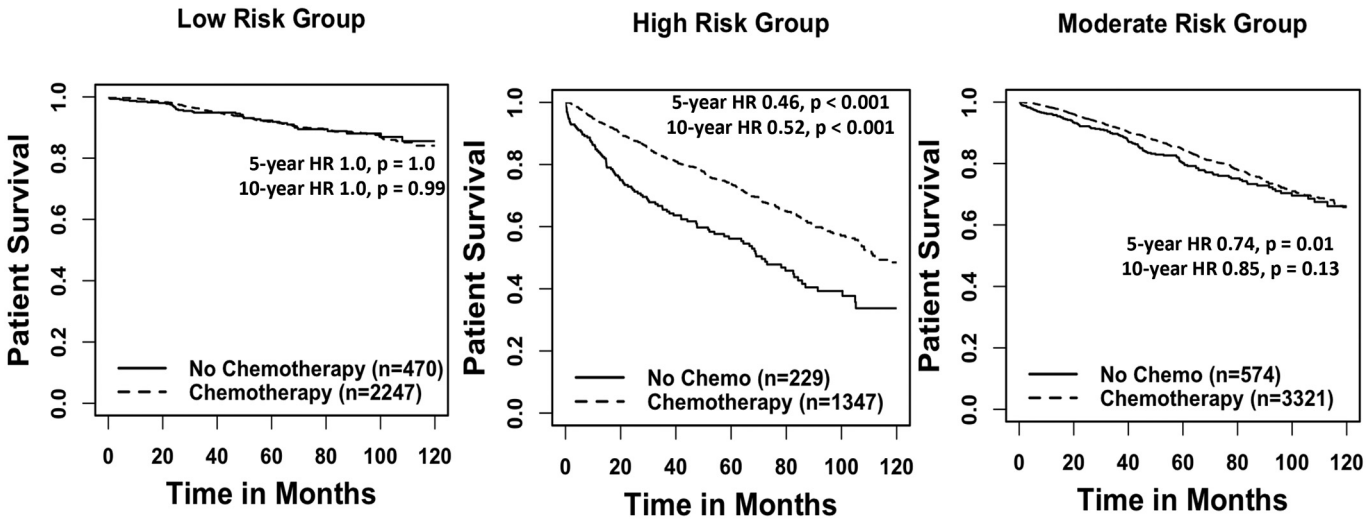


Fig. 3. Kaplan- Meier survival curves comparing those were treated *versus* not treated among the low, high, and moderate risk groups. The low risk group had no benefit of treatment at both 5 (HR 1.0, 95%CI 0.66–1.51, p = 1.0) and 10 years (HR 1.0, 95%CI 0.70–1.42, p = 0.99). The moderate risk group had a treatment benefit at 5 (HR 0.74, 95%CI 0.58–0.93, p = 0.01) years but not at 10 years (HR 0.85, 95%CI 0.70–1.05, p = 0.13). The high risk group benefited from treatment at both 5 (HR 0.46, 95%CI 0.40–0.54, p < 0.001) and 10 years (HR 0.52, 95%CI 0.42–0.65, p < 0.001).

comment on whether those with favorable prognosis benefit from adjuvant treatment [4].

Inferring from these prior trials, it would appear possible that there is a subset of patients with high-risk early-stage ovarian cancer who may not benefit from treatment. The designed calculator included age, stage, grade, histology, tumor size, number of pelvic and paraaortic lymph nodes examined, presence of ascites, and CA125. This combination was able to delineate those who would benefit from chemotherapy in a retrospective dataset. This scoring system performed very similar in the validation set lowering the chance of overfitting. Last, it was also applied to a hold set of 320 patients who had declined chemotherapy. The model showed excellent prediction in this cohort as well. These findings together indicate a robust model that should be validated in a prospective setting.

When considering what was found in the ACTION trial and by Chan et al., this calculator is comprehensive regarding clinical characteristics. It includes adequacy of staging, using the surrogate of number of lymph nodes examined. This recognizes the finding from the ACTION trial that those who were completely surgically staged did not benefit from chemotherapy. The calculator further combined the knowledge from prior work that has shown age, grade, ascites, and overall stage are also important prognostic factors [4]. Therefore, it is reasonable to consider applying this calculator to the ACTION and ICON1 datasets to potentially alter the recommendation for adjuvant treatment in all high-risk, early-stage ovarian cancer patients.

Interestingly, our calculator showed three distinct risk groups. While the low and high risk groups contained patients whose prognosis was almost universally good or bad, the moderate risk group contained patients with heterogeneous survival. We felt that this moderate risk group was important to include because it demonstrates a juxtaposition with the low and high risk groups. The low and moderate risk group comparison shows that clinical characteristics without molecular information may be sufficient to predict prognosis in some patient populations. However, when comparing the moderate to the high risk group, you can see that both groups would more strongly benefit from molecular insights than the low risk group. In the moderate risk group, molecular information could better help refine the prognosis prediction and treatment targets. While in the high risk group, molecular data should focus on providing new targets to improve outcomes rather than refining prognosis in a group that does almost universally poor.

Despite the number of strengths of this study, there were several limitations that need to be acknowledged. These include the retrospective nature and the inherent treatment bias to those who were treated *versus* those who were not assigned to receive chemotherapy. While propensity score weighting was used to reduce this bias, propensity score weighting cannot account for variables not within the dataset, such as BRCA status or homologous recombination deficiency. Second, when designing the calculator it was important to limit the data to a specific patient population. This may have caused loss of data or limited generalizability. Furthermore, the NCDB lacks whether patients were staged by a gynecologic oncologist, the number of treatment cycles, type of chemotherapy, how recurrences were treated, genomic data, progression free survival information or if patients died due to a cancer related death, among other clinically pertinent variables. This could result in poor algorithm performance when applied to a prospective population.

In summary, to our knowledge, our clinical calculator is the first algorithm which can both predict prognosis and treatment benefit among high-risk early-stage epithelial ovarian cancer patients. It may aid in patient-centered counseling regarding potential treatment benefits for those with high-risk early-stage ovarian cancer. Furthermore, this calculator may be applied to both the ICON1 and ACTION patient populations allowing validation in data that was collected as part of a prospective, randomized clinical trial. Last, a web app, https://davidmysona.shinyapps.io/HighRisk-EarlyStage-OVCA-TreatmentCalculator/, was created which allows for reproducible implementation and distribution of this algorithm.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.08.012.

Declaration of Competing Interest

None of the authors have conflicts of interest as it relates to the submitted work. Outside of the submitted work, Dr. Ghamande has received compensation from GlaxoSmithKline for consulting and from Merck as part of their speaker bureau. Dr. Chan has received compensation from Astra Zeneca, Aravive, Clovis, Eisai, GlaxoSmithKline Merck, Myriad, Roche/GenentechSeagen.

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