Clinicopathologic factors predictive of platinum resistance in advanced stage epithelial ovarian cancer; development and validation of a prediction model using a nationwide registry

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ABSTRACT

Objective

To identify clinicopathologic factors predictive of platinum resistance in advanced stage epithelial ovarian cancer (EOC) and to develop and internally validate a risk prediction model for platinum resistance after first-line of treatment in advanced stage EOC.

Methods

In this retrospective population-based study, all consecutive patients diagnosed with advanced stage EOC between 1st January 2008 and 31st December 2015 were identified from the Netherlands Cancer Registry. Patients who underwent cytoreductive surgery combined with platinum-based chemotherapy as initial EOC treatment were selected. Two risk prediction models, a pretreatment and a postoperative model, were developed and validated. Candidate predictors of platinum resistance were based on expert opinion and previous studies. These candidate predictors were fitted into multivariable logistic regression models. Models' selection was performed using a backward selection procedure based on the likelihood ratio test. Models' discrimination was estimated with the area under the receiver operating characteristic curve (AUC) and models' calibration was assessed using calibration plots and the Hosmer-Lemeshow goodness of fit test. Internal validation of the final models was performed using a bootstrap resampling method, which provided an estimate of model optimism and a shrinkage factor for each model.

Results

A total of 4,557 advanced stage EOC patients were identified, including 3,196 platinum sensitive patients and 1,361 platinum resistant patients. Platinum resistant patients were more likely to have FIGO stage IV, mucinous or clear cell type of ovarian cancer, presence of ascites, suboptimal (> 1 cm of residual tumor) residual disease, and more likely to have undergone interval cytoreductive surgery. The final pretreatment prediction model included age at diagnosis, FIGO stage, histologic subtype, presence of ascites, and pretreatment serum levels of CA-125. The AUC of the final pretreatment model was 0.65 [95% CI 0.64 – 0.67]. Calibration plots and Hosmer-Lemeshow test might suggest the pretreatment model was not perfectly calibrated. Bootstrap validation revealed an estimate of 0.003 of optimism in the pretreatment model's performance and a shrinkage factor of 0.94. The final postoperative prediction model included FIGO stage, histologic subtype, presence of ascites, type of surgery performed, and residual disease after surgical treatment. The AUC of the postoperative model was 0.72 [95% confidence interval 0.70 – 0.73]. Calibration plots and the Hosmer-Lemeshow test did not show evidence for miscalibration of the final postoperative model. Bootstrap validation revealed an estimate of 0.001 of optimism in the postoperative model's performance and a shrinkage factor of 0.96.

Conclusion

A good discriminative clinical model has been developed that predicts the risk of platinum resistance following first-line of treatment in advanced EOC based on FIGO stage, histologic subtype, presence of ascites, type of surgery performed, and residual disease after surgical treatment. Even though external validation is still required, this prediction model can support treatment decision making in daily clinical practice.

Keywords

Epithelial ovarian cancer; platinum resistance; platinum-based chemotherapy; population-based study; prediction model.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy in the western world [1, 2]. Worldwide, there are approximately 240,000 new cases and 185,000 disease-related deaths annually from ovarian cancer (OC) [2]. The annual mortality rate remains high due to the lion's share of patients who are diagnosed at an advanced stage (i.e. International Federation of Gynecology and Obstetrics (FIGO) stages IIB-IV) along with the patients who develop recurrent disease as a result of platinum chemotherapy resistance [3-5]. In advanced stage EOC, the mainstay of treatment includes cytoreductive surgery combined with platinum-based chemotherapy. Although most patients initially respond to this treatment, approximately 15-20% have intrinsic resistance toward platinum and succumb to the disease shortly after being diagnosed [6]. In addition, other patients may experience disease recurrence (~60-80%) due to resistance (often toward multiple drugs) after repeated lines of treatment, and unfortunately, one-fourth of these recurrences occur less than six months after completing first-line of treatment [3]. In recent years, research has increasingly focused on identifying factors that contribute to the development of platinum resistance in advanced stage EOC patients, however, it remains poorly understood and difficult to predict which patients with advanced disease develop platinum resistance and which do not.

Prior studies on predictive factors of platinum resistance have primarily focused on biomarkers, molecular or genetic factors that contribute to the occurrence of platinum resistance [4, 5, 7, 8]. While various prognostic factors have been studied for disease-free and overall survival in advanced ovarian cancer, it is still uncertain whether these factors could be predictive of platinum resistance. For instance, some studies have suggested that neoadjuvant chemotherapy followed by cytoreductive surgery as well as a residual tumor mass of more than 1 cm leads to an increased risk of platinum resistance [9, 10]. However, these studies are often hampered due to the limited sample size and the extent of missing data. To the best of our knowledge, no studies that quantify the association between clinicopathologic factors and platinum resistance or chemotherapy response using population-based data have been conducted.

If women who are expected to derive little benefit from standard platinum-based treatment are identified, then early intervention with alternative approaches such as novel therapies targeting molecular pathways could be considered. Therefore, the aim for this study is to elucidate clinicopathologic factors predictive of platinum resistance in advanced stage epithelial ovarian cancer patients. Moreover, we sought to develop and internally validate a prediction model for platinum resistance in advanced epithelial ovarian cancer using data from a population-based cancer registry.

METHODS

Data collection

In this retrospective cohort study, data from a population-based database comprising all consecutive patients diagnosed with epithelial ovarian cancer (EOC) between the 1st of January 2008 and the 31st of December 2015 from the Netherlands Cancer Registry (NCR) were used. The NCR is a nationwide registry which covers all patients diagnosed with cancer in the Netherlands since 1989. For registration and research purposes, trained registrars have routinely reviewed and extracted various data on patients, tumor and treatment characteristics using a standardized case record form. Furthermore, the registration team obtained complementary patient (e.g. performance score and comorbidity) and follow-up data (e.g. date of recurrent disease). The registry is notified of all newly histologically confirmed malignancies through an automated nationwide pathology archive (PALGA) on a weekly basis. In addition, the registry is annually linked to hospital discharge diagnoses and municipality registries to obtain recent data on vital status. Ethical approval for this study has been acquired from the NCR's Committee of Privacy.

Study population

Patients diagnosed with advanced stage EOC (i.e. FIGO stage IIB-IV) and who have undergone cytoreductive surgery combined with platinum-based chemotherapy as their initial EOC treatment were selected. Patients who received solely neo-adjuvant chemotherapy followed by cytoreductive surgery (i.e. NACT-ICS patients who did not continue chemotherapy after cytoreductive surgery) had inadequate treatment, and therefore, were excluded from this study. Similarly, patients who did not receive chemotherapy or cytoreductive surgery did not undergo the complete standard of EOC treatment, consequently, these patients were also excluded from further analyses.

Definitions

Platinum resistance was defined as disease recurrence or progression of disease developed within six months after completion of platinum-based chemotherapy. Progression of disease has previously been defined as clinical signs of tumor growth, i.e. an increase in CA-125 serum levels (greater than or equal to twice the upper normal limit of CA-125 on two separate occasions at least one week apart) or tumor lesions visible on imaging techniques (either regrowth of pre-existing lesions or growth of new lesions), combined with the clinical judgement of the treating medical oncologist or gynecologist [11]. Patients did not have routine CA-125 follow up after completing first-line therapy providing they were well and had no symptoms suggesting progressive or recurrent disease. Residual disease was defined as the maximum diameter of the largest tumor nodule remaining after cytoreductive surgery (classified as: no macroscopic disease, largest lesion being <1 cm, or >1 cm).

Statistical analyses

The patients' characteristics were summarized using descriptive statistics. The platinum-free interval (PFI) defined as the time between the date of completion of platinum-based chemotherapy and the date of disease recurrence or disease progression was calculated. Patients were divided into two groups based on their platinum-free interval; platinum sensitive group (PFI > 6 months) or platinum resistant group (PFI ≤ 6 months). Pearson χ^2 test or Fisher's exact test was used for categorical variables and two sample Wilcoxon rank-sum test for continuous

variables to compare the two groups. Logistic regression models were used to quantify associations between variables and platinum resistance. All statistical analyses were performed using STATA/SE, version 14.1 (Stata-Corp, College Station, Texas, USA) and R, version 3.6.1.(http://www.r-project.org).

Development of the prediction models

Two risk prediction models, a pretreatment model (also referred to as model 1) and a postoperative model (also referred to as model 2) were developed and validated using the seven steps described by Steyerberg *et al.* [12]. Candidate predictors selected for the multivariable logistic regression models were based on expert opinion and available literature on possible predictors in an effort to reduce the likelihood of including noise variables (i.e. variables that have no true relationship to the outcome of platinum resistance) in the models. The first model is solely based on clinicopathologic factors that are available before starting EOC treatment to assess whether platinum resistance can be predicted using these factors before receiving EOC treatment. Candidate predictors considered for this pretreatment risk prediction model included age at diagnosis, FIGO stage, histologic subtype, tumor type (i.e. ovarian, extra ovarian or fallopian tumor), tumor grade, pretreatment serum levels of CA-125, and presence of ascites. Concerning the postoperative risk prediction model, candidate predictors considered for this logistic regression model included age at diagnosis, FIGO stage, histologic subtype, tumor type, tumor grade, BRCA status, performance status (i.e. Karnofsky performance score), pretreatment serum levels of CA-125, presence of ascites, type of surgery performed (i.e. primary debulking or interval debulking), and residual disease after cytoreductive surgery. Candidate predictors initially selected but missing data on more than 50% of the observations were eliminated from both models. The backward selection procedure based on the likelihood ratio (LR) test was conducted in order to identify the most important predictors. A less strict *p*-value stopping rule ($p<0.20$) was selected to prevent premature exclusion of potentially important predictors. After selection, the risk prediction models were estimated.

Performance and internal validation of the models

The ability of the models to predict the patients' risk of developing platinum resistance after initial ovarian cancer treatment was based on the area under the receiver operating characteristic curve (AUC). A larger AUC indicates a higher discriminative power of a prediction model (i.e. the model's ability to distinguish patients who are platinum resistant from those who are platinum sensitive). In addition, the calibration of the models was evaluated using the Hosmer-Lemeshow (H-L) goodness-of-fit test. Differences between observed and predicted risks were plotted to assess the calibration of both models. Internal validation of the models was performed using the bootstrap resampling method, where samples were drawn with replacement from the development sample of the models. The number of bootstrap iterations was set to 1,000 for both models. This approach provides a shrinkage factor that can be used to correct for overfitting of a model (i.e. the occurrence where a model performs well for the patients used to develop it, but not for new patients) by shrinking the regression coefficients towards zero. The model intercept for each model was re-estimated after shrinkage. In addition, this internal validation approach yields measures of optimism in the performance of a model in the development data, which can subsequently be used to compute optimism-corrected indices of performance.

RESULTS

Study population

A total of 6,503 patients were diagnosed with advanced stage epithelial ovarian cancer between the 1st of January 2008 and the 31st of December 2015 in the Netherlands. Of these patients, 4,654 patients underwent cytoreductive surgery combined with platinum-based chemotherapy as initial ovarian cancer treatment. Among those patients, a total of 3,196 patients were recognized as platinum sensitive patients and 1,361 patients as platinum resistant patients. Data on disease recurrence or follow up status were unknown for 97 patients, accordingly, these patients were omitted from further analyses (see figure 1).

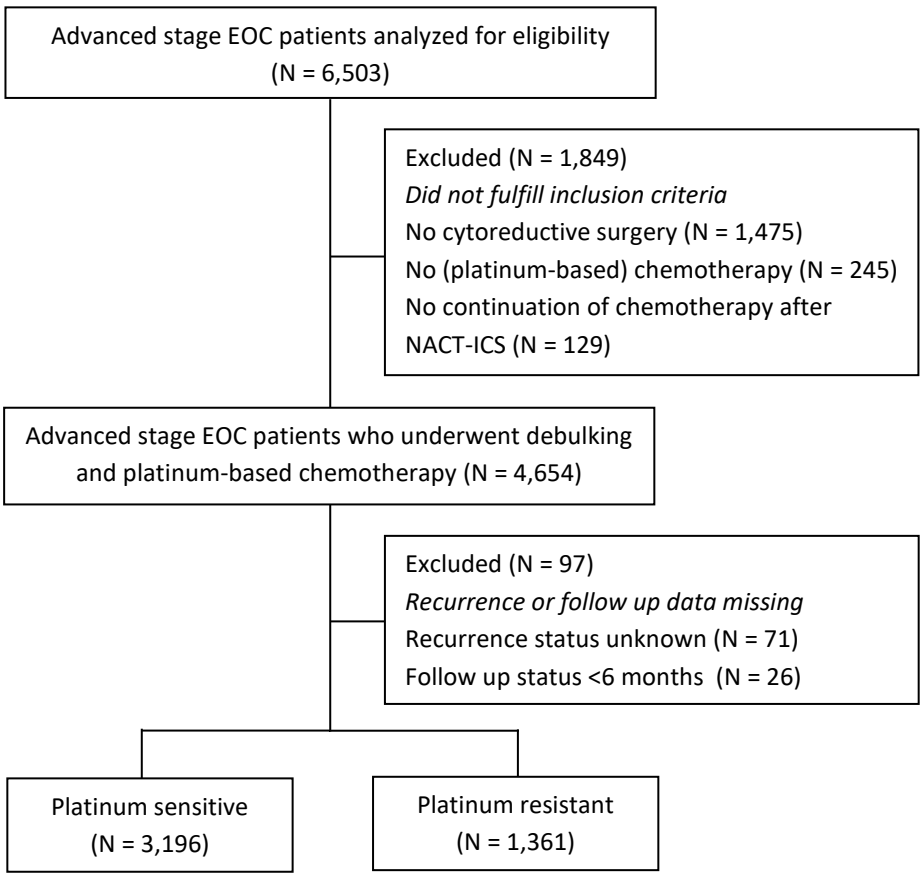


Figure 1. Flow chart of the study population

The patients' characteristics are summarized in table 1. For the platinum resistant group, the median age at diagnosis was 65 years (range, 20-91) compared to 64 years (range, 20-88) for the platinum sensitive group. Platinum resistant patients were more likely to have FIGO stage IV, whereas the platinum sensitive group comprised more patients with FIGO stage IIB-IIC (p<0.001). Serous type of ovarian cancer (OC) was the predominant histologic subtype for both groups followed by adenocarcinoma not otherwise specified. Only 3.5% of platinum resistant patients had endometrioid type of OC, whereas 6.0% of platinum sensitive patients had endometrioid type of OC (p<0.001).

The type of surgery performed varied significantly between the groups, the platinum resistant group consisted of more patients who underwent interval debulking (73.1% vs. 56.3%, p<0.001). Similarly, the platinum resistant group comprised more patients with residual tumor of more than 1 cm (19.8% vs. 6.7%) and less patients with macroscopic free residual disease (35.1% vs. 60.2%, p<0.001). Also, concerning the FIGO stage IV patients,

platinum resistant patients consisted of more patients with pleural malignant effusion than the platinum sensitive patients (14.4% and 7.6%, respectively), however this difference was statistically insignificant (p<0.244). Moreover, recurrent disease after a platinum-free interval of at least six months was observed in approximately two-thirds of the platinum sensitive patients.

Table 1. Characteristics of study population (N = 4557)

	Platinum sensitive group [n=3196 70.1%]		**Platinum resistant group [n= 1361 29.9%]**		
Characteristic	No. of patients or Mean/Median	% or Range	No. of patients or Mean/Median	% or Range	*p*-value
Age at diagnosis (in yrs)					**0.002***
Median (range)	64	20-88	65	20-91	
≤64	1622	50.8	641	47.1	**0.029**†
65-74	1078	33.7	472	34.7	
≥75	496	15.5	248	18.2	
FIGO stage					**<0.001**†
Stage IIB-IIC	372	11.6	34	2.5	
Stage IIIA-IIIB	279	8.7	76	5.6	
Stage IIIC	1936	60.6	824	60.5	
Stage IV	609	19.1	427	31.4	
Tumor type					**0.047**†
Ovarian tumor	2735	85.6	1151	84.6	
Extra ovarian tumor	311	9.7	160	11.8	
Fallopian tumor	150	4.7	50	3.7	
Tumor grade					**<0.001**†
Grade I	168	5.3	46	3.4	
Grade II	351	11.0	126	9.3	
Grade III	1692	52.9	681	50.0	
Unknown (n=1493)	985	30.8	508	37.3	
Histologic subtype					**<0.001**†
Serous	2488	77.8	1037	76.2	
Mucinous	57	1.8	52	3.8	
Endometrioid	193	6.0	47	3.5	
Clear cell	105	3.3	65	4.8	
Adenocarcinoma NOS	318	10.0	133	9.8	
Other[a]	35	1.1	27	2.0	
Karnofsky score (PS)					0.169†
10-50	14	0.4	10	0.7	
60-100	1575	49.3	613	45.0	
Unknown (n=2349)	1607	50.3	738	54.2	
Pretreatment CA-125 serum level					**<0.001***
Mean (kU/L)	1500		1900		
Median (kU/L / range)	512	3-56704	761	4-60000	
Unknown (n=369)	240		80		
BRCA status					**<0.001**†
Negative	893	27.9	277	20.4	
BRCA 1	203	6.4	36	2.7	
BRCA 2	119	3.7	6	0.4	
Unknown (n=3023)	1981	62.0	1042	76.6	
Presence of ascites					**<0.001**†
No	2102	65.8	724	53.2	
Yes	1093	34.2	637	46.8	
Unknown (n=1)	1	0	0	0	

Type of surgery performed					**<0.001†**
Primary debulking	1398	43.7	366	26.9	
Interval debulking	1798	56.3	995	73.1	
Residual disease after debulking					**<0.001†**
Macroscopic free	1923	60.2	477	35.1	
<1 cm	1011	31.6	596	43.8	
>1 cm	215	6.7	269	19.8	
Unknown (n=66)	47	1.5	19	1.4	
Intraperitoneal chemotherapy[b]					**0.022†**
No	3061	95.8	1323	97.2	
Yes	135	4.2	38	2.8	
Sites of metastasis					<0.244†
Pleural malignant effusion	242	7.6	196	14.4	
Intra-abdominal	172	5.4	107	7.9	
Lymph nodes	107	3.4	65	4.8	
Other[c]	86	2.7	59	4.3	
Not applicable[d] (n=3431)	2587	80.9	934	68.6	
Unknown (n=3)	2	0.1	0	0.0	
Recurrence					**<0.001†**
No	969	30.3	0	0	
Yes	1742	54.5	685	50.3	
Not applicable[e]	484	15.1	676	49.7	
Unknown (n=1)	1	0.0	0	0	

*Wilcoxon rank-sum test

†Fisher's exact or Pearson χ^2 test.

Abbreviations: BRCA, breast cancer gene; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NOS, not otherwise specified; PS, performance score;

[a] The subcategory 'other' of the category 'histological subtype' comprises the patients with other histological subtypes than noted such as Brenner, undifferentiated, mixed or other carcinoma.

[b] This variable includes both intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy.

[c] The subcategory 'other' of the category 'sites of metastasis' include metastasis such as one to the bone, brain, skin, breasts, and female reproductive organs.

[d] The subcategory 'not applicable' of the category 'sites of metastasis' comprises the patients who had FIGO stage IIB up to IIIC.

[e] The subcategory 'not applicable' of the category 'recurrence' comprises the patients who had partial remission, progression of disease or stable disease after initial treatment.

Associations between candidate predictors and platinum resistance

Due to limited available data, the candidate predictors BRCA status and performance status were excluded from further analyses. A total of 4,236 and 4,176 patients had complete cases and were initially included in the multivariable logistic regression analysis for the pretreatment and postoperative prediction model respectively. For the final pretreatment model, the following variables were independently associated with platinum resistance: age at diagnosis, FIGO stage, histologic subtype, presence of ascites, and pretreatment serum levels of CA-125. Not being independently associated with platinum resistance in the multivariable logistic regression analysis for the first model, tumor grade and tumor type were excluded from the final pretreatment model. Regarding the postoperative model; age at diagnosis, tumor type, tumor grade, and pretreatment serum levels of CA-125 were not independently associated with platinum resistance when corrected for covariates, neither did these variables improve the model performance. As a result, these variables were omitted from the postoperative model. The final postoperative model included FIGO stage, histologic subtype, presence of ascites, type of surgery performed, and residual disease after cytoreductive surgery. The final pretreatment and postoperative model listing their most important predictors and their odd ratios are demonstrated in tables 2 and 3 respectively.

Table 2. Final pretreatment prediction model (N = 4,236)*

Characteristic	Odds ratio (OR)	95% CI
Age at diagnosis (in yrs)		
≤64	Reference	
65-74	1.16	1.01 – 1.36
≥75	1.34	1.11 – 1.61
FIGO stage		
Stage IIB-IIC	Reference	
Stage IIIA-IIIB	3.29	2.06 – 5.24
Stage IIIC	4.88	3.28 – 7.25
Stage IV	8.31	5.52 – 12.51
Histologic subtype		
Serous	Reference	
Mucinous	3.13	2.01 – 4.86
Endometrioid	1.01	0.70 – 1.48
Clear cell	2.53	1.76 – 3.62
Adenocarcinoma NOS	0.97	0.77 – 1.21
Other	2.60	1.48 – 4.56
Presence of ascites		
No	Reference	
Yes	1.54	1.34 – 1.77
Pretreatment level of CA-125		
	1.00	1.00 – 1.00
Model intercept	0.06	0.04 – 0.09

Abbreviations: CI, confidence interval.

*An additional 321 patients were excluded from the final pretreatment model with reference to Figure 1, since these patients had unknown data on one or more variables included in the model.

Table 3. Final postoperative prediction model (N = 4,490)*

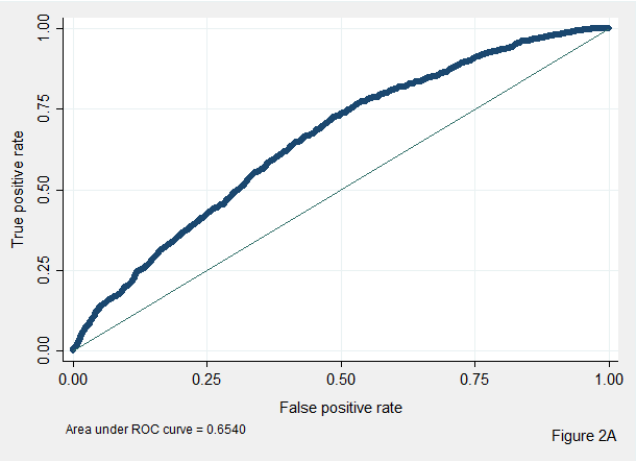
Characteristic	Odds ratio (OR)	95% CI
FIGO stage		
Stage IIB-IIC	Reference	
Stage IIIA-IIIB	2.57	1.62 – 4.06
Stage IIIC	3.14	2.11 – 4.68
Stage IV	4.49	2.96 – 6.83
Histologic subtype		
Serous	Reference	
Mucinous	4.17	2.70 – 6.45
Endometrioid	1.24	0.86 – 1.79
Clear cell	3.02	2.09 – 4.37
Adenocarcinoma NOS	0.98	0.78 – 1.24
Other	3.12	1.78 – 5.50
Presence of ascites		
No	Reference	
Yes	1.19	1.03 – 1.38
Type of surgery performed		
Primary debulking	Reference	
Interval debulking	1.91	1.61 – 2.28
Residual disease after debulking		
Macroscopic free	Reference	
<1 cm	2.26	1.94 – 2.62
>1 cm	4.84	3.90 – 6.00
Model intercept	0.04	0.03 – 0.06

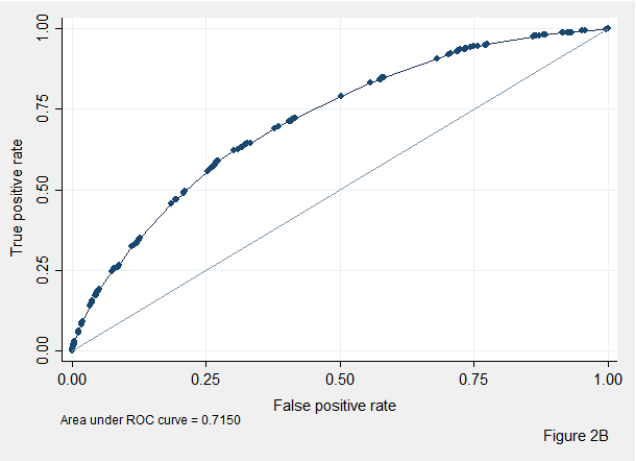
Abbreviations: CI, confidence interval.

*An additional 67 patients were excluded from the final postoperative model with reference to Figure 1, since these patients had unknown data on one or more variables included in the model.

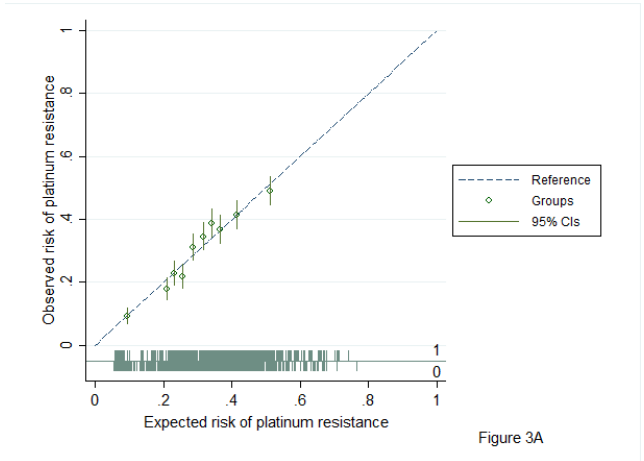
Models' performance

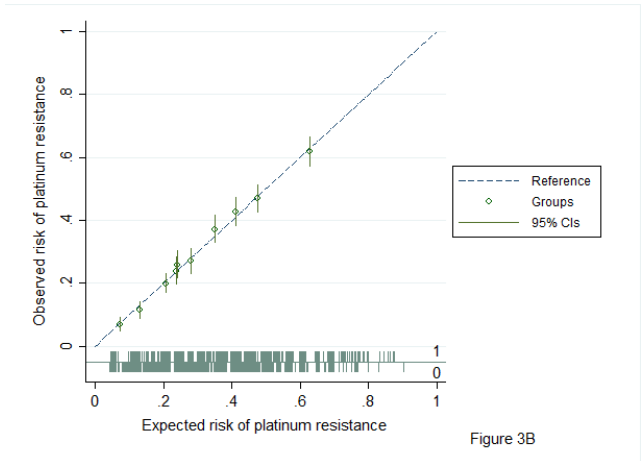
The AUC of the final pretreatment model was 0.65 [95% CI 0.64 – 0.67], indicating a moderate discriminative ability of the model (see figure 2A). The Hosmer-Lemeshow goodness of fit test was non-significant (p=0.114), which suggests good overall calibration of the model. However, the calibration plot demonstrated that 95% confidence interval around the observed rate of outcome in each decile group of predicted risk did not cross the perfect fit line for all groups, which could demonstrate that the model might not be as well calibrated (see figure 3A). Moreover, the AUC of the final postoperative model was 0.72 [95% CI 0.70 – 0.73], indicating good discriminative ability of the model (see figure 2B). In addition, the Hosmer-Lemeshow goodness of fit test was statistically not significant (p=0.845), which indicates good calibration of the model. Similarly, the calibration plot demonstrated that the 95% confidence interval around the observed rate of outcome in each decile group of predicted risk crossed the perfect fit line, illustrating that the model was well calibrated (see figure 3B).





Figures 2A and 2B. Area under the receiver operating characteristic curve for the final pretreatment (Figure 2A) and postoperative (Figure 2B) models on the predicted risk towards platinum resistance after first-line treatment of ovarian cancer treatment in advanced disease.





Figures 3A and 3B. Calibration plots of the developed pretreatment (Figure 3A) and postoperative (Figure 3B) model.

Particularly, table 4 shows that the performance of the final postoperative model (in this case the model with the higher predictive ability) is highly dependent on the chosen threshold for a positive test. As the threshold used to define high-risk of platinum resistance increases, the sensitivity decreases but the specificity and positive predictive value increase. For instance, for a given cut-off value of 70%, the specificity is estimated at 99.6%, indicating that 0.4% of the patients will be incorrectly classified as platinum resistant patients with this model.

Depending on the clinical implications and the role of patients' preferences in treatment decision, an optimal and acceptable threshold for a positive test can be selected.

Table 4. Risk stratification table to assess the performance of the final postoperative model at different thresholds for a positive test*

Cut-off value for a positive test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+
5%	99.3	4.7	30.8	94.3	1.04
10%	98.7	8.5	31.5	93.7	1.08
20%	93.1	28.0	35.5	90.5	1.29
30%	63.6	68.0	45.7	81.4	1.99
40%	47.0	80.6	50.8	78.1	2.42
50%	24.7	92.5	58.4	74.2	3.29
60%	13.9	96.7	63.9	72.5	4.21
70%	2.5	99.6	72.3	70.6	6.25
80%	0.5	99.9	77.8	70.2	8.67
90%	0	100	-	70.1	-
100%	0	100	-	70.1	-

Abbreviations: LR+, positive likelihood ratio (calculated using the equation: sensitivity/1-speficity); PPV, positive predictive value; NPV, negative predictive value

*A positive test indicates a positive outcome of developing platinum resistance.

Models' validation

Bootstrapping of the final pretreatment model revealed an estimate of 0.003 of model optimism. Internal validation using 1,000 bootstrap iterations revealed a shrinkage factor of 0.94 when all modeling steps (including the backward selection procedure) were repeated and deleted the pretreatment serum levels of CA-125 from the final pretreatment model. The model optimism of the final postoperative model was estimated as 0.001 after 1,000 iterations of bootstrapping, suggesting minimal overfitting of the postoperative model. Furthermore, internal validation revealed a shrinkage factor of 0.96 of the postoperative model. Both shrinkage factors were used to adjust the regression coefficients and the intercept estimates of each model to correct for overfitting, so that future predictions will be better.

DISCUSSION

In this large population-based study, we developed and internally validated two prediction models, based on clinicopathologic factors, that estimate the risk of platinum resistance in advanced epithelial ovarian cancer after initial treatment. In our study, significant associations between platinum resistance (defined as a platinum free interval of less than 6 months) and FIGO stage, histologic subtype, presence of ascites, type of cytoreductive surgery performed, and residual disease after cytoreductive surgery were found in multivariable logistic regression analysis and a prediction model (nomogram) has been built using the internally validated estimates of the postoperative model and presented on an open accessible web-based platform.

Concerning tumor biology, it has been established that clear cell and mucinous type of ovarian cancers are generally less responsive to platinum-based chemotherapy compared to serous type of ovarian cancer [13, 14]. Our current data showed that patients with clear cell and mucinous type of ovarian cancers have a tendency to be more platinum resistant in comparison to those with serous type of ovarian cancer. Although there was no significant independent association between tumor grade and platinum resistance, the combination of both tumor grade and histologic subtype could lead to a more accurate predictor of platinum resistance in advanced stage EOC patients. Studies have reported that, even though less common, low grade serous cancers also tend to be more resistant to platinum-based chemotherapy compared to high grade serous cancer (most common type of EOC). A further subclassification of our serous EOC patient cohort into high grade serous cancer (HGSC) versus low grade serous cancer (LGCS) patients did not reveal a significant difference in risk of platinum resistance between both groups. Nonetheless, this analysis was limited due to the considerable amount of unknown data on tumor grade in patients with serous type of EOC.

In addition, type of cytoreductive surgery performed revealed to be an important predictor of platinum resistance in our analysis. Specifically, platinum resistant patients were more likely to have undergone interval cytoreductive surgery following neo-adjuvant chemotherapy (NACT-ICS) rather than primary cytoreductive surgery (PCS) (OR 1.91; 95% CI 1.61 – 2.28). Similarly, Luo *et al.* showed that NACT-ICS patients had a higher occurrence of platinum resistant disease at first relapse compared to PCS patients in FIGO stage IIIC and IV disease (50.0% vs 35.0%, respectively) (OR 2.95; 95% CI 1.57 – 5.54) [9]. However, even though other studies initially showed a significant association between NACT-ICS and platinum resistant disease after first line treatment in univariable analyses [10, 15, 16], most studies failed to show a significant difference in platinum resistant disease between NACT-ICS and PCS patients when corrected for covariates in multivariable analysis [10, 15].

The decision to schedule a patient for PCS or NACT-ICS is mostly based on pre-operative imaging in relation to the probability of a successful cytoreductive surgery (i.e. no macroscopic or <1 cm residual tumor), even though it has been specified that the outcome of cytoreductive surgery cannot be reliably predicted with pre-operative imaging [17]. Other important reasons to opt for NACT-ICS as opposed to PCS include FIGO stage IV disease, poor performance status, and high perioperative risk (e.g. recent pulmonary embolism) [17]. Herewith, we can possibly conclude that platinum resistant patients may consist of more patients who initially present with worse conditions, and consequently, clinicians are more inclined to choose NACT-ICS as a treatment approach for them.

Though, it has also been stated that in clinical practice patients who are deemed fit for PCS with potentially resectable disease, either NACT-ICS or PCS may be offered based on studies that concluded that NACT-ICS was non-inferior to PCS regarding progression-free survival and overall survival in advanced EOC [17-19]. Nevertheless, the aforementioned studies that reported inconsistent results regarding the association between NACT-ICS and platinum resistance were hampered due to their limited sample size. Our results indicate that NACT-ICS is significantly associated with platinum resistance, and thus, NACT-ICS should probably not be considered for patients with a high likelihood of achieving complete or optimal cytoreduction and deemed fit for upfront surgery.

In addition, our study further confirms that the aim of cytoreductive surgery should be complete cytoreduction since patients with macroscopic free residual disease were less likely to be platinum resistant compared to those with residual disease of <1 and >1 cm. Even though it remains unclear whether NACT-ICS can induce platinum resistant disease, studies have implied that undergoing chemotherapy before debulking (rather than ICS itself) might contribute to the development of platinum resistant disease [9, 20]. It has been hypothesized that the higher the tumor burden when chemotherapy is initiated, the greater the likelihood of development of mutations and chemoresistance [9, 10, 13, 21].

It is important to note that the lack of sufficient data on *BRCA1/2* mutation status has prevented us from including this variable without substantially reducing the usability of the study population in the postoperative model development. Nevertheless, this did not hamper us from assessing the impact of *BRCA1/2* mutation status on platinum resistance in advanced EOC. A sensitivity analysis, including only patients with an identified *BRCA1/2* mutation status (N = 1,534), revealed that patients with a *BRCA*-negative mutation status (OR 6.05; 95% CI 2.59 – 14.15) as well as patients with a *BRCA1* mutation status (OR 3.3; 95% CI 1.34 – 8.41) were more likely to be platinum resistant compared to those with a *BRCA2* mutation status when corrected for covariates. Consistently, several reports found that patients with *BRCA2* mutation status have an increased response to platinum-based chemotherapy compared to those with *BRCA1* mutation status, and therefore, *BRCA* mutation status could be another important predictor of platinum resistance [13, 22-24]. Nevertheless, similar to these previous reports our finding is also based on a relatively small number of patients and events (only six platinum resistant patients in our *BRCA2* mutation cohort). Thus, given the potential impact on response to platinum-based chemotherapy, information about *BRCA* status should be documented whenever possible to confirm its influence on platinum resistance [13]. Similarly, performance status was left out of the model development due to the high number of unknown data. Exploratory analyses, including performance status as a candidate predictor in the postoperative model development, failed to show a significant relationship between performance status and platinum resistance, possibly due to its colinearity with age at diagnosis weakening any probable association.

Despite the good discriminative ability of our final postoperative model and population-based design, several other limitations apply to our study. Although internal validation using the bootstrap method allowed us to use the entire study population in model development, bootstrap sampling with reintroduction does not exclude that some observations are considered several times during the same bootstrap iteration, whereas others never. This in combination with the large amount of data could have resulted into minimal model optimism of both models,

however, bootstrapping is still considered one of strongest methods of internal validation and the size of the study population makes it highly unlikely that the optimism of either model is underestimated.

Furthermore, NACT-ICS patients who did not continue chemotherapy after surgery were excluded from the study, because it was difficult to distinguish patients who did not resume chemotherapy due to the non-responsiveness to platinum-based treatment from those who discontinued chemotherapy for other reasons (i.e. those who would have been wrongly categorized as platinum resistant patients). As a result, patients who were platinum resistant might have been excluded from our study. In contrast, patients who do not respond to treatment or progress very early on treatment are often classified as platinum refractory patients, so exclusion of this subset of patients is appropriate [6, 13]. Namely, patients with platinum refractory disease are believed to have intrinsic drug resistance and are inclined to have minimum to no benefit from the platinum-based chemotherapy, while platinum resistant patients relatively seem to benefit slightly more from platinum containing chemotherapy [13]. Unfortunately, the overall inconsistent reporting of data regarding the number of cycles of platinum-based chemotherapy received did not allow us to accurately differentiate between platinum refractory and platinum resistant patients. Subsequently, the platinum resistant patients in our study consist of both platinum refractory as well as platinum resistant patients. Although the study population included advanced stage EOC patients who received intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) added to their standard EOC treatment, the limited number of patients restricted us from fully analyzing this factor for our study.

Even though our pretreatment and postoperative model showed moderate and good performance respectively, one might argue their clinical usefulness. Currently, there is no viable alternative to platinum-based therapy in the armamentarium for treatment of advanced EOC. Nonetheless, even if not perfect at ruling in or ruling out high risk of platinum resistant disease after completing first-line treatment in patients, both models do give insight into clinicopathologic characteristics of platinum resistant patients which enhances our knowledge on which patients will develop platinum resistance. Having low response rates to subsequent chemotherapy (<15%) with a progression free survival of three to four months and median survival of less than a year [13], the net benefit of receiving additional systemic treatment accompanied with high toxicity should be assessed for these patients. The use of a prediction model as tool along with clinical assessment could be helpful in the shared decision making process of continuing (or even starting) treatment or not. Unfortunately, it remains difficult to accurately predict the risk of platinum resistance before starting any EOC treatment. Despite its lower predictive ability, the final pretreatment model could represent a benchmark for development of more accurate predictive models that include biomarkers, genetic or molecular factors alone or in combination with the clinicopathologic factors we have described. Moreover, the postoperative model could serve as a tool to decide whether patients are more inclined to gain from clinical trials rather than the standard of care and even help in selecting the right target patients for those studies with the aim to develop therapies suitable for them.

In conclusion, a good discriminative model that estimates the risk of platinum resistance after completing first-line treatment in advanced stage EOC patients was developed and internally validated. An improved understanding of factors that contribute to the development of platinum resistance could aid in the accurate prediction of patient prognosis and outcome. Thus, identifying which patients are more likely to be platinum resistant could help in

individual counselling of patients and quantifying risks and benefits of standard care of EOC treatment. After external validation, our developed postoperative prediction model may improve patient selection towards those that may actually benefit from platinum-based treatment from those (hopefully in the near future) who benefit from novel therapies.

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