Cancer Epidemiology 75 (2021) 102008

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Clinicopathologic predictors of early relapse in advanced epithelial ovarian cancer: development of prediction models using nationwide data

Sherin A. Said [a,b,*], Reini W. Bretveld [a], Hendrik Koffijberg [c], Gabe S. Sonke [d], Roy F.P. M. Kruitwagen [e,f], Joanne A. de Hullu [b], Anne M. van Altena [b], Sabine Siesling [a,c], Maaike A. van der Aa [a]

[a] Department of Research and Development, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands
[b] Department of Obstetrics and Gynecology, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Department of Health Technology and Services Research, Technical Medical Centre, University of Twente, Enschede, the Netherlands
[d] Department of Medical Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[e] Department of Obstetrics and Gynecology, Maastricht University Medical Centre, Maastricht, the Netherlands
[f] GROW – School for Oncology and Developmental Biology, University of Maastricht, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Epithelial ovarian cancer
Early relapse
Platinum-based chemotherapy
Population-based study
Prediction model

ABSTRACT

Objective: To identify clinicopathologic factors predictive of early relapse (platinum-free interval (PFI) of ≤6 months) in advanced epithelial ovarian cancer (EOC) in first-line treatment, and to develop and internally validate risk prediction models for early relapse.

Methods: All consecutive patients diagnosed with advanced stage EOC between 01-01-2008 and 31-12-2015 were identified from the Netherlands Cancer Registry. Patients who underwent cytoreductive surgery and platinum-based chemotherapy as initial EOC treatment were selected. Two prediction models, i.e. pretreatment and postoperative, were developed. Candidate predictors of early relapse were fitted into multivariable logistic regression models. Model performance was assessed on calibration and discrimination. Internal validation was performed through bootstrapping to correct for model optimism.

Results: A total of 4,557 advanced EOC patients were identified, including 1,302 early relapsers and 3,171 late or non-relapsers. Early relapsers were more likely to have FIGO stage IV, mucinous or clear cell type EOC, ascites, >1 cm residual disease, and to have undergone NACT-ICS. The final pretreatment model demonstrated subpar model performance (AUC = 0.64 [95 %-CI 0.62−0.66]). The final postoperative model based on age, FIGO stage, pretreatment CA-125 level, histologic subtype, presence of ascites, treatment approach, and residual disease after debulking, demonstrated adequate model performance (AUC = 0.72 [95 %-CI 0.71−0.74]). Bootstrap validation revealed minimal optimism of the final postoperative model.

Conclusion: A (postoperative) discriminative model has been developed and presented online that predicts the risk of early relapse in advanced EOC patients. Although external validation is still required, this prediction model can support patient counselling in daily clinical practice.

1. Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy in the western world [1,2] Worldwide, approximately 240,000 new cases and 185,000 disease-related deaths from EOC occur annually [2]. The mortality rate remains high as the vast majority of patients is still diagnosed with advanced stage (i.e. International Federation of Gynecology and Obstetrics (FIGO) stages IIB-IV) disease and a very high likelihood to develop recurrent disease [3–5]. In advanced EOC, standard treatment includes cytoreductive surgery combined with platinum-based chemotherapy. While most patients respond to treatment, 15–20 % have intrinsic resistance toward platinum and often succumb to the disease shortly after diagnosis [6]. Many others experience disease recurrence after initial response to treatment (~60−80%). One-fourth of these recurrences occur within six months after completing first-line treatment [3]. Quantifying risk of early relapse in patients with advanced disease could assist in the

* Corresponding author at: P.O. Box 9101, Geert Grooteplein Zuid 10, 6500 HB, Nijmegen, the Netherlands.
E-mail address: sherin.said@radboudumc.nl (S.A. Said).

https://doi.org/10.1016/j.canep.2021.102008
Received 22 March 2021; Received in revised form 3 August 2021; Accepted 8 August 2021
Available online 9 September 2021

counselling of individual EOC patients, leading into a more personalized care for them.

Prior studies on prognostic factors of early relapse (defined as a PFI ≤ 6 months) have primarily focused on biomarkers, molecular or genetic factors that contribute to the development of early progressive or recurrent disease [4,5,7,8]. While numerous clinicopathologic factors have been studied for progression-free and overall survival in advanced EOC, it is uncertain if these factors could also be used to accurately predict the risk towards early relapse. For instance, studies have suggested that widespread disease that is inaccessible for primary cytoreductive surgery and >1 cm residual disease after surgery lead to an increased risk of early relapse [9,10]. However, these studies are often hampered by their limited sample size and their extent of missing data. No studies that quantify associations between clinicopathologic factors and early relapse (defined as a PFI ≤ 6 months) to develop clinical prediction models using population-based data have been conducted.

If patients who are expected to derive little to no benefit from standard platinum-based treatment are identified early, then intervention with alternative approaches (e.g. novel targeting therapies or dose-dense chemotherapy) or even discontinuation of chemotherapy might be considered. Therefore, the aim of this study is to develop and internally validate two prediction models (a pretreatment and a post-operative model) for early relapse in advanced stage EOC patients during or after first-line treatment using nationwide data.

2. Methods

2.1. Data collection

All consecutive patients diagnosed with advanced stage EOC (FIGO stages IIB-IV) between 01-01-2008 and 31-12-2015 were identified from the Netherlands Cancer Registry (NCR). This population-based registry is weekly notified of all recent histologically confirmed malignancies through an automated nationwide pathology archive (PALGA). Trained registrars have previously reviewed and extracted various data on patient, tumor and treatment characteristics using standardized case report forms. Complementary patient (e.g. performance score) and follow-up (e.g. date of recurrence) data were recently collected for a Dutch Cancer Society's project (IKNL2014-6838). The NCR is annually linked to municipality registries to obtain recent information on vital status. Ethical approval for this study has been acquired from the NCR's Committee of Privacy.

2.2. Study population

Patients diagnosed with advanced EOC and who have undergone cytoreductive surgery combined with platinum-based chemotherapy as their initial EOC treatment were selected. Patients who underwent less than four cycles of platinum-based chemotherapy or no cycles after interval debulking were excluded. Patients who did not undergo debulking or platinum-based chemotherapy were also excluded.

2.3. Definitions

Early relapse was defined as progressive disease during first-line platinum-based chemotherapy, progressive or recurrent disease developed within four to six weeks after receiving the last platinum dose, or recurrent disease developed within six months after completing platinum-based chemotherapy. Progressive and recurrent disease have previously been defined as clinical signs of tumor growth, i.e. increase in CA-125 serum levels (greater than or equal to twice the upper limit of CA-125 serum level on two separate occasions at least one week apart) or tumor lesions visible on imaging (either (re)growth of pre-existing or new lesions), combined with the clinical judgement of the treating medical oncologist or gynecologist [11]. The majority of patients did not undergo routine follow-up of CA-125 levels. For those, it was only determined when they experienced symptoms suggesting progressive or recurrent disease according to Dutch protocol, while post-treatment CA-125 surveillance might be standard in other countries. Residual disease was defined as the maximum diameter of the largest tumor nodule remaining after debulking (classified as no macroscopic, ≤1 or >1 cm residual disease).

2.4. Statistical analyses

Patients' characteristics were summarized using descriptive statistics. The platinum-free interval (PFI) defined as the time between the date of last platinum dose and the date of disease recurrence or disease progression was calculated. Patients were divided into two groups based on their PFI; late or non-relapsers (PFI > 6 months) or early relapsers (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. Differences in overall survival (OS) were analyzed using Kaplan-Meier survival curves and log-rank tests. Overall survival (OS) was defined as the time between the date of diagnosis and the date of death, or last follow-up for patients who were still alive (31-01-2020). Logistic regression models were used to quantify associations between variables and early relapse. 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).

2.5. Model development

Two prediction models, a pretreatment and a postoperative model, were developed and internally validated following the seven steps outlined in 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. Candidate predictors considered for the pretreatment model included age at diagnosis, FIGO stage, pretreatment CA-125 level, performance status (Karnofsky score), and presence of ascites. Concerning the postoperative model, the same candidate predictors were considered in addition to histologic subtype, *BRCA* status, treatment approach (i.e. primary cytoreductive surgery (PCS) or neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT-ICS)), and residual disease after debulking. Candidate predictors initially selected but missing data on more than 50 % of the observations were eliminated from the model.

After model selection, the risk prediction models were estimated.

2.6. Model performance and internal validation

The ability of the models to predict the patients' risk of early relapse during or after first-line EOC treatment was based on the area under the receiver operating characteristic curve (AUC). A larger AUC indicates a higher discriminative power (i.e. the model's ability to distinguish early relapsers from late or non-relapsers). Calibration of the models was evaluated using calibration plots. Internal validation was performed using the bootstrap method, where samples are drawn with replacement from the development sample. Bootstrap iterations were set to 1,000. This approach, in which the entire model building process is repeated,

yielded estimates of optimism in model performance applied to the development data, which were used to compute optimism-corrected indices of performance. To correct for overfitting (i.e. the occurrence where a model performs well for the development sample, but not for new patients), regression coefficients were shrunk towards zero and model intercepts were re-estimated after shrinkage.

3. Results

3.1. Study population

A total of 6,408 patients were diagnosed with advanced EOC between 01−01−2008 and 31−12−2015 in the Netherlands. Of these patients, 4,563 patients underwent cytoreductive surgery and platinum-based chemotherapy as part of their first-line EOC treatment. Among those patients, 1,302 patients were classified as early relapsers and 3,171 patients as late or non-relapsers. Data on disease recurrence or follow-up were unknown for 90 patients whom were excluded from this study (see Fig. 1).

Patients' characteristics are summarized in Table 1. For the early relapsers, median age at diagnosis was 65 years (range 20−91) compared to 64 years (range 20−88) for the late or non-relapsers. Early relapsers were more likely to have FIGO stage IV, whereas late or non-relapsers comprised more often FIGO stage IIB-IIC ($p < 0.001$). Serous type of EOC was the predominant histologic subtype in both groups. Only 3.5 % of early relapsers had endometrioid type of EOC compared to 6.0 % of late or non-relapsers ($p < 0.001$). Early relapsers consisted of more patients who underwent NACT-ICS (76.1 % vs. 56.5 %, $p < 0.001$). Similarly, early relapsers comprised more patients with >1 cm residual disease (18.9 % vs. 6.7 %) and less patients with macroscopic free residual disease (35.3 % vs. 60.3 %, $p < 0.001$).

3.2. Survival outcomes

Early relapsers demonstrated a median OS of 11 months (range 0–83 months, N = 1,299), whereas late or non-relapsers demonstrated a median OS of 43 months (range 9–123 months, N = 3,164) ($p < 0.001$). The Kaplan-Meier estimates of OS of late or non-relapsers and the early relapsers are demonstrated in Fig. 2.

3.3. Models' performance

Due to limited available data, the predictors *BRCA* status and performance status (i.e. Karnofsky score) were eliminated from the model development process. A total of 4,166 and 4,109 patients had complete cases and were included in the pretreatment and postoperative model development respectively. The AUC of the pretreatment model was 0.64 [95 %-CI 0.62–0.66]. The calibration plot of the pretreatment model demonstrated that the 95 %-CI around the observed rate of outcome by deciles of predicted risk often did not cross the perfect fit line (see Fig. 3).

The AUC of the postoperative model was 0.72 [95 %-CI 0.71–0.74]. The calibration plot of the postoperative model showed that the 95 %-CI around the observed rate of outcome by deciles of predicted risk crossed the perfect fit line for all groups (see Fig. 4).

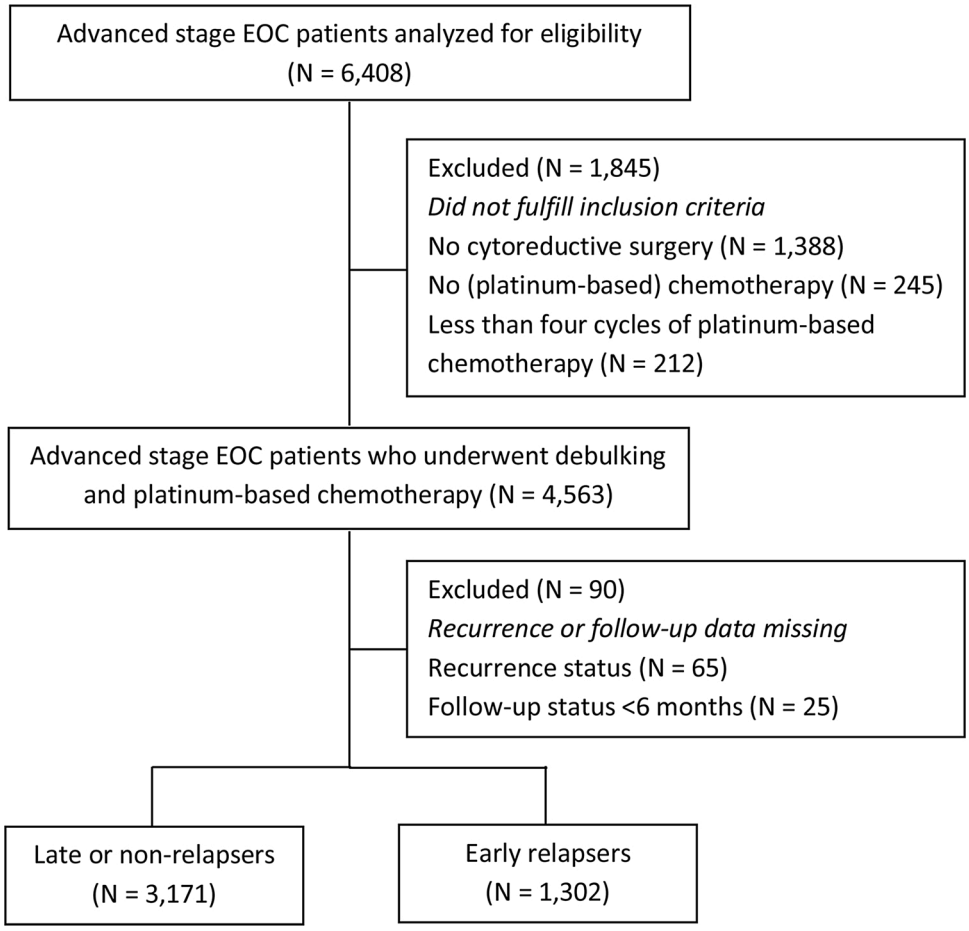


Fig. 1. Flow chart of the study population.

Table 1
Characteristics of study population (N = 4473).

Characteristic	Late or non-relapsers [N = 3,171 70.9 %]		Early relapsers [N = 1,302 29.1 %]		*p*-value
	No. of patients or Median	% or Range	No. of patients or Median	% or Range	
Age at diagnosis (in yrs)					**<0.020**[†,*]
Median (range)	64	20–88	65	20–91	
≤64	1607	50.7	611	46.9	
65–74	1077	33.7	452	34.7	
≥75	487	15.4	239	18.4	
FIGO stage					**<0.001**[†]
Stage IIB-IIC	366	11.5	27	2.1	
Stage IIIA-IIIB	274	8.6	68	5.2	
Stage IIIC	1921	60.6	789	60.6	
Stage IV	610	19.2	418	32.1	
Tumor type					**0.022**[†]
Ovarian tumor	2711	85.5	1096	84.2	
Extra ovarian tumor	311	9.8	159	12.2	
Fallopian tube tumor	149	4.7	47	3.6	
Tumor grade					**<0.001**[†]
Grade 1	167	5.3	41	3.2	
Grade 2	339	10.7	115	8.8	
Grade 3	1753	55.3	684	52.5	
Unknown (N = 1,374)	912	28.8	462	35.5	
Histologic subtype					**<0.001**[†]
Serous	2472	77.9	1019	78.3	
Mucinous	56	1.8	41	3.2	
Endometrioid	191	6.0	39	3.0	
Clear cell	101	3.2	55	4.2	
Adenocarcinoma NOS	316	10.0	125	9.6	
Other[a]	35	1.1	23	1.8	
Karnofsky score (PS)					0.166[†]
10–50	14	0.4	10	0.8	
60–100	1566	49.4	595	45.7	
Unknown (N = 2,288)	1591	50.2	697	53.5	
Pretreatment CA-125 level (in kU/L)					**<0.001**[*]
Median (range)	512	3-56704	793	4-60000	
Unknown (N = 306)	232		74		
***BRCA*status**					**<0.001**[†]
Negative	894	28.2	271	20.8	
BRCA1 mutation	202	6.4	36	2.5	
BRCA2 mutation	117	3.7	6	0.5	
Unknown (N = 2,950)	1958	61.8	1042	76.2	
Presence of ascites					**<0.001**[†]
No	2080	65.6	681	52.3	
Yes	1090	34.4	621	47.7	
Unknown (N = 1)	1	0	0	0	
Treatment approach					**<0.001**[†]
PCS	1378	43.5	311	23.9	
NACT-ICS	1793	56.5	991	76.1	
Residual disease after debulking					**<0.001**[†]
Macroscopic free	1911	60.3	459	35.3	
≤1 cm	1000	31.5	581	44.6	
>1 cm	213	6.7	246	18.9	
Unknown (N = 63)	47	1.5	16	1.2	
Intraperitoneal chemotherapy[b]					**0.020**[†]
No	3037	95.8	1266	97.2	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Late or non-relapsers [N = 3,171 70.9 %]		Early relapsers [N = 1,302 29.1 %]		*p*-value
	No. of patients or Median	% or Range	No. of patients or Median	% or Range	
Yes	134	4.2	36	2.8	
Sites of metastasis					<0.174[†]
Extra-abdominal lymph nodes	107	3.4	65	5.0	
Pleural malignant effusion	243	7.7	195	15.0	
Intra-abdominal parenchymal	172	5.4	100	7.7	
Other[c]	86	2.7	58	4.5	
Not applicable[d] (N = 3,445)	2561	80.8	884	67.9	
Unknown (N = 2)	2	0.1	0	0.0	
Recurrence					**<0.001**[†]
No	964	30.4	0	0	
Yes	1728	54.5	664	51.0	
Not applicable[e] (N = 1,117)	479	15.1	638	49.0	

Abbreviations: BRCA, breast cancer gene; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PCS, primary cytoreductive surgery; PS, performance score.

[*] Wilcoxon rank-sum test.

[†] Fisher's exact or Pearson χ^2 test.

[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.

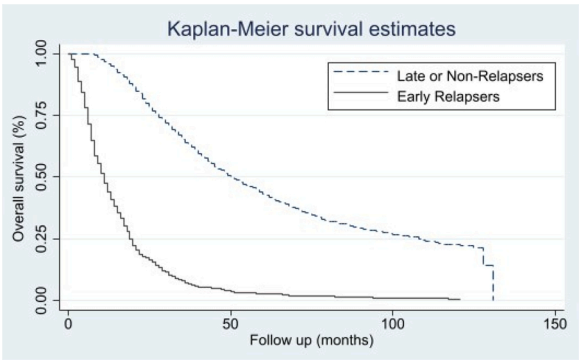


Fig. 2. Kaplan-Meier estimates of the overall survival (OS) of late or non-relapsers (N = 3,164, dash line) and early relapsers (N = 1,299, solid line). The late or non-relapsers had a median OS of 43 months and the early relapsers had a median OS of 11 months.
A statistically significant difference in OS was observed with the log-rank test ($p < 0.001$).
*An additional 10 patients were excluded from the survival analysis with reference to Fig. 1, since these patients had unknown follow-up or survival data.

3.4. Models' validation

Due to the overall subpar model performance of the final pretreatment model, no internal validation of this model was performed. Bootstrapping using 1,000 iterations revealed a calibration slope of 0.97 for the final postoperative model. To correct this minimal overfitting, a shrinkage factor of 0.97 was used to adjust the odds ratios and intercept estimates of the final model.

3.5. Nomogram

An online score calculator based on the internally validated estimates of the final postoperative model was developed and presented on a freely accessible web-based platform (see Fig. 5). For instance, for a 65-year-old FIGO stage IIIC patient who presented with mucinous EOC, a pretreatment CA-125 level of 1230 kU/L, ascites, and who underwent suboptimal (i.e. $\leq$ 1 cm residual disease) NACT-ICS; the risk towards early relapse is estimated at 92 %,which is relevant information in the counselling of individual patients. In a subgroup of patients (e.g. vulnerable patients), other options such as dose-dense chemotherapy (i.e. shortening the time-intervals between chemotherapy doses) or even discontinuation of platinum-based chemotherapy should also be discussed besides the

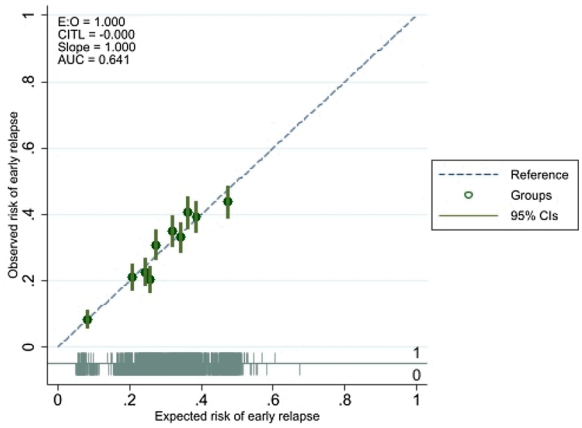


Fig. 3. Calibration plot of the final pretreatment model.

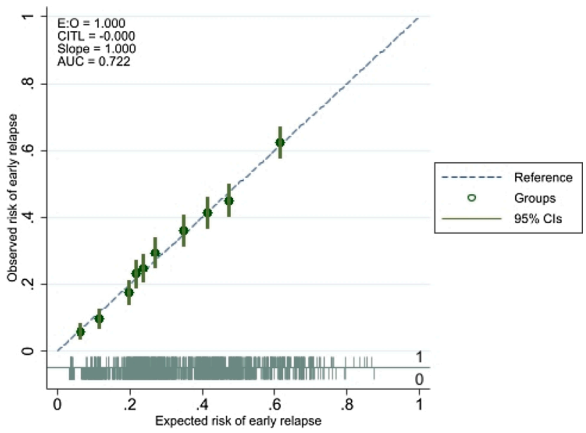


Fig. 4. Calibration plot of the final postoperative model.

continuation of standard platinum-based chemotherapy.

3.6. Risk stratification

Table 2 shows that the performance of the final postoperative model is highly dependent on the chosen threshold for a positive test. As the threshold used to define high-risk of early relapse increases, the sensitivity decreases but the specificity and positive predictive value increase. 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. For the patient example, at a cut-off value of 70 %, one minus positive predictive value is estimated at 33.9 %, indicating the percentage of patients who are incorrectly classified as early relapsers.

3.7. Sensitivity analysis

In a sensitivity analysis, including solely patients with a known *BRCA* status (N = 1,504), *BRCA* status was added to the postoperative model developing process as an additional predictor. A total of 1,397 patients had complete cases in the *BRCA* model development. The AUC of the *BRCA* model was 0.76 [95 %-CI 0.73–0.79]. The calibration plot of the *BRCA* model showed that the 95 %-CI around the observed rate of outcome by deciles of predicted risk crossed the perfect fit line for all groups (see Fig. 6). Bootstrap internal validation demonstrated a calibration slope of 0.88 for the final *BRCA* model. This shrinkage factor of 0.88 was used to adjust the odds ratios and intercept estimates of the final *BRCA* model. The final models with their unadjusted (training set) and adjusted (test set) odds ratios and intercept estimates are listed in supplementary tables A.3, A.4, and A.5.

4. Discussion

In this population-based study, two prediction models, based on clinicopathologic factors, were developed that estimate the risk of early relapse in advanced EOC during or after first-line treatment. Significant associations between early relapse (i.e. a PFI $\leq$ 6 months) and FIGO stage, histologic subtype, presence of ascites, treatment approach, and residual disease after debulking were found. A nomogram has been built of the final postoperative model and presented on a freely accessible online platform.

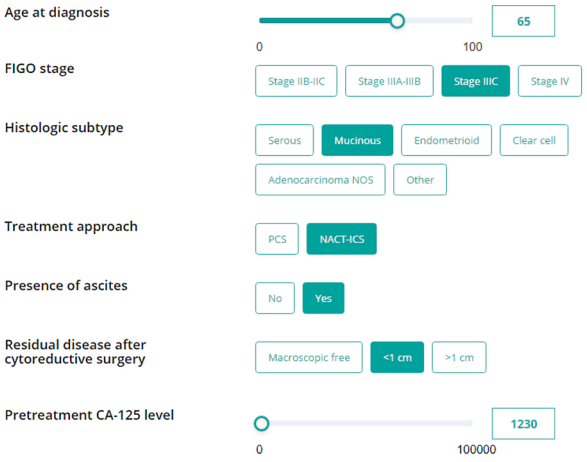
4.1. Early relapse and tumor histology

In accordance with literature, our data showed that patients with clear cell and mucinous cell type indeed have a higher tendency to become early relapsers compared to those with serous type of EOC [13,14]. Studies have reported that, while less common, low grade serous cancer (LGSC) tends to be more intrinsically resistant to platinum-based chemotherapy compared to high grade serous cancer (HGSC). A further subclassification of our serous cancer type patients into LGCS and HGCS patients did not reveal a significant difference in risk of early relapse possibly due to the indolent behavior of LGSC [13,14]. Still, this requires central revision of serous histopathologies which was not feasible considering the extensive database covering patients from many Dutch hospitals over several years.

4.2. Early relapse and treatment approach

In addition, treatment approach revealed to be an important predictor of early relapse in our analysis. Specifically, patients who did not qualify for primary cytoreductive surgery (PCS), but who received neoadjuvant chemotherapy preceding interval cytoreductive surgery (NACT-ICS) instead, demonstrated shorter platinum-free intervals. Similarly, Luo et al. showed that NACT-ICS patients had a higher occurrence of developing progressive or recurrent disease within six months after first-line treatment 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]. Conversely, most studies failed to show a significant difference in progressive or recurrent disease within six months after treatment between NACT-ICS and PCS patients when corrected for covariates [10,15,16].

Besides the probability of a successful cytoreductive surgery (i.e. no



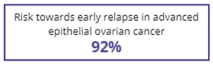


Fig. 5. Online score calculator with a patient example.
The above shown parameters were set for the 65-year-old patient example described in the text to demonstrate the results of the nomogram. The risk towards early relapse is estimated at 92 % for the patient using our online nomogram. Table 2 shows that at a cut-off value of 90 % for a positive test, 0% of the patients will be incorrectly classified as early relapsers. Depending on the clinical implications and this patient's treatment preference, treatment options can be discussed.

Table 2
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 (%)	1-Specificity (%)	1-PPV (%)	NPV (%)	LR+
5 %	99.1	93.1	69.2	94.8	1.06
10 %	98.4	88.6	68.0	95.0	1.11
15 %	95.1	74.5	65.2	92.6	1.28
20 %	91.9	68.3	63.9	90.4	1.35
25 %	71.8	39.9	57.0	83.6	1.80
30 %	62.3	30.2	53.7	81.6	2.06
35 %	57.5	26.6	52.5	80.5	2.16
40 %	47.2	19.7	49.9	78.4	2.40
45 %	32.6	11.4	45.7	75.8	2.86
50 %	23.9	6.9	41.8	74.5	3.46
55 %	16.7	4.1	36.8	73.3	4.07
60 %	12.5	2.9	35.9	72.6	4.31
65 %	6.8	1.6	35.7	71.6	4.25
70 %	2.4	0.5	33.6	70.9	4..80
75 %	0.8	0.2	33.3	70.6	4.00
80 %	0.5	0	14.3	70.6	16.3
90 %	0	0	–	70.5	–
100 %	0	0	–	70.5	–

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

* A positive test indicates a positive outcome of developing early relapse.

Table 2 shows that the performance of the final postoperative model is highly dependent on the chosen threshold for a positive test. As the threshold used to define high-risk of early relapse increases, the sensitivity decreases but the specificity and positive predictive value increase. For instance, for a cut-off value of 80 %, one minus positive predictive value is estimated at 14.3 %, indicating the percentage of patients who are incorrectly classified as early relapsers. 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.

macroscopic or ≤1 cm residual disease), other important reasons to opt for NACT-ICS rather than PCS include FIGO stage IV disease, poor performance status, and high perioperative risk [17]. Herewith, we can possibly conclude that early relapsers initially present with worse conditions, and consequently, clinicians are more inclined to choose NACT-ICS as a treatment approach for them. Our results suggest that NACT-ICS is significantly associated with early relapse; however, it remains unclear if this is due to our patient selection towards NACT-ICS as a treatment approach or attributable to other reasons. Geographical external validation of our postoperative model may give better insights into this finding and its implication for the Dutch clinical practice.

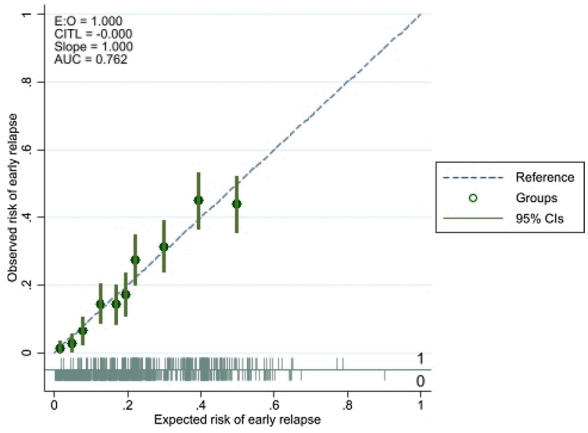


Fig. 6. Calibration plot of the final *BRCA* model.

4.3. Early relapse and BRCA status

Insufficient data on *BRCA* status (mainly over the first period of the study when it was not clinical practice) has prevented us from including this variable without substantially reducing the usability of the study population in the postoperative model development. Nonetheless, a sensitivity analysis, including only patients with an known *BRCA* status (N = 1,504), revealed that patients with a *BRCA-negative* mutation status (OR 5.43; 95 %-CI 2.15–13.77) along with patients with a *BRCA1* mutation status (OR 2.91; 95 %-CI 1.07–7.95) were more likely to be early relapsers compared to those with a *BRCA2* mutation status. Consistently, several reports found that patients with a *BRCA2* mutation have an increased response to platinum-based chemotherapy, and therefore, *BRCA* status could be another important predictor of prolonged platinum-free interval [13,18–20]. Thus, information about *BRCA* status should be determined for all newly diagnosed EOC patients as recommended in current guidelines to confirm its effect on patients' platinum-free interval in addition to more important reasons (i.e. familial cancer risk and PARP inhibitors' indication) [13,21,22]. Furthermore, exploratory analyses, including performance status in the postoperative model development, failed to show a significant relation between performance status and early relapse, possibly due to its colinearity with age at diagnosis weakening any probable association.

4.4. Strength and limitations

Despite the adequate discriminative ability of our final postoperative model and population-based study design, several limitations apply to our study. Insufficient data on the post-chemotherapy CA-125 nadir, a parameter of which its association with the (un)favorable progression-free and overall survival of EOC has been established, did not allow for this parameter to be included in the postoperative model development [23]. Moreover, bootstrap resampling does not exclude that some observations are considered several times during the same bootstrap iteration, whereas others are never. That occurrence along with the large dataset could have resulted into minimal model optimism. However, bootstrapping is still considered one of the strongest methods of internal validation and the size of the study population makes it highly unlikely that the optimism of the model is underestimated. Nevertheless, there are alternative model-building approaches that might lead to better performing models. To assess this, the models were also built using gradient boosting decision trees (GBDT) with a random 70/30 (i.e. train/test) sample split. However, the model performance of the GBDT models were found to be similar as the logistic regression models (data not shown).

Furthermore, patients who received less than four cycles of platinum-based chemotherapy or no cycles after interval cytoreductive surgery were excluded from our study, since these patients received inadequate treatment. Thus, early relapsers might have been excluded from this study. Nevertheless, the far majority of those patients discontinued chemotherapeutic treatment for reasons other than non-responsiveness to platinum-based treatment (e.g. adverse reactions, postoperative complications, or patient refusal). Consequently, most of those patients would have been wrongly categorized as early relapsers.

4.5. Future implications

Despite its adequate model performance, one might argue the clinical usefulness of our final postoperative model. Currently, there is no viable alternative to platinum-based therapy in the armamentarium of advanced EOC treatment. Nonetheless, the model does give insight into which patients may develop platinum resistant relapse using clinicopathologic characteristics that are often available to treating gynecologic and medical oncologists. 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 additional systemic treatment accompanied with high toxicity should be discussed with these

patients. A prediction model along with clinical assessment could be helpful in the shared decision-making process of continuing, altering (e.g. dose-dense chemotherapy) or even discontinuing chemotherapeutic treatment. Also, it could serve as a useful tool to decide whether patients are more inclined to gain from clinical trials rather than the standard treatment and even help in selecting the right target patients for those studies. It remains difficult to accurately predict the risk of early relapse before starting any treatment. Despite its subpar predictive ability, the final pretreatment model could represent a benchmark for the development of more accurate predictive models that include biomarkers, genetic or molecular factors, and even other clinicopathologic factors (e.g. comorbidity status).

4.6. Conclusion

Concluding, an improved understanding of contributing factors to the development of early relapse in advanced EOC could aid in an accurate prediction of patients' prognosis and outcome. Thus, identifying which patients are more likely to become early relapsers could help in the individual counselling of patients by quantifying the risks and benefits of standard chemotherapeutic treatment in the shared decision-making process. After external validation, our postoperative prediction model may improve patient selection towards those that may actually benefit from platinum-based treatment from those who may not but rather may benefit from novel therapies.

Authorship contribution statement

Study concepts: SAS, RB, HK, RK, GS, SS, MvdA.
Study design: SAS, RB, HK, SS, MvdA.
Data acquisition: SAS, RB, MvdA.
Quality control of data and algorithms: SAS, RB, HK, SS, MvdA.
Data analysis and interpretation: SAS, RB, HK, RK, GS, AvA, SS, MvdA.
Statistical analysis: SAS, RB, HK.
Manuscript preparation: SAS.
Manuscript editing: SAS, RB, HK, RK, GS, JdH, AvA, SS, MvdA.
Manuscript review: SAS, RB, HK, RK, GS, JdH, AvA, SS, MvdA.

Author disclosure statement

No disclosures for all authors.

Funding

This work was supported by Dutch Cancer Society [IKNL2014-6838].

CRediT authorship contribution statement

Sherin A. Said: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Reini W. Bretveld:** Conceptualization, Software, Supervision. **Hendrik Koffijberg:** Conceptualization, Methodology, Supervision, Visualization, Writing - review & editing. **Gabe S. Sonke:** Conceptualization, Supervision, Writing - review & editing. **Roy F.P.M. Kruitwagen:** Conceptualization, Supervision, Writing - review & editing. **Joanne A. de Hullu:** Writing - review & editing. **Anne M. van Altena:** Conceptualization, Visualization, Supervision, Writing - review & editing. **Sabine Siesling:** Conceptualization, Methodology, Supervision, Visualization, Writing - review & editing. **Maaike A. van der Aa:** Conceptualization, Methodology, Supervision, Visualization, Writing - review & editing.

Acknowledgements

The authors thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry. Also, the authors would like to gratefully acknowledge Dr. Marissa van Maaren for her helpful advice in the statistical analysis and model validation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2021.102008.

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