TOWARDS **PERSONALIZED CARE** IN **ADVANCED EPITHELIAL OVARIAN CANCER**

TREATMENT RESPONSE AND PREDICTORS OF SURVIVAL

SHERIN ABDO SAID

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Sherin Abdo Said

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For reasons of consistency within this dissertation, some terms and abbreviations have been standardized throughout the text, and may therefore slightly differ from the original publications.

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Bismillahi al-Rahman al-Rahim
In the name of Allah, the Most Gracious, the Most Merciful

To my parents, Abdo and Zahra,
for giving me every opportunity they never had and for their endless sacrifices.

To my siblings, Mohamed, Sherihan, Mustafa, Aisha, and Munira,
for their unconditional love and support.

To my nieces, Sumaya and Amanah,
for their joy, which has been a constant reminder of what truly matters.

To the people of Palestine,
may we live to see a free Palestine, where justice, dignity, and peace are the rights of all.

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CHAPTER 1

General Introduction and Dissertation Outline

General Introduction

Epithelial ovarian cancer (EOC) is the second most common gynecologic cancer and remains the leading cause of death among gynecologic malignancies, with over 324,000 new cases and approximately 207,000 deaths reported worldwide in 2022 [1]. In the Netherlands, approximately 1,400 new cases and 1,000 deaths are reported annually [2]. Accounting for nearly 90% of all ovarian cancer cases, EOC predominantly affects postmenopausal women [3–5].

EOC comprises several histologic subtypes, each with distinct origins and clinical behavior [3, 6–9]. High-grade serous carcinoma, the most common and aggressive type, is thought to arise from the fallopian tube epithelium and usually presents at an advanced stage [9–11]. Low-grade serous carcinoma is also linked to the fallopian tube epithelium but follows a more indolent course, often developing from serous borderline tumors [8–10, 12, 13]. Endometrioid and clear cell carcinomas are frequently associated with endometriosis and generally present at an early stage [9]. Mucinous carcinoma presents diagnostic challenges, as many cases once classified as primary ovarian cancers are now considered metastases from gastrointestinal origins [9, 14–16]. True primary mucinous tumors, typically large and unilateral, often arise from pre-existing benign or borderline lesions, although exceptions occur and require careful evaluation [16].

EOC diagnosis typically involves clinical evaluation, imaging techniques (e.g., transvaginal ultrasound and computed tomography scans), serum tumor marker CA-125 assessment, and histopathologic confirmation via biopsy [3]. More than 75% of patients present with advanced-stage disease, classified as International Federation of Gynecology and Obstetrics (FIGO) stages IIB through IV, due to the nonspecific nature of early symptoms, such as bloating and abdominal discomfort [6]. Currently, there are no reliable screening methods for early detection of EOC, leading to increasing interest in prevention and risk-reduction strategies, such as risk-reducing salpingo-oophorectomy for high-risk individuals [17–19].

In advanced-stage EOC, standard treatment involves a multimodal approach combining cytoreductive surgery and platinum- and taxane-based chemotherapy [4, 20]. The treatment approach depends on the feasibility of achieving complete cytoreduction, which is influenced by factors such as the patient's overall condition and tumor burden [20, 21]. Patients eligible for upfront surgery undergo primary cytoreductive surgery (PCS) followed by six cycles of adjuvant chemotherapy [4, 5]. In contrast, when complete cytoreduction is deemed not feasible at initial presentation, treatment starts with

three cycles of neoadjuvant chemotherapy, followed by interval cytoreductive surgery (NACT-ICS) and three additional cycles of adjuvant chemotherapy [4, 5]. Over the past decade, the use of targeted therapies, i.e., anti-angiogenic therapy and poly(ADP-ribose) polymerase (PARP) inhibitors, has transformed the management of EOC in both primary and recurrent settings [22].

Intraperitoneal (IP) chemotherapy, which delivers chemotherapy directly into the peritoneal cavity, has been introduced for selected patients to enhance drug exposure to residual disease [23–25]. However, its use is limited due to toxicity, tolerability concerns, and technical challenges (e.g., catheter-related complications) [23–25]. Additionally, hyperthermic intraperitoneal chemotherapy (HIPEC), administered during cytoreductive surgery, combines heated chemotherapy with surgical resection to target microscopic disease and improve outcomes [25–27]. In the Netherlands, HIPEC is currently offered in the NACT-ICS setting.

Outline of this Dissertation

This dissertation explores the factors influencing the management and survival of advanced-stage EOC. By assessing clinical and hematologic prognostic markers, treatment adherence, and the impact of surgical and clinical interventions, it aims to identify determinants of overall survival and early relapse. Furthermore, this research focuses on developing and validating predictive models to guide individualized treatment approaches and improve patient counseling. The following chapters address these aims in detail.

Part I: Clinical and treatment factors affecting advanced-stage EOC survival
Despite advancements in treatment, survival rates for advanced EOC have only modestly improved over the past decades, with five-year survival remaining between 29 and 47% [3, 28, 29]. Approximately 15% of patients survive beyond 10 years, with long-term survival associated with factors such as younger age, lower FIGO stage, lower tumor grade, non-serous histology, absence of ascites, primary cytoreductive surgery, and complete cytoreduction [30]. However, predicting individual survival outcomes remains challenging. Pretreatment anemia, thrombocytosis, and leukocytosis are common hematologic abnormalities in advanced-stage EOC. These markers are linked to a poorer prognosis in several cancers, though their specific prognostic value in EOC remains underexplored [31–34]. **Chapter 2** investigates the association of these hematologic parameters with overall survival and develops predictive models

incorporating these markers alongside established prognostic factors to estimate the probability of ≤3-, ≥5-, and ≥10-year overall survival.

In an effort to improve survival outcomes for patients with advanced-stage EOC, there has been growing interest in the role of the immune system, particularly in the balance between immune-activating and immune-suppressing mechanisms. Targeting a single immune pathway has proven inadequate for eradicating ovarian cancer [35, 36], highlighting the need for a more comprehensive approach [8]. A remarkable case of spontaneous regression in FIGO stage IIIC EOC was observed in a patient who developed sepsis following a bowel perforation during diagnostic workup [37]. The patient experienced tumor regression without undergoing standard treatment [37]. Though rare, such clinical cases suggest that immune activation may play a role in tumor control. **Chapter 3** evaluates the association of sepsis with oncologic outcomes in advanced-stage EOC, exploring its impact on overall and progression-free survival and its potential to inform novel immunotherapeutic strategies.

The spleen also plays an important role in the immune response, contributing to both immune activation and suppression, which may influence tumor progression. In advanced-stage EOC, splenectomy is sometimes required to achieve complete cytoreduction, particularly in cases involving extensive upper abdominal disease or metastatic splenic involvement. However, the impact of splenectomy on long-term survival outcomes in these patients remains unclear. While some studies suggest that splenectomy facilitates complete cytoreduction with acceptable perioperative complications, others report inconsistent findings. **Chapter 4** investigates the association of splenectomy with oncologic outcomes, including progression-free and overall survival, in patients with advanced-stage EOC undergoing cytoreductive surgery.

For advanced-stage EOC, guidelines recommend combining cytoreductive surgery with six cycles of carboplatin and paclitaxel as the standard first-line treatment. However, adherence to these guidelines in real-world practice remains unclear. **Chapter 5** investigates patterns of chemotherapy adherence and modifications, such as dose reduction, interruption, and reduction in the number of cycles, in the Netherlands. This nationwide study, using data from the Netherlands Cancer Registry, evaluates the reasons for deviations from guidelines and their association with overall survival, highlighting potential gaps between clinical practice and guideline-recommended care.

Part II: Predictive models for early relapse in advanced-stage EOC

While most patients initially respond to first-line treatment, 60–80% will relapse after successful frontline therapy [38]. One-quarter of these relapses occur within six

months, during or shortly after first-line chemotherapy [39]. Early relapse is associated with poor prognosis, with low response rates to subsequent chemotherapy (<20%) and a median overall survival of less than a year [40]. Identifying patients at high risk for early relapse is essential for tailoring individualized care and facilitating shared decision-making regarding treatment options, toxicity, and quality of life. **Chapter 6** focuses on developing prediction models that estimate the risk of early relapse using clinicopathologic factors. These models could aid clinicians in counseling individual patients and making informed decisions about follow-up care and treatment adjustments, ultimately supporting more personalized care.

Before these models can be incorporated into routine clinical practice, it is important to validate them using a cohort distinct from the one used during their development. **Chapter 7** externally validates the models developed in **Chapter 6** using independent cohorts from Australia and the Netherlands.

Finally, **Chapter 8** provides a comprehensive discussion of the key findings, their clinical relevance, and implications for future research and practice in the management of advanced-stage EOC. **Chapter 9** offers a concise summary of the dissertation, highlighting the study designs, main findings, and brief conclusions in both English and Dutch.

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PART I

Clinical and Treatment Factors Affecting Advanced-Stage EOC Survival

CHAPTER 2

Development and Internal Validation of Prediction Models for Survival of Advanced Epithelial Ovarian Cancer Based on Established Prognostic Factors and Hematologic Parameters

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Abstract

Objective

To assess the association between pretreatment thrombocytosis, anemia, and leukocytosis and overall survival (OS) of advanced-stage EOC. Furthermore, to develop predictive models using established prognostic factors and pretreatment hematologic parameters to estimate the OS of advanced-stage EOC patients.

Methods

Advanced-stage EOC patients treated between January 1, 1996 and January 1, 2010 in the eastern Netherlands were included. Survival outcomes were compared between patients with and without pretreatment thrombocytosis (≥450,000 platelets/μL), anemia (hemoglobin level of <7.5 mmol/L), or leukocytosis (≥11.0 × 10^9 leukocytes/L). Three predictive models (for ≤3-, ≥5- and ≥10-year OS) were developed. Candidate predictors were fitted into multivariable logistic regression models. Multiple imputation was conducted. Model performance was assessed on calibration, discrimination, and Brier scores. Bootstrap validation was used to correct for model optimism.

Results

A total of 773 advanced-stage (i.e., FIGO stages IIB–IV) EOC patients were included. The median [interquartile range, IQR] OS was 2.3 [1.3–4.2] and 3.0 [1.4–7.0] years for patients with and without pretreatment thrombocytosis (p<0.01). The median OS was not notably different for patients with and without pretreatment leukocytosis (p=0.58) or patients with and without pretreatment anemia (p=0.07). The final models comprised established predictors with either pretreatment leukocyte or platelet count. The ≥5- and ≥10-year OS models demonstrated good calibration and adequate discrimination with optimism-corrected *c*-indices [95% CI] of 0.76 [0.72–0.80] and 0.78 [0.73–0.83], respectively. The ≤3-year OS model demonstrated suboptimal performance with an optimism-corrected *c*-index of 0.71 [0.66–0.75].

Conclusion

Pretreatment thrombocytosis is associated with poorer EOC survival. Two well-performing models predictive of ≥5-year and ≥10-year OS in advanced-stage EOC were developed and internally validated.

**QR codes linking to the online score calculators are provided in the Supplementary section.*

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecologic cancers in the Western world [1]. In 2020, approximately 314,000 new cases of EOC and 207,000 EOC-related deaths were reported worldwide [2]. In advanced-stage EOC, standard treatment includes cytoreductive surgery combined with platinum- and taxane-based chemotherapy [3]. In the past decade, the anti-angiogenic agent bevacizumab and poly(ADP-ribose) polymerase (PARP) inhibitors have been introduced as maintenance therapy for advanced-stage EOC [4]. While most patients achieve complete remission, 60–80% experience disease relapse and often succumb to the disease within 5 years after being diagnosed [5, 6]. Nevertheless, a subgroup of patients may be long-term survivors, beyond 5–10 years [6–12]. This may depend on multiple factors including FIGO stage, age, histologic subtype, tumor grade, performance status, or residual disease.

In addition to more established prognostic factors for EOC, there has been accumulating evidence on the prognostic value of high platelet counts (i.e., preoperative thrombocytosis) in EOC [13–15]. Specifically, malignant EOC cells were demonstrated to produce thrombopoietic cytokines (i.e., IL-6) that lead to paraneoplastic thrombocytosis, which in turn contributes to tumor growth and metastatic development or growth [14, 16, 17]. Pretreatment thrombocytosis was associated with extensive initial disease burden, macroscopic residual disease after cytoreductive surgery, postoperative morbidity, and shortened survival [14–16, 18]. Similarly, pretreatment leukocytosis and anemia, being linked to cancer progression, were also poor prognostic factors for EOC patients [14, 19, 20]. However, prior studies evaluating pretreatment anemia, leukocytosis, and thrombocytosis in EOC presented limited cohort sizes or clinical data. Therefore, it remains unclear whether these easily available parameters could really aid in predicting survival of individual advanced-stage EOC patients in clinical practice.

The aim of this study was to assess whether the aforementioned pretreatment hematologic parameters are associated with overall survival (OS) of advanced-stage EOC patients. In addition, the aim was to develop and internally validate three models predictive of ≤3-, ≥5- and ≥10-year OS in advanced-stage EOC in which established prognostic factors and pretreatment hematologic parameters are considered as predictors. These predictive models may be helpful for clinicians in estimating patients' probabilities of ≤3-, ≥5-, and ≥10-year OS.

Methods

Data collection

Patients who underwent treatment for advanced-stage EOC (i.e., FIGO stages IIB–IV) between January 1, 1996 and January 1, 2010 in the eastern part of the Netherlands were selected. These patients were identified through a multicenter database that covers 1,554 EOC patients from eleven participating Dutch hospitals and were selected since the time after their date of diagnosis exceeded 10 years. Extensive data on patient, tumor, and treatment characteristics were previously collected from patients' medical records for registration and research purposes [21]. Survival data of the patients were obtained through the Netherlands Cancer Registry (NCR). The NCR is a nationwide cancer registry that is annually linked with municipality registries to update patients' mortality status.

Study population

Patients diagnosed with FIGO stages IIB–IV EOC were identified. Patients who underwent cytoreductive surgery and received at least one cycle of platinum-based (neo)adjuvant chemotherapy as part of their EOC treatment were included to ensure the study population underwent adequate treatment with a curative intent, enabling a proper assessment of the association between pretreatment hematologic parameters and overall survival of EOC.

Definitions

Pretreatment thrombocytosis was defined as a platelet count of ≥450,000 platelets per microliter (consistent with Stone et al. who demonstrated a significant association between thrombocytosis and shortened survival [16]). Pretreatment anemia was defined as a hemoglobin level of <7.5 mmol per liter [22, 23]. Pretreatment leukocytosis was defined as a leukocyte count of $\geq 11.0 \times 10^9$ per liter [14, 19]. Treatment approach was defined as primary cytoreductive surgery (PCS) followed by adjuvant chemotherapy, or neoadjuvant chemotherapy followed by interval cytoreductive surgery and adjuvant chemotherapy (NACT-ICS). Platinum-based chemotherapy is generally initiated within six weeks after diagnosis and/or cytoreductive surgery. In addition, patients who were initially scheduled to undergo primary cytoreductive surgery but whose procedure was aborted, and subsequently received platinum-based chemotherapy followed by cytoreductive surgery, were considered NACT-ICS patients. Residual disease was defined as the maximum diameter of the largest remaining tumor nodule after cytoreductive surgery, classified as no macroscopic disease (complete cytoreduction), macroscopic disease ≤1 cm (optimal cytoreduction), or >1 cm (incomplete cytoreduction).

Statistical analysis

Clinicopathologic characteristics were summarized using descriptive statistics. The OS was calculated as the time between the date of diagnosis and the date of death, or the date of last follow-up for patients who were still alive (censoring date: January 31, 2023). To assess whether pretreatment anemia, leukocytosis, or thrombocytosis was associated with OS, Kaplan–Meier survival curves and log-rank tests were used. For the log-rank tests, the Kaplan–Meier survival curves were censored at ten years of follow-up. Characteristics were demonstrated for the entire study population and patients with ≤3-, ≥5-, and ≥10-year OS. The cutoff point of ≤3-year OS was selected since the median OS of advanced-stage EOC patients is estimated at ~36 months [24]. The ≥5-year OS was selected to facilitate comparison with similar studies and FIGO reports [25–28]. Lastly, the ≥10-year OS was selected as a cutoff point for exceptionally long-term survival of advanced-stage EOC [7, 8, 11, 12]. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines were followed to report this study [29]. All statistical analyses were performed using STATA/SE (version 17.0) and R (version 4.0.3) (http://www.r-project.org) [30, 31]. The following R packages were used for the analyses: "Hmisc" (version 4.7.0), "rms" (version 6.3.0), and "caret" (version 6.0.93) [32-35].

Model development

Three prediction models were developed and internally validated using the seven steps outlined in Steyerberg et al. [36]. The models were developed to predict probabilities of ≤3-, ≥5-, and ≥10-year OS. Candidate predictors considered included nine established prognostic factors (i.e., age at diagnosis, FIGO stage, tumor grade, histologic subtype, pretreatment CA-125 level, Karnofsky score, ascites volume, treatment approach, and residual disease after cytoreductive surgery) along with the following pretreatment hematologic parameters: hemoglobin level, platelet count, and leukocyte count, both as continuous and dichotomous variables. Continuous variables were transformed using logarithmic transformations when required. Multiple imputation was conducted using 30 imputations and 200 iterations. Candidate predictors were fitted into multivariable logistic regression models. Predictors were selected using backward selection (p<0.50) to avoid using noise predictors in the models [37]. The results were pooled using Rubin's rules [38]. Model performance was assessed on discrimination, calibration, and Brier scores.

I. Discrimination, i.e., the model's ability to distinguish between patients with and without the survival outcome of interest, was assessed using Harrell's concordance index (*c*-index) [39]. A value of 0.5 indicates that the model predicts outcomes no better than random chance. Conversely, a value of 1 indicates that

the model perfectly predicts who will experience a certain outcome from those who will not.

II. Calibration, i.e., the agreement between the predicted and observed rates at the (sub)group level, was assessed with calibration plots, calibration intercepts, and slopes.

III. The Brier score is an overall performance measure calculated as the mean squared difference between the observed and the predicted outcomes. The lower the score, the better the predictions reflect the observed data. A score near 0 indicates perfect accuracy.

Model validation

Internal validation was performed using the boot-MI method as proposed by Bartlett and Hughes [38]. A total of 100 bootstrap samples were drawn from the development sample. The entire model development process, including multiple imputation, was repeated in each bootstrap sample. Bootstrapping was used to estimate and correct for optimism in *c*-indices, calibration, and Brier scores and to estimate shrinkage factors for the final models. After internal validation, the shrinkage factors were used to re-estimate the regression coefficients and model intercepts.

Ethical approval

Ethical approval from the NCR's Committee of Privacy was obtained for this study [K17-245].

Results

Study population

A total of 1,045 patients were diagnosed with advanced-stage EOC between January 1, 1996 and January 1, 2010 in the eastern part of the Netherlands (**Figure 1**). Of these, 773 patients underwent cytoreductive surgery (PCS or NACT-ICS) in combination with platinum-based chemotherapy. Overall, 415 of 773 patients survived ≤3 years (53.7%), 238 of 773 (30.8%) survived ≥5 years, and 127 of 773 (16.4%) survived ≥10 years.

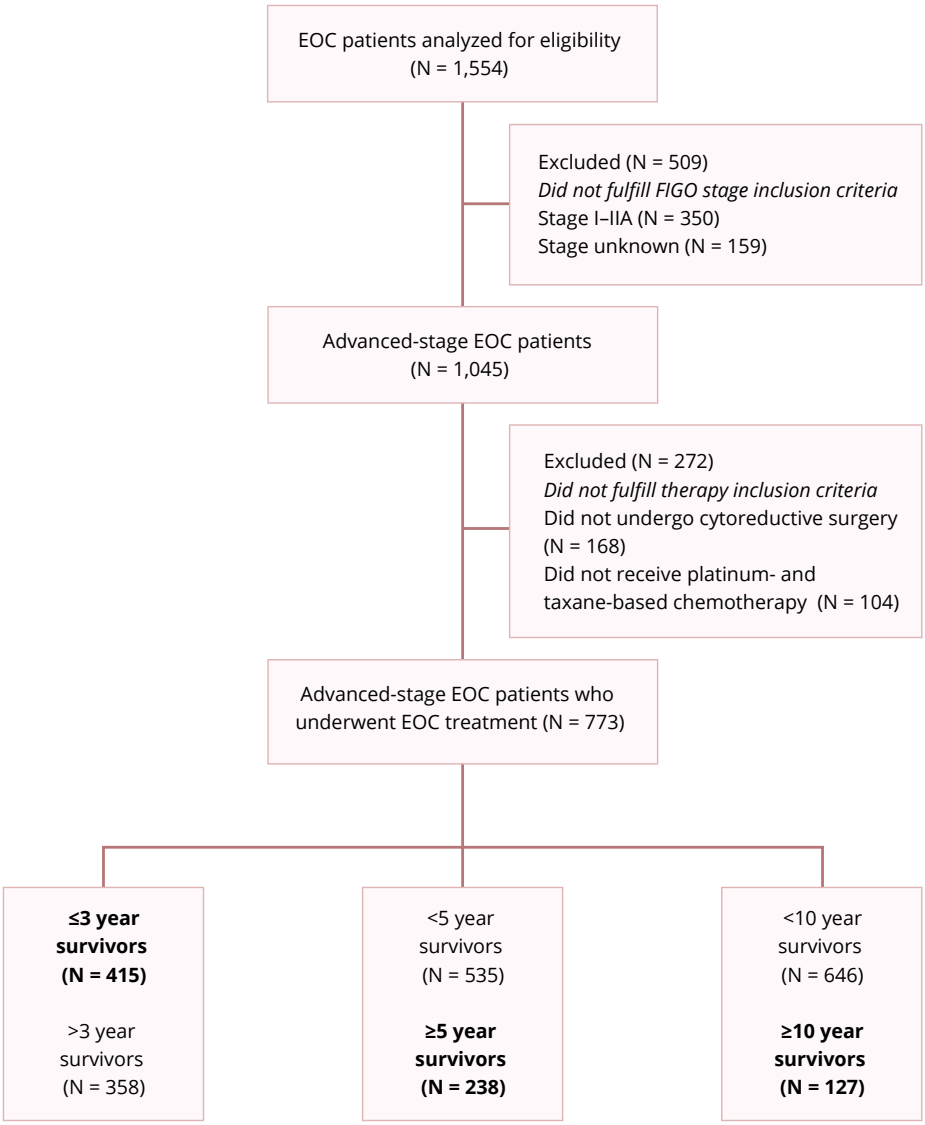

Figure 1. Flowchart of the study population.

Patient, tumor, and treatment characteristics

The patient, tumor, and treatment characteristics are summarized in **Table 1**. The ≤3-year survivors were slightly older than the ≥5- and ≥10-year survivors. In addition, the ≤3-year survivors consisted of relatively more patients with FIGO stages IIIC and IV and fewer patients with FIGO stages IIB–IIIB. The serous type of EOC was the most common histologic subtype among the ≤3-, ≥5-, and ≥10-year survivors. However, the ≥5- and

≥10-year survivors comprised relatively more patients with the endometrioid type of EOC than the ≤3-year survivors. Moreover, the ≤3-year survivors consisted of more patients with Karnofsky scores of 50 to 70 and fewer patients with 80 to 100 than the ≥5- and ≥10-year survivors. The ≤3-year survivors also comprised more patients with pretreatment thrombocytosis compared with the ≥5- and ≥10-year survivors. Similarly, the ≤3-year survivors comprised a slightly higher proportion of patients with pretreatment anemia and leukocytosis than the ≥5- and ≥10-year survivors. Lastly, the ≤3-year survivors comprised relatively fewer patients who underwent PCS or complete cytoreduction compared with the ≥5- and ≥10-year survivors.

Table 1. Patient, tumor, and treatment characteristics of the study population (N = 773).

	Total (N = 773)	**≤3-year OS (N = 415)**	**≥5-year OS (N = 238)**	**≥10-year OS (N = 127)**
Characteristic	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]
Age at diagnosis (in yrs)				
Median	61 [21–84]	63 [28–84]	60 [27–80]	59 [38–77]
FIGO stage				
Stage IIB–IIC	83 (10.7)	16 (3.9)	61 (25.6)	48 (37.8)
Stage IIIA–IIIB	87 (11.3)	41 (9.9)	31 (13.0)	18 (14.2)
Stage IIIC	506 (65.5)	292 (70.4)	134 (56.3)	60 (47.2)
Stage IV	97 (12.5)	66 (15.9)	12 (5.0)	1 (0.8)
Tumor grade				
Grade 1	42 (5.4)	15 (3.6)	21 (8.8)	19 (15.0)
Grade 2	172 (22.3)	83 (20.0)	63 (26.5)	34 (26.8)
Grade 3	452 (58.5)	259 (62.4)	125 (52.5)	64 (50.4)
Unknown	107 (13.8)	58 (14.0)	29 (12.2)	10 (7.9)
Histologic subtype				
Serous	445 (57.6)	251 (60.5)	118 (49.6)	54 (42.5)
Mucinous	29 (3.8)	20 (4.8)	6 (2.5)	4 (3.2)
Endometrioid	92 (11.9)	40 (9.7)	41 (17.2)	27 (21.3)
Clear cell	23 (3.0)	12 (2.9)	9 (3.8)	8 (6.3)
Adenocarcinoma NOS*	146 (18.9)	72 (17.4)	51 (21.4)	28 (22.1)
Other	35 (4.5)	19 (4.6)	12 (5.0)	6 (4.7)
Unknown	3 (0.4)	1 (0.2)	1 (0.4)	0 (0)
Karnofsky score				
10–40	3 (0.4)	2 (0.5)	0 (0)	0 (0)
50–70	187 (24.2)	128 (30.8)	35 (14.7)	18 (14.2)
80–100	492 (63.7)	224 (54.0)	184 (77.3)	96 (75.6)
Unknown	91 (11.8)	61 (14.7)	19 (8.0)	13 (10.2)

Table 1. (Continued)

	Total (N = 773)	**≤3-year OS (N = 415)**	**≥5-year OS (N = 238)**	**≥10-year OS (N = 127)**
Characteristic	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]
Pretreatment CA-125 serum level (kU/L)				
Median	484 [9–25,784]	666 [24–13,995]	334 [9–9,219]	259 [10–4,180]
Unknown	43 (5.6)	26 (6.3)	8 (3.4)	4 (3.1)
Pretreatment hemoglobin level (mmol/L)				
Median	7.9 [4.6–9.9]	7.8 [4.6–9.6]	8.1 [5.7–9.7]	8.1 [5.9–9.7]
No anemia	505 (65.3)	257 (61.9)	167 (70.2)	82 (64.6)
Anemia	225 (29.1)	134 (32.4)	58 (24.4)	34 (26.8)
Unknown	43 (5.6)	24 (5.8)	13 (5.5)	11 (8.7)
Pretreatment platelet count (× 10^3/μL)				
Median	370 [144–898]	390 [158–749]	336 [169–637]	324 [194–590]
No thrombocytosis	369 (47.7)	185 (44.6)	126 (52.9)	69 (54.3)
Thrombocytosis	155 (20.1)	95 (22.9)	34 (14.3)	16 (12.6)
Unknown	249 (32.2)	135 (32.5)	78 (32.8)	42 (33.1)
Pretreatment leukocyte count (× 10^9/L)				
Median	8.4 [3.6–20.2]	8.6 [4.5–16.8]	8.1 [4–17.8]	8.3 [4.6–14.8]
No leukocytosis	461 (59.6)	255 (61.5)	136 (57.1)	68 (53.5)
Leukocytosis	119 (15.4)	67 (16.1)	32 (13.5)	16 (12.6)
Unknown	193 (25.0)	93 (22.4)	70 (29.4)	43 (33.9)
Presence of ascites				
No	142 (18.4)	46 (11.1)	75 (31.5)	45 (35.4)
Yes	608 (78.7)	355 (85.5)	158 (66.4)	80 (63.0)
Unknown	23 (3.0)	14 (3.4)	5 (2.1)	2 (1.6)
Ascites volume (mL)				
Median	700 [0–18,000]	2,000 [0–14,000]	100 [0–7,000]	50 [0–6,000]
Unknown	172 (22.2)	91 (22.0)	53 (22.2)	25 (19.7)
Treatment approach				
PCS	523 (67.7)	264 (63.6)	187 (78.6)	105 (82.7)
NACT-ICS	250 (32.3)	151 (36.4)	51 (21.4)	22 (17.3)
Residual disease after cytoreductive surgery				
No macroscopic	285 (36.9)	102 (24.6)	138 (58.0)	85 (66.9)
≤1 cm	265 (34.3)	153 (36.9)	70 (29.4)	31 (24.4)
>1 cm	186 (24.1)	137 (33.0)	22 (9.2)	8 (6.3)
Unknown	37 (4.8)	23 (5.5)	8 (3.4)	3 (2.4)

Abbreviations: CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; No., number; NOS, not otherwise specified; OS, overall survival; PCS, primary cytoreductive surgery.

*The subcategory 'adenocarcinoma NOS' comprises the patients who had epithelial ovarian cancer without further specification on the histologic subtype of the epithelial ovarian cancer.

†The subcategories labeled 'unknown' of the different variables refer to the unknown or missing data of that specific variable within the study cohort.

OS and pretreatment hematologic parameters

Figure 2 demonstrates the Kaplan–Meier survival curves used to calculate the median OS for the patients with and without pretreatment thrombocytosis, leukocytosis, and anemia. The median [IQR] OS was 3.0 [1.4–7.0] years for the patients without pretreatment thrombocytosis compared with 2.3 [1.3–4.2] years for the patients with pretreatment thrombocytosis (p<0.01). Furthermore, the median [IQR] OS was 2.7 [1.4–5.6] years for the patients without pretreatment leukocytosis compared to 2.5 [1.3–5.5] years for the patients with pretreatment leukocytosis (p=0.58). In addition, median [IQR] OS was 2.9 [1.5–6.3] years for the patients without pretreatment anemia compared with 2.3 [1.4–5.3] years for the patients with pretreatment anemia (p=0.07).

Final prediction models and their parameters

After the variable selection processes, the three prediction models comprised different sets of predictors. The most predictive ≤3-year OS model contained pretreatment leukocyte count, age at diagnosis, FIGO stage, tumor grade, histologic subtype, Karnofsky score, ascites volume, treatment approach, and residual disease after cytoreductive surgery. The most predictive ≥5-year OS model included the same predictors as the ≤3-year OS model, but excluded tumor grade and histologic subtype as predictors. Lastly, the ≥10-year OS model included pretreatment platelet count, FIGO stage, tumor grade, Karnofsky score, treatment approach, and residual disease after cytoreductive surgery. The final OS models are listed in **Supplementary Tables 1**–**3**.

Model performance

The *c*-indices of the ≤3-year, ≥5-year, and ≥10-year OS prediction models were estimated at 0.74, 0.78, and 0.82, respectively. Additionally, the Brier scores were estimated at 0.21, 0.17, and 0.11, respectively. The calibration plots of all models showed that the calibration curves of the different models were close to the perfect fit line (**Supplementary Figures S1**–**S3**).

Internal validation

Internal validation using 100 bootstrap iterations estimated the optimism-corrected *c*-indices at 0.71 [95% CI 0.66–0.75], 0.76 [95% CI 0.72–0.80], and 0.78 [95% CI 0.73–0.83] for the ≤3-year, ≥5-year, and ≥10-year OS models, respectively. In addition, the Brier scores were re-estimated at 0.22 [95% CI 0.20–0.23], 0.18 [95% CI 0.17–0.19], and 0.12 [95% CI 0.10–0.13], respectively. The optimism-corrected calibration slopes (i.e., shrinkage factors) were estimated to be 0.85 [95% CI 0.82–0.88], 0.87 [95% CI 0.85–0.89], and 0.82 [95% CI 0.79–0.86], respectively. These shrinkage factors were used to re-estimate the regression coefficients and the intercepts of the respective final

shrunken models. The final OS models and the odds ratios of the included parameters before and after internal validation are listed in **Supplementary Tables 1–3**.

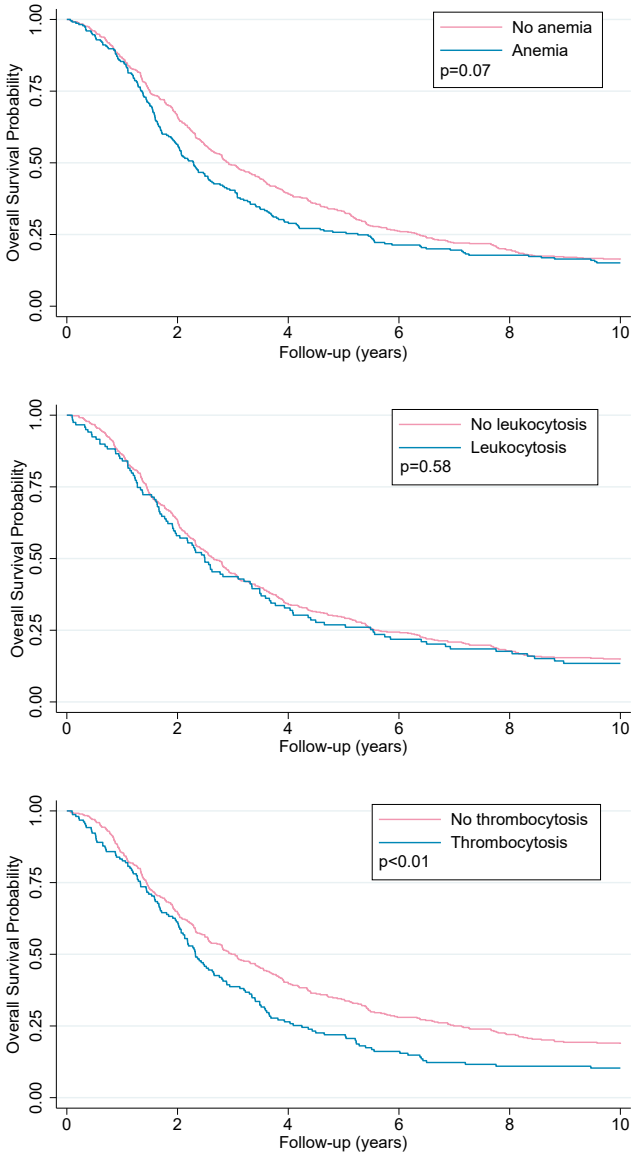

Figure 2. Kaplan–Meier survival curves for the overall survival of the different pretreatment hematologic parameter subgroups. The patients with pretreatment anemia (N = 225), leukocytosis (N = 119), or thrombocytosis (N = 155) are illustrated in blue, whereas patients without pretreatment anemia (N = 505), leukocytosis (N = 461), or trombocytosis (N = 369) are illustrated in pink. The *p*-values are provided at the different Kaplan–Meier survival curves.

Risk stratification

Risk stratification tables show the sensitivities, specificities, positive and negative predictive values, and the positive likelihood ratios according to different cutoffs for the predicted probabilities of the final prediction models. Predicted probabilities greater than or equal to the cutoff are defined as fulfilling the prediction of surviving at least 10 years. **Table 2** shows that when the cutoff for patients' probability of ≥10-year OS is set at 25%, the final ≥10-year OS model has a sensitivity of 55.9%, a specificity of 87.5%, a positive predictive value of 46.7%, and a negative predictive value of 91.0%. The risk stratification table of the final ≥5-year OS model is listed in **Supplementary Table 4**.

Table 2. Risk stratification table to assess the performance of the final ≥10-year overall survival model for different predicted probabilities*.

Predicted probability	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+
≥5%	97.6	31.0	21.8	98.5	1.4
≥10%	88.2	55.6	28.1	96.0	2.0
≥15%	73.2	71.8	33.8	93.2	2.6
≥20%	62.2	83.3	42.2	91.8	3.7
≥25%	55.9	87.5	46.7	91.0	4.5
≥30%	48.0	91.3	52.1	89.9	5.5
≥35%	40.2	94.1	57.3	88.9	6.8
≥40%	37.0	95.2	60.2	88.5	7.7
≥45%	35.4	95.8	62.5	88.3	8.4
≥50%	33.1	96.3	63.6	88.0	8.9
≥55%	30.0	97.4	69.0	87.6	11.5
≥60%	23.6	98.0	69.8	86.7	11.8
≥65%	13.4	98.9	70.8	85.3	12.2
≥70%	6.3	99.7	80.0	84.4	21.0
≥75%	4.7	99.7	75.0	84.2	15.7
≥80%	3.9	100	100	84.1	-
≥85%	-	-	-	-	-
≥90%	-	-	-	-	-
≥95%	-	-	-	-	-
≥100%	-	-	-	-	-

Abbreviations: LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.
*Predicted probability of having ≥10-year OS.
†LR+ was calculated using the equation: sensitivity ÷ (1 – specificity), with sensitivity and specificity expressed in proportions.

Online score calculators

Online score calculators are built using the internally validated estimates of the final ≥5-year or ≥10-year OS models and are freely accessible at Evidencio.com. To calculate the probabilities of ≥5-year or ≥10-year OS for an advanced-stage EOC patient who underwent cytoreductive surgery, each calculator requires the relevant parameter values of that patient. An example of the online score calculator that predicts the probability of ≥10-year OS is shown in **Figure 3**. An example of the online score calculator of the ≥5-year model is illustrated in **Supplementary Figure 4**.

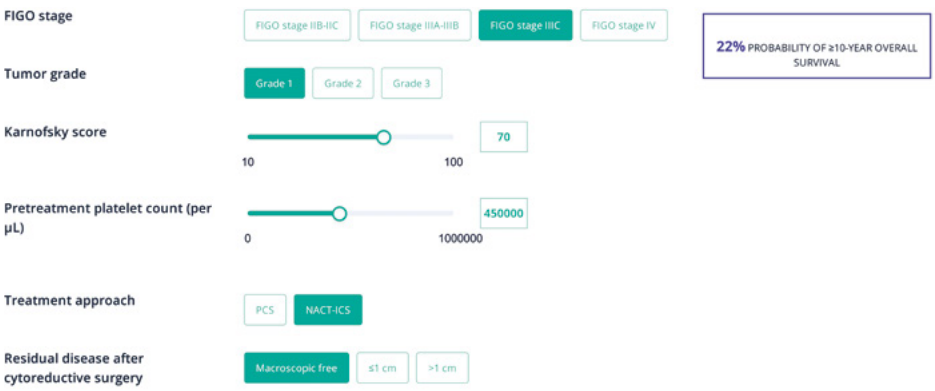

Figure 3. Screenshot of the online score calculator for the ≥10-year OS model. The online score calculator allows clinicians to estimate the probability of ≥10-year overall survival. For example, for a patient with FIGO stage IIIC EOC who presented with a low-grade tumor, a Karnofsky score of 70, a pretreatment platelet count of 450,000 per µL, and who underwent NACT-ICS with complete cytoreduction, the calculator predicts a probability of 22% for ≥10-year OS.

Discussion

In this population-based study, the prognostic value of three pretreatment hematologic parameters (i.e., pretreatment anemia, leukocytosis, and thrombocytosis) was assessed. Our data confirm that pretreatment thrombocytosis is associated with worse overall survival of advanced-stage EOC. No significant association was found between pretreatment anemia or leukocytosis and overall survival. In addition, three prediction models were developed and internally validated using established prognostic factors along with either pretreatment leukocyte count or platelet count as predictors. Online score calculators were built for the models that predict the probabilities of ≥5-year or ≥10-year OS for individual advanced-stage EOC patients on a freely accessible online platform (Evidencio.com).

Pretreatment thrombocytosis was shown to be associated with higher initial disease burden, postoperative morbidity, disease progression, and decreased OS of EOC [13–19, 40, 41]. Our data confirm this last finding. This might further support the theory that high platelet counts at diagnosis contribute to tumor or metastatic growth, which could hamper patients from demonstrating long-term survival. Accordingly, pretreatment platelet count was selected as a useful predictor in the ≥10-year OS model. Specifically, patients who do not present with pretreatment thrombocytosis (i.e., patients with low or normal platelet counts) have a higher probability of long-term survival.

Furthermore, pretreatment anemia was linked with low performance status, chemotherapy delays, chemotherapy dose reductions, and decreased quality-of-life for cancer patients [42, 43]. Our data did not show a significant difference in the OS of patients with pretreatment anemia compared to those without pretreatment anemia. Gerestein et al. (N = 118) incorporated pretreatment hemoglobin level into their nomogram to predict probabilities of 5-year OS of advanced-stage EOC patients [27]. Despite demonstrating survival differences up to a follow-up of five years, our data did not show that pretreatment anemia is significantly associated with overall survival. Pretreatment hemoglobin level was also not selected as a final predictor in any of our three final OS models since other combinations of predictors resulted in better-performing predictive models. The inclusion of pretreatment hemoglobin level in the model of Gerestein et al. is likely due to the slightly different combination of candidate predictors (e.g., albumin and lactate dehydrogenase levels) incorporated in their model or a different study population. Nevertheless, the *c*-index of their nomogram was estimated at 0.67 (0.62 at external validation) compared with a higher *c*-index of 0.76 for our ≥5-year OS model [27].

Contrary to the two aforementioned hematologic parameters, the prognostic value of pretreatment leukocytosis in advanced-stage EOC remains unclear due to inconsistent findings in the literature [20, 44, 45]. For instance, So et al. demonstrated an independent association between pretreatment leukocytosis and shortened PFS and OS. Their study (N = 155) was solely based on patients who underwent primary cytoreductive surgery [20]. Chen et al. (N = 816), on the other hand, did not demonstrate an independent association between pretreatment leukocytosis and decreased EOC survival [14]. In line with Chen et al., our data did not demonstrate a difference in median OS of patients with or without pretreatment leukocytosis. Nevertheless, pretreatment leukocyte count did add to the prediction of ≤3-year and ≥5-year OS for advanced-stage EOC patients.

Several prognostic models have been developed for predicting EOC survival [25-28, 46, 47]. However, most of these models did not include patients who underwent NACT-ICS

(except Rutten et al.) [26–28, 47, 48]. In addition, existing models predominantly focus on the 5-year OS of EOC patients and do not provide predictions of the ≤3-year and ≥10-year OS of advanced-stage EOC patients. The inclusion of advanced-stage EOC patients, encompassing all histologic subtypes and undergoing NACT-ICS or PCS combined with platinum- and taxane-based chemotherapy in our models, enhances the generalizability of our findings to a broader population of EOC patients. Although external validation of the models is required, our prognostic models are expected to be inexpensive and readily applicable tools for obtaining more reliable prognostic information for individual advanced-stage EOC patients after cytoreductive surgery than the current models that are available. In addition to more individualized patient counseling on prognosis, these prediction models may be useful in postoperative counseling of patients and perhaps in the assessment of patients' eligibility for clinical trials.

Regarding the limitations of our study, it is essential to acknowledge that the ≤3-year OS model exhibited inadequate performance, resulting in a high rate of patients being incorrectly classified as ≤3-year survivors. Therefore, this model is unsuitable for predicting the probability of ≤3-year OS. Furthermore, due to the retrospective nature of the data, the lack of sufficient data on other possible predictors (e.g., *BRCA* status, postoperative CA-125 level, CA-125 nadir, or the use of HIPEC) did not allow for these factors to be included in the model development. In addition, the data used in our study dated back to the era before PARP inhibitors. Therefore, PARP inhibitor usage could not be used as a potential predictor in the development of the current prediction models. Namely, different phase III trials (i.e., SOLO-1, PAOLA-1, PRIMA, and VELIA) demonstrated significant improvement in progression-free survival of advanced-stage EOC [4]. However, long-term overall survival data from these trials are still pending. Therefore, it is important to update the models when these data become available to assess their impact on patients' survival.

Conclusion

In conclusion, pretreatment thrombocytosis is significantly associated with poorer EOC survival. However, no significant association was observed between pretreatment anemia or leukocytosis and overall survival. Two adequately performing models were developed and internally validated to predict the probabilities of ≥5-year and ≥10-year OS for individual advanced-stage EOC patients.

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Supplementary

Online score calculators

The online score calculators for the ≥5-year OS model and the ≥10-year OS model can be accessed using the QR codes below:

≥5-year OS model

≥10-year OS model

Supplementary Table 1. Final ≤3-year OS model (≤3 year survivors (N = 415) and >3 year survivors (N = 358)).

	Original model*	**Shrunken model***
Characteristic	Odds ratio [95% CI]	Odds ratio [95% CI]
Age at diagnosis		
≤74 yrs	Reference	Reference
≥75 yrs	2.08 [1.21–3.57]	1.86 [1.08–3.19]
FIGO stage		
Stage IIB–IIC	Reference	Reference
Stage IIIA–IIIB	2.31 [1.10–4.85]	2.03 [0.97–4.27]
Stage IIIC	2.46 [1.27–4.74]	2.14 [1.10–4.13]
Stage IV	3.88 [1.76–8.53]	3.15 [1.43–6.93]
Tumor grade		
Grade 1	Reference	Reference
Grade 2	1.15 [0.54–2.45]	1.12 [0.53–2.39]
Grade 3	1.61 [0.79–3.31]	1.50 [0.73–3.08]
Histologic subtype		
Serous	Reference	Reference
Non-serous	1.29 [0.86–1.95]	1.24 [0.83–1.87]
Adenocarcinoma NOS	0.77 [0.50–1.17]	0.80 [0.52–1.22]
Karnofsky score (per 10 points)		
	0.82 [0.69–0.96]	0.84 [0.72–0.99]
Pretreatment leukocyte count (ln)		
	1.87 [1.06–3.32]	1.70 [0.96–3.02]
Ascites volume (ln)		
	1.06 [1.01–1.13]	1.05 [1.00–1.11]
Treatment approach		
PCS	Reference	Reference
NACT-ICS	1.34 [0.92–1.94]	1.28 [0.88–1.85]
Residual disease after cytoreductive surgery		
No macroscopic	Reference	Reference
≤1 cm	1.99 [1.36–2.91]	1.79 [1.22–2.62]
>1 cm	3.30 [1.06–3.32]	2.75 [1.73–4.38]
Model intercept	0.16 [0.02–1.35]	0.21 [0.03–1.84]

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; ln, natural log; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; OS, overall survival; PCS, primary cytoreductive surgery.
*The original model comprises the results before internal validation, and the shrunken model comprises the results after internal validation where the shrinkage factor of 0.85 was used to shrink the coefficients, including the intercept.

Supplementary Table 2. Final ≥5-year OS model (<5 year survivors (N = 535) and ≥5 year survivors (N = 238)).

	Original model*	**Shrunken model***
Characteristic	Odds ratio [95% CI]	Odds ratio [95% CI]
Age at diagnosis		
≤74 yrs	Reference	Reference
≥75 yrs	0.54 [0.28–1.03]	0.58 [0.31–1.12]
FIGO stage		
Stage IIB–IIC	Reference	Reference
Stage IIIA–IIIB	0.33 [0.16–0.68]	0.39 [0.19–0.78]
Stage IIIC	0.35 [0.19–0.64]	0.40 [0.22–0.74]
Stage IV	0.13 [0.06–0.31]	0.17 [0.07–0.40]
Karnofsky score (per 10 points)		
	1.28 [1.07–1.54]	1.24 [1.03–1.49]
Pretreatment leukocyte count (ln)		
	0.46 [0.24–0.86]	0.50 [0.27–0.95]
Ascites volume (ln)		
	0.92 [0.87–0.98]	0.93 [0.88–0.99]
Treatment approach		
PCS	Reference	Reference
NACT-ICS	0.53 [0.35–0.81]	0.57 [0.38–0.88]
Residual disease after cytoreductive surgery		
No macroscopic	Reference	Reference
≤1 cm	0.52 [0.34–0.78]	0.57 [0.37–0.85]
>1 cm	0.23 [0.13–0.41]	0.28 [0.16–0.50]
Model intercept	2.82 [0.31–25.57]	2.25 [0.24–20.38]

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; ln, natural log; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; OS, overall survival; PCS, primary cytoreductive surgery.

*The original model comprises the results before internal validation, and the shrunken model comprises the results after internal validation where the shrinkage factor of 0.87 was used to shrink the coefficients, including the intercept.

Supplementary Table 3. Final ≥10-year OS model (<10 year survivors (N = 646) and ≥10 year survivors (N = 127)).

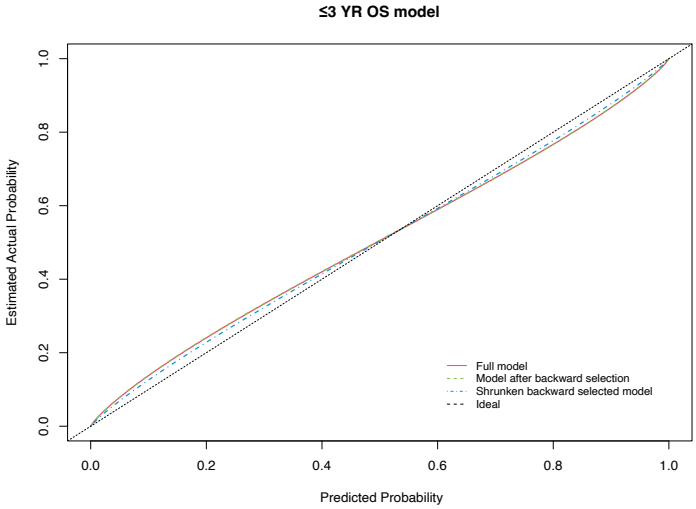
	Original model*	**Shrunken model***
Characteristic	Odds ratio [95% CI]	Odds ratio [95% CI]
FIGO stage		
Stage IIB–IIC	Reference	Reference
Stage IIIA–IIIB	0.29 [0.14–0.59]	0.35 [0.17–0.73]
Stage IIIC	0.25 [0.14–0.46]	0.32 [0.17–0.58]
Stage IV	0.02 [0.00–0.17]	0.04 [0.01–0.33]
Tumor grade		
Grade 1	Reference	Reference
Grade 2	0.42 [0.19–0.93]	0.48 [0.22–1.08]
Grade 3	0.37 [0.17–0.77]	0.44 [0.21–0.92]
Pretreatment platelet count (ln)		
	0.81 [0.66–1.00]	0.84 [0.68–1.03]
Karnofsky score (per 10 points)		
	1.26 [1.00–1.60]	1.21 [0.96–1.53]
Treatment approach		
PCS	Reference	Reference
NACT–ICS	0.58 [0.33–1.03]	0.64 [0.36–1.13]
Residual disease after cytoreductive surgery		
No macroscopic	Reference	Reference
≤1 cm	0.42 [0.25–0.71]	0.49 [0.29–0.82]
>1 cm	0.21 [0.09–0.46]	0.27 [0.12–0.61]
Model intercept	1.01 [0.10–9.96]	0.81 [0.08–7.95]

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; ln, natural log; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; OS, overall survival; PCS, primary cytoreductive surgery.
*The original model comprises the results before internal validation, and the shrunken model comprises the results after internal validation where the shrinkage factor of 0.82 was used to shrink the coefficients, including the intercept.

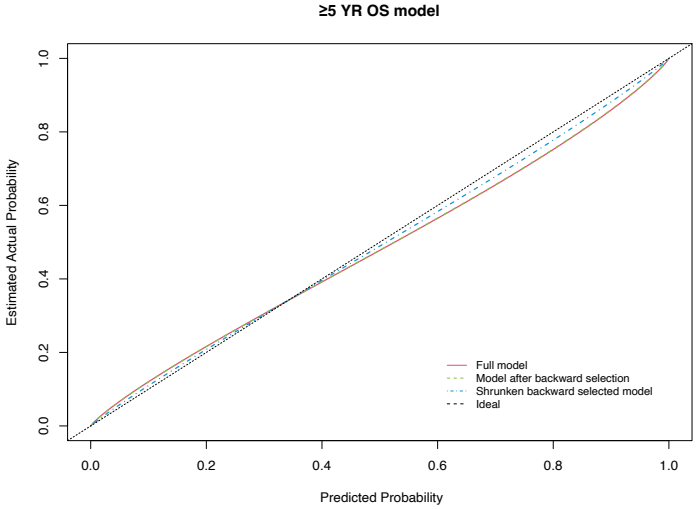
Supplementary Table 4. Risk stratification table to assess the performance of the final ≥5-year overall survival model for different predicted probabilities*.

Predicted probability	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+
≥5%	99.6	5.6	31.9	96.8	1.1
≥10%	98.7	21.5	35.9	97.4	1.3
≥15%	93.7	37.9	40.2	93.1	1.5
≥20%	89.1	52.0	45.2	91.4	1.9
≥25%	80.2	62.8	49.0	87.7	2.2
≥30%	71.4	70.1	51.5	84.7	2.4
≥35%	63.4	77.6	55.7	82.7	2.8
≥40%	50.0	83.6	57.5	79.0	3.0
≥45%	42.4	87.9	60.8	77.4	3.5
≥50%	38.2	90.7	64.5	76.7	4.1
≥55%	32.8	93.5	69.0	75.8	5.0
≥60%	27.3	95.1	71.4	74.6	5.6
≥65%	23.1	96.1	72.4	73.7	5.9
≥70%	18.9	97.8	78.9	73.0	8.6
≥75%	15.1	98.5	81.8	72.2	10.1
≥80%	11.3	98.9	81.8	71.5	10.3
≥85%	4.2	99.8	90.9	70.1	21.0
≥90%	-	-	-	-	-
≥95%	-	-	-	-	-
≥100%	-	-	-	-	-

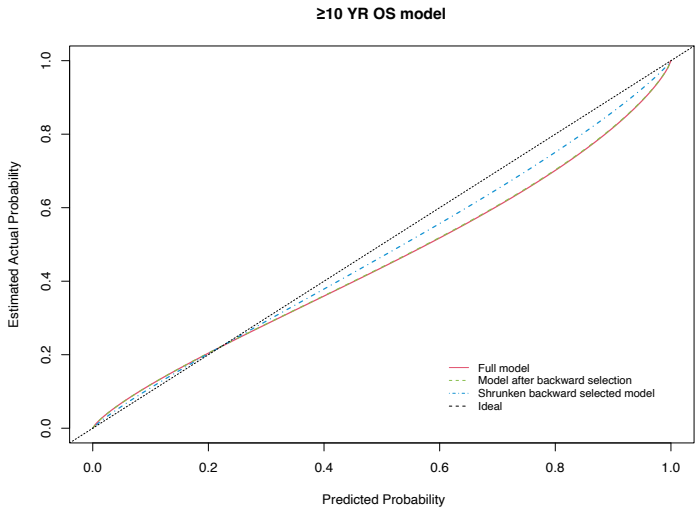
Abbreviations: LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.
*Predicted probability of having ≥5-year OS.
†LR+ was calculated using the equation: sensitivity ÷ (1 – specificity), with sensitivity and specificity expressed in proportions.



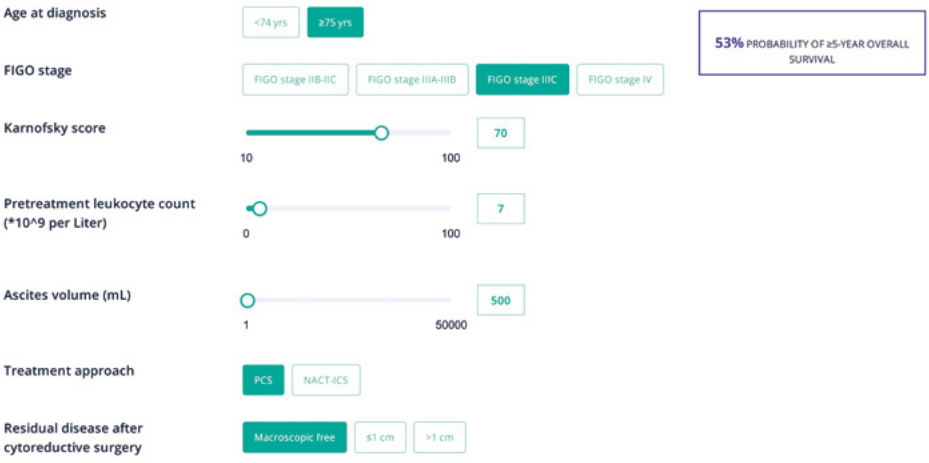
Supplementary Figure 1. Calibration plot of the ≤3-year OS model before and after internal validation. The ideal line represents the perfect fit line. The model after backward selection represents the model before internal validation (green dashed line). The shrunken backward selection model represents the model after internal validation (blue dot-dashed line). The full model represents the model with all the candidate predictors (red solid line). The calibration plot demonstrates that the final ≤3-year OS model is well-calibrated.



Supplementary Figure 2. Calibration plot of the ≥5-year OS model before and after internal validation. The ideal line represents the perfect fit line. The model after backward selection represents the model before internal validation (green dashed line). The shrunken backward selection model represents the model after internal validation (blue dot-dashed line). The full model represents the model with all the candidate predictors (red solid line). The calibration plot demonstrates that the final ≥5-year OS model is well-calibrated.



Supplementary Figure 3. Calibration plot of the ≥10-year OS model before and after internal validation. The ideal line represents the perfect fit line. The model after backward selection represents the model before internal validation (green dashed line). The shrunken backward selection model represents the model after internal validation (blue dot-dashed line). The full model represents the model with all the candidate predictors (red solid line). The calibration plot demonstrates that the final ≥10-year OS model is well-calibrated.



Supplementary Figure 4. Screenshot of the online score calculator for the ≥5-year OS model. The online score calculator allows clinicians to estimate the probability of ≥5-year OS. For example, for an 81-year-old patient with FIGO stage IIIC EOC who presented with a Karnofsky score of 70, a pretreatment leukocyte count of 7 × 10^9/L, and 500 mL of ascites volume, and who underwent primary cytoreductive surgery with complete cytoreduction, the calculator predicts a probability of 53% for ≥5-year OS.

CHAPTER 3

Impact of Sepsis on the Oncologic Outcomes of Advanced Epithelial Ovarian Cancer Patients: A Multicenter Observational Study

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Abstract

Objective

The sepsis-induced inflammatory response may potentially affect malignant cells. Recently, a case of spontaneous regression of a histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) stage IIIC epithelial ovarian cancer (EOC) following sepsis was reported. The aim of our study was to explore the impact of sepsis on the oncologic outcomes of advanced-stage EOC patients.

Methods

Gynecologic oncology patients admitted to the Intensive Care Units of three oncologic centers between January 1, 2006 and January 1, 2019 were identified and patients who experienced sepsis following the advanced-stage EOC diagnosis selected. Survival outcomes were compared with advanced-stage EOC patients from the Netherlands Cancer Registry (NCR). To correct for case-mix differences, propensity score matching (using 1:3 nearest neighbor matching) was conducted, after which survival analyses were repeated.

Results

A total of 18 of 207 patients with advanced-stage EOC experienced sepsis. The sepsis patients had similar distribution of patient, tumor, and treatment characteristics to the 3,988 patients from the NCR cohort. A total of 3 out of 18 patients died from the complications of sepsis. While the remaining patients initially responded to treatment, 14 of 15 patients relapsed. The median [interquartile range, IQR] overall survival was 31 [24–44] and 35 [20–60] months for the sepsis and unmatched NCR cohort (p=0.56), respectively. The median [IQR] progression-free survival was 16 [11–21] and 16 [11–27] months (p=0.90), respectively. Survival outcomes did not differ following propensity matching (for overall survival, 31 [24–44] vs. 36 [20–56] months, p=0.40; for progression-free survival, 16 [11–21] and 16 [12–21] months, p=0.72).

Conclusion

In this observational study, the occurrence of sepsis did not affect the oncologic outcomes of advanced-stage EOC patients.

Introduction

The vast majority of patients with epithelial ovarian cancer (EOC) are diagnosed at an advanced stage [1]. Despite enhancements in treatment strategies, such as more radical surgery, combination chemotherapy, intraperitoneal chemotherapy, or targeted molecular therapy, the long-term survival of advanced-stage EOC patients has only improved slightly over the past three decades [2–4]. Hence, EOC remains the leading cause of gynecologic cancer-related death in the Western world [5, 6]. The role of the immune system in ovarian cancer has been an important focus of research [1, 4, 7, 8]. It has become clear that instead of being targeted for immune destruction, ovarian cancer has the ability to escape the immune system [4, 9, 10]. The foremost mechanism behind this evasion of immunosurveillance is the creation of a highly immunosuppressive environment in the peritoneal cavity [4, 9, 10]. The immunologic response against ovarian cancer is a critical balance between immune-activating and immune-suppressing mechanisms [1, 4, 8, 10–12].

Recently, the first case of spontaneous regression of advanced-stage EOC following sepsis illustrated the interplay between immunity and cancer prognosis [13]. Briefly, a 79-year-old patient developed sepsis due to a bowel perforation after a biopsy that confirmed a high-grade serous FIGO stage IIIC EOC diagnosis. She was admitted to the Intensive Care Unit (ICU) and treated for her sepsis. She was later discharged with supportive care. In the following six months, she showed no signs of EOC. She underwent an uncomplicated bilateral salpingo-oophorectomy after which histopathologic examination only confirmed a microscopic residual tumor in one ovary. To date, seven years after diagnosis, without undergoing any adjuvant systemic chemotherapy, the patient shows no signs of recurrent disease.

Spontaneous regression of cancer is defined as partial or complete disappearance of a histologically proven malignant tumor, either in the absence of treatment, or in the presence of therapy considered inadequate to exert a significant influence on the disease [14]. This phenomenon has been reported for cancers such as acute myeloid leukemia, lymphoma, melanoma, and sarcoma, but not for EOC prior to the aforementioned case [15–18]. Spontaneous regression of cancer has mostly been observed following infections (including sepsis) with various pathogens [14]. It is hypothesized that the systemic inflammatory response, triggered by sepsis, could elicit an antitumor response, which can lead to favorable oncologic outcomes. However, in theory, it is also possible that a persistent immunosuppressive response, observed in sepsis patients, may lead to unfavorable oncologic outcomes of cancer patients [17].

Therefore, the aim of this pilot study was to explore the impact of sepsis on the course and oncologic outcomes of advanced-stage EOC patients.

Methods

Study population

To identify advanced-stage EOC patients who experienced sepsis, gynecologic oncology patients admitted to the ICU between January 1, 2006 and January 1, 2019 (to allow last follow-up date: January 31, 2022) were selected from the following three Dutch hospitals: Radboud University Medical Center, Catharina Hospital, and Maastricht University Medical Center. Patients were identified from the hospitals' electronic patient records using the search terms 'neoplasm' and 'gynecology as the referring medical specialty'. Subsequently, patients were cross-checked with a list of all consecutive ovarian cancer patients who underwent treatment in the participating hospitals. Moreover, the study's eligibility criteria required patients:

I. To be diagnosed with a histologically confirmed EOC;
II. To have FIGO stage IIB or higher (i.e., advanced-stage EOC);
III. To be admitted to the ICU;
IV. To be diagnosed with sepsis [19, 20] following their primary or recurrent EOC diagnosis;
V. To have an abdominal focus for their sepsis.

Patients who did not meet all of the aforementioned criteria were excluded from this study.

In addition, data of advanced-stage EOC patients were obtained from the Netherlands Cancer Registry (NCR) to gain insights into the survival of advanced-stage EOC patients in general and to compare survival outcomes with the sepsis patients identified in this study. The NCR is a nationwide population-based registry that is notified weekly of all newly histologically confirmed malignancies in the Netherlands through an automated nationwide pathology archive (PALGA). Dedicated registrars previously collected data on patient, tumor, and treatment characteristics from patients' medical records. No additional data were collected for the NCR cohort in this study. Further details on the NCR and the nationwide cohort used in the survival analyses were reported earlier [21].

Definitions

Sepsis was defined according to the Sepsis-2 (introduced in 2001) or Sepsis-3 (introduced in 2016) definition; as the criteria for sepsis changed throughout the period in which data were collected for this study [19, 20]. According to the Sepsis-2 definition, sepsis is defined

as a proven or suspected infection accompanied by at least two Systemic Inflammatory Response Syndrome (SIRS) criteria (**Supplementary Table 1**) [19]. According to the Sepsis-3 definition, sepsis is defined as organ dysfunction caused by a dysregulated host response to an infection. In this definition, organ dysfunction is characterized by an increase in Sequential Organ Failure Assessment (SOFA) score of 2 or greater (**Supplementary Table 2**) [20]. The severity of sepsis was assessed on the requirement of a vasopressor to maintain an adequate mean arterial pressure (i.e., vasopressor-dependent sepsis or non-vasopressor-dependent sepsis). Septic shock was defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities were associated with a greater risk of mortality than with sepsis alone [20]. These patients are characterized by a need for a vasopressor, as well as an elevated lactate level.

Data collection

Data were collected from patients' medical records for the sepsis cohort. The collected data included information regarding the EOC diagnosis and treatment, e.g., age at diagnosis, FIGO stage, histologic subtype, treatment approach, surgical procedures performed during cytoreductive surgery, residual disease after cytoreductive surgery, hospital length of stay, chemotherapy regimen, and EOC treatment response. In addition, collected data included information on the sepsis diagnosis and treatment, e.g., site of infection, the time between the date of cytoreductive surgery and the onset of sepsis, the severity of sepsis, antibiotic treatment, type of medical intervention, and ICU length of stay. Furthermore, follow-up data, i.e., recurrence status and date, survival status, cause of death, and date of death or last follow-up date, were collected. The cause of death was identified and was presumed cancer-related if the patient had advanced recurrent disease at the time of death. If applicable, further data on patients' recurrent EOC diagnosis and treatment were collected.

Oncologic outcomes

Overall survival (OS) was defined as the time between the date of diagnosis and death or the last follow-up date (censoring date: January 31, 2022). Progressive or recurrent disease was defined as clinical signs of tumor growth, i.e., either an increase in CA-125 serum levels (twice the upper limit of CA-125 serum level on two separate occasions at least one week apart) or the presence of tumor lesions visible on imaging (either growth of pre-existing lesions or development of new lesions), combined with the clinical judgement of the treating medical oncologist or gynecologic oncologist. Progression-free survival (PFS) was defined as the time between the date of diagnosis and the date of disease progression or recurrence or the date of death, whichever occurred first. The last follow-up date, instead of date of death, was used to calculate the PFS and OS of patients who were still alive and did not experience progressive or recurrent disease.

Statistical analysis

Patient, tumor, and treatment characteristics were summarized. Differences in clinicopathologic characteristics between patients were assessed in a descriptive manner. The PFS and OS of patients were calculated. In addition, to correct for possible differences in case-mix, sepsis patients were compared to a propensity-score-matched group from the NCR in a sensitivity analysis. Patients were matched using 1:3 nearest neighbor matching based on age, FIGO stage, histologic subtype, grade, treatment approach, bowel surgery, residual disease after cytoreductive surgery, and year of diagnosis. Survival curves using the Kaplan–Meier method were plotted to assess possible differences in OS and PFS between the sepsis patients (who consisted solely of FIGO stage IIIC and IV EOC) and unmatched or matched FIGO stage IIIC and IV EOC patients from the NCR. In addition, Cox regression analyses were conducted to assess differences in OS and PFS between the sepsis and unmatched or matched patients from the NCR. The hazard ratios (HRs) and their associated 95% confidence intervals [95% CI] were reported. The Cox regression analysis was stratified by the matching group variable for the analysis using matched patients from the NCR. All statistical analyses were performed using STATA/SE, version 17 (StataCorp, College Station, Texas, USA) and R, version 4.0.3 (http://www.r-project.org).

Ethical approval

Ethical approval for this study was acquired from the Medical Ethical Committees (CMO 2019-5390) of all participating centers. The requirement for obtaining informed consent was waived by the committees, since additional privacy protection measures were taken to ensure collected data were not traceable to individual patients. This study was carried out in accordance with the applicable rules concerning the review of research ethics committees and informed consent in the Netherlands.

Results

Study population

A total of 207 patients with advanced-stage EOC were admitted to the ICU between January 1, 2006 and January 1, 2019 at one of the three hospitals. Among this group, 18 patients experienced sepsis with an abdominal focus (**Figure 1**). In addition, a total of 3,988 FIGO stage IIIC and IV patients who underwent standard treatment for EOC were identified from the NCR (**Figure 1**). This group of advanced-stage EOC patients from the NCR was used as a control group. In an additional sensitivity analysis, a smaller subgroup of patients (N = 54) from the NCR was matched (1:3) based on prognostic factors and demographic characteristics (**Figure 1**).

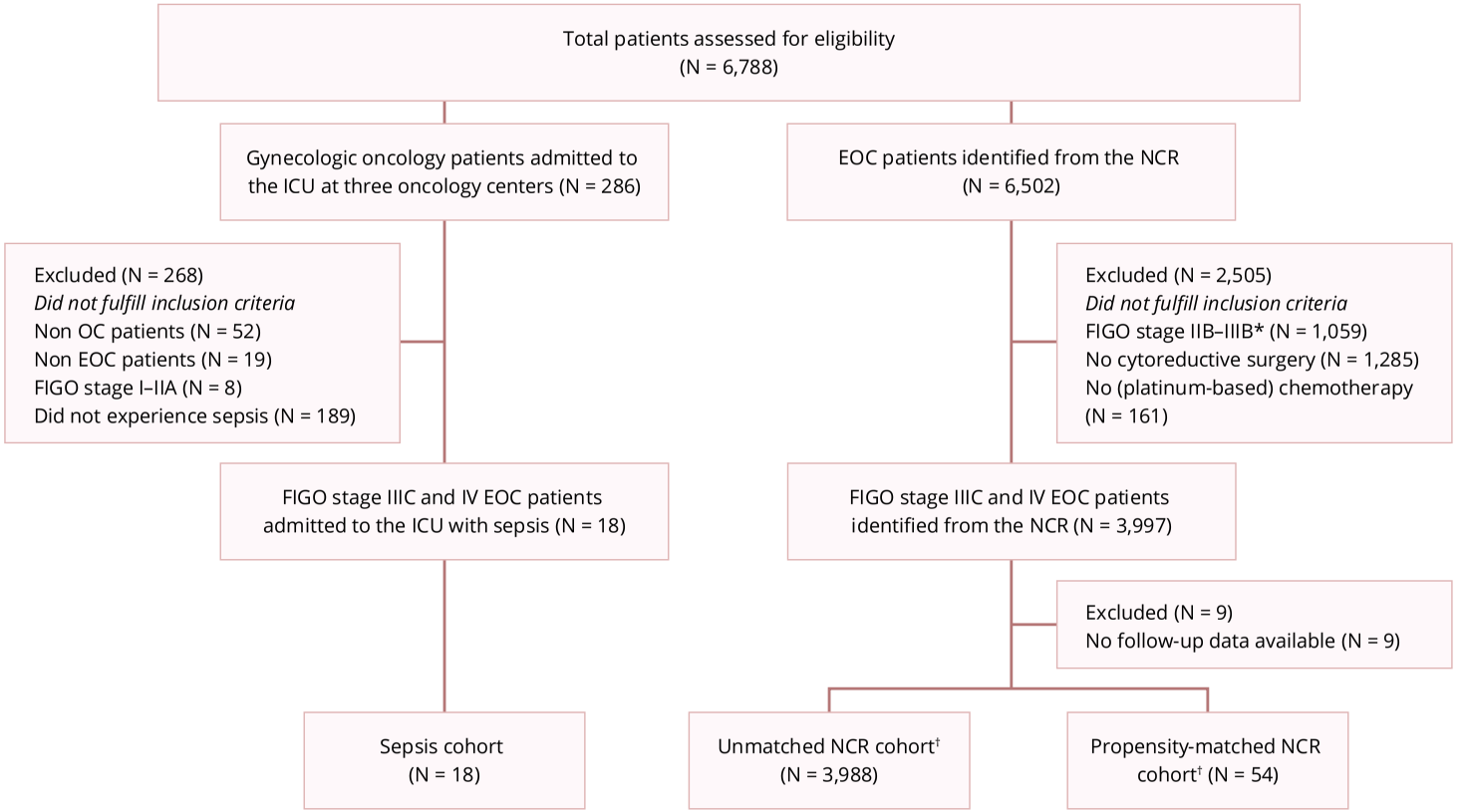

Figure 1. Flowchart of the study population (sepsis and NCR cohort).

*FIGO stage IIB–IIIB patients were excluded from the NCR cohort to align with the sepsis cohort (FIGO IIIC–IV only) for comparability.
†The unmatched and propensity-matched NCR cohorts are separate; the 54 matched patients are a subset of the 3,988 unmatched patients.

Patient, tumor, and treatment characteristics

Patient, tumor, and treatment characteristics of the sepsis and NCR cohorts are summarized in **Table 1**. The median [interquartile range, IQR] age of the patients was 65 [60–73] years for the sepsis cohort. Thirteen patients had FIGO stage IIIC and five had FIGO stage IV EOC. Serous EOC type was the predominant histologic subtype (16/18). The sepsis patients underwent either primary cytoreductive surgery (PCS, 4/18) or interval cytoreductive surgery after neoadjuvant chemotherapy (NACT-ICS, 14/18). Similar proportions were observed in the unmatched NCR cohort. However, 13 sepsis patients (72%) underwent bowel surgery as part of cytoreductive surgery, which was higher than in the unmatched NCR cohort (815/3,988; 21%). Five sepsis patients did not receive adjuvant chemotherapy after interval cytoreductive surgery due to prior chemotherapy resistance (1/18), prolonged postoperative recovery (1/18), and postoperative mortality (3/18). All other sepsis patients completed their platinum-based chemotherapy as part of their primary EOC treatment. The differences in case-mix between the unmatched NCR cohort and the sepsis cohort were minimized in the propensity-matched NCR cohort. Full details on the EOC characteristics of the 18 sepsis patients are provided in **Supplementary Table 3**.

Sepsis characteristics

The patients' sepsis characteristics are summarized in **Table 2**. Most patients experienced sepsis after treatment for primary EOC (16/18), whereas two patients experienced sepsis after surgical treatment for recurrent disease. Sepsis occurred within a fortnight of cytoreductive surgery for all patients except for one (Patient E). Patient E developed urosepsis approximately five months after secondary cytoreductive surgery due to a blocked nephrostomy catheter that was inserted to manage a urinoma caused by an iatrogenic ureter injury. In most patients (13/18), sepsis was caused by bowel complications such as anastomotic leakage or bowel perforation. Four patients (Patients C, E, G, and O) developed sepsis due to a vaginal cuff abscess (which led to infective endocarditis), urosepsis, pancreatic fluid leakage, and gastric perforation, respectively. The exact site of infection was unclear for one patient (Patient F) since she experienced both pulmonary and abdominal complaints. All patients were treated with broad-spectrum antibiotics and underwent some type of source control, such as a relaparotomy (including bowel surgery and/or abscess drainage) or drainage. Most patients (15/18) recovered from sepsis, while three patients died from the complications of their sepsis during their hospital stay. Full details on patients' sepsis characteristics are provided in **Supplementary Table 4**.

Table 1. EOC characteristics of the sepsis cohort (N = 18), unmatched NCR cohort (N = 3,988), and propensity-unmatched NCR cohort (N = 54).

	Sepsis cohort (N = 18)	**Unmatched NCR cohort (N = 3,988)**	**Propensity-matched NCR cohort* (N = 54)**
Characteristic	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]
Age at diagnosis (in yrs)			
Median	65 [60–73]	65 [20–88]	63 [43–79]
FIGO stage			
Stage IIIC	13 (72)	2,884 (72)	38 (70)
Stage IV	5 (28)	1,104 (28)	16 (30)
Histologic subtype			
Serous	16 (89)	3,211 (80)	46 (85)
Mucinous	0 (0)	72 (2)	0 (0)
Endometrioid	0 (0)	124 (3)	5 (9)
Clear cell	0 (0)	104 (3)	0 (0)
Adenocarcinoma NOS	2 (11)	428 (11)	3 (6)
Other	0 (0)	49 (1)	0 (0)
Treatment approach			
PCS	4 (22)	1,144 (29)	16 (30)
NACT-ICS	14 (78)	2,844 (71)	38 (70)
Bowel surgery			
No	5 (28)	3,075 (77)	14 (26)
Yes	13 (72)	851 (21)	40 (74)
Unknown	0 (0)	62 (2)	0 (0)
Residual disease after cytoreductive surgery			
No macroscopic	12 (67)	1,939 (49)	38 (70)
≤1 cm	6 (33)	1,487 (37)	14 (26)
>1 cm	0 (0)	500 (12)	2 (4)
Unknown	0 (0)	62 (2)	0 (0)
Chemotherapy (primary treatment)			
Yes, adjuvant	4 (22)	1,144 (29)	16 (30)
Yes, neoadjuvant and adjuvant	9 (50)	2,725 (68)	37 (68)
Yes, neoadjuvant only	5 (28)	119 (3)	1 (2)

Abbreviations: EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; IQR, interquartile range; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NCR, Netherlands Cancer Registry; NOS, not otherwise specified; PCS, primary cytoreductive surgery.
*The patients were matched according to the following variables: year of diagnosis, age, FIGO stage, histologic subtype, tumor grade, treatment approach, bowel surgery, and residual disease after cytoreductive surgery.

Table 2. Sepsis characteristics of the sepsis cohort (N = 18).

Characteristic	No. of patients (%)/ Median [IQR]
Sepsis diagnosed during	
Primary EOC treatment	16 (89)
Recurrent EOC treatment	2 (11)
Time between surgery and sepsis onset (days)	
Median	7 [5–9]
Severity of sepsis	
Non-vasopressor-dependent sepsis	13 (72)
Vasopressor-dependent sepsis	5 (28)
Site of infection	
Bowel complications	13 (72)
Gastric perforation	1 (5.5)
Pancreatic fluid leakage	1 (5.5)
Urosepsis	1 (5.5)
Vaginal cuff abscess	1 (5.5)
Unclear	1 (5.5)
Source control	
Abscess drainage	3 (17)
Laparotomy including abscess drainage	13 (72)
Insertion of nephrostomy catheter	1 (5.5)
Mechanical ventilation	1 (5.5)
Antibiotic treatment duration (days)	
Median	10 [6–10]
ICU length of stay (days)	
Median	3 [1–8]
Hospital length of stay (days)	
Median	24 [18–42]

Abbreviations: EOC, epithelial ovarian cancer; ICU, intensive care unit; IQR, interquartile range.

Oncologic outcomes

Of the 15 patients who recovered from sepsis, 13 patients experienced sepsis during primary EOC treatment. Among them, only Patient A had not developed disease recurrence after finishing treatment more than 13 years ago. Other patients did develop progressive or recurrent disease often within a year after completing primary EOC treatment or later (Patients B, O, and R). The remaining two patients (Patients D and E) developed sepsis after secondary cytoreductive surgery in the treatment of EOC relapse. Both patients died within 18 months after treatment. The timeline of the

different patients and their oncologic outcomes is presented in **Figure 2**. Full details on patients' oncologic outcomes are provided in **Supplementary Table 5**.

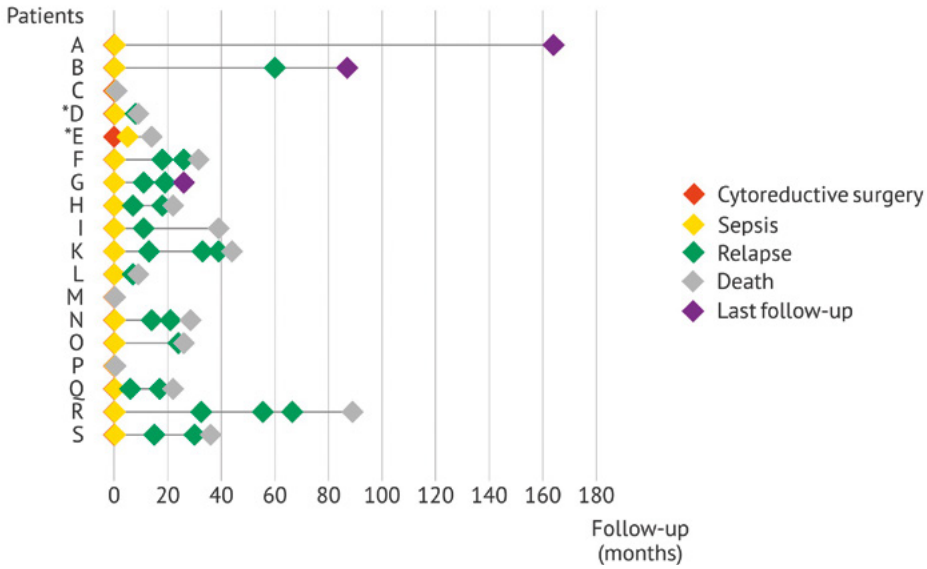

Figure 2. Timeline of the sepsis patients that outlines their oncologic outcomes. The timeline starts at the time of cytoreductive surgery. Sepsis occurred within a fortnight of cytoreductive surgery for 17/18 patients. As a result, the red diamond (indicative of cytoreductive surgery) is less noticeable for these patients. Patients C, M, and P died from the complications of sepsis.*Patients D and E experienced sepsis during treatment after cytoreductive surgery for first and second relapse, respectively.

Survival outcomes

Figures 3A and **3B** demonstrate the Kaplan–Meier survival curves used to calculate the median OS and PFS for the sepsis and unmatched NCR patients, respectively. The median [IQR] OS was 31 [24–44] months for the sepsis cohort compared to 35 [20–60] months for the unmatched NCR cohort (p=0.56). The median [IQR] PFS was 16 [11–21] months for the sepsis cohort and 16 [11–27] months for the unmatched NCR cohort (p=0.90). The Cox regression analyses demonstrated an HR of 1.16 [95% CI 0.70–1.93] for the OS and an HR of 1.03 [95% CI 0.61–1.75] for the PFS.

Sensitivity analysis

Figures 3C and **3D** demonstrate the Kaplan–Meier survival curves of the median OS and PFS for the sepsis and propensity-matched NCR cohorts, respectively. The median [IQR] OS was 31 [24–44] months for the sepsis cohort compared to 36 [20–56] months for the propensity-matched NCR cohort (p=0.40). The median [IQR] PFS was 16 [11–21]

months for the sepsis cohort and 16 [12–21] months for the propensity-matched NCR cohort (p=0.72). The Cox regression analyses demonstrated an HR of 1.42 [95% CI 0.72–2.80] for the OS and an HR of 1.01 [95% CI 0.49–2.10] for the PFS. The results from the propensity score matching analysis are demonstrated in **Figure 4**.

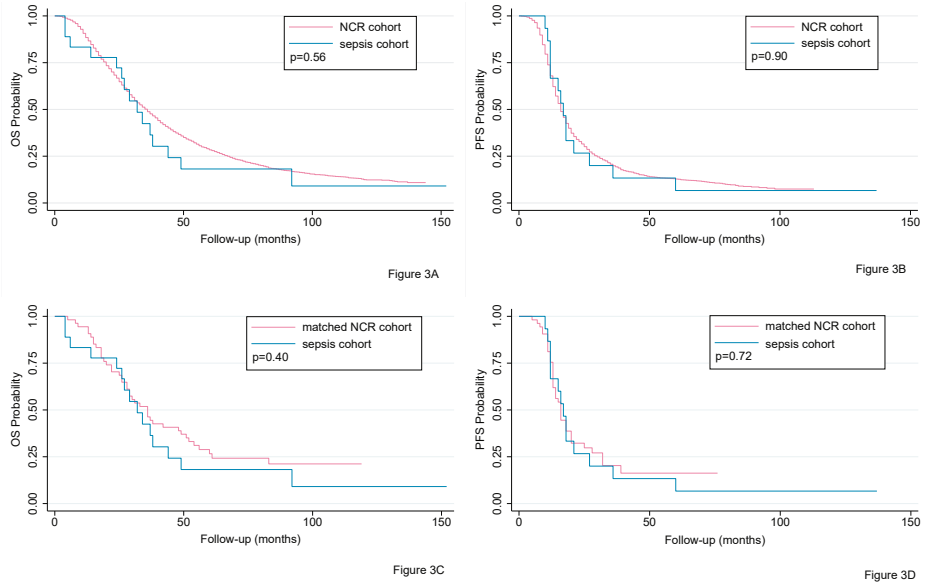

Figure 3. Kaplan–Meier curves of the sepsis and unmatched NCR cohort, and the propensity-matched NCR cohort. The Kaplan–Meier curves of OS for the sepsis cohort (N = 18) and the unmatched NCR cohort (N = 3,988) are depicted (**3A**). The median [IQR] OS was 31 [24–44] months for the sepsis cohort and 35 [20–60] months for the NCR cohort (p=0.56). Kaplan–Meier curves of progression-free survival (PFS) for the sepsis cohort (N = 18) and unmatched NCR cohort (N = 3,852)* are depicted (**3B**). The median [IQR] PFS was 16 [11–21] and 16 [11–27] months, respectively (p=0.90). The Kaplan–Meier curves of OS for the sepsis cohort (N = 18) and the propensity-matched NCR cohort (N = 54) are depicted (**3C**). The median [IQR] OS was 31 [24–44] months for the sepsis cohort and 36 [20–56] months for the propensity-matched NCR cohort (p=0.40). Kaplan–Meier curves of PFS for the sepsis cohort and the propensity-matched NCR cohort are depicted (**3D**). The median [IQR] PFS was 16 [11–21] and 16 [12–21] months, respectively (p=0.72).

*A total of 136 patients were excluded from this analysis compared to Figures 1 and 3A, due to missing follow-up data regarding recurrence status.

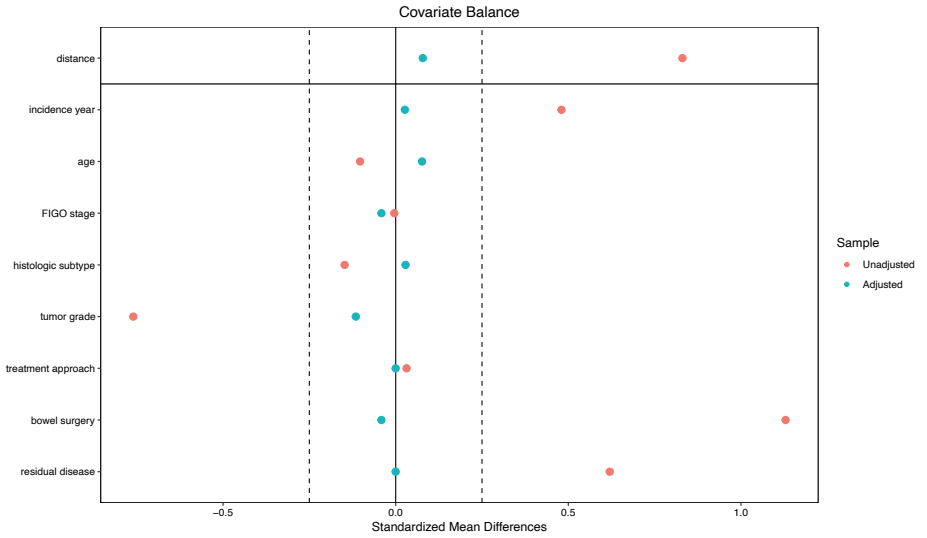

Figure 4. The Love plot demonstrates the absolute standardized mean differences of each variable in the unadjusted data (before propensity score matching) and adjusted data (after propensity score matching). The plot demonstrates that the covariates showed better balance in the adjusted data.

Discussion

During sepsis, the initial activation of the immune response may potentially be beneficial, while sepsis-induced immunosuppression may theoretically also harm cancer patients. To investigate the interplay between sepsis and ovarian cancer, our multicenter observational study provides a descriptive analysis of advanced-stage EOC patients who experienced sepsis after primary or recurrent EOC diagnosis. Our data indicate that, overall, sepsis does not influence the prognosis of advanced-stage EOC patients in terms of progression-free and overall survival. Apart from our finding that 3/18 (~17%) of the advanced-stage EOC patients died from the complications of sepsis, consistent with the current in-hospital mortality rate of 20–40% of cancer patients with sepsis or septic shock [17, 22], the development of sepsis, overall, did not benefit or harm EOC patients.

It is recognized that the immune response in sepsis can be characterized by the simultaneous activation of pro-inflammatory and anti-inflammatory processes [15, 17]. Specifically, the initially dominant hyper-inflammatory response, also known as the 'cytokine storm', in the first few days is characterized by increased levels of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) [15]. These proinflammatory cytokines are generally responsible for immune response activation (such as IL-6), cytotoxic and cytostatic effects against cancer cells (such

as TNF-α), and the recruitment and activation of immune cells along with other pro-inflammatory cytokines (such as IL-1β) [23]. Simultaneously, both the innate and adaptive immune system will start to dampen this hyper-inflammatory phase. As a result, patients may undergo either a controlled anti-inflammatory response, which enables them to return to immune homeostasis, or an uncontrolled anti-inflammatory response, which may lead them into a sustained immunosuppressed phase [15]. These immune processes may be related to reported favorable and unfavorable oncologic outcomes of cancer patients who experience sepsis [12]. Thus, it might be possible that overall there is no effect, but a subgroup of patients does benefit, while another subgroup experiences harm from this variable immune response.

This notion is illustrated by observations that the hyper-inflammatory phase of sepsis exerts a negative effect on the antitumor-responsive capacity in tumor-bearing mice who were pre-exposed to chemotherapy prior to sepsis when compared to those who were not [15, 24–26]. Conversely, upfront cytoreductive surgery in EOC was demonstrated to reduce circulating regulatory T-cells (Tregs) and to increase $CD8^+$ T-cell function, which resulted in a surgically induced reduction of the immunosuppressive environment [4, 27, 28]. These changes in the immune cells and their function were not observed in patients who underwent neoadjuvant chemotherapy or in those with recurrent disease [27]. In line with this, sepsis patients who underwent neoadjuvant chemotherapy before undergoing cytoreductive surgery, or patients who experienced sepsis after cytoreductive surgery for recurrent disease in our study, did not demonstrate favorable oncologic outcomes. Contrarily, sepsis patients who underwent primary cytoreductive surgery included two patients who demonstrated prolonged EOC survival and one patient who did not. However, no definite conclusions can be drawn due to the small number of these patients.

Another concept is that sepsis-induced immunosuppression can be compartmentalized as shown in murine models [16, 29]. Tissue-resident memory $CD8^+$ T cells that reside in non-lymphoid tissues, contrary to the circulatory $CD8^+$ T cells, do not experience loss in numbers or function after sepsis probably due to their secluded localization and the inability of produced cytokines to reach them [16, 29].

In addition, injections of anaerobic bacteria administered in the intraperitoneal cavity demonstrated better tumor targeting than when administered intravenously in ovarian-cancer-bearing murine models [26]. Since EOC predominantly operates in the intraperitoneal cavity, this seems to be the localization where the antitumor immune response needs to happen. Consequently, it could be that a systemic inflammatory

response related to other sites of infection was insufficiently able to target the tumor or elicit a strong antitumor response in some of our cases.

Nevertheless, it is important to note that, contrary to the aforementioned case report, most patients in our study underwent successful EOC treatment often leaving microscopic or no residual disease. In addition, EOC treatment often consisted of adjuvant chemotherapy for the patients. Thus, it appears plausible that the immunosuppressive effects of chemotherapy might have diminished the antitumor-responsive capacity of sepsis in our patients. Hence, it remains unclear to what extent the patients could have benefited from the pro-inflammatory response of sepsis and to what extent sepsis essentially impacted the patients' oncologic outcomes. Particularly, it is speculative whether sepsis could have induced an antitumor response in the two patients who demonstrated prolonged EOC survival or whether their increased survival was within the normal variation or due to other favorable factors.

Certain limitations apply to our study. Our study was mainly limited by its observational nature and the small group of EOC patients admitted to the ICU. To ensure the inclusion of patients who experienced fulminant sepsis, patients were identified through ICU departments. Therefore, sepsis patients without an ICU admission may have been missed. In addition, the small group of patients comprised a heterogeneous group, which may have impacted the statistical power to detect an association between sepsis and EOC survival. As a result, no definite conclusions can be drawn from our study. In addition, it remains possible that the occurrence of sepsis could be beneficial in a selected group of advanced-stage EOC patients, while there may be a harmful effect in another subgroup. This may be related to different factors, such as the site of infection, the extent of the inflammatory response, and the timing of sepsis relative to EOC diagnosis. Moreover, the impact of sepsis in EOC patients with high tumor burden may be different. Nevertheless, this is the first study to assess the impact of sepsis on advanced-stage EOC in which detailed information was collected on patients' EOC and sepsis. The use of nationwide data to compare differences in survival outcomes between the sepsis patients and the unmatched and propensity-matched patients from the NCR represents a strength of this study.

To further investigate the impact of sepsis (and the earlier mentioned aspects of timing, severity, and so forth) on the antitumor response in advanced-stage EOC and its impact on EOC growth and development, it would be interesting to explore this in EOC-bearing mice experiencing cecal ligation and puncture-induced sepsis compared to EOC-bearing mice in which sepsis was not induced. An experimental study might eventually lead to a new immunotherapeutic strategy for a specific group of EOC patients who have not

received prior treatment. Current ongoing clinical trials (e.g., FIRST trial, NCT03602859) so far focus on combining immunotherapy with chemotherapy, anti-angiogenic drugs, immune checkpoint inhibitors, or other immunotherapies in an effort to enhance the antitumor activity of immunotherapeutic agents [30, 31]. While other promising approaches such as chimeric antigen receptor (CAR)- and T-cell receptor (TCR)-engineered T cells, dendritic vaccinations, and oncolytic viruses are still emerging, response rates to immunotherapy remain modest among EOC patients [7, 31], and our study adds to the notion that sepsis or the subsequent immune response does not substantially influence the prognosis of patients with EOC.

Conclusion

In conclusion, no indications were found in our observational study that postoperative sepsis may affect cancer prognosis or survival in patients with advanced-stage EOC.

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Supplementary

Supplementary Table 1. Definitions of sepsis.

	Sepsis-2	Sepsis-3
SIRS	At least 2 of the following: - temperature >38°C or <36°C, - heart rate >90/min, - respiratory rate >20/min or $PaCO_2$ <32 mmHg, - white cell count >12,000/mm³ or <4000/mm³ or >10% immature (bands) forms	Not applicable
SOFA (**Supplementary Table 2**)	Not applicable	Respiratory (PaO_2/FiO_2), Nervous (Glasgow Coma Scale), Cardiovascular (mean arterial pressure or vasopressor), Liver (bilirubin), Coagulation (platelets), Renal (creatinine)
Sepsis	SIRS + suspected infection	Increase in SOFA score ≥2 points + suspected infection
Septic shock	SBP <90 mmHg, reduction in SBP ≥40 mmHg from baseline, or MAP <60 mmHg despite fluid resuscitation	Vasopressors to maintain MAP ≥65 mmHg and lactate ≥2 mmol/dL despite adequate volume resuscitation

Abbreviations: FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; SBP, systolic blood pressure; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment.

Supplementary Table 2. Sequential Organ Failure Assessment (SOFA) Score System.

	Score				
System	**0**	**1**	**2**	**3**	**4**
Respiration					
PaO_2/FiO_2, mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, × 10^3/μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular					
Mean arterial pressure or vasopressor	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system					
Glasgow Coma Scale (score)	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen in arterial blood.

Supplementary Table 3. EOC diagnosis and treatment characteristics of the study patients.

Patients	Age	Incidence date	FIGO stage	Histologic subtype	Tumor grade	Treatment approach	Bowel surgery	Type of bowel surgery	Residual disease	Type of chemotherapy	Completion of chemotherapy	Response to chemotherapy
Patient A	68	2008	IV	Serous	Grade 3	PCS	Yes	Ileocecal resection; rectosigmoid resection with end colostomy	No	Adjuvant 6 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient B	68	2014	IIIC	Serous	Grade 3	PCS	Yes	Tumor deposits removed from mesentery of the ascending colon	No	Adjuvant 6 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient C	75	2015	IIIC	Serous	Grade 3	NACT-ICS	No	-	≤1 cm	Neoadjuvant 3 cycles of carboplatin/ paclitaxel	No (patient died)	-
Patient D	32	2009	IIIC	Serous	Grade 1	NACT-ICS	Yes	Resection of terminal ileum; rectosigmoid resection with temporary colostomy	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel	No (due to chemotherapy resistance)	Progressive disease (during neoadjuvant chemotherapy)
Patient E	40	2009	IIIC	Serous	Grade 2	PCS	Yes	Appendectomy	≤1 cm	Adjuvant 6 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient F	60	2011	IIIC	Serous	Grade 2	NACT-ICS	Yes	Right hemicolectomy; en bloc partial ileal and rectosigmoid resection with temporary colostomy	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel OVHIPEC with cisplatin Adjuvant 3 cycles of carboplatin	Yes (no adjuvant paclitaxel given due to adverse reactions)	Complete remission
Patient G	61	2019	IIIC	Serous	Grade 3	NACT-ICS	No	(Splenectomy)	≤1 cm	Neoadjuvant 2 cycles of carboplatin/ paclitaxel; then Neoadjuvant 6 cycles of dose-dense carboplatin/paclitaxel OVHIPEC with cisplatin Adjuvant 2 cycles of dose-dense carboplatin/paclitaxel	Yes	Partial remission
Patient H	73	2016	IVA	Serous	Grade 3	NACT-ICS	Yes	Transverse colon serosal injury sutured; no other bowel surgery performed	≤1 cm	Neoadjuvant 6 cycles of carboplatin/ paclitaxel Adjuvant 3 cycles of carboplatin/ paclitaxel	Yes	Stable disease

Supplementary Table 3. (Continued)

Patients	Age	Incidence date	FIGO stage	Histologic subtype	Tumor grade	Treatment approach	Bowel surgery	Type of bowel surgery	Residual disease	Type of chemotherapy	Completion of chemotherapy	Response to chemotherapy
Patient I	73	2015	IV	Serous	Grade 3	NACT-ICS	No	-	No	Neoadjuvant 6 cycles of carboplatin/ paclitaxel Adjuvant 3 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient K	80	2015	IIIC	Serous	Grade 3	NACT-ICS	Yes	Tumor deposits removed from mesentery of the transverse colon	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel Adjuvant 3 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient L	64	2015	IIIC	Serous	Grade 3	NACT-ICS	Yes	Lower anterior resection; extended right hemicolectomy and ileal resection (end-to-end anastomosis); appendectomy	≤1 cm	Neoadjuvant 6 cycles of carboplatin/ paclitaxel Adjuvant 3 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient M	70	2016	IIIC	Serous	Grade 3	NACT-ICS	Yes	Reversal of ileostomy (side-to-side anastomosis)	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel	No (patient died)	-
Patient N	64	2011	IIIC	Adenocar-cinoma NOS	Unknown	NACT-ICS	No	-	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel Adjuvant 3 cycles of carboplatin. Followed by 8 cycles of bevacizumab/ cyclophosphamide	Yes	Complete remission
Patient O	66	2008	IVB	Adenocar-cinoma NOS	Unknown	NACT-ICS	No	-	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel	No (due to postoperative complications)	Complete remission
Patient P	67	2019	IIIC	Serous	Grade 3	NACT-ICS	Yes	Tumor deposits removed from mesentery; no other bowel surgery performed	≤1 cm	Neoadjuvant 3 cycles of carboplatin/ paclitaxel	No (patient died)	-

Supplementary Table 3. (Continued)

Patients	Age	Incidence date	FIGO stage	Histologic subtype	Tumor grade	Treatment approach	Bowel surgery	Type of bowel surgery	Residual disease	Type of chemotherapy	Completion of chemotherapy	Response to chemotherapy
Patient Q	64	2015	IIIC	Serous	Grade 3	NACT-ICS	Yes	Ileocecal resection (side-to-side anastomosis); lower anterior resection with end colostomy	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel OVHIPEC (cisplatin) Adjuvant 3 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient R	48	2011	IVA	Serous	Grade 3	NACT-ICS	Yes	Excision of multiple lesions on the sigmoid and ascending colon (primary closure of the wounds)	No	Neoadjuvant 3 cycles of carboplatin/ paclitaxel Adjuvant 4 cycles of carboplatin/ paclitaxel	Yes	Complete remission
Patient S	61	2012	IIIC	Serous	Grade 3	PCS	Yes	Sigmoid resection; ileocecal resection (side-to-end anastomosis of the transverse colon and ileum)	No	Adjuvant 6 cycles of carboplatin/ paclitaxel	Yes	Complete remission

Supplementary Table 4. Sepsis diagnosis and treatment characteristics of the study patients.

	ICU admission for sepsis	Sepsis after primary treatment	Days between surgery and sepsis	Cause of sepsis	Severity of sepsis	Antibiotic treatment for sepsis	Bacterial culture obtained	Days between sepsis and intervention	Type of intervention	Treatment response (for sepsis)	Length of stay ICU (days)	Length of stay hospital (days)
Patient A	Yes	Yes	9	Anastomotic leakage of the colorectal anastomosis (no bowel ischemia)	Non-vasopressor-dependent sepsis	10 days Piperacillin/ Tazobactam (2 days); Switch to Meropenem (8 days)	Yes, multidrug-resistant *E. coli* (peritoneal fluid)	0	Relaparotomy; abscess drainage; creation of double-loop ileostomy	Full recovery	1	26
Patient B	Yes	Yes	7	Bowel perforation at the distal site of the ascending colon (no bowel ischemia)	Non-vasopressor-dependent sepsis	8 days Piperacillin/ Tazobactam (7 days); Switch to Ciprofloxacin (1 day)	Yes, no bacteria found in pleural fluid and blood culture. Not determined for the peritoneal fluid.	1	Relaparotomy; abdominal lavage; right hemicolectomy; creation of end ileostomy	Full recovery	1	18
Patient C	Yes	Yes	14	Vaginal cuff abscess; followed by persistent sepsis due to infective mitral valve endocarditis	Vasopressor-dependent sepsis (septic shock)	23 days Piperacillin/ Tazobactam (7 days); Switch to Teicoplanin/ Metronidazole (17 days)	Yes, *P. mirabilis* (blood culture) Yes, multidrug-resistant *E. coli* and *E. faecium* (vaginal cuff debris)	3	Drainage of vaginal cuff abscess	No recovery; (patient died in the ICU)	4 (1st ICU admission for sepsis) 4 (2nd ICU admission for sepsis	44
Patient D	Yes	No (after surgery for 1st relapse)	11	Ileal anastomotic leakage of the 2nd anastomosis of the ileum	Vasopressor-dependent sepsis	>10 days Piperacillin/ Tazobactam	Yes, multidrug-resistant *E. coli* (peritoneal fluid)	0	1st: Relaparotomy; Vorlagerung procedure; abdominal drains placed 2nd: Operative drainage of peritoneal fluid	Delayed recovery (2nd intervention was needed)	4	31

Supplementary Table 4. (Continued)

	ICU admission for sepsis	Sepsis after primary treatment	Days between surgery and sepsis	Cause of sepsis	Severity of sepsis	Antibiotic treatment for sepsis	Bacterial culture obtained	Days between sepsis and intervention	Type of intervention	Treatment response (for sepsis)	Length of stay ICU (days)	Length of stay hospital (days)
Patient E	Yes	No (after surgery for 2nd relapse)	>150	Urosepsis due to a blocked nephrostomy catheter and urinoma	Non-vasopressor-dependent sepsis	>10 days Ceftriaxone (1 day); Switch to Amoxicillin/ Clavulanic acid	Yes, multidrug-resistant *E. coli* (urine)	0	Nephrostomy catheter replacement	Full recovery	1	63
Patient F	Yes	Yes	7	Bacterial translocation due to ileus or pneumosepsis due to aspiration pneumonia (pneumosepsis more likely)	Vasopressor-dependent sepsis	5 days Ceftazidime/ Metronidazole (5 days)	Yes, *E. faecium* (peritoneal fluid)	0	Intubation for mechanical ventilation No surgical intervention needed	Delayed recovery (after mechanical ventilation at the ICU)	9	42
Patient G	No (postop ICU due to OVHIPEC)	Yes	2	Pancreatic fluid leakage which led to intra-abdominal fluid collections	Non-vasopressor-dependent sepsis	7 days Ceftriaxone/ Metronidazole (1,5 days) Switch to Piperacillin/ Tazobactam (5 days)	Yes, *S. epidermidis* (blood culture; possible contamination)	1	Drain placement for pancreatic fluid drainage	Delayed recovery (after long-term drainage of the pancreatic fluid)	0 (for sepsis)	10
Patient H	Yes	Yes	4	Bowel perforation of the transverse colon; followed by intra-abdominal abscess 10 days after relaparotomy	Non-vasopressor-dependent sepsis	5 days Cefuroxime/ Metronidazole (5 days)	Yes, *P. aeruginosa and E. faecium* (peritoneal fluid)	0	1st: Relaparotomy; segmental resection considered (not performed); defect sutured 2nd: Ultrasound-guided drainage of intra-abdominal abscess	Delayed recovery (2nd intervention was needed)	2	18

Supplementary Table 4. (Continued)

	ICU admission for sepsis	Sepsis after primary treatment	Days between surgery and sepsis	Cause of sepsis	Severity of sepsis	Antibiotic treatment for sepsis	Bacterial culture obtained	Days between sepsis and intervention	Type of intervention	Treatment response (for sepsis)	Length of stay ICU (days)	Length of stay hospital (days)
Patient I	Yes	Yes	5	Bowel perforation of the rectosigmoid colon	Non-vasopressor-dependent sepsis	6 days Ceftriaxone/ Metronidazole (6 days)	Yes, Gram-negative rods (not further specified) combined with anaerobic gut flora (peritoneal fluid)	0	1st: Relaparotomy; rectosigmoid defect sutured; creation of double-loop transverse colostomy 2nd: Sedation and intubation for mechanical ventilation (4 days)	Delayed recovery (2nd intervention was needed)	4	18
Patient K	Yes	Yes	2	Bowel perforation of the jejunum	Non-vasopressor-dependent sepsis	11 days Ceftriaxone/ Metronidazole (5 days) Switch to Cefuroxime/ Metronidazole (6 days)	Yes, anaerobic gut flora (peritoneal fluid)	0	1st: Relaparotomy; jejunal defect sutured 2nd: Platzbauch repaired with mesh	Delayed recovery (2nd surgical reintervention needed for Platzbauch)	7 (after 1st intervention) 4 (after 2nd intervention)	29
Patient L	Yes	Yes	4	Anastomotic leakage of the ileotransverse colon anastomosis due to bowel ischemia	Non-vasopressor-dependent sepsis	4 days Cefotaxime/ Metronidazole (4 days)	Yes, *B. fragilis* (blood culture) Yes, *S. aureus* and anaerobic gut flora (pus and wound fluid)	0	Relaparotomy; creation of ileotransversostomy	Full recovery	2	13

Supplementary Table 4. (Continued)

	ICU admission for sepsis	Sepsis after primary treatment	Days between surgery and sepsis	Cause of sepsis	Severity of sepsis	Antibiotic treatment for sepsis	Bacterial culture obtained	Days between sepsis and intervention	Type of intervention	Treatment response (for sepsis)	Length of stay ICU (days)	Length of stay hospital (days)
Patient M	Yes	Yes	6	Anastomotic leakage of the sigmoid colon due to bowel ischemia	Vasopressor-dependent sepsis	5 days Cefuroxime/ Metronidazole (1 day) Switch to Cefotaxime/ SDD (1 day) Switch to Meropenem/ Metronidazole/ Vancomycin (3 days)	Yes, *P. aeruginosa* and anaerobic gut flora (peritoneal fluid)	0	1st: Relaparotomy; fecal fluid drainage; no leak or ischemia found; Abthera closure 2nd: Relaparotomy; sigmoid resection at leak site; creation of end colostomy	No recovery; (patient died in the ICU)	4	11
Patient N	Yes	Yes	8	Bowel perforation of the sigmoid colon due to bowel ischemia	Non-vasopressor-dependent sepsis	10 days Cefuroxime/ Metronidazole/ Gentamycin	Yes, *E. coli* and *B. fragilis* (blood culture) Yes, *B. fragilis* (peritoneal fluid)	0	1st: Relaparotomy; fecal fluid drainage; creation of end colostomy 2nd: Ultrasound-guided drainage of abdominal fluid	Delayed recovery (2nd intervention was needed)	8	49

Supplementary Table 4. (Continued)

	ICU admission for sepsis	Sepsis after primary treatment	Days between surgery and sepsis	Cause of sepsis	Severity of sepsis	Antibiotic treatment for sepsis	Bacterial culture obtained	Days between sepsis and intervention	Type of intervention	Treatment response (for sepsis)	Length of stay ICU (days)	Length of stay hospital (days)
Patient O	Yes	Yes	7	Suspected gastric perforation (CT showed signs of perforation. Even though the site of perforation was not found, an infiltrate was observed near antrum of the stomach)	Non-vasopressor-dependent sepsis	9 days Cefuroxime/ Metronidazole (4 days) Switch to Piperacillin/ Tazobactam/ Vancomycin (5 days)	Yes, *E. coli* and *S. aureus* (pus and wound fluid) Yes, *E. cloacae, E. faecium,* and *C. albicans* (peritoneal fluid)	0	1st: Relaparotomy; yellow pus found, no perforation or fecal fluid found 2nd: Relaparotomy; drain placement near gastric antrum	Delayed recovery (2nd intervention was needed)	3 (after 1st intervention) 2 (after 2nd intervention)	60 (transferred to another hospital)
Patient P	Yes	Yes	6	Bowel ischemia of the transverse colon	Vasopressor-dependent sepsis	>10 days Piperacillin/ Tazobactam/ Anidulafungin (1 day) Switch to Cefotaxime/ Metronidazole (6 days) Switch to Meropenem/ Vancomycin/ Anidulafungin/ SDD (selective digestive decontamination) (>3 days)	Yes, *E. faecalis* (peritoneal fluid)	5	Relaparotomy; creation of end colostomy; fecal fluid drainage	No recovery; (patient died in the ICU)	15	16

Supplementary Table 4. (Continued)

	ICU admission for sepsis	Sepsis after primary treatment	Days between surgery and sepsis	Cause of sepsis	Severity of sepsis	Antibiotic treatment for sepsis	Bacterial culture obtained	Days between sepsis and intervention	Type of intervention	Treatment response (for sepsis)	Length of stay ICU (days)	Length of stay hospital (days)
Patient Q	No (post-op ICU due to OVHIPEC)	Yes	9	Spontaneous bacterial peritonitis (no anastomotic leakage, bowel ischemia, or bowel perforation)	Non-vasopressor-dependent sepsis	10 days Cefuroxime/ Metronidazole (10 days)	No bacteria found in drain fluid (peritoneal fluid)	0	1st and 2nd: Ultrasound-guided abdominal fluid drainage (excess peritoneal fluid, no fecal fluid found)	Delayed recovery (2nd Ultrasound-guided drainage was needed)	0	18
Patient R	Yes	Yes	7	Bowel perforation of the caecum or ascending colon	Non-vasopressor-dependent sepsis	10 days Cefuroxime/ Metronidazole (10 days)	Yes, *E. faecalis* and *E. coli* (peritoneal fluid)	1	1st: Relaparotomy; right hemicolectomy; creation of end ileostomy and mucus fistula (split stoma) 2nd: CT-guided abdominal fluid drainage	Delayed recovery (patient needed CT-guided drainage for paracolic abscess)	1	22
Patient S	Yes	Yes	10	Bowel perforation and fecal leakage of the colon due to bowel ischemia	Non-vasopressor-dependent sepsis	14 days Gentamycin (1 dose) Piperacillin/ Tazobactam (5 days) Switch to Amoxicillin/ Clavulanic acid (2 days) Switch back to Piperacillin/ Tazobactam (7 days)	Yes, *E. coli* (peritoneal fluid)	0	1st: Relaparotomy; creation of colostomy 2nd: VAC system placement	Delayed recovery (patient needed multiple washings and a VAC system for a wound infection)	1	31

Supplementary Table 5. Oncologic outcomes of the study patients.

	EOC recurrence	PFI* (months) (last FU date if no recurrence)	Secondary cytoreductive surgery	Residual disease after secondary surgery	Chemotherapy for EOC recurrence	Type of chemotherapy for recurrence	Completion of chemotherapy for recurrence	Response after chemotherapy for recurrence	Death	Cause of death	OS (months)	PFS (months)
Patient A	No	131 months	-	-	-	-	-	-	No	-	153	137
Patient B	Yes	56 months	No	-	Yes	1 cycle of carboplatin/ paclitaxel Switch to 5 cycles carboplatin/ gemcitabine (No paclitaxel due to neuropathy)	Yes	Complete remission	No	-	85	60
Patient C	*NA*	-	-	-	-	-	-	-	Yes	Septic shock†	-	-
Patient D	Yes	1st relapse: 9 months 2nd relapse: 6 months	Yes (for 1st relapse)	≤1 cm	Yes	1st relapse: 3 cycles of doxorubicin (Caelyx) 2nd relapse: none	No (patient wish to discontinue)	1st relapse: Progression of disease	Yes	Cancer related	24	PFS1: 12 months PFS2: 11 months
Patient E	Yes	1st relapse: 7 months 2nd relapse: 3 months	Yes (for 2nd relapse)	No	Yes	1st relapse: 6 cycles of carboplatin/ paclitaxel 2nd relapse: None	Yes	1st relapse: Complete remission 2nd relapse: Complete remission	Yes	Cancer related	37	PFS1: 12 months PFS2: 7 months PFS3: 18 months
Patient F	Yes	1st relapse: 13 months 2nd relapse: 3 months	No	-	Yes	1st relapse: 6 cycles of carboplatin 2nd relapse: None	No (patient refusal after 2nd relapse)	1st relapse: Stable disease for 3 months then Progressive disease	Yes	Cancer related	35	21
Patient G	Yes	1st relapse: 8 months 2nd relapse: 4 months	No	-	Yes	1st relapse: 6 cycles of carboplatin/ gemcitabine Switch to maintenance therapy with Niraparib (PARP inhibitor) 2nd relapse: 3 cycles doxorubicin/ bevacizumab	Yes	1st relapse: Stable disease for 4 months then Progressive disease	No	-	27	15

Supplementary Table 5. (Continued)

	EOC recurrence	PFI* (months) (last FU date if no recurrence)	Secondary cytoreductive surgery	Residual disease after secondary surgery	Chemotherapy for EOC recurrence	Type of chemotherapy for recurrence	Completion of chemotherapy for recurrence	Response after chemotherapy for recurrence	Death	Cause of death	OS (months)	PFS (months)
Patient H	Yes	1st relapse: 4 months 2nd relapse: 3 months	No	-	Yes	1st relapse: 1 cycle of doxorubicin (Caelyx), and 2 cycles of paclitaxel/ bevacizumab Switch to 6 cycles of carboplatin/ paclitaxel 2nd relapse: 2 cycles of gemcitabine	Yes (patient died during chemotherapy for 2nd relapse)	1st relapse: Stable disease	Yes	Cancer related	27	13
Patient I	Yes	7.5 months	No	-	Yes	1 cycle of carboplatin/ paclitaxel	No (patient wish to discontinue)	Progressive disease	Yes	Cancer related	44	17
Patient K	Yes	1st relapse: 9 months 2nd relapse: 6 months	No	-	Yes	1st relapse: maintenance therapy of carboplatin/ cyclophosphamide 2nd relapse: 6 cycles of doxorubicin (Caelyx) Switch to maintenance therapy with tamoxifen	Yes	1st relapse: Partial remission 2nd relapse: Progressive disease	Yes	Cancer related	48	17
Patient L	Yes	3 months	No	-	Yes	1 cycle of doxorubicin (Caelyx)	No (patient wish to discontinue)	Progressive disease	Yes	Cancer related	14	12
Patient M	*NA*	-	-	-	-	-	-	-	Yes	Septic shock†	6	-
Patient N	Yes	1st relapse: 7 months 2nd relapse: 4 months	No	-	Yes	1st relapse: 4 cycles of carboplatin/ paclitaxel 2nd relapse: 3 cycles of doxorubicin (Caelyx)	Yes	1st relapse: Progressive disease 2nd relapse: Progressive disease	Yes	Cancer related	32	17
Patient O	Yes	23 months	No	-	Yes	Not reported	Not reported	Not reported	Yes	Cancer related	29	24
Patient P	*NA*	-	-	-	-	-	-	-	Yes	Septic shock†	4	-

Supplementary Table 5. (Continued)

	EOC recurrence	PFI* (months) (last FU date if no recurrence)	Secondary cytoreductive surgery	Residual disease after secondary surgery	Chemotherapy for EOC recurrence	Type of chemotherapy for recurrence	Completion of chemotherapy for recurrence	Response after chemotherapy for recurrence	Death	Cause of death	OS (months)	PFS (months)
Patient Q	Yes	1st relapse: 6 months 2nd relapse: 11 months	No	-	Yes	1st relapse: 6 cycles carboplatin/ paclitaxel (3 months after recurrence) 2nd relapse: 1 cycle of doxorubicin (Caelyx) Palliative radiotherapy for necrotizing vaginal cuff mass	No (patient refusal after 2nd relapse)	1st relapse: Stable disease 2nd relapse: Progressive disease	Yes	Cancer related	26	10
Patient R	Yes	1st relapse: 28 months 2nd relapse: 18 months 3rd relapse: 11 months	No	-	Yes	1st relapse: 6 cycles carboplatin/ doxorubicin (Caelyx) 2nd relapse: 6 cycles of carboplatin/ gemcitabine 3rd relapse: maintenance therapy with tamoxifen; followed by 4 cycles of carboplatin/ doxorubicin	No (carboplatin discontinued at 3rd relapse due to allergic reaction)	1st relapse: Complete remission 2nd relapse: Complete remission 3rd relapse: Progressive disease	Yes	Cancer related	93	36
Patient S	Yes	1st relapse: 15 months 2nd relapse: 15 months	No	-	Yes	1st relapse: tamoxifen -> Progressive disease then start 6 cycles carboplatin/ paclitaxel 2nd relapse: 6 cycles of carboplatin/ doxorubicin (Caelyx)	Yes	1st relapse: Partial remission 2nd relapse: Stable disease	Yes	Cancer related	38	17

*Platinum-free interval (PFI) was defined as the time between the date of receiving the last chemotherapy dose and the date of progressive or recurrent disease, or the date of death.

†Sepsis deaths: Three of the eighteen patients (Patients C, M, and P) died from complications of septic shock during their hospital admission. Patient C developed sepsis due to a vaginal cuff abscess, which caused a fulminant infective endocarditis, leading to septic shock and ultimately death. Patient M developed sepsis from an anastomotic leak. Although CT imaging showed signs of anastomotic leakage, no leak was observed during an initial relaparotomy. The following day, the patient's condition deteriorated rapidly. During a second relaparotomy, the site of anastomotic leak and ischemia of the colon was detected and managed with a sigmoid resection and colostomy. Nevertheless, she developed septic shock, which led to her death. Lastly, Patient P developed sepsis without any clear signs of anastomotic leakage or bowel perforation on CT imaging. The sepsis was initially managed with broad-spectrum antibiotics. However, the patient's health worsened, after which a colonoscopy confirmed bowel ischemia. She underwent a relaparotomy with bowel resection and creation of a colostomy. Nonetheless, the patient's sepsis did not respond to further treatment, leading to septic shock and ultimately death.

CHAPTER 4

Oncologic Outcomes after Splenectomy during Initial Cytoreductive Surgery in Advanced Epithelial Ovarian Cancer: A Nationwide Population-Based Cohort Study

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Abstract

Objective

Epithelial ovarian cancer (EOC) patients undergoing splenectomy during cytoreductive surgery represent a small subgroup of patients. Splenic metastases or technical reasons due to extensive upper abdominal disease may require splenectomy. It remains unclear whether splenectomy during cytoreductive surgery is justified to achieve complete cytoreduction. The aim of this study was to assess the association between splenectomy and perioperative outcomes, as well as survival, in patients with advanced-stage epithelial ovarian cancer (EOC).

Methods

In this nationwide population-based study, all consecutive patients diagnosed with FIGO stage IIIC and IV EOC between January 1, 2008 and December 31, 2015 were identified from the Netherlands Cancer Registry. Patients who underwent cytoreductive surgery combined with platinum-based chemotherapy as primary treatment were selected. Differences in clinicopathologic characteristics between splenectomy and non-splenectomy patients were assessed. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan–Meier survival curves and log-rank tests. Cox proportional hazards models were used to adjust for covariates that influence survival.

Results

A total of 3,911 patients were identified: 99 splenectomy and 3,812 non-splenectomy patients. Splenectomy patients were more likely to undergo extensive surgery or surgical reintervention, to receive intraperitoneal chemotherapy, intraoperative and postoperative blood transfusions, to experience postoperative infections, and to be admitted to an Intensive Care Unit (all $p<0.002$). No significant differences in PFS and OS were observed between splenectomy and non-splenectomy patients after adjusting for covariates.

Conclusion

Although advanced-stage EOC patients who undergo splenectomy during cytoreductive surgery have less favorable perioperative outcomes, no adverse impact of splenectomy on the survival of advanced-stage EOC patients was observed. Splenectomy during cytoreductive surgery seems to be justified to achieve complete cytoreduction in advanced-stage EOC patients.

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecologic malignancies in the Western world [1]. It has generally been accepted that EOC patients who underwent complete cytoreduction have better survival than those who undergo an optimal or incomplete cytoreduction (i.e., residual disease ≤1 or >1 cm, respectively) [2]. Accordingly, radical surgery has been increasingly adopted to achieve no macroscopic residual disease status. In some cases, extensive upper abdominal disease (e.g., omental cake or metastatic splenic involvement) may even require splenectomy to ensure complete cytoreduction. However, there is limited knowledge about the impact of splenectomy on the long-term outcome of patients. It has been hypothesized that as the antitumor-immunologic functions of the spleen may inhibit cancer growth, splenectomy may promote the growth of residual disease during the postoperative period as observed in murine models of other cancer types [3–6]. Nevertheless, the role of the spleen in the antitumor immune response remains only partly understood due to the contradictory literature on the relation between the function of the spleen and cancer growth [7].

Similarly, studies on the impact of splenectomy on the perioperative and survival outcomes of advanced-stage EOC patients have also reported inconsistent results. For instance, some have stated that splenectomy at the time of cytoreductive surgery may contribute to achieving complete cytoreduction with low perioperative complications, implying survival benefit [8–11]. Conversely, another study suggested that although splenectomy during upfront cytoreductive surgery is associated with acceptable perioperative complications, the added procedure appears to be associated with a shortened survival that seems to be unrelated to perioperative morbidity [12]. Nonetheless, the impact of splenectomy on the progression-free or overall survival, while adjusting for other prognostic factors, could often not reliably be demonstrated due to the low sample sizes of these studies [8–10, 12]. Moreover, their outcomes were mostly based on institution-based data (rather than population-based data), so it remains unclear to what extent patient selection for (surgical) treatment approaches might have affected their study outcomes. Their studies also did not report data on patients who underwent neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT-ICS) but solely on patients who underwent primary cytoreductive surgery (PCS). It thus remains to be determined whether the impact of splenectomy on perioperative and survival outcomes differs per treatment approach.

Although the impact of splenectomy on the surgical outcome of cytoreductive surgery may improve survival, the increased complication rate and/or the suppressed immunologic

effect may negatively influence the prognosis of advanced-stage EOC patients. Therefore, the aim of this study was to assess the association between splenectomy during initial cytoreductive surgery and perioperative outcomes and survival of FIGO stage IIIC and IV EOC patients.

Methods

Data collection

In a nationwide cohort study, all patients consecutively diagnosed with FIGO stage IIIC and IV EOC, including peritoneal, ovarian, and fallopian tube cancers (International Classification of Disease for Oncology (ICD-O) codes C48.1, C48.2, C56.9, and C57.0), between January 1, 2008 and December 31, 2015 were identified from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry that is weekly notified of all newly histologically confirmed malignancies in the Netherlands through an automated nationwide pathology archive (PALGA). The NCR contains extensive data on all newly diagnosed malignancies in the Netherlands. It covers more than 95% of all histologically confirmed malignancies [13]. Dedicated registrars have previously extracted data on patient, tumor, and treatment characteristics from patients' medical records. The data collected include information on surgical procedures and perioperative outcomes. Complementary patient (e.g., Charlson Comorbidity Index) and follow-up data (e.g., date of recurrence) were recently collected for a Dutch Cancer Society's project (IKNL2014-6838). To obtain recent information on vital status and the date of death, the NCR is annually linked to municipality registries (where citizens' data on death is registered by government officials as mandated by Dutch law).

Study population

Solely FIGO stage IIIC and IV EOC patients who had undergone cytoreductive surgery combined with platinum-based chemotherapy were selected. Surgical care for EOC patients is publicly available to all citizens owing to the Dutch healthcare system and is centralized in the Netherlands, where cytoreductive surgery is only performed in 16 high-volume hospitals (i.e., secondary and tertiary centers) by experienced gynecologic oncologists. Splenectomy procedures were performed by surgical oncologists from the Departments of General Surgery who joined gynecologic oncologists during cytoreductive surgery. Patients who underwent partial splenectomy were excluded from this study, since it is unclear to what extent this procedure affects the function of the spleen. Patients with missing information on the execution of splenectomy during cytoreductive surgery were also excluded. Finally, patients with unknown survival or recurrence data were excluded from the survival analyses.

Definitions

Residual disease after cytoreductive surgery was defined as the maximum diameter of the largest tumor nodule remaining after the procedure, classified as no macroscopic (complete), ≤1 cm (optimal), or >1 cm (incomplete) residual disease. Progressive or recurrent disease was defined as clinical signs of tumor growth, i.e., an increase in CA-125 serum levels (greater than or equal to twice the upper limit on two separate occasions at least one week apart), or the appearance of tumor lesions on imaging (either growth of pre-existing lesions or development of new lesions), combined with the clinical judgement of the treating medical oncologist or gynecologic oncologist [14]. Progression-free survival (PFS) was defined as the time between the date of diagnosis and the date of progressive or recurrent disease, or death (whichever occurred first). Patients who were alive without a record of progressive or recurrent disease were censored at the date of their last hospital visit. Overall survival (OS) was defined as the time between the date of diagnosis and the date of death, or last follow-up date for patients who were still alive (censoring date: January 31, 2020). Postoperative complications were recorded if they occurred within 30 days after cytoreductive surgery, and included complications such as infections, surgical complications, thromboembolic events, reinterventions, and Intensive Care Unit (ICU) admissions.

Statistical analysis

Patient characteristics were summarized using descriptive statistics. Patients were divided into a splenectomy group and a non-splenectomy group. The Pearson χ^2 test or Fisher's exact test was used for categorical variables and the two-sample Wilcoxon rank-sum test for continuous variables to compare the two groups. Kaplan–Meier survival curves, log-rank tests, and Cox proportional hazards models were used to analyze the PFS and OS. To assess whether splenectomy is independently associated with PFS or OS, the following established prognostic factors were included in the multivariable model: age, FIGO stage, tumor grade, treatment approach, and residual disease after cytoreductive surgery. All of the covariables were treated as categorical variables except for age at diagnosis, which was treated as a continuous variable. The proportional hazards assumption was tested for both survival analyses using the Schoenfeld residual test. If the assumption was violated, time-varying covariates were included in the Cox proportional hazards models. Interaction effects were assessed using interaction terms and interaction plots were generated using margins plots to obtain the predicted hazard ratios of PFS or OS at each combination of the two variables which demonstrated interaction effects. If an interaction effect was statistically significant, that interaction term was included in the multivariable model. All statistical analyses were performed using STATA/SE, version 14.1 (StataCorp, College Station, Texas, USA) and a *p*-value of less than 0.05 was considered statistically significant.

Study outcomes

Primary outcomes of our study were the perioperative and survival outcomes (PFS and OS). Secondarily, the survival of the two groups was assessed by stratification by treatment approach (NACT-ICS and PCS) and by the presence of solid splenic metastases (these included both clinically (CT imaging) and pathologically (splenic tissue) confirmed splenic metastases).

Ethical approval

Ethical approval for this study was obtained from the NCR's Committee of Privacy [K20.157].

Results

Study population

A total of 6,502 patients were diagnosed with FIGO stage IIB–IV EOC between January 1, 2008 and December 31, 2015 in the Netherlands (~810 patients annually). Specifically, 5,443 patients were diagnosed with FIGO stage IIIC or IV EOC. Of these, 3,997 patients underwent cytoreductive surgery combined with platinum-based chemotherapy. The 19 patients who underwent partial splenectomy were excluded from this study. Data on the splenectomy procedure were unavailable for 67 patients, who were therefore also excluded. Finally, 99 patients were classified as splenectomy patients and 3,812 patients as non-splenectomy patients (**Figure 1**).

Patient, tumor, and treatment characteristics

Patient, tumor, and treatment characteristics are summarized in **Table 1**. For the splenectomy group, the median age at diagnosis was 63 years [range, 24–79] compared with 65 years [range, 20–91] for the non-splenectomy group. Splenectomy patients comprised a similar percentage of patients with omental cake as the non-splenectomy group (100% vs. 99.1%, p=0.352). Splenectomy patients more often underwent extensive surgical procedures (i.e., bowel resection (56.6% vs. 20.8%), diaphragmatic stripping (38.4% vs. 12.0%), or distal pancreatectomy (18.2% vs. 0.1%)), and relatively more often received intraperitoneal chemotherapy compared with the non-splenectomy patients (11.1% vs. 4.0%) (all p<0.002).

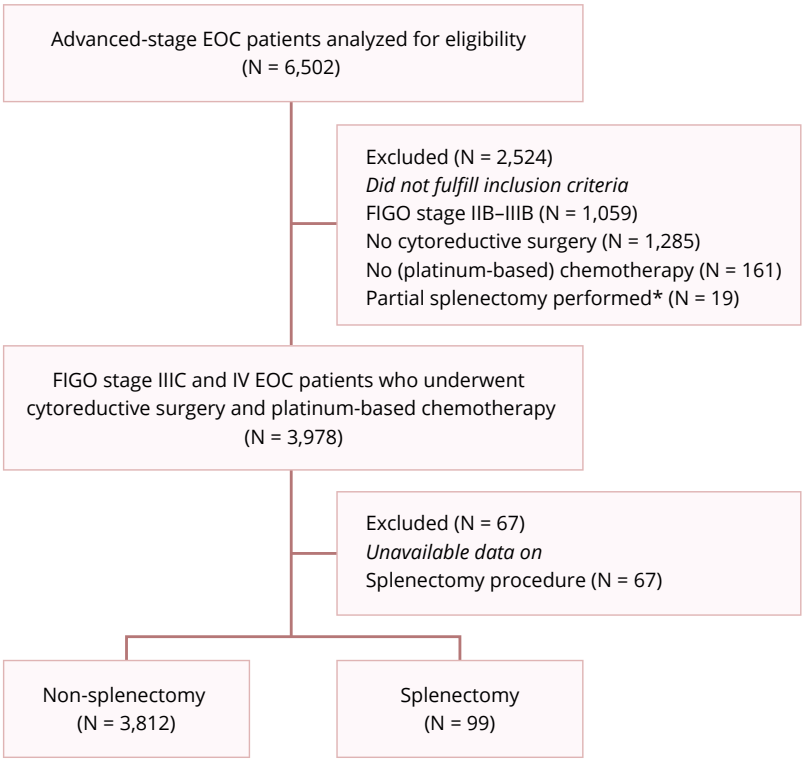

Figure 1. Flowchart of the study population.

*A partial splenectomy refers to a procedure in which only a part of the spleen is removed to preserve the spleen and its functions.

Table 1. Characteristics of the study population (N = 3,911).

	Non-splenectomy group (N = 3,812)	**Splenectomy group (N = 99)**	
Characteristic	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]	*p*-value
Age at diagnosis (in yrs)			<0.140*
Median	65 [20–91]	63 [24–79]	
FIGO stage			0.211†
Stage IIIC	2,762 (72.5)	66 (66.7)	
Stage IV	1,050 (27.5)	33 (33.3)	
Tumor grade			**0.036†**
Grade 1	135 (3.5)	8 (8.1)	
Grade 2	341 (9.0)	6 (6.1)	
Grade 3	1,987 (52.1)	43 (43.4)	
Unknown (N = 1,391)	1,349 (35.4)	42 (42.4)	
Histologic subtype			0.317†
Serous	3,071 (80.6)	90 (90.9)	
Mucinous	68 (1.8)	0 (0)	
Endometrioid	118 (3.1)	1 (1.0)	
Clear cell	100 (2.6)	1 (1.0)	
Adenocarcinoma NOS[a]	407 (10.7)	7 (7.1)	
Other[a]	48 (1.2)	0 (0)	
Karnofsky score (PS)			0.447†
10–50	24 (0.6)	0 (0)	
60–100	1,865 (48.9)	45 (45.5)	
Unknown (N = 1,977)	1,923 (50.5)	54 (54.5)	
Pretreatment CA-125 level (in kU/L)			**<0.049***
Median	665 [3–60,000]	809 [18–22,300]	
Unknown (N = 147)	142 (3.7)	5 (5.1)	
BRCA status			0.946†
BRCA-negative	977 (25.6)	28 (28.3)	
BRCA1 mutation	204 (5.3)	5 (5.1)	
BRCA2 mutation	101 (2.7)	3 (3.0)	
Unknown (N = 2,593)	2,530 (66.4)	63 (63.6)	
Presence of ascites			0.354†
No	1,619 (42.5)	37 (37.4)	
Yes	2,192 (52.5)	62 (62.6)	
Unknown (N = 1)	1 (0)	0 (0)	
CCI (in points)[b]			0.255†
0	280 (7.3)	11 (11.1)	
1–2	1,730 (45.4)	47 (47.5)	
≥3	1,802 (47.3)	41 (41.4)	
Solid splenic metastases[c]			**<0.001†**
No	3,787 (99.3)	81 (81.8)	

Table 1. (Continued)

Characteristic	Non-splenectomy group (N = 3,812) No. of patients (%)/ Median [range]	Splenectomy group (N = 99) No. of patients (%)/ Median [range]	*p*-value
Yes	25 (0.7)	18 (18.2)	
Presence of omental cake			0.352†
No	33 (0.9)	0 (0)	
Yes	3,777 (99.1)	99 (100)	
Unknown (N = 2)	2 (0)	0 (0)	
Treatment approach			0.501†
PCS	1,091 (28.6)	25 (25.3)	
NACT-ICS	2,721 (71.4)	74 (74.7)	
Bowel resection			**<0.001‡**
No	3,017 (79.1)	43 (43.4)	
Yes	791 (20.8)	56 (56.6)	
Unknown (N = 4)	4 (0.1)	0 (0)	
Diaphragmatic stripping			**<0.001†**
No	3,348 (87.8)	61 (61.6)	
Yes	457 (12.0)	38 (38.4)	
Unknown (N = 7)	7 (0.2)	0 (0)	
Lymphadenectomy			0.760†
No	3,322 (87.2)	88 (88.9)	
Yes	484 (12.7)	11 (11.1)	
Unknown (N = 6)	6 (0.1)	0 (0)	
Distal pancreatectomy			**<0.001†**
No	3,806 (99.8)	81 (81.8)	
Yes	4 (0.1)	18 (18.2)	
Unknown (N = 2)	2 (0.1)	0 (0)	
Intraperitoneal chemotherapy[d]			**<0.002‡**
No	3,661 (96.0)	88 (88.9)	
Yes	151 (4.0)	11 (11.1)	

Abbreviations: *BRCA*, breast cancer gene; CA-125, cancer antigen 125; CCI, Charlson Comorbidity Index; 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.

[a] The subcategory 'other' of the category 'histologic subtype' comprises the patients with other histologic subtypes than those noted such as Brenner, undifferentiated, mixed, or other carcinomas. The subcategory 'adenocarcinoma NOS' may consist of a large part of 'serous' type of EOC.

[b] In accordance with the National Cancer Institute's Charlson Comorbidity index, patients only received points for solid or metastatic tumors if other cancer types (with an incidence date of 5 years prior to or 30 days after the diagnosis date of advanced EOC) were present.

[c] Solid splenic metastases were defined based on clinically (CT imaging) and pathologically (splenic tissue) confirmed metastases.

[d] This variable includes both intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy. Inconsistent data on chemotherapy regimen did not allow for these two regimens to be analyzed separately.

*Wilcoxon rank-sum test

†Fisher's exact or Pearson χ^2 test

Perioperative outcomes

The perioperative outcomes are shown in **Table 2**. A slightly higher percentage of patients with complete cytoreduction (56.6% vs. 48.4%) and a lower percentage of patients with incomplete cytoreduction (7.1% vs. 12.6%) were observed in the splenectomy group than the non-splenectomy group. However, these discrepancies were not statistically significant (p=0.156). Splenectomy patients had relatively more intraoperative blood loss compared with the non-splenectomy patients (median 1,545 vs. 600 mL). Accordingly, the splenectomy group received more intraoperative (44.5% vs. 21.6%) and postoperative blood transfusions (44.5% vs. 21.1%) compared with the non-splenectomy group. Splenectomy patients were also more likely to experience postoperative infections (15.2% vs. 4.2%), to undergo surgical reintervention (12.1% vs. 3.0%), and to be admitted to an ICU (28.3% vs. 8.5%). The median hospital length of stay (10 vs. 7 days) and time to start adjuvant chemotherapy after cytoreductive surgery (35.5 vs. 29 days) were prolonged for the splenectomy patients when compared with the non-splenectomy patients (all p<0.001).

Table 2. Perioperative outcomes (N = 3,911).

	Non-splenectomy group (N = 3,812)	**Splenectomy group (N = 99)**	
Characteristic	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]	p-value
Residual disease after cytoreductive surgery			0.156†
No macroscopic	1,846 (48.4)	56 (56.6)	
≤1 cm	1,433 (37.6)	35 (35.3)	
>1 cm	481 (12.6)	7 (7.1)	
Unknown (N = 53)	52 (1.4)	1 (1.0)	
Intraoperative estimated blood loss (mL)			**<0.001***
Median	600 [50–4,600]	1,545 [400–6,900]	
Unknown (N = 270)	265 (7.0)	5 (5.1)	
Intraoperative blood transfusion			**<0.001‡**
No	2,550 (66.9)	43 (43.4)	
Yes	824 (21.6)	44 (44.5)	
Unknown (N = 450)	438 (11.5)	12 (12.1)	
Intraoperative blood transfusion (mL)			**<0.001***
Median	600 [100–6,000]	1,150 [300–5,100]	
Not applicable (N = 2,593)	2,550 (66.9)	43 (43.4)	
Unknown (N = 450)	438 (11.5)	12 (12.1)	
Postoperative blood transfusion			**<0.001‡**
No	2,538 (66.6)	43 (43.4)	
Yes	805 (21.1)	44 (44.5)	
Unknown (N = 481)	469 (12.3)	12 (12.1)	

Table 2. (Continued)

Characteristic	Non-splenectomy group (N = 3,812) No. of patients (%)/ Median [range]	Splenectomy group (N = 99) No. of patients (%)/ Median [range]	*p*-value
Postoperative infection[a]			**<0.001†**
No	3,650 (95.8)	84 (84.8)	
Yes	162 (4.2)	15 (15.2)	
Thromboembolic events[b]			0.318†
No	3,774 (99.0)	99 (100)	
Yes	38 (1.0)	0 (0)	
Surgical reintervention			**<0.001†**
No	3,696 (97.0)	87 (87.9)	
Yes	114 (3.0)	12 (12.1)	
Unknown (N = 2)	2 (0)	0 (0)	
Postoperative ICU stay			**<0.001†**
No	3,389 (88.9)	68 (68.7)	
Yes	325 (8.5)	28 (28.3)	
Unknown (N = 101)	98 (2.6)	3 (3.0)	
Length of stay at ICU (days)			0.193*
Median	2 [2–30]	3 [1–15]	
Not applicable (N = 3,457)	3,389 (88.9)	68 (68.7)	
Unknown (N = 101)	98 (2.6)	3 (3.0)	
Length of stay at hospital (days)			**<0.001***
Median	7 [1–123]	10 [4–55]	
Unknown (N = 2)	2 (0)	0 (0)	
TTC (days)[c]			**<0.001***
Median	29 [0–307]	35.5 [20–136]	
Unknown (N = 161)	156 (4.1)	5 (5.1)	
30-day mortality			0.703†
No	3,785 (99.3)	99 (100)	
Yes	23 (0.6)	0 (0)	
Unknown (N = 4)	4 (0.1)	0 (0)	
Recurrent or progressive disease			0.906†
No	738 (19.4)	20 (20.2)	
Yes	3,068 (80.5)	79 (79.8)	
Unknown (N = 6)	6 (0.1)	0 (0)	

Abbreviations: ICU, intensive care unit; TTC, time to start adjuvant chemotherapy.
[a]The variable 'postoperative infection' includes postoperative infections ranging from surgical site infections to systemic infections.
[b]The variable 'thromboembolic events' includes both deep venous thrombosis and pulmonary embolism.
[c]The variable 'time to start adjuvant chemotherapy' comprises the time interval between cytoreductive surgery and the start of adjuvant chemotherapy.
*Wilcoxon rank-sum test
†Fisher's exact or Pearson χ^2 test.

Survival outcomes

No significant differences in PFS and OS were observed between the splenectomy and non-splenectomy patients. When adjusted for FIGO stage, tumor grade, treatment approach, and residual disease after cytoreductive surgery, splenectomy was not independently associated with PFS (hazard ratio (HR) 0.60 [95% confidence interval (CI) 0.36–1.02]). Multivariable analysis demonstrated that the effect of splenectomy on PFS was dependent on treatment approach. The joint effect of splenectomy and treatment approach on the hazard estimates of PFS is demonstrated in the interaction plot (**Supplementary Figure 1**). Moreover, when adjusted for age, FIGO stage, tumor grade, treatment approach, and residual disease after cytoreductive surgery, splenectomy was also not independently associated with OS (HR 0.97 [95% CI 0.77–1.22]). The Kaplan–Meier curves of the progression-free survival and overall survival are demonstrated in **Figures 2** and **3**, respectively. The Cox proportional hazards models for PFS and OS with their crude and adjusted hazard ratios are listed in **Tables 3** and **4**, respectively.

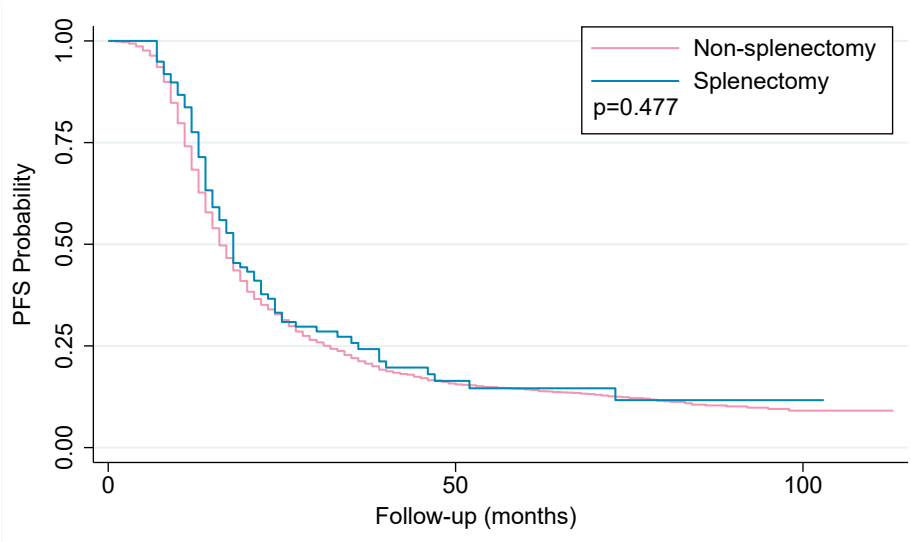

Figure 2. Kaplan–Meier curves of the progression-free survival (PFS) of non-splenectomy patients (N = 3,654, pink line) and splenectomy patients (N = 94, blue line). The median PFS was 16 and 18 months for the non-splenectomy and splenectomy patients, respectively. No significant difference in PFS was observed with the log-rank test (p=0.477).

*An additional 163 patients were excluded from the survival analysis with reference to Figure 1, because these patients had unknown follow-up or survival data.

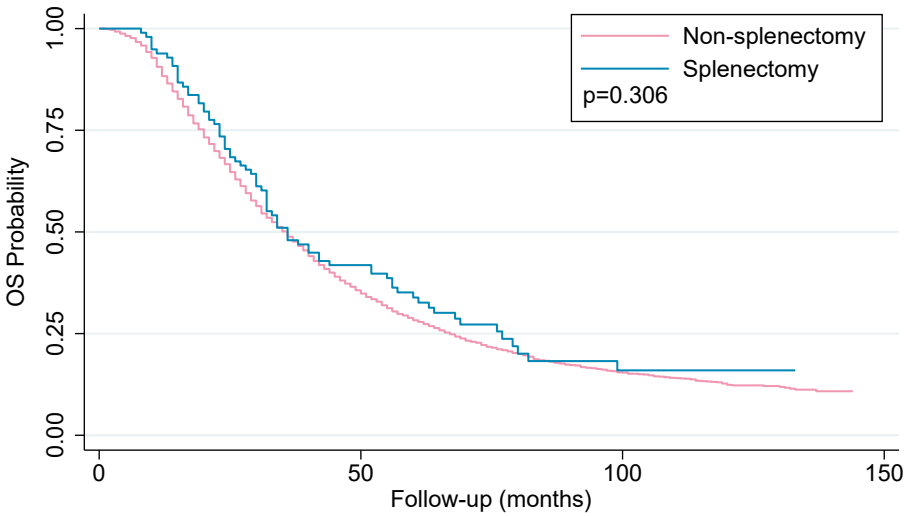

Figure 3. Kaplan–Meier curves of the overall survival (OS) of non-splenectomy patients (N = 3,805, pink line) and splenectomy patients (N = 98, blue line). The median OS was 36 months for both the non-splenectomy and splenectomy patients. No significant difference in OS was observed with the log-rank test (p=0.306).

*An additional 8 patients were excluded from the survival analysis with reference to Figure 1, because these patients had unknown follow-up or survival data.

Survival outcomes stratified by treatment approach

Stratification by treatment approach demonstrated a prolonged median PFS of patients who underwent PCS with splenectomy (N = 23, median PFS of 32 months) compared with patients who underwent PCS without splenectomy (N = 1,038, median PFS of 20 months) (p=0.043). However, no increase in median PFS was observed for patients who underwent NACT-ICS with splenectomy (N = 71, median PFS of 16 months) compared with patients who underwent NACT-ICS without splenectomy (N = 2,616, median PFS of 15 months) (p=0.614). No statistically significant difference in median OS was demonstrated between patients who underwent PCS with splenectomy (N = 25, median OS of 63 months) and patients who underwent PCS without splenectomy (N = 1,091, median OS of 48 months) (p=0.134). Consistently, no difference in median OS was found between patients who underwent NACT-ICS with splenectomy (N = 73, median OS of 32 months) and patients who underwent NACT-ICS without splenectomy (N = 2,714, median OS of 32 months) (p=0.804) (**Supplementary Figures 2** and **3**).

Table 3. Cox proportional hazards model reporting crude hazard ratios (N = 3,748)* and adjusted hazard ratios (N = 3,702)* for progression-free survival.

Characteristic	Crude HR [95% CI]	Adjusted HR [95% CI]
FIGO stage†		
Stage IIIC	Reference	Reference
Stage IV	1.29 [1.19–1.40]	1.37 [1.18–1.59]
Tumor grade		
Grade 1	Reference	Reference
Grade 2	1.46 [1.17–1.84]	1.38 [1.10–1.74]
Grade 3	1.33 [1.09–1.63]	1.27 [1.04–1.56]
Unknown	1.50 [1.22–1.84]	1.28 [1.04–1.58]
Treatment approach‡		
PCS	Reference	Reference
NACT-ICS	1.52 [1.40–1.65]	3.02 [1.69–5.39]
Residual disease after cytoreductive surgery†		
No macroscopic	Reference	Reference
>1 cm	1.69 [1.56–1.82]	0.71 [0.58–0.83]
≤1 cm	2.60 [2.32–2.90]	1.24 [1.05–1.44]
Splenectomy‡		
No	Reference	Reference
Yes	0.92 [0.74–1.16]	0.60 [0.36–1.02]
Treatment approach × Splenectomy		
NACT-ICS & Splenectomy	*NA*	1.95 [1.08–3.49]

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NA, not applicable; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; PCS, primary cytoreductive surgery.

*An additional 163 and 209 patients were excluded from the univariable and multivariable Cox regression analyses, respectively, with reference to Figure 1, because these patients had unknown data on recurrence status or one of the other variables included in the multivariable model.

†These variables (FIGO stage and residual disease after cytoreductive surgery) are time-varying covariates and were included in the multivariable model as such.

‡These variables (treatment approach and splenectomy) demonstrated interaction effects. Therefore, the interaction term 'Treatment approach × Splenectomy' was included in the model.

Table 4. Cox proportional hazards model reporting crude hazard ratios (N = 3,903)* and adjusted hazard ratios (N = 3,848)* for overall survival.

Characteristic	Crude HR [95% CI]	Adjusted HR [95% CI]
Age at diagnosis (in yrs)†		
	1.02 [1.01–1.02]	1.02 [1.01–1.03]
FIGO stage†		
Stage IIIC	Reference	Reference
Stage IV	1.33 [1.23–1.44]	1.35 [1.17–1.56]
Tumor grade		
Grade 1	Reference	Reference
Grade 2	1.51 [1.21–1.89]	1.33 [1.06–1.67]
Grade 3	1.36 [1.11–1.66]	1.21 [0.99–1.48]
Unknown	1.57 [1.28–1.92]	1.25 [1.02–1.54]
Treatment approach		
PCS	Reference	Reference
NACT-ICS	1.56 [1.44–1.69]	1.57 [1.44–1.71]
Residual disease after cytoreductive surgery†		
No macroscopic	Reference	Reference
≤1 cm	1.65 [1.53–1.78]	2.15 [1.90–2.42]
>1 cm	2.86 [2.58–3.19]	4.24 [3.53–5.10]
Splenectomy		
No	Reference	Reference
Yes	0.89 [0.71–1.12]	0.97 [0.77–1.22]

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; PCS, primary cytoreductive surgery.

*An additional 8 and 63 patients were excluded from the univariable and multivariable Cox regression analyses, respectively, with reference to Figure 1, because these patients had unknown data on follow-up or one of the other variables included in the multivariable model.

†These variables (age at diagnosis, FIGO stage, and residual disease after cytoreductive surgery) are time-varying covariates and were included in the multivariable model as such.

Survival outcomes stratified by splenic metastases

Stratification by solid splenic metastases did not demonstrate a statistically significant difference in median OS between patients with splenic metastases who underwent splenectomy (N = 18, median OS of 52 months) and those who did not undergo splenectomy (N = 25, median OS of 33 months) (p=0.162). Similarly, no statistically significant difference in median OS between patients without splenic metastases who underwent splenectomy (N = 80, median OS of 34 months) and those who did not undergo splenectomy (N = 3,780, median OS of 36 months) was found (p=0.759) (**Supplementary Figure 4**).

Discussion

In this nationwide study, the association between splenectomy during cytoreductive surgery and perioperative outcomes and survival of FIGO stage IIIC and IV EOC patients was assessed. Patients who underwent splenectomy had significantly more extensive surgical procedures, likely due to widespread (upper) abdominal disease, and consequently experienced more perioperative complications compared with non-splenectomy patients. Survival analyses suggested that patients who underwent PCS with splenectomy had a longer median PFS compared with those who underwent PCS without splenectomy. No other significant differences in PFS and OS were observed between splenectomy and non-splenectomy patients after adjustment for other prognostic factors.

In accordance with the literature, our data show that splenectomy during cytoreductive surgery is indeed rarely performed in patients with advanced-stage EOC. In this study, ~2.5% of patients with advanced EOC underwent splenectomy during initial cytoreductive surgery, similar to the previously reported incidences of 1.3%–13.8% of other population-based studies [9, 12, 15]. Conversely, recent studies in which patients were selected based on their feasibility of achieving complete cytoreduction reported higher proportions of patients undergoing splenectomy during cytoreductive surgery, likely due to their low proportion of NACT-ICS patients or inclusion of periods characterized by more radical surgical approaches [16].

Furthermore, ~1.1% of the study population had isolated splenic metastases (N = 43), confirming that this occurrence is uncommon in EOC. Although the nationwide registry did not provide data on the exact indication of splenectomy in each patient, information was available on which patients had splenic metastases and which had omental cake. Most patients probably underwent splenectomy due to technical reasons relating to perisplenic disease (82%) instead of direct metastatic involvement of the spleen (18%). Consistently, Magtibay et al. also reported that patients were more likely to undergo splenectomy for technical reasons (42 of 66 patients, 63.6%) than for splenic metastases (24 of 66 patients, 36.4%) during primary treatment [10]. Other studies did not disclose whether splenectomy was performed for splenic metastases or technical reasons [8, 9, 11, 12, 17].

Splenectomy patients were more likely to undergo other extensive upper abdominal surgical procedures (e.g., bowel resection or diaphragmatic stripping) in addition to splenectomy. Accordingly, relatively fewer patients with incomplete cytoreduction and slightly more patients with complete cytoreduction were observed in the splenectomy

group than in the non-splenectomy group (p=0.156). Although no data were available to more precisely quantify the extent of disease prior to surgery, such as the Sugarbaker's peritoneal cancer index (PCI), these findings suggest that splenectomy is mainly performed during cytoreductive surgery when it is expected to increase the likelihood of achieving complete cytoreduction [10, 18, 19]. Similarly, Zapardiel et al. did not find significant differences in residual disease after cytoreduction between splenectomy and non-splenectomy patients, which may also be due to case matching in their study [8]. Other studies did not report the rates of complete cytoreduction among splenectomy patients compared with non-splenectomy patients [10, 12].

On account of the more radical surgical procedures being performed, higher rates of perioperative complications were observed in the splenectomy group. In particular, the rate of postoperative infections, varying from surgical site infections to sepsis, was higher among splenectomy patients. Specifically, six splenectomy patients developed sepsis (6.1%), compared to 47 non-splenectomy patients (1.2%) (p<0.001). Nevertheless, it remained unclear to what extent sepsis was a direct result of splenectomy itself or other concurrent surgical procedures (e.g., bowel resection). Other studies also reported slightly higher rates of patients developing sepsis in the splenectomy group compared to the non-splenectomy group (3%–12.2% vs. 1%–9%, respectively) [8, 12, 17]. Magtibay et al. reported that five of the 112 patients who underwent splenectomy during primary or secondary cytoreductive surgery (4.5%) developed sepsis, three of whom died from septic shock [10]. However, no cases of sepsis could be directly attributed to splenectomy. Despite a relatively more complicated postoperative recovery period (i.e., a prolonged hospital length of stay), no differences in 30-day mortality were found between the groups in our study. These findings are consistent with those of previous reports [8, 12, 17].

Joneborg et al. found that upper abdominal surgery does not delay the initiation of adjuvant chemotherapy, despite a higher rate of postoperative complications and a longer hospital stay [20]. In contrast, our results suggest that splenectomy patients experience a longer time to adjuvant chemotherapy compared with non-splenectomy patients, likely due to prolonged recovery following more extensive surgical procedures and a higher rate of complications. Delayed initiation of adjuvant chemotherapy after complete cytoreductive surgery has been identified as an independent prognostic factor for shortened overall survival [21]. Nevertheless, the median time to adjuvant chemotherapy of splenectomy patients in our study remained within the recommended five to six weeks after cytoreductive surgery [21].

McCann et al. demonstrated that patients who underwent PCS with splenectomy resulting in maximum ≤1 cm residual disease had shorter OS than patients who underwent PCS without splenectomy (median OS 30 vs. 45 months (p<0.045)) [12]. Our results suggested a favorable median PFS for patients who underwent PCS with splenectomy compared with those without. Patients who underwent PCS with splenectomy included a higher proportion of individuals younger than 64 years and fewer patients older than 75 years, compared with non-splenectomy patients who underwent PCS. In addition, patients who underwent PCS with splenectomy more often underwent aggressive cytoreductive abdominal procedures (e.g., bowel resection and diaphragmatic stripping). Therefore, it is possible that these patients underwent more radical procedures in which the gynecologic oncologists aimed to achieve the maximum surgical effort, potentially explaining the prolonged PFS. Another, albeit speculative, explanation might be that splenectomy inhibited tumor growth or the development of metastases of EOC by modulating antitumor adaptive and innate immune responses as observed in murine models of other cancer types (e.g., lung cancer, mammary cancer, or hepatocellular cancers) [7, 22, 23]. Nevertheless, this finding is based on a small number of patients, and no significant differences in median OS were observed between splenectomy and non-splenectomy patients, even after stratification by treatment approach. Other studies also did not observe an independent association between splenectomy and either PFS or OS in patients with advanced-stage EOC [8, 9, 17].

Our results suggested that patients who underwent NACT-ICS had worse PFS (adjusted HR 3.02 [95% CI 1.69–5.39]) and OS (adjusted HR 1.57 [95% CI 1.44–1.71]) compared with patients who underwent PCS. However, it remains unclear whether this is due to the NACT-ICS approach itself or to other factors (e.g., aggressive tumor biology). Ongoing trials, such as the 'Trial of Radical Upfront Surgical Therapy' (TRUST), may help clarify this issue [24].

Two studies have reported that the presence of a solitary splenic metastasis is associated with shorter OS in advanced-stage EOC patients [15, 25]. However, stratification of survival outcomes by splenic metastases in our data did not demonstrate a decrease in OS of patients with splenic metastases compared to those without. This finding suggests that the amount of residual disease after cytoreductive surgery, rather than the initial tumor burden, may be more critical in determining oncologic outcomes in this patient population [8].

This population-based study reports the largest cohort of patients undergoing splenectomy as part of primary treatment of advanced-stage EOC. Additionally, our data demonstrate the association of splenic metastases and treatment approach with survival

outcomes in EOC patients. Nonetheless, several limitations should be acknowledged. Despite the strength of a robust population-based registry and large overall sample size, the number of patients who underwent splenectomy during initial cytoreductive surgery was relatively small. Furthermore, the absence of data on surgical complexity scores (e.g., Sugarbaker's PCI or Mayo Surgical Complexity Score) limited our ability to adjust for the extent of disease prior to surgery, which may reduce the external validity of our findings. Similarly, lack of information on chemotherapy regimens beyond the primary treatment limited the survival analysis. Incomplete data on thromboembolic events restricted a thorough assessment of thromboembolic events in advanced-stage EOC patients undergoing splenectomy. Additionally, information on the occurrence of certain infections (e.g., pneumonia) or other long-term effects of splenectomy was not available.

Conclusion

Despite the small number of patients who underwent splenectomy as part of initial cytoreductive surgery and the increased rate of perioperative complications, splenectomy at the time of cytoreductive surgery does not appear to be negatively associated with oncologic outcomes in patients with advanced-stage EOC. Therefore, it may be considered a justified procedure to achieve complete cytoreduction.

Acknowledgements

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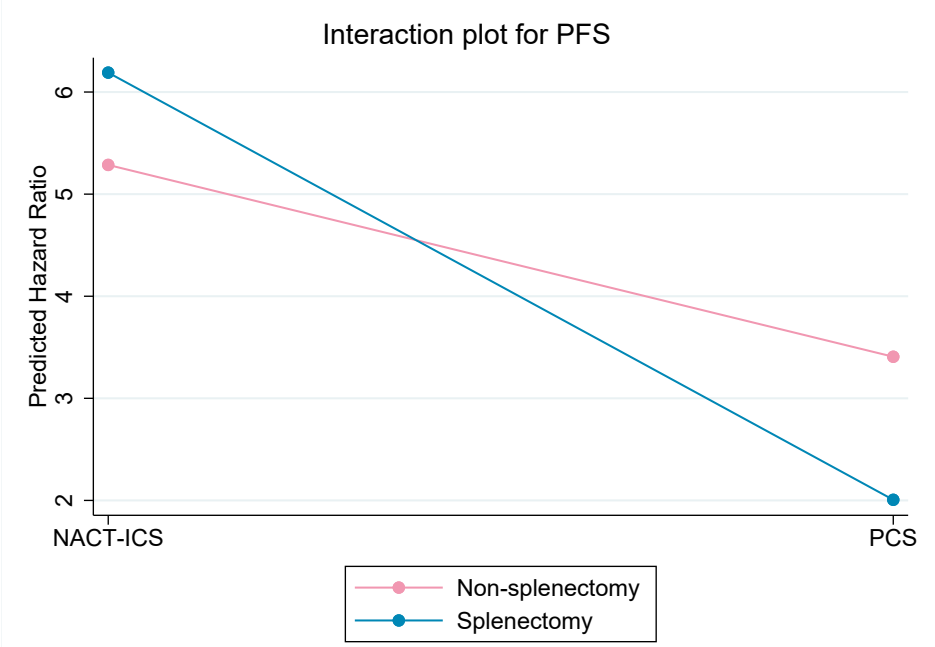
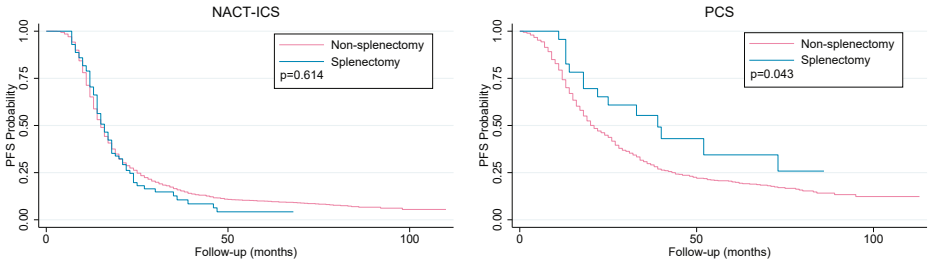
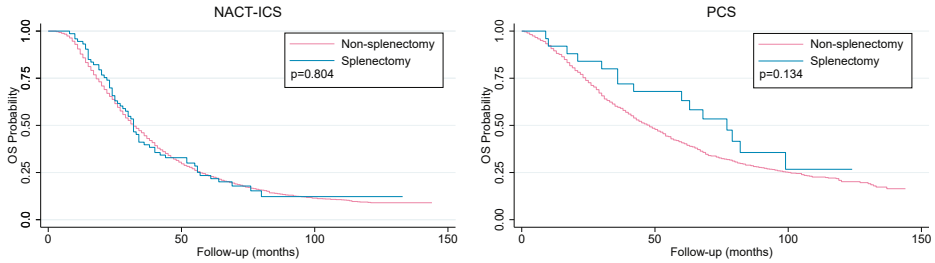
Supplementary



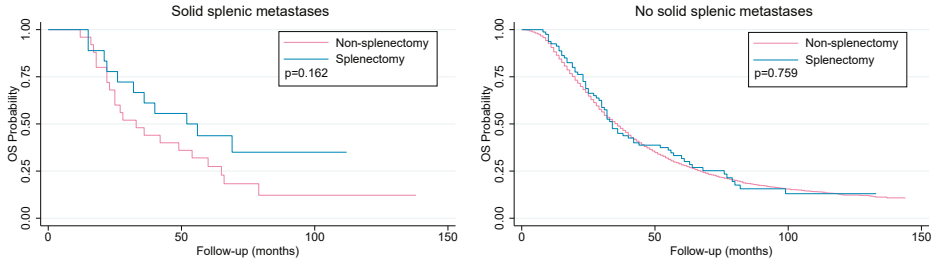
Supplementary Figure 1. The interaction plot demonstrating the estimated hazard ratios for progression-free survival for NACT-ICS patients with or without splenectomy, and PCS patients with or without splenectomy.



Supplementary Figure 2. Kaplan–Meier curves of progression-free survival of non-splenectomy patients (pink lines) and splenectomy patients (blue lines) for patients who underwent NACT-ICS (left) and PCS (right).



Supplementary Figure 3. Kaplan–Meier curves of overall survival of non-splenectomy patients (pink lines) and splenectomy patients (blue lines) for patients who underwent NACT-ICS (left) and PCS (right).



Supplementary Figure 4. Kaplan–Meier curves of overall survival of non-splenectomy patients (pink lines) and splenectomy patients (blue lines) for patients who had solid splenic metastases (left) and no solid splenic metastases (right).

CHAPTER 5

Adherence to Chemotherapy among Patients with Advanced Epithelial Ovarian Cancer in the Netherlands and Its Impact on Survival: A Nationwide Cohort Study

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Submitted

Abstract

Objective

Population-based information regarding adherence to first-line chemotherapy in epithelial ovarian cancer (EOC) is scarce. This study aimed to evaluate chemotherapy adherence, reasons for chemotherapy modifications, and associations with overall survival (OS).

Methods

Advanced-stage EOC patients diagnosed between January 1, 2015 and December 31, 2021 were identified from the Netherlands Cancer Registry. Patients who underwent cytoreductive surgery combined with platinum- and taxane-based chemotherapy were included. Patients were categorized into two groups: adherent (patients without modifications) and non-adherent (patients with modifications: dose reduction, chemotherapy interruption, and/or reduction in chemotherapy cycles). Reasons for modifications were assessed. Kaplan–Meier survival curves and Cox proportional hazards models were used to analyze OS.

Results

Among the cohort (N = 3,687), 54% of patients underwent chemotherapy modifications. Dose reduction (38%) was the most common, followed by interruption (24%) and reduction in chemotherapy cycles (9%). Non-adherence was associated with poorer performance scores, higher comorbidity indices, and undergoing primary cytoreductive surgery. Neurotoxicity and hematologic toxicity were the primary reasons for modifications in platinum agents (33% and 37%) and taxane agents (47% and 35%). No association with survival was found for dose reduction and interruption. However, reduction in chemotherapy cycles was associated with lower 5-year OS (32% [95% CI 26%–38%] vs. 36% [95% CI 34%–38%]), remaining significant after multivariable adjustment (hazard ratio 1.36 [95% CI 1.17–1.59]).

Conclusion

A significant proportion of Dutch advanced-stage EOC patients undergo chemotherapy modifications. No impact on OS was found for dose reduction or chemotherapy interruption, warranting prospective studies. Reduction in chemotherapy cycles was negatively associated with OS, possibly reflecting underlying treatment ineffectiveness.

Introduction

Chemotherapy is one of the cornerstones in the treatment of primary epithelial ovarian cancer (EOC) [1]. In advanced-stage EOC, the European guidelines state primary cytoreductive surgery (PCS) followed by six cycles of chemotherapy as the gold standard of treatment [1, 2]. First-line chemotherapy consists of paclitaxel (175 mg/m^2) and carboplatin (AUC of 5−6) administered every three weeks for a total of six cycles [1, 2]. Alternatively, when complete cytoreduction is not deemed feasible (e.g., due to spread of disease or the patient's general condition), three cycles of neoadjuvant chemotherapy, followed by interval cytoreductive surgery (NACT-ICS) and three adjuvant chemotherapy cycles, are recommended [1, 2].

Despite clear guidelines, variation in chemotherapy administration has been reported for EOC [3]. For instance, a French multicenter study disclosed that only 44% of patients underwent guideline-recommended chemotherapy [4]. In an Australian nationwide study, Jordan et al. reported that 68% of patients received platinum-based chemotherapy combined with taxanes [5]. Furthermore, it was reported that only 50% of patients completed the recommended six cycles without modifications, and 68% of patients aged over 70 did not undergo the standard chemotherapy regimen [5]. Most studies, except for Jordan et al., are not nationwide investigations or are limited by small sample sizes [3–7]. The lack of nationwide studies may imply the potential existence of disparities in clinical practices that remain inadequately explored in the current literature.

Therefore, the aim of this nationwide study was to assess the adherence of advanced-stage EOC patients to first-line chemotherapy, as recommended by the European guidelines, in the Netherlands. Furthermore, reasons for chemotherapy modifications (i.e., dose reduction, chemotherapy interruption, or reduction in the number of chemotherapy cycles) and their impact on patients' overall survival were assessed.

Methods

Data collection

In this retrospective cohort study, patients with peritoneal, ovarian, and fallopian tube cancers (i.e., International Classification of Disease for Oncology [ICD-O-3] codes C48.1, C48.2, C56.9, and C57.0), diagnosed between January 1, 2015 and December 31, 2021 were identified from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry that receives weekly notifications of all cytologically and histologically

confirmed malignancies in the Netherlands through an automated nationwide pathology archive (PALGA). Dedicated data managers extract data on patient, tumor, and treatment characteristics from medical records. To obtain recent information on vital status and date of death, the NCR is annually linked to the Personal Records Database (BRP).

Study population

Patients primarily diagnosed with advanced-stage EOC (i.e., International Federation of Gynecology and Obstetrics [FIGO] stages IIB–IV) were identified from the NCR. Solely advanced-stage EOC patients who underwent cytoreductive surgery combined with at least one cycle of platinum- and taxane-based chemotherapy were included. Patients who underwent another form of treatment were excluded. In addition, patients with missing data on chemotherapy regimens or modifications were also excluded from this study.

Definitions

Chemotherapy modifications comprised chemotherapy dose reduction, chemotherapy interruption, and/or reduction in the number of chemotherapy cycles. Dose adjustments based on the decreased estimated glomerular filtration rates or patients' weight changes after ascites drainage were not considered dose reductions. 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 (censoring date: January 31, 2024). The World Health Organization (WHO) performance score was used as a performance status. Residual disease was defined as the maximum diameter of the largest tumor nodule remaining after cytoreductive surgery, classified as no macroscopic (complete), ≤1 cm (optimal), or >1 cm (incomplete) residual disease.

Statistical analysis

Patient, tumor, and treatment characteristics were summarized using descriptive statistics. Patients who had chemotherapy modifications, along with the reasons for these modifications, were identified. Patients were divided into adherent (patients without chemotherapy modifications) and non-adherent (patients with chemotherapy modifications) groups. To compare the two groups, Pearson χ^2 or Fisher's exact tests were used for categorical variables, and two-sample Wilcoxon rank-sum tests were used for continuous variables. To assess whether chemotherapy modifications affect overall survival (OS), survival analyses were conducted using Kaplan–Meier survival curves and multivariable Cox proportional hazards models. Survival was adjusted for performance status, histologic subtype, tumor grade, FIGO stage, treatment approach (i.e., PCS or NACT-ICS), residual disease, type of chemotherapy modification, use of hyperthermic

intraperitoneal chemotherapy (HIPEC), and use of poly(ADP-ribose) polymerase (PARP) inhibitors. Furthermore, a subgroup analysis was conducted to compare survival between patients who received five chemotherapy cycles and those who received six cycles. This analysis evaluated whether omitting the final chemotherapy cycle impacts patient survival, as this is often considered in clinical practice for several reasons. Two-sided *p*-values of less than 0.05 were considered statistically significant. All statistical analyses were performed using STATA/SE, version 17.1 (StataCorp, College Station, TX, USA).

Ethical approval

Ethical approval for this study was obtained from the NCR's Committee of Privacy [K23.306].

Results

Study population

A total of 9,082 patients were diagnosed with primary EOC between January 1, 2015 and December 31, 2021. Of these, 3,687 (41%) had advanced-stage EOC and underwent cytoreductive surgery combined with platinum- and taxane-based chemotherapy. Among them, 1,713 patients (46%) underwent treatment without chemotherapy modifications (adherent group), while 1,974 patients (54%) underwent treatment with chemotherapy modifications (non-adherent group) (**Figure 1**).

Patient, tumor, and treatment characteristics

Table 1 presents the patient, tumor, and treatment characteristics of the study cohort. The median age at diagnosis was 66 years [interquartile range [IQR], 59–72], and the most common WHO performance score was 0 (45%). Serous type EOC was the most prevalent histologic subtype (84%). The majority of patients underwent NACT-ICS (72%). Compared with patients who did not undergo chemotherapy modifications, those with modifications generally had more comorbidities, worse performance scores, and were more likely to undergo PCS.

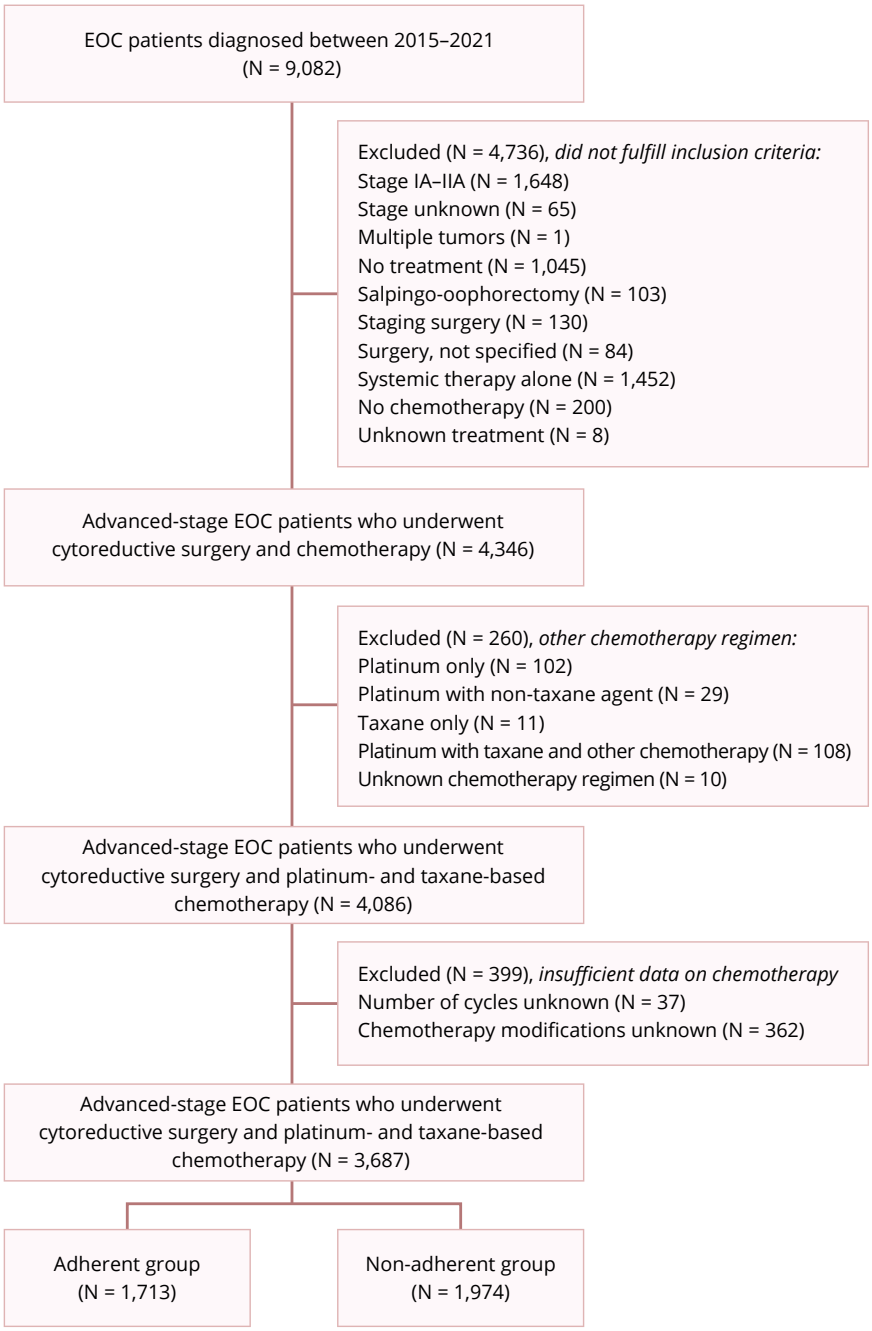

Figure 1. Flowchart of the study population.

Table 1. Patient, tumor, and treatment characteristics of the entire study cohort (N = 3,687), also stratified by chemotherapy adherence.

		Chemotherapy adherence		
	Entire cohort (N = 3,687)	**Yes (N = 1,713)**	**No (N = 1,974)**	
Characteristic	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	*p*-value
Age at diagnosis (in yrs)				**0.013**
Median	66 [59–72]	66 [58–72]	67 [59–73]	
FIGO stage				**<0.001**
IIB–IIIB	724 (20)	298 (17)	426 (22)	
IIIC	1,865 (50)	859 (50)	1,006 (51)	
IV	1,098 (30)	556 (32)	542 (27)	
Histologic subtype				0.74
Serous	3,114 (84)	1,459 (85)	1,655 (84)	
Mucinous	49 (1)	20 (1)	29 (1)	
Endometrioid	104 (3)	48 (3)	56 (3)	
Clear cell	151 (4)	67 (4)	84 (4)	
Adenocarcinoma NOS	132 (4)	54 (3)	78 (4)	
Other	137 (4)	65 (4)	72 (4)	
Tumor grade				0.83
Grade 1	215 (6)	102 (6)	113 (6)	
Grade 2	91 (2)	40 (2)	51 (3)	
Grade 3	2,869 (78)	1,310 (76)	1,559 (79)	
Unknown	512 (14)	261 (15)	251 (13)	
BRCA status				0.71
BRCA-negative	2,144 (58)	1,032 (60)	1,112 (56)	
BRCA1 mutation	287 (8)	131 (8)	156 (8)	
BRCA2 mutation	155 (4)	75 (4)	80 (4)	
BRCA1 and BRCA2 mutation	4 (<1)	1 (<1)	3 (<1)	
No mutation analysis performed	588 (16)	262 (15)	326 (17)	
Unknown	509 (14)	212 (12)	297 (15)	
Performance status (WHO score)				**0.009**
0	1,661 (45)	807 (47)	854 (43)	
1	971 (26)	441 (26)	530 (27)	
2	220 (6)	94 (5)	126 (6)	
3	45 (1)	12 (1)	33 (2)	
4	4 (<1)	3 (<1)	1 (<1)	
Unknown	786 (21)	356 (21)	430 (22)	

Table 1. (Continued)

		Chemotherapy adherence		
	Entire cohort (N = 3,687)	**Yes (N = 1,713)**	**No (N = 1,974)**	
Characteristic	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	No. of patients (%)/ Median [IQR]	*p*-value
Charlson Comorbidity Index				**<0.001**
0	2,241 (61)	1,071 (63)	1,170 (59)	
1	754 (20)	322 (19)	432 (22)	
2	206 (6)	70 (4)	136 (7)	
Unknown	486 (13)	250 (15)	236 (12)	
Treatment approach				**<0.001**
NACT-ICS	2,659 (72)	1,333 (78)	1,326 (67)	
PCS	1,028 (28)	380 (22)	648 (33)	
HIPEC administered				0.80
No	3,267 (89)	1,515 (88)	1,752 (89)	
Yes	420 (11)	198 (12)	222 (11)	
PARP inhibitor administered				0.07
No	3,449 (94)	1,616 (94)	1,833 (93)	
Yes	238 (6)	97 (6)	141 (7)	
Vital status				0.29
Alive	1,646 (45)	747 (44)	899 (46)	
Deceased	2,032 (55)	959 (56)	1,073 (54)	
Unknown	9 (<1)	7 (<1)	2 (<1)	

Abbreviations: *BRCA*, breast cancer gene; FIGO, International Federation of Gynecology and Obstetrics; HIPEC, hyperthermic intraperitoneal chemotherapy; IQR, interquartile range; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PARP, poly(ADP-ribose) polymerase; PCS, primary cytoreductive surgery; WHO, World Health Organization.

Chemotherapy cycles

In the entire study cohort, patients were more likely to receive the guideline-recommended six cycles of platinum than six cycles of taxane. **Supplementary Figures 1**–**3** demonstrate the number of chemotherapy cycles administered after PCS, and before and after ICS, respectively. In the PCS setting (N = 1,028, 28%), six cycles of adjuvant platinum were administered to 89% of patients, while six cycles of taxane were administered in 81% of the patients (p<0.001) (**Supplementary Figure 1**).

In the ICS setting (N = 2,659, 72%), the proportion of patients undergoing the recommended three cycles of neoadjuvant chemotherapy was similar for both agents (platinum 79% vs. taxane 78%) (**Supplementary Figure 2**). However, the proportion of patients who

underwent the recommended three cycles of adjuvant chemotherapy after NACT-ICS was higher for platinum (83%) than taxane (78%) (p<0.001) (**Supplementary Figure 3**).

Chemotherapy modifications

Table 2 demonstrates the types of chemotherapy modifications across the entire cohort, as well as stratified by chemotherapy agent. Dose reduction was the most commonly reported chemotherapy modification (38%), followed by chemotherapy interruption (24%), and reduction in the number of chemotherapy cycles (9%). Multiple types of chemotherapy modifications were reported for 624 patients (17%). Dose reduction (31% vs. 36%, p<0.001) and reduction in the number of chemotherapy cycles (4% vs. 8%, p<0.001) were less frequently reported for platinum agents than taxane agents. **Supplementary Table 1** further stratifies the chemotherapy modifications by chemotherapy timing (neoadjuvant versus adjuvant).

Table 2. The types of chemotherapy modifications across the entire cohort (N = 3,687), also stratified by chemotherapy agent.

		Chemotherapy agent		
	Entire cohort	**Platinum**	**Taxane**	
	No. of patients (%)	No. of patients (%)	No. of patients (%)	p-value
Dose reduction				**<0.001**
No	2,271 (62)	2,532 (69)	2,368 (64)	
Yes	1,416 (38)	1,155 (31)	1,319 (36)	
Chemotherapy interruption				0.32
No	2,785 (76)	2,804 (76)	2,841 (77)	
Yes	902 (24)	883 (24)	846 (23)	
Reduction in the number of cycles				**<0.001**
No	3,362 (91)	3,533 (96)	3,400 (92)	
Yes	325 (9)	154 (4)	287 (8)	

*A patient may have undergone multiple chemotherapy modifications. Consequently, if a patient experienced, for instance, both dose reduction and chemotherapy interruption, they will be presented twice in this table.

Reasons for chemotherapy modifications

The reasons for chemotherapy modifications in patients are listed in **Figure 2**. Neurotoxicity was the predominant reason for modifications involving taxane agents (47%) and the second most common for platinum agents (33%). Conversely, hematologic toxicity was the most common reason for modifications involving platinum agents (37%) and the second most frequent for taxane agents (35%). The reasons for each modification type are detailed in **Supplementary Figures 4**–**6**. Neurotoxicity was the most frequently reported reason for dose reduction (51% for platinum vs. 63% for

taxane) and for reduction in the number of chemotherapy cycles for taxane agents (52%). In contrast, reasons other than those listed were most commonly reported for reduction in chemotherapy cycles for platinum agents (39%). Hematologic toxicity was the predominant reason for chemotherapy interruption in both platinum (64%) and taxane (63%) agents.

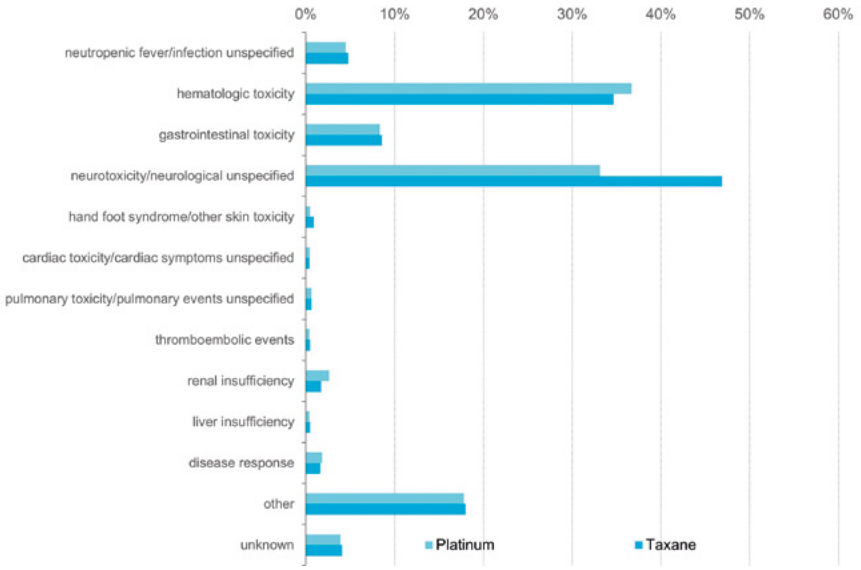

Figure 2. The reasons for chemotherapy modifications (i.e., dose reduction, chemotherapy interruption, or reduction in the number of cycles combined) of the entire cohort.

*Patients could have had chemotherapy modifications due to more than one reason.
†The other category comprises reasons for chemotherapy modifications other than one of the listed reasons.

Survival analyses

Kaplan–Meier survival curves are presented in **Figure 3**. The 5-year survival rate of the entire cohort was 36% [95% CI 34%–38%]. The 5-year survival rates of patients with and without dose reduction were similar (36% [95% CI 33%–39%] vs. 35% [95% CI 33%–38%]). Similarly, no significant difference in the 5-year survival was found between patients with and without chemotherapy interruption (36% [95% CI 32%–39%] vs. 36% [95% CI 33%–38%]). However, patients with reduction in the number of chemotherapy cycles had significantly lower 5-year survival rates than those without (32% [95% CI 26%–38%] vs. 36% [95% CI 34%–38%]), even after multivariable adjustment (hazard ratio (HR) 1.36 [95% CI 1.17–1.59]).

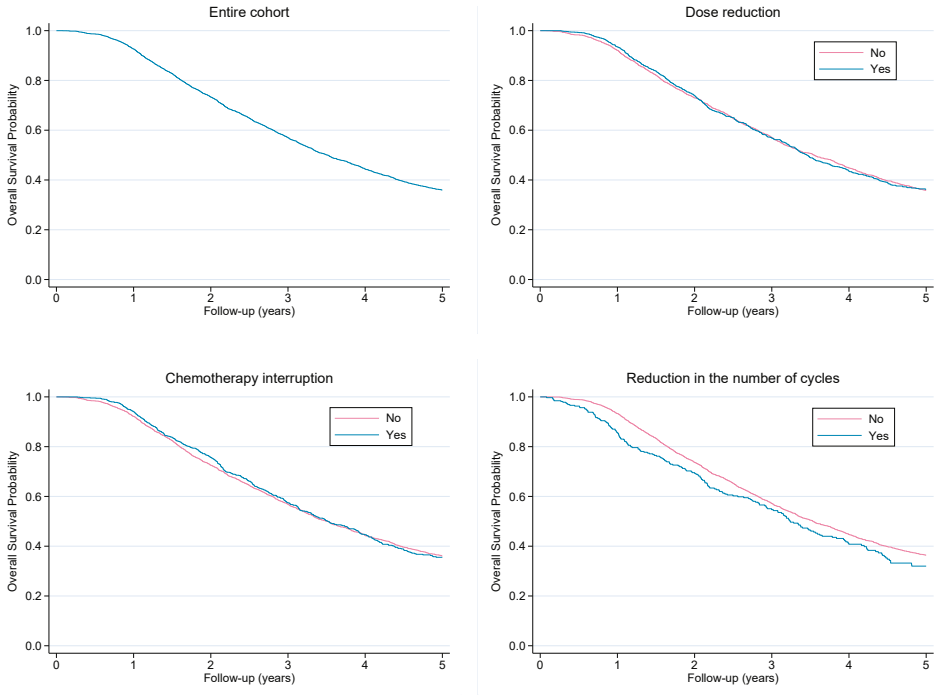

Figure 3. Kaplan–Meier survival curves for the entire cohort and for patients with or without dose reduction, chemotherapy interruption, or reduction in the number of chemotherapy cycles.

*Hazard ratios (HRs) from multivariable Cox proportional hazards models: dose reduction (HR 1.09 [95% CI 0.98–1.19]); chemotherapy interruption (HR 0.98 [95% CI 0.88–1.09]); reduction in the number of chemotherapy cycles (HR 1.36 [95% CI 1.17–1.59]).

Subgroup analysis

A subgroup analysis was conducted to determine whether omitting the final chemotherapy cycle affects patient survival, as reducing the number of cycles is often considered in clinical practice to minimize toxicity or manage side effects. The Kaplan–Meier survival curves for patients receiving either five or six chemotherapy cycles in the PCS and NACT-ICS setting are presented in **Figure 4**. No notable survival difference was observed between patients who received five or six chemotherapy cycles in the PCS setting (HR 1.53 [95% CI 0.84–2.76]). Similarly, no significant difference in survival was found between patients who received five or six chemotherapy cycles in the NACT-ICS setting (HR 1.25 [95% CI 0.88–1.76]).

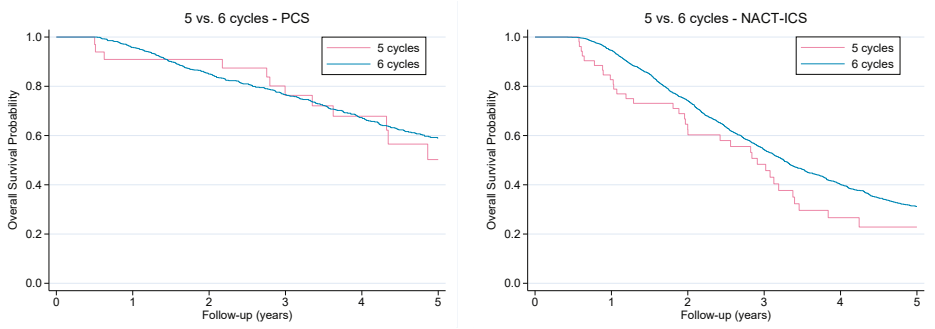

Figure 4. Kaplan–Meier survival curves for the patients who received either 5 or 6 chemotherapy cycles in the primary cytoreductive surgery (PCS; N = 278) and interval cytoreductive surgery (NACT-ICS; N = 1,030) setting.

*Hazard ratios (HRs) from multivariable Cox proportional hazards models: PCS setting (HR 1.53 [95% CI 0.84–2.76]); NACT-ICS setting (HR 1.25 [95% CI 0.88–1.76]).

Discussion

This nationwide cohort study provides significant insights into chemotherapy adherence among advanced-stage EOC patients in the Netherlands. Our findings confirm that variability in chemotherapy administration is common among EOC patients, with more than half of patients (54%) experiencing adjustments to their treatment regimens. While dose reduction and chemotherapy interruption (or delay) do not appear to negatively impact OS, reduction in the number of chemotherapy cycles, specifically more than one omitted cycle, may be associated with decreased OS.

Dose reduction emerged as the most common chemotherapy modification among patients, often attributed to neurotoxicity. Surprisingly, despite receiving lower doses than initially intended, these patients did not experience worse survival outcomes. This finding is consistent with the results of Lee et al. (N = 102) and Nagel et al. (N = 175), who also found no negative impact of dose reductions on OS in patients with EOC [8]. Notably, Lee et al. demonstrated that even dose reductions of ≥60% did not adversely affect overall or progression-free survival in advanced-stage EOC [8]. These findings prompt further investigation into whether the initial dosing regimens may be higher than necessary, given that dose reduction does not appear to compromise OS and may be associated with avoidable adverse events.

While reports on the impact of chemotherapy interruption or delay on EOC survival have been inconsistent [9–12], our results suggest that it is feasible to manage adverse effects without compromising the efficacy of treatment. Similarly, Starbuck et al.

(N = 505) demonstrated comparable survival between patients without chemotherapy delays and those with a prolonged treatment duration of less than four weeks. However, their study showed that survival probabilities decreased when the total delay in treatment exceeded six weeks [12]. In addition, Searle et al. (N = 205) reported that a chemotherapy interruption of more than ten weeks was associated with poorer survival [10]. The lack of association with survival in our cohort may be attributed to better management of treatment intervals in the Netherlands.

The number of patients undergoing a reduction in chemotherapy cycles was relatively low (4% for platinum vs. 8% for taxane). Among all chemotherapy modifications, only a decrease in the number of chemotherapy cycles was associated with poorer OS. The proportion of patients with disease progression or lack of treatment response was higher among those with reduced chemotherapy cycles compared to those with dose reductions or chemotherapy interruptions. Therefore, the poorer survival outcomes observed in patients with reduced chemotherapy cycles may be attributed to treatment response rather than the reduced number of cycles alone. However, it is important to note that after adjusting for performance status, histologic subtype, tumor grade, FIGO stage, treatment approach, residual disease, and type of chemotherapy modification, no significant difference in survival was found between patients receiving five or six cycles. This suggests that a reduction of more than one chemotherapy cycle may be necessary to negatively impact survival outcomes.

Our findings suggest that standard dosing and treatment duration of six cycles may not always be necessary, emphasizing the need to tailor treatment plans to optimize both efficacy and tolerability in advanced-stage EOC patients. Clinical recommendations are often derived from studies that may not fully represent the diverse patient population seen in real-world clinical practice. If a substantial proportion of patients deviates from standard treatment regimens, recommendations based solely on those regimens may have limited practicality. Bridging the gap between clinical research and real-world practice using population-based research is crucial for improving chemotherapy adherence and outcomes. This may involve inclusive study designs, guidelines that accommodate patient variability, and supportive interventions to address adherence barriers. Personalized treatment approaches, considering patient factors while adhering closely to guidelines, are essential. Additionally, strategies to manage chemotherapy-related toxicities could help mitigate the need for treatment modifications.

Our study is strengthened by its large sample size and nationwide population-based design, offering a representative overview of chemotherapy adherence among EOC patients in the Netherlands. Moreover, it provides comprehensive insights into

chemotherapy modifications, serving as one of the first nationwide studies to explore the reasons behind these modifications and their impact on survival. Nonetheless, limitations of our study include the lack of data on the extent of dose reduction and the absence of detailed information regarding the median duration of chemotherapy interruption. Furthermore, due to the retrospective, observational nature of the data, the ability to draw definitive conclusions is limited.

Conclusion

In conclusion, this nationwide study highlights significant variability in chemotherapy adherence among advanced-stage EOC patients in the Netherlands, with a substantial proportion of patients undergoing chemotherapy modifications. Chemotherapy dose reduction and interruption were not negatively associated with OS, suggesting the need for further prospective studies to evaluate potential adjustments to dosing schedules. Conversely, reduction in the number of chemotherapy cycles, specifically more than one omitted cycle, was associated with worse OS, possibly due to an inadequate response to chemotherapy.

Acknowledgements

The authors thank the Netherlands Cancer Registry for collecting and providing the data used in this study.

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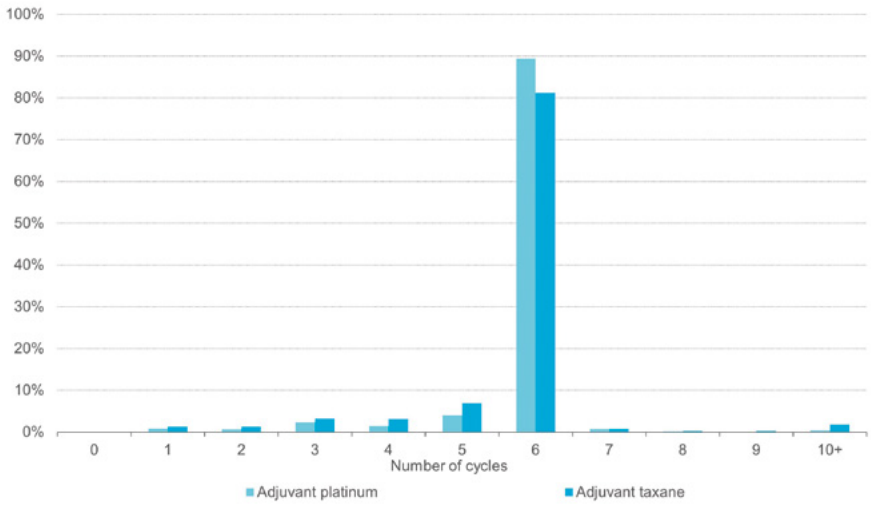
Supplementary

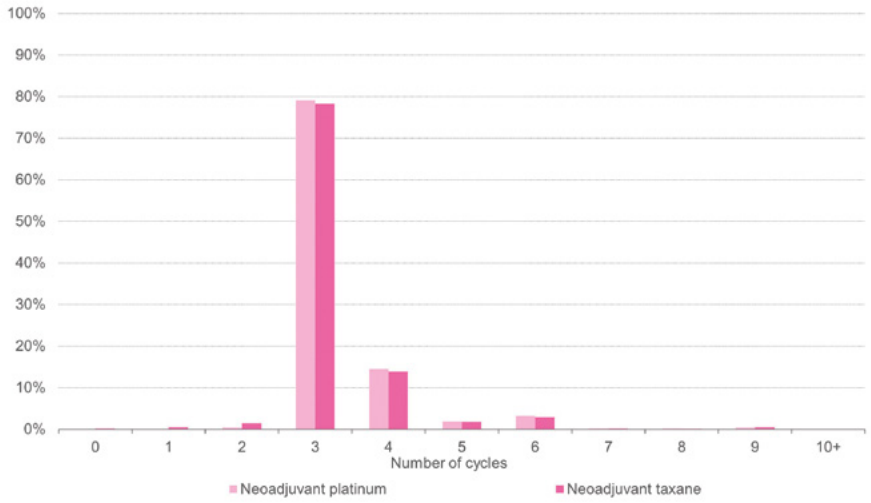
Supplementary Table 1. Types of chemotherapy modifications reported for patients who underwent neoadjuvant (N = 2,659) and/or adjuvant (N = 3,545)* chemotherapy, stratified by chemotherapy agent.

	Neoadjuvant				Adjuvant			
	Total	**Platinum**	**Taxane**		**Total**	**Platinum**	**Taxane**	
	No. of patients (%)	No. of patients (%)	No. of patients (%)	*p*-value	No. of patients (%)	No. of patients (%)	No. of patients (%)	*p*-value
Dose reduction				**0.002**				**<0.001**
No	1,723 (65)	1,891 (71)	1,783 (67)		2,170 (61)	2,424 (68)	2,265 (64)	
Yes	936 (35)	768 (29)	876 (33)		1,375 (39)	1,121 (32)	1,280 (36)	
Chemotherapy interruption				0.49				0.31
No	2,036 (77)	2,047 (77)	2,069 (78)		2,670 (75)	2,689 (76)	2,726 (77)	
Yes	623 (23)	612 (23)	590 (22)		875 (25)	856 (24)	819 (23)	
Reduction in the number of cycles				**<0.001**				**<0.001**
No	2,478 (93)	2,578 (97)	2,499 (94)		3,227 (91)	3,393 (96)	3,265 (92)	
Yes	181 (7)	81 (3)	160 (6)		318 (9)	152 (4)	280 (8)	

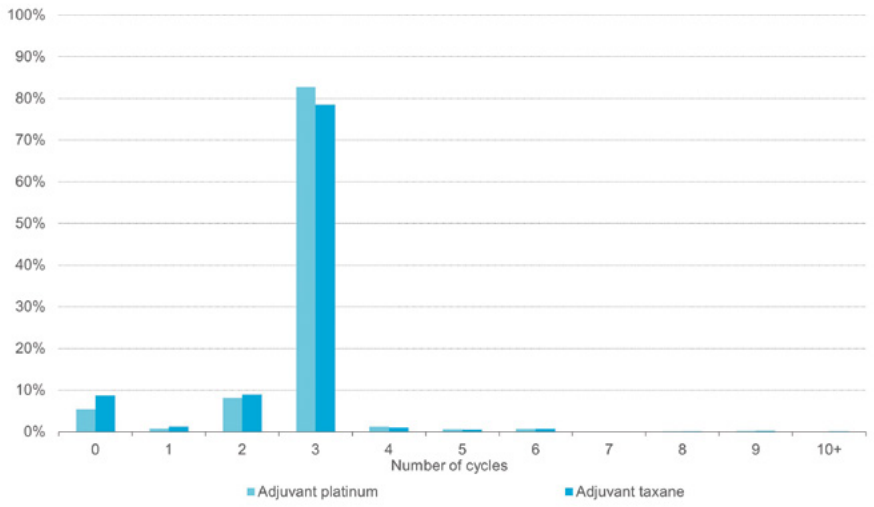
*A total of 142 patients who received only neoadjuvant chemotherapy were excluded from the adjuvant group, with reference to Figure 1 and Table 2.



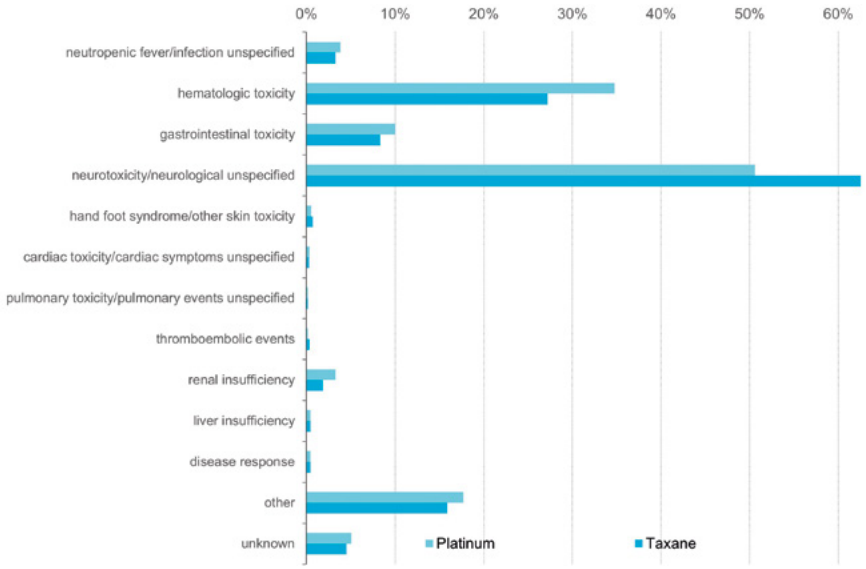
Supplementary Figure 1. The proportion of patients by the number of adjuvant chemotherapy cycles in the primary cytoreductive setting (N = 1,028).



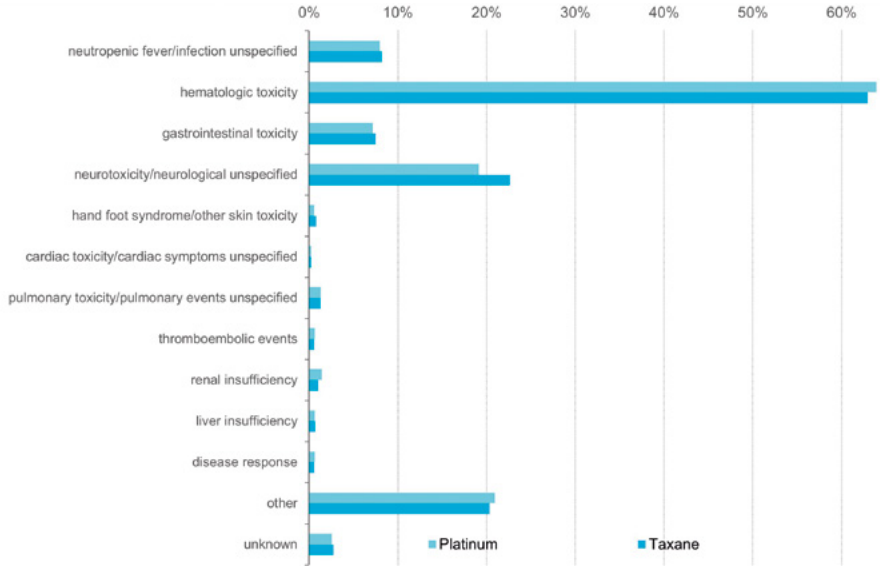
Supplementary Figure 2. The proportion of patients by the number of neoadjuvant chemotherapy cycles in the interval cytoreductive setting (N = 2,659).



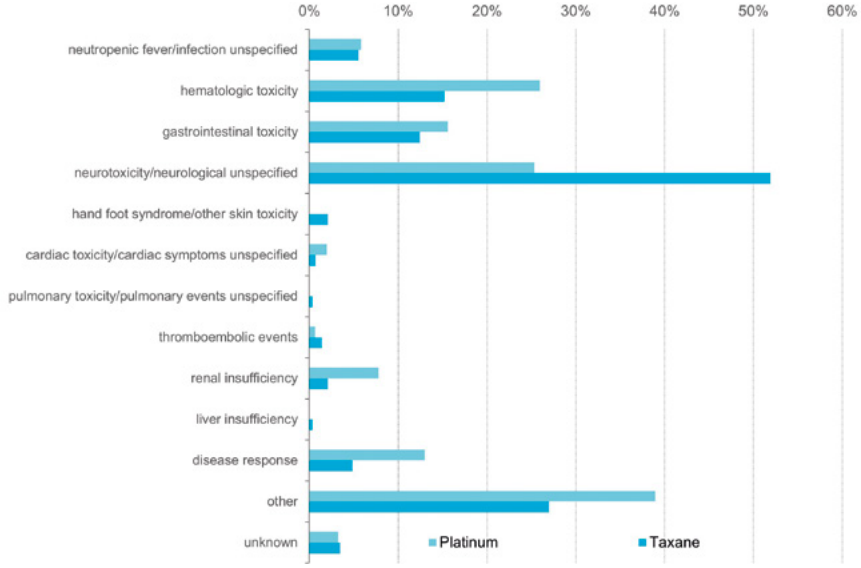
Supplementary Figure 3. The proportion of patients by the number of adjuvant chemotherapy cycles in the interval cytoreductive setting (N = 2,659).



Supplementary Figure 4. Reasons for dose reduction in the entire cohort.



Supplementary Figure 5. Reasons for chemotherapy interruption in the entire cohort.



Supplementary Figure 6. Reasons for reduction in the number of chemotherapy cycles in the entire cohort.

PART II

Predictive Models for Early Relapse in Advanced-Stage EOC

CHAPTER 6

Clinicopathologic Predictors of Early Relapse in Advanced Epithelial Ovarian Cancer: Development of Prediction Models using Nationwide Data

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Abstract

Objective

To identify clinicopathologic factors predictive of early relapse (platinum-free interval [PFI] of ≤6 months) in advanced epithelial ovarian cancer (EOC) during 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 January 1, 2008 and December 31, 2015 were identified from the Netherlands Cancer Registry. Patients who underwent cytoreductive surgery and platinum-based chemotherapy as initial treatment for EOC 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 in terms of calibration and discrimination. Internal validation was performed through bootstrapping to correct for model optimism.

Results

A total of 4,473 advanced-stage 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 of 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 cytoreductive surgery, demonstrated adequate model performance (AUC of 0.72 [95% CI 0.71–0.74]). Bootstrap validation revealed minimal optimism in the final postoperative model.

Conclusion

A postoperative discriminative model has been developed and made available online to predict the risk of early relapse in patients with advanced-stage EOC. Although external validation is still required, this model can support patient counseling in daily clinical practice.

**QR codes linking to the online score calculators are provided in the Supplementary section.*

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 are still diagnosed at an advanced stage (i.e., International Federation of Gynecology and Obstetrics [FIGO] stages IIB–IV) with a very high likelihood of developing 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 to platinum and often succumb to the disease shortly after diagnosis [6]. Many others experience disease recurrence after the initial response to treatment (~60–80%), with one-fourth of these recurrences occurring within six months of completing first-line therapy [3]. Quantifying the risk of early relapse in patients with advanced disease could support individualized counseling, contributing to more personalized care.

Prior studies on prognostic factors of early relapse (defined as a platinum-free interval [PFI] of ≤6 months) have primarily focused on biomarkers, as well as 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 in relation to progression-free and overall survival in advanced EOC, it remains uncertain whether these factors can accurately predict the risk of early relapse. For instance, studies have suggested that widespread disease not amenable to primary cytoreductive surgery and >1 cm residual disease after cytoreductive surgery are associated with an increased risk of early relapse [9, 10]. However, these studies are often hampered by their limited sample size and a high degree of missing data. To date, no studies have quantified the association between clinicopathologic factors and early relapse (defined as a PFI of ≤6 months) to develop clinical prediction models using population-based data.

If patients who are expected to derive little to no benefit from standard platinum-based treatment can be identified early, alternative approaches, such as novel targeted 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 model and a postoperative model) for early relapse in patients with advanced-stage EOC during or after first-line treatment, using nationwide data.

Methods

Data collection

All consecutive patients diagnosed with advanced-stage EOC (FIGO stages IIB–IV) between January 1, 2008 and December 31, 2015 were identified from the Netherlands Cancer Registry (NCR). This population-based registry receives weekly notifications of all recently histologically confirmed malignancies through an automated nationwide pathology archive (PALGA). Trained registrars have previously reviewed and extracted data on patient, tumor, and treatment characteristics using standardized case report forms. Additional data, such as performance status and follow-up details (e.g., date of recurrence), were collected recently as part of a Dutch Cancer Society project (IKNL2014-6838). The NCR is linked annually to municipal registries to obtain up-to-date information on patients' vital status.

Study population

Patients diagnosed with advanced-stage EOC who underwent cytoreductive surgery combined with platinum-based chemotherapy as initial treatment were selected. Patients who received fewer than four cycles of platinum-based chemotherapy or no cycles after interval cytoreductive surgery were excluded. Patients who did not undergo cytoreductive surgery or platinum-based chemotherapy were also excluded.

Definitions

Early relapse was defined as progressive disease during first-line platinum-based chemotherapy, progressive or recurrent disease occurring within four to six weeks after the last platinum dose, or recurrent disease within six months of completing platinum-based chemotherapy. Progressive and recurrent disease were defined as clinical signs of tumor growth, either an increase in CA-125 serum levels (greater than or equal to twice the upper limit of normal CA-125 serum levels on two separate occasions at least one week apart) or tumor lesions visible on imaging (i.e., growth of pre-existing lesions or development of new lesions), in combination with the clinical judgement of the treating medical oncologist or gynecologic oncologist [11]. The majority of patients did not undergo routine CA-125 surveillance. In accordance with Dutch guidelines, CA-125 was only measured in symptomatic patients with suspected progressive or recurrent disease, whereas post-treatment CA-125 monitoring may be standard practice in other countries. Residual disease was defined as the maximum diameter of the largest tumor nodule remaining after cytoreductive surgery and classified as no macroscopic, ≤1 cm, or >1 cm residual disease.

Statistical analysis

Patient characteristics were summarized using descriptive statistics. The platinum-free interval (PFI), defined as the time between the last platinum dose and the date of disease recurrence or disease progression, was calculated. Patients were categorized into two groups based on their PFI: late or non-relapsers (PFI of >6 months) and early relapsers (PFI of ≤6 months). Pearson χ^2 test or Fisher's exact test was used to compare categorical variables, and the two-sample Wilcoxon rank-sum test was used for continuous variables to compare the two groups. Differences in overall survival (OS) were analyzed using Kaplan–Meier survival curves and log-rank tests. OS was defined as the time from diagnosis to death or last follow-up for patients who were still alive (censoring date: January 31, 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 (StataCorp, College Station, Texas, USA), and R, version 3.6.1 (http://www.r-project.org).

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 the available literature, with the aim of minimizing the inclusion of noise variables. For the pretreatment model, candidate predictors included age at diagnosis, FIGO stage, pretreatment CA-125 level, performance status (Karnofsky score), and presence of ascites. In 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 cytoreductive surgery. Candidate predictors with more than 50% missing data were excluded from the model. After predictor selection, the risk prediction models were estimated.

Model performance and internal validation

The ability of the models to predict patients' risk of early relapse during or after first-line EOC treatment was assessed using the area under the receiver operating characteristic curve (AUC). A higher AUC indicates greater discriminative power (i.e., the model's ability to distinguish early relapsers from late or non-relapsers). Calibration was evaluated using calibration plots. Internal validation was performed with the bootstrap method, where samples were 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, provided estimates of optimism in model performance when applied to the development data, which were used to compute optimism-corrected performance

indices. To correct for overfitting (i.e., when a model performs well on the development sample but poorly on new data), regression coefficients were shrunk towards zero, and model intercepts were re-estimated after shrinkage.

Ethical approval

Ethical approval for this study was obtained from the NCR's Committee of Privacy [K19.121].

Results

Study population

A total of 6,408 patients were diagnosed with advanced-stage EOC between January 1, 2008 and December 31, 2015 in the Netherlands. Of these, 4,563 patients underwent cytoreductive surgery and platinum-based chemotherapy as part of first-line treatment. Among them, 3,171 patients were classified as late or non-relapsers and 1,302 patients as early relapsers. Data on disease recurrence or follow-up were unavailable for 90 patients, who were excluded from the study (**Figure 1**).

Patient, tumor, and treatment characteristics

Patient, tumor, and treatment 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 were more frequently diagnosed with FIGO stage IIB–IIC (p<0.001). The serous type of EOC was the predominant histologic subtype in both groups. Only 3.0% of early relapsers had endometrioid type EOC, compared with 6.0% of late or non-relapsers (p<0.001). Early relapsers were more likely to have undergone 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 fewer patients with no macroscopic residual disease (35.3% vs. 60.3%, p<0.001).

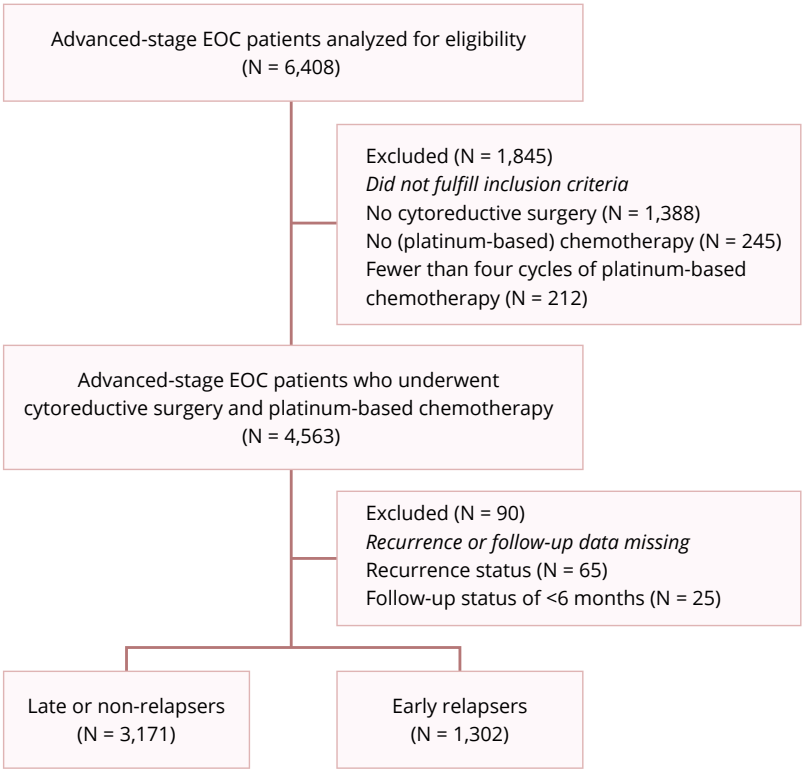

Figure 1. Flowchart of the study population.

Table 1. Characteristics of the study population (N = 4,473).

	Late or non-relapsers (N = 3,171)	**Early relapsers (N = 1,302)**	
Characteristic	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]	*p*-value
Age at diagnosis (in yrs)			**<0.020*†**
Median	64 [20–88]	65 [20–91]	
≤64	1,607 (50.7)	611 (46.9)	
65–74	1,077 (34.0)	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	1,921 (60.6)	789 (60.6)	
Stage IV	610 (19.2)	418 (32.1)	
Tumor type			**0.022†**
Ovarian tumor	2,711 (85.5)	1,096 (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	1,753 (55.3)	684 (52.5)	
Unknown (N = 1,374)	912 (28.8)	462 (35.5)	
Histologic subtype			**<0.001†**
Serous	2,472 (77.9)	1,019 (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	1,566 (49.4)	595 (45.7)	
Unknown (N = 2,288)	1,591 (50.2)	697 (53.5)	
Pretreatment CA-125 level (in kU/L)			**<0.001***
Median	512 [3–56,704]	793 [4–60,000]	
Unknown (N = 306)	232 (0.1)	74 (0.1)	
BRCA status			**<0.001†**
BRCA-negative	894 (28.2)	271 (20.8)	
BRCA1 mutation	202 (6.4)	33 (2.5)	
BRCA2 mutation	117 (3.7)	6 (0.5)	
Unknown (N = 2,950)	1,958 (61.8)	992 (76.2)	

Table 1. (Continued)

	Late or non-relapsers (N = 3,171)	**Early relapsers (N = 1,302)**	
Characteristic	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]	*p*-value
Presence of ascites			**<0.001†**
No	2,080 (65.6)	681 (52.3)	
Yes	1,090 (34.4)	621 (47.7)	
Unknown (N = 1)	1 (0)	0 (0)	
Treatment approach			**<0.001†**
PCS	1,378 (43.5)	311 (23.9)	
NACT-ICS	1,793 (56.5)	991 (76.1)	
Residual disease after cytoreductive surgery			**<0.001†**
No macroscopic	1,911 (60.3)	459 (35.3)	
≤1 cm	1,000 (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	3,037 (95.8)	1,266 (97.2)	
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)	2,561 (80.8)	884 (67.9)	
Unknown (N = 2)	2 (0)	0 (0)	
Recurrence			**<0.001†**
No	964 (30.4)	0 (0)	
Yes	1,728 (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.

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

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

[c] The subcategory 'other' of the category 'sites of metastasis' includes metastases 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.

*Wilcoxon rank-sum test

†Fisher's exact or Pearson χ^2 test.

Survival outcomes

Early relapsers had a median OS of 11 months [range, 0–83 months; N = 1,299], whereas late or non-relapsers had a median OS of 43 months [range, 9–123 months; N = 3,164] (p<0.001). The Kaplan–Meier curves of OS for late or non-relapsers and early relapsers are shown in **Figure 2**.

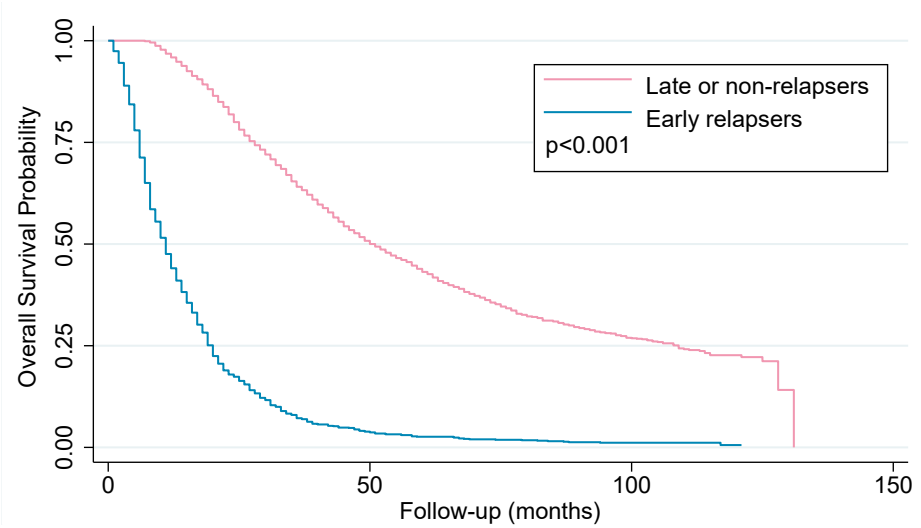

Figure 2. Kaplan–Meier curves of overall survival (OS) for late or non-relapsers (N = 3,164; pink line) and early relapsers (N = 1,299; blue line). Late or non-relapsers had a median OS of 43 months, while early relapsers had a median OS of 11 months. A statistically significant difference in OS was observed using the log-rank test (p<0.001).

*An additional 10 patients were excluded from the survival analysis (with reference to Figure 1) due to unknown follow-up or survival data.

Models' performance

Due to limited data availability, the predictors *BRCA* status and performance status (Karnofsky score) were excluded from the model development process. A total of 4,166 and 4,109 patients had complete cases and were included in the development of the pretreatment and postoperative models, respectively. The AUC of the pretreatment model was 0.64 [95% CI 0.62–0.66]. The calibration plot of the pretreatment model showed that the 95% CI around the observed outcome rate by deciles of predicted risk often did not cross the perfect fit line (**Figure 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 outcome rate by deciles of predicted risk crossed the perfect fit line for all groups (**Figure 4**).

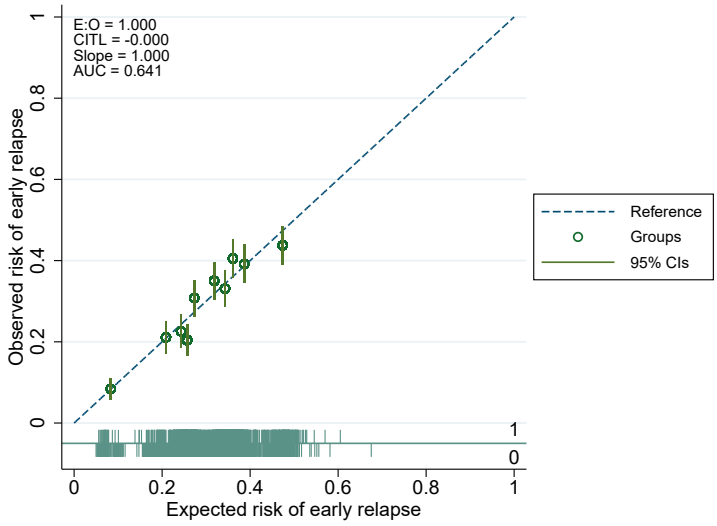

Figure 3. Calibration plot of the final pretreatment model.

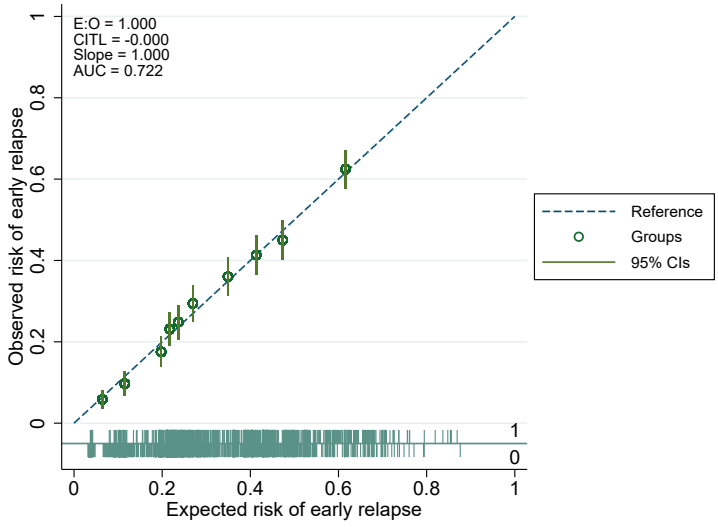

Figure 4. Calibration plot of the final postoperative model.

Models' validation

Due to the overall subpar model performance of the final pretreatment model, no internal validation of this model was performed. Bootstrapping with 1,000 iterations revealed a calibration slope of 0.97 for the final postoperative model. To correct for this

minimal overfitting, a shrinkage factor of 0.97 was applied to adjust the odds ratios (and regression coefficients) as well as the intercept estimates of the final model.

Online score calculator

An online score calculator based on the internally validated estimates of the final postoperative model was developed and made available on a freely accessible web-based platform (**Figure 5**). For example, for a 65-year-old FIGO stage IIIC patient with mucinous EOC, a pretreatment CA-125 level of 1,230 kU/L, ascites, and who underwent suboptimal NACT-ICS (i.e., ≤1 cm residual disease after cytoreductive surgery), the estimated risk of early relapse is 70.4%.

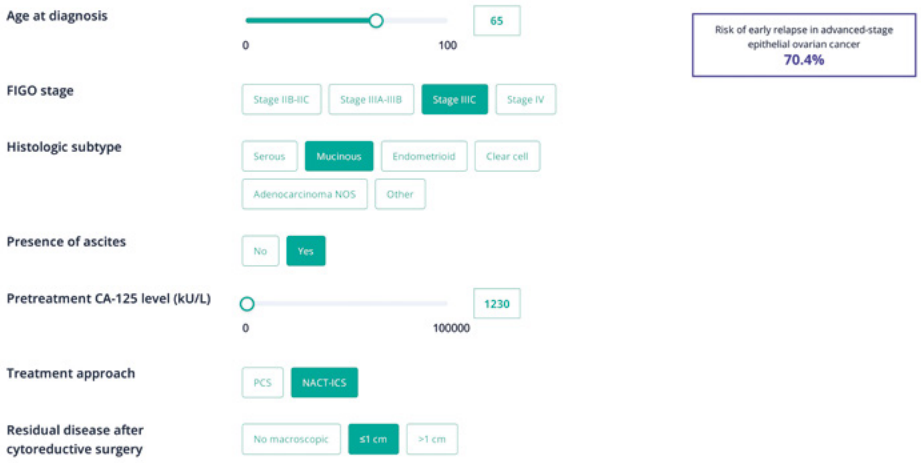

Figure 5. Screenshot of the online score calculator for the postoperative model. The parameters shown above were set for the 65-year-old patient example described in the text to demonstrate the results of the prediction model. Using our online score calculator, the risk of early relapse for this patient is estimated at 70.4%.

Risk stratification

Table 2 shows that the performance of the final postoperative model is highly dependent on the threshold chosen for a positive test. As the threshold for defining high risk of early relapse increases, sensitivity decreases, while specificity and positive predictive value increase. Depending on the clinical implications and the role of patient preferences in treatment decisions, an optimal and acceptable threshold for a positive test can be selected. For the patient example, at a 70% cutoff value, 1 minus the positive predictive value is estimated at 33.6%, indicating the percentage of patients who are incorrectly classified as early relapsers.

Table 2. Risk stratification table to assess the performance of the final postoperative model at different thresholds for a positive test*.

Cutoff value for a positive test	Sensitivity (%)	1-Specificity (%)	1-PPV (%)	NPV (%)	LR+
≥5%	99.1	93.1	69.2	94.8	1.1
≥10%	98.4	88.6	68.0	95.0	1.1
≥15%	95.1	74.5	65.2	92.6	1.3
≥20%	91.9	68.3	63.9	90.4	1.4
≥25%	71.8	39.9	57.0	83.6	1.8
≥30%	62.3	30.2	53.7	81.6	2.1
≥35%	57.5	26.6	52.5	80.5	2.2
≥40%	47.2	19.7	49.9	78.4	2.4
≥45%	32.6	11.4	45.7	75.8	2.9
≥50%	23.9	6.9	41.8	74.5	3.5
≥55%	16.7	4.1	36.8	73.3	4.1
≥60%	12.5	2.9	35.9	72.6	4.3
≥65%	6.8	1.6	35.7	71.6	4.3
≥70%	2.4	0.5	33.6	70.9	4.8
≥75%	0.8	0.2	33.3	70.6	4.0
≥80%	0.5	0	14.3	70.6	16.3
≥90%	0	0	-	70.5	-
≥100%	0	0	-	70.5	-

Abbreviations: LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.
*Predicted risk of early relapse.
†LR+ was calculated using the equation: sensitivity ÷ (1 – specificity), with sensitivity and specificity expressed in proportions.

Sensitivity analysis

In a sensitivity analysis, only patients with a known *BRCA* status (N = 1,504) were included, and *BRCA* status was added as an additional predictor in the postoperative model development process. 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 outcome rate by deciles of predicted risk crossed the perfect fit line for all groups (**Figure 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 regression coefficients) as well as the 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 1**–**3**.

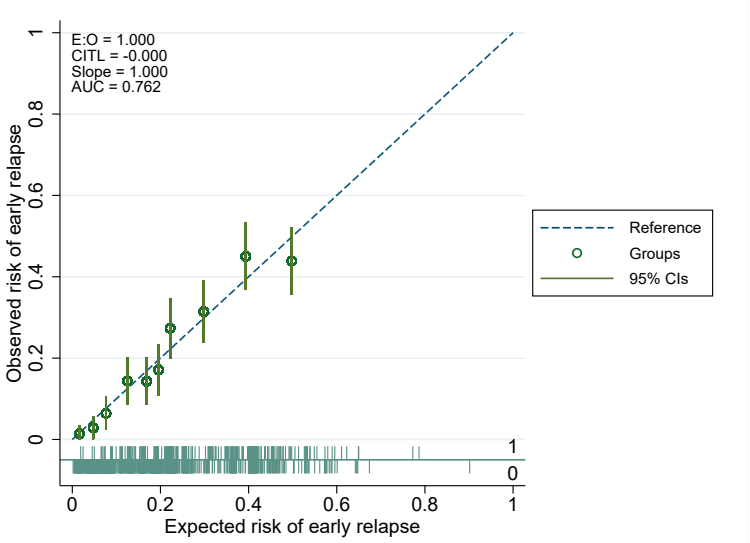

Figure 6. Calibration plot of the final *BRCA* model.

Discussion

In this population-based study, two prediction models were developed using clinicopathologic factors to estimate the risk of early relapse in advanced-stage EOC, during or after first-line treatment. Significant associations were found between early relapse (i.e., a PFI of ≤6 months) and FIGO stage, histologic subtype, presence of ascites, treatment approach, and residual disease after cytoreductive surgery. An online score calculator based on the final postoperative model was created and made available on a freely accessible platform.

Early relapse and tumor histology

In accordance with the literature, our data showed that patients with clear cell and mucinous histologic subtypes had a higher tendency to experience early relapse compared to those with serous EOC [13, 14]. Although less common, studies have reported that low-grade serous carcinoma (LGSC) tends to be more intrinsically resistant to platinum-based chemotherapy compared to high-grade serous carcinoma (HGSC). A further subclassification of our serous EOC cases into LGSC and HGSC did not reveal a significant difference in the risk of early relapse, possibly due to the indolent behavior of LGSC [13, 14]. However, this would require central revision of serous histopathology, which was not feasible given the extensive database covering patients from numerous Dutch hospitals over several years.

Early relapse and treatment approach

In addition, treatment approach proved to be an important predictor of early relapse in our analysis. Specifically, patients who did not qualify for primary cytoreductive surgery (PCS), but instead underwent neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT-ICS), demonstrated shorter platinum-free intervals. Similarly, Luo et al. showed that NACT-ICS patients had a higher incidence of progressive or recurrent disease within six months after first-line treatment compared with PCS patients with 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 achieving successful cytoreductive surgery (i.e., no macroscopic or ≤1 cm residual disease), other important reasons for opting for NACT-ICS rather than PCS include FIGO stage IV disease, poor performance status, and high perioperative risk [17]. These findings suggest that early relapsers may initially present in worse clinical condition, and consequently, clinicians may be more inclined to choose NACT-ICS as their treatment approach. Our results suggest that NACT-ICS is significantly associated with early relapse; however, it remains unclear whether this association stems from patient selection for NACT-ICS or other underlying factors. Geographical external validation of our postoperative model may offer further insight into this observation and its implications for Dutch clinical practice.

Early relapse and *BRCA* status

Insufficient data on *BRCA* status (particularly in the earlier years of the study, when testing was not yet part of standard clinical practice) prevented us from including this variable in the postoperative model without substantially reducing the usable study population. Nonetheless, a sensitivity analysis including only patients with known *BRCA* status (N = 1,504) revealed that patients with a *BRCA*-negative status (OR 5.43 [95% CI 2.15–13.77]) along with those with a *BRCA1* mutation (OR 2.91 [95% CI 1.07–7.95]) were more likely to be early relapsers compared to patients with a *BRCA2* mutation. These findings are consistent with several reports indicating that patients with a *BRCA2* mutation have an increased response to platinum-based chemotherapy. Therefore, *BRCA* status may be another important predictor of prolonged platinum-free interval [13, 18–20]. Thus, information on *BRCA* status should be determined for all newly diagnosed EOC patients, as recommended by current guidelines, to confirm its effect on patients' platinum-free interval, in addition to other important reasons (i.e., familial cancer risk and indications for PARP inhibitors) [13, 21, 22]. Furthermore, exploratory analyses, which included performance status in the postoperative model development,

failed to show a significant association with early relapse, possibly due to collinearity with age at diagnosis, which may have weakened any potential association.

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 whose association with both favorable and unfavorable progression-free and overall survival in EOC has been established, hindered its inclusion in the postoperative model development [23]. Moreover, bootstrap resampling allows for the possibility that some observations are considered multiple times during the same iteration, while others may not be considered at all. This occurrence, combined with the large dataset, could have contributed to minimal model optimism. However, bootstrapping remains one of the strongest methods of internal validation, and the size of the study population makes it highly unlikely that the model's optimism is underestimated. Still, alternative model-building approaches might yield better-performing models. To explore this, the models were also developed using gradient boosting decision trees (GBDT) with a random 70/30 (train/test) sample split. However, the performance of the GBDT models was found to be similar to that of the logistic regression models (data not shown).

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

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 provides insight into which patients may develop platinum-resistant relapse, using clinicopathologic characteristics that are often available to treating gynecologic and medical oncologists. Given that subsequent chemotherapy has low response rates (<15%) and a progression-free survival of three to four months, with a median overall survival of less than a year [13], the net benefit of additional systemic treatment accompanied by high toxicity should be carefully 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. It could also serve as a useful tool to decide whether patients are more likely to benefit from clinical trials rather than standard treatment, and even help in selecting the right target patients for these studies. Although it remains difficult to accurately predict the risk of early relapse before starting any treatment, the final pretreatment model, despite its subpar predictive ability, could serve as a benchmark for developing more accurate predictive models that include biomarkers, genetic or molecular factors, and even other clinicopathologic factors (e.g., comorbidity status).

Conclusion

In conclusion, an improved understanding of factors contributing to early relapse in advanced-stage EOC could aid in more accurate prediction of patients' prognosis and outcomes. Identifying patients at higher risk of early relapse could support individual counseling by helping quantify the risks and benefits of standard chemotherapeutic treatment within the shared decision-making process. After external validation, our postoperative prediction model may improve patient selection for those who may actually benefit from platinum-based treatment, as opposed to those who may not but rather may benefit from novel therapies.

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 on the statistical analysis and model validation.

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Supplementary

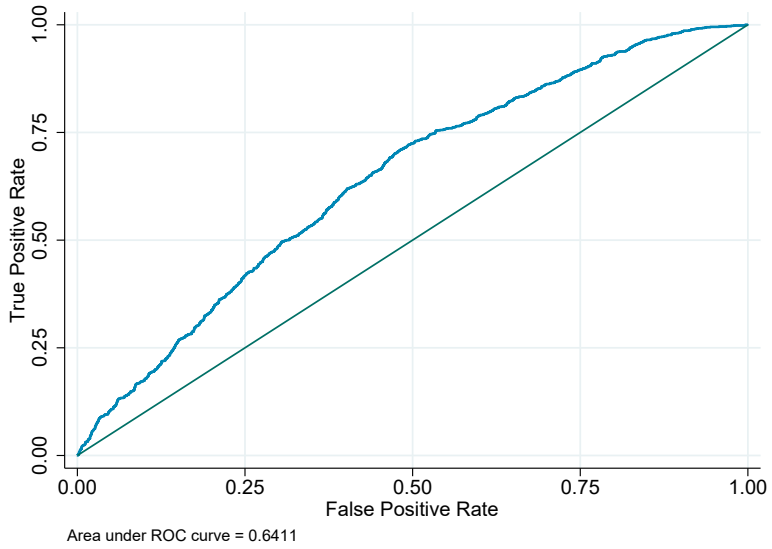
Online score calculators

The online score calculators for the postoperative model and the *BRCA* model can be accessed using the QR codes below:

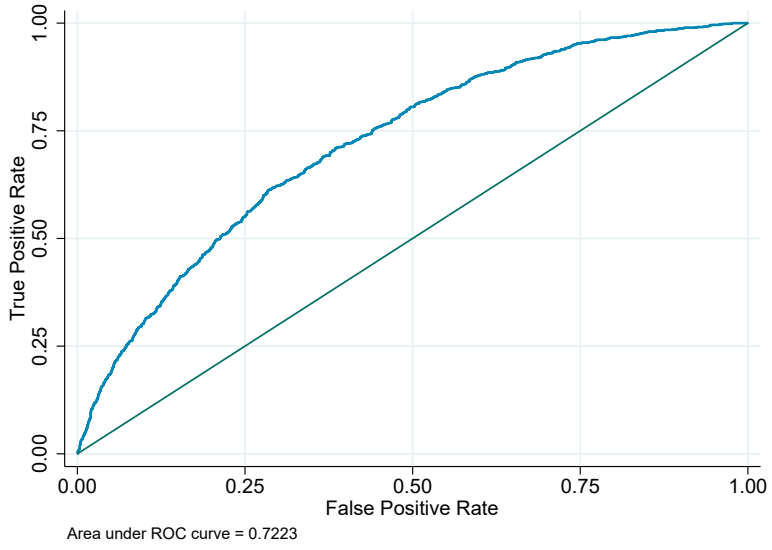
Postoperative model

BRCA model

**Note: The score calculator for the BRCA model was developed for demonstration purposes only in this dissertation and is not publicly accessible. Access is restricted and available solely via the provided QR code.*



Supplementary Figure 1. Area under the receiver operating characteristic curve for the final pretreatment model.



Supplementary Figure 2. Area under the receiver operating characteristic curve for the final postoperative model.

Supplementary Table 1. Final pretreatment prediction model (N = 4,166)*.

	Training set†
Characteristic	Odds ratio [95% CI]
Age at diagnosis (in yrs)	
	1.15 [1.04–1.26]
FIGO stage	
Stage IIB–IIC	Reference
Stage IIIA–IIIB	3.26 [1.99–5.35]
Stage IIIC	4.68 [3.08–7.11]
Stage IV	8.05 [5.24–12.36]
Presence of ascites	
No	Reference
Yes	1.52 [1.32–1.75]
Pretreatment level of CA-125 (in kU/L)	
	1.02 [1.00–1.05]
Model intercept	0.04 [0.02–0.07]

Abbreviations: CA-125, cancer antigen 125; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics

*An additional 307 patients were excluded from the final pretreatment model with reference to Figure 1, because these patients had unknown data for one or more variables included in the final model.

†Internal validation was not conducted for this model due to its subpar model performance.

Supplementary Table 2. Final postoperative prediction model (N = 4,109)*.

	Training set†	Test set†
Characteristic	Odds ratio [95% CI]	Odds ratio [95% CI]
Age at diagnosis (in yrs)		
	1.07 [0.96–1.19]	1.07 [0.96–1.19]
FIGO stage		
Stage IIB–IIC	Reference	Reference
Stage IIIA–IIIB	2.90 [1.72–4.88]	2.81 [1.67–4.73]
Stage IIIC	3.17 [2.00–5.00]	3.06 [1.93–4.83]
Stage IV	4.61 [2.86–7.42]	4.40 [2.73–7.09]
Histologic subtype		
Serous	Reference	Reference
Mucinous	3.42 [2.08–5.64]	3.30 [2.00–5.43]
Endometrioid	1.02 [0.67–1.56]	1.02 [0.67–1.56]
Clear cell	2.80 [1.86–4.21]	2.71 [1.81–4.08]
Adenocarcinoma NOS	0.94 [0.74–1.19]	0.94 [0.74–1.20]
Other	2.81 [1.51–5.25]	2.73 [1.46–5.09]
Presence of ascites		
No	Reference	Reference
Yes	1.19 [1.02–1.39]	1.19 [1.02–1.38]
Pretreatment level of CA-125 (in kU/L)		
	1.02 [0.99–1.05]	1.01 [0.99–1.04]
Treatment approach		
PCS	Reference	Reference
NACT-ICS	2.12 [1.76–2.55]	2.07 [1.72–2.49]
Residual disease after cytoreductive surgery		
No macroscopic	Reference	Reference
≤1 cm	2.35 [2.01–2.75]	2.29 [1.96–2.68]
>1 cm	4.97 [3.95–6.25]	4.73 [3.76–5.96]
Model intercept	0.03 [0.02–0.05]	0.03 [0.01–0.05]

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

*An additional 364 patients were excluded from the final postoperative model with reference to Figure 1, because these patients had unknown data for one or more variables included in the final model.

†The training set data comprise the results of the developmental dataset, and the test set data comprise the results of the internal validation dataset.

Supplementary Table 3. Final *BRCA* prediction model (N = 1,397)*.

	Training set†	Test set†
Characteristic	Odds ratio [95% CI]	Odds ratio [95% CI]
Age at diagnosis (in yrs)		
	0.87 [0.72–1.05]	0.88 [0.73–1.07]
FIGO stage		
Stage IIB–IIC	Reference	Reference
Stage IIIA–IIIB	4.68 [0.96–22.89]	3.88 [0.79–18.96]
Stage IIIC	5.94 [1.37–25.74]	4.78 [1.10–20.71]
Stage IV	7.20 [1.63–31.83]	5.66 [1.28–25.01]
BRCA status		
BRCA-negative	6.88 [2.72–17.42]	5.43 [2.15–13.77]
BRCA1 mutation	3.38 [1.24–9.22]	2.91 [1.07–7.95]
BRCA2 mutation	Reference	Reference
Histologic subtype		
Serous	Reference	Reference
Mucinous	6.13 [2.03–18.46]	4.91 [1.63–14.80]
Endometrioid	0.71 [0.24–2.13]	0.74 [0.25–2.22]
Clear cell	2.42 [0.92–6.39]	2.17 [0.82–5.74]
Adenocarcinoma NOS	1.02 [0.64–1.61]	1.02 [0.64–1.61]
Other	2.40 [0.64–8.87]	2.15 [0.58–7.97]
Presence of ascites		
No	Reference	Reference
Yes	1.17 [0.87–1.57]	1.15 [0.85–1.54]
Pretreatment CA-125 level (in kU/L)		
	1.03 [0.98–1.10]	1.03 [0.97–1.09]
Treatment approach		
PCS	Reference	Reference
NACT-ICS	3.13 [2.09–4.69]	2.72 [1.81–4.08]
Residual disease after cytoreductive surgery		
No macroscopic	Reference	Reference
≤1 cm	2.49 [1.84–3.36]	2.22 [1.65–3.00]
>1 cm	4.18 [2.47–7.06]	3.51 [2.08–5.93]
Model intercept	0.00 [0.00–0.02]	0.00 [0.00–0.02]

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

*An additional 107 patients were excluded from the final *BRCA* model with reference to the 1,504 patients with known *BRCA* status, since these patients had unknown data for one or more variables included in the final model.

†The training set data comprise the results of the developmental dataset, and the test set data comprise the results of the internal validation dataset.

CHAPTER 7

External Validation of Prediction Models for Early Relapse in Advanced Epithelial Ovarian Cancer using Australian and Dutch Population-Based Data

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Abstract

Objective

To externally validate the published postoperative and *BRCA* models predictive of early relapse in patients with advanced-stage epithelial ovarian cancer (EOC) using independent Australian and Dutch cohorts.

Methods

Advanced-stage EOC patients diagnosed between January 1, 2002 and June 1, 2006 in Australia and between January 1, 2016 and December 31, 2017 in the Netherlands were included. Data from patients who underwent cytoreductive surgery and platinum-based chemotherapy were used to validate both models. Missing data were addressed through multiple imputation. Model updates included recalibration-in-the-large, recalibration, and model revision, with a closed testing procedure to identify the most suitable approach. Model performance was assessed for calibration, discrimination, and the Brier score.

Results

The Australian cohort (N = 1,334) included 475 early relapsers and 859 late or non-relapsers, showing baseline differences compared to the development cohort. Discrimination was adequate for both the postoperative and *BRCA* models (*c*-indices of 0.69 and 0.70, respectively). The postoperative model required full revision, while recalibration-in-the-large was sufficient for the *BRCA* model in the Australian cohort. The Dutch cohort (N = 1,212) included 283 early relapsers and 929 late or non-relapsers, with baseline characteristics similar to those of the development cohort. Both models demonstrated adequate discrimination (*c*-indices of 0.71 and 0.70, respectively). Recalibration-in-the-large corrected miscalibration in the Dutch cohort.

Conclusion

The postoperative and *BRCA* models were successfully validated for predicting early relapse in advanced-stage EOC patients, confirming their robustness. However, local data updates are advised to enhance accuracy across clinical settings. Online calculators were built for clinical use.

**QR codes linking to the online score calculators are provided in the Supplementary section.*

Introduction

In advanced-stage epithelial ovarian cancer (EOC), nearly one-fourth of patients experience early relapse, defined as progressive or recurrent disease that develops during first-line treatment or within six months after the last dose of platinum-based chemotherapy [1–4]. Early relapse is associated with an unfavorable prognosis, as patients' response rates to subsequent chemotherapy are low (~10–20%) [4, 5]. Consequently, these patients have a median progression-free survival of three to four months and a median overall survival of less than a year [4, 5]. Identification of patients at risk for early relapse could aid in individualizing care and providing adequate counseling. This personalized approach is particularly relevant in EOC, where the majority of patients are older than 65 years and may have multiple comorbidities. Additionally, platinum-based chemotherapy, part of standard primary treatment, carries the potential for significant toxicity.

Results from our previous Dutch population-based study (using data from 2008 to 2015), in which three risk prediction models were developed, suggested that the risk of early relapse can be reliably predicted using clinicopathologic predictors for advanced-stage EOC patients [6]. A pretreatment model was developed to estimate the risk of early relapse before commencing EOC treatment, while a postoperative and *BRCA* model were designed for the postoperative setting [6]. The *BRCA* model extends the postoperative model by including *BRCA* status as an additional predictor. This extended model was developed separately because *BRCA* status was considered a contributing predictor, but it was not consistently available in routine clinical practice in the past (although it is now routinely assessed). The pretreatment model demonstrated subpar performance before internal validation (AUC of 0.64) and was not further validated. Conversely, the postoperative and *BRCA* models showed adequate performance after internal validation (AUC of 0.72 and 0.76, respectively) [6]. These models were well-calibrated and corrected for optimism. Online score calculators were built for the postoperative and *BRCA* models. However, evaluating the performance of a prediction model with external data remains crucial before it can be implemented in clinical practice [7].

Therefore, the aim of this study was to externally validate the postoperative and *BRCA* models using independent data from two distinct cohorts. Geographical validation was achieved using an Australian cohort, which dates back to 2002–2006 and represents a population with different demographic and healthcare characteristics. To address the limitation of using older Australian data, a Dutch cohort from 2016–2017 was included to serve as a temporal validation set.

Methods

Previously developed models

The postoperative model included age at diagnosis, FIGO stage (IIB–IIC, IIIA–IIIB, IIIC, or IV), pretreatment CA-125 level, histologic subtype (serous, mucinous, endometrioid, clear cell, adenocarcinoma NOS, or other), presence of ascites (yes or no), treatment approach (primary cytoreductive surgery [PCS] followed by adjuvant chemotherapy, or neoadjuvant chemotherapy followed by interval cytoreductive surgery [NACT-ICS] and adjuvant chemotherapy), and residual disease after cytoreductive surgery (no macroscopic, macroscopic ≤1 cm, or macroscopic >1 cm). The *BRCA* model was developed using patients with known *BRCA* status from the postoperative model development sample. It included the same predictors as the postoperative model, with *BRCA* status (*BRCA1* mutation, *BRCA2* mutation, or *BRCA*-negative) added as an additional predictor [6]. Additional details about the development sample are provided in the left two columns of **Table 1** in the Results section.

Data collection

For this study, advanced-stage (i.e., FIGO stage IIB–IV) EOC patients were identified from the Australian Ovarian Cancer Study (AOCS) cohort. The AOCS is an Australia-wide, population-based study that prospectively recruited patients newly diagnosed with histologically confirmed epithelial ovarian, peritoneal, or fallopian tube cancer between January 1, 2002 and June 1, 2006 [8, 9]. Detailed clinical and follow-up data, including recurrence and survival information, were collected from patients' medical records. Mortality status was updated approximately every six months for up to five years, and annually thereafter [8, 9]. In addition, advanced-stage EOC patients diagnosed between January 1, 2016 and December 31, 2017 were identified from the Netherlands Cancer Registry (NCR). Further details on the NCR can be found in a previous publication [6].

Study population

In line with the development study, advanced-stage EOC patients who underwent cytoreductive surgery combined with platinum-based chemotherapy as their initial treatment were included. Patients who received fewer than four cycles of platinum-based chemotherapy or no platinum-based chemotherapy following interval cytoreductive surgery were excluded.

Definitions

Early relapse was defined as progressive disease during first-line platinum-based chemotherapy, or progressive or recurrent disease that developed within six months after receiving the last dose of platinum-based chemotherapy. Progressive and

recurrent disease were defined as clinical signs of tumor growth, i.e., an increase in CA-125 serum levels (greater than or equal to twice the upper limit of CA-125 on two separate occasions at least one week apart) or tumor lesions visible on imaging (either increased growth of pre-existing lesions or development of new lesions), combined with the clinical examination of the treating medical oncologist or gynecologic oncologist. Platinum-free interval (PFI) was defined as the time between the date of last platinum dose and the date of progressive or recurrent disease. All of the aforementioned definitions are consistent with those used in the development study [6].

Statistical analysis

Patient characteristics were summarized using descriptive statistics. The Australian and Dutch validation cohorts were compared with the Dutch development cohort. Categorical variables were analyzed using the Pearson χ^2 test or Fisher's exact test, and continuous variables were analyzed with the two-sample Wilcoxon rank-sum test. The PFI was calculated for the Australian and Dutch cohorts, dividing patients into two subgroups: early relapsers (PFI of ≤6 months) and late or non-relapsers (PFI of >6 months).

Model validation

The postoperative and *BRCA* models were externally validated following the steps outlined in Vergouwe et al. [10]. Their proposed method involves selecting the optimal updating technique for a prediction model based on a closed testing procedure, ensuring that extensive updates are only made if they significantly improve model performance. The closed testing procedure assessed whether the model's intercept should be updated (recalibration-in-the-large), both the intercept and slope should be updated (recalibration), all regression coefficients and the intercept should be re-estimated (model revision), or the original model should be retained [10]. This procedure uses the likelihood ratio test to determine if the updated model provides a statistically significantly better fit than the original model in the validation cohort [10]. Model performance of the updated models was assessed in terms of calibration, discrimination, and the Brier score. Calibration, i.e., the agreement between predicted and observed risks at the (sub)group level, was assessed with calibration plots and the estimated calibration intercept and slope. Discrimination, i.e., the model's ability to distinguish between patients with and without early relapse, was assessed with Harrell's concordance (*c*) index. The Brier score is a metric used to evaluate the accuracy of probabilistic predictions by calculating the mean squared difference between predicted probabilities and actual outcomes (i.e., whether early relapse occurred).

To address missing data in the validation datasets, multiple imputation was performed using the MICE method as proposed by van Buuren et al. [11]. Each dataset was imputed

three times. Complete case and imputed case validation results were compared to assess the impact of imputation. Results for each imputation and the complete case validation are reported separately (**Supplementary File 1**).

All statistical analyses were conducted using STATA/SE (version 17) (StataCorp, College Station, Texas, USA), and R (version 4.0.3) (http://www.r-project.org), with the R packages "Hmisc" (version 4.7.0), "rms" (version 6.3.0), and "caret" (version 6.0.93) [12-17]. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines were followed to report this study [18].

Ethical privacy

Ethical approval for this study was obtained from the Netherlands Cancer Registry's Committee of Privacy [K19.212].

Results

Study population

In Australia, 1,389 advanced-stage EOC patients underwent initial treatment between January 1, 2002 and June 1, 2006. Of these, 1,334 patients received at least four cycles of platinum-based chemotherapy. The Australian validation cohort included 475 early relapsers and 859 late or non-relapsers (**Figure 1**). In the Netherlands, 1,246 advanced-stage EOC patients underwent cytoreductive surgery and platinum-based chemotherapy between January 1, 2016 and December 31, 2017. Of these, 1,212 patients received at least four cycles of platinum-based chemotherapy. The Dutch validation cohort included 283 early relapsers and 929 late or non-relapsers (**Figure 1**).

Patient, tumor, and treatment characteristics

Table 1 summarizes the patient, tumor, and treatment characteristics for the Dutch development cohort and the Dutch and Australian validation cohorts. The median age was 61 years for the Australian validation cohort, 66 years for the Dutch validation cohort, and 65 years for the development cohort.

Concerning FIGO stages, the Australian validation cohort had a higher percentage of patients with FIGO stage IIIC (70.8% vs. 60.6% in the development cohort) and a lower percentage with FIGO stage IV (15.1% vs. 23.0%) compared with the development cohort. In contrast, the Dutch validation cohort had a slightly lower percentage of patients with FIGO stage IIIC (52.5% vs. 60.6%) and a higher percentage with FIGO stages IIIA–IIIB (13.6% vs. 7.7%) compared with the development cohort.

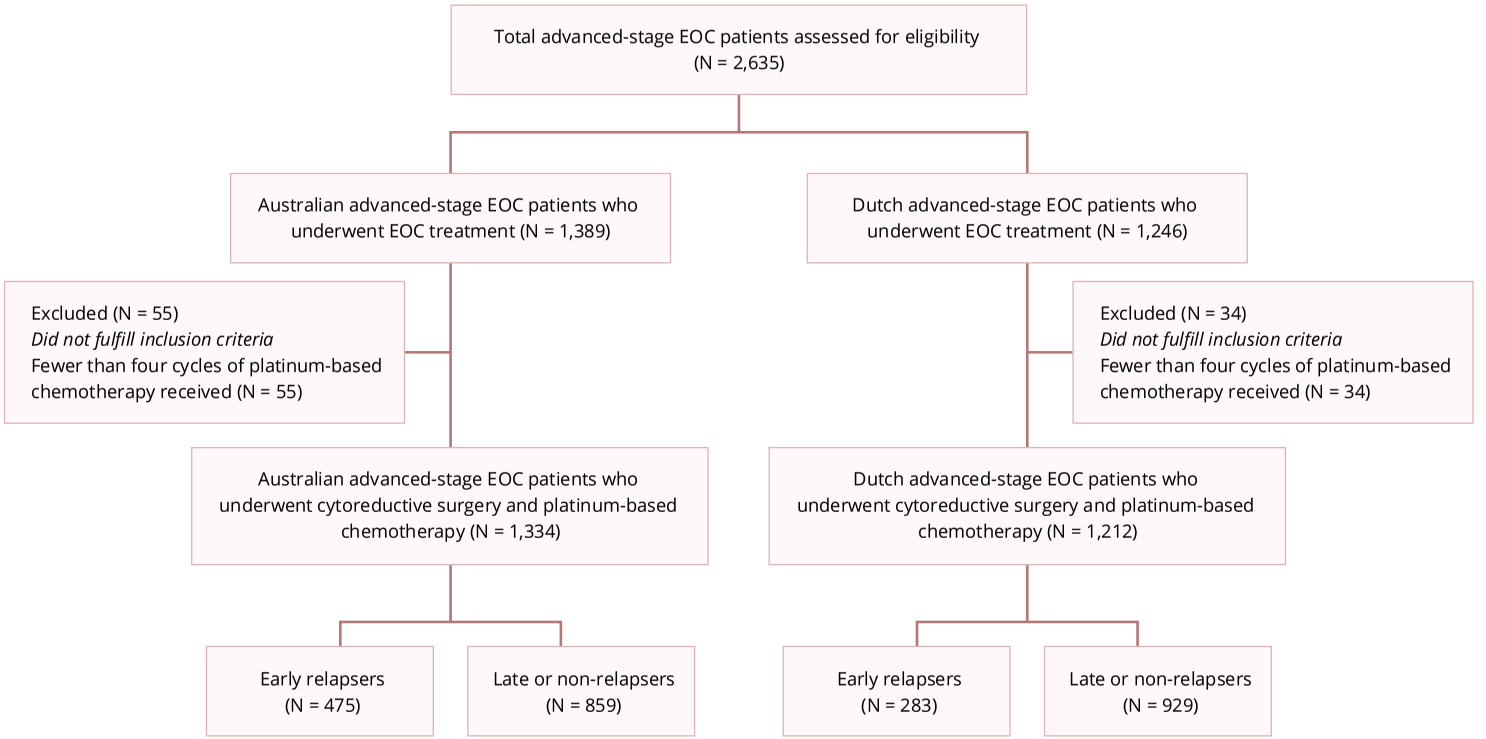

Figure 1. Flowchart of the Australian and Dutch validation cohort.

Table 1. Characteristics of the Dutch development cohort (N = 4,473), the Australian validation cohort (N = 1,334), and Dutch validation cohort (N = 1,212).

	Dutch cohort (N = 4,473) Development	**Australian cohort (N = 1,334) Validation**	**Dutch cohort (N = 1,212) Validation**
Characteristic	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]
Age at diagnosis (in yrs)			
Median	65 [20–91]	61 [24–86]	66 [17–89]
≤64	2,218 (49.6)	869 (65.1)	513 (42.3)
65–74	1,529 (34.2)	354 (26.6)	494 (40.8)
≥75	726 (16.2)	111 (8.3)	205 (16.9)
FIGO stage			
Stage IIB–IIC	393 (8.8)	81 (6.1)	97 (8)
Stage IIIA–IIIB	342 (7.7)	107 (8.0)	165 (13.6)
Stage IIIC	2,710 (60.6)	945 (70.8)	636 (52.5)
Stage IV	1,028 (23.0)	201 (15.1)	314 (25.9)
Tumor grade*			
Grade 1	209 (7.0)	0 (0)	65 (6.4)
Grade 2	462 (15.4)	256 (19.2)	44 (4.3)
Grade 3	2,328 (77.6)	1,078 (80.8)	914 (89.3)
Unknown	1,474 (33.0)	0 (0)	189 (15.6)
Histologic subtype			
Serous	3,491 (78.1)	1,142 (85.6)	1,016 (83.8)
Mucinous	97 (2.2)	9 (0.7)	19 (1.6)
Endometrioid	230 (5.1)	51 (3.8)	38 (3.2)
Clear cell	156 (3.5)	29 (2.2)	50 (4.1)
Adenocarcinoma NOS	441 (9.9)	56 (4.2)	44 (3.6)
Other	58 (1.3)	47 (3.5)	45 (3.7)
Pretreatment CA-125 level (in kU/L)			
Median	591 [3–60,000]	714 [0–93,000]	764 [2–27,200]
Unknown	306 (6.8)	167 (12.5)	583 (48.1)
BRCA status*			
BRCA-negative	1,165 (76.5)	766 (80.0)	677 (85.3)
BRCA1 mutation	235 (15.4)	130 (13.6)	75 (9.5)
BRCA2 mutation	123 (8.1)	62 (6.5)	41 (5.2)
Unknown	2,950 (66.0)	376 (28.2)	419 (34.6)
Presence of ascites*			
No	2,761 (61.7)	385 (33.3)	41 (44.6)
Yes	1,711 (38.3)	769 (66.6)	51 (55.4)
Unknown	1 (0.0)	180 (13.5)	1,120 (92.4)

Table 1. (Continued)

	Dutch cohort (N = 4,473) Development	Australian cohort (N = 1,334) Validation	Dutch cohort (N = 1,212) Validation
Characteristic	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]	No. of patients (%)/ Median [range]
Treatment approach			
NACT-ICS	2,784 (62.2)	294 (22.0)	812 (67.0)
PCS	1,689 (37.8)	1,040 (78.0)	400 (33.0)
Residual disease after cytoreductive surgery*			
No macroscopic	2,370 (53.7)	416 (32.9)	810 (67.5)
≤1 cm	1,581 (35.9)	506 (40.1)	307 (25.6)
>1 cm	459 (10.4)	341 (27.0)	83 (6.9)
Unknown	63 (1.4)	71 (5.3)	12 (1.0)

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.
*The "unknown" categories were excluded from the percentage calculations of the respective variables to enable accurate comparisons across cohorts without distortion from differing amounts of missing data. The percentage following each "unknown" category reflects the proportion of missing data for that specific variable.

Serous type EOC was the most common histologic subtype in all three cohorts. The Australian validation cohort had a higher proportion of patients who underwent PCS (78.0% vs. 37.8%) and a lower proportion who underwent NACT-ICS (22.0% vs. 62.2%) compared with the development cohort. In contrast, the Dutch validation cohort had a similar proportion of patients who underwent NACT-ICS (67.0% vs. 62.2%) and PCS (33.0% vs. 37.8%) compared to the development cohort.

Regarding residual disease, the Australian cohort had a higher percentage of patients with macroscopic >1 cm residual disease (27.0% vs. 10.4%) or ≤1 cm residual disease (40.1% vs. 35.9%) and fewer with no macroscopic residual disease (32.9% vs. 53.7%) compared with the development cohort. Conversely, the Dutch validation cohort had more patients with no macroscopic residual disease (67.5% vs. 53.7%) and fewer with macroscopic residual disease ≤1 cm (25.6% vs. 35.9%) or >1 cm (6.9% vs. 10.4%) compared with the development cohort.

Australian external validation

Table 2 presents the external validation results of the postoperative model (N = 1,334) and the *BRCA* model (N = 958) for the Australian validation cohort after missing data imputation. The closed testing procedure selected 'model revision' as the preferred method to update the postoperative model, while 'recalibration-in-the-large' was selected to update the *BRCA* model for this cohort.

Table 2. Results of the Australian external validation of the postoperative model (N = 1,334) and the *BRCA* model (N = 958).

	Postoperative model (N = 1,334)		***BRCA* model (N = 958)**	
	Original	Model revision	Original	Recalibration-in-the-large
Model performance				
Calibration intercept	0.20	0	0.68	0
Calibration slope	0.86	1	0.87	0.87
c-index	0.69	0.71	0.70	0.70
Brier score	0.21	0.20	0.22	0.20
Coefficients				
Intercept	-1.751	-0.879	-2.059	-1.194
Age at diagnosis (in yrs)	0.004	0.004	-0.009	-0.009
FIGO stage				
Stage IIB–IIC (Ref.)				
Stage IIIA–IIIB	1.035	-0.436	1.339	1.339
Stage IIIC	1.120	0.358	1.545	1.545
Stage IV	1.485	0.861	1.712	1.712
BRCA status				
BRCA-negative (Ref.)	*NA*	*NA*		
BRCA1 mutation	*NA*	*NA*	-0.616	-0.616
BRCA2 mutation	*NA*	*NA*	-1.673	-1.673
Histologic subtype				
Serous (Ref.)				
Mucinous	1.196	0.551	1.572	1.572
Endometrioid	0.024	-0.329	-0.297	-0.297
Clear cell	1.001	1.456	0.766	0.766
Adenocarcinoma NOS	-0.061	-0.427	0.015	0.015
Other	1.006	0.559	0.758	0.758
Presence of ascites				
Yes (Ref.)				
No	-0.170	-0.358	-0.134	-0.134
Pretreatment CA-125 (U/L)	0.010	0.035	0.018	0.018
Treatment approach				
PCS (Ref.)				
NACT-ICS	0.729	0.983	0.990	0.990
Residual disease after cytoreductive surgery				
>1 cm (Ref.)				
≤1 cm	-0.726	-0.452	-0.450	-0.450
No macroscopic	-1.558	-1.123	-1.240	-1.240

Abbreviations: *BRCA*, breast cancer gene; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PCS, primary cytoreductive surgery; Ref., reference category.
*The closed testing procedure determined 'model revision' as the preferred update for the postoperative model, while 'recalibration-in-the-large' was selected for the *BRCA* model.
†The calibration intercept and slope quantify the extent of miscalibration in the models, indicating the adjustments required to improve their alignment with observed outcomes.

Figure 2 shows the calibration plots of both the original and updated postoperative and *BRCA* models for the Australian validation cohort. In these plots, the predicted rates of early relapse are compared to the observed rates in the Australian cohort. The calibration plots demonstrated that the original postoperative and *BRCA* models were notably miscalibrated, showing significant misalignment between the predicted and observed early relapse rates.

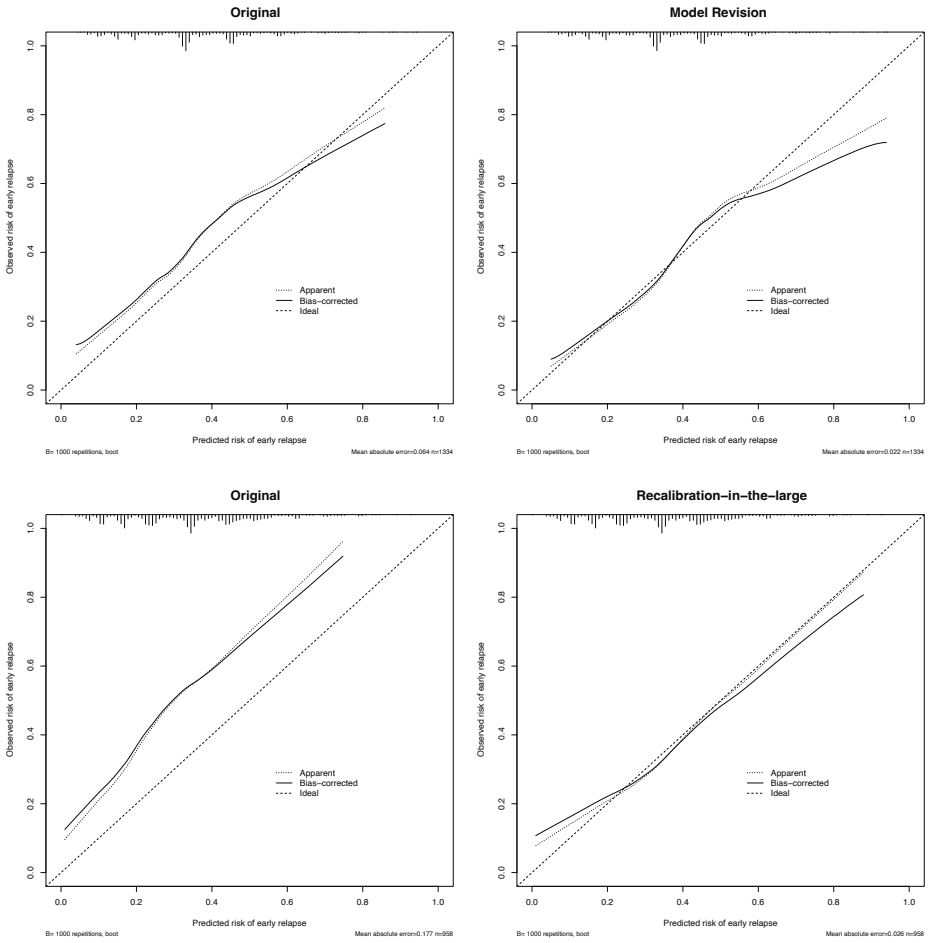

Figure 2. Calibration plots of the original and updated postoperative models for the Australian validation cohort (N = 1,334, top two plots) and the original and updated *BRCA* models (N = 958, bottom two plots). The dashed 45-degree line represents perfect calibration (i.e., ideal line), where predicted and observed probabilities are equal.

Addressing this misalignment with a complete model revision, going beyond recalibration-in-the-large and recalibration, was valuable, as it significantly further improved the

performance of the postoperative model. In contrast, moving beyond recalibration-in-the-large did not significantly improve the performance of the *BRCA* model.

The full validation results for the Australian validation cohort can be found in **Supplementary Tables 1** and **2**, and **Supplementary Figures 1** and **2**. Updating was more limited in the complete case analyses, with the closed testing procedure selecting 'recalibration-in-the-large' for both the postoperative model (N = 981) and the *BRCA* model (N = 709) (**Supplementary File 1**).

Dutch external validation

Table 3 presents the external validation results of the postoperative model (N = 1,212) and the *BRCA* model (N = 793) for the Dutch validation cohort after missing data imputation. The closed testing procedure selected 'recalibration-in-the-large' as the preferred method to update both the postoperative and *BRCA* models for this cohort.

Table 3. Results of the Dutch external validation of the postoperative model (N = 1,212) and the *BRCA* model (N = 793).

	Postoperative model (N = 1,212)		***BRCA* model (N = 793)**	
	Original	Recalibration-in-the-large	Original	Recalibration-in-the-large
Model performance				
Calibration intercept	-0.28	0	0.05	0
Calibration slope	1.02	1.02	0.84	0.84
c-index	0.71	0.71	0.70	0.70
Brier score	0.16	0.16	0.17	0.17
Coefficients				
Intercept	-1.751	-2.045	-2.059	-1.816
Age at diagnosis (in yrs)	0.004	0.004	-0.009	-0.009
FIGO stage				
Stage IIB–IIC (Ref.)				
Stage IIIA–IIIB	1.035	1.035	1.339	1.339
Stage IIIC	1.120	1.120	1.545	1.545
Stage IV	1.485	1.485	1.712	1.712
BRCA status				
BRCA-negative (Ref.)	*NA*	*NA*		
BRCA1 mutation	*NA*	*NA*	-0.616	-0.616
BRCA2 mutation	*NA*	*NA*	-1.673	-1.673

Table 3. (Continued)

	Postoperative model (N = 1,212)		***BRCA* model (N = 793)**	
	Original	Recalibration-in-the-large	Original	Recalibration-in-the-large
Histologic subtype				
Serous (Ref.)				
Mucinous	1.196	1.196	1.572	1.572
Endometrioid	0.024	0.024	-0.297	-0.297
Clear cell	1.001	1.001	0.766	0.766
Adenocarcinoma NOS	-0.061	-0.061	0.015	0.015
Other	1.006	1.006	0.758	0.758
Presence of ascites				
Yes (Ref.)				
No	-0.170	-0.170	-0.134	-0.134
Pretreatment CA-125 (U/L)	0.010	0.010	0.018	0.018
Treatment approach				
PCS (Ref.)				
NACT-ICS	0.729	0.729	0.990	0.990
Residual disease after cytoreductive surgery				
>1 cm (Ref.)				
≤1 cm	-0.726	-0.726	-0.450	-0.450
No macroscopic	-1.558	-1.558	-1.240	-1.240

Abbreviations: *BRCA*, breast cancer gene; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PCS, primary cytoreductive surgery; Ref., reference category.
*The closed testing procedure determined 'recalibration-in-the-large' as the preferred method for updating both the postoperative and *BRCA* models.
†The calibration intercept and slope quantify the extent of miscalibration in the models, indicating the adjustments required to improve their alignment with observed outcomes.

Figure 3 shows the calibration plots of both the original and updated postoperative and *BRCA* models for the Dutch validation cohort. The original postoperative and *BRCA* models' predicted rates of early relapse did not align well with the observed rates, indicating miscalibration. However, after recalibration-in-the-large, the models' calibration improved, and further adjustments to the models were not statistically significant.

The full validation results for the Dutch validation cohort can be found in **Supplementary Tables 3** and **4**, and **Supplementary Figures 3** and **4**. Updating was more limited in the complete case analyses, with the closed testing procedure selecting 'retaining the

original model' for both the postoperative model (N = 92) and the *BRCA* model (N = 88) (**Supplementary File 1**).

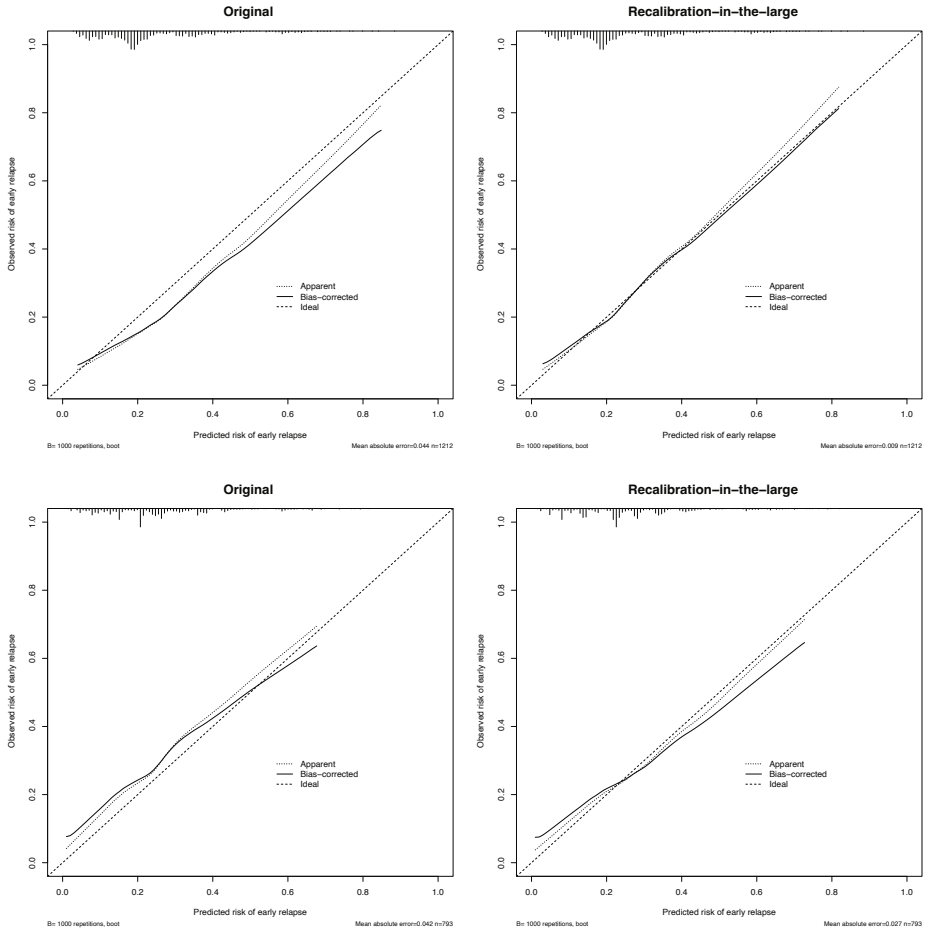

Figure 3. Calibration plots of the original and updated postoperative models for the Dutch validation cohort (N = 1,212, top two plots) and the original and updated *BRCA* models (N = 793, bottom two plots). The dashed 45-degree line represents perfect calibration (i.e., ideal line), where predicted and observed probabilities are equal.

Online score calculators

To facilitate clinical application, the results from the Dutch validation cohort (selected for its more recent data compared to the Australian validation cohort) were used to update the online score calculators for the postoperative model and the *BRCA* model.

Discussion

This study externally validated the previously developed postoperative and *BRCA* models predictive of early relapse in patients with advanced-stage EOC using independent Australian and Dutch cohorts. Both models demonstrated adequate discriminative performance and were successfully updated using data from the Dutch validation cohort. However, differences in clinical practice between the Australian and Dutch cohorts required a more extensive revision of the models for the Australian cohort. Furthermore, validation using more recent Australian data is necessary before these models can be reliably applied in Australia.

Australian validation

The Australian validation cohort, collected between 2002 and 2006, showed notable differences from the development cohort, primarily due to variations in treatment and diagnostic practices. For instance, the higher proportion of patients with macroscopic residual disease in the Australian cohort, likely due to the preference for PCS over NACT-ICS, contributed to the higher early relapse rate (35.6% vs. 28.6%). This preference reflects past global treatment trends, which have evolved over time [19]. In addition, the higher percentage of FIGO stage IIIC patients and the lower percentage of FIGO stage IV patients in the Australian cohort may be attributed to the differences in diagnostic practices. During this period, Australia relied more on cytology or histology for a FIGO stage IV diagnosis, while current practice often uses radiological evidence alone. These variations necessitated a full revision of the postoperative model, which, after updating, showed better performance compared to the original model in the Australian cohort. Despite these updates, the older nature of the Australian dataset limits the relevance of the updated models for current clinical practice in Australia. Therefore, it is crucial to conduct further research and validate these models on more recent Australian data before they can be used confidently there.

Dutch validation

In contrast, the more-up-to-date Dutch validation cohort showed similar characteristics to those of the development cohort, with a lower observed early relapse rate (23.3% vs. 28.6%), likely due to a higher proportion of patients with FIGO stages IIIA–IIIB, a lower proportion with stage IIIC, and more patients with no macroscopic residual disease. As a result, only minor adjustments were needed to align the models' predictions with the observed outcomes, specifically an intercept update to account for the lower early relapse rate in this cohort. This suggests that the original models were robust and adaptable with minimal modification.

Early relapse and *BRCA* status

The *BRCA* model demonstrated a discriminative performance similar to the postoperative model in both validation cohorts (*c*-index of 0.70 vs. 0.71). While the *BRCA* model performed better than the postoperative model in the development study (*c*-index of 0.76 vs. 0.72) [6], this validation study indicates that the additional prognostic value of *BRCA* status is more modest. This discrepancy may be due to the smaller and more selective development subset for the *BRCA* model in the development study, whereas the validation cohorts had more balanced sample sizes and were more heterogeneous. Nevertheless, assessing *BRCA* status remains essential for newly diagnosed EOC patients. While the *BRCA* model does not outperform the postoperative model in predicting early relapse, it may still be valuable in clinical settings, particularly where *BRCA* testing is routine.

Future implications

The discrepancies observed in the model performance between the Australian and Dutch cohorts underscore the importance of considering regional and temporal variations in clinical practice. Factors such as tumor characteristics, treatment regimens, diagnostic practices, and demographics can significantly impact the accuracy and generalizability of prediction models. The significant differences between the Australian and Dutch cohorts likely led to differences in predictor–outcome relationships. These differences were pivotal in determining the extent of model updating required. While the Australian cohort necessitated a full revision of the postoperative model, only minimal adjustments were needed for the Dutch cohort, which more closely mirrored the development cohort. These cohort-specific differences, however, may have diminished over time as clinical practices have evolved. This emphasizes the need for region-specific adjustments and for regular updates to predictive models to ensure they remain accurate and relevant in diverse healthcare settings.

Strengths and limitations

This study has several strengths, including the use of large, independent validation cohorts, which enhance the generalizability and reliability of the results. The use of robust statistical methods, such as multiple imputation of missing data, ensured that the models were built on comprehensive datasets. Additionally, the development of online score calculators based on the Dutch cohort makes the models readily accessible for clinical use, facilitating their integration into routine practice. The postoperative model, in particular, relies on routinely collected clinical parameters, which enhances its practical applicability across diverse settings. A key limitation is the old nature of the Australian dataset (2002–2006), which may reflect outdated clinical practices that are not representative of current protocols. Therefore, the models revised using the

Dutch validation cohort have been made available online. Further research is needed to validate the models with more recent Australian data to ensure their relevance and applicability in current clinical practice.

Conclusion

This study successfully validated the postoperative and *BRCA* models for predicting early relapse in advanced-stage EOC, confirming their robustness and clinical utility. Although the models performed well across validation cohorts, differences in regional demographics and clinical practices may influence their accuracy. Further validation with local data can support widespread implementation, while regular model updating is relevant to keep implemented models accurate and valuable to clinicians and patients.

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Supplementary

Online score calculators

The online score calculators for the postoperative model and the *BRCA* model can be accessed using the QR codes below:

Postoperative model

BRCA model

Supplementary File 1

Supplementary File 1 can be downloaded from the website hosting the online score calculators (Evidencio) for both the postoperative and *BRCA* models. This file is located under the 'Related files' section, accessible by selecting the 'Details' option positioned at the top right corner of each calculator's title. Alternatively, the file can be accessed directly using the QR code below:

Supplementary File 1

Supplementary Table 1. Model performance of the original model (Postoperative model) and the updated models for the Australian cohort (N = 1,334).

	Original	Recalibration-in-the-large	Recalibration	Model revision
Model performance				
Calibration intercept	0.20	0	0	**0**
Calibration slope	0.86	0.86	1	**1**
c-index	0.69	0.69	0.69	**0.71**
Brier score	0.21	0.21	0.21	**0.20**
Coefficients				
Intercept	-1.751	-1.435	-1.311	**-0.879**
Age at diagnosis (in yrs)	0.004	0.004	0.004	**0.004**
FIGO stage				
Stage IIB–IIC (Ref.)				
Stage IIIA–IIIB	1.035	1.035	0.894	**-0.436**
Stage IIIC	1.120	1.120	0.968	**0.358**
Stage IV	1.485	1.485	1.284	**0.861**
Histologic subtype				
Serous (Ref.)				
Mucinous	1.196	1.196	1.034	**0.551**
Endometrioid	0.024	0.024	0.021	**-0.329**
Clear cell	1.001	1.001	0.865	**1.456**
Adenocarcinoma NOS	-0.061	-0.061	-0.053	**-0.427**
Other	1.006	1.006	0.869	**0.559**
Presence of ascites				
Yes (Ref.)				
No	-0.170	-0.170	-0.147	**-0.358**
Pretreatment CA-125 (U/L)	0.010	0.010	0.009	**0.035**
Treatment approach				
PCS (Ref.)				
NACT-ICS	0.729	0.729	0.630	**0.983**
Residual disease after cytoreductive surgery				
>1 cm (Ref.)				
≤1 cm	-0.726	-0.726	-0.628	**-0.452**
No macroscopic	-1.558	-1.558	-1.346	**-1.123**

Abbreviations: CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PCS, primary cytoreductive surgery; Ref., reference category.

*The closed testing procedure selected 'model revision' as the preferred method for updating the postoperative model.

†The calibration intercept and slope quantify the extent of miscalibration in the models, indicating the adjustments required to improve their alignment with observed outcomes.

Supplementary Table 2. Model performance of the original model (*BRCA* model) and the updated models for the Australian cohort (N = 958).

	Original	Recalibration-in-the-large	Recalibration	Model revision
Model performance				
Calibration intercept	0.68	**0**	0	0
Calibration slope	0.87	**0.87**	1	1
c-index	0.70	**0.70**	0.70	0.71
Brier score	0.22	**0.20**	0.20	0.20
Coefficients				
Intercept	-2.059	**-1.194**	-1.113	-0.511
Age at diagnosis (in yrs)	-0.009	**-0.009**	-0.008	-0.005
FIGO stage				
Stage IIB–IIC (Ref.)				
Stage IIIA–IIIB	1.339	**1.339**	1.164	-0.458
Stage IIIC	1.545	**1.545**	1.343	0.512
Stage IV	1.712	**1.712**	1.489	0.883
BRCA status				
BRCA-negative (Ref.)				
BRCA1 mutation	-0.616	**-0.616**	-0.536	-0.654
BRCA2 mutation	-1.673	**-1.673**	-1.454	-1.013
Histologic subtype				
Serous (Ref.)				
Mucinous	1.572	**1.572**	1.367	-4.280
Endometrioid	-0.297	**-0.297**	-0.258	-0.524
Clear cell	0.766	**0.766**	0.666	1.203
Adenocarcinoma NOS	0.015	**0.015**	0.013	-0.255
Other	0.758	**0.758**	0.659	0.631
Presence of ascites				
Yes (Ref.)				
No	-0.134	**-0.134**	-0.116	-0.446
Pretreatment CA-125 (U/L)	0.018	**0.018**	0.016	0.007
Treatment approach				
PCS (Ref.)				
NACT-ICS	0.990	**0.990**	0.860	1.182
Residual disease after cytoreductive surgery				
>1 cm (Ref.)				
≤1 cm	-0.450	**-0.450**	-0.392	-0.399
No macroscopic	-1.240	**-1.240**	-1.078	-0.923

Abbreviations: *BRCA*, breast cancer gene; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PCS, primary cytoreductive surgery; Ref., reference category.
*The closed testing procedure selected 'recalibration-in-the-large' as the preferred method for updating the *BRCA* model.
†The calibration intercept and slope quantify the extent of miscalibration in the models, indicating the adjustments required to improve their alignment with observed outcomes.

Supplementary Table 3. Model performance of the original model (Postoperative model) and the updated models for the Dutch validation cohort (N = 1,212).

	Original	Recalibration-in-the-large	Recalibration	Model revision
Model performance				
Calibration intercept	-0.28	**0**	0	0
Calibration slope	1.02	**1.02**	1	1
c-index	0.71	**0.71**	0.71	0.72
Brier score	0.16	**0.16**	0.16	0.16
Coefficients				
Intercept	-1.751	**-2.045**	-2.061	-1.612
Age at diagnosis (in yrs)	0.004	**0.004**	0.004	0.005
FIGO stage				
Stage IIB–IIC (Ref.)				
Stage IIIA–IIIB	1.035	**1.035**	1.052	0.384
Stage IIIC	1.120	**1.120**	1.139	0.825
Stage IV	1.485	**1.485**	1.510	1.048
Histologic subtype				
Serous (Ref.)				
Mucinous	1.196	**1.196**	1.216	1.785
Endometrioid	0.024	**0.024**	0.024	0.465
Clear cell	1.001	**1.001**	1.017	1.431
Adenocarcinoma NOS	-0.061	**-0.061**	-0.062	-0.152
Other	1.006	**1.006**	1.022	1.408
Presence of ascites				
Yes (Ref.)				
No	-0.170	**-0.170**	-0.173	0.155
Pretreatment CA-125 (U/L)	0.010	**0.010**	0.010	0.043
Treatment approach				
PCS (Ref.)				
NACT-ICS	0.729	**0.729**	0.741	0.718
Residual disease after cytoreductive surgery				
>1 cm (Ref.)				
≤1 cm	-0.726	**-0.726**	-0.738	-1.160
No macroscopic	-1.558	**-1.558**	-1.583	-1.993

Abbreviations: CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PCS, primary cytoreductive surgery; Ref., reference category.

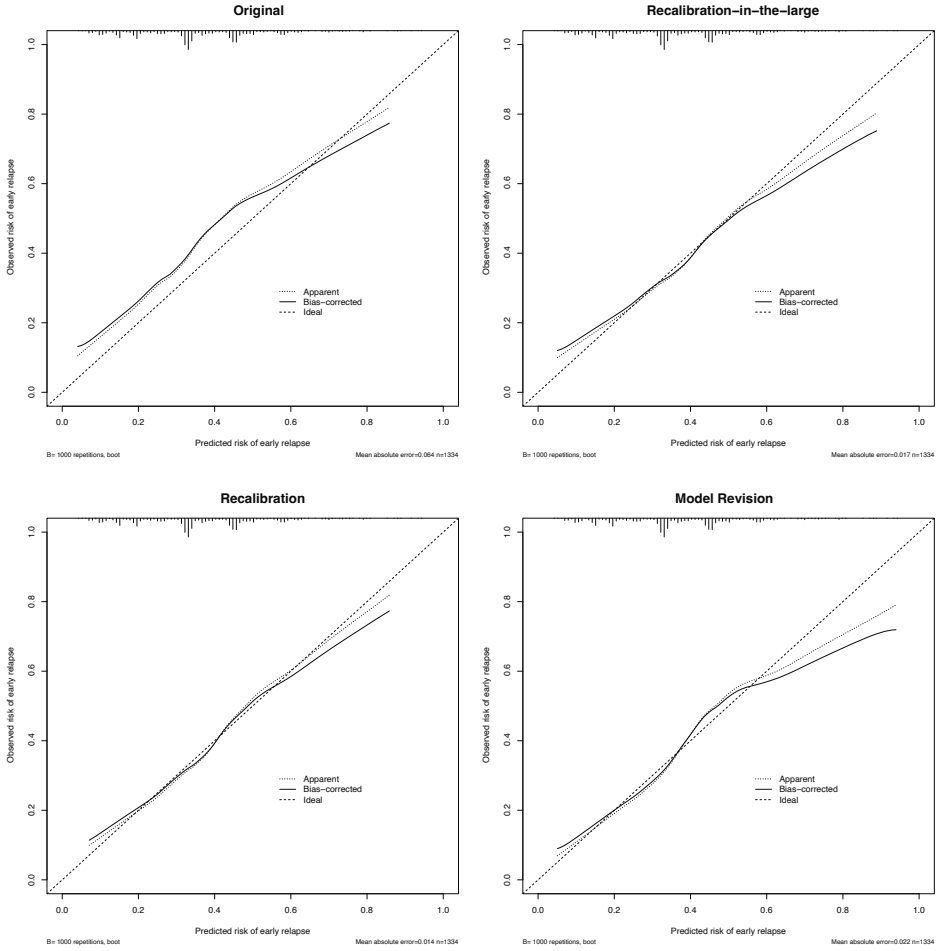
*The closed testing procedure selected 'recalibration-in-the-large' as the preferred method for updating the postoperative model.

†The calibration intercept and slope quantify the extent of miscalibration in the models, indicating the adjustments required to improve their alignment with observed outcomes.

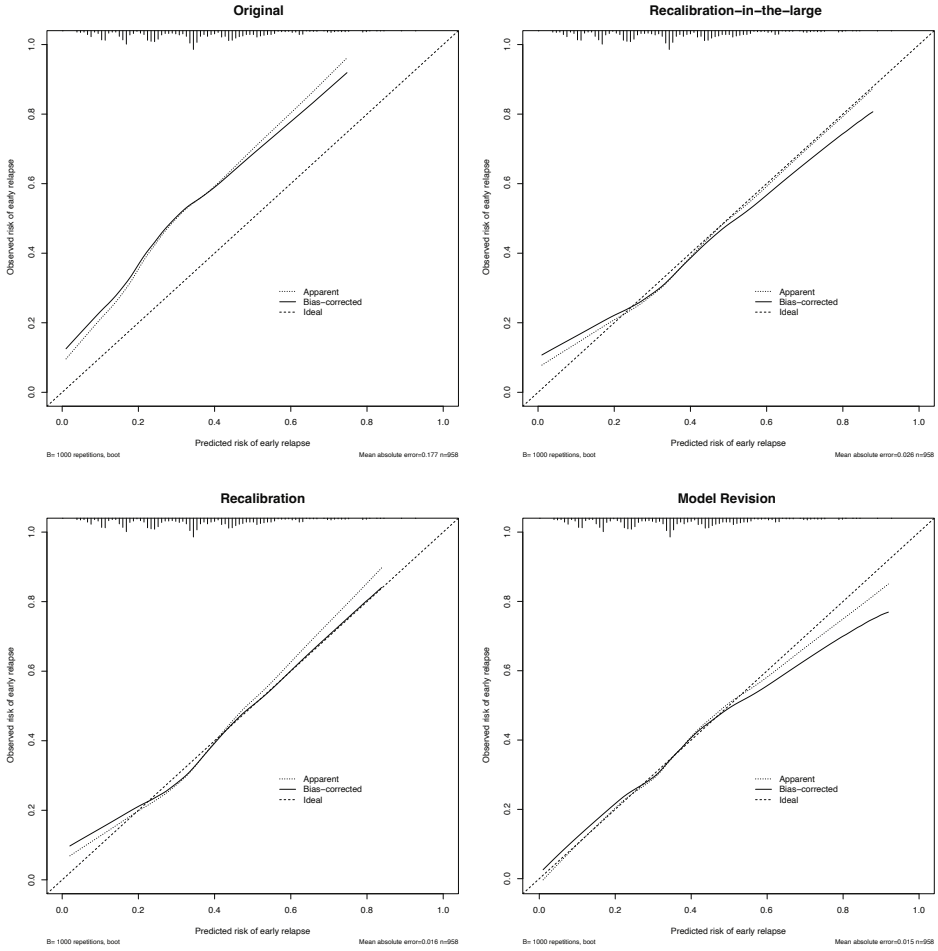
Supplementary Table 4. Model performance of the original model (*BRCA* model) and the updated models for the Dutch cohort (N = 793).

	Original	Recalibration-in-the-large	Recalibration	Model revision
Model performance				
Calibration intercept	0.05	**0**	0	0
Calibration slope	0.84	**0.84**	1	1
c-index	0.70	**0.70**	0.70	0.70
Brier score	0.17	**0.17**	0.17	0.17
Coefficients				
Intercept	-2.059	**-1.816**	-1.670	-1.517
Age at diagnosis (in yrs)	-0.009	**-0.009**	-0.007	-0.001
FIGO stage				
Stage IIB–IIC (Ref.)				
Stage IIIA–IIIB	1.339	**1.339**	1.121	0.607
Stage IIIC	1.545	**1.545**	1.293	1.238
Stage IV	1.712	**1.712**	1.433	1.509
BRCA status				
BRCA-negative (Ref.)				
BRCA1 mutation	-0.616	**-0.616**	-0.516	-0.708
BRCA2 mutation	-1.673	**-1.673**	-1.400	-0.934
Histologic subtype				
Serous				
Mucinous	1.572	**1.572**	1.316	0.973
Endometrioid	-0.297	**-0.297**	-0.248	0.556
Clear cell	0.766	**0.766**	0.641	0.969
Adenocarcinoma NOS	0.015	**0.015**	0.013	-0.280
Other	0.758	**0.758**	0.635	1.730
Presence of ascites				
Yes (Ref.)				
No	-0.134	**-0.134**	-0.112	0.055
Pretreatment CA-125 (U/L)	0.018	**0.018**	0.015	0.033
Treatment approach				
PCS (Ref.)				
NACT-ICS	0.990	**0.990**	0.828	0.570
Residual disease after cytoreductive surgery				
>1 cm (Ref.)				
≤1 cm	-0.450	**-0.450**	-0.377	-0.981
No macroscopic	-1.240	**-1.240**	-1.038	-1.571

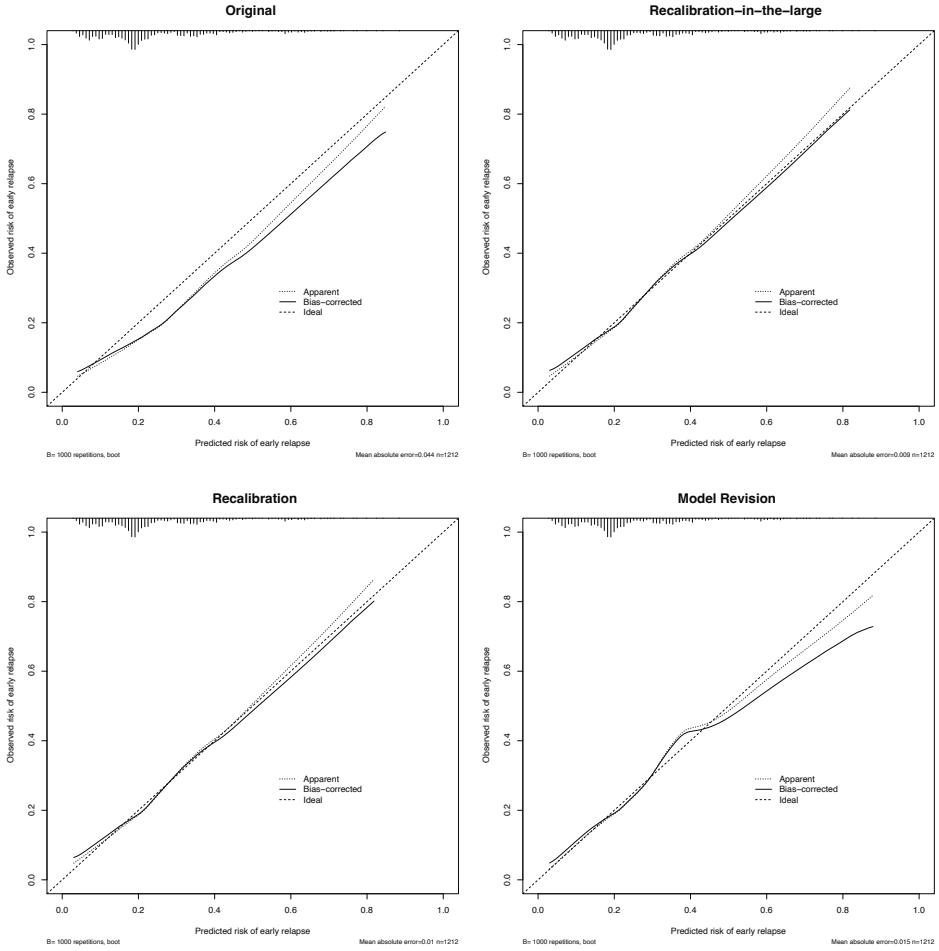
Abbreviations: *BRCA*, breast cancer gene; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; NA, not applicable; NACT-ICS, neoadjuvant chemotherapy followed by interval cytoreductive surgery; NOS, not otherwise specified; PCS, primary cytoreductive surgery; Ref., reference category.
*The closed testing procedure selected 'recalibration-in-the-large' as the preferred method for updating the *BRCA* model.
†The calibration intercept and slope quantify the extent of miscalibration in the models, indicating the adjustments required to improve their alignment with observed outcomes.



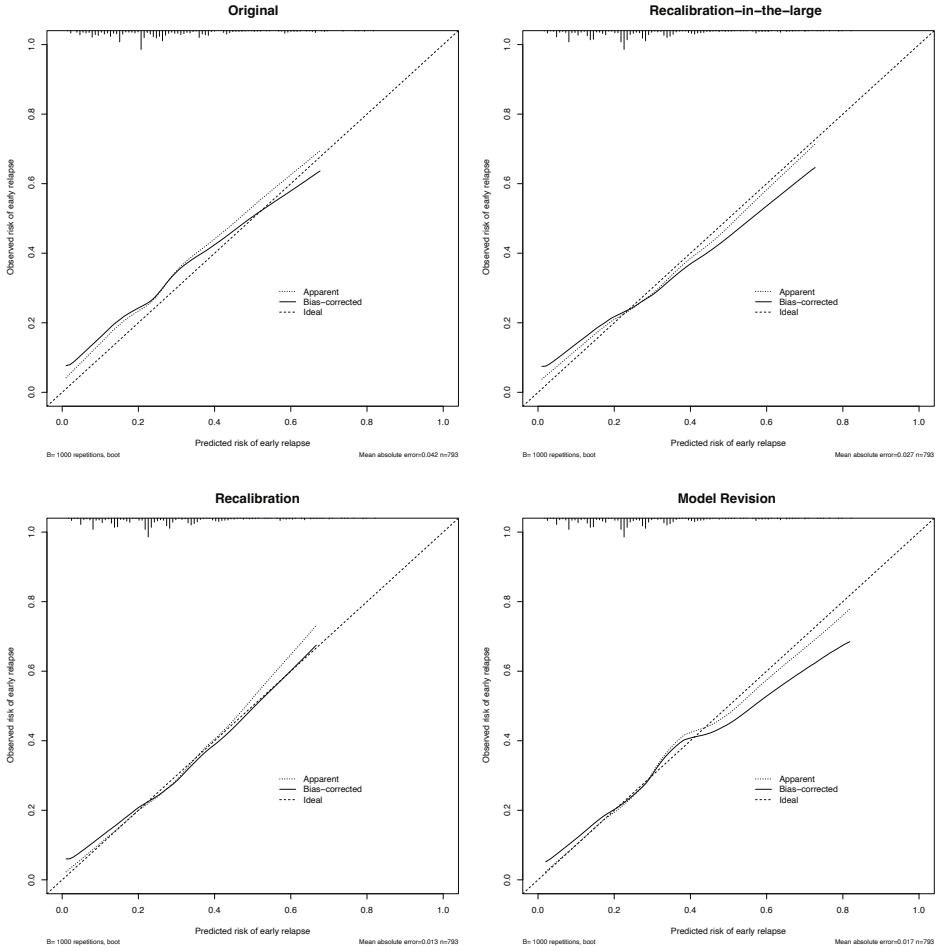
Supplementary Figure 1. Calibration plots of the original and updated postoperative models in the Australian validation cohort (N = 1,334). The dashed 45-degree line represents perfect calibration (i.e., ideal line), where predicted and observed probabilities are equal.



Supplementary Figure 2. Calibration plots of the original and updated *BRCA* models in the Australian validation cohort (N = 958). The dashed 45-degree line represents perfect calibration (i.e., ideal line), where predicted and observed probabilities are equal.



Supplementary Figure 3. Calibration plots of the original and updated postoperative models in the Dutch validation cohort (N = 1,212). The dashed 45-degree line represents perfect calibration (i.e., ideal line), where predicted and observed probabilities are equal.



Supplementary Figure 4. Calibration plots of the original and updated *BRCA* models in the Dutch validation cohort (N = 793). The dashed 45-degree line represents perfect calibration (i.e., ideal line), where predicted and observed probabilities are equal.

CHAPTER 8

General Discussion and Future Perspectives

General Discussion

This dissertation explored various factors influencing survival and the risk of early relapse in advanced epithelial ovarian cancer (EOC). The findings presented in the previous chapters highlight the complexity of managing this disease and emphasize the need for more personalized treatment approaches. This chapter will discuss the broader implications of these findings, contextualize them within the current literature, and outline potential directions for clinical practice and future research.

Evolution of treatment strategies in EOC

The management of advanced EOC has evolved gradually over the past four decades, transitioning from standardized treatments (i.e., cytoreductive surgery and chemotherapy) to more tailored strategies. This shift has been driven by a growing understanding of EOC's heterogeneity, advancements in tumor biology, and the development of novel therapeutic options. The progression towards individualized treatment reflects broader trends in oncology and highlights the crucial role of clinical and translational research in improving patient outcomes.

Cisplatin, introduced in the 1970s, revolutionized EOC treatment by improving response rates and survival outcomes [1, 2]. However, its severe toxicities, including neurotoxicity, ototoxicity, nephrotoxicity, myelosuppression, and gastrointestinal side effects, prompted a search for alternatives [1–3]. Carboplatin, introduced in 1985, provided similar efficacy but with less toxicity, becoming the standard platinum-based agent for EOC treatment [1–3]. In the 1990s, the addition of paclitaxel further improved outcomes, enhancing progression-free and overall survival compared to platinum-based therapy alone [2, 4, 5]. By the early 2000s, this combination became the standard first-line therapy for advanced EOC [1, 6, 7].

Since its establishment in the 1970s, primary cytoreductive surgery (PCS) followed by adjuvant chemotherapy was the sole treatment approach for advanced EOC [8]. However, in the early 2000s, neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT-ICS) emerged as an alternative approach [8]. The EORTC 55971 trial (2010) and the CHORUS trial (2015) demonstrated that NACT-ICS resulted in survival outcomes comparable to PCS, particularly in patients with high tumor burden or poor performance status [9, 10]. Consequently, a paradigm shift occurred in clinical practice, with NACT-ICS becoming the predominant approach for the treatment of advanced EOC, especially for these patient subgroups [11–14]. However, these trials faced criticism regarding patient selection, low complete resection rates, and low overall survival outcomes [15–18]. Concerns have been raised about whether surgeries in these

trials reflected the high-quality procedures typically conducted in specialized centers, potentially introducing bias towards NACT-ICS [15, 16, 18]. The ongoing TRUST trial (NCT02828618), which compares PCS and NACT-ICS in advanced EOC, is expected to address these concerns [19].

In 2006, intraperitoneal chemotherapy was recommended in the United States after the GOG 172 trial demonstrated a 16-month overall survival benefit over systemic chemotherapy [6, 20, 21]. However, its widespread implementation was limited due to concerns about toxicity, catheter complications, and patient discomfort [6, 20]. In 2018, the GOG 252 trial found no survival advantage when combined with bevacizumab, leading to a further decline in its use [6, 20, 22]. Hyperthermic intraperitoneal chemotherapy (HIPEC) in the NACT-ICS setting gained attention following the OVHIPEC-1 trial, published in 2018, which showed improvements in both progression-free and overall survival for FIGO stage III patients [23]. While promising, the use of HIPEC varies due to concerns about the generalizability of the study's findings [6, 24, 25]. The role of HIPEC in the PCS setting is currently under investigation [26, 27].

In the 2010s and beyond, targeted therapies began to play an increasingly important role in EOC management [28–30]. Bevacizumab was approved for recurrent EOC in 2014 and later for frontline treatment of FIGO stage III and IV EOC in 2018 [31]. The introduction of maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib and niraparib, further transformed treatment for tumors with *BRCA* mutations and homologous recombination deficiencies (HRD), significantly improving progression-free survival in both primary and recurrent settings [28, 30, 32–34]. With ongoing research into these novel therapies and a growing shift towards personalized treatment strategies, the landscape of EOC management continues to evolve.

Personalizing standardized chemotherapy protocols

While uniform standardized protocols offer a structured approach, the need to tailor therapies based on individual patient factors, such as tumor resistance in different histologic subtypes or toxicity, requires flexibility within these protocols. This flexibility, however, can result in variations in clinical practice, highlighting the challenge of ensuring consistent application of treatment strategies. The impact of incorporating individualized approaches into established protocols on EOC survival outcomes remains uncertain.

Chapter 5 of this dissertation demonstrated that over half of patients with advanced EOC underwent chemotherapy modifications for various reasons, with 38% of them experiencing dose reductions. These dose reductions did not significantly impact overall survival, suggesting that toxicity concerns can be addressed safely without

compromising patient outcomes. Additionally, no significant difference in survival was observed between patients who received five or six chemotherapy cycles. Nonetheless, the lack of detailed information on the extent of dose reductions or the initial doses administered to patients limits the ability to draw definitive conclusions regarding whether prescribed doses exceed therapeutic requirements or if reductions can be implemented without compromising survival outcomes. Future research should explore optimal dosing strategies to identify dose reduction thresholds that improve quality of life without compromising survival. Moreover, investigating whether lower chemotherapy doses or a total of five cycles can be safely administered to selected patients (or potentially all patients) without compromising efficacy could provide valuable insights into more personalized treatment approaches. Target trial emulation using detailed observational data could be a valuable approach for investigating these questions, enabling the simulation of a randomized controlled trial when conducting one is not feasible or ethical [35–38].

As previously noted, **Chapter 5** highlighted that clinical practice often involves adjustments to standardized protocols to address toxicity or other concerns, though the manner in which these adjustments are applied may vary. Traditional dosing strategies, such as flat dosing or body surface area-based calculations, fail to account for important factors influencing chemotherapy tolerance, including age, race, comorbidities, organ function, and metabolism [39, 40]. Moreover, clinical trials evaluating dosing regimens predominantly enroll patients with excellent performance status and minimal comorbidities, leading to the underrepresentation of older and more vulnerable populations [39, 40]. As a result, trial findings may not fully translate to real-world settings, underscoring the need for alternative methodologies, such as target trial emulation, to determine optimal dosing in heterogeneous patient populations [35, 36]. In line with this, emerging strategies in precision oncology, including dose adjustments based on individual patient characteristics, offer a promising approach to optimizing chemotherapy regimens [39]. For instance, starting at reduced doses and using intra-patient dose escalation may enable safe and effective personalized dosing, particularly for novel drug combinations lacking formal phase I trials [39].

Beyond individualized dose adjustments, the timing and intensity of chemotherapy administration also play a crucial role in optimizing treatment outcomes. In this context, dose-dense chemotherapy regimens have been explored as an alternative to standard schedules, aiming to enhance efficacy by shortening the interval between chemotherapy cycles. However, their efficacy in routine clinical practice remains uncertain [41]. Studies in Asian populations have shown improved progression-free survival and overall survival with weekly paclitaxel administration, while the ICON8 trial

in European populations found weekly dose-dense chemotherapy feasible but without significant progression-free survival benefit over standard three-weekly regimens [42–44]. These discrepancies highlight the challenges of generalizing findings across diverse populations. Notably, further analysis on the dataset of the ICON8 trial suggested that dose-dense chemotherapy regimens could benefit patients with poor prognostic characteristics, i.e., lower tumor chemosensitivity assessed by the modeled cancer antigen 125 (CA-125) elimination rate constant and incomplete cytoreductive surgery [45]. Nevertheless, its impact on overall survival and quality of life in routine clinical practice, as well as its practical implementation, remains unclear [45]. Addressing these gaps through further research is essential for defining the role of dose-dense strategies in personalized treatment approaches.

Immunotherapy challenges in EOC

Developing individualized approaches for EOC, particularly in the context of immunotherapy, poses major challenges due to the complex interaction between tumor biology and treatment responses. The inherent heterogeneity of EOC, with distinct histologic subtypes comprising different molecular and genetic profiles, complicates the development of effective therapeutic strategies [46–48]. Furthermore, the immunosuppressive nature of the EOC tumor microenvironment, characterized by a low tumor mutational burden, limited immunogenicity, and a high presence of regulatory T cells, reduces the efficacy of immune checkpoint inhibitors [47–49].

Given the growing interest in immune modulation as a therapeutic strategy, investigating real-world scenarios where immune activation occurs naturally may provide novel insights. In line with this, **Chapter 3** of this dissertation explored the impact of sepsis on the oncologic outcomes of EOC patients. In a cohort of 18 patients, sepsis did not appear to influence survival outcomes: three patients succumbed to the complications, two demonstrated exceptionally long survival, and the remainder showed no significant impact on survival. While these findings suggest that sepsis may not affect oncologic outcomes in EOC, the limited sample size and observational nature of the study highlight the difficulty of drawing definitive conclusions. Larger, prospective studies are needed to better understand immune responses in this context.

A significant challenge in EOC is the lack of reliable predictive biomarkers. In particular, programmed death ligand-1 (PD-L1) expression has not proven sufficient to identify patients who may benefit from immune checkpoint inhibitors [49-52]. This reflects the broader challenge of overcoming EOC's highly immunosuppressive tumor microenvironment, which limits the efficacy of single-pathway approaches such as PD-1/PD-L1 targeting [47, 53]. The heterogeneity between primary tumors and peritoneal

metastases further complicates the effectiveness of single-pathway approaches [53]. Moreover, the optimal integration of immunotherapy into current treatment protocols remains unclear, with unresolved questions about its timing, sequencing, and potential role in combination or maintenance strategies.

Given these challenges, immune checkpoint inhibitors have shown only limited efficacy in EOC, both as monotherapy and in combination with chemotherapy [47, 49, 50, 53, 54]. Resistance mechanisms further hinder the effectiveness of single-pathway immune therapies in targeting tumors, highlighting the need for therapeutic strategies that incorporate multi-pathway targeting or combination approaches [47-49, 55]. To address these challenges, ongoing trials focus on promising combination strategies, such as pairing immune checkpoint inhibitors with anti-angiogenic agents and PARP inhibitors [49, 51, 55]. For instance, the DUO-O trial (NCT03737643) is evaluating the efficacy and safety of a combination regimen that includes standard platinum-based chemotherapy, bevacizumab, olaparib, and durvalumab (an anti–PD-L1 antibody) in patients with newly diagnosed EOC [56]. Moreover, future research should refine combination strategies and improve patient stratification methods to identify those patients most likely to benefit from immunotherapy [48, 49]. Ongoing efforts to explore immunotherapeutic approaches, including vaccines (e.g., the NEODOC trial, NCT05773859), adoptive cell therapies, antibody-drug conjugates, and the development of novel targets (e.g., TROP-2, FRα, TIGIT, TIM-3, or LAG-3) are crucial for improving immunotherapy outcomes in EOC [47, 57].

Role of prediction models in EOC management

Prediction models are emerging as valuable tools for identifying patients who may benefit from specific therapies, leading to a growing emphasis on integrating prognostic models, biomarkers, and genetic information to optimize individualized treatment strategies. As demonstrated in **Chapters 2** and **6** of this dissertation, our models were developed using clinicopathologic predictors and conventional statistical methods. Apart from improving survival and prognosis predictions, our models may also guide treatment selection by assessing the suitability of standard treatments for vulnerable patient groups and facilitating the choice of tailored treatments that better match individual needs. By utilizing readily available clinicopathologic data, our models provide transparent and interpretable insights that could support personalized counseling on survival and the risk of early relapse. Their strength lies in their simplicity and accessibility, particularly through online score calculators, which may enhance their utility in daily clinical practice.

However, as demonstrated in **Chapters 2**, **6**, and **7**, our models showed room for improvement in predictive performance, as the *c*-indices did not exceed 0.80. Recent

advancements suggest that machine learning approaches have the potential to enhance predictive accuracy by uncovering complex patterns within large datasets [58]. These techniques can identify patients most likely to benefit from specific therapies, enabling more precise and targeted interventions. Nevertheless, conventional statistical models maintain their relevance due to their simplicity, accessibility, and ease of interpretation [59]. Conventional models also require less data and computational resources, making them a practical choice in resource-constrained settings [58]. Although **Chapter 6** did not explicitly present the data, it discussed how gradient boosting decision trees, a machine learning technique, did not outperform logistic regression in predictive accuracy. This finding underscores the importance of considering the specific clinical context and available data when selecting models. Developing models that balance accessibility, accuracy, and interpretability is vital for their successful implementation in clinical practice.

Another important consideration for the successful implementation of prediction models is external validation [60-62]. Existing prediction models of EOC often rely on data from single-institution cohorts, raising concerns about their generalizability across diverse clinical settings. External validation requires access to high-quality, comprehensive datasets, which are not always readily available during model development [62]. Unfortunately, current practices tend to prioritize the development of new models over the assessment and validation of existing ones [62, 63]. This approach may lead to an accumulation of models that lack thorough evaluation and practical applicability [63].

As treatment strategies continue to evolve, it is essential to regularly update prediction models to incorporate the latest therapeutic advancements and their potential impact on patient outcomes. This ongoing process is vital not just during external validation but also as part of continuous model refinement [62]. As demonstrated in **Chapter 7**, it is crucial to assess a model's performance within a specific clinical setting before it is applied. Treatment protocols, patient demographics, and regional variations in healthcare practices can all influence the predictive accuracy of a model. Therefore, regular updates within the same clinical setting are also necessary, as changes in treatment strategies and evolving care approaches can affect model performance. Regularly revisiting and refining prediction models ensures they remain relevant, effective, and aligned with the evolving treatment landscape, thereby maintaining their utility in guiding shared decision-making [62]. In addition, incorporating newly identified prognostic factors, biomarkers, or genetic data into established models is essential for assessing their added prognostic or predictive value, ultimately enabling the development of more powerful and accurate prediction tools.

Future Perspectives

As the field of EOC treatment continues to evolve, there is an increasing emphasis on the role of personalized medicine to optimize outcomes. Tailoring treatment strategies to the individual patient is crucial in improving survival while also prioritizing quality of life.

Based on the findings from this dissertation, the following recommendations for clinical practice and future research are proposed:

- **Chapter 2** highlighted that the selected clinicopathologic predictors were sufficiently predictive of five- and ten-year overall survival. However, it was also demonstrated that these predictors were insufficient for predicting short-term survival (i.e., less than three years of overall survival). The first two models should undergo external validation before they are implemented in daily clinical practice. Once validated, these models could serve as valuable tools for patient counseling. Additionally, incorporating new predictive factors and adapting models to account for evolving standard treatments should be considered to improve their accuracy and applicability.
- **Chapter 3** investigated the impact of postoperative sepsis on overall survival in advanced EOC patients. While no significant evidence suggesting that sepsis affects survival was found, the observational nature of the study limits the ability to draw definitive conclusions. Further research is needed to explore the potential effects of sepsis on the antitumor response in EOC, considering factors such as timing, severity, and underlying mechanisms. Experimental studies using EOC-bearing mice, with and without sepsis, could provide insights into the role of sepsis in tumor growth and development, even if they do not directly lead to novel therapeutic strategies for EOC patients.
- **Chapter 4** did not observe a statistically significant difference in progression-free or overall survival between advanced-stage EOC patients who underwent splenectomy as part of cytoreductive surgery and those who did not. Splenectomy can be performed when necessary, but its perioperative risks should be carefully considered.
- **Chapter 5** found no statistically significant difference in overall survival between patients who had chemotherapy regimens interrupted (including delays) and those who did not, nor between patients who had chemotherapy dose reductions and those who did not. These findings suggest that interrupting or reducing chemotherapy doses can be feasible and safe without compromising survival. However, further research is required to evaluate the impact of specific time intervals of interruptions or the extent of dose reductions on survival outcomes, as no such data were available in our study.

- Additionally, **Chapter 5** showed that omitting the sixth chemotherapy cycle did not negatively affect survival, offering reassurance that patients can safely forgo this cycle because of toxicity or other concerns. However, the study also suggested that further reducing the number of chemotherapy cycles was associated with impaired overall survival. Further investigation is needed to determine whether five cycles could be considered the new standard treatment duration for a specific subgroup of patients.
- **Chapter 6** highlighted the difficulty of predicting early relapse risk in the pretreatment setting using clinicopathologic predictors alone. However, **Chapters 6** and **7** demonstrated that risk of early relapse can be estimated in the postoperative setting. Our postoperative and *BRCA* models have now been validated in the Dutch clinical setting and are ready for broader clinical implementation. Nonetheless, external validation in other countries' clinical settings is essential to ensure their accuracy across diverse populations.

Looking ahead, as genomic profiling advances, identifying molecular subtypes may become a cornerstone in tailoring therapies for individual EOC patients [64, 65]. Detecting specific mutations, such as those in the *BRCA* gene alterations or other HRD markers, could enable a more refined approach to treatment selection, helping to predict which patients will benefit most from targeted therapies or immunotherapies [64, 65]. Future research should expand the use of molecular diagnostics and integrate these findings with clinical parameters to develop more robust risk stratification models that guide EOC treatment decisions.

While platinum- and taxane-based chemotherapy remains the foundation of EOC management, ongoing research into chemotherapy alternatives and optimization is crucial. Despite current treatment options, the five-year survival rate remains low [66, 67]. Personalizing chemotherapy dosing based on age, comorbidities, and genetic profiles may reduce toxicity while preserving efficacy [39]. Similarly, further evaluation of PARP inhibitors is needed to address ongoing challenges in optimizing their effectiveness.

The immunosuppressive tumor microenvironment remains a significant challenge in EOC treatment. As noted earlier, EOC tumors have a low mutational burden and are often resistant to immune checkpoint inhibitors. However, the evolving landscape of immunotherapy offers hope, particularly through combination approaches [47, 49, 50]. Pairing immune checkpoint inhibitors with PARP inhibitors or anti-angiogenic agents is currently being explored in clinical trials and may help overcome the immunosuppressive environment [47, 49, 51, 55]. Nevertheless, these combinations could lead to increased toxicity, raising concerns about their impact on future treatment

options, particularly when multiple agents are used concurrently in initial therapy. Moreover, emerging strategies, such as tumor-infiltrating lymphocyte therapies or personalized cancer vaccines, could potentially boost the immune response against EOC cells [47]. Continuing research into these areas, alongside the development of refined biomarkers, is essential for identifying patients most likely to benefit from immunotherapy and to understanding the resistance mechanisms that limit their effectiveness [53, 57]. Additionally, antibody-drug conjugates, which selectively target and deliver cytotoxic agents directly to tumor cells, hold great promise for improving EOC treatment outcomes [57].

Another promising direction for improving EOC treatment is the growing role of liquid biopsies in monitoring treatment response and early relapse detection [68–71]. Liquid biopsy, which allows for the non-invasive detection of circulating tumor DNA or cells in ascites or blood samples, could provide a way to track tumor progression more effectively than conventional imaging or traditional biopsy [68–70]. Incorporating liquid biopsy into routine clinical practice could enable more precise monitoring of EOC progression, potentially identifying relapses earlier and allowing for more timely interventions [68–71]. Additionally, liquid biopsy could help identify patients who may require fewer chemotherapy cycles. Future research should focus on validating liquid biopsy as a tool for real-time patient monitoring, particularly when combined with imaging techniques or tumor markers like CA-125, to improve both detection and treatment response assessment. Similarly, the use of ex vivo 3D micro-tumor testing platforms has shown promise in predicting patient-specific responses to platinum-based therapies and second-line treatments, allowing for better patient stratification and more informed treatment decisions in both first- and second-line therapies [72].

Finally, to optimize prediction model use in clinical practice, promoting multidisciplinary collaboration is important. The complexity of EOC requires input from a diverse group of specialists, including medical oncologists, pathologists, radiologists, clinical geneticists, and gynecologic oncologists, to provide a comprehensive approach to treatment management. Incorporating advanced computational methods into clinical workflows will allow for the continuous refinement of predictive tools and better patient stratification. By ensuring that these models integrate a broad range of clinical and molecular data, personalized care can become more precise and adaptable, adjusting as new information on patient response and disease progression becomes available. In line with this, a national biobank for EOC patients has been initiated in the Netherlands, with the potential for expansion or replication in other countries, offering a valuable resource to further enhance research and collaboration [73, 74].

Concluding Remarks

In conclusion, while some progress has been made in the management of EOC, there is still much work to be done. The future of EOC treatment lies in the development of personalized, targeted approaches, with a focus on biomarkers, molecular profiling, and innovative combination therapies. By continuing to refine these strategies and validating their effectiveness across diverse populations, patient outcomes and quality of life in EOC can be improved. The ongoing integration of advanced technology, along with multidisciplinary care, will ultimately provide clinicians with the tools necessary to manage this complex disease more effectively.

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CHAPTER 9

Summary | Samenvatting

Summary

This chapter summarizes the findings of this dissertation, which explored factors influencing the management and survival of advanced epithelial ovarian cancer (EOC). By assessing clinical and hematologic prognostic markers, chemotherapy adherence, and the impact of surgical and clinical interventions, this research identified determinants of overall survival (OS) and early relapse. Furthermore, it presented the development and validation of predictive models to support personalized treatment strategies and improve patient counseling.

Part I: Clinical and treatment factors affecting advanced-stage EOC survival

In **Chapter 2**, we assessed the association of pretreatment hematologic abnormalities (i.e., anemia, leukocytosis, and thrombocytosis) with OS in advanced-stage EOC patients. A cohort of 773 patients treated between 1996 and 2010 in the eastern Netherlands was analyzed. Pretreatment thrombocytosis was significantly associated with poorer OS, while leukocytosis and anemia demonstrated no notable survival impact. In addition, predictive models incorporating established clinicopathologic and hematologic parameters were developed for ≤3-, ≥5-, and ≥10-year OS. The ≥5- and ≥10-year models demonstrated good calibration and discrimination, while the ≤3-year model showed suboptimal performance. These findings underscore the prognostic value of pretreatment thrombocytosis and provide a basis for further validation of long-term survival models in advanced EOC.

In **Chapter 3**, we explored the impact of sepsis on oncologic outcomes in advanced-stage EOC patients. A cohort of 18 patients who developed sepsis following EOC diagnosis and were admitted to the Intensive Care Unit (ICU) across three oncologic centers was identified and compared to 3,988 patients from the Netherlands Cancer Registry (NCR). After adjusting for case-mix differences using propensity score matching, survival outcomes were analyzed. Three patients died from sepsis-related complications, while the remaining patients initially responded to treatment; however, most (14/15) relapsed, with two showing exceptional survival. No significant differences in OS or progression-free survival (PFS) were observed between the sepsis and NCR cohorts, irrespective of propensity score matching. These findings suggest that sepsis does not influence survival outcomes in advanced-stage EOC. However, given the observational nature of the study and the small sample size, further research is warranted to clarify its potential impact on disease progression and survival.

In **Chapter 4**, we investigated the association between splenectomy and perioperative and survival outcomes in advanced-stage EOC. A nationwide study using the NCR identified

FIGO stage IIIC–IV EOC patients who underwent cytoreductive surgery with platinum-based chemotherapy between 2008 and 2015. Among 3,911 patients, 99 underwent splenectomy, while 3,812 did not. Compared with non-splenectomy patients, those who underwent splenectomy were more likely to undergo extensive surgery, require surgical reintervention, receive intraperitoneal chemotherapy and blood transfusions, and had higher rates of postoperative infections and ICU admission. Despite these less favorable perioperative outcomes, no significant differences in PFS or OS were observed between the two groups. These findings suggest that while splenectomy is associated with increased surgical morbidity, it does not appear to adversely affect survival, supporting its use when necessary to achieve complete cytoreduction in advanced-stage EOC.

In **Chapter 5**, we evaluated chemotherapy adherence, reasons for treatment modifications, and their associations with OS in advanced-stage EOC. A nationwide study using the NCR identified 3,687 patients diagnosed between 2015 and 2021 who underwent cytoreductive surgery with platinum- and taxane-based chemotherapy. Patients were categorized as adherent (patients without modifications) or non-adherent (patients with modifications: dose reduction, chemotherapy interruption, and/or reduction in the number of cycles). Overall, 54% of patients underwent chemotherapy modifications, with dose reduction (38%) being the most common, followed by interruption (24%) and reduction in the number of cycles (9%). Non-adherence was associated with poorer performance status, higher comorbidity indices, and primary cytoreductive surgery. Neurotoxicity and hematologic toxicity were the main reasons for modifications. While dose reduction and interruption did not impact OS, reduction in the number of chemotherapy cycles was associated with lower 5-year OS and remained statistically significant after multivariable adjustment. However, no significant difference in survival was observed between patients who received five or six chemotherapy cycles. These findings highlight the high prevalence of chemotherapy modifications and suggest that while some modifications may be safe, further studies are needed to validate these results.

Part II: Predictive models for early relapse in advanced-stage EOC

In **Chapter 6**, we identified clinicopathologic factors predictive of early relapse in advanced-stage EOC and developed prediction models for early relapse. A cohort of 4,473 patients diagnosed between 2008 and 2015, identified from the NCR, was analyzed, 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 histologic subtypes, ascites, >1 cm residual disease after cytoreductive surgery, and to have undergone neoadjuvant chemotherapy. Two prediction models were developed: one for the pretreatment setting and another for the postoperative setting. The final pretreatment model demonstrated suboptimal performance, suggesting the need for further refinement in predicting early

relapse. Conversely, the postoperative model, incorporating age, FIGO stage, CA-125 levels, histologic subtype, ascites, treatment approach, and residual disease, showed better model performance. Internal validation using bootstrapping confirmed minimal optimism in the postoperative model. Additionally, a sensitivity analysis incorporating *BRCA* status further improved the predictive power of the postoperative model.

In **Chapter 7**, we externally validated the postoperative and *BRCA* models developed in **Chapter 6** for predicting early relapse in advanced-stage EOC using independent Australian and Dutch cohorts. Patients diagnosed between 2002 and 2006 in Australia and between 2016 and 2017 in the Netherlands, who underwent cytoreductive surgery and platinum-based chemotherapy, were included. Missing data were addressed through multiple imputation, and model updates involved recalibration-in-the-large, recalibration, or model revision. In the Australian cohort (N = 1,334), both models showed adequate discrimination. However, the postoperative model required full revision due to miscalibration, whereas the *BRCA* model only required recalibration-in-the-large. The Dutch cohort (N = 1,212) demonstrated similar findings, with both models showing adequate discrimination. Recalibration-in-the-large effectively updated both models in the Dutch cohort. These findings confirm the robustness of both the postoperative and *BRCA* models for predicting early relapse in advanced-stage EOC. To enhance the models' accuracy across various clinical settings, further regional updates are recommended. Online score calculators have been developed to facilitate clinical implementation.

**The online score calculators for the prediction models developed in this dissertation can be accessed using the following QR codes:*

≥5-year OS model

≥10-year OS model

Postoperative model *validaded*

BRCA model *validaded*

Samenvatting

Deze samenvatting geeft een overzicht van de belangrijkste bevindingen uit dit proefschrift, waarin factoren zijn onderzocht die van invloed zijn op de behandeling en overleving van patiënten met gevorderd epitheliaal ovariumcarcinoom (EOC). Door klinische en hematologische prognostische markers, de toepassing van chemotherapeutische richtlijnen en de impact van chirurgische en klinische interventies te analyseren, zijn factoren geïdentificeerd die samenhangen met overleving en vroegtijdig recidief. Daarnaast zijn voorspellende modellen ontwikkeld en gevalideerd die kunnen bijdragen aan gepersonaliseerde behandelstrategieën, maar ook aan betere voorlichting en begeleiding van patiënten.

Deel I: Klinische en therapiegerelateerde factoren die de overleving bij gevorderd EOC beïnvloeden

In **Hoofdstuk 2** onderzochten we de relatie tussen hematologische afwijkingen voorafgaand aan de behandeling (d.w.z. anemie, leukocytose en trombocytose) en de algehele overleving. In een cohort van 773 patiënten, behandeld tussen 1996 en 2010 in Oost-Nederland, bleek trombocytose voorafgaand aan de behandeling geassocieerd met een slechtere algehele overleving. Leukocytose en anemie hadden daarentegen geen significante invloed. Voorspellende modellen voor de algehele overleving werden ontwikkeld op basis van klinisch-pathologische en hematologische parameters. De modellen die een minimale overleving van vijf en tien jaar vanaf diagnose voorspelden, presteerden goed, terwijl het model dat de overleving binnen de eerste drie jaar moest voorspellen minder betrouwbaar bleek. Deze resultaten benadrukken de voorspellende waarde van trombocytose voorafgaand aan de behandeling en bieden een basis voor verdere ontwikkeling van overlevingsmodellen voor de lange termijn.

In **Hoofdstuk 3** richtten we ons op de invloed van sepsis op de oncologische uitkomsten. Een cohort van 18 patiënten die sepsis doormaakten werd daarin vergeleken met 3.988 patiënten uit de Nederlandse Kankerregistratie (NKR). Na correctie voor een aantal patiëntkenmerken (middels propensity score matching) werden de overlevingsuitkomsten vergeleken. Van de sepsispatiënten overleden drie aan sepsisgerelateerde complicaties; de overige 15 patiënten reageerden aanvankelijk goed op de behandeling, hoewel bij 14 van hen een recidief optrad. Er werden geen significante verschillen in algehele of progressievrije overleving gevonden tussen het sepsis- en het NKR-cohort, ongeacht het gebruik van propensity score matching. Deze bevindingen suggereren dat sepsis de overleving bij gevorderd EOC niet beïnvloedt, al is aanvullend onderzoek gewenst.

In **Hoofdstuk 4** onderzochten we de rol van splenectomie tijdens de behandeling van patiënten met gevorderd EOC, waarbij het doel is om zoveel mogelijk tumorweefsel te verwijderen (cytoreductieve chirurgie). In een landelijke studie op basis van data uit de NKR werden patiënten met FIGO-stadium IIIC en IV onderzocht. Deze patiënten ondergingen tussen 2008 en 2015 cytoreductieve chirurgie, in combinatie met platinumhoudende chemotherapie. Van de 3.911 patiënten ondergingen er 99 een splenectomie. Deze patiënten ondergingen vaker uitgebreide operaties, intraperitoneale chemotherapie, bloedtransfusies en hadden vaker postoperatieve complicaties zoals infecties en Intensive Care opnames. Toch vonden we geen significante verschillen in algehele of progressievrije overleving ten opzichte van patiënten waarbij de milt niet was verwijderd. De resultaten ondersteunen het verrichten van splenectomie wanneer dit nodig is om complete cytoreductie te bereiken, ondanks het verhoogde risico op perioperatieve complicaties.

In **Hoofdstuk 5** evalueerden we de mate waarin chemotherapeutische richtlijnen werden gevolgd, en onderzochten we de redenen voor aanpassingen in de chemotherapieschema's en de invloed daarvan op de algehele overleving. Van de 3.687 patiënten uit de NKR die tussen 2015 en 2021 werden behandeld met cytoreductieve chirurgie gevolgd door platinum- en taxaanhoudende chemotherapie, onderging 54% aanpassingen in het chemotherapieschema (zoals een dosisverlaging (38%), een onderbreking van de chemokuren (24%) en een vermindering van het aantal kuren (9%)). Dosisverlaging en kuuronderbreking hadden geen invloed op de algehele overleving. Een vermindering van het aantal kuren, daarentegen, werd wel geassocieerd met een lagere 5-jaars overleving. Een aanvullende analyse liet daarbij zien dat er geen verschil in de algehele overleving werd gevonden tussen patiënten die vijf of zes kuren ontvingen. Deze resultaten laten zien dat de praktijk vaak afwijkt van de standaardaanbevelingen binnen de richtlijnen, maar dat sommige chemotherapie aanpassingen mogelijk geen negatief effect hebben op de overleving.

Deel II: Voorspellende modellen voor vroegtijdig recidief bij gevorderd EOC

In **Hoofdstuk 6** identificeerden we klinisch-pathologische factoren die geassocieerd zijn met het vroegtijdig optreden van een recidief. Een vroegtijdig recidief werd gedefinieerd als progressieve ziekte tijdens eerstelijns platinumhoudende chemotherapie, of als progressieve of recidiverende ziekte binnen zes maanden na de laatste dosis chemotherapie. Van de 4.473 patiënten die tussen 2008 en 2015 werden gediagnosticeerd en geselecteerd uit de NKR, ontwikkelden 1.302 patiënten (29%) een vroegtijdig recidief. Risicofactoren waren onder andere FIGO-stadium IV, een mucineuze of clear cell tumor, ascites, restziekte van meer dan 1 cm na cytoreductieve chirurgie en het starten met neoadjuvante chemotherapie. Er werden twee voorspellende modellen

ontwikkeld: één voor de fase voorafgaand aan de behandeling en één voor de fase na de operatie. Het model voor de start van de behandeling presteerde suboptimaal, terwijl het postoperatieve model een hogere voorspellende waarde liet zien. Het toevoegen van de *BRCA* status aan het postoperatieve model verbeterde de voorspellende waarde. Deze modellen bieden waardevolle ondersteuning bij het inschatten van het risico op een vroegtijdig recidief.

In **Hoofdstuk 7** valideerden we de in **Hoofdstuk 6** ontwikkelde modellen met behulp van andere patiëntcohorten, uit Australië en Nederland. Patiënten die tussen 2002 en 2006 in Australië (N = 1.334) en tussen 2016 en 2017 in Nederland (N = 1.212) werden gediagnosticeerd en behandeld met cytoreductieve chirurgie in combinatie met platinumhoudende chemotherapie werden geanalyseerd. Na het aanvullen van ontbrekende gegevens en het aanpassen van het model door de interceptwaarde te herkalibreren, bleek het *BRCA* model in beide cohorten robuust. In het Australische cohort was een volledige herziening van het postoperatieve model nodig vanwege miskalibratie, terwijl in het Nederlandse cohort een eenvoudige herkalibratie van de interceptwaarde volstond. Beide modellen bleken goed toepasbaar in verschillende klinische omgevingen. Online score calculators zijn ontwikkeld om de implementatie in de praktijk te ondersteunen, met de aanbeveling om het model per land opnieuw te kalibreren voor een optimale nauwkeurigheid.

**De online score calculators voor de predictiemodellen ontwikkeld in dit proefschrift zijn toegankelijk via de onderstaande QR-codes:*

≥5-jaar OS model

≥10-jaar OS model

Postoperatief model *gevalideerd*

BRCA-model *gevalideerd*

APPENDICES

List of Abbreviations
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List of Abbreviations

Abbreviation	Definition
AOCS	Australian Ovarian Cancer Study
AUC	area under the receiver operating characteristic curve
BRCA	breast cancer gene
CA-125	cancer antigen 125
CAR	chimeric antigen receptor
caret	classification and regression training (R package)
CCI	Charlson comorbidity index
$CD8^+$	T cells expressing the CD8 glycoprotein; cytotoxic T cells involved in immune defense
CHORUS	CHORUS trial (NCT00075712)
CI	confidence interval
c-index	Harrell's concordance index
CT	computed tomography
DNA	deoxyribonucleic acid
DUO-O	DUO-O trial (NCT03737643)
EOC	epithelial ovarian cancer
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
FIRST	FIRST trial (NCT03602859)
FRα	folate receptor alpha
GBDT	gradient boosting decision trees
GOG	Gynecologic Oncology Group
HGSC	high-grade serous carcinoma
HIPEC	hyperthermic intraperitoneal chemotherapy
Hmisc	Harrell miscellaneous (R package)
HR	hazard ratio
HRD	homologous recombination deficiency
ICON8	ICON8 trial (NCT01654146)
ICU	intensive care unit
IKNL	Netherlands Comprehensive Cancer Organization
IL-1β	interleukin-1 beta
IL-6	interleukin-6
IP	intraperitoneal
IQR	interquartile range
LAG-3	lymphocyte-activation gene 3
LGSC	low-grade serous carcinoma
LR+	positive likelihood ratio
MAP	mean arterial pressure
N	number

NA	not applicable
NACT-ICS	neoadjuvant chemotherapy followed by interval cytoreductive surgery
NCR	Netherlands Cancer Registry
NCT	National Clinical Trial
NEODOC	NEODOC trial (NCT05773859)
No.	number
NOS	not otherwise specified
NPV	negative predictive value
OR	odds ratio
OS	overall survival
OVHIPEC	OVHIPEC trial (NCT00426257)
PALGA	Pathological Anatomical National Automated Archive
PAOLA-1	PAOLA-1 trial (NCT02477644)
PARP	poly(ADP-ribose) polymerase
PCS	primary cytoreductive surgery
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PPV	positive predictive value
PRIMA	PRIMA trial (NCT02655016)
PS	performance status or performance score
R	statistical software and programming language/environment
rms	regression modeling strategies (R package)
SBP	systolic blood pressure
SIRS	systemic inflammatory response syndrome
SOFA	sequential organ failure assessment
SOLO-1	SOLO-1 trial (NCT01844986)
STATA/SE	statistical software (Stata Special Edition)
TCR	T-cell receptor
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TNF-α	tumor necrosis factor-alpha
Tregs	regulatory T cells
TRIPOD	transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
TRUST	TRUST trial (NCT02828618)
TTC	time to start adjuvant chemotherapy
TROP-2	trophoblast cell-surface antigen 2
VAC	vacuum-assisted closure system
VELIA	VELIA trial (NCT02470585)
yrs	years


A

List of Publications

Said, S.A., IntHout, J., Koffijberg, H., de Hullu, J.A., Hyde, S.E., van der Aa, M.A., & van Altena, A.M. (2025). External validation of prediction models for early relapse in advanced epithelial ovarian cancer using Australian and Dutch population-based data. *Cancer Epidemiology*, 97, 102824. PMID: 40315577

Said, S.A., IntHout, J., den Ouden, J.E., Walraven, J.E.W., van der Aa, M.A., de Hullu, J.A., & van Altena, A.M. (2024). Development and internal validation of prediction models for survival of advanced epithelial ovarian cancer based on established prognostic factors and hematologic parameters. *Journal of Clinical Medicine*, 13(10), 2789. PMID: 38792332

Said, S.A., de Hullu, J.A., van der Aa, M.A., Walraven, J.E.W., Bekkers, R.L.M., Slangen, B.F.M., Pickkers, P., & van Altena, A.M. (2023). Impact of sepsis on the oncologic outcomes of advanced epithelial ovarian cancer patients: A multicenter observational study. *Cancers (Basel)*, 15(18), 4642. PMID: 37760610

Said, S.A., van der Aa, M.A., Veldmate, G., de Hullu, J.A., & van Altena, A.M. (2022). Oncologic outcomes after splenectomy during initial cytoreductive surgery in advanced epithelial ovarian cancer: A nationwide population-based cohort study. *Acta Obstetricia et Gynecologica Scandinavica*, 101(1), 56–67. PMID: 34719790

Said, S.A., Bretveld, R.W., Koffijberg, H., Sonke, G.S., Kruitwagen, R.F.P.M., de Hullu, J.A., van Altena, A.M., Siesling, S., & van der Aa, M.A. (2021). Clinicopathologic predictors of early relapse in advanced epithelial ovarian cancer: Development of prediction models using nationwide data. *Cancer Epidemiology*, 75, 102008. PMID: 34509380

Said, S.A.*, Wenzel, H.H.B.*, van Altena, A.M., Walraven, J.E.W., in 't Hout, J., de Hullu, J.A., & van der Aa, M.A. Adherence to chemotherapy among patients with advanced epithelial ovarian cancer in the Netherlands and its impact on survival: A nationwide cohort study. *[Manuscript submitted for publication]*, *Shared first authorship.

Research Data Management

Ethics and privacy

This dissertation is based on the results of research involving human participants, which was conducted in accordance with relevant national and international legislation and regulations, guidelines, codes of conduct, and Radboud University Medical Center policy.

Ethical approval for **Chapters 2**, **4**, **5**, **6**, and **7** was obtained from the Privacy Committee of the Netherlands Cancer Registry (NCR) with the following reference numbers: K17-245 (**Chapter 2**), K20.157 (**Chapter 4**), K23.306 (**Chapter 5**), and K19.121 (**Chapters 6** and **7**).

For **Chapter 3**, ethical approval was obtained from the Medical Ethics Committees of the participating centers: Radboud University Medical Center (CMO 2019-5390), Maastricht University Medical Center (METC 2019-1412), and Catharina Hospital (nWMO-2020.054). All committees concluded that the study did not fall under the Medical Research Involving Human Subjects Act (WMO) and, therefore, waived the requirement for informed consent, as strong privacy protection measures ensured that data could not be traced to individual patients. Informed consent was obtained to collect and process participants' data for this research project.

The privacy of the participants in all these studies was ensured through the use of pseudonymization by the Netherlands Comprehensive Cancer Organization.

Data collection and storage

For **Chapter 2**, data were collected from patients' medical records and stored in a STATA file for analysis. All research chapters (**Chapters 2**–**7**) involved data from the Netherlands Cancer Registry (NCR). For these chapters, previously collected and curated datasets were utilized. For **Chapter 7**, data from the Australian Ovarian Cancer Study (AOCS) group were used, which had also been previously collected and curated. However, the dataset was anonymized and limited to the variables necessary for the analysis. All data were analyzed using R or STATA.

Study data are securely stored either on the servers of the Department of Obstetrics and Gynecology (**Chapters 2** and **3**) or on the servers of the Netherlands Comprehensive Cancer Organization, where they are managed by the gynecologic cancer research team (**Chapters 2**–**7**).

Data sharing according to the FAIR principles

All data and analytical codes are documented in either Dutch or English in accordance with the FAIR principles, ensuring they are findable, accessible, interoperable, and reusable. The data will be retained for 15 years following the completion of each study. All published articles from this dissertation are available open access. The data used for **Chapters 2**–**7** include the Netherlands Cancer Registry (NCR) data, which are not owned by Radboud University Medical Center. These data are archived and managed by the Netherlands Comprehensive Cancer Organization (IKNL). Any questions regarding the data can be directed to Dr. Maaike van der Aa (M.vanderAa@iknl.nl).

PhD Portfolio

PhD Candidate: **Drs. S.A. Said**
Department: **Department of Obstetrics and Gynecology**
PhD period: **01/01/2020 – 22/09/2025**
PhD supervisor: **Dr. J.A. de Hullu**
PhD co-supervisors: **Dr. A.M. van Altena, Dr. M.A. van der Aa, and Dr. J. in 't Hout**

Training activities	Hours
Courses	
• Radboudumc — General Introduction to Radboudumc for Research Personnel (2020)	9.00
• RIHS — Introduction Course for PhD Candidates (2020)	15.00
• EpidM — Missing Data: Consequences and Solutions (2021)	56.00
• Radboudumc — R Introduction Course (2021)	24.00
• Radboudumc — eBROK Course (for researchers working with human subjects) (2021)	26.00
• RU — Writing Scientific Articles (2021)	84.00
• RIHS — Writing a Rebuttal Workshop (2021)	2.00
• Radboudumc — Scientific Integrity (2021)	20.00
• RU — Project Management for PhD Candidates (2021)	56.00
• RIHS — Design Your New Year Workshop (2022)	2.00
• RIHS — Boost Your Writing Skills Workshop (2022)	2.00
• RIHS — Prepare Your Defense: Answering Questions Workshop (2022)	4.00
Seminars	
• Resident Peer Review Evening (2020) at the Department of Obstetrics and Gynecology, oral presentation	14.00
• Radboudumc — Research Integrity Round (2020)	3.00
• Peer Review and Presentation Meetings at the Netherlands Comprehensive Cancer Organization (2021), oral presentation	14.00
• PhD Retreat (2022), oral presentation	28.00
• Radboudumc — Research Integrity Round (2022)	3.00
• Pizza and Science Evening (2022) at the Department of Obstetrics and Gynecology, oral presentation	14.00
• Peer Review and Presentation Meetings at the Netherlands Comprehensive Cancer Organization (2024), oral presentation	14.00

Conferences	
• International Society of Gynecologic Cancer (IGCS) Congress (2020), oral presentation	28.00
• Netherlands Cancer Registry (NCR) Symposium (2020)	6.00
• European Society of Gynecologic Oncology (ESGO) Congress (2021), live participation in Prague, two poster presentations	28.00
• Netherlands Cancer Registry (NCR) Symposium (2021), oral presentation and moderator	10.00
• International Society of Gynecologic Cancer (IGCS) Congress (2022), two poster presentations	28.00
• Netherlands Cancer Registry (NCR) Symposium (2022)	8.00
• European Society of Gynecologic Oncology (ESGO) Congress (2025), poster presentation	28.00
Other	
• Monthly research meetings of the Gynecologic Oncology team at the Netherlands Comprehensive Cancer Organization (2020–2022)	30.00
• Chairing PhD candidates meetings at the Department of Obstetrics and Gynecology (2020–2022)	14.00
Teaching activities	
Lecturing	
• Presentation on prediction models at the Netherlands Comprehensive Cancer Organization (2020)	6.00
• Gynecologic oncology educational meetings for Master's students in Medicine (2020–2022)	28.00
Supervision of internships	
• Supervision of one Master's student in Medicine during research internship (2020)	28.00
• Supervision of three Bachelor's students in Medicine during research project (2020)	84.00
Total	
	716.00


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About the Author

Sherin Said was born on February 1, 1993, in Mogadishu, Somalia. She grew up in Enschede, the Netherlands, with her parents, Abdo and Zahra, and her siblings: Mohamed, Sherihan, Mustafa, Aisha, and Munira. She is also the proud aunt of her nieces Sumaya and Amanah.

After completing secondary education at Het Stedelijk Lyceum Zuid in Enschede, she was admitted to medical school at Radboud University Nijmegen through decentralized selection. During her studies, she completed a research internship on ovarian cancer, supervised by Dr. Anne van Altena. She also completed medical electives in Obstetrics and Gynecology and Anesthesiology at Horacio Oduber Hospital in Aruba and Radboud University Medical Center.

After graduating from medical school, she pursued a second Master's degree in Health Sciences at the University of Twente. She remained actively involved in various research projects and served as president of a student association. Following her internship at the Netherlands Comprehensive Cancer Organization (IKNL), supervised by Dr. Maaike van der Aa, she was offered the opportunity to combine her research projects into a PhD trajectory focused on ovarian cancer at Radboud University Medical Center in collaboration with IKNL.

In January 2023, she began working as a junior doctor in the Intensive Care Unit at Gelderse Vallei Hospital, a position she held alongside completing her PhD research. Starting in fall 2025, she will begin residency training in Anesthesiology at University Medical Center Utrecht.

Over de auteur

Sherin Said werd geboren op 1 februari 1993 in Mogadishu, Somalië. Zij groeide op in Enschede, samen met haar ouders, Abdo en Zahra, en haar broers en zussen: Mohamed, Sherihan, Mustafa, Aisha en Munira. Zij is de trotse tante van haar nichtjes Sumaya en Amanah.

Na het behalen van haar gymnasiumdiploma aan Het Stedelijk Lyceum Zuid in Enschede werd zij via decentrale selectie toegelaten tot de opleiding Geneeskunde aan de Radboud Universiteit Nijmegen. Tijdens haar studie voerde zij een wetenschappelijke stage uit over ovariumcarcinoom onder begeleiding van dr. Anne van Altena. Daarnaast liep zij keuzecoschappen Gynaecologie en Anesthesiologie bij het Horacio Oduber Hospital op Aruba en het Radboudumc.

Na het afronden van haar geneeskundestudie volgde zij een tweede masteropleiding Health Sciences aan de Universiteit Twente. Daarnaast bleef zij actief betrokken bij verschillende wetenschappelijke projecten en vervulde zij de rol van voorzitter binnen een studentenvereniging. Na haar stage bij het Integraal Kankercentrum Nederland (IKNL), onder supervisie van dr. Maaike van der Aa, kreeg zij de mogelijkheid haar onderzoeksprojecten te combineren tot een promotietraject gericht op ovariumcarcinoom in het Radboudumc in samenwerking met IKNL.

In januari 2023 is zij gestart als arts niet in opleiding tot specialist (ANIOS) Intensive Care in het Ziekenhuis Gelderse Vallei, een functie die zij combineerde met het afronden van haar promotieonderzoek. Vanaf de herfst 2025 zal zij beginnen aan de opleiding tot anesthesioloog aan het UMC Utrecht.

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