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Prediction of 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer

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ABSTRACT

Objective: Treatment in advanced stage epithelial ovarian cancer (EOC) is based on primary cytoreductive surgery followed by platinum-based chemotherapy. Successful cytoreduction to minimal residual tumour burden is the most important determinant of prognosis. However, extensive surgical procedures to achieve maximal debulking are inevitably associated with postoperative morbidity and mortality. The objective of this study is to determine predictors of 30-day morbidity after primary cytoreductive surgery for advanced stage EOC.

Methods: All patients in the South Western part of the Netherlands who underwent primary cytoreductive surgery for advanced stage EOC between January 2004 and December 2007 were identified from the Rotterdam Cancer Registry database. All peri- and postoperative complications within 30 days after surgery were registered and classified according to the definitions of the National Surgical Quality Improvement Programme (NSQIP).

To investigate independent predictors of 30-day morbidity, a Cox proportional hazards model with backward stepwise elimination was utilised. The identified predictors were entered into a nomogram.

Results: Two hundred and ninety-three patients entered the study protocol. Optimal cytoreduction was achieved in 136 (46%) patients. 30-day morbidity was seen in 99 (34%) patients. Postoperative morbidity could be predicted by age ($P = 0.007$; odds ratio [OR] 1.034), WHO performance status ($P = 0.046$; OR 1.757), extent of surgery ($P = 0.1308$; OR = 2.101), and operative time ($P = 0.017$; OR 1.007) with an optimism corrected c-statistic of 0.68.

Conclusion: 30-day morbidity could be predicted by age, WHO performance status, operative time and extent of surgery. The generated nomogram could be valuable for predicting operative risk in the individual patient.

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1. Introduction

Currently, treatment in advanced stage epithelial ovarian cancer (EOC) is based on primary cytoreductive surgery followed by platinum-based chemotherapy.

Successful cytoreduction to minimal residual tumour burden is the most important determinant of prognosis.[1–4] However, extensive surgical procedures to achieve maximal debulking are inevitably associated with postoperative morbidity and mortality. Reported 30-day morbidity after primary cytoreductive surgery for advanced stage EOC ranges from 11 to 67%.[5–16] Postoperative mortality (POM) rates vary between 0 and 6.7%, with a mean POM rate of 2.8%.[17]

Predictive parameters for postoperative complications after primary cytoreduction for advanced stage EOC are age, performance status, co-morbidity and extent of surgery. Risk-adjustment models for postoperative morbidity and mortality after major surgical procedures, developed for inter- and intra-institutional audits, have shown to improve surgical outcome.[18]

We currently know of only one study on risk-adjustment for surgical outcome in EOC patients.[13] Prediction models for 30-day morbidity could facilitate prediction of surgical outcome in daily clinical practice and provide objective parameters to identify those patients who might benefit from alternative treatment approaches.

The objective of this study was to identify predictive parameters for 30-day morbidity after primary cytoreductive surgery for advanced stage EOC and to develop a nomogram to predict 30-day morbidity.

2. Material and methods

2.1. Selection of patients and study design

From January, 2004 to December, 2007 all patients with primary surgery for EOC were retrieved from the Rotterdam Cancer Registry database.

The Rotterdam Cancer Registry covers the South Western part of the Netherlands. This region comprises one university hospital, four teaching hospitals and 11 non-teaching hospitals serving a population of 2.4 million inhabitants. All newly diagnosed cases of cancer are reported to the Registry by pathology laboratories and by the hospital administration for discharge records. Patients with advanced stage EOC, defined as International Federation of Gynaecology and Obstetrics (FIGO) stage III/IV, who underwent primary cytoreductive surgery were eligible for this study. For all patients, information was sent to the hospitals to obtain access to the medical records for review by two clinicians (CG and GMN). General case notes, surgical reports and pathology reports were reviewed.

The study was approved by the Medical Ethical Committee of the Erasmus University Medical Center and was performed according to the standards outlined in the Declaration of Helsinki.

2.2. Pre-operative assessments

Standard preoperative work-up of the patients consisted of patients' history, physical examination and transvaginal sonography (TVS). CT-scans were electively made at the discretion of the attending physician. Blood samples for measurement of CA125, blood platelet count and haemoglobin concentrations were withdrawn within 1 week prior to surgery. CA125 was assessed by enzyme immunoassay (Roche E170) using a sandwich method with chemo luminescence (Roche Diagnostics BV, Almere, the Netherlands). The blood platelet count and haemoglobin were assessed by a Sysmex XE 2100 system (Sysmex Corporation, Kobe, Japan).

2.3. Treatment regimen

Primary cytoreductive surgery was performed using an abdominal midline incision and included total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy and resection of all visible and palpable bulky tumour. The aim of this procedure was to resect all macroscopic tumour or at least to lesions <1 cm.[1,2] Bowel resection, pancreas resection, splenectomy, diaphragmatic stripping, partial liver resection and lymphadenectomy were performed if warranted to achieve an optimal cytoreduction, defined as residual disease <1 cm.

2.4. Histo-pathological assessment

Histology was classified as serous, mucinous, endometrioid, clear cell, and undifferentiated adenocarcinoma. Differentiation was classified in grade 1 to 3, according to the Silverberg criteria.[19] Subsequently, stage of the disease was determined according to FIGO guidelines.[20]

2.5. Study parameters and outcome measures

Preoperative parameters for analysis were patients' age, clinical condition according to the WHO performance scale, comorbidity status, presence of ascites prior to surgery, CA125-, blood platelet- and haemoglobin concentrations. Ascites was defined as the presence of pelvic fluid on ultrasound, CT-scan and/or at laparotomy. Comorbidity was scored and categorised using a modification of the Charlson comorbidity index (CCI) (Table 1).[21]

Postoperative parameters for analysis were residual disease, type of surgeon, extent of surgical procedures, operative time, histology, histological differentiation and FIGO stage. To assess the extent of surgical procedures, the surgical complexity score (SCS) described by Aletti and colleagues was adopted.[13] Based on number and complexity of the surgical procedures performed, patients were assigned to one of three groups: low-, intermediate and complex surgery (Table 2).

All peri- and postoperative complications were registered and classified according to the definitions of the National Surgical Quality Improvement Programme (NSQIP).[22–24] Postoperative mortality (POM) was defined as death from any cause within 30 days of operation. Cause of death was systematically described by applying the methodology proposed by Waljee and colleagues. In this classification the complication that attributed most to the patient's death during a postoperative course has to be assigned[23] (Table 7).

Postoperative morbidity included the following selection of adverse events seen within 30 days after surgery: POM,

Table 1 – The modified Charlson comorbidity index.[21]

Comorbid condition	Index points
Coronary artery disease[a]	1
Congestive heart failure	1
Cerebrovascular disease	1
Peripheral vascular disease	1
Hypertension	1
Dementia	1
Diabetes (mild or moderate)	1
Pulmonary disease	1
Renal disease	1
Any prior malignant tumour	2
Hepatic disease	3

[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris.

Table 2 – Surgical complexity score and complexity score groups developed by Alleti and colleagues. SCS = Surgical complexity score;TH-BSO = Total hysterectomy and bilateral-salpingo-oophorectomy.[13]

Operative procedure	SCS
TH-BSO	1
Omentectomy	1
Pelvic lymphadenectomy	1
Para-aortic lymphadenectomy	1
Pelvic peritoneum stripping	1
Abdominal peritoneum stripping	1
Small bowel resection	1
Large bowel resection	2
Liver resection	2
Splenectomy	2
Diaphragm stripping	2
Recto-sigmoidectomy T-T anastomosis	3

Complexity score groups.
SCS $\leqslant$ 3: Low complex surgery.
SCS 4–7: Intermediate complex surgery.
SCS $\geqslant$ 8: High complex surgery.

bleeding requiring>4 U of transfused blood, sepsis, pneumonia, venous thrombo-embolism (pulmonary embolus or deep venous thrombosis), any type of complication requiring re-operation, any bowel injury (leak, fistula, anastomotic leakage), prolonged ileus (>6 days), urinary complications (ureteral fistula, obstruction or leak), failure to wean from the ventilator >48 h after operation, renal failure requiring dialysis, myocardial infarction, stroke, and unplanned intubation.

The primary outcome measure was 30-day morbidity.

3. Analysis

Data analysis, utilising the software package SPSS 14.0 (SPSS, Chicago, IL, USA), was performed on all patients fulfilling in- and exclusion criteria of the study. The Student *t*-test was utilised to compare patients' age, operative time and preoperative serum concentrations of log CA125, blood platelet and haemoglobin between the group of patients with 30-day morbidity and those patients with an uncomplicated postoperative course. Chi square tests were used to compare the preoperative presence of ascites, WHO performance status, CCI, FIGO stage, residual disease, extent of surgical procedures performed, type of surgeon, histological differentiation and histology between the groups of patients with 30-day morbidity to the group of patients with an uncomplicated postoperative course. Based on the univariate analysis, initial predictive parameters for 30-day morbidity with $P < 0.50$ were selected to be assessed by multivariate Cox regression analysis with backward stepwise elimination. In order to prevent overestimation and to achieve a better model performance, parameters with $P < 0.15$ were entered into our prognostic model.[25] We accounted for missing values by multiple imputation.[26]

The discriminative ability of the prognostic model, or the ability to distinguish patients with a poor outcome from patients with a favourable outcome, was expressed by means of the c-statistic.[27] The internal validity of the model was tested by a bootstrapping method in which the selection and estimation process was repeated 200 times. Each of these repetitions consisted of creating a new dataset (bootstrap sample) by drawing cases with replacement from the original data. The backward stepwise elimination process was performed on this dataset, yielding a set of selected predictors and parameter estimates.[27,28] Resulting model estimates of each bootstrap sample were evaluated on the original data, and a shrinkage factor was estimated to correct for statistical over optimism. In addition, a correction for optimism in the c-statistic was derived from the bootstrap method.

A nomogram was generated with the identified predictive parameters.

4. Results

4.1. *Recruitment and demographic characteristics of the patients*

Between January 2004 and December 2007, 494 patients underwent primary surgery for EOC. One hundred and eighty-eight patients with early stage EOC and 13 patients with emergency surgery were excluded. Finally, 293 patients with advanced stage EOC who underwent primary cytoreductive surgery entered the study protocol.

Median age was 64 years (range 15.0–90.5 years), with 91 patients (31%) aged $\geqslant$70 years at time of surgery. Fourteen (4.8%) patients were diagnosed with FIGO stage IIIA, 23(7.8%) patients with FIGO stage IIIB, 208(71.0%) patients with FIGO stage IIIC and 48(16%) patients with stage IV disease. Sixty-seven patients (22.9%) were cytoreduced to no gross residual disease; optimal cytoreduction (residual disease <1 cm) was achieved in another 69 patients (23.5%).

30-day morbidity was seen in 99 patients (34%). POM was 4.8% (N = 14). Causes of death are listed in Table 3. Further patients characteristics are depicted in Tables 4–6.

4.2. *Initial predictive parameters for 30-day morbidity*

Median age was higher in the group of patients with 30-day morbidity when compared to the group of patients without complications, 66.7 ± 12.2 versus 62.5 ± 11.3 years with

Table 3 – Tabulation of causes of death. CCI = Charlson comorbidity index; SCS = surgery complexity score; VTE = venous thromboembolism.

	Age (years)	WHO	CCI	FIGO	Residual tumour	SCC	Cause of death
1	43	1	1	IIIC	>1 cm	1	Sepsis
2	81	0	0	IV	>1 cm	1	Haemorrhage
3	50	1	0	IIIC	>1 cm	2	VTE
4	67	0	1	IV	<1 cm	1	Pulmonary failure
5	67	1	2	IIIC	<1 cm	1	Pulmonary failure
6	82	0	1	IV	>1 cm	1	Pulmonary failure
7	78	3	2	IIIC	>1 cm	2	Progressive disease
8	76	2	2	IIIC	>1 cm	1	Haemorrhage
9	78	0		IIIC	>1 cm	1	Progressive disease
10	74	1	2	IV	>1 cm	1	Sepsis
11	66	1	0	IIIC	>1 cm	2	Anastomotic leakage
12	84	1	0	IIIC	>1 cm	1	Progressive disease
13	81	1	2	IIIC	>1 cm	1	Anastomotic leakage
14	70	1	0	IIIC	>1 cm	1	Renal failure

Table 4 – Preoperative characteristics of study population. Differences, if any, between the group of patients with 30-day morbidity and those with an uncomplicated postoperative course are tested with Student *t* and Chi square tests, when applicable. SD = standard deviation, CCI = Charlson comorbidity index.

	Study population	No complications	30-day morbidity	*P*-value
Preoperative characteristics of the study population of patients with advanced stage ovarian cancer (FIGO III–IV)				
Number of patients (*n*)	293	194(66%)	99 (34%)	
Preoperative parameters				
Age, n (%)				
Median (range)	64.7 (15.9–90.5)	62.5 (31.0–90.5)	66.7 (15.9–81.1)	0.012
<50 years	34 (11.6)	25 (73.5)	9 (26.5)	
50–59 years	80 (27.3)	60 (75.0)	20 (25.0)	
60–69 years	88 (30.0)	57 (64.8)	31 (35.2)	
>70 years	91 (31.0)	52 (57.1)	39 (42.9)	
WHO performance, *n* (%)				0.043
WHO 0	161 (54.9)	118 (73.3)	43 (26.7)	
WHO I	117 (39.9)	68 (58.1)	49 (41.9)	
⩾WHO II	15 (5.1)	8 (53.3)	7 (46.7)	
CCI, *n* (%)				0.981
0	129 (44.0)	89 (69.0)	40 (31.0)	
1	84 (28.7)	55 (65.5)	29(34.5)	
⩾2	80 (27.3)	50 (62.5)	30(37.5)	
Presence of ascites, *n* (%)	174 (59.3)	109 (62.6)	65 (37.4)	0.665
Preoperative serum parameters				
Haemoglobin (mmol/L) ± SD	7.9 ± 0.99	8.0 ± 0.98	7.6 ± 0.99	0.051
Platelet count (*109/L) ± SD	381 ± 140	380 ± 142	388 ± 137	0.221
Log CA125 (kU/L) ± SD	2.80 ± 3.90	2.67 ± 3.98	2.98 ± 3.40	0.459

$P = 0.012$. WHO performance status was significantly better in the group of patients with an uncomplicated postoperative course ($P = 0.043$). Co-morbidity status, preoperative haemoglobin, serum CA125 level, platelet count, and presence of ascites were comparable in both groups (Table 4).

Mean operative time differed markedly between those patients with 30-day major morbidity and those without complications, 189 ± 93 versus 124 ± 61 min with $P < 0.0001$. SCS was >1 in 22 (22.2%) patients with 30-day morbidity versus 12 (6.2%) patients without complications with $P < 0.0001$ (Table 5).

Optimal cytoreduction rate, type of surgeon, histology, histological differentiation and FIGO stage were similar in both groups (Table 6).

4.3. *Uni- and multivariate analysis of predictors for 30-day major morbidity*

The results of the univariate analyses are depicted in Table 7. The variables with $P < 0.50$ in the univariate analysis were assessed by multivariate Cox regression, utilising a backward elimination procedure. Postoperative morbidity could be predicted by age ($P = 0.007$; odds ratio [OR] 1.034), WHO performance status ($P = 0.046$; OR 1.757), extent of surgery ($P = 0.1308$; OR = 2.101), and operative time ($P = 0.017$; OR 1.007) with a c-statistic of 0.73. In other words, our model accurately discriminated patients with and without 30-day morbidity 73% of the time. Because our model was developed and evaluated on the same data, the performance of the

Table 5 – Perioperative characteristics of study population. Differences, if any, between the group of patients with 30-day morbidity and those with an uncomplicated postoperative course are tested with Student *t* and Chi square tests, when applicable. Min = minutes, SCS = surgical complexity score.

	Study population	No complications	30-day morbidity	*P*-value
Perioperative characteristics of the study population of patients with advanced stage ovarian cancer (FIGO III–IV)				
Type of surgeon, n (%)				0.217
Gynaecologic oncologist	109(37.2)	77(70.6)	32(29.4)	
General gynaecologist	184(62.8)	117(63.5)	67(36.4)	
Operative time				<0.0001
Mean (range)	152 min (40–384)	124 min (40–327)	189 min (40–384)	
SCS, n (%)				<0.0001
1	259 (88.4)	182 (70.3)	77 (29.7)	
2	32 (10.9)	12 (37.5)	20 (62.5)	
3	2 (0.7)	0 (0)	2 (100)	

Table 6 – Postoperative characteristics of study population. Differences, if any, between the group of patients with 30-day morbidity and those with an uncomplicated postoperative course are tested with Student *t* and Chi square tests, when applicable.

	Study population	No complications	30-day morbidity	*P*-value
Postoperative characteristics of the study population of patients with advanced stage ovarian cancer (FIGO III–IV)				
Number of patients (n)				
Postoperative parameters				
FIGO, *n* (%)				0.228
III	245 (83.6)	162 (66.1)	83 (33.9)	
IV	48 (16.4)	32 (66.7)	16 (33.3)	
Differentiation, *n* (%)				0.051
1	17 (5.8)	8(47.1)	9 (52.9)	
2	96(32.8)	55 (57.3)	41 (42.7)	
3	139(47.4)	97 (69.8)	42 (30.2)	
unknown	41(14.0)	34(82.9)	7 (17.1)	
Residual disease, *n* (%)				0.991
No macroscopic disease	67 (22.9)	45 (67.2)	22 (32.8)	
<1 cm	69 (23.5)	45 (65.2)	24 (34.8)	
>1 cm	157 (53.6)	104 (66.2)	53(33.8)	
Histology, *n*(%)				0.162
Serous	209(71.3)	142 (67.9)	67 (32.1)	
Endometrioid	22(7.5)	14 (63.6)	8 (36.4)	
Mucinous	17 (5.8)	7 (41.2)	10 (58.8)	
Clear cell	10(3.4)	7 (70.0)	3 (30.0)	
Undifferentiated adenocarcinoma	26 (8.9)	20 (76.9)	6 (23.1)	

model is too optimistic. To correct for the optimism in discriminative ability, the steps taken in Cox regression were internally validated by 200 random bootstrap samples. The optimism corrected c-statistic was 0.68 (Table 5). A shrinkage factor of 0.79 was estimated from the bootstrap procedure. This indicates that in case of replication of this analysis, the resulting coefficients of the final model are on average 0.79 smaller. The generated nomogram, consisting of age, WHO performance status, extent of surgery, and operative time, for the probability of 30-day morbidity is depicted in Fig. 1.

5. Discussion

In the above study we identified predictors for postoperative morbidity and mortality after primary cytoreductive surgery for advanced stage EOC. Age, WHO performance status, operative time and extent of surgery were predictive for 30-day morbidity. With these parameters a nomogram was generated to predict operative risk in the individual patient.

The ability to perform cytoreduction to minimal residual disease determines disease free interval and survival in patients with advanced stage EOC.[1,2] Aggressive surgical procedures including upper abdominal procedures increase optimal cytoreduction rates, resulting in improved overall survival.[29,30] However, extensive surgical procedures are inevitably related to operative morbidity and mortality.

Postoperative morbidity after primary cytoreductive surgery for advanced stage ovarian cancer is reported inconsistently, without standard definitions of postoperative morbidity. Unadjusted morbidity rates range between 11

Table 7 – Univariate analysis of the potential predictors of 30-day morbidity. Parameters with P<0.50 were included in the multivariate Cox regression analysis. OR = odds ratio; NS = not significant; CI = confidence interval; CCI = Charlson comorbidity index; SCS = surgery complexity score.

Variable	Significance	OR (95% CI)
Univariate analysis of predictors of 30-day morbidity		
Preoperative parameters		
Age	0.013	1.028 (1.006–1.050)
WHO performance status	0.018	1.977 (1.191–3.280)
CCI	0.913	1.173 (0.654–2.110)
Presence of ascites	0.947	0.976 (0.480–1.990)
Preoperative serum parameters		
Haemoglobin	0.062	0.976 (0.952–1.000)
Platelet count	0.366	1.001 (0.999–1.000)
Log CA125	0.430	1.069 (0.905–1.260)
Postoperative parameters		
Residual tumour <1 cm	0.991	0.997 (0.614–1.620)
Histological differentiation	0.080	1.304 (0.770–2.210)
Histology	0.324	0.662 (0.241–1.820)
FIGO stage	0.942	0.976 (0.506–1.880)
Type of surgeon	0.218	1.378 (0.827–2.290)
SCS	<0.0001	4.333 (2.042–9.190)
Operative time	0.002	1.008 (1.003–1.010)

and 67%.[5–8,10,12–16,31] In our study one out of three patients experienced a major complication.

Although overall POM is low with a mean POM rate of 2.8%, POM rates in the elderly are significantly higher ranging from 5.4% to 11.7%.[17,32–34]

To provide accurate reference figures, an international standard for data collection and reporting of 30-day morbidity needs to be established. In our opinion these standards could be derived from the NSQIP methodology.[22,24] This risk-adjustment programme started in 1994 and generates periodically observed/expected ratios for 30-day morbidity and mortality after major surgical procedures. With these data inter- and intra-institutional audits are performed to identify structural and procedural failures at the participating hospitals. Ten years after its introduction the overall morbidity and mortality rates after major surgery decreased significantly.

Predictive parameters for postoperative complications after primary cytoreduction for advanced stage EOC are age, performance status, co-morbidity and extent of surgery. Aletti and colleagues developed a risk-adjustment model for primary surgery in advanced stage EOC. Independent predictors of 30-day morbidity were serum albumin level, performance status (ASA) and surgical complexity.[18] In our study those parameters were also predictive for morbidity. Unfortunately, albumin level was not available in most patients and for this reason not included in our analysis. Our generated nomogram facilitates prediction of 30-day morbidity in daily clinical practice and provides objective parameters to identify those patients who might benefit from an alternative treatment approach with neoadjuvant chemotherapy followed by interval debulking surgery. The actual value of this approach is still under debate, but several studies show comparable survival outcomes with less operative morbidity at least in a subgroup of patients.[35–38]

The importance of individual risk assessment is even more important in the elderly.

Cytoreductive surgery for EOC at higher age is associated with increased morbidity and mortality. Exclusion criteria may, however, seriously confound comparisons and information on co-morbidity and performance status is necessary to interpret results in elderly series. In our opinion maximal cytoreduction is feasible in the majority of patients at an

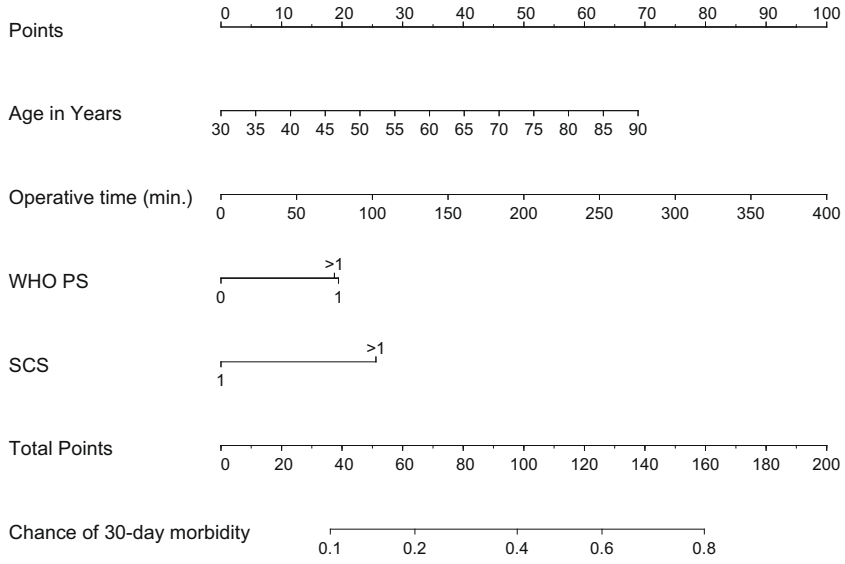

Fig. 1 – Nomogram for prediction of 30-day morbidity. For each level of predictive factor there is a number of points allocated on the point scale above. By adding together the points of each parameter, the total points can be calculated. This number represents the probability of 30-day morbidity. For example, in an 80-year-old patient [57 points] with, respectively, a WHO 0 performance status [0 points], a SCS of 1 [0 points] and an operative time of 150 min [37 points], the total score is 94 points (57+37+0+0) representing a 38% chance of 30-day morbidity.

older age. Prediction models for operative risk can improve management in this growing subgroup of patients by determining individual risk profiles.[39]

Our study has several limitations. First, due to the retrospective nature of data collection, the actual rate of complications could be underscored.

Second, the optimal cytoreduction rate in our study was lower when compared to reports from specialised centres. This supports the general opinion that treatment of patients with an advanced stage EOC should be performed in high volume hospitals with specialised surgeons.[1] However, after its insidious onset, heterogeneous presentation, and clinical course, the vast majority of patients will be referred after an initial examination in a general hospital by a general gynaecologist. An accurate preoperative assessment on resectability and operative risk is therefore essential to guarantee proper decision making and management of these patients. As suggested by other authors, risk-adjustment models should be developed in a general population rather than in a selection of patients treated in specialised high volume hospitals.[13]

Finally, our nomogram was internally validated by bootstrapping. However, before applying the nomogram in daily clinical practise, the nomogram needs to be externally validated.

In conclusion, we developed and internally validated a nomogram predicting 30-day morbidity after primary cytoreductive surgery for advanced stage EOC.

This nomogram is valuable for predicting operative risk in the individual patient.

Conflict of interest statement

None declared.

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REFERENCES

1. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;**20**(5):1248–59.
2. du Bois A, Reuss A, Pujade-Lauraine E, et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer* 2009.
3. Allen DG, Heintz AP, Touw FW. A meta-analysis of residual disease and survival in stage III and IV carcinoma of the ovary. *Eur J Gynaecol Oncol* 1995;**16**(5):349–56.
4. Winter 3rd WE, Maxwell GL, Tian C, et al. Tumor residual after surgical cytoreduction in prediction of clinical outcome in stage IV epithelial ovarian cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2008;**26**(1):83–9.
5. Chen SS, Bochner R. Assessment of morbidity and mortality in primary cytoreductive surgery for advanced ovarian carcinoma. *Gynecol Oncol* 1985;**20**(2):190–5.
6. Suzuki M, Ohwara M, Sekiguchi I, Sato I. Radical cytoreductive surgery combined with platinums-carboplatin and cisplatin chemotherapy for advanced ovarian cancer. *Int J Gynecol Cancer* 1999;**9**(1):54–60.
7. Heintz AP, Hacker NF, Berek JS, et al. Cytoreductive surgery in ovarian carcinoma: feasibility and morbidity. *Obstet Gynecol* 1986;**67**(6):783–8.
8. Eisenkop SM, Spirtos NM, Montag TW, Nalick RH, Wang HJ. The impact of subspecialty training on the management of advanced ovarian cancer. *Gynecol Oncol* 1992;**47**(2):203–9.
9. Eisenkop SM, Spirtos NM, Friedman RL, et al. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. *Gynecol Oncol* 2003;**90**(2):390–6.
10. Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. *Gynecol Oncol* 1999;**72**(3):278–87.
11. Engelen MJ, Kos HE, Willemse PH, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer* 2006;**106**(3):589–98.
12. Bristow RE, Montz FJ. Complete surgical cytoreduction of advanced ovarian carcinoma using the argon beam coagulator. *Gynecol Oncol* 2001;**83**(1):39–48.
13. Aletti GD, Santillan A, Eisenhauer EL, et al. A new frontier for quality of care in gynecologic oncology surgery: multi-institutional assessment of short-term outcomes for ovarian cancer using a risk-adjusted model. *Gynecol Oncol* 2007;**107**(1):99–106.
14. Piver MS, Baker T. The potential for optimal (less than or equal to 2 cm) cytoreductive surgery in advanced ovarian carcinoma at a tertiary medical center: a prospective study. *Gynecol Oncol* 1986;**24**(1):1–8.
15. Guidozzi F, Ball JH. Extensive primary cytoreductive surgery for advanced epithelial ovarian cancer. *Gynecol Oncol* 1994;**53**(3):326–30.
16. Michel G, De Iaco P, Castaigne D, et al. Extensive cytoreductive surgery in advanced ovarian carcinoma. *Eur J Gynaecol Oncol* 1997;**18**(1):9–15.
17. Gerestein CG, Damhuis RA, Burger CW, Kooi GS. Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: a systematic review. *Gynecol Oncol* 2009.
18. Khuri SF. The NSQIP: a new frontier in surgery. *Surgery* 2005;**138**(5):837–43.
19. Shimizu Y, Kamoi S, Amada S, et al. Toward the development of a universal grading system for ovarian epithelial carcinoma I. Prognostic significance of histopathologic features–problems involved in the architectural grading system. *Gynecol Oncol* 1998;**70**(1):2–12.
20. Changes in definitions of clinical staging for carcinoma of the cervix and ovary: International Federation of Gynecology and Obstetrics, . *Am J Obstet Gynecol* 1987;**156**(1):263–4.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**(5):373–83.

22. Khuri SF, Daley J, Henderson W, et al. The Department of Veterans Affairs' NSQIP: the first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. *Ann Surg* 1998;**228**(4):491–507.
23. Waljee JF, Windisch S, Finks JF, Wong SL, Birkmeyer JD. Classifying cause of death after cancer surgery. *Surg Innov* 2006;**13**(4):274–9.
24. Daley J, Khuri SF, Henderson W, et al. Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: results of the National Veterans Affairs Surgical Risk Study. *J Am Coll Surg* 1997;**185**(4):328–40.
25. Steyerberg EW, Eijkemans MJ, Harrell Jr FE, Habbema JD. Prognostic modelling with logistic regression analysis: a comparison of selection and estimation methods in small data sets. *Stat Med* 2000;**19**(8):1059–79.
26. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med* 1999;**18**(6):681–94.
27. Harrell Jr FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**15**(4):361–87.
28. Van Houwelingen JC, Le Cessie S. Predictive value of statistical models. *Stat Med* 1990;**9**(11):1303–25.
29. Chi DS, Franklin CC, Levine DA, et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. *Gynecol Oncol* 2004;**94**(3):650–4.
30. Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stages IIIC-IV epithelial ovarian cancer. *Gynecol Oncol* 2006;**103**(3):1083–90.
31. Venesmaa P, Ylikorkala O. Morbidity and mortality associated with primary and repeat operations for ovarian cancer. *Obstet Gynecol* 1992;**79**(2):168–72.
32. Alphs HH, Zahurak ML, Bristow RE, Diaz-Montes TP. Predictors of surgical outcome and survival among elderly women diagnosed with ovarian and primary peritoneal cancer. *Gynecol Oncol* 2006;**103**(3):1048–53.
33. Diaz-Montes TP, Zahurak ML, Giuntoli 2nd RL, et al. Surgical care of elderly women with ovarian cancer: a population-based perspective. *Gynecol Oncol* 2005;**99**(2):352–7.
34. Cloven NG, Manetta A, Berman ML, Kohler MF, DiSaia PJ. Management of ovarian cancer in patients older than 80 years of Age. *Gynecol Oncol* 1999;**73**(1):137–9.
35. Vergote I, De Wever I, Tjalma W, et al. Neoadjuvant chemotherapy or primary debulking surgery in advanced ovarian carcinoma: a retrospective analysis of 285 patients. *Gynecol Oncol* 1998;**71**(3):431–6.
36. Vergote I, Trope C, Amant F, et al. EORTC-GCG/NCIC-CTG Randomised trial comparing primary debulking surgery with neoadjuvant chemotherapy in stage IIIC/IV ovarian, fallopian tube and peritoneal cancer. In: 12th Biennal Meeting International Gynecologic Cancer Society. Bangkok, Thailand; 2008.
37. Schwartz PE, Chambers JT, Makuch R. Neoadjuvant chemotherapy for advanced ovarian cancer. *Gynecol Oncol* 1994;**53**(1):33–7.
38. Huober J, Meyer A, Wagner U, Wallwiener D. The role of neoadjuvant chemotherapy and interval laparotomy in advanced ovarian cancer. *J Cancer Res Clin Oncol* 2002;**128**(3):153–60.
39. Janda M, Youlden DR, Baade PD, Jackson D, Obermair A. Elderly patients with stage III or IV ovarian cancer: should they receive standard care? *Int J Gynecol Cancer* 2008;**18**(5):896–907.