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ORIGINAL RESEARCH

Impact of health-related quality of life (HRQoL) on short-term mortality in patients with recurrent ovarian, fallopian or peritoneal carcinoma (the NOGGO-AGO QoL Prognosis-Score-Study): results of a meta-analysis in 2209 patients

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Objective: Recurrent ovarian cancer is an incurable disease with variable but poor prognosis. Health-related quality of life (HRQoL) is a patient-reported outcome measure generally applied to measure effects of therapies. Our aim was the development and validation of a risk score for the prediction of short-term mortality using the combination of sociodemographic and clinical factors and HRQoL.

Methods: For exploratory and validation analysis, the North-Eastern German Society of Gynecological Oncology (NOGGO) and Working Group Gynecological Oncology (AGO) study databases were screened for trials. Only trials which obtained defined HRQoL measurements were included in the final analysis. Multivariable logistic regression analyses were used to identify risk factors and their weighting for the risk score. Modulation with cubic regression analyses revealed median survival and short-term mortality defined as 1-year mortality for each value.

Results: For exploration, 974 patients from three clinical studies of the NOGGO and for validation, 1235 patients from several clinical studies of the AGO were eligible. The risk score included platinum-free interval, performance status, age, global QoL and nausea/vomiting. Receiver operating characteristic analysis showed a good predictive value with an area under the curve of 0.81 for model 1 in the exploration and 0.74 in the validation. Short-term mortality in model 1 was 8.2%, 23.5% and 58.4% in the exploration sample, and 19.7%, 38.1% and 63.4% in the validation sample for patients under low, medium and high risk, respectively.

Conclusions: This risk score discriminates well between recurrent ovarian cancer patients under low, medium and high risk of short-term mortality. It may help to identify a risk group under high risk for short-term mortality that can be used for randomization in clinical trials and may support decision making for palliative chemotherapy.

Key words: recurrent ovarian cancer, quality of life, patient-reported outcome measures

INTRODUCTION

Recurrent ovarian cancer (rOC) is an incurable and chronic disease with poor prognosis. The median survival of platinum-resistant patients is 12-18 months and for platinum-sensitive patients about 3 years.[1,2] The estimation of the individual prognosis of a respective patient is important for therapeutic decision making. However, patient communication, especially on predictive and prognostic outcome measurements and their value remains challenging. A large international survey showed that most ovarian cancer patients want information on their individual prognosis in primary and recurrent disease to be as precise as possible.[3]

For decision making, platinum sensitivity and performance status are widely used.[4,5] Social epidemiological studies in the 1980s showed that self-reported health or health-related quality of life (HRQoL) variables have independent prognostic power for survival.[6,7] This could also be shown for several groups of patients including cancer patients.[8-11] In a review, almost all studies of different cancer types showed a significant relation of HRQoL variables with survival. The most important predictors were global QoL, functioning scales and symptoms such as fatigue, appetite

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loss and pain, even after adjusting for sociodemographic and clinical factors.[12] The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) summary score, physical functioning and global QoL were strong predictors for mortality in a large sample of nearly 7000 patients with 12 different cancer types.[13] However, there are conflicting data in ovarian cancer patients. Two studies revealed that physical well-being of the Functional Assessment of Cancer Therapy - General (FACT-G) or the treatment outcome index of the FACT-Ovarian at baseline are significant predictors of mortality.[14-16] In addition, another two trials demonstrated that all functioning scales of the EORTC QLQ-C30, except global QoL, were univariable and significantly related to mortality.[1,4] In contrast, Gupta et al.[17] could not show any significant association of functioning scales at baseline with mortality in ovarian cancer patients. In multivariable analyses adjusted for clinical factors, performance status, global QoL and cognitive functioning, physical functioning and abdominal/gastrointestinal problems remained significant predictors for survival.[1,4]

These different results may be attributed to the heterogeneous cohorts of primary and rOC patients with early and advanced stage disease. Also, in multivariable analyses, inconsistency may be caused by an intercorrelation of HRQoL variables and clinical variables complicating the identification of the most important predictors.[18] The aim of this study is the identification of prime predictors for short-term survival of only rOC patients in a large cohort from different controlled clinical trials and to create a risk score for this 1-year mortality, including HRQoL variables and clinical variables. This newly created North-Eastern German Society of Gynecological Oncology-Working Group Gynecological Oncology (NOGGO-AGO) QoL prognosis score was then validated in another independent large cohort from different controlled clinical trials of rOC patients. This is so far the first and largest trial trying to define a validated risk score-dependent prediction model for short-term mortality in rOC patients, including HRQoL measurements alongside clinical variables.

METHODS

Measures

Outcome. Short-term mortality was defined as 1-year mortality or death within 12 months after assessment of QoL. Censored cases with follow-up of <12 months were excluded from analysis of short-term mortality.

Sociodemographic and clinical variables. Age, body mass index (BMI), performance status [Eastern Cooperative Oncology Group (ECOG)], histology, grading, presence of ascites, tumor size (non-measurable, tumor size <5 cm, ≥5 cm) and preexisting diseases such as cardiovascular diseases, pulmonary diseases, gastrointestinal diseases, depression, pain or anemia (hemoglobin concentration) were derived from examination at study entry.

From tumor history, we included tumor stage at first diagnosis [International Federation of Gynecology and Obstetrics (FIGO)], number of relapses and platinum sensitivity. Platinum sensitivity was categorized as resistant (interval from end of last platinum-based chemotherapy until relapse <6 months), partially sensitive (interval 6-12 months) and sensitive (interval >12 months). For those cases only with a documented cut-off of 12 months, an interval from first diagnosis to randomization <12 months was categorized as platinum-resistant, an interval ≥15 months as partially sensitive for the first relapse, an interval <15 months as resistant and an interval >24 months as partially sensitive.

HRQoL. HRQoL was assessed before the start of treatment using the EORTC QLQ-C30. This 30-item questionnaire has been developed in several countries including Germany and Austria and has been validated in several cancer patients including ovarian cancer patients.[19,20] The EORTC QLQ-C30 is the most frequently used HRQoL instrument in clinical trials.[21] A global QoL scale, five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea and vomiting) and six single-item symptoms (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial impact) can be obtained from the questionnaire. All scales and single-item symptoms were constructed and transformed to values from 0 to 100 according to the recommendation of the EORTC QoL group.[22]

A summary score including all scales and symptoms (excluding the financial impact) can also be computed.[23] Higher values of functional scales, global QoL and the summary score indicate a better QoL, whereas higher values of the symptoms indicate a worse QoL.

Cohorts

Exploration set. Three studies of the NOGGO meta database of rOC with baseline assessment of QoL using EORTC QLQ-C30 were selected: Topotecan phase III, Hector and TRIAS.

Topotecan phase III study—non-platinum topotecan combinations versus topotecan alone for rOC. This phase III trial compared topotecan monotherapy with two topotecan combinations, topotecan-etoposide and topotecan-gemcitabine, in recurrent epithelial ovarian cancer patients after primary surgery and first-line platinum-based chemotherapy. Between September 1999 and November 2004, 502 platinum-resistant rOC patients, according to the trial protocol defined as progressive disease within 12 months after end of first-line therapy, and platinum-sensitive patients were included. The primary objective of this randomized, multicenter trial was the overall survival. Secondary endpoints were progression-free survival, response rates, toxicity and QoL.[24]

Hector study—carboplatin in combination with topotecan versus standard platinum-based combinations in rOC. In this phase III trial, 550 patients with platinum-sensitive ovarian, peritoneal and fallopian tube carcinoma were included between March 2007 and December 2009. They were randomly assigned to receive either topotecan and carboplatin or a standard platinum-based combination with paclitaxel, gemcitabine or pegylated doxorubicin. The primary endpoint was progression-free survival and secondary endpoints were overall survival, response rates, toxicity and QoL.[25]

TRIAS—a randomized, double-blind, placebo-controlled, multicenter phase II study to assess the efficacy and safety of sorafenib added to standard treatment with topotecan in patients with platinum-resistant rOC. In this double-blind, placebo-controlled phase II trial, the combination of topotecan with sorafenib was compared with the combination of topotecan with a placebo. From January 2010 until September 2013, 174 patients with platinum-resistant rOC, defined as progression within 6 months after platinum-based therapy, were randomly assigned to receive topotecan with sorafenib or with placebo. The primary endpoint was progression-free survival and secondary endpoints were overall survival, response rates, toxicity and QoL.[26]

Overall, 974 (80%) out of 1220 patients with rOC with baseline assessment of the EORTC QLQ-C30 from the three trials could be included (Table 1). Six cases from Hector were excluded due to double randomization.

Validation set. The validation sample was selected from the AGO (Arbeitsgemeinschaft gynäkologische Onkologie) database. The database was screened for studies with rOC patients, with assessment of EORTC QLQ-C30 at baseline and data about age at randomization, performance status (ECOG), survival and platinum sensitivity categorized as resistant, partially sensitive or sensitive. Nine studies recruiting from August 1996 until September 2014 could be identified and fulfilled inclusion criteria (for details see publication list on http://85.158.4.112/ago-ovar.de/profil-publizierte-studien-16.html). A total of 1235 out of 1437 patients (86%) filled out the EORTC QLQ-C30 questionnaire and were eligible for analysis. Included trials were: Ovar 2.1 ($n = 66$); Ovar 2.2 ($n = 46$), Ovar 2.3 ($n = 280$), Ovar 2.5 ($n = 321$), Ovar 2.7 ($n = 31$), Ovar 2.9 ($n = 238$), Ovar 2.15 ($n = 52$), Ovar 2.20-P1 ($n = 44$) and Ovar 2.20-P2 ($n = 147$).

Statistics

For continuous variables, receiver operating characteristic (ROC) curve analyses were applied to find cut-off values to discriminate patients with short-term mortality from those with longer survival. Established cut-offs were preferred when the best cut-off computed was nearby.

Univariate logistic regression analyses were used to assess the risk of short-term mortality for categorical and continuous variables. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were computed for HRQoL variables per 10 points reflecting clinically important differences.[27] Multivariate stepwise logistic regression models ($p_{in} = 0.05$ and $p_{out} = 0.10$) were used to identify the most important independent predictors of short-term mortality and to receive the weights for computation of the risk score. The risk score was categorized into low, medium and high risk for short-term mortality using ROC curve analysis. Sensitivity, specificity, positive predictive value and negative predictive value were computed.

Kaplan—Meier survival curves were computed to show the differences in survival of the three risk groups graphically.

To approximate 1-year mortality rates and median survival for each risk score value, we modulated the mortality rate and the median survival derived from several Kaplan—Meier analyses with the corresponding mean risk score using cubic regression models. The 95% CIs were computed for both samples separately. The more extreme values of both samples were used to show the probable range of 1-year mortality rates and the median survival for each risk score value.

All analyses were done with IBM SPSS Statistics 25 (SPSS an IBM company, Chicago, IL). A two-sided P value of <0.05 was considered statistically significant.

RESULTS

Patients' characteristics

Median age of the 974 eligible patients was 61 years, ranging from 25 to 84 years, one-third were overweight (BMI 25-30 kg/m^2) and 23% obese (BMI $>$ 30 kg/m^2). Most of the patients had advanced-stage disease at first diagnosis (85%), with serous histology (76%) and poorly differentiated (G3) tumor (58%). The majority of the patients had their first recurrence (83%). Four hundred and fourteen patients (43%) had platinum-sensitive, 257 (26%) platinum-resistant and 228 (23%) partially sensitive carcinoma. Only 47 patients (5%) had impaired performance status (ECOG $>$ 1). One-year mortality was 31% with 10% cases not eligible (censored within the first 12 months).

The patients of the validation sample were of similar age, with most of them aged $<$65 years (62%). The majority had advanced (69%), serous (54%) and poorly differentiated (56%) ovarian cancer. The percentage of platinum-sensitive patients (45%) was similar and of platinum-resistant patients (21%) lower than in the exploration sample. Only a few patients (6%) had an impaired performance status of ECOG $>$ 1 (6%). One-year mortality was higher (35%) than in the exploration sample. Patients' characteristics are shown in detail in Table 1.

Physical and social functioning, global QoL and C30 summary score were higher, and some symptoms, dyspnea, fatigue and pain, were lower in the validation sample than in the exploration sample.

Table 1. Patients' characteristics

Characteristics	Exploration sample ($N = 974$)		Validation sample ($N = 1235$)	
	n	%	*n*	%
Age (years)				
<65	607	62.3	834	67.5
65-74	302	31.0	348	28.2
≥75	65	6.7	52	4.2
Unknown			1	0.1
Study inclusion				
1996-1999	0		236	19.1
2000-2009	841	86.3	756	61.2
2010-2014	133	13.7	243	19.7
Recurrence				
First	808	83.0		
Second	147	15.1		
Third	19	2.0		
FIGO stage				
I	65	6.7	35	2.8
II	64	6.6	304	24.6
III	690	70.8	600	48.6
IV	134	13.8	271	21.9
Unknown	21	2.2	25	2.0
Histology				
Serous	740	76.0	682	55.2
Mucinous	26	2.7	22	1.8
Endometrioid	72	7.4	57	4.6
Others/not specified	136	13.9	474	38.4
Grading				
Well differentiated	38	3.9	51	4.1
Moderately differentiated	297	30.5	339	27.4
Poorly differentiated	569	58.4	709	57.4
Undifferentiated	0		17	1.4
Grade cannot be assessed	9	0.9	39	3.2
Unknown	61	6.3	80	6.5
Platinum-free interval				
<6 months	257	26.4	267	21.6
6-12 months	228	23.4	405	32.8
>12 months	414	42.5	546	44.2
Classification not possible	75	7.7	17	1.4
ECOG				
0	454	46.6	597	48.3
1	467	47.9	542	43.9
2	47	4.8	79	6.4
3	0		2	0.2
Unknown	6	0.6	15	1.2
BMI				
<25	421	43.2		
25-30	327	33.6		
>30	223	22.9		
Unknown	3	0.3		
Anemia				
Hb <7.4 mmol/l	369	37.9		
Hb ≥7.4 mmol/l	581	59.7		
Unknown	24	2.5		
Ascites				
Yes	290	29.8		
No	554	56.9		
Unknown	130	13.3		
Tumor size				
Only non-measurable	252	25.9		
<5 cm	348	35.7		
≥5 cm	175	18.0		
Unknown	199	20.4		
Preexisting disease				
CVD	422	43.3		
Diabetes	60	6.2		
Gastrointestinal	54	5.5		
Depression	97	10.0		
Pain	307	31.5		
Respiratory	46	4.7		

Continued

Table 1. Continued				
Characteristics	**Exploration sample ($N = 974$)**		**Validation sample ($N = 1235$)**	
	n	%	*n*	%
Mortality				
<12 months	268	30.7	409	35.0
≥12 months	605	69.3	759	65.0
Not applicable	101		67	

BMI, body mass index; CVD, cardiovascular disease; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

Exploration

Univariate risks for short-term mortality. Several of the sociodemographic and clinical variables were univariate associated with short-term mortality. The highest risks were observed for platinum-resistant patients (OR 8.3, 95% CI 5.6-12.3) and partially sensitive patients (OR 1.6, 95% CI 1.0-2.4) compared with platinum-sensitive patients, for ECOG > 1 (OR 6.7, CI 3.4-13.3) and ECOG = 1 (OR 2.2, CI 1.6-3.0) compared with ECOG 0, presence of ascites (OR 2.8, CI 2.0-3.9), and age >75 years (OR 2.7, CI 1.5-4.6) compared with age <65 years. For BMI and number of relapses, no predictive value was observed.

All functioning and symptom scales of the EORTC QLQ-C30, except diarrhea, cognitive functioning and financial difficulties, were predictive for 1-year mortality. The strongest predictor was the summary score (OR per 10 points 0.77, 95% CI 0.69-0.87) followed by global QoL (OR per 10 points 0.80, 95% CI 0.75-0.86) and physical functioning (OR per 10 points 0.83, CI 0.78-0.88). The strongest effect was observed for the symptoms nausea/vomiting (OR 1.3, 95% CI 1.2-1.3), fatigue (OR 1.2, CI 1.1-1.3) and appetite loss (OR 1.2, CI 1.1-1.2).

Multivariate logistic regression. In the multivariate stepwise logistic regression model 1, platinum sensitivity was included in the first step, global QoL in the second step, ECOG in the third step, nausea/vomiting in the fourth step and age in the fifth step. In model 2, global QoL and nausea/vomiting were substituted with the QLQ-C30 summary score (Table 2).

The logistic regression formulas were used to calculate risk indices and subsequently the risk score, the probability of short-term mortality in %:

Table 2. Logistic regression for short-term mortality (stepwise $p_{in} = 0.05$; $p_{out} = 0.10$)

Predictor	B	*P*	OR	Lower	Upper	B	*P*	OR	Lower	Upper
Age (years)		0.005					0.002			
65-74	0.45	0.029	1.56	1.05	2.33	0.51	0.016	1.67	1.10	2.54
≥75	0.97	0.005	2.63	1.35	5.14	1.14	0.003	3.12	1.49	6.54
Platinum-free interval		<0.001					<0.001			
<6 months	2.27	<0.001	9.64	6.20	15.00	2.15	<0.001	8.59	5.46	13.51
6-12 months	0.55	0.025	1.73	1.07	2.80	0.38	0.139	1.46	0.88	2.42
ECOG		<0.001					<0.001			
ECOG = 1	0.44	0.025	1.56	1.06	2.29	0.54	0.009	1.71	1.14	2.57
ECOG > 1	1.77	<0.001	5.89	2.63	13.17	2.17	<0.001	8.76	3.56	21.52
Global QoL	−0.17	0.000	0.84	0.77	0.92					
Nausea and vomiting	0.13	0.002	1.14	1.05	1.24					
C30 summary score						−0.19	0.000	0.83	0.75	0.92
Constant	−1.76	<0.001	0.17			−1.18	0.006	0.31		

Short-term mortality for the risk groups

Risk score	Exploration			Validation		
	N	Short-term mortality		*N*	Short-term mortality	
		%	95% CI		%	95% CI
Model 1						
Low (<15%)	329	8.5	5.5-11.5	533	19.7	16.3-23.1
Medium (15%-40%)	227	24.2	18.6-29.8	318	38.1	32.8-43.4
High (>40%)	222	61.7	55.3-68.1	246	63.6	57.6-69.6
Model 2						
Low (<15%)	310	10.3	6.9-13.7	495	20.2	16.7-23.7
Medium (15%-40%)	192	22.4	16.5-28.3	294	39.5	33.9-45.1
High (>40%)	199	61.3	54.5-68.1	211	64.9	58.5-71.3

QoL scores were analyzed per 10 points. Model 1 with combination of QoL scores. Model 2 with QoL summary score.
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; QoL, quality of life; B, beta.

Model 1:

$$\text{Risk index 1} = -1.76 + 0.45 \times (\text{age } 65-74 \text{ years}) + 0.97 \times (\text{age} \geq 75 \text{ years}) + 2.27 \times (\text{platinum-resistant}) + 0.55 \times (\text{partially sensitive}) + 0.44 \times (\text{ECOG} = 1) + 1.77 \times (\text{ECOG}>1) - 0.17 \times (\text{GQoL10}) + 0.13 \times (\text{nausea10}).$$

$$\text{Riskscore1} = [\text{EXP}(\text{risk index 1})]/\{1 + [\text{EXP}(\text{risk index 1})]\} \times 100.$$

Model 2:

$$\text{Risk index 2} = -1.18 + 0.51 \times (\text{age } 65-74 \text{ years}) + 1.14 \times (\text{age} \geq 75 \text{ years}) + 2.15 \times (\text{platinum-resistant}) + 0.38 \times (\text{partially sensitive}) + 0.54 \times (\text{ECOG} = 1) + 2.17 \times (\text{ECOG}>1) - 0.19 \times (\text{C30Summary10}).$$

$$\text{Riskscore2} = [\text{EXP}(\text{risk index 2})]/\{1 + [\text{EXP}(\text{risk index 2})]\} \times 100.$$

ROC analysis of the two risk scores showed a good predictive value with an area under the curve (AUC) of 0.81 for model 1 and 0.80 for model 2. The sample was divided into patients under low risk with a risk score <15 ($n = 329$, 42%), medium risk with a risk score of 15-40 ($n = 227$, 29%) and high risk with a risk score of >40 ($n = 222$, 29%). The distribution of the three groups was similar for model 2 (Table 2). One-year mortality was 8.5% for low risk, respectively, 10% for low risk according to model 2, for medium risk 24%, respectively, 22% and for high risk 62%, respectively, 61%. Both models showed good specificity and negative predictive value of 85% and acceptable sensitivity and positive predictive value of 62% for the group under high risk.

Validation

ROC analysis of the two risk scores showed a satisfactory predictive value a little lower than in the exploration sample, with an AUC of 0.74 for model 1 and 0.73 for model 2. The high-risk group was smaller (22% versus 21%) and the low-risk group greater (49% versus 49.5%) than in the exploration sample. One-year mortality for the low-risk group was ($n = 533$ versus $n = 495$ for model 2) 20%, for the medium-risk group ($n = 318$, 18% versus $n = 294$) 38% versus 39.5% and for the high-risk group ($n = 246$ versus $n = 211$) 63% versus 65%. Both models showed a good specificity of >85% for high risk, a satisfactory negative predictive value of 73% and an acceptable positive predictive value of 63% versus 65%, but sensitivity was low with 41% versus 39%.

Survival analyses and calibration

For further analyses, we focused on risk score 1 with global QoL and nausea/vomiting and we excluded patients with a start of treatment before the year 2000, because they received more contemporary medication, and the results may be more representative for the last years.

The survival curves of the different risk groups were clearly distinguished both in the exploration sample and in the validation sample (Figure 1A and B). Median survival was 30 months (95% CI 26-34 months), 22 months (95% CI 19-25 months) and 10 months (95% CI 9-11.5 months) for low, medium and high risk, respectively, in the exploration sample. In the validation sample, the median survival was shorter: 23 months (95% CI 21-25 months), 17 months (95% CI 15-19 months) and 8.5 months (95% CI 7-10 months) for patients under low, medium or high risk, respectively.

The short-term mortality in all risk groups of the exploration sample was equivalent to the mean risk score (probability of short-term mortality), only under high risk was the mean risk score a little bit higher (61%) than the short-term mortality (58%, 95% CI 52%-65%). The estimated 1-year mortality of 63% (95% CI 56%-70%) was equivalent to the mean risk-score of 62.5% in the validation sample only in the patient group under high risk. However, in the groups under low and medium risk, the estimated short-term mortality was 19% (95% CI 15%-23%) and 35% (95% CI 30%-41%) significantly higher than the mean risk score of 9% and 23%, respectively.

After modulation using cubic regression analyses, we approximated lower and upper limits for short-term mortality and median survival for each value of the risk score 1 for both samples separately. The extreme values of both are shown in Figure 2. Up to a risk score of 60%-65% the upper limit for the median survival and the lower limit for the short-term mortality of the exploration sample and the lower limit for median survival and the upper limit for short-term mortality of the validation sample were used; this was the other way round for a higher risk score.

The range of lower and upper limits of short-term mortality was 17%-18% for a risk score between 10% and 60%, and of median survival 5 months for a risk score between

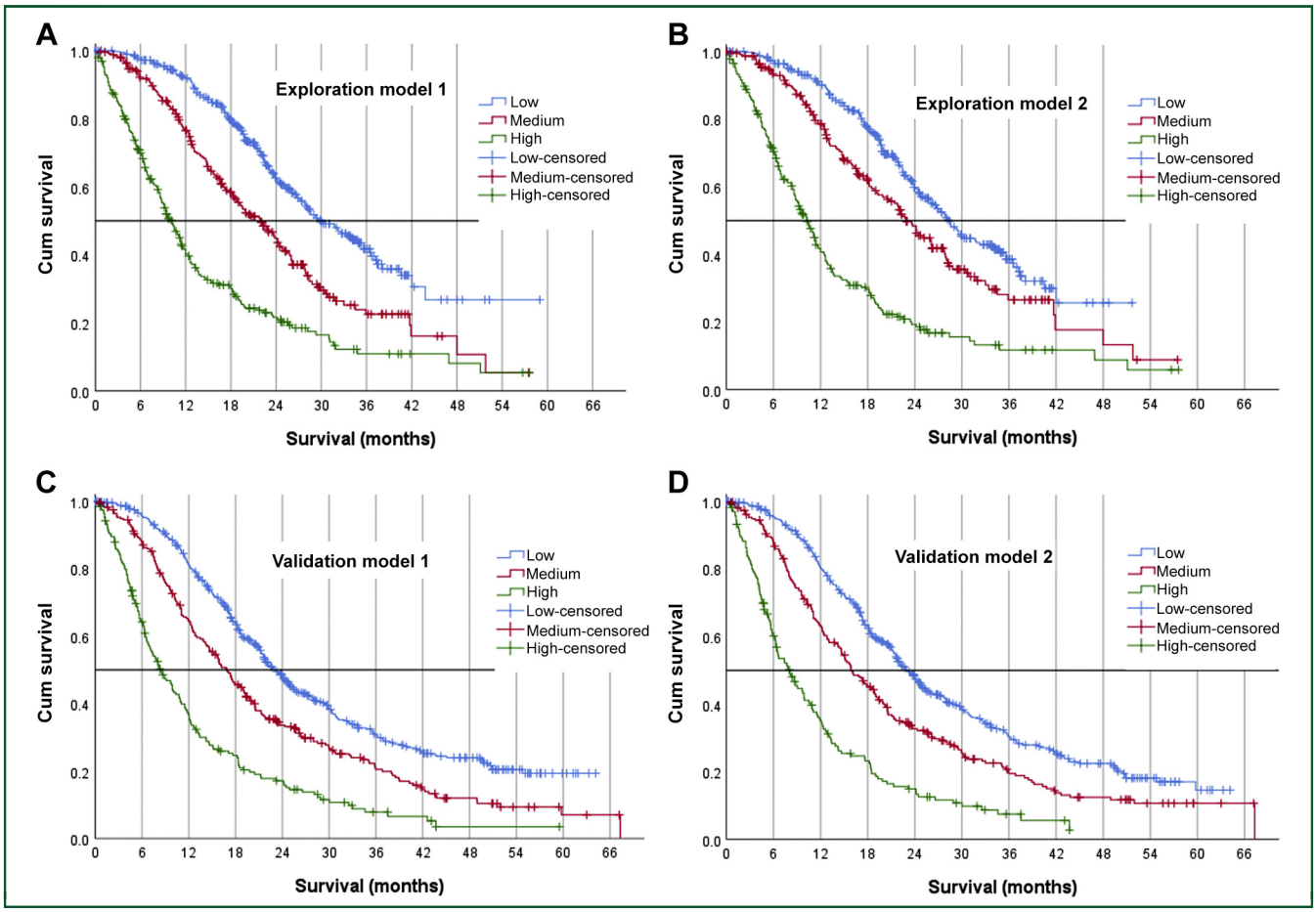

Figure 1. **Survival of patients under low, medium and high risk of the exploration sample (A, B) and the validation sample (C, D) for model 1 and model 2.**

40% and 60%. A risk score of 10%, 50% or 70% was associated with a short-term mortality of 7%-25%, 40%-57% or 57%-79%, respectively, and a median survival of 20-37, 11-16 or 5-12 months, respectively.

DISCUSSION

A risk score can be computed with the EORTC QLQ-C30 global QoL and its nausea/vomiting symptom scale in combination with platinum sensitivity, ECOG and age with good prediction (AUC = 0.81) in the exploration cohort and satisfactory prediction in the validation cohort (AUC = 0.74). The second model with the QLQ-C30 summary score instead of global QoL and nausea/vomiting was only a little worse (AUC 0.80 versus 0.73). The NOGGO-AGO QoL-prognosis score clearly discriminates rOC patients under low, medium and high risk for short-term survival. The high-risk group shows good specificity, satisfactory to good negative predictive value, acceptable positive predictive value with low to acceptable sensitivity.

Platinum sensitivity is the most important single predictor of survival but is not good enough alone for precise estimation of life expectancy. Although the definition for platinum sensitivity was recently modified,[28] the usefulness of platinum resistance defined as <6 months before progression was confirmed by a subgroup analysis, with no difference in survival between platinum-free intervals <3 months and 3-6 months (data not shown). In two studies of platinum-sensitive patients, a platinum-free interval of <12 months was included in nomograms for prediction of overall survival or progression-free survival.[29,30] The platinum-free interval categorized in three groups (<6 months, 6 to <12 months and ≥12 months) in an additional analysis showed a better predictive value than the continuous variable of completed months (data not shown).

In the aforementioned studies, ECOG PS was also significantly predictive for overall survival, as well as for primary advanced ovarian cancer,[15,31,32] even in combination with global QoL[4] and for platinum-resistant rOC patients.[33] Only a non-significant trend was observed in two studies with few cases of ECOG PS > 1.[16,34]

Age is the weakest but significant predictor for short-term mortality in our models. Other findings of the influence of age on survival of ovarian cancer patients are inconsistent. Some studies use age only for adjustment in their multivariable analysis without reporting the effect (e.g. von Gruenigen et al.[14] and Gupta et al.[35]), some showed a significant relation[13,15,31,32] and others no association of age and survival.[4,34] Our results showed no steady increase of mortality with increasing age; up to the age of 60 years the mortality of ovarian cancer does not increase. However, for older patients there is a higher risk of short-term mortality, especially for those older than 75 years.

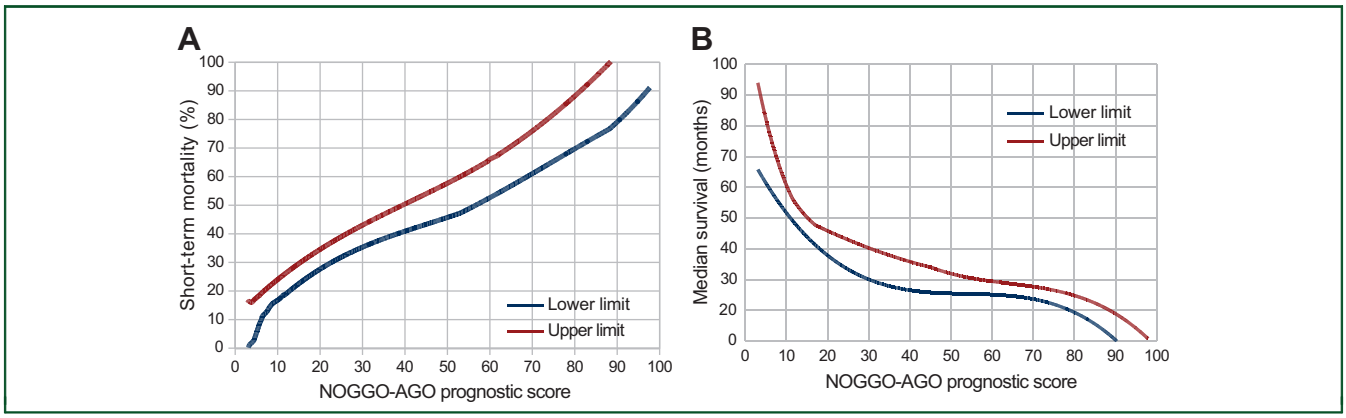

Figure 2. NOGGO-AGO prognostic score and short-term mortality (A) or median survival (B), the more extreme limit of the 95% CI in the exploration or validation sample.

The inclusion of HRQoL measures improved the prediction of survival significantly; global QoL or the EORTC QLQ-C30 summary score were the second factor included in our stepwise regression models. Patient-reported symptoms and clinical physician-reported symptoms differ, and both contribute independently to a better prediction of survival.[36] HRQoL might give a better more sensitive account of individual well-being and might indicate personal characteristics like coping strategies, depression and anxiety, which are both related to patient-reported QoL and to mortality.[13]

The QLQ-C30 summary score is the strongest predictor, followed by global QoL when only a single QoL-measure was analyzed in multivariable regression models (also in a large study with different cancer types by Husson et al.[13]). Other studies using the EORTC QLQ-C30 also showed a significant relation of survival and nausea/vomiting[13,34,37] in ovarian cancer patients or abdominal/gastrointestinal problems measured by EORTC QLQ Ovar28 in platinum-resistant and platinum-sensitive rOC patients.[1,30] Despite improved antiemetic medication, nausea/vomiting remained a great problem for most ovarian cancer patients impeding daily life activities.[38] These findings highlight the importance of nausea/vomiting for rOC patients. Nausea/vomiting is not of minor concern; in fact these patient-reported symptoms are related to mortality. Physicians should pay more attention to abdominal problems. Adequate antiemetic comedication, less toxic chemotherapy, counseling on nutrition and intake of probiotics[39] may help to improve patients' well-being and further extend life expectation.

The predictive score in this form with validated acceptable goodness of fit can already be used. The NOGGO-AGO QoL prognosis score is developed in a large sample of >900 rOC patients eligible for analysis and validated in a sample of >1200 rOC patients with more early stages, less serous histology and platinum resistance and better HRQoL in some aspects than in the exploration sample. Many potential risk factors such as FIGO stage, grading, histology, ascites, tumor size, preexisting diseases and BMI, and the well-validated and most frequently used HRQoL measure the EORTC QLQ-C30 in addition were included in the exploration process. Inclusion only of rOC patients in clinical trials is on one hand an advantage, because they received state-of-the-art therapy, but on the other hand they may not be representative for all rOC patients. Mostly patients with good ECOG PS of 0/1 participate, and some preexisting diseases also lead to exclusion from participation. Patients not responding to QoL assessment may have a worse HRQoL than patients who filled out the questionnaire. But in the exploration sample, there was no difference in short-term mortality between patients responding to baseline HRQoL assessment and those not responding.

Patients with rOC represent an inhomogeneous group; they vary in many characteristics. Therefore, the prediction of short-term mortality and median survival with the risk score is derived from two large samples separately. The differences between these two samples with different mortality rates result in a range of a minimal 5 months for median survival and 17% for 1-year mortality for the corresponding value of the risk score. However, the majority of the included patients had their first relapse, so the score could be less valid in second or third relapses. This represents a limitation of the study. Nonetheless, the multivariate regression analyses showed that the number of relapses as a single marker has no predictive value.

Although the accuracy and differentiation of prediction with the risk score outweighs that of platinum sensitivity alone, there is room for improvement. Other well-known sociodemographic factors, such as living with a partner or socioeconomic status,[40,41] may possibly improve the predictive value. In some studies the course of HRQoL was predictive for survival.[14,15,17] Furthermore, it should be mentioned that the obtained data are from the era before the introduction of PARP inhibitors, which could be a limitation of the present analysis.

In conclusion, the risk score from model 1 discriminates well between low, medium and high risk for short-term mortality of rOC patients, and the prediction of short-term mortality and median survival is precise within a range of a minimal 17% or 5 months, respectively. The NOGGO-AGO QoL prognosis score can be used for stratification or randomization in clinical trials and for

identification of a group under high risk for short-term mortality. As a concrete consequence, clinicians can balance the impact of systemic therapy against supportive and symptom-led treatment. This may also help the decision making for chemotherapy or best supportive care and more precise information of further life expectation for rOC patients. This could help both physicians and patients in therapy decision making. Further studies are warranted to also validate this score for targeted therapies.

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DISCLOSURES

The authors have declared are no conflicts of interest.

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