GYNECOLOGY

Development and validation of a risk-calculator for adverse perioperative outcomes for women with ovarian cancer

Stephanie Cham, MD; Ling Chen, MD, MPH; Caryn M. St. Clair, MD; June Y. Hou, MD; Ana I. Tergas, MD, MPH; Alexander Melamed, MD, MPH; Cande V. Ananth, PhD, MPH; Alfred I. Neugut, MD, PhD; Dawn L. Hershman, MD; Jason D. Wright, MD

BACKGROUND: Primary cytoreduction followed by platinum-based chemotherapy is the primary treatment for advanced ovarian cancer. However, neoadjuvant chemotherapy followed by interval debulking is an alternative option, particularly in those who may be poor surgical candidates.

OBJECTIVE: The objective of this study was to determine factors associated with short-term, significant perioperative morbidity and mortality for women undergoing surgery for ovarian cancer and to create a nomogram to predict the risk of adverse perioperative outcomes.

STUDY DESIGN: We used the National Surgical Quality Improvement Program database to identify women with ovarian, fallopian tube, or primary peritoneal cancer who underwent surgery from 2011 to 2015. Demographic factors, clinical characteristics, comorbidity, functional status, and the extent of surgery were used to predict the risk of severe perioperative complications or death using multivariable models. Multiple imputation methods were employed for missing data. A nomogram was developed based on the final model. The discrimination ability of the model was assessed with a calibration plot and discrimination concordance index.

RESULTS: We identified a total of 7029 patients. Overall, 5.8% of patients experienced a Clavien-Dindo IV complication, 9.8% of patients were readmitted, 3.0% of patients required a reoperation, and 0.9% of patients died within 30 days. Among the baseline variables assessed, increasing age, emergent surgery, ascites, bleeding disorder, low albumin, higher American Society of Anesthesiology classification score, and a higher extended procedure score were associated with serious perioperative morbidity or mortality. Of these factors, performance of $\geq$3 cytoreductive procedures (adjusted odds ratio 4.53, 95% confidence interval 3.01−6.82), American Society of Anesthesiology classification score $\geq$ class 4 (adjusted odds ratio 2.89, 95% confidence interval 1.17−7.14), bleeding disorder (adjusted odds ratio 2.73, 95% confidence interval 1.82−4.10), and age $\geq$80 years (adjusted odds ratio 2.46, 95% confidence interval 1.66−3.63) were most strongly associated with risk of an event. The final nomogram included the above variables and had an internal discrimination concordance index of 0.71, with accurate predictions in an internal validation set, indicating a 71% correct identification of patients across all possible pairs.

CONCLUSION: Women undergoing surgery for ovarian cancer are at significant risk for the occurrence of adverse perioperative outcomes. Using readily identifiable characteristics, this nomogram can predict adverse outcomes.

Key words: complication, cytoreduction, debulking, ovarian cancer

The primary treatment for advanced-stage ovarian cancer is cytoreductive surgery followed by adjuvant platinum-based chemotherapy. Optimal or complete resection of disease is associated with improved survival outcomes.[1−4] In addition to hysterectomy, bilateral salpingo-oophorectomy, and omentectomy, complete resection of disease may also require radical surgery, including bowel resection, diaphragm stripping, splenectomy, liver resection, and other complex procedures.[5−9]

While aggressive surgery may be associated with increased overall survival, this benefit must be balanced against the significant risk of perioperative morbidity and mortality associated with radical cytoreductive surgery.[10,11] Patients diagnosed with ovarian cancer are often elderly, have multiple comorbidities, and may experience less benefit from cytoreduction than is reported in clinical trials of highly selected patients.[11−15] Surgical complications in women with ovarian cancer are associated with significant pain and suffering, are costly to treat, and may lead to delay in the receipt of adjuvant chemotherapy.[16]

There has been an increasing interest in identifying patients who may be poor surgical candidates, given the risks associated with surgery. Neoadjuvant chemotherapy (NACT) followed by interval debulking is an alternative to primary cytoreduction. In clinical trials, NACT has been associated with similar survival as primary cytoreduction but is accompanied by significantly less perioperative morbidity and mortality.[17] A number of models have attempted to predict perioperative morbidity and mortality as a method of identifying patients who may benefit from NACT. Most models have used single-institution data to determine factors associated with short-term morbidity and mortality and have included factors such as age, American Society of Anesthesiology (ASA) classification score, surgical complexity, and tumor characteristics, such as stage, grade, and histology.[18−24]

Cite this article as: Cham S, Chen L, St Clair CM, et al. Development and validation of a risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019;220:571.e1-8.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2019.02.019

AJOG at a Glance

Why was this study conducted?

Prediction of patients who are at high risk of adverse perioperative outcomes may help stratify patients between primary debulking and neoadjuvant chemotherapy.

Key findings

Overall, 5.8% of patients experienced a Clavien-Dindo IV complication and 0.9% of patients died within 30 days. Among the baseline variables assessed, increasing age, emergent surgery, ascites, bleeding disorder, low albumin, higher American Society of Anesthesiology classification score, and a higher extended procedure score were associated with serious perioperative morbidity or mortality and were included in our nomogram. The final nomogram had an internal discrimination concordance index of 0.71.

What does this add to what is known?

Using readily identifiable characteristics, this validated nomogram may help predict patients at high risk of adverse outcomes and assist in stratifying ovarian cancer patients to primary debulking or neoadjuvant chemotherapy.

The objective of our study was to use a large, national dataset to determine factors associated with short-term, significant perioperative morbidity and mortality and to create a nomogram to predict the risk of adverse perioperative outcomes. Using this nomogram, we hope to create a prediction tool for patients who are being considered for primary debulking or NACT.

Materials and Methods

We examined patients who underwent surgery for primary ovarian, fallopian tube, or peritoneal cancer in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database between 2011 and 2015. NSQIP collects preoperative, intraoperative, and 30-day postoperative data of patients undergoing major surgical procedures from participating hospitals to measure surgical quality. Data are abstracted from medical charts under a systematic sampling process that requires each participating hospital to submit data from 42 of the 46 8-day cycles equally spaced throughout the year. Data quality is ensured by conducting inter-rater reliability audits regularly.[25]

All patients in our cohort underwent oophorectomy with or without hysterectomy. For patients who had additional procedures for cytoreduction, we developed a surgical complexity score. For the procedure score, we assigned 1 point each for lymph node dissection; small bowel, colon, rectosigmoid, liver, bladder, or diaphragm resection; and debulking. Each patient was thereby classified with a score of 0, 1, 2, or $\geq$3.

Demographic characteristics included age (<50, 50−59, 60−69, 70−79, ≥80 years), race/ethnicity (white, black, other), and whether the surgery was elective (yes, no). For each woman, the following preoperative conditions were recorded: body mass index (BMI; normal <25 kg/m^2, overweight 25 to <30 kg/m^2, obese ≥30 kg/m^2), diabetes mellitus (insulin-dependent or non-insulin-dependent), tobacco use within 1 year, history of severe chronic obstructive pulmonary disease, ascites, congestive heart failure within 30 days before surgery, hypertension requiring medication, bleeding disorder, ASA classification score (≤1, 2, 3, ≥4), serum albumin (>4, 3.5−4, <3.5 g/dL), and hematocrit (<36%, ≥36%). Year of operation, length of stay (0, 1, 2, ≥3 days), and discharge status (home, dead, facility) were reported descriptively. Missing data were reported as the "unknown" category. The primary outcome was Clavien-Dindo IV complications (including postoperative sepsis, shock, cardiac arrest, myocardial infarction, pulmonary embolism, ventilation >48 hours, or unplanned intubation) or death within 30 days after surgery.[26]

Fifteen predictors were initially evaluated for statistically significant associations (P value < .05) with the outcome using bivariate logistic regression models. Missing data were noticed in race/ethnicity, elective surgery, BMI, albumin, and hematocrit and were accounted for using multiple imputation with chained equations with $M = 100$ imputations. The discriminant function method was used to impute the categorical variables of race/ethnicity and elective surgery. Height, weight, albumin, and hematocrit were imputed using linear regression models assuming normality, and then categorized as BMI, albumin, and hematocrit groups. To avoid bias, all the variables in the analysis model, including height, weight, each cytoreductive procedure (yes/no) from the procedure score, and the outcome variable were included in the imputation model, along with year of operation.[27,28] Race, BMI, preoperative diabetes mellitus, tobacco use, chronic obstructive pulmonary disease, and congestive heart failure were excluded because of P values ≥ .05. All 2-way interaction terms were evaluated between the remaining predictors. The interactions between ascites and hematocrit, and between hypertension and bleeding disorder, had a P value < .1, but neither showed clinically differentiable odds ratios; therefore, only the main predictors were included in the multivariable model. Hypertension and hematocrit were no longer significant (P value < .05) after adjusting for the other covariates and were excluded. The final model included procedure score, age, elective surgery, preoperative ascites, bleeding disorder, albumin, and the ASA classification score.

A nomogram was developed based on the final model. The discrimination ability of the model was reported as the calibration plot with the 95% confidence interval (CI). The concordance index (C-index) was reported as a measure of internal validation using both 10-fold cross-validation repeated for 20 times, and bootstrap validation of 200 resamples the same size as the original cohort with replacement. We performed sensitivity analysis with complete cases excluding patients with missing data, or

classifying them as the unknown group. All analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

We identified a total of 7029 patients for whom surgeries were performed between 2011 and 2015. Age was well represented across all groups, with 19.4% of patients aged <50 years, 26.5% 50–59 years, 29.3% 60–69 years, and 24.8% ≥70 years (Table 1). Most patients were white, overweight or obese, nonsmokers, and nondiabetic. Preoperatively, most patients had no ascites, had a normal albumin, and were not anemic. Most patients underwent 1 extended procedure (49.7%), with the most common being debulking (49.8%) and lymph node dissection (43.4%), followed by rectosigmoid resection (6.8%), other large bowel resection (3.9%), and small bowel resection (3.1%). Postoperatively, most patients had a hospital length of stay of 3 days or longer and 92.4% of patients were discharged home (Table 1).

Overall, 5.8% of patients experienced a Clavien-Dindo IV complication, 9.8% of patients were readmitted, and 3.0% of patients required a reoperation. Of the Clavien-Dindo IV complications, the most common were sepsis (2.4%) and pulmonary embolism (1.7%) (Table 2). The perioperative mortality rate within 30 days of surgery was 0.9%.

Among the baseline variables assessed in multivariable models, increasing age, emergent surgery, ascites, bleeding disorder, low albumin, higher ASA, and a higher extended procedure score were significantly associated with serious perioperative morbidity or mortality. Of these factors, performance of ≥3 cytoreductive procedures (adjusted odds ratio [aOR] 4.53, 95% CI 3.01–6.82), ASA ≥ class 4 (aOR 2.89, 95% CI 1.17–7.14), bleeding disorder (aOR 2.73, 95% CI 1.82–4.10), and age ≥80 years old (aOR 2.46, 95% CI 1.66–3.63) were most strongly associated with risk of an event (Table 3).

The final nomogram included the above variables and had an initial

TABLE 1
Descriptive statistics of patient characteristics

	N	%
All	7029	(100.0)
Year of operation		
2011	878	(12.5)
2012	1082	(15.4)
2013	1510	(21.5)
2014	1606	(22.9)
2015	1953	(27.8)
Age (in years)		
<50	1366	(19.4)
50–59	1864	(26.5)
60–69	2057	(29.3)
70–79	1291	(18.4)
≥80	451	(6.4)
Race/ethnicity		
White	5380	(76.5)
Black	445	(6.3)
Other	384	(5.5)
Unknown	820	(11.7)
Elective surgery		
Yes	6370	(90.6)
No	632	(9.0)
Unknown	27	(0.4)
BMI		
Normal	2435	(34.6)
Overweight	2056	(29.3)
Obese	2495	(35.5)
Unknown	43	(0.6)
Diabetes		
Insulin	221	(3.1)
Non-insulin	555	(7.9)
No	6253	(89.0)
Tobacco use	928	(13.2)
COPD	190	(2.7)
Ascites	1323	(18.8)
CHF	19	(0.3)
Hypertension	2852	(40.6)
Bleeding disorder	183	(2.6)
Albumin (g/dL)		

Cham et al. Risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019.

(continued)

TABLE 1
Descriptive statistics of patient characteristics *(continued)*

	N	%
<3.5	1033	(14.7)
3.5–4	1902	(27.1)
>4	1974	(28.1)
Unknown	2120	(30.2)
Hematocrit		
<36%	2780	(39.6)
≥36%	4073	(58.0)
Unknown	176	(2.5)
ASA classification score		
≤1	204	(2.9)
2	2959	(42.1)
3	3595	(51.2)
≥4	271	(3.9)
Procedure score		
0	1586	(22.6)
1	3493	(49.7)
2	1618	(23.0)
≥3	332	(4.7)
Extended procedures		
LND	3047	(43.4)
Small bowel resection	217	(3.1)
Colon resection	272	(3.9)
Rectosigmoid resection	475	(6.8)
Liver resection	123	(1.8)
Bladder resection	21	(0.3)
Diaphragm resection	154	(2.2)
Debulking	3503	(49.8)
Length of stay		
0	110	(1.6)
1	498	(7.1)
2	619	(8.8)
≥3	5798	(82.5)
Unknown	4	(0.06)
Discharge status		
Home	6494	(92.4)
Dead	40	(0.6)
Facility	480	(6.8)
Unknown	15	(0.2)

ASA, American Society of Anesthesiology; *BMI*, body mass index; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *LND*, lymphadenectomy.

Cham et al. Risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019.

discrimination C-index of 0.71, indicating a 71% correct identification of patients across all possible pairs. A 10-fold cross validation with 20 replications resulted in a C-index of 0.70 and the bootstrap validation with 200 resamples resulted in a C-index of 0.71, indicating acceptable discriminatory ability. The bias-corrected C-index with these validation sets closely matched the initial C-index. The final model showed good internal calibration, with predicted outcomes matching closely with observed outcomes (Figure 1). The nomogram seen in Figure 2 uses individual patient characteristics to predict risk of a Clavien-Dindo IV event or 30-day mortality postoperatively. Complete case analyses showed similar results.

In 1 example, an 82-year-old woman undergoing elective surgery for an ovarian mass with an ASA score of 2, normal albumin >4, no bleeding disorder, no ascites, and a procedure score of 1 (standard surgery with debulking) would be assigned 60 points for age ≥80, 23 points for a procedure score of 1, 17 points for an ASA of 2, and 0 points for an elective procedure, normal albumin, no ascites, and no bleeding disorder. Her total points would be 100 and her risk of a Clavien-Dindo IV complication or mortality would be 4.6%.

In contrast, a 65-year-old woman with medical comorbidities including poorly controlled diabetes and hypertension and an ASA class of 3, undergoing elective surgery for widely disseminated disease with an anticipated procedure score of ≥3 (debulking, rectosigmoid, small bowel, and diaphragm resection), ascites, and hypoalbuminemia, but without a bleeding disorder would be assigned 22 points for age, 31 points for ASA of 3, 100 points for her procedure score, 31 points for ascites, 44 points for hypoalbuminemia, and 0 points for an elective procedure and no bleeding disorder. Her total points would be 228 and her risk of a Clavien-Dindo IV complication or mortality would be 25.1%.

Comment

We noted that women undergoing surgery for ovarian cancer are at significant risk for the occurrence of adverse

TABLE 2
Morbidity and mortality outcomes of patients

	N	%
Readmission	688	(9.8)
Reoperation	214	(3.0)
Death	64	(0.9)
Clavien-Dindo IV complications	409	(5.8)
Sepsis	166	(2.4)
Shock	63	(0.9)
Cardiac arrest	15	(0.2)
Myocardial infarction	22	(0.3)
Pulmonary embolism	116	(1.7)
Ventilation > 48 hours	69	(1.0)
Unplanned intubation	65	(0.9)
Death or Clavien-Dindo IV complications	434	(6.2)

Cham et al. Risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019.

perioperative outcomes. Cytoreduction with performance of multiple extended surgical procedures, higher ASA score, and advanced age were among the factors most strongly associated with adverse outcomes. Using readily identifiable clinical characteristics, we were able to develop a nomogram to predict adverse outcomes that was associated with strong internal calibration with a C-index of 0.71, indicating that in 71% of cases the nomogram was able to correctly predict the actual outcome when tested across risk groups.

Cytoreductive surgery for ovarian cancer is associated with substantial morbidity. A systematic review of women who underwent surgery for ovarian cancer found that the overall risk of mortality was 3.7% in population-based studies and 2.5% in single-center studies.[10] One study using the Surveillance Epidemiology and End-Results (SEER) database indicated that the 30-day mortality risk for stage II–IV epithelial ovarian cancer was 8.7%, with worse outcomes in the elderly, those with stage IV disease, and those with increasing comorbidity scores.[14] In our prior published work using the NSQIP database, we found a perioperative complication rate of 9.5% with worsening outcomes in those with hypoalbuminemia or multiple cytoreductive procedures.[29]

NSQIP has a publicly available universal risk calculator that allows up to 20 variables to be input for a specified procedure but in prior studies has shown poor performance for gynecologic oncology patients.[30,31] The strengths of our nomogram as compared to the universal risk calculator are that it includes only factors statistically and clinically associated with the primary outcomes, uses a surgical complexity score to account for multiple procedures during debulking surgery, and uses multiple imputation methods to complete data where missing.

Prior studies have attempted to create predictive models for both short- and long-term postoperative outcomes in patients undergoing ovarian debulking surgery. One study of 620 patients with stage III/IV epithelial ovarian cancer reported a 22.3% rate of 30-day Clavien-Dindo III or higher complications and an 8.9% rate of 90-day mortality. Clavien-Dindo complications were significantly associated with age, BMI, ASA, albumin, stage, and surgical complexity (internal validation with C-index of 0.78). Stage and surgical complexity were no longer significant in 90-day mortality outcomes.[19] Similarly,

TABLE 3
Multivariable model for predictors of death or Clavien-Dindo IV complication

	aOR
Procedure score	
0	Referent
1	1.41 (1.04–1.92)[a]
2	2.26 (1.63–3.11)[a]
≥3	4.53 (3.01–6.82)[a]
Age (years)	
<50	1.32 (0.94–1.85)
50–59	Referent
60–69	1.39 (1.04–1.87)[a]
70–79	1.81 (1.32–2.46)[a]
≥80	2.46 (1.66–3.63)[a]
Elective surgery	
Yes	Referent
No	1.72 (1.29–2.29)[a]
Ascites	1.58 (1.26–1.99)[a]
Bleeding disorder	2.73 (1.82–4.10)[a]

Cham et al. Risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019. *(continued)*

TABLE 3
Multivariable model for predictors of death or Clavien-Dindo IV complication
(continued)

	aOR
Albumin	
>4	Referent
3.5–4	1.42 (1.06–1.90)[a]
<3.5	1.93 (1.39–2.70)[a]
ASA classification score	
≤1	Referent
2	1.28 (0.55–2.98)
3	1.61 (0.70–3.72)
≥4	2.89 (1.17–7.14)[a]

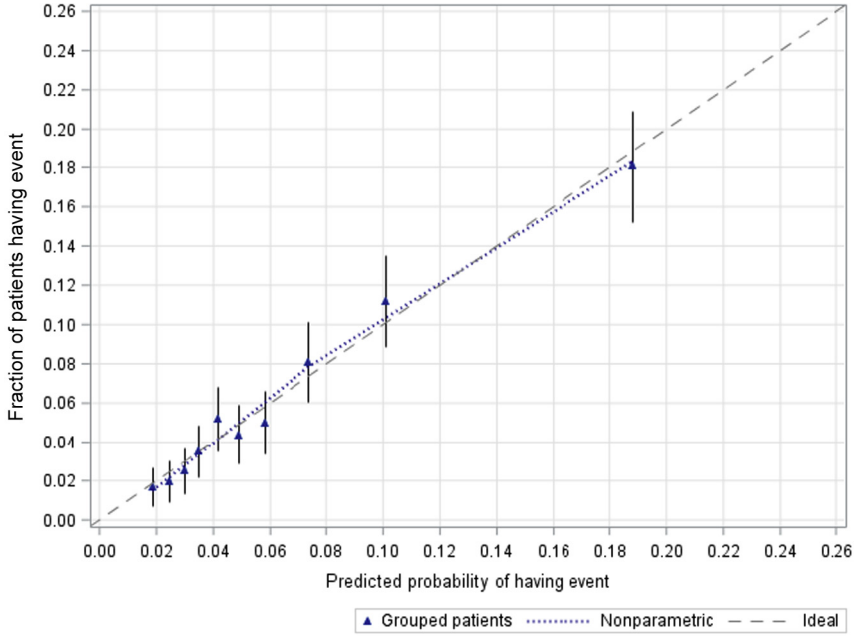
The final multivariable logistic regression model included age, elective surgery, preoperative ascites, bleeding disorder, albumin level, ASA classification score, and procedure score. Multiple imputation using chained equations with $M = 100$ imputations were performed for patients with missing data in demographic characteristics.

ASA, American Society of Anesthesiology.

[a] P value $< .05$.

Cham et al. Risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019.

FIGURE 1
Calibration of the nomogram for Clavien-Dindo IV complication or mortality



Dashed line (the 45-degree line) indicated the ideal reference line where the predicted probabilities of having an event would match the observed factions. Blue triangles represented nomogram-predicted probabilities vs the actual probability grouped for each of the 10 decile groups, along with the 95% confidence intervals (error bars). The distance between the pair of nomogram-predicted vs observed and the ideal line showed the absolute error of the nomogram's prediction.

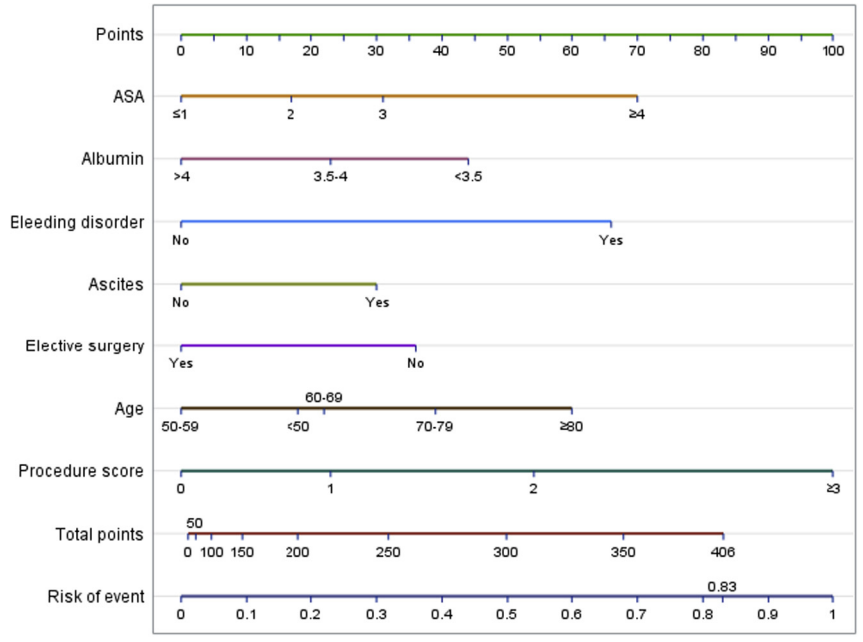
Cham et al. Risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019.

in another study of 219 patients, ASA score, surgical complexity score (based on difficulty and number of procedures performed), and age contributed to short-term morbidity, while residual disease was the only factor contributing to 90-day mortality.[18] One long-term survival nomogram examined 424 patients with bulky stage IIIC ovarian carcinoma and found age and residual disease were the greatest factors that contributed to 5-year survival probability (internal validation with C-index of 0.67).[20] Our model using readily identifiable factors was associated with high internal and with a random holdout sample external validity.

An important goal of developing predictive nomograms for ovarian cancer is to help facilitate the triage of women at high risk for adverse perioperative outcomes to NACT. Similar to prior work, our nomogram found that the performance of extended cytoreductive procedures weighed more heavily than hypoalbuminemia, advanced age, ascites, or emergent surgery.[11] An important goal of NACT is to reduce the need for extended cytoreductive procedures. In a randomized trial studying NACT, patients who underwent NACT had a lower perioperative mortality rate (0.7% vs 2.5%) and grade 3 and 4 hemorrhage (4% vs 7%).[17] A second randomized trial also found a 10% increased rate of perioperative death or severe complications in those who underwent primary debulking surgery.[32] A study of the National Cancer Database found that the increased regional use of NACT significantly reduced short- and long-term mortality within 3 years after diagnosis.[33] Given that both morbidity and mortality are lower with NACT compared to primary cytoreduction, there is a strong rationale to offer primary chemotherapy to the highest-risk women. Using our nomogram, we were able to create a standardized objective algorithm to determine which patients may be at high risk who may be considered for NACT.

We recognize a number of important limitations. First, NSQIP lacks data on clinical and tumor characteristics, such as CA-125 levels, histology, and the

FIGURE 2
Nomogram for Clavien-Dindo IV complication or mortality



Risk points for each variable are obtained by vertically mapping a patient's category to the scale labeled "Points." The predicted risk of Clavien-Dindo IV complication or mortality is obtained by vertically mapping the totaled points on the scale labeled "Total points" to the scale labeled "Risk of event."

Cham et al. Risk-calculator for adverse perioperative outcomes for women with ovarian cancer. Am J Obstet Gynecol 2019.

amount of residual tumor at the completion of surgery. However, the focus of the current study was immediate postoperative morbidity and mortality and not long-term outcomes. Similarly, we lack data on other diagnostic modalities, such as imaging and laparoscopic assessment of disease, which might be useful in further improving the performance of our nomogram, if available.[34–37] Lastly, we are unable to distinguish whether a patient underwent primary or interval cytoreduction or the stage at time of diagnosis. A priori, the goal of this analysis was only to examine factors associated with complications, regardless of the timing of surgery. However, the overall complication rate would likely have been higher if our study were limited to women who underwent primary surgery or had strictly stage III/IV disease.

In summary, these data demonstrate that it is feasible to create a highly predictive nomogram for adverse outcomes among women undergoing surgery for ovarian cancer. Extended cytoreductive procedures, ASA score, bleeding disorder, and age were all predictive of poor outcomes. Our nomogram is among the first to use nationwide data and its strengths include a large patient sample size and a strong C-index of 0.71. This nomogram may be a valuable tool for decision making in guiding providers when considering primary debulking or NACT. ■

References

1. Chi DS, Eisenhauer EL, Lang J, et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol 2006;103:559–64.

2. Aletti GD, Dowdy SC, Gostout BS, et al. Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol 2006;107:77–85.

3. Winter WE 3rd, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:3621–7.

4. Colombo PE, Mourregot A, Fabbro M, et al. Aggressive surgical strategies in advanced ovarian cancer: a monocentric study of 203 stage IIIC and IV patients. Eur J Surg Oncol 2009;35:135–43.

5. Tsolakidis D, Amant F, Van Gorp T, Leunen K, Neven P, Vergote I. Diaphragmatic surgery during primary debulking in 89 patients with stage IIIB-IV epithelial ovarian cancer. Gynecol Oncol 2010;116:489–96.

6. Mourton SM, Temple LK, Abu-Rustum NR, et al. Morbidity of rectosigmoid resection and primary anastomosis in patients undergoing primary cytoreductive surgery for advanced epithelial ovarian cancer. Gynecol Oncol 2005;99:608–14.

7. 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;103:1083–90.

8. Magtibay PM, Adams PB, Silverman MB, Cha SS, Podratz KC. Splenectomy as part of cytoreductive surgery in ovarian cancer. Gynecol Oncol 2006;102:369–74.

9. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol 2006;100:283–7.

10. 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;114:523–7.

11. Wright JD, Lewin SN, Deutsch I, et al. Defining the limits of radical cytoreductive surgery for ovarian cancer. Gynecol Oncol 2011;123:467–73.

12. Langstraat C, Aletti GD, Cliby WA. Morbidity, mortality and overall survival in elderly women undergoing primary surgical debulking for ovarian cancer: a delicate balance requiring individualization. Gynecol Oncol 2011;123:187–91.

13. Mahdi H, Lockhart D, Maurer KA. Impact of age on 30-day mortality and morbidity in patients undergoing surgery for endometrial cancer. Gynecol Oncol 2015;137:106–11.

14. Thrall MM, Goff BA, Symons RG, Flum DR, Gray HJ. Thirty-day mortality after primary cytoreductive surgery for advanced ovarian cancer in the elderly. Obstet Gynecol 2011;118:537–47.

15. Walters CL, Schneider KE, Whitworth JM, et al. Perioperative morbidity and mortality in octogenarians with ovarian cancer. Int J Gynecol Cancer 2013;23:1006–9.

16. Wright JD, Herzog TJ, Neugut AI, et al. Effect of radical cytoreductive surgery on omission and delay of chemotherapy for advanced-stage ovarian cancer. Obstet Gynecol 2012;120:871–81.

17. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in

stage IIIC or IV ovarian cancer. N Engl J Med 2010;363:943–53.
18. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. Am J Obstet Gynecol 2007;197:676 e1–7.
19. Kumar A, Janco JM, Mariani A, et al. Risk-prediction model of severe postoperative complications after primary debulking surgery for advanced ovarian cancer. Gynecol Oncol 2016;140:15–21.
20. Chi DS, Palayekar MJ, Sonoda Y, et al. Nomogram for survival after primary surgery for bulky stage IIIC ovarian carcinoma. Gynecol Oncol 2008;108:191–4.
21. Stashwick C, Post MD, Arruda JS, et al. Surgical risk score predicts suboptimal debulking or a major perioperative complication in patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. Int J Gynecol Cancer 2011;21:1422–7.
22. Suidan RS, Leitao MM Jr, Zivanovic O, et al. Predictive value of the Age-Adjusted Charlson Comorbidity Index on perioperative complications and survival in patients undergoing primary debulking surgery for advanced epithelial ovarian cancer. Gynecol Oncol 2015;138:246–51.
23. Orskov M, Iachina M, Guldberg R, Mogensen O, Mertz Norgard B. Predictors of mortality within 1 year after primary ovarian cancer surgery: a nationwide cohort study. BMJ Open 2016;6:e010123.
24. Di Donato V, Kontopantelis E, Aletti G, et al. Trends in mortality after primary cytoreductive surgery for ovarian cancer: a systematic review and metaregression of randomized clinical trials and observational studies. Ann Surg Oncol 2017;24:1688–97.
25. 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;228:491–507.
26. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13.
27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30:377–99.
28. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. J Clin Epidemiol 2006;59:1087–91.
29. Patankar S, Burke WM, Hou JY, et al. Risk stratification and outcomes of women undergoing surgery for ovarian cancer. Gynecol Oncol 2015;138:62–9.
30. Rivard C, Nahum R, Slagle E, Duininck M, Isaksson Vogel R, Teoh D. Evaluation of the performance of the ACS NSQIP surgical risk calculator in gynecologic oncology patients undergoing laparotomy. Gynecol Oncol 2016;141:281–6.
31. Szender JB, Frederick PJ, Eng KH, Akers SN, Lele SB, Odunsi K. Evaluation of the National Surgical Quality Improvement Program Universal Surgical Risk Calculator for a gynecologic oncology service. Int J Gynecol Cancer 2015;25:512–20.
32. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet 2015;386:249–57.
33. Melamed A, Fink G, Wright AA, et al. Effect of adoption of neoadjuvant chemotherapy for advanced ovarian cancer on all cause mortality: quasi-experimental study. BMJ 2018;360:j5463.
34. Rutten MJ, van Meurs HS, van de Vrie R, et al. Laparoscopy to predict the result of primary cytoreductive surgery in patients with advanced ovarian cancer: a randomized controlled trial. J Clin Oncol 2017;35:613–21.
35. Rodriguez N, Rauh-Hain JA, Shoni M, et al. Changes in serum CA-125 can predict optimal cytoreduction to no gross residual disease in patients with advanced stage ovarian cancer treated with neoadjuvant chemotherapy. Gynecol Oncol 2012;125:362–6.
36. Pelissier A, Bonneau C, Chereau E, et al. CA125 kinetic parameters predict optimal cytoreduction in patients with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy. Gynecol Oncol 2014;135:542–6.
37. Eoh KJ, Yoon JW, Lee JY, et al. A novel algorithm for the treatment strategy for advanced epithelial ovarian cancer: consecutive imaging, frailty assessment, and diagnostic laparoscopy. BMC Cancer 2017;17:481.

Author and article information

From the Columbia University College of Physicians and Surgeons, New York, NY (Drs Cham, Chen, St Clair, Hou, Tergas, Neugut, Hershman, and Wright); the Joseph L. Mailman School of Public Health, Columbia University, New York, NY (Drs Tergas, Ananth, Neugut, and Hershman); the Herbert Irving Comprehensive Cancer Center, Columbia University College of Physicians and Surgeons, New York, NY (Drs St Clair, Hou, Tergas, Neugut, Hershman, and Wright); New York Presbyterian Hospital, New York, NY (Drs Cham, St Clair, Hou, Tergas, Neugut, Hershman, and Wright); and Massachusetts General Hospital, Boston, MA (Dr Melamed).

Received Nov. 21, 2018; revised Jan. 6, 2019; accepted Feb. 7, 2019.

A.I.N. has served as a consultant to Pfizer, Teva, Eisai, Otsuka, and United Biosource Corporation, and is on the medical advisory board of EHE, Intl. D.L.H. is the recipient of a grant from the Breast Cancer Research Foundation/Conquer Cancer Foundation. J.D.W. is a recipient of grants from the National Cancer Institute (NCI R01CA169121-01A1) and has served as a consultant for Tesaro and Clovis Oncology. No other authors report any conflicts of interest or disclosures.

Corresponding author: Jason D. Wright, MD. jw2459@columbia.edu