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Development and Validation of a Risk-Calculator for Adverse Perioperative Outcomes for Women with Ovarian Cancer

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Abstract

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 2011-2015. 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 C-index.

Results—We identified a total of 7,029 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,

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Condensation: A nomogram developed and validated from a nationwide database may predict perioperative adverse outcomes in ovarian cancer debulking

and 0.9% of patients died within 30 days. Among the baseline variables assessed, increasing age, emergent surgery, ascites, bleeding disorder, low albumin, higher ASA, and a higher extended procedure score were associated with serious perioperative morbidity or mortality. Of these factors, performance of ≥3 cytoreductive procedures (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. The final nomogram included the above variables and had an internal discrimination C-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.

Introduction

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 salpingoophorectomy, 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 followed by interval debulking is an alternative to primary cytoreduction. In clinical trials, neoadjuvant chemotherapy 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 neoadjuvant chemotherapy. Most models have used single institutional data to determine factors associated with short term morbidity and mortality and have included factors, such as age, ASA score, surgical complexity and tumor characteristics, such as stage, grade, and histology.[18–24]

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 neoadjuvant chemotherapy.

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 (ACS NSQIP) database between 2011-2015. 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 which 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 one 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 ≥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 one year, history of severe chronic obstructive pulmonary disease (COPD), ascites, congestive heart failure (CHF) within 30 days before surgery, hypertension requiring medication, bleeding disorder, American Society of Anesthesiology (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) 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 <0.05) 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, COPD and CHF were excluded because of *P*-values ≥0.05. All two-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 <0.1, but neither showed clinically differentiable ORs; therefore, only the main predictors were included in the multivariable model. Hypertension and hematocrit were no longer significant (*P*-value <0.05) 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. 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 7,029 patients for whom surgeries were performed between 2011-2015. Age was well represented across all groups with 19.4% of patients age <50 years, 26.5% 50-59 years old, 29.3% 60-69 years, and 24.8% ≥70 years (Table 1). Most patients were white, overweight or obese, non-smokers, and non-diabetic. Preoperatively, most patients had no ascites, a normal albumin, and were not anemic. Most patients underwent one 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 re-admitted, 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 (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) a were most strongly associated with risk of an event (Table 3).

The final nomogram included the above variables and had an initial 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 one example, an 82 year old 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, 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, 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 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 the 30 day mortality risk for stage II-IV epithelial ovarian cancer was 8.7%, with worse outcomes in the elderly, 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 been 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 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, 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 neoadjuvant chemotherapy. Similar to prior work, our nomogram found the performance of extended cytoreductive procedures weighed more heavily than hypoalbuminemia, advanced age, ascites, or emergent surgery.[11] An important goal of neoadjuvant chemotherapy 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 three years after diagnosis. [33] Given that both morbidity and mortality are lower with neoadjuvant chemotherapy 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 neoadjuvant chemotherapy.

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

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AJOG at a Glance:

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

B. 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 ASA, 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 C-index of 0.71.

C. 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

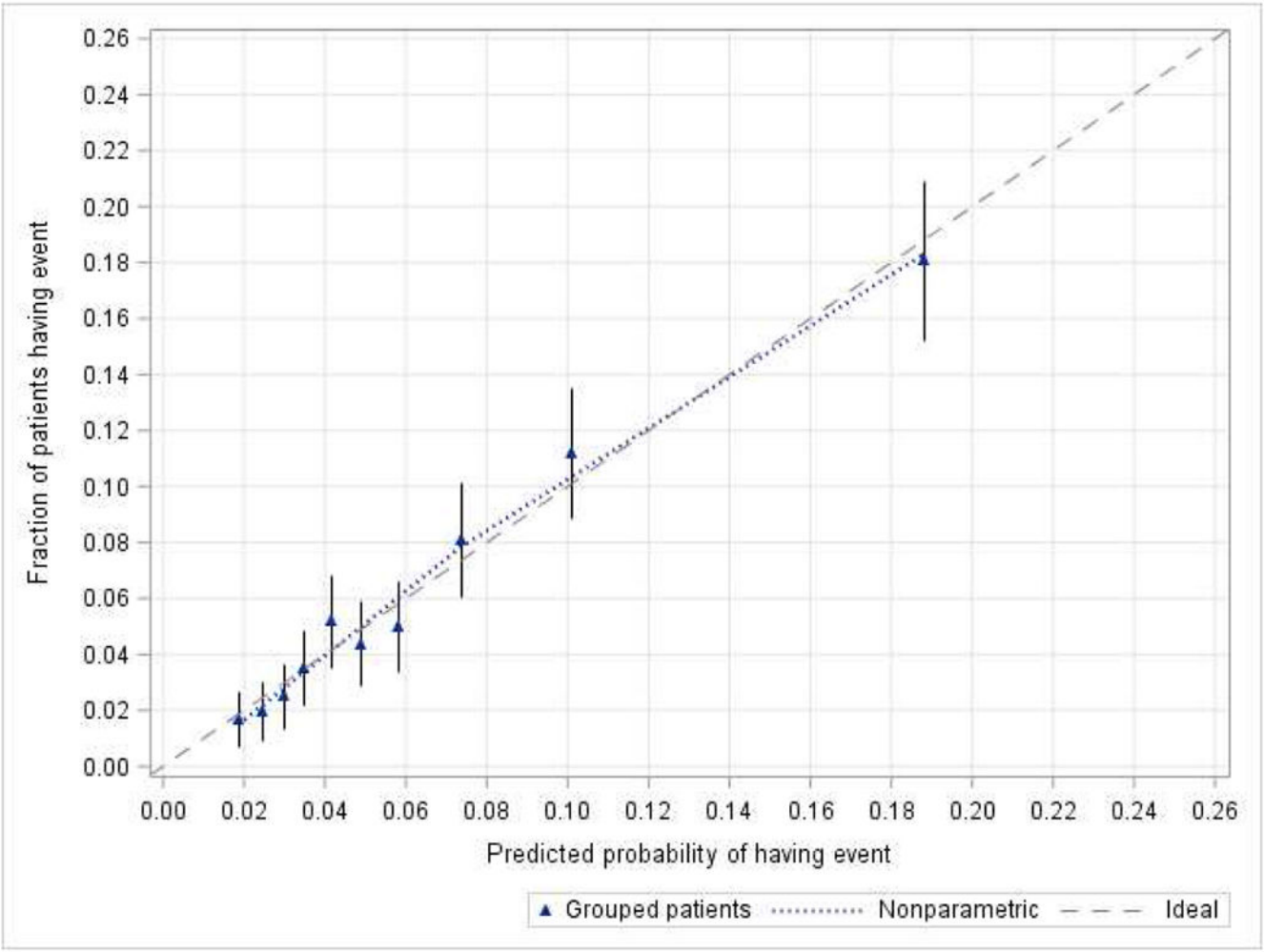

Figure 1.

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 versus the actual probability grouped for each of the ten decile groups, along with the 95% confidence intervals (error bars). The distance between the pair of nomogram-predicted versus observed and the ideal line showed the absolute error of the nomogram's prediction.

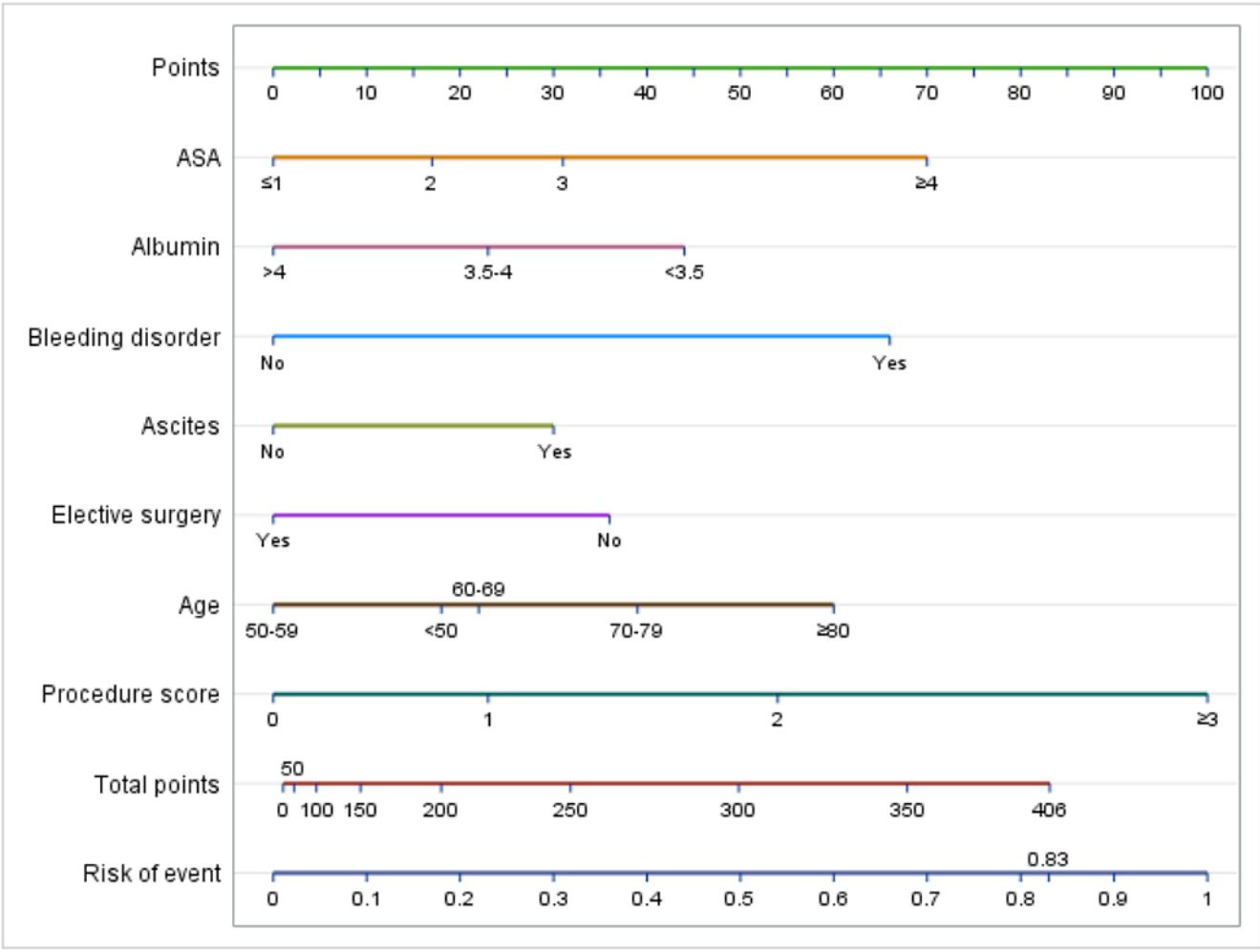

Figure 2.

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".

Table 1.

Descriptive statistics of patient characteristics

	N	%
All	7,029	(100.0)
Year of operation		
2011	878	(12.5)
2012	1,082	(15.4)
2013	1,510	(21.5)
2014	1,606	(22.9)
2015	1,953	(27.8)
Age (in years)		
<50	1,366	(19.4)
50-59	1,864	(26.5)
60-69	2,057	(29.3)
70-79	1,291	(18.4)
≥80	451	(6.4)
Race/ethnicity		
White	5,380	(76.5)
Black	445	(6.3)
Other	384	(5.5)
Unknown	820	(11.7)
Elective surgery		
Yes	6,370	(90.6)
No	632	(9.0)
Unknown	27	(0.4)
BMI		
Normal	2,435	(34.6)
Overweight	2,056	(29.3)
Obese	2,495	(35.5)
Unknown	43	(0.6)
Diabetes		
Insulin	221	(3.1)
Non-insulin	555	(7.9)
No	6,253	(89.0)
Tobacco use	928	(13.2)
COPD	190	(2.7)
Ascites	1,323	(18.8)
CHF	19	(0.3)
Hypertension	2,852	(40.6)
Bleeding disorder	183	(2.6)
Albumin (g/dL)		
<3.5	1,033	(14.7)

	N	%
3.5-4	1,902	(27.1)
>4	1,974	(28.1)
Unknown	2,120	(30.2)
Hematocrit		
<36%	2,780	(39.6)
≥36%	4,073	(58.0)
Unknown	176	(2.5)
ASA classification score		
≤1	204	(2.9)
2	2,959	(42.1)
3	3,595	(51.2)
≥4	271	(3.9)
Procedure score		
0	1,586	(22.6)
1	3,493	(49.7)
2	1,618	(23.0)
≥3	332	(4.7)
Extended procedures		
LND	3,047	(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	3,503	(49.8)
Length of stay		
0	110	(1.6)
1	498	(7.1)
2	619	(8.8)
≥3	5,798	(82.5)
Unknown	4	(0.06)
Discharge status		
Home	6,494	(92.4)
Dead	40	(0.6)
Facility	480	(6.8)
Unknown	15	(0.2)

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)

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) *
2	2.26 (1.63-3.11) *
≥3	4.53 (3.01-6.82) *
Age (in years)	
<50	1.32 (0.94-1.85)
50-59	Referent
60-69	1.39 (1.04-1.87) *
70-79	1.81 (1.32-2.46) *
≥80	2.46 (1.66-3.63) *
Elective surgery	
Yes	Referent
No	1.72 (1.29-2.29) *
Ascites	1.58 (1.26-1.99) *
Bleeding disorder	2.73 (1.82-4.10) *
Albumin	
>4	Referent
3.5-4	1.42 (1.06-1.90) *
<3.5	1.93 (1.39-2.70) *
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) *

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 (MICE) with m=100 imputations were performed for patients with missing data in demographic characteristics.

* p-value <0.05.