

Validation of a risk-based algorithm to reduce poor operative outcomes after complex surgery for ovarian cancer

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HIGHLIGHTS

- ⇒ The Mayo triage algorithm identifies patients at high risk of morbidity/mortality after cytoreductive surgery.
- ⇒ We previously validated the algorithm internally and externally using a low complexity national cohort.
- ⇒ In this study we validated the algorithm in a high complexity international surgical setting.

ABSTRACT

Objective We developed an algorithm that identifies patients at high risk of morbidity/mortality after cytoreductive surgery for advanced ovarian cancer. We have previously shown that the Mayo triage algorithm reduces operative mortality internally, followed by validation using an external low complexity national dataset. However, validation in a higher complexity surgical setting is required before widespread acceptance of this approach, and this was the goal of our study.

Methods We included patients who underwent debulking surgery (including primary or interval debulking surgery) for stage IIIC/IV ovarian cancer between October 2011 and November 2019 (SCORPION trial patients until May 2016 and non-trial patients thereafter) at Fondazione Policlinico A Gemelli, Italy. Using the algorithm, we classified patients as either high-risk or triage-appropriate and compared 30-day grade 3+ complications and 90-day mortality using a χ^2 test or Fisher's exact test.

Results A total of 625 patients were included. The mean age was 58.7 ± 11.4 years, 73.6% (n=460) were stage IIIC, and 63.0% (n=394) underwent primary debulking surgery. Surgical complexity was intermediate or high in 82.6% (n=516) of patients (95.7% (n=377) for primary surgery and 60.2% (n=139) for interval surgery), and 20.3% (n=127) were classified as high-risk. When compared with triage-appropriate patients, high-risk patients had (1) a threefold higher rate of 90-day mortality (6.3% vs 2.0%, p=0.02); (2) a higher likelihood of 90-day mortality following a grade 3+ complication (25.9% vs 10.0%, p=0.05); and (3) comparable rates of grade 3+ complications (21.3% vs 16.1%, p=0.17).

Conclusion The evidence-based triage algorithm identifies patients at high risk of morbidity/mortality after cytoreductive surgery. Triage high-risk patients are poor candidates for surgery when complex surgery is required. This algorithm has been validated in heterogeneous settings (internal, national, and international) and degree of surgical complexity. Risk-based decision making should be standard of care when planning surgery for patients

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Mayo triage algorithm identifies patients at high risk of morbidity/mortality after cytoreductive surgery for advanced ovarian cancer. The triage algorithm identifies patients at highest risk of mortality following a major complication. We previously validated the algorithm using a temporally independent internal cohort, followed by validation using an external low complexity national dataset.

WHAT THIS STUDY ADDS

⇒ This study adds further external validation (international and high complexity setting) to a previously validated algorithm.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The Mayo algorithm performs robustly in a variety of settings and can be used widely. Risk-based decision making may be considered when planning surgery for patients with advanced ovarian cancer.

with advanced ovarian cancer, whether primary or interval surgery.

INTRODUCTION

Performing complex cytoreductive surgery often results in post-operative morbidity, and in patients with co-morbid conditions can culminate in death. However, withholding primary or interval debulking surgery and non-targeted use of neoadjuvant chemotherapy for advanced ovarian cancer is equally concerning, given the consistently observed benefit associated with complete cytoreduction. The decision to offer surgery for advanced ovarian cancer should be chosen based on individual patient and disease factors which are known to predict poor post-operative outcomes.

Original research

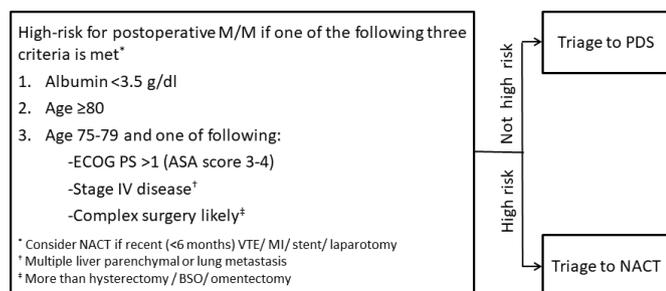


Figure 1 Mayo triage algorithm to predict morbidity/mortality (M/M) after cytoreductive surgery for advanced ovarian cancer. ASA, American Society of Anesthesiologists; BSO, bilateral salpingo-oophorectomy; ECOG, Eastern Cooperative Oncology Group; MI, myocardial infarction; NACT, neoadjuvant chemotherapy; PI, predictive index; VTE, venous thromboembolism.

A large body of research by our group and others¹⁻⁵ investigating outcomes after ovarian cancer cytoreductive surgery and risk factors for complications have led to the proposed triage algorithm (Figure 1). We previously demonstrated the value of the Mayo triage algorithm in a temporally separate internal cohort.⁶ Most notably, the implementation of the triage algorithm resulted in a reduction in 90-day mortality from 8.9% to 2.6%; most women (81.5%) in that study underwent intermediate or high complexity surgery. External validation in a variety of settings is a prerequisite for international adoption of an algorithm. We previously performed external validation using the National Surgical Quality Improvement Program database primarily consisting of low complexity surgery for advanced stage ovarian cancer.⁷ Our objective in the current study was to demonstrate the value and generalizability of the triage algorithm by validating it in an independent international setting with moderate to high complexity surgery.

METHODS

We included patients who underwent either primary or interval debulking surgery for stage IIIC/IV ovarian cancer between October 2011 and November 2019 at Fondazione Policlinico A Gemelli, Italy. This cohort included patients in the SCORPION trial^{8,9} until May 2016 (end of trial enrollment) and non-trial patients thereafter. The SCORPION study and data collection on non-study patients were approved by the institutional review board at Fondazione Policlinico A Gemelli, Italy. The Mayo Clinic institutional review board waived review of the study because it included de-identified patient data.

The inclusion and exclusion criteria for the SCORPION study are described elsewhere but are briefly summarized for reader convenience.^{8,9} Women aged 18–75 years with stage IIIC/IV ovarian cancer with estimated life expectancy of at least 4 weeks, Eastern Cooperative Oncology Group performance status ≤2, and predictive index (PI) score ≥8 or ≤12 on staging laparoscopy were included.^{10,11} All data were prospectively obtained. Pre-operative albumin levels were defined as albumin levels drawn within 30 days before the surgical procedure. No interventions were made to supplement patients with low albumin. Surgical complexity score was assigned using a previously published scoring system.¹² Post-operative complications within 30 days of surgery were graded

using the modified Accordion classification 0–4 scale.¹³ Accordion grade 3+ complications were considered to be severe post-operative complications.¹³

We retrospectively applied criteria from the algorithm and classified women as high-risk if they met at least one of the three criteria listed or triage-appropriate if they had no high-risk factors at the time of cytoreductive surgery (Figure 1). The primary outcomes of interest for comparison between the high-risk and triage-appropriate groups were the presence of 30-day postoperative Accordion grade 3+ complications (including death <30 days) and 90-day mortality following surgery. Comparisons between the groups were evaluated using the two-sample t-test or Wilcoxon rank-sum test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. P values <0.05 were considered statistically significant. All statistical analyses were performed using the SAS version 9.4 software package (SAS Institute, Cary, North Carolina, USA).

RESULTS

The mean age of the 625 included women was 58.7±11.4 years; 73.6% (n=460) had stage IIIC disease and 63.0% underwent primary debulking surgery (Table 1). Surgical complexity was intermediate or high in 82.6% (n=516) of patients. As anticipated, surgical complexity was higher for patients who underwent primary debulking than for those who underwent interval debulking surgery (95.7% vs 60.2%, respectively). Mean (SD) operative time was 377 (140) min. Pre-operative albumin was normal (≥3.5 g/dL) in 67.8%, low (<3.5 g/dL) in 14.4%, and not available in 17.8% of patients (Table 1). Residual disease at the end of surgery was absent/microscopic for 78.7% (n=492), and sub-optimal (>1 cm) in only 4.0% (25/625). Overall, severe post-operative complications occurred in 17.1% (n=107) and 90-day mortality in 2.9% (n=18) of women.

On retrospectively applying the algorithm criteria (Figure 1), 20.3% (n=127) of women would have been classified as high risk for surgical morbidity/mortality pre-operatively and the remaining 79.7% (n=498) classified as triage-appropriate. Characteristics of included women by risk classification are shown in Table 1. High-risk women were older (mean 64.3 vs 57.3 years), more likely to have low pre-operative serum albumin (<3.5 g/dL, 70.9% vs 0%; p<0.001) and more frequently had Eastern Cooperative Oncology Group performance score of 2 or higher (7.2% vs 1.8%, p=0.004). These differences were expected based on the variables used in the algorithm. Body mass index, International Federation of Obstetrics and Gynecology staging, surgical complexity, and operative time were not significantly different between the high-risk women and triage-appropriate women, suggesting minimal bias.

Women classified as high risk by the algorithm had a threefold higher rate of 90-day mortality (6.3% vs 2.0%, p=0.02) compared with those identified as triage-appropriate for cytoreductive surgery (Table 2, Main analysis). Rates of 30-day severe post-operative complications (21.3% vs 16.1%, p=0.17) were comparable for the two groups. Rates of complete cytoreduction were 73.2% and 80.3% (p=0.08) for high-risk and triage-appropriate patients, respectively. Of the 625 women, 111 (17.8%) did not have a pre-operative albumin measure available within 30 days prior to surgery. For the initial analysis, these women were considered as

Table 1 Characteristics of 625 women who underwent surgery for stage IIIC or IV ovarian cancer between October 12, 2011 and 26 November, 2019

Characteristic	Total (n=625)	High-risk sub-group (n=127)	Triage-appropriate sub-group (n=498)	P value*
Age at surgery (years), mean (SD)	58.7 (11.4)	64.3 (13.4)	57.3 (10.4)	<0.001
Race				0.99
White	624 (99.8)	127 (100.0)	497 (99.8)	
Non-white	1 (0.2)	0 (0.0)	1 (0.2)	
Body mass index (kg/m ²)				0.94
<25.0	350 (56.2)	72 (57.1)	278 (55.9)	
25.0–39.9	267 (42.9)	53 (42.1)	214 (43.1)	
≥40.0	6 (1.0)	1 (0.8)	5 (1.0)	
Unknown	2	1	1	
Pre-operative albumin (g/dL)				<0.001
≥3.5	424 (67.8)	30 (23.6)	394 (79.1)	
<3.5	90 (14.4)	90 (70.9)	0 (0.0)	
Not available	111 (17.8)	7 (5.5)	104 (20.9)	
Eastern Cooperative Oncology Group performance score				0.004
0–1	604 (97.1)	116 (92.8)	488 (98.2)	
2+	18 (2.9)	9 (7.2)	9 (1.8)	
Unknown	3	2	1	
FIGO stage				0.09
IIIC	460 (73.6)	86 (67.7)	374 (75.1)	
IV	165 (26.4)	41 (32.3)	124 (24.9)	
Surgical complexity				0.08
Low	109 (17.4)	17 (13.4)	92 (18.5)	
Intermediate	207 (33.1)	36 (28.3)	171 (34.3)	
High	309 (49.4)	74 (55.3)	235 (47.2)	
Operative time (min), mean (SD)	377 (140)	382 (138)	376 (141)	0.68
Type of surgery				<0.001
Primary debulking surgery	394 (63.0)	100 (78.7)	294 (59.0)	
Interval debulking surgery	231 (37.0)	27 (21.3)	204 (41.0)	

Results are reported as N (%) unless otherwise stated.

*Comparisons between groups were evaluated using two-sided tests; the two-sample t-test for age and operative time and the χ^2 test or Fisher's exact test for categorical variables ignoring the unknown category.

FIGO, International Federation of Gynecology and Obstetrics.

triage-appropriate in the absence of other high-risk factors (n=104). If other high-risk factors were present (n=7), they were considered high risk. To be sure that missing pre-operative albumin values was not a source of bias, we performed a sensitivity analysis excluding women with no documented pre-operative albumin and no other high-risk criteria. Of the remaining 521 women, 127 (24.4%) met the high-risk criteria. The sensitivity analysis showed similar results with a threefold higher rate of 90-day mortality (6.3% vs 1.8%, p=0.01) for the high-risk women, and rates of 30-day severe post-operative complications (21.3% vs 15.7%, p=0.15) were not significantly different (Table 2, Sensitivity analysis). Lastly, we performed a similar analysis using women who underwent primary debulking surgery only and observed a similar trend in 90-day mortality (2.5%

vs 5.4%, p=0.15) but the results were not statistically significant due to smaller sample size. We independently analyzed the impact of isolated low albumin in 89 patients whose only high-risk factor was low albumin: 90-day mortality was 5.6% versus 2% (low vs normal range).

We observed that the 90-day mortality following a severe post-operative complication was much higher in high-risk women compared with triage-appropriate women (25.9% (7/27) vs 10.0% (8/80); p=0.05) (Table 3). These observations confirm that the criteria used in the algorithm identify women who are less resilient to complications. By comparison, in the absence of a severe post-operative complication, the 90-day mortality was not significantly different in the two groups: 1.0% (1/100) among

Original research

Table 2 Outcomes after cytoreductive surgery for ovarian cancer among high-risk women compared with triage-appropriate women

Outcome	Main analysis*			Sensitivity analysis†		
	High-risk sub-group (n=127)	Triage-appropriate sub-group (n=498)	P value‡	High-risk sub-group (n=127)	Triage-appropriate sub-group (n=394)	P value‡
30-day post-operative Accordion grade 3+ complications§	27 (21.3)	80 (16.1)	0.17	27 (21.3)	62 (15.7)	0.15
90-day mortality	8 (6.3)	10 (2.0)	0.02	8 (6.3)	7 (1.8)	0.01
Residual disease			0.21			0.05
No gross disease or microscopic	93 (73.2)	399 (80.3)		93 (73.2)	326 (83.0)	
Measurable (0.1–1 cm)	28 (22.0)	79 (15.9)		28 (22.0)	57 (14.5)	
Sub-optimal (>1 cm)	6 (4.7)	19 (3.8)		6 (4.7)	10 (2.5)	
Unknown	0	1		0	1	

Results are reported as N (% of column).

*Main analysis: Assumes albumin was ≥ 3.5 g/dL for those without documented albumin levels.

†Sensitivity analysis: Patients with undocumented albumin who did not meet the high-risk criteria based on their other characteristics were excluded, leaving 521 of the 625 in this analysis.

‡Comparisons between the two groups were evaluated using the two-sided χ^2 test or Fisher's exact test, ignoring the unknown category.

§Memorial Sloan Kettering Cancer Center Surgical Secondary Events Database Classifications.

high-risk women and 0.5% (2/418) among triage-appropriate women ($p=0.48$).

Finally, we looked at the impact of surgical complexity on outcomes. The rate of 30-day grade 3+ complications increased with increasing surgical complexity independent of risk group (Table 4). We also observed a trend towards a higher rate of 90-day mortality associated with high complexity surgery in high-risk women compared with triage-appropriate women (90-day mortality 8.1% vs 3.0%, $p=0.09$), although power was limited due to the small number of deaths.

DISCUSSION

Summary of Main Results

The algorithm identified a high-risk sub-group of women who were at a threefold increased risk of 90-day mortality after cytoreductive surgery. High-risk women were also more likely to die within 90 days following a severe complication (25.9% vs 10.0%, $p=0.05$).

Results in the Context of Published Literature

We observed a similar increase in mortality in high-risk women in the current study (6.3% vs 2.0%), which was comparable to our previously published internal validation study (6.0% vs 1.2%).⁶ This increased risk in high-risk women was observed even in the low complexity National Surgical Quality Improvement Program (NSQIP) cohort, although the absolute risk reduction was smaller and only 30-day mortality data were available (1.4% vs 0.5%).⁷ In addition, we again confirmed that mortality was more likely after a severe post-operative complication in the high-risk group (less resilient) compared with the triage-appropriate group (resilient) (25.9% vs 10.0%; $p=0.05$). Most recently, others have independently validated the performance of the algorithm in an Asian population.¹⁴ They observed that high-risk women had higher rates of 30-day complications (28% vs 5%, $p<0.01$), inability to undergo adjuvant chemotherapy after primary debulking surgery (22% vs 2%, $p<0.01$), and 90-day mortality (6% vs 1%, $p=0.15$) compared with triage-appropriate women. The present study supports the validity and generalizability of our findings.

Table 3 Comparison of 90-day mortality between high-risk women and triage-appropriate women, separately among women with and without 30-day post-operative Accordion grade 3+ complications

Sub-set	High-risk sub-group (n=127)	Triage-appropriate sub-group (n=498)	P value*
Women with 30-day post-operative Accordion grade 3+ complications	7/27 (25.9)	8/80 (10.0)	0.05
Women without 30-day post-operative Accordion grade 3+ complications	1/100 (1.0)	2/418 (0.5)	0.48

Results are reported as N (% of column) within each stratum.

*Comparisons between the two groups were evaluated using the two-sided Fisher's exact test.

Table 4 Relationship between surgical complexity, triage-risk classification, and outcomes

Strata/outcome	Low surgical complexity sub-group (n=109)	Intermediate surgical complexity sub-group (n=207)	High surgical complexity sub-group (n=309)	P value*
All women (n=625)				
30-day grade 3+ complications	3/109 (2.8)	18/207 (8.7)	86/309 (27.8)	<0.001
90-day mortality	2/109 (1.8)	3/207 (1.4)	13/309 (4.2)	0.14
High-risk sub-group (n=127)				
30-day grade 3+ complications	1/17 (5.9)	3/36 (8.3)	23/74 (31.1)	0.006
90-day mortality	1/17 (5.9)	1/36 (2.8)	6/74 (8.1)†	0.59
Triage-appropriate sub-group (n=498)				
30-day grade 3+ complications	2/92 (2.2)	15/171 (8.8)	63/235 (26.8)	<0.001
90-day mortality	1/92 (1.1)	2/171 (1.2)	7/235 (3.0)†	0.44

Results are reported as N (% of column) within each stratum.
 *Comparisons between the three groups were evaluated using the two-sided χ^2 test or Fisher's exact test.
 †8.1% vs 3.0%; p=0.09.

Surgical complexity plays an important role in the risk of complications (Table 4). Even high-risk patients can tolerate low-complexity surgery (after neoadjuvant chemotherapy or in early stage disease). However, patient selection becomes critical when intermediate- or high-complexity surgery is required irrespective of primary or interval setting. Neoadjuvant chemotherapy for high-risk women, ideally coupled with pre-habilitation efforts, has the dual benefits of improving performance and nutritional status as well as reducing tumor burden (decreasing needed surgical complexity). Indeed, in this study, only 21.3% of women after neoadjuvant chemotherapy were deemed high risk compared with 78.7% in the primary debulking surgery group ($p<0.001$). For those rare patients who still require higher complexity surgery after neoadjuvant chemotherapy, use of the algorithm can help with decision making regarding the risk versus theoretical benefit of adding surgery.

Other published models to predict post-operative morbidity/mortality are not specific for ovarian cancer,^{15 16} use intra-operative factors which limit utility for pre-operative decision making,^{17–19} or lack external validation.²⁰ Only the model developed by Cham et al²¹ to predict Clavien–Dindo grade IV complications or death within 30 days has been validated in an external setting.²² A limitation of the Cham model is derivation from the low-risk NSQIP dataset. The effect was apparent in the single institution validation study where the authors concluded that the model performed well at predicting lower likelihood of complications but felt it needed enhancement to help identify patients at higher risk for serious complications.

Strengths and Weaknesses

The strengths of our study include the use of data from an independent international high complexity surgical center. The data were collected prospectively, which decreases the risk of bias from retrospective data collection where the outcome is already known. Additional strengths include large sample size and inclusion of only advanced ovarian cancer. Limitations include the application of the triage algorithm retrospectively. There may be some heterogeneity between patients enrolled in the SCORPION study and the non-study patients. Institutional practices on diagnosis and management of complications may have changed over time that

may impact outcomes. Additionally, albumin levels may have been collected at different times during the 30 days before the operation. Lastly, data on morbidity and mortality may not be complete for patients lost to follow-up.

Implications for Practice and Future Research

Triage high-risk patients have a high risk of poor outcomes when complex surgery is required to achieve optimal cytoreduction. In our practice, women who meet any of the triage criteria are considered high risk and are triaged to neoadjuvant chemotherapy, whereas those who are not at high risk are offered primary debulking surgery if considered resectable. Concerning interval debulking surgery, the same tool can likely be used to identify high-risk patients for moderate- to high-complexity surgery. Risk-based decision making should be standard of care when evaluating surgical risks/benefits for patients with advanced ovarian cancer and can be incorporated into practice using the evidence-based Mayo triage algorithm.

CONCLUSIONS

The evidence-based Mayo triage algorithm identifies patients at high risk of morbidity/mortality after debulking surgery. We previously validated the algorithm internally at our institution, followed by validation using an external low-complexity national dataset. Others have independently validated the performance of the algorithm in an Asian population. In the current study we have validated the algorithm using an international high-complexity surgical setting. The proposed algorithm performs robustly in a variety of settings.

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