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International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery

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GYNECOLOGY

International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery

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BACKGROUND: Enhanced Recovery After Surgery Society publishes guidelines on perioperative care, but these guidelines should be validated prospectively.

OBJECTIVE: To evaluate the association between compliance with Enhanced Recovery After Surgery Gynecologic/Oncology guideline elements and postoperative outcomes in an international cohort.

STUDY DESIGN: The study comprised 2101 patients undergoing elective gynecologic/oncology surgery between January 2011 and November 2017 in 10 hospitals across Canada, the United States, and Europe. Patient demographics, surgical/anesthesia details, and Enhanced Recovery After Surgery protocol compliance elements (pre-, intra-, and postoperative phases) were entered into the Enhanced Recovery After Surgery Interactive Audit System. Surgical complexity was stratified according to the Aletti scoring system (low vs medium/high). The following covariates were accounted for in the analysis: age, body mass index, smoking status, presence of diabetes, American Society of Anesthesiologists class, International Federation of Gynecology and Obstetrics stage, preoperative chemotherapy, radiotherapy, operating time, surgical approach (open vs minimally invasive), intraoperative blood loss, hospital, and Enhanced Recovery After Surgery implementation status. The primary end points were primary hospital length of stay and complications. Negative binomial regression was used to model length of stay, and logistic regression to model complications, as a function of compliance score and covariates.

RESULTS: Patient demographics included a median age 56 years, 35.5% obese, 15% smokers, and 26.7% American Society of Anesthesiologists Class III-IV. Final diagnosis was malignant in 49% of patients. Laparotomy was used in 75.9% of cases, and the remainder minimally invasive surgery. The majority of cases (86%) were of low complexity (Aletti score $\leq$3). In patients with ovarian cancer, 69.5% had a medium/high complexity surgery (Aletti score 4—11). Median length of stay was 2 days in the low- and 5 days in the medium/high-complexity group. Every unit increase in Enhanced Recovery After Surgery guideline score was associated with 8% (IRR, 0.92; 95% confidence interval, 0.90—0.95; $P<.001$) decrease in days in hospital among low-complexity, and 12% (IRR, 0.88; 95% confidence interval, 0.82—0.93; $P<.001$) decrease among patients with medium/high-complexity scores. For every unit increase in Enhanced Recovery After Surgery guideline score, the odds of total complications were estimated to be 12% lower ($P<.05$) among low-complexity patients.

CONCLUSION: Audit of surgical practices demonstrates that improved compliance with Enhanced Recovery After Surgery Gynecologic/Oncology guidelines is associated with an improvement in clinical outcomes, including length of stay, highlighting the importance of Enhanced Recovery After Surgery implementation.

Key words: compliance, ERAS, gynecologic surgery, gynecologic oncology, length of stay, perioperative care

Enhanced Recovery After Surgery (ERAS) brings together unimodal, evidence-based interventions into a combined program with the aim of improving recovery through a reduction in surgical stress response.[1] This ultimately leads to a decrease in length of hospital stay and complications with commensurate improvements in patient satisfaction.[2] ERAS has been implemented successfully in many different surgical disciplines globally.[3] The ERAS Society has helped to develop protocols specific to many of these surgical specialties.[1]

Unlike other disciplines, there is a wide range of complexity within inpatient gynecologic surgery: interventions vary from simple hysterectomy to advanced cytoreductive cancer surgery. Reviews of enhanced recovery programs in both benign and gynecologic oncology surgery found that although protocol elements in the studies showed benefit, there were marked dissimilarities among the protocols, which made it difficult to compare results and draw conclusions.[4,5] This highlighted the need to develop a formalized, evidence-based guideline for patients undergoing gynecologic surgery. In 2016, the ERAS Society guidelines for gynecologic surgery were published.[6,7]

Despite the benefits, introduction of ERAS protocols can be demanding and require major changes in daily clinical practice. The protocol comprises more than 20 different items, and although many are now considered standard of care, substantial effort may be required for implementation. Therefore, the effect of each individual ERAS intervention as well as the importance of adherence to the complete protocol may be questioned. Compliance with the program has been shown to be crucial to achieve optimal care for the surgical

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AJOG at a Glance

Why was this study conducted?

The aim of this study was to investigate the influence of compliance to Enhanced Recovery After Surgery Society gynecologic/oncologic guideline elements on postoperative outcomes in an international cohort.

Key findings

Increased Enhanced Recovery After Surgery guideline compliance was associated with a decrease in length of hospital stay across all patients and showed lower odds of complications among low-complexity patients.

What does this add to what is known?

Compliance with Enhanced Recovery After Surgery Society guidelines are associated with improved outcomes in gynecologic surgery in an international cohort.

patient in other specialties.[8−10] This also has been shown for gynecologic surgery in single institutions.[11,12]

The aim of this study was to evaluate the association between compliance with pre- and intraoperative ERAS Society gynecologic/oncologic guideline elements and postoperative outcomes following elective gynecologic surgery in an international cohort.

Material and Methods

The study was an international multicenter cohort study including patients undergoing elective gynecologic surgery in 10 centers across the United States, Canada, Switzerland, and Sweden between January 3, 2011, and November 29, 2017 (Supplemental Table 1). All centers except 1 implemented the ERAS guidelines in clinical practice at some point during the study period. The guidelines are described in detail elsewhere.[6,7] The cohort contained patients entered consecutively into the web-based ERAS Interactive Audit System (EIAS; www.erassociety.org; Encare, Kista, Sweden). The population included patients operated on for both malignant and benign indications. Although most patients were entered after implementation of ERAS, a smaller portion of patients were entered before an ERAS implementation process was initiated. Pre-ERAS patient data were in part collected retrospectively, whereas all other data were entered prospectively.

EIAS collects information on patient demographics, surgical and anesthesia details, diagnosis, and postoperative outcomes as well as compliance with ERAS protocol elements. Data were entered by trained staff in each center.

Information on all surgical procedures was collected from the database (including diaphragmatic stripping but with the exception of pelvic/abdominal stripping, which was not captured in EIAS). Surgical complexity was stratified in accordance with the Aletti scoring system into low $\leq$3 vs medium/high $\geq$4 groups.[13]

The primary outcomes were postoperative hospital length of stay (LOS), defined as the time spent in hospital during primary stay, from the day of operation to discharge, and total complications, defined as complications during primary stay and/or within 30 days after discharge. Complications were registered and classified according to the Clavien−Dindo system.[14]

Total compliance score was calculated as the number of interventions fulfilled from the guideline recommendations. Elements of pre- and intraoperative care were included, since they are almost completely under the control of the caregiver, whereas several postoperative elements also can be regarded as outcomes.[8] Since not clearly recommended in the guidelines for low-complexity surgery, compliance with epidural use was only registered for the medium/high-complexity group. This resulted in inclusion of the following 11 (low-complexity group) vs 12 (medium/high-complexity group) perioperative interventions in the calculations: systematic preadmission information and counseling given, preoperative oral carbohydrate drink treatment, no oral bowel preparation prescribed, long-acting sedatives not given as premedication, treatment with antibiotic prophylaxis, thrombosis prophylaxis, postoperative nausea and vomiting prophylaxis administered, treatment of active warming with upper-body forced-air heating cover used, avoidance of resection site drainage, amount of intravenous fluid day 0, and mobilization patient out of bed at all on day 0. For categorical elements compliance were marked as yes/no. The reason for limiting the testing to only the 11 and 12 elements in the pre- and intraoperative period was based on the fact that elements of compliance in the later phase could be regarded as outcomes and are more or less dependent of the earlier elements of the protocol. The ones tested are basically all under the control of the caregivers and are the ones that are commonly tested for other guidelines.[8] The cutoff for compliance to the continuous variable, intravenous fluid day 0, were set to 4 mL/kg/hour during surgery + perioperative bleeding in milliliters + no more than 1500 mL during the rest of the day of surgery. Total amounts of $\leq$2000 mL, in total day 0, were regarded compliant, regardless of time of surgery.

Data analyses

Descriptive data were presented as numbers and percentages, mean and standard deviation, or median and ranges. Patient and surgical characteristics as well as outcomes (LOS, readmissions, complications), were tabulated by operation complexity score (ie, Aletti low [1-3] vs medium/high [$\geq$4] scores), and compared using the χ^2 test for categorical variables or the median test for continuous measures. All further analyses also were stratified by low vs medium/high scores.

The impact of individual ERAS elements was evaluated in unadjusted analyses and adjusted for covariates. The role of the total compliance score was investigated and plotted in analyses

TABLE 1
Patient and surgical characteristics

Characteristics	Low-complexity score n=1816	Medium/high-complexity score n=285	*P* value[a]	Total n=2101
Age, y, median (range)	54 (18–93)	62 (27–86)	<.001[b]	55 (18–93)
BMI, kg/m^2, n (%)	28 (15–69)	26 (18–52)	<.001	28 (15–69)
<18	34 (1.9)	6 (2.1)		40 (1.9)
18.1–25.0	554 (30.5)	123 (43.2)		677 (32.2)
25.1–30.0	555 (30.5)	84 (29.5)		639 (30.4)
>30	673 (37.1)	72 (25.3)		745 (35.5)
Smoker, n, (%)	277 (15.3)	35 (12.3)	.061	312 (14.9)
Diabetes mellitus, n, (%)	175 (9.6)	28 (9.8)	.963	203 (9.6)
ASA class, n, (%)			.066	
I-II	1343 (73.9)	196 (68.8)		153 (73.3)
III-IV	473 (26.0)	89 (31.2)		562 (26.7)
Diagnosis, n, (%)			<.001	
Ovarian cancer	293 (16.1)	198 (69.5)		491(23.4)
Uterine cancer	416 (22.9)	62 (21.8)		478 (22.8)
Other gynecologic cancer	50 (2.8)	2 (0.7)		52 (2.5)
Benign indication	1057 (58.2)	23 (8.1)		1080 (51.4)
FIGO stage, n, (%)			<.001	
Not applicable, benign	1057 (58.2)	23 (8.1)		1080 (51.4)
FIGO I	379 (20.9)	58 (20.4)		437 (20.8)
FIGO II	75 (4.1)	16 (5.6)		918 (4.3)
FIGO III	215 (11.8)	134 (47.0)		349 (16.6)
FIGO IVa	36 (2.0)	20 (7.0)		56 (2.7)
FIGO IVb	40 (2.2)	29 (10.2)		69 (3.3)
Recurrence/unknown	14 (0.8)	5 (1.8)		19 (0.9)
Preoperative chemotherapy, n, (%)	150 (8.3)	80 (28.1)	<.001	230 (10.9)
Radiotherapy,[c] n, (%)	22 (1.2)	6 (2.1)	.221	28 (1.3)
Surgical approach, n, (%)			<.001	
Open surgery	1316 (72.5)	279 (97.9)		1595 (75.9)
Laparoscopic/robot	500 (27.5)	6 (2.1)		506 (24.1)
Operating time, min, median (range)	99 (13–492)	213 (55–581)	<.001[b]	108 (13–581)
Intraoperative blood loss, mL, median (range)	150 (0–8000)	500 (0–3800)	<.001[b]	200 (0–8000)

ASA, American Society of Anesthesiologists; *FIGO*, International Federation of Gynecology and Obstetrics.

[a] *P* values are from the χ^2 test; [b] *P* values are from median test; [c] Previous radiotherapy to operating field.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

adjusted for covariates. Adjustment variables were prespecified and included in the multivariable analyses based on their clinical relevance to outcome measures irrespective of their statistical significance. The covariates accounted for in the analysis were age, body mass index, smoking status, presence of diabetes mellitus, American Society of Anesthesiologists class, International Federation of Gynecology and Obstetrics stage, preoperative chemotherapy, previous radiotherapy to operating field, operating time, surgical approach (open vs minimally invasive), intraoperative blood loss, and ERAS implementation status and individual ERAS elements. The multivariable

TABLE 2
Patient outcomes

Outcomes	Low-complexity score n=1816	Medium/high-complexity score n=285	*P* value[a]	Total n=2101
LOS, d, median (range)	2 (0–44)	5 (1–46)	<.001[b]	2 (0–46)
Readmissions, n (%)	72 (4.0)	20 (7.0)	.020	92 (4.4)
Total LOS, d, median (range)	2 (0–44)	5 (1–46)	<.001[b]	3 (0–46)
Complications, primary stay, n (%)	166 (9.1)	89 (31.2)	<.001	255 (12.1)
Grade 1–3a	129 (7.1)	73 (25.6)		202 (9.6)
Grade 3b–5	37 (2.0)	16 (5.6)		53 (2.5)
Complications after discharge,[c] n (%)	242 (13.3)	72 (25.3)	<.001	314 (15.0)
Grade 1–3a	225 (12.4)	67 (24.0)		292 (14.0)
Grade 3b–5	17 (0.9)	5 (1.8)		22 (1.1)
Total complications, n (%)	362 (19.9)	131 (46.0)	<.001	493 (23.5)[d]
Grade 1–3a	309 (17.0)	110 (38.6)		419 (20.0)
Grade 3b–5	53 (2.9)	21 (7.4)		74 (3.5)
Total compliance score, median (range)	10 (3–11)	9 (5–12)	<.001[b]	10 (3–12)

LOS, length of primary stay from operation day until discharge; *Total LOS*, including readmissions.

[a] *P* values are from the χ^2 test; [b] *P* values are from median test; [c] After discharge: within 30 days; [d] 76 patents had complications both in primary stay and after discharge.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

fractional polynominal method was used to assess whether total compliance score and continuous covariates can be modeled as linear measures. To account for the within-stratum variation on operation complexity score, adjusted analyses also included the within-stratum Aletti score. All models were adjusted for hospitals (including the "unadjusted" model) to allow for differences across hospitals and to adjust the standard errors for the potential lack of independence of within-hospital observations.

Since LOS had a highly non-normal (right-skewed) distribution, was recorded as a minimum of zero day and there was an evidence of over dispersion (ie, variance exceeds the mean), negative binomial regression was used to model LOS as a function of compliance score and covariates. In addition, logistic regression was used to model prolonged hospital stay, defined as LOS > median LOS (that is >2 days for low-complexity group and >5 days for medium/high-complexity group).

The effect of explanatory variables on development of complications was modeled using logistic regression. Results are presented as odds ratio (OR) and 95% confidence interval (CI). The statistical software used was Stata version 14/SE for Windows (Stata Corp, College Station, TX). Tests were 2-sided and statistical significance was defined as $P<.05$.

Study approval was obtained from the local ethics board at each site (HCA Centennial Hospital and London Health Sciences Centre were approved as Quality Improvement projects).

Results

Demographic and surgical characteristics

From the EIAS register, we identified 2375 patients of 18 years of age and older who underwent elective gynecological surgery between January 2011 and November 2017. We excluded patients with missing data on adherence status to the ERAS interventions (n=195) and/or covariates in the adjusted model (n=79), leaving 2101 patients for the analyses. There were 427 patients operated before systematic ERAS implementation (pre-ERAS) and 1674 patients after implementation. Demographic and surgical characteristics are presented in Table 1 in total and stratified for low- vs medium/high-complexity surgery.

Final diagnosis was malignant in 49% (n=1021) and benign in 51% (n=1080) of patients. Laparotomy was used in 75.9% of cases (the remainder underwent minimally invasive surgery). The majority of cases (86%) were of low complexity (Aletti score range 1– 3). Fourteen percent underwent more complex procedures (Aletti score range 4–11). Patients who had medium/high complexity operations were older but had lower body mass index scores. They were more likely to have gynecologic cancer (92% vs 42%), particularly stage III/IV ovarian cancer, and more likely to have been treated with neoadjuvant chemotherapy.

LOS and complications

Mean LOS overall was 2.9 days in the low- and 6.3 days in the medium/high-complexity group (Table 2). Thirty-one patients (1%) underwent reoperation during their primary stay for hemorrhage, wound rupture, anastomotic

leakage, intra-abdominal abscess, or bowel obstruction and were more common in the medium/high-complexity group. Ninety-two (4%) were readmitted to hospital; 23 of these underwent reoperation for similar reasons as those during primary stay. The proportion of patients with LOS of 10 or more days comprised 14% (n=39) in the medium/high-complexity group as opposed to 2% (n=43) in the low-complexity group.

Two hundred fifty-five (12%) had a complication during their primary hospital stay, of whom 2 patients died (1 in each complexity group) and 314 (15%) had a complication after discharge. The majority of complications were of low grade (1−3a) according to Clavien−Dindo classification; 79% during primary stay, 93% after discharge, and 85% overall. Among patients with complication during primary stay, 55% had excessive bleeding, during or after operation, 26% infections, 26% from gastrointestinal tract, 18% respiratory, and 16% cardiovascular complications. Complications after primary stay was dominated by infectious complications (73% of those with complication), mostly urinary tract and wound infections, followed by surgical complications and gastrointestinal tract complications.

Compliance with ERAS elements

The cohort comprised patients with a wide range of total compliance with the prespecified individual perioperative ERAS elements (3−12) with a median of 10 (Table 2). More than 90% of the ERAS elements were fulfilled for 48% of the patients in the total population; 54% for low-complexity group and 8% for medium/high-complexity group (Table 3). Compliance with individual ERAS elements (11 in the low-complexity group and 12 in medium/high-complexity group) are presented in Figure 1. For the low complexity group, the lowest compliance was found for balanced intravenous fluids (59%), whereas for the medium/high-complexity group, the lowest compliance was found for oral carbohydrate loading (48%), balanced intravenous fluids (20%), mobilization on day 0 (49%), and use of epidurals (29%).

TABLE 3
Compliance with ERAS elements presented in groups of stratified compliance

Compliance with elements	Low-complexity score n=1816	Medium/high-complexity score n=285	Total n=2101
<75%	490 (27%)	134 (47%)	624 (30%)
≥75%−90%	345 (19%)	129 (45%)	474 (22%)
>90%	981 (54%)	22 (8%)	1003 (48%)

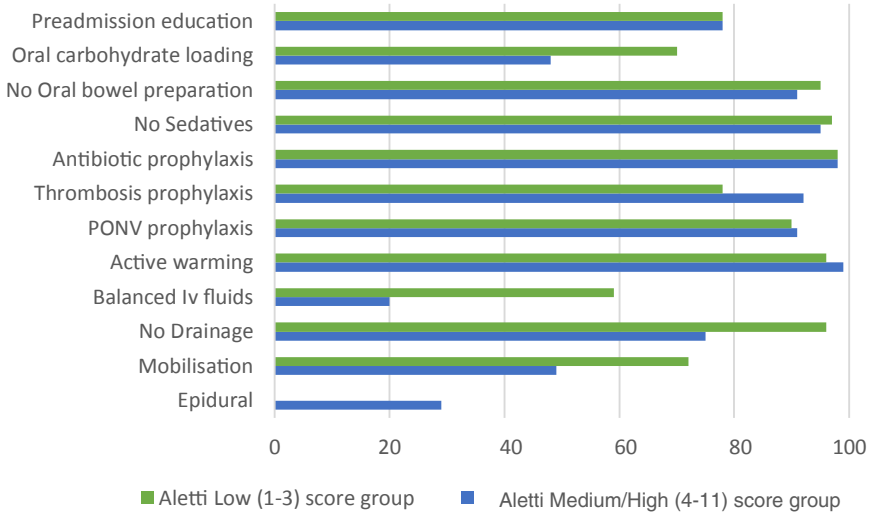
ERAS, Enhanced Recovery After Surgery.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

Association between compliance and LOS

Table 4 displays the associations of individual ERAS elements with the length of primary hospital stay obtained from the negative binomial regression model. Eight of eleven ERAS elements were statistically significantly associated with shorter LOS in the low-complexity group. No sedatives, no drainage, and mobilization day 0 remained statistically significant also in the adjusted analyses. In the medium/high-complexity group, statistically significant associations with shorter LOS were observed for 6 of 12 elements of which preadmission counseling, no bowel preparation, and mobilization day 0 remained statistically significant also after adjustment. In the medium/high-complexity group, usage of epidurals was correlated with pro-

FIGURE 1
Compliance with individual ERAS elements



Compliance with individual pre- and intraoperative ERAS elements stratified by Aletti operation complexity group. Epidural anesthesia is not considered for the group with low score. Values are proportions with fulfilled ERAS element.

ERAS, Enhanced Recovery After Surgery; *PONV*, postoperative nausea and vomiting; *IV*, intravenous.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

TABLE 4
Associations between compliance with individual ERAS element and length of stay

Compliance elements	Low-complexity score group		Medium/high-complexity score group	
	Unadjusted[a]	Adjusted[b]	Unadjusted[a]	Adjusted[b]
Preoperative compliance				
1 Preadmission counseling	−0.16[c] (−0.24 to −0.07)	−0.08 (−0.19 to 0.04)	−0.33[c] (−0.53 to −0.14)	−0.27[d] (−0.53 to −0.01)
2 Oral carbohydrate loading	−0.20[c] (−0.28 to −0.12)	0.02 (−0.07 to 0.12)	−0.21[d] (−0.41 to −0.02)	0.01 (−0.21 to 0.20)
3 No Oral bowel preparation	−0.18 (−0.36 to 0.01)	0.02 (−0.16 to 0.19)	−0.62[c] (−0.96 to −0.28)	−0.34[d] (−0.63 to −0.06)
4 No long-acting sedatives	−0.45[c] (−0.61 to −0.28)	−0.22[e] (−0.37 to −0.08)	−0.01 (−0.35 to 0.33)	−0.06 (−0.31 to 0.19)
5 Antibiotic prophylaxis	0.14 (0.08 to 0.37)	0.14 (−0.07 to 0.35)	0.08 (−0.56 to 0.71)	0.06 (−0.44 to 0.56)
6 Thrombosis prophylaxis	−0.16[d] (−0.28 to −0.04)	−0.03 (−0.15 to 0.09)	−0.27 (−0.55 to 0.02)	−0.16 (−0.37 to 0.05)
7 PONV prophylaxis	−0.28[c] (−0.38 to −0.18)	−0.06 (−0.16 to 0.04)	−0.12 (−0.43 to 0.18)	−0.01 (−0.25 to 0.23)
Perioperative compliance				
8 Active warming	0.05 (−0.12 to 0.22)	0.09 (−0.07 to 0.24)	−0.39 (−1.07 to 0.29)	−0.36 (−0.85 to 0.12)
9 Balanced IV fluids	−0.26[c] (−0.34 to −0.19)	−0.07 (−0.14 to 0.00)	−0.47[c] (−0.70 to −0.25)	−0.14 (−0.32 to 0.04)
10 No drainage	−0.65[c] (−0.78 to −0.52)	−0.17[d] (−0.30 to −0.04)	−0.45[c] (−0.64 to −0.27)	−0.13 (−0.28 to 0.01)
11 Mobilization day 0	−0.44[c] (−0.51 to −0.37)	−0.22[c] (−0.29 to −0.15)	−0.48[c] (−0.63 to −0.33)	−0.17[d] (−0.31 to −0.04)
12 Epidural analgesia	N/A	N/A	0.27[d] (0.05 to 0.49)	0.03 (−0.14 to 0.21)

Results are coefficients and 95% confidence intervals from the analysis using negative binomial regression analyses.

ERAS, Enhanced Recovery After Surgery; *IV*, intravenous; *N/A*, not available; *PONV*, postoperative nausea and vomiting.

[a] Unadjusted for covariates or other ERAS items but adjusted for hospitals; [b] Adjusted for hospitals, age, body mass index, smoking status, diabetes, American Society of Anesthesiologists class, surgical approach, blood loss, operation duration, chemotherapy, radiotherapy, International Federation of Gynecology and Obstetrics stage, ERAS implementation status and Aletti score, and other ERAS elements; [c] $P<.001$; [d] $P<.05$; [e] $P<.01$.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

longed LOS in the unadjusted analysis, but this association did not remain after adjustment for covariates.

The relationship between total compliance score and LOS by complexity groups is presented as the predicted average LOS for each compliance value (Figure 2). Every unit increase in total compliance score was associated with 8% (IRR, 0.92; 95% CI, 0.90−0.95; $P<.001$) decrease in days in hospital among patients with Alleti low score, and 12% (IRR, 0.88; 95% CI, 0.82−0.93; $P<.001$) decrease among patients with Alleti medium/high score, while holding the other variables in the model constant.

Adjusted logistic regression analyses associated greater total compliance score with lower odds of prolonged (hospital stay > median hospital stay) hospitalization (low-complexity group: n=1815; OR, 0.77; 95% CI, 0.68−0.88, $P<.001$; medium/high-complexity group: n=282; OR, 0.65; 95% CI, 0.41−1.02; $P=.061$).

Association between compliance and complications

Table 5 shows associations of single ERAS elements with complications in total obtained from the logistic regression model. In unadjusted analyses, 5 of 11 single elements were associated with lower odds for complications in the low-complexity group, whereas in the medium/high complexity group, statistically significant inverse association was observed only in relation to mobilization on day 0. In the analyses adjusted for covariates and ERAS interventions, preadmission counseling and thrombosis prophylaxis were statistically significantly associated with lower odds of total complications in the low-complexity group. In the medium/high-complexity group, epidural analgesia was associated with greater odds of total complications.

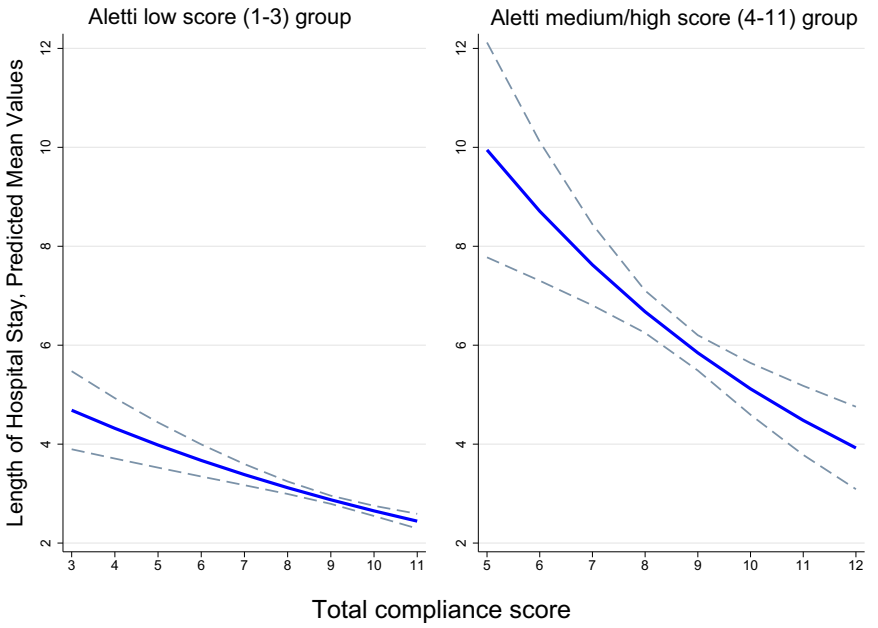
Figure 3 shows estimated ORs from the adjusted logistic regression analyses examining the relationship between total ERAS guideline compliance score and total complications. For every unit increase in total compliance score, the odds of total complications were estimated to be 12% lower (OR, 0.88; 95% CI, 0.78−1.00; $P<.05$) among low-complexity patients but not reaching significance among medium/high-complexity patients (OR, 0.94; 95% CI, 0.69−1.28; $P=.704$).

Discussion

Principal findings

In this international multicenter observational study of more than 2000 patients undergoing planned gynecological surgery, we found an association between increased compliance with ERAS Society guidelines and shorter LOS, regardless of the magnitude of the surgery. In addition, the risk of having a

FIGURE 2
Compliance vs predicted LOS



Association between total compliance score and length of primary hospital stay by operation complexity groups. Mean values of hospital stay were predicted by the negative binomial regression model adjusted for covariates. *Dashed lines* indicate 95% CIs.

LOS, length of stay; *CI*, confidence interval.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

complication was lower with greater compliance with the ERAS guidelines.

Results

Enhanced recovery programs have demonstrated improvements in clinical outcome, including faster recovery and shortened hospital stay, after gynecological surgery for both benign and malignant indications. Equivalent or fewer complications and decreased cost also have been described. In these reports, the enhanced recovery protocols have been diverse, and the question arises as to which interventions are the most important to gain the desired effect.[4,5,15] In this study, we chose to evaluate the ERAS Society Gynecologic/Oncology Guidelines. These guidelines are based on the recommendations from the current literature using a standardized way of evaluating and grading each care item in the protocol.[6,7] This approach has been used before when testing ERAS guidelines for colonic and rectal surgery.[8,9,16,17] The approach to testing is based on the fact that the care of the patient must be regarded as a continuum rather than a series of individual care items, since most of the care items influence those that follow. This makes it harder to discriminate the importance of any individual element. In addition, what may be a key factor for one hospital to adhere to may not be the same in another hospital, since the variation in care processes vary tremendously between hospitals.[18] For example, avoiding fasting, use of preoperative drinks, choice of pain medication, and early mobilization all affect the development of insulin resistance, which has been shown to have an impact on recovery.[19] Likewise, avoiding overnight fasting, oral bowel preparation, fluid overload, opioids, and promoting early mobilization and postoperative nausea and vomiting prophylaxis are all linked to recovery of bowel function.[20] In this study, most of the ERAS interventions significantly decreased LOS in univariate analysis but failed to do so individually after adjustment for confounders in the multivariate analyses. However, when studying all care elements together, the results show a dose−response relationship between the number of elements adhered to and the LOS. This indicates that it is the combination of all the different elements that makes an effective regimen rather than the single element on its own. This is in accordance with previous single-center and multicenter studies in colorectal surgery and in gynecology.[8,11,17] This also supports the multimodal approach of ERAS where combinations of interventions with different mechanisms of action work synergistically to improve recovery and is the strongest indicator for the effect to be genuine. This interpretation also is supported by the fact that the same trend was found both for low and high complexity surgery.

In this study, we chose to evaluate pre- and intraoperative ERAS interventions only. The reason for this choice is because these interventions are under the sole control of the care giver. This is not the case for several post-operative elements. Elements such as intake of oral nutrition and mobilization can just as well be regarded as outcomes that may be confounded by comorbidities and complications. This is also in accordance with previous studies.[8,17] Nevertheless, the postoperative elements serve a very important purpose in securing that this phase of the care pathway is also optimized.

Multimodal treatment of pain is a central tenet of ERAS. The use of mid-thoracic epidurals (TEAs) has been shown to decrease surgical stress by reducing the development of insulin resistance and reducing the need for opioids. For these reasons, epidurals have been a natural intervention in colorectal ERAS programs particularly for open surgery.[21] However, in gynecological ERAS studies, the use of TEA

TABLE 5
Associations between compliance with individual ERAS element and complications

Compliance elements	Low-complexity score group		Medium/high-complexity score group	
	Unadjusted[a]	Adjusted[b]	Unadjusted[a]	Adjusted[b]
Preoperative compliance				
1 Preadmission counseling	0.78 (0.57–1.06)	0.56[c] (0.34–0.94)	0.65 (0.33–1.27)	0.23 (0.05–1.11)
2 Oral carbohydrate loading	0.73[c] (0.54–0.98)	0.89 (0.60–1.33)	0.96 (0.50–1.84)	1.31 (0.42–4.03)
3 No oral bowel preparation	0.95 (0.47–1.93)	1.39 (0.64–3.03)	0.24 (0.05–1.18)	0.45 (0.07–2.76)
4 No long-acting sedatives	0.77 (0.39–1.52)	1.06 (0.51–2.20)	0.34 (0.10–1.15)	0.54 (0.12–2.42)
5 Antibiotic prophylaxis	1.22 (0.53–2.80)	1.22 (0.52–2.90)	0.35 (0.05–2.65)	0.38 (0.03–5.25)
6 Thrombosis prophylaxis	0.56[c] (0.35–0.89)	0.54[c] (0.32–0.91)	0.62 (0.22–1.70)	0.52 (0.13–2.07)
7 PONV prophylaxis	0.59[d] (0.40–0.87)	0.71 (0.47–1.09)	1.14 (0.41–3.17)	1.11 (0.30–4.14)
Perioperative compliance				
8 Active warming	1.06 (0.55–2.04)	1.09 (0.55–2.17)	0.33 (0.03–4.10)	0.15 (0.01–3.19)
9 Balanced IV fluids	0.96 (0.72–1.29)	1.15 (0.84–1.59)	0.66 (0.31–1.37)	1.43 (0.56–3.62)
10 No drainage	0.51[c] (0.29–0.88)	0.98 (0.52–1.84)	0.75 (0.40–1.42)	1.97 (0.84–4.59)
11 Mobilization day 0	0.66[d] (0.50–0.87)	0.88 (0.64–1.19)	0.39[e] (0.22–0.68)	0.56 (0.27–1.16)
12 Epidural analgesia	N/A	N/A	2.90[c] (1.25–6.71)	4.01[c] (1.23–13.15)

Results are odds ratios and 95% confidence intervals from the analysis using logistic regression analyses.

ERAS, Enhanced Recovery After Surgery; *IV*, intravenous; *N/A*, not available; *PONV*, postoperative nausea and vomiting.

[a] Unadjusted for covariates or other ERAS items but adjusted for hospitals; [b] Adjusted for hospitals, age, body mass index, smoking status, diabetes, American Society of Anesthesiologists class, surgical approach, blood loss, operation duration, chemotherapy, radiotherapy, International Federation of Gynecology and Obstetrics stage, ERAS implementation status and Aletti score and other ERAS elements; [c] $P<.05$; [d] $P<.01$; [e] $P<.001$.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

has not been uniform, and the necessity for this is now challenged due to the risk for TEA to potentially impair ambulation, increase urinary retention, and increase the risk of fluid overload especially in complex surgery.[7,22] In contrast to previous reports, 1 study has shown an increased risk of ileus with TEA compared with other multimodal analgesia regimens.[23] In our study, the use of epidurals was negatively associated with complications for the group of complex surgery. Meyer et al[24] and Wijk et al[11] both showed a clear reduction in opioid consumption after introducing an ERAS protocol with multimodal pain treatment without epidurals, whereas Bergstrom et al[25] found a reduction in opioids in the ERAS population with an increased use of epidural. Approaches with multimodal oral pain management, often combined with alternative locoregional analgesia such as continuous lidocaine infusions, spinal analgesia or transversus abdominis plane blocks, or incisional injection also have been used successfully in gynecological ERAS protocols.[12,26,27] It is clear that introduction of an ERAS protocols influences opioid consumption using many different approaches.

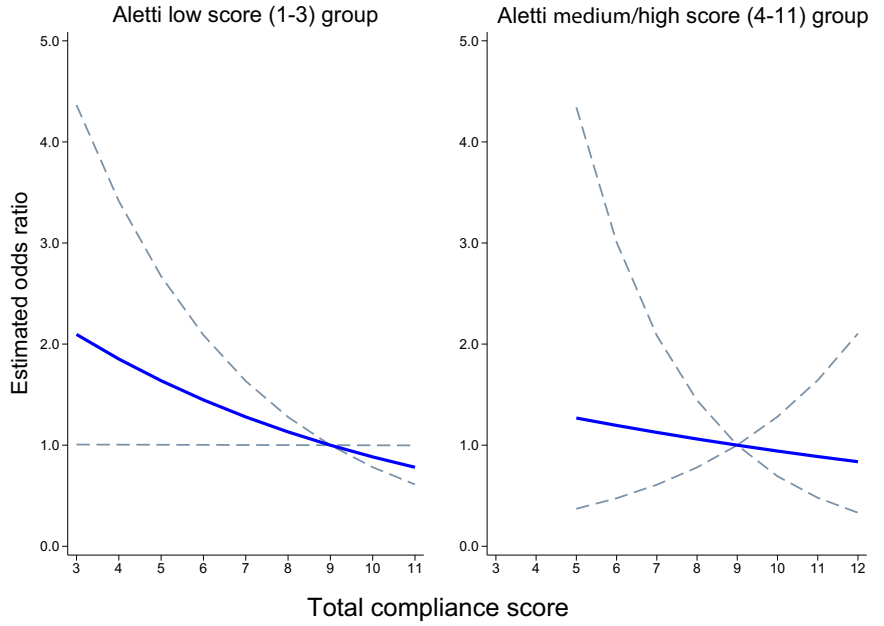
Even more important than the impact of ERAS on short-term clinical outcomes are the effects in oncological surgery, specifically the potential effect on progression-free survival and overall survival. One study in colorectal surgery showed a positive association between ERAS and 5-year survival.[28] Also, perioperative epidural use has been suggested as a prognostic factor in solid tumor malignancies due to positive effects on surgical stress response and the immune system.[29] Epidural anesthesia is believed to decrease the stress response of surgery, unlike general anesthesia and systemic opioids, which inhibit cell-mediated immunity. Also, studies on ovarian cancer surgery demonstrate an association between epidural anesthesia and improved progression-free survival and overall survival.[29,30]

ERAS protocols in colorectal surgery have resulted in a reduction of complications up to 50%.[2,31] In gynecology, the results have either shown a decrease or no change in complications.[5,12,26] Our study demonstrates a significant association between the reduction in complications and compliance with protocol for low-complexity surgery and a similar trend in the medium/high-complexity group, which is also in accordance with studies in colorectal surgery.[8,17] This may be due to the lower number of patients in the medium/high group.

Clinical implications

Apart from the benefit with enhanced recovery for the individual patient, a large proportion of patients with gynecological malignancies will require

FIGURE 3
Compliance vs complications



Association between total compliance score and complications in total by operation complexity groups. The reference point used for the plot is total compliance score equal to 9. Presented as estimated odds ratio and 95% CI (*dashed lines*), adjusted for covariates.

CI, confidence interval.

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.

additional postoperative adjuvant treatment such as radiation and/or chemotherapy. Since delays in the initiation of adjuvant therapy have been associated with decreased survival, enhancing time to recovery is therefore especially crucial for this population.[32,33]

Research implications

Further prospective and randomized studies of specific ERAS interventions are needed in gynecologic surgery, particularly with regards to use of regional analgesia, intraoperative fluid monitoring, and interventions to improve postoperative mobilization.

Strengths and limitations

This is the first international multicenter analysis of the relation between ERAS and outcome after gynecological surgery. The study has the limitation of being an observational study and comprising a mixed population. However, to decrease the risk of bias, we studied consecutive patients and adjusted for a large number of relevant confounders and the difference in surgical complexity has been accounted for by using Aletti scoring.[13]

Conclusions

In conclusion, this study has shown that improved compliance with ERAS Society gynecologic/oncology guidelines results in improved outcomes by reducing recovery time and LOS. The dose–response relationship between the number of elements adhered to and the LOS indicates that it is the combination of all the different elements that makes an effective regimen rather than a single element on its own. ■

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Dr Ljungqvist has an appointment with Nutricia Advisory Board and has given advice to MSD, Abbot, and Advanced medical Nutrition. He has received speaker honoraria from Nutricia, MSD, Braun; Medtronic; and Fresenius-Kabi. He is the current Chairman of the ERAS Society. He founded, serves on the Board, and owns stock in Encare AB, which runs the ERAS Society Interactive Audit System (EIAS). Dr Nelson is the secretary of the ERAS Society, and Dr Elias serves on the Executive Committee for ERAS USA. The remaining authors report no conflict of interest.

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SUPPLEMENTAL TABLE 1
Included patients from each center

	No. patients	Date ranges
Mayo Clinic, Rochester, MN	97	October 19, 2015, to December 14,2016
Örebro University Hospital, Örebro, Sweden	509	January 3, 2011, to January 30, 2017
Royal Alexandra Hospital, Edmonton, AB, Canada	114	June 14, 2016, to September 28, 2017
Foothills Medical Centre, Calgary, AB, Canada	357	Mars 2, 2016, to June 30, 2017
Lausanne University Hospital, Lausanne, Switzerland	370	October 2, 2012, to Mars 20, 2017
Brigham and Women's Hospital, Boston, MA	188	Mars 2, 2017, to November 29, 2017
London Health Sciences Centre, London, ON, Canada	51	February 14, 2017, to June 28, 2017
Weill Cornell Medical College, New York, NY	24	November 22, 2016, to April 20, 2017
HCA Centennial Hospital, Nashville, TN	336	May 18, 2017, to November 29, 2017
Winnipeg Health Sciences Centre, Winnipeg, MB, Canada	55	February 3, 2013, to June 8, 2016

Wijk et al. International validation of Enhanced Recovery After Surgery Society guidelines on enhanced recovery for gynecologic surgery. Am J Obstet Gynecol 2019.