



Nomogram predicting the likelihood of complications after surgery for deep endometriosis without bowel involvement

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ABSTRACT

Study Objective: To describe complications following surgery for deep endometriosis (DE) without bowel involvement and to develop a nomogram for predicting postoperative complications.

Design: Retrospective study

Setting: Tertiary referral university hospital and expert center in endometriosis

Patients: Two-hundred and twenty patients with DE without bowel involvement

Interventions: Laparoscopic resection for DE without bowel involvement

Measurements and Main Results: Operative complications were evaluated using the Clavien-Dindo classification. Voiding dysfunction was defined as a need for bladder self-catheterization lasting >1 month. Fifty-three patients (24%) had postoperative complications: 31 (14%) had a Clavien-Dindo grade I–II complication (3 grade I and 28 grade II); 11 (5%) had a grade III complication (2 grade IIIa and 9 grade IIIb); and 11 (5%) had voiding dysfunction. No grade IV–V complications were observed. Age, Enzian classification risk group, and previous surgery for endometriosis were significantly associated with postoperative complications. The predictive model had an AUC of 0.72 (95% CI, 0.70–0.74) before and 0.70 (95% CI, 0.68–0.72) after bootstrap sample correction. The average difference and maximal difference in predicted and calibrated probabilities of recurrence were 0.023 and 0.089% respectively.

Conclusion: Surgery for DE without bowel resection is associated with a relatively high incidence of voiding dysfunction and postoperative complications mainly corresponding to Clavien-Dindo grade I–II. Age, risk group of Enzian classification, and previous surgery for endometriosis are significantly associated with postoperative complications and voiding dysfunction. Our results allowed us to build a nomogram which can be used to better inform patients about the risk of DE surgery without bowel involvement

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Introduction

Endometriosis is a gynecological disorder defined by the histological presence of endometrial glands and stroma outside the uterus [1]. It is estimated to affect 10–15 % of women of reproductive age [2,3].

Three types of endometriosis have been identified although they are often associated: peritoneal, ovarian (also called endometrioma), and deep endometriosis (DE). Based on the relation between the depth of infiltration and intensity of pain,

DE has been defined as endometriosis infiltrating beneath the peritoneum over 5 mm [4,5]. However, in accordance with previous reports, DE should be defined by the infiltration of anatomical structures and organs regardless of the depth of penetration [6,7]. The most common locations of pelvic DE are the uterosacral ligaments, vagina, rectovaginal septum, colorectal junction and bladder [8–10].

First intention treatment of DE is based on hormonal contraception, progestins, and GnRH analogues. Surgery is restricted to patients who do not respond to medical treatment. This strategy is supported by previous studies as well as national and international guidelines [11–13] highlighting the risk of severe complications after DE resection. However, in contrast to colorectal endometriosis, few data have focused on surgical morbidity using the standardized Clavien-Dindo classification in patients with

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pelvic DE without bowel involvement [14,15]. Moreover, few data are available to determine whether the Enzian and ASRM (American Society for Reproductive Medicine) classifications are useful to predict postoperative complications [16,17].

Hence, the objectives of this study were to evaluate the incidence of complications after surgery for DE without bowel involvement, and to develop a nomogram for predicting their occurrence.

Materials and methods

Patients

We conducted a retrospective analysis of our prospective database using information from women with DE without bowel involvement who underwent surgery from January 2006 to December 2014 at Tenon University Hospital in Paris, France.

For each woman, the following parameters were recorded: age at surgery, body mass index (BMI), smoking status, presence of endometrioma and adenomyosis on magnetic resonance imaging (MRI), fertility before surgery, symptoms, previous surgery for endometriosis, type of surgery, surgical route (laparoscopy or laparotomy), Enzian and ASRM scores calculated during surgery. All patients gave their consent to participate in the study.

The study was approved by the Ethics Committee (CEROG) of the College National des Gynécologues et Obstétriciens Français (CNGOF) (reference number: CEROG 2012-GYN-10-03).

Preoperative diagnosis and surgery

All the patients underwent transvaginal sonography and MRI to evaluate the locations of DE using previously published criteria, and the presence of endometrioma and adenomyosis [5,18]. Indication for surgery was based on symptoms, failure of medical treatment, and associated infertility.

Endometriosis surgery was performed by laparoscopy by three experienced surgeons. The first step of the surgery consisted of exploring the abdominopelvic cavity to exhaustively assess the endometriotic lesions and calculate the ASRM and Enzian scores. Adhesiolysis and salpingo-ovariolysis were performed if necessary. The endometrioma were treated by cystectomy, Plasmajet® vaporization or expectant management depending on lesion size and preoperative ovarian reserve evaluation. The ureters were systematically identified before dissection in the case of major infiltration, and uni- or bilateral ureterolysis was performed when required. Once the external lateral surface of the uterosacral ligament had been fully liberated, the rectovaginal space and the ipsilateral pararectal fossa were opened. The uterosacral ligaments and torus were removed if infiltrated. When the vaginal wall was involved, an en bloc resection including the uterosacral ligaments and a partial colectomy was performed. All patients underwent a first postoperative visit 4–6 weeks after surgery. When data were not available in the hospital medical records, the patients were contacted by phone or by e-mail.

Outcome measures

All intra- and postoperative complications were recorded. In accordance with the Clavien-Dindo classification, complications were classified as minor when of grade I–II (deviation from the normal postoperative course without the need for surgical, endoscopic or radiological interventions) and major when of grade IIIa (requiring surgical, endoscopic or radiological intervention without general anesthesia), IIIb (requiring surgical, endoscopic or radiological intervention under general anesthesia), IV (life-threatening complication, including central nervous system

complications or requiring intermediate or intensive care unit management) and V (death). In addition, *de novo* voiding dysfunction requiring self-catheterization lasting more than 1 month was considered a major complication.

For statistical analysis, the primary composite endpoint was the occurrence of any Clavien-Dindo complication or voiding dysfunction lasting more than 1 month.

Statistical analysis

Development and predictive accuracy of the model

A nomogram was developed for predicting the likelihood of complications after surgery for DE without bowel involvement. We considered three groups at risk of postoperative complications according to the Enzian classification (Table 1); (i) a low-risk group with only location A0, A1, B1 and C0, (ii) an intermediate risk group with A2 and/or B2 location, and (iii) a high-risk group with at least A3, B3 or C1 location.

A multivariate analysis was performed using the logistic regression model and including all the factors that were statistically significant on univariate analysis or clinically relevant from the literature [19]. The complexity of the model was controlled using the Akaike information criterion [20]. A P-value of 0.05 was considered significant. The final model equation was then organized as a nomogram designed to calculate patient-specific probabilities of complications after surgery for DE without bowel involvement. Values for each of the model covariates were mapped to points on a scale ranging from 0 to 100, with total points obtained for each model covariate mapped to the probability of a live birth associated with the area under the receiver-operating characteristic curve (AUC) to measure the model's discriminatory power. It is generally accepted that an AUC of 1.0 indicates perfect accuracy between cases with or without a live birth, an AUC of 0.7–0.8 indicates satisfactory discrimination, values of 0.8 represent good discrimination whereas an AUC of 0.5 indicates no relationship [21]. Calibration was assessed using plots that overlap the prediction model.

A bootstrapping technique to obtain relatively unbiased estimates (200 repetitions) was used for internal validation. The bootstrapping method is based on resampling obtained by randomly drawing data and replacing them with samples from the original dataset. It provides an estimate of the average optimism of the AUC of the receiver-operating characteristics (AUC-ROC) [22]. Calibration was assessed using plots that overlapped the prediction model.

Additional statistical tests

The categorical and numerical variables were analyzed using the chi2 test and the Student t test, respectively. Differences were considered significant at a P-value of 0.05. All analyses were

Table 1
Distribution of surgical complications according to Enzian risk groups.

ENZIAN classification (N = 220)	N (%)
Low risk	53 (24.1)
- Grade I–II Clavien-Dindo complications	4 (7.5)
- Grade III Clavien-Dindo complications	2 (3.8)
- Voiding dysfunction	1 (1.9)
Intermediate risk	87 (39.5)
- Grade I–II Clavien-Dindo complications	7 (8)
- Grade III Clavien-Dindo complications	2 (2.3)
- Voiding dysfunction	4 (4.6)
High risk	80 (36.4)
- Grade I–II Clavien-Dindo complications	20 (25)
- Grade III Clavien-Dindo complications	7 (8.75)
- Voiding dysfunction	6 (7.5)

performed using the R package with the Design, Hmisc, Presence/absence (<http://lib.stat.cmu.edu/R/CRAN>).

Results

Description of the study population

During the study period, 370 women with DE without bowel involvement underwent a resection for DE. One hundred and fifty women for whom it was impossible to evaluate the ASRM or Enzian scores were excluded resulting in a study population of 220 women. The median age of the patients was 32 years (range 19–53 years). The BMI was 22.5 kg/m² (range: 14.1–35.8). The majority of the patients were nulliparous (73%). Epidemiological and clinical characteristics of the population are summarized in Table 2 and Table 3.

Surgical procedures (Table 4)

The main indication for surgical management was pain (155 patients, 70%), followed by the association of pain and infertility (60 patients, 27%), and infertility (five patients, 3%).

Nearly all the patients (97%) underwent laparoscopic management. Only one conversion to laparotomy (0.5%) was required due to extensive abdominopelvic adhesions. The remaining 2.5% of the patients underwent a laparotomy due to the association of DE with uterine fibroids requiring a multiple myomectomy.

The median operating time was 125 min (range: 40–320 minutes). No intraoperative transfusions were required.

Complications (Supplementary data 1)

The mean hospital stay was 3.7 days (range: 1–19).

Intraoperative complications

Two hundred twelve patients (96.4%) did not experience any intraoperative complications. The intraoperative complications

Table 2

Characteristics of the 220 patients with deep endometriosis.

Characteristics (N = 220)	Items
Age (years) median (range)	32 (19–53)
BMI (Kg/m ²) median (range)	22.5 (14.1–35.8)
Smoking N (%)	55 (25)
Parity median (range)	0.48 (0–5)
- 0 N (%)	159 (72.3)
- 1 N (%)	27 (12.3)
- ≥ 2 N (%)	34 (15.5)
Previous surgery for endometriosis	
- No N (%)	149 (67.7)
- Yes N (%)	71 (32.3)
1	48
≥ 2	23
Preoperative symptoms N (%)	
- Gynecologic	
dysmenorrhea	180 (81.8)
dyspareunia	149 (67.7)
chronic pelvic pain	99 (45)
- Digestive	
dyschezia	83 (37.7)
- Urinary	
mvoiding dysfunction	19 (8.6)
urinary infection	23 (10.5)
Clinical lesion N (%)	
- Vagina	35 (15.9)
- Uterosacral ligaments	167 (75.9)
- Torus uterinum	141 (64.1)
- Parametrium	15 (6.8)
- Rectum	24 (10.9)

Table 3

Location of deep endometriosis by MRI of the 220 patients.

Lesion location (N = 220)	N (%)
Vagina	41 (18.6)
Torus Uterinum	186 (84.5)
Utero-sacral ligaments	206 (92.3)
- right	43
- left	27
- bilateral	136
Rectum	15 (6.8)
Other digestive lesion	2 (0.9)
Bladder	13 (5.9)
Parametrium	19 (8.6)
- right	5
- left	14
Ureterohydronephrosis	9 (4.1)
- right	2
- left	7
Endometrioma	80 (36.4)
- right	26
- left	29
- bilateral	25
Associated adenomyosis	50 (22.7)

observed in the remaining eight patients included: three cases of digestive injury requiring laparoscopic suture; two of vaginal injury; one bladder injury; one ureteral injury requiring a suture with JJ stent; and one intra-abdominal hemorrhage with abdominal wall hematoma subsequent to epigastric vessel injury and treated by transparietal suture.

Postoperative complications

One hundred sixty-seven patients (76%) did not experience any postoperative complications. Among the 53 patients (24%) presenting at least one postoperative complication: 31 patients had a Clavien-Dindo grade I-II complication (minor); 11 had a grade III complication (major); and 11 patients had voiding dysfunction. No grade IV-V complications were observed.

Three of the 31 minor complications were of Clavien-Dindo grade I: two cases of seizure episodes and one case of pelvic hematoma. The remaining 28 patients had a grade II complication: 10 cases of urinary infection; nine cases of pyelonephritis; four of pelvic abscess; four cases of fever of unknown cause and treated by antibiotics; and one case of deep venous thrombosis.

Two of the 11 major complications were of Clavien-Dindo grade IIIa: one pelvic abscess treated by radiological drainage; and one uretero-hydronephrosis treated by nephrostomy followed by ureteral reimplantation. The remaining nine patients had a grade IIIb complication: three cases of pelvic peritonitis requiring an ileostomy (one case subsequent to ileal injury treated by segmental small bowel resection and ileostomy, one ileal injury treated by simple ileostomy, and one case of rectovaginal fistula); three cases of vaginal bleeding due to leakage and treated by simple suture; one case of uretero-vaginal fistula treated by JJ stent; one laparoscopic drainage of pelvic hematoma; and one case of abdominal wall hematoma treated by drainage.

Six of the 11 patients experiencing voiding dysfunction lasting more than 1 month required self-catheterization for less than 6 months. The remaining five required self-catheterization for more than 6 months.

In addition, three patients had late complications corresponding to two cases of vaginal granuloma treated by silver nitrate and one case of incisional hernia requiring a second surgery.

Table 4

Surgical procedures for DE resection for the 220 patients.

Surgical characteristics (N = 220)	N (%)
Indication for resection	
- Pain	155 (70.4)
- Infertility	5 (2.3)
- Pain and infertility	60 (27.3)
Surgical approach	
- Laparotomy	5 (2.3)
- Laparoscopy	214 (97.3)
- Laparoconversion	1 (0.5)
Operating time (min) median (range)	125 (40–320)
Resection of Gynecologic lesions	
- Ovarian fenestration	9 (4.1)
- Ovarian cystectomy	54 (23.2)
right	25
left	21
bilateral	8
- Salpingectomy	30 (13.6)
right	16
left	9
bilateral	5
- Adnexectomy	18 (8.2)
right	6
left	6
bilateral	6
- Hysterectomy	36 (16.4)
- Torus uterinum resection	170 (77.3)
- Uterosacral ligaments resection	201 (91.4)
right	30
left	28
bilateral	143
- Partial colpectomy	37 (16.8)
Resection of urinary lesions	
- Partial bladder resection	9 (4.1)
- Ureterolysis	155 (70.5)
right	22
left	43
bilateral	90
- Ureterolysis with parametrectomy	41 (18.6)
right	10
left	19
bilateral	12
- Ureteroneocystostomy	4 (1.8)
right	1
left	3
Resection of bowel lesions	
- Superficial rectal shaving	56 (25.5)
- Appendectomy	4 (1.8)

Relation between ASRM and Enzian classifications and the occurrence of postoperative complication

The distribution of postoperative complications according to the Enzian classification is given in Supplementary data 2. Based on the three Enzian classification risk groups: 53 (24.1%) patients were at low risk; 87 (39.5%) at intermediate risk; and 80 (36.4%) at

high risk. A relation was observed between the Enzian risk groups and the occurrence of complications (Table 5).

According to the ASRM classification, 15 patients had stage I, 86 stage II, 50 stage III, and 69 stage IV. Among the patients with stage I disease, one patient had a grade I-II complication and one had a grade III complication. Among the patients with stage II disease, 10 patients had a grade I-II complication, two had a grade III complication and three had voiding dysfunction. Among the patients with stage III disease, 10 patients had a grade I-II complication, two had a grade III complication and seven had voiding dysfunction. Among the patients with stage IV disease, 10 patients had a grade I-II complication, six patients had a grade III complication and one voiding dysfunction. No statistical relation was observed between the ASRM classification and the occurrence of complications. Moreover, no differences in the complication rate was observed between ASRM stages I and II or between ASRM stages III and IV.

Model to predict complications after surgery for DE without bowel involvement

In multivariate analysis (Table 5), a p-value below 0.20 was considered significant. Age, Enzian risk group, and previous surgery for endometriosis were significantly associated with postoperative complication after surgery and were included in the logistic regression model.

The predictive model (Fig. 1) had an AUC of 0.72 (95% CI, 0.70–0.74) before the 200 repetitions of bootstrap sample corrections and 0.70 (95% CI, 0.68–72) afterwards (Fig. 2). No significant difference was observed between the predicted probability obtained from the bootstrap correction and the actual probabilities of postoperative complications ($p=0.19$), implying that the nomogram was well calibrated. The average difference and the maximal difference in predicted and calibrated probabilities of recurrence were 0.023 and 0.089%, respectively (Supplementary data 3)

Discussion

The present retrospective study of complications following surgery for women with DE without bowel involvement, allowed us to develop a nomogram to predict postoperative complications based on three simple criteria: the patient's age, previous surgery for DE and the Enzian classification. We found a postoperative complication rate of 24% during the first postoperative month. Most of these complications corresponded to Clavien-Dindo grade I-II complications were classified as minor according to the Clavien-Dindo classification. Among these, 90% were grade II mainly related to urinary tract infection and treated by antibiotics. Eleven patients (5%) experienced a major complication (two grade IIIa requiring a radiological intervention and nine grade IIIb

Table 5

Risk factors associated with occurrence of postoperative complications: univariate and multivariate analysis.

H	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p	OR (95 % CI)	p
Age	1.036 (0.982 – 1.093)	0.446	1.022 (0.968 – 1.079)	0.447
Previous surgical procedure for endometriosis				
- Non	0.33 (0.155 – 0.702)	0.007	0.343 (0.157 – 0.751)	0.007
- Oui	1		1	
Risk group of Enzian classification				
- Low risk	1		1	
- Intermediate risk	1.413 (0.413 – 4.84)	0.6308	1.359 (0.389 – 4.745)	
- High risk	4.083 (1.309 – 12.741)	0.0209	3.918 (1.229 – 12.484)	0.011

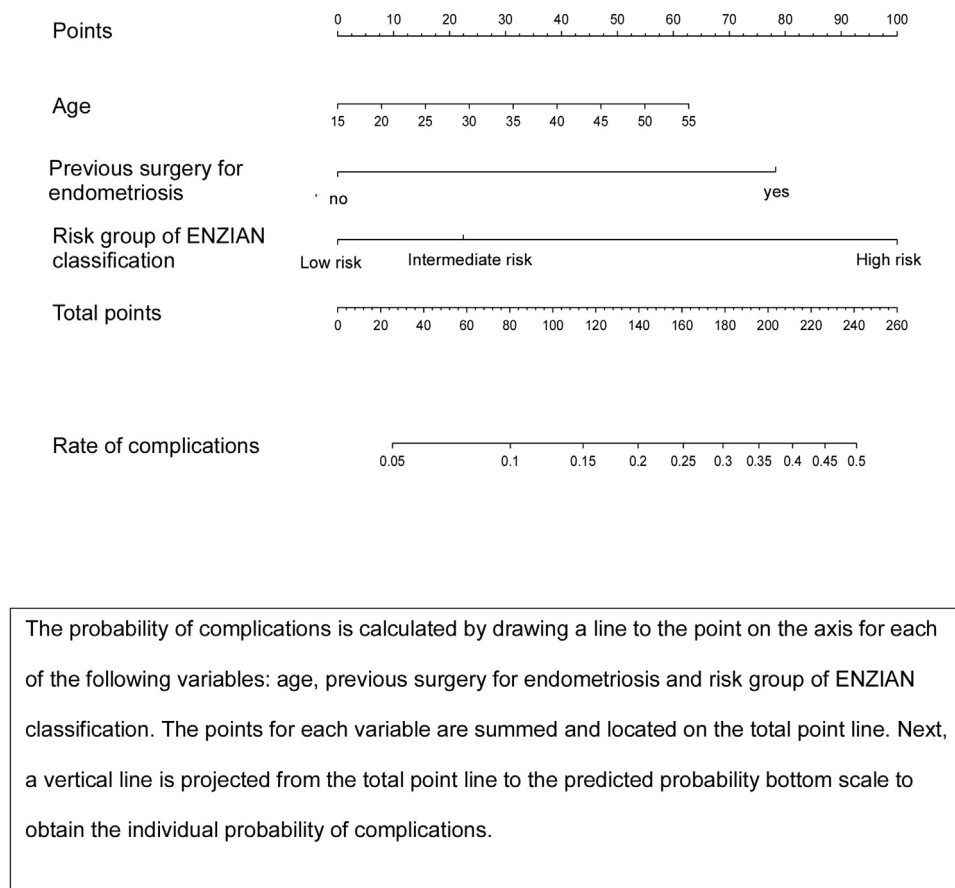


Fig. 1. Predictive model of complications after surgery for DE without bowel involvement.

The probability of complications is calculated by drawing a line to the point on the axis for each of the following variables: age, previous surgery for endometriosis and risk group of ENZIAN classification. The points for each variable are summed and located on the total point line. Next, a vertical line is projected from the total point line to the predicted probability bottom scale to obtain the individual probability of complications.

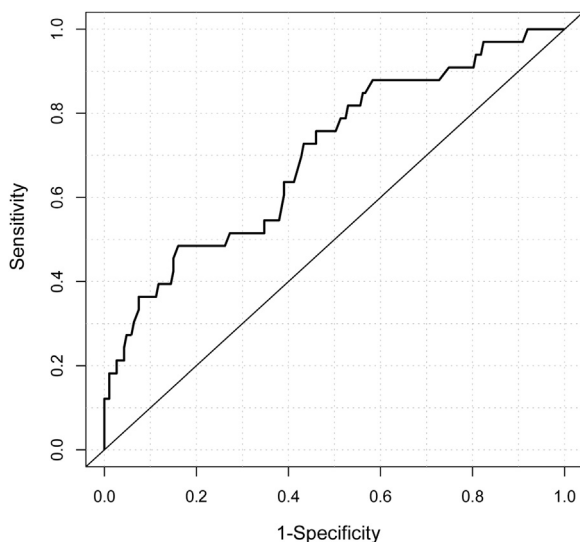


Fig. 2. ROC curve.

requiring a second surgery) while no grade IV or V complications were observed. A further 11 patients required bladder self-catheterization.

In contrast to DE with bowel involvement [14,23–25], relatively few data focusing on complications of DE without bowel

endometriosis are available. In a series of 568 patients with DE, Kondo et al [26] reported an overall complication rate of 13.9% (with 9.5% minor and 4.6% major complications) but did not describe these complications. In contrast, De La Hera-Lazaro observed a complication rate of 30.4% [27]. However, it is difficult to compare our series with previous studies because the reports do not systematically distinguish DE resection with and without bowel involvement. Moreover, most of the studies did not use the Clavien-Dindo classification to report the complication rates. In a prospective series of 203 patients with moderate to severe endometriosis according to the ASRM classification, Meuleman et al reported 1% of Clavien-Dindo grade I–II and 2% of grade \geq III complications in the 127 patients without bowel involvement [14]. This apparent discrepancy in complication rates could be explained by several factors such as the inclusion in the group of patients with severe endometriosis those exhibiting endometrioma of more than 3 cm in diameter or with extensive adhesions without true DE. Moreover, the rate of voiding dysfunction was not reported while this complication represented 5% of our postoperative complications. The difficulties to compare morbidity of DE resection according to series impose the use a consensual scoring system such as the Clavien-Dindo classification but adapted to patients with endometriosis to take into account the specific risk of voiding dysfunction. Finally, although inclusion criteria excluded patients with colorectal endometriosis, it is important to note that some patients required a rectal shaving probably linked to an underestimation of serosal rectal involvement. However, none of our patients required a discoid or segmental colorectal resection.

Moreover, in accordance with previous studies [28], appendicular endometriosis was ignored by preoperative IRM in four patients.

Few data exist on urinary dysfunction after surgery of DE without bowel resection. Dubernard et al [29], comparing the incidence of voiding dysfunction according to uni- or bilateral uterosacral ligament resection, demonstrated an increased risk correlated with the extent of the resection. In a literature review on urinary dysfunction, despite the absence of a consensual definition of bladder voiding dysfunction, Bonneau et al [30] reported that DE surgery was associated with a risk of urinary dysfunction, mainly corresponding to *de novo* voiding dysfunction, in 1.4%–29.2% of cases with a mean value of 4.8%. This is in agreement with our results.

However, complications should be evaluated not only by the percentage but also according to the extent of the DE lesions. In the present study, both ASRM and Enzian classifications were used to evaluate the extent of the DE lesions. Although a trend for a relation was observed between ASRM classification and the occurrence of postoperative complications, it is interesting to note that this difference was not significant between stages I and II or between stages III and IV implying that it cannot be used as a predictor of postoperative complications. In contrast, using uni- and multivariate analysis, a relation was found between the Enzian score and Enzian risk groups and the occurrence of postoperative complications. Indeed, all Clavien-Dindo grade III complications occurred in patients with Enzian grade A3 or B3. Moreover, using three simple items – the age of the patient, previous surgery for DE and the Enzian classification – it was possible to build a nomogram to predict the occurrence of severe postoperative complications. The usefulness of the Enzian score in predicting the risk of surgical complications associated with DE resection is supported by a recent study by Di Paola et al [31] who demonstrated a high correlation between the preoperative MRI Enzian score and the intraoperative Enzian score.

Some limits of the present study deserve to be mentioned. First, the retrospective nature of the study cannot exclude the risk of biases. Second, the long study period and the exclusion of patients with incomplete data on the exact location of DE on MRI and due to the lack of ASRM or Enzian values from the initial population is another limit of the present study. Third, we included voiding dysfunction requiring self-catheterization for more than 1 month as a severe complication although this complication cannot be clearly categorized according to Clavien-Dindo classification. Fourth, the Enzian score calculation was based on intraoperative evaluation of DE but not on MRI. While all DE lesions were clearly distinguished on MRI, the lesion size was not systematically measured. Fifth, we classified the Enzian score into three risk groups. This approach is not subject to consensus but reflects the extent of the disease and the requirement for multiple surgical procedures. Finally, although the calibration of the model was good, the ROC curve was only 0.72. Taking into account these limitations, further studies are required to externally validate and assess the robustness the present nomogram.

Conclusion

The nomogram developed by this study based on three simple criteria – the age of the patient, previous surgery for DE and the Enzian classification – could be used to evaluate the risk of severe postoperative complications associated with the resection of DE without bowel involvement. This is important in a context where clinicians are increasingly interested in supporting women to make an informed decision based on individual criteria.

Conflict of interest

None.

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