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Markers of deep infiltrating endometriosis in patients with ovarian endometrioma: a predictive model

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ABSTRACT

Objective: The purpose of the study was to develop an easily applicable predictive model to predict deep infiltrating endometriosis in patients with ovarian endometrioma.
Study design: We performed a retrospective analysis of 178 consecutive women with ovarian endometrioma who underwent surgery, with histological confirmation and complete removal of endometriosis in the Hospital Clinic of Barcelona. Several markers were prospectively obtained and compared between the group of patients presenting deep infiltrating endometriosis associated with ovarian endometrioma and women with only ovarian endometrioma. Multiple logistic regression analysis was performed to create a model to predict the presence of deep infiltrating endometriosis and internal validation was later performed.
Results: Of the 178 patients studied, 80 (45%) were classified in the ovarian endometrioma group and 98 (55%) in the group of patients presenting deep infiltrating endometriosis associated with ovarian endometrioma. The independent variables to predict deep infiltrating endometriosis were: at least one previous pregnancy, a past history of surgery for endometriosis and the mean endometriosis-associated pelvic pain score. The area under the ROC curve was 0.91 (95% confidence interval: 0.86–0.94), with an optimal cut-off of the predicted probability of 0.54. The sensitivity of the model was 80% and the specificity 84%.
Conclusions: This model predicts the development of deep infiltrating endometriosis in patients with ovarian endometriomas allowing prioritization of women for referral to specialized centers.

Introduction

Endometriosis is a chronic disease characterized by the presence of endometrial tissue outside the uterine cavity, causing pain and reproductive failure [1].

The two most important manifestations of endometriosis are ovarian endometrioma (OE) and deep infiltrating endometriosis (DIE), being OE the most common (17–44% of patients with endometriosis) [2]. DIE has the most aggressive presentation, penetrating to more than 5 mm under the peritoneal surface. It is a multifocal disease primarily affecting the posterior area, and frequently involves the uterosacral ligaments and the torus uterinus, as well as the posterior vaginal and anterior rectal walls. Furthermore, the bladder and urinary system may also be affected [3,4].

Surgery in DIE is usually more complex than in other types of endometriosis and requires a multidisciplinary approach. Thus, failure to remove all of the endometriotic tissue may result in recurrence and persistent symptoms, and thus, referral of patients with DIE to a center with the necessary expertise is strongly recommended [5]. However, the preoperative assessment is complex and therefore it is not rare to find unexpected DIE in patients with OE undergoing scheduled surgery [6,7]. The presence of DIE significantly increases the difficulty of the procedure, thereby making preoperative suspicion of DIE in patients with OE very important to avoid underdiagnosis and undertreatment [8]. DIE associated with OE may be detected by transvaginal ultrasound as a first-line approach but also by transrectal

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ultrasound and magnetic resonance imaging (MRI) [9,10]. However, this is an expensive technique, and skilled radiologists are needed.

Some authors have suggested that several circumstances presented during adolescence may predict DIE [11,12]. Additionally, the presence of certain interleukins has been associated with higher severity of the disease [13–15]. Recently, preoperatively assessed severe pelvic pain has been associated with DIE in women presenting OE [16]. Nevertheless, despite previous attempts to develop noninvasive predictive models [17,18], the presurgical diagnosis of DIE remains suboptimal. Indeed, Chapron et al. [19] and Lafay Pillet et al. [20] created a standardized questionnaire specifically designed to identify posterior DIE. However, recent reports have suggested the need to develop better diagnostic tools for predicting DIE [21]. Therefore, the aim of the present study was to evaluate the predictive value of a novel equation developed with three easily obtainable markers in order to identify among patients diagnosed with OE those with a high risk of associated DIE.

Materials and methods

We assessed a total of 196 consecutive patients undergoing surgery for complete removal of endometriosis in the Service of Gynecology of the Hospital Clínic of Barcelona, from January 2011 to December 2013. The indication for surgery was: infertility in 58 patients (33%), pain and infertility in 32 patients (18%) and isolated pain in 88 (49%) patients (Fig. 1).

The exclusion criteria were: the impossibility to perform complete removal of the lesions and lack of histological confirmation of endometriosis. This study finally included 178 patients.

All the patients underwent an extensive preoperative work-up fully described elsewhere [9], including clinical examination, MRI and transvaginal sonography. Surgery was performed by two experienced surgeons (MAMZ, FC) and all the patients underwent a complete surgical exploration in order to confirm or exclude DIE. Based on the results of the surgical exploration, the women were then distributed into two groups: patients with isolated OE (OE-only group) and patients with DIE associated with OE (OE-DIE group), and thereafter a retrospective analysis was performed. According to the local regulations the Institutional Ethics Committee of our hospital approved this study. All participants provided written informed consent for data collection.

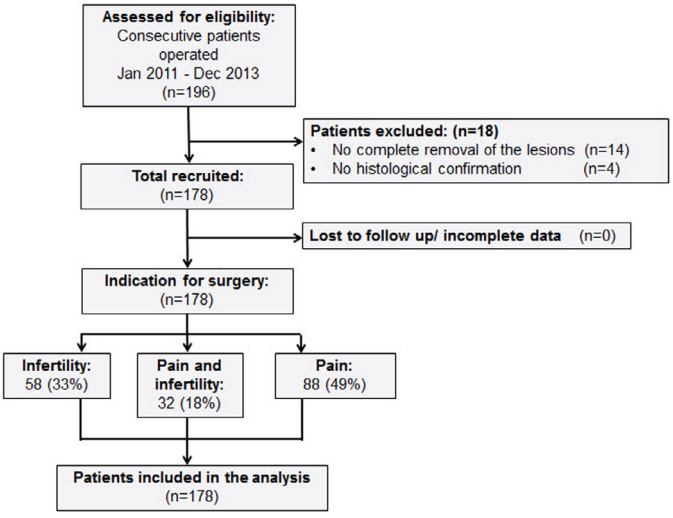

Fig. 1. Flow chart of the patients included.

The clinical data were prospectively recorded for each patient from surgical and pathological medical reports, and included the age at first visit, body mass index (BMI), previous pregnancies, past history of surgical treatment for endometriosis and the use of hormone treatment. Histological confirmation of all endometriotic lesions was obtained and a description of the location of the DIE lesions was recorded. Pain symptoms including dysmenorrhea, dyschezia, dyspareunia and pelvic pain were assessed using a VAS before surgery, regardless of the indication of the surgery (i.e. pain, infertility), and were also classified by each patient as the presence or absence of each pain. Women graded their feeling for each type of pain on a 10-cm line, from 0 "no pain" to 10 "unbearable pain". The mean VAS value for all previous types of pain was calculated for each patient and defined as the endometriosis-associated pelvic pain (EAPP) score. Disease-related data included the presence or absence of associated DIE, laterality of OE, multiplicity, size of the OE or sum of the sizes of OEs in the case of multiplicity. The origin of the patients was also recorded as follows: "out of area" women, in cases of referral from other gynecological centers because of the severity of the disease, and "in area" patients attended directly in our department as our hospital acts as a primary care center for some districts of Barcelona.

Descriptive analysis of the qualitative variables was performed using frequencies and percentages and the quantitative variables using mean and standard deviation (SD) or median and interquartile range (IQR). Categorical characteristics were compared between DIE and non-DIE patients using the χ^2 tests, and quantitative variables were compared using the *t*-test or the Wilcoxon rank-sum test.

In order to identify a logistic predictive regression model of DIE, clinical and statistical judgment led to the assessment of the following characteristics: age, BMI, clinical examination, previous pregnancies (yes/no), past history of surgical treatment of endometriosis (yes/no), dysmenorrhea (yes/no), dyschezia (yes/no), dyspareunia (yes/no), non cyclic pelvic pain (yes/no) and mean EAPP, hormone treatment (yes/no), laterality (unilateral/bilateral), multiplicity (single/multiple) and the sum of the sizes of OE. The log-likelihood ratio test and the Akaike's and Schwarz's Bayesian Information Criteria (AIC and SBIC, respectively) were used to choose among different logistic regression models allowing the identification of the variables included in the final multiple model (those with the lowest AIC and SBIC value) [22,23]. The goodness-of-fit model was assessed using the Hosmer–Lemeshow test along with an observed vs. predicted probabilities graph with a Lowess smoothing curve. The performance of the model was based on its discrimination ability and calibration. The area under receiver operating characteristic (AUC) curve was estimated. In order to estimate the optimal cutpoint, two methods were used: the Liu method that maximizes the product of the sensitivity and specificity, and the nearest to (0,1) method that finds the cutpoint on the ROC curve closest to (0,1). The positive (LR+) and negative likelihood ratios (LR−) were calculated as a measure of the extent to which pre-model odds were altered by the model result [24].

The model was developed of the whole dataset, and its performance was internally validated choosing the AUC as the prognostic indicator. By means of the non-parametric bootstrap technique, the bias-corrected confidence interval (CI) of the AUC was estimated. One thousand bootstrap replications were performed drawing with replacement samples of 178 patients from the initial sample, and the final predictive model was plotted using a nomogram.

To further validate the model, we split the sample into two groups defined by the origin of the patients and we re-assessed our model in the "in area" sub-sample.

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