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ORIGINAL RESEARCH

Factors and Regional Differences Associated with Endometriosis: A Multi-Country, Case–Control Study

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ABSTRACT

Introduction: The present study aimed to investigate clinical, lifestyle, and environmental factors associated with endometrioma (OMA) and/or deep infiltrating endometriosis (DIE) as determined by case–control comparison [women with superficial peritoneal endometriosis (SUP) or no endometriosis], and compare differences between factor associated with endometriosis at a national level.

Methods: This was three countries (China, Russia, and France), case–control study in 1008 patients. Patients were identified and enrolled during their first routine appointment with their physician post-surgery for a benign gynecologic indication, excluding pregnancy. Retrospective information on symptoms and previous medical history was collected via face-to-face interviews; patients also completed

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a questionnaire to provide information on current habits. For every DIE patient recruited ($n = 143$), two women without endometriosis ($n = 288$), two SUP patients ($n = 288$), and two OMA patients ($n = 288$) were recruited.

Results: For the overall population, factors significantly associated ($P \leq 0.05$) with DIE or OMA [Odds ratio (OR) >1] were: previous use of hormonal treatment for endometriosis [OR 6.66; 95% confidence interval (CI) 4.05–10.93]; previous surgery for endometriosis (OR 1.95; 95% CI 1.11–3.43); and living or working in a city or by a busy area (OR 1.66; 95% CI 1.09–2.52). Differences between regions with regard to the diagnosis, symptomatology, and treatment of endometriosis exist.

Conclusion: The findings provide insight into potential risk factors for endometriosis and differences between regions in terms of endometriosis management and symptomatology. Further investigations are required to confirm the associations found in this study.

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Keywords: Environmental factors; Diagnosis; Endometriosis phenotypes; Lifestyle factors; Infertility; Multi-national study; Painful symptoms; Risk factors

INTRODUCTION

Endometriosis is an enigmatic disease characterized by the development of functional endometrial tissue outside the uterine cavity [1]. At a population level, an estimated 2–11% of women of reproductive age has endometriosis [2, 3] often experiencing substantial burden of disease, including chronic pelvic pain and infertility [4, 5].

Symptoms of endometriosis can be non-discriminatory, so the initial indication of disease is normally based on a constellation of symptoms [6]. As such, endometriosis is characterized by long delays in diagnosis [7], with up to 74% of patients receiving at least one false diagnosis [8]. Histologically, there are three phenotypes of endometriotic lesions: superficial peritoneal endometriosis (SUP), cystic ovarian endometriosis or endometrioma (OMA), and deep infiltrating endometriosis (DIE). The pathogenesis of endometriosis is unclear, and it is unknown why different patients present with SUP, OMA, or DIE lesions, and sometimes all the types present in the same patient. The fact that endometriosis phenotype pathogenesis remains elusive suggests that multifactorial mechanisms are involved [9], including hormonal [10], inflammatory [11, 12], immunologic [13, 14], genetic [15–17], epigenetic [18], environmental [19], and other influences.

There is a need to recognize whether endometriosis presents in different ways in different populations. Population-based studies exploring the SUP, OMA, and DIE phenotypes have confirmed the genetic heterogeneity of endometriosis [15], but offer little insight into the potential for regional variation.

The FEELING (Factors associated with the development of Endometrioma and dEep infiLtratING endometriosis) study (NCT01351051) aimed to identify clinical, lifestyle, and environmental factors associated with OMA and/or DIE. As the study took place over three diverse geographic regions, differences in endometriosis presentation were also compared descriptively.

METHODS

Study Design

This was three countries, incident case–control study conducted at seven hospital gynecologic departments in China (four centers), Russia (two centers), and France (one center) between May 2011 and April 2013. Females aged 18–41 years who had undergone surgery (laparoscopy or laparotomy) for a benign gynecologic indication in the last 3 months were considered for enrollment at their first routine post-surgical appointment with their usual physician (study visit).

Patients were eligible if they showed either no visible endometriosis lesions (control patient) or histologically confirmed endometriosis lesions. Histologically proven endometriotic lesions were classified into three groups: [20] SUP (control patient), OMA (case patient), or DIE (case patient). Endometriotic lesions were considered as DIE when the muscularis (bladder, intestine, and intrinsic ureter) was infiltrated by endometriotic tissue after radical surgery (e.g., bowel resection, partial cystectomy, and ureteral resection) [21]. For other endometriotic locations [uterosacral ligament(s), vagina, and extrinsic ureter], DIE was arbitrarily defined as endometriotic tissue infiltrating beneath the peritoneum surface deeper than 5 mm [22]. Patients can exhibit variable degrees of endometriotic infiltration, potentially harboring tissue characteristics of multiple subgroups; thus, patients were arbitrarily classified according to the most severe condition. By definition, endometriotic lesions were ranked from least to worst as follows: SUP, OMA, and DIE [20]. Patients were excluded in the event of pregnancy or if surgical findings showed suspicion or evidence of malignancy. To ensure absolute certainty of the presence or the absence of endometriosis, patients lacking histologic confirmation of endometriosis were ineligible [20].

Investigators enrolled all consecutive patients fulfilling the eligibility criteria during the specified period (~2 years). The planned enrollment was 546 patients in China, 308 patients in Russia, and 154 patients in France, with half as many DIE patients recruited to SUP, OMA, or no endometriosis patients at each center. Cases and controls were recruited to achieve the targeted recruitment numbers for each group and to maintain the group ratio within each site along the recruitment process. Furthermore, within each site, DIE patients with uterosacral lesions could only comprise 20% of the DIE population. There were no matching factors.

Enrolled patients participated in a face-to-face interview with the investigator at the study visit to obtain retrospective data on symptoms and previous medical history, including pre-surgical complaints, endometriosis surgery details, endometriosis status, endometriosis history, additional medical history, gynecologic history, and family medical history using an internet-based electronic data capture (EDC) case report form (Supplemental Data Table S1). Patients then completed a paper questionnaire to provide prospective information on their current habits, including environment, dietary habits, and health and mood during the post-surgical visit (Supplemental Data Table S2). Investigators also completed a questionnaire using EDC (age, gender, years in practice in gynecology, practice site information, number of newly diagnosed subjects with endometriosis per year, total number of endometriosis cases followed per year, and number of assisted reproductive technologies for endometriosis per year). The investigator was responsible for

the validity of all data collected at each site. A study sponsor monitor regularly checked that the data were accurately reported. Documents, including questionnaires (non-validated), were translated at a country level to ensure accuracy and cultural competency.

Objectives and Assessments

The primary objective of this study was to identify clinical, lifestyle, and environmental factors associated with OMA and/or DIE, as determined by case–control comparison. Evidence suggests that SUP may occur intermittently in all women and may not represent true endometriotic disease [23]; thus, because uncertainties arise regarding the precise clinical significance of SUP [9], for the purpose of the primary analysis, both women with no endometriosis and women with SUP were considered control cases. As suggested by Holt and Weiss [24], in this study, only the ovarian (OMA) and deep forms (DIE) were considered as 'definite disease' (case group). The primary analysis was to determine whether significant differences emerged between OMA or DIE vs SUP and no endometriosis groups when the following variables were analyzed: demographics, pre-surgery complaints, endometriosis history, associated diseases, uterine surgical history, menstrual and ovulation history, contraception history, gestation and parity, birth data, family medical history, environment, dietary habits, health, and mood. The secondary objective was to identify factors associated with endometriosis, including the determination of any comparative differences between descriptive variables emerging at a national level and the analysis of patient profiles by endometriosis status in women who had recently undergone surgery for a benign gynecologic indication. Some variables were analyzed for regional differences across different endometriosis phenotypes.

Besides the completion of the patient and investigator questionnaires, no additional assessments, tests, or safety evaluations were performed. The decision to perform surgery was made according to local routine clinical practice, prior to and independently from the decision to enroll the patient into the study. The study did not interfere with any decision made by the physician related to therapeutic management. Histologic evaluation was performed locally at each study hospital.

Statistical Analysis

It was planned to enroll a total of 1008 patients (no endometriosis $n = 288$; SUP $n = 288$; OMA $n = 288$; DIE $n = 144$) to detect odds ratios (ORs) ≥ 2 with a significance level of 5% and a power of 90%, and allowing for 20% missing/non-evaluable questionnaires.

In the primary analysis, patients with SUP were regarded as controls and pooled with the no endometriosis group because of the uncertainties surrounding the real clinical significance of SUP [9]. Likewise, OMA and DIE were considered 'definite disease' and pooled [24].

Univariate logistic regression analyses were performed at the first stage to screen all factors potentially associated with OMA or DIE. All variables with a P value below the 20% significance level in the univariate regressions were retained for the subsequent correlation analyses. Association between these retained variables was then tested using the appropriate method, depending on the nature of the variables. Association between a quantitative variable and a qualitative one was tested using an analysis of variance with the quantitative

variable as the dependent variable and the qualitative variable as the covariate. The association between two continuous variables was tested using the Spearman correlation coefficient. The association between two qualitative variables was tested using Chi-square test, or Fisher's exact test [if expected count(s) <5]. Significant associations were determined at a $P < 0.0001$ level. In the case of a strongly significant association between two variables, the variable to keep for the multivariate regression was selected based on a clinical rationale by the principal investigator and the study team (comprising the medical director, project manager, and statistician).

These variables, as well as the variables 'hormonal treatment for endometriosis', 'infertility', and 'previous surgical diagnosis', were then introduced in the construction of the final multivariate logistic regression model. A stepwise elimination analysis was followed using a significance level of 10% to entry variables in the model and a significance level of 5% to retain variables in the model. The Hosmer and Lemeshow goodness-of-fit test for the final selected model was presented, and 95% confidence intervals (CI) for the OR, estimated by the logistic model, were calculated [25].

Comparisons between countries for qualitative variables were conducted using Chi-squared tests.

All statistical analyses were performed by the biostatistics unit of LINCOLN using the SAS® software, version 9.1 (SAS Institute Inc., Cary, North Carolina, USA, 2004).

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Patients provided written informed consent to allow their medical data to be collected, analyzed, and shared with regulatory authorities. The study identifier for clinicaltrials.gov is NCT01351051. Prior to initiating the study, the investigator/institution had approval from the Independent Ethics Committee/Institutional Review Board as applicable in the country of study

RESULTS

Patients

In total, 1008 surgically screened patients were enrolled between May 26, 2011 and April 30, 2013 and 1007 were analyzed [one DIE patient from Russia was not evaluated (age outside range)]. Baseline characteristics and endometriosis phenotype distribution are presented in total and by country in Table 1.

Primary Objective

Factors Associated with OMA or DIE

Clinical, lifestyle, and environmental factors found to be potentially associated with OMA or DIE in the overall population and by country are presented in Table 2 (univariate analysis) and Table 3 (multivariate analysis). In the overall population, factors significantly associated ($P \leq 0.05$) with DIE or OMA (OR >1) were: the previous use of hormonal treatment for endometriosis (OR 6.66; 95% CI 4.05–10.93), the previous history of surgery for endometriosis (OR 1.95; 95% CI 1.11–3.43), and living in a city or by a busy area (OR 1.66; 95% CI 1.09–2.52). Of note, data indicate that predictive factors may vary between different

Table 1 Baseline characteristics

Characteristic	China ($n = 546$)	Russia ($n = 307$)	France ($n = 154$)	Total ($N = 1007$)
Mean age (years) on visit day (range)	31.80 (18–41)	30.28 (19–41)	31.58 (18–41)	31.30 (18–41)
Mean BMI ± SD, kg/m^2	21.37 ± 3.27	22.22 ± 4.01	22.23 ± 4.07	21.76 ± 3.66
Ethnicity (%)				
Asian	546 (100)	0	4 (2.6)	550 (54.6)
Caucasian/white	0	306 (99.7)	124 (80.5)	430 (42.7)
Black/African American	0	0	14 (9.1)	14 (1.4)
Other	0	1 (0.3)	12 (7.8)	13 (1.3)
Marital status, n/N (%)				
Single	80 (14.7)	43 (14.0)	52 (33.8)	175 (17.4)
Married	450 (82.4)	204 (66.4)	47 (30.5)	701 (69.6)
Free union*	14 (2.6)	44 (14.3)	47 (30.5)	105 (10.4)
Divorced/separated	2 (0.4)	15 (4.9)	7 (4.5)	24 (2.4)
Widowed	0	1 (0.3)	1 (0.6)	2 (0.2)
Education level, $n/N^{\dagger}$ (%)				
Primary school	20 (3.7)	3 (1.0)	0	23 (2.3)
High school	112 (20.6)	2 (0.7)	7 (4.5)	121 (12.0)
Vocational or professional school	59 (10.8)	39 (12.7)	7 (4.5)	105 (10.4)
Polytechnic or equivalent (+2 years)	38 (7.0)	21 (6.8)	31 (20.1)	90 (8.9)
University or business school (+4 to 5 years)	316 (58.0)	242 (78.8)	109 (70.8)	667 (66.3)
Missing	1	0	0	1
Smoking status, n/N (%)				
Smoker	12 (2.2)	50 (16.3)	45 (29.2)	107 (10.6)
Never smoker	530 (97.1)	200 (65.1)	91 (59.1)	821 (81.5)
Ex-smoker	4 (0.7)	57 (18.6)	18 (11.7)	79 (7.8)
Endometriosis type (%)				
No endometriosis	156 (29)	88 (29)	44 (29)	288 (29)
SUP, n	156 (29)	88 (29)	44 (29)	288 (29)
OMA, n	156 (29)	88 (29)	44 (29)	288 (29)
DIE, n	78 (14)	43 (14)	22 (14)	143 (14)

BMI body mass index, *DIE* deep infiltrating endometriosis, *OMA* endometrioma, *SD* standard deviation, *SUP* superficial peritoneal endometriosis

*A union that lacks any publicly recognized bond

† $n = 1006$ ($n = 545$ for China)

Table 2 Odds ratios [95% CI] for risk factors potentially associated with OMA or DIE vs control (no endometriosis and SUP) patients from univariate analysis

Factor	China	Russia	France	Overall
BMI on the day of visit (kg/m^2)				
≥18.5 to <22	–	Ref	–	Ref
<18.5	–	2.20 [1.11–4.37]	–	1.45 [1.00–2.11]
≥22 to <25	–	0.63 [0.35–1.14]	–	0.86 [0.63–1.18]
≥25	–	0.50 [0.26–0.97]	–	0.65 [0.44–0.96]
Marital status				
Married	–	Ref	–	–
Single	–	4.84 [2.34–10.00]	–	–
Free union females	–	2.05 [1.06–3.96]	–	–
Divorced or separated or widowed	–	1.12 [0.39–3.22]	–	–
Education level				
University or business school	–	–	–	Ref
Primary and high school	–	–	–	0.60 [0.41–0.88]
Vocational or professional school	–	–	–	0.68 [0.44–1.04]
Polytechnic or equivalent	–	–	–	1.05 [0.68–1.63]
Non-cyclic chronic pelvic pain				
No	Ref	Ref	–	Ref
Yes	2.30 [1.40–3.78]	5.20 [3.18–8.51]	–	2.44 [1.84–3.23]
Dysmenorrhea pain at intensities				
0	Ref	Ref	Ref	Ref
≥1 to ≤4	2.77 [1.77–4.34]	1.72 [0.71–4.14]	6.50 [1.00–42.31]	2.56 [1.76–3.73]
≥5 to ≤7	3.31 [2.00–5.46]	2.59 [1.37–4.88]	1.67 [0.63–4.39]	2.47 [1.74–3.50]
≥8 to ≤10	6.96 [4.02–12.07]	4.81 [2.63–8.81]	4.95 [1.91–12.80]	5.41 [3.79–7.72]
Deep dyspareunia				

Table 2 continued

Factor	China	Russia	France	Overall
No	Ref	Ref	–	Ref
Yes	3.09 [1.81–5.27]	2.56 [1.61–4.07]	–	2.05 [1.56–2.70]
Pain at time of ovulation				
No	–	Ref	–	Ref
Yes	–	1.77 [1.11–2.82]	–	1.48 [1.09–2.01]
GI symptoms during menstruation				
No	Ref	Ref	–	Ref
Yes	3.40 [2.23–5.19]	3.46 [2.15–5.55]	–	2.70 [2.06–3.52]
Urinary symptoms during menstruation				
No	Ref	Ref	–	Ref
Yes	4.34 [1.91–9.85]	2.17 [1.14–4.16]	–	2.47 [1.60–3.81]
Infertility				
No	–	Ref	–	Ref
Yes	–	0.23 [0.14–0.37]	–	0.56 [0.43–0.73]
Previously surgical diagnosis				
No	Ref	Ref	Ref	Ref
Yes	7.07 [3.10–16.14]	8.47 [3.15–22.73]	2.37 [1.05–5.37]	4.92 [3.06–7.90]
Hormonal treatment for endometriosis				
No	Ref	Ref	Ref	Ref
Yes	22.32 [7.97–62.52]	12.54 [5.68–27.71]	2.64 [1.23–5.69]	8.41 [5.39–13.12]
Lifelong menstrual cycles				
Always/generally regular	Ref	Ref	Ref	Ref
Irregular	0.37 [0.17–0.84]	0.36 [0.17–0.76]	0.23 [0.08–0.73]	0.34 [0.21–0.55]
Time since age at menarche	1.47 [1.06–2.03]	–	–	–

Table 2 continued

Factor	China	Russia	France	Overall
Progestin-only oral contraceptive				
No	Ref	–	–	Ref
Yes	0.26 [0.07–0.90]	–	–	0.39 [0.16–0.99]
Previous uterine surgery				
No	Ref	–	–	–
Yes	1.57 [1.03–2.39]	–	–	–
Pregnancy				
No	Ref	Ref	–	–
Yes	1.42 [1.00–2.02]	0.60 [0.38–0.95]	–	–
Breastfed				
Yes	Ref	–	–	–
No	0.48 [0.26–0.88]	–	–	–
Birth premature				
No	–	–	–	Ref
Yes	–	–	–	1.70 [1.04–2.78]
History of endometriosis in first-degree relatives				
No	Ref	Ref	–	Ref
Yes	4.12 [1.10–15.39]	2.76 [1.31–5.80]	–	2.37 [1.38–4.08]
Drinking alcohol				
No	Ref	Ref	–	–
Yes	9.83 [1.02–95.06]	0.08 [0.01–0.57]	–	–
Number of fish consumed per week	–	–	0.01 [0.00–0.40]	–
Exercise done				
No	–	–	Ref	–

Table 2 continued

Factor	China	Russia	France	Overall
Yes	–	–	0.45 [0.23–0.89]	–
Health status				
Excellent, very good, good	–	Ref	–	Ref
Fair	–	2.14 [1.33–3.43]	–	1.62 [1.25–2.09]
Poor	–	1.82 [0.25–13.22]	–	1.78 [0.90–3.53]

Statistically significant ($P \leq 0.05$) odds ratios only shown for all groups (overall population, China, Russia, and France)
BMI body mass index, *CI* confidence interval, *DIE* deep infiltrating endometriosis, *GI* gastrointestinal, *OMA* endometrioma, *Ref* reference level, *SUP* superficial peritoneal endometriosis

countries, such as greater importance of the previous use of hormonal treatment in China (OR 17.95; 95% CI 5.92–54.43), or gastrointestinal symptoms during menstruation in China (OR 3.18; 95% CI 1.90–5.31) and Russia (OR 3.85; 95% CI 2.13–6.97).

Secondary Objectives—Overall Population

At study entry, for the overall population, a suspicion of endometriosis was the surgical indication for 51.3% ($n = 517$) of patients. Following surgery, endometriosis was histologically confirmed in 71.4% ($n = 719$) of patients leading to a rate of unsuspected endometriosis of 20.1% ($n = 202$ patients). In the cases of unsuspected endometriosis, the final histologic diagnosis was SUP in the majority of cases, with similar values observed in each of the three countries.

Secondary Objectives—Comparative Differences Between Regions

Gynecologic History

Table 4 summarizes the gynecologic history of patients in China, Russia, and France. Differences were seen between countries with regard to regular menstrual cycles, regular use of tampons, vaginal douching practice, menstrual and ovulatory disorders, contraception use, previous pregnancy, and infertility. For all but pregnancy and infertility, these variables were highest in French patients; pregnancy was highest in Chinese patients, and infertility highest in Russian patients.

Infertility was reported in fewer subjects in the OMA group (27.1%) compared with the DIE (42.0%), SUP (51.4%), and control (39.9%) groups. Infertility occurred in approximately one-third of patients in China regardless of

Table 3 Odds ratios [95% CI] for variables associated with OMA and DIE vs control (no endometriosis and SUP) patients from multivariate analysis

Factor	China	Russia	France	Overall
Previous use of hormonal treatment for endometriosis	17.95 [5.92–54.43]	7.54 [2.90–19.57]	3.04 [0.88–10.45]	6.66 [4.05–10.93]
Previous surgery for endometriosis	3.06 [1.21–7.73]	5.46 [1.46–20.38]	1.05 [0.28–3.90]	1.95 [1.11–3.43]
Does not live in city or near a busy area	2.14 [1.27–3.60]	NS	NS	1.66 [1.09–2.52]
GI symptoms during menstruation	3.18 [1.90–5.31]	3.85 [2.13–6.97]	NS	NS
Lives or works in a busy area	NS	NS	NS	1.66 [1.09–2.52]
Infertility	0.55 [0.34–0.87]	0.19 [0.10–0.36]	0.78 [0.38–1.63]	0.46 [0.35–0.62]
Irregular lifelong menstrual cycles	0.36 [0.13–0.96]	NS	0.19 [0.06–0.63]	NS
Not breastfed	0.33 [0.16–0.69]	NS	NS	NS
Practice of vaginal douching	0.39 [0.16–0.97]	NS	NS	0.58 [0.35–0.98]
Pregnancy	NS	0.49 [0.27–0.91]	NS	NS
Units of alcohol per week (10 u increase)	NS	0.05 [0.00;0.67]	NS	NS

Statistically significant ($P \leq 0.05$) odds ratios shown for all groups (overall population, China, Russia, and France). The overall population values are from the primary efficacy analysis

Reference values: previous hormonal treatment for endometriosis, ref = no; previous surgery for endometriosis, ref = no; Live/work in city/busy area/smoky area, ref = no; GI symptoms during menstruation, ref = no; infertility, ref = no; lifelong menstrual cycles, ref = always and generally regular; breastfed, ref = yes; douching, ref = no; pregnancy, ref = no

CI confidence interval, *DIE* deep infiltrating endometriosis, *GI* gastrointestinal, *NS* not selected for analysis, *OMA* endometrioma, *SUP* superficial peritoneal endometriosis

Table 4 Between-country differences in gynecologic clinical history

Factor	China	Russia	France	Statistical comparison between countries, Chi^2 test (where applicable)	Total
Mean age of menarche [95% CI]	13.60 [13.48–13.72] $n = 545$	12.96 [12.81–13.10] $n = 307$	12.68 [12.42–12.95] $n = 154$		13.26 [13.17–13.35] $N = 1006$
Lifelong menstrual cycles, *n/N* (%)					
Always regular	344/545 (63.1)	144/307 (46.9)	129/154 (83.8)	F vs R, $P < 0.0001$	617/1006 (61.3)
				C vs F, $P < 0.0001$	
				C vs R, $P < 0.0001$	
Generally regular	166/545 (30.5)	120/307 (39.1)	2/154 (1.3)		288/1006 (28.6)
Irregular	35/545 (6.4)	43/307 (14.0)	23/154 (14.9)		101/1006 (10.0)
Missing	1	0	0		1
Tampon used regularly during menstruation, *n/N* (%)	77/545 (14.1)	76/307 (24.8)	94/154 (61.0)	F vs R, $P < 0.0001$	247/1006 (24.6)
				C vs F, $P < 0.0001$	
				C vs R, $P = 0.0001$	
Vaginal douching practised regularly, *n/N* (%)	38/545 (7.0)	20/307 (6.5)	32/154 (20.8)	F vs R, $P < 0.0001$	90/1006 (8.9)
				C vs F, $P < 0.0001$	
				C vs R, $P = 0.7989$	
Menstrual and ovulatory disorders, *n/N* (%)	45/545 (8.3)	56/307 (18.2)	89/154 (57.8)	F vs R, $P < 0.0001$	190/1006 (18.9)
				C vs F, $P < 0.0001$	
				C vs R, $P < 0.0001$	
Contraception use, *n/N* (%)	384/546 (70.3)	239/307 (77.9)	143/154 (92.9)	F vs R, $P < 0.0001$	766/1007 (76.1)
				C vs F, $P < 0.0001$	
				C vs R, $P = 0.0175$	

Table 4 continued

Factor	China	Russia	France	Statistical comparison between countries, Chi^2 test (where applicable)	Total
Pregnancy, *n*/*N* (%)	326/546 (59.7)	137/307 (44.6)	52/154 (33.8)	F vs R, $P = 0.0254$ C vs F, $P < 0.0001$ C vs R, $P < 0.0001$	515/1007 (51.1)
Gestations					
1 to 3, *n*/*N* (%)	279/326 (85.6)	124/137 (90.5)	48/52 (92.3)		451/515 (87.6)
4 to 8, *n*/*N* (%)	47/326 (14.4)	13/137 (9.5)	4/52 (7.7)		64/515 (12.4)
Gestations with delivery (parity)					
1 to 3, *n*/*N* (%)	221/326 (67.8)	76/137 (55.5)	30/52 (57.7)		327/515 (63.5)
Gestations without delivery					
1 to 3, *n*/*N* (%)	246/326 (75.5)	104/137 (75.9)	27/52 (51.9)		377/515 (73.2)
4 to 7, *n*/*N* (%)	21/326 (6.4)	7/137 (5.1)	2/52 (3.8)		30/515 (5.8)
Miscarriage, *n*/*N* (%)	77/267 (28.8)	34/111 (30.6)	19/29 (65.5)		130/407 (31.9)
Voluntary abortion, *n*/*N* (%)	184/267 (68.9)	54/111 (48.6)	12/29 (41.4)		250/407 (61.4)
Therapeutic abortion, *n*/*N* (%)	21/267 (7.9)	26/111 (23.4)	0/29		47/407 (11.5)
Ectopic pregnancy, *n*/*N* (%)	8/267 (3.0)	18/111 (16.2)	1/29 (3.4)		27/407 (6.6)
Infertility, *n*/*N* (%)	154/546 (28.2)	197/307 (64.2)	50/154 (32.5)	F vs R, $P < 0.0001$ C vs F, $P = 0.3039$ C vs R, $P < 0.0001$	401/1007 (39.8)
Primary, *n*/*N* (%)	85/154 (55.2)	117/197 (59.4)	32/50 (64.0)		234/401 (58.4)
Secondary, *n*/*N* (%)	69/154 (44.8)	80/197 (40.6)	18/50 (36.0)		167/401 (41.6)

C China, *CI* confidence interval, *F* France, *R* Russia

Table 5 Between-country differences in endometriosis-associated clinical history

Factor	China	Russia	France	Statistical comparison between countries, Chi^2 test (where applicable)	Total
Laparoscopy/laparotomy, *n*	509/37	306/1	127/27		942/65
	$n = 546$	$n = 307$	$n = 154$		$N = 1007$
Reason for surgery, *n*/*N* (%)					
Suspicion of endometriosis	196/546 (35.9)	82/307 (26.7)	89/154 (57.8)		367/1007 (36.4)
Other gynecologic indication*	290/546 (53.1)	151/307 (49.2)	49/154 (31.8)		490/1007 (48.7)
Previous uterine surgery, *n*/*N* (%)	108/545 (19.8)	39/307 (12.7)	8/154 (5.2)	F vs R, $P = 0.0120$ C vs F, $P < 0.0001$ C vs R, $P = 0.0083$	155/1006 (15.4)
Previously surgically diagnosed with endometriosis, *n*/*N* (%)	47/479 (9.8)	31/307 (10.1)	30/154 (19.5)	F vs R, $P = 0.0050$ C vs F, $P = 0.0014$ C vs R, $P = 0.8960$	108/940 (11.5)
Mean age first endometriosis symptoms (years [95% CI])	28.15 [27.37–28.93] $n = 331$	27.66 [26.92–28.39] $n = 180$	22.54 [20.65–24.43]† $n = 63$		27.38 [26.82–27.94] $N = 574$
Mean time between first medical attention and visit day (years [95% CI])	1.81 [1.48–2.14] $n = 366$	1.93 [1.53–2.33] $n = 190$	3.67 [2.66–4.67]† $n = 63$		2.04 [1.78–2.29] $N = 619$
Mean time between first medical attention and diagnosis (years [95% CI])	1.07 [0.28–1.85] $N = 46$	0.50 [0.10–0.90] $N = 30$	5.76 [3.69–7.83] $N = 29$		2.20 [1.42–2.98] $N = 105$
Mean time between first endometriosis symptoms and first medical attention (years [95% CI])	2.13 [1.62–2.64] $n = 330$	0.78 [0.43–1.13] $n = 180$	5.06 [3.66–6.47]† $n = 63$		2.03 [1.67–2.39] $N = 573$

Table 5 continued

Factor	China	Russia	France	Statistical comparison between countries, Chi^2 test (where applicable)	Total
Previous hormonal treatment for endometriosis, *n*/*N* (%)	64/497 (12.9)	57/307 (18.6)	36/154 (23.4)	F vs R, $P = 0.2248$ C vs F, $P = 0.0016$ C vs R, $P = 0.0284$	157/958 (16.4)
History of endometriosis in a first-degree relative, *n*/*N* (%)	12/546 (2.2)	34/307 (11.1)	13/153 (8.5)	F vs R, $P = 0.3897$ C vs F, $P = 0.0002$ C vs R, $P < 0.0001$	59/1006 (5.9)

C China, *CI* confidence interval, *F* France, *R* Russia

* Other indications include benign ovarian cysts (except endometrioma), uterine myomas, bleeding, request for tubal ligation, infection

† Non-overlapping 95% CI values

phenotype (OMA, SUP, or DIE) and, in France, in approximately one-quarter with OMA and 40% with SUP or DIE. However, in Russia, most patients with SUP or DIE had infertility (86.4% and 62.8%, respectively), but only one-third of patients with OMA.

Endometriosis History

In terms of endometriosis history (Table 5), mean [±standard deviation (SD)] age of subjects at the presentation of their first endometriosis symptoms was lower in France (22.54 ± 7.50 years) compared with China (28.15 ± 7.22 years) and Russia (27.66 ± 5.01 years). The mean ± SD time between first endometriosis symptoms and first medical attention sought was considerably shorter in Russia (0.78 ± 2.38 years) compared with China (2.13 ± 4.67 years) and France (5.06 ± 5.58 years). Similarly, the mean ± SD time between first seeking medical attention and diagnosis was shorter in Russia (0.50 ± 1.07 years) compared with China (1.07 ± 2.64 years) and France (5.76 ± 5.45 years). Finally, the mean ± SD time since first endometriosis symptoms and the visit day was shorter in Russia (2.76 ± 3.88 years) compared with China (4.08 ± 5.56 years) and France (8.73 ± 6.79 years).

The previous uterine surgery was highest in China, while more patients in France were previously surgically diagnosed with endometriosis, and hormonal treatment for endometriosis was also highest in France. Finally, more patients in Russia had a history of endometriosis in a first-degree relative.

Pre-Surgery Symptoms

Differences in pain reporting were observed between countries, with an overall trend towards the highest symptom reporting in the French group and the lowest symptom

Table 6 Between-country differences in pre-surgical symptoms

Factor	China	Russia	France	Statistical comparison between countries, Chi^2 test (where applicable)	Total
Non-cyclic chronic pelvic pain, *n*/*N* (%)	76/546 (13.9)	129/307 (42.0)	73/154 (47.4)	F vs R, $P = 0.3574$ C vs F, $P < 0.0001$ C vs R, $P < 0.0001$	278/1007 (27.6)
Mean intensity out of 10 [95% CI]	3.74 [3.28–4.20] $n = 76$	5.64 [5.24–6.04] $n = 129$	5.40 [4.94–5.86] $n = 73$		5.05 [4.78–5.32] $N = 278$
Dysmenorrhea, *n*/*N* (%)	308/546 (56.4)	147/307 (47.9)	120/154 (77.9)	F vs R, $P = 0.3574$ C vs F, $P < 0.0001$ C vs R, $P = 0.0166$	575/1007 (57.1)
Primary, *n*/*N* (%)	99/308 (32.1)	112/147 (76.2)	73/120 (60.8)		284/575 (49.4)
Secondary, *n*/*N* (%)	209/308 (67.9)	35/147 (23.8)	47/120 (39.2)		291/575 (50.6)
Mean intensity out of 10 [95% CI]	5.39 [5.10–5.67] $n = 308$	6.99 [6.59–7.39] $n = 147$	7.34 [7.03–7.65]* $n = 120$		6.21 [6.00–6.41] $N = 575$
Dysmenorrhea impacting life, *n*/*N* (%)	136/308 (44.2)	95/147 (64.6)	98/120 (81.7)	F vs R, $P = 0.0020$ C vs F, $P < 0.0001$ C vs R, $P = 0.0002$	329/575 (57.2)
Use of oral contraceptive in dysmenorrhea, primary, *n*/*N* (%)	4/99 (4.0)	16/112 (14.3)	33/73 (45.2)		53/284 (18.7)
Use of oral contraceptive in dysmenorrhea, secondary, *n*/*N* (%)	11/209 (5.3)	11/35 (31.4)	6/47 (12.8)		28/291 (9.6)
Pain at time of ovulation, *n*/*N* (%)	30/546 (5.5)	119/307 (38.8)	65/154 (42.2)	F vs R, $P = 0.4761$ C vs F, $P < 0.0001$ C vs R, $P < 0.0001$	214/1007 (21.3)

Table 6 continued

Factor	China	Russia	France	Statistical comparison between countries, Chi^2 test (where applicable)	Total
Mean intensity out of 10 [95% CI]	3.50 [2.72–4.28] $n = 30$	4.52 [4.13–4.91] $n = 119$	4.48 [3.96–5.00] $n = 65$		4.36 [4.08–4.65] $N = 214$
Deep dyspareunia, n/N (%)	69/545 (12.7)	140/307 (45.6)	86/154 (55.8)	F vs R, $P = 0.0380$ C vs F, $P < 0.0001$ C vs R, $P < 0.0001$	295/1006 (29.3)
Mean intensity out of 10 [95% CI]	3.91 [3.50–4.33] $n = 68$	4.71 [4.38–5.05] $n = 140$	5.50 [4.99–6.01] $n = 86$		4.76 [4.51–5.00] $N = 294$
GI symptoms during menstruation, n/N (%)	123/546 (22.5)	144/307 (46.9)	81/154 (52.6)	F vs R, $P = 0.2488$ C vs F, $P < 0.0001$ C vs R, $P < 0.0001$	348/1007 (34.6)
Mean intensity out of 10 [95% CI]	3.43 [3.08–3.77] $n = 120$	4.60 [4.19–5.02] $n = 144$	5.58 [5.09–6.07]* $n = 79$		4.42 [4.16–4.67] $N = 343$
Urinary symptoms at menstruation, n/N (%)	32/546 (5.9)	44/307 (14.3)	21/154 (13.6)	F vs R, $P = 0.8395$ C vs F, $P = 0.0013$ C vs R, $P < 0.0001$	97/1007 (9.6)
Mean intensity out of 10 [95% CI]	3.41 [2.69–4.13] $n = 32$	4.89 [4.09–5.68] $n = 44$	4.76 [3.60–5.92] $n = 21$		4.37 [3.87–4.87] $N = 97$

C China, *CI* confidence interval, *F* France, *GI* gastrointestinal, *R* Russia

* Non-overlapping 95% CI values

reporting in the Chinese group (Table 6). In the overall population of patients, 57.2% ($n = 329$) considered dysmenorrhea to have a real impact on their daily quality of life. This impact was significantly more important in France (81.7%, $n = 98$), compared with Russia (64.6%, $n = 95$) and China (44.2%, $n = 136$). In the overall population, oral contraception was prescribed to treat intensity of primary dysmenorrhea in 18.7% of the cases ($n = 53$). This result is significantly correlated to the country: 4.0% in China ($n = 4$), 14.3% in Russia ($n = 16$), and 45.2% in France ($n = 33$) (Table 6).

In the overall population, painful symptoms were more frequently reported in patients with endometriosis when compared to those without endometriosis. The frequency of painful symptoms seemed to be correlated with the endometriosis phenotype and increased with the severity of the lesions: SUP, OMA, and DIE (Fig. 1a). Similar trends were observed for the intensity of pain/discomfort symptoms according to the visual analog scale, with Chinese patients reporting the lowest intensities (Fig. 1b). While the incidence of symptoms appeared to be correlated with

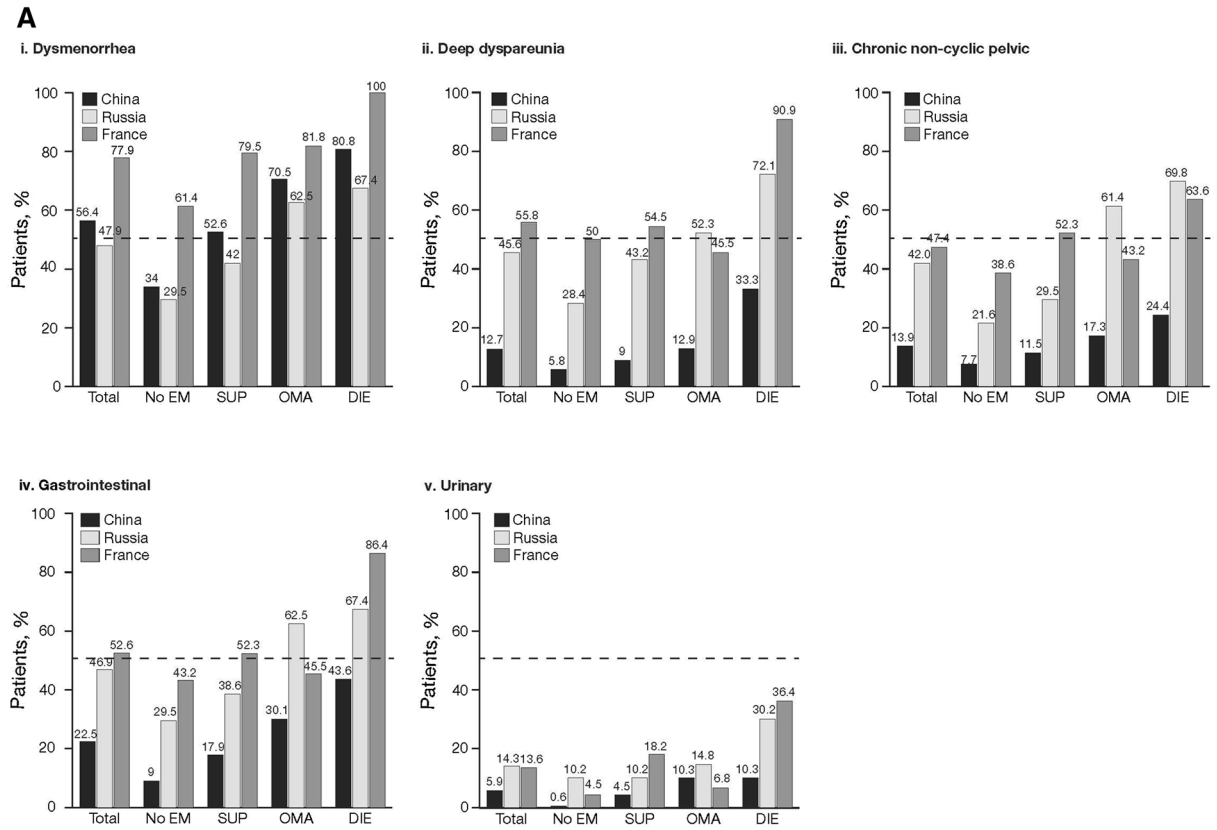

Fig. 1 **a** Complaint frequency illustrated by endometriosis type and country for (*i*) dysmenorrhea, (*ii*) deep dyspareunia, (*iii*) chronic non-cyclic pelvic pain, (*iv*) gastrointestinal symptoms during menstruation, and (*v*) urinary symptoms during menstruation. **b** Pain or discomfort intensity as rated on Visual Analog Scale for (*i*) chronic non-cyclic pelvic pain, (*ii*) dysmenorrhea, (*iii*) deep dyspareunia, (*iv*) gastrointestinal symptoms during menstruation, and (*v*) urinary symptoms during menstruation. *EM* endometriosis, *DIE* deep infiltrating endometriosis, *OMA* endometrioma, *SUP* superficial peritoneal endometriosis

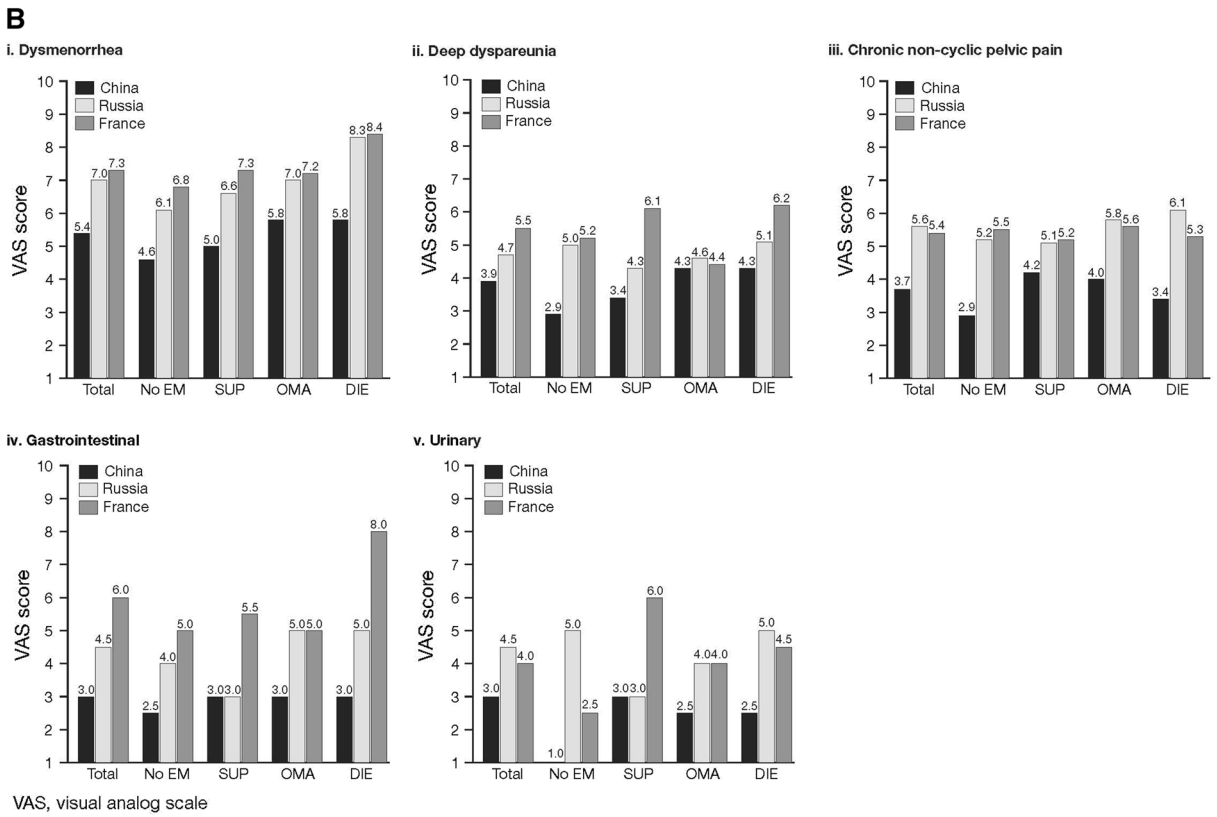

Fig. 1 continued

countries and phenotypes, their intensity differed largely according to country but not to phenotype.

Other Variables

Living or working in a busy area was recorded for 96.7% of patients from Russia, 89.0% from France, and 80.6% from China (France vs Russia, $P < 0.0008$; China vs France, $P = 0.0159$). Living or working in a smoky atmosphere was reported by 54.7% of patients from Russia, 22.6% from China, and 14.4% from France (France vs Russia, $P < 0.0001$; China vs France, $P = 0.0267$). In Russia and China, 92.2% and 89.5% of patients had been breastfed, respectively, compared with only 52.0% of patients from France. Finally, the mean (95% CI) units of alcohol consumed per week were 0.68 (0.58–0.78) for the total population ($N = 988$), with 0.20 (0.12–0.28) for China, 1.03 (0.88–1.17) for Russia, and 1.63 (1.20–2.06) for France.

DISCUSSION

This multi-country, case–control study demonstrates important wide-ranging clinical and environmental factors that may be associated with DIE or OMA, compared with SUP and no endometriosis, in women who had recently undergone surgery for a benign gynecologic indication across three diverse regions. This is the first study, to our knowledge, to examine the relationship between such factors and endometriosis, and supports the theory that DIE and OMA have complex, multifaceted origins. The data highlight interesting regional differences,

potentially influenced by health care and cultural practices specific to the local environment, in the diagnosis, symptomatology, and treatment practices of endometriosis.

Pain reporting varied between countries, possibly related to cultural influences, rather than actual differences in pain experienced. Indeed, most (82%) French patients reported that dysmenorrhea impacted their lives vs only 44% of Chinese patients. Furthermore, deep dyspareunia was more frequent in French women without endometriosis (50%) than in Chinese women with endometriosis (15.4%). These findings suggest potentially different health care experiences and/or expectations between patients from different regions. In addition, multiple studies suggest that cultural norms may influence individual conceptualization of pain and affect health-seeking behavior [26–28]. Although French patients reported more pain, they also tolerated longer duration between pain and treatment, which may reveal differences in treatment acceptability and/or health care system efficiencies.

Studies of Western patients with endometriosis report infertility rates of 30–50% [29]. However, 64.2% of Russian patients in our study reported infertility, vs 32.5% and 28.2% in France and China, respectively. The participating Russian centers are specialists in fertility treatment, suggesting that infertility rates seen in Russian patients, particularly with SUP histology (86% of Russian SUP patients had infertility), may have been affected by referral biases. We hypothesize that infertility was the main indication for surgery among the controls/SUP cases (and tubal ligation was the main indication in other prospective cohorts), and speculate that only the best cases of infertility (i.e., young patients with good ovarian reserve) are operated on; other patients with poor infertility prognosis should receive assisted reproductive technologies without surgery.

The key strengths of this study are the inclusion of many patients ($N = 1008$) from three ethnically, culturally, socially, and economically different countries. In addition, each patient had been histologically diagnosed according to endometriosis phenotype, and all patients without endometriosis had been surgically explored to exclude asymptomatic endometriosis. To avoid recruitment bias, all consecutive patients who met the eligibility criteria during the specified period were included. To overcome the limitations of selecting a control group for patients with endometriosis [24], a case–control design was used to enable identification of associated factors and to avoid under-representation of DIE patients. All women included had recently undergone surgery for a benign gynecologic indication; however, any non-endometriosis pathology—benign ovarian cyst, uterine myoma, salpingitis, polycystic ovary syndrome, and tubal infertility treatment—was not taken into account when analyzing factors associated with endometriosis. Clinical presentation was chosen, as endometriosis is a heterogeneous disease with three different entities: SUP, OMA, and DIE [30]. The two main benefits for this approach are that treatment modalities are decided according to the clinical appearance of endometriotic lesions; and identifying risk factors for endometriosis contribute to reducing the delay for the diagnosis especially for the most severe phenotypes (OMA and DIE). The difficulties and limitations of this approach are that the three phenotypes can be present in the same patient [31]. Some specific study limitations exist. Data collection occurred at the post-operative visit when patients received the outcome of their surgical investigation. Patient behavior can

change—particularly in the short term—following a clinical diagnosis [32, 33], and we cannot rule out the possibility that some patient responses regarding current behaviors were influenced by their surgery results. This might partly explain why only predictable factors (e.g., factors of diagnosis) were associated with OMA and/or DIE and not etiologic factors. Ideally, these data would have been collected prior to revealing the surgery results. In addition, a large quantity of data was collected retrospectively at the study visit, which makes causality and temporality difficult to assess, and is subject to recall bias.

The main objective of this study was not inter-country comparison. Thus, no formal monitoring of translations or assessment of literal translation accuracy across sites was carried out; however, translations were carried out at a country level, so translation accuracy and cultural competencies can be assumed. Low patient numbers in national groups by endometriosis type limit both inter- and intra-country comparisons; although numeric within-country differences were noted across endometriosis types, few were significant. Nevertheless, the importance of our findings should not be underestimated.

CONCLUSION

In conclusion, we show substantial differences in the symptoms and management of endometriosis phenotypes across three diverse countries, which suggest that this multifactorial, complex condition cannot be generalized on a global scale. Larger studies, taking into account geographic, cultural, and health care differences between patients, are required to confirm the initial findings reported here, with the goal of assisting investigators in achieving earlier patient risk stratification and diagnosis within routine clinical practice.

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Participation in study design [all authors], execution [all authors], statistical analysis [Pascal Maisonobe], manuscript drafting and critical discussion [all named authors].

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Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Patients provided written informed consent to allow their medical data to be collected, analyzed, and shared with regulatory authorities. The study identifier for clinicaltrials.gov is NCT01351051. Prior to initiating the study, the investigator/institution had approval from the Independent Ethics Committee/Institutional Review Board as applicable in the country of study

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