

The impact of anemia on treatment management and clinical outcomes of women hospitalized for uterine leiomyomas

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ABSTRACT

Objectives: Uterine leiomyomas are the most common benign gynecological tumors. Symptomatic leiomyomas represent a major cause of hospitalization, particularly those associated with abnormal uterine bleeding (AUB) and anemia. The aim of this study was to identify predictors of anemia in women hospitalized due to uterine leiomyomas and evaluate its impact on treatment management and clinical outcomes.

Material and methods: Population-based retrospective study of women hospitalized for uterine fibroids in public hospitals in mainland Portugal between 2010 and 2015. Data were extracted from the national database of the Central Administration of the Portuguese Health System. Comparative and multivariable logistic regression analysis was performed to assess outcomes.

Results: A total of 36 295 patients were hospitalized due to uterine leiomyomas during this period. Of those, 11.5% presented with anemia. Age, obesity, intramural type of leiomyoma and AUB are independent predictors of anemia ($p < 0.001$, AUC 0.7056). Anemia was associated with a high risk of inpatient hospitalization (OR: 5.161, 95% CI: 4.376–6.085), urgent admission (OR: 1.953, 95% CI: 1.797–2.121), radical surgical approach (OR: 2.559, 95% CI: 2.298–2.849), laparoscopic hysterectomy (OR: 1.575, 95% CI: 1.393–1.780) and intra- and post-operative complications (OR: 5.285, 95% CI: 4.332–6.448). It was also associated with longer hospital stays ($p < 0.001$). These outcomes were more pronounced in acute anemic patients.

Conclusions: Anemia has a significant impact on treatment approaches and clinical outcomes of women hospitalized for uterine leiomyomas. Age, obesity, intramural leiomyomas and AUB are some predictors of anemia that could represent a risk-stratification opportunity, allowing for its prompt identification and correction, therefore improving patient care.

Key words: leiomyoma; anemia; hysterectomy; uterine myomectomy; endoscopy; hospitalization

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INTRODUCTION

Uterine leiomyomas are the most common benign gynecological tumors, affecting up to 70% of women of reproductive age [1, 2].

The exact prevalence of uterine leiomyomas is unknown as most of them are asymptomatic and often incidentally found [2, 3]. However, it is estimated that about 2 million Portuguese women are affected by this disease [1, 4–6].

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Nevertheless, approximately 1/3 of leiomyomas are associated with a variety of symptoms including abnormal uterine bleeding (AUB), pelvic pressure or pain and possibly reproductive dysfunction, mainly subfertility and recurrent pregnancy loss [1–3, 5, 7]. The clinical complaints may differ significantly depending on size, location and number of leiomyomas. According to the International Federation of Gynecology and Obstetrics (FIGO) Classification System, there are nine types of leiomyomas (submucosal: types 0–2; intramural: types 3, 4; subserous: types 5–7; other locations — cervical, round or broad ligaments, parasitic: type 8) [8]. Those that involve the endometrial cavity (types 0–3) are the most likely to contribute to AUB and consequent anemia [8–10].

Moreover, symptomatic leiomyomas can significantly impair the patient's quality of life eventually leading to absenteeism and decreased productivity in the workplace, having also been described as a major cause of hospitalization and surgery for gynecologic disorders [1, 2, 5, 6]. Indeed, surgical treatment has long been the standard for symptomatic leiomyomas, which can be radical (hysterectomy) or conservative/uterus-sparing approach (uterine myomectomy and uterine artery embolization). Medical therapies such as gonadotropin-releasing hormone (GnRH) agonists or antagonists and selective progesterone receptor modulators (SPRMs) can also be used as an alternative to surgery or as a pre-operative ancillary to improve and optimize surgical outcomes by reducing size of leiomyomas and/or AUB [2–5, 7, 11].

Preoperative anemia has been associated with longer hospital stays and increased post-operative morbimortality in some surgical specialties [12]. However, there is insufficient published evidence regarding the effect of anemia in patients hospitalized for uterine leiomyomas.

Objectives

The aim of this study was to identify predictors of anemia in women hospitalized due to uterine leiomyomas and evaluate its impact on treatment management and clinical outcomes of these patients.

MATERIAL AND METHODS

Study design and population

We performed a population- and register-based retrospective study of women who were hospitalized with a primary diagnosis of uterine fibroid in public hospitals in mainland Portugal between 2010 and 2015.

The Central Administration of the Portuguese Health System — *Administração Central do Sistema de Saúde* (ACSS) — approved the study and provided the database containing information related to all public hospitals in mainland Portugal.

Data collection

Patient data regarding hospital codes based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), age, admission and discharge dates, type of hospitalization, diagnoses, procedures and complications were extracted from the national database of ACSS.

The primary diagnosis, defined as the condition after study which occasioned the admission to the hospital, was classified by ICD-9-CM as submucous leiomyoma of uterus (218.0), intramural leiomyoma of uterus (218.1), subserous leiomyoma of uterus (218.2) and unspecified leiomyoma of uterus (218.9). The existence of anemia was characterized by women with the following ICD-9-CM diagnoses: anemia due to chronic blood loss (280.0), acute posthemorrhagic anemia (285.1) and non-specified blood loss anemia (285.9), considering the World Health Organization (WHO) definition of anemia that comprises a hemoglobin threshold of < 12 g/dL for non-pregnant woman [13, 14]. Procedures included medical and surgical treatments which can be divided in conservative (uterine myomectomy, hysteroscopy, curettage and/or embolization) or radical (hysterectomy) approaches. The surgical route (laparotomy, endoscopy or vaginal) was also reported. Intra- and post-operative complications such as dehiscence of the surgical wound, post-operative infection, hemorrhage, hematoma and/or seroma were also analyzed.

Outcomes

We intended to determine if there are any identifiable risk factors associated with the presence of anemia in women hospitalized for uterine leiomyomas such as age, obesity, type of uterine leiomyoma or presence of AUB. Additionally, we sought to study the impact of anemia in the treatment approaches and clinical outcomes of these women, comparing those with and without anemia regarding the need of surgical treatment, surgical management (conservative/radical), surgical route (laparotomy/endoscopy/vaginal), type of hospitalization (inpatient/outpatient, elective/urgent), number of hospitalization days and intra- and post-operative complications. A secondary analysis considering chronic versus acute anemia was also conducted.

Ethical compliance

The database is blinded relative to patient identification in order to disenable the investigator from identifying the subjects and to maintain anonymity. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

Statistical analysis

Normality of continuous variables was assessed by histogram observation and the Kolmogorov-Smirnov test.

Continuous variables were expressed as mean \pm standard deviation and categorical variables as percentages. Student's *t*-test and χ^2 test were used for group comparisons in continuous and categorical variables, respectively. Multivariable logistic regression models and Receiver-Operating Characteristic (ROC) Analysis were also performed to achieve predictors of anemia and assess its independent effect on treatment approaches and clinical outcomes of women hospitalized for uterine leiomyomas. A two-sided *p*-value < 0.05 was considered statistically significant. All calculations were performed using STATA software version 16.0.

RESULTS

National trends and prevalence of anemia in women hospitalized for uterine leiomyomas

A total of 36 295 patients were admitted in public hospitals in Portugal due to uterine leiomyomas between 2010 and 2015. There was a decrease in the number of hospitalizations for uterine leiomyomas from 6358 in 2010 to 5449 in 2015, representing a decline of 14.3% (Fig. 1).

During this period, 11.5% ($n = 4155$) of hospitalized women presented with anemia, of which 50.7% ($n = 2108$) had chronic anemia, 17.0% ($n = 707$) had acute anemia and 32.3% ($n = 1340$) had non-specified blood loss anemia.

Characterization of women hospitalized for uterine leiomyomas and prediction of anemia

According to Table 1, anemic patients were younger and more obese than patients without anemia. The presence of AUB, intramural leiomyomas and coexistence of more than one type of leiomyoma were also associated with anemic patients.

A multivariable regression model including variables with clinical significance revealed that age, obesity, intramural type of leiomyoma and presence of AUB were all independent predictors of anemia in hospitalized women (Tab. 2). The ROC curve analysis of this model was associated with predictive power to forecast the presence of anemia (Fig. 2).

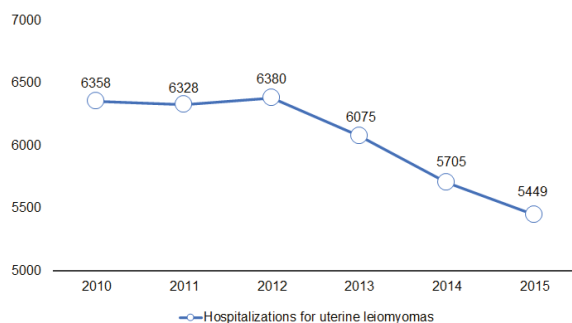


Figure 1. Number of hospitalizations due to uterine leiomyomas between 2010 and 2015

Impact of anemia on treatment management and clinical outcomes of women hospitalized for uterine leiomyomas

The inpatient hospitalization was more frequent in women with anemia comparing to those without this condition (95.7% vs 81.1%, $p < 0.001$). Similarly, the urgent admissions to the Hospital were also more frequent in this group (26.4% vs 11.3%, $p < 0.001$) (Tab. 1).

Regarding treatment, 92.4% ($n = 3838$) of anemic women were submitted to a surgical procedure. Of those, a radical approach (hysterectomy) was performed in the majority of women [82.4% ($n = 3161$)], mainly by laparotomy. However, the laparoscopic hysterectomy was more common in patients with anemia than in non-anemic patients (12.3% vs 8.3%, $p < 0.001$) (Tab. 1).

The mean hospitalization days were higher in anemic patients (4.5 ± 3.4 vs 3.4 ± 2.8 days, $p < 0.001$), as well as the rate of intra- and post-operative complications (4.7% vs 1.0%, $p < 0.001$) (Tab. 1).

After multivariable analysis adjusting for potential confounders, anemia remained independently and significantly associated with inpatient hospitalization, urgent admission to the Hospital, radical surgical approach, laparoscopic hysterectomy and intra- and post-operative complications (Tab. 3).

Secondary analysis for acute and chronic anemia

A subgroup analysis considering patients with acute versus chronic anemia revealed that the first one was associated with more inpatient hospitalizations, more urgent admissions to the Hospital and longer hospital stays. Although there were no statistical differences between both groups regarding radical surgeries, the laparoscopic route was more frequent in chronic anemic patients submitted to hysterectomy than in patients with acute anemia (Tab. 4).

Of all hospitalized patients due to uterine leiomyomas, 4.6% ($n = 1630$) received a blood transfusion. As presented in Table 4, the need for transfusion was higher in acute anemic patients than those with chronic anemia (53.6% vs 18.9%, $p < 0.001$), as well as the rate of intra- and post-operative complications (17.5% vs 1.8%, $p < 0.001$).

DISCUSSION

This study highlights three main findings considering hospitalization due to uterine leiomyomas. First, a significant percentage of hospitalized women presented with anemia, and we identified some independent predictors of this condition, namely age, obesity, intramural type of leiomyoma and the presence of AUB. Second, adjusting for the presence of potential confounders, we still observed that anemia has a substantial impact on treatment management and clinical outcomes of patients hospitalized due to

Table 1. Characteristics, treatment approaches and clinical outcomes of women hospitalized for uterine leiomyomas with and without anemia				
	Total population (n = 36 295)	With anemia (n = 4155)	Without anemia (n = 32 140)	P
Panel A: Characteristics of hospitalized women with and without anemia				
Age, mean \pm SD, years	47.3 \pm 8.6	45.7 \pm 7.0	47.5 \pm 8.8	< 0.001
Obesity, % (n)	6.2 (2252)	8.3 (345)	5.9 (1907)	< 0.001
No. of different leiomyomas, % (n)				
Only 1 type of leiomyoma	82.2 (29 832)	76.7 (3188)	82.9 (26 644)	< 0.001
\geq 2 types of leiomyomas	17.8 (6463)	23.3 (967)	17.1 (5496)	
Submucous leiomyoma, % (n)	38.3 (13 886)	37.0 (1538)	38.4 (12 348)	0.080
Intramural leiomyoma, % (n)	57.1 (20 706)	65.7 (2729)	55.9 (17 977)	< 0.001
Other type of leiomyomas, % (n)*	26.8 (9712)	26.5 (1103)	26.8 (8609)	0.743
Abnormal uterine bleeding, % (n)	18.9 (6862)	47.0 (1952)	15.3 (4910)	< 0.001
Panel B: Treatment approaches and clinical outcomes				
Type of hospitalization, % (n)				
Inpatient	82.8 (30 055)	95.7 (3977)	81.1 (26 078)	< 0.001
Outpatient	17.2 (6240)	4.3 (178)	18.9 (6062)	
Admission to hospital, % (n)				
Urgent	13.1 (4735)	26.4 (1097)	11.3 (3638)	< 0.001
Elective	86.9 (31 560)	73.6 (3058)	88.7 (28 502)	
Surgical treatment, % (n)	95.2 (34 563)	92.4 (3838)	95.6 (30 725)	< 0.001
Surgical management, % (n)				
Conservative approach	31.3 (10820)	17.6 (677)	33.0 (10 143)	< 0.001
Radical approach	68.7 (23 743)	82.4 (3161)	67.0 (20 582)	
Surgical route, % (n)				
Hysterectomy				< 0.001
Laparotomy	87.7 (20 821)	83.4 (2667)	88.2 (18 154)	
Laparoscopy	8.8 (2094)	12.3 (390)	8.3 (1704)	
Vaginal	3.5 (828)	3.3 (104)	3.5 (724)	
Uterine myomectomy				< 0.001
Laparotomy	0.3 (96)	0.5 (20)	0.2 (76)	
Laparoscopy	0.4 (140)	0.2 (10)	0.4 (130)	
Resectoscopy	13.5 (4799)	8.2 (339)	14.1 (4460)	
Hysteroscopy and curettage	13.6 (4865)	3.7 (151)	13.9 (4392)	< 0.001
Uterine artery embolization	0.1 (48)	0.2 (9)	0.1 (39)	0.112
Hospitalization days, mean \pm SD	3.5 \pm 2.9	4.5 \pm 3.4	3.4 \pm 2.8	< 0.001
Intra- and post-operative complications, % (n)				
Dehiscence of the surgical wound	1.4 (492)	4.7 (182)	1.0 (310)	< 0.001
Post-operative infection	0.2 (71)	0.5 (20)	0.2 (51)	
Hemorrhage, hematoma and/or seroma	0.3 (95)	0.5 (18)	0.3 (77)	
	1.1 (369)	4.1 (156)	0.7 (213)	

*Subserous and unspecified uterine leiomyomas; SD — standard deviation

Table 2. Multivariable logistic regression analysis considering the prediction of anemia in women hospitalized for uterine leiomyomas								
	OR_{unadj}	95%CI		P	OR_{adj}	95%CI		P
Age	0.973	0.970	0.977	< 0.001	0.973	0.968	0.977	< 0.001
Obesity	1.436	1.274	1.618	< 0.001	1.387	1.223	1.573	< 0.001
No. of different leiomyomas	1.470	1.361	1.589	< 0.001	1.059	0.846	1.325	0.619
Submucous leiomyoma	0.942	0.881	1.007	0.080	1.174	0.992	1.389	0.063
Intramural leiomyoma	1.508	1.409	1.613	< 0.001	1.532	1.280	1.833	< 0.001
Other type of leiomyomas	0.988	0.918	1.063	0.743	1.105	0.926	1.319	0.266
Abnormal uterine bleeding	4.914	4.591	5.260	< 0.001	4.702	4.389	5.036	< 0.001

OR_{unadj} — unadjusted/crude odds ratio; OR_{adj} — adjusted odds ratio according to the other variables presented in the table; CI — confidence interval

uterine leiomyomas, particularly on inpatient hospitalizations, urgent admissions, radical surgeries, laparoscopic hysterectomies, mean hospitalization stays as well as intra- and post-operative complications. Third, these effects were worsened by acute anemia.

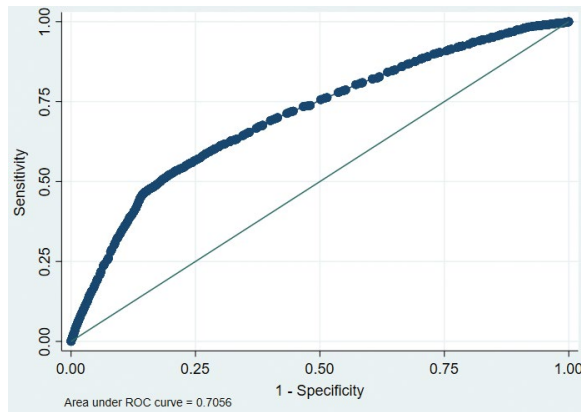


Figure 2. Receiver-Operating Characteristic (ROC) curve for multivariable logistic regression analysis for the prediction of anemia (Area under the ROC curve = 0.7056). The predictive model includes the following variables: age, obesity, number of different leiomyomas, submucous leiomyoma, intramural leiomyoma, other type of leiomyomas and abnormal uterine bleeding

In the context of the current literature, uterine leiomyomas are one of the leading causes of hospitalization for gynecological disorders and one of the most frequent reasons for hysterectomy. Although the number of hospitalizations for uterine leiomyomas has been decreasing over the years in Portugal, probably due to new effective medical therapies, this pathology is still associated with a large impact on healthcare systems, representing a growing public health issue worldwide [1, 2, 7, 15]. The AUB is the most common presenting symptom associated with uterine leiomyomas, which can lead to anemia. In our study, the prevalence of anemia in women hospitalized due to uterine leiomyomas was 11.5%, which did not differ significantly with the published data [12, 16–18].

Considering the prediction of anemia, in a retrospective cohort study of 149 women with severe anemia from heavy menstrual bleeding, the patient's mean age was 41.6 years (range, 19–55 years) with 67.6% of the population being obese or overweight [19]. Our findings also revealed that anemic patients are younger and more obese than non-anemic women, demonstrating that age and obesity are both independent predictors of this condition. Furthermore, a sonohysterography-based study concluded that both intramural and submucous leiomyomas were fairly equally

Table 3. Multivariable logistic regression models considering the impact of anemia on treatment approaches and clinical outcomes of women hospitalized due to uterine leiomyomas

Outcome	Anemia ^a								
	OR _{unadj}	95%CI		p	OR _{adj}	95%CI		AUC	p
Inpatient	5.194	4.458	6.051	< 0.001	5.161	4.376	6.085	0.728	< 0.001
Urgent admission	2.810	2.602	3.036	< 0.001	1.953	1.797	2.121	0.716	< 0.001
Radical surgical approach	2.301	2.111	2.508	< 0.001	2.559	2.298	2.849	0.723	< 0.001
Laparoscopic hysterectomy	1.825	1.627	2.047	< 0.001	1.575	1.393	1.780	0.710	< 0.001
Complications	4.884	4.054	5.884	< 0.001	5.285	4.332	6.448	0.712	< 0.001

^aPatients without anemia constituted the reference population; OR_{unadj} — unadjusted/crude odds ratio; OR_{adj} — adjusted odds ratio according to the model adjusted for age, obesity, number of different leiomyomas, submucous leiomyoma, intramural leiomyoma, other type of leiomyomas and abnormal uterine bleeding; CI — confidence interval; AUC — area under curve

Table 4. Comparison of treatment approaches and clinical outcomes of hospitalized women with acute versus chronic anemia

	Acute anemia (n = 707)	Chronic anemia (n = 2108)	p
Inpatient hospitalization, % (n)	99.6 (704)	94.5 (1993)	< 0.001
Urgent admission, % (n)	42.6 (301)	30.8 (650)	< 0.001
Radical surgical approach, % (n)	81.7 (490)	82.4 (1620)	0.663
Laparoscopic hysterectomy, % (n)	8.0 (39)	15.6 (253)	< 0.001
Hospitalization days, mean ± SD	6.0 ± 5.2	4.1 ± 2.7	< 0.001
Complications, % (n)	17.5 (105)	1.8 (36)	< 0.001
Need of blood transfusion, % (n)	53.6 (379)	18.9 (399)	< 0.001

SD — standard deviation

related to bleeding [20]. Other studies also demonstrated that submucous leiomyomas were associated with a high risk of heavy menstrual bleeding and anemia [9–11]. However, in our study, only the intramural type of leiomyoma demonstrated an independent and significant relation to anemia, which may have resulted from an earlier therapeutic intervention on submucous lesions. In fact, myomectomy by resectoscopy is an easy and safe procedure, which could prevent the occurrence of anemia in patients with leiomyomas that involve the endometrial cavity. Nevertheless, myomectomy of intramural leiomyomas is technically challenging and incomplete excisions are more frequent, what contributes to a higher prevalence of anemia in this type of lesions. On the other hand, some imprecise classification regarding the FIGO Classification System [8] may occur.

With respect to the impact of anemia on treatment management, in our study, non-anemic patients were more frequently submitted to a surgical treatment. This could be explained by the existence of some effective and safe pharmacological agents like GnRH analogs and SPRMs that can be used to control bleeding and correct anemia prior to surgery. These drugs will improve surgical outcomes and are also an option when fertility preservation is the goal. In some cases, the surgery can be avoided if medical therapy is completely successful [3, 21–25].

In our study, anemic patients were submitted more frequently to a radical surgery. On the contrary, in a retrospective study including 96 852 hospitalized patients with a baseline diagnosis of uterine leiomyoma, those with menstrual disorders and anemia were 1.5 and 1.3 times more likely to perform uterine-sparing procedures over hysterectomy, respectively ($p < 0.001$) [18].

As in our study, the published evidence suggests that minimally invasive procedures should be preferred in anemic patients in order to reduce the risk of surgical bleeding and decrease perioperative morbidity. Due to the optimal intraoperative visualization and exposition conditioned by pneumoperitoneum and the better assessment of hemostasis and bleeding control, minimally invasive surgical techniques, namely laparoscopic approaches, are associated with less intra and post-operative complications than laparotomy, particularly regarding surgical bleeding and other possible organ damage, hospital stay and recovery time, which could justify the preference of this surgical option in anemic patients. In fact, the surgical management should be decided based on the patient's preference, size, number and location of leiomyomas as well as the personal experience of the Gynecologist and available equipment [3, 7, 26].

Regarding perioperative complications, a published retrospective cohort study including 12 836 women submitted to a gynecological surgery concluded that preoperative anemia and blood transfusion were associated with worse

postoperative outcomes [12]. Likewise, in our study, anemia was also an independent predictor of intra- and post-operative complications such as dehiscence of the surgical wound, infection, hemorrhage, hematoma and/or seroma.

The loss of blood volume and the iron deficiency associated with anemia are probably the potential mechanisms that predispose to worse hospitalization outcomes and higher rates of complications. These conditions are exacerbated in cases of acute anemia where a physiological response is not as fast and efficient to answer to the clinical and surgical demands.

The findings of this study may have important implications on clinical practice and healthcare assistance, as the identification of preventable predictors of anemia could lead to its prompt correction and therefore prevent its occurrence. Additionally, the earlier diagnosis of anemia and its efficient treatment may avoid its prejudicial effects on treatment approaches and hospitalization outcomes.

A major strength of the present study is that it is a large, reliable, nationwide sample that, in fact, corresponds to the best available data on leiomyoma-related hospital care in a country with a dominant public health system. Moreover, anemia is a potential risk factor in women hospitalized for uterine leiomyomas that can be readily and easily detectable. This could represent a risk-stratification opportunity considering the identified predictors described above, allowing its prompt correction and the improvement of pre-operative status and clinical outcomes, while also reducing associated costs. Additionally, it could also promote primary preventative measures as iron supplementation, blood transfusion and/or bleeding inhibition with GnRH analogs or SPRMs, as already suggested in other studies [21–24].

Nevertheless, the conclusions from this study should be evaluated within the context of its potential limitations. First, its retrospective design might have introduced inherent bias with a dataset which depends on coding accuracy. For example, considering the rate of obesity in our country, it is estimated that obesity was underreported in our study, thus limiting our results. In the same way, other comorbidities or medical conditions that could be important to our research were not registered in the national database, conditioning our findings. Besides, our research was based on the principal diagnosis and other diseases, or symptoms may have been overvalued at the expense of underreporting leiomyoma.

CONCLUSIONS

In conclusion, our results indicate that anemia has a significant impact on treatment approaches and clinical outcomes of women hospitalized for uterine leiomyomas. Some predictors such as age, obesity, intramural leiomyomas and AUB promptly accounted for will improve clinical outcomes and minimally invasive surgical approaches.

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Conflict of interest

All authors declare no conflict of interest.

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