Original Article

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Levonorgestrel-releasing intrauterine system versus oral progestogens for non-atypical endometrial hyperplasia: predictors for treatment failure

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Objective: This study aims to compare treatment outcomes of a levonorgestrel-releasing intrauterine system (LNG-IUS) or oral progestogens in women with non-atypical endometrial hyperplasia (EH). Additionally, the predictors for EH non-regression were determined.
Methods: Medical records of women diagnosed with non-atypical EH between April 2016 and March 2022 at Tuen Mun Hospital were retrieved. These patients were offered LNG-IUS as the first-line option or oral progestogens if they refused or had LNG-IUS contraindications such as submucosal fibroid distorting endometrial cavity. The rate of EH non-regression at 12 months and the rate of EH relapse at 24 and 36 months between groups were compared. Univariate and multivariate analyses were conducted to identify predictors for EH non-regression.
Results: The median follow-up duration was 24 months for the LNG-IUS group and 19 months for the oral progestogens group. The rate of EH regression at 12 months was higher in the LNG-IUS group (93.9% vs 71.2%, p<0.001). The rate of EH relapse was higher in the oral progestogens group at 24 months (21.1% vs 1.1%, p=0.003) and 36 months (33.3% vs 2.3%, p=0.014). The incidence of hysterectomy for treatment failure was higher in the oral progestogens group (13.7% vs 4.2%, p=0.005). No EH relapse occurred in either group after 36 months post-treatment. Predictors for EH non-regression were postmenopausal status (odds ratio=5.80, p=0.022) and oral progestogens treatment (odds ratio=7.51, p<0.001).
Conclusion: In women with non-atypical EH, treatment with LNG-IUS leads to a higher regression rate at 12 months, a lower relapse rate within 36 months, and a lower rate of hysterectomy due to treatment failure, compared with treatment with oral progestogens. Postmenopausal status and treatment with oral progestogens are risk factors for treatment failure. Regular endometrial surveillance should be provided to women at risk. Hysterectomy is recommended for postmenopausal women.

Keywords: Endometrial hyperplasia; Levonorgestrel; Medroxyprogesterone; Metrorrhagia; Norethisterone; Recurrence

Introduction

Endometrial hyperplasia (EH) is the precursor to endometrial cancer (EC), which is the most common gynaecological malignancy in the developed world[1]. The incidence of EH is 133 per 100 000 women and peaks in women in their early 50s and 60s[2]. The main symptom of EH is abnormal uterine bleeding[3]. Early diagnosis and treatment of EH can prevent progression to EC.

Non-atypical EH accounts for about 90% of all EH, whereas atypical EH accounts for the remaining 10%[2]. For women with non-atypical EH, the cumulative long-term risk for progression to EC is <5%[4]. Although spontaneous regression of EH can occur[5], progestogen treatment leads to higher regression rates than observation alone and reduces the need for a hysterectomy and progression to EC[6,7]. Hence, treatments with progestogens are recommended. In particular, the levonorgestrel-releasing intrauterine system (LNG-IUS) is recommended as the first-line medical treatment for EH because it leads to a higher disease regression rate, more favourable bleeding profile, and fewer adverse effects, compared with oral progestogens[8-12].

We aimed to compare the clinical outcomes of women treated with LNG-IUS or oral progestogens, particularly the rate of disease non-regression at 12 months and the rate of disease relapse at 24 and 36 months. Additionally, the predictive factors for disease non-regression were determined.

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Materials and methods

Medical records of women diagnosed with non-atypical EH (according to the World Health Organization's 1994 classification[1]) between April 2016 and March 2022 at Tuen Mun Hospital, Hong Kong, were retrieved from the clinical notes and electronic patient record system. These patients were offered LNG-IUS as the first-line option or oral progestogens if they refused or had LNG-IUS contraindications such as submucosal fibroid distorting endometrial cavity. The LNG-IUS (Mirena; Bayer HealthCare Pharmaceuticals) has a steroid reservoir containing 52 mg levonorgestrel, with a release rate of 21 μg/day for the first 24 days and 11 μg/day for 5 years. The LNG-IUS should be kept in place for at least 6 months and to 5 years if tolerable. The oral progestogen options were either medroxyprogesterone or norethisterone 10 mg oral daily for 6 months. Treatment compliance was checked in follow-up sessions; non-compliant women were excluded.

Patients underwent endometrial biopsies at 6 and 12 months with LNG-IUS in situ. Patients were cleared from surveillance if these two biopsy results showed disease regression. For patients with a body mass index (BMI) ≥30 kg/m^2, with or without a history of chronic anovulation, endometrial biopsies were repeated annually thereafter. Patients were counselled for a hysterectomy if EH persisted after 12 months of LNG-IUS or 6 months of oral progestogens plus 6 months of LNG-IUS, or if the disease progressed or relapsed, or if patients had persistent bleeding, declined endometrial surveillance, or were non-compliant to medical treatment.

Primary outcomes were rates of disease regression and relapse after treatment. Disease regression was defined as the absence of endometrial hyperplasia at 12 months. Disease relapse was defined as the presence of non-atypical EH, atypical EH, or EC after the initial regression at 12 months. Secondary outcomes were predictors for disease non-regression at 12 months.

The sample size was calculated based on a study of regression rates after LNG-IUS or oral progestogen treatment.[6] A minimum of 172 women was required to have 80% power to detect statistical significance. The LNG-IUS and oral progestogen groups were compared using Pearson's Chi-squared test or Fisher's exact test for categorical data and Mann-Whitney *U* tests for non-parametric data. Continuous skewed variables were presented as median and interquartile ranges. Binary logistic regression analysis was performed. Among women whose treatment was successful, relapse rates were compared using time-to-failure methods with Kaplan–Meier plots and log-rank tests. Data analysis was performed using SPSS (Windows version 26.0; IBM Corp, Armonk [NY], US). A p value of <0.05 was considered statistically significant.

Results

Over the 6-year study period, 381 women were diagnosed with non-atypical EH and 285 of them completed 6 months' treatment with LNG-IUS (n=212) or oral progestogens (n=73), specifically medroxyprogesterone (n=63) and norethisterone (n=10) [Figure 1]. We excluded 96 women who were lost to follow-up after the initial diagnosis of EH (n=12), opted for observation (n=14) or hysterectomy (n=40), did not complete the 6-month treatment (n=20), or had changed treatment method within the first 6 months (n=10).

The median duration from diagnosis to the last histological follow-up was 24 months for the LNG-IUS group and 19 months for the oral progestogen group. The two groups were comparable in terms of demographics and uterine conditions, except that women treated with LNG-IUS were more likely to be multiparous (66.5% vs 47.9%, p=0.005) and absent of fibroids or adenomyosis (58.5% vs 45.2%, p=0.049), compared with those treated with oral progestogens (Table 1).

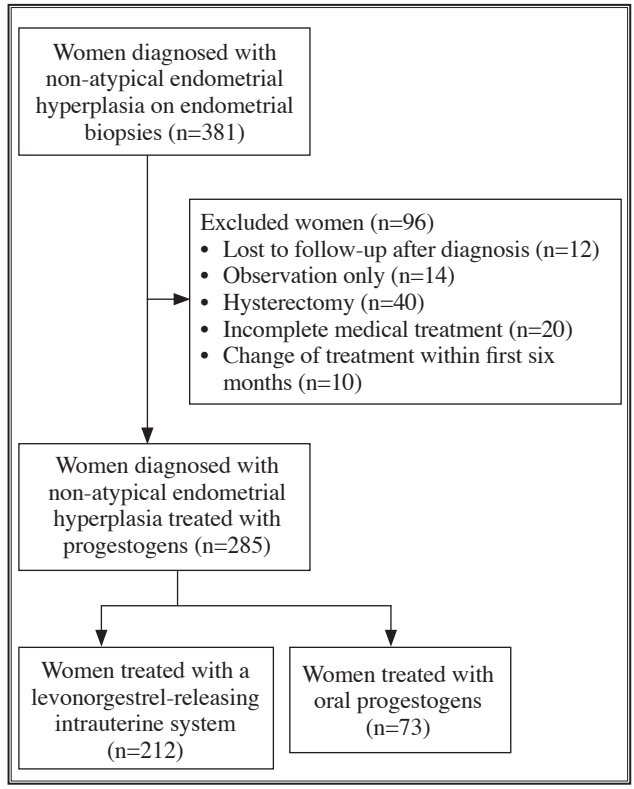

Figure 1. Flowchart of inclusion of patients.

Table 1. Baseline characteristics of women with non-atypical endometrial hyperplasia treated with a levonorgestrel-releasing intrauterine system (LNG-IUS) or oral progestogens

Characteristic	LNG-IUS (n=212)*	Oral progestogen (n=73)*	p Value
Age, y	46±9	43±12	0.166
Menopausal status			>0.99
Premenopausal	203 (95.8)	70 (95.9)	
Postmenopausal	9 (4.2)	3 (4.1)	
Presence of fibroids and/or adenomyosis			0.049
Yes	88 (41.5)	40 (54.8)	
No	124 (58.5)	33 (45.2)	
Uterine size			0.096
Normal size	142 (67.0)	41 (56.2)	
Enlarged	70 (33.0)	32 (43.8)	
Endometrial cavity length, cm	8.0±1.0	8.0±1.8	0.192
≤10	199 (93.9)	65 (89.0)	
>10	13 (6.1)	8 (11.0)	
Time from diagnosis to treatment, d	41±38	36±21	0.305
≤4 weeks	51 (24.1)	22 (30.1)	
>4 weeks	161 (75.9)	51 (69.9)	
Smoking status			0.573
Smoker	14 (6.6)	3 (4.1)	
Non-smoker	198 (93.4)	70 (95.9)	
Parity			0.005
Nulliparous	71 (33.5)	38 (52.1)	
Multiparous	141 (66.5)	35 (47.9)	
Body mass index, kg/m^2	26.5±7.8	25.9±7.6	0.819
<30	148 (69.8)	52 (71.2)	
≥30	64 (30.2)	21 (28.8)	
Ethnicity			0.526
Chinese	201 (94.8)	71 (97.3)	
Filipino	3 (1.4)	2 (2.7)	
Pakistani	3 (1.4)	0	
Indonesian	3 (1.4)	0	
Indian	1 (0.5)	0	
Vietnamese	1 (0.5)	0	
Concurrent use of Tamoxifen			>0.99
Yes	2 (0.9)	0	
No	210 (99.1)	73 (100)	
Concurrent use of hormonal replacement therapy			>0.99
Yes	1 (0.5)	0	
No	211 (99.5)	73 (100)	
Diabetes mellitus			0.634
Yes	30 (14.2)	12 (16.4)	
No	182 (85.8)	61 (83.6)	
Hypertension			0.686
Yes	39 (18.4)	15 (20.5)	
No	173 (81.6)	58 (79.5)	
Polycystic ovary syndrome			0.143
Yes	19 (9.0)	11 (15.1)	
No	193 (91.0)	62 (84.9)	
Family history of endometrial, ovarian, breast, or colorectal malignancy			0.551
Yes	16 (7.5)	4 (5.5)	
No	196 (92.5)	69 (94.5)	
Carrier of hereditary nonpolyposis colorectal cancer genes			>0.99
Confirmed	2 (0.9)	0	
Unknown	210 (99.1)	73 (100)	

* Data are presented as mean ± standard deviation or No. (%) of patients

At 12-month post-treatment, more women had achieved disease regression in the LNG-IUS group than in the oral progestogens group (93.9% vs 71.2%, p<0.001, Figure 2). Among the 251 women achieving disease regression, 137 had further endometrial biopsies beyond the initial 12 months. At 24 months, five (4.4%) of 114 women who had endometrial biopsies were diagnosed with EH relapse. At 36 months, four (7.7%) of 52 women who had endometrial biopsies were diagnosed with EH relapse. The risk of EH relapse was higher in the oral progestogens group than in the LNG-IUS group at 24 months (21.1% vs 1.1%, p=0.003) and 36 months (33.3% vs 2.3%, p=0.014). Figure 3 shows the Kaplan–Meier curves for EH relapse; the difference in EH relapse between the two groups was significant (p<0.001). The oral progestogens group had a higher rate of hysterectomy (13.7% vs 4.2%, p=0.005) performed for non-regression, relapse, or progression, compared with the LNG-IUS group. The incidence of EC was similar between groups (2.8% vs 4.1%, p=0.698, Figure 2).

Women with EH non-regression were more likely to be postmenopausal (41.7% vs 10.6%, p=0.008) and in the oral progestogens group (28.8% vs 6.1%, p<0.001) [Table 2]. In a multivariate analysis, postmenopausal status (odds ratio [OR]=5.80, 95% confidence interval [CI]=1.28-26.18, p=0.022) and treatment with oral progestogens (OR=7.51, 95% CI=3.28-17.20, p<0.001) were identified as predictors for EH non-regression at 12-month post-treatment.

Discussion

In the present study, women in the LNG-IUS group had a higher rate of EH regression at 12 months and a lower rate of EH relapse at 24 and 36 months and fewer hysterectomy performed due to treatment failure, compared with women in the oral progestogens group. Postmenopausal status and treatment with oral progestogens were significant risk factors for EH non-regression at 12-month post-treatment. These findings are consistent with those in other studies[6,7,13,14]. Nonetheless, the optimal type, dosage, and duration of progestogens have not been

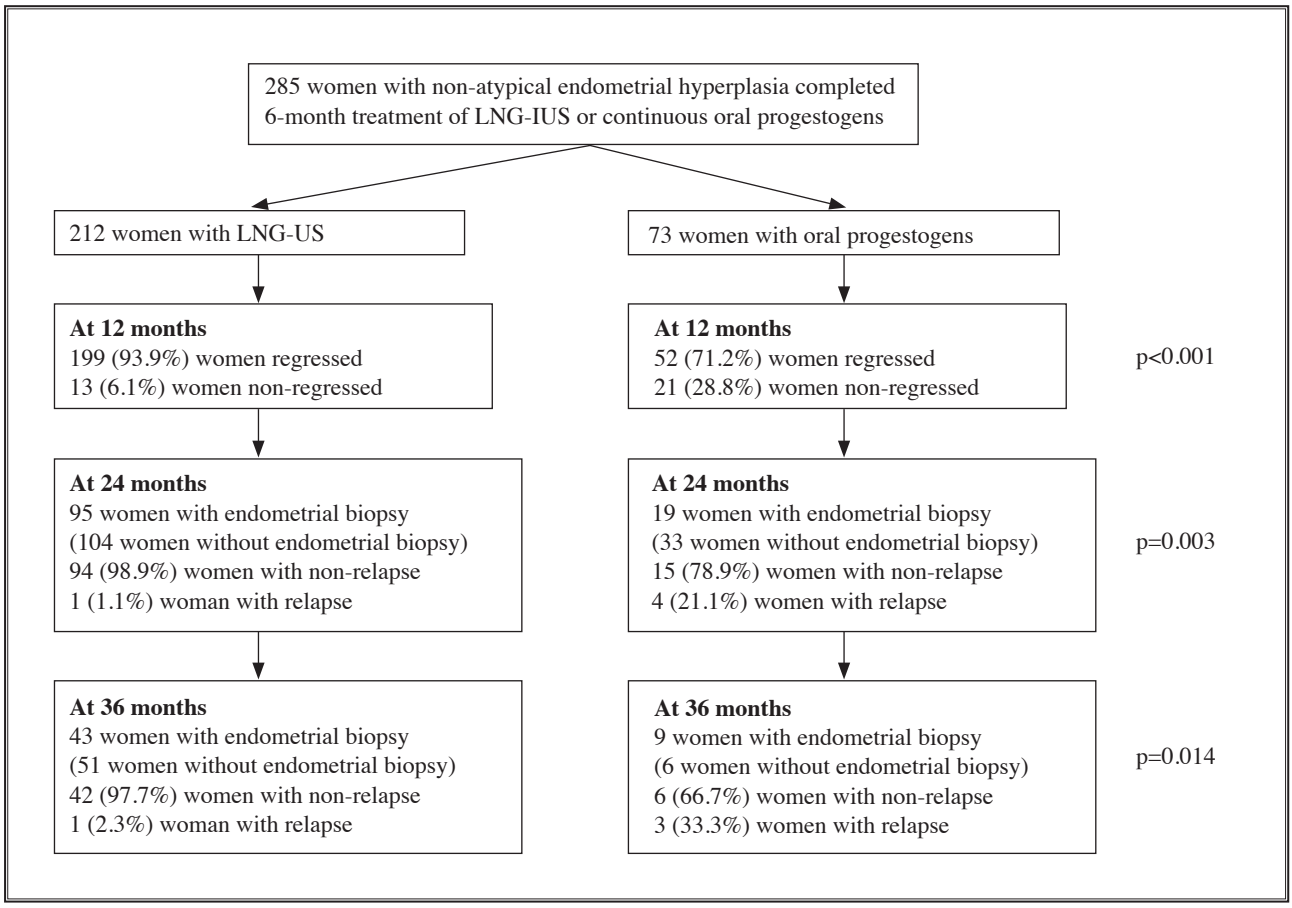

Figure 2. Flowchart of outcomes of women treated with a levonorgestrel-releasing intrauterine system (LNG-IUS) or oral progestogens.

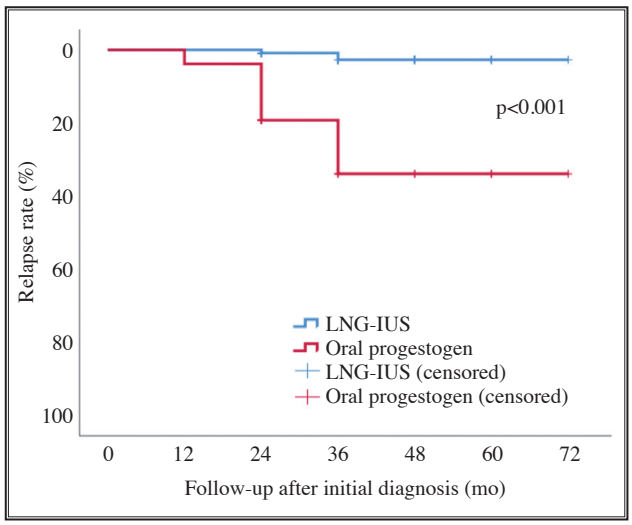

Figure 3. Kaplan–Meier survival curves for endometrial hyperplasia relapse over the course of 72 months in women with regression after treatment with a levonorgestrel-releasing intrauterine system (LNG-IUS) or oral progestogens.

identified in the literature.

The continuous slow release of progestogens onto the endometrium by the LNG-IUS is suggested to contribute to its higher efficacy than oral progestogens[7,15]. In addition, the relatively favourable adverse effect profile of the LNG-IUS might improve women's tolerance and compliance with treatment, compared with oral progestogens. Nevertheless, 73 (25.6%) of 285 women preferred oral progestogens; these women were more likely to be nulliparous or have uterine fibroids or adenomyosis. Five women with repeated dislodgements and two women with pelvic infections requested a change to oral progestogens treatment. Thus, it is important to emphasise the higher efficacy of LNG-IUS in achieving disease regression to these women. Some nulliparous women might be reluctant to opt for LNG-IUS because of fertility concerns; they should be reassured that there is no delay in fertility after LNG-IUS removal[16-18].

Table 2. Univariate and multivariate analyses for disease regression after 12 months of treatment

Variable	Univariate analysis			Multivariate analysis	
	Women with regression (n=251)*	Women with non-regression (n=34)*	p Value	Adjusted odds ratio (95% confidence interval)	p Value
Age at diagnosis, y	46.0 (10)	45.5 (10)	0.347	1.014 (0.951-1.081)	0.681
Menopausal status			0.008	5.796 (1.283-26.180)	0.022
Premenopausal (n=273)	244 (89.4)	29 (10.6)			
Postmenopausal (n=12)	7 (58.3)	5 (41.7)			
Parity			0.451	1.555 (0.580-4.168)	0.380
Nulliparous (n=109)	98 (89.9)	11 (10.1)			
Multiparous (n=176)	153 (86.9)	23 (13.1)			
Body mass index, kg/m^2			0.393	0.811 (0.321-2.051)	0.659
<30 (n=200)	174 (87.0)	26 (13.0)			
≥30 (n=85)	77 (90.6)	8 (9.4)			
Diabetes mellitus			0.305	1.704 (0.624-4.654)	0.299
Yes (n=42)	35 (83.3)	7 (16.7)			
No (n=243)	216 (88.9)	27 (11.1)			
Endometrial cavity length			0.151	1.675 (0.480-5.847)	0.419
≤10 cm (n=264)	235 (89.0)	29 (11.0)			
>10 cm (n=21)	16 (76.2)	5 (23.8)			
Polycystic ovary syndrome			>0.99	0.915 (0.207-4.052)	0.907
Yes (n=30)	27 (90.0)	3 (10.0)			
No (n=255)	224 (87.8)	31 (12.2)			
Progestogen treatment			<0.001	7.509 (3.277-17.203)	<0.001
Levonorgestrel-releasing intrauterine system (n=212)	199 (93.9)	13 (6.1)			
Oral progestogens (n=73)	52 (71.2)	21 (28.8)			

* Data are presented as No. (%) of patients

In addition, they should be encouraged to conceive after disease regression in at least one endometrial sample. Women with fibroids or adenomyosis also preferred oral progestogens. Although women's wishes should be respected, we would recommend LNG-IUS as the first-line treatment for all women, except for those with distorted anatomy of the uterine cavity or a significantly increased cavity length.

One (1.1%) of 95 women in the LNG-IUS group and four (21.1%) of 19 women in the oral progestogens group had a EH relapse at 24 months despite disease regression. This finding differs from that in a multicentre randomised trial in which the relapse rate after 6 months of treatment with LNG-IUS was 41% and was similar between the two treatment arms at 24-month post-treatment[19]. This discrepancy may be due to differences in the duration of the treatment with LNG-IUS, which was kept in place for 5 years if tolerated by our patients. Among those diagnosed with EH, the incidence of EC was higher (but not significantly) in the oral progestogens group than the LNG-IUS group (4.1% vs 2.8%). The non-significance may be due to the small sample size in women with endometrial biopsies after the initial 12 months' treatment. Owing to a higher risk of disease relapse and hysterectomy rate due to treatment failure, we recommend regular annual surveillance in women after oral progestogens treatment. Further long-term surveillance should be considered in those with significant risk factors. Because oral progestogen is a one-off 6-month treatment, LNG-IUS is recommended for long-term endometrial protection after completion of initial oral treatment, especially for those with additional risk factors.

Postmenopausal status was identified as a risk factor for EH non-regression at 12 months, after adjusting for age and BMI. This finding is consistent with that in a previous study[19]. Disease regression was not associated with age, obesity, nulliparity, diabetes, hypertension, and size of endometrial cavity. This finding is consistent with that in other studies[20-23]. Increased incidence of progression to EC in postmenopausal women is possibly because obese older women have increased susceptibility to unopposed oestrogen[24]. We believe that the pathophysiology of EH in postmenopausal women is likely more complex than it is currently understood[25-28].

Apart from standard progestogen treatment, surgical treatment (hysterectomy with bilateral salpingo-oophorectomy) should be considered as the definitive management for postmenopausal women with EH. Yet, women should consider the surgical risks and the risk factors for EH when making decision to undergo a hysterectomy. Women who are reluctant to undergo a hysterectomy should receive annual endometrial biopsies after disease regression to monitor disease relapse or progression.

There are several limitations to this study. There may be recall bias in this retrospective study. The lack of a central pathology review to identify women with non-atypical EH might affect the overall outcome of the study. Not all women had long-term endometrial biopsies because some were diagnosed and treated recently. According to our centre's practice, regular endometrial surveillance after 12 months is offered to those with symptom recurrence or at a higher risk of relapse. Hence, we may unintentionally omit those with EH relapse or EC or mild symptoms such that the relapse went undetected. Similarly, we could not provide the median duration of the LNG-IUS treatment in asymptomatic women with disease regression who were discharged from monitoring at 12 months. Although no women had EH relapse after 36 months, the sample size after censor was small. Owing to the small number of women with EH relapse, our study lacks the power to identify other predictors for EH relapse.

Conclusions

In women with non-atypical EH, treatment with LNG-IUS leads to a higher regression rate at 12 months, a lower relapse rate within 36 months, and a lower rate of hysterectomy due to treatment failure, compared with treatment with oral progestogens. Postmenopausal status and treatment with oral progestogens are risk factors for treatment failure. Regular endometrial surveillance should be provided to women at risk. Hysterectomy is recommended for postmenopausal women.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics approval

The study was approved by the New Territories West Cluster Research Ethics Committee (reference: CIRB-2022-062-1). The patients were treated in accordance with the tenets of the Declaration of Helsinki.

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