Research Square

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Short-Interval, Low-Dose versus High-Dose Cyclophosphamide for Menstrual Disorders in Systemic Lupus Erythematosus: A Multicenter Real-World Study

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Abstract

Background

Cyclophosphamide (CYC) is a commonly used therapy for severe, life-threatening Systemic lupus erythematosus (SLE), but its gonadotoxicity may lead to menstrual disorder. This study compared the risk of menstrual disorders between short-interval, low-dose intravenous CYC (SILD IV-CYC) and conventional high-dose intravenous CYC (HD IV-CYC) in reproductive-aged SLE patients.

Methods

We analyzed clinical parameters from 469 female SLE patients (aged 16 to 45 years) across 25 Chinese hospitals. 282 patients received IV-CYC at 400 mg every two weeks(short-interval, low dose cyclophosphamide, SILD IV-CYC), and the other 187 patients received 500 mg/m²of body surface area every month (high-dose intravenous cyclophosphamide, HD IV-CYC). Menstrual disturbances were compared between groups.

Results

The incidence of menstrual disorders was significantly lower in the SILD IV-CYC group (25.18% [71/282]) versus the HD IV-CYC group (41.18% [77/187]) ($P < 0.001$). Decreased menstrual volume was more commonly observed in the HD IV-CYC group (26.74% versus 10.99%, $P < 0.001$), particularly in patients aged 21–40 years. Multivariable logistic regression analysis confirmed that SILD IV-CYC was associated with a reduced risk of menstrual disorders (OR 0.400, 95% CI 0.262 to 0.612, $P < 0.001$), while longer CYC course increased this risk (OR 1.147, 95%CI 1.002 to 1.312, $P = 0.046$).

Conclusions

SILD IV-CYC demonstrates a superior safety profile regarding menstrual preservation compared to HD IV-CYC in reproductive-aged SLE patients, may supporting its clinical preference to minimize gonadal toxicity.

Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multiorgan involvement that predominantly affects women of childbearing age, making reproductive health an important clinical concern in these patients.[1] Studies suggest SLE patients exhibit higher rates of menstrual irregularities. For instance, Medeiros et al showed that the menstrual abnormalities were observed in 63% of Juvenile SLE patients, which was higher than the 10% observed in healthy controls[2]. Beyond menstrual irregularities, accumulating evidence indicates that SLE itself may adversely affect ovarian reserve. A recent systematic review and meta-analysis found significantly lower serum anti-Müllerian hormone (AMH) levels and antral follicle counts in women with SLE compared with healthy controls, while ovarian reserve impairment has also been observed in patients with SLE who had regular menstruation and no exposure to alkylating agents[3][4]

Although there are many new and promising treatments, cyclophosphamide (CYC) remains an important induction therapy for severe SLE manifestations, such as lupus nephritis, neuropsychiatric SLE, hematological involvement, pulmonary involvement. And high dose intravenous cyclophosphamide (HD IV-CYC) has long been the standard induction therapy for lupus nephritis (LN)[5]. Current EULAR and KDIGO recommendations continue to include IV-CYC among the treatment options for severe lupus nephritis while emphasizing strategies to minimize cumulative cyclophosphamide exposure [6][7]. The gonadotoxicity of cyclophosphamide is clinically important, with a recent systematic review and meta-analysis estimating a pooled prevalence of premature ovarian insufficiency of approximately 15% among women with SLE exposed to cyclophosphamide[8].

Considering the toxicity associated with high-dose cyclophosphamide, the feasibility of low-dose administration warrants further investigation. More recent meta-analytic evidence has also suggested a lower risk of amenorrhea and gonadal toxicity with low-dose cyclophosphamide regimens compared with conventional high-dose regimens [9]. Long-term follow-up of the Euro-Lupus Nephritis Trial demonstrated comparable long-term renal outcomes between low-dose and high-dose IV-CYC regimens, supporting the clinical feasibility of reducing cumulative cyclophosphamide exposure[10]. Although existing meta-analytic evidence suggests that low-dose cyclophosphamide may reduce the risk of menstrual or gonadal toxicity[11], large multicenter real-world studies specifically evaluating menstrual disturbances as the primary outcome remain scarce. Therefore, the comparative effects of short-interval low-dose and high-dose IV-CYC on menstrual outcomes in women with SLE

necessitate additional research. Importantly, menstrual status should not be regarded as an equivalent measure of ovarian reserve, as subclinical ovarian damage may occur despite regular menstrual cycles [4][12].

Methods

Patient population

We retrospectively screened 834 female patients with SLE who met the 1997 revised classification criteria of the American College of Rheumatology and were treated at 25 hospitals in China from March 2017 to July 2023 with complete case records. All patients received intravenous cyclophosphamide (IV-CYC) and patients in combination with other immune suppressants (such as mycophenolate mofetil, azathioprine, ciclosporin, rituximab, etc) were unacceptable. Patients were excluded if they were younger than 16 years, older than 45 years, or had irregular menstruation before IV-CYC. Finally, 469 patients aged 16 to 45 years were included in this study. Among them, `282 patients received short-interval, low-dose (SILD) IV-CYC at a dose of 400 mg every 2 weeks, and 187 received high-dose (HD) IV-CYC at a dose of 500 mg/m2 of body surface area every month. (Fig. 1)The study was approved by Peking University People's Hospital Ethics Committee (reference number: 2015PHB004-01).

Data collection

Clinical data were retrospectively collected from inpatient and outpatient electronic medical records systems. Data collected included demographics, age at disease onset, systemic involvement, laboratory parameters (e.g., complement, anti-dsDNA antibodies), IV-CYC treatment duration, cumulative cyclophosphamide dose, and prior immunosuppressive therapies (glucocorticoids/other agents). Menstrual information was collected from the patients' medical records. Menstrual cycle and volume were compared with the previous cycle and volume of the same patient before IV-CYC treatment. The primary outcome was menstrual disorders, defined as the presence of any of the following: menstrual cycle change, menstrual volume change, or amenorrhea. Menstrual cycle change was characterized by an increase or decrease of ≥ 7 days from the individual baseline cycle length, whereas a change in menstrual volume was defined as an approximately 20% increase or decrease from the individual baseline menstrual volume. Amenorrhea was defined as the absence of menstruation for more than 3 consecutive months. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), as recorded in the medical records.

Statistical analysis

The statistical analyses were performed using Statistical Product and Service Solutions (SPSS) V.26.0. Continuous variables were expressed as mean ± standard deviation (SD), and comparison between the two groups was performed with the Student's t-test. Discrete variable data were presented as median (IQR), and statistical significance between two groups was assessed using a Mann-Whitney U test.

Categorical data were compared using $\chi 2$ or Fisher's exact test. Spearman's correlation analysis was applied to analyze relationship between the two groups. Backward stepwise multivariable logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for menstrual disorders. In univariate analysis, the factors related to menstrual disorder at $p < 0.1$ were entered into the multivariate logistic model. A value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The characteristics of the patients were summarized in Table 1. The mean age of the patients was 32.04 ± 7.02 years, with the median course of CYC being 6.00 (4.00, 10.00) months. The accumulated dose of CYC was 5.60 (3.20, 8.00) grams. There were no statistically significant differences between the SILD IV-CYC and HD IV-CYC groups in age, organ involvement, CYC duration, cumulative CYC dose, prior immunosuppressive therapy, or disease activity.

Table 1
The characteristics of female SLE patients in this study

Age (years)	SLE patients(n = 469)	SILD IV-CYC (n = 282)	HD IV-CYC (n = 187)	P value
	32.04 ± 7.02	**32.49 ± 7.35**	**31.37 ± 6.46**	**0.083**
Age of onset (years)	26.11 ± 7.53	26.24 ± 7.93	25.91 ± 6.90	0.637
CYC course(Months)	6.00 (4.00, 10.00)	7.00 (4.00, 11.63)	6.00 (4.00, 9.00)	0.115
Accumulated dose of CYC (g)	5.60 (3.20, 8.00)	5.60 (3.20, 9.30)	6.00 (3.20, 8.00)	0.125
Lupus nephritis	297 (63.32)	169 (59.93)	128 (68.45)	0.061
Leukocytopenia	76 (16.20)	44 (15.60)	32 (17.11)	0.664
Thrombocytopenia	38 (8.10)	21 (7.45)	17 (9.09)	0.523
Lung disease	33 (7.04)	16 (5.67)	17 (9.09)	0.157
Pulmonary arterial hypertension	23 (4.90)	14 (4.96)	9 (4.81)	0.941
NPSLE	69 (14.71)	41 (14.54)	28 (14.97)	0.897
Decreased C3	254 (54.16)	144 (51.06)	110 (58.82)	0.099
Decreased C4	234 (49.89)	131 (46.45)	103 (55.08)	0.067
Increased anti-dsDNA antibody	156 (33.26)	85 (30.14)	71 (37.97)	0.078
Glucocorticoid dose (mg/d)	20.00 (10.00, 40.00)	20.00 (10.00, 41.25)	15.00 (10.00, 37.50)	0.066
HCQ	425 (90.62)	252 (89.36)	173 (92.51)	0.252
MMF	92 (19.62)	49 (17.38)	43 (22.99)	0.134
AZA	8 (1.71)	6 (2.13)	2 (1.07)	0.386
CSA	11 (2.35)	8 (2.84)	3 (1.60)	0.388
TAC	12 (2.56)	9 (3.19)	3 (1.60)	0.286
LEF	16 (3.41)	13 (4.61)	3 (1.60)	0.079
RTX	3 (0.64)	2 (0.71)	1 (0.53)	0.817
MTX	5 (1.07)	4 (1.42)	1 (0.53)	0.362
SLEDAI	7.00 (2.00, 12.00)	6.00 (2.00, 12.00)	8.00 (4.00, 12.00)	0.124

Data were presented as mean ± standard deviation (SD), median (interquartile range) or count (percentage). CYC, cyclophosphamide; NPSLE, neuropsychiatric SLE; C3, complement 3; C4, complement 4; dsDNA, double-stranded DNA; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; AZA, azathioprine; CSA, cyclosporine; TAC, tacrolimus; MTX, Methotrexate; LEF, leflunomide; RTX, rituxima(these immunosuppressants were administered prior to the initiation of intravenous cyclophosphamide therapy).

Patients in the SILD IV-CYC group had fewer menstrual disorders than those in the HD IV-CYC group.

A total of 71 (25.18%) patients in the SILD IV-CYC group and 77 (41.18%) patients in the HD IV-CYC group had menstrual disorder (P < 0.001). To identify risk factors for menstrual disturbance, we performed logistic regression analysis. When patients were divided into two groups—those without menstrual disorder (n = 321) and those with menstrual disorder (n = 148)—patients with menstrual disorder had older age(years) [33.00 (28.25, 38.00) vs 32.00(27.00,37.00), P = 0.050], longer IV-CYC course(months) [8.00 (6.00, 11.00) vs 6.00 (3.00, 10.00), P < 0.001], higher accumulated dose of CYC(g) [6.40 (4.20, 8.95) vs 4.80 (2.40, 8.00), P < 0.001] and HD IV-CYC regimen [41.18% vs 25.18%, P < 0.001] compared to those without menstrual disorder(Table 2).

Multivariate analysis revealed that patients who received SILD IV-CYC had a significantly lower risk of menstrual disorders than those who received HD IV-CYC (OR 0.400, 95%CI 0.262 to 0.612, P < 0.001,). In addition, the IV-CYC course was also independently associated with menstrual disorder (OR 1.147, 95%CI 1.002 to 1.312, P = 0.046)(Fig. 2).

Decreased menstrual volume was more common in patients receiving HD IV-CYC

The menstrual volume and cycle parameters were compared between SILD and HD IV-CYC groups to assess differences in menstrual characteristics. The menstrual volume changes were shown in Fig. 3. In the 282 patients who received SILD IV-CYC, 31 (10.99%) patients experienced a reduction in menstrual volume, while only one (0.35%) patient reported an increase. The majority, 250 (88.65%), maintained unchanged menstrual volume throughout the treatment period. Among the 187 patients in the HD IV-CYC group, 50 (26.74%) patients had decreased menstrual volume and 3 (1.60%) patients with increased volume, while 134 (71.66%) patients remained unchanged. There is no difference in menstrual cycle and the rate of amenorrhea between the two groups (6.38% in SILD IV-CYC group versus 6.42% in HD IV-CYC group).

We further divided the patients into four age-based groups: 16 to 20 years, 21 to 30 years, 31 to 40 years, 41 to 45 years. The difference in the incidence of menstrual disorders between the two groups was most pronounced among patients aged 21 to 40 years (Fig. 4A). Compared with patients who received HD IV-CYC treatment in the 21 to 30 years group (n = 73, Fig. 4B), the SILD IV-CYC group (n = 85) exhibited significantly lower incidence of menstrual disturbance (20.00% versus 39.73%, P = 0.007) and decreased menstrual volume (8.24% vs 21.92%, P = 0.015). Among patients aged 31 to 40 years (Fig. 3C), the incidences of menstrual disturbance in the SILD IV-CYC (n = 131) and HD IV-CYC (n = 84) groups were 25.19% and 41.67%(P = 0.011), respectively. In addition, sixteen (12.21%) patients in the SILD IV-CYC group and 23 patients (27.38%) in the HD IV-CYC group had a decreased menstrual volume (P = 0.005).

Table 2 Risk factors for menstrual disturbances in SLE patients receiving IV CYC.

				Multivariate analysis	
	Without menstrual disorder (n=321)	With menstrual disorder (n=148)	P value	OR (95%CI)	P value
Age (years)	32.00 (27.00, 37.00)	33.00 (28.25, 38.00)	0.050	1.007 (0.963, 1.053)	0.770
Age onset (years)	26.00 (20.00, 31.00)	26.00 (22.00, 34.00)	0.039*	1.031 (0.989, 1.074)	0.150
CYC course（Months）	6.00 (3.00, 10.00)	8.00 (6.00, 11.00)	<0.001*	1.147 (1.002, 1.312)	0.046*
Accumulated dose of CYC (g)	4.80 (2.40, 8.00)	6.40 (4.20, 8.95)	<0.001*	0.875 (0.739, 1.038)	0.125
Lupus nephritis	202 (62.93)	95 (64.19)	0.792		
Leukocytopenia	45 (14.02)	31 (20.95)	0.058	1.472 (0.866, 2.500)	0.153
Thrombocytopenia	27 (8.41)	11 (7.43)	0.718		
Lung disease	23 (7.17)	9 (6.08)	0.583		
Pulmonary arterial hypertension	16 (4.98)	6 (4.05)	0.563		
NPSLE	48 (14.95)	20 (13.51)	0.828		
Decreased C3	178 (55.45)	76 (51.35)	0.408		
Decreased C4	168 (52.34)	66 (44.59)	0.119		
Increased anti-dsDNA antibody	101 (31.46)	55 (37.16)	0.224		
SLEDAI	8.00 (2.00, 12.00)	6.00 (2.25, 12.00)	0.512		
CYC protocols					
SILD IV-CYC	74.82% (211/282)	25.18% (71/282)	<0.001*	0.400 (0.262, 0.612)	0.001*
HD IV-CYC	58.82% (110/187)	41.18% (77/187)		1.00 (reference)	
Glucocorticoid dose (mg/d)	20.00 (10.00, 40.00)	22.50 (10.00, 40.00)	0.597		

Disscussion

Menstrual disturbances in women with SLE are likely multifactorial, reflecting the combined effects of underlying disease activity, therapeutic exposure, and patient-specific factors. Increasing evidence indicates that SLE itself may adversely affect ovarian function. A recent systematic review and meta-analysis demonstrated significantly lower AMH levels and antral follicle counts in women with SLE compared with healthy controls[3]. Importantly, subclinical impairment of ovarian reserve has also been reported in women with SLE who had regular menstruation and no exposure to alkylating agents, suggesting that ovarian dysfunction may occur independently of cyclophosphamide exposure[4]. In addition, menstrual disturbances have been associated with higher disease activity in women with SLE who have not received alkylating

therapy, further supporting a potential intrinsic contribution of active SLE to menstrual dysfunction[13]. Therefore, the effect of cyclophosphamide on menstrual outcomes should be interpreted in the context of both disease-related and treatment-related factors.

In addition, therapeutic interventions, including glucocorticoids and immunosuppressive agents, are believed to influence ovarian reserve [14, 15]. CYC is one of the best-established and most important therapies for treating severe, organ-threatening SLE. However, CYC mediates its ovarian toxicity through DNA crosslinking, which damages chromosomes in mitotically active cells and irreversibly harms the limited ovarian germ cell reserve. The drug's principal action targets primordial follicle granulosa cells, inhibiting estrogen synthesis while enhancing gonadotropin release. This endocrine alteration triggers excessive follicular recruitment, significantly amplifying the cohort of follicles susceptible to the cytotoxic effects of CYC and precipitating premature ovarian exhaustion.[16][17] Besides, in many studies, serum anti-Müllerian hormone (AMH) levels, a marker of ovarian reserve, are lower in patients with SLE without cyclophosphamide exposure than in healthy comparators[18][19]. Knight et al. reported that patients treated with cyclophosphamide had a two-fold higher prevalence of menstrual disturbance than cyclophosphamide-naive patients[20]. Another systematic review and meta-analysis revealed that CYC influenced gonadal function in patients with SLE[15].

In the present multicenter real-world cohort, SILD IV-CYC was associated with a significantly lower risk of menstrual disturbances than HD IV-CYC. This finding is consistent with previous evidence suggesting that lower-dose cyclophosphamide regimens may reduce gonadal toxicity. A 2017 systematic review and meta-analysis reported a lower risk of menstrual disorders with low-dose cyclophosphamide in lupus nephritis (RR 0.46, 95% CI 0.31–0.69), while a more recent 2026 meta-analysis similarly found a lower risk of amenorrhea or gonadal toxicity with low-dose compared with high-dose IV-CYC (RR 0.51) [9][11]. However, these studies have generally focused on gonadal toxicity or amenorrhea across heterogeneous treatment regimens, and direct evidence from large multicenter real-world cohorts specifically evaluating menstrual disturbances remains limited. Our findings therefore provide complementary real-world evidence. The Euro-Lupus Nephritis Trial also provides important evidence supporting lower-dose cyclophosphamide exposure[21]. In a subsequent subgroup analysis, serum AMH levels did not show a significant decline following the Euro-Lupus regimen, suggesting a relatively limited effect on ovarian reserve[22]. However, the AMH analysis was conducted in a relatively small subgroup, and further evidence is needed.

Our findings are also consistent with previous evidence from a randomized single-center study conducted by our group, in which lower-dose IV-CYC was associated with fewer menstrual disturbances than high-dose IV-CYC[23]. The present study extends these observations by providing multicenter real-world data from 25 hospitals. Nevertheless, given the retrospective and non-randomized nature of the present study, the observed association should not be interpreted as establishing a causal effect of SILD IV-CYC on ovarian function.

To minimize confounding from physiological hormonal changes, we excluded patients younger than 16 years or older than 45 years. Although we observed an increased rate of menstrual disorders with age in both groups, patients aged 21 to 40 in SILD IV-CYC group were less prone to menstrual disorders. This protective effect of SILD IV-CYC was particularly evident in reproductive-aged patients (21–40 years), suggesting this regimen may be preferable for fertility preservation.

Conclusions

Collectively, our multicenter real-world study suggests that SILD IV-CYC is associated with a lower risk of menstrual disturbances than HD IV-CYC in reproductive-aged women with SLE, particularly among those aged 21–40 years. These findings may support the potential clinical value of limiting cumulative cyclophosphamide exposure, while prospective studies incorporating objective ovarian reserve markers and long-term reproductive outcomes are warranted to determine whether these menstrual benefits translate into preservation of ovarian reserve and fertility.

Limitations

Our study has several inherent limitations related to its retrospective design. First, because the data were collected primarily for routine clinical care rather than research purposes, some clinical information was incomplete or unavailable. Second, patients who were lost to follow-up, had missing or irretrievable key clinical information, or had potential hormonal factors that could affect menstrual status were excluded, which may have introduced selection bias. Furthermore, menstrual status cannot be considered equivalent to ovarian reserve, as regular menstrual cycles may coexist with reduced AMH levels or antral follicle counts in women with SLE[4][12]. Finally, serum AMH levels were not available in our cohort, limiting our ability to comprehensively assess ovarian reserve and detect potential subclinical ovarian damage[3][24].

Abbreviations

AMH
anti-Müllerian hormone
AZA

azathioprine
C3
complement 3
C4
complement 4
CI
confidence interval
CSA
cyclosporine
CYC
Cyclophosphamide
dsDNA
double-stranded DNA
EULAR
European Alliance of Associations for Rheumatology
HCQ
hydroxychloroquine
HD IV-CYC
conventional high-dose intravenous CYC
IQR
interquartile range
KDIGO
Kidney Disease:Improving Global Outcomes
LEF
leflunomide
LN
lupus nephritis
MMF
mycophenolate mofetil
MTX
Methotrexate
NPSLE
neuropsychiatric SLE
OR
odds ratio
RTX
rituximab
SD
standard deviation
SILD IV-CYC
short-interval, low-dose intravenous CYC
SLE
Systemic Lupus Erythematosus
SLEDAI
Systemic Lupus Erythematosus Disease Activity Index
SPSS
Statistical Product and Service Solutions
TAC
tacrolimus

Declarations

Ethics approval and consent to participate

This study involves human participants and was conducted in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. The approval (reference no 2015PHB004-01) was obtained from the Peking University People's Hospital Ethics Committee for this study. Participants gave informed consent to participate in the study before taking part.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Peking University People's Hospital (Approval Number: 2015PHB004-01). Given the retrospective nature of the study and the use of anonymized data, the requirement for written informed consent was waived by the Ethics Committee.

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Author Contribution

ZGL RL and MS conceived and designed the study. MS and all other authors collected the clinical data. MS and CLT performed the statistical analyses. MS and CLT drafted the manuscript. ZGL and MS critically reviewed and revised the manuscript for intellectual content. All authors interpreted the data, revised the manuscript critically for important intellectual content, and read and approved the final manuscript.

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Not applicable.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available because they contain patient-level clinical information from multiple hospitals. De-identified data may be available from the corresponding author on reasonable request, subject to hospital data-sharing policies.

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Figures

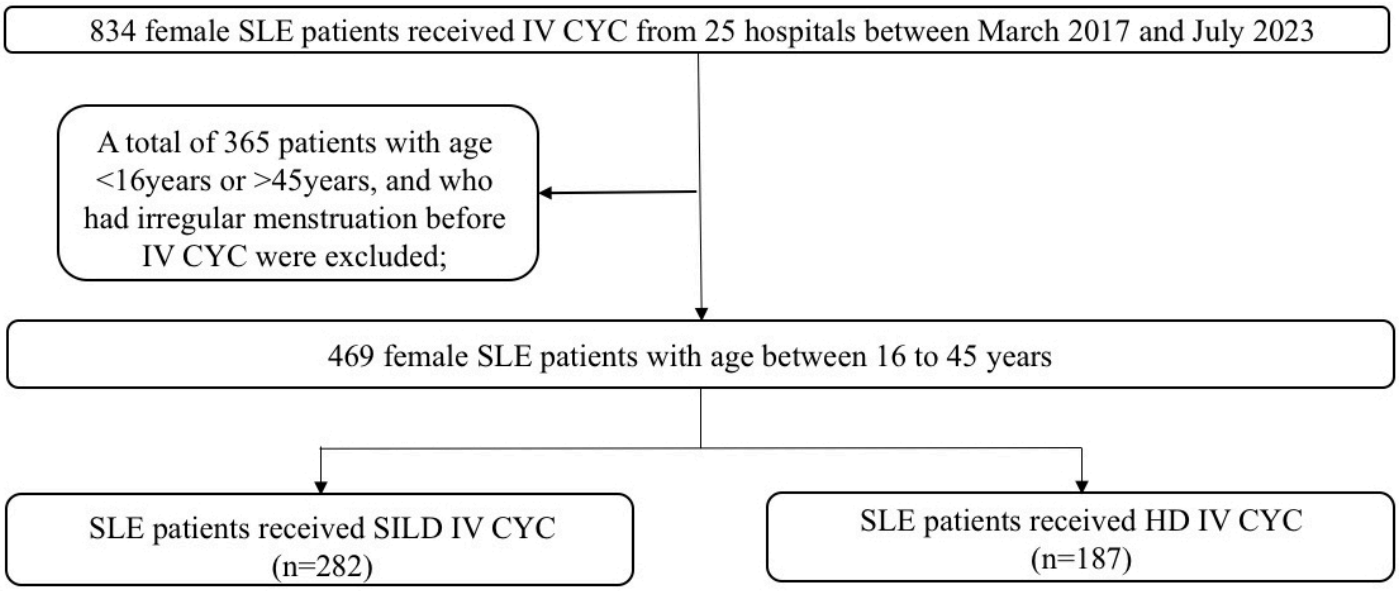


Figure 1

Flow diagram of the SLE patients.

IV CYC, SILD, short-interval lower-dose intravenous cyclophosphamide; HD IV CYC, high-dose intravenous cyclophosphamide; n, number of patients.

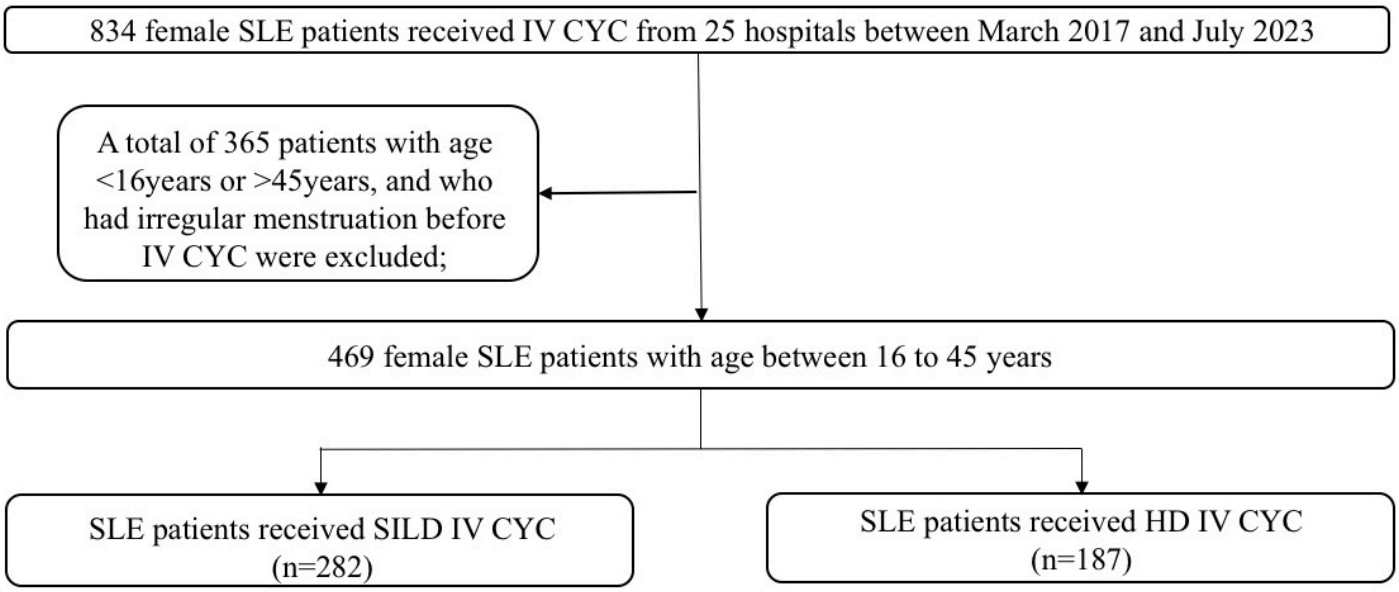


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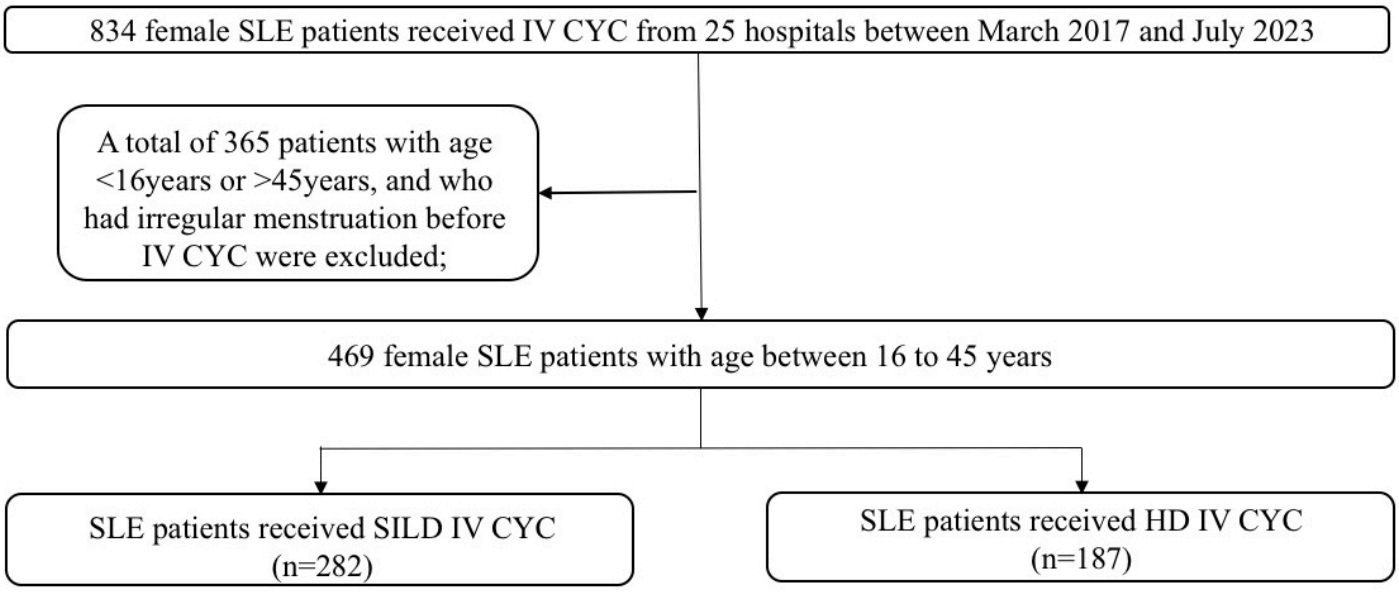


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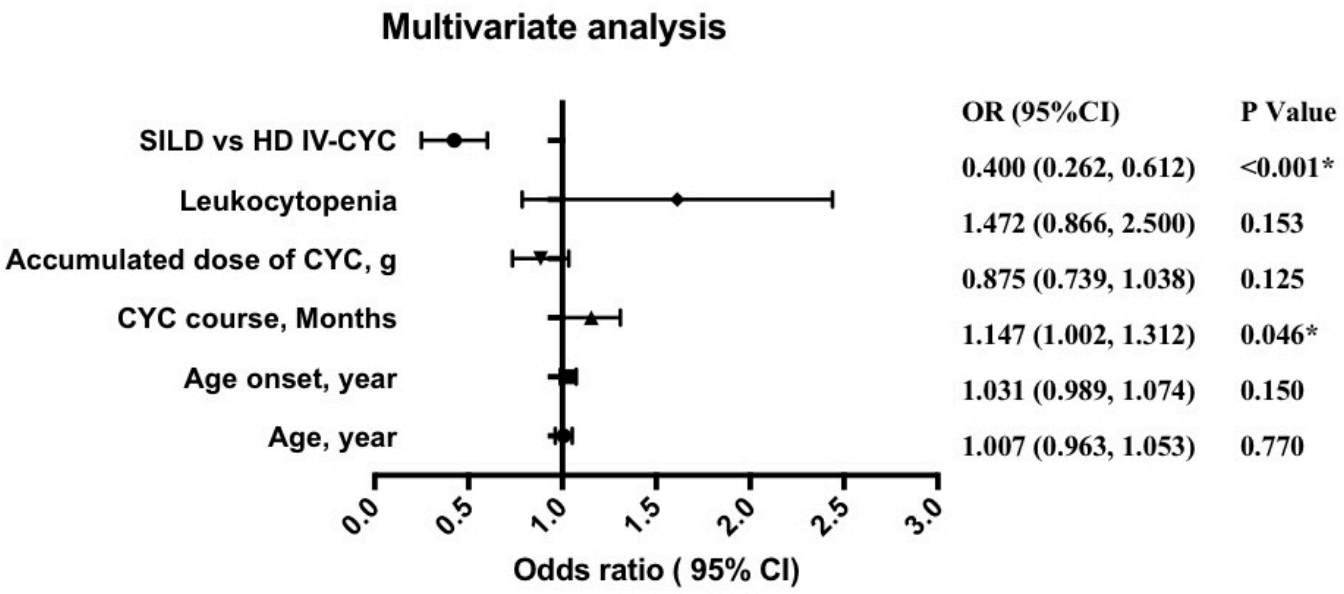


Figure 2

Risk factors for menstrual disturbances in SLE patients receiving IV CYC.

Data were presented as median (interquartile range) or n count (percentage). * P <0.05.

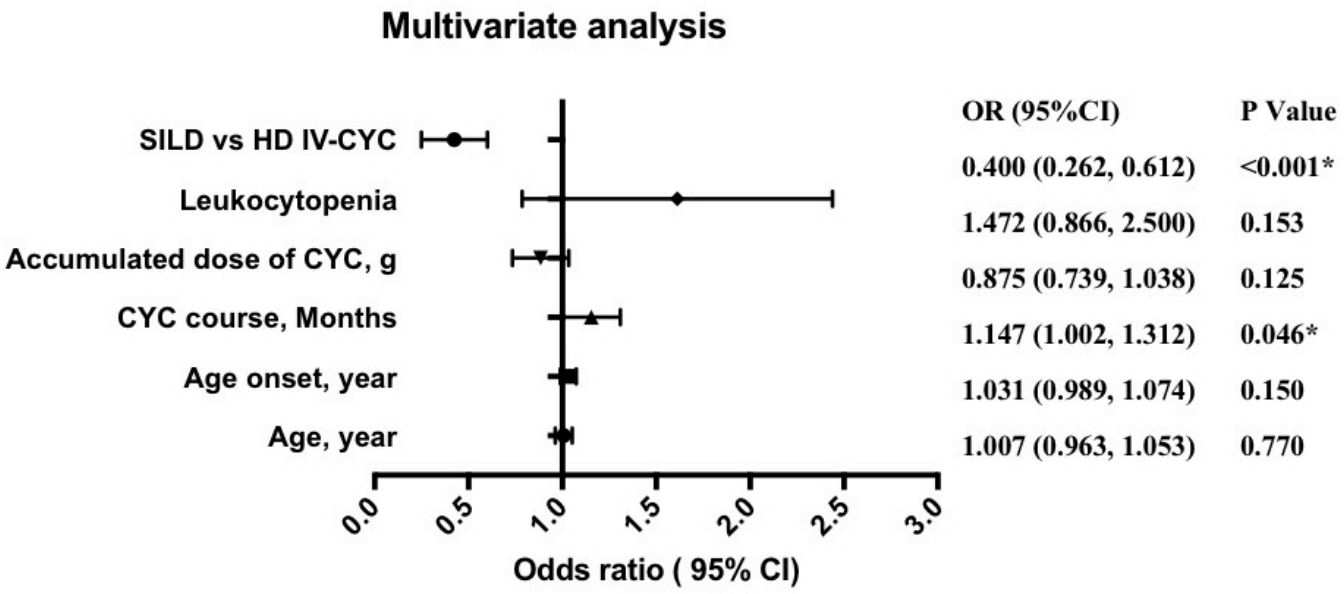


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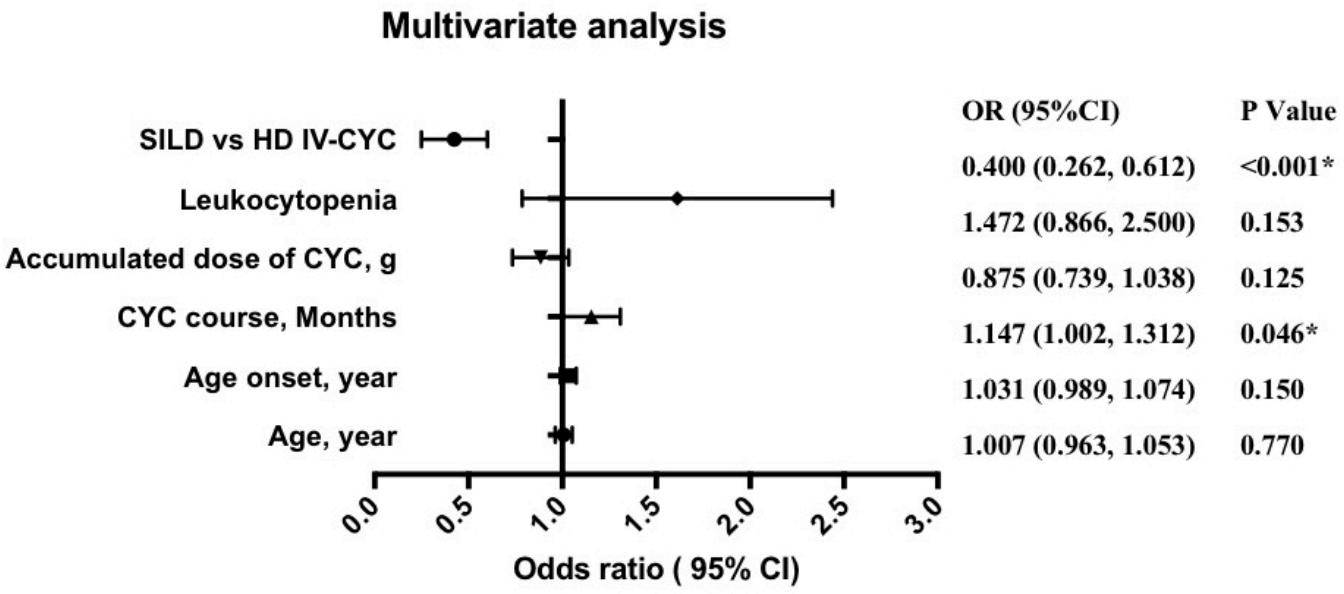


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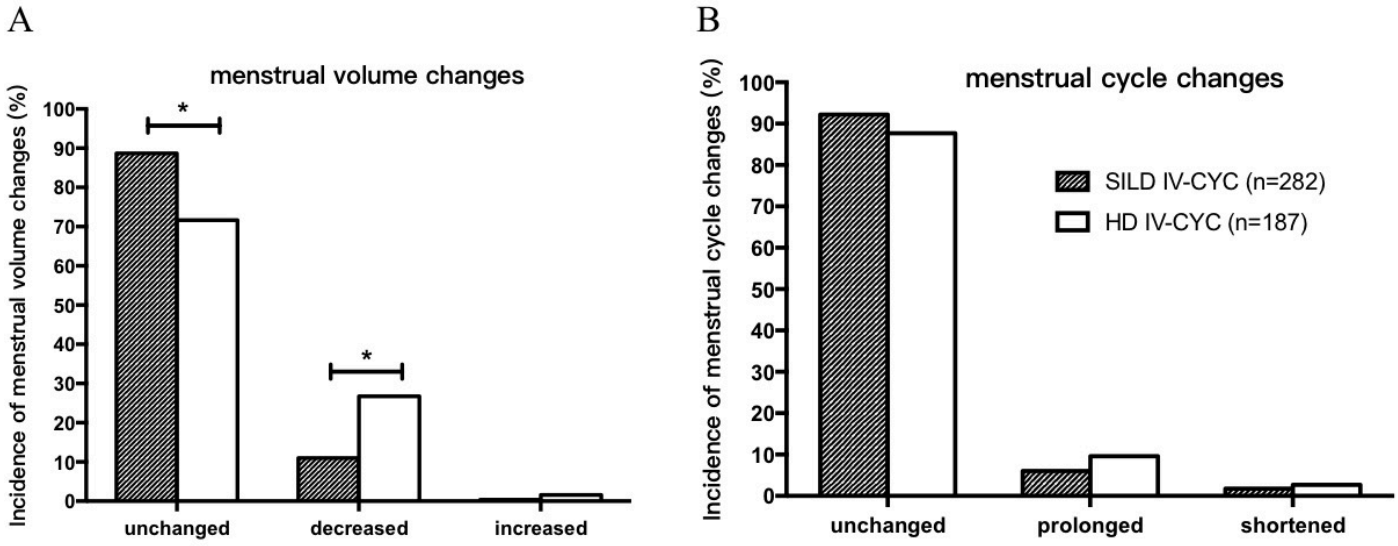


Figure 3

The comparison of menstrual disturbance in SLE patients receiving SILD IV-CYC and HD IV-CYC treatment.

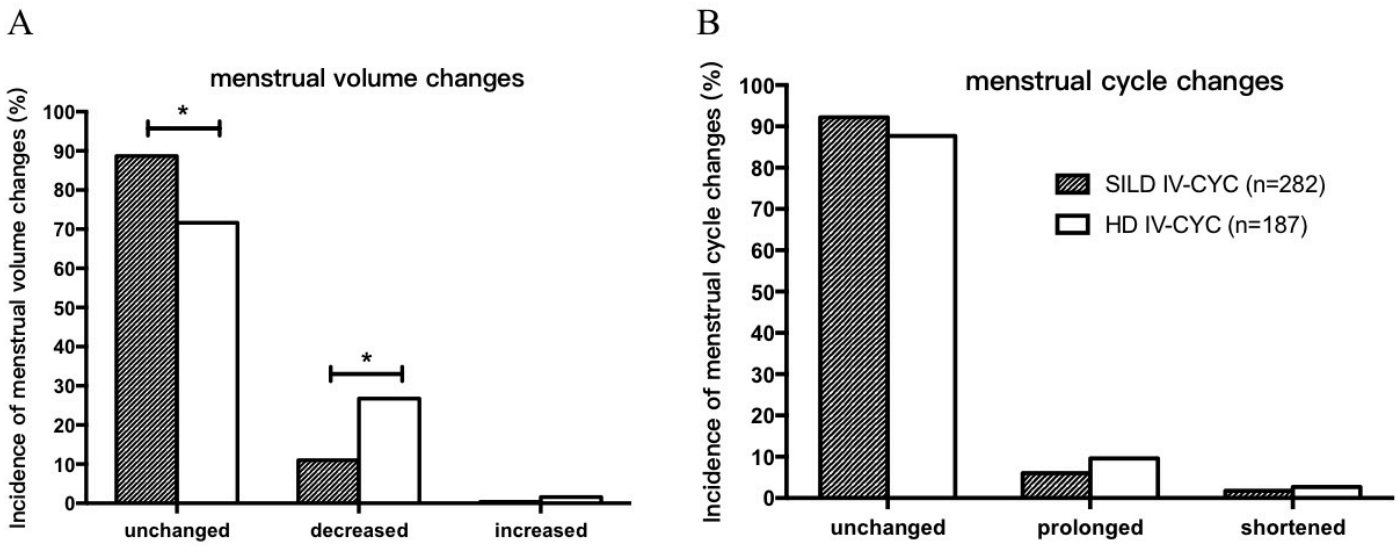


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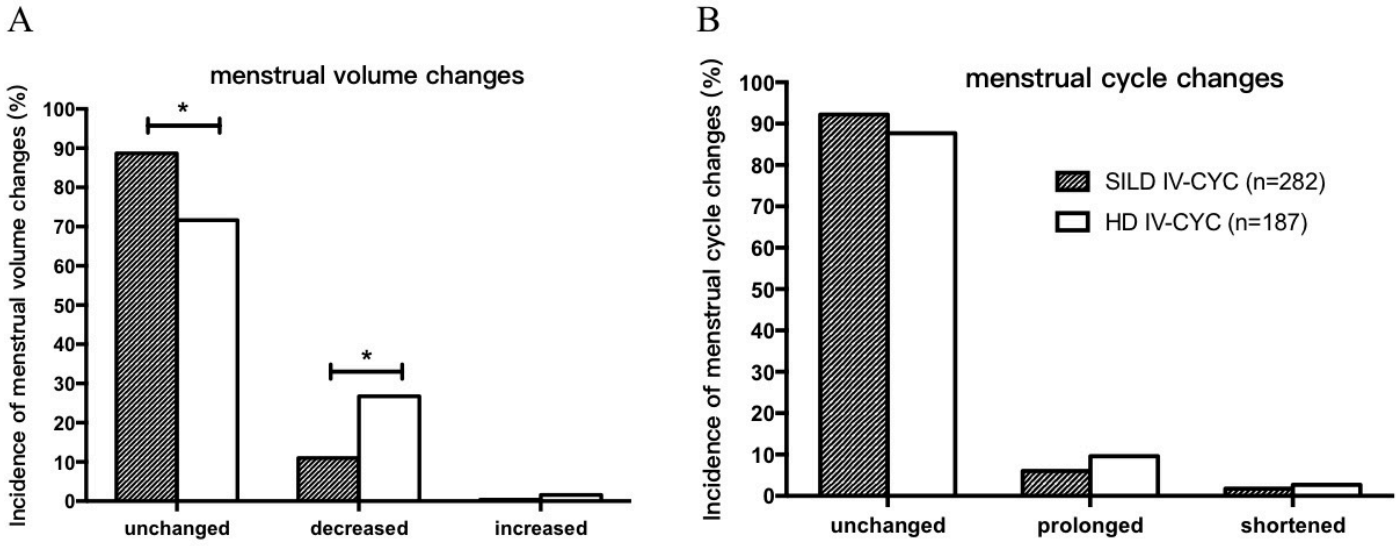


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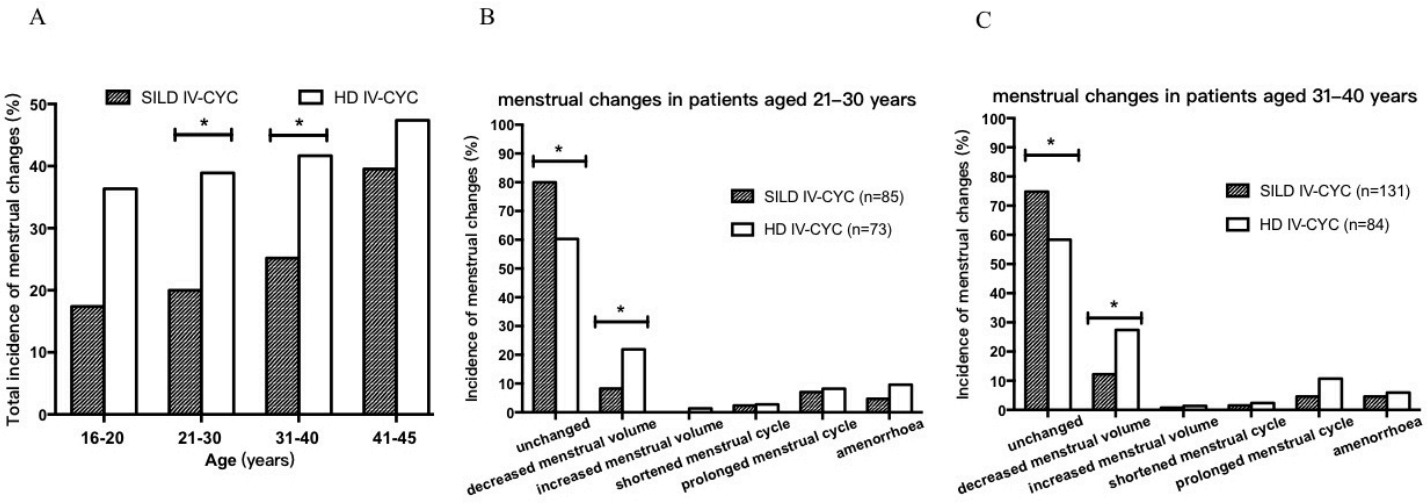


Figure 4

Age-stratified analysis of menstrual disturbance in SLE patients receiving SILD IV-CYC and HD IV-CYC treatment.

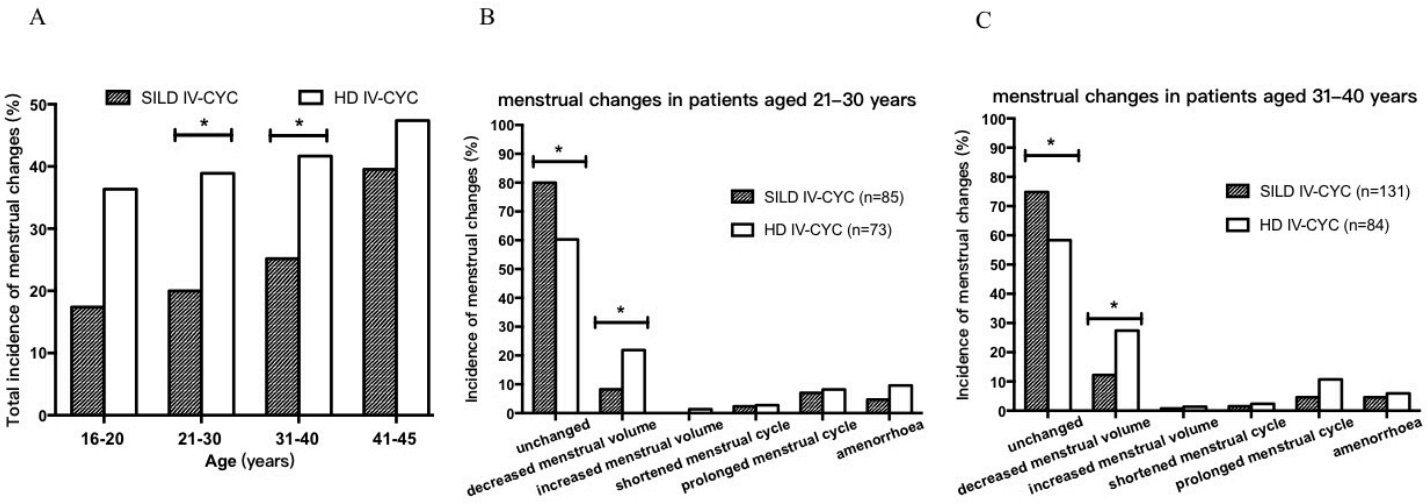


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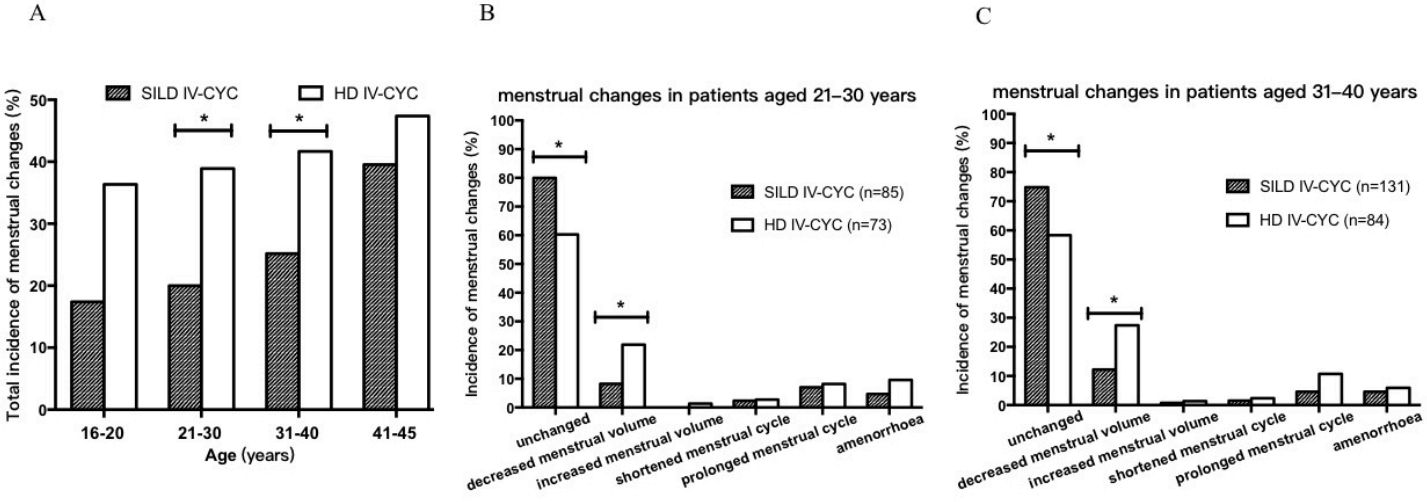


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