



# Letrozole vs clomiphene citrate in Sudanese patients with infertility secondary to polycystic ovary syndrome

Warda Salah Elkhalfa<sup>a</sup>, Hayat Mohamed Suliman<sup>b,\*</sup>, Iman H. Abdoon<sup>b</sup>,  
Walaa Mohamed<sup>c</sup>, Bashier Osman<sup>b</sup>

<sup>a</sup> Clinical Pharmacy, Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, Sudan

<sup>b</sup> Pharmacology, Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, Sudan

<sup>c</sup> Khartoum North Teaching Hospital, Sudan

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## ABSTRACT

PCOS is a cluster of metabolic, hormonal, and environmental factors coupled with infertility in patients within reproductive age. This cross-sectional study compared letrozole (LTZ) vs Clomiphene citrate (CC) as ovulation inducers in infertile Sudanese patients with PCOS. Follicles  $\geq 18$  mm and pregnancy tests were used for comparison. SPSS version 23 was used for analysis. Significance was calculated with Chi-square, *t*-test, and logistic regression.  $P \leq 0.05$  was considered significant.

Our results showed 49% of the patients were 20–30 years old, 60% had secondary infertility 98.4% were secondary to PCOS and 64% had a family history of infertility. Comparable results on positive pregnancy tests of 26% ( $P \leq 0.017$ ) and 17% ( $P \leq 0.027$ ) were observed for LTZ vs CC respectively. Similar strengths ( $P \leq 0.000$ ) in compacting the ovarian cysts were recorded. LTZ showed less activity ( $P \leq 0.013$ ) on follicles size maturation compared to ( $P \leq 0.000$ ) with CC. The endometrial thickness was increased with LTZ (51.87%) but reduced with CC (25.54%). The positive pregnancy test was associated with age and BMI.

**Conclusion:** Letrozole 20 mg single dose showed comparable results on positive pregnancy tests but less significance on follicle maturation compared to CC100mg. Both drugs compacted the ovarian cysts' sizes. letrozole significantly increased the endometrial lining thickness.

## 1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder that occurs in approximately 1 in 15 women of reproductive age [1]. The condition is characterized by signs and symptoms of hyperandrogenism including acne, hirsutism, male pattern baldness, menstrual disturbances (oligomenorrhea or amenorrhea), and acanthosis nigricans (dark/velvety skin) [2,3]. PCOS is a cluster of symptoms resulting from complex interactions of hormonal, genetic, metabolic, and environmental factors [4]. The association between metabolic disorders such as insulin resistance and PCOS is well-reported [5]. Insulin could play a key role in the manifestation of hyperandrogenism as it synergistically induces the release of the luteinizing hormone (LH) and the sex hormone-binding globulin (SHBG) protein from the liver [6]. SHBG is a binding protein for the transport of sex hormones including testosterone, and estradiol

\* Corresponding author. Department of Pharmacology, Faculty of Pharmacy, University of Khartoum, 1111 Al Qasr Avenue, Khartoum Sudan, P. O.B 1996,

E-mail address: [hayatibrahimsuliman19@gmail.com](mailto:hayatibrahimsuliman19@gmail.com) (H.M. Suliman).

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with a higher affinity to testosterone. Hyperandrogenism is directly associated with circulating testosterone metabolites [7], and with increased responsiveness of 17-hydroxyprogesterone to gonadotropin stimuli [4] SHBG is considered an early biomarker and a signaling molecule with a promising therapeutic potential in the treatment of PCOS [8].

The most common tool for the diagnosis of PCOS is the Rotterdam Criteria. 2 of 3 signs including oligo-anovulation, and clinical or biochemical signs of hyperandrogenism are needed for diagnosis. More recent criteria acknowledged that PCOS may occur without obvious signs of hyperandrogenism, [9]. Female infertility is affected by many factors with advancing maternal age as the prominent influential factor. In contrast, infertility due to PCOS often presents in young patients and is generally associated with genetic/chromosomal defects, congenital abnormalities, spontaneous abortion, and PCOS. Infertility could also be affected by the patient's past medical history including pelvic inflammatory disease secondary to infections with Chlamydia, premature ovarian failure, endometriosis, diminished ovarian reserve, and some other environmental factors, [10,11].

Treatment of infertility secondary to PCOS has to be directed to restore menses followed by treatment of hyperandrogenism, control of insulin resistance, and therapeutic assistance of fertility. Clomiphene citrate (CC) -the first-line therapeutic agent-acts through the hypothalamic-pituitary-ovarian axis by competitively binding to estrogen receptors [12]. The dosing schedule is 50 or 100 mg from the second day to the fifth day of the menstrual cycle. The most common side effects are hot flashes, tenderness of the abdomen/breast and mood swings [13]. It is also associated with multiple gestations in about 3–8% of pregnancies [14]. The Aromatase inhibitors (AIs) (letrozole and anastrozole) emerge as alternative to CC as ovulation inducers. The main adverse effects of AIs include headache, gastro-intestinal complaints, joint pain, flushing, sweating, and edema. LTZ recommended doses were 2.5 or 5 mg daily for 5 days starting from the second day of the menstrual cycle [15]. LTZ as a single loading dose of 20 mg or 25 mg was reported, [16,17]. AIs facilitate conception by reducing the hypothalamic-pituitary estrogen feedback mechanisms. Consequently, follicles growth and ovulation would be stimulated by the high release of gonadotropins [18]. LTZ mediate an agonistic activity on increasing the follicle stimulating hormone (FSH) levels and decreasing estrogen release from the ovary maintaining the negative feedback mechanisms without depleting the estrogen receptors. This activity may be behind the development of one dominant follicle (mono-ovulation) by LTZ [19]. In comparison, the mean number of mature follicles was significantly higher in CC compared to the letrozole group while the number of mono-follicular cycles and the mean of the endometrial lining thickness were significantly higher in the LTZ group [20]. This may be related to the agonistic activity on the endometrial estrogen receptors which stimulate the increase in thickness. In contrast, the antagonistic activity that block the estrogen receptors and the central feedback mechanisms mediated by CC has been claimed to be behind the week activity of CC on the endometrium [21]. A controlled clinical trial in infertile patients with PCOS showed the number of dominant follicles as an insignificant variable and statistically comparable results for LTZ and CC in the association between the endometrial thickness vs positive pregnancy outcome [20,22].

This study was designed to compare letrozole vs CC as ovulation inducers in Sudanese patients with infertility secondary to PCOS. The rationale of this study was based on the fact that infertility secondary to PCOS is increasing among Sudanese patients, [23]. Despite the wide acceptance of CC citrate as first-line drug for treatment, a significant proportion of patients do not respond positively [3]. In addition, LTZ 20 mg as a single dose prescribing is increasing in recent years.

### 1.1. Objective

A retrospective cross-sectional study to compare LTZ vs CC as ovulatory inducers in the treatment of Sudanese patients diagnosed with infertility secondary to PCOS according to Rotterdam criteria. The outcome measure includes the follicles maturation to size  $\geq 18$  mm, positive pregnancy tests outcome, change in the ovarian cyst dimensions, and effects on the endometrial lining thickness.

## 2. Methods

### 2.1. Ethical clearance

Ethical clearance was granted by the faculty of Pharmacy, University of Khartoum Research Committee, (a copy is added as supplementary material). Permission from the medical authorities of the 3 private infertility centers were gained before the start of the study. Informed patient's consent was not needed as the data was collected from patients' records.

### 2.2. Inclusion and exclusion criteria

#### 2.2.1. Inclusion criteria

- Infertile Sudanese patients 16–40 years old
- Diagnosed with PCOS according to clinical signs (anovulation) and ultrasound scanning as indicated by Rotterdam criteria
- Were prescribed LTZ or CC as ovulation inducers

#### 2.2.2. Exclusion criteria

- Patients younger than 16 or older than 40 years old
- Infertility due to the male partner or due to other co-morbidities
- Patients who have naturally conceived within the last two years

- Incomplete medical records

### 2.3. Study design

This is a cross-sectional retrospective study to assess LTZ vs CC success rates as ovulation inducers in Sudanese patients with infertility secondary to PCOS at 3 private infertility centers in Khartoum City.

The study covers the records of patients diagnosed with PCOS between January 2015 to January 2020 (5 years), and were treated with LTZ or CC. The files were sorted out according to the inclusion and exclusion criteria. A total of 100 files were separated. After further sorting, the patients who were prescribed LTZ 25 mg (6 patients), and those prescribed CC 50 mg (3 patients) were included in the demographics and patient past medical history but not in the outcome measures analysis (due to small sizes). Consequently, 44 patients on LTZ 20 mg and 47 patients on CC100mg were included in the study analysis.

The treatment regimen for both drugs were started at the second day of the menstrual cycle. LTZ was given as a single loading dose of 20 mg and CC as 100mg per day for 5 days.

Patients had been medically monitored on monthly bases through the first 3 month after induction. A transvaginal ultrasound was arranged on day one and day 10 of the menstrual cycle for follicular tracking. The scans were done to calculate the number of mature follicles, to measure the size of follicles, to measure the endometrial thickness and ovarian cyst dimensions. Pregnancy test was performed 6 weeks after the last tablet taken then repeated one week later for confirmation. For each patient the pregnancy test was repeated two times at each point of checking. The number of detected mature follicles  $\geq 18$  mm, effects on the ovarian cyst dimensions and endometrial lining thickness in addition to positive pregnancy test were used as outcome measures.

### 2.4. Data collection and analysis

Data were collected using a self-structured collection sheet between the 10th of October to the December 10, 2020 (3 months). Data was entered into an excel sheet as coded numerical values before handling statistically. SPSS version 23 was used for analysis. Descriptive statistic frequencies, percentages and mean  $\pm$  Standard Error of the Mean (M $\pm$ SEM) or standard deviations (SD) were calculated. Statistical significance was calculated with independent *t*-test and Chi-square.  $P \leq 0.05$  was considered significant. Association between variables was assessed with logistic regression.

## 3. Results

### 3.1. Demographics of patients with infertility secondary to PCOS at 3 infertility centers at Khartoum City

The duration of marriage was found to be less than 5 years in 65% of the patients. 59% were of a moderate educational level, 65% were housewives and 52% of the husbands were self-employed as shown in [Table 1](#).

### 3.2. History of patients with infertility secondary to PCOS at 3 infertility centers in Khartoum City

The mean age of the patients 20–25 years old was  $23.9 \pm 0.55$  (26%), the group of 25–30 years (23%) had a mean age of  $27 \pm 0.25$ , and 6% were less than 20 years old with a mean age of  $18.0 \pm 0.53$ .

The BMI of  $18.8 \pm 0.47$  was scored by 7 patients, 33 patients scored  $22.8 \pm 0.02$ , 50 patients scored  $26.60 \pm 0.26$ , and 10 patients score  $30.9 \pm 0.12$  as shown in [Table 2](#).

From the investigated patients 64% had secondary infertility of which 98.4% was secondary to PCOS. The menstrual cycle pattern was observed to be irregular in 64% of the patients. 26% had a history of miscarriages of which 54% had a history of at least one episode, and 27% had 2 episodes of spontaneous abortion. 74 patients had a family history of infertility, 45.95%, (34) within mothers and 50% (37) within sisters as shown in [Table 2](#).

### 3.3. Outcome measures comparing LTZ vs CC as ovulation inducers in Sudanese patients with PCOS

A significant ( $P \leq 0.000$ ) increase of 51.9% on the thickness of the endometrial lining was observed with LTZ 20 mg single dose, while CC100mg mediated a significant ( $P \leq 0.000$ ) reduction of 25.5%. Both drugs compacted the ovarian cysts' sizes with similar statistical significance ( $P \leq 0.000$ ). LTZ 20 mg showed less activity ( $P \leq 0.013$ ) on the number of mature follicles ( $\geq 18$  mm) compared to ( $P \leq 0.000$ ) by CC100mg. LTZ vs CC on positive pregnancy tests showed comparable results with 26% ( $P \leq 0.017$ ) and 17% ( $P \leq 0.027$ ) respectively as shown in [Table 3](#).

**Table 1**

Demographics of Sudanese patients with infertility secondary to PCOS in Khartoum City, (n = 100).

Marriage duration in years	Patient education	Wife occupation	Husband occupation
$\leq 5$ : 65%	University: 17%	Housewife: 65%	Self-employed: 52%
5-10: 27%	Secondary: 59%	Employed: 35%	Employed: 48%
$\geq 10$ : 8%	Primary: 24%		

**Table 2**

History of patients treated with LTZ 20 mg or CC100mg for the treatment of infertility secondary to PCOS, (n = 100).

Variables	≤20 years	20–25 years	25–30 years	30–40 years
Age in years (mean ± SEM)	18.0 ± 0.53	23.9 ± 0.55	27 ± 0.25	34.9 ± 0.38
BMI in Kg/M <sup>2</sup> (Mean ± SEM)	7 (18.8 ± 0.47)	33 (22.8 ± 0.02)	50 (26.6 ± 0.26)	10 (30.9 ± 0.12)
Menstrual cycle pattern	Regular	Yes = 36%	No = 64%	
Type of Infertility within patients	Primary 36%	Secondary 64%	Secondary 98.4%	PCOS (n = 64)
Infertility within family, (n = 74)	Mother (34) 45.95%	Sister (37) 50%	Aunt (3) 4.05%	
Miscarriages within Patients (n = 26)	Once (14) 53.84%	Twice (7) 27%	Thrice (5) 19.2%	

#### 4. Associations between the investigated clinical parameter and LTZ vs CC as ovulation inducers in PCOS patients

No significant association was observed between LTZ vs CC and cycle patterns, type of infertility, number of miscarriages or duration of marriage as shown by Chi-square analysis in Table 4.

##### 4.1. Factor associated with positive pregnancy test outcome by LTZ 20 mg vs CC 100 mg in Sudanese patients with infertility secondary to PCOS

A significant correlation ( $P \leq 0.009$ ) was observed between age and positive pregnancy tests outcomes. The patients within the age range of 20–30 years old have a better rate of positive pregnancy tests with 10 times more likely to get pregnant (OR.10.3, 95%, CI.1.78–59.9) compared to those 30–40 years old. Although the age group less than 20 years were not significantly associated with positive pregnancy tests ( $p \leq 0.115$ ), yet this group had 7-fold chance to get pregnant (OR = 7.2) compared to the senior group.

A significant association was observed between BMI and positive pregnancy tests ( $p \leq 0.049$ ). The overweight is 17 times more likely to get pregnant compared to the obese group.

LTZ showed a significant ( $P \leq 0.007$ ) association with positive pregnancy tests with CC as reference.

No association was observed between positive pregnancy tests and cycle pattern, type of infertility, number of miscarriages, family history of infertility or duration of marriage as shown in Table 5.

##### 4.2. Discussion

Polycystic ovary syndrome is an endocrine/metabolic disorder that commonly presents with hyperandrogenism, and disability to conceive in young patients within reproductive age [10]. This study was designed to compare the successes rate of LTZ 20 mg as a single loading does and CC100mg as ovulatory inducers in Sudanese patients diagnosed with infertility secondary to PCOS.

Our study showed that almost two thirds of the patients had a duration of marriage less than 5 years. This result is in contrast to some previous reports that raised concern about Sudanese patients not seeking medical intervention early after marriage [3]. Half the investigated patients were in the age range of 20–30 of whom 98.4% has infertility secondary to PCOS. As reported by Witchel et al., 2019; that 6%–20% of patients within reproductive age were affected by PCOS [5]. More than 50% of the included patient's BMI was within the overweight range ( $26.60 \pm 0.26$ ), while 10 patients were obese ( $30.9 \pm 0.12$ ). High BMI increases the chance for a poor fertility prognosis, [24]. In addition, central obesity and high BMI are considered major factors for the development of insulin resistance and hyperandrogenism, which are determinant factors in PCOS [25]. About two thirds had family history of infertility in close family members including mothers and sisters which reflect a genetic or an environmental element. Many studies had showed the association between PCOS with genetics, and environmental factors [26].

LTZ 20 mg vs CC100mg reliability in improving positive pregnancy tests rate were statistically similar ( $P \leq 0.017$ ) and ( $P \leq 0.027$ ) respectively. CC100mg showed more potent activity in enhancing follicles' size maturation to  $\geq 18$  mm ( $P \leq 0.000$ ) compared to ( $P \leq 0.013$ ) by Letrozole 20 mg. However, letrozole showed a significant association ( $P \leq 0.007$ ) with positive pregnancy tests when CC100 was used as reference as shown by logistic regression. In contrast, LTZ was also reported as effective as CC in inducing pregnancy although it produces fewer follicles [22]. Liu et al. 2017; reported no significant difference between LTZ and CC in terms of positive pregnancy and live birth rates [27]. Interestingly, LTZ has been claimed as more effective than CC in achieving better pregnancy rates

**Table 3**

Outcome measures comparing LTZ vs CC in Sudanese patients with PCOS.

Variable	Clomiphene Citrate group (n = 47) Mean (SD)	P value	Letrozole group (n= (44) Mean (SD)	P value		
Endometrial thickness, mm	Before	8.2213 (1.59)	P ≤ 0.000	Before	4.8455 (1.31)	P ≤ 0.000
	After	↓6.1213 (1.36)		After	↑ 7.3591 (1.9)	
Ovarian cyst sizes, mm	Before	4.8532 (2.11)	P ≤ 0.000	Before	5.6750 (2.01)	P ≤ 0.000
	After	↓ 4.4255 (2.07)		After	↓5.3341 (2.05)	
Number of follicles ≥18 mm	–	18.7 (0.55)	P ≤ 0.000	–	18.2 (1.23)	P ≤ 0.013
Positive pregnancy tests	(n = 188)	8 ± 00 (17%)	P ≤ 0.027	(n = 176)	13 ± 00 (26%)	P ≤ 0.017

SD = standard deviation.

**Table 4**  
Associations between LTZ vs CC and the investigated clinical parameters.

Variables		Pregnancy test after induction		Pearson Chi-Square P value
		Positive	Negative	
Cycle pattern	Irregular	8 12.50%	56 87.50%	0.110*
	Regular	9 25.00%	27 75.00%	
Type of infertility	Primary	8 17.40%	38 82.60%	0.923*
	Secondary	9 16.70%	45 83.30%	
Miscarriage	Yes	4 15.40%	22 84.60%	0.799*
	No	13 17.60%	61 82.40%	
Duration of marriage	<5 years	13 20.00%	52 80.00%	0.551*
		5–10 years	3 11.10%	
	>10 years	1 12.50%	7 87.50%	

**Table 5**  
Logistic regression analysis of positive pregnancy tests and LTZ 20 mg vs CC100mg in patients with PCOS in Khartoum City.

Variables	S.E.	Sig.	Exp(B)	95% C.I. for EXP(B)	
				Lower	Upper
<b>Age in years</b>					
<20 years	1.244	0.120	6.918	.604	79.299
20–30 years	.884	0.010	9.756	1.726	55.143
>30–40 years (Ref.)		1			
<b>Cycle pattern</b>					
Regular	.681	0.383	.552	.145	2.098
Irregular (Ref.)		1			
<b>Type of infertility</b>					
Primary	.850	0.560	1.641	.310	8.683
Secondary (Ref.)		1			
<b>Miscarriage</b>					
Family history of Infertility (PCOS)	.980	0.663	1.532	.224	10.470
No	.704	0.863	1.129	.284	4.483
Yes		1			
<b>Drugs for induction</b>					
Letrozole	.833	0.007	9.533	1.862	48.798
Clomiphene citrate (ref)		1			
<b>BMI</b>					
Normal	1.278	0.157	6.110	.499	74.757
Overweight	1.435	0.049	16.914	1.015	281.841
Obese (Ref.)		1			
<b>Marriage duration</b>					
<5 years	1.451	0.925	.872	.051	14.988
5–10 years	1.464	0.685	.552	.031	9.731
>10 years (Ref.)		1			

SEM = standard error of the mean, OR = odd ratio, 95%CI: 95% confidence interval.  
Sig = statistical significance ( $P \leq 0.05$ ).

and live birth rates as reported by Sakar and Oglak 2020; [18]. A meta-analysis by Liu et al. 2023; reported similar findings but the authors concluded that there is still mixed quality of evidence [28]. According to Chi-square and logistic regression analysis in this study, no association was observed between the outcome measures and the patients’ clinical parameters which supports eliminating the confounding factors that may influence the efficacy of the two drugs. This interpretation is supported by the study of Sakar and Oglak 2023; [18].

Both drugs showed similar potency ( $P \leq 0.000$ ) in compacting the ovarian cysts sizes. This may be explained by the fact that both drugs interact with insulin and ovarian androgens metabolic pathway through which they reduce the hormonal levels and consequently regulate the hormonal homeostasis and improve ovulation. Insulin plays a key role in regulating the ovarian functions. Hence, high insulin increase the release of androgens that may precipitate anovulation and block follicular normal development [29].

The two drugs showed different modes of activities on the endometrial lining thickness. CC 100 mg reduced the endometrial lining

thickness by almost a quarter (25.54%) while an increase of almost 52% was observed with LTZ. This may be due to the fact that LTZ increases the endometrial receptivity and has an agonistic effects on the estrogen receptors on the endometrium which stimulate the increase in thickness, unlike CC antagonistic activity that block the estrogen receptors and consequently inhibit the normal central feedback mechanisms [21]. It is also reported that CC antagonistic activity may suppresses the endometrial receptivity and responsiveness to central signals and stimuli [30]. In addition, CC has a long half-life and a high affinity to exhaust the estrogen receptors in the endometrium which precipitates a negative impact on the mucosal layer and consequently the endometrial thickness. These factors may be behind the low pregnancy rates by CC in spite of the high number of mature follicles produced [18]. Although the endometrial lining thickness has no direct effects on enhancing positive pregnancy outcome, but it is considered among the factors that may help to facilities conception. As reported by Saeed B. et al. 2018; that an increase of 5 mm or more in the endometrial thickness would facilitates higher pregnancy rates [31].

Our results showed that positive pregnancy test was significantly associated with age and BMI. The younger groups of patients were 7–10 times more likely to get pregnant compared to the older group of 30–40 years old. The overweight patients were 17 times more likely to get pregnant compared to the obese group. Poor fertility prognosis and lower chance of clinical pregnancy has been associated with high BMI and obesity [24]. Furthermore, some reports linked obesity to spontaneous abortion and negative pregnancy outcomes, [32,33].

#### 4.3. Conclusion

LTZ mediated comparable results on positive pregnancy tests but less activity on follicle size maturation compared to CC. Effects on the ovarian cysts' sizes of both drugs were statistically similar. CC mediated more potent activity on follicles size maturation and LTZ showed more activity on increasing the endometrial lining thickness. Positive pregnancy tests rates were significantly associated with patient's age and BMI.

#### 4.4. Strengths and limitations

##### The Strengths.

- This study showed an improvement in Sudanese patients' awareness to pursue medical interventions for infertility treatment compared to a pervious study on 2017; [3]. Our results showed that half the patients attempted medical treatment for infertility at younger age and shorter duration after marriage
- A high percentage of the included patients in this study had infertility secondary to PCOS as a running disease in the family which consolidate other reports linking genetic factor to infertility due to PCOS
- This study consolidated the reports about the effects of the two drugs on the thickness of the endometrial lining

##### The Limitations.

- The small sample size is the main limitation in this study which could be justified as many patients would refrain from private treatment as it is highly expensive for the general public in Sudan
- The study was conducted in private sector centers only, and the state hospitals departments were not included due to some logistic difficulties
- The study was bound by a narrow time window and specific inclusion/exclusion criteria
- Incomplete medical records led to the exclusion of many files from the study
- Recommendations
  - Prospective research to investigate and follow up the patients being treated with loading doses of LTZ 20 mg or 25 mg as a single doe to monitor the long-term effects on mother and baby
  - A study to investigate the outcome of positive clinical pregnancies and number of full term live birth rates after LTZ 20 mg vs CC100mg as treatment for PCOS in Sudanese patients

#### Author contribution statement

Hayat Ibrahim Mohamed Suliman; Iman Hassan Abdoon: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Warda SALah Elkhailifa: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Bashier Ibrahim Osman: Conceived and designed the experiments; Wrote the paper.

Walaa Mohamed Mohamed: Performed the experiments; Contributed reagents, materials, analysis tools or data.

#### Data availability statement

Data associated with this study has been deposited at Mendeley data repository under the accession number 10.17632/bbjkmpkgms.1.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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