# Clinical correlation between volume of placental lakes and non-reassuring fetal status: a retrospective cohort study

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**Abstract. – OBJECTIVE:** This study evaluated the correlation between placental lakes and non-reassuring fetal status.

**SUBJECTS AND METHODS:** We analyzed data from pregnant women who underwent fetal echocardiography at the Fujian Maternity and Child Health Hospital. Women with singleton pregnancies at a gestational age of 20-24 weeks were included. Sociodemographic and clinical data were collected. Pregnant women with (case group) and without (control group) placental lakes were screened, and their placental Doppler ultrasound data and pregnancy outcome were recorded. Univariate and multivariable analyses were done to evaluate the correlation between the volume of placental lakes and the non-reassuring fetal status.

**RESULTS:** A total of 1,728 pregnant women (156 with placental lakes) were included in this study. There were no significant differences in age of delivery and BMI between the pregnant women with placental lakes and the control group. The non-reassuring fetal status rate in the case group was higher than that in the control population, without statistical significance (5.8% *vs.* 3.5%, *p*=0.226). Subgroup analysis showed that a higher volume of placental lakes was positively associated with non-reassuring fetal status risk, with an odds ratio (OR) (95% CI) of 1.90 (1.29-2.66) (*p* for trend < 0.001). This positive correlation persisted even after adjustment for confounding factors.

**CONCLUSIONS:** Taken together, our analyses demonstrated a graded increase in the non-reassuring fetal status rate with increased volume of placental lakes. Thus, robust clinical monitoring of placental lakes would help in timely detection of non-reassuring fetal status.

*Key Words:*
Placental lakes, Non-reassuring fetal status, Pregnancy outcome.

### Abbreviations

BMI: Body Mass Index; CS: Caesarean Section; IQR, interquartile range; SD, standard deviation; ORs: Odd Ratios; CI: confidence interval; PROM, premature rupture of the membranes; GDM, Gestational Diabetes Mellitus; HBV, hepatitis B virus; SGA, small for gestational age; VD, Vaginal delivery.

## Introduction

The placenta is an essential and a highly specialized organ that plays an important role in the growth and development of the fetus during pregnancy. Placental abnormalities have serious consequences in the development of the fetus, as they affect the exchange of oxygen, nutrients, and metabolic waste between the mother and the fetus[1]. Increased use of obstetrical sonography has led to discovery of many subtle abnormalities. Since these discoveries could be normal or abnormal variants, the diagnostic confusion may lead to over-examination, thus increasing the economic burden. One of these potential abnormalities, the placental lakes, characterized by the formation of hypoechoic cystic spaces centrally within the placenta, were first reported in the late 1970s and early 1980s[2]. With the continuous advancement in diagnostic tools, especially resolution enhancement in medical ultrasound imaging, there is a higher detection rate for placental lakes. Indeed, recent reports[3,4] have shown that the detection rate for the placental lakes could reach 17.8%. However, clinical significance of the placental lakes remains controversial. For instance, previous studies[4,5] showed

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that the placental lakes are not associated with adverse effects on pregnancy outcomes, which disagreed with other studies[6] that showed a correlation with poorer pregnancy outcomes.

Previous studies[7-9] demonstrated that the non-reassuring fetal status (fetal distress), an abnormal fetal heart rate which results from insufficient oxygen supply[7], is a risk factor for neonatal developmental disorders[8,9]. Here, we present new evidence on the effects of placental lake volume on non-reassuring fetal status.

## Subjects and Methods

### Study Design and Data Acquisition

This retrospective observational study obtained data from a case register at the Fujian Maternity and Child Health Hospital between September 2017 and January 2018. We extracted data, such as maternal outpatient card number, ID card, maternal birthdate, maternal ethnicity, gravidity, parity, BMI (Body Mass Index), and prenatal history. The medical records were taken when performing fetal echocardiogram at a gestational age between 20 and 24 weeks. A unique resident identity card number was used to obtain follow up data on the placental Doppler ultrasound results and pregnancy outcome. Data collection and definition of covariates were acquired from both electronic medical records and paper medical charts.

### Selection Criteria

Women with multiple gestations and nonviable pregnancies, no follow-up data or pregnancies with unknown outcomes as well as those with serious physical illness, substance abuse or other mental disorders that were not suitable for pregnancy (Figure 1) were excluded. All other pregnant women who underwent fetal echocardiogram at the Fujian Maternity and Child Health Hospital were included in the study. The included pregnant women underwent color Doppler ultrasound examination at around 31 weeks of gestation, before the delivery.

### Definition and Measurement

A placental lake was defined as an anechoic area measuring at least 1 cm without demonstrable flow on Doppler interrogation, surrounded by normally appearing placental tissue[10]. The placental lake diagnosis from other space-occupying lesions in the placenta was based on conventional ultrasonography. The volume of the placental lakes was calculated using the standard formula: volume =

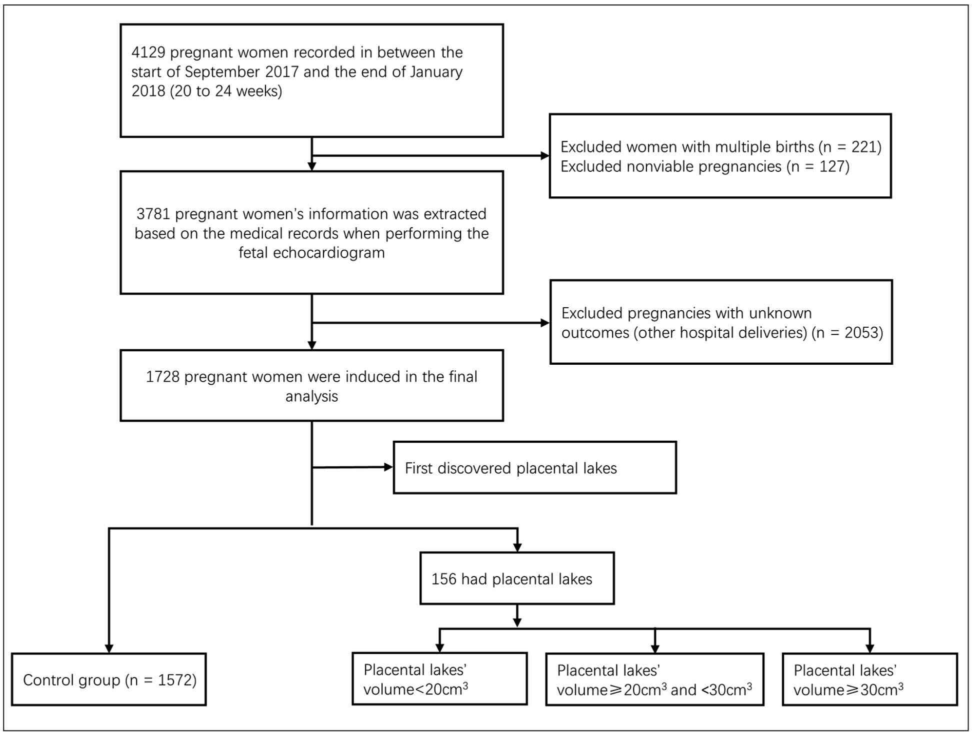


**Figure 1.** Flowchart of the enrolled women.

length×width×height×0.52[11]. If more than one lesion existed, the final total volume was calculated from the summation of each placental lake. Non-reassuring fetal status was defined as persistent or worsening category II fetal heart rate (FHR), or Category III FHR[7].

### Study Outcomes/Perinatal Outcomes

Primary outcome was non-reassuring fetal status. Secondary outcomes included analysis of maternal features, such as post-partum hemorrhage, complications during pregnancy, and delivery method. Neonatal outcomes included mortality, birth weight, and neonatal asphyxia (defined as 5-minute Apgar score ≤7).

### Predictors/Covariates

The study considered potential confounders, such as age (on delivery date), pre-pregnancy weight, maternal BMI at delivery, gravidity, parity, gestational age, and pregnancy complications.

### Statistical Analysis

Normal distribution data were expressed as mean (standard deviation), while non-normally distributed data were expressed as median [IQR, Interquartile Range]. Counting data were expressed as Frequency (Percentage) /n (%). We examined the relationship between volume of the placental lakes and pregnancy outcome. Comparisons between demographic and clinical features were performed based on the outcome status, using One-way analysis of variance (One-way ANOVA) or chi-square test. Unconditional logistic regression was used to obtain adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association between the different volumes of placental lakes and non-reassuring fetal status. Ordinal trend tests used logistic regression with the dependent variable of interest and an ordinal independent variable. The analyses were performed in R software (V3.6.2) and all the statistical inferences were based on a 0.05 significance level.

### Ethical Approval

This study was approved by the local institutional review boards and ethical committees (YCXQ 18-34). Due to the retrospective design of the study, only nonwritten patient consent was required.

## Results

### Characteristics of the Cohort

Medical records of 4,129 pregnant women were collected at the Fujian Maternity and Child Health Hospital between September 2017 and January 2018. We excluded women with multiple births (n=221), nonviable pregnancies (n=127) and pregnancies with unknown outcomes (n=2,053). A total of 1,728 pregnant Asian women were included in the final analysis (Figure 1). Of them, 156 (9.0%) women had placental lakes. Women were divided into subgroups based on the presence and the size of the placental lakes: control (no placental lakes, n=1,572), small (<20 $cm^3$; n=129), medium-sized (≥ 20 and < 30 $cm^3$; n=10) and large (>30 $cm^3$; n=17) placental lakes. Among the women with placental lakes, 44 (28.2%) had the last obstetric ultrasound examination before the delivery and indicated disappearance of abnormality signals after 8-12 weeks. Approximately half of intermediate size (20-30 $cm^3$) placental lakes vanished. New-onset placental lakes developed in 1.1% of the control group (the initial fetal echocardiogram examination without the placental lakes), and the volumes of placental lakes were not high (Table I). The mean maternal age of the participants at delivery was 29.79 (SD 4.52) years while their BMI was 25.92 $kg/m^2$ (SD 2.77). There were no differences between the groups in terms of the age of delivery, BMI, platelet count and previous preform birth history. The haemoglobin levels of the pregnant women with small placental lakes were slightly higher compared to the other groups, while the white blood cell count in the medium-sized placental lakes group was higher than in the other groups.

### Pregnancy Complications and Outcomes

Our analysis showed that there was no difference in the HBV infection and Hypertensive disorders in pregnancy among the four groups ($p$>0.05) (Table II). There was a statistically significant difference in the incidence of premature rupture of the membranes (PROM) and non-reassuring fetal status between women with and without placental lakes ($p$<0.05). Large placental lakes (volume≥30 $cm^3$) appeared to increase the risks of placenta previa and placenta accrete ($p$<0.001, 0.07, respectively).

The volume of placental lakes correlated with some of the pregnancy outcomes, such as 2h postpartum haemorrhage, gestational week at delivery, and the occurrence of non-reassuring

**Table I.** Basic characteristics according to different volume of placental lakes.

| First discovered | | Control group (n = 1,572) | < 20 cm³ (n = 129) | ≥ 20 & < 30 cm³ (n = 10) | ≥ 30 cm³ (n = 17) | *p*-value* |
|---|---|---|---|---|---|---|
| Age (years) | | 29.75 (4.53) | 30.19 (4.19) | 31.50 (4.60) | 29.35 (5.81) | 0.444 |
| G (times) | | 2.00 [1.00, 3.00] | 2.00 [1.00,3.00] | 2.00 [2.00, 2.75] | 200 [2.00, 3.00] | 0.414 |
| P (times) | | 1.00 [0.00, 1.00] | 1.00 [1.00, 2.00] | 1.00 [1.00, 1.75] | 2.00 [1.00, 3.00] | < 0.001 |
| BMI(kg/m²) | | 25.92 (2.80) | 26.11 (2.58) | 26.03 (1.99) | 25.19 (2.05) | 0.611 |
| WBC (×10^9) | | 10.53 (3.39) | 9.39 (2.93) | 11.18 (1.99) | 9.94(3.36) | 0.002 |
| HGB (g/L) | | 117.73 (13.02) | 121.27 (11.82) | 113.90 (13.58) | 117.12 (15.60) | 0.019 |
| PLT (×10^9) | | 212.35 (54.59) | 209.26 (64.80) | 194.50 (20.22) | 219.53 (66.63) | 0.641 |
| Previous preterm | NO | 1,538 (97.8) | 128 (99.2) | 9 (90.0) | 16 (94.1) | 0.155 |
| birth history | YES | 34 (2.2) | 1 (0.8) | 1 (10.0) | 1 (5.9) | |
| Placental lakes | NO | 1,548 (98.9) | 37 (28.9) | 5 (50.0) | 2 (11.8) | < 0.001 |
| volume of last | ≤ 20 | 18 (1.1) | 78 (60.9) | 5 (50.0) | 10 (58.8) | |
| measuring(cm³) | > 20 | 0 (0.0) | 13 (10.2) | 0 (0.0) | 5 (29.4) | |
| Placental lakes | NO | 1,554 (99.2) | 37 (28.9) | 5 (50.0) | 2 (11.8) | < 0.001 |
| volume of last | ≤ 30 | 12 (0.8) | 87 (68.0) | 5 (50.0) | 10 (58.8) | |
| measuring (cm³) | > 30 | 0 (0.0) | 4 (3.1) | 0 (0.0) | 5 (29.4) | |

*One-way ANOVA or chi-square test; Wilcoxon signed-rank test was applied for Non-normally distributed data.

fetal status. The intensity of the 2h postpartum haemorrhage was highest in the group with large placental lakes. One patient in the large placental lakes group experienced massive haemorrhage (7,005 ml) caused by complete placenta previa. In addition, our data showed that the rate of cae-

**Table II.** Pregnancy complications and outcomes according to different volume of placental lakes.

| First discovered | | Control group (n = 1,572) | < 20 cm³ (n = 129) | ≥ 20 & < 30 cm³ (n = 10) | ≥ 30 cm³ (n = 17) | *p*-value* |
|---|---|---|---|---|---|---|
| Postpartum 2h hemorrhage (ml) | | 283.91 (170.41) | 461.56 (448.82) | 496.50 (244.73) | 784.94 (1609.09) | < 0.001 |
| Gestational week at delivery(W) | | 39.40 [38.70,40.30] | 39.00 [37.00, 40.00] | 38.15 [36.25, 39.88] | 35.00 [34.00, 38.40] | <0.001 |
| Nonreassuring | NO | 1517 (96.5) | 125 (96.9) | 8 (80.0) | 13 (76.5) | < 0.001 |
| fetal status | YES | 55 (3.5) | 4 (3.1) | 2 (20.0) | 4 (23.5) | |
| Delivery method | VD | 1,026 (65.3) | 63 (48.8) | 2 (20.0) | 5 (29.4) | < 0.001 |
| | CS | 546 (34.7) | 66 (51.2) | 8 (80.0) | 12 (70.6) | |
| PROM | NO | 1275 (81.1) | 113 (87.6) | 6 (60.0) | 17 (100.0) | 0.016 |
| | YES | 297 (18.9) | 16 (12.4) | 4 (40.0) | 0 (0.0) | |
| GDM | NO | 1,320 (84.0) | 122 (94.6) | 10 (100.0) | 15 (88.2) | 0.006 |
| | YES | 252 (16.0) | 7 (5.4) | 0 (0.0) | 2 (11.8) | |
| HBV infection | NO | 1,413 (89.9) | 122 (94.6) | 9 (90.0) | 16 (94.1) | 0.351 |
| | YES | 159 (10.1) | 7 (5.4) | 1 (10.0) | 1 (5.9) | |
| Hypertensive | NO | 1,533 (97.5) | 124 (96.1) | 10 (100.0) | 17 (100.0) | 0.648 |
| disorders in pregnancy | YES | 39 (2.5) | 5 (3.9) | 0 (0.0) | 0 (0.0) | |
| Placenta accrete | NO | 1,557 (99.0) | 124 (96.1) | 9 (90.0) | 14 (82.4) | < 0.001 |
| | YES | 15 (1.0) | 5 (3.9) | 1 (10.0) | 3 (17.6) | |
| Placenta increta/ | NO | 1,560 (99.2) | 129 (100.0) | 10 (100.0) | 16 (94.1) | 0.070 |
| percreta | YES | 12 (0.8) | 0 (0.0) | 0 (0.0) | 1 (5.9) | |
| Stillbirth | NO | 1,571 (99.9) | 129 (100.0) | 10 (100.0) | 17 (100.0) | 0.992 |
| | YES | 1 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| SGA | NO | 1,542 (98.1) | 116 (90.6) | 10 (100.0) | 16 (94.1) | < 0.001 |
| | YES | 30 (1.9) | 12 (9.4) | 0 (0.0) | 1 (5.9) | |

PROM, premature rupture of the membranes; GDM, Gestational Diabetes Mellitus; HBV, hepatitis B virus. SGA, small for gestational age; VD, Vaginal delivery; CS, Cesarean section.

sarean section in all the placental lakes groups was higher than in the control group ($p$<0.001). The occurrence of severe bleeding was higher after caesarean compared to the normal vaginal delivery. Increase in the volume of placental lakes led to the decrease in the gestational week at delivery ($p$<0.001). Among the pregnant women with large placental lakes, half delivered before 35 weeks of pregnancy. Compared with the other groups, the gestational week at delivery in the large placental lakes group was significantly lower (large *vs.* small and medium placental lakes, all $p$-values were less than 0.05). The chi-square tests showed that the non-reassuring fetal status was statistically different between the four groups ($p$<0.001) (Table II).

### Association Between the Volume of Placental Lakes and Non-Reassuring Fetal Status

We used the odd ratios (ORs) and 95% confidence intervals (CIs) to assess the correlation between non-reassuring fetal status and the volume of placental lakes after adjusting for potential confounding factors (Table III). Our data showed that there was an 8-fold increase in the risk of non-reassuring fetal status associated with large placental lakes compared with the control group (OR = 8.49, 95% CI = 2.33-24.88, $p$ for trend < 0.001). Adjustment for the pre-pregnancy weight, age, BMI, and parity did not affect the correlation between the placental lakes and the non-reassuring fetal status (OR = 8.09, 95% CI = 1.93-28.68, $p$ for trend = 0.002). Since the non-reassuring fetal status had more influencing factors, we carefully adjusted for possible patient demographic and clinical confounders. There was no difference in the association after adjustment for potential confounders such as pre-pregnancy weight, age, BMI, parity, WBC, HB, PROM, GDM, Hypertensive disorders in pregnancy, placenta accrete (OR = 7.26, 95% CI = 1.53-29.84, $p$ for trend = 0.005).

## Discussion

Non-reassuring fetal status is a leading cause of fetal asphyxiation[12], and an important indication for the caesarean section[13]. Potential risk factors for the non-reassuring fetal status may include pregnancy complications and abnormal placentation[7,14]. However, data on the association between the volume of placental lakes and non-reassuring fetal status remains limited. Our study demonstrated a significant correlation between large placental lakes and the non-reassuring fetal status. According to our results, placental lakes may be used as a clinical indicator for the non-reassuring fetal status.

In a previous study by Inubashiri et al[3] large placental lakes in 11 women were monitored by three-dimensional high-definition flow during the second visit. The huge placental lakes persisted in only five women after 4-10 weeks. Of them, four (80%) were in the labor period with respiratory fetal distress, while one (20%) had a small gestational age (SGA) fetus. In the remaining cases, obstetric ultrasound confirmed that the placental

**Table III.** Odd ratios and 95% confidence interval for nonreassuring fetal status according to different volume of placental lakes.

| | | OR/aORs [95%CI] | | | |
|---|---|---|---|---|---|
| | Control group (n = 1572) | < 20 $cm^3$ (n = 129) | ≥ 20 & < 30 $cm^3$ (n = 10) | ≥ 30 $cm^3$ (n = 17) | $p$ for trend |
| Model 1 | 1 | 0.88 [0.26, 2.20] | 6.90 [1.02,28.31] | 8.49 [2.33,24.88] | < 0.001 |
| $p$-value | - | 0.812 | 0.016 | <0.001 | |
| Model 2 | 1 | 0.89 [0.25,2.43] | 7.09 [1.01,31.16] | 8.09 [1.93,28.68] | 0.002 |
| $p$-value | - | 0.832 | 0.018 | 0.002 | |
| Model 3 | 1 | 0.87 [0.24,2.43] | 6.15 [0.86,28.04] | 6.58 [1.40,26.80] | 0.009 |
| $p$-value | - | 0.805 | 0.032 | 0.011 | |
| Model 4 | 1 | 0.95 [0.26,2.68] | 5.90 [0.83,26.94] | 7.26 [1.53,29.84] | 0.005 |
| $p$-value | - | 0.929 | 0.036 | 0.008 | |

Model 1: No adjustment. Model 2: Adjusting for pre-pregnancy weight, age, BMI, parity. Model 3: Adjusting for pre-pregnancy weight, age, BMI, parity, gestational age, PROM, GDM, Hypertensive disorders in pregnancy, placenta accrete. Model 4: Adjusting for pre-pregnancy weight, age, BMI, parity, WBC, HB, PROM, GDM, Hypertensive disorders in pregnancy, placenta accrete.

lakes shrank or disappeared. Thus, the persistence of placental lakes is likely to be clinically informative, which agrees with other previous studies[15]. This might be due to the strong compensatory function of the placenta[16]. The placental lakes were not mentioned in the first fetal echocardiogram examination probability because the proportion of the large placental lakes was small.

Previous studies[4,17] showed absence of clinical significance of the placental lakes in pregnancy. However, Hwang et al[15] estimated the diameters of the placental lakes and classified them into different types. They showed that, unlike in small placental lakes, fetal SGA status significantly correlated with large placental lakes. A subsequent study[18] which grouped women according to the placental lake volume made similar conclusions about the link between fetal umbilical venous circulation with the volume of the placental lakes. Our study analyzed the electronic fetal heart monitoring in the different volumes of placental lakes. After adjusting for potential confounding factors, we showed that large placental lakes could indeed lead to non-reassuring fetal status. Therefore, we explored the relationship between the risk factors for non-reassuring fetal status, and adjusted models for potential confounders[19].

Our results showed a linear correlation between the volume of placental lakes and the rate of non-reassuring fetal status. We used standard integer and simple calculation formulas to estimate the volumes. Based on the results of this study, we suggest that if the second trimester examination reveals a volume of placental lakes greater than 30 $cm^3$, there is need for strengthened fetal heart rate monitoring during the third trimester. Electronic fetal heart monitoring (CTG) emerged as a convenient, low-costs method that is now considered essential in the obstetrics diagnostic approach[20], which makes the implementation of our suggestions easy in all clinical settings. Previous studies[15,21] have revealed a significant relationship between large placental lakes and the SGA diagnosis of the fetus, which plays an important role in the non-reassuring fetal status[3]. There is, however, a need for a large sample size to better assess the association among the two factors.

Non-reassuring fetal status may be related to factors, such as myometrial contractions, blood redistribution, changes in fetal heart rate patterns or maternal exposure to hypoxic events[7,12,22-24]. This might increase fetal troponin in the absence or presence of hypoxia, which ultimately affects fetal cardiovascular dysfunction as well as changes in fetal heart monitoring[25]. Chronic non-reassuring fetal status can lead to a compensatory response that manifests as an increase in chorionic fetal vessels before the appearance of clinical symptoms[26,27]. Large placental lakes may affect blood redistribution in the chorionic fetal vessels, leading to increased incidence of non-reassuring fetal status.

## Conclusions

Taken together, our analysis demonstrates that large placental lakes are an independent risk factor for non-reassuring fetal status. To the best of our knowledge, this is the first study that, using Doppler ultrasound, showed that placental lakes with a volume greater than 30 $cm^3$ need dynamic evaluation of the size of placental blood pool and strengthened monitoring. These findings contribute to timely clinical detection of non-reassuring fetal status.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Ethical Approval

Ethical approval for this study was granted by the Ethics Committee of the Fujian Maternity and Child Health Hospital. Permission to access the data was granted by the Fujian Provincial Maternity and Children's Hospital Database steering committee.

### Consent for Publication

All the data were anonymous, thus individual consent for publication was not required.

### Availability of Data and Materials

Data were anonymized, and no patient information was included to preserve confidentiality. All the data are available for scientific purposes, if needed.

### Funding

The funding sources had no role in the study design, data collection, data analysis, data interpretation, or preparation of the manuscript.

### Authors' Contribution

ZDL and YB conceptualized the study. SSZ and XQZ acquired the data. XWL designed the analyses. XQZ performed the analyses. YB and ZDL wrote the draft manuscript. All authors read and approved the final draft of the manuscript.

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