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Preterm birth and stillbirth: total bile acid levels in intrahepatic cholestasis of pregnancy and outcomes of twin pregnancies: a retrospective cohort study from 2014 to 2022

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Abstract

Background Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disorder characterized by maternal pruritus and elevated serum bile acids. Twin pregnancies, as a type of high-risk pregnancy, present additional complexities when complicated by ICP compared to singleton pregnancies. Our study aims to investigate the relationship between bile acid levels in intrahepatic cholestasis of pregnancy and adverse pregnancy outcomes such as preterm birth and stillbirth in twin pregnancies.

Methods This retrospective single-center cohort study was conducted at the Second Hospital of Sichuan University from January 2014 to July 2022, focusing on twin pregnancies complicated by ICP. Patients were grouped based on peak levels of total bile acids during pregnancy. Differences among these groups in gestational weeks at delivery, preterm birth, fetal growth restriction, fetal distress, stillbirth, premature rupture of membranes, meconium-stained amniotic fluid, and newborn birth weight were observed as pregnancy outcome indicators.

Results In 1156 twin pregnancies complicated by ICP, were 430 cases classified as mild, 392 as moderate-low, 292 as moderate-high, and 42 as severe. Regarding pregnancy outcomes, significant differences were observed among the four groups of pregnant women in terms of gestational weeks at delivery ($P < 0.001$), rate of preterm birth ($P < 0.001$), newborn birth weight ($P < 0.001$), incidence of meconium-stained amniotic fluid ($P < 0.001$), and proportion of low birth weight infants ($P < 0.001$).

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Conclusion The study results indicate that the severity of intrahepatic cholestasis of pregnancy (ICP) is associated with adverse pregnancy outcomes such as preterm birth, newborn birth weight, and meconium-stained amniotic fluid contamination. Additionally, among different bile acid level groups, gestational weeks at delivery showed varying trends in stillbirth occurrence.

Keywords Intrahepatic cholestasis of pregnancy, Twin pregnancy, Neonatal outcomes, Maternal complications

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is one of the severe complications unique to pregnancy, primarily manifested by varying degrees of skin itching, jaundice, and abnormally elevated serum total bile acid (TBA) concentrations, which may also be accompanied by elevated liver enzymes, and both serum total bile acids and liver enzymes can return to normal levels postpartum [1]. The incidence of ICP worldwide is approximately 0.3–15% [2], while the overall prevalence of ICP in China is 6.06% [3], particularly in regions such as Chongqing, Sichuan, and the Yangtze River basin, where the prevalence can reach 4–10% [4].

However, the pathogenesis of ICP remains unclear and may be associated with factors such as genetics, estrogen levels, and the environment. One significant characteristic of metabolic adaptation during pregnancy is the gradual elevation of serum bile acid levels. Therefore, the increase in bile acid levels in most pregnant women is considered a normal physiological change that stays within the normal reference range. Nonetheless, if there is an abnormal increase in bile acids in the pregnant woman, it could result in intrahepatic cholestasis of pregnancy [5]. Existing studies suggest a strong correlation between ICP and negative pregnancy outcomes, including stillbirth, preterm delivery, and fetal distress. Furthermore, children born to mothers with ICP are at an increased risk of developing conditions such as diabetes, obesity, and dyslipidemia [6].

Preterm birth (PTB) is defined as the birth of an infant before 37 weeks of gestation. The global incidence of preterm birth ranges from 5–18% [7], and it is a leading cause of perinatal mortality worldwide [8]. Surviving preterm infants are also at risk of neurological, respiratory, and gastrointestinal complications, as well as metabolic syndrome and cardiovascular diseases [9–11]. The incidence of preterm birth in twin pregnancies is nearly ten times higher than in single pregnancies [12], and it significantly increases the incidence and mortality rates of severe fetal and neonatal diseases [13]. Twin pregnancies also increase the risk of perinatal complications and comorbidities, such as gestational diabetes, gestational hypertension, premature rupture of membranes, and postpartum hemorrhage [14].

Elevated serum TBA concentration (> 10 mmol/L) can serve as an early diagnostic marker and is often used for grading the severity of ICP [15]. The clinical progression of ICP complicates diagnosis because pruritus often precedes TBA elevation by several weeks. Therefore, even with normal TBA levels, patients require close follow-up. Once an increase in TBA levels is observed, research indicates that maternal bile acids readily cross the placental barrier and accumulate in fetal circulation and amniotic fluid, which is believed to be the basis for inferring the aforementioned fetal risks [16]. ICP can be classified into early-onset and late-onset types based on the timing of onset. Previous studies have shown that early-onset ICP is associated with worse pregnancy outcomes [17], and bile acid metabolism shows significant changes between 28 and 31 weeks of gestation [18].

Additionally, research shows that the risk of adverse pregnancy outcomes is higher in pregnancies complicated by ICP. While peak TBA levels during pregnancy impact single fetal ICP outcomes, data on the effects of TBA levels on twin pregnancy outcomes are currently lacking. Therefore, investigating the impact of different TBA levels on adverse outcomes in twin pregnancies is beneficial for increasing clinical awareness and improving maternal health management, which is crucial for bettering maternal and fetal outcomes. This study retrospectively analyzed data from patients with twin pregnancies complicated by ICP at West China Second Hospital, Sichuan University, focusing on the effects of TBA levels during pregnancy on twin pregnancy outcomes.

Materials and methods

Study population

The data for this study were collected from pregnant women diagnosed with ICP who underwent antenatal care and delivery at the West China Second University Hospital from January 2014 to July 2022. Diagnostic criteria included unexplained pruritus in pregnancy, normal liver function tests, normal or elevated TBA levels, absence of other liver diseases, and postpartum recovery to normal levels.

The inclusion criteria were twin pregnancies complicated by ICP. Exclusion criteria included incomplete case data, comorbidities such as pre-existing cardiovascular disease, autoimmune disorders, HIV, syphilis, or missing data.

ICP severity was categorized based on peak pregnancy TBA levels (μmol/L) as follows: mild (TBA < 20), moderate-low (20 ≤ TBA < 40), moderate-high (40 ≤ TBA < 100), and severe (TBA ≥ 100). Given the clinical relevance of

bile acids, peak TBA levels were used for analysis [1, 2, 19].

Data collection

Data collection included demographic and clinical variables. Demographic characteristics comprised age, pre-pregnancy body mass index (BMI), gravidity, parity, in vitro fertilization with embryo transfer (IVF-ET), the proportion of dichorionic diamniotic twin pregnancies, and uterine scar percentage. Maternal outcomes encompassed gestational weeks at ICP diagnosis, TBA levels at onset of ICP, delivery gestational age, TBA levels before delivery, peak pregnancy TBA levels, intraoperative blood loss, placental abruption, premature rupture of membranes (PROM), fetal distress, stillbirth, gestational diabetes, and preeclampsia. Neonatal outcomes include birth weight, low birth weight infant, 1-minute Apgar scores, 5-minute Apgar scores, and 10-minute Apgar scores, meconium-stained amniotic fluid.

Statistical analysis

All data was analyzed in SPSS, version 26.0. Continuous variables are presented as medians (interquartile ranges) because they did not conform to a normal distribution, and categorical variables are expressed as frequency n (%). Then, the Kruskal-Wallis test or chi-square test was used to compare 4 groups. A value of $p < 0.05$ was considered statistically significant.

Results

Comparison of baseline characteristics

Baseline data analysis was conducted on four groups of pregnant women. The differences in age ($P = 0.117$), pre-pregnancy BMI ($P = 0.381$), gestational weight gain ($P = 0.124$), parity ($P = 0.424$), gravidity ($P = 0.924$), IVF-ET usage ($P = 0.395$), dichorionic diamniotic twin pregnancies ($P = 0.767$), and uterine scar proportion ($P = 0.301$) among the groups were not statistically significant (Table 1).

Comparison of pregnancy outcomes among the four groups

Significant differences were observed among the four groups of pregnant women in terms of gestational age at intrahepatic cholestasis of pregnancy (ICP) diagnosis ($P < 0.001$), TBA levels at diagnosis ($P < 0.001$) and before delivery ($P < 0.001$), gestational age at termination ($P < 0.001$), vaginal delivery($P = 0.037$), and preterm birth rate ($P < 0.001$). In this study, we defined preterm birth based on the Chinese guidelines as gestational age greater than or equal to 28 weeks but less than 37 weeks [20]. Additionally, gestational weeks 28 to 31 were classified as early preterm, and gestational weeks 32 to 36 as late preterm. In terms of specific gestational weeks at delivery, the proportion of full-term pregnancies in the severe and moderate-high groups (7.5%, 4.8%, $P < 0.001$) was lower than that in the mild group. Meanwhile, the proportion of late preterm births in the moderate-low and moderate-high groups (79.3%, 85.6%, $P < 0.001$) was significantly higher than that in the mild group.

However, our study did not find significant differences in maternal-fetal complications among the four groups. Rates of placental abruption ($P = 0.717$), premature rupture of membranes ($P = 0.354$), fetal growth restriction ($P = 0.109$), fetal distress ($P = 0.669$), stillbirth ($P = 0.679$), preeclampsia ($P = 0.382$), operative blood loss ($P = 0.210$), and gestational diabetes ($P = 0.705$) did not differ significantly (Table 2).

Comparison of neonatal data among the four groups

Statistically significant differences were observed among the four groups in terms of neonatal birth weight ($P < 0.001$), proportion of low birth weight infants ($P < 0.001$), and meconium-stained amniotic fluid occurrence ($P < 0.001$). Moreover, the severe and moderate to severe groups had significantly higher rates of low birth weight and meconium-stained amniotic fluid compared to the mild group (Table 3).

Table 1 Maternal baseline information of 4 groups

Description	mild($n = 430$)	Moderate-low($n = 392$)	Moderate-high ($n = 292$)	severe($n = 42$)	*P*-Value
Age, median(P_{25}-P_{75})	31(28,33)	31(28,34)	31(28,34)	30(27,34)	0.236
Advanced age (≥ 35 years), n(%)	81(18.8%)	73(18.6%)	71(24.3%)	10(23.8%)	0.125
BMI before pregnancy, median(P_{25}-P_{75})	21.36(19.53,23.15)	21.19 (19.59,23.10)	20.80 (19.50,22.92)	20.70 (18.70,22.87)	0.355
Gravidity, median(P_{25}-P_{75})	2(1,3)	2(1,3)	2(1,3)	2(1,4)	0.514
Parity, median(P_{25}-P_{75})	0(0,0)	0(0,0)	0(0,0)	0(0,0)	0.867
IVF-ET, n(%)	263(61.2%)	249(63.5%)	172(58.9%)	22(52.4%)	0.407
Dichorionic twins, n(%)	335(77.9%)	320(81.6%)	226(77.4%)	33(78.6%)	0.492
Scarred uterine, n(%)	27(6.3%)	30(7.7%)	26(8.9%)	1(2.4%)	0.340

Table 2 Maternal outcomes of 4 groups

Description	mild($n=430$)	Moderate-low($n=392$)	Moderate-high ($n=292$)	severe($n=42$)	*P*-Value
GA at diagnosis, median(P_{25}-P_{75})	34(31,35) a	32(30,34) b	32(29,33) c	30(27,33)c	0.000
TBA at diagnosis, median(P_{25}-P_{75})	12.7(11.0,15.4) a	20.0(13.2,26.7) b	39.1(20.4,52.9) c	67.6(24.7,125.2) c	0.000
Vaginal delivery	19(4.4%)a, b	6(1.5%)b	16(5.5%)a	2(4.8%)a, b	0.037
TBA at peak	14.0(12.0,16.7) a	27.6(23.8,32.4) b	56.1(47.8,69.8) c	139.5(116.0,174.7) d	0.000
TBA at delivery, median(P_{25}-P_{75})	11.2(8.2,14.2) a	20.4(12.4,26.0) b	37.1(20.3,52.2) c	70.5(30.5,111.2) c	0.000
Delivery week, median(P_{25}-P_{75})	36(34,37) a	35(34,36) a	35(34,36) b	34(33,35) c	0.000
Delivery week 28–31	21(4.9%)a, b	9(2.3%)b	17(5.8%%)a, b	6(14.3%)a	0.002
Delivery week 32–36	296(68.8%)a	311(79.3%)b	250(85.6%)b	33(78.6%)a, b	0.000
Delivery week ≥ 37	110(25.6%)a	72(18.4%)a, b	22(7.5%)c	2(4.8%)b, c	0.000
Preterm birth, n(%)	317(73.7%)a	320(81.6%)b	267(91.4%)c	39(92.9%)b, c	0.000
Intraoperative blood loss, median(P_{25}-P_{75})	400(400,500)	400(400,600)	400(400,500)	400(400,500)	0.210
Placental abruption, n(%)	7(1.6%)	5(1.3%)	6(2.1%)	0(0%)	0.717
PROM, n(%)	78(18.1%)	67(17.1%)	40(13.7%)	5(11.9%)	0.354
Fetal growth restriction, n(%)	23(5.3%)	9(2.3%)	14(4.8%)	3(7.1%)	0.109
Fetal distress, n(%)	21(4.9%)	17(4.3%)	18(6.2%)	3(7.1%)	0.669
stillbirth, n(%)	8(1.9%)	6(1.5%)	7(2.4%)	0(0%)	0.679
Preeclampsia, n(%)	42(9.8%)	50(12.8%)	37(12.7%)	3(7.1%)	0.382
gestational diabetes, n(%)	117(27.2%)	116(29.6%)	88(30.1%)	10(23.8%)	0.705

Table 3 Neonatal outcomes of 4 groups

Description	Mild($n=842$)	Moderate-low($n=770$)	Moderate-high ($n=565$)	severe($n=82$)	*P*-Value
birth weight, median(P_{25}-P_{75})	2320 (2050,2560)a	2330 (2060,2560)a	2210 (1940,2440)b	1980 (1760,2260)c	0.000
low birth weight infants(< 2500 g), n(%)	585(69.5%)a	523(67.9%)a	452(80.0%)b	76(92.7%)c	0.000
very low birth weight(< 1500 g), n(%)	45(5.3%)a	17(2.2%)b	41(7.3%)a	10(12.2%)a	0.000
extremely low birth weight(< 1000 g), n(%)	11(1.3%)a	1(0.1%)b	3(0.5%)a, b	1(1.2%)a, b	0.037
amniotic fluid	62(7.4%)a	101(13.1%)b	138(24.5%)c	20(24.4%)c	0.000
Apgar score ≤ 7 at 1 min, n(%)	37(4,4%)	25(3.2%)	31(5.5%)	7(8.5%)	0.063
Apgar score ≤ 7 at 5 min, n(%)	11(1.3%)	5(0.6%)	9(1.6%)	1(1.2%)	0.413

Analysis of intrauterine fetal death cases in ICP twin pregnancies

In this cohort, a total of 21 cases of intrauterine fetal death occurred, with a rate of 1.82% (95% CI: 1.05-2.59%). Of these, 19 cases were singletons and 2 cases were twins. The interval between ICP diagnosis and intrauterine fetal death was 3.96 ± 1.18 weeks of gestation, with the majority (73.9%) occurring within one month of diagnosis. We calculated the risk of intrauterine fetal death at late pregnancy among three groups of patients (no intrauterine fetal deaths occurred in the severe group) by dividing the number of specific gestational week deaths by the number of ongoing pregnancies at that gestational week (see Fig. 1).

Discussion

Our study is the first to uncover the relationship between peak TBA levels in ICP and outcomes of twin pregnancies, based on data from 1156 patients. This large-scale, single-center cohort study aims to elucidate the association between peak TBA levels in ICP and adverse pregnancy outcomes, including preterm birth, stillbirth, and fetal distress.

Over the past decades, the rate of multiple pregnancies has markedly increased due to the rise in assisted reproductive technologies [21]. However, recent studies indicate a decrease in twin pregnancy rates since 2014 [22, 23]. Twin pregnancies not only result in higher rates of cerebral palsy, stillbirth, and neonatal morbidity and mortality [24–26], but also elevate the risk of maternal complications such as hypertension [27]. Moreover, the risk of stillbirth is greater and occurs earlier in multiple pregnancies [28, 29]. In our study, the stillbirth rate was 1.82%, which is higher than the previously reported 0.28% for severe ICP pregnancies [19]. The incidence of intrauterine death for singletons in our study was 1.64%, which is consistent with the 0.5–6.8% range reported in earlier studies [30]. Additionally, our analysis of stillbirth rates at different gestational ages indicates a relatively stable rate between 32 and 36 weeks of gestation for overall ICP. Among the three groups, the incidence increased in the mild group, whereas it decreased in the moderate-low and moderate-high groups. This indicates that when managing patients with twin pregnancies complicated by ICP, enhanced fetal monitoring should be considered

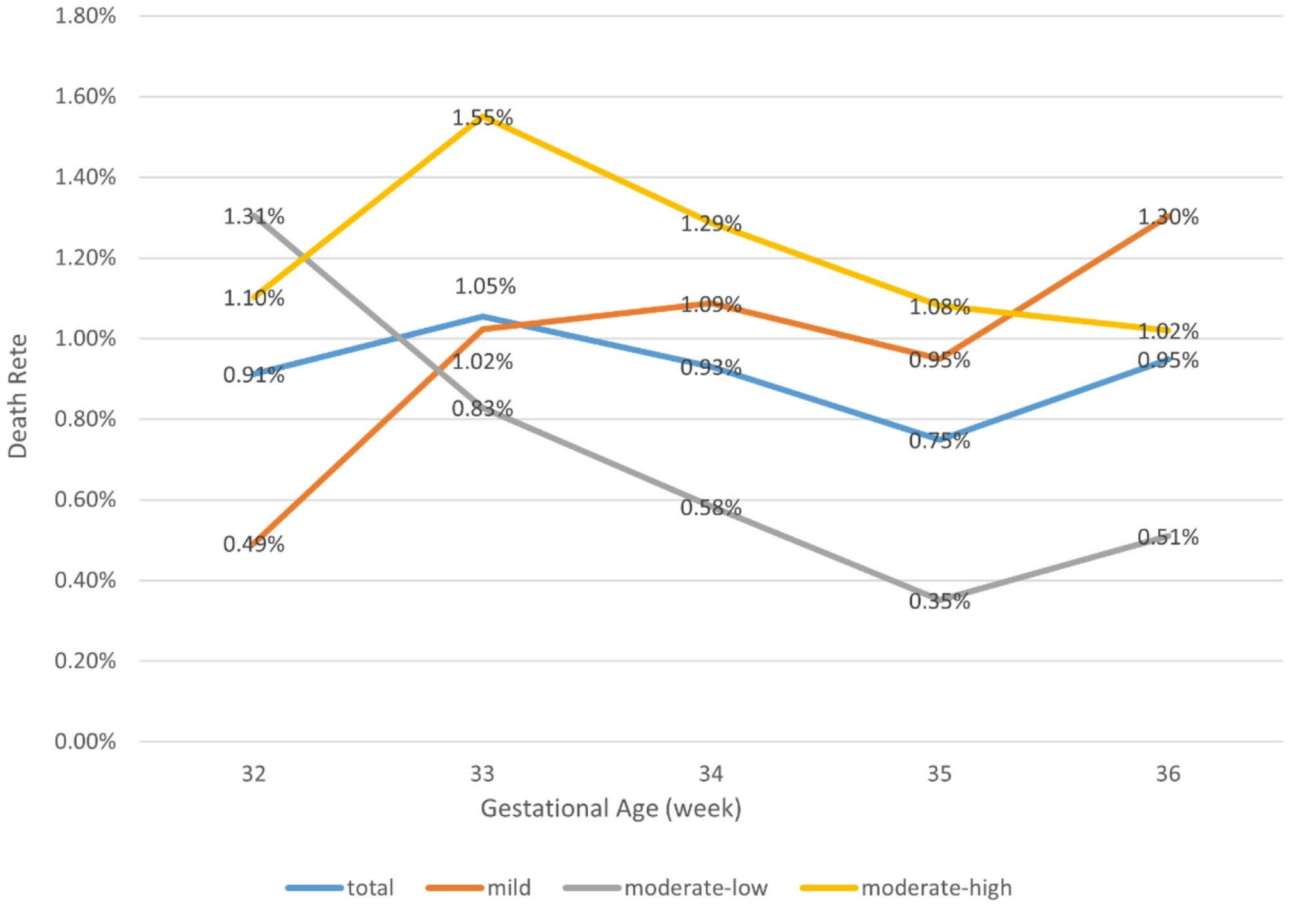

Fig. 1 Risk of stillbirth at expectant week

in late pregnancy, particularly for single chorionic twin pregnancies [31].

Severe ICP is a common cause of fetal complications. When TBA > 40, each 1 μmol/L increase in TBA increases the risk of fetal complications by 1–2% [32, 33], and the fetal myocardium is also more prone to damage [34]. Fetal complications include spontaneous preterm birth, fetal distress, arrhythmias, pulmonary insufficiency, meconium-stained amniotic fluid, and intrauterine death [35, 36]. The relationship between ICP severity and meconium-stained amniotic fluid may indicate underlying fetal distress. The pathophysiological mechanisms of stillbirth due to ICP remain unclear [37], with some studies suggesting that bile acids may cause fetal arrhythmias and placental vascular spasms, leading to acute fetal hypoxia [38, 39].

PTB is conventionally defined as being born before 37 weeks of pregnancy. It is classified further into extreme preterm (before 28 weeks), very preterm (from 28 to 32 weeks), and moderate to late preterm (from 32 to 36 weeks) [12]. It is estimated that 15 million infants are born preterm each year, representing one-tenth of the total number of newborns, while approximately 1 million children die from complications related to prematurity each year [40, 41]. Preterm birth is the leading cause of perinatal death and morbidity in multiple pregnancies, and the underlying mechanisms of preterm birth are complex and multifactorial [42–44], and our understanding of these mechanisms is still insufficient. Therefore, the available interventions for preventing preterm birth show inconsistent benefits [45, 46]. Research on pregnant women with ICP has acknowledged the association between elevated bile acids and the increased risk of preterm birth [19, 35]. A meta-analysis shows a significant correlation between increased TBA levels and a higher risk of spontaneous preterm birth; a clear dose-response relationship can be observed above the threshold of 20 μmol/L [47]. Our study cohort also displayed the same trend, where the proportion of full-term births declined significantly as bile acid levels increased. Given the differing stillbirth risks associated with various chorionic types and the influence of complications, it is essential to further discuss recommendations for the timing of pregnancy termination in twin pregnancies associated with ICP, to reduce the impacts of preterm birth on newborns [48, 49].

At present, ICP is primarily linked to adverse pregnancy outcomes, and its major symptoms usually alleviate within 48 h post-treatment or after delivery; hence, current studies on ICP mainly concentrate on perinatal management and fetal outcomes [50]. Nevertheless, as a pregnancy-specific complication, there is a relative scarcity of research on maternal and neonatal outcomes following the incidence of ICP; recent cohort studies show that patients with ICP face an increased risk of liver diseases, such as cholangiocarcinoma, liver cancer, gallstones, cirrhosis, autoimmune disorders, and cardiovascular diseases [51–53]. Therefore, in addition to enhancing prenatal monitoring, postpartum follow-up for mothers and assessment of liver disease risk are also important measures to improve long-term outcomes [54].

Our research provides additional evidence on the relationship between the severity of ICP and the occurrence of preterm birth in twin pregnancies, as well as an analysis of the variations in stillbirth rates among different groups at different anticipated delivery weeks. Further research with larger cohort studies is necessary to investigate the relationship between bile acid levels and the prognosis of twin pregnancies, which will assist clinicians in making more informed decisions.

Conclusion

Our retrospective cohort study involving 1156 patients demonstrated a correlation between peak TBA levels in ICP and adverse outcomes in twin pregnancies. This study provides evidence for the clinical management of subsequent twin pregnancies complicated by ICP, highlighting the need for further research to refine management strategies for ICP during twin pregnancies.

Abbreviations

ICP	Intrahepatic cholestasis of pregnancy
IVF-ET	In vitro fertilization with embryo transfer
PTB	Preterm birth
TBA	Total bile acid
GA	Gestational age

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Author contributions

Design of the work: Xinghui Liu and Guolin He. Data collection: Qianwen Zhang, Yongzhao Zhao and Yuting Sheng. Data analysis and interpretation: Man Zhang and Yongzhao Zhao. Drafting and critical revision of the article: Yongzhao Zhao and Xinghui Liu. All authors read and approved the final manuscript.

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Data availability

The data of study are not publicly available due to ethical and legal restrictions. However, upon request, data may be available from the Institutional Review Board of West China Second University Hospital.

Declarations

Ethics approval and consent to participate

The study has been performed in accordance with the principles of the Declaration of Helsinki. All of the participants provided written informed consent, and the study was approved by the Research Ethics Committee of the West China Second University Hospital of Sichuan University. Trial registration: 2024380. The authors confirm that all methods were carried out in accordance with relevant guidelines and regulations along with ethical approval statement and informed consent to participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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