

# Effects of the Timing of Labour Induction on Maternal and Neonatal Outcomes in Low-risk Nulliparous Chinese Women

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## Research article

**Keywords:** pregnancy, labour induction, gestational age, maternal outcomes, neonatal outcomes

**Posted Date:** December 28th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-133412/v1>

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# Abstract

**Background:** When labour induction should be offered to women at or beyond term is unclear. This work aimed to investigate the effects of the timing of labour induction on maternal and neonatal outcomes in low-risk pregnancies.

**Methods:** This retrospective case-control study involved low-risk primigravid pregnant mothers in whom labour was induced at 40-41+6 weeks at our two hospitals between January and December 2017. According to the gestational age at labour induction, participants were categorized into the study group (40-40+6 weeks, n=284) or to the control group (41-41+6 weeks, n=172), and maternal and neonatal outcomes were compared.

**Results:** The study group showed significantly shorter labour in the first stage (391.8±225.7 vs. 472.0±268.9 min, P=0.006), second stage (65.41±38.66 vs. 53.73±31.58 min, P= 0.008) and total stage (453.0±235.8 vs. 535.7±259.8 min, P=0.005). The two groups showed no significant differences in the methods of labour induction or in the rates of failure of labour induction, of caesarean delivery, of postpartum haemorrhage, or of admission to the neonatal intensive care unit.

**Conclusions:** Our retrospective study suggests that inducing labour at 40-40+6 weeks does not increase the risk of adverse maternal or foetal outcomes, and that it shortens labour. These results suggest that labor induction at 40-40+6 weeks was feasible for low-risk primiparas.

**Trial registration:** The research has been approved by the Ethics Committee of West China Second Hospital of Sichuan University and Chengdu Women and Children's Central Hospital, China. Patients gave written informed consent for their anonymized medical data to be analyzed and published for research purposes.

## Introduction

Induction of labour is defined as the process of artificially stimulating the uterus to start labour<sup>1</sup>. It is usually performed by administering oxytocin or prostaglandins to the pregnant woman or by manually rupturing the amniotic membranes<sup>2</sup>. Induction of labour is the most common procedure in obstetrics<sup>2</sup>. Over the past several decades, the incidence of labour induction for shortening the duration of pregnancy has continued to rise<sup>2</sup>. Induction of labour is widely practised to improve health outcomes for women and their infants. In 2015 in the USA, approximately 24% of births were induced<sup>3</sup>. The rate of induction may be as high as 52% for gestations  $\geq$  41 weeks (late-term and post-term pregnancies)<sup>4</sup>. In 2018, a systematic review showed that, compared with expectant management, induction of labour after full term ( $\geq$  39weeks) was associated with fewer perinatal deaths, higher Apgar scores at 5 min after birth, fewer admissions to the neonatal intensive care unit (NICU), and fewer caesarean sections. It was also associated with a higher rate of assisted vaginal births without an increase in the risk of maternal death<sup>5</sup>. That review also highlighted the need for further work to determine the best time for labour induction in women at or beyond term.

The generally recognised timing of labour induction in low-risk pregnancies is  $\geq$  41 weeks<sup>2,6-7</sup>. The American College of Obstetrics and Gynecology (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) define "term" in such a way to prevent unnecessary induction of labour and caesarean sections earlier than 39 weeks of gestation and to emphasize the health risks for perinatal infants after 41 weeks of gestation<sup>8</sup>: early term is

defined as from 37 through 38<sup>+6</sup> weeks of gestation; full term, 39 through 40<sup>+6</sup> weeks; late term, 41 through 41<sup>+6</sup> weeks; and post-term, 42 weeks and beyond. Generally, induction of labour has merit as a therapeutic option when the benefits of expeditious delivery outweigh the risks of continuing the pregnancy. The benefits of labour induction must be weighed against the potential risks to mother and foetus<sup>7</sup>. Studies have shown that perinatal mortality rate gradually decreases after 37 weeks and reaches a minimum at 40 weeks, after which it steadily increases<sup>9</sup>. This raises the question: do we have to wait until 41 weeks of gestation to induce labour? Therefore, some have advocated induction of even uncomplicated singleton gestations once they reach full term (39–40<sup>+6</sup> weeks)<sup>10–11</sup>.

We conducted a retrospective cohort study of nulliparous women with low-risk pregnancies to compare the maternal and neonatal outcomes between labour induction at 40 to 40<sup>+6</sup> weeks or at 41 to 41<sup>+6</sup> weeks.

## Methods

### Study population

Medical records were retrospectively analysed for low-risk nulliparous pregnancies in the Departments of Obstetrics at West China Second Hospital of Sichuan University and at the Chengdu Women and Children's Central Hospital in which labour had been induced at 40–41<sup>+6</sup> weeks between January and December 2017. A total of 9,873 pregnancies delivered in 2017, high-risk pregnancies accounted of 81.8% (8,074 cases). High-risk pregnancies were excluded, such as those involving gestational hypertension and preeclampsia 519 cases (5.3%), placenta previa 9,98 case (10.1%), gestational diabetes mellitus 1,945 case (19.7%), intrahepatic cholestasis of pregnancy 781 cases (7.9%), preterm labor and premature rupture of membranes 2,198 cases (22.3%), multiple pregnancies 601 cases (6.1%), oligohydramnios 246 cases (2.5%), and foetal growth restriction 177 cases (1.8%), and others 609 cases (6.2%). Low-risk pregnancies who delivered naturally without labour induction were 1018 cases (10.3%). Pregnancies requiring caesarean section without surgical indications during labour induction were also excluded 325 cases (3.3%). At last, 456 women (4.6%) were collected and divided into the study group, defined as those in whom labour was induced at a gestational age of 40–40<sup>+6</sup> weeks, and a control group, defined as those in whom labour was induced at 41–41<sup>+6</sup> weeks.

### Data collection

Demographic and clinical data of the study subjects were collected retrospectively, and included general demographic data (maternal age, pre-pregnancy body mass index (BMI), prenatal BMI, etc), obstetric specialty (gestational age at induced labour, bishop score before labour induction, etc), labour induction method (artificial membrane rupture, low-dose oxytocin drip), delivery method (vaginal delivery or cesarean section), labour stage (total, first, second and third stage of labour), perinatal outcomes and complications of labour induction (neonatal birth weight, Apgar scores at 1 and 5 min, the NICU admission rate within 24 h, severe neonatal asphyxia or perinatal death, second- or third-degree meconium-stained amniotic fluid, uterine hyperstimulation, foetal heart rate abnormalities, postpartum haemorrhage, placental abruption, threatened uterine rupture, etc.).

### Promotion of cervical ripening and induction of labour

Before labour induction, all women underwent vaginal examination by a senior obstetrician, who determined the cervical Bishop score. Women with scores  $\leq 6$  were treated first with dinoprostone suppositories (scores  $\leq 4$ ), a

cervical ripening balloon (scores 5–6), or a sequential combination of both (first suppositories, then balloon) if the Bishop score was no higher than 7 after suppositories<sup>12</sup>. After these interventions, the cervical Bishop score was re-assessed. Patients with a Bishop score of  $\geq 7$  who did not undergo spontaneous labour were induced using artificial membrane rupture. If no regular and effective uterine contractions occurred within 30 min of rupture, intravenous low-dose oxytocin drip was initiated<sup>12</sup>.

The first cervical Bishop score was performed by vaginal examination on the day the balloon was placed, and the Cook cervical ripening balloon was placed at 18:00–21:00 that night. The steps are as follows: Check whether the balloon catheter is intact, and check whether the balloon is damaged and leaking by aerating the empty needle. After emptying the bladder, the pregnant woman take the lithotomy position, place the speculum, strictly disinfect the vagina and cervix, and cervical forceps hold the anterior or posterior lips of the cervix for traction and fixation. Gently insert the double balloon catheter and ensure that both balloons pass through the cervical orifice. Gradually inject 40 ml physiological saline into the uterine balloon catheter (marked U in red) and pull the catheter outward to make the expanded uterine balloon against the cervical orifice and the vaginal balloon expose the external cervix. Gradually inject 20 ml physiological saline into the vaginal balloon catheter (marked with green in V). At this time, the two inflated balloons are located inside and outside the cervix. Remove the speculum and continue to inject saline into the two balloon catheters at a time of 20 ml to reach 80 ml, and the maximum is not more than 120 ml. Fix the catheter on the inside of the thigh of the pregnant woman with tape, without restricting movement. If there is discomfort or uterine hyperstimulation, the balloon can be removed at any time, otherwise the balloon will be removed at 8:00–9:00 in the next morning, and the cervical Bishop score will be evaluated again.

The first cervical Bishop score was performed by vaginal examination on the day of dinoprostone vaginal suppositories placed, and it was placed on the same day at 8:00–9:00. The steps are as follows: pregnant women empty the bladder, after disinfecting the vulva, wear sterile gloves, hold the suppository to the depth of the posterior fornix of vaginal, and then rotate 90°, make the suppository transverse to the posterior fornix, and place the termination tape in the vagina, so as not to bring it out during activity. Ask the patient to lie down for two hours to allow the suppository to fully absorb water and expand. Review after 2 hours, the drug is still in place and can be moved out of bed. If there are regular uterine contractions (3 times in 10 minutes) accompanied by cervical maturation, or uterine hyperstimulation, fetal heart rate abnormalities, suppository should be take out at any time, otherwise it will be get out after 24 hours, and the cervical Bishop score will be evaluated again.

Intravenous infusion pump was used for low-dose oxytocin drip which starting at 8:00–9:00 in the morning. The steps are as follows: 2U of oxytocin was added to 500 ml crystalline liquid (0.004 U/ml) and pumped into the liquid at a rate of 15–30 ml/h. Adjust the drip rate according to the uterine contractions and adjust it every 15–30 min with an increase of 15–30 ml/h until effective contractions occur (3 contractions within 10 minutes, each lasting 30–60 seconds). Usually the drip rate is 30–75 ml/h, and the maximum drip rate is 300 ml/h. If the maximum drop rate is not enough to induce effective contractions, then the drop rate is readjust after the concentration of oxytocin is increased to 1U/100 ml. The midwife monitors the fetal heart rate and contractions during the administration of oxytocin. If the regular contractions have not yet been delivered for 8 hours, stop the oxytocin infusion and rest until the next morning to infuse intravenous again.

## **Statistical analysis**

Data were analysed using SPSS 19.0 (IBM, Armonk, NY, USA). Inter-group differences in data that showed a normal distribution and homogeneous variance were assessed for significance using the independent-samples *t* test. Inter-group differences in data not meeting these conditions were assessed for significance using the Mann-Whitney U test. Differences in composition ratio and rate were assessed using the chi-squared test. Odds ratio and corresponding 95% CI were calculated for binary outcomes. Logistic regression analysis was used to evaluate the influence of induced gestation week on delivery mode (vaginal delivery and cesarean section). Confounded factors included maternal age, neonatal birth weight, pre-pregnancy BMI, Bishop score before labour induction, and meconium-stained amniotic fluid. Multiple linear regression analysis was used to compare the effects of different gestational age groups on each stage of labour, taking into account confounders such as maternal age, pre-pregnancy BMI, and neonatal birth weight. Differences were considered significant if they were associated with  $P < 0.05$ .

## Results

### Characteristics of the study population

A total of 456 pregnant women were included in the analysis: 284 in the study group (40–40<sup>+6</sup> weeks), with a mean gestational age of  $40.50 \pm 0.28$  weeks at labour induction; and 172 in the control group (41–41<sup>+6</sup> weeks), with a mean gestational age of  $41.14 \pm 0.18$  weeks at induction ( $P < 0.001$ ). There were no statistically significant differences between the two groups in maternal age, pre-pregnancy BMI, prenatal BMI, or Bishop score before labour induction (Table 1).

Table 1

Comparison of demographic and clinical characteristics between the two groups with different timing of labour induction\*

Characteristic	Control group (n = 172)	Study group (n = 284)	P**
Gestational age at induced labour (weeks)	$41.14 \pm 0.18$	$40.50 \pm 0.28$	0.000
Maternal age (years)	$28.71 \pm 3.05$	$28.35 \pm 3.04$	0.216
Pre-pregnancy BMI (kg/m <sup>2</sup> )	$20.52 \pm 2.47$	$20.22 \pm 3.09$	0.274
Prenatal BMI (kg/m <sup>2</sup> )	$26.61 \pm 2.73$	$26.21 \pm 3.46$	0.206
Bishop score before labour induction (points)	$4.51 \pm 1.30$	$4.59 \pm 1.08$	0.389
Values are as mean $\pm$ standard deviation .			
Abbreviation: BMI, body mass index.			
* Labour was induced in the study group at 40–40 <sup>+6</sup> weeks of gestation, and in the control group at 41–41 <sup>+6</sup> weeks of gestation.			
** Based on Student's <i>t</i> test and Mann-Whitney U test.			

## Induction of labour

Cervical Bishop scores before induction of labour were < 7 points in all cases. The two groups showed no statistically significant differences in the rates of treatment with dinoprostone suppositories, cervical ripening balloon or sequential application of both for promotion of cervical maturation between the two groups. There were no significant differences in the rates of artificial membrane rupture or oxytocin intravenous drip to induce labour (Table 2).

Table 2

Comparison of the mode of promoting cervical ripening and labour induction between the two groups.

Characteristic		Control group (n = 172)	Study group (n = 284)	P*
Mode of promotion of cervical ripening	Dinoprostone suppositories	64 (37.21)	83 (29.23)	0.206
	Cervical mature balloon	101 (58.72)	189 (66.55)	
	Sequential application of both	7 (4.07)	12 (4.23)	
Mode of labour induction	Artificial membrane rupture	88 (51.16)	150 (52.82)	0.732
	Oxytocin intravenous drip	92 (53.49)	163 (57.39)	0.415
Values are n (%).				
* Based on the chi-squared test.				

## Caesarean section rate and labour status of vaginal delivery

Those who did not enter the labour process after induction of labour were considered as induction failures. Seven failures (2.46%) occurred in the study group, similar to the two cases (1.16%) in the control group (Odds ratio 0.534, 95% CI 0.441–10.460, P = 0.534). In the study group, 88 women (30.99%) underwent a caesarean section and 196 (69.01%) had vaginal delivery, 11 of whom (5.61%) received vaginal midwifery. In the control group, 65 mothers (37.79%) underwent a caesarean section and 107 (62.21%) had vaginal delivery, 8 of whom (7.48%) received vaginal midwifery. The two groups did not differ significantly in delivery mode (Odds ratio 1.353, 95% CI 0.909–2.014, P = 0.136). Compared with the control group, the study group showed significantly shorter labour in the first stage (P = 0.006), second stage (P = 0.008) and overall (P = 0.005; Table 3). The groups did not, however, differ significantly in labour duration in the third stage.

Table 3  
Comparison of caesarean section rate and stages of labour between the two groups.

Characteristic		Control group (n = 172)	Study group (n = 284)	P*	OR (95% CI)
Caesarean section		65 (37.79)	88 (30.99)	0.1360	1.353(0.909–2.014)
Failed labour induction		2 (1.16)	7 (2.46)	0.534	2.148(0.441–10.460)
Labour duration of vaginal delivery (min)	Total labour duration	535.75 ± 259.80	452.98 ± 235.84	<b>0.005</b>	
	First labour stage	471.99 ± 268.86	391.84 ± 225.73	<b>0.006</b>	
	Second labour stage	65.41 ± 38.66	53.73 ± 31.58	<b>0.008</b>	
	Third labour stage	7.17 ± 4.27	7.41 ± 4.55	0.655	
Values are as mean ± standard deviation or n (%).					
* Based on Student's <i>t</i> test, Mann-Whitney U test or chi-squared test.					

To control for bias, logistic regression analysis was used to evaluate the influence of induced gestation week on delivery mode (vaginal delivery and cesarean section). After controlling for confounding factors such as maternal age, neonatal birth weight, pre-pregnancy BMI, Bishop score before labour induction, and meconium-stained amniotic fluid, it can be seen from Logistic regression analysis that compared with those induced at 41–41 + 6 weeks, there was no increase in cesarean section rate at 40–40 + 6 weeks (OR: 1.345, 95%CI: 0.865–2.092) (Table 4). Multiple linear regression analysis was used to compare the effects of different gestational age groups on the stage of labour (Table 5). After controlling for confounding factors (including maternal age, pre-pregnancy BMI, and neonatal birth weight), compared with pregnant women who were induced at 40–40<sup>+6</sup> weeks, the total, first, and second stages of labor were increased by an average of 130 minutes (P < 0.001), 118 minutes (P = 0.001), and 13 minutes (P = 0.008) at 41–41<sup>+6</sup> weeks respectively.

Table 4

Logistic regression analysis to identify the effect of gestational week at induced labour on cesarean section

Variables	OR	95%CI	P *
Maternal age (years)	1.107	1.028–1.192	0.007
Birth weight (g)	1.001	1.000-1.001	0.005
Pre-pregnancy BMI (kg/m <sup>2</sup> )	1.123	1.034–1.219	0.006
Bishop score before labour induction (points)	0.872	0.721–1.053	0.154
Meconium-stained amniotic fluid (ref = No)	9.797	2.323–6.203	0.000
Gestational age at induced labour (weeks) (ref = 40–40 + 6 weeks)	1.345	0.865–2.092	0.188
Dependent variable: Cesarean section			
* Based on the Logistic regression.			

Table 5

Multivariate analysis of the influence of gestational week at induced labour on different stages of labor

Model	Dependent variable	Coefficient	t	P *
Model 1	Total labour duration	130.805	3.683	0.000
Model 2	First labour stage	118.183	3.441	0.001
Model 3	Second labour stage	13.217	2.667	0.008
Model 4	Third labour stage	-0.569	-0.898	0.370
The confounding factors controlled by model 1, model 2, model 3 and model 4 were the same, including maternal age, pre-pregnancy BMI and birth weight.				
* Based on the Multiple linear regression.				

## Peri- and postnatal outcomes

The total number of female newborns in the two groups was 238 (52.19%). There were 134 female newborns in the study group (47.18%) and 104 in the control group (60.47%), a difference that was statistically significant (Odds ratio 1.712, 95% CI 1.166–2.514, P = 0.006). There was no significant difference between the two groups in birth weight, Apgar scores at 1 or 5 min, or the NICU admission rate within 24 h (Table 6). No severe neonatal asphyxia or perinatal death occurred in either group. There were no significant differences between the two groups in the ratio of second- or third-degree meconium-stained amniotic fluid, uterine hyperstimulation, foetal heart rate abnormalities, postpartum haemorrhage, or the use of second-line uterotonics. In the study group, five

women (1.76%), all of whom suffered placental abruption, had serious complications, as well as three mothers in the control group (1.74%), one of whom experienced placental abruption and two of whom threatened uterine rupture. There was no significant difference between the two groups in the proportion of serious complications ( $P = 0.999$ ; Table 7). No maternal deaths occurred in either group.

Table 6  
Comparison of perinatal outcomes between the two groups.

Characteristic	Control group (n = 172)	Study group (n = 284)	P*	OR (95% CI)
Birth weight(g)	3482.70 ± 371.53	3438.71 ± 361.75	0.224	
Female neonate	104 (60.47)	134 (47.18)	<b>0.006</b>	1.712(1.166–2.514)
Apgar score ≤ 7 at 1 minute	2 (1.16)	1 (0.35)	0.319	3.329(0.300-36.995)
Apgar score ≤ 7 at 5 minutes	0	0	-	
NICU admission	26 (15.12)	32 (11.27)	0.232	1.402(0.804-.446)
Values are as mean ± standard deviation or n (%).				
Abbreviation: NICU, neonatal intensive care unit.				
* Based on Student's <i>t</i> test, Mann-Whitney U test or chi-squared test.				

Table 7  
Comparison of induced labour complications and other abnormalities between the two groups.

Characteristic	Control group (n = 172)	Study group (n = 284)	P*
0-3 degrees of meconium-stained amniotic fluid	44 (25.58)	63 (22.18)	0.407
Uterine hyperstimulation	25 (14.53)	30 (10.56)	0.207
Foetal heart rate abnormalities	26 (15.12)	44 (15.49)	0.914
Postpartum haemorrhage	4 (2.33)	7 (2.46)	0.925
Use of second-line uterotonics	49 (28.49)	86 (30.28)	0.682
Serious complications	3 (1.74)	5 (1.76)	0.999
Values are as n (%).			
* Based on the chi-squared test.			

## Discussion

In our study, duration of the total labour, the first labour and the second labour stage was significantly shorter in those in whom labour was induced at 40–40<sup>+6</sup> weeks than in those who were induced at 41–41<sup>+6</sup> weeks, yet the

two groups showed similar peri- and postnatal outcomes, including Apgar scores and rates of induction failure, caesarean section, complications and NICU admission.

It is well known that the risk of placental dysfunction and meconium-stained amniotic fluid increases after 41 weeks of gestation, as well as the risk of foetal distress and even foetal death<sup>13-14</sup>. Therefore, induction of labour after 41 weeks in low-risk pregnancies has become a global obstetric consensus to reduce perinatal mortality and neonatal meconium aspiration syndrome<sup>2,6-7</sup>. In recent years, a number of systematic reviews have shown that full-term (39–40<sup>+6</sup> weeks) labour induction does not increase the risk of caesarean section or adverse maternal or foetal outcomes, regardless of cervical conditions<sup>5,15-16</sup>. In fact, those reviews suggest that full-term induction can actually reduce the risk of caesarean section and NICU admission. A large study conducted in the UK found that the risk of stillbirths was 0.86–1.08 per 1,000 cases at 40–41 weeks of gestation, while it increased to 1.2–1.27 per 1000 cases at 41–42 weeks<sup>17</sup>. Another study showed that, compared with those who gave birth at 39–41 weeks, those who delivered at 41–42 weeks were at significantly higher risk of postpartum anaemia, meconium aspiration, neonatal Apgar score < 5 at 1 min, and caesarean section due to foetal distress<sup>18</sup>. Therefore, since maternal-foetal risk increases after 41 weeks of gestation, and the induction of labour after full term does not increase the rate of caesarean section or of adverse maternal or foetal events in low-risk pregnancies without complications, many obstetricians wonder whether to wait until 41 weeks or to induce labour earlier.

Our results suggest that earlier induction is not associated with significantly higher risk of adverse maternal or foetal events, but is associated with shorter labour, which may bring several advantages. Labour at later gestational stages can be complicated due to higher foetal weight, skull deformation, and amniotic fluid reduction. Prolonged labour can consume the physical strength of the mother, aggravate her anxiety and that of her family members, increase the rate of unindicated caesarean sections and increase risk of uterine atony, foetal distress and postpartum haemorrhage. Therefore, our results suggest that shortening labour is likely to bring several advantages without additional risks. For determining the choice of induction at 40–40<sup>+6</sup> weeks rather than 41–41<sup>+6</sup> weeks in the low risk women, the factors include nulliparous women receiving standard prenatal care, singleton pregnancy, no obstetrics complications, no medical and surgical complications.

Limitations of the study include the fact as follows: First, our hospital, as a large tertiary-care medical center in western China, admission and treatment of difficult and serious diseases in the surrounding area, and high-risk pregnancy accounts for nearly 80%. Therefore, the number of pregnant women with low-risk is relatively small, which causes the number of cases finally included in this study relatively small. Second, there was no statistically significant difference in neonatal birth weight between the two groups. Analysis the reason may be that all the cases included in the study were pregnant women who received regular prenatal care in our hospital, the weight gain of them during pregnancy was reasonable and the fetal growth was normal. Third, we found that the proportion of female newborns was significantly higher at 41–41<sup>+6</sup> weeks than at 40–40<sup>+6</sup> weeks; we looked at the literature and there was no research on this problem. This result should be confirmed in further studies, and the reasons should be explored. Last and most important, this is a retrospective cohort study, all of these factors above may have influenced the results to some extent. To control the bias and confounding factors, logistic regression analysis and multiple linear regression analysis were used to adjust the potential confounding biases.

## Conclusions

In summary, our retrospective study suggests that inducing labour at 40–40<sup>+6</sup> weeks does not increase the risk of adverse maternal or foetal outcomes, and that it shortens labour. It may be an appropriate option for nulliparous women with low-risk pregnancies. Multicenter large sample study, preferably with a prospective and randomised design, are needed to verify and extend our findings.

## Abbreviations

BMI: body mass index, NICU: neonatal intensive care unit.

## Declarations

### Ethics approval and Consent to participate

The research has been approved by the Ethics Committee of West China Second Hospital of Sichuan University and Chengdu Women and Children's Central Hospital, China. Patients gave written informed consent for their anonymized medical data to be analyzed and published for research purposes.

### Consent for publication

Written informed consent was obtained from the patient for publication of the case details.

### Availability of data and materials

All data generated or analysed during this study are included in this published article. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors declare that they have no competing interests.

### Funding

This work was supported by the the Science and Technology Foundation of Sichuan Province (2019YFS0410).

### Acknowledgements

We are grateful to all the subjects of the patients for their participation in this study.

### Author contributions

Qiang Wei, Qin-yan Cao,: data acquisition and analysis, manuscript writing. Li Zhang: study design, manuscript writing. Mei-fan Duan, Yi Xu: data acquisition and analysis. All authors read, reviewed, and approved the submitted version of the manuscript.

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