Delivery, maternal and neonatal outcomes in nulliparous women with gestational diabetes undergoing epidural labour analgesia: a propensity score-matched analysis

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ABSTRACT

Objective This study aimed to retrospectively analyse the influence of epidural labour analgesia (ELA) on delivery and maternal and neonatal outcomes in nulliparous women with gestational diabetes mellitus (GDM) using propensity score-matched analysis.

Design Retrospective cohort analysis.

Setting Primary care practices in a teaching hospital from March 2018 to October 2021.

Participants A total of 816 delivery records of nulliparous women with GDM were collected and retrospectively analysed.

Interventions ELA and non-ELA (NELA) cohorts were assessed.

Main outcome measure The primary outcome assessed was delivery type (spontaneous, assisted vaginal or caesarean). The secondary outcomes assessed included labour duration and maternal and neonatal outcomes.

Results A total of 137 propensity score-matched pairs of ELA and NELA patients were analysed. ELA was associated with a decreased rate of caesarean section (18.3% vs 46.0% in the ELA vs NELA cohort, respectively; p<0.05) and an increased occurrence of assisted vaginal delivery (35.8% vs 12.4% in the ELA vs NELA cohort, respectively; p<0.05). The duration of the first and total stages of labour was prolonged, the occurrence of postpartum fever increased, and the duration of hospital stay was shortened in those receiving ELA (all p<0.05).

Additionally, neonatal birth weight, plasma glucose levels and neonatal macrosomia occurrence increased, while neonatal intensive care unit admissions and neonatal hypoglycaemia decreased in the ELA versus the NELA group (all p<0.05). With respect to other maternal and neonatal outcomes, both cohorts were similar.

Conclusions The use of ELA decreases the rate of caesarean section and improves maternal and neonatal outcomes in nulliparous women with GDM.

Trial registration number ChiCTR-2000033091.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance or hyperglycaemia with onset or first recognition in the second or third trimester of pregnancy. The social and economic burden of the condition is significant.1 GDM is a common complication caused by insulin resistance due to contrainsulin hormones secreted by the placenta (oestrogen, cortisol and human placental lactogen) with advancing gestation. GDM affects approximately 10%–15% of all pregnancies worldwide and approximately 17.5% of pregnancies in China.2 3 Since convincing clinical evidence has revealed that the development of GDM is associated with an increased risk of maternal and neonatal complications, ever-growing efforts from multidisciplinary collaborative teams have aimed to minimise complications and improve personalised healthcare standards and the comfort of women with GDM during labour.4 A large body of evidence suggests that epidural labour analgesia (ELA) is the global gold standard for pain relief during labour. ELA provides physical wellness, minimises stress and provides pain relief in a

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Propensity score matching was used to assess possible imbalances in parameters considered when epidural labour analgesia (ELA) and non-epidural labour analgesia (NELA) participants were compared.

⇒ ELA and NELA participants were matched based on age, gestational age, body mass index, risk factors and gestational diabetes mellitus (GDM) classification.

⇒ It is possible that non-included variables will remain confounding factors.

⇒ Given the retrospective nature of this study, the effects of additional confounders cannot be ruled out.

⇒ Studies that assess the impact of ELA on long-term outcomes of neonates and their mothers with GDM are needed.
manner that is superior to alternatives in women without contraindications. Clinical evidence has clearly demonstrated that in normal pregnancies early or late initiation of epidural analgesia for labour has similar effects on instrumental birth risk, duration of the second stage of labour and risk of Apgar scores less than 7 at 1 and 5 min. \(^{6-8}\) However, in patients with a pathological condition such as GDM, clinical data are almost non-existent. Maternal GDM is an independent risk factor for fetal macrosomia, large-for-gestational-age fetuses, shoulder dystocia and neonatal injury. \(^ {9,10}\) Given that mothers with GDM tend to have larger babies than those with normal pregnancies, it is likely that vaginal delivery in women with GDM will be more difficult, with correspondingly increased rates of instrumentally assisted delivery and conversion to urgent caesarean section. Therefore, an indwelling epidural catheter is a better choice for labour analgesia should a caesarean delivery become necessary. \(^ {11}\) One recent retrospective study analysed factors associated with successful trial of labour after caesarean (TOLAC) among mothers with GDM and no prior vaginal delivery in comparison with TOLAC in mothers without GDM. The results indicated that ELA was independently associated with TOLAC success in mothers with GDM (adjusted OR 3.32, 95% CI 1.31 to 8.69, \(p=0.011\)). Further, ELA was the only modifiable independent predictor of TOLAC success. \(^ {12}\) Considering that clinical evidence is not yet sufficient for researchers to determine whether use of ELA during labour positively or negatively affects maternal and neonatal outcomes, we conducted the current retrospective study to analyse labour outcomes associated with ELA in nulliparous women with GDM using propensity score matching.

**METHODS**

The study was registered at ChiCTR.org.cn (ChiCTR-2000033091). The requirement for written informed consent was waived by the Institutional Ethics Committee. This manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. \(^ {13}\)

**Participant selection**

All nulliparous women with GDM and patient data in the electronic medical database were considered for inclusion in this retrospective study. Patients meeting the following inclusion criteria were included: aged 20–35 years, singleton pregnancy and admitted to the Department of Obstetrics and Gynecology between March 2018 and October 2021. The diagnostic criteria for GDM employed in the study were as follows: (1) any diabetic symptoms (eg, excessive thirst, extreme hunger, frequent urination, unusual weight loss or increased fatigue) during pregnancy accompanied with a random plasma glucose level \(>11.1 \text{ mmol/L} (200 \text{ mg/dL})\) if confirmed on a subsequent day; (2) a fasting plasma glucose level \(>7.0 \text{ mmol/L} (126 \text{ mg/dL})\) if confirmed on a subsequent day; and (3) a plasma glucose level \(>10.0 \text{ mmol/L} (180 \text{ mg/dL})\) 60 min after an oral glucose tolerance test using a 75 g glucose load at 24–28 weeks of gestation. For all hospitalised participants, plasma glucose levels were monitored daily and diabetes treatment regimens were followed according to the recommendations of a multidisciplinary team, if necessary. Parturients with evidence of accidental dural puncture with an epidural needle, failure in epidural administration or catheterisation, obstetric emergencies, or intrauterine fetal demise were excluded.

**Epidural labour analgesia**

In the ELA cohort, ELA was not initiated until it was requested by the parturients and a comprehensive evaluation was performed by the attending obstetrician. With standard monitoring, the epidural catheter was inserted at L2–L3 or L3–L4 in the lateral position by an experienced anaesthesiologist using a standard sterile technique. An 18 G epidural needle (TuoRen, Henan Tuoren Medical Device, China) was used and the epidural space was identified using the loss of resistance technique. A 20 G epidural catheter (TuoRen, Henan Tuoren Medical Device) was inserted 5 cm into the epidural space. Following a 3 mL test dose of 1% lidocaine with 1:200 000 epinephrine, the epidural catheter was fixed. The standardised ELA protocol was initiated with 8–10 mL 0.1% ropivacaine and 0.5 µg/mL sufentanil. Thereafter, the same mixture was used for the programmed intermittent epidural bolus, with a dose of 5–8 mL intermittent bolus for every 45 min. The patient-controlled analgesia system was programmed to deliver a 5–8 mL bolus of local anaesthetic with a lockout interval of 20 min.

**Data collection**

The medical records of eligible parturients were manually reviewed. Parturients’ demographic and obstetric characteristics reviewed included the following: age, gestational age, height, weight, body mass index (BMI), high-risk factors (eg, overweight or obesity, family history of diabetes, maternal age \(>25\) years, impaired glucose tolerance, polycystic ovary syndrome (PCOS), history of recurrent abortions, essential hypertension, pregnancy-related hypertension, pre-eclampsia or eclampsia) and classification (A1: a fasting plasma glucose level \(<5.8 \text{ mmol/L} (105 \text{ mg/dL})\) and a 2-hour postprandial plasma glucose level \(<6.7 \text{ mmol/L} (120 \text{ mg/dL})\) after receiving medical nutrition therapy and exercise; A2: a fasting plasma glucose level \(\geq 5.8 \text{ mmol/L} (105 \text{ mg/dL})\) and a 2-hour postprandial plasma glucose \(\geq 6.7 \text{ mmol/L} (120 \text{ mg/dL})\) after receiving medical nutrition therapy and exercise, and initiation of insulin therapy). Anaesthetic characteristics including the date and time of ELA, type and dose of epidural medication administered, pain rating before and after ELA evaluated using a 10-point Numeric Rating Scale, and the need for additional analgesia were noted. Delivery outcomes, including mode of
delivery (spontaneous, assisted vaginal, caesarean), and duration of the first, second and total stages of labour were recorded. Maternal outcomes including blood loss during and 2-hour after delivery, length of stay after delivery, and any complications during and after delivery were analysed. Neonatal outcomes considered included the following: birth weight, plasma glucose level, occurrence of an Apgar score <7 at 1 and 5 min after birth, rate of neonatal macrosomia, and neonatal intensive care unit (NICU) admission.

Outcome measurement
The primary outcome assessed was delivery mode. The secondary outcomes considered included duration of labour as well as the maternal and neonatal outcomes described in the Data collection section.

Sample size calculation
An overall caesarean section rate of 47.1% in women with GDM was assumed for both cohorts, based on recent average 3-year statistical data of Fujian Provincial Hospital, which was close to the 46.2% rate reported in a domestic survey and the WHO. In addition, the inferiority margin was set at 20%, α at 0.05 and β at 0.20, yielding a power of 80%. Therefore, to demonstrate that there was a statistical difference between patients who did and did not undergo ELA, a total of 255 patients were determined to be required for researchers to be 80% sure that the upper limit of a two-sided 95% CI would exclude a difference more than 20% in favour of the ELA cohort, assuming a loss to follow-up rate of 20%.

Propensity score-matched analysis
Propensity score matching is a method that is used to minimise selection bias when estimating causal interventional effects in non-randomised controlled trials. ‘Intervention’ (eg, ELA) and ‘control’ (eg, non-ELA (NELA)) cohorts are paired based on characteristics that would otherwise confound between-group comparisons. Once a matched cohort has been formed, interventional effects can be estimated by directly comparing the outcomes of the intervention and the control group.

In the current study, propensity scores were developed, accounting for all factors significantly associated with ELA occurrence via logistic regression analysis. Accordingly, individual propensity scores were calculated using logistic regression modelling based on the following five covariates for demographic and obstetric characteristics: age, gestational age, BMI, risk factors (eg, being overweight or obese, family history of diabetes, maternal age >25 years, impaired glucose tolerance, PCOS, history of recurrent abortions, essential hypertension, pregnancy-related hypertension, pre-eclampsia or eclampsia) and GDM classification. ELA and NELA parturients were then paired 1:1 using exact propensity score matching. A standard calliper size of 0.2 × log (SD of the propensity score) was used. Standardised differences were estimated before and after matching to evaluate the balance of covariates. These analyses revealed small absolute values (<10%), indicating a balanced baseline between the two cohorts.

Data analysis
Demographic characteristics, obstetric characteristics, and delivery, maternal and neonatal outcomes are presented as mean±SD or median (M) (IQR) for continuous variables, and absolute number (percentage) for categorical variables. Following 1:1 propensity score matching, McNemar’s test was performed to evaluate categorical variables for univariate comparisons and pooled using ORs with corresponding 95% CIs. Alternatively, a paired t-test and Wilcoxon rank-sum test were used for normally and non-normally distributed continuous variables, respectively. Thereafter, backward logistic regression analysis identified covariates associated with the use of ELA (p<0.05 for entry and p>0.10 for removal). Propensity score-matched analysis was performed using IBM SPSS Statistics V.22 software and data were analysed with GraphPad Prism V.8.0 for Windows (GraphPad Software, San Diego, California, USA; www.graphpad.com). All p values presented were two-sided and values <0.05 were considered statistically significant.

Patient and public involvement
Neither patients nor the public were involved in the design, conduct, reporting or dissemination of this study.

RESULTS
A flow chart summarising participant inclusion is detailed in figure 1. In addition, comparisons of demographic and obstetric characteristics among ELA and NELA cohorts before and after propensity score matching are presented in table 1. Before propensity score matching, 816 parturients, 149 in the ELA cohort (18.3%) and 667 in the NELA cohort (81.7%), met the criteria for inclusion in the study. To better control for confounders regarding the selection of patients undergoing ELA, parturients were matched 1:1 based on the demographic and obstetric characteristics of the unmatched cohort. The propensity score-matched cohort from the primary analysis included 274 patients: 137 in the ELA cohort (50.0%) and 137 in the NELA cohort (50.0%). Previously observed covariate imbalances between cohorts with respect to age, height, BMI and risk factors associated with GDM, including elevated BMI and older maternal age, were diminished after matching absolute standardised differences to <10% for all covariates.

Comparisons of delivery and maternal and neonatal outcomes between the NELA and ELA cohorts after propensity score matching are presented in table 2. After propensity score matching, there was a markedly decreased occurrence of caesarean section and a significantly increased occurrence of assisted vaginal delivery in the ELA versus the NELA cohort. No between-matched cohort differences in spontaneous delivery and the second stage of labour were observed. In addition, the
ELA cohort had an increased duration of the first and total stages of labour.

Maternal and neonatal outcomes of matched cohorts were also compared. Blood loss during and 2 hours after delivery was significantly reduced and length of stay was shortened in the ELA versus the NELA cohort; however, there was an increased occurrence of postpartum fever (defined as body temperature above 38°C during the postpartum period) in the ELA versus the NELA cohort. Further, when the ELA and NELA groups were compared, no significant between-cohort differences were observed in terms of consumption of oxytocin, application of lateral episiotomy, or other complications including postpartum haemorrhage, infection, deep venous thrombosis or amniotic fluid embolism.

Significantly increased neonatal birth weight and occurrence of neonatal macrosomia as well as decreased NICU admissions rates were observed when the ELA cohort was compared with the NELA cohort. Significantly increased neonatal plasma glucose and decreased occurrence of neonatal hypoglycaemia were also observed when the ELA cohort was compared with the NELA cohort. The ELA cohort had non-inferior outcomes when compared with the NELA cohort in terms of occurrence of an Apgar score <7 at 1 and 5 min after birth, and other neonatal complications including hyperbilirubinaemia, neonatal respiratory distress syndrome and perinatal mortality.

The logistic regression of cohorts of nulliparous women with GDM who underwent caesarean section is presented in Table 3. Variables that significantly varied via univariate comparisons of maternal and neonatal outcomes of the ELA and NELA cohorts were entered into a multivariable model to identify predictors of caesarean section. Increased neonatal birth weight (OR 1.8, 95% CI 1.1 to 3.1; p=0.04) was independently associated with undergoing caesarean section. Notably, receiving ELA (OR 0.2, 95% CI 0.1 to 0.4; p<0.001) and elevated neonatal plasma glucose levels (OR 0.6, 95% CI 0.5 to 0.8; p<0.001) were independently associated with reduced occurrence of caesarean section.

**DISCUSSION**

This study demonstrated that the use of ELA decreased the rate of caesarean section and improved maternal and neonatal outcomes (blood loss reduction, shortened length of stay, and decreased neonatal hypoglycaemia and NICU admission rates) in 137 pairs of matched nulliparous women with GDM. To comprehensively control for biases associated with the selection of particular demographic and obstetric characteristics for ELA, we matched ELA and NELA parturients using a propensity score matching method. Logistic regression analysis also revealed that an increased neonatal birth weight was independently associated with undergoing caesarean section, while receiving ELA and an increased neonatal plasma glucose level were associated with reduced occurrence of caesarean section.

Epidural analgesic techniques are widely used as the gold standard for labour analgesia, with advantages that include high level of effectiveness, consistent analgesia and high level of patient satisfaction. However, it remains uncertain whether women with medical pregnancy complications, including GDM, who use ELA are at increased risk of undergoing caesarean section or instrumental delivery, negative maternal and neonatal outcomes, or severe complications.

Theoretically, ELA using local anaesthetics prolongs the first stage of labour by decreasing the intensity and frequency of uterine contractions in women with normal pregnancies; however, whether ELA prolongs the first stage of labour and increases the risk of emergency caesarean section for dystocia, as well as the incidence of instrumental delivery, remains debatable, especially in nulliparous women with GDM. Discrepancies with previously published data are likely due to variations in...
analgesic strategy. This includes the method of ELA used (epidural, spinal and combined spinal-epidural), as well as the categories, dosages and concentrations of local anaesthetics and/or opioids administered. 6 20–24

Interestingly, ELA is also associated with an increased rate of fever during labour.25 Similarly, we also found the incidence of fever increased in the ELA group compared with that of patients who did not receive ELA in the present study. Although the mechanisms by which intrapartum fever develops as a result of ELA remain unclear, numerous studies suggest that maternal fever during delivery may be a consequence of non-infectious inflammatory resulting from central neuraxial blockade.26–28

Fever during labour with ELA may be associated with adverse maternal outcomes and increased risk of neonatal complications. Recent studies have shown that among those receiving ELA, women who developed intrapartum fever had a significantly longer first stage of labour and a higher incidence of caesarean deliveries, assisted vaginal delivery, intrapartum haemorrhage and turbid amniotic fluid than those with no intrapartum temperature elevation.29 30 Other studies indicated that neonates of women who developed intrapartum fever were at increased risk of hypotonia, assisted ventilation, reduced 1 and 5 min Apgar scores, and early-onset seizures when compared with neonates of women with no intrapartum temperature elevation.29–31 However, considering the limited sample size of the subgroup of mothers with ELA who developed intrapartum fever, the data in the present study cannot reach statistical significance.

In women with GDM, neonatal complications including macrosomia, neonatal hypoglycaemia, hyperbilirubinaemia, neonatal respiratory distress syndrome and increased perinatal mortality are associated with a high risk of adverse events.32 Our results show that mothers with GDM who chose ELA have an increased incidence of macrosomia versus those who did not. Possible reasons for this finding are that women with macrosomia experience...
sharper labour pain and more severe stress during delivery than those without; thus, women with macrosomia were more willing to undergo ELA than those without. Moreover, mothers with GDM who chose ELA were at decreased risk of neonatal hypoglycaemia and NICU admission. A previous study reported that although well-controlled GDM has potentially significant detrimental effects on the fetal acid-base status at birth in uncomplicated pregnancies and deliveries, ELA reduces cord arterial glucose and lactate.33 Maternal hyperglycaemia leads to neonatal hyperinsulinaemia and increased utilisation of glucose,

**Table 2** Comparison of delivery and maternal and neonatal outcomes among ELA and NELA cohorts after propensity score matching

| Outcomes                     | ELA (n=137) | NELA (n=137) | P value |
|------------------------------|-------------|--------------|---------|
| **Delivery**                 |             |              |         |
| Mode of delivery             |             |              |         |
| Spontaneous                  | 63 (46.0)   | 57 (41.6)    | 0.47    |
| Assisted vaginal             | 49 (35.8)   | 17 (12.4)    | <0.001  |
| Caesarean                    | 25 (18.3)   | 63 (46.0)    | <0.001  |
| **Stage of labour (min)**    |             |              |         |
| First stage of labour        | 532.9±202.7 | 411.3±160.4  | <0.001  |
| Second stage of labour       | 57.5±31.4   | 53.1±31.9    | 0.41    |
| Total duration of labour     | 591.7±214.9 | 465.9±161.9  | <0.001  |
| **Maternal**                 |             |              |         |
| Blood loss (mL)              | 287.2±89.3  | 319.9±103.4  | 0.005   |
| Total dose of oxytocin (IU)  | 14.7±5.0    | 14.1±5.1     | 0.28    |
| Lateral episiotomy           | 39/112 (34.8)| 17/74 (23.0)| 0.10    |
| Length of stay (days)        | 3.9±1.1     | 5.1±1.6      | <0.001  |
| **Maternal complications**   |             |              |         |
| Maternal fever               | 31 (22.6)   | 14 (10.2)    | 0.01    |
| Postpartum haemorrhage       | 1 (0.7)     | 2 (1.5)      | >0.99   |
| Infection                    | 0 (0.0)     | 1 (0.7)      | >0.99   |
| DVT                          | 1 (0.7)     | 4 (2.9)      | 0.37    |
| Amniotic fluid embolism      | 0 (0.0)     | 1 (0.7)      | >0.99   |
| **Neonatal**                 |             |              |         |
| Birth weight (kg)            | 3.5±0.6     | 3.3±0.5      | <0.001  |
| Plasma glucose level (mmol/L)| 5.5±1.9     | 4.9±1.7      | 0.01    |
| Apgar score <7 points        |             |              |         |
| At 1 min after birth         | 16 (11.7)   | 14 (10.2)    | 0.85    |
| At 5 min after birth         | 6 (4.4)     | 7 (5.1)      | >0.99   |
| Neonates transferred to NICU | 11 (8.0)    | 26 (19.0)    | 0.01    |
| **Neonatal complications**   |             |              |         |
| Macrosomia                   | 28 (20.4)   | 11 (8.0)     | 0.005   |
| Neonatal hypoglycaemia       | 5 (3.7)     | 16 (11.7)    | 0.02    |
| Hyperbilirubinaemia          | 47 (34.3)   | 44 (32.1)    | 0.80    |
| Neonatal respiratory distress syndrome | 3 (2.2) | 7 (5.1)      | 0.33    |
| Perinatal mortality          | 0 (0.0)     | 0 (0.0)      | >0.99   |

DVT, deep venous thrombosis; ELA, epidural labour analgesia; NELA, non-epidural labour analgesia; NICU, neonatal intensive care unit.

**Table 3** Logistic regression for cohorts of nulliparous women with GDM undergoing caesarean section

| Variables                  | OR   | 95% CI     | P value |
|----------------------------|------|------------|---------|
| Larger neonatal birth weight| 1.8  | 1.1 to 3.1 | 0.04    |
| Receiving ELA              | 0.19 | 0.09 to 0.41| <0.001  |
| Higher neonatal plasma glucose | 0.56 | 0.45 to 0.75 | <0.001  |

ELA, epidural labour analgesia; GDM, gestational diabetes mellitus.
and hence increased neonatal adipose tissue, according to Pedersen’s hypothesis.\textsuperscript{34} After delivery, neonates maintain a high level of insulin, while they no longer have a high level of plasma glucose from their mothers, resulting in neonatal hypoglycaemia. However, since labour pain is diminished and delivery stress is reduced after initiating ELA, maternal hyperglycaemia is more easily controlled, resulting in alleviation of neonatal hypoglycaemia and reduced occurrence of neonatal hypoglycaemia.

Although substantial effort was devoted to controlling for selection bias via the use of propensity score-matched analysis, the study has some limitations that should be emphasised. First, we should recognise the potential for selection bias since the decision to use ELA is rarely made at random. ELA is more likely to be used when labour is particularly long or painful, especially when there is an increased likelihood that operative intervention will be needed. Second, although obstetricians conformed to the guidelines that strictly describe indications for assisted vaginal delivery and caesarean section, some differences among individual caregivers in clinical practice may occur since guideline interpretation may vary among individuals. Finally, it was determined that the cohort would require 128 matched pairs (256 total) to demonstrate the superiority of ELA to NELA (power=80\%, \( \alpha =0.05 \)). Moreover, we also provided the posteriori calculation that according to the 46.0\% of caesarean section rate in the subgroup of patients who had no epidural analgesia, a total of 248 patients should be determined to be required to be 80\% sure, assuming a loss to follow-up rate of 20\%. However, only 112 and 74 parturients in the ELA and NELA cohorts, respectively, had delivery and maternal outcome data regarding stage of labour and occurrence of lateral episiotomy since other parturients underwent caesarean section. Therefore, the analysis is slightly underpowered. Future prospective randomised clinical trials with sample sizes sufficient for providing adequate power will be indispensable for determining whether ELA improves delivery and maternal and neonatal outcomes in nulliparous women with GDM.

To the best of our knowledge, the current study is the first of its kind to compare delivery characteristics and maternal and neonatal outcomes in parturients with GDM who did and did not receive ELA using a propensity score matching methodology. Our findings demonstrate that the use of ELA decreases the occurrence of caesarean sections and improves maternal and neonatal outcomes in nulliparous women with GDM.

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Contributors YCh and XW conceived the study, designed the experiments, interpreted and analysed the data, and wrote the manuscript. HW, XueY and XiaY conceived the study. HuW, XW and YaC designed the experiments, supervised the work and edited the manuscript. All authors have read and approved this manuscript prior to submission. HuW is the study guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Institutional Ethics Committee (IEC) of Fujian Provincial Hospital (no: K2020-04-047). The waiver of written informed consent was allowed by the IEC.

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Data availability statement Data are available upon reasonable request. All data relevant to the study are included in the article.

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