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The assessing of clinical relevance of chromosomal microarray analysis in the prenatal diagnosis of fetal growth restriction

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Abstract

Objective Chromosomal variations are known to play a role in the etiology of fetal growth restriction (FGR). Here, we intend to investigate the significance of Chromosomal Microarray Analysis (CMA) in the prenatal diagnosis of definite FGR.

Method 182 pregnant women with FGR participated in our study, undergoing CMA to identify chromosomal abnormalities. The cohort was categorized into isolated FGR, FGR with ultrasound soft marker abnormalities, and FGR associated with structural malformations.

Results The detection rates of PCNVs in FGR with structural anomalies are significantly higher than those in the isolated FGR group and the FGR group with abnormal ultrasound soft markers (19.0% vs. 2.1%, 19% vs. 1.5%; χ^2=9.33, p=0.005). Compared to FGR with a single system malformation, the diagnostic rate of chromosomal variations in FGR with multiple system malformations is markedly increased (60% vs. 6.3%; p=0.028). Advanced maternal age, early-onset FGR, and severe FGR do not appear to influence the diagnostic rate of chromosomal variations (p>0.05).

Conclusion Chromosomal variations pose a significant risk in FGR with structural abnormalities, associated with the number of organ systems involved. Notably, advanced maternal age, early-onset FGR, and severe FGR do not affect the diagnostic rate of chromosomal variations in FGR.

Keywords Fetal growth restriction, Chromosomal microarray analysis, Prenatal diagnosis, Ultrasound abnormalities, Copy number variation

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Introduction

Fetal Growth Restriction (FGR) refers to a pathological condition where intrauterine fetal growth fails to achieve its genetic potential due to maternal, fetal, or placental factors [1]. FGR is typically characterized by an estimated fetal weight (EFW) or abdominal circumference below the 10th percentile for gestational age, with severe FGR defined as measurements below the 3rd percentile [1]. Prenatal ultrasonography is extensively employed for fetal anomaly screening, enabling detection of various fetal abnormalities including structural anomalies, soft markers, FGR, and amniotic fluid abnormalities [2]. Fetal ultrasound abnormalities typically indicate an increased risk of chromosomal abnormalities [10]. The etiology of FGR is multifactorial [3]. While maternal and uteroplacental factors primarily relate to obstetric management, genetic disorders play a crucial role among fetal factors [4]. Fetal ultrasound abnormalities serve as primary indicators for invasive prenatal genetic testing, with genetic etiology investigated through Chromosomal Microarray Analysis (CMA) [3]. In prenatal diagnosis, soft marker abnormalities may correlate with fetal chromosomal anomalies (aneuploidy and P/LP CNVs) and are utilized in risk assessment [5]. Common ultrasonographic soft markers include nuchal translucency (NT) thickening, ventriculomegaly, nasal bone hypoplasia, hyperechogenic cardiac foci, renal pyelectasis, choroid plexus cysts, hyperechogenic bowel, shortened long bones, single umbilical artery, renal pelvic dilatation, and tricuspid regurgitation [6]. Research indicates that NT thickening (44.5%) is the most prevalent soft marker abnormality, followed by ventriculomegaly (15.9%) and nasal bone hypoplasia (13.2%) [2]. The detection rate of chromosomal abnormalities (aneuploidy and P/LP CNVs) in fetuses with soft marker abnormalities is 9.9%, with rates of 9.7% and 11.8% for single and multiple soft marker abnormalities, respectively [2]. Over recent decades, conventional karyotyping and CMA have become standard genetic diagnostic tools for FGR, revealing various chromosomal and submicroscopic disorders [7]. This study conducts a retrospective analysis of fetuses with fetal growth restriction (FGR) who underwent invasive prenatal diagnostic testing, examining the differences in the detection rates of chromosomal abnormalities among three groups: isolated FGR, FGR with abnormal ultrasound soft markers, and FGR with structural fetal anomalies. Our aim is to explore the application value of chromosomal microarray analysis (CMA) in establishing prenatal genetic diagnoses for FGR, providing valuable insights for the management of pregnancies involving FGR fetuses with ultrasound abnormalities.

Materials and methods

Subjects

This single-center, prospective cohort study enrolled 182 singleton pregnancies diagnosed with FGR at Jining Medical University Affiliated Hospital from January 2020 to December 2023. In the study, cases of multiple pregnancies, preeclampsia, chronic nephritis, TORCH infections(Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus, and Others), and substance abuse were all excluded. The study received approval from the ethical committee of Jining Medical University Affiliated Hospital, and all participants provided written informed consent.

Chromosome karyotyping and CMA

In accordance with the principle of surgical asepsis, we performed amniocentesis by ultrasound at 18^{+0}-32^{+6} weeks' gestation in all subjects, extracting 30 ml of amniotic fluid. Out of this, 20 ml was designated for chromosome karyotyping, while the remaining 10 ml was allocated for chromosomal microarray analysis. The samples intended for karyotype analysis were prepared following the standard cell culture procedures based on G-banding techniques. DNA extraction was conducted using the QIAamp DNA Blood Kit (QIAGEN, Hilden, Germany), adhering to the protocol outlined in the kit manual (www.qiagen.com). The CMA was performed per the established experimental procedures of the Affymetrix CytoScan 750 K chip kit. The pathogenicity of copy number variations was interpreted with reference to databases such as DGV (http://dgv.tcag.ca/dgv), OMIM (https://omim.org/), DECIPHER (https://decipher.sanger.ac.uk/), and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/).

Diagnostic standard

The gestational age is calculated based on the last menstrual period and the crown-rump length (CRL) measured by ultrasound at $11–13^{+6}$ weeks. The estimated fetal weight (EFW) was calculated using biparietal diameter, head circumference, abdominal circumference, and femoral length derived from mid-pregnancy obstetric ultrasound based on Hadlock's formula 3. In cases affected by pathological factors, an EFW or abdominal circumference below the 10th percentile corresponding to the gestational age indicates fetal growth restriction (FGR), while values below the 3rd percentile reflect severe FGR. In this study, we categorized subjects into three groups based on ultrasound indications of abnormal soft markers and fetal structural anomalies to investigate the differences in chromosomal abnormalities among them. Generally, structural anomalies refer to morphological defects of one or multiple organ systems in the fetus, such as cleft lip and palate, or spina bifida,

Table 1 Kappa consistency test

CMA Karyotyping	Negative	Positive	Cases	Detection	Rates	*P*	Kappa Value
Negative	95	10	110	4.5%	12.7%	0.012	0.379
Positive	1	4					

Table 2 Comparative analysis of detection rates of chromosomal variations among different FGR groups

Groups	Cases	PCNVs	VOUS	PCNVs detection rates	χ^2	*P*	CMA detection rates	χ^2	*P*
Isolated FGR	94	2	7	2.1%	9.33	0.005	9.6%	8.89	0.012
FGR with abnormal soft markers	67	1	3	1.5%			6.0%		
FGR with structure anomalies	21	4	2	19.0%			28.6%		

The detection rates of PCNVs pertained solely to pathogenic and likely pathogenic cases, while the detection rates of CMA encompassed pathogenic, likely pathogenic, and variants of uncertain significance (VOUS)

Table 3 Stratified analysis of the FGR group with soft indicators and the FGR group with structural anomalies

FGR with abnormal soft markers	Cases	PCNVs	VOUS	PCNVs detection rates	χ^2	*P*	CMA detestion rates	χ^2	*P*
individual items	44	0	3	0.0%	-	0.343	6.8%	0.00	1.000
Merge two or more items	23	1	0	4.3%			4.3%		
FGR with structual anomalies	Cases	PCNVs	VOUS	PCNVs detection rates	χ^2	P	CMA detestion rates	χ^2	P
individual items	16	1	1	6.3%	-	0.028	12.5%	-	
Merge two or more items	5	3	1	60%			80%	0.011	

while non-structural anomalies are defined as abnormal soft markers, including nuchal translucency (NT) thickening, ventriculomegaly, nasal bone hypoplasia, hyperechogenic cardiac foci, renal pyelectasis, choroid plexus cysts, hyperechogenic bowel, shortened long bones, single umbilical artery, renal pelvic dilatation, and tricuspid regurgitation.

Statistical analysis

Statistical analysis of the data was performed with SPSS software. I selected either the Pearson chi-squared test, continuity correction, or Fisher's exact probability test to compare the detection rates of chromosomal abnormalities across different groups, with $P<0.05$ being deemed statistically significant.

Results

We included data from 182 cases of FGR pregnancies at the Affiliated Hospital of Jining Medical University, among which 110 had results from both karyotype analysis and CMA as prenatal diagnostic methods. To investigate whether there is a discrepancy in detection rates between the two approaches in FGR pregnancies, we employed the Kappa consistency test (Table 1). A Kappa value of less than 0.4 indicates a poor level of agreement between the two methods. Our findings revealed that the consistency between chromosomal karyotype analysis and CMA is indeed low (Kappa = 0.379). The detection rate for CMA was 12.7%, significantly higher than that of karyotype analysis (4.5%), with a statistically significant difference ($P<0.05$). This suggests that compared to traditional chromosomal karyotype analysis, CMA significantly enhances the diagnostic rate of chromosomal abnormalities in FGR pregnancies.

Based on the distinctive diagnostic advantages of CMA for FGR pregnancies, we continue to investigate the differences in the detection rates of chromosomal variations among various FGR groups (Table 2). In conjunction with ultrasound findings, we categorized FGR pregnancies into three groups: isolated FGR, FGR with abnormal ultrasound soft markers, and FGR with fetal structural anomalies. The detection rates of PCNVs pertained solely to pathogenic and likely pathogenic cases, while the detection rates of CMA encompassed pathogenic, likely pathogenic, and variants of uncertain significance (VOUS). The PCNV detection rates for the three groups were 2.1%, 1.5%, and 19.0%, respectively, whereas the CMA detection rates were 9.6%, 6.0%, and 28.6%. Significant differences were observed in both PCNV detection rates (χ^2=9.33, $P=0.005$) and CMA detection rates (χ^2=8.89, $P=0.012$) across the three groups. Post-hoc multiple comparison analysis revealed that there were significant differences in PCNV detection rates ($P=0.010$) and CMA detection rates (χ^2=3.915, $P=0.048$) between the FGR with fetal structural anomalies group and the isolated FGR group. Similarly, significant differences were also found in PCNV detection rates ($P=0.011$) and CMA detection rates (χ^2=6.020, $P=0.014$) between the FGR with structural anomalies group and the FGR with abnormal soft markers group.

We conducted stratified analyses on the FGR with soft marker abnormalities group and the FGR with structural malformations group simultaneously (Table 3). In the FGR group with structural malformations, we found that the detection rates of PCNVs and CMA were significantly

Table 4 Differentiated comparison of chromosomal variations in other respects

Factors	Subgroups	Cases	PCNVs	VOUS	PCNVs detection rates	χ^2	*P*	CMA detestion rates	χ^2	*P*
Maternal age	< 35years	159	6	9	3.8%	-	1.000	9.4%	0.64	0.423
	≥ 35years	23	1	3	4.3%			17.4%		
Gestational age at onset of FGR	Early-onset FGR(<32 weeks)	171	6	10	3.5%	-	0.359	9.4%	1.51	0.220
	Late-onset FGR(≥32 weeks)	11	1	2	9.1%			27.3%		
Severity of FGR	FGR	130	6	10	4.6%	0.18	0.670	12.3%	1.51	0.193
	Severe FGR	52	1	2	2.0%			5.8%		

Table 5 Binary logistic regression of PCNVs

Factors	B	*P*	OR	PCNVs OR [95%CI]	
				95%CI low	95%CI up
Severe FGR	-0.771	0.489	0.462	0.052	4.112
Advanced maternal age	0.077	0.953	1.080	0.084	13.855
Pregnancy weeks of onset	1.407	0.290	4.085	0.301	55.411
FGR groups	1.378	0.013	3.966	1.338	11.754

higher in the multi-system structural malformations group compared to the single-system structural malformations group. Interestingly, when comparing the FGR group with multiple soft marker abnormalities to the group with a single soft marker abnormality, there was no significant increase in the detection rates of PCNVs and CMA, which was completely unexpected. This finding may hold critical implications for clinical prenatal diagnostic practices.

Furthermore, We conduct the effects of maternal age, gestational week at the onset of FGR, and the severity of FGR on the rate of chromosomal variations in FGR cases (Table 4). Unexpectedly, we did not find statistically significant impacts of advanced maternal age, early-onset FGR, and severe FGR on the chromosomal variations ($P > 0.05$).

Ultimately, we employed binary logistic regression analyses on PCNVs to validate the aforementioned perspective that advanced maternal age, early-onset FGR, and severe FGR appear to be independent of chromosomal variations in FGR (Table 5). However, when FGR is coupled with structural anomalies, the incidence of chromosomal variations significantly increases, particularly among those with multi-system structural abnormalities. Compared to isolated FGR, the risk of detecting PCNVs in the cohort presenting with FGR alongside structural anomalies is elevated by 2.97 times (OR = 3.97; $P = 0.01$).

We also aimed to investigate the relationship between the onset timing of FGR and chromosomal variations. As shown in Table 6, our findings indicate that there is no significant difference in the rate of chromosomal variations among FGR cases with different onset timings.

According to the CNV interpretation guidelines released by the American College of Medical Genetics and Genomics [8], we classified CNV results into five categories: pathogenic, likely pathogenic, variants of uncertain significance, likely benign, and benign CNVs. We identified a total of 20 cases of chromosomal abnormalities, with 19 deriving from CMA, while only one case of "chromosomal polymorphism" was identified through karyotyping analysis (Table 7). Chromosomal microvariations such as "1qh+," "13pass," and "14pstk+" are referred to as "chromosomal polymorphisms." Recent studies have suggested that these polymorphisms may contribute to difficulties in homologous chromosome pairing and chromosome nondisjunction, leading to the formation of abnormal gametes or zygotes, and could therefore be associated with clinical conditions such as infertility, azoospermia, miscarriage, and stillbirth [9]. However, among the CNV results, only 7 cases (3.85%) represent genuinely pathogenic or likely pathogenic CNVs, which is significantly lower than the findings reported in other similar studies [10, 11].

Pregnancy outcomes

Among 20 cases of chromosomal abnormalities associated with FGR, 8 opted for pregnancy termination, while the remaining 12 successfully delivered without significant abnormalities. In cases involving PCNVs, only 1 chose to continue the pregnancy, and among cases involving VOUS, only 2 opted for termination. Among

Table 6 Stratified analysis of the onset timing of FGR

Pregnancy weeks of onset	Cases	PCNVs	VOUS	PCNVs detection rates	χ^2	*P*	CMA detection rates	χ^2	*P*
18–23^{+6}w	53	1	2	1.9%	0.81	0.71	5.7%	2.05	0.36
24–27^{+6}w	63	3	4	4.8%			11.1%		
28–32^{+6}w	66	3	6	4.5%			13.6%		

Table 7 Comparison of chromosomal abnormalities identified through karyotype analysis and CMA detection

Karyotyping	CMA	Groups	Meaning	Pregnancy outcome
47,XN,+18	arr(18)x3	structural	Path	TOP
46,XN	arr[GRCh37] 9p24.3p13.3(208454_33391202)x3,22q11.1q11.21(16888899_19732140)x3	structural	Path	TOP
/	arr[GRCh37] 22q11.21(18648855_21800471)x1	structural	Path	TOP
46,XN	arr[GRCh38] Xp22.33(251,888_2,778,721)x3,Xq28(153,294,365_156,003,433)x1; Yp11.2(2,782,384-3,214,403)x1	Isolated	Path	Born
/	arr[GRCh38] 16p13.11(15,589,894_16,201,939)x1	Isolated	Path	TOP
46,XN	arr[GRCh37]16p11.2(28763849_29051191)x1,16p12.2(21841353_22442007)x1	Non-structural	L-Path	TOP
46,XN, der(4)t(3;4)(q24;q35)mat	arr[GRCh37] 3q24q29(143413622_197851444)x3,4q34.3q35.2(179118352_190816266)x1	structural	L-Path	TOP
46,XN,1qh+	arr(1–22)x2,(X, N)X1	Non-structural	/	Born
46,XN	arr[GRCh37] 20q11.23q12(37507115_38519582)x3	Isolated	VOUS	Born
46,XN	arr[GRCh37] Xq28(153334710_153736115)x3	Isolated	VOUS	Born
46,XN,14pstk + mat	arr[GRCh37]12q14.1(59507892–60206788)x1	Isolated	VOUS	Born
46,XN	arr[GRCh37] 15q13.1q13.2(28965218_30370018)x3	Isolated	VOUS	Born
46,XN	arr[GRCh37] Xp22.33(217329_1234634)x3	Isolated	VOUS	Born
/	arr[GRCh37] 3p26.3(319825_2204325)x3	structural	VOUS	Born
46,XN, dup(4)(p15)	arr[GRCh37] 4p15.31p15.1(19267282_28387475)x3	Isolated	VOUS	Born
46,XN	arr[GRCh37] 4p16.1(9837055_10895802)x3	Isolated	VOUS	TOP
/	arr[GRCh37] Xp22.31(6455151_8143509)x1	Non-structural	VOUS	Born
/	arr[GRCh37] 2q32.2q33.3(191838203_205881252)x2 hmz	structural	VOUS	TOP
46,XN	arr[GRCh38] 2q37.3(237,150,088_237,802,873)x1	Non-structural	VOUS	Born
46,XN	arr[GRCh38] 7p22.2p22.1(3,387,054_4,508,910)x3	Non-structural	VOUS	Born

TOP, termination of pregnancy; VOUS, variants of unknown significance;
Path, Pathogenic; L-Path, Likely Pathogenic

the malformed fetuses identified through prenatal ultrasound or amniocentesis, only one case confirmed fetal femoral curvature, while the others appeared to show no developmental abnormalities. In this study, approximately 58.9% (107/182) of the cases of fetal growth restriction (FGR) were confirmed to be small for gestational age.

Discussion

Fetal Growth Restriction (FGR) is a multifaceted obstetric condition affected by a myriad of factors, with the genetic dimensions of its prenatal diagnosis presenting a significant challenge for obstetricians [12]. The genetic etiology of FGR may be linked to fetal chromosomal anomalies, localized placental chromosomal irregularities, or maternal chromosomal abnormalities [12]. Although these genetic causes constitute a minor proportion of FGR cases, some studies suggest a higher prevalence of genetic anomalies in cases of severe and early-onset FGR [13]. However, our research did not yield similar finding, raising the possibility that the discrepancy may be associated with sample size. Furthermore, not all pregnant women with abnormal ultrasound findings related to FGR underwent amniocentesis, suggesting the presence of selection bias. In our study, we observed that the detection rates of PCNVs and CMA significantly increased in cases of FGR with structural anomalies. In contrast, the chromosomal variations between the isolated FGR group and the group with soft marker abnormalities were not significantly different. This aligns with various clinical guidelines. According to the 2016 guidelines from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine, CMA is recommended as the first-line prenatal diagnostic tool when ultrasound detects fetal structural anomalies, superseding traditional chromosomal karyotyping [14]. Structural anomalies visualized via ultrasound necessitate direct CMA, whereas soft marker anomalies indicate that either karyotyping or CMA could be considered [14].

Compared to traditional chromosomal karyotyping, the primary advantage of CMA lies in its higher resolution and precise localization of submicroscopic imbalances [15]. CMA offers additional diagnostic benefits

by accurately revealing submicroscopic imbalances or CNVs that are often too subtle to be detected in standard G-band chromosomal preparations [15]. These submicroscopic imbalances, commonly referred to as microdeletions and microduplications, provide significant guidance for prenatal diagnostic work when they involve specific genomic regions associated with clinical outcomes [16]. In this study, CMA improved the diagnostic rate of genetic variations in pregnant women with FGR by 8.2%, clearly showcasing its clinical value in the prenatal diagnosis of FGR. We identified a total of seven pathogenic or potentially pathogenic cases, with Trisomy 18 being the most prevalent etiology among chromosomal non-aneuploid sources of FGR [17]. Prior research has identified a microdeletion at 22q11.21 in cases of FGR associated with structural anomalies, which aligns with our findings [13]. The Xp22.33 microduplication could be associated with congenital heart defects, short stature, and male infertility [18, 19]. The Xq28 microdeletion is closely linked to ovarian insufficiency, Barth syndrome, and neuromuscular diseases [20–22]. Interestingly, the submicroscopic imbalances at Xp22.33 and Xq28 were frequently observed in our study, leading us to hypothesize that they are closely associated with the pathogenesis of FGR.

Variants of Uncertain Significance (VOUS) can either be benign alterations with no clinical impact or rare pathogenic variants that result in clinical phenotypes [23]. Typically, chromosomal variations inherited from asymptomatic parents usually have a more favorable prognosis, whereas those originating from the fetus's own chromosomes are more likely to be clinically significant [23]. Consequently, parameters such as the size of CNVs, gene content, and inheritance patterns assist in distinguishing whether a VOUS is more likely to be benign or pathogenic [24]. In this study, the genetic chip results indicated arr[GRCh37] 4p16.1(9837055_10895802)x3 for a pregnant woman with incomplete family analysis, leading to a request for induced termination of pregnancy. Additionally, the genetic chip results showed arr[GRCh37] 2q32.2q33.3(191838203_205881252)x2 hmz (VOUS) for another pregnant woman at 28 weeks gestation, where ultrasound findings suggested fetal aortic coarctation, abnormal development of the right kidney, and fetal growth restriction, prompting her request for induced termination of pregnancy.

Our study revealed that genetic variations linked to Fetal Growth Restriction (FGR) are correlated with the number of organ systems affected by malformations. The diagnostic rate of chromosomal anomalies in cases of single-system malformations associated with FGR is significantly lower than that for malformations affecting two or more systems (6.3% vs. 60%). Previous studies have indicated that the gestational age at which FGR develops and its severity can affect the diagnostic rate of chromosomal distortions; however, we did not observe a significant risk associated with advanced maternal age, early-onset FGR, or severe FGR concerning chromosomal variations. The latest guidelines from the Society for Maternal-Fetal Medicine (SMFM) state that late-onset FGR is not considered an indication for invasive diagnostic procedures [25]. Table 4 indicates that there are no significant differences in chromosomal variations between late-onset FGR and early-onset FGR. Therefore, we propose that genetic assessment should also be considered in cases of late-onset FGR. Additionally, advanced maternal age has consistently been identified as an independent risk factor for amniocentesis in prenatal diagnostics [26]. Considering the limitations of our study, including a small sample size and being a single-center prospective investigation, we continue to advocate for the use of CMA as a primary prenatal diagnostic method for older mothers or those with severe FGR. Furthermore, we encourage additional research to explore the value of CMA in FGR cases with concurrent ultrasound soft marker abnormalities.

Conclusion

Compared to the isolated FGR group and the FGR group with ultrasound soft marker abnormalities, chromosomal abnormalities present a significant risk in pregnant women with structural anomalies associated with FGR, and this risk correlates with the number of affected organ systems. Advanced maternal age, early-onset FGR, and severe FGR do not appear to affect the diagnostic rate of chromosomal variations in FGR cases. We recommend routine genetic assessments for cases of FGR that develop after 32 weeks of gestation, and we hypothesize that submicroscopic imbalances at Xp22.33 and Xq28 are closely linked to the pathogenesis of FGR.

Abbreviations

FGR	Fetal growth restriction
CMA	Chromosomal Microarray Analysis
CNVs	Copy Number Variants
P CNVs	Pathogenic Copy Number Variants
EFW	Estimated Fetal Weight
LP CNVs	Likely Pathogenic Copy Number Variants
NT	Nuchal translucency
TORCH	Toxoplasmosis, Rubella, Cytomegalovirus, Herpes simplex virus, and Others
CRL	Crown-Rump Length
VOUS	Variants Of Uncertain Significance

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Author contributions

P.L.: Conceptualization, Writing–original draft. F.G.W.: Investigation, Writing–review and editing. D.M.M.: Investigation, Writing–review and editing. Y.P.W.: Data curation, Resources, Writing–review and editing. X.Y.Z.: Data curation, Resources, Writing–review and editing. M.L.: Data curation, Resources, Writing–

review and editing. W.L.W.: Formal analysis, Writing–review and editing. Y.T.L.: Formal analysis, Writing–review and editing.

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Data availability
The datasets generated and/or analysed during the current study are not publicly available due to privacy or ethical restrictions but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures involving human participants in this study comply with the Helsinki Declaration (revised in 2013). The study involving human participants were reviewed and approved by the Logic Committee of the Affiliated Hospital of Jining Medical College. The patients/participants provided their written informed consent to participate in this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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