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Original Research

Fertility outcome of patients with CBAVD: a single-institution experience

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Abstract

Background and objective: Congenital bilateral absence of the vas deferens (CBAVD) is not common and fertility outcome is not clear. This study is to report fertility outcomes of infertile male with CBAVD. **Material and methods**: Our study cohort comprised CBAVD males who were enrolled from 2005 to 2019. Baseline information was collected including mean age, previous medical history, duration of infertility, sex hormone assays, ejaculate volume/pH, parameters of sperm retrieved by percutaneous epididymal sperm aspiration (PESA), development of seminal vesicle TRUS, follow up fertility outcomes of the patients with intracytoplasmic sperm injection (ICSI) and compared the impact of varies male factors on fertility outcomes. **Results**: 172 participants with CBAVD were analyzed. A total of 211 ICSI cycles were performed and the live birth rate was 46.92%. Among 126 live births, 57 (45.24%) were boy and 69 (54.76%) were girl. The neonatal weight and height are 3036.83 $\pm$ 672.17 g, 49.43 $\pm$ 2.49 cm, respectively. There were no significant differences between successes group of couples and fail group of couples for first ICSI cycles cases in terms of age ($P = 0.09$), testicle volume (left $P = 0.96$, right $P = 0.41$), sex hormones ($P > 0.05$), ejaculate volume ($P = 0.79$), ejaculate pH ($P = 0.78$) or sperm quality parameters from PESA ($P > 0.05$). **Conclusions**: This study indicates that the clinical characteristics of male with CBAVD had no impact on fertility outcomes.

Keywords: Male infertility; CBAVD; Fertility outcome; Percutaneous epididymal sperm aspiration; Intracytoplasmic sperm injection

1. Introduction

Congenital bilateral absence of the vas deferens (CBAVD) is a relatively rare anomaly that may contribute to male infertility in most instances [1]. The prevalence of CBAVD in the general population is 0.1%, accounting for most of infertile males with cystic fibrosis and 1–2% of all male infertility [2,3]. One study revealed that ~44% of patients with CBAVD were found ΔF508/R117H mutations and CFTR mutations might affect male fertility through other mechanisms than obstruction of the genital tract [4]. The condition is presented in 4–17% of male with azoospermia and 17–30% of male with obstructive azoospermia (OA) [5,6]. In the earlier years, patients with CBAVD have traditionally been considered desperate and sterile. With the development of intracytoplasmic sperm injection (ICSI), the use of surgical methods to get sperm from the testis or epididymis can achieve pregnancy, allowing azoospermia patients to restore their patrilineal hope [7,8].

Sex of offspring is reported to be affected by social, environmental, and biological factors, such as hypertension, parental age, war, natural disaster, toxins, consanguineous marriages and economic/policy conditions [9–14]. But research shows that there is no obvious indication that semen quality is related to sex determination of offspring [15].

With the advance of ICSI and success of sperm retrieval techniques for CBAVD males, fertilizing and pregnancy rates are generally high because spermatogenesis in the testis is not affected by abnormal development of spermatogenic ducts, in general. In some studies, fertilization rates [2] and pregnancy rates [16] have been reported for patients with CBAVD. The main endpoint for couples is to get a child. However, few studies have evaluated the role of clinical characteristics in men with CBAVD on the outcome of ICSI. Up to now, it is lack of this information about live birth rates, sex of offspring, and their relationship with the clinical characteristics in available scientific literature.

2. Methods

2.1 Participants

The study participants were recruited from the department of urology, Peking Union Medical College Hospital (PUMCH). All patients attended our clinic with the complaint of infertility and underwent a series of clinical examination including palpation of the testis, epididymis and

vas deferens. We recorded the medical history of patients and every patient written informed consent to participation. According to clinical examination, ultrasound examination of the seminal vesicles and vas deferens and azoospermia at least two semen analyses it was diagnosed as CBAVD. This study obtained ethics approval from ethics committee of PUMCH.

Between January 2005 and December 2019, there were 432 men were diagnosed CBAVD. In order to achieve complete patient information, we only included 172 patients with complete clinical information and fertility outcome finally after following all patients. Clinical information and fertility outcomes include: age, volume of both testes, duration of infertility (the time from marriage to be diagnosed), sex hormones [testosterone (T), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2) and prolactin (PRL)], semen analysis results before Percutaneous Epididymal Sperm Aspiration (PESA), development of vas deferens and seminal vesicle, the presence of varicocele, outcomes of PESA, and fertility information of offspring. Karyotype analysis was advised for all patients and the cases with abnormal karyotype were excluded. In order to eliminate the influence of gynecological problems on fertility outcomes, we included the female partners of 172 patients with a normal fertility profile (established by evidence from hysterosalpingogram, follicular ultrasound, FSH, antimullerian hormone and examined for CFTR mutations) and were negative for cystic fibrosis.

2.2 PESA

PESA procedures were carried out to get sperm retrieval. All patients received 1% lidocaine hydrochloride seals the spermatic cord and local anesthesia at the scrotal skin. Use a 2 mL syringe to absorb 0.5 mL of HEPES culture solution, fix one side of the epididymis with the left hand, and hold the syringe with the right hand to puncture the epididymal head through the skin, and pull the syringe to 1.5 mL Form negative pressure, gently massage the epididymis while slowly withdrawing the needle until it leaves the epididymis. Pour the aspiration fluid into a petri dish and look for sperm under an inverted microscope (400×). The aspirate was evaluated to determine sperm count, sperm motility, sperm vitality, and normal sperm morphology. If no spermatozoa were found, the same procedure was performed repeated puncture on the same or the contralateral side. If more than one progressively motile sperm could be observed in 10 visual fields, freezing was applicable; if one progressively motile sperm could be seen on the whole slide, the sperm would meet the ICSI standard. In of these cases, we only included patients with CBAVD who successfully obtained sperm enough to perform ICSI.

2.3 ICSI

Routine stimulation was adopted according to the patients' partners' case requirements. Transvaginal ultrasound was used to monitor the follicles continuously. Oocyte maturation was triggered by human chorionic gonadotropin (hCG) 5000–10,000 IU. After 36 hours, the oocytes were retrieved through the vagina under the guidance of B-ultrasound. ICSI was performed 2 to 4 hours after oocytes collection, and embryo transfer was performed 72 hours after oocytes collection. Use the Hoffman modulation contrast system to perform ICSI on the platform of an inverted microscope and inject fixed motile sperm into the oocyte. We defined the live birth rate as: number of births/total transplantation cycles with live births. The outcomes of ICSI cycles, weight and length of the new born baby were recorded.

2.4 Data analysis

After extraction, all data were used with the SPSS software (version 22, IBM Corp., Chicago, IL, USA) performs an analysis. Outcomes of continuous variables were compared by Mann-Whitney U or Student's *t* test and expressed as mean difference (MD) with 95% CI. Qualitative variables were used Fisher's test and a chi-squared test. $P < 0.05$ is considered statistically significant.

3. Results

3.1 Baseline characteristics of patients

This retrospective cohort study included 172 infertile patients due to CBAVD. Mean age was 30 years (range 20–49 years).The mean volume of both testes was also measured: left 13.25 $\pm$ 2.30 mL and right 13.20 $\pm$ 2.49 mL. Ejaculate volumes were 1.04 $\pm$ 0.85 mL and ejaculate pH values were 6.59 $\pm$ 0.39. Bilateral epididymis development is normal. 94 of 172 males with CBAVD (54.65%) had seminal vesicle absent/dysplasia. Some of the evaluated endocrine and semen analysis parameter retrieval of PESA are presented in Table 1.

3.2 Previous medical history

One case had a history of testicular torsion and performed a right testicular resection. One case had a history of cryptorchidism. Three cases had a history of hernia repair (two cases were left and one case was right). 17.57% CBAVD patients were coexisted varicocele and three patients had to be carried out varicocelectomy. 17.57% of CBAVD patients have a history of varicocele. Nine cases had a history of mumps. 1 case had bilateral hydrocele surgery at the age of 14.

3.3 The duration of infertility

The distribution of durations of infertility after marriage is shown in Fig. 1. 37.16% of the patients were more than 3-years duration of infertility.

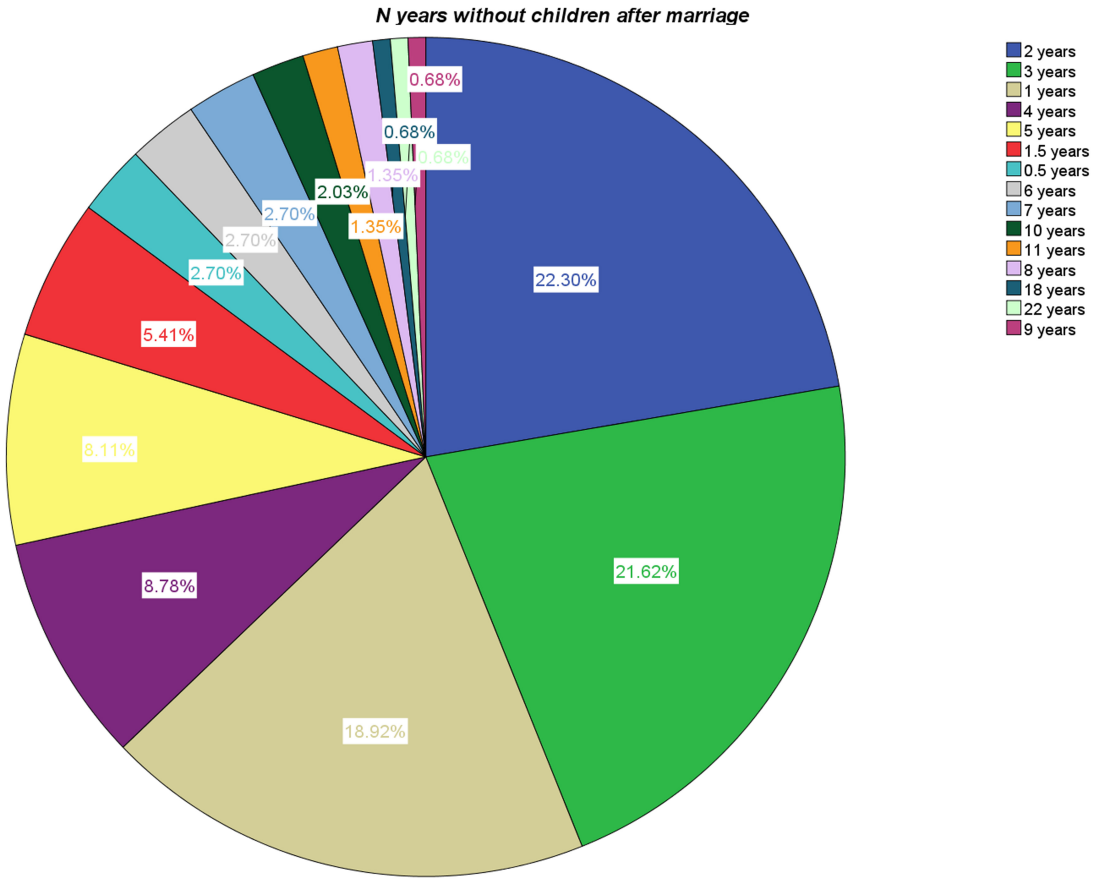

Fig. 1. The distribution duration of infertility after marriage.

Table 1. General characteristic and laboratory data of the 172 cases with CBAVD.

Parameters	Mean ± SD	Parameters	Mean ± SD
Age (years)	29.68 ± 4.55	Once ejaculation	
Testicle volume (mL)		Volume (mL)	1.04 ± 0.85
Left	13.25 ± 2.3	pH	6.59 ± 0.39
Right	13.20 ± 2.49	PESA (sperm)	
Hormone		Motility (A), %	6.55 ± 9.41
FSH (IU/L)	4.84 ± 2.17	Motility (B), %	8.67 ± 6.34
LH (mIU/mL)	3.60 ± 1.68	Motility (C), %	22.88 ± 14.78
PRL (ng/mL)	9.27 ± 3.97	Motility (D), %	62.65 ± 21.86
T (ng/mL)	4.05 ± 1.42	Concentration (10^6)	88.84 ± 73.57
E2 (pmol/L)	34.35 ± 15.82	Deformity rate (%)	66.42 ± 24.23

FSH, follicle-stimulating hormone (normal range: 1.27–12.96 mIU/mL); LH, luteinizing hormone (normal range: 1.24–8.62 mIU/mL); PRL, prolactin (normal range: 2.64–13.13 ng/mL); T, testosterone (normal range: 4–8 ng/mL); E2, estradiol (normal range: 20–75 pg/mL).

3.4 Family history

The older brother of one case and twin brother of another case had been diagnosed with CBAVD, which the study of familial evidence has been published [17].

3.5 Results of PESA

149 (86.63%) of 172 patients could be successfully retrieved spermatozoa when were conducted for the first time of PESA. The remaining 23 patients obtained sperm successfully after three months of treatment with HCG/HMG for the second/third time of PESA.

3.6 ICSI outcomes and neonatal condition

As showed in Fig. 2, a total of 211 ICSI cycles were performed in couples in which the man with CBAVD. 75 cases of the first ICSI cycles were successfully to birth infant(s). Among 97 males with a history of failed first ICSI cycles, 17 cases succeeded; and 92 cases were successful finally. For all ICSI cycles, the live birth rate was 46.92%.

No significant effect on sex ratio was found based on the use of ICSI for CBAVD couples: Among 126 lives births, 57 (54.76%) were boys and 69 (45.24%) were girls, which including 29 boys with a singleton birth and 31 girls with a singleton birth, 14 boys with single sex twins' birth and 24 girls with single sex twins' birth, and 28 boys/girls

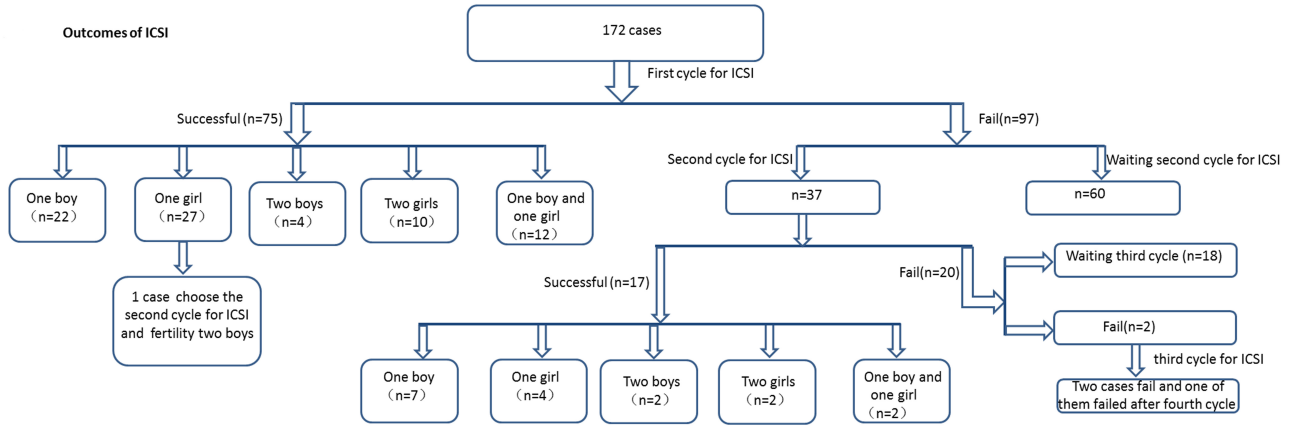

Fig. 2. Fertility outcomes in ICSI cycles in couples with CBAVD.

with twins of different sex birth. Neonatal weight and height are 3036.83 ± 672.17 g, 49.43 ± 2.49 cm, respectively.

3.7 Difference for male factors between the successful and failure of ICSI

For first ICSI cycles, there were no significant differences between success group of couples and failure group of couples in terms of age ($P = 0.09$), testicle volume (left $P = 0.96$, right $P = 0.41$), FSH ($P = 0.65$), LH ($P = 0.58$), PRL ($P = 0.62$), T ($P = 0.82$) and E2 ($P = 0.18$), ejaculate volume ($P = 0.79$), ejaculate pH ($P = 0.78$) or sperm quality parameters (the concentration, motility and deformity rate of sperm retrieved) ($P > 0.05$). The same outcomes were found when comparing the success group of couples for first ICSI cycles with repeated failure group (≥2 times ICSI cycles) in terms of male factors ($P > 0.05$) (Table 2).

4. Discussion

CBAVD is not common in clinics of male infertility and often overlooked in clinical work, which delays diagnosis and gives patients unnecessary examinations and treatments. Due to the advancement of ICSI, patients with CBAVD may have their own offspring, but the abnormal development in male reproductive duct brought about concerns about the outcome of ICSI and the health of next generations, which triggered the report in this article and also answered urgent clinical perplexes. This study tries to evaluate the reproductive outcomes (including live birth rate and sex of offspring) of patients with CBAVD, and compare success group of couples with failure group of couples in terms of male factors. No significant differences were found between success group of couples and failure group of couples in terms of age, testicle volume, sex hormone, ejaculate volume, ejaculate pH or sperm quality parameters ($P > 0.05$). We found that the live birth rate was 46.92%, in agreement with literature data (live birth rate 30–50%) had published due to male/non-male factors infertile [18,19]. Among 126 live births, 54.76% were boy and 45.24% were girls. These results were similar to status of infant born naturally [20]. The change in sex ratio after ICSI might be due to genetic abnormalities or due to the use of more immature germ cells or rather to an increased stress of the male cells, extracted from the epididymis or testicular tissue [21].

Clinically, it usually manifests as missing vas deferens and epididymis that cannot be touched on both sides [22]. Low volume ejaculate and acidic ejaculate pH are leading signs of CBAVD, azoospermia, pH <7.2 and semen volume <1.5 mL are common performance in semen analysis. In this study, the mean volume of both testes was left 13.25 ± 2.3 mL and right 13.20 ± 2.49 mL; the evaluated reproductive hormones were within normal range; ejaculate volumes were 1.04 ± 0.85 mL, ejaculate pH values were 6.59 ± 0.39. These results were consistent with prior research findings, in which testis volume and serum gonadotropins are usually normal [6].

Couples who want to achieve their offspring have to adopt ICSI with sperm extraction from epididymis (PESA) or testis (TESA). In this study, 86.63% of patients could successfully have retrieved spermatozoa when conducted for the first time of PESA. It is commonly believed that epididymal spermatozoa should be selected firstly compare to testicular spermatozoa [23,24].

In theory, CBAVD was considered purely "obstructive" azoospermia. However, after a left was plus right testicular volume <30 mL could remind us of the existence of possible testicular hypotrophy, though it was observed that the mean testicular volume in the normal range in our series. This finding suggests the presence of a mixed pathology, with both obstructive damage and testicular failure. PESA outcomes justify these; both in terms of activity or vitality were low and abnormality rates were high [25].

It is generally believed that defective spermatogenesis in man with non-OA affects the outcomes of ICSI [26]. However, for CBAVD patients with OA, the potential impact of spermatogenesis quality on the results of ICSI is un-

Table 2. General characteristic of the 172 cases.

Parameters	Mean ± SD (A/B)	*P*	Mean ± SD (A/C)	*P*
Age (years)	29.03 ± 4.34/30.31 ± 4.66	0.09	29.03 ± 4.34/29.53 ± 4.06	0.67
Testicle volume (mL)				
Left	13.24 ± 2.20/13.26 ± 2.42	0.96	13.24 ± 2.20/13.47 ± 2.00	0.69
Right	13.02 ± 2.60/13.36 ± 2.42	0.41	13.02 ± 2.60/13.65 ± 1.99	0.35
Hormone				
FSH (IU/L)	4.96 ± 2.11/4.80 ± 2.23	0.65	4.96 ± 2.11/4.15 ± 1.40	0.15
LH (mIU/mL)	3.68 ± 1.83/3.52 ± 1.57	0.58	3.68 ± 1.83/3.28 ± 1.25	0.42
PRL (ng/mL)	9.40 ± 3.87/9.07 ± 4.07	0.62	9.40 ± 3.87/9.50 ± 5.17	0.93
T (ng/mL)	4.02 ± 1.59/4.08 ± 1.29	0.82	4.02 ± 1.59/4.10 ± 1.44	0.87
E2 (pmol/L)	36.34 ± 15.68/32.66 ± 16.06	0.18$^{\#}$	36.34 ± 15.68/32.11 ± 19.18	0.36$^{\#}$
Once ejaculate				
Volume (mL)	1.07 ± 0.92/1.02 ± 0.82	0.79	1.07 ± 0.92/0.93 ± 0.39	0.65
pH	6.60 ± 0.40/6.58 ± 0.39	0.78	6.60 ± 0.40/6.55 ± 0.37	0.71
PESA (sperm)				
Motility (A), %	7.11 ± 7.37/6.16 ± 11.09	0.59$^{\#}$	7.11 ± 7.37/10.50 ± 20.79	0.32$^{\#}$
Motility (B), %	9.49 ± 6.88/7.82 ± 5.70	0.20$^{\#}$	9.49 ± 6.88/10.00 ± 4.63	0.84$^{\#}$
Motility (C), %	22.08 ± 13.55/23.84 ± 16.32	0.56$^{\#}$	22.08 ± 13.55/19.38 ± 9.43	0.59$^{\#}$
Motility (D), %	61.87 ± 21.55/63.40 ± 22.63	0.73$^{\#}$	61.87 ± 21.55/63.38 ± 13.99	0.75$^{\#}$
Concentration (10^6)	92.70 ± 78.98/87.13 ± 69.24	0.67$^{\#}$	92.70 ± 78.98/118 ± 79.48	0.27$^{\#}$
Deformity rate (%)	68.40 ± 20.70/64.64 ± 27.25	0.58$^{\#}$	68.40 ± 20.70/73.33 ± 24.01	0.61$^{\#}$

(A/B: success of couples for first ICSI cycles versus failure of couples for first ICSI cycles; A/C: success of couples for first ICSI cycles versus failure of couples for ≥2 times ICSI cycles; $^{\#}$ Mann-Whitney U).
FSH, follicle-stimulating hormone; LH, luteinizing hormone; PRL, prolactin; T, testosterone; E2, estradiol.

known. In our study, whether it is live birth rate or sex of offspring, there is no significant different from other published literature.

It was revealed that the pregnancy, spontaneous abortion rates, fertilization rate, and implantation are encountered the impact of sperm quality [27–30]. When we tried to explore whether there were male factors affecting fertility outcomes of ICSI, no difference was found by comparing success group of couples with failure group of couples. For mean age, testicle volume, sex hormone and ejaculate volume/pH, there were no difference at all. However, total motility, A-level (active forward) sperm motility and B-level (slow forward) sperm motility in success group of couples for first ICSI cycles were significantly better than failure group of couples though the *P*-value were no significance.

In our cases, 17.57% CBAVD patients had coexisting varicocele, this result was similar to the incidence in the normal population. Over one third of the patients were more than 3-years duration of infertility. It may be the lack of basic attention and physical examination in clinical work, although physical examination can find most of the vas deferens, especially bilateral deficiencies. Meanwhile, TRUS test results can give us more detailed tips that 94 of 152 males with CBAVD (61.84%) had seminal vesicle absence/dysplasia. Considering the family history, the older brother of one case and twin brother of another case had been diagnosed with CBAVD. This enlightenment to us is that if there are brothers in the family, the corresponding absence of the vas deferens can be coexisting for the same time.

All factors involved in the analysis were evaluated in 172 patients, and were performed in a single center and small samples. It was reported that 20–30% of patients with CBAVD present with renal agenesis due to developmental characteristics [31]. With the main orientation towards fertility, our study did not include the information of CBAVD coexist with renal agenesis. The majority of patients with mutations occur in the *CFTR* gene [32]; the combination of phenotype/genetic molecular mechanism and fertility outcomes is a better idea, which is the shortcoming of this article and we will explore this part of the following research.

5. Conclusions

In this study, we demonstrated that CBAVD is generally diagnosed when evaluating infertility with low volume ejaculate and acidic ejaculate pH in men in apparent good health. The mean volume of the testes, reproductive hormones and bilateral epididymal development usually are normal. More than half of patients with CBAVD (54.65%) had seminal vesicle absent/dysplasia. Qualified sperm was easily retrieved from CBAVD males with PESA,

and 86.63% of patients could be successfully retrieved spermatozoa when conducted the first PESA try. Semen parameters in retrieval by PESA are relatively successful and good enough for ICSI. The clinical factors of male with CBAVD were no-impact on fertility outcomes for success or failure of ICSI.

Author contributions

CM and HL designed the study. CM, ZS, JW, BW and HL performed the data collection and analyzed the data. CM wrote the paper.

Ethics approval and consent to participate

This study was approved by the Ethics committee of the Peking Union Medical College Hospital (PUMCH) (project number 2021–25) and conformed to the principles of Good Clinical Practice. Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and materials

Data are available upon reasonable request. If needed during the review process, we could provide datasets to the editor or editorial staff upon request. Please contact lihongjun@pumch.cn.

Consent for publication

All participants and legal guardians (for participants under the age of 18 years) gave written informed consent or assent.

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