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Study on the clinical characteristics, persistent infection capability, and viral load of human papillomavirus type 82 single infection

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Abstract

Background Human papillomavirus (HPV) infection is a key factor in the development of cervical cancer and HPV genotyping is crucial for screening. There are significant differences in the pathogenic potential of the various HPV types. Currently, clinical data on HPV82 are scarce, and the relationship between its viral load, pathogenicity, and persistence is unknown. This study analyzed the characteristics of HPV82 single infection.

Methods Cervical samples were collected to determine the positivity rate of HPV82 and its clinical features in a single infection and examined the association between viral load, persistent infection, and pathogenicity.

Results The positive rate of HPV82 among women attending hospitals for gynecological physical examination or medical consultation was approximately 0.24% (1,033/435,072). Among 335 cases of HPV82 single infection, the number of patients with lesion-free tissue biopsy results, cervical intraepithelial neoplasia (CIN) 1, CIN2, CIN3, and cervical cancer were 263, 42, 11, 18, and one, respectively. A follow-up of 210 patients showed that 21.21% (7/33) of patients with CIN1 progressed to high-grade lesions, whereas 7.34% (13/177) of lesion-free patients progressed to CIN. The viral load in the CIN and cervical cancer group was significantly higher than that in the lesion-free group ($p < 0.001$), and the viral load in the persistent infection group was higher than that in the viral clearance group ($p < 0.001$).

Conclusion The pathogenicity of single HPV82 infection ranks in the middle among high-risk HPV types, and it can lead to cervical cancer, warranting the inclusion of HPV82 in expanded screening for HPV. High viral load is a significant factor that improves the persistent infection ability and pathogenicity of HPV82. Viral load is expected to serve as a screening risk factor for persistent infection and disease progression associated with HPV82.

Keywords HPV, Cervical cancer, CIN, Viral persistence, Viral load

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Introduction

Cervical cancer is the fourth most common cancer in women globally [1]. The high incidence of cervical cancer is closely related to inadequate screening [2]. Persistent infection with the high-risk human papillomavirus (HPV) is a key factor in the development of cervical cancer [3]. Currently, there are more than 20 major high-risk types of HPV, and their carcinogenic abilities vary greatly [4]. Thus, HPV genotyping is crucial for cervical cancer screening and predicting disease progression [5]. To guide the clinical application of HPV genotyping and subsequent research, the International Agency for Research on Cancer has classified the 20 major high-risk HPV types into three groups: "carcinogenic to humans", "probably carcinogenic to humans," and "possibly carcinogenic" [6]. HPV82 has been primarily recognized as a high-risk type, described as having "limited evidence in humans for cervical cancer", and classified as "possibly carcinogenic" [6].

HPV82 is phylogenetically related to other high-risk HPV types, and is originally suspected to be carcinogenic. In vitro molecular experiments have shown that the HPV82 genome may have functions similar to those of other high-risk HPV types [7]. Previous studies on the clinical characteristics of HPV82 have been extremely limited. Although HPV82 has been mentioned in some studies, they often made no distinction between single infections and multiple infections, making it difficult to measure the pathogenicity of HPV82 individually [8, 9, 10]. Additionally, the few studies that involved single HPV82 infections have small sample sizes, lacking sufficient evidence of the correlation between HPV82 and cervical cancer [8, 9, 11].

Viral load is closely associated with the persistence and pathogenicity in virus infections, with higher viral loads often correlating with persistent infection, which is a critical factor in the carcinogenic mechanism of HPV [12]. Therefore, quantitative analysis of the HPV82 viral load could aid in the assessment of its pathogenic potential.

The genotyping detection of HPV has been continuously expanding from initial detection of only HPV16 and HPV18. HPV82 has received increasing attention and has increasingly appeared in commercial detection kits and cervical cancer prevention strategies [13, 14]. However, clinical data on single HPV82 infections remain limited, and research on the relationship between its viral load and clinical characteristics has been almost non-existent, which hinders the application of HPV82-related tests and examinations in cervical cancer prevention. This highlights the necessity of conducting further in-depth research on HPV82. Therefore, this study aimed to investigate the infection characteristics of HPV82 among women attending hospitals for physical examination or medical consultation, examine the pathogenicity of single infections with HPV82, and explore the relationship between viral load, pathogenicity, and persistent infection. The results of this study aim to provide a basis for the development of diagnostic and therapeutic strategies.

Methods

Study population and criteria

(1) Female participants were recruited from the Affiliated Hospital of Zunyi Medical University, Nanchuan Hospital of Chongqing Medical University, Chengdu Huada Hospital, Chongqing Changshou District Traditional Chinese Medicine Hospital, and Chongqing Tongnan Maternal and Child Health Hospital. (2) Samples were collected from January 1, 2014, to December 31, 2023. (3) The inclusion criteria were as follows: female participants attending hospitals for gynecological physical examinations or medical consultations. (4) The exclusion criteria were as follows: women who had undergone total hysterectomy, had no sexual history, had used uterine or vaginal medications/surgeries in the past 3 d, or were currently menstruating.

Sample collection

Female patients underwent gynecological examination, and their samples were collected by gynecologists in the Department of Gynecology. Cervical cells were collected using a cervical swab and preserved in cell preservation solution (Chaozhou Kaipu Biochemical Co., China, catalog number: KJ010). After collection, samples were temporarily stored at 4 °C and were subjected to HPV genotyping within 24 h. The study was approved by the Ethics Committee of Affiliated Hospital of Zunyi Medical University (ZYFYLS2018(81)). Written consents were obtained from patients or their guardians, the study complied with medical ethics norms.

HPV genotyping

An HPV nucleic acid gene typing detection kit (National Medical Device Registration Certificate No. 20143402188, Chaozhou Kaipu Biochemical Co., China; detection limit: 20 copies/reaction; specificity: 100%, catalog number: 06942221700359) was used for nucleic acid extraction and HPV genotyping [15]. This kit allows for the typing of major HPV types (high-risk: HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82; low-risk: HPV 6, 11, 42, 43, 44, 81). All tests were carried out according to the instructions and using the supporting equipment and consumables recommended in the manual. The automatic nucleic acid extractor used for nucleic acid extraction by magnetic bead method was: HBNP-9601 A (Guangdong province Medical Device Registration License No. 20210042, Chaozhou Kaipu Biochemical Co., Ltd.), and the PCR instrument used for real-time

fluorescence PCR was SLAN96P (National Medical Device Registration License No. 20183401659, Shanghai Hongshi Medical Technology Co., Ltd.). Quality control was performed for each batch.

Sample quantification

The human papillomavirus nucleic acid genotyping detection kit (fluorescent PCR method) (National Medical Device Registration Certificate No. 20153400364, Jiangsu BioPerfectus Co., China, detection limit: 20 copies/reaction, specificity: 99.6%. catalog number: JC80301) was used to determine the viral load of HPV82 [16]. This kit employs real-time fluorescent PCR to simultaneously quantify the HPV genome and human housekeeping genes in different reaction tubes [16]. The HPV82 viral load was calculated per 10,000 cells based on the concentration of the housekeeping genes. The automatic nucleic acid extractor used for nucleic acid extraction by magnetic bead method was SSNP-9600 A (Jiangsu province Medical Device Registration License No. 20200158, Jiangsu BioPerfectus Co., Ltd.), and the real-time fluorescence PCR instrument is SLAN96P.

Pathological examination, re-examination, and follow-up

Cross-sectional and follow-up studies were designed following the protocols used in previous studies [17, 18, 19, 20]. HPV82 single infection were selected for the cross-sectional study, with the following exclusion criteria: human immunodeficiency virus infection, use of immunosuppressive medications, or refusal of tissue pathological biopsy. After gynecological colposcopy or pathological ThinPrep™ Pap Test PreservCyt (TCT) examination, patients with abnormalities underwent histopathological examination to distinguish between lesion-free tissue, cervical intraepithelial neoplasia (CIN) grades 1–3, and cervical cancer.

Cervical cancer, CIN3, and CIN2 were considered disease endpoints requiring treatment; therefore, no further follow-up was conducted. CIN1 and lesion-free patients were included during the follow-up period. The inclusion criteria for follow-up were as follows: HPV82-positive women were advised to undergo re-examination and HPV retesting every six months from the initial examination, with follow-up lasting 6–24 months. The exclusion criteria for follow-up were cervical surgery, loss to follow-up, or concurrent high-risk infections.

Data analysis

Data analysis was performed using SPSS version 26.0. Independent sample t-tests were used to compare the means of different groups, and chi-square tests were used to assess differences between categorical data. Statistical significance was set at $p < 0.05$.

Results

HPV82 positivity rate

A total of 435,072 samples were tested with 76,821 positive results. Owing to the presence of multiple infections in some samples, the HPV detection number was 103,608, including 1,033 cases of HPV82. The positive rate for HPV82 among women attending hospitals for gynecological physical examination or medical consultation was approximately 0.24% (1,033/435,072). Among the HPV types detected, the detection rate of HPV82 was 1.00% (1,033/103,608). Of the 1,033 women infected with HPV82, 342 had a single infection. Detailed information of the 342 HPV82 single infections in this study is presented in Supplementary material 1.

Among all the detected types, the detection rates of high-risk types were as follows: HPV52 (18.07%), 16 (11.89%), 58 (10.67%), 53 (8.48%), 39 (6.48%), 51 (5.13%), 68 (4.59%), 56 (3.90%), 18 (3.74%), 33 (3.54%), 66 (3.20%), 59 (2.96%), 31 (2.65%), 35 (1.24%), 82 (1.00%), 45 (0.91%), 73 (0.59%), 26 (0.37%). The detection rate of HPV82 ranked fifteenth among the high-risk types.

Cross-sectional study results

Seven patients refused biopsy after abnormal results from colposcopy and/or TCT; therefore, 335 participants (mean age 39.74 ± 10.53 years, age range 22–74 years) were included in the cross-sectional study. The results showed that 263 patients were lesion-free, 42 had CIN1, 11 had CIN2, 18 had CIN3, and 1 had cervical cancer. The study design is illustrated in Fig. 1.

Follow-up results

In total, 210 patients completed the follow-up (mean follow-up duration 12.46 ± 3.25 months, range 6.90–22.73 months). Among the 42 patients with CIN1, three underwent surgery and six were lost to follow-up. Therefore, 33 patients were included in the analysis: four maintained CIN1, seven progressed to CIN2, and 22 regressed to lesion-free status (with HPV82 becoming negative). Among the 263 lesion-free patients, seven underwent cervical surgery, one had concurrent high-risk infections, 76 were lost to follow-up, and two refused biopsy. Therefore, 177 patients were included in the analysis: 12 progressed to CIN1, one progressed to CIN2, and 164 remained lesion-free (37 had persistent infections and 127 tested negative for HPV82).

The progression rate of patients with CIN1 to more severe cervical lesions (21.21%, 7/33) was significantly higher than that of lesion-free patients (7.34%, 13/177) (relative risk = 2.89, 95% confidence interval = 1.25–6.69, χ^2=6.21, $p = 0.013$).

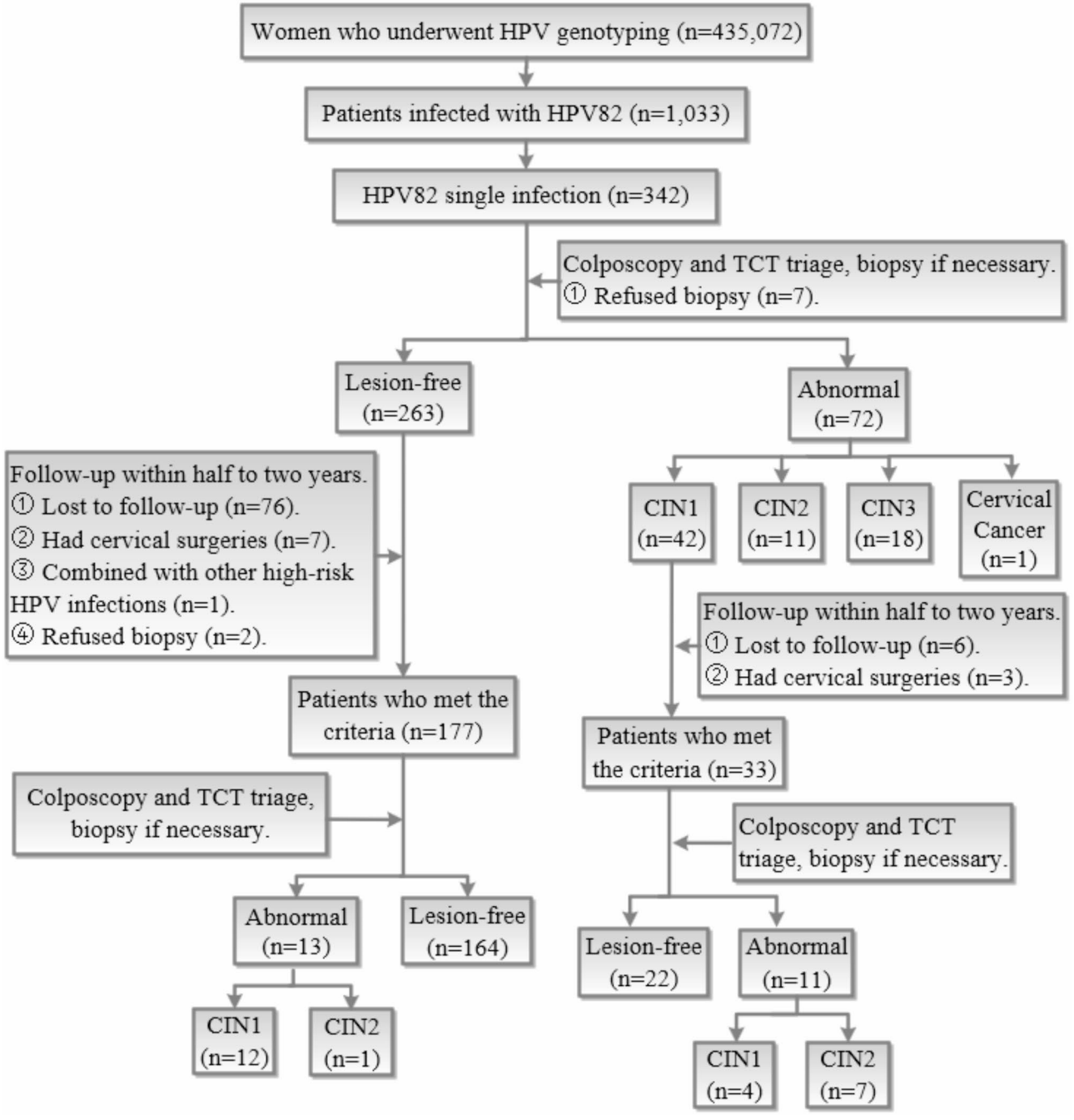

Fig. 1 Study design of HPV82 single infection characteristics. Note: Flow chart representing the details of population recruitment, HPV genotyping, and follow-up till cancer detection. HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia. TCT: ThinPrep™ Pap Test PreservCyt

Viral load comparison

The mean logarithmic value of viral load (units: $\log_{10}$ copies per 10,000 cells) in patients with cervical cancer and CIN was significantly higher (4.41) than that in the lesion-free group (3.90) ($t = 3.79$, $p < 0.001$).

In the follow-up phase, the average log viral load in the progression group (CIN1 progressing to CIN2, lesion-free progressing to CIN1 or CIN2) (4.53) was significantly higher than that in the maintenance and regression group (3.79) ($t = 3.11$, $p = 0.002$).

Furthermore, the log viral load of the persistent HPV82 infection group (4.53) was significantly higher than that of the non-persistent infection group (3.79) ($t = 4.70$, $p < 0.001$).

Discussion

Different HPV types exhibit significant differences in their capacities to promote the development of CIN and cervical cancer. This necessitates tailored follow-up and treatment protocols based on HPV type, which relies on extensive clinical research data [21]. However, the infection rate of HPV82 is low, making it challenging to obtain clinical data on its infections. Although studies on HPV distribution have mentioned HPV82, they often do not distinguish between single and multiple infections. Even when distinctions are made, sample sizes are typically small and there is a lack of follow-up and viral load studies specifically addressing HPV82. Using a multicenter approach with a large sample size, this study identified 335 cases of HPV82 single infection for cross-sectional analysis and obtained follow-up data from 210 patients. The results of this study indicate that the infection rate of HPV82 among women attending hospitals for gynecological physical examinations or medical consultations in Southwest China is low. However, a HPV82 single infection can lead to cervical cancer, and its pathogenic potential is moderate among the high-risk types. Additionally, a positive correlation was confirmed between the HPV82 viral load and its pathogenicity and persistent infection ability.

Different HPV types also show significant distribution differences across various countries and regions, necessitating diagnostic and preventive strategies based on HPV distribution characteristics. The high-prevalence and high-pathogenicity types are focal points for detection and prevention. With advances in technology, HPV screening has expanded from detecting only HPV16 and 18 to including a broader range of HPV types, with HPV82 receiving increasing attention [22]. Numerous studies have highlighted the geographical characteristics of HPV distribution, mainly focusing on commonly known high-risk types such as 16, 18, 33, 52, and 58. In contrast, HPV82, which has a low detection rate, is generally regarded as a rare type, with fewer relevant analyses [23, 24, 25]. In our study, the detection rates of the three most common high-risk types were HPV52 (18.07%), 16 (11.89%), and 58 (10.67%) respectively. The detection rate of HPV82 (1.00%) was far lower than that of the most common high-risk types, ranking fifteenth among all high-risk types, indicating that it is a rare high-risk HPV type across multiple regions. In terms of prevalence, HPV82 may not be a clinically significant type in these regions. However, as more and more types are included in HPV-related testing and examination for cervical cancer prevention, the fact that HPV82 ranks fifteenth still makes it an option worthy of further exploration. What's more, in some areas, HPV82 is very common and warrants attention [26, 27, 28].

Phylogenetic analysis has revealed that HPV82 belongs to the HPV α-5 family and has close relationships with the highly carcinogenic α-7 (represented by HPV18) and α-9 families (represented by HPV16, 33, 52, and 58), placing it in the category of possibly carcinogenic types [6, 20]. HPV51 from the α-5 family has been recognized as a carcinogenic HPV, and HPV82 is most closely related to HPV51 among all HPV types. Previous studies have reported the presence of HPV82 in cervical cancer within the context of mixed infections or without distinguishing between single and multiple infections [8, 9, 10]. However, owing to the limited sample size when differentiating single infections, there is little evidence of a correlation between HPV82 single infections and cervical cancer [8, 9, 11], highlighting the need for more clinical research data on HPV82 single infections. Previous studies have suggested that HPV82 accounts for approximately 0.1% of cervical cancer cases, ranking 20th among the high-risk HPV types, indicating that it results in the minimum number of cancer cases in 20 estimated HPV types [29]. Among carcinogenic HPVs, HPV16 and HPV18 are considered the most pathogenic, followed by HPV31, 33, 45, 52, and 58, whereas, HPV39, 51, 53, 56, and 59 are regarded as lower-risk within the high-risk category [29]. HPV53, a common high-risk type, was estimated in early studies to contribute to approximately 0.5% of cervical cancer cases [29]. Recent research on HPV53 single infections, involving 419 cases, showed no instances of cervical cancer, with a lesion-free cervical condition ratio of 82.3% and a slow progression of cervical lesions post-infection [30]. This cross-sectional study on HPV82 suggests that a HPV82 single infection can lead to cervical cancer, with a notably high proportion of CIN3 among cervical lesions. Follow-up data indicated a high progression rate of persistent HPV82 infections, along with the emergence of high-grade cervical lesions from initially lesion-free conditions. Overall, the pathogenicity of HPV82 was significantly higher than that of HPV53; however, it was still much lower than that of HPV16 [31]. Therefore, HPV82 is characterized as a high-risk HPV with moderate pathogenic potential.

Viral load is a crucial indicator of viral infection, with an elevated viral load potentially increasing both the capacity for persistent infection and pathogenicity [32, 33]. Persistent infections with the same high-risk HPV types are widely accepted to be necessary for the development of CIN and cervical cancer. The longer the duration of persistent infection with a specific high-risk HPV type, the longer the development time of cervical lesions, which likely leads to more severe complications. Higher levels of HPV viral load are associated with greater difficulty in viral clearance, possibly indicating stronger persistent infection capabilities. Additionally, higher viral loads suggest increased viral activity within the host,

which may correlate with enhanced pathogenicity [32, 33, 34]. Theoretically, the HPV viral load could serve as a vital indicator of persistent infection and pathogenicity in high-risk HPV types. Current cross-sectional studies mainly examining the relationship between HPV viral load and cervical disease show that the viral load of α-9 family HPVs increases in correlation with the severity of cervical disease, exhibiting a positive association with more severe cervical lesions. In contrast, the viral load of other high-risk HPV types, such as HPV18, does not show a significant correlation with the severity of cervical lesions [35, 36, 37]. This suggests that the relationship between HPV viral load, persistent infection, and pathogenicity varies across HPV types, warranting specific studies to determine whether viral load can predict disease progression or serve as an auxiliary criterion for assessing cervical disease severity based on certain HPV types. There is limited research concerning the viral load of rare high-risk HPV types, such as HPV82. The results of this cross-sectional study confirmed that the viral load of HPV82 in the CIN group was significantly higher than that in the lesion-free group. Furthermore, during follow-up, the viral load of HPV82 in the persistent infection group was found to be significantly higher than in the HPV82 clearance group. A positive association between HPV82 viral load and disease progression were confirmed, reflecting characteristics similar to that of the α-9 family represented by HPV16.

Conclusion

HPV82 is a rare high-risk HPV type. Its pathogenic potential from a single infection ranks in the middle among high-risk types and can lead to cervical cancer. A high proportion of CIN3 cases was observed in HPV82 single infections. HPV82 should be included in the expanded screening for HPV. High viral load is a significant factor that improves the persistent infection ability and pathogenicity of HPV82. Viral load is expected to serve as a screening risk factor for persistent infection and disease progression associated with HPV82.

Abbreviations

HPV	Human papillomavirus
CIN	Cervical intraepithelial neoplasia
TCT	ThinPrep™ Pap Test PreservCyt

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12985-025-02688-9.

Supplementary Material 1

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Author contributions

ZC, QL, ZD and XZ conceived and designed the study. ZC, QC, XZ, FT, GL, XM, MZ, ZD and QL performed the experiments. ZC, QL, ZD, NL, QC, FT and XZ analyzed the data. ZC, XZ and QL wrote the paper. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Affiliated Hospital of Zunyi Medical University, the approval number was ZYFYLS2018(81). Written informed consents were obtained from all the patients or their guardians. This study was conducted in strict compliance with medical ethics norms.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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