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ORIGINAL RESEARCH

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Clinical efficacy of CO_2 laser therapy combined with photodynamic therapy in male patients with condyloma acuminatum

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Abstract

This study investigated the clinical efficacy of Carbon dioxide (CO_2) laser therapy combined with photodynamic therapy in male patients with condyloma acuminatum. A retrospective analysis was conducted on 120 male patients with genital warts treated at our hospital. Based on different treatment methods, they were divided into a control group and an observation group, each consisting of 60 cases. The control group received CO_2 laser treatment, while the observation group received photodynamic therapy and CO_2 laser treatment. Levels of lymphocyte chemotactic factor (LTN), human beta-defensin-2 (HBD-2), B-cell lymphoma-2 (Bcl-2), interleukin-12 (IL-12), tumor necrosis factor-alpha (TNF-α), T lymphocytes ($CD3^+$), inducible T cells ($CD4^+$), suppressive T cells ($CD8^+$), Male Sexual Function Index (MSFI) scores, Chinese version of the Genital Warts Quality of Life Scale (CECA10) scores, incidence of adverse reactions, recurrence rate, and total treatment effectiveness were compared between groups. After therapy, both groups showed reduced levels of Bcl-2 and TNF-α, but increased levels of IL-12. The observation group had significantly lower Bcl-2, TNF-α and greater IL-12 levels than the control group ($p < 0.05$). After therapy, both groups showed increased levels of $CD3^+$ and $CD4^+$ but lower levels of $CD8^+$ than before treatment. The observation group had significantly greater $CD3^+$ and $CD4^+$ levels, but lower $CD8^+$ levels than the control group ($p < 0.05$). The observation group had significantly higher $CD3^+$ and $CD4^+$ levels and lower $CD8^+$ levels compared to the control group ($p < 0.05$). The incidence of complications in the observation group was significantly lower than in the control group ($p < 0.05$). CO_2 laser therapy combined with 5-aminolevulinic acid photodynamic therapy demonstrates efficacy in treating male genital warts. This therapy can significantly reduce inflammation, improve immune function, and help improve quality-of-life.

Keywords

CO_2 laser therapy; Photodynamic therapy; Male; condyloma acuminatum; Clinical efficacy

1. Introduction

Condyloma acuminatum, commonly known as genital warts, is primarily caused by human papillomavirus infection, which is highly contagious. The primary route of infection is sexual transmission. The anogenital region is the most common site of infection. The clinical manifestations of the disease are pain, local bleeding, pressure, *etc*.

Progression of the disease is associated with an increased risk of cancer [1]. While conventional treatments such as electrocautery, laser therapy, cryotherapy and topical medications demonstrate some efficacy, they are often limited by adverse effects, high recurrence rates, and suboptimal clinical outcomes [2]. CO_2 laser therapy aims to achieve therapeutic effect through irradiation of the affected area. However, it is difficult to achieve the purpose of complete eradication, and it is very easy to have adverse reactions [3]. 5-Aminolevulinic acid photodynamic therapy utilises a specific wavelength of light to activate a photosensitiser, selectively targeting and destroying abnormal proliferative cells while sparing healthy tissue. This therapy is a unique, non-invasive treatment option. Upon exposure to light of the appropriate wavelength, the photosensitiser within the target tissue generates reactive oxygen species, primarily singlet oxygen. Compared to earlier photodynamic therapies, the use of 5-aminolevulinic acid has substantial advantages in terms of both dependability and originality. At present, the clinical efficacy of CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy for the treatment of this disease has been reported, but there are relatively few reports on the treatment of male patients [4].

We investigated the clinical efficacy of CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy in 120 male patients with condyloma acuminatum treated at our hospital.

2. Information and methods

2.1 General information

A retrospective analysis was conducted on 120 male patients with genital warts admitted to our hospital between January 2021 and December 2022. The patients were divided into a control group and an observation group based on different treatment methods, with 60 patients in each group. The average age of the control group was 42.95 ± 16.07 years; the average disease duration was 1.68 ± 0.54 years. The average age of the observation group was 39.53 ± 17.34 years; the average disease duration was 1.72 ± 0.52 years. Baseline characteristics did not differ significantly between groups ($p > 0.05$).

2.2 Inclusion and exclusion criteria

Inclusion criteria: ① all showed clinical symptoms such as bleeding, odor, itching, *etc.*; ② the diameter of a single wart at the urethral opening ranges from 2.0 cm to 5.0 cm; ③ psychological dysfunction; ④ all signed the informed consent form.

Exclusion criteria: ① immune system disorders; ② allergy to the drugs used in this study; ③ mental dysfunction; ④ patients with serious organ function abnormalities; ⑤ patients with cognitive dysfunction; ⑥ patients with cardiovascular disease; ⑦ malignant tumor disease; ⑧ patients who withdrew during the study.

2.3 Methods

Patients were advised to abstain from sexual activity during treatment, maintain a healthy diet and avoid alcohol consumption.

2.3.1 Control group

CO_2 laser treatment: Local anesthesia was administered preoperatively using lidocaine. Following delineation of the treatment area, disinfection was performed using 0.5% iodine tincture. The CO_2 laser treatment was applied with a wavelength of 10.6 μm and a maximum power of 22.4 W ± 10%. After identifying the wart location, coagulation and vaporization were performed, including coagulation and vaporization of skin and mucous membranes that tested positive for acetic acid, until the basal damage was within a 2 mm range. Postoperatively, an antibiotic ointment was applied to prevent infection. Once the wound healed, Imiquimod cream (Manufacturer: Zhuhai Federal Pharmaceutical Co., Ltd., Zhongshan Branch, National Medicine Standard H20040283, Specification: 0.25 g:12.5 mg, Chengdu, Sichuan, China) was applied.

2.3.2 Observation group

In addition to the CO_2 laser treatment, 5-aminolevulinic acid photodynamic therapy was administered. The damaged skin area was identified, and 20% 5-aminolevulinic acid moisturizing gel was administered topically, covering an area larger than the lesion. After application, the area was immediately covered with plastic wrap and uncovered after 180 minutes. Following exposure of the lesion, photodynamic therapy was administered using a light source with the following parameters: irradiance of 80 mW/cm^2, wavelength of 633 ± 10 nm, spot diameter of 3 cm, and irradiation time of 30 minutes per spot. Treatment was performed once a week, with intervals of 6 days between treatments, for a total of 3 sessions.

2.4 Observation indicators

(1) Before and after treatment, 3 mL of venous blood was drawn in the morning (8:00–10:00), patients were instructed to fast before blood sample collection and maintain the fasting state, after blood collection. After centrifuging the blood for 10 minutes at 3000 rpm, 12 cm of radius, and −20 °C to retain the supernatant, the sample was ready for analysis—detection index: LTN, HBD-2; detection method: enzyme immunoassay.

(2) The levels of Bcl-2, interleukin-12 (IL-12), and tumor necrosis factor-α (TNF-α) were measured before and after treatment in both groups, and the method of blood sample collection and centrifugation were the same as mentioned in (1). The detection method was an enzyme-linked immunoassay.

(3) Flow cytometry was employed to assess immune function in both groups before and after treatment, measuring the percentages of $CD3^+$ T lymphocytes, $CD4^+$ T helper cells, and $CD8^+$ suppressor T cells.

(4) The two groups were compared for the incidence of adverse reactions, including edema, scarring and mucosal damage.

(5) The Male Function Inventory (MSFI) and the Chinese version of the Acromegaly Quality of Life Assessment Scale (CECA10) were administered before and after treatment. The MSFI has a total of 44 points, with higher scores indicating better sexual function; the CECA10 has a score of 10–50 points, and the score is positively proportional to the quality of life.

(6) Recurrence rates were compared between the two groups.

(7) Following World Health Organization (WHO) diagnostic criteria for sexually transmitted infections [5], the overall effectiveness rate of the two groups was compared. If the wart area was reduced by more than 60% and there was no recurrence upon follow-up, it was considered effective. If the wart area was reduced by more than 20% but less than 60% after treatment, it was considered partially effective. If the wart area was reduced by less than 20% after treatment, it was considered ineffective. The overall effectiveness rate is calculated as 1 − (ineffective cases/total cases) × 100%.

2.5 Calculation of sample size

Based on preliminary research results, the changes in CECA10 scores for the observation group and the control group were 19.35 ± 1.65 and 9.65 ± 0.95 points, respectively, with an effect size of 0.82. Using the two-sample *t*-test (assuming unequal variances) in PASS 15.0 software (International Business Machines Corporation, Armonk, NY, USA), the sample size was calculated with a two-sided significance level of α =

0.05 and a power of $1 - p = 0.9$. To maintain group balance, the calculated sample size was 50 per group. Considering an approximate dropout rate of 10%, this study enrolled 60 patients per group to meet the clinical research requirements.

2.6 Statistical methods

Data were analyzed using SPSS 27.0 (International Business Machines Corporation, Armonk, NY, USA). Measurement data conforming to a normal distribution were described as ($\bar{x} \pm s$), while those not conforming to a normal distribution were described using the median (quartiles) [M (Q1, Q3)]. Comparisons were made using *t*-tests for normally distributed data and rank-sum tests for non-normally distributed data. Categorical data were described by frequency and percentage (n (%)) and compared between groups using chi-square tests. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Comparison of LTN and HBD-2 levels between the two groups

As shown in Table 1, both LTN and HBD-2 levels were significantly elevated following treatment in both groups ($p < 0.05$). Notably, the observation group exhibited significantly higher levels of these markers compared to the control group ($p < 0.05$).

3.2 Comparison of Bcl-2, IL-12 and TNF-α levels between the two groups

As shown in Table 2, there was a significant difference ($p < 0.05$) between the mean values of Bcl-2, TNF-α and IL-12 in the two groups after treatment, compared to their pre-treatment values. Furthermore, significant differences were observed in IL-12, Bcl-2 and TNF-α levels between the observation and control groups.

3.3 Comparison of cellular immune function index levels between the two groups

As shown in Table 3, there was a significant difference ($p < 0.05$) between the two groups' $CD3^+$, $CD4^+$ and $CD8^+$ levels before and after treatment. Moreover, the observation group's $CD3^+$ and $CD4^+$ levels were higher than those of the control group, and its $CD8^+$ levels were lower.

3.4 Comparison of the incidence of adverse reactions between the two groups

As shown in Table 4, the observation group experienced a significantly lower complication rate compared to the control group ($p < 0.05$).

3.5 Comparison of sexual function and CECA10 scores of the 2 groups

As shown in Table 5, after treatment, the sexual function and CECA10 scores of the 2 groups were higher than those before treatment, and the observation group was higher than that of the control group, and the difference was significant ($p < 0.05$).

3.6 Comparison of the total effective rate and recurrence rate between the two groups

As shown in Table 6, the observation group exhibited a significantly higher total effective rate (96.67%) compared to the control group (83.33%), while also demonstrating a significantly lower recurrence rate (3.33% *vs.* 15.00%). The total effective rate of the observation group was higher than that of the control group, and the recurrence rate of the observation group was lower than that of the control group, with a significant difference ($p < 0.05$).

4. Discussion

Condyloma acuminatum causes proliferative lesions in the pharynx, perianal area, genitals and other parts of the body, which are dominated by small DNA viruses [6]. Globally, an estimated 30 million new cases of condyloma acuminatum occur annually, including an estimated 150,000 cases in China annually. Condyloma acuminatum is highly prevalent, ranking second among sexually transmitted infections [7]. Human papillomavirus infection is the primary cause of this disease, leading to papillomatous proliferation in areas such as the genital and anal regions. Despite the availability of treatments, condyloma acuminatum is characterized by a high recurrence rate. Research has found that among patients with genital warts, 40% to 60% of male patients experience recurrence within 3 months after treatment, with warts having a diameter of ≥5.0 cm [8]. Due to the disease's covert nature and its impact on sexual function, most patients experience significant psychological stress, which severely affects their quality of life. Clinical treatment primarily focuses on local removal

TABLE 1. Comparison of LTN and HBD-2 between the two groups ($\bar{x} \pm s$).

Group	LTN (pg/mL)		HBD-2	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 60)	278.45 ± 26.12	311.59 ± 30.78	123.36 ± 11.48	147.55 ± 13.46
Observation group (n = 60)	278.69 ± 26.34	418.37 ± 40.71	123.28 ± 11.57	171.29 ± 16.44
t	0.050	16.206	0.038	8.655
p (Between groups)	0.960	<0.001	0.970	<0.001

Note: Compared to before treatment within the group, $p < 0.05$. LTN: lymphocyte chemotactic factor; HBD-2: human beta-defensin-2.

TABLE 2. Comparison of Bcl-2, IL-12 and TNF-α between the two groups ($\bar{x} \pm s$).

Group	Bcl-2		IL-12 (pg/mL)		TNF-α (pg/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 60)	8.24 ± 0.71	7.01 ± 0.65	55.43 ± 4.48	64.79 ± 5.39	297.67 ± 28.81	98.89 ± 8.81
Observation group (n = 60)	8.35 ± 0.74	4.57 ± 0.41	55.56 ± 4.72	75.73 ± 6.19	297.38 ± 28.57	122.26 ± 11.69
t	0.831	24.593	0.155	10.324	0.055	12.367
p (Between groups)	0.408	<0.001	0.877	<0.001	0.956	<0.001

Note: Compared to before treatment within the group, $p < 0.05$. Bcl-2: B-cell lymphoma-2; IL-12: interleukin-12; TNF-α: tumor necrosis factor-alpha.

TABLE 3. Comparison of cellular immune function indexes between the two groups ($\bar{x} \pm s$).

Group	$CD3^+$		$CD4^+$		$CD8^+$	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 60)	58.49 ± 5.48	62.29 ± 6.15	28.89 ± 2.54	33.67 ± 3.62	31.11 ± 3.47	29.86 ± 2.49
Observation group (n = 60)	58.29 ± 5.61	68.87 ± 6.94	28.57 ± 2.52	40.22 ± 4.83	31.62 ± 3.38	26.51 ± 2.43
t	0.198	5.497	0.693	8.406	0.816	7.458
p (Between groups)	0.844	<0.001	0.490	<0.001	0.416	<0.001

Note: Compared to before treatment within the group, $p < 0.05$. $CD3^+$: T lymphocytes; $CD4^+$: inducible T cells; $CD8^+$: suppressive T cells.

TABLE 4. Comparison of the incidence rate of adverse reactions between the two groups (n, (%)).

Group	Number of cases	Edema	Scarring	Mucous Membrane Injury	Incidence rate
Control group	60	3 (5.00)	4 (6.67)	2 (3.34)	9 (15.01)
Observation group	60	1 (1.67)	1 (1.67)	0 (0.00)	2 (3.34)
χ^2					4.904
p (Between groups)					0.027

TABLE 5. Comparison of sexual function and quality of life scores between the two groups ($\bar{x} \pm s$, points).

Group	Sexual Function		CECA10 Score	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n = 60)	41.23 ± 4.47	60.38 ± 6.41	22.26 ± 2.87	32.39 ± 3.27
Observation group (n = 60)	41.36 ± 4.15	74.46 ± 7.17	22.16 ± 2.57	39.83 ± 3.55
t	0.165	11.340	0.201	11.940
p (Between groups)	0.869	<0.001	0.841	<0.001

Note: Compared to before treatment within the group, $p < 0.05$. CECA10: Chinese version of the Genital Warts Quality of Life Scale.

TABLE 6. Comparison of total effective rate and recurrence rate between the two groups (n, (%)).

Group	Number of cases	Effective	Effective	Ineffective	Total Effective Rate	Recurrence Rate
Control group	60	14 (23.33)	36 (60.00)	10 (16.67)	50 (83.33)	9 (15.00)
Observation group	60	35 (58.33)	23 (38.34)	2 (3.33)	58 (96.67)	2 (3.33)
χ^2					5.926	4.904
p (Between groups)					0.015	0.027

of lesions and boosting the body's immune response. This paper aims to analyze the effects and objectives of combining CO_2 laser therapy with 5-aminolevulinic acid photodynamic therapy in treating male patients with genital warts, specifically addressing issues related to inflammation and decreased immune function.

CO_2 laser therapy uses far-infrared technology with a high energy density. It works by irradiating the warts, converting the energy into heat, which raises the temperature at the treatment site and burns the diseased tissue [9]. This therapy is easy to cause wart surface damage when irradiated, increasing the risk of infection. Photodynamic therapy mainly produces cytotoxicity under the action of single-linear oxygen, damaging abnormally active cells to cause apoptosis, and then achieving the therapeutic purpose. This therapy exhibits strong specificity, enabling rapid identification and destruction of virus-infected tissue, viral load reduction, and lesion elimination [10]. 5-amino ketoglutaric acid photodynamic therapy is a new technology of clinical photodynamic therapy, which can have a therapeutic effect on the proliferative lesion tissue. To accomplish the therapeutic goal, the photosensitizer 5-amino ketoglutaric acid is used in conjunction with light sources and devices to create damage to the lesion tissue. This destruction process is highly selective [11].

The body's immune cells are the main cells that secrete chemokines, and in the transfer of inflammatory cells, chemokines can participate in the transfer process and induce the activation of leukocytes. Chemokines are implicated in numerous immune processes, such as pathogen infection, inflammatory response, trauma repair and other immune processes [12]. LTN is secreted by immune cells, which can influence the immune system and regulate the balance of the system. HBD-2 belongs to the β-defensin, which has a strong inducing effect, can regulate the immune response, and has the functions of antiviral and bactericidal effects [13]. In this study, it was found that the comparison of LTN and HBD-2 index levels between the two groups was higher in the observation group, indicating that CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy can effectively regulate the levels of LTN and HBD-2 indexes as a way to improve the immune function. The main reason is that CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy can quickly regulate the balance of the immune system, play a bactericidal, and antiviral effect, accelerate the wound repair, and prompt the immune cells to secrete LTN, HBD-2, and thus improve the levels of TN, and HBD-2 indicators.

This study found that by comparing the Bcl-2, IL-12 and TNF-α levels of the two groups, the improvement of the observation group was more significant, indicating that CO_2 laser combined with 5-amino ketoglutaric acid photodynamic therapy can play a stronger role in improving the levels of Bcl-2, IL-12 and TNF-α indexes, to enhance the immunoregulation. CO_2 laser resection of lesions followed by 5-aminolevulinic acid photodynamic therapy can play a strong role in inducing apoptotic proteins around the cells by reducing the content of Bcl-2, thereby lowering the level of this indicator and prompting the rapid apoptosis of condyloma acuminatum cells, which is closely related to the role of mitochondria and the death receptor mediation. This variation may be attributed to the differing levels of humoral and cellular immunity observed in patients with condyloma acuminatum [14]. Some scholars have found that 5-amino ketoglutaric acid photodynamic therapy can change IL-12 and TNF-α levels [15].

This study demonstrated a significantly higher total effective rate and a lower recurrence rate in the observation group compared to the control group, indicating that CO_2 laser combined with 5-amino ketoglutaric acid photodynamic therapy could reduce the recurrence and improve the therapeutic effect. The primary cause is that normal tissue does not sustain as much damage, has fewer negative reactions, and heals quickly when CO_2 laser photodynamic therapy is paired with 5-aminolevulinic acid photodynamic therapy. Within normal cells, 5-aminolevulinic acid is metabolized into protoporphyrin IX via the haem biosynthesis pathway. During the treatment period, the lesion tissues continuously absorb 5-aminolevulinic acid. At the same time, the content of protoporphyrin IX is rapidly increased in the lesion cells due to the inability of the abnormal proliferating cells to convert hemoglobin [16]. Upon light activation, this photosensitive compound transitions to an excited state, increasing the levels of reactive oxygen species and singlet oxygen. This intensifies the damage to the cellular structure of the lesion, inducing apoptosis and thereby improving the therapeutic effect [17]. At the same time, due to the tendency of porphyrin IX to aggregate, it can accumulate in the lesion tissue, leading to apoptosis of the diseased cells and helping to reduce the recurrence rate.

T lymphocytes are important effector cells in cell-mediated immunity and can accurately reflect immune function while effectively regulating immune responses. In a normal population, these cells are in a balanced state. However, during viral infections, T lymphocyte subgroups become disordered, making it difficult to establish an immune regulation mechanism. $CD3^+$ cells provide essential support and contribute to the induction of suppressor T lymphocytes (Ts cells), reflecting the state of cell-mediated immunity. The cellular immune system is accurately reflected by $CD4^+$ cells, and tracking alterations in T lymphocyte subsets can aid in determining how a disease is progressing. Research has found that $CD8^+$ cells, which secrete inhibitory factors, have a strong suppressive effect on immune responses. This study found that compared to the control group, the observation group had higher levels of $CD3^+$ and $CD4^+$ and lower levels of $CD8^+$, indicating that CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy significantly improves immune function. This finding is consistent with foreign research [18] which observed that in male patients with genital warts, the combined treatment group had better immune function than the control group ($p < 0.05$).

CO_2 laser can effectively regulate T cell immune responses by vaporizing wart tissue at high temperatures, thereby enhancing immune defense capabilities. Since the recurrence rate of genital warts is closely related to immune function, a decrease in recurrence rate is associated with a significant improvement in immune function. 5-aminolevulinic acid photodynamic therapy rapidly destroys diseased cell tissues, induces apoptosis, and damages the blood vessels of the lesions, thereby achieving therapeutic effects. This therapy has minimal adverse reactions, is easy to perform, and has high

reproducibility, which helps to reduce recurrence rates and improve immune function.

Patients in the observation group exhibited significantly improved sexual function and quality of life, as evidenced by higher CECA10 scores, compared to the control group. This improvement is primarily due to the fact that 5-aminolevulinic acid, with its strong hydrophilicity, generates singlet oxygen upon irradiation, increasing the content of oxygen free radicals, which leads to cellular damage and targets the diseased cells. While this therapy causes significant damage to the diseased tissue, it does not cause substantial harm to the surrounding normal tissue and has low toxicity, resulting in minimal damage to the body.

During treatment, the use of deeply penetrating laser can prevent damage to the body, which helps improve sexual function and quality of life. This study shows that the incidence of adverse reactions was lower in the observation group compared to the control group, indicating that the combined therapy of CO_2 laser and 5-aminolevulinic acid photodynamic therapy has fewer adverse reactions and higher safety, reducing treatment risks for patients. This provides valuable data for clinical treatment and has a positive impact on future clinical research and applications. Photodynamic therapy, as a relatively novel treatment method, shows significant potential prospects in the treatment of genital warts due to its ability to generate singlet oxygen and other reactive oxygen species under specific wavelengths of laser light.

This study included 120 patients, all of whom had chronic diseases and were treated with CO_2 laser combined with 5-aminolevulinic acid photodynamic therapy, requiring regular treatments. However, each treatment differed slightly, and anxiety during treatment periods reduced the number of cases. This study focuses solely on treatment modalities and their efficacy on condyloma acuminatum, without comprehensive analysis of its diverse subtypes. Future research should prioritize larger sample sizes, incorporate objective evaluation indicators for prospective symptomatic analysis, and explore diverse condyloma acuminatum subtypes to enhance treatment precision and patient outcomes.

5. Conclusions

In summary, the combination of CO_2 laser and 5-aminolevulinic acid photodynamic therapy shows significant efficacy in treating male genital warts. It has a favorable impact on patients' inflammatory responses and immune function, rapidly alleviates inflammation, enhances immune function, and helps prevent recurrence. This approach has potential for widespread application.

AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

AUTHOR CONTRIBUTIONS

YHW—designed the study and carried them out. YHW, LJL, CLZ, HL and SFW—supervised the data collection, analyzed the data, interpreted the data. YHW and SFW—prepared the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Qingyuan County People's Hospital (Approval no. 202403) and the Ethics Committee of Lishui Central Hospital (Approval no. 2024272). Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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