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Effect of Mitochondrial Function of Ovarian Granulosa Cells on *In Vitro* Fertilization and Embryo Transfer Outcomes in Obese Polycystic Ovary Syndrome Patients

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Abstract: *Objective:* To investigate the effect of abnormal ovarian granulosa cell metabolism on *in vitro* fertilization and embryo transfer (IVF-ET) outcomes in obese polycystic ovary syndrome (PCOS) patients. *Methods:* Patients with PCOS who met the study criteria were screened according to the inclusion criteria. A total of 32 patients with obese PCOS were recruited into the study group, and 39 patients with non-obese PCOS were recruited into the control group. The general data (age, body mass index, and years of infertility), insulin resistance index (HOMA-IR), follicle-stimulating hormone (FSH), luteinizing hormone (LH), granulosa cell mitochondrial function, and IVF-ET outcome of patients in the study group and control group were retrospectively analyzed. *Results:* The differences in age and years of infertility between the study group and the control group were insignificant ($P > 0.05$), and the body mass index (BMI) of the study group and control group was 30.5 ± 1.24 kg/m^2 and 22.3 ± 1.12 kg/m^2, respectively, in which the difference was statistically significant ($P < 0.05$); the HOMA-IR of the study group was significantly higher than that of the control group ($P < 0.05$); the reactive oxygen species (ROS) in the study group was significantly higher than that in the control group ($P < 0.05$), and the ATP content in the study group was significantly lower than that in the control group ($P < 0.05$); comparing the FSH and LH levels between the two groups, the difference was not statistically significant ($P > 0.05$); the rate of IVF-ET failure was significantly higher in the study group than in the control group. *Conclusion:* PCOS is a complex endocrine disorder, and obesity is one of the independent risk factors for the development of PCOS.

Keywords: Polycystic ovary syndrome; Mitochondrial function; Ovarian granulosa cell; *In vitro* fertilization and embryo transfer

Online publication: April 17, 2023

1. Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by oligo-ovulation or anovulation, polycystic ovarian changes, hyperandrogenemia, and/or hyperinsulinemia, and it is a common cause of infertility. Obesity (body mass index ≥ 30 kg/m^2) is an independent risk factor for PCOS and is strongly associated with the clinical outcomes in patients with PCOS; weight gain and increased risk of obesity-related diseases have been reported in patients with PCOS. Due to abnormal ovarian function in patients with PCOS, patients with fertility requirements are usually treated clinically by *in vitro* fertilization and embryo transfer (IVF-ET); however, the incidence of IVF-ET failure in patients with PCOS is as high

as 30%–50%. It is now believed that endocrine disruption in PCOS patients in IVF-ET can affect IVF-ET outcomes by affecting granulosa cell mitochondrial function [1-6]. It has been shown that abnormal mitochondrial function is associated with decreased ovarian reserve and granulosa cell apoptosis due to abnormal mitochondrial function plays an important role in the development of PCOS [7]. However, no studies related to obesity and abnormal mitochondrial function in ovarian granulosa cells of PCOS patients have been reported in literature. Therefore, we intend to analyze the relationship between obesity and abnormal ovarian granulosa cell mitochondrial function in patients with PCOS and provide new ideas to improve IVF-ET outcomes in PCOS patients.

2. Data and method

2.1. General data

Patients with PCOS who met the study criteria were screened according to the inclusion criteria. The exclusion criteria included (1) presence of endometriosis, endometrial lesions, or ovarian tumors; (2) presence of insulin resistance or hyperinsulinemia; (3) family history of tumors; and (4) a history of PCOS-related diseases. A total of 32 patients with obese PCOS who met the criteria were recruited into the study group, and 39 women with non-obese PCOS, who were outpatients and hospitalized during the same period, were recruited into the control group.

2.2. Methods

(1) All study subjects were tested by drawing venous blood on the 5th day of menstruation, and urine specimens were collected for biochemical analysis. General clinical data and laboratory indices were recorded, and BMI was calculated using the formula.

(2) Controlled ovarian hyperstimulation (COH) was performed using the standard long protocol in all participants. Pituitary descending regulation was routinely started at mid-luteal phase (18–21 d of menstruation) with the administration of gonadotropin-releasing hormone agonist (GnRH-a) Diphereline (IpsenPharma Biotech, France) 0.05 mg/d or 0.1 mg/d subcutaneously. Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) levels were measured after 10–14 days of dosing, and follicle development was monitored by vaginal ultrasound. When FSH < 5 mIU/mL, LH < 5 mIU/mL, E2 < 50 pg/mL, and sinus follicle diameter < 5 mm, meeting the criteria for downregulation, ovulation treatment was started with recombinant human gonadotropin (Gonal-f, Merck Serono, Switzerland) 150-300 IU/d subcutaneously. Based on the patient's age, BMI, antral follicle count (AFC) of both ovaries, and anti-Müllerian hormone (AMH), basal FSH and LH were used to determine the starting dose and medication time of gonadotropin (Gn). Serum LH, E2, and progesterone (P) levels, as well as follicle and endometrial development were monitored regularly during the dosing period, and the dose was adjusted according to the hormone levels and follicle development. Gn was discontinued when 60%–70% of follicles ≥ 18 mm or ≥ 14 mm in diameter or 40%–50% of follicles ≥ 20 mm or ≥ 14 mm in diameter and 200–300 pg/mL of serum E2/14 mm follicles were measured in both ovaries, and 250 μg of recombinant human chorionic gonadotropin (rhCG, Ovidre, Merck Serono Switzerland) was injected subcutaneously at around 2100 hour on the same night. Vaginal ultrasound-guided ovulation was performed 36 hours later. Patients' blood and follicular fluid were collected, fasting plasma insulin concentration was measured, luteinized granulosa cells were extracted, and the corresponding kits were used to detect and assess granulosa cell mitochondrial function (*e.g.*, adenosine triphosphate [ATP] content and reactive oxygen species [ROS] levels).

2.3. Observational index

The general clinical data, including age, BMI, and years of infertility, were compared and analyzed between

the two groups; FSH, LH, insulin resistance index (HOMA-IR), granulosa cells mitochondrial function, and IVF-ET outcomes were compared and analyzed between patients in the study group and the control group.

2.4. Statistical analysis

All data in this study were processed using SPSS 22.0 statistical software. Measurement data were expressed by mean ± standard deviation (s) and tested by t test; counting data adopted rate (%) to express and were tested by chi-squared test (χ^2).

3. Results

3.1. Comparison of clinical data between the two groups

The differences in age and years of infertility between the study group and the control group were insignificant ($P > 0.05$). The BMI of the control group (22.3 ± 1.12 kg/m^2) was lower than that of the study group (30.5 ± 1.24 kg/m^2), and the difference was statistically significant ($P < 0.05$). **Table 1** shows the comparison of clinical data between the two groups.

Table 1. Comparison of clinical data between the two groups

Group	Age (years)	Years of infertility (years)	Body mass index (kg/m^2)
Control group (n = 39)	24.3 ± 2.12	3.3 ± 1.13	22.3 ± 1.12
Study group (n = 32)	26.3 ± 2.12	3.4 ± 1.22	30.5 ± 1.24
t	1.232	1.469	8.234
P	> 0.05	> 0.05	< 0.05

3.2. Comparison of mitochondrial function in granulosa cells between the two groups

ROS in the study group was significantly higher than that in the control group ($P < 0.05$). The ATP content in the study group, compared with the control group, was significantly lower than that in the control group ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of mitochondrial function in granulosa cells between the two groups

Group	ATP (pmol/mg)	ROS (DCF fluorescence intensity)
Control group (n = 39)	1.64 ± 0.34	27,339 ± 4,684
Study group (n = 32)	0.35 ± 0.04	46,825 ± 5,352
t	11.232	11.369
P	< 0.05	< 0.05

Abbreviations: ATP, adenosine triphosphate; DCF, dichlorofluorescein; ROS, reactive oxygen species.

3.3. Comparison of *in vitro* fertilization and embryo transfer outcomes between the two groups

The FSH and LH levels in IVF-ET cycles between obese and non-obese individuals were not statistically significant ($P > 0.05$); HOMA-IR was significantly higher in the study group than in the control group ($P < 0.05$); and the rate of IVF-ET failure was significantly higher in the study group than in the control group ($P < 0.05$), as shown in **Table 3**.

Table 3. Comparison of IVF-ET outcomes between the two groups of patients

Group	FSH (u/L)	LH (mIU/ml)	Failure rate of IVF-ET (n, %)	HOMA-IR (mU/L)
Control group (n = 39)	8.3 ± 2.12	15.3 ± 1.12	2 (5.13)	0.36 ± 0.06
Study group (n = 32)	6.3 ± 2.12	14.3 ± 1.22	9 (24.13)	0.89 ± 0.12
t	1.232	1.369	8.234	6.987
P	> 0.05	> 0.05	< 0.05	< 0.05

Abbreviations: FSH, follicle-stimulating hormone; HOMA-IR, insulin resistance index; IVF-ET, *in vitro* fertilization and embryo transfer; LH, luteinizing hormone.

4. Discussion

Infertility is defined as the absence of pregnancy after more than 12 months of regular unprotected intercourse. Infertility is a major global reproductive health problem with an incidence of 10%–15%. Anovulation is an important cause of infertility in women, in which PCOS is the second leading cause after tubal infertility. PCOS is the most important disease related to reproductive endocrine and metabolic disorders in Chinese women of reproductive age, and its prevalence rate is 5%–10%, with a gradually increasing trend. In PCOS, the follicles are in a state of abnormal development, mainly due to follicle over-recruitment, dominant follicle selection disorder, and pre-ovulation follicle failure. These problems can cause ovarian dysfunction, which in turn can affect pregnancy outcomes. However, we have found that the quality of eggs obtained and embryos formed in infertile PCOS patients is reduced during IVF, resulting in low fertilization rates, low pregnancy rates, and high miscarriage rates. Therefore, there is an urgent scientific need to investigate how to improve the quality of eggs and embryos by improving the clinical symptoms of PCOS, thus increasing the success rate of IVF-ET.

Granulosa cells play an important role in the development, maturation, fertilization, and embryonic development of oocytes, which require large amounts of ATP to provide energy. When granulosa cells surround oocytes, they not only affect the cytoplasmic maturation of oocytes during follicular development, but also complete the response to gonadotropin through their own unique FSH and LH receptors, as well as participate in the maturation promoting effect of gonadotropin on oocyte nucleus. Data from several studies have suggested that abnormal ovarian granulosa cell function is closely associated with abnormal folliculogenesis in PCOS. Obesity increases the degree of sex hormone disorders and metabolic dysfunction, which may have an impact on reproductive performance in obese women. Fat cells secrete cytokines that contribute to a pro-inflammatory state and the initiation of oxidative damage. In this study, the mitochondrial function of ovarian granulosa cells in obese PCOS patients and non-obese PCOS patients was analyzed, and it was found that the mitochondrial function of ovarian granulosa cells in obese PCOS patients was significantly lower than that in non-obese PCOS patients. Abnormal mitochondrial function is a common mechanism in the occurrence and development of various metabolic diseases. Obesity may lead to the disturbance of cell energy metabolism by causing insulin resistance and hyperinsulinemia, thus resulting in abnormal mitochondrial function and affecting the metabolism and development of granulosa cells [8-11]. In addition, obesity may also lead to impaired function of post-insulin receptor signaling pathway, thus inducing hyperinsulinemia and insulin resistance. This may be related to the pathogenesis of PCOS and follicle maturation disorder. Some studies have shown that in obese PCOS patients, mitochondrial function abnormalities can be found in some of these patients by observing the morphology of granulosa cells and the insulin level in culture medium. Mitochondria are important sites for energy metabolism and substance metabolism in cells. Cell metabolism disorders caused by obesity and hyperinsulinemia may lead to mitochondrial dysfunction and affect the development process of granulosa cells. Animal model studies have demonstrated that high-fat diet can induce the overgrowth and abnormal expression of mitochondrial

proteins in mouse ovarian granulosa cells as well as granulosa cell apoptosis. This study found that the mitochondrial function of ovarian granulosa cells in obese PCOS patients decreased, which may interfere with oocyte development and ultimately affect the outcome of IVF-ET [12-15]. However, due to the small sample size of this study, there may be statistical errors.

In the present study, human luteinized ovarian granulosa cells were extracted, and the corresponding kits were used to detect and assess granulosa cell mitochondrial function (*e.g.*, ATP content and ROS levels) as well as to analyze the correlation with IVF-ET outcomes. We found that obesity affects ovarian granulosa cell mitochondrial function in PCOS patients and may be associated with abnormal ovarian function and reproductive endocrine disorders in PCOS patients. We also analyzed the possible factors involved in the high follicular rate and low embryo quality in infertile PCOS patients. There was a limitation due to the small sample size; thus, further expansion of the sample size is needed. Meanwhile, relevant animal experiments can be conducted to further investigate the mechanisms related to follicular development and maturation.

In conclusion, PCOS is a complex endocrine disorder, and obesity is one of the independent risk factors in its development.

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Disclosure statement

The authors declare no conflict of interest.

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Correlation Analysis of Traditional Chinese Medicine Syndrome Types and Influencing Factors of Asthmatic Bronchitis in Children

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Abstract: *Objective:* To explore the correlation between traditional Chinese medicine (TCM) syndrome types and the influencing factors of asthmatic bronchitis in children, as well as to provide clinical syndrome differentiation basis and reference for the treatment of children with asthmatic bronchitis. *Methods:* The clinical data of 197 inpatients with asthmatic bronchitis in our hospital from March 2021 to March 2022 were collected, referring to "Zhu Futang Practical Pediatrics" (7th Edition, 2002) and "Chinese Medicine Industry Standards – Standards for Diagnosis and Efficacy of Pediatric Diseases and Syndromes of Traditional Chinese Medicine" (1994, State Administration of Traditional Chinese Medicine) for diagnosis, classification, and analysis of TCM syndrome types and the influencing factors of asthmatic bronchitis in children. *Results:* (i) cold asthma syndrome contributed to the majority of TCM syndrome types of pediatric asthmatic bronchitis; (ii) gender had a great influence on TCM syndromes types in children with asthmatic bronchitis, and the differences among the TCM syndrome types were statistically significant ($P < 0.05$); (iii) there was no significant difference in the distribution of TCM syndrome types of pediatric asthmatic bronchitis among different age groups ($P > 0.05$); (iv) birth status had no effect on the distribution of TCM syndrome types of pediatric asthmatic bronchitis ($P > 0.05$); (v) no significant correlation was observed between the mode of delivery and the distribution of TCM syndrome types in children with asthmatic bronchitis ($P > 0.05$); (vi) children with cold asthma syndrome, heat asthma syndrome, and mixed cold and heat syndrome were not breastfed, and there was no significant difference in the feeding methods of children with mixed deficiency and excess syndrome ($P > 0.05$); (vii) no significant correlation was observed between the TCM syndrome types of pediatric asthmatic bronchitis and family history of asthma/allergy ($P > 0.05$); (viii) a significant correlation was observed between different TCM syndrome types and history of drug and food allergy ($P < 0.05$); (ix) normal or high eosinophil percentage was commonly observed in children with asthmatic bronchitis, and there was no significant difference among the different TCM syndrome types ($P > 0.05$). *Conclusion:* The TCM syndrome types of pediatric asthmatic bronchitis are related to gender, feeding history, allergy history, and other factors, which may be influencing factors of the TCM syndrome types of pediatric asthmatic bronchitis.

Keywords: Asthmatic bronchitis; Children; TCM syndrome types; Influencing factors

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1. Introduction

Pediatric asthmatic bronchitis, also known as asthmatic bronchitis, refers to a common bronchial-pulmonary disease in infants and young children. Its clinical manifestations include wheezing, coughing, shortness of breath, and difficulty in breathing.

Chinese medicine classifies pediatric asthmatic bronchitis into categories such as "wheeze" and "lung carbuncle" [1]. According to modern medicine, asthmatic bronchitis usually occurs after upper respiratory tract infection, wherein the infection spreads to the bronchi, causing congestion and edema of the bronchial mucosa. The smooth muscle spasm of the wall, causing the narrowing of airway, is the main pathological mechanism. At the same time, the disease is also triggered by various factors, such as dust mites, house dust, pollen, mold, and other inhaled allergens; feather, paint, and other contact allergens; food allergens; and sports or physical factors [2]. In Western medicine, this disease is treated with anti-inflammatory, antispasmodic, and asthma-relieving medications. Although there are many methods of control, patients with asthmatic bronchitis are prone to repeated attacks and may develop side effects. Treating this disease with Chinese medicine has obvious curative effect, whether it is in relieving the symptoms of the attack or in improving the state of recurrence [3].

In this study, through TCM syndrome differentiation and classification of children with asthmatic bronchitis under the Pediatric Department of our hospital, the correlation between TCM syndrome types of pediatric asthmatic bronchitis and the influencing factors of asthmatic bronchitis in children was explored, so as to provide a clinical basis for treatment.

2. Materials and methods

2.1. General information

The clinical data of 197 children with asthmatic bronchitis admitted to our hospital from March 2021 to March 2022 were collected, referring to "Zhu Futang Practical Pediatrics" (7th Edition, 2002) and "Chinese Medicine Industry Standards – Standards for Diagnosis and Efficacy of Pediatric Diseases and Syndromes of Traditional Chinese Medicine (1994, State Administration of Traditional Chinese Medicine) for diagnosis, classification, and analysis of the influence of factors such as age, gender, birth status, delivery method, feeding method, genetic history, allergy history, *etc*., on the diagnosis and syndrome types of traditional Chinese medicine (TCM).

Inclusion criteria: (i) complete clinical data, with informed consent obtained from parents; (ii) children under 3 years old; (iii) in compliance with "Zhu Futang Practical Pediatrics" (7th Edition, 2002) and "Chinese Medicine Industry Standards – Standards for Diagnosis and Efficacy of Pediatric Diseases and Syndromes of Traditional Chinese Medicine [4]" (1994, State Administration of Traditional Chinese Medicine). Exclusion criteria: (i) unstable patients or complicated with other diseases at the time of admission; (ii) patients with incomplete clinical data; (iii) patients with major organ dysfunction, such as heart, liver, and kidney, and patients uncooperative with laboratory examinations.

2.2. Methods

On the day when the children were admitted to the hospital, the items for analysis were collected according to the asthmatic bronchitis questionnaire, including the patients' (i) general condition (age, gender, *etc*.), clinical symptoms, and clinical signs; (ii) past medical history (such as infantile diarrhea, eczema, allergic rhinitis, *etc*.); (iii) family history; and (iv) laboratory tests, in which 3 mL of peripheral blood was collected and centrifuged at a speed of 3000 r/min for 10 min, and the plasma was then separated to measure serum C-reactive protein (CRP) and serum amyloid A (SAA) by immunoturbidimetry, as well as serum procalcitonin (PCT) by emulsion-enhanced immunoturbidimetry. The tests were carried out on the same day the blood samples were drawn according to the operating specifications.

2.3. Statistical analysis

The collected data were sorted out as follows: recorded – organized – input – listed – statistically analyzed. SPSS 16.0 was used for processing; count data were expressed in percentage (%), and χ^2/F-test was

performed.

3. Results

3.1. Distribution of TCM syndromes in children with asthmatic bronchitis

Among the 197 children with asthmatic bronchitis, the proportions of children cold asthma syndrome, heat asthma syndrome, mixed cold and heat syndrome, and mixed deficiency and excess syndrome accounted for 48.22%, 36.04%, 10.66%, and 5.08%, respectively, suggesting that the majority of children with asthmatic bronchitis have cold asthma syndrome (**Table 1**).

Table 1. Distribution of TCM syndromes in children with asthmatic bronchitis

TCM syndrome	Number of cases	Percentage (%)
Cold asthma	94	47.72
Febrile asthma	69	35.03
Mixed cold and heat	21	10.66
Mixed deficiency and excess	13	6.59

3.2. Correlation analysis of TCM syndrome types and influencing factors in children with asthmatic bronchitis

Among the 197 children, there were 143 males and 54 females; χ^2 test showed $P = 0.0439$ (< 0.05), suggesting that gender has a significant influence on the TCM syndromes of asthmatic bronchitis in children. Among the children, 77 cases were 0–1 year old, accounting for 39.08%; 69 cases were 1–2 years old, accounting for 35.02%; and 51 cases were 2–3 years old, accounting for 25.88%; χ^2 test showed $P > 0.05$, indicating no significant difference in the distribution of TCM syndromes of pediatric asthmatic bronchitis among the different age groups. There were 185 cases of full-term children, accounting for 93.91%, and 12 cases of premature children, accounting for 6.09%; χ^2 test showed $P > 0.05$, indicating that birth status has no effect on the distribution of TCM syndromes of asthmatic bronchitis in children. Among the cases, 94 children were delivered naturally, accounting for 47.72%, while 103 cases were delivered via cesarean section, accounting for 52.28%; χ^2 test showed $P > 0.05$, indicating that there is no correlation between the mode of delivery and the distribution of TCM syndromes in children with asthmatic bronchitis. The majority of children with cold asthma syndrome, heat asthma syndrome, and mixed cold and heat syndrome were not exclusively breastfed, and there was no significant difference in the feeding method of children with mixed deficiency and excess syndrome ($P > 0.05$). Among children with cold asthma syndrome, 21 cases had family history of asthma/allergy, whereas 73 cases had no family history of asthma/allergy; among children with heat asthma syndrome, 6 cases had family history of asthma/allergy, whereas 63 cases had no family history of asthma/allergy; among children with mixed cold and heat syndrome, 4 cases had family history of asthma/allergy, whereas 17 cases had no family history of asthma/allergy; among children with mixed deficiency and excess syndrome, 1 case had family history of asthma/allergy, whereas 12 cases had no family history of asthma/allergy; χ^2 test showed $P > 0.05$, indicating no significant correlation between the TCM syndromes of pediatric asthmatic bronchitis and family history of asthma/allergy. Among the 197 cases of asthmatic bronchitis, 78 had history of drug and food allergy, accounting for 39.59%, whereas 119 cases had no history of drug or food allergy, accounting for 60.41%; χ^2 test showed $P < 0.05$, suggesting a significant correlation between different TCM syndromes and history of drug and food allergy. In children with asthmatic bronchitis, the most common picture was normal or decreased eosinophils ($0 \leq E\% \leq 5\%$), and there was no significant difference among the syndromes ($P > 0.05$).

Table 2. Correlation between TCM syndromes and influencing factors in children with asthmatic bronchitis

		Cold asthma (94)	Heat asthma (69)	Mixed cold and heat (21)	Mixed deficiency and excess (13)	χ^2/F	*P*
Gender	Male	74	41	17	9	8.3139	0.0400
	Female	20	28	4	4		
Age	0–1 year old	43	22	7	5	8.8205	0.1839
	1–2 years old	24	29	11	5		
	2–3 years old	27	18	3	3		
Birth status	Full term	89	64	20	12	2.5570	0.0834
	Premature	5	5	1	1		
Mode of delivery	Vaginal delivery	45	31	12	6	0.9767	0.8069
	Caesarean section	49	38	9	7		
Feeding method	Breastfeeding	28	19	10	4		
	Mixed feeding	50	43	9	4	1.5822	0.2577
	Artificial feeding	16	7	2	5		
Family history of asthma/allergy	Yes	21	6	4	1	2.0481	0.0865
	No	73	63	17	12		
History of drug/food allergy	Yes	27	34	9	8	10.0594	0.0181
	No	67	35	12	5		
Percentage of eosinophils	Low	9	5	2	1	3.1174	0.0936
	Normal	59	44	12	10		
	High	26	20	7	2		

4. Discussion

Asthmatic bronchitis is a common respiratory disease in children, and it mostly occurs in infants and young children. In recent years, with the influence of environmental pollution, climate change, malnutrition, immune function deficiency, and other factors, the incidence of the disease is on the rise, and it has a tendency to affect younger children [5]. The onset of this disease is related to the child's physiological make-up and the invasion of the human body by wind-cold, wind-heat, and dryness. As recorded in "On the Origin and Symptoms of Various Diseases," "For those with lung diseases, phlegm retention is in the lungs." According to "Pediatric Medicine and Syndrome Zhi Jue," "Those who cough with sputum retention, wheeze and cough with phlegm ringing, and even with mucus obstructing the heart orifices...the treatment should be to dissipate phlegm and detoxify. It should be based on clearing away heat and resolving phlegm [6]." According to modern medicine, asthmatic bronchitis usually occurs after upper respiratory tract infection. When the infection spreads to the bronchus, it causes congestion and edema of the bronchial mucosa, spasm of the smooth muscle wall, and wheezing due to bronchial narrowing. This is the main pathological mechanism of asthmatic bronchitis. In order to find a safe and effective method of treatment, it is necessary to further study the TCM syndromes of this disease and the related factors.

Through statistical analysis of the clinical data of 197 inpatients with asthmatic bronchitis in our hospital, we aimed to provide an objective basis for determining the factors related to TCM syndromes of pediatric asthmatic bronchitis and to carry out standardized TCM diagnosis and treatment. The findings of this study are presented below.

(i) Among the 197 children with asthmatic bronchitis, the majority of cases had cold asthma syndrome, accounting for 48.22%. Most of the patients are male, and although the disease can occur across all four

seasons, there are significant correlations with temperature changes, family history, previous medications, and food allergy history.

(ii) Among the 197 children, 77 were 0–1 year old, accounting for 39.08%; 69 were 1–2 years old, accounting for 35.02%; and 51 were 2–3 years old, accounting for 25.88%; χ^2 test showed $P > 0.05$, indicating no significant difference in the distribution of TCM syndromes of asthmatic bronchitis in children among different age groups. There were 185 full-term children, accounting for 93.91%, and 12 premature children, accounting for 6.09%; χ^2 test showed $P > 0.05$, indicating that birth status has no effect on the distribution of TCM syndromes of pediatric asthmatic bronchitis. Among the children, 94 were delivered naturally, accounting for 47.72%, and 103 were delivered by cesarean section, accounting for 52.28%; χ^2 test showed $P > 0.05$, suggesting that there is no correlation between the mode of delivery and the distribution of TCM syndromes in children with asthmatic bronchitis. Children with cold asthma syndrome, heat asthma syndrome, and mixed cold and heat syndrome were not exclusively breastfed, and there was no significant difference in the feeding method of children with mixed deficiency and excess syndrome ($P > 0.05$). In terms of family history of asthma/allergy, 21 cases with cold asthma syndrome had family history, whereas 73 cases had no family history; 6 cases with heat asthma syndrome had family history, whereas 63 cases had no family history; 4 cases with mixed cold and heat syndrome had family history, whereas 17 cases had no family history; 1 case with mixed deficiency and excess syndrome had family history, whereas the other 12 cases had no family history; χ^2 test showed $P > 0.05$, indicating that there is no significant correlation between the TCM syndromes of asthmatic bronchitis in children and family history of asthma/allergy. Among the 197 children with asthmatic bronchitis, 78 cases had history of drug and food allergy, accounting for 39.59%, whereas 119 cases had no history of drug or food allergy, accounting for 60.41%; χ^2 test showed $P < 0.05$, suggesting a significant correlation between different TCM syndromes and history of drug and food allergy. A picture of normal or high eosinophil percentage is common in children with asthmatic bronchitis, and there was no statistically significant difference among the syndrome types in the present study ($P > 0.05$).

Due to the small number of cases in this study and the small sample size, there may be some deviations in the statistical results. We hope that the sample size and geographical scope will be further expanded in future studies to further clarify the pathogenesis and influencing factors of pediatric asthmatic bronchitis and the correlation with other TCM syndrome types, so as to provide a clinical basis for rescue work and effectively manage children with asthmatic bronchitis in clinical practice.

Disclosure statement

The authors declare no conflict of interest.

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Dosimetric Comparative Analysis of Volumetric Modulated Arc Therapy and Intensity-Modulated Radiation Therapy in Cervical Cancer

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Abstract: *Objective:* To carry out dosimetric comparison between volumetric modulated arc therapy (VMAT) and intensity-modulated radiation therapy (IMRT) in cervical cancer. *Methods:* 50 postoperative cervical cancer patients were included in this study. The patients were admitted for treatment from January 2021 to January 2022. VMAT and IMRT plans were designed for each patient to analyze the dose distribution in the target area of the two treatment techniques. *Results:* Comparing the monitor unit for single treatment (638.21 ± 116.21 MU) and time of single treatment (143.21 ± 23.14 s) in the observation group and the monitor unit for single treatment (932.14 ± 74.11 MU) and time of single treatment (223.14 ± 17.26 s) in the control group, there was significant difference ($P < 0.05$); there was also significant difference ($P < 0.05$) between the normal tissue (bladder and rectum) of the observation group and that (bladder and rectum) of the control group. *Conclusion:* VMAT is more effective in cervical cancer, and it has a certain protective effect on normal tissues in patients and can reduce the radiation dose.

Keywords: Volumetric modulated arc therapy, Intensity-modulated radiation therapy; Radiotherapy for cervical cancer; Dose

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1. Introduction

Cervical cancer is a common malignant tumor of the female reproductive system. With the widespread application of cervical screening in recent years, cervical cancer can be detected and treated early. The peak period of cervical cancer incidence is bimodal; the first peak is between 40 and 50 years old, while the second peak is between 60 and 70 years old. Abnormal vaginal bleeding, abnormal vaginal discharge, and some late symptoms of compression are clinical manifestations of cervical cancer [1], of which contact vaginal bleeding is the main symptom. This disease is also related to human papillomavirus (HPV) infection. There are high-risk types of HPV viruses, such as HPV 16 and 18, both of which are the main types that cause cervical cancer. In the treatment of cervical cancer, the three main methods are surgery, chemotherapy, and radiotherapy. The surgery that is commonly performed in patients with cervical cancer is known as extensive radical surgery. According to the patient's condition, fertility and the pelvic nerves can be preserved; especially in the early stages of cervical cancer, the ovaries are often preserved [2]. Intensity-modulated radiation therapy (IMRT) is a radiotherapy technique. For patients with early-stage cervical cancer, postoperative adjuvant radiotherapy can effectively inhibit local recurrence. The prolonged treatment time of IMRT in the static field may easily lead to the increase in uncertainty factors in the

treatment process and affect the curative process. In addition, postoperative radiotherapy for cervical cancers may also lead to complications. Patients may develop certain reactions, such as gastrointestinal reactions, while other patients may have bowel adhesions as a result of radiotherapy. In severe cases, symptoms such as intestinal obstruction, radiation proctitis, hematochezia, tenesmus, *etc*., will affect the health of patients [3]. On the basis of image-guided radiation therapy, volumetric modulated arc therapy (VMAT) is an advanced radiation therapy technique under the guarantee of three-dimensional dose verification by the reverse optimization treatment planning system and high-precision accelerator. VMAT uses a single arc or multiple arcs to irradiate the tumor at any angle. During the rotation of the ray beam, parameters such as dose rate, rack speed, and blade position can be dynamically adjusted. This technology has a larger irradiation range, more flexibility and precision, better dose focusing effect, and advantage in the irradiation of early-stage and complex tumors [4]. Compared with IMRT, rotating IMRT (VMAT) can effectively reduce the treatment time, while ensuring that the radiation dose to normal organs is low. Therefore, we analyzed the dosimetric difference between VMAT and IMRT in cervical cancer in this study to provide reference for clinical radiotherapy.

2. Materials and methods

2.1. Data

A total of 50 postoperative patients with cervical cancer were included in this study. The patients were admitted for treatment from January 2021 to January 2022. The average age of the patients was 56.17 ± 6.17 (40–70) years old. Inclusion criteria: (i) informed consent given; (ii) patients with complete clinical data. Exclusion criteria: (i) patients with other serious diseases; (ii) non-cooperative to postoperative treatment. The differences in baseline data between the two groups of patients were not statistically significant ($P > 0.05$).

2.2. Methods

Fixed body position, computed tomography (CT) simulation: All patients were required to empty their bladders 1 hour before the scan, drink 500 mL of water, and retain their urine; they were fixed with a thermoplastic body film, and CT was used to acquire plain and enhanced images; the range of the scan included the patient's perineum, pelvis, and middle and lower abdomen, with a slice thickness of 5 mm; the images were then transmitted to the Monaco planning system.

Radiotherapy plan design: (i) observation group (the starting angle of the gantry was 180°, and the arc was rotated 360° to and fro for irradiation); (ii) control group (5 fields were coplanarly irradiated, and the rack angles were 40°, 110°, 180°, 250°, and 320°).

2.3. Observation indicators

The doses to organs at risk and normal tissues were compared between the two groups.

2.4. Statistical analysis

SPSS 26.0 was used for statistical processing. $P < 0.05$ indicates significant difference in the data.

3. Results

3.1. Comparison of monitor unit and planned treatment time between the two groups

The monitor unit for single treatment (638.21 ± 116.21 MU) and single treatment time (143.21 ± 23.14 s) of the observation group were better than those of the control group (932.14 ± 74.11 MU; 223.14 ± 17.26 s), and the difference was statistically significant ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of monitor unit and planned treatment time between the two groups

Group	Number of cases (n)	CI	HI	Monitor unit for single treatment (MU)	Single treatment time (s)
Observation group	25	0.81 ± 0.10	0.08 ± 0.01	638.21 ± 116.21	143.21 ± 23.14
Control group	25	0.71 ± 0.02	0.08 ± 0.02	932.14 ± 74.11	223.14 ± 17.26
t	–	2.0127	1.0123	16.4417	9.1728
P	–	0.0714	0.0918	0.0000	0.0000

Abbreviations: CI, conformity index; HI, homogeneity index.

3.2. Comparison of normal tissue dose between the two groups of patients

The normal tissue dose (bladder and rectum) of the observation group was significantly lower than that of the control group (P <0.05), as shown in **Table 2**.

Table 2. Comparison of doses to normal tissues between two groups of patients

Group	Number of cases (n)	Bladder		Rectum	
		$D_{10\%}$ (cGy)	D_{max} (cGy)	$D_{10\%}$ (cGy)	D_{max} (cGy)
Observation group	25	3366.14 ± 228.14	4091.21 ± 317.26	4176.21 ± 556.14	4576.23 ± 536.11
Control group	25	4932.17 ± 187.21	5064.21 ± 23.14	4951.17 ± 109.14	4576.51 ± 531.24
t	–	21.1627	24.1128	23.2614	27.2914
P	–	0.0000	0.0000	0.0000	0.0000

4. Discussion

According to relevant research [4], cervical cancer mainly refers to canceration that occurs in female epithelium or glands. Among the different types of cervical cancer (cervical adenocarcinoma, squamous cell carcinoma, *etc*.), squamous cell carcinoma is the most common. The occurrence of cervical cancer is closely related to HPV infection, prolificacy, and long-term inflammatory stimulation. Commonly, there is no clinical manifestation in early cervical cancer, and the malignancy is often identified through inspection. Among the symptoms, bleeding after intercourse is the earliest symptom in the early stage of cervical cancer [5]. Cervical exfoliative cytology examination and HPV screening are generally performed in clinical practice to screen for cervical cancer, while pathological tissue biopsy and colposcopy are performed to confirm the diagnosis. If cervical cancer is not treated in time, there will be worsening of vaginal bleeding and irregular vaginal bleeding [6]. Once contact bleeding or postmenopausal bleeding occurs, it is necessary to seek medical attention, so that relevant examinations can be carried out in time to rule out the possibility of cervical lesions. In the treatment of cervical cancer, the treatment methods vary depending on the patient. In addition, different patients also have different prognoses. Clinically, surgical methods are usually used for cervical cancer, and they are generally suitable for patients with early cervical cancer. Surgery and postoperative adjuvant therapy are effective when the tumor has not invaded the parauterine tissue or metastasized. In such cases, the curative effect is high [7]. However, in most cases, when patients are diagnosed with cervical cancer, there is regional spread; hence, patients would have lost the best opportunity for surgery. For such patients, radiation therapy is the treatment of choice. Radiation therapy has been widely used in clinical practice. For early-stage cervical cancer, such as stage IA, stage IB, and stage IIA, hysterectomy is commonly performed, with adjuvant radiotherapy and chemotherapy after surgery. However, for advanced cervical cancer, such as stage IIB and above, radiotherapy can be performed.

With the advancements in treatment methods, the survival rate of cancer patients is increasing. Controlling the tumor while reducing the incidence and severity of side effects is one of the key issues that need to be considered in radiotherapy. The top priority in postoperative radiotherapy for patients with cervical cancer is to reduce the incidence and severity of bladder and bowel reactions. Radiotherapy is beneficial to postoperative patients with cervical cancer. In cervical cancer, radiation therapy mainly refers to three-dimensional conformal radiation therapy based on CT positioning. It can achieve high curative effect, high dose, high-precision irradiation on the tumor, and optimal protection of normal tissues and organs around the tumor. Three-dimensional conformal radiation therapy is constantly maturing and is considered to be a major breakthrough in radiation therapy for cancer. In traditional radiotherapy for cervical cancer, due to the influence of various factors, the tissue in the patient's pelvic cavity is easily exposed to high doses of radiation, which can cause severe acute and chronic side effects. There are different types of IMRT, including step-and-shoot IMRT, sliding window IMRT, volumetric IMRT, and tomotherapy, which can be divided into two types: (i) conventional tomotherapy and helical tomotherapy; and (ii) multi-leaf grating, which has many clinical applications. In clinical practice, the most appropriate and suitable treatment method should be used according to conditions to achieve the effect of treating tumors while protecting normal tissues and organs and reducing complications. The aforementioned IMRT types have been used clinically, rendering positive effects. Nowadays, with the extensive application of VMAT in clinical practice, certain effects have been achieved. During the rotation of the gantry, the volumetric intensity-modulated radiation produces beams continuously, and the shape and dose rate of the radiation field are also adjusted according to the requirements. Thus, reasonable dose distribution can be achieved.

Compared with the three-dimensional conformal technology, IMRT can improve the dose distribution in the target area, but the treatment time is significantly lengthened, resulting in a significant decrease in treatment accuracy. VMAT is optimized by dynamic multi-leaf grating through a rotating beam to achieve the required clinical dose; the intensity-modulated plan is then made to select the arcs of rotation, and the irradiation field, the beam, and the angle of incidence are optimized in the planning system. After optimization, the required dose distribution is achieved and transferred back to the computer manual planning system for treatment. VMAT is a novel technique that allows the precise control of multiple-parameter information during the rotation process of the accelerator frame, such as the position and dose of multi-level cell (MLC) and the angle of the frame at each control point. By adjusting the speed of the rotating gantry and the shape and weight of the field of view at the corresponding angle, it is possible to achieve ideal dose distribution. In general clinical cases, VMAT usually uses two arcs to achieve the ideal treatment plan. VMAT can reduce the number of machine jumps of the accelerator [8]. In the present study, VMAT was used. VMAT shields the radiation when the radiation field is aimed at normal tissues, and although the gantry keeps rotating at a constant speed, it does not emit beams, thereby reducing the low-dose exposure of normal tissues on the radiation field path.

In the present study, the intensity modulation scheme of 5 fields was selected. In the actual treatment process, it takes a certain amount of time to switch the angle of the treatment field. If the field increases, the treatment time will also increase. In the VMAT plan, two irradiation arcs are selected. The end angle of the first treatment field becomes the starting angle of the next treatment field. There is no need to switch the angle of the treatment field, thereby preventing time wastage. According to statistics, for each patient treated, the VMAT plan can save about 8 minutes on average, which is of great significance to improving clinical efficacy.

Our research showed that there was significant difference ($P < 0.05$) in single treatment monitor unit and single treatment time between the observation group (638.21 ± 116.21 MU; 143.21 ± 23.14 s) and the control group (932.14 ± 74.11 MU; 223.14 ± 17.26 s); there was also significant difference ($P < 0.05$) in

normal tissue dose (bladder and rectum) between the observation group and the control group.

In conclusion, VMAT has a shorter treatment time and certain protective effect on normal tissues and can reduce the radiation dose in radiotherapy for cervical cancer; thus, it is worthy of promotion and application in clinical practice.

Disclosure statement

The authors declare no conflict of interest.

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In Silico Evaluation of Potential Ligands of Cancer Cells for Surfactin from *Bacillus* spp.

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Abstract: Cancer is one of the most prevalent diseases worldwide, which causes significant morbidity and mortality. Designing and developing a potential anti-cancer drug is an active field of research worldwide. Microorganisms have been considered a potential source of anti-cancer drugs. One such microbe-derived compound is surfactin, which shows potential anti-cancer activities. In this study, we evaluated the binding potential of surfactin with several cancer cell ligands via an *in-silico* approach. Hence, molecular docking studies were performed to test the binding potential of surfactin against four targets. The analyses revealed that surfactin from *Bacillus* sp. can bind with the targeted ligands (coenzyme A, D-leucine, glycerol, and (R)-3-hydroxytetradecanal) with significant affinity. Surfactin showed the highest binding affinity (-7.7 kcal mol^{-1}) to coenzyme A among the targeted ligands. These results may be useful for developing anti-cancer drugs. Nevertheless, further experimental studies are needed to investigate the ligand binding capacity and anti-cancer potential of such surfactin-like molecules.

Keywords: Molecular docking; Cancer; Ligand; Surfactin; *Bacillus*

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1. Introduction

Cancer may develop when cells in one part of the body grow and reproduce uncontrollably. Cancerous cells can invade healthy tissue, including organs and then wreak havoc. Males are more likely to develop cancer of the prostate, lung, colon, and urinary bladder, whereas females are more likely to develop cancer of the breast, lung, colon, uterine corpus, and thyroid gland [1-3]. Cancer treatment with anticancer drugs is costly and can result in cell mutations, thus making them resistant to anticancer drug therapy [1,4]. Numerous studies are being conducted to identify potential anticancer drugs with comparable efficacy. Several studies have suggested that bacteria-derived therapeutic agents are effective in the treatment of cancer [5-7].

Certain specific tumor-targeting bacterial bioactive metabolites have demonstrated impressive efficacy in cancer treatment [8]. Surfactin, iturin, bacillomycin D, and fengycin are well known for their potent anticancer action against various cancer cell lines [9,10]. Surfactin, a cyclic lipopeptide that is also a bacteria-derived biosurfactant, has been demonstrated to elicit cytotoxicity against various malignancies [11]. It has been reported that surfactin has cytotoxic effect on several human cancer cell lines but lower toxicity to normal human fibroblast cells [12]. Other studies have reported similar findings, with surfactin exhibiting a

greater degree of toxicity toward cancer cells compared to normal cells.

Bacillus subtilis, *Bacillus amyloliquefaciens*, and *Bacillus velezensis* are the primary bacterial sources of lipopeptides, including surfactin [11]. These bacteria are safe, renowned for various biological activities, available in nature, and simple to isolate, cultivate, and manipulate in laboratories [13-15]. In their use as alternatives for the treatment of various cancers, more research is needed to fully understand the potential of surfactin and its mode of action.

Surfactin, among other lipopeptides, has a generalized effect and significantly benefits from its ability to penetrate the cell membranes of both gram-positive and gram-negative bacteria. It has both hydrophilic (water-loving) and hydrophobic (water-fearing) properties that keep it stable in both conditions and allow its interaction with cell membranes, which also have hydrophilic and hydrophobic regions. Several mechanisms have been suggested as the anti-cancer mechanisms of surfactin, including apoptosis induction, anti-proliferation of cancer cells, inhibition of angiogenesis, immune response modulation, *etc*. [16,17].

The binding mechanism of surfactin with cancer cells has not been fully understood, but it is believed that the interaction between the lipopeptide and the cell membrane is involved. Studies have suggested that surfactin can bind to the cell membrane of cancer cell through its hydrophobic tail, which can penetrate the membrane and interact with the lipid bilayer [18]. This would disrupt the structure and function of the membrane, thus leading to cell death. The specific receptors of cancer cells for surfactin binding have not been clearly identified or characterized. Additionally, surfactin has been shown to affect the function of membrane proteins and receptors, including those involved in cell signaling pathways and apoptosis [18]. For example, surfactin has been found to modulate the activity of epidermal growth factor receptor (EGFR), which is often overexpressed in cancer cells and involved in tumor growth and survival [19].

In addition, modifications to the structure of surfactin, such as changing the amino acid sequence or modifying the hydrophobic tail, may also lead to ligands with improved binding affinity for cancer cells [20-22]. Hence, further explorations and investigations are needed to identify the specific ligands of cancer cells for surfactin binding and modify the structure of surfactin to improve its anti-cancer properties.

The aim of the current study was to visualize the three-dimensional (3D) structure of surfactin; the processing of surfactin and ligands, coenzyme A ($C_{21}H_{36}N_7O_{16}P_3S$), D-leucine ($C_6H_{13}NO_2$), glycerol ($C_3H_8O_3$), and (R)-3-hydroxytetradecanal ($C_{14}H_{28}O_2$); and the molecular docking of surfactin and ligands to discover the potential binding sites.

2. Methods

2.1. Preparation of surfactin structure

In order to visualize the binding domain and identify the amino acids in the binding pocket, the crystal structure of surfactin (PDB ID: 2VSQ) was imported into chimera from Protein Data Bank (**Figure 1**). As previously reported, an analysis of the amino acid residues in the binding domain of the inhibitor binding site was conducted [23,25]. The ionization and tautomeric states of the amino acid residues were altered in the protein by adding hydrogen atoms. Prior to docking, the water molecules and complexes attached to the receptor molecules were dislodged. Using a virtual screening application, AutoDock Vina, the modified protein was saved in PDBQT format and loaded into PyRx for molecular docking [25,26].

2.2. Generation of ligand dataset

The three-dimensional structures of different target ligand molecules, namely coenzyme A ($C_{21}H_{36}N_7O_{16}P_3S$), D-leucine ($C_6H_{13}NO_2$), glycerol ($C_3H_8O_3$), and (R)-3-hydroxytetradecanal ($C_{14}H_{28}O_2$) were obtained from Protein Data Bank (www.rcsb.org) with the following PDB ID: 1PGP, 1USK, GOL, and 2NPV, respectively [27-29]. Before molecular docking studies were carried out, the protein structure as determined by PDB was modified. The energy of the molecules was reduced, and the water molecules were

eliminated (**Figure 2**).

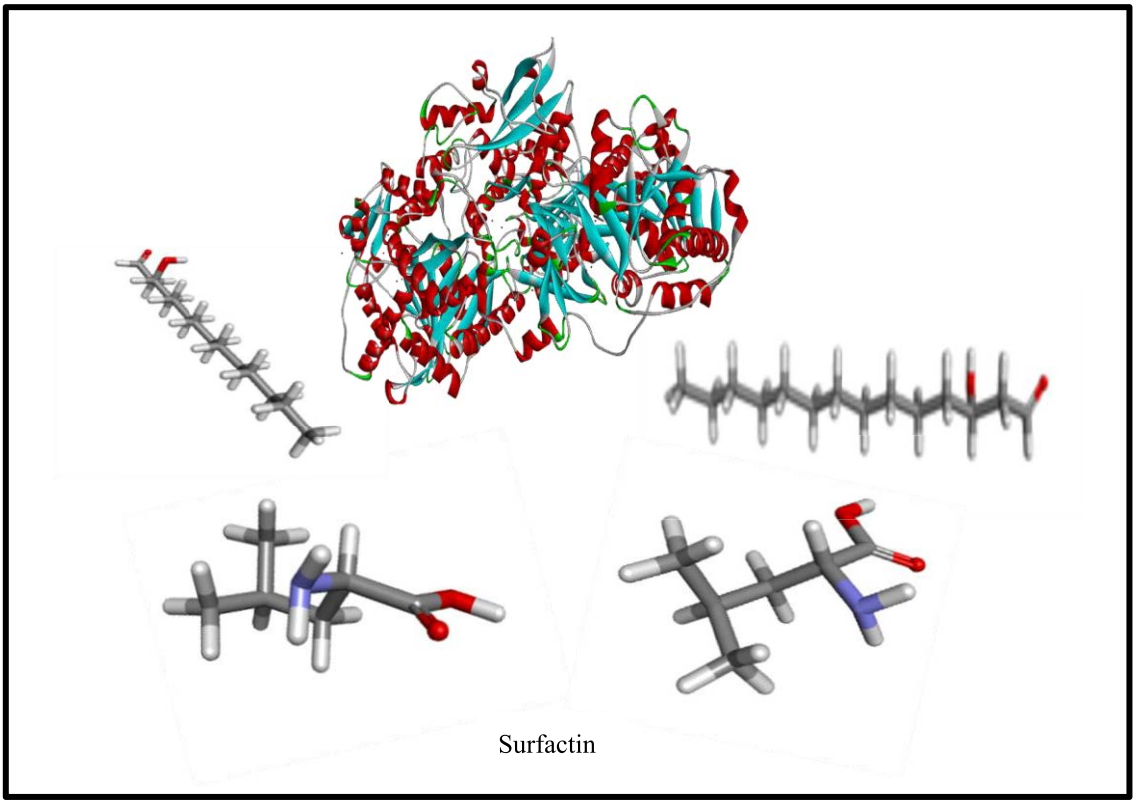

Figure 1. Three-dimensional crystal structure and chemical structure of surfactin

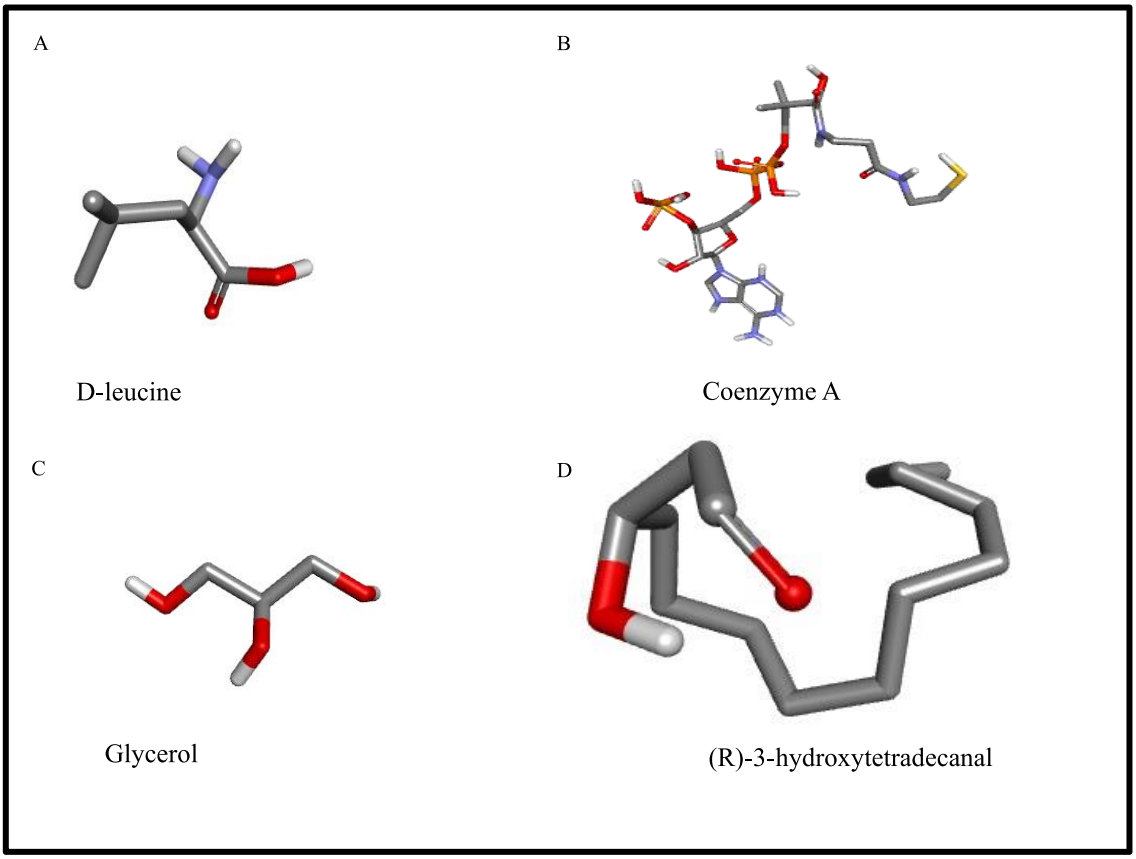

Figure 2. Three-dimensional configuration of ligands before docking

2.3. Docking strategy

The processed PDB files of proteins were loaded into PyRx and converted into macromolecules using the autodock option. Ligand structures were imported using PyRx, and the energy in ligand structures was minimized using an off-force field and conjugate gradient optimization algorithm. Post-energy minimization, ligands were converted into the autodock ligand format. Using Vina Wizard, both the molecule and the ligands were selected, and autodock was initiated. After docking binding affinity for two-dimensional (2D) and 3D binding, the root mean square deviation/upper bound (rmsd/ub) and lower bound (rmsd/lb) were observed. The visualization of receptor-ligand interaction on BIOVIA Discovery Studio and the selection of receptor and ligand were performed. Although docking can ensure binding with available binding sites, knowing the affinity for particular amino acids is desirable.

3. Results and discussions

Drug design is the process of identifying new drugs based on knowledge of their biological targets. Drug design can be categorized into structure-based drug design and ligand-based drug design [30,31]. In structure-based drug design, the 3D structure of the receptor or the target protein is known, whereas in ligand-based drug design, the structure of molecules (ligands) that bind to the target protein of interest is known [32-34]. Interaction between ligands and binding sites is simulated *in silico* drug design and homology modeling. *In silico* drug design employs computer simulation to discover and develop new drugs. However, the complex structures of lipopeptides render this method difficult. When paired with a receptor lipopeptide, particular ligands must be found for physiological reactions to take place [35-37]. Ligands are particles that form complexes with biomolecules to serve biological functions. The orientation of the 3D shape is altered when a ligand binds to a receptor protein, altering the conformation [35-37].

Surfactin has been reported to have anti-proliferative effects on human colon cancer cells, with a significant increase in apoptosis [22]. Six ligands of surfactin have been identified. Among them, D-leucine, the D-alpha-enantiomer of leucine, is a bacterial metabolite. The non-polymer (R)-3-hydroxytetradecanal is covalently linked to polymers or other heterogeneous groups [38]. Around 4% of cellular enzymes use coenzyme A as a substrate. It is known for its function in production and oxidation of fatty acids, as well as the oxidation of pyruvate in the citric acid cycle [39]. Following the identification of surfactin ligands, the molecular docking of these ligands with the lipopeptide was performed for *in silico* drug design with reference to Parween *et al*. and Qasaymeh *et al*. [40,41]. The aim of the current study was to visualize the 3D structure of surfactin; the processing of surfactin and ligands (coenzyme A [$C_{21}H_{36}N_7O_{16}P_3S$], D-leucine [$C_6H_{13}NO_2$], glycerol [$C_3H_8O_3$], and (R)-3-hydroxytetradecanal [C14H28O2]); and the molecular docking of surfactin and ligands to discover potential binding sites.

After docking, nine binding sites with varying affinity were found for D-leucine, coenzyme A, glycerol, and (R)-3-hydroxytetradecanal (**Figure 3**). As shown in **Figure 3**, surfactin binds better with D-leucine and coenzyme A compared to glycerol and (R)-3-hydroxytetradecanal. The binding of surfactin with the selected ligands is illustrated in **Figures 4–5**. In the case of D-leucine, surfactin formed van der Waals bonds (GLY, A: 273, 311; SER, A: 272, 437, 309; VAL, A: 264, 436; GLU, A: 310; ASN, A:792; ILE, A: 312), conventional hydrogen bonds (ARG, A: 268; GLU, A: 793), a carbon-hydrogen bond (SER, A: 267), and an alkyl bond (LEU, A: 308). In the case of coenzyme A, surfactin formed van der Waals bonds (ILE, A: 612, 626, 632; ASN, A: 625, 631; THR, A: 628, 759; SER, A: 814; LYS, A:815), conventional hydrogen bonds (TYR, A: 611; ALA, A: 610), carbon-hydrogen bonds (PRO, A: 609; ASN, A: 631), and covalent bonds (ILE, A: 626; THR, A: 628). In the case of glycerol, surfactin formed only conventional hydrogen bonds (LYS, ARG, THR, TYR), carbon-hydrogen bonds (GLU, PRO), and unfavorable donor-donor bonds (LEU). With (R)-3-hydroxytetradecanal, surfactin formed only unfavorable bonds (ARG, PHE). From these binding analyses, D-leucine and coenzyme A are predicted to be better and stronger ligands for

surfactin.

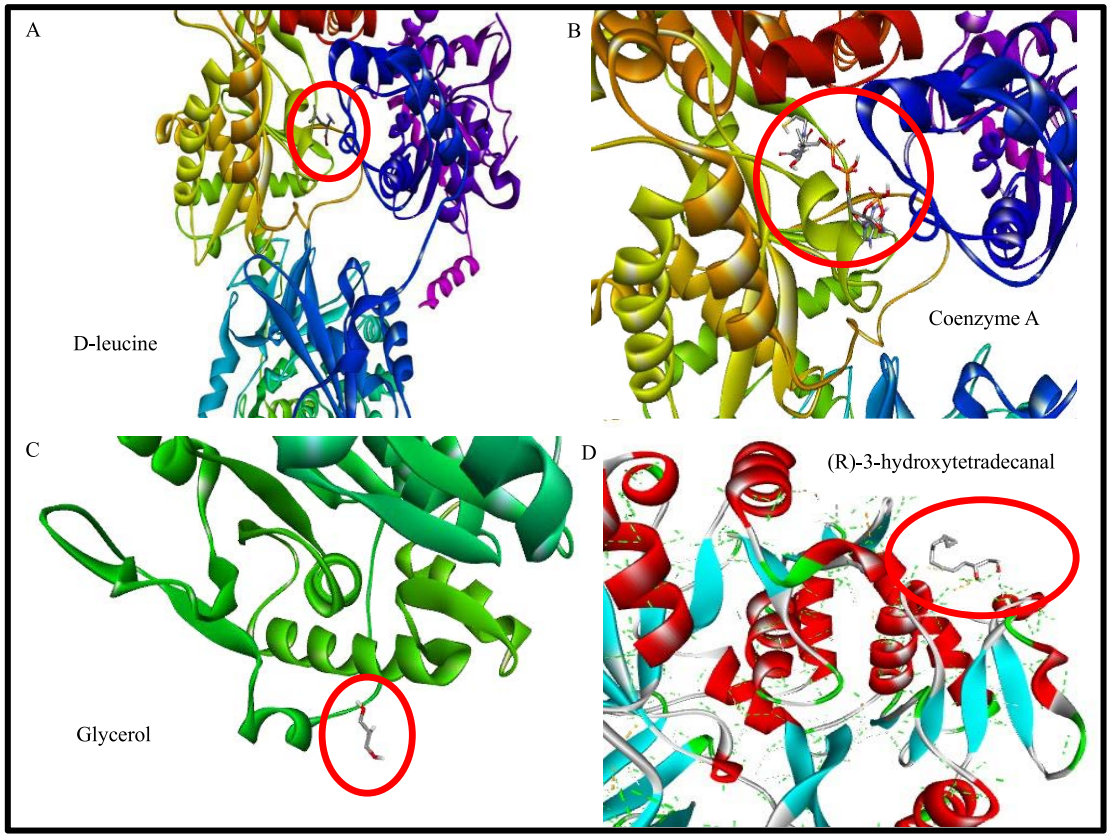

Figure 3. Binding of surfactin with ligands

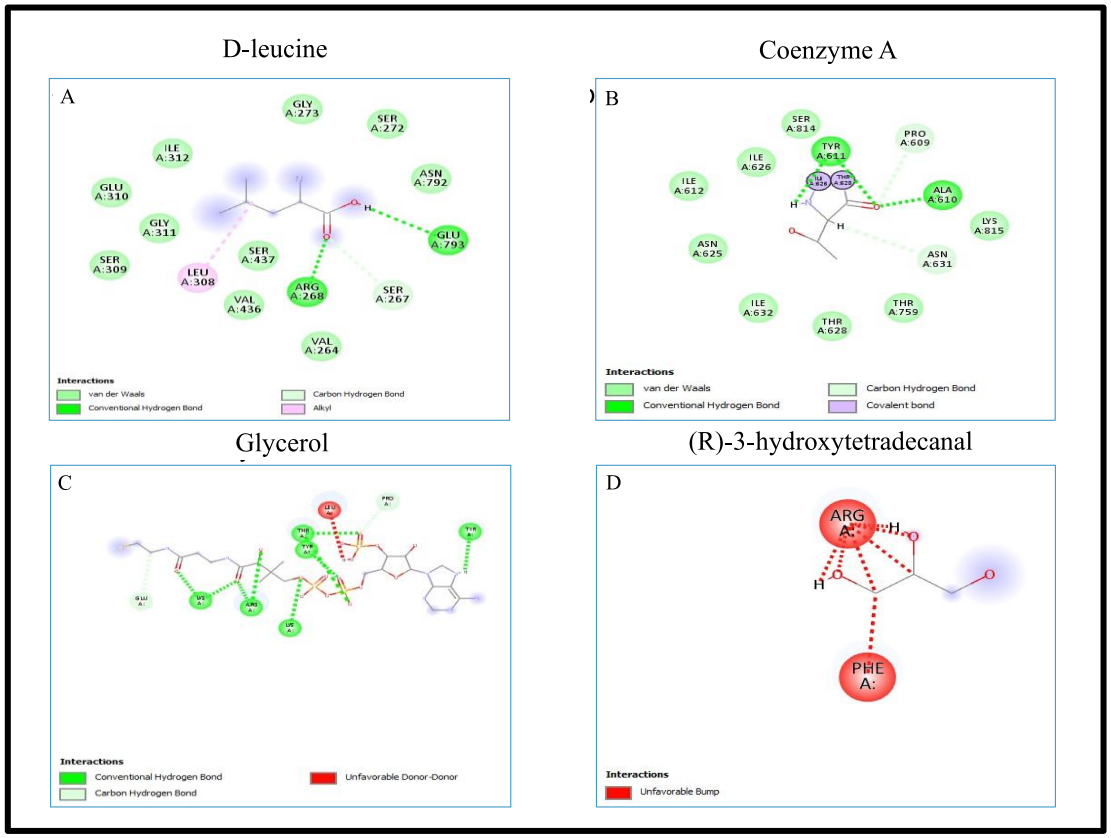

Figure 4. Amino acid binding site of surfactin with ligands

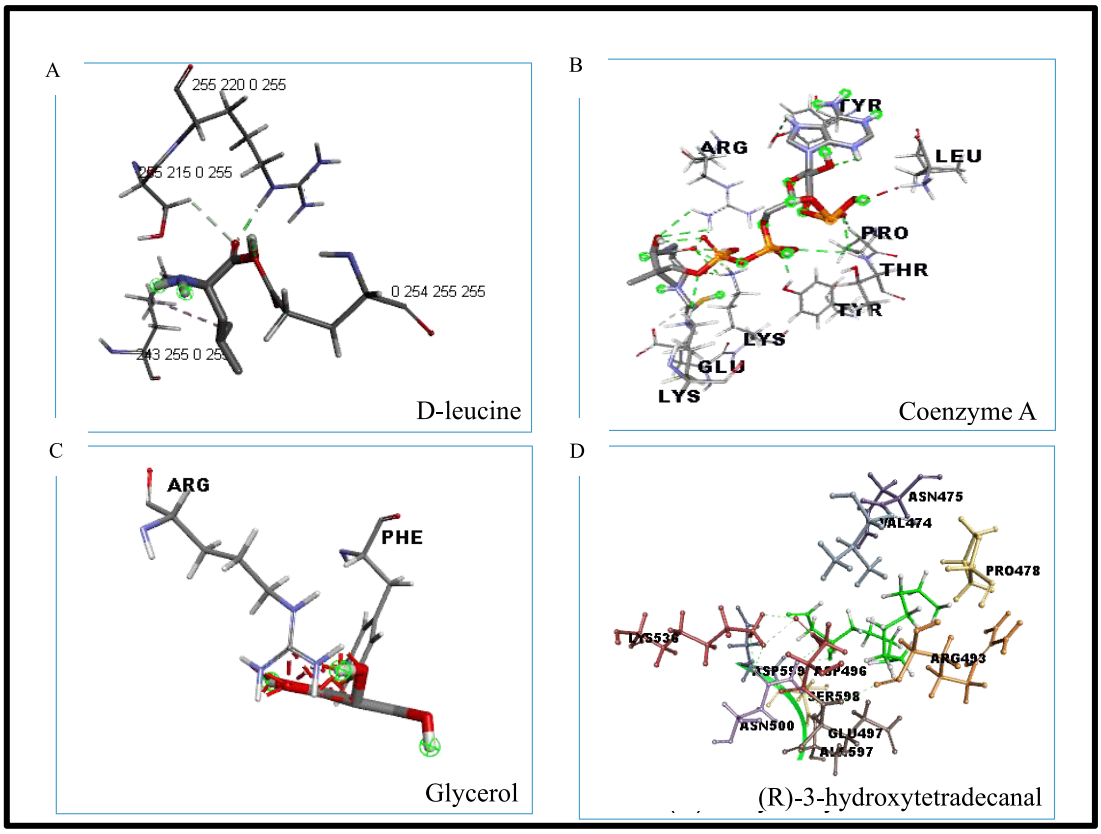

Figure 5. Binding affinity of surfactin with ligands

The docking study revealed that surfactin from *Bacillus* spp. has the highest binding affinity (Ca. -7.5 kcal mol^{-1}) with coenzyme A among the tested ligands but the lowest binding affinity with (R)-3-Hydroxytetradecanal (Ca. -3.5 kcal mol^{-1}). Surfactin was observed to have moderate binding affinity with D-leucine (approximately -4.4 kcal mol^{-1}) and glycerol (approximately -4.1 kcal mol^{-1}). **Table 1** shows the binding affinity of those ligands with surfactin in various conformations, as well as the root mean square deviation (RMSD) of the interacting molecules (protein and ligand).

Table 1. Binding affinity of surfactin with ligands

Ligand	Binding affinity (kcal mol^{-1})	rmsd/ub (root mean square deviation/upper bound)	rmsd/lb (root mean square deviation/lower bound)
D-leucine	-4.6	0	0
	-4.5	2.577	2.216
	-4.4	25.399	24.194
	-4.4	29.603	29.158
	-4.4	64.989	63.672
	-4.3	63.683	62.843
	-4.3	31.076	30.266
	-4.3	28.558	27.722
	-4.3	57.221	56.019

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Ligand	Binding affinity (kcal mol^{-1})	rmsd/ub (root mean square deviation/upper bound)	rmsd/lb (root mean square deviation/lower bound)
Coenzyme A	-7.7	0	0
	-7.6	43.203	40.274
	-7.6	46	42.974
	-7.6	44.764	41.141
	-7.6	11.762	6.135
	-7.5	48.812	45.186
	-7.5	41.543	38.881
	-7.4	10.308	7.804
	-7.4	7.879	5.444
Glycerol	-4.1	0	0
	-4	27.277	26.221
	-4	2.324	0.689
	-4	27.36	26.286
	-3.9	51.725	51.252
	-3.8	20.862	20.14
	-3.8	24.046	23.339
	-3.8	24.179	23.483
	-3.7	2.275	1.486
(R)-3-hydroxytetradecanal	-3.9	0	0
	-3.8	19.391	17.209
	-3.8	3.302	1.626
	-3.5	15.995	13.512
	-3.5	5.453	2.825
	-3.5	16.391	13.991
	-3.4	18.358	16.644
	-3.4	16.969	14.778
	-3.3	16.688	14.711

Due to their high availability as metabolites and low binding affinity, D-leucine, and coenzyme A are highly applicable as binding ligands for surfactin. In order to test the effectiveness of these peptides, *in vivo* studies on animal models can be carried out following the completion of drug design.

4. Conclusions

We conducted a computational study to assess the binding potential of surfactin from *Bacillus* spp. to identify new potential candidates for the treatment of cancer. Thus, according to our *in silico* study, surfactin may act as a potential drug that can be used as a promising anti-cancer agent. Nevertheless, further experimental studies are needed to investigate the ligand binding and anti-cancer potentials of such surfactin-like molecules. While these studies are promising, more research is needed to fully understand the potential of surfactin as an anticancer agent. Additionally, the use of surfactin in cancer treatment would require further testing and evaluation to determine its safety and efficacy in humans.

Disclosure statement

The authors declare no conflict of interest.

Author contributions

M.A.A., U.T.F., M.F., S.D., and M.A.S. were involved in research conceptualization and design; M.A.A. and U.T.F. took part in the collection and/or assembly of data; U.T.F., M.F., S.D., and M.A.S. were involved in data analysis and interpretation; M.F. and M.A.S. took part in manuscript writing; and M.F., S.D., and M.A.S. were involved in the critical revision of the manuscript. All authors read and approved the final manuscript.

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Application of Pelvic Peritoneum Closure Combined with Extraperitoneal Colostomy in Laparoscopic Surgery for Low Rectal Cancer

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Abstract: *Background:* In the treatment of colorectal cancer, laparoscopic surgery has seen a significant amount of success. Reducing the risk of postoperative complications and improving patients' quality of life can be accomplished by appropriately employing pelvic peritoneal repair and sigmoid colostomy when appropriate. *Objective:* To compare fusion closure of pelvic peritoneum combined with extraperitoneal colostomy with non-closure of pelvic peritoneum combined with intraperitoneal colostomy in patients with low rectal cancer who had permanent colostomy. *Methods:* Low rectal cancer patients admitted to Hengshui People's Hospital for permanent colostomy were evaluated. The participants were divided into two groups: an observation and a control group. All 30 cases in the observation group underwent pelvic peritoneum closure and extraperitoneal colostomy, while the other 30 cases in the control group underwent intraperitoneal colostomy. The C-reactive protein (CRP) levels of the participants in both groups were evaluated for 6 months to 2 years (24 h before, 24 h after, 48 h after, 96 h after surgery). *Results:* Comparing the colostomy operative time, time to first passage of flatus postoperatively, time to first defecation postoperatively, length of hospital stay, laboratory indicators, stoma-related complications, colostomy function, *etc*., the colostomy operative time significantly differed between the two groups ($P < 0.05$); the observation group did considerably better than the control group in terms of stoma-related complications and bowel movement control 6 months after surgery ($P < 0.05$); and although serum CRP levels increased in both groups 48 h after surgery, the difference was significant ($P < 0.05$). *Conclusion:* Extraperitoneal colostomy can improve the quality of life of patients with permanent stoma and reduce the occurrence of stoma-related complications. Thus, this technique is worthy of promotion in clinical practice.

Keywords: Low rectal cancer; Closure of pelvic peritoneum; Permanent colostomy; Extraperitoneal colostomy via rectus abdominis

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1. Background

Colorectal cancer is one of the common malignant tumors of the intestines in China. In terms of the incidence rate and mortality rate, colorectal cancer is the third most common malignant tumor and fourth deadliest cancer worldwide. This cancer not only affects the patient's health, but also places a significant financial burden on the patient. The continuous deepening of cancer research and improvement of diagnosis and treatment have significantly improved the five-year survival rate of patients with colorectal cancer. In China, the incidence of colorectal cancer is increasing every year [1,2]. The persistent development of medical standards enables early detection, diagnosis, and treatment of colorectal cancer, all of which can help improve the quality of life of patients. In China, middle and low rectal cancers have higher incidence

rates. Unfortunately, since middle and low rectal cancers are not easily detected and diagnosed in time, permanent colostomy is required in some patients whose anus cannot be preserved during surgical treatment. As colorectal cancer research deepens, complete surgical treatment options are used. Colorectal cancer surgery has evolved from open to laparoscopic to robotic. Laparoscopic approach has become the standard surgical procedure for colorectal cancer surgery due to its minimal invasiveness, clear vision, and finer dissection [3-5]. The reasonable use of pelvic peritoneal reconstruction and sigmoid colostomy can help reduce postoperative complications and improve the quality of life of patients. However, surgical treatment will inevitably result in some complications [6]. Standardized and improved surgical procedures can reduce complications and improve patients' quality of life. In the present study, we compared 60 patients with low rectal cancer admitted to Hengshui People's Hospital from January 2019 to January 2021 for surgery. The aim of this study was to compare the advantages and disadvantages of pelvic peritoneum closure and colostomy, as well as to follow-up to observe the bowel movement control in the patients with colostomy. We performed pelvic peritoneum closure combined with extraperitoneal colostomy under laparoscopic surgery for low rectal cancer to evaluate its benefits and improve the patients' quality of life. This study provides guidance for future clinical work and to improve the quality of life of patients after surgery.

2. Materials and methods

2.1. Baseline information

We selected 60 patients with low rectal cancer (tumor < 5 cm from the anus) who were admitted to the Department of General Surgery of Hengshui People's Hospital from January 2019 to January 2021. These patients were diagnosed with rectal adenocarcinoma via pathological examination, and all of them underwent laparoscopic Miles' surgery (abdominoperineal resection combined with rectal cancer resection). According to the type of surgical method used, the patients were divided into two groups: an observation group and a control group. The observation group composed of 30 cases who were treated with pelvic peritoneum closure combined with tunnel colostomy via rectus abdominis. There were 18 male and 12 female patients, age ranging from 26 to 68 years, with an average age of 48.6 ± 6.24 years. In terms of postoperative pathological examination and staging, there were 22 cases with tumor diameter less than 5 cm, 17 cases with TNM stage I–II, and 13 cases with TNM stage III–IV. The control group composed of 30 cases who were treated with non-closure of pelvic peritoneum combined with intraperitoneal colostomy. The control group consisted of 14 male and 16 female patients, age ranging from 25 to 69 years, with an average age of 43.6 ± 5.68 years. In terms of postoperative pathological examination and staging, there were 18 cases with tumor diameter < 5 cm, 16 cases with TNM stage I–II, and 14 cases with TNM stage III–IV. There was no significant difference in the baseline parameters between the two groups ($P > 0.05$). This study was approved by the medical ethics committee of Hengshui People's Hospital (Approval No. 2020-2-007). Informed consent was obtained from the patients and their family members before being recruited for this study.

2.2. Methods

Both groups of patients received general anesthesia, and their heads were positioned lower than their feet. Dissociation, specimen removal, and perineum suture were the same. The surgery followed total mesorectal excision (TME). In the observation group, pelvic peritoneum closure was paired with extraperitoneal colostomy via rectus abdominis, whereas in the control group, intraperitoneal colostomy was employed. The sacrum was drained in both groups. After suturing the perineal incision, 2-0 barbed suture (Johnson & Johnson SAPP1A405) was used with 1 cm stitches and a 0.5 cm margin. The pelvic peritoneum was sutured continuously from the bladder or uterine rectal lacuna to the pelvic entry above the iliac crest without producing pores. In the lateral sigmoid colon extraperitoneum, forceps were used to bluntly detach the

extraperitoneal space from the lateral abdominal wall to produce an extraperitoneal tunnel. Extraperitoneal colostomy was performed via rectus abdominis. The patient circumstances influenced the preoperative positioning. The navel and left anterior superior iliac spine make up around 1/3 to 1/2 of the flat abdominal wall. A 2–3-cm circular incision was performed to remove the skin and subcutaneous fat to reveal the anterior rectus sheath and rectus abdominis (blunt dissection to protect the integrity of muscle fibers). Dissection was made from the posterior rectus sheath to the peritoneum. The peritoneum on the side of the blunt tunnel separation outside the peritoneum would merge with the peritoneum on the side of the intestinal tube exiting the stoma. The tunnel's width was modified based on the intestine and mesentery, and the sigmoid colon was led out along the tunnel to avoid twisting or folding of the mesentery. There was moderate intestinal tube tension near the stoma. The intestinal stoma was sutured with the rectus abdominis anterior sheath, subcutaneous tissue, and dermis, and an ostomy bag was externally fixed. Intraperitoneal colostomy via rectus abdominis was performed. The navel and the left anterior superior iliac spine 1/3 to 2/3 of the abdominal wall were selected as the fistula location, and layer-by-layer dissection was used to expose the peritoneum. Given a tight sigmoid colon, the intestine and abdominal wall were repaired in layers (**Figure 1**).

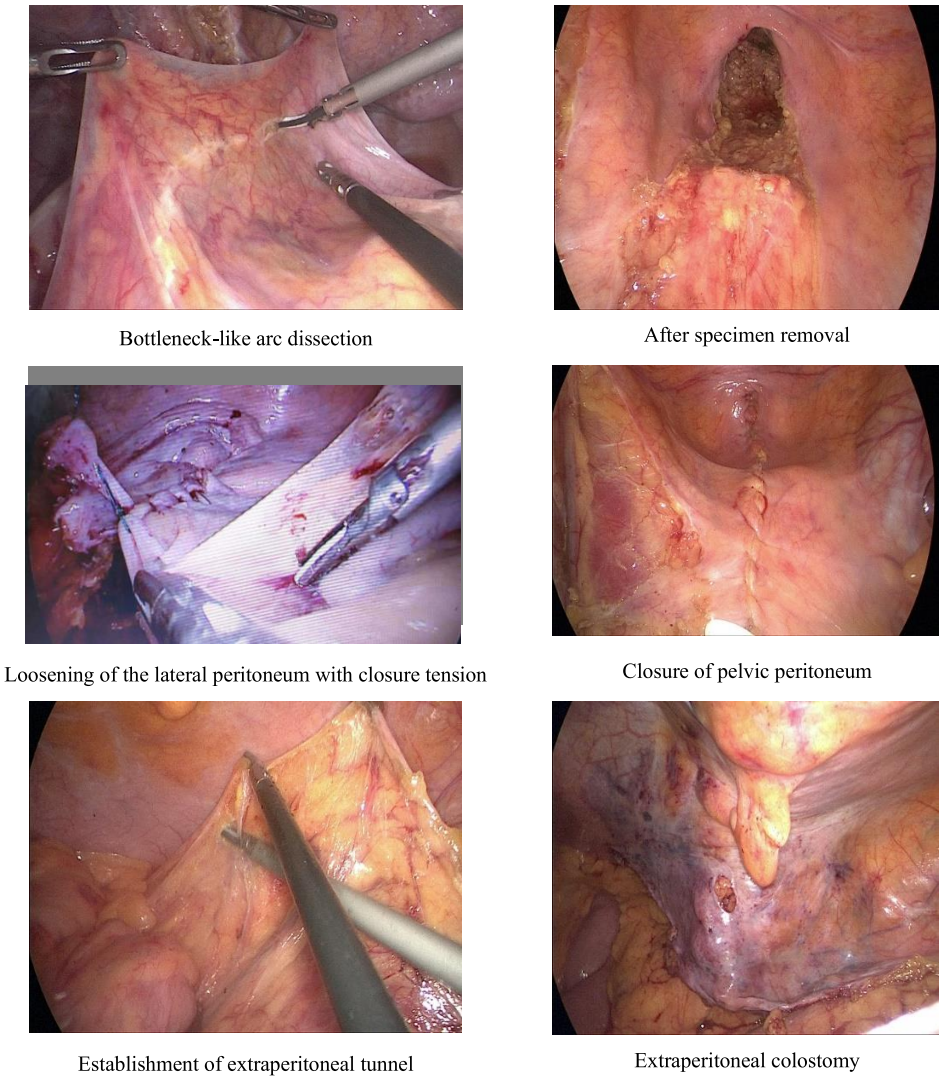

Figure 1. Dissociation, specimen removal, and perineum suture. The surgery followed total mesorectal excision (TME). In the observation group, pelvic peritoneum closure was paired with extraperitoneal colostomy via rectus abdominis, while in the control group, intraperitoneal colostomy was employed.

2.3. Observation indicators

(1) Surgery-related indicators: colostomy operative time, time to first passage of flatus postoperatively, time to first defecation postoperatively, and length of hospital stay.

(2) Laboratory indicators: serum C-reactive protein (CRP) levels 24 h before operation and 24 h, 48 h, and 96 h after surgery; the CRP levels were determined using the turbidimetric method (normal reference value 0–8 mg/L; reagents were purchased from Goldsite Co., Ltd., Shenzhen, China).

(3) Follow-up indicators: stoma-related complications (stoma bleeding, stoma separation, dermatitis around the stoma, stoma stenosis, stoma retraction, stoma prolapse, intestinal obstruction, and parastomal hernia) were evaluated for at least 6 months to 2 years (through follow-up visits, telephone follow-up, WeChat follow-up, *etc.*); bowel movement control was evaluated by interviewing the patients about their bowel movement control ability and any signals (abdominal distension, bowel sounds, and peristalsis of the left lower abdominal wall) before defecation at 2 months, 4 months, and 6 months after surgery; stoma function was evaluated based on three aspects: (i) whether the patients can detect defecation signals before bowel movement, (ii) whether the patients can distinguish flatus from feces, and (iii) whether the patients can perceive the whole process of defecation.

2.4. Statistical analysis

Statistical Package for Social Sciences (SPSS) version 21.0 was used to analyze and process all data. Measurement data were expressed in mean ± standard deviation (SD) and analyzed using *t* test. Count data were expressed in percentage (%) and analyzed using chi-square (χ^2) test or Fisher's exact test (when the number of cases was 0 or less than 5). $P < 0.05$ indicates statistically significant difference.

3. Results

3.1. Surgery-related indicators

The colostomy operative time was significantly different between the observation group and the control group ($P < 0.05$). There were no significant differences in the time to first flatus, time to first defecation, and length of hospital stay ($P > 0.05$), as shown in **Table 1**.

Table 1. Comparison of surgery-related indicators between the observation group and the control group

Group	Colostomy operative time (min)	Time to first flatus (h)	Time to first defecation (h)	Length of hospital stay (days)
Observation group	26.64 ± 2.45	30.28 ± 4.38	52.48 ± 4.78	14.42 ± 3.68
Control group	24.86 ± 2.78	29.44 ± 3.46	53.26 ± 4.86	15.18 ± 2.46
t	2.854	0.824	0.627	0.94
P	0.000	0.413	0.553	0.351

3.2. Laboratory indicators

There was no significant difference in serum CRP level between the observation group and the control group at 24 h before surgery, 24 h after surgery, and 96 h after surgery ($P > 0.05$). At 48 h after surgery, the serum CRP levels of the two groups increased, and the difference was statistically significant ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of laboratory indicators after colostomy between the two groups

	CRP levels (mg/L)			
	24 h before surgery	**24 h after surgery**	**48 h after surgery**	**96 h after surgery**
Observation group	4.54 ± 0.78	30.78 ± 3.98	47.75 ± 4.38	25.46 ± 6.15
Control group	4.67 ± 0.82	31.52 ± 4.13	53.16 ± 5.19	28.88 ± 7.43
t	0.629	0.708	4.363	1.942
P	0.532	0.482	0.000	0.057

3.3. Stoma-related complications

Based on the analysis of stoma-related complications in the two groups, the patients in the observation group had no parastomal hernias, and the total number of stoma-related complications in the observation group was fewer than that in the control group; there was statistical difference between the two groups ($P < 0.05$). In terms of bleeding, stoma separation, dermatitis around stoma, stoma retraction, stoma stenosis, stoma prolapse, intestinal obstruction, and parastomal hernia, there was no statistical difference between the two groups ($P > 0.05$), as shown in **Table 3**. (Note: There could be one or more stoma-related complications in the same patient, and thus the total complication rate was relatively high.)

Table 3. Comparison of stoma-related complications between the two groups

Group	Stoma bleeding	Stoma separation	Dermatitis around stoma	Stoma retraction	Stoma stenosis	Stoma prolapse	Intestinal obstruction	Parastomal hernia	Total number of complications (%)
A	0	2	4	1	1	0	0	0	8 (24.2%)
B	1	4	4	1	2	2	4	4	22 (73.3%)
χ^2		0.19*	0.14	0.52*	0.00*	0.52	2.41*	2.41*	13.07
P	1.000	0.667	0.704	0.472	1.000	0.472	0.121	0.121	0.000

The blanks indicate Fisher's exact test. *Yates-corrected chi-square test was used. Abbreviations: A, observational group; B, control group.

3.4. Follow-up indicators

After postoperative follow-up for 2 months, 4 months, and 6 months, the patients could detect defecation signals before bowel movement; their stomas were evaluated based on whether they could distinguish flatus from feces as well as perceive the whole process of defecation. The number of cases in the observation group was generally more than that in the control group. The indicators were not significantly different between the timepoints at 2 months after surgery and at 4 months after surgery ($P > 0.05$), but there were statistical differences in the follow-up indicators 6 months after surgery ($P < 0.05$), as shown in **Table 4**.

Table 4. Comparison of stoma function at 2 months, 4 months, and 6 months after surgery

	2 months after surgery		*P*	4 months after surgery		*P*	6 months after surgery		*P*
	Observation	**Control**		**Observation**	**Control**		**Observation**	**Control**	
A	6	10	0.243	13	19	0.121	19	26	0.037
B	4	8	0.197	8	15	0.063	15	24	0.015
C	2	5	0.421	6	14	0.028	14	22	0.035

Abbreviations: A, defecation signals before bowel movement; B, ability to distinguish between flatus and feces; C, ability to perceive the whole process of defecation. Observation refers to the observation group, and control refers to the control group.

4. Discussion

At present, whether the pelvic peritoneum should be closed after laparoscopic Miles' surgery in low rectal cancer is still debatable [7-9]. The present study cannot prove the association between pelvic peritoneum reconstruction and the occurrence of postoperative intestinal obstruction. However, 4 cases of intestinal obstruction were observed in the control group whose pelvic peritoneum was unclosed. Among them, one case was examined in a second surgery. Partial small bowel resection was performed in view of severe bowel adhesions to the pelvic group. Hence, we believe that closing the pelvic peritoneum has clinical significance. (2) Some patients with rectal cancer require postoperative radiotherapy due to their condition. If the pelvic floor and peritoneum are not sutured, the small intestine that has herniated into the pelvic floor is prone to radiation enteritis, which may trigger intestinal obstruction. Severe cases require surgical treatment, and subsequent surgeries may be more challenging. The recovery of patients after surgery may be difficult, which increases the physical and mental burden on patients. (3) In many instances after Miles' surgery, infection or even dehiscence of the perineal wound occurs. If the pelvic floor and peritoneum are not sutured, perineal inflammation may occur, causing pelvic infection and small bowel obstruction. Closure of the pelvic peritoneum is a routine operation in Miles' open abdomen surgery. In this study, presacral drainage tube was routinely placed through the perineum to reduce the risk of retrograde infection, and the closure of pelvic peritoneum was performed in this study. The main points of the operation are summarized as follows: (i) taking into account of individual differences, tension was reduced when closing the peritoneum; (ii) TME principle was adhered to during lateral dissection in order to properly retain the lateral peritoneum in preparation for closure [10-13]; when the tension was high and the peritoneum could not be closed, ultrasonic knife gasification was used to dissect the peritoneum and subperitoneal fascia to properly loosen the lateral peritoneum, maintain the continuity of the subperitoneal fascia, and achieve tension-free closure of the pelvic peritoneum; (3) regarding the pelvic floor design, Denonvilliers' fascia was dissected in the avascular area about 0.5 cm above the peritoneal reflex, and 2-0 barbed suture was used to close the pelvic peritoneum from the pelvic floor to the proximal end; the end of the thread was clamped using Hem-o-lok clip. Through the aforementioned methods, pelvic peritoneal reconstruction was successfully completed in all cases of the present study. Based on the findings of this study, there are several advantages of extraperitoneal colostomy of sigmoid colon. (1) Through sigmoid colon extraperitoneal colostomy, the abdominal organ pressure on the abdominal wall is diffused and buffered, and the stoma form is altered. This minimizes the colon-abdominal wall space and parastomal hernia. No patient in the observation group reported parastomal hernia, although the number of cases and follow-up period were found to be associated. Thus, further clinical research is necessary. Similar results have been observed by Tomasz [14]. (2) The intestinal stoma and peritubular tissue may become connected and fixed, supporting and stabilizing the tunnel colon and decreasing retraction or prolapse of the colostomy tube. Peritubular tissue presses on the colostomy tube to improve feces control. (3) The intestinal stoma's parietal peritoneum is nerve-rich. During intestinal expansion caused by gas or feces, nerve terminals in the parietal peritoneum are stimulated, triggering the defecation reflex. This allows patients to detect and control bowel motions, unlike intraperitoneal colostomy. Extraperitoneal colostomy should be every surgeon's first choice, although this approach should be thoroughly assessed based on the patient's condition. The present study's small sample size and short follow-up period are limitations. To compare the long-term consequences of the two colostomy procedures and the function of artificial anus, a large sample study and extended follow-up are needed. This would contribute to finding a better laparoscopic permanent sigmoid colostomy technique to improve patients' quality of life.

Colostomy may cause complications, among which parastomal hernia is a complex problem. Treatment is determined by the size of the inguinal ring and hernia contents. Some patients would require hernia surgery. Foreign body reaction from postoperative patch implantation, along with feces contamination and

infection, causes operation failure and recurrence. In severe cases, intestines may block. The subsequent surgery is more demanding and expensive. Effective methods to decrease parastomal hernia after a permanent colostomy are clinically significant. The incidence rate of parastomal hernia varies [15]. In order to reduce the occurrence of parastomal hernia, some surgeons place a patch in the muscle layer of the stoma in advance to prevent the occurrence of parastomal hernia [16,17]. However, infection may occur since the patch is a foreign body. In addition, the implanted patch increases the treatment cost. Performing complex operation in laparoscopic surgery is not practical, as it requires surgeons with high technical skills. In theory, extraperitoneal colostomy via rectus abdominis can reduce the incidence of parastomal hernia. In line with results reported in other literature, this study demonstrated that the incidence of parastomal hernia in the extraperitoneal colostomy group was significantly lower than that in the intraperitoneal colostomy group [18]. When performing colostomy, it is necessary to ensure that the intestinal tube and its mesentery pass through the preset tunnel anteriorly, without squeezing or twisting. The tension of the colon in the tunnel should be reduced as much as possible to ensure sufficient blood supply to the intestinal stoma and unobstructed intestinal cavity. Therefore, choosing an appropriate colostomy method, upgrading nursing education on stoma, reducing stoma-related complications, and further improving the quality of life of patients after surgery are the issues that clinical surgeons should address and continue to explore. In the present study, we evaluated the patients' CRP levels before and after surgery. A significant rise in CRP suggests acute inflammation or infection, prompting doctors or nurses to take appropriate action. This study suggests that surgical stress and inflammation are behind the increase in postoperative CRP levels, which indicates incision inflammation. After inflammation reduces, CRP returns to normal [19].

5. Conclusion

In recent years, laparoscopic surgery for colorectal cancer has become more refined and standardized following the intense development of this technique. Laparoscopic surgery is commonly employed in most of the colorectal cancer surgeries in our hospital. Extraperitoneal colostomy via rectus abdominis is associated with good clinical outcomes in the treatment of low rectal cancer and anal cancer. This colostomy method is used as the routine in laparoscopic Miles' surgery. However, owing to the small number of samples and short follow-up period in the present study, clinical studies involving larger samples are needed for confirmation. Closure of pelvic peritoneum combined with extraperitoneal colostomy via rectus abdominis can reduce postoperative complications and improves the patient's ability to control defecation after the surgery. Therefore, this technique can provide solace to the patients and improve their quality of life. On this basis, this technique is worthy of further improvement and promotion in clinical practice.

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Disclosure statement

The authors declare no conflict of interest.

Author contributions

H.Y. and C.S. contributed in the study conception, as well as the design and writing of the first draft of the manuscript; C.W. and J.L. collected and analyzed the data; Y.L and L.L interpreted the results; and B.Z. and J.L. supervised the whole research and revised the final draft of the manuscript. All authors agreed to be accountable for all aspects of the work.

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Clinical Analysis of Patients with Cervical Cancer After Adequate Radiotherapy and Surgery

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Abstract: *Objective:* To explore the effect of giving adequate radiotherapy before surgery on the recovery of patients with cervical cancer. *Methods:* An experimental study was carried out in Aviation General Hospital (hereafter referred as our hospital) from March 2022 to March 2023. Fifty patients with cervical cancer were retrospectively analyzed. The patients underwent surgery 15–20 days after adequate external radiotherapy, and the clinical effect was analyzed. *Results:* The symptoms of the patients were relieved, among which contact bleeding and irregular vaginal bleeding completely resolved in 27 patients and 19 patients, respectively; although intermittent vaginal bleeding persisted in 3 patients, the symptom improved compared with before treatment; for 1 patient, the treatment was ineffective, as there was no significant improvement in symptoms. For patients with stage IB2 cancer, the tumor reduction rate after treatment was about 50%–70%, but the reduction in 2 patients was insignificant. *Conclusion:* Cervical cancer is a serious condition. Adequate radiotherapy before surgery has a significant effect. It reduces the difficulty of surgery and creates an opportunity for patients to undergo surgery, thus improving the treatment effect. Therefore, it is worthy of clinical promotion.

Keywords: Cervical cancer; Adequate radiotherapy; Surgical treatment; Clinical effect

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1. Introduction

Cervical cancer is a common malignancy among women. Its incidence is relatively high, and there has been a continuous increase in recent years. Cervical cancer has garnered widespread clinical attention in recent years. Judging from the current situation, the clinical treatment of such patients is usually surgery, but for some patients in the advanced stage, due to the severity of their condition, comprehensive therapy including radiotherapy and chemotherapy is often used on the basis of surgery in order to improve the symptoms and prolong the survival period of patients [1]. With medical advancements in recent years, clinical research has strengthened. Data have shown that giving adequate radiotherapy to patients with cervical cancer before surgery can enhance the therapeutic effect on patients with advanced disease. On this basis, taking patients in our hospital as research subjects, adequate radiotherapy before surgery was performed, and the effect was analyzed.

2. Materials and methods

2.1. Data analysis

This study was carried out in our hospital from March 2022 to March 2023. The subjects of the study were 50 patients with advanced cervical cancer under the care of our hospital during this period. All patients were female, with the oldest being 70 years old, and the youngest 35 years old; the mean age of the patients

was 50.45 ± 3.23. Among them, 30 cases were stage IB2, while 20 cases were stage IIB2. The patients were diagnosed based on the diagnostic criteria for cervical cancer. The clinical symptoms of the patients were mainly contact bleeding and irregular vaginal bleeding. All patients in the study were informed about the experimental process and expressed their willingness to cooperate with the study. The study was approved by the hospital ethics committee. The possibility of patients with other major diseases and psychiatric history can be excluded.

2.2. Research methods

After the patients were admitted to the hospital, various investigations were performed, including routine blood examination, liver and kidney function, electrocardiography, chest radiography, and pelvic computed tomography (CT). The patients were given adequate radiotherapy before surgery. The The patients underwent whole pelvic irradiation based on external irradiation of 6 MV X-rays. The dose was controlled at 20–50 Gy, and the irradiation was performed five times a week, from Monday to Friday. The course of the treatment was four weeks. After the completion of the scheduled radiotherapy, the patients were examined for parametrial infiltration. Given the improvement or disappearance of the surrounding infiltration and the increased elasticity of parametrial tissue, surgery was performed 15–22 days after completion of radiotherapy. The surgical procedures included radical hysterectomy, pelvic lymph node dissection, and bilateral adnexectomy.

2.3. Observation indicators

The patients in this study were observed and followed-up on their treatment and prognosis.

3. Results

3.1. Treatment effect

The symptoms experienced by the patients were relieved after adequate radiotherapy and surgery; among them, contact bleeding and irregular vaginal bleeding completely resolved in 27 patients and 19 patients, respectively; although intermittent vaginal bleeding persisted in 3 patients, the symptom improved compared with before treatment; in 1 patient, the treatment was ineffective, as there was no significant improvement in symptoms. Gynecological bimanual and trimanual examinations showed that the parametrial tissue softened and the parametrial space widened in these patients. For those with stage IB2 cancer, the tumor reduction rate after treatment was about 50%–70%, but there were 2 patients whose tumor reduction was insignificant.

3.2. Surgical situation

The surgery for all 50 patients went smoothly, without any major complications, such as massive bleeding. The average bleeding volume was about 600 mL.

3.3. Pathological analysis

None of the patients had parametrial invasion after surgery; there was no invasion to the vaginal stump, and the patients showed no signs of lymph node metastasis.

3.4. Postoperative follow-up

All 50 patients were followed-up for 1 year after surgery. Among them, 3 patients died of lung metastasis, while the other 47 patients survived. No patient had pelvic recurrence or lymph node metastasis.

4. Discussion

Cervical cancer is a common malignancy in clinical practice, and it continues to be listed among the top gynecological malignancies in our country. The symptoms of cervical cancer are mainly irregular vaginal bleeding and contact bleeding on sexual intercourse, both of which have a great impact on the quality of life of patients. If patients are not timely treated, their condition may deteriorate and metastasis may even occur, thus reducing the survival period of patients and posing a serious threat to their health. With the country's development in recent years, many people are now adopting unhealthy lifestyles, leading to an increase in number of cervical cancer cases in our country. Cervical cancer has become a major disease that poses a serious threat to women's health. However, clinical research on the treatment of cervical cancer has also been strengthened in recent years, with new treatment methods being introduced, updated, and improved, so as to ensure the improvement of treatment effect and prolong the survival period of cervical cancer patients.

Comprehensive therapy including chemotherapy, radiotherapy, and surgery is usually used for the treatment of cervical cancer. It is believed that any one of these methods can achieve better therapeutic effect. Among them, radiotherapy can reduce the tumor area, gradually promote the recovery of patients, prevent metastasis, and effectively control the disease; surgery, on the other hand, can be used to remove the lesion directly, block the development of cancer cells, and promote the recovery of patients. According to research data, the 5-year survival rate of patients with early cervical cancer is as high as 80% after surgery or radiotherapy alone, but the combined treatment can enhance the clinical effect and prolong the survival time of patients [2]. However, despite clinical advancements, there are still some patients who have poor awareness, and when the disease is detected, it is already in the middle and advanced stage. Such patients usually have parametrial invasion or regional lymph node metastasis, which makes surgery more difficult, patients more prone to massive bleeding during surgery, and reduces the treatment effect, resulting in high postoperative recurrence rate and mortality; in addition, the 5-year survival rate after treatment is only about 50%.

On this basis, it has been clinically suggested that adequate radiotherapy should be performed before surgery. Preoperative radiotherapy can create operative opportunities for patients who are unable to undergo surgery, promote parametrial cancer cell death, widen the parametrial space, and reduce the tumor volume. It provides treatment opportunities to patients who are unable to undergo surgery. Clinical research data have shown that in patients with stage IB2 or stage II cervical cancer, the benefits of preoperative radiotherapy can only be observed when the tumor area is 4 cm or more than 6 cm [3]. Among the patients with stage IB2 cancer in this study, a significant reduction in tumor volume and intraoperative blood loss was observed. In addition, the tumor volume reduction in patients with squamous cell carcinoma was found to be more significant than that in patients with adenocarcinoma [4], suggesting that cervical adenocarcinoma has poor radiosensitivity. At the same time, through preoperative radiotherapy, local lesions may reduce or disappear, the parametrial tissue becomes softer, and the parametrial space becomes wider, which can reduce the scope of surgical resection and risk of damage to the patient. This would not only be less traumatic to the patients, but also improve the thoroughness of surgical resection, thereby increasing the success of surgery and reducing the recurrence rate [5]. At the same time, adequate preoperative radiotherapy has a certain toxic effect on cancer cells and can seal the patient's lymphatic vessels and microvessels, thus preventing cancer cell proliferation or metastasis during surgery [6]. Among the patients in the present study, lung metastases occurred in 3 cases, with no other metastases found. For patients with stage IB2 and stage IIB cancer, surgical intervention after radiotherapy can reduce the need for long-term radiotherapy, thereby reducing the occurrence of cervical adhesions, endometritis, intrauterine effusion, and empyema [7]. It can reduce the pain caused by the disease itself or treatment, the economic burden on the patient, and the incidence of complications, such as radiation proctitis and radiation

cystitis; these benefits are of positive significance for improving the treatment effect and promoting the recovery of patients [8]. From the perspective of surgery, the results of the present study showed that the average intraoperative blood loss was 600 mL, with no serious complications occurring during the surgery, and all operations were successfully completed. The sutures were removed within 7 days after surgery, and the patients were discharged from the hospital 8–10 days after surgery. The incisions healed well; none of the patients had delayed wound healing or failure of proper wound healing, indicating that preoperative radiotherapy and surgery have positive significance for cervical cancer patients. In the postoperative follow-up period, ThinPrep cytology test (TCT) of the vaginal stump and CT scan were regularly performed. The results showed good postoperative recovery effect. Although 3 patients died from lung metastasis, the quality of life and survival rate of the remaining patients were good.

In conclusion, patients with advanced cervical cancer are in severe states. The quality of life of some patients are poor due to their intolerability to surgery. With preoperative radiotherapy, the tumor size can be reduced before surgery, the patient's surgical adaptability can be improved, patients are provided with the opportunity for surgery, and the surgery can be carried out smoothly, thus reducing the risk of complications. Preoperative radiotherapy is of great significance to alleviating symptoms, ensuring the effectiveness of surgical removal, and improving the survival rate of patients after surgery. Through this study, we recommend the popularization of preoperative radiotherapy.

Disclosure statement

The authors declare no conflict of interest.

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Correlation Between NLRP3 Inflammasome and GP73 Levels and Hepatitis B Cirrhosis with Esophageal Varices Rupture

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Abstract: *Objective:* To investigate the correlation between NOD-like receptor family protein 3 (NLRP3) inflammasome and Golgi protein 73 (GP73) levels and hepatitis B cirrhosis with esophageal varices (EV) rupture. *Methods:* The subjects of this study were 145 patients with hepatitis B cirrhosis and varices who were treated in our hospital in recent years. Endoscopic examination was performed on the patients. The patients were divided into two groups according to whether there was EV rupture: rupture group and non-rupture group. The correlation between plasma NLRP3 and GP73 levels and hepatitis B cirrhosis with EV rupture was analyzed. *Results:* Through observation, comparing the levels of NLRP3 and GP73 between the two groups, the levels of NLRP3 and GP73 were significantly higher in the rupture group than in the non-rupture group ($P < 0.05$). Logistic regression analysis showed that NLRP3 and GP73 levels and Child-Pugh classification were related risk factors of hepatitis B cirrhosis with EV rupture. *Conclusion:* NLRP3 inflammasome and GP73 levels are closely related to hepatitis B cirrhosis with EV rupture. The corresponding evaluation aids in predicting EV rupture and bleeding in patients with hepatitis B cirrhosis.

Keywords: Hepatitis B cirrhosis; Esophageal varices; NLRP3 inflammasome; GP73; Correlation

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1. Introduction

Liver cirrhosis is a transition period from chronic liver disease to liver cancer. The co-existence of liver cirrhosis with other diseases affects the survival period and quality of life of patients. Esophageal varices (EV) are considered a serious complication of liver cirrhosis. Patients often present with massive hematemesis without symptoms or tarry stools. Clinical studies have shown that NOD-like receptor family protein 3 (NLRP3) is associated with the occurrence of various diseases and highly expressed in liver cell injury, which may be associated with liver cell apoptosis and related to vascular aging and vascular rupture [1]. Golgi protein 73 (GP73) is a new type of serum marker that has been confirmed to be highly correlated with liver cirrhosis [2] and liver cancer in recent years. It has high sensitivity to liver cell damage [3] and a certain relationship with the occurrence of EV [4]. Therefore, NLRP3 and GP73 may be associated with liver cirrhosis and EV rupture [5] and may become relevant markers for predicting the risk of EV rupture [6].

The main cause of liver cirrhosis in China is hepatitis B [7]. In this study, 145 patients with hepatitis B cirrhosis complicated with varices in our hospital were selected to determine the correlation between the levels of NLRP3 inflammasome and GP73 and hepatitis B cirrhosis with EV rupture.

2. Materials and methods

2.1. General information

The subjects of this study were 145 patients with hepatitis B cirrhosis and varices admitted to the Department of Infectious Diseases and Gastroenterology of Shaanxi Provincial People's Hospital from January 2020 to December 2022. The diagnosis complied with the Chinese Guidelines for the Diagnosis and Treatment of Liver Cirrhosis (2019 Edition) and the Chinese Guidelines on the Management of Liver Cirrhosis [8]. The patients underwent endoscopic examination and then divided into two groups according to the presence or absence of EV rupture, namely the rupture group and the non-rupture group. There were 75 patients in the rupture group, including 52 male and 23 female patients, age ranging from 41 to 60; there were 70 patients in the non-rupture group, including 51 male and 19 female patients, with age ranging from 42 to 62. There were no significant differences in the baseline data of the two groups of patients ($P > 0.05$). The research protocol was approved by the Ethics Committee of Shaanxi Provincial People's Hospital, and all the patients signed the informed consent.

2.2. Methods

Venous blood was extracted from each patient and placed in a 5 mL vacuum anticoagulant tube. The anticoagulant tube was inverted twice to ensure sufficient contact between the blood and the tube wall. After standing for 1 hour, a pipette was used to extract the upper layer of plasma, and it was then stored in an environment of -80°C. Every 6 months, concentration detection was performed, and the levels of NLRP3 and GP73 in the two groups of patients were detected by enzyme-linked immunosorbent assay (ELISA).

2.3. Statistical analysis

Statistical software SPSS 21.0 was used to process the relevant data in this study; the measurement data were expressed as mean ± standard deviation, and *t*-test was performed. $P < 0.05$ indicates statistically significant difference.

3. Results

3.1. NLRP3 and GP73 levels

Comparing the levels of NLRP3 and GP73 between the two groups, the rupture group had significantly higher NLRP3 and GP73 levels than the non-rupture group ($P < 0.05$). See **Table 1** for details.

Table 1. Comparison of NLRP3 and GP73 levels between the two groups of patients

Group	Number of cases	NLRP3 (ng/L)	GP73 (ng/L)
Rupture group	75	614.62 ± 59.25	183.85 ± 22.61
Non-rupture group	70	546.26 ± 67.12	131.05 ± 21.32
t	–	6.152	14.443
P	–	< 0.001	< 0.001

3.2. Multivariate analysis of liver cirrhosis with EV rupture

Multivariate analysis showed that Child-Pugh classification, NLRP3, and GP73 are related risk factors of liver cirrhosis with EV rupture. See **Table 2** for details.

Table 2. Multivariate logistic regression analysis of liver cirrhosis with EV rupture

Variable	beta	SE	Wald χ^2 value	*P*-value	OR (95%CI)
Child-Pugh classification	2.269	0.785	1.748	0.017	1.839 (1.516–2.589)
NLRP3	2.201	0.783	4.069	0.005	1.993 (1.846–2.765)
GP73	0.063	0.146	16.745	< 0.001	1.865 (1.487–2.697)

Abbreviations: χ^2, chi-square; OR, odds ratio; SE, standard error.

4. Discussion

When chronic liver disease is not effectively controlled [9], it gradually develops into liver cirrhosis, resulting in a more serious degree of liver fibrosis, which promotes an increase in portal venous pressure and blood flow in the gastric or esophageal vessels [10]. Varices [11], which may progress to EV rupture and bleeding, is a risk factor that threatens the life of patients with liver cirrhosis [12]. For patients with rupture and bleeding caused by portal hypertension, they are usually in the decompensated stage of liver cirrhosis and are prone to various complications. Early diagnosis and appropriate intervention can improve the survival rate of patients and disease effect. In order to improve the early diagnostic efficiency of liver cirrhosis with EV rupture, we selected 145 patients with hepatitis B cirrhosis and varices in our hospital as the research subjects [13].

In the human immune system, inflammasome is a relatively important component, most of which are proteolytic complexes, which can recognize pathogens and then transfer signals to promote cell activation and release related inflammatory factors, playing a certain anti-inflammatory effect. NLRP3 is an important member of the inflammasome family that can recognize endogenous and exogenous pathogens and signaling pathways. Studies have shown that excessive intraluminal pressure contributes to the expression of NLRP3 and is closely related to vascular endothelial injury and angiotensin II (AngII) dysfunction [14]. GP73, on the other hand, is a transmembrane glycoprotein in the Golgi apparatus. Unlike NLRP3, which is basically not expressed in normal human tissues, the expression of GP73 decreases if the disease progresses into liver cirrhosis. The increase is most significant in connective tissues and liver cells near cirrhotic nodules [15]. Our results showed that the levels of NLRP3 and GP73 in the rupture group were significantly higher than in the non-rupture group ($P < 0.05$). The reasons are as follows: (i) the number of patients with Child-Pugh C in the rupture group was significantly higher, indicating that the liver reserve capacity of the rupture group was weaker and the liver cirrhosis was relatively more serious, which may be the cause of the rupture; (ii) EV rupture may be due to the increased local vascular pressure, leading to inflammatory response and thus the increase in NLRP3 and GP73 levels.

In order to analyze the correlation between plasma NLRP3 and GP73 levels and hepatitis B cirrhosis with EV rupture, logistic regression analysis was conducted in this study [16]. The results showed that NLRP3 and GP73 levels and Child-Pugh classification are risk factors of hepatitis B cirrhosis with EV rupture. Analysis of the reason may be that NLRP3, as an inflammasome, not only identifies local vascular inflammation, but also promotes inflammatory response, thus causing damage to vascular endothelium. GP73 may be associated with the triggering of inflammatory reactions. A high expression of GP73 is associated with the degree of damage to the nucleus and cell structure, promoting the destruction of local blood vessels, which may be an independent cause of hepatitis B cirrhosis with EV rupture [17].

In conclusion, there is a close relationship between plasma NLRP3 and GP73 levels and hepatitis B cirrhosis with EV rupture, and this evaluation is conducive to the prediction of EV rupture and bleeding in patients.

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Disclosure statement

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Observation on the Effect of Integrated Medical and Nursing Care in Patients with Pulmonary Tuberculosis Combined with Lung Cancer

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Abstract: *Objective:* To explore the effect of integrated medical and nursing care in patients with pulmonary tuberculosis combined with lung cancer. *Methods:* From August 2021 to August 2022, 60 patients with pulmonary tuberculosis combined with lung cancer were admitted. All patients were diagnosed with pulmonary tuberculosis according to the Guidelines for the Diagnosis and Treatment of Pulmonary Tuberculosis and with lung cancer by pathology. The patients were randomly divided into two groups, with 30 cases in each group. The control group received daily nursing care, whereas the study group received integrated medical and nursing care. The sputum conversion rate, tumor remission rate, and quality of life of patients were observed and analyzed. *Results:* The item function score and symptom function score of the observation group were higher than those of the control group ($P < 0.05$); the total effective rate of the observation group was significantly higher than that of the control group ($P < 0.05$); the sputum conversion rate of the observation group was significantly higher than that of the control group ($P < 0.05$). *Conclusion:* For patients with pulmonary tuberculosis combined with lung cancer, the application of integrated medical and nursing care can help consolidate the treatment effect and improve the quality of life of patients; thus, it is worthy of promotion and application.

Keywords: Medical care integration; Pulmonary tuberculosis; Lung cancer

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1. Introduction

Lung cancer is the most common malignant tumor in medical oncology, and chemotherapy is one of the fundamental treatment methods [1]. Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*. Its main clinical manifestations are cough, sputum, chest tightness, shortness of breath, fever, hot flashes in the afternoon, night sweats, and weight loss [2]. The incidence of lung cancer combined with pulmonary tuberculosis is not high, but its treatment poses a challenge. Regarding the relationship between tuberculosis and lung cancer, some think that they are related, some think that they are not, and some think that they are antagonistic. As early as the 19th century, there were records of lung cancer combined with pulmonary tuberculosis. According to autopsy statistics, the coexistence rate of tuberculosis and lung cancer is 0.44%–0.75%. General clinical data have shown that the incidence of tuberculosis combined with

lung cancer is 2%–8%, of which 89.8% are men and 84.6% are over 50 years old; the coexistence of the two diseases is more common in the same lung lobe on the same side; carcinoma is more common, followed by undifferentiated carcinoma; 78% of cases suffer from pulmonary tuberculosis for more than 5–20 years, and most lung cancers are detected in the late stage. In short, with the aging of tuberculosis patients and the rising incidence of lung cancer, the coexistence of lung cancer and tuberculosis has shown an increasing trend. The current epidemic of tuberculosis combined with lung cancer in China is relatively severe and lacks a standardized nursing intervention model. The resulting nursing-related problems are particularly prominent. The integrated medical and nursing care model allows physicians and nurses to actively participate in medical and nursing care, nursing staff to actively participate in medical activities, and medical staff to actively participate in nursing activities, so as to help patients and their families to understand the conditions and actively cooperate with treatment [3]. The aim of the present study was to explore the effect of integrated medical and nursing care in patients with lung cancer combined with pulmonary tuberculosis.

2. Materials and methods

2.1. General information

Sixty patients with pulmonary tuberculosis and lung cancer admitted from August 2021 to August 2022 were included in the study. All 60 patients were diagnosed with pulmonary tuberculosis with reference to the Guidelines for the Diagnosis and Treatment of Tuberculosis and also pathologically confirmed with lung cancer. They were randomly divided into two groups, with 30 patients in each group. The observation group consisted of 18 males and 12 females, age ranging from 23 to 71 years, with an average age of 49.1 ± 4.2 years; there were 9 cases of adenocarcinoma, 8 cases of squamous cell carcinoma, and 13 cases of adenosquamous carcinoma. The control group included 20 males and 10 females, age ranging from 25 to 65 years, with an average age of 48.6 ± 4.1 years; there were 10 cases of adenocarcinoma, 9 cases of squamous cell carcinoma, and 11 cases of adenosquamous carcinoma. There was no statistically significant difference in general information between the two groups of patients ($P > 0.05$).

2.2. Methods

The patients in the control group received daily nursing care. The patients were given environmental introduction, chemotherapy drugs, dietary and activity advice, rest, related examinations, medications, and rehabilitation guidance before leaving the hospital.

The experimental group received the integrated medical and nursing care intervention. (1) Establishment of a comprehensive medical and health responsibility group: After dividing the medical staff of each medical institution into several groups, each of which has an attending physician and a nurse-in-charge, and forming a stable team, appropriate arrangements are made for each squad, while implementing an 8-hour and 24-hour shift system. (2) Comprehensive check-up: All medical staff participate in the check-up, all medical workers communicate with the patients and their family members, physicians check for changes in patients' condition and ask about their physical conditions; nurses ask about patients' care needs and record the changes in their conditions; the nursing staff discusses the treatment and care plan with the patients and their families and designs a personalized treatment and care plan. (3) Integration education of medical personnel: Physicians educate patients and their family members about the pathogenesis and prognosis of tuberculosis combined with lung cancer, as well as inform them of the treatment plan, so as to enhance patients' understanding of these conditions and thus improve their compliance and initiative in the treatment of tuberculosis combined with lung cancer, while nurses provide detailed nursing care to patients; in this process, given the requirement for physical examinations and treatments, patients are informed of the relevant examinations and treatments, and nurses actively accompany patients during the examinations

and treatments, while providing corresponding guidance to ensure a smooth examination. (4) Comprehensive spiritual counseling in healthcare: Medical workers communicate the concerns of patients about the subject matter and skillfully communicate the thoughts of patients based on the patients' personality, education level, and other factors, and they detect patients' negative emotions in a timely manner; physicians take the initiative to help patients understand the disease, counsel patients, and treat the condition appropriately; nurses actively seek to support patients spiritually, create a good medical environment, relieve the mental pressure of the external environment on patients, guide family members to provide care and support to the patients, and improve patients' self-confidence; with significant negative emotions, a psychiatrist is consulted, and appropriate treatment measures are developed. (5) Life counseling with integrated medical care: Medical practitioners assess the nutritional status of patients and develop corresponding meal plans; physicians inform the patient of the importance of following the medically prescribed diet; nurses devise a detailed meal plan, such as the way of eating, the amount of food eaten, and the type of food to be consumed, so as to ensure nutritional balance. (6) Comprehensive hospitalization guidance and follow-up treatment: Medical work and patients are followed-up before hospitalization. During hospitalization, medical staff seeks to understand the changing status of patients' condition and gives patients targeted medication and review guidance, while nursing staff gains insights into patients' psychological and living status and provides guidance on physical exercise, psychology, diet, and so on.

2.3. Observation indicators

The observation indicators in this study included sputum conversion rate, tumor remission rate, and quality of life of patients. The sputum bacteriology conversion rate was recorded as negative sputum test results for 3 consecutive months; after treatment and nursing, ≥ 3 specimens were selected every month, and sputum smear examination was performed ≥ 1 time per month. The tumor remission rate was divided into four according to the new standard of solid tumor efficacy evaluation: complete remission, partial remission, stable disease, and progressive disease; total curative rate = complete remission rate + partial remission rate. The quality of life of patients was evaluated by the cancer patient quality of life score (QOL), in which the full score is 60 points, followed by 51–60 points indicating well, 41–50 points indicating good, 31–40 points indicating fair, 21–30 points indicating poor, and < 20 points indicating extremely poor.

2.4. Statistical analysis

SPSS 24.0 was used for data analysis; measurement data were expressed as mean ± standard deviation, and t-test was performed; count data were expressed as percentages, and chi-squared test (χ^2) test was performed. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of the quality of life between the two groups of patients

Before the intervention, the QOL item function score and symptom function score of patients in the observation group were 56.19 ± 10.58 points and 62.58 ± 10.95 points, respectively, whereas those in the control group were 55.73 ± 11.03 points and 62.15 ± 11.12 points, respectively; there were no statistically significant differences in comparison (t = 0.165, $P = 0.870$; t = 0.151, $P = 0.881$). After the intervention, the item function score and symptom function score of the observation group were 69.01 ± 11.26 points and 76.17 ± 11.92 points, respectively, both of which were higher than those of the control group (62.87 ± 10.59 points and 69.27 ± 12.01 points), and the difference was statistically significant (t = 2.176, $P = 0.034$; t = 2.233, $P = 0.029$).

3.2. Comparison of short-term curative effect between the two groups of patients

In the control group, 1 case (3.33%) had complete remission, 16 cases (53.33%) had partial remission, 8 cases (26.67%) had stable disease, and 5 cases (13.33%) had progressive disease; the total curative rate was 56.67%. In the observation group, 3 cases (10.00%) had complete remission, 23 cases (76.67%) had partial remission, 2 cases (6.67%) had stable disease, and 2 cases (6.67%) had disease progression; the total curative rate was 86.67%. The total curative rate of the observation group was significantly higher than that of the control group ($\chi^2 = 6.648$, $P = 0.010$).

3.3. Comparison of sputum conversion rate between the two groups of patients

After treatment, the sputum examination turned negative in 26 cases (86.7%) in the observation group and 19 cases (63.3%) in the control group; the difference was statistically significant ($P < 0.05$).

4. Discussion

With the development of society, the level of medical care and living standards continue to improve, and the demands for nursing care are increasing. The traditional nursing model can no longer meet the demands of patients due to untimely communication of medical and nursing information and the fact that communication with patients is not open and timely [5]. Integrated medical and nursing care is a new type of nursing mode that is patient centered. Physicians and nursing staff communicate with each other in a timely manner to objectively assess patients' condition in detail and maximize patient's care through a collaborative and cooperative approach [6,7]. Tuberculosis and lung cancer are both difficult to treat and have a long treatment course, thereby requiring high clinical care [8,9]. Most of these patients have low self-immunity and have a certain fear of the disease. In the integrated medical and nursing care, the medical staff will explain the disease-related knowledge to patients from a professional perspective, improve their awareness of the disease, and eliminate their fear. Patients are also given appropriate psychological counseling, so that they can maintain a good mental state while receiving anti-tuberculosis treatment and chemotherapy and build confidence in overcoming the disease [10-15]. Medical care integration is an advanced nursing concept at present. It focuses on the combination of clinical and nursing operations and comprehensively considers the needs of patients to improve the quality of care, so as to facilitate rapid recovery. Improvements in nursing practice are accompanied by advances in nursing research. However, due to business in the work schedule of nurses and the lack of understanding of the integration of medical care, many scientific research results have not been applied or even understood. Practicing medical care integration allows for more efficient use of medical and nursing resources, improves nursing practice by introducing evidence from nursing research, updates nursing knowledge, changes traditional nursing concepts and methods, and promotes nursing research.

With the continuous adjustment of the nursing model, the integrated medical and nursing care model has been applied in clinical nursing, especially in certain diseases that require higher nursing care. The treatment of pulmonary tuberculosis combined with lung cancer is difficult and harmful to the patients themselves, thereby requiring high clinical care. The nursing staff can carry out a series of nursing work, such as psychological care, basic care, life care, and health education. Effective communication between doctors and nursing staff enables both parties to be aware of the patients' current situation at the same time, which would not only benefit in the effort of rescuing and treating patients in a timely manner when problems occur, but also improve the relevance of the nursing staff's work. The establishment of clinical diagnosis and treatment pathways can help patients achieve continuous and targeted nursing care, which is important for improving treatment outcomes and patients' quality of life.

In conclusion, for patients with pulmonary tuberculosis and lung cancer, the application of integrated medical and nursing care can help consolidate the treatment effect and improve the quality of life of patients;

thus, its application is worth promoting.

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Performance Evaluation of Combined Detection of Serum CEA, CYFRA21-1, CA125, and NSE in Patients with Lung Cancer by Fluorescence Flow Cytometry

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Abstract: *Objective:* To investigate the effect of combined detection of serum carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), cancer antigen 125 (CA125), and neuron-specific enolase (NSE) in patients with lung cancer by fluorescence flow cytometry. *Methods:* From August 2019 to July 2022, 200 patients with lung cancer diagnosed by pathology in our hospital were retrospectively analyzed. 2 mL venous blood was collected in a fasting state and centrifuged to separate the serum (containing human chorionic gonadotropin antibody [anti-hCG antibody], hepatitis B surface antibody [anti-HBs antibody], and CEA). *Results:* The sensitivities of CEA and CYFRA21-1 detected via enzyme-linked immunosorbent assay (ELISA) were 100%, and the detection limits were 0.5 ng/mL and 0.1 ng/mL, respectively; the sensitivities of CA125 and NSE detected via flow cytometry were 100%, and the detection limits were 10 U/mL and 2 ng/mL, respectively. Compared with ELISA, the sensitivities of CA125 and NSE detected via flow cytometry were higher. When the concentration of CEA was 10–40 ng/mL, the sensitivities of the three markers CYFRA21-1, CA125, and NSE showed no significant changes ($P > 0.05$); when the concentration of CEA was 40–80 ng/mL, the sensitivity of CEA significantly decreased ($P < 0.01$), but the sensitivities of the three markers CYFRA21-1, CA125, and NSE showed no significant changes ($P > 0.05$); when the concentration of CEA was 80–200 ng/mL, the sensitivities of all four markers showed no significant changes ($P > 0.05$). *Conclusion:* Compared with the double-antibody sandwich ELISA, fluorescence flow cytometry has certain advantages, including high sensitivity, good precision, short detection time, low sample usage, and low medical cost; thus, it is worthy of clinical promotion.

Keywords: Fluorescence flow cytometry; Lung cancer; Serum

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1. Introduction

Lung cancer is a malignant tumor with the highest global incidence. The incidence and mortality of lung cancer are on the rise globally. Lung cancer is one of the most common malignant tumors in China among which its morbidity and mortality rank first in our country. Lung cancer has surpassed liver cancer as the leading cause of death from malignant tumors. It has always been one of the malignant tumors that seriously threatens human health and life. There are about 450,000 new lung cancer cases and about 500,000 deaths in our country every year. Therefore, it is particularly important to raise awareness of the symptoms of lung cancer and its early diagnosis, considering the cruciality of lung cancer prevention and screening. Studies

have shown that 80%–90% of lung cancer patients have elevated serum carcinoembryonic antigen (CEA). CEA is related to the prognosis of lung cancer [1]. At present, commonly used tumor marker detection methods include immunochromatography, enzyme-linked immunosorbent assay (ELISA), colloidal gold immunochromatography assay [2], chemiluminescence immunoassay [3,4], *etc*. However, these methods have varying degrees of limitations, especially for the detection of markers, such as CEA, cytokeratin 19 fragment (CYFRA21-1), cancer antigen 125 (CA125), and neuron-specific enolase (NSE) [5-8]. Therefore, in our study, serum CEA, CYFRA21-1, CA125, and NSE in patients with lung cancer were detected, and a comparative analysis was conducted based on commonly used clinical tumor markers. Five serum samples from patients with lung cancer were measured in parallel, and the results were compared and analyzed by double-antibody sandwich ELISA and fluorescence flow cytometry to verify the accuracy and stability of the methods. In this study, 200 serum samples from lung cancer patients were collected, including 70 single-positive serum samples and 130 double-positive serum samples. Fluorescence flow cytometry was used to detect CEA, CYFRA21-1, CA125, and NSE in lung cancer patients.

2. Materials and methods

2.1. Specimen collection

From August 2019 to July 2022, 200 patients with lung cancer in our hospital, including 128 males and 72 females, were retrospectively analyzed. All cases were confirmed by histopathological examination: 27 cases of stage I cancer, 67 cases of stage II cancer, 30 cases of stage III cancer, and 76 cases of stage IV cancer. Patients with vital organ involvement, including the heart, liver, and kidney, were excluded. 2 mL of venous blood were collected under fasting state and centrifuged to separate the serum (including human chorionic gonadotropin antibody [anti-hCG antibody], hepatitis B surface antibody [anti-HBs antibody], and CEA).

2.2. Reagents and instruments

The assay reagents were provided by Beijing Wantai Biotechnology Co., Ltd., and the fluorescence flow cytometry method was provided by Beijing Beckman Technology Co., Ltd. The instrument used was Hitachi 7020 automatic biochemistry analyzer; ELISA was provided by Shanghai Anpu Analytical Instrument Co., Ltd., and the double-antibody sandwich ELISA kit was manufactured by Hangzhou Haide Biotechnology Co., Ltd.

2.3. Methods

Five portions of fresh serum (containing CEA, CYFRA21-1, CA125, and NSE) were taken in 1–2 mL each and placed in 2 mL Eppendorf (EP) tubes. The sample-containing tubes were placed in a refrigerator at 4°C overnight and subsequently taken and placed on plate A. Parallel samples were made on plate A with 5×10^4/L alkaline phosphatase (ALP)-labeled gold secondary antibody (20 μL in each well). The results were determined by double-antibody sandwich ELISA and flow cytometry, respectively, and the result of the double-antibody sandwich ELISA were taken as the standard.

2.4. Statistical analysis

All data were processed and analyzed by SPSS 19.0. The measurement data were expressed as mean ± standard deviation (s), and t-test was used; the count data were expressed as percentages, and chi-squared (χ^2) test was used; $P < 0.05$ in one-way analysis of variance (ANOVA) was considered statistically significant.

3. Results

Under ELISA, the sensitivities of CEA and CYFRA21-1 were 100%, and the detection limits were 0.5 ng/mL and 0.1 ng/mL, respectively; the sensitivities of CA125 and NSE were 78.96% and 81.39%, respectively, with detection limits of 10 U/mL and 2 ng/mL, respectively. Compared with ELISA, for detection by flow cytometry, the sensitivities of CA125 and NSE were 100.00%, and the detection limits were 10 U/mL and 2 ng/mL, respectively; the sensitivities of CEA and CYFRA21-1 were 100%, with detection limits of 0.5 ng/mL and 0.1 ng/mL, respectively. The sensitivities of CA125 and NSE detected via flow cytometry were higher. When the concentration of CEA was 10–40 ng/mL, the sensitivities of the four markers showed no significant changes ($P > 0.05$); when the concentration of CEA was 40–80 ng/mL, the sensitivity of CEA significantly decreased ($P < 0.01$), but the sensitivities of CYFRA21-1, CA125, and NSE showed no significant changes ($P > 0.05$); when the concentration of CEA was 80–200 ng/mL, the sensitivities of all four markers showed no significant changes ($P > 0.05$), as shown in **Table 1**.

Table 1. Sensitivity of CEA, CYFRA21-1, CA125, and NSE detected by flow cytometry

Concentration	CEA	CYFRA21-1	CA125	NSE
10–40 ng/mL	87.12%	89.21%	85.36%	84.69%
40–80 ng/mL	67.98%	89.29%	86.23%	88.99%
80–200 ng/mL	81.36%	84.36%	87.21%	87.23%

4. Discussion

In recent years, the detection of tumor markers has been a common clinical practice, as people's understanding of the occurrence and development of tumors has grown. Since tumor cells or tissues in the human body have special structures and functions, different from normal cells, their metabolites or active substances are significantly different from normal tissues, so the detection of tumor markers is of great significance for clinical diagnosis and treatment. Currently, commonly used clinical tumor markers include CA125, CYFRA21-1, NSE, cytokeratin 7 (CK7), fibroblast growth factor 13 (FGF13), and tumor necrosis factor receptor superfamily 2. In the present study, CEA, CYFRA21-1, CA125, and NSE in the serum of patients with lung cancer were detected by flow cytometry. This method has a good correlation with ELISA; the linear range of CEA is 0.20–1.00 μg/L, the linear range of CYFRA21-1 is 0.40–1.00 μg/L, the linear range of CA125 is 0.40–1.00 μg/L, and the linear range of NSE is 0.40–1.00 μg/L.

Lung cancer serum is a relatively special tumor marker. By detecting lung cancer cells in the serum, we can determine if the patient is suffering from lung cancer. The diagnosis with lung cancer serum has certain similarities with that of other tumors, but its specificity is not high; hence, it is not a good diagnostic method. Lung cancer serum is a special type of tumor marker that has certain value in the diagnosis of lung cancer. In order to determine whether a particular type of tumor marker will affect the diagnosis, the first step is to determine which other tumors this tumor marker shares features with. For instance, both liver cancer and pancreatic cancer share common features of hepatocellular carcinoma; epithelial cell carcinoma shares a common feature with bowel cancer; and squamous cell carcinoma shares common features with both breast cancer and cervical cancer. Only in this way can its diagnostic value be determined according to the characteristics of different tumors. Lung cancer, like other tumors, is characterized by abnormal changes in cell differentiation, proliferation, or apoptosis. In terms of pathological types, lung cancer not only shares the same characteristics as adenocarcinoma, but also shares similar changing patterns with squamous cell carcinoma and small cell carcinoma. Lung cancer serum, as a special type of tumor marker, can reflect the possibility of a patient suffering from lung cancer and whether the patient will deteriorate after suffering from this cancer.

With more tumor cells in the serum, the patient's condition will be more severe. In clinical diagnosis, the tumor cell content in serum has a certain relationship with lung tumors. If tumor metastasis occurs in a patient with lung cancer, the tumor cell content in serum will show a sharp rise. Therefore, if there is an abnormal increase in the patient's serum, it is necessary to be alert of the likelihood that the cancer has metastasized. However, it may also be related to other problems, such as cancer recurrence. Therefore, tumor cell content in serum cannot be used as a basis for diagnosis. When a patient is diagnosed with lung cancer, related examinations and surgical treatment should be performed in time. If the condition worsens, it should be controlled and treated. The current state of medicine cannot determine whether a patient is suffering from lung cancer; rather, it can only determine the extent of the condition through relevant markers. Proteins in serum often change over time. Some of these proteins may show abnormalities even in normal conditions, such as molecules and other biologically active substances on the surface of cells that change over time. Therefore, if a patient's serum protein is abnormal, it indicates that the patient may be suffering from lung cancer.

The method of using serum to detect lung cancer is increasingly used in clinical practice, especially in the diagnosis of early lung cancer. This detection method of lung cancer has high application value. Serum testing for different cancers yields different data that can be used to determine the need for treatment. This method can be used for the prognosis of lung cancer, in addition to the diagnosis of early lung cancer. By analyzing the number and size of tumor cells in serum, it is possible to determine whether a patient is suffering from lung cancer. However, it is impossible to determine whether treatment is required solely based on the number of cancer cells in serum, mainly because malignant tumors have strong genetic characteristics. In many cases, the number of cancer cells in serum does not show obvious changes. In addition, even if an increase in number of cancer cells in serum is detected, but the patient does not show any symptoms or obvious discomfort, then no treatment is required.

Lung cancer is one of the most common malignant tumors in clinical practice. According to statistics, its incidence rate and mortality rate rank first among all malignant tumors, showing an increasing trend year by year. Patients with early lung cancer generally have no obvious symptoms, so most patients are already at an advanced stage when they are diagnosed, thus missing the best time for treatment. Therefore, early detection and early diagnosis are particularly important. At present, the tumor markers commonly used in clinical practice mainly include CEA, carbohydrate antigen 19-9 (CA19-9), glycosyltransferase (CAGT), cytokeratin-18, *etc*. These tumor markers have high value in early screening, but their specificity and sensitivity are limited. In recent years, with the development of China's medical and health services, tumor markers have been widely used in clinical practice, but the accuracy and stability of the test require further improvement. In recent years, as a high-sensitivity and high-specificity detection technology [9], fluorescence flow cytometry has garnered widespread attention in the field of tumor marker detection. CEA is generally elevated in the serum of lung cancer patients [10-12], and NSE, which is a highly specific nucleoprotein factor comprising a small molecular protein composed of 26 amino acids, is significantly elevated in lung cancer tissues [13-15].

In conclusion, compared with double-antibody sandwich ELISA, fluorescence flow cytometry has certain advantages, including high sensitivity, good precision, short detection time, less sample consumption, and low medical cost; thus, it is worthy of clinical promotion.

Disclosure statement

The authors declare no conflict of interest.

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Role of CST1 in Promoting Gastric Cancer Metastasis and Analysis of Its Mechanism

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Abstract: *Objective:* To elucidate the role and mechanism of cysteine protease inhibitor SN (CST1) in promoting the metastasis of gastric cancer. *Methods:* (1) Firstly, 6 pairs of cancer and paracancer tissue samples from gastric cancer patients without distant metastasis and 5 pairs of cancer and paracancer tissue samples from gastric cancer patients with peritoneal metastasis were collected for transcriptome sequencing. Statistical analysis was performed on the sequencing results to identify significantly upregulated differential genes. (2) Another 75 pairs of cancer and paracancer tissue samples were collected from gastric cancer patients, and the protein and total RNA of gastric cancer tissue samples were extracted. Western blot and quantitative reverse transcription polymerase chain reaction (qRT-PCR) were used to detect the expression of CST1 protein and messenger RNA (mRNA) in gastric cancer and adjacent tissues. (3) The total protein and total RNA of AGS, BGC823, HGC-27, MGC803, MKN45, SGC7901, and SNU-1 gastric cancer cells and normal gastric mucosal epithelial cells GES-1 were extracted. Western blot and qRT-PCR were used to detect CST1 protein and mRNA expression. *Results:* (1) The significantly upregulated differential gene *CST1* was screened, and the expression of CST1 in gastric cancer tissues was significantly higher than that in adjacent tissues. (2) Compared with normal gastric mucosal epithelial cells GES-1, the expression of CST1 in gastric cancer cell lines was upregulated, and the expression of CST1 in HGC-27 and SNU-1 was relatively low, while the expression of CST1 in AGS and MKN45 was relatively high. At the same time, a stable cell line of HGC-27 overexpressing CST1 and MKN45 knocking down CST1 was successfully constructed. (3) Overexpression or knockdown of CST1 did not significantly change the proliferation ability of gastric cancer cells, but can promote the migration and invasion of gastric cancer cells. (4) CST1 may promote the metastasis of gastric cancer cells by activating the epithelial–mesenchymal transition (EMT) signaling pathway. *Conclusion: CST1* gene promotes the migration of gastric cancer cells, and we found through animal experiments that CST1 can affect the metastasis and invasion function of gastric cancer and is negatively correlated with the level of E-cadherin.

Keywords: CST1; Gastric cancer; Mechanism

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1. Introduction

Gastric cancer metastasis is an important factor affecting the prognosis of patients with gastric cancer and is one of the main causes of mortality in these patients. Studies have shown that inhibiting the expression of extracellular matrix (ECM) components can promote tumor cell migration and epithelial-mesenchymal

transition (EMT) is involved in the regulation of gastric cancer metastasis. Transcription factor CST1 is a highly conserved transcription factor that plays an important role in various malignant tumors. However, the role and mechanism of CST1 in gastric cancer remain unclear. Our research group has found that the expression of CST1 protein is upregulated in gastric cancer tissues and its expression level is closely related to disease progression as well as the prognosis of patients with gastric cancer [1-5]. Recently, we have found a new protein in gastric cancer tissue: CST1. Its expression in gastric cancer tissue has been found to be significantly higher than that in normal gastric mucosal epithelium and primary tumor ($P < 0.05$). We have further proven that CST1 is a new tumor-promoting factor by Western blotting, immunofluorescence, flow cytometry, and other methods. Further studies have found that CST1 is highly expressed in gastric cancer specimens and cell lines *in vitro* and its high expression is closely related to poor prognosis in patients. Experiments on CST1 knockout mice have shown that CST1 overexpression can significantly inhibit tumor growth and metastasis, indicating that it is closely related to distant metastasis in gastric cancer. At the same time, we have verified its transcriptional activation function by luciferase reporter assay. In the study, reverse transcription polymerase chain reaction (RT-PCR), Western blot, immunohistochemistry, and other methods were used to verify the hypothesis that CST1 can promote the migration of gastric cancer cells under the condition of high expression in the stomach. By immunofluorescence staining, we have also found that the *CST1* gene is located between the gastric mucosa cell layer and the epithelial cell layer, as well as in the nucleus; through bioinformatics analysis, it has been found that this gene may encode a new protein complex protein: transcription activator. The results of immunofluorescence staining have shown that CST1, its interacting proteins (Krüppel-like factor 4 [KLF4], [KLF5], and matrix metalloproteinase-2 [MMP-2]), and E-cadherin (N-cadherin) are localized in the nucleus; *in vitro* experiments have found that this gene can promote the upregulation of EMT-related molecules (E-cadherin) in cancer cells; animal experiments have also proven that it can promote tumor metastasis. Therefore, CST1 is considered a new gastric cancer metastasis-related regulatory protein, which may promote gastric cancer metastasis by regulating EMT in cancer cells and affecting the invasion ability of tumor cells.

2. Materials and methods

2.1. Materials

(1) The cell line used in this study was derived from human gastric cancer tissue, and it was acquired from the gastric tissue of gastric cancer patients after surgical resection. (2) In this experiment, we used human gastric cancer cell line SGC-7901 and RT-PCR to detect the transcription factor CST1; Western blot was used to detect the expression of CST1 protein; the cells were cultured on the basis of ordinary medium and phosphate-buffered saline (PBS) in the prepared Dulbecco's Modified Eagle Medium (DMEM) buffer. (3) The kits used in this experiment, including all reagents and accessories, were produced by Shanghai Aladdin Biochemical Technology Co., Ltd., who also provided supporting consumables and instruments. (4) The main reagents and consumables used were as follows: PCR primers and probe primers, synthesized by Beijing Aidi Biotechnology Co., Ltd.; Western blot, immunohistochemistry, and fluorescence in situ hybridization, purchased from American Gibco Company; reverse transcription PCR, purchased from American Tener Company; immunofluorescence microscope, purchased from American Affymetrix Company; electrophoresis buffer dimethyl sulfoxide (DMSO) + 5% sodium dodecyl sulfate (SDS) prepared from DMSO, with DMSO at pH 7.4; gel purification solution, agar sugar gel purification solution, 4',6-diamidino-2-phenylindole (DAPI) gel purification solution, and agarose gel, produced by Sigma Company. (5) The main equipment used was as follows: microplate reader (WSTY-1P/ST5000S, Shimadzu, Japan); fluorescence microscope (WST-100, Shimadzu, Japan).

2.2. Methods

The expression of CST1 in gastric cancer tissues was detected by immunohistochemical method. Immunohistochemistry (IHC) staining and ELISA were used to detect the changes in clinicopathological features caused by the high expression of CST1 and its impact on the prognosis of gastric cancer patients. We screened differential genes in human gastric cancer specimens by RT-PCR. The stably cultured cell lines were isolated from human gastric cancer cell lines by Western blot, and the protein was extracted for future use. *CST1* mRNA level was detected by RT-PCR, and the corresponding primers for reverse transcription were selected to synthesize copy DNA (cDNA) according to its expression level. The stable cultured cell line was isolated from human gastric cancer tissue specimens by Western blot, and the protein was extracted, purified, and separated after Tricine-SDS-PAGE electrophoresis. The isolated protein was further verified by Western blot. CST1 and its interacting proteins (Klf4, Klf5, Mmp2) and E-cadherin (N-cadherin) were identified in the nucleus. The localization of the above cytokines (interleukin 4 [IL-4], IL-6, interferon gamma [IFN-γ], tumor necrosis factor alpha [TNF-α]) in the nucleus was detected by IHC staining, and the above cytokines and TNF-α were detected by ELISA. The content of its downstream related cytokines (IL-4 and IL-6) was in the nucleus. The effect of CST1 protein on the expression levels of the above cytokines and the combination of CST1 and E-cadherin protein were observed by Western blot. We also applied real-time PCR to detect the changes in the transcription levels of related genes, and the interaction between CST1 and KLF4 protein was verified by luciferase reporter gene detection experiments.

3. Results

3.1. Screening of differentially upregulated gene *CST*1 in gastric cancer

In 6 pairs of gastric cancer and adjacent tissues without distant metastasis, a total of 3,904 differentially expressed genes were screened out, and the results showed that a large number of upregulated and downregulated differentially expressed genes. A total of 2,243 differentially expressed genes were screened out in 5 pairs of gastric cancer and adjacent tissues with peritoneal metastasis, and the results showed a large number of upregulated and downregulated differential genes. The upregulated differentially expressed genes screened out by the above two groups were intersected, and Venn diagram analysis showed that there were 768 shared differentially expressed genes. Among the 768 common upregulated differentially expressed genes, CST1 was upregulated 55.38 times in the non-metastatic gastric cancer group and 105.89 times in the gastric cancer group with peritoneal metastasis, and the *P*-value was less than 0.05, suggesting a statistical difference.

3.2. High expression of CST1 protein and messenger RNA in gastric cancer tissues

Western blot was used to detect the expression of CST1 in 75 pairs of gastric cancer and adjacent tissues; it was found that the expression level of CST1 in gastric cancer tissues, compared to the corresponding adjacent tissues, was significantly upregulated ($P < 0.05$). qRT-PCR was then used to detect the *CST1* mRNA expression level in the same 75 pairs of gastric cancer and adjacent tissues; it was found that the *CST1* mRNA level in gastric cancer tissues was significantly higher than that in adjacent tissues ($P < 0.05$).

3.3. Local expression of CST1 in gastric cancer cell lines

In order to study the expression levels of CST1 protein and its mRNA in gastric cancer cell lines and normal gastric mucosal epithelial cells, Western blot and qRT-PCR were used to detect CST1 protein and mRNA expressions, respectively, in normal gastric epithelial cells GES-1 and gastric cancer cells AGS, BGC823, HGC-27, MGC803, MKN45, SGC7901, and SNU-1. The trend of CST1 protein and mRNA expressions in eight cell lines was basically the same, that is, the protein expression and mRNA level of CST1 in gastric

cancer cells were significantly higher than those in normal gastric mucosal epithelial cells. In gastric cancer cell lines, the expression of CST1 in AGS and MKN45 were relatively the highest, while the expression of CST1 in SNU-1 and HGC-27 were relatively the lowest ($P < 0.05$).

3.4. CST1 activates epithelial–mesenchymal transition signaling pathway

In order to determine the effect of CST1 expression on EMT signaling pathway, we used Western blot to detect the expression of EMT pathway-related proteins in HGC-27 overexpressing CST1 and CST1-knocked down MKN45 cell lines. Compared with HGC-27-mock, CST1 overexpression can upregulate the expression of vimentin, Snail, and MMP-2 proteins in HGC-27-CST1 cells; compared with MKN45-shcontrol, knockdown of CST1 can downregulate the expression of vimentin, Snail, and MMP-2 proteins ($P < 0.05$). The results indicated that CST1 activates the EMT signaling pathway in gastric cancer cells.

4. Discussion

Gastric cancer is one of the most common malignant tumors in China, and about 50% of patients will have local or distant metastasis. Therefore, elucidating the mechanism of distant metastasis of gastric cancer is an important part of the treatment and prognosis of gastric cancer. CST1 is a new protein whose high expression is thought to play an important role in the progression of gastric cancer. However, the significance of CST1 expression in gastric cancer and its relationship with gastric cancer invasion and metastasis are still unclear. Although there are a number of studies on the mechanism of invasion and metastasis of gastric cancer, no effective diagnostic markers and therapeutic targets of gastric cancer have been discovered [6-8]. The transcription factor CST1 is a highly conserved transcription factor, which has functions of inhibiting cell proliferation and promoting cell apoptosis. The expression of *CST1* gene is closely related to the occurrence and development of tumors, and its expression is higher in gastric cancer. In the present study, we found that highly expressed *CST1* gene in the stomach can affect the migration ability of gastric cancer cells and has an upregulation effect on the level of E-cadherin through *in vitro* experiments; our mouse experiments confirmed that it regulates the migration and invasion of gastric cancer stem cells and tumor stem cells. Our previous research has demonstrated that the transcription factor E-cadherin can upregulate the expression of *CST1* gene and promote EMT in cancer cells. In addition, we found through bioinformatics analysis that CST1 is highly expressed in gastric cancer tissues and it may be a new gastric cancer metastasis-related regulatory protein. In addition, we found that CST1 can promote ubiquitination and degradation of E-cadherin while inhibiting its degradation *in vitro* and E-cadherin may be an important factor in the occurrence of EMT, which is one of the important mechanisms in tumor metastasis. We verified that CST1 has a regulatory role in EMT development in gastric cancer cells by *in vitro* experiments. At the same time, the animal experiments also showed that CST1 plays a role in gastric cancer metastasis [9-15].

The results showed the following: (1) the expression of CST1 protein in gastric cancer tissue was significantly higher than that in normal gastric mucosa and normal gastric mucosa, and the proliferation of tumor cells in the high-expression group was significantly higher than that in the low-expression control group; (2) RT-PCR results showed that transcription factor CST1 is highly expressed in gastric cancer tissues and is related to the prognosis of gastric cancer patients, and multiple mutation sites were observed in the promoter region of the *CST1* gene in gastric cancer patients retrieved from the transcription factor database; (3) Western blot showed that cells with high expression of CST1 were distributed in G1 phase, whereas the cell cycle distribution was wider in the low expression group; (4) IHC results showed that high expression of CST1 can promote cell proliferation; (5) immunofluorescence staining results showed that the high-expression group KLF4, KLF5, and E-cadherin were localized in the nucleus, while the low-expression group was localized in the cytoplasm; (6) bioinformatics analysis predicted that CST1 may

encode a new protein complex protein: transcriptional activator V1-E3; gene structural and functional predictions revealed that the protein complex may be involved in the regulation of tumor metastasis and invasion. This study verified the role of *CST1* gene in promoting the migration of gastric cancer cells through a series of molecular biology and immunohistochemical methods. At the same time, through animal experiments, we found that CST1 could affect the metastasis and invasion function of gastric cancer and is negatively correlated with E-cadherin levels.

In conclusion, we believe that transcription factor CST1 promotes tumor cell migration by inhibiting the expression of ECM components and E-cadherin, as an important molecule of EMT, participates in the regulation of cancer cell invasion and metastasis.

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Retrospective Analysis of the Effect of Auricular Acupuncture on Pain and Gastrointestinal Motility Recovery After Laparoscopic Surgery for Colorectal Cancer

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Abstract: *Objective:* To investigate the effect of auricular acupuncture on postoperative pain and gastrointestinal motility recovery after laparoscopic surgery for colorectal cancer. *Methods:* The clinical data of patients who underwent laparoscopic radical surgery for colorectal cancer in our hospital from April 2020 to December 2021 were collected. Based on the inclusion and exclusion criteria, 76 patients were included in the retrospective analysis. Depending on whether they received auricular acupuncture or not, the patients were divided into two groups: 46 patients in the experimental group (auricular acupuncture) and 30 patients in the control group. The differences between the two groups were analyzed. *Results:* The time to first flatus of the experimental group was significantly shorter than that of the control group (52.2 ± 7.36 h versus 66.3 ± 7.83 h; $P < 0.001$). Similarly, the time to first defecation of the experimental group was significantly shorter than that of the control group (76.3 ± 7.76 h versus 86.1 ± 10.79 h; $P < 0.001$). The time to first fluid intake of the auricular group was significantly shorter than that of the control group (90.4 ± 8.92 h versus 107.3 ± 9.66 h, $P < 0.001$). Compared with the control group, the experimental group scored significantly lower on the visual analogue scale on postoperative days 2 and 3 ($P < 0.001$). *Conclusion:* Auricular acupuncture is an effective traditional Chinese medicine external treatment method. It can promote gastrointestinal motility recovery in patients after laparoscopic radical surgery for colorectal cancer and also reduce postoperative pain and discomfort. Furthermore, this therapy is easy to operate and well-accepted by patients. Therefore, it should be strongly promoted in clinical practice.

Keywords: Auricular acupuncture; Colorectal cancer; Laparoscopy; Pain; Postoperative gastrointestinal motility

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1. Introduction

Acupuncture, a traditional Chinese medicine therapy, has garnered widespread attention in research as a promising intervention for rapid postoperative recovery [1]. Postoperative pain is a crucial determinant of postoperative recovery, and studies have demonstrated that acupuncture can effectively alleviate pain and reduce the need for analgesics while mitigating the side effects of drugs [2]. In addition, acupuncture has shown potential in promoting the recovery of bowel function after surgery [3], as evidenced by shorter bowel

transit times, reduced hospital stays, and lesser complications. Since postoperative patients often present with psychological issues, such as anxiety, depression, and sleep disturbances, acupuncture has emerged as a feasible solution to improving their emotional state and sleep quality while reducing related symptoms [4].

Auricular acupuncture, a form of acupuncture point therapy, is performed by applying pressure on precise areas of the ear to activate the body's nervous and meridian systems, thereby regulating bodily functions and treating illnesses. According to traditional Chinese medicine (TCM) theory, the ear acts as a reflex zone that corresponds to various parts and organs of the body, allowing stimulation of certain organs and parts through the application of pressure on the corresponding auricular points. The therapeutic technique of auricular acupuncture involves the use of specialized tools or fingers to apply pressure on auricular points, with targeted treatment that aligns with the patient's symptoms and constitution. This therapy is broadly utilized in managing a range of conditions, including headaches [5], insomnia [6], indigestion [7], depression [8], and smoking cessation [9]. Several studies have demonstrated the effectiveness of auricular acupuncture in mitigating pain [10] and alleviating symptoms like nausea, vomiting, and fatigue in cancer patients [11].

The efficacy of auricular acupuncture as a potential method for alleviating postoperative pain and promoting the recuperation of postoperative gastrointestinal motility in colorectal cancer remains undetermined. In order to address this gap in literature, we conducted a retrospective analysis of patient data from our hospital spanning between April 2020 and December 2021. Specifically, we compared the differences in postoperative outcomes between colorectal cancer patients who received auricular acupuncture and those who did not. The aim of this study was to evaluate the effect of auricular acupuncture on postoperative pain management and gastrointestinal motility recovery.

2. Data and methods

2.1. Study population

The clinical data of patients who underwent laparoscopic radical surgery for colorectal cancer in our hospital from April 2020 to December 2021 were collected, including gender, age, body mass index (BMI), whether neoadjuvant therapy was given, pathological stage of tumor, time of surgery, time to first defecation postoperatively, time to first flatus postoperatively, time to first fluid intake postoperatively, and postoperative days 1–5 visual analogue scale (VAS) score.

Inclusion criteria: (i) age 18–80; (ii) underwent laparoscopic radical surgery for colorectal cancer; (iii) first abdominal surgery; (iv) American Society of Anesthesiologists (ASA) class I–III.

Exclusion criteria: (i) combined organ resection or intermediate open surgery; (ii) those with stoma; (iii) severe cardiac, pulmonary, hepatic, or renal insufficiency; (iv) psychiatric disorders; (v) severe postoperative complications; (vi) second postoperative surgery; (vii) early inflammatory bowel obstruction; (viii) incomplete data, including the main observation indicators.

This study was reviewed by the ethical review committee of Shaanxi Provincial People's Hospital (2020R007), and the patients were informed of the details of the procedure.

2.2. Grouping and treatment methods

Depending on whether they received auricular acupuncture or not, the patients were divided into two groups: the experimental (auricular acupuncture) group and the control group.

In the experimental group, auricular acupressure was performed using ear seeds. First, the corresponding auricular points (including the subcortex, shenmen, stomach, large intestine, small intestine, triple energizer, and sympathy) were located and cleaned with 75% ethanol or iodine swabs. Using forceps, vaccaria seeds were then placed on these points. The auricular points were pressed with light to heavy pressure until the sensations of heat, pain, swelling, numbness, and soreness appeared. Each acupoint was

pressed for 5 min each time and pressed again after an interval of 8 h. The intervention was stopped upon restoration of bowel movement after 5 days; other factors that caused abnormal bowel movement, such as early inflammatory bowel obstruction, were considered and excluded.

2.3. Efficacy observation indicators

The efficacy observation indicators of the patients were as follows: (i) time to first flatus and defecation postoperatively; (ii) time to first fluid intake postoperatively; (iii) VAS scores on postoperative days 1–5.

2.4. Statistical analysis

SPSS 23.0 was used for statistical analysis. Data including age, BMI, operation time, time to first flatus and defecation, and time to first fluid intake were in accordance with the normal distribution by Shapiro-Wilk test. These data were expressed as mean ± standard deviation (SD). The differences in these data between the experimental group and the control group were compared using Student's t-test. The VAS scores that failed to conform to the normal distribution after normality test were expressed as medians (interquartile range), and Mann-Whitney U test was used to test the difference between the two groups. Count data including gender and whether neoadjuvant treatment was given were expressed by frequency, and the difference between the two groups was compared by chi-square (χ^2) test. $P < 0.05$ indicated that the difference was statistically significant.

3. Results

3.1. General clinical data

A total of 76 patients (41 males and 35 females) were included in the study based on the inclusion and exclusion criteria. The experimental group consisted of 46 patients, while the control group consisted of 30 patients. The mean age of the patients was 63.4 ± 10.9. There were no significant differences between the two groups in their baseline characteristics: gender, age, BMI, whether neoadjuvant therapy was given, pathological stage of tumor, and duration of surgery (**Table 1**).

Table 1. Comparison of general clinical data of colorectal cancer patients between the two groups

Characteristic	Experimental group	Control group	t/χ^2	*P*
Age (mean ± SD)	61.7 ± 10.9	66.1 ± 10.6	1.755	0.083
Gender (n, %)			0.00752	0.931
Female	21	14		
Male	25	16		
BMI (kg/m^2; mean ± SD)	21.7 ± 4.9	23 ± 4.5	1.181	0.241
Neoadjuvant therapy given			0.133	0.716
Yes	28	17		
No	18	13		
Tumor staging			0.217	0.897
I	16	9		
II	15	10		
III	15	11		
Duration of surgery	2.99 ± 1.04	3.1 ± 0.83	-0.475	0.637

3.2. Effect of auricular acupressure on gastrointestinal motility recovery

In order to determine the effect of auricular acupuncture on gastrointestinal motility recovery, we compared

the differences in terms of time to first flatus, time to first defecation, and time to first fluid intake after surgery between the experimental group and the control group (**Table 2**). The time to first flatus was significantly shorter in the auricular acupressure group than in the control group (52.2 ± 7.36 h versus 66.3 ± 7.83 h; $P < 0.001$). The time to first defecation (76.3 ± 7.76 h versus 86.1 ± 10.79 h; $P < 0.001$) and first fluid intake (90.4 ± 8.92 h versus 107.3 ± 9.66 h; $P < 0.001$) was also significantly shorter in the experimental group than in the control group. These results indicate that auricular acupuncture can markedly enhance the recovery of gastrointestinal motility and reduce the feeding time.

Table 2. Comparison of postoperative gastrointestinal motility recovery time between the two groups

	Gastrointestinal motility recovery time		
	Time to first flatus (h)	**Time to first defecation (h)**	**Time to first fluid intake (h)**
Experimental group	52.2 ± 7.36	76.3 ± 7.76	90.4 ± 8.92
Control group	66.3 ± 7.83	86.1 ± 10.79	107.3 ± 9.66
t	7.98	4.6	7.82
P	< 0.001	< 0.001	< 0.001

3.3. Effect of auricular acupressure on postoperative pain

We assessed the VAS scores from postoperative day 1 to day 5 (**Table 3**) and found that the experimental group had significantly lower VAS scores than the control group on postoperative days 2 and 3 ($P < 0.001$), indicating that auricular acupuncture can substantially alleviate postoperative pain.

Table 3. Comparison of postoperative VAS scores between the two groups

	VAS score (median, interquartile range)				
	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Experimental group	8 (3)	4 (2)	4 (2)	4 (2)	3 (2)
Control group	8 (3)	6 (2)	6 (2)	4 (1)	3 (1)
U-value	559	173	161	603	605
P	0.159	< 0.001	< 0.001	0.339	0.351

4. Discussion

According to TCM theory, the ear has specific zones that reflect the organs in the body, which are known as auricular points. When a part of the body is ill, it often responds to the relevant auricular point. Thus, stimulating these points can prevent and cure diseases. Auricular acupressure is believed to regulate autonomic function by stimulating acupoints on the ear [12]. In the present study, we examined the effect of auricular acupressure on gastrointestinal recovery and pain following surgery for colorectal cancer. Based on TCM theory, auricular acupressure balances the sympathetic and parasympathetic nervous systems [13], promotes gastrointestinal motility and digestive secretions [14], inhibits visceral reflexes, increases pain threshold [15], improves microcirculation, and promotes wound healing. We stimulated the following auricular points: subcortex, shenmen, stomach, large intestine, small intestine, triple energizer, and sympathy. Stimulating the subcortex acupoint regulates autonomic function and relieves pain [16]. Stimulating the shenmen acupoint promotes blood circulation, reduces inflammation, and relieves abdominal pain [17]. Stimulating the sympathy acupoint regulates sympathetic function, reduces anxiety, and alleviates pain. Stimulating the stomach, large intestine, and small intestine acupoints directly improves gastrointestinal recovery.

Postoperative pain affects sleep, bed activity, coughing, expectoration, and ultimately postoperative recovery. Multimodal postoperative analgesic management using intravenous analgesic pumps, nonsteroidal anti-inflammatory drugs (NSAIDs), epidural analgesia, peripheral nerve blocks, and incisional infiltration is currently advocated. Although analgesic pumps are used to relieve postoperative pain, they tend to cause significant gastrointestinal response and prolong postoperative gastrointestinal recovery. The use of NSAIDs, a simple and effective method, is currently recommended for the management of postoperative pain in colorectal cancer; however, literature has suggested an increased risk of anastomotic fistula [18,19]. It has been found that postoperative pain can be significantly reduced by targeting specific auricular points with analgesic and tranquilizing effects [20]. This finding coincides with the results of the present study. Our study showed that the pain experienced by the experimental group was relieved on postoperative days 2 and 3, suggesting that auricular acupuncture can effectively relieve postoperative pain.

Auricular acupuncture is a distinctive TCM method that is generally well-tolerated by patients. It is not only a safe and painless method that has minimal side effects and complications, but also a simple and convenient method that does not require specialized equipment or skills, as it can be self-administered with materials such as medicinal seeds. Moreover, it is an economical method that does not entail much cost or time. However, there are some precautions and contraindications to this method. For instance, the ears and fingers should be cleaned before use; moisture contact should be avoided during use; the medicinal seeds or other materials should be replaced promptly after use; and the intervention should be discontinued immediately in case of allergic reactions or other discomfort. Furthermore, it should be used cautiously or avoided in cases of skin infection or injury, pregnancy, and severe heart disease.

In conclusion, auricular acupuncture has a significant effect on pain and gastrointestinal motility recovery, especially in terms of time to first flatus and defecation after laparoscopic surgery for colorectal cancer. In addition to its low cost, it is safe and simple to operate. Moreover, it effectively promotes rapid postoperative rehabilitation of patients with colorectal cancer. Therefore, this method should be promoted in clinical practice.

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Disclosure statement

The authors declare no conflict of interest.

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Note: When referencing an entry from a dictionary or an encyclopedia with no author there is no requirement to include the source in the reference list. In these cases, only cite the title and year of the source in-text. For an authored dictionary/encyclopedia, treat the source as an authored book.

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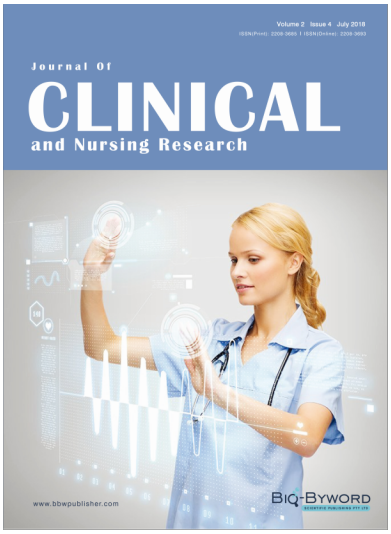

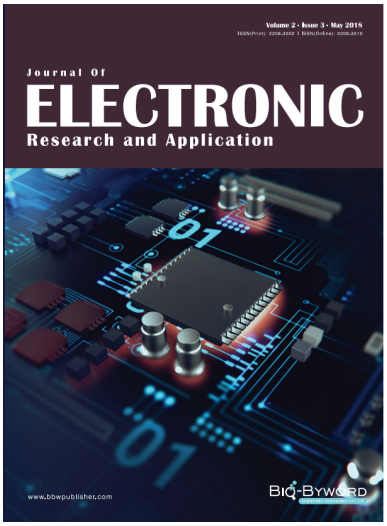

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