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Evaluating the Efficacy of Fecal Occult Blood Test and Tumor Marker Combined Screening for Colorectal Cancer

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Abstract: *Objective:* To analyze the screening effectiveness of combining the fecal occult blood test with tumor marker detection for colorectal cancer. *Methods:* A total of thirty patients with colorectal cancer and thirty patients with benign colon hyperplasia who received treatment from January 2020 to January 2023 were selected. These patients were assigned to the observation group and the control group, respectively. All patients in both groups underwent both fecal occult blood tests and tumor marker detection. The levels of tumor markers between the two groups were compared, the tumor marker levels in different stages were assessed within the observation group, and the positive detection rates for single detection and combined detection were compared. *Results:* The levels of various tumor markers in the observation group were significantly higher than those in the control group ($P < 0.05$). Furthermore, as the Duke stage increased within the observation group, the levels of various tumor markers also increased ($P < 0.05$). The positive detection rate of the combined test was notably higher than that of single detection ($P < 0.05$). *Conclusion:* Combining the fecal occult blood test with tumor marker detection in colorectal cancer screening can significantly improve the overall detection rate.

Keywords: Colorectal cancer; Fecal occult blood test; Tumor marker detection

Online publication: November 7, 2023

1. Introduction

Colorectal cancer is a relatively common malignant tumor of the digestive system. In recent years, significant changes in people's lifestyles and dietary habits have led to a notable increase in the incidence of this disease compared to previous years. In the early stages of the disease, there are typically no specific symptoms. As the disease progresses and the tumor grows in size, various adverse symptoms, such as diarrhea, abdominal pain, and increased bowel movements, become more prominent. In the advanced stages of the disease, anemia and various other complications may occur. Early diagnosis is crucial for improving prognosis.

Tumor markers are vital substances for analyzing and assessing the development of malignant tumors. Their dynamic changes can reflect the progression of the disease [1]. Early monitoring of tumor marker levels can help determine the disease's status. Other studies have demonstrated that combining tumor marker detection

with fecal occult blood tests can further enhance the diagnostic accuracy of colorectal cancer [2]. This study aims to analyze the role of combined fecal occult blood tests and tumor marker detection in colorectal cancer screening. To achieve this, 30 patients with confirmed colorectal cancer and 30 patients diagnosed with benign colon hyperplasia were selected as the research subjects.

2. Materials and methods

2.1. General information

Thirty patients with colorectal cancer were enrolled to comprise the observation group, all admitted between January 2020 and January 2023. Additionally, 30 patients with benign colon hyperplasia who received treatment during the same period were selected for the control group.

The observation group comprised 19 males and 11 females, with an age range of 48–79 years and an average age of 63.26 ± 5.17 years. The control group comprised 18 males and 12 females, with an age range of 46–78 years and an average age of 63.12 ± 5.23 years. Disease types included 9 cases of colon adenoma, 7 cases of colon polyps, 8 cases of rectal adenoma, and 6 cases of rectal polyps. Duke stage distribution included 10 cases in Stage I, 8 cases in Stage II, 7 cases in Stage III, and 5 cases in Stage IV. Statistical analysis was conducted on the data from both groups, yielding a conclusion of $P > 0.05$.

Inclusion criteria included all 30 patients in the observation group who were pathologically diagnosed with colorectal cancer, and they had primary adenocarcinomas, patients who could actively cooperate with various examinations, and patients with complete examination data. Exclusion criteria included patients with contraindications to surgery, patients with concurrent ascites or peritoneal inflammatory reactions, patients with serious underlying diseases, and patients with a history of major abdominal surgery.

2.2. Methods

(1) Fecal occult blood test procedure: Utilizing the fecal occult blood colloidal gold detection test paper technique, the process involves using a sample rod to add the collected stool specimen into a sample collection tube containing 1.5 mL of a 0.85% normal saline sample diluent. The test strip/card is taken out of its aluminum foil bag and laid flat on the table for marking. The next steps include unscrewing the tip of the sample collection tube and vertically adding approximately 80 μL (3 drops) of sample diluent to the test strip's designated area or the sampling hole of the test card. Results are then observed and displayed within a 10-minute timeframe, where a positive outcome is indicated by the presence of two red reaction lines, while a negative result is denoted by a single red reaction line.

(2) Serum tumor marker detection method: A fasting morning venous blood sample of 3 mL was collected, and serum was obtained after centrifugation. A fully automatic biochemical analyzer was used to measure carcinoembryonic antigen (CEA; positive standard: ≥ 5.0 **μg**/L), carbohydrate antigen 50 (CA50; positive standard: ≥ 25 U/L), carbohydrate antigen 199 (CA199; positive standard: ≥ 37 U/L), and carbohydrate antigen 724 (CA724; positive standard: ≥ 6.9 U/L) levels.

2.3. Observation indicators

(1) Comparison of tumor marker levels between the control group and the observation group.
(2) Comparison of tumor marker levels among patients with different Duke stages in the observation group.
(3) Comparison of the positive detection rates of fecal occult blood test, single diagnostic method,

and combined diagnostic method of tumor marker detection in diagnosing the 30 patients in the observation group.

2.4. Statistical methods

Data from the study were entered into SPSS 25.0 statistical software for analysis. Measurement data were represented as mean ± standard deviation (SD) when in line with normal distribution, and count data were represented as [*n* (%)]. Independent sample *t*-tests were conducted (*F*-tests for data with three groups or more), as well as χ^2 tests. If $P < 0.05$ was obtained, it indicated statistical significance in the compared date.

3. Results

3.1. Comparison of tumor marker levels between the two groups

As depicted in **Table 1**, the levels of various tumor markers in the observation group were significantly higher than those in the control group ($P < 0.05$).

Table 1. Comparison of tumor marker levels between the two groups (mean ± SD)

Group	*n*	CEA (μg/L)	CA50 (U/L)	CA199 (U/L)	CA724 (U/L)
Control group	30	13.20 ± 1.16	17.52 ± 2.15	31.54 ± 3.29	4.51 ± 0.48
Observation group	30	33.25 ± 4.17	45.36 ± 5.29	79.52 ± 7.13	20.26 ± 2.17
t	-	25.372	26.704	33.467	38.816
P	-	0.000	0.000	0.000	0.000

3.2. Comparison of tumor marker levels among patients with different Duke stages in the observation group

As illustrated in **Table 2**, the comparison of various tumor marker levels revealed a pattern: Stage IV > Stage III > Stage II > Stage I ($P < 0.05$).

Table 2. Comparison of tumor marker levels among patients with different Duke stages in the observation group (mean ± SD)

Group	*n*	CEA (μg/L)	CA50 (U/L)	CA199 (U/L)	CA724 (U/L)
Phase I	10	15.10 ± 2.13	23.52 ± 3.31	38.47 ± 4.10	10.14 ± 2.26
Phase II	8	20.14 ± 2.20	32.57 ± 3.16	52.05 ± 5.13	16.36 ± 2.69
Stage III	7	27.46 ± 4.14	41.50 ± 4.52	73.54 ± 5.29	24.52 ± 3.38
Stage IV	5	45.17 ± 5.39	55.35 ± 5.74	95.05 ± 9.15	37.46 ± 3.10
F	-	6.264	5.457	8.416	7.965
P	-	0.000	0.000	0.000	0.000

3.3. Comparison of positive detection rates between single detection and combined detection

As displayed in **Table 3**, there is no notable difference in the positive detection rate between the fecal occult blood test and tumor marker detection ($P > 0.5$). However, the positive detection rate of the combined test was significantly higher than that of the single test result ($P < 0.05$).

Table 3. Comparison of positive detection rates between single detection and combined detection [*n* (%)]

Detection method	*n*	Positive	Negative
Fecal occult blood test	30	22 (73.33)	8 (26.67)
Tumor marker detection	30	23 (76.67)	7 (23.33)
Joint testing	30	29 (96.67)	1 (3.33)
Comparison of single test results (χ^2/*P*)	-	0.089/0.766	
Comparison of joint detection results (χ^2/*P*)	-	6.537/0.038	

4. Discussion

Colorectal cancer stands as the most common malignant tumor in the digestive system worldwide. According to the latest global cancer burden data released by IARC in 2020, there are approximately 1.9 million new cases of colorectal worldwide (around 560,000 cases in China) and about 935,000 deaths caused by colorectal cancer (about 290,000 cases in China). It ranks as the third most prevalent cancer globally in terms of incidence and the second most prevalent cancer in China. Colorectal cancer's incidence and mortality in China are ranked second and fifth, respectively [3,4], making its prevention and control a pressing concern. Studies have demonstrated that early screening and timely intervention significantly improve the five-year survival rate and may even lead to complete cures [5]. Therefore, early screening, diagnosis, and treatment for colorectal cancer are of paramount importance.

Presently, there are numerous methods for clinically screening colorectal cancer. Aside from pathological examination, colonoscopy is the most effective and widely used diagnostic method. During colonoscopy, colorectal lesions can be visually identified, and entities such as adenomas and polyps can be removed during the procedure. However, colonoscopy necessitates rigorous bowel preparation, can cause discomfort, and carries the risk of complications such as bleeding. Additionally, it is relatively costly, limiting its clinical applicability and patient compliance [6]. There is a need to explore alternative, safer, more convenient, affordable, and accurate screening methods. The fecal occult blood test serves as a significant non-invasive screening technology for early colorectal cancer. It can be classified into chemical and immunological fecal occult blood tests. Among the former, the guaiac fecal occult blood test is the most commonly used, based on the hemoglobin content. Hemoglobin possesses peroxidase activity, generating new oxygen during catalysis, which triggers color development in the reagent. Test results are determined by this color development. While this method is simple and cost-effective, it is susceptible to dietary influences before the test [7]. For instance, the consumption of lean meat, iron supplements, or large leafy vegetables before the test can interfere with results, leading to relatively low sensitivity and an increased risk of false positives. The immunological fecal occult blood test relies on the antigen-antibody reaction principle to detect antibodies against globin components in fecal blood [8], with methods such as enzyme-linked immunoassay, latex agglutination turbidimetric method, and the colloidal gold test paper method being more commonly used. In this study, the colloidal gold test paper method was employed. Immunological fecal occult blood tests are not affected by dietary factors and have fewer interfering variables. The results indicate a positive detection rate of 73.33% for a single fecal occult blood test, highlighting the potential for further improvement in detection rates.

Tumor markers are substances produced due to the upregulation of tumor-related gene expression or the body's response to tumor tissue. Tumor markers are present only in small amounts or absent in normal tissues but are significantly elevated in tumor tissues. The quantitative and qualitative detection of tumor markers can

help screen for malignant tumors, determine prognosis, and play a critical role in treatment plan development, efficacy prediction, and recurrence monitoring [9]. The most commonly used tumor markers in colorectal cancer detection include CEA, CA50, CA199, and CA724. CEA is a specific tumor marker for colorectal adenocarcinoma, classified as a tumor embryonic antigen. In colorectal cancer, CEA interacts with cells and has associations with extramatrix adhesion, causing elevated levels that inhibit cell differentiation and disrupt tissue structure. CA50 is a sialoglycoprotein highly expressed in most colon cancer patients [10]. CA199 is associated with tumor cell gangliosides and is used in diagnosing various digestive tract tumors, such as pancreatic cancer. CA724 is a mucin antigen [11], with a higher sensitivity in colon cancer as compared to CEA and CA199 [12]. The results in this study indicate that the levels of various tumor markers in patients with colorectal cancer in the observation group are higher than those in patients with benign colon hyperplasia in the control group. Furthermore, higher Duke stages in the observation group correlate with higher levels of various tumor markers, demonstrating the markers' potential to distinguish between benign and malignant colorectal tumors and assess disease severity. When comparing the positive detection rates of the fecal occult blood test, single tumor marker detection, and combined detection, the results reveal that the positive detection rate of single detection does not significantly differ, while the positive detection rate of combined detection surpasses that of single detection. This underscores the enhancement of the positive detection rate through the combination of these two detection methods.

In conclusion, colorectal cancer represents a relatively high-incidence malignant tumor of the digestive tract. Various detection methods for colorectal cancer screening have their own advantages and limitations. It is recommended to employ both the fecal occult blood test and tumor marker detection simultaneously to boost the positive detection rate, which holds great significance for early disease diagnosis and treatment.

Disclosure statement

The author declares no conflict of interest.

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A Review of Textile Fabrication Using Bioactive Compounds Derived from Natural Products

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Abstract: Antimicrobial-treated textiles should exhibit efficacy against a broad spectrum of bacterial and fungal species, all while maintaining user safety with a non-toxic profile. Natural antimicrobial compounds play a vital role in textile finishing processes. The proliferation of synthetic antimicrobial agents introduces environmental and consumer safety concerns. Given these potential hazards associated with synthetic agents, the utilization of natural antimicrobial agents is gaining traction, as they tend to have fewer adverse effects on users and are more environmentally sustainable. Numerous natural antimicrobial compounds, sourced from plants such as neem, basil, turmeric, aloe vera, and clove oil, have been developed, showcasing inherent antimicrobial properties. This review article highlights the importance of incorporating bioactive components in the creation of antibacterial textile fabrics.

Keywords: Antimicrobial-treated textile; Bioactive compounds; Natural products

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1. Introduction

Recent studies investigating antimicrobial compounds for textiles have been primarily driven by an increasing public concern regarding hygiene [1,2]. The growth of microorganisms on textile materials can have various adverse consequences for both the textiles themselves and the individuals using them [3]. Textiles not only serve as a platform for the proliferation of microbes but also actively facilitate their growth [4]. With a growing awareness among the general public about the risks associated with microbial infections, there is a rising demand for products equipped with antimicrobial properties to combat germ contamination [5]. The pursuit of a healthier lifestyle has led to a surge in scientific interest in antimicrobial finishing for textiles. As a result, numerous synthetic and natural antimicrobial treatments for textiles have emerged over time [6] malodors and stain formations caused by microorganisms, there is an increasing need for antibacterial materials in many application areas like medical devices, health care, hygienic application, water purification systems, hospital, dental surgery equipment, textiles, food packaging, and storage.(Shahidi et al, 2007. The global

output of antimicrobial fabrics surpassed 100,000 tons in 2000 [7]. The production of antimicrobial textiles has experienced a remarkable surge in recent years, establishing itself as one of the fastest-growing segments within the textile industry [8]. According to recent industry research conducted by textile experts, the global market for antimicrobial agents, encompassing various consumer applications including textiles, is projected to witness an annual growth rate exceeding 12% [9]. Over the past two decades, antimicrobial fabrics have garnered considerable attention and widespread acceptance in both markets and everyday life. Textile manufacturers are continually exploring innovative production methods to enhance product quality and satisfy customer demands. The heightened competition in the industry has spurred the development of numerous synthetic antibacterial agents. However, despite their widespread adoption, these synthetic compounds pose potential risks to both human health and the environment. In response to these substantial concerns, several environmental organizations have implemented regulations restricting the use of synthetic chemicals. In contrast, natural antimicrobial compounds pose fewer risks to human health and exhibit greater environmental friendliness. Various natural substances, including turmeric (containing curcumin), neem (with active limonoids such as nimbinin and azadirachtin), basil (featuring eugenol as one of its active agents), pomegranate, onion, chitosan, aloe vera, sericin, and clove oil, are known for their antimicrobial properties [10].

2. The effect of microbes on textiles

The term “biodegradation” refers to “any undesirable alteration in the properties of a material resulting from the life processes of organisms.” Microbes encompass a range of microorganisms, including algae, fungi, bacteria, and viruses. Ramachandran *et al.* characterized bacteria as unicellular organisms that thrive in warm, moist environments [11]. Textile fibers possess inherent features that create an environment conducive to the growth of microorganisms. Microbes can flourish due to factors such as substrate structure and chemical processes, with humidity and warmth further exacerbating this condition.

Microbial infestation can lead to both pathogen transmission and the generation of unpleasant odors when textiles are worn close to the skin [11]. Furthermore, microbial attack can result in discoloration and a deterioration of performance attributes of textile materials. Natural fiber textiles are often more susceptible to biodegradation compared to synthetic (man-made) fibers. This susceptibility arises from the porous and hydrophilic nature of textile structures, which readily absorb water, oxygen, and nutrients, providing an ideal environment for bacterial growth [12]. According to a survey, 61% of women reported taking extra measures to purchase antibacterial or antimicrobial products [13]. People have significant concerns regarding issues such as stains, odors, degradation, and human health, including the risk of infectious diseases and allergies (**Table 1**).

3. Antimicrobial agents for textiles

Antimicrobial technology encompasses a wide range of approaches that offer varying levels of protection against microbes for various products. Antimicrobials exhibit significant diversity in terms of their chemical origins, mechanisms of action, impact on human health and the environment, handling characteristics during manufacturing, stability on different surfaces, cost considerations, and interactions with both beneficial and harmful microorganisms. These antimicrobial agents find applications in the management of microbial issues in textiles [14]. They serve to bolster resistance against microorganisms, enhance textile durability, and safeguard fabrics from colonization by odor-causing bacteria [15,16]. Additionally, antimicrobial treatments can reduce the frequency of laundering, resulting in substantial reductions in energy and water consumption, as well as a decreased demand for chemical additives in textile care [17]. An effective antimicrobial agent should possess

Table 1. Microorganisms and the disease caused by microorganisms

Microorganism	Diseases or conditions
Gram-positive bacteria	
Staphylococcus aureus	Pyrogenic infections
Staphylococcus epidermis	Body odor
Corynebacterium diphtheriae	Body odor
Brevibacterium ammoniagenes	Diaper rash
Streptococcus pneomoniae	Bacterial pneumonia
Mycobacterium tuberculosis	Tuberculosis
Gram-negative bacteria	
Escherichia coli	Infections of the urinogenital tract
Pseudomonas aeruginosa	Infections of wounds and burns
Proteus mirabilis	Urinary infections
Fungi	
Candida albicans	Diaper rash
Epidermophyton floccosum	Infections of skin and nails
Trichophyton interdigitale	Athletes foot
Trichophyton rubrum	Chronic infection of skin and nails
Aspergillus niger	Damage cotton
Viruses	
Poliomyelitis virus	Poliomyelitis
Vaccinia virus	Local disease induced by vaccination against smallpox
Protozoa	
Trichomonas vaginalis	Vaginal infections

broad-spectrum activity against a variety of bacterial and fungal species while posing minimal risks to humans and the environment, and being free from allergens and irritants.

The cytotoxicity, irritation, and sensitization test levels would be lowered for textiles treated with an antimicrobial agent, and they would also meet the following criteria, as outlined by [18]:

(1) Adherence to the regulatory standards established by governing bodies
(2) Resilience to repeated washing throughout the textile's lifespan
(3) Compatibility with chemical substances employed in textile finishing processes
(4) No requirement to eliminate non-pathogenic bacterial flora naturally occurring on the wearer's skin
(5) No adverse impact on the textile's appearance or properties, including its physical durability and handling
(6) Versatility and resistance to sterilization/disinfection processes
(7) Absence of negative consequences for the user, manufacturer, or environment [9]

There exist several methods for imparting antibacterial characteristics to fabrics [14]:

(1) Coagulants such as halogens and primary alcohols
(2) Oxidizing agents like aldehydes
(3) Compounds featuring quarternary ammonium
(4) Triclosan-based products (derivatives of bis-phenyl)
(5) Chitosan, derived from chitin, as well as natural alternatives from, herbs, shrubs, and plants
(6) Complex metallic compounds based on mercury, silver, and cadmium

4. Natural antimicrobial agents

The majority of diverse natural antibacterial substances are derived from plants. Globally, there are an estimated 5,000,000 different plant species, with less than 1% of these possessing any therapeutic properties [5,19]. Natural alternatives hold greater promise for research due to their eco-friendliness, low toxicity, suitability for use in next-to-skin innerwear, the extensive study aimed at combating antimicrobial-resistant bacteria, and safe handling [14]. In contrast, synthetic substances like quaternary ammonium compounds, triclosan, and nanosilver materials are available for the antimicrobial finishing of textiles. Notably, the production of nanoparticles is more cost-intensive compared to other synthetic options (**Table 2**) [10].

Table 2. Active phytochemical agents from plants [10]

Class	Subclass	Example	Mechanism
Alkaloids		Berberine Piperine	Interactive into the cell wall and/or DNA
Terpenoids		Capsaicin	Membrance disruption
Phenolic	Simple phenols	Catechol	Substrate deprivation
	Flavonoids	Chrysin	Bind to adhesins complex with cell wall
	Flavones	Abyssinone	Interact with enzymes
	Flavonols tannins	Ellagitannin	Bind to proteins Bind to adhesion Substrate deprivation Membrane disruption
	Coumarins	Warfarin	Interaction with eukaryotic DNA
Lectins and polypeptides		Mannose	Block viral fusion or adsorption

5. Natural versus synthetic materials

The oil industry stands as the largest contributor to environmental pollution, closely followed by the textile sector. As the world increasingly emphasizes sustainability, it has become imperative for the textile industry to cease the use of hazardous materials and transition towards natural alternatives. Stringent regulations governing textile production have been enacted by numerous countries, compelling manufacturers to explore safer substitutes. Natural materials are consistently favored over synthetic ones due to their benevolence toward the users and the environment. Synthetic antimicrobial agents pose significant challenges owing to their harmful nature, which can result in adverse effects on human health and environmental contamination. While synthetic antimicrobial agents exhibit exceptional effectiveness, durability, and a broad spectrum of activity, their

natural counterparts may not match this efficacy but are considered safe for both humans and the environment. To achieve a level of effectiveness similar to synthetic agents, there is a need to further field research on combinations of these natural antibacterial agents. Consequently, the future significance of natural antibacterial compounds derived from plant sources cannot be overstated. The preservation and protection of the natural ecosystem are essential steps towards restoring global sustainability [10].

6. The impact on normal microflora

The regular use of topical antimicrobial drugs on the skin poses primary concerns related to the development of allergies, irritating dermatitis, and alterations in the environmental stability of both the natural (resident) and host (transient) microflora. It is worth noting that there has been relatively less research dedicated to understanding the impact of antimicrobial agents on the microflora residing on human skin [21], despite the pivotal role of the skin microbiota in acting as a crucial barrier against potential pathogenic microorganisms and the proliferation of existing opportunistic microorganisms [20]. The majority of studies investigating the effects of antimicrobial agents on normal microflora have predominantly focused on the intestinal flora [20]. Further processing of free fatty acids, skin proteins, and sebum has also been proposed as beneficial roles [22]. Additionally, there has been limited exploration into the adverse effects of antimicrobial clothing, particularly form-fitting athletic and leisure lingerie, on the ecological balance of bacteria present on human skin.

To assess the potential negative impacts on the healthy skin microbiota, a placebo-controlled trial was conducted, comparing antimicrobial clothing with textiles having a similar structure but with lower antimicrobial properties. This study involved sixty participants, each provided with form-fitting T-shirts featuring two sides: a non-antibacterial control side and an antibacterial half exhibiting a 3–5 log-step reduction in bacterial activity due to the inclusion of silver-loaded or silver-finished fibers. Over the course of six weeks, the microflora on the scapular skin was assessed weekly for the presence of aggressive and pathogenic bacteria. The results indicated that the antibacterial halves did not disturb the quantity or composition of the microflora. However, a deodorant-containing silver did lead to a temporary disruption. Additionally, measurements of skin morphology and function (such as moisture, pH, and transepidermal water loss) did not reveal any significant changes. In summary, wearing antimicrobial clothing did not adversely affect the ecological balance of healthy skin microflora [23].

Disclosure statement

The authors declare no conflict of interest.

Reference

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Coexistence of Pseudotumor Cerebri and Chiari Malformation Type 1

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Abstract: *Objective:* To identify different radiological markers for the diagnosis of the coexistence of pseudotumor cerebri and Chiari malformation type 1. *Method:* Patients who were clinically suspected to have Chiari malformation type 1 and were referred to the Department of Radiology between 2007 and 2020, and whose diagnosis was radiologically confirmed through magnetic resonance imaging (MRI), were retrospectively evaluated. A total of 49 Chiari malformation type 1 patients with both cervical and cerebral examinations and 49 control subjects of the same age and gender without a diagnosis of Chiari malformation type 1 were included in the study. In Chiari malformation type 1 diagnosed patients, the presence of pseudotumor cerebri, the presence of syringomyelia in cervical spinal MRI images, and the distance of cerebellar tonsils and obex according to McRae line were evaluated in millimeters. *Result:* In Chiari malformation type 1 clinically and radiologically diagnosed cases, the cerebellar tonsils and obex were located lower in patients with a radiological diagnosis of pseudotumor cerebri compared to those without, and the rate of accompanying syringomyelia appeared to be higher. However, no statistically significant difference was observed between the two groups. *Conclusion:* The coexistence of pseudotumor cerebri and Chiari malformation type 1 is more common than previously estimated. Different treatment protocols in the coexistence of pseudotumor cerebri and Chiari malformation type 1 emphasize the importance of making this diagnosis. Further radiological imaging studies are needed to identify different radiological markers for the diagnosis of the coexistence of pseudotumor cerebri and Chiari malformation type 1.

Keywords: Pseudotumor cerebri; Chiari malformation type 1; Coexistence; Radiological markers

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1. Introduction

Chiari malformation type 1 (CM1) originates from embryonic developmental abnormalities of the brainstem and cerebellum, characterized by the displacement of cerebellar tonsils 5 mm or more caudally from the foramen magnum. This definition is purely radiological, and in the literature, patients with CM1 clinical features and cerebellar tonsillar displacement exceeding 3 mm from the foramen magnum are also observed [1,2]. The prevalence of CM1 is reported to be approximately 1% in the population [3]. CM1 is the mildest form of

Chiari malformations. While it is more common in females, it typically manifests symptoms in the third and fourth decades of life, hence it is also referred to as the adult form of Chiari malformations. Despite numerous hypotheses, its etiology remains unclear. Some of these hypotheses include primary mesodermal insufficiency, hypoplasia of the basal part of the occipital bone, or a small posterior cranial fossa (PCF) due to platybasia [4-6].

Headache is the most common symptom in CM1. In CM1, the classic type of headache is a suboccipital headache or neck pain triggered or worsened by Valsalva-like maneuvers (such as coughing or straining) [7]. Approximately 14% to 21% of CM1 patients are asymptomatic and are incidentally diagnosed through imaging methods [8,9].

The compression of cerebellar tonsils, brainstem, and upper cervical spine at the foramen magnum can lead to symptoms of lower cranial nerve paralysis, such as limb weakness, dysphagia, and dysphonia. In CM1, the dynamics of cerebrospinal fluid (CSF) flow can be disrupted, and approximately 20%–72% of CM1 cases can lead to the development of syringomyelia in the cervical region due to CSF flow disturbance [10,11]. Syringomyelia is the most commonly associated disorder with CM1. Syringomyelia refers to the formation of CSF cavities within the spinal cord [12]. Syringomyelia, due to spinal cord compression, causes paresthesia, hyperesthesia, or anesthesia in a classic shawl-like pattern that does not involve a specific dermatome in the neck and shoulders. The widening of the central canal leads to dissociation loss of pain and temperature sensation, but light touch and proprioception are initially preserved. Weakness, non-radicular pain, and spasticity can also be observed primarily in the upper extremities. Untreated chronic syringomyelia can cause scoliosis and myelopathy in 18%–42% of CM1 patients [7,13,14].

According to the modified Dandy criteria, pseudotumor cerebri (PTC) is a syndrome characterized by an increase in intracranial pressure (ICP) with normal CSF content and the absence of focal neurologic findings, except for isolated sixth cranial nerve palsy [15]. PTC is classified into two types: idiopathic intracranial hypertension (IIH) and secondary PTC syndrome associated with specific causes such as venous sinus thrombosis [16]. The incidence of idiopathic intracranial hypertension is 19/100,000 [17,18]. Patients with idiopathic intracranial hypertension most commonly present with headache, which is seen in 68%–98% of cases. Other clinical features include pain, pulsatile tinnitus, and visual disturbances that can lead to blindness [17,19].

Idiopathic intracranial hypertension, despite being a clinical diagnosis based on high opening pressure (>20 cm H_2O in non-obese patients, > 25 cm H_2O in obese patients with a body mass index of 30 or higher) in conjunction with normal CSF content, has associated supportive neuroimaging findings described. These imaging findings include flattening of the posterior sclera, tortuosity of the optic nerve sheath, empty sella syndrome, dilated Meckel's cave, and constriction of transverse venous sinuses. Neuroimaging methods can assist in clinical diagnosis or support, especially for clinicians unfamiliar with the diagnosis [20,21].

The goal of this study is to identify different radiological markers for the diagnosis of the coexistence of PTC and CM1.

2. Materials and methods

In this study, 49 CM1 patients (age range 20–59 years with an average of 37.82 ± 10.53 years, 44 females, and 5 males) with both cervical and cerebral MRI examinations and a confirmed diagnosis through magnetic resonance imaging (MRI) who were referred from the Department of Neurosurgery to the Department of Radiology with a clinical pre-diagnosis of CM1 between 2007 and 2020 were included. Additionally, 49 control subjects of the same age and gender without a diagnosis of CM1 were also included. The magnetic resonance images were retrospectively evaluated. Ethical approval was obtained from the Mersin University Ethics Committee (no. 2022/60) before the measurements began.

The CM1 patient and control groups were scanned using a 1.5 Tesla (T) General Electric (Milwaukee, Wisconsin, U.S.A.) Excite II device and a 1.5 T Siemens (Erlangen, Germany) Magneton Area device with a 16-channel head and neck coil. The axial and sagittal slice thicknesses for cervical MRI examinations were set to 3 mm. The presence of PTC was radiologically evaluated from cerebral MRI images, including findings such as empty sella syndrome, expansion in Meckel's cave, tortuosity of the optic nerve sheath, widening of the CSF space adjacent to the optic nerve, and flattening of the posterior sclera (**Figure 1**) [20,21]. The presence of syringomyelia was assessed from cervical spinal MRI images, and the distances in mm of the cerebellar tonsils and obex were measured according to the McRae line (a line extending from Basion to Opistion; **Figure 2**) [22].

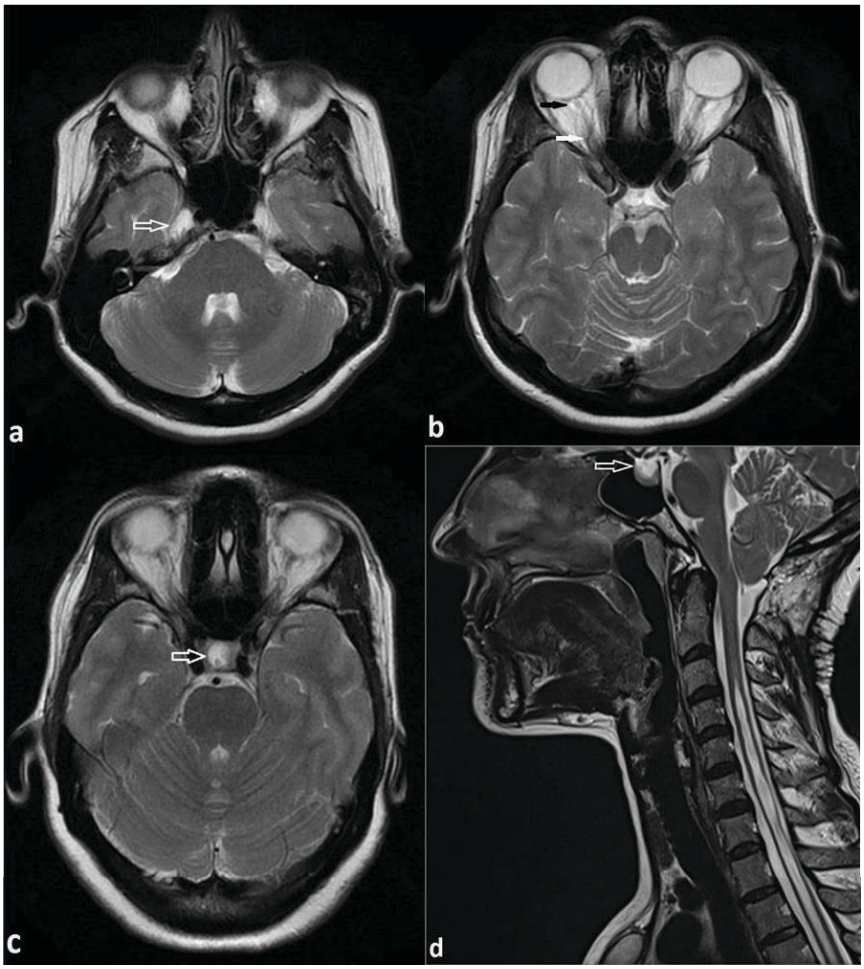


Figure 1. Radiological assessment of pseudotumor cerebri (PTC) presence from cerebral MRI images. **(a)** Expansion in Meckel's cave; **(b)** tortuosity of the optic nerve sheath (white arrow) and widening of cerebrospinal fluid space adjacent to the optic nerve (black arrow); and **(c, d)** empty sella syndrome.

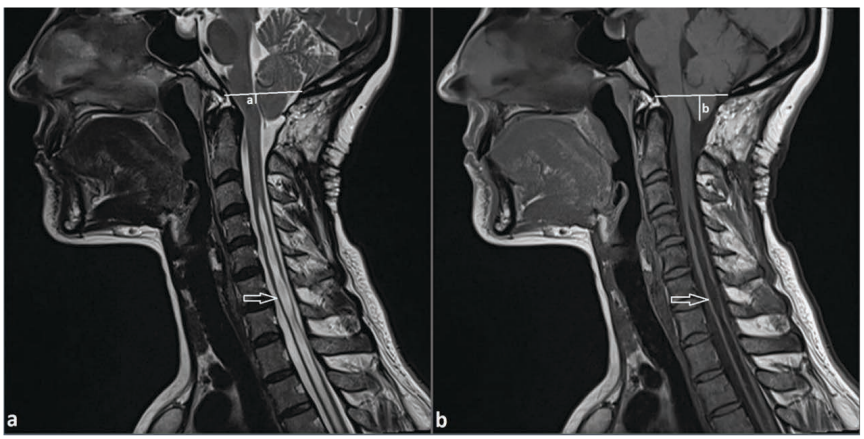


Figure 2. The presence of syringomyelia (arrow), **(a)** the distance of obex (a marker for the cervicomedullary junction, where the fourth ventricle becomes the central canal in the cervical spinal cord) measured in mm according to the McRae line (a line extending from Basion to Opistion), and **(b)** the distance of the cerebellar tonsils were assessed from cervical spinal MRI images. Measurements performed above the McRae line were evaluated as negative values, while measurements performed below were considered positive.

Measurements performed above the McRae line were evaluated as negative values, while measurements performed below were considered positive. Patients in the CM1 group had no intracranial space-occupying pathology that could affect the measurements. In the control group, there were no congenital or systemic diseases related to the craniovertebral junction that could affect the measurements. Patients diagnosed with CM1 clinically and radiologically were categorized into two groups, similar to those with PTC and those without PTC, based on tonsillar herniation exceeding 5 mm. The Shapiro-Wilk test was used to check whether the measurements had a normal distribution, which was confirmed. Descriptive statistics provided mean and standard deviation for continuous variables and number and percentage for categorical variables. Student *t*-test was used to compare the means between the two groups. Analysis of variance (ANOVA) was applied for comparisons of more than two groups. For pairwise comparisons between groups, the Dunnet test was preferred for comparisons against the control group, and the Tukey test was used for all other comparisons. Receiver operating curve (ROC) analysis was used to evaluate the success of the parameters in distinguishing cases with syringomyelia from cases without syringomyelia. Descriptive statistics included the area under the curve, sensitivity and specificity values, and confidence intervals. A significance level of $P < 0.05$ was considered statistically significant.

3. Result

In the PTC (-) CM1 group, the number of females was 34 (89.5%), and males were 4 (10.5%). In the PTC (+) CM1 group, there were 10 females (90.9%) and 1 male (9.1%), while in the control group, there were 44 females (89.8%) and 5 males (10.5%). The distribution of males and females in the groups was homogeneous ($P = 0.990$). Female patients predominated in both PTC (+) and (-) CM1 groups. The average age in the PTC (+) CM1 group was 46.27 ± 8.51 years, and in the PTC (-) CM1 group, it was 35.37 ± 9.84 years (**Table 1**).

Table 1. The mean age of patients according to groups and mean cerebellar tonsillar and obex distances relative to the McRae line (mean ± standard deviation)

	Group			*P*-value
	Control (*n* = 49)	PTC (+) CM1 (*n* = 11)	PTC (-) CM1 (*n* = 38)	
Cerebellar tonsillar distance relative to McRae line (mm)	-1.20 ± 2.42	8.05 ± 3.07*	7.98 ± 3.30*	< 0.001
Obex distance relative to McRae line (mm)	-7.47 ± 1.83	0.59 ± 6.31*	-1.12 ± 5.20*	< 0.001
Age (years)	37.82 ± 10.53	46.27 ± 8.51*	35.37 ± 9.84	0.009

*Statistical difference compared to the normal group. Abbreviation: PTC, pseudotumor cerebri; CM1, Chiari malformation type 1.

In this study, PTC was present in 11 out of 49 CM1 cases (22.45%). In the PTC (-) CM1 group, nine (23.7%) had syringomyelia, while in the PTC (+) CM1 group, five (45.5%) had syringomyelia. There were no cases of syringomyelia in the control group (0%). The rate of syringomyelia in both PTC (+) and (-) CM1 groups was higher than in the control group ($P < 0.05$). Although the rate of syringomyelia was higher in PTC (+) CM1 patients compared to PTC (-) CM1 patients, there was no statistically significant difference between the two groups ($P > 0.05$).

In this study, the position of the cerebellar tonsils in control patients was above the McRae line (-1.20 ± 2.42 mm). For PTC (+) and (-) CM1 patients, the position of cerebellar tonsils and obex according to the McRae line was significantly lower than that of the control group ($P < 0.001$) (**Table 1**). While PTC (+) CM1 patients had

cerebellar tonsils and obex positioned lower than PTC (-) CM1 patients, there was no statistically significant difference in the distance of cerebellar tonsils and obex according to the McRae line between PTC (+) and (-) CM1 patients ($P = 0.997$, 0.437, respectively).

In patients with syringomyelia, the distance of cerebellar tonsillar and obex according to the McRae line was significantly lower than in the group without syringomyelia ($P < 0.001$, 0.004, respectively) (**Table 2**). In this study, ROC analysis was performed to evaluate the value of the distance of cerebellar tonsils and obex according to the McRae line in patients with and without syringomyelia. According to the McRae line, the distance of cerebellar tonsils in patients without syringomyelia had a cut-off value of ≤ 2.6 mm and the obex distance had a cut-off value of ≤ -5.5 mm (**Table 3**). There was no statistically significant difference in distinguishing between patients with and without syringomyelia in terms of the distance of obex according to the McRae line ($P = 0.1185$).

Table 2. Cerebellar tonsillar and obex distances relative to the McRae line between groups with and without syringomyelia (mean ± standard deviation)

	Group		*P*-value
	Syringomyelia (+) (*n* = 14)	**Syringomyelia (-) (*n* = 84)**	
Cerebellar tonsillar distance relative to McRae line (mm)	9.41 ± 4.09	2.39 ± 4.95	< 0.001
Obex distance relative to McRae line (mm)	-0.39 ± 5.11	-4.72 ± 5.07	0.004

Table 3. ROC analysis of cerebellar tonsillar and obex distance values relative to the McRae line between cases with and without syringomyelia

Parameter	ROC [CI]	*P*	Cut-off	Sensitivity	95% CI	Specificity	95% CI
Obex distance relative to McRae line (mm)	0.762 [0.666–0.843]	0.0001	≤ -5.5	58.33	47.1–69.0	92.86	66.1–99.8
Cerebellar tonsillar distance relative to McRae line (mm)	0.835 [0.747–0.903]	< 0.0001	≤ 2.6	58.33	11.3–29.1	100.00	76.8–100.0

Abbreviation: CI, confidence interval.

4. Discussion

In the literature, as in this study, CM1 is reported to be more common in females [4-6]. The findings in this study are consistent with the literature, which indicates that CM1 generally causes symptoms in the third and fourth decades [4-6].

In the treatment protocol for CM1, posterior fossa decompression is performed, while in the PTC treatment protocol, ventriculoperitoneal shunt therapy is applied. For the complete resolution of symptoms and prevention of recurrence in patients with PTC and CM1 coexistence, both treatment procedures should be performed together [23]. Therefore, the importance of diagnosing PTC and CM1 coexistence is significant.

Aiken and colleagues observed cerebellar herniation of more than 5 mm in 9 out of 43 IIH patients (21%) [23]. Johnston *et al*. reported that 6% of IIH patients had radiological criteria for CM1 (cerebellar herniation of more than 5 mm) [24]. Banik *et al*. found that more than 2 mm of cerebellar ectopia was present in 24% of IIH patients, while more than 5 mm of cerebellar herniation was observed in 11% of patients [25]. Fagan and colleagues described the coexistence of CM1 with IIH and the difficulty of its treatment, defining it as Chiari Pseudotumor

Cerebri Syndrome [26]. The percentage of PTC-CM1 coexistence in this study is similar to the result found by Aiken and colleagues [23].

The coexistence of CM1 with syringomyelia in the PTC (-) and (+) CM1 groups is consistent with the literature's reported rate of 20%–72% for syringomyelia in CM1 [27]. To date, there is no other study on the prevalence of syringomyelia in PTC and CM1 coexistence.

Huang *et al*. and Işik *et al*. found the position of cerebellar tonsils to be located 1 and 2.9 mm above the McRae line, respectively, which is consistent with this study [28,29]. Aiken and colleagues found the distance of obex according to the McRae line to be lower in IIH patients ($P < 0.01$) [23]. They even observed that similar to CM1 cases, the obex in IIH patients who exhibited herniation with a hook-like protrusion into the cervical canal was significantly lower than in the control group. Therefore, they suggested that obex distance could be a discriminating factor in distinguishing patients with PTC and CM1 from those with only PTC [23]. In this study, although PTC (+) CM1 patients had cerebellar tonsils and obex positioned lower than PTC (-) CM1 patients, there was no statistically significant difference in the distance of cerebellar tonsils and obex according to the McRae line between PTC (+) and (-) CM1 patients ($P = 0.997$, 0.437, respectively). Therefore, it is believed that investigating the distance of cerebellar tonsils and obex according to McRae line may not provide a significant contribution to the diagnosis of PTC coexistence in CM1 patients. Aiken and colleagues may have come to a different conclusion due to the small sample size of five patients with PTC-CM1 coexistence, which is much smaller than the 11 patients in this study.

Bogdanov and colleagues found the inferior herniation of cerebellar tonsils according to the McRae line to be approximately 7.6 ± 1.5 mm in CM1 cases with syringomyelia, which is similar to this study [30].

5. Conclusion

The coexistence of PTC and CM1 is more common than previously estimated. Different treatment protocols for PTC-CM1 coexistence highlight the importance of establishing the diagnosis. In PTC (+) CM1 patients, cerebellar tonsils and obex are located lower compared to PTC (-) CM1 patients, and the rate of syringomyelia appears to be higher. However, no statistically significant difference is observed between the two groups. The main limitation of this study is that the diagnosis of PTC is supported by radiological images rather than the gold standard, which is the opening CSF pressure [15]. Another limitation is that while this study investigates the coexistence of PTC on the basis of CM1 cases, in some studies that were compared to, PTC cases was investigated in the context of CM1 coexistence [23-25]. Therefore, a direct comparison of the studies may not be entirely appropriate. To identify different radiological markers for the diagnosis of PTC-CM1 coexistence, more radiological imaging studies are needed.

Disclosure statement

The authors declare no conflict of interest.

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Effects of Neuromuscular Electrical Stimulation in Combination with Glutamine Administration on Skeletal Muscle Atrophy in Colon-26 Tumor-Bearing Mice

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Abstract: The depressed protein synthetic response, a phenomenon termed anabolic resistance, has been shown to be involved in muscle wasting induced by cancer cachexia. Moreover, a positive relationship between the protein synthetic rate and intracellular glutamine (GLN) concentration has been found in skeletal muscles. This study investigated the effects of neuromuscular electrical stimulation (ES) and GLN administration on muscle wasting and GLN metabolism in colon-26 (C-26) tumor-bearing mice. CD2F1 mice were divided into 8 groups: control (CNT), CNT+ES, CNT+GLN, CNT+ES+GLN, C-26, C-26+ES, C-26+GLN, C-26+ES+GLN. Cancer cachexia was induced by subcutaneous injection of C-26 cells and developed for four weeks. ES was performed on the left plantar flexor muscles every other day, and GLN (1 g/kg) was administered daily intraperitoneally starting one day after the C-26 injection. Tumor-free body mass and fast-twitch gastrocnemius (Gas) muscle weight were lower in the C-26 group than in the CNT group (-19% and -17%, respectively). Neither ES training nor GLN administration, alone or in combination, ameliorated the loss of Gas muscle weight in the C-26 mice. However, ES training in combination with GLN administration inhibited the increased expression of GLN synthetase (GS) in the C-26 muscles. Thus, it is likely that GLN plays a critical role in muscle protein metabolism and, therefore, can be targeted as a tentative treatment of cancer cachexia.

Keywords: Cancer cachexia; Anabolic resistance; Muscle atrophy; Glutamine; Neuromuscular electrical stimulation

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1. Introduction

Cancer cachexia is a progressive metabolic disorder characterized by significant skeletal muscle atrophy [1]. Unlike the relatively preserved skeletal muscle mass and decreased fat tissue in a state of starvation [2], cancer-induced muscle atrophy is reported to be difficult to improve with conventional nutritional support [3]. Furthermore, muscle wasting due to cancer cachexia not only deteriorates physical function and quality of life but also leads to a loss of resilience to undergo comprehensive treatment [4]. Additionally, recent studies have

shown that the reduction in skeletal muscle mass in cancer patients and cancer model animals is associated with poor prognosis [5,6], making the inhibition of muscle atrophy associated with cancer cachexia an important challenge in cancer rehabilitation.

In cancer cachexia, resistance to muscle protein assimilation has been observed [7]. This resistance, which reduces the rate of muscle protein synthesis in addition to increased resistance training and amino acid intake, is a phenomenon where the synthesis of muscle protein decreases compared to normal conditions [8,9]. Muscle resistance to assimilation with age is believed to involve decreased translation from mRNA to protein, hindrance in amino acids uptake in muscle, and insulin resistance [9]. Furthermore, in cancer cachexia, it has been shown that the reactivity of the mammalian target of the rapamycin complex 1 (mTORC1) signaling pathway, which plays a crucial role in regulating muscle protein translation, is diminished in response to muscle contraction and glucose administration [10].

Glutamine (GLN), the most abundant non-essential amino acid in the body, is primarily produced in skeletal muscles through the action of glutamine synthetase (GS) and accounts for approximately 60% of the free amino acid pool within muscle cells [11]. In conditions like sepsis or trauma, the demand for GLN in the body exceeds the supply from skeletal muscles, causing a maximum decrease of up to 50% in muscle and up to 30% in blood GLN concentrations, necessitating external supplementation [12]. Therefore, despite being a non-essential amino acid, GLN is sometimes referred to as a conditionally essential amino acid. Interestingly, MacLennan *et al*. demonstrated that increasing GLN concentration in muscle cells by reinfusing a high-concentration GLN solution into muscles increased the muscle protein synthesis rate [13]. Furthermore, with tumor growth, the release of GLN from skeletal muscles increases twofold [14], leading to a decrease in muscle GLN concentration [15]. GLN supplementation has been shown to prevent the decrease in GLN concentration in skeletal muscles of cancer model rats and improve the reduced rate of muscle protein synthesis [16-18]. On the other hand, some reports suggest that there is no clear connection between muscle GLN concentration and protein synthesis rate. Damink *et al*. demonstrated that even when muscle GLN concentration was reduced by 40% using GS inhibitors, there was no change in muscle protein synthesis rate [19]. Therefore, the causal relationship between the increased GS expression in muscle cells and decreased GLN concentration in cancer cachexia and muscle protein assimilation resistance has not yet been fully elucidated.

Cancer-induced muscle atrophy is notably observed in fast-twitch muscles, which are generally less prone to inactivity-induced atrophy [20]. Therefore, to prevent muscle atrophy through exercise, it is believed that high-intensity training that recruits fast-twitch muscles is necessary. However, in many cases, it is difficult to actively prescribe high-intensity exercise therapy that can mobilize fast-twitch muscles to cancer patients who experience a decline in physical strength and fatigue. Neuromuscular electrical stimulation (ES) is a method that induces involuntary muscle contractions by electrically stimulating peripheral nerves and muscles and is widely used for rehabilitation and training purposes [21]. ES has the advantage of recruiting both slow and fast-twitch muscle fibers without following the size principle and can be performed even in a resting state [22]. However, in reports where ES training was applied to the quadriceps muscles of lung cancer patients, no suppression of muscle atrophy was observed [23]. Furthermore, in previous studies that investigated the effects of isometric and concentric contractions by ES training in cancer model mice, it was reported that muscle atrophy was not reduced [24,25]. It is believed that the involvement of muscle protein assimilation resistance in cancer cachexia is responsible for these results, but whether muscle cell GLN metabolism is involved in this mechanism has not been sufficiently studied.

Thus, this study aimed to clarify the role of GLN metabolism in cancer-induced muscle atrophy and investigate the effects of ES training and GLN administration, alone and in combination, on muscle mass and

GS expression in colon-26 (C-26) tumor-bearing mice, a widely used model for cancer cachexia.

2. Methods

2.1. Ethical Considerations

This study was conducted with the approval of the Sapporo Medical University Animal Experiment Committee (Approval No. 15-044_17-078) and in accordance with the regulations set by the committee.

2.2. Experimental animals and protocol

Five-week-old male CD2F1 mice were used in this study. They were randomly divided into control (CNT) mice and C-26 mice, further subdivided into GLN non-administration groups (CNT group and C-26 group) and GLN administration groups (CNT+GLN group and C-26+GLN group), with each group containing 5 mice. The right hind limbs of these groups were designated as the non-training side, and the left hind limbs were designated as the training side (CNT+ES group, C-26+ES group, CNT+GLN+ES group, and C-26+GLN+ES group), resulting in a total of 8 groups. The mice had *ad libitum* access to water and food and were kept in a room maintained at a constant temperature of 24 ± 2°C with a 12-h light-dark cycle. C-26 cells were cultured at 37°C under 5% CO_2 in RPMI-1640 medium containing 10% fetal bovine serum (FBS) and 1% penicillin/streptomycin, and tumor induction was performed by injecting 5×10^5 C-26 cells suspended in phosphate-buffered saline (PBS) into the subcutaneous region of the abdomen, following the method of Murphy *et al*. [26]. The GLN administration group received GLN (1 g/kg; HyClone) dissolved in PBS via intraperitoneal injection daily from the day following C-26 seeding until the day of dissection, following the method of Meador *et al*. [27]. The group without GLN administration received an equivalent amount of PBS in the same manner. ES was performed every other day from the day following C-26 seeding for a total of 14 sessions. After 24 hours from the final ES session (28 days after cancer cell seeding), the body weight of each mouse was measured, and the tumor mass and gastrocnemius muscle were collected. Additionally, the weight of the collected tumor mass and gastrocnemius muscle was measured, and the gastrocnemius muscle was rapidly frozen in liquid nitrogen and stored at -80°C until analysis.

2.3. ES load

The left hind limb of the mouse was fixed using tape in the dorsally recumbent position in an ankle dorsiflexion torque measurement system under isoflurane inhalation anesthesia (2%, 2 L/min). The dorsiflexion angle of the ankle joint during fixation was set at 20° dorsiflexion (**Figure 1**). To minimize the influence of body movement induced by exercise, the trunk was taped to immobilize it. To reduce skin resistance to electrical stimulation, the left hind limb of the mouse was shaved immediately before each ES session, and surface electrodes connected to an electrical stimulator (Nihon Kohden Co., Ltd.) were attached to the posterior and anterior aspects of the lower leg. The electrical signal of the maximal isometric torque (MIT) for ankle dorsiflexion was amplified by an amplifier and observed as a waveform using data analysis software (LabChart, Ver. 8, ADInstruments). ES training was modified based on the method of Gondin *et al*. [28]. MIT was measured under the stimulation conditions of a stimulation frequency of 50 Hz and a stimulation intensity of 45 V (maximal upper stimulation). Subsequently, MIT was gradually increased to 60% of the obtained MIT as the target torque under the conditions of a stimulation frequency of 50 Hz, a stimulation time of 2 s, and a rest time of 4 s, until the voltage reached 45 V. The stimulation was terminated when the torque of 60% MIT could no longer be exerted even at 45 V. This was considered one set, and three sets were performed in 1 day, with a 1-minute break between sets.

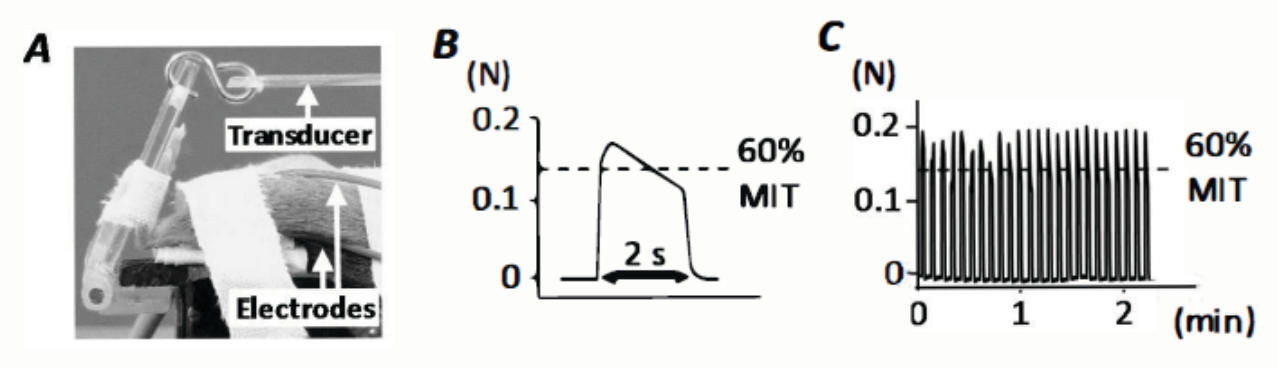


Figure 1. Procedure for neuromuscular electrical stimulation training on mouse plantar flexor muscles. **(A)** Under anesthesia, the animal was placed in a supine position and the experimental limb was attached to a footplate connected to a force transducer. The foot was placed at 20° angle of dorsal flexion. Surface electrodes were placed on the front and back surfaces of plantar flexor muscles. **(B and C)** Torque traces were displayed on a monitor and the stimulation intensity was progressively increased throughout the stimulation period to maintain a peak torque corresponding to 60% of the maximal isometric torque (MIT).

2.4. Open field test

To account for the influence of ES training, the measurement day was set as 2 days before the dissection day without ES training (26 days after cancer cell seeding). Since mice are nocturnal, the open field test was conducted in the dark at night. The method was modified from Shimada *et al.* [29]. A 60 cm^2 field was divided into nine regions of 3×3 (each 20 cm^2), and the number of times the mouse crossed the dividing lines within 10 minutes was recorded. During the measurement, the observer avoided moving and took great care not to affect the mouse's behavior. The equipment was cleaned after each measurement to eliminate any lingering odors.

2.5. Western blotting

Gastrocnemius muscles (approximately 20 mg) were homogenized in 40-fold Tris solution (10 mM Tris maleate, 35 mM NaF, 1 mM $NaVO_4$, 1% Triton X 100, 1 tablet of protease inhibitor/50 mL). Protein concentration was quantified using the Bradford method [30]. Total muscle proteins were loaded onto gels (4–15% Mini-PROTEAN TGX Stain-Free™ Gels, Bio-Rad) at 20 µg per lane and electrophoresed at 150 V for 45 minutes. All bands on the gel were visualized using a Stain-Free imager (Bio-Rad) and the band intensity of the myosin heavy chain (MyHC) was calculated as a ratio to the total band intensity of each lane using Image Lab Software (Bio-Rad). Subsequently, proteins were transferred from the gel to a membrane using a cell (Mini PROTEAN II Cell, Bio-Rad) at 100 V for 180 minutes. The membrane was blocked in a washing solution (40.3 mM Tris-HCl, 9.7 mM Tris-base, 150 mM NaCl, 0.02% Tween 20) containing 3% (w/v) skim milk for 1 hour and then incubated overnight at 4°C with primary antibodies (anti-GS antibody, 20,000-fold dilution, GeneTex; anti-GAPDH antibody, 2,000-fold dilution, Wako). After three washes with washing solution for 10 minutes each, the membrane was incubated with a secondary antibody, diluted 10,000-fold, at room temperature for 1 hour, followed by further washing. A chemiluminescence reagent (Immobilon, Millipore) was used for visualizing the target proteins, and band detection and quantification were performed using a chemiluminescence detection device. The expression level of GS was corrected by the expression level of GAPDH.

2.6. Statistical analysis

All data are presented as mean ± standard error (SEM). The comparison of tumor weights in the C-26 group and

C-26+GLN groups was performed using an unpaired *t*-test. On the other hand, a two-way analysis of variance (ANOVA) was used to compare the body weight and activity level in each group, while a three-way ANOVA was used to compare gastrocnemius muscle weight, GS, and MyHC expression levels. In case of significance, a Student-Newmann-Keuls test was performed as a post-hoc test. Statistical analysis was conducted using Statview 5 (SAS Institute Inc.), and the significance level was set at 5%.

3. Result

3.1. Changes in body mass and tumor mass

Table 1 shows the values of body mass and tumor mass in each group. In terms of body mass, a two-way analysis of variance with C-26 seeding and GLN administration as factors showed a significant main effect of C-26 seeding ($P < 0.05$), but no significant interaction was observed ($P > 0.05$). Multiple comparison tests revealed that the body mass in C-26 mice was 19% lower compared to CNT mice, and C-26+GLN mice had a 21% lower body mass compared to CNT mice ($P < 0.05$).

Table 1. Effects of tumor-bearing and glutamine administration on body and tumor mass in control and colon-26 mice

	CNT ($n = 5$)	CNT+GLN ($n = 5$)	C-26 ($n = 5$)	C-26+GLN ($n = 5$)
Tumor-free body mass (g)	23.8 ± 0.4	23.2 ± 0.5	19.2 ± 1.0*†	18.7 ± 0.5*†
Tumor mass (g)	-	-	6.5 ± 0.7	4.5 ± 0.7

Values are means ± SEM. Abbreviations: CNT, control; C-26, colon-26; GLN, glutamine. $P < 0.05$ versus *CNT and †CNT+GLN.

In the case of gastrocnemius muscle wet weight, a three-way ANOVA with C-26 seeding, GLN administration, and ES load as factors showed significant main effects of C-26 seeing and GLN administration ($P < 0.05$), while no significant second-order interactions or first-order interactions were observed. Multiple comparison tests indicated that the gastrocnemius muscle wet weight in the C-26 group was 17% lower than the CNT group ($P < 0.05$) (**Figure 2**). Contrary to expectations, both GLN administration and the combination of ES training and GLN administration did not prevent the decrease in gastrocnemius muscle wet weight in C-26 mice.

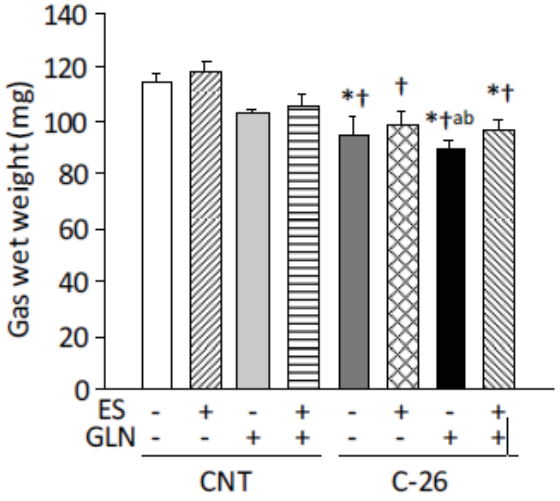


Figure 2. The wet weight of gastrocnemius (Gas) muscles from control (CNT) and colon-26 (C-26) mice with or without neuromuscular electrical stimulation (ES) training and/or glutamine (GLN) administration. Bars show the mean and SEM results from 5 mice per group. Statistical significance was set at $P < 0.05$ versus *CNT, †CNT+ES, [a]CNT+GLN, and [b]CNT+GLN+ES.

3.2. Changes in activity level

In the open field test, the number of times mice crossed the dividing lines within 10 minutes was 129 ± 12 times for CNT mice, 134 ± 15 times for CNT+GLN mice, 79 ± 21 times for C-26 mice, and 105 ± 11 times for C-26+GLN mice. A two-way ANOVA with C-26 seeding and GLN administration as factors showed a significant main effect of C-26 seeding ($P < 0.05$), but no significant interaction was observed ($P > 0.05$).

3.3. Changes in GS expression level

Figure 3A shows typical electrophoresis results of GS in each group. In a three-way ANOVA with C-26 seeding, ES load, and GLN administration as factors, significant main effects of C-26 seeding and ES load were observed ($P < 0.05$), and a first-order interaction between C-26 seeding and GLN administration was observed ($P < 0.05$). Multiple comparison tests revealed that GS expression in the CNT+ES group was approximately halved compared to the CNT group ($P < 0.05$). In contrast, the GS expression in the C-26 group, C-26+ES group, and C-26+GLN group was higher than that in the CNT group ($P < 0.05$). No significant difference was observed between the GS expression in the C-26+ES group as well as the C-26+GLN group and the C-26 group. However, GS expression in the C-26+GLN+ES group was lower than in the C-26 group ($P < 0.05$) (**Figure 3B**).

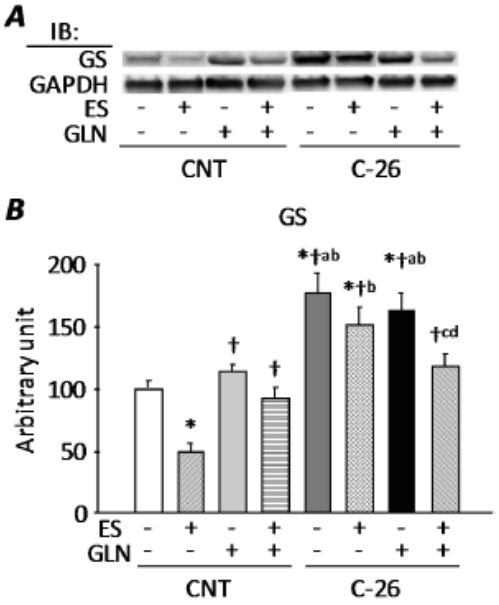


Figure 3. (A) Representative immunoblots (IB) for glutamine synthetase (GS) expression in gastrocnemius muscles from control (CNT) and colon-26 (C-26) mice with or without neuromuscular electrical stimulation (ES) training and/or glutamine (GLN) administration. **(B)** The expression levels of GS were quantified as arbitrary units normalized to GAPDH content. Data show the mean and SE< results from 5 muscles per group. Statistical significance was set at $P < 0.05$ versus *CNT, †CNT+ES, ^{a}CNT+GLN, ^{b}CNT+GLN+ES, ^{c}C-26, and ^{d}C-26+GLN.

3.4. Changes in MyHC expression level

Figure 4A displays typical electrophoresis results of MyHC in each group. The proportion of MyHc in total muscle protein quantified from Stain-Free images showed a significant main effect of GLN administration in a three-way ANOVA with GLN administration as a factor ($P < 0.05$), while no significant interactions were observed. The distribution of MyHC in whole muscle cell proteins is not altered in gastrocnemius muscles from colon-26 mice, as shown in **Figure 4B**.

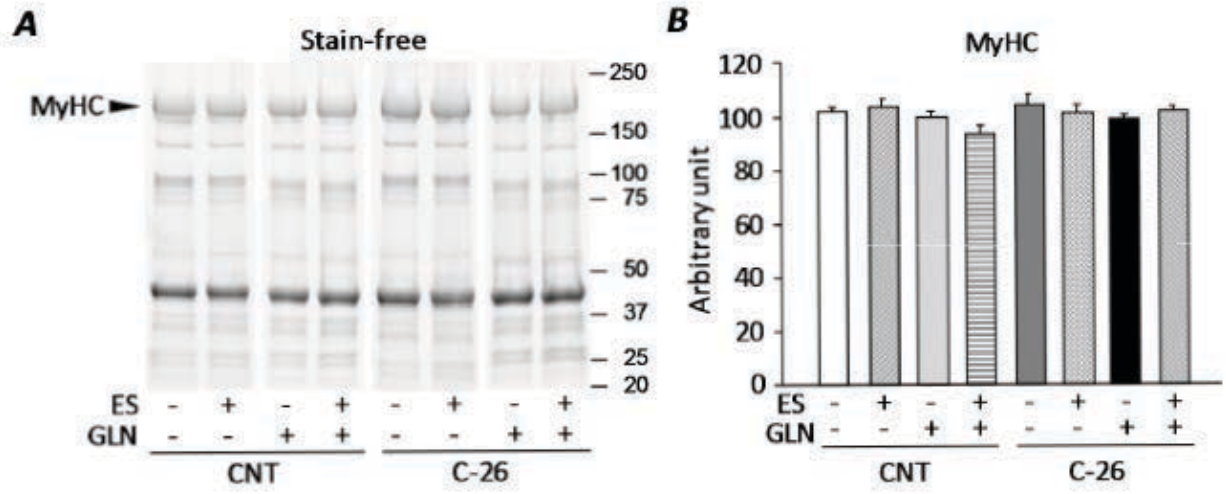


Figure 4. (A) Representative Stain-Free Image for myosin heavy chain (MyHC) in gastrocnemius muscles from control (CNT) and colon-26 (C-26) mice with or without neuromuscular electrical stimulation (ES) training and/or glutamine (GLN) administration. **(B)** The expression levels of MyHC were quantified as arbitrary units normalized to whole muscle proteins in Stain-Free images. Data show the mean and SEM results from 5 muscles per group.

4. Discussion

In this study, mice on the 28th day after seeding with C-26 cancer cells experienced a significant decrease in their body weight, approximately 20%, concomitant with tumor growth. Unintentional weight loss exceeding 5% within 6 months is one of the diagnostic criteria for cancer cachexia in humans [31]. Therefore, it is reasonable to assume that cancer cachexia occurred in this study due to the seeding of C-26 cells. It should be noted that mice subcutaneously seeded with C-26 cancer cells are reported to succumb to the disease in about 32 days [32], suggesting that the 28th day represents an advanced stage of the disease.

Under stressful conditions such as cancer cachexia, immune cells and the gastrointestinal tract have increased GLN consumption, leading to an increased release of GLN from the major GLN-producing organ, skeletal muscle [15,18]. Previous studies have demonstrated that increased GS activity in the skeletal muscles of methylcholanthrene-induced cancer model mice is associated with increased GLN release and decreased GLN concentration in the muscle [14]. This study is also consistent with previous studies as there was an increase in GS expression in the skeletal muscles of C-26 mice, a widely used model for cancer cachexia. Therefore, although this study did not measure GLN concentrations in the muscles, it is suggested that, in C-26 mice, the increased demand for GLN associated with cancer cachexia leads to an increase in GS synthesis in skeletal muscles and a decrease in intramuscular GLN concentration.

The mechanism behind this phenomenon is unclear, but it has been shown that endurance running exercise suppresses the increase in GS expression in mice skeletal muscle [33]. In line with these findings, this study showed that ES training suppressed GS expression in the skeletal muscles of CNT mice. However, in the skeletal muscles of C-26 mice, ES training showed a tendency to suppress the increase in GS expression, but no statistical difference was observed. Moreover, external GLN administration has been shown to prevent the decrease in intramuscular GLN concentration and the increase in GS activity in skeletal muscles of methylcholanthrene-induced cancer model mice [14]. However, in this study, GLN administration did not suppress the increase in GS expression in the skeletal muscles of C-26 mice. The reasons for these differences

are unclear but may be related to variations in GLN dosage and administration methods, as previous studies have utilized 2% GLN in free drinking water.

Multiple previous studies have reported a high correlation between the synthesis rate of muscle protein and intramuscular GLN concentration [13,34]. Additionally, GLN administration has been shown to improve ribosome size and distribution in skeletal muscle after surgical trauma [35], prevent the reduction of GLN content in the skeletal muscles of diabetic model mice, and suppress the inactivation of the mTORC1 signaling pathway, a major muscle protein synthesis pathway [36]. On the other hand, the fact that muscle protein synthesis rate does not change when intramuscular GLN concentration is significantly decreased over a certain period by GS inhibitors suggests that muscle protein synthesis rate may not be determined by intramuscular GLN concentration [19]. Supporting this idea, in this study, the combination of ES training and GLN administration suppressed the increase in GS expression in the skeletal muscles of C-26 mice but did not prevent the decrease in muscle weight. Additionally, the combination of GLN administration and low-intensity swimming exercise did not improve the atrophy of the gastrocnemius muscle in Walker 256 cancer model mice [37]. Therefore, based on these findings, it is highly likely that there is no causal relationship between intracellular GLN concentration and muscle protein synthesis rate.

Consistent with the results of this study, previous studies have reported that isometric or concentric contraction ES training does not prevent the atrophy of the gastrocnemius muscle in C-26 mice [24,25]. On the other hand, recent research has shown that ES training involving eccentric contractions, which can increase mechanical stress on muscles more than isometric contractions, enhances the mTORC1 signaling in the skeletal muscles of C-26 cancer model mice without causing muscle damage and counteracts muscle protein anabolic resistance [24,38,39]. Furthermore, a study comparing the effects of ES training with different contraction modes on muscle hypertrophy in normal mice demonstrated that eccentric contractions, as opposed to isometric contractions, result in higher activation of the mTORC1 signaling pathway and muscle hypertrophy, and this is determined not by the type of contraction but by the torque exerted during contraction [40]. Thus, if ES training is carried out to reduce muscle atrophy due to anabolic resistance in cancer, it is important to increase the intensity of the load, and training using eccentric contractions is suggested to be effective. Nevertheless, it should be noted that with the progression of cancer cachexia, the susceptibility of skeletal muscles to damage from eccentric contractions may increase, and hence, this aspect should be carefully considered in future studies.

In cancer-related muscle atrophy, reports indicated both selective reductions in MyHC and uniform decreases in muscle proteins other than MyHC [41-43]. In this study, no significant changes in the proportion of MyHC in total muscle proteins were observed. Hence, it is suggested that the muscle atrophy observed in C-26 mice does not involve selective reductions in MyHC and instead results in a uniform decrease in cytoplasmic and myofibrillar proteins. Supporting this notion, glucocorticoids, which are considered one of the factors contributing to muscle protein anabolic resistance in cancer cachexia, have been shown not to affect MyHC mRNA and protein expression levels [44].

5. Research limitations

The balance between muscle protein synthesis and degradation is regulated by food intake. Previous studies have reported that C-26 mice are a cancer model that does not exhibit reduced food intake [39,45]. Thus, while it is considered unlikely that differences in food intake played a role in the observed changes in muscle mass in this study, the food intake was not measured, so its involvement cannot be completely ruled out.

6. Conclusion

In this study, the effects of isometric ES training and GLN supplementation on skeletal muscle were investigated in C-26 cancer model mice. ES training and GLN supplementation individually did not suppress the increased expression of GS in C-26 mice's skeletal muscles. However, when used in combination, they prevented this increase. On the other hand, neither ES training nor GLN supplementation, alone or in combination, prevented muscle atrophy in C-26 mice. While there have been reports suggesting a relationship between increased GS expression and decreased GLN concentration in skeletal muscle and resistance to muscle protein anabolism in muscle atrophy [13,46], there are also reports suggesting no relationship [19,47]. The results of this study support the latter. Therefore, nutritional and exercise therapies aimed at normalizing GLN metabolism in skeletal muscle do not appear to be effective in improving muscle atrophy associated with cancer cachexia.

Disclosure statement

The authors declare no conflict of interest.

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Correlation between HBeAg and Hepatitis B Virus DNA and RNA Levels in Diverse Liver Disease Cohorts

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Abstract: *Objective:* To investigate the disparities and associations between HBV DNA and HBV RNA in various liver disease groups with respect to HBeAg status. *Methods:* Between September 2020 and September 2023, 90 patients diagnosed with chronic hepatitis B (CHB), 74 patients diagnosed with liver cirrhosis (LC), and 102 patients diagnosed with hepatocellular carcinoma (HCC) from the Department of Gastroenterology or Infection at the First Affiliated Hospital of Xi'an Jiaotong University were selected. HBV DNA, HBV RNA, and HBeAg quantitative tests were conducted using serum samples from the same patients. *Results:* In the three groups of cases, the HBV RNA load was higher when HBeAg was positive than when HBeAg was negative, and this difference was statistically significant. Only in the HCC group was the HBV DNA load significantly higher when HBeAg was positive than when HBeAg was negative. Additionally, there was a positive correlation between HBV DNA and HBV RNA regardless of HBeAg status. *Conclusion:* During HBeAg conversion, HBV RNA demonstrates a more sensitive response than HBV DNA. As CHB progresses to LC or HCC, HBV RNA exhibits better diagnostic value than HBV DNA.

Keywords: Hepatitis B virus DNA; Hepatitis B virus RNA; HBeAg

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1. Introduction

Human hepatitis B virus (HBV) is a small group of hepatophilic DNA viruses that infect more than 258 million people worldwide [1]. Chronic HBV infection is the primary cause of viral hepatitis, with approximately one-third of HBV carriers developing liver cirrhosis (LC), and 11% progressing to hepatocellular carcinoma (HCC) [2]. While prophylactic vaccines are available to prevent HBV infection, there is currently no cure for patients with chronic hepatitis B (CHB) [3].

Hepatitis B e antigen (HBeAg) is produced from the core pre-mRNA of HBV. It is an unstructured protein that can be released from infected hepatocytes into the bloodstream, where it functions as a soluble protein [4]. HBeAg can act as a tolerogen, modulating the host immune response and inhibiting the cytotoxic activity of host T-cells, leading to immune tolerance against HBV infection. Additionally, HBeAg acts as an immunogen, protecting hepatocytes from apoptosis by interfering with hepatocyte signaling pathways as a target of the

immune response. While HBeAg is not essential for viral replication or infection, it plays a crucial role in virus-hepatocyte interactions and the establishment of chronic HBV infection. It also serves as a marker of HBV replication and infectivity [5].

HBV DNA reflects the extent of active replication of the hepatitis B virus. A higher viral load indicates more active replication and increased infectivity. Serum HBV RNA is directly transcribed from covalently closed circular DNA (cccDNA) in infected hepatocytes, and most of it is reverse-transcribed into HBV DNA and released into the serum. Serum HBV RNA levels can reflect the presence of cccDNA and its transcriptional activity in hepatocytes [6]. However, the biological significance and clinical relevance of serum HBV RNA in the course of HBV infection remain unclear. An early study suggested that serum HBV RNA might be a valuable marker for distinguishing the stages of chronic HBV infection [7]. In this study, the levels of HBV DNA and HBV RNA before and after HBeAg conversion were compared separately in different disease groups, aiming to assess the clinical utility of these two assays.

2. Materials and methods

2.1. General information

A total of ninety patients diagnosed with CHB, 74 patients diagnosed with LC, and 102 patients diagnosed with HCC who had sought treatment at the Department of Gastroenterology or the Department of Infection at the First Affiliated Hospital of Xi'an Jiaotong University from September 2020 to September 2023 were selected.

The inclusion criteria included patients with HBV infection for more than half a year, patients aged between 18–80 years, and patients willing to provide informed consent.

The exclusion criteria included patients with severe liver-related complications (including decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation) and patients co-infected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV).

This study adhered to the ethical principles of the Declaration of Helsinki, and the protocol received approval from the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. All patients provided informed consent.

2.2. Laboratory testing

HBV DNA and HBV RNA were quantified using real-time fluorescence quantitative polymerase chain reaction (PCR), following the reagent instructions (Zhongshan Daan, Guangzhou, China). An ABI7500 fluorescence quantitative PCR instrument from the USA was used. The lower limit of detection for HBV DNA was 20 IU/mL, and for HBV RNA, it was 100 copies/mL.

HBeAg was detected using the chemiluminescence method with the fully automatic chemiluminescence immunoassay analyzer (ALINITYI, Abbott, USA), and the associated reagents for HBeAg detection. The test unit was S/CO, with results considered negative if < 1 and positive if ≥ 1.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (IBM, Chicago, IL, USA). Data are presented as mean ± standard deviation (SD), and differences in means were analyzed using Student's *t*-test. According to the reagent manufacturer's instructions, HBV DNA was compared to HBV RNA using a conversion factor of 1 IU = 5 copies. Correlation tests were analyzed using Pearson's correlation analysis. Significance levels were denoted as follows: * for $P < 0.05$, ** for $P < 0.01$, *** for $P < 0.001$, **** for $P < 0.0001$, and ns for $P > 0.05$. A significance level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. HBV DNA and HBV RNA in CHB in relation to HBeAg in the CHB group

In the hepatitis group, the HBV DNA load in the HBeAg-positive group was higher than that in the HBeAg-negative group, but this difference was not statistically significant ($P > 0.05$). However, the HBV RNA load in the HBeAg-positive group was significantly higher than that in the HBeAg-negative group ($P < 0.0001$), as shown in **Figure 1**.

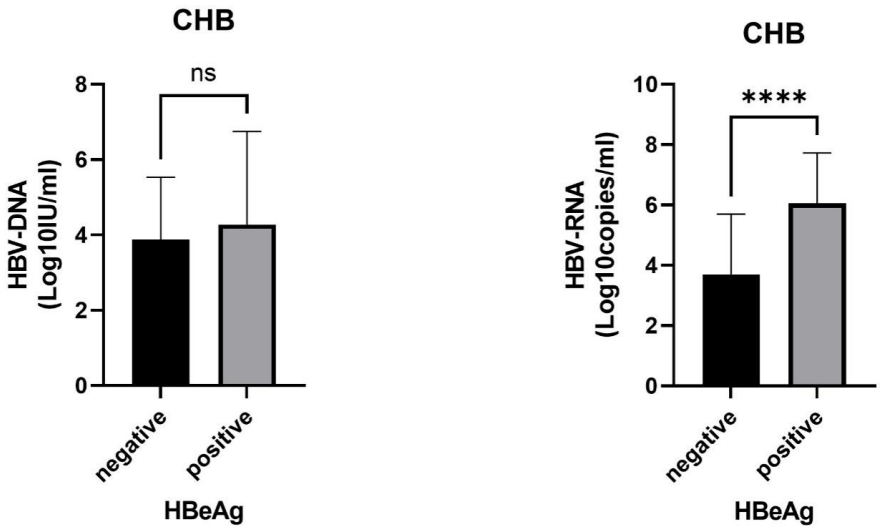


Figure 1. HBV DNA and HBV RNA load changes before and after HBeAg conversion in the CHB group

3.2. HBV DNA and HBV RNA in relation to HBeAg in the LC group

In the cirrhosis group, the HBV DNA load in the HBeAg-positive group was higher than that in the HBeAg-negative group, but this difference was not statistically significant ($P > 0.05$). However, the HBV RNA load in the HBeAg-positive group was significantly higher than that in the HBeAg-negative group ($P < 0.001$), as shown in **Figure 2**.

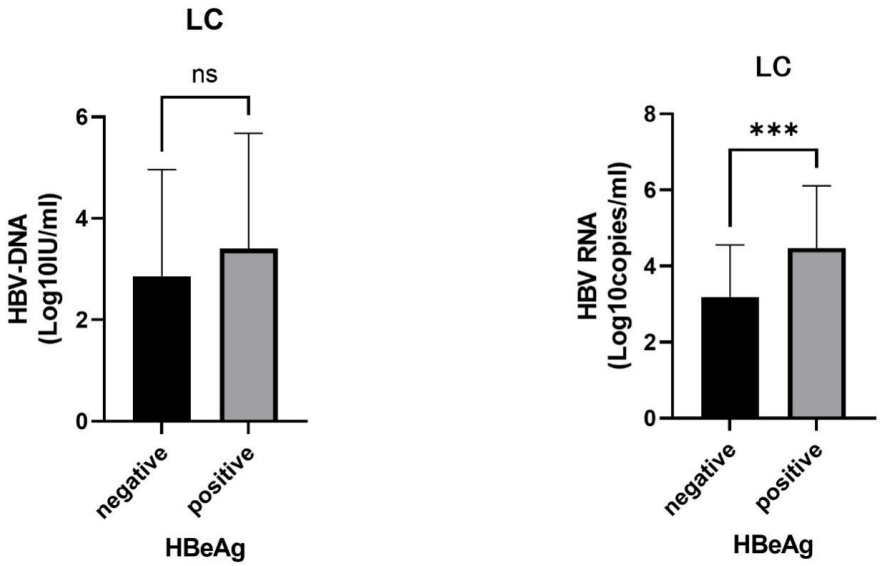


Figure 2. HBV DNA and HBV RNA load changes before and after HBeAg conversion in the LC group

3.3. HBV DNA and HBV RNA in relation to HBeAg in the HCC group

In the hepatocellular carcinoma group (**Figure 3**), the HBV DNA load in the HBeAg-positive group was substantially higher than that in the HBeAg-negative group ($P < 0.01$), while the HBV RNA load in the HBeAg-positive group was significantly higher than that in the HBeAg-negative group ($P < 0.0001$).

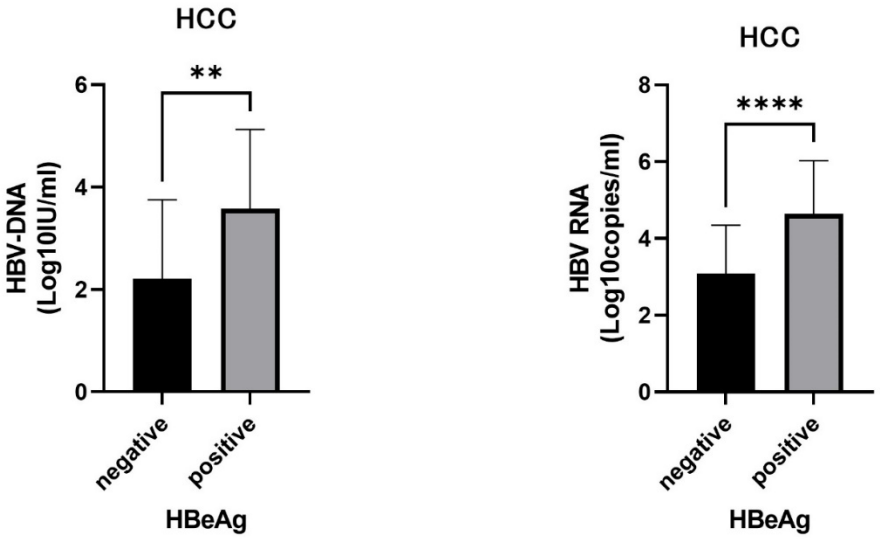


Figure 3. HBV DNA and HBV RNA load changes before and after HBeAg conversion in the HCC group

3.4. Correlation of HBV DNA with HBV RNA

The correlation between HBV DNA and HBV RNA was further examined. The results indicated a positive correlation between HBV DNA and HBV RNA, both in the HBeAg-negative group ($r = 0.6085$) and the HBeAg-positive group ($r = 0.5741$).

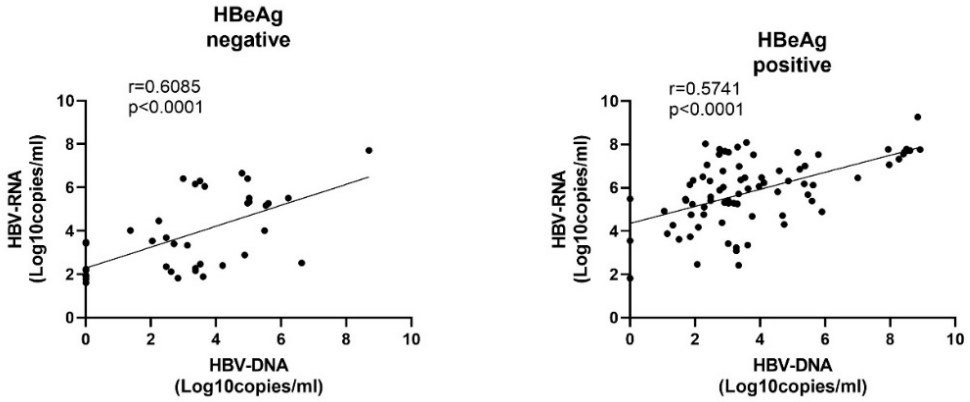


Figure 4. Correlation analysis of HBV DNA and HBV RNA before and after HBeAg conversion

4. Discussion

The core HBV gene encodes HBeAg, which is secreted from infected hepatocytes and serves as a marker of active viral replication. Both HBeAg and its antibody, HBeAb, can be quantitatively measured through immunoassays. HBeAg typically becomes detectable 6–12 weeks after exposure to HBV, indicating a high level of HBV DNA and infectivity. Seroconversion from HBeAg to anti-HBe is a crucial milestone in disease

progression, often signaling the transition to an inactive infection state [8]. The seroconversion of HBeAg is a key prognostic factor. Persistent HBeAg positivity in patients with CHB is indicative of ongoing HBV infection, which is associated with active hepatitis and an increased risk of LC. High serum HBeAg levels are correlated with the progression to LC and HCC [9].

In this study, higher HBV DNA and HBV RNA loads were observed in the HBeAg-positive group compared to the HBeAg-negative group within the CHB cohort. Notably, the difference in HBV DNA load was not statistically significant, but the difference in HBV RNA load was statistically significant (**Figure 1**). The HBeAg-positive phase in the context of long-term persistent HBV infection is characterized by immune-mediated liver injury and fluctuating HBV titers. High HBV titers and active viral replication are observed in this phase [10]. The transition to an anti-HBeAg-positive status signifies the entry into the inactive HBV-carrying phase, known as HBeAg-negative chronic hepatitis, characterized by lower HBV titers and slower progression of liver injury compared to the previous immune response phase [11].

A small subset of CHB patients may ultimately clear HBV, entering the HBsAg-negative phase in which serum HBV DNA becomes undetectable [12], marking a "functional cure." However, since viral cccDNA persists in the liver, HBV can reactivate with certain immunosuppressive treatments. Typically, end-stage liver diseases related to HBV (including LC and HCC) may develop within a few decades after this stage [13]. When HBV infection tends to resolve, clinical symptoms may become less apparent and easily overlooked. Symptoms that arise before treatment often indicate advanced liver cancer, which is challenging to treat at this stage. HBV DNA positivity in HBeAg-negative patients suggests viral mutations that escape immune surveillance, increasing the risk of cancerous cell formation and the likelihood of developing cirrhosis and liver cancer.

In this study, the HBV DNA load in HBeAg-positive patients in the LC group was higher than in HBeAg-negative patients, although this difference was not statistically significant. However, the HBV RNA load in the LC group was significantly higher in the HBeAg-positive group compared to the HBeAg-negative group (**Figure 2**). In contrast, in the HCC group, both HBV DNA and HBV RNA levels were higher in the HBeAg-positive group than in the HBeAg-negative group, and these differences were statistically significant, with HBV RNA demonstrating a slightly stronger difference compared to HBV DNA (**Figure 3**). These findings suggest that HBV RNA is more responsive to HBeAg conversion in earlier stages of the disease, such as CHB and LC. However, as the disease progresses to HCC, both HBV DNA and HBV RNA become equally valuable in assessing changes before and after HBeAg conversion.

HBV RNA levels were correlated with HBV DNA levels, varying with the stage of infection. The highest levels were observed during the immune tolerance period, whereas patients with inactive HBV infection had the lowest levels [14]. This study found a positive correlation between HBV DNA and HBV RNA, regardless of HBeAg status (**Figure 4**). This indicates that HBeAg conversion does not alter the relationship between HBV DNA and HBV RNA. Some studies have investigated whether measuring HBeAg levels can serve as a substitute for quantifying HBV DNA. In a study of 82 patients in Malaysia, HBeAg levels were correlated with HBV DNA levels above 300 IU/mL ($r = 0.893$) but not with HBsAg levels [15].

While seroconversion of HBeAg is widely regarded as a treatment endpoint [16], it is important to note that HBeAg presence primarily indicates active viral replication and active liver disease. In a subset of HBeAg-negative patients, detectable HBV-DNA and active hepatitis may still be present when using low-sensitivity molecular hybridization techniques for serum HBV DNA detection [17]. Furthermore, first-line antiviral agents (e.g., nucleotide analogs) can reduce serum HBV DNA to undetectable levels by interfering with the viral transcription process, but HBV RNA quantification remains unaffected [18]. Thus, serum HBV RNA is considered a novel marker for monitoring antiviral efficacy, especially in virologically suppressed patients who

cannot achieve HBV DNA suppression under nucleotide analogs therapy [19]. This study illustrates that while HBV DNA and HBV RNA exhibit a certain degree of correlation, HBV RNA demonstrates greater sensitivity and superior predictive value in disease assessment compared to HBV DNA.

Disclosure statement

The authors declare no conflict of interest.

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Expert Consensus on Clinical Management of T2DM Combined with Obesity Reversal Treatment in China (2023 Edition)

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Abstract: With lifestyle changes, the incidence of type 2 diabetes (T2DM) and obesity has significantly increased, becoming major chronic diseases that seriously threaten the health of China's residents. Both domestic and international guidelines and consensus exist regarding the diagnosis and management of this disease. In recent years, T2DM treatment has focused more on new tactics that lean towards a patient-centered comprehensive management approach, replacing the traditional glucose-centered approach. Additionally, an increasing amount of evidence in medicine suggests that the reversal of diabetes is possible. However, there is currently no expert consensus on the clinical management of T2DM combined with obesity reversal treatment. Therefore, experts and scholars in China with extensive experience in T2DM combined with obesity reversal treatment have been invited to develop this consensus. The content includes early identification and diagnosis of T2DM combined with obesity, definition and mechanisms of diabetes reversal, disease assessment and grading, staging of diabetes and goals of reversal, the 2+N reversal strategy, inpatient system treatment combined with comprehensive outpatient management (including weight control, precise nutrition, scientific exercise, glucose-lowering medication, psychological intervention, rehabilitation therapy, and remote follow-up through online platforms), and evaluation of post-reversal efficacy. The aim is to further improve the level of T2DM combined with obesity reversal diagnosis, treatment, and management in China, and to implement the Healthy China strategy.

Keywords: Type 2 diabetes mellitus (T2DM); Obesity; Reversal treatment; Clinical management; Expert consensus

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1. Introduction

As people's lifestyles evolve and population aging accelerates, the prevalence of type 2 diabetes mellitus (T2DM)

and obesity is on a rapid incline. The initial *Diabetes Map of China*, released by the Chinese Center for Disease Control and Prevention in 2022, indicates that the overall prevalence of T2DM in China surged to 14.92% between 2015 and 2019, ranking it first globally. This is in stark contrast to the 1.29% recorded from 1980 to 1984 [1]. Obesity is intricately linked with T2DM. The 2023 *Obesity Map of China* reveals a 36.8% prevalence of diabetes among obese/overweight individuals in China [2], with 58% of diabetes patients being overweight or obese [3]. Therefore, obesity emerges as the primary cause of T2DM.

Traditionally considered an incurable chronic progressive disease, T2DM's best-expected outcome through conventional hypoglycemic therapy has been to manage hyperglycemia and delay inevitable complications. Unfortunately, the compliance rate for diabetes control has been historically low, leading to a worsening public health situation related to diabetes. Recent years have witnessed a shift in the traditional "hypoglycemic-centered" approach to T2DM treatment, with a growing recognition of the "patient-centered" integrated management concept. Simultaneously, the previously considered irreversible cognitive pattern of T2DM is transforming [4].

Mounting evidence suggests that diabetes can be reversed. Numerous studies confirm that managing body weight through lifestyle intervention, certain drug treatments, and metabolic weight loss surgery can enhance insulin sensitivity, improve insulin secretion, foster B cell redifferentiation, and repair and reverse pancreatic function, thereby delaying or even reversing diabetes progression. In 2016, the World Health Organization (WHO) acknowledged that diabetes could be reversed through weight loss and calorie restriction. Most experts posit that, in the absence of hypoglycemic drugs, maintaining blood glucose levels lower than diabetes diagnostic criteria for an extended period and glycosylated hemoglobin (HbA1c) below 6.5% fulfill the requirements for diabetes remission [5,6]. The concept of "reversal of diabetes" aims to prevent the progression of diabetes into a destructive cycle, repair or even reverse islet β cell function, delay or prevent disease progression, reduce or cease the use of diabetes drugs, enhance patient's quality of life, alleviate the medical burden on patients and society, and reverse the severe health crisis of diabetes.

Over the past decade, more than one hundred experts from the Specialized Committee of Obesity Reversal of the Guangdong Provincial Geriatric Health Association and the Specialized Committee of Diabetes Management of the Guangdong Provincial Hospital Association have affirmed that T2DM patients with obesity can undergo reversal through extensive clinical practices. This draft refined through multiple revisions after extensive discussions and then consensus-seeking while acknowledging differences, serves as a clinical pathway guide for reversal therapy. It integrates the latest theories and clinical practices related to diabetes globally, offering valuable insights to domestic counterparts.

2. Significance and purpose of reversing T2DM combined with obesity

Diabetes can lead to chronic complications such as vasculopathy and neuropathy, as well as acute complications such as infection and ketoacidosis, necessitating lifelong medication treatment for patients. According to the 2017 National Medical Insurance Sampling Database, Chinese diabetic patients incur an average annual personal expenditure of 18,785 CNY (including inpatients), while the corresponding annual personal expenditure covered by medical insurance is 41,682 CNY [1]. This imposes a substantial economic burden on patients, their families, and society.

Increased body weight or waist circumference can exacerbate insulin resistance, complicating blood glucose control [7,8]. Weight loss proves effective in improving insulin resistance, managing blood glucose, reducing cardiovascular and cerebrovascular disease risk factors, and enhancing overall quality of life. Within a certain range, greater weight loss correlates with more significant health benefits [9]. Obesity heightens the risk of

chronic complications in T2DM patients independently. It serves as a key risk factor for diabetic kidney disease, contributing to the progression of chronic kidney disease. Moreover, weight loss proves advantageous in reducing proteinuria in chronic kidney disease patients and slowing down the decline in renal function [10,11]. Obesity also substantially elevates the risk of cardiovascular and cerebrovascular diseases [12]. Therefore, reinforcing weight management in T2DM patients with obesity while concurrently addressing blood glucose is of paramount importance.

In 2016, the Endocrinology Branch of the Chinese Medical Association established *An Expert Consensus on the Comprehensive Management of T2DM Complicated with Obesity in China* [13]. In 2021, Professor Zou Dajin and Professor Ji Linong collaboratively formulated China's inaugural *Chinese Expert Consensus on Alleviating T2DM*. In 2022, Professor Wu Yiming and a team of 13 experts nationwide issued t*he Expert Consensus on Weight Management of Patients with T2DM in China* [14], guiding the systematic management of T2DM patients complicated with obesity. The economic and social value of reversing diabetes and obesity is substantial as it reduces medication dependency, alleviates complications, and diminishes personal, family, and socio-economic burdens.

The purpose of formulating a reversal therapy clinical expert consensus on T2DM complicated with obesity is to further standardize clinical management processes, improve blood glucose compliance rates and diabetes-related weight control, reduce the risk of complications, enhance patients' overall quality of life, and alleviate personal and social economic burdens.

3. Diagnostic criteria for T2DM complicated with obesity

The diagnostic criteria and classification of T2DM adhere to the standards set by the WHO in 1999 [15]. The diagnostic criteria for obesity are derived from *the Expert Consensus on Chinese Adult Obesity Prevention (2011 Edition)* [16], and the criteria for abdominal obesity outlined in the *Chinese Type 2 Diabetes Prevention Guide (2020 Edition)* [17]. Patients meeting the diagnostic criteria for both conditions are managed in accordance with T2DM complicated with obesity. **Tables 1** and **2** present the diagnostic criteria for diabetes and obesity, respectively.

Table 1. Diagnostic criteria for diabetes

Diagnostic criteria	Venous plasma glucose level (mmol/L)
Typical symptoms of diabetes (polydipsia, polyuria, polyphagia, weight loss) and random blood glucose testing	≥ 11.1
Fasting blood glucose detection	≥ 7.0
Blood glucose testing 2 h after glucose loading (for those without diabetes symptoms, the testing should be repeated on some other day)	≥ 11.1

Table 2. Diagnostic criteria for obesity

Score index	Score
Body mass index (kg/m^2)	
Overweight	≥ 24
Obesity	≥ 28
Abdominal obesity - waistline (cm)	
Male	≥ 90
Female	≥ 85

4. Definition of diabetes reversal

Presently, there exists no uniform standard for the definition of T2DM reversal. In 2017, the DiRECT study delineated diabetes remission as the withdrawal of anti-diabetic drugs for a minimum of 2 months and an HbA1c level below 6.5% at the one-year mark [18]. In 2009, the definition of T2DM remission within the pertinent consensus of the American Diabetes Association (ADA) categorized it into partial remission, complete remission, and long-term remission (**Table 3**). The 2021 Consensus Report titled "Definitions and Explanations for T2DM Remission," drafted by the International Expert Group of the ADA, proposed the use of an HbA1c level below 6.5% after at least 3 months of discontinuation of hypoglycemic drugs as a diagnostic criterion for T2DM remission.

In China, the domestic standard for T2DM remission has incorporated the postprandial blood glucose level index, and the requirement for HbA1c levels is relatively lenient. Professor Li Guangwei and Professor Weng Jianping applied the same criteria to assess the remission of T2DM patients undergoing intensive insulin therapy [19]: in the absence of medication after intensive treatment, fasting blood glucose should be below 7.0mmol/L, and blood glucose two hours post-meal should be below 10 mmol/L, with this state maintained for over a year.

Table 3. T2DM remission criteria in 2009 ADA expert consensus

Category	Definition	Criterion
Partial remission	The blood glucose level is below the diagnostic threshold of diabetes for at least 1 year without active drug intervention or some other interventions.	Without active drug intervention or ongoing intervention, HbA1c < 6.5%, and fasting blood glucose is 5.6–6.9 mmol/L for at least 1 year.
Complete remission	Normal blood glucose level lasts for at least 1 year, with no active drug intervention or other ongoing interventions	Without active drug intervention or ongoing intervention, HbA1c is within the normal range, and fasting blood glucose is less than 5.6 mmol/L for at least 1 year.
Long-term remission	Complete remission lasts at least 5 years	

5. Mechanisms of diabetes reversal

Insulin resistance and islet β-cell dysfunction represent the primary pathophysiological characteristics of T2DM complicated with obesity. In skeletal muscle, lipid accumulation diminishes blood glucose utilization, concurrently escalating insulin secretion. The heightened insulin concentration in the portal vein triggers liver fat deposition, further exacerbating liver insulin resistance. Additionally, synthesized fat infiltrates pancreatic tissue, resulting in impaired pancreatic β-cell function, β-cell dedifferentiation, and a subsequent decline in insulin response to ingested glucose, thereby elevating postprandial blood glucose levels. Notably, insulin resistance impacting blood glucose control predominantly originates from the liver rather than skeletal muscle [20].

Recent studies challenge the notion that β cells in T2DM patients undergo apoptosis; instead, they lose key β-cell characteristics due to dedifferentiation. Consequently, these cells lose their normal secretory regulation function, rendering them incapable of metabolic regulation in glucose homeostasis [21].

Research indicates that lifestyle intervention and comprehensive treatments, such as hypoglycemic drug application and nutritional adjustment, stand out as primary effective measures for diabetes reversal. Lifestyle intervention not only delays the onset of T2DM but also diminishes the risk of cardiovascular and cerebrovascular adverse events, microvascular complications, and cardiovascular and all-cause mortality, thereby prolonging life expectancy [22-24]. Short-term intensive insulin therapy in the early stages of diabetes

alleviates the condition and contributes to the recovery of β-cell functions [25]. GLP-1 receptor agonists (GLP-1RAs), through multiple mechanisms, reduce insulin resistance and play a role in diabetes reversal [26]. Precise nutritional therapy, meanwhile, contributes to weight reduction and the partial restoration of insulin function [27].

6. Reversal methods and processes

6.1. Reversal mode

(1) 2+N reversal mode: "2" signifies the integration of traditional Chinese medicine and Western medicine, as well as the fusion of drug and non-drug approaches. "N" encompasses a range of comprehensive measures, including precise nutritional therapy, scientific exercise, correction of detrimental lifestyle habits, and mental conditioning.

(2) In-hospital treatment: Recommended for new-onset diabetes, patients experiencing unstable blood glucose fluctuations (fasting blood glucose > 10mmol/L, random blood glucose > 15 mmol/L), and those with severe complications.

(3) Out-of-hospital comprehensive management: Appropriate for patients with stable conditions post short-term hospitalization, individuals whose severe complications are under control, and those whose blood glucose levels meet the standard.

6.2. Reversal process – main operational steps of clinical management standard

6.2.1. Establishment and personnel allocation of multidisciplinary diagnosis and treatment team

The comprehensive management of T2DM patients with obesity/overweight necessitates a multidisciplinary diagnosis and treatment team. The team's formation involves professionals and the acquisition of necessary hardware equipment. Led by diabetes specialists, the multidisciplinary team includes nutritionists, health managers, psychologists, weight loss surgeons, sports medicine doctors, rehabilitation physiotherapists, diabetes specialist nurses, and network managers. Hardware equipment comprises common medical tools such as a glucometer, instantaneous continuous blood glucose monitoring system, sphygmomanometer, computer, height and weight instrument, tape, nylon wire, tuning fork, human body fat composition analyzer, non-mydriatic ophthalmoscope, Doppler stethoscope, and peripheral nerve sensory threshold detector.

The medical staff at primary medical institutions, outpatient departments of hospitals at all levels, physical examination centers, weight loss centers, nutrition departments, and health care institutions should be trained to conduct diabetes screening, focusing on families with a history of diabetes.

Endocrine doctors with specialized reversal training formulate a reversal plan, oversee the entire reversal process, and guide health management institutions, nutritionists, rehabilitation physiotherapists, health managers, psychologists, and sports fitness coaches, all of whom have received professional reversal training, to jointly supervise patients in completing the reversal work.

6.2.2. Screening of high-risk population

Screening for adults (> 18 years old) with high-risk diabetes complicated with obesity includes measuring body mass index and waist circumference, blood glucose screening, glucose tolerance testing, differential diagnosis of etiology, understanding of diabetes and obesity-related complications, and testing and inquiring about related medical history.

6.2.3. Confirmation of patients

Diagnosis of T2DM patients complicated with obesity/overweight adheres to the diagnostic criteria of both

T2DM and obesity/overweight. The diagnosis of abdominal obesity primarily utilizes waist circumference, with diagnostic criteria of male ≥ 90 cm and female ≥ 85 cm.

6.2.4. Improvement of auxiliary examination and establishment of files for reversed patients

The perfect auxiliary examination involves filing and measuring height, weight, waist circumference, hip circumference, body fat content, and body mass index, as well as taking photos. Biochemical tests include blood lipids, blood glucose, HbA1c, insulin and C-peptide levels, urinary microalbumin, thyroid function, adrenocortical hormone, and sex hormones. Peripheral nerve electrophysiological examination, fundus examination, electrocardiogram, abdominal ultrasound, chest X-ray, and body fat composition analysis should be performed.

Filing involves the collection of patients' basic information, evaluation of islet β-cell function and complications, and establishment of personal medical records through hospitals, community health service centers, or health management institutions.

6.2.5. Evaluation and grading of patients

Assessment and grading include disease assessment, lifestyle assessment, and psychological assessment. Disease assessment can be summarized as ABCD, where A represents Age and HbA1c; B represents BMI and blood pressure; C represents Cholesterol and Cigarettes; D represents Diet and Duration. Patient condition is divided into 4 grades based on weight and blood glucose control level (see **Table 4**), where a higher grade indicates a more severe disease.

Table 4. Diabetic and obesity/overweight classification

Patient classification	Classification of diabetes (HbA1c)			
Classification of obesity (BMI: kg/m^2)	Early stage of diabetes	Diabetes level 1 (≤ 7.5%)	Diabetes level 2 (7.5%–9.0%)	Diabetes level 3 (> 9.0%)
Overweight (24.0–27.9)	Level 1	Level 2	Level 2	Level 3
Obesity level 1 (28.0–32.9)	Level 2	Level 2	Level 3	Level 3
Obesity level 2 (33.0–37.9)	Level 2	Level 3	Level 3	Level 4
Obesity level 3 (≥ 38)	Level 3	Level 3	Level 4	Level 4

Note: The obesity grading standard refers to the grading standard on obesity of the WHO, and it is adjusted according to the weight of the Chinese people.

Lifestyle assessment encompasses various aspects such as diet, exercise habits, exercise willingness, exercise feasibility, and smoking and drinking habits. Sports feasibility includes physical function feasibility and environmental feasibility. Psychologists should also evaluate patients based on quality of life, sleep status, and anxiety status.

6.2.6. Formulation of intervention schemes

An individualized reversal intervention plan should be formulated based on the evaluation of the patient's condition. The plan sets control objectives such as ideal weight, blood glucose, and complications. Lifestyle, drug intervention, and bariatric surgery schemes are then developed. Diabetes reversal treatment sets goals according to different stages of the disease (see **Table 5**).

Table 5. Staging and reversal targets of diabetes

High-risk stage	Earlier stage	Early stage	Middle stage	Late stage
Carry out interventions during the obesity and insulin resistance stages to restore normal body weight and eliminate insulin resistance.	In IGT and IFG stages, reverse to normal glucose tolerance and normal fasting blood glucose.	Within 3 years of the new onset of diabetes, islet function is better. After reversal, 90% can reach normal blood glucose, and no need for medication.	The course of the disease is more than 3 years, the islet function is good, no obvious complications, the antidiabetic drug cannot well control blood glucose, 50% of patients can stop the drug, and their blood glucose is normal.	The course of the disease is more than 10 years, the islet function is poor, there are obvious complications, a variety of drugs cannot control blood glucose, and can make the blood glucose stable. When reducing drugs, complications are alleviated.

The ideal control targets for blood glucose, blood pressure, and blood lipid should be determined according to different stages. In the middle and late stages of diabetes, blood glucose control is relatively loose (refer to **Tables 6** and **7** for specific control targets).

Table 6. Comprehensive control objectives after reversal

Reversal targets	1	Early stage: HbA1c (%) < 6.5–7.0 Middle and late stage: HbA1c (%) 7.0–7.5
	2	Early stage: fasting blood glucose and postprandial blood glucose are completely normal Middle and late stage: fasting blood glucose (mmol/L): 4.4–7.0, non-fasting: < 10.0
	3	Blood pressure (mmHg): < 140/90 BMI (kg/m^2): < 24 Waist circumference (cm): < 85 (male), < 80 (female)
	4	TG (mmol/L): < 1.7 LDL without coronary heart disease (mmol/L): < 2.6 LDL with coronary heart disease (mmol/L) < 1.8 CH (mmol/L): < 4.5; HDL-C (mmol/L): > 1.0 (male), > 1.3 (female)

Table 7. Blood glucose control targets

Blood glucose control targets	HbA1c level	Description
Strict	< 6.5%	Newly diagnosed, less than 65 years old, no complications and severe concomitant diseases, and no adverse reactions such as hypoglycemia or weight gain in hypoglycemic therapy; Planning pregnancy or combined pregnancy; No need for hypoglycemic drug intervention
Standard	6.5%–7.0%	Under 65 years old, oral hypoglycemic drugs can not meet the standard, combined with insulin therapy or switching to insulin therapy; More than 65 years old, no risk of hypoglycemia, good organ function, expected survival for more than 15 years; Planning pregnancy based on insulin treatment for diabetes
Loose	7.0%–9.0%	Have cardiovascular disease (CVD) or CVD with very high risk; Equal to or more than 65 years old, expected survival for more than 15 years; high-risk groups of hypoglycemia; Patients with difficulties in implementing treatment programs such as mental or intellectual or visual impairment; Too poor medical conditions.

6.2.7. Implementation of intervention measures

When implementing intervention treatment schemes for diabetic patients, individualized choices are made according to different conditions. Drug intervention scheme choices consider improving insulin resistance and protecting β-cell function, prioritizing drugs with comprehensive metabolic benefits. Hypoglycemic drugs with significant weight loss effects are preferred, followed by those with minimal impact on body weight. Drugs that

increase body weight should be used sparingly, with weight loss drugs and surgery considered if necessary.

Several key intervention treatment issues:

(1) Lifestyle intervention: Lifestyle intervention, a pivotal part of the reversal process, includes dietary adjustments, exercise routines, habit corrections, and psychological therapy. Successful intervention requires collaborative efforts from Western medicine practitioners, Chinese medicine practitioners, and healthcare managers. The integration of Internet+ is instrumental in achieving optimal results. The 5+2 reversal treatment model, combining the traditional "five carriages" with co-management and Internet+, proves effective where traditional methods fall short.

(2) Weight management: Effective weight management is crucial for diabetic patients with obesity. Early weight loss goals range from 5% to 10%, with the ultimate target being a BMI < 24 kg/m^2.

(3) Precise nutrition: A scientifically sound diet forms the foundation of diabetes reversal therapies. Patients with T2DM and obesity require precise, personalized, and systematic nutrition therapy. The selection of nutritional interventions should align with metabolic indicators such as obesity degree, blood glucose, blood pressure, blood lipid, and uric acid. Recommended dietary modes include the ketogenic diet, low-carbohydrate diet, Mediterranean diet, and Paleo diet, flexibly adapted to the patient's condition. Diet therapy principles include:

   (a) Determine total calorie intake based on body mass index and weight loss goals;

   (b) Adjust the proportion of carbohydrate intake according to blood glucose control, choose foods with a low glycemic index (GI) and/or low glycemic load (GL) such as coarse grains and vegetables, and avoid the intake of refined rice and flour foods and refined sugars;

   (c) Appropriately adjust the total amount of protein intake and avoid a long-term high-protein diet;

   (d) Avoid the intake of trans-fatty acids, and appropriately intake high-quality fat;

   (e) Increase dietary fiber intake;

   (f) Appropriately select types and quantities of fruits according to the control of blood glucose;

   (g) Ensure the intake of rich vitamins, minerals, and antioxidants;

   (h) Reasonably allocate dieting time to reduce the stimulation of the pancreas;

   (i) Chewing slowly is conducive to digesting food;

   (j) Pay attention to intestinal health and appropriately supplement probiotics and/or prebiotics.

(4) Scientific exercise therapy: Exercise enhances insulin sensitivity, improves skeletal muscle function, and positively impacts metabolic disorders. Principles of exercise therapy for T2DM with obesity include:

   (a) Medical evaluation before exercise therapy and strict control of indications and contraindications;

   (b) Individualized exercise prescriptions according to the patient's course of disease, degree of illness, severity of complications, etc., by considering a variety of factors such as age, family status, exercise habits, and cultural background; the exercise prescription should include five elements: exercise frequency, exercise intensity, exercise duration, exercise type, and amount of exercise;

   (c) Focusing on moderate intensity and aerobic exercises, at least 3 times a week, not less than 20 minutes each time. Aerobic exercise and resistance exercise should be carried out alternately, integrating outdoor and indoor activities. They should exercise at any time and anywhere according to their specific living and working environment. Meanwhile, they should integrate the concept of exercise into life and work, persist in a personalized, continuous, and systematic exercise mode, and walk at least 5,000–10,000 steps every day (depending on the patient's

physical condition);

(d) They should follow the principles of from light to heavy, from less to more, from slow to fast, and from sparse to dense to adjust their own sports scheme;

(e) They should adjust the exercise scheme in time according to blood glucose monitoring and weight loss.

(5) Mental intervention: Obesity and diabetes increase the psychological burden on patients. Strengthening psychological intervention, guided by professional psychologists or diabetes specialists, helps patients adjust their mentality, improve their life attitude, and boost their confidence. Weight loss not only overcomes psychological barriers but also fosters self-confidence, contributing to enhanced life satisfaction.

(6) Developing good living habits: A poor lifestyle is a significant factor leading to diabetes and obesity. A good lifestyle is essential for reversing diabetes complicated with obesity. Doctors play a crucial role in helping patients identify existing problems, providing corrective training, and ensuring patients form and maintain good living habits.

(7) Chinese medicine acupuncture and rehabilitation therapy: Traditional Chinese medicine offers advantages in regulating metabolic disorders caused by diabetes and treating diabetic complications. "Obesity or overweight - spleen-warm syndrome - Xiaoke - Xiaoke complications" is the natural development process of obese diabetes. The effect of the "Kaiyu Qingre method" is significant in the treatment of early and middle diabetes [28]. Compound preparations such as Dahuang Huanglian Xiexin Decoction, Gegen Qinlian Decoction, and Dachaihu Decoction can appropriately reduce blood glucose and reduce risk factors for complications [29]. Therefore, Chinese medicine conditioning, tailored to blood glucose, constitution, and Chinese medicine dialectical methods, significantly improves physical condition, stabilizes blood glucose, and enhances the reversal effect of diabetes.

By stimulating the corresponding acupoints, acupuncture plays a role in dredging the channel, balancing yin and yang, regulating Zang and Fu, and running qi and blood, and ultimately achieves the purpose of weight loss and blood glucose regulation [30]. Acupuncture can also inhibit the occurrence of hunger and reduce food intake by adjusting the activity of neurotransmitters. Meanwhile, it can promote the adrenal medulla to secrete adrenaline, enhance fat mobilization and decomposition, and reduce the content of growth hormone and insulin, thereby reducing weight, lowering blood glucose, and reversing diabetes.

Major acupoints of acupuncture therapy included Yishu, Pishu, and Sanyinjiao. Matching acupoints for patients with damp-heat retention in the spleen may include Quchi and Neiting. Functional acupuncture, moxibustion, and ultrasonic energy meter can dredge the channel, relieve diabetic complications, and activate stem cells to repair islet function [31-33]. Therefore, it has a very important adjuvant therapeutic effect on the reversal of T2DM patients complicated with obesity.

(8) Rational use of drug therapy: In the early stage of diabetes reversal, drugs should be applied rationally based on blood glucose and complications. **Tables 10** to **12** show the characteristics and types of related drugs. However, in the late reversal, medication should be minimized to prevent hypoglycemia.

(9) Surgical treatment: Metabolic surgery can be considered for T2DM patients with obesity/overweight if blood glucose control or weight loss is unsatisfactory after comprehensive reversal therapy. Surgical methods and types are individually selected based on the patient's condition and willingness, following corresponding guidelines.

Table 10. Types of hypoglycemic drugs for weight loss

	Metformin	SGLT-2 inhibitor	GLP-1 receptor agonist
Mechanism of action	Reduce liver glucose output, improve insulin resistance	Inhibit renal glucose reabsorption, increase urinary glucose excretion, negatively balance energy metabolism	Promote insulin secretion, inhibit glucagon secretion, and delay gastric emptying
Representative drugs	Metformin	Dapagliflozin, Ertugliflozin	Exenatide, Liraglutide
Advantages	Reduce HbA1c, low risk of hypoglycemia, mild weight loss, cardiovascular protection.	Reduce HbA1c, lose weight, lower systolic blood pressure, possible cardiovascular and renal benefits	Reduce HbA1c, lose weight, low risk of hypoglycemia, lower blood pressure, decrease fasting and postprandial blood glucose fluctuations

Table 11. Types of hypoglycemic drugs that have little effect on body weight

	DPP-4 inhibitor 1	α-Glycosidase inhibitor
Mechanism of action	Increase glucose-dependent insulin secretion by delaying GLP-1 degradation	Inhibit the absorption of carbohydrates in the upper small intestine
Representative drugs	Sitagliptin, Saxagliptin, Linagliptin, Alogliptin, Vildagliptin	Acarbose, Voglibose
Advantages	Moderate reduction of HbA1c, low risk of hypoglycemia	Moderate reduction of HbA1c, low risk of hypoglycemia, protective effect of cardiovascular on patients with impaired glucose tolerance and diabetes

Table 12. Types of weight loss drugs

	Orlistat	Lorcaserin hydrochloride	Phentermine / Topiramate extended-release agent	Naltrexone extended-release agent / Bupropion extended-release agent
Mechanism of action	Gastrointestinal lipase inhibitor	5-hydroxytryptamine 2c receptor agonist	Promote the release of norepinephrine (Phentermine) and regulation of GAB receptor (Topiramate)	Opioid receptor agonist (Naltrexone); Dopamine and norepinephrine reuptake inhibitors (Bupropion)

(10) Control of multiple risk factors: Assessment of risk factors for cardio-cerebro-renal vascular disease (such as carotid ultrasound, peripheral nerve sensory threshold, fundus, urinary microprotein, liver and kidney function) should be conducted annually. Treatment plans should be adjusted based on examination results.

(11) Monitoring and follow-up:

(a) Monitoring: FPG and PG 2 hours after the meal should be detected at each follow-up, and HbA1C, blood lipids, body weight, and other risk factors of cardiovascular, cerebrovascular, and renal vascular diseases should be monitored regularly. OGTT and islet function tests should be performed at least once a year.

(b) Follow-up: Face-to-face or telephone follow-up should be carried out at least once a week to understand the patient's diet and exercise situation, complications, blood glucose control, symptom improvement, etc. The physical examination should be recorded to conduct a dynamic comparison and formulate a diagnosis and treatment plan.

(c) Efficacy evaluation after reversal: 3–6 months after reversal, the blood glucose stability of patients should be evaluated. All indicators before reversal should be re-examined to compare the differences before and after treatment and evaluate the therapeutic effect. Meanwhile, patient satisfaction, medical expenses, and medical insurance payments should be evaluated.

Disclosure statement

The authors declare no conflict of interest.

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The Role of Endoplasmic Reticulum Stress Sensor Protein CREB3L2 in the Development of Tissues and Tumors

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Abstract: The endoplasmic reticulum plays an extremely important role in the process of cellular protein secretion. The cyclic AMP-responsive element-binding protein 3 (CREB3) transcription factor family is closely associated with the secretion and transport of proteins within the endoplasmic reticulum. As a member of the CREB3 transcription factor family, cyclic AMP-responsive element-binding protein 3-like protein 2 (CREB3L2) stands out as a non-classical sensor within the endoplasmic reticulum. CREB3L2 can detect and regulate endoplasmic reticulum pressure, exert control over the processes of protein transport and secretion, participate in the development of tumor cells, and is also closely linked to the development of certain human tissues and organs. This article aims to review the role of CREB3L2 in tissue development and disease, shedding light on the related mechanisms of CREB3L2 in cancer development. The goal is to provide insights and directions for further analysis of CREB3L2.

Keywords: CREB3L2; Endoplasmic reticulum stress sensor; CREB3

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1. Introduction to endoplasmic reticulum stress sensors

The endoplasmic reticulum (ER) assumes a crucial role in cellular life activities, particularly in the context of protein secretion, which is intricately linked to the ER [1-6]. Most proteins undergo initial entry into the ER, where they undergo storage, folding, and assembly processes. Only correctly assembled proteins proceed from the ER to the cell surface, emphasizing the significance of quality control within the ER. This quality control mechanism ensures that accurately folded proteins are packaged into ER exit vesicles and transported to the cell surface, while misfolded proteins are retained in the ER and subsequently degraded by the cytoplasmic proteasome – an event recognized as ER-associated degradation (ERAD) [7,8].

Throughout these processes, cells dynamically regulate the folding capacity of proteins in the ER as

required. The ER responds to the burden of unfolded proteins in its lumen, known as ER stress, by activating intracellular signal transduction pathways collectively termed the unfolded protein response (UPR). The canonical UPR consists of three branches, with distinct signal transduction mechanisms, that collectively regulate the expression of numerous genes to maintain ER homeostasis. Alternatively, they induce apoptosis in instances where ER stress remains unresolved [9,10]. The UPR signal sensors on these branches include protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6). These three signal transduction families sense protein folding conditions in the ER lumen and transmit this information. This leads to the production of basic leucine zipper transcription factors (bZIP), which enter the nucleus and drive the transcription of UPR target genes. The distinct pathways employ varied signal transduction mechanisms: ATF6 regulates proteolysis, PERK controls the translation process, and IRE1 regulates non-spliced messenger ribonucleic acid (mRNA). Both PERK and IRE1 reduce ER folding load by down-regulating translation and degrading ER-bound mRNAs respectively [11-14].

The cyclic adenosine 3',5'-monophosphaste (cAMP)-responsive element-binding protein 3 (CREB3) transcription factor family comprises ER-localized proteins belonging to the bZIP family. They are transported from the ER to the Golgi apparatus, where they are cleaved by site-1 proteases (S1P) and site-2 proteases (S2P) in intramembrane proteases. This cleavage releases the N-terminal domain, which acts as a transcription factor [15]. Consequently, CREB3 family members regulate the expression of multiple genes and play roles in acute phase response, lipid metabolism, cell development, cell differentiation, and protein secretion. The ER stress response is initiated by CREB3 sensor proteins detecting organelle function deficiencies. These sensors activate one or more transcription factors, inducing the transcription of genes involved in organelle function regulation [16].

2. Functional study of CREB3L2 in sensing and regulating endoplasmic reticulum stress

The cAMP-responsive element-binding protein 3-like protein 2 (*CREB3L2*) gene was initially identified as part of the *FUS/CREB3L2* chimeric gene specific for low-grade fibromyxoid sarcoma (LGFMS). Spanning over 120 kbp, the gene comprises 12 exons and is expressed in most human tissues. As a member of the CREB3 family of transcription factors, the CREB3L2 protein consists of an N-terminal transactivation part, a basic DNA binding domain, a leucine zipper region, a transmembrane hydrophobic region, and a cavity domain [17]. Operating as a transmembrane protein within the ER, the CREB3L2 protein undergoes cleavage on the membrane under ER stress. In the luminal segment, intramembrane hydrolytic protein (RIP) cleaves CREB3L2, and the resulting cleaved fragment of the protein, which contains the N-terminal transactivation domain, basic DNA binding domain, and leucine zipper region, is transported into the nucleus. There, it binds to corresponding sites, activating the transcription of CREB3L2 target genes [18].

Throughout this process, unfolded proteins amass in the ER, prompting the transmission of signals from the ER to the cytoplasm and nucleus by the ER pressure sensors IRE1, PERK, and ATF6. Some scholars have identified astrocyte-specific inducing substance (OASIS) as an ER stress sensor of astrocytes. Interestingly, CREB3L2 exhibits structural homology to OASIS and undergoes cleavage during the ER stress response [19]. The cleaved fragments of CREB3L2 are then transported into the nucleus, binding to the cyclic AMP response element site and activating the transcription of target genes. Moreover, under normal conditions, CREB3L2 protein remains unexpressed; however, it is significantly induced at the translation level during ER stress. Other researchers have observed that in neuroblastoma cell lines, CREB3L2 overexpression inhibits cell death induced by ER stress, while small interfering RNA knockdown of CREB3L2 promotes ER stress-induced cell death. In summary, CREB3L2 emerges as an ER stress sensor, playing a pivotal role in preventing the accumulation of unfolded proteins [20].

3. Functional study of CREB3L2 in controlling protein transport and secretion

As a regulator of cellular secretion capacity, CREB3 members actively participate in ER and Golgi stress responses and contribute to cell differentiation processes. Research has uncovered their crucial role in the differentiation of endometrial stromal cells (EnSCs) into secretory cells during decidualization, a process vital for embryo implantation. Decidualization involves the release of numerous factors, necessitating the remodeling of extensive secretory pathways. Both CREB3L1 and CREB3L2 transcription factors are up-regulated during decidualization. Notably, simultaneous down-regulation of CREB3L1 and CREB3L2 damages the Golgi apparatus, resulting in reduced protein secretion. Thus, both CREB3L1 and CREB3L2 are indispensable for Golgi remodeling and efficient protein secretion [21].

Another study further supports the role of CREB3L2 in controlling protein transport and secretion. Liver fibrosis, stemming from an excessive wound-healing response to chronic injury, progresses to cirrhosis. During fibrosis, inflammatory cytokines induce the differentiation of hepatic stellate cells (HSCs) into myofibroblasts. This process entails an expansion of the ER and Golgi apparatus, indicating heightened protein synthesis and secretion in activated HSCs. The study observes isoform-specific upregulation of the transmembrane bZIP transcription factor CREB3L2, as well as components Sec23a and Sec24d of the endocoat protein complex II (COPII), during HSC activation. Knockout of these components hinders successful HSC activation, emphasizing the necessity of Sec23a/Sec24d-mediated transport from the endoplasmic reticulum to the Golgi apparatus for this process [22].

CREB3L2's role in controlling protein transport and secretion extends to cartilage development. Following cleavage, the N-terminal of CREB3L2 promotes the secretion of extracellular matrix proteins by inducing the expression of Sec23a, functioning as a transcription factor. The C-terminal part of the protein regulates the parathyroid hormone-related protein signaling pathway, promoting chondrocyte proliferation and inhibiting hypertrophic differentiation. CREB3L2 also acts on the transcriptional activation axis during chondrocyte differentiation to accelerate the secretion of cartilage matrix proteins. Additionally, its expression increases during the transformation of human B-cells into antibody-secreting cells, suggesting a crucial role in the secretory pathway during this process [23-25].

4. Research on the function of CREB3L2 in tumor progression

The pivotal role of CREB3L2 in cancer primarily stems from the chromosome-specific translocation t(7;16)(q33;p11), giving rise to the chimeric gene *FUS/CREB3L2*. In instances like LGFMS, a rare, slow-growing cancer typically found in the deep soft tissues of the legs or trunk, this chimeric gene is implicated in the regulation of CD24 expression [26]. Additionally, in malignant glioma, the RAS/MAPK signaling pathway cascade, activated by the FRS2/PAK1 oncogene, induces the upregulation of CREB3L2. CREB3L2 then directly binds to the ATF5 promoter, resulting in ATF5 transcription – a transcription factor pivotal for cell survival. The activation of HSCs in liver cancer is also closely associated with CREB3L2. In essence, CREB3L2 assumes a critical role in tumor development [27-29].

5. Functional studies of CREB3L2 during development

CREB3L2 assumes a crucial role in development, particularly in neural and skeletal development.

Nerve growth factor (NGF) stimulates various cellular physiological processes, such as growth, differentiation, and survival, maintaining the phenotypes of multiple neuron types. The CREB3 transcription factor acts as a signaling hub, regulating numerous genes associated with the secretory pathway and Golgi

homeostasis. It integrates signals from various sources to oversee protein secretion, post-translational modification, and transport. Scholars utilized NGF-induced differentiation of PC12 cells, a commonly used neural cell line, to scrutinize the expression and signaling mechanisms of CREB3 transcription factor family members. The outcomes revealed that NGF treatment induced an enlargement of the Golgi apparatus, coupled with an increase in the expression of proteins and mRNAs essential for membrane transport. In addition, a significant elevation in CREB3L2 protein and mRNA levels was observed in response to NGF. This response necessitated mitogen-activated protein kinase (MAPK) and cAMP signaling pathways, and CREB3L2 overexpression impeded NGF-induced synaptic growth. In summary, this study underscores CREB3L2 as a crucial downstream effector in the NGF activation pathway, promoting neuronal differentiation [30,31].

In the context of cartilage formation, CREB3L2 plays a vital role. Many tissues possess specific signaling systems for ER dysfunction. As an ER-localized basic leucine zipper transcription factor, CREB3L2 activates in response to ER stress and is expressed in cartilage, with high expression in proliferating chondrocytes. These chondrocytes, under ER stress, exhibit abnormal expansion of ER and can secrete aggregated type II collagen (Col2) and cartilage oligomeric matrix protein (COMP). Sec23a, responsible for transporting proteins from the ER to the Golgi apparatus, is a target of CREB3L2. CREB3L2 directly binds to the promoter region of Sec23a, activating its transcription. Introduction of Sec23a into CREB3L2 chondrocytes fully restored damaged cartilage matrix protein transport and secretion. This highlights the pivotal role of the CREB3L2-Sec23a pathway in cartilage development and formation through the activation of protein secretion [32,33].

6. Research on the functions of CREB3L2 in other life processes

Beyond its contribution to nerve and cartilage development, CREB3L2 plays a pivotal role in various organs and life processes.

Liver fibrosis, a common feature in chronic liver diseases leading to cirrhosis and hepatocellular carcinoma (HCC), has been linked to the *microRNA 92b* (*miR-92b*) gene in HCC progression. Research indicated that miR-92b-3p is highly expressed in fibrotic liver tissues, as well as in human hepatic cell line LX-2 under transforming growth factor beta 1 (TGF-β1) stimulation. In addition, researchers also found that miR-92b-3p mimics can promote the activation, proliferation, and migration of LX-2 and HSC-T6 cells. TargetScan database analysis identified CREB3L2 as a potential target of miR-92b-3p, and luciferase assays confirmed that miR-92b-3p inhibits CREB3L2 expression. Mechanistically, miR-92b-3p activates the Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway through CREB3L2, thereby promoting liver fibrosis progression, and providing novel insights into liver fibrosis diagnosis and treatment [34].

During progesterone stimulation, EnSCs undergo decidualization, releasing factors crucial for embryo implantation. This process requires significant remodeling of the secretory pathway, particularly the Golgi complex. Transcriptomic analysis of decidualized EnSCs *in vitro* revealed a set of co-regulated genes related to vesicle trafficking and early secretion, sharing CREB3L1 and CREB3L2 binding elements in their promoter region. Simultaneous down-regulation of CREB3L1 and CREB3L2 during decidualization adversely affects Golgi remodeling, resulting in drastic changes, including Golgi apparatus fragmentation and expanded endothelial cells. This leads to collagen accumulation in reticulum cisterns and an overall reduction in protein secretion. Hence, both CREB3L1 and CREB3L2 are crucial for Golgi remodeling, efficient protein secretion, and successful decidualization [35].

In prostate cancer (PCa), where the androgen receptor (AR) drives progression, CREB3L2 collaborates with AR to mediate transport from the ER to the Golgi apparatus. Single-cell transcriptome analysis reconstructing the transcriptional network of AR in Pca revealed direct regulation of genes in the ER-to-Golgi

protein vesicle-mediated transport pathway by AR. The expression of these genes relies on androgen transport from the ER to the Golgi apparatus, highlighting the key role of CREB3L2 in the cooperation with AR-mediated expression and dysfunction of ER-to-Golgi transport in PCa progression [36].

Lastly, in Alzheimer's disease (AD), β-amyloid acts as a trigger, promoting the formation of pathological CREB3L2-ATF4 transcription factor heterodimers in neurons. Examination of AD datasets and a chemical genetics approach to genomic binding profiles of heterodimeric transcription factors (ChIPmera) revealed that CREB3L2-ATF4 activates a transcriptional pathway interacting with about half of the genes differentially expressed in AD, including subsets associated with beta-amyloid and tau neuropathology. CREB3L2-ATF4 activation drives hyperphosphorylation and secretion of tau protein in neurons and misregulates reverse transcriptase, a complex implicated in AD pathogenesis. This suggests that differential transcription factor CREB3L2-ATF4 dimerization is a crucial mechanism in the development of pathogenic cell states in AD [37].

7. Summary

In previous studies, researchers have obtained a preliminary understanding of the functions and roles of the CREB3 family. As transcription factors located in the ER, they play crucial roles in acute phase response, lipid metabolism, cell development, cell differentiation, organelle autoregulation, and protein secretion. Consequently, they are closely linked to specific human diseases and life processes. As a member of the CREB3 family, CREB3L2 has been unequivocally associated with the onset of liver cirrhosis, nervous system development, and chondrocyte formation. Presently, scholars have delved into *in vitro* and animal model experiments related to CREB3L2, particularly its connection with cancer metastasis, sparking heightened research interest.

While exploring novel functions of CREB3L2 in various contexts is intriguing, a more critical endeavor involves accurately analyzing the underlying mechanisms through which CREB3L2 finely regulates diverse biological events and pathways in distinct cell types. A comprehensive understanding of CREB3L2 and its regulatory modes will contribute to unraveling how the ER stress-sensing mechanism orchestrates multiple cellular components to maintain tissue homeostasis and impact disease progression. This knowledge will further elucidate CREB3L2's role in cancer development, providing novel targets and insights for cancer treatment.

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Disclosure statement

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Laparoscopic Surgery and Modified Xiaoyan Lidan Decoction: An Effective Combination for Treating Cholecystitis with Cholelithiasis

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Abstract: *Objective:* To assess the clinical effects of combining laparoscopic surgery with Modified Xiaoyan Lidan Decoction in patients diagnosed with cholecystitis and cholelithiasis. *Methods:* Following the guidelines of the double-blind method, 86 cases of cholecystitis with cholelithiasis were randomly divided into two groups, each comprising 43 cases. Both groups underwent laparoscopic surgery, with the observation group additionally receiving Modified Xiaoyan Lidan Decoction. A comparative analysis was conducted on clinical treatment effectiveness, general observation indicators, Traditional Chinese Medicine (TCM) syndrome scores, and the occurrence of adverse reactions between the two groups. *Results:* The observation group demonstrated a significantly higher overall clinical treatment effectiveness compared to the control group ($P < 0.05$). The clinical symptom improvement time and hospitalization time were shorter in the observation group, and the pain score and TCM syndrome score after treatment were lower than those in the control group ($P < 0.05$). No statistically significant difference was observed in the total reaction values ($P > 0.05$). *Conclusion:* The combined application of laparoscopic surgery and Modified Xiaoyan Lidan Decoction can enhance clinical treatment efficiency for patients with cholecystitis and cholelithiasis. It facilitates a quicker improvement in clinical symptoms without causing serious adverse reactions, suggesting its potential for widespread adoption.

Keywords: Laparoscopic surgery; Xiaoyan Lidan decoction; Cholecystitis; Cholelithiasis

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1. Introduction

Cholecystitis stands as a highly prevalent digestive system ailment within clinical practice. In recent years, the escalating incidence of this disease can be attributed to shifts in national dietary habits and lifestyles. Compounded by its frequent association with cholelithiasis, patients often endure acute attacks marked by severe upper right abdominal pain, accompanied by symptoms such as nausea, vomiting, fever, and chills. Without timely and effective intervention, the progression of this condition may lead to severe complications such as purulent infection and localized perforation, posing a significant threat to the individual's life safety [1].

Laparoscopic surgery, a minimally invasive procedure widely adopted in recent clinical practice,

has gradually supplanted traditional laparotomy. It effectively facilitates lesion removal without causing substantial physical trauma. However, for patients grappling with cholecystitis and cholelithiasis, even when the implementation of laparoscopic surgery, the removal of the gallbladder and the inevitable varying degrees of damage to the bile duct during the operation can impede postoperative recovery. Consequently, combining pertinent traditional Chinese medicine (TCM) therapies is recommended to enhance the patient's clinical symptoms, expedite recovery, and significantly improve prognostic outcomes [2].

Xiaoyan Lidan Decoction, a renowned prescription in TCM, exhibits notable heat-clearing, detoxifying, soothing, and choleretic effects. When applied in conjunction with laparoscopic surgery, it proves instrumental in attenuating the body's inflammatory response and expediting the amelioration of related diseases [3]. This study focuses on 86 confirmed cases of cholecystitis accompanied by cholelithiasis, examining the actual therapeutic impact following the incorporation of Modified Xiaoyan Lidan Decoction during laparoscopic surgery.

2. Materials and methods

2.1. General information

A total of 86 cases diagnosed with cholecystitis and cholelithiasis were enrolled in the study, all of whom underwent treatment within the specific timeframe set by the institute (commencing in September 2021 and concluding in September 2023). The treatment procedures adhered to the relevant standards of the double-blind method. Following group allocation, the control group comprised 43 cases, with 18 males and 25 females. The age range spanned from 34 to 69 years, with an average age of 51.58 ± 6.59 years. The observation group also included 43 cases, with 20 males and 23 females. The age range spanned from 33 to 70 years, with an average age of 51.49 ± 6.51 years. Upon comparing inter-group data, no significant differences were observed ($P > 0.05$).

Inclusion criteria encompassed patients meeting the diagnostic standards outlined in the "China Consensus Opinions on the Medical Diagnosis and Treatment of Chronic Cholecystitis and Cholecystolithiasis (2018)" [4]. Diagnosis was based on clinical symptoms, imaging, laboratory, and other examinations. Patients eligible for inclusion had surgical indications in line with laparoscopic surgery requirements, maintained complete medical records, and provided informed consent.

Exclusion criteria comprised patients with concomitant functional failure of vital organs, coagulation disorders, immune system diseases, malignant tumors, or a history of mental, cognitive, or psychological disorders. Additionally, individuals with contraindications related to laparoscopic surgery, intolerance to the study medication, allergic reaction, or those departing from the study midway were excluded.

2.2. Methods

Both groups of patients underwent laparoscopic surgery, wherein they assumed a supine position and received general anesthesia with tracheal intubation. Once the anesthesia took effect, artificial pneumoperitoneum was established, maintaining pressure between 12–14 mmHg, followed by the application of the four-hole method. During laparoscopic surgery, if the gallbladder body exhibited enlargement accompanied by edema symptoms, initial puncture and subsequent removal were performed. In cases of adhesions in the gallbladder neck, effective separation was executed before addressing the cystic artery and cystic duct. When stones were present in the cystic duct, stone removal took precedence, followed by cholecystectomy. After confirming the complete removal of all stones, the abdominal cavity was flushed, a drainage tube was inserted, and the incision was sutured. Relevant antibiotics were administered postoperatively, with extubation typically occurring around 24–28 hours after the procedure.

For the observation group, in addition to the aforementioned treatment, the Modified Xiaoyan Lidan Decoction was introduced. The basic prescription included 30 g of desmodium, 15 g of chicken gizzards membranes, 15 g of *Polygonum cuspidatum*, 12 g of bupleurum, 12 g of white peony, 9 g of turmeric, 9 g of corydalis, 9 g of *Melia azadirachta*, 9 g of *Lygodium japonicum*, 6 g of costus, and 5 g of licorice, with adjustments based on the syndrome. Additional ingredients were incorporated based on specific symptoms: for severe abdominal pain, 9 g of turmeric was added; for dry mouth and thirst, 15 g of *Ophiopogon japonicus*, 15 g of *Adenophora japonicus*, and 15 g of dendrobium were added; for those with a thick and greasy tongue coating, 9 g of *Magnolia officinalis*, 9 g of atractylodes, and 9 g of *Rhizoma atractylodis* were added; and for individuals with severe dampness and heat, 18 g of *Artemisia chinensis*, 15 g of gypsum, 9 g of anemarrhena, and 9 g of gardenia were added. The prescribed dosage involved boiling the mixture with 800 mL of water until approximately 400 mL of mixture remained, to be taken warm twice daily in the morning and evening for a duration of 2 weeks.

2.3. Observation indicators

(1) Effective clinical treatment:
   (a) Markedly effective: Abdominal pain, nausea, vomiting, and other symptoms have been observed and have essentially disappeared. B-ultrasound results indicate that at least two indicators of gallbladder or cystic duct wall thickness, roughness, and sound transmission have returned to normal.
   (b) Effective: Relevant clinical symptoms have significantly improved, and B-ultrasound indicates substantial improvement, with at least one of the aforementioned three indicators returning to normal.
   (c) Ineffective: The relevant content does not meet the above standards.

(2) General observation indicators: The improvement time of clinical symptoms and hospitalization time for both groups were effectively observed. Simultaneously, the Visual Analog Scale (VAS) was employed before and after treatment. Zero points were assigned for no pain, while severe pain was scored as ten points. Scores were calculated based on the degree of pain, showing a positive correlation between the score and the degree of pain.

(3) TCM syndrome scores: In accordance with the "Guideline Principles for Clinical Research of New Traditional Chinese Medicines" [5], TCM syndrome scores for both groups were employed before and after treatment. This scoring primarily focused on right upper quadrant pain, nausea and belching, fever, chills, and other symptoms. Each item could be scored from 0 to 3 points, with scores reflecting the severity of symptoms.

(4) Occurrence of adverse reactions: Adverse reactions that emerged during the treatment of both groups were meticulously documented, encompassing infections, gastrointestinal reactions, rashes, etc. Total values were compared to assess the overall occurrence of adverse reactions.

2.4. Statistical analysis

The statistical analysis employed SPSS 25.0 for Windows software as the foundation. All acquired data were categorized by nature. If the data fell under the measurement category, it was presented as mean ± standard deviation (SD), and a parallel *t*-test was conducted. For count data, it was represented as percentage (%), and simultaneously, the chi-squared test was applied. A final *P* value less than 0.05 signified a significant difference, establishing statistical significance.

3. Results

3.1. Comparison of clinical treatment effectiveness between the two groups

Table 1 illustrates that the total clinical treatment effective rates were 69.77% and 93.02% for the control and observation groups, respectively. The observation group demonstrated a significantly higher rate ($P < 0.05$).

Table 1. Comparison of clinical treatment effectiveness observations [n (%)]

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control group ($n = 43$)	12 (27.91)	18 (41.86)	13 (30.23)	30 (69.77)
Observation group ($n = 43$)	15 (34.88)	25 (58.14)	3 (6.98)	40 (93.02)
χ^2	-	-	-	7.679
P	-	-	-	0.006

3.2. Comparison of general observation indicators between the two groups

Table 2 reveals that, upon comparing clinical symptom improvement time and hospitalization time between the two groups, the observation group exhibited significantly lower values ($P < 0.05$). No statistically significant difference was found in the pain scores between the two groups before treatment ($P > 0.05$). However, the pain score of the observation group after treatment was markedly lower than that of the control group ($P < 0.05$).

Table 2. Comparison of general indicator observation results (mean ± SD)

Group	Time to improve clinical symptoms (d)	Length of stay (d)	Pain score (points)	
			Before treatment	After treatment
Control group ($n = 43$)	7.31 ± 2.68	12.87 ± 5.58	6.21 ± 2.14	3.56 ± 1.24
Observation group ($n = 43$)	5.02 ± 1.54	8.45 ± 3.19	6.18 ± 2.11	2.25 ± 0.89
t	4.858	4.509	0.065	5.628
P	0.001	0.001	0.948	0.001

3.3. Comparison of TCM syndrome scores between the two groups

Table 3 demonstrates that, prior to treatment, there was no statistically significant difference in the integrated TCM syndromes between the two groups ($P > 0.05$). Following treatment, the total TCM syndrome score of the observation group was significantly lower than that of the control group ($P < 0.05$).

Table 3. Comparison of TCM syndrome scores before and after treatment (mean ± SD, points)

Group	Time	Right upper quadrant pain	Nausea and belching	Fever	Chills	Total score
Control group ($n = 43$)	Before	2.61 ± 1.12	2.01 ± 0.82	1.78 ± 0.77	1.65 ± 0.65	7.86 ± 3.25
	After	1.24 ± 0.42	0.78 ± 0.34	0.62 ± 0.25	0.54 ± 0.21	3.89 ± 1.24
Observation group ($n = 43$)	Before	2.59 ± 1.09	2.03 ± 0.84	1.75 ± 0.74	1.62 ± 0.63	7.81 ± 3.22
	After	0.34 ± 0.12	0.28 ± 0.09	0.15 ± 0.05	0.08 ± 0.02	1.78 ± 0.42
t	Before	0.084	0.112	0.184	0.217	0.072
	After	13.511	9.322	12.089	14.299	10.568
P	Before	0.933	0.911	0.854	0.828	0.943
	After	0.001	0.001	0.001	0.001	0.001

3.4. Comparison of adverse reactions between the two groups

Table 4 shows that there is no statistically significant difference in the total values of adverse reactions between the two groups ($P > 0.05$).

Table 4. Comparison of incidence rates of adverse reactions [n (%)]

Group	Infection	Gastrointestinal reactions	Rash	Total incidence rate
Control group ($n = 43$)	1 (2.33)	2 (4.65)	1 (2.33)	4 (9.30)
Observation group ($n = 43$)	0 (0.00)	1 (2.33)	0 (0.00)	1(2.23)
χ^2	-	-	-	1.911
P	-	-	-	0.167

4. Discussion

Cholecystitis with cholelithiasis is a prevalent condition in clinical practice, and surgery remains the most direct and efficient treatment method. Laparoscopic surgery, in particular, offers advantages such as minimal invasiveness and safety, surpassing traditional laparotomy. It proves effective in lesion removal, substantially reducing patient pain during treatment. Despite the efficacy of surgery, its inherently invasive nature necessitates integration with high-quality treatment options to enhance patient prognosis [6].

In recent years, the integration of traditional Chinese and Western medicine has emerged as a mainstream trend. From a Western medicine perspective, laparoscopic surgery effectively eliminates known lesions, and when combined with TCM, it further controls the body's inflammatory response [7]. TCM views cholecystitis and cholelithiasis through categories such as "gallbladder bloating" and "costal pain." Their occurrence is closely linked to factors such as improper diet, poor mood, and exogenous dampness. Hindered excretion and drainage of gallbladder organs lead to bile stagnation, blockage, and over time, the formation of gallbladder stones. Treatment strategies focus on soothing the liver, promoting gallbladder function, anti-inflammation, analgesia, and softening and clearing stones. The Modified Xiaoyan Lidan Decoction plays a pivotal role in this treatment [8]. Components such as *Desmodium japonica* and *Polygonum cuspidatum* reduce jaundice and swelling, induce diuresis, and detoxify; Chicken gizzard membranes and acosta strengthen the spleen, eliminate food, and relieve stranguria; Bupleurum addresses external and internal issues, soothes the liver, and alleviates stagnation; White peony root softens the liver and relieves pain. Turmeric dissipates blood stasis and replenishes qi; *Melanium japonica* and corydalis promote qi and blood circulation, relieve heat, and ease pain; *Lygodium japonicum* relieves dampness, heat, stranguria, and pain; Licorice harmonizes various medicines. The combined use of these ingredients functions to break qi, eliminate accumulation, disperse pimples, soften hardness, soothe the liver, promote gallbladder function, clear away heat, and detoxify [9-11]. As evidenced by the results in the tables in this article, the observation group achieved a high total clinical treatment effectiveness of 93.02%, with only 2.23% experiencing adverse reactions. Moreover, the clinical symptom improvement time and hospitalization time were shorter, and both pain and TCM syndrome scores were lower. These findings suggest that combining laparoscopic surgery with the Modified Xiaoyan Lidan Decoction can yield satisfactory treatment outcomes for patients.

In summary, the application of Modified Xiaoyan Lidan Decoction during laparoscopic surgery for patients with cholecystitis and cholelithiasis can significantly reduce the improvement time of related symptoms, enhance the clinical treatment's effectiveness, and improve overall treatment safety. This approach holds considerable promise for wider application and promotion.

Disclosure statement

The author declares no conflict of interest.

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The Role and Mechanism of Unfolded Protein Response Pathway in Tumor Drug Resistance

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Abstract: In the process of tumor proliferation and metastasis, tumor cells encounter hypoxia, low glucose, acidosis, and other stressful environments. These conditions prompt tumor cells to generate endoplasmic reticulum stress (ERS). As a signal mechanism that mitigates ERS in eukaryotic cells, the unfolded protein response (UPR) pathway can activate cells and tissues, regulating pathological activities in various cells, and maintaining ER homeostasis. It forms the most crucial adaptive and defensive mechanism for cells. However, under the continuous influence of chemotherapy drugs, the quantity of unfolded proteins and erroneous proteins produced by tumor cells significantly increases, surpassing the normal regulatory range of UPR. Consequently, ERS fails to function properly, fostering tumor cell proliferation and the development of drug resistance. This review delves into the study of three UPR pathways (PERK, IRE1, and ATF6), elucidating the mechanisms of drug resistance and research progress in the signal transduction pathway of UPR related to cancers. It provides a profound understanding of the role and relationship between UPR and anti-tumor drugs, offering a new direction for effective clinical treatment.

Keywords: Unfolder protein response (UPR); Tumor resistance; Activating transcription factor 6 (ATF6); Protein kinase RNA-like endoplasmic reticulum kinase (PERK); Inositol requiring enzyme 1 (IRE1)

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1. Introduction

In eukaryotic cells, the endoplasmic reticulum (ER) is a membranous organelle intricately woven throughout the cell, primarily responsible for the composition, folding, modification, and secretion of proteins. The ER, resembling a microcosm of the entire cell, operates as a dynamic system meticulously controlling the processes of protein synthesis and folding. Its homeostasis is finely tuned but susceptible to disruption. Various stimuli such as hypoxia, nutrient deficiency, high cell proliferation rates, abnormal redox homeostasis, or exposure to chemical drugs can prompt protein misfolding in the ER and the accumulation of unfolded proteins. An imbalance in ER homeostasis leads to a form of cellular disease. A protective stress response, preventing the

aggregation of unfolded proteins, is termed endoplasmic reticulum stress (ERS) [1].

The unfolded protein response (UPR), functioning as a signaling mechanism to alleviate ERS in eukaryotic cells, is the primary reaction in numerous cascade pathways activated by ERS, extensively researched. The UPR pathway mobilizes cells and tissues to regulate the pathological activities of various cells, playing a pivotal role in safeguarding and restoring ER homeostasis. It forms the most crucial adaptability and defense mechanism for cells. When the ER's protein folding capacity is disrupted or cellular demands are excessive, misfolded proteins accumulate in the ER. At this juncture, the UPR transmits signals about the ER's health to the nucleus by upregulating the activity of several transcription factors. Post-UPR activation, these transcription factors elevate the expression of related genes, reestablishing protein homeostasis and restoring ER through multiple mechanisms: (1) transient attenuation of protein translation, (2) augmentation of protein folding capacity, and (3) clearance of unfolded/misfolded proteins through protein quality control systems [2].

Overcoming ERS primarily depends on stress sensors that detect ERS: protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme 1 (IRE1), and activating transcription factor 6 (ATF6) [3-6]. These three effector proteins can each activate their signaling cascades to induce UPR. In periods of low ERS, UPR activation correctly expresses folded proteins, alleviating the burden of ERS, safeguarding cells, promoting tumor cell survival, and preventing tumors from progressing adversely. Conversely, active tumor cells increase the demand for translation, modification, folding, and secretion of proteins in the ER, resulting in elevated ERS levels. Limited blood vessel supply cannot match the rapid tumor proliferation, restricting tumor growth. Uncontrolled tumor cell proliferation and metabolism compromise ER integrity, causing misfolded proteins and improper reflections in the membrane cavity. This, combined with imbalanced Ca^{2+} distribution, triggers a novel endogenous apoptosis pathway, known as the ERS apoptosis pathway, inducing cell death [7-10].

As research on UPR has deepened in recent years, elucidating the signal transduction pathways in UPR offers a new direction for understanding tumor drug resistance mechanisms and effective treatments [11].

2. General mechanisms of tumor drug resistance

The mechanisms underlying tumor drug resistance are intricate and varied. Recent studies have underscored the significance of ERS as a potential influential factor in the drug resistance of tumor cells [9,10]. Moreover, the UPR plays a pivotal role in tumor progression and resistance to treatment [1,5,12-18], involving processes such as DNA damage repair, apoptosis inhibition, autophagy, and more [18].

In instances of DNA damage within tumors, UPR-regulated cells induced by ERS activate related recovery mechanisms to facilitate DNA repair. This ensures that the tumor microenvironment reaches a "steady state" during this period. Most anti-tumor drugs inflict damage on cellular DNA, leading to a reduction in the proportion of unfolded and misfolded proteins produced through cellular transcription and translation. This disruption affects the intracellular protein balance and compromises the adaptation of ERS. The UPR, however, can override the original adaptive environment, reasserting its role. Consequently, it maintains cellular protein balance and accelerates the induction of cell apoptosis.

Nevertheless, with the sustained use of chemotherapeutic drugs, the increase in DNA damage corresponds to an escalation in DNA repair function. The unfolded and misfolded proteins produced during post-transcriptional translation undergo a significant surge, surpassing the normal regulatory range of UPR. The adaptability of ERS is severely impaired once again, rendering it incapable of functioning normally. This ultimately promotes tumor cell proliferation and the development of drug resistance.

In summary, ERS exhibits a dual role: it can activate early cancer cells while also contributing to the

transformation of late-stage cancer cells into drug-resistant entities [19].

2.1. The role of the PERK-ATF4 pathway in tumor drug resistance

PERK functions as a eukaryotic translation initiation factor 2 (eIF2α) and belongs to the upstream kinase family. It is a type I transmembrane protein housing a serine/threonine kinase domain, constituting the most crucial pathway in the UPR against ERS [20,21]. ATF4, a stress-induced transcription factor, also known as cyclic AMP (cAMP)-linked response element 2 (CREB2), holds a pivotal role in the integrated stress response pathway [21]. Controlling a wide array of adaptive genes, ATF4 equips cells to withstand stress.

Upon ERS in eukaryotic cells, numerous unfolded or misfolded proteins set off a series of reactions. This prompts PERK to oligomerize and activate in the ER membrane, inducing cell phosphorylation and activating the kinase domain. This, in turn, promotes the upregulation of ATF4 expression, aiding tumor cells in recognizing and processing external stimuli. It enhances their adaptability to adverse factors in the surroundings, effectively resisting external damage, and consequently, fostering the survival and spread of tumors [22,23]. However, under prolonged stress conditions, ATF4 promotes the induction of apoptosis [24].

Compared to normal tissues, ATF4 is up-regulated in tumor cells. As a vital member of the transcription factor family, its primary function is to activate the transcription of genes related to oxidative stress response, amino acid synthesis, cell differentiation, angiogenesis, and other processes regulating tumor progression. This suggests that ATF4 may present a novel opportunity for tumor treatment [22,25,26].

UPR activates the PERK-eIF2α-ATF4 pathway, resulting in the constitutive activation of PERK signaling at the epithelial-mesenchymal transition (EMT), inducing malignant tumors [27]. Although PERK inhibition does not affect EMT cell survival or growth, research indicates that inhibiting PERK activity heightens EMT cell sensitivity to ERS. EMT cells rely on PERK signaling to form tumors and migrate. Additionally, both dedifferentiated cancer cells and cancer stem-like cells generated by EMT exhibit resistance to various chemotherapy treatments [28]. Extensive experimental data indicates a robust positive correlation between the expression of EMT genes and PERK pathway genes.

The PERK-eIF2α-ATF4 pathway has been suggested to play a crucial role in promoting tumor cell apoptosis and resistance to chemotherapeutic drugs. This has been explored in various diseases, including ovarian cancer, colorectal cancer, pancreatic cancer, breast cancer, and cervical cancer, among others [29-33]. Notably, Shi *et al*. discovered an upregulation of PERK-eIF2α-ATF4 pathway activity in colon cancer cells, leading to increased resistance to 5-fluorouracil (5-FU). Genetic intervention or pharmacological inhibition of this pathway effectively heightened the sensitivity of colorectal cancer cells to 5-FU in mouse experiments, offering promise in overcoming chemotherapy drug resistance in colorectal cancer [29]. Subsequent studies revealed that inhibiting PERK accelerated the apoptosis of colon cancer cells, reducing the expression of eIF2α and ATF4, thereby increasing cancer cell sensitivity to 5-FU [32].

Acriflavine was found to inhibit the PERK-eIF2α-ATF4 pathway by blocking eIF2α phosphorylation and reducing ATF4 translation. This restoration effectively revived drug sensitivity in acquired drug-resistant pancreatic cancer cell lines [34,35]. Consequently, targeting the PERK-eIF2α-ATF4 pathway holds promise in diminishing or inhibiting tumor cell drug resistance, improving the efficacy of drug chemotherapy, and enhancing patient prognosis.

2.2. The role of the IRE1α-XBP1 pathway in tumor drug resistance

Similar to PERK, IRE1 is a type I transmembrane protein featuring a serine/threonine kinase domain and an endoribonuclease domain situated on the cytoplasmic side of the protein. As a primary pathway in the

UPR, the IRE1α-XBP1 pathway has received extensive study. Following UPR activation by ERS, IRE1α is activated, inducing the cleavage of the transcription factor splicing X-box binding protein 1 (XBP1) mRNA. This process generates the XBP1 variant (XBP1s), initiating a series of gene transcription events. These genes primarily contribute to protein refolding or promote the degradation of unfolded proteins, positively regulating ER chaperones, genes encoding endoplasmic reticulum-associated protein degradation (ERAD), and liposome metabolism. Consequently, this eases the pressure on the ER [20].

Continual stimulation of IRE1α-XBP1 signaling can trigger tumor cell proliferation, metastasis, and chemoresistance. However, existing pharmacological technologies face limitations in producing effective XBP1 inhibitors. Consequently, targeting its upstream regulator, IRE1α, presents a potential new avenue for tumor treatment [36]. IRE1α inhibitor was discovered to significantly inhibit the proliferation of breast tumor cells. Furthermore, the combination of the IRE1α inhibitor MKC 8866 and paclitaxel effectively enhanced its efficacy in triple-negative breast cancer, leading to improved therapeutic effects. This underscores that the expression of XBP1 impacts the treatment resistance of tumors, offering breakthroughs in cancer drug resistance research [37-39].

Endocrine therapy often leads to drug resistance in breast cancer patients, resulting in disease progression and mortality. Targeting XBP1 is considered a promising approach to overcoming endocrine drug resistance in breast cancer. Ming *et al*. observed up-regulation of XBP1 at the mRNA and protein levels in breast cancer cells. The IRE1α inhibitor, STF-083010, in combination with tamoxifen, significantly reversed endocrine resistance in breast cancer. This improved the response of tumor cells to chemotherapy drugs, enhancing the therapeutic effect [40].

In summary, treatment resistance frequently allows cancer cells to evade the effects of monotherapy. The IRE1α-XBP1 pathway may play a role in tumor cell resistance. The combined use of IRE1α inhibitors and chemotherapy drugs can effectively enhance the efficacy of chemotherapy drugs and alter the drug resistance of tumor cells [20].

2.3. The role of ATF6 in tumor drug resistance

ATF6, a type II transmembrane glycoprotein and transcriptional activator, plays a pivotal role in initiating UPR signaling during ERS. When unfolded proteins are detected, full-length ATF6 (p90) undergoes transportation to the Golgi apparatus for processing and cleavage. The cleaved p90 releases the N-terminal cAMP-dependent ATF6 alpha form (p50) into the cytoplasm, translocates to the nucleus, binds to DNA on the endoplasmic reticulum stress response element (ERSE), and regulates ERAD and UPR genes.

Recent studies have identified ATF6 as playing a crucial role in tumor drug resistance, making it a potential new target. High-grade serous ovarian cancer (HGSOC), the most lethal ovarian cancer histotype, faces limited treatment options for chemotherapy-resistant disease. Elevated ATF6 expression in HGSOC has been linked to poor survival rates, particularly in the context of resistance to poly-ADP ribose polymerase (PARP) inhibitors. Targeted treatment of PARP inhibitors, along with RNA sequencing and short hairpin RNA (shRNA) screening, has established ATF6 as a mediator of DNA damage response and PARP inhibitor resistance [41].

In the case of gastric cancer drug resistance, ER and autophagy are recognized mechanisms. Research on the JAK2/STAT3 pathway in 5-FU-resistant AGS cells revealed that agents inhibiting JAK2 or STAT3 significantly altered protein expression and suppressed ATF6 promoter activity. Targeting the JAK2/STAT3 pathway emerges as a potential strategy to diminish cancer resistance to 5-FU, offering new insights into the molecular mechanisms of gastric cancer resistance to this drug [36].

Benedetti's team recently uncovered that inhibiting ATF6 enhances the anticancer effect of DNA-damaging agents. Doxorubicin, a widely used DNA-damaging drug for colon cancer treatment, exhibited increased

cytotoxicity in ERS cancer cells when ATF6 is inhibited. This suggests a potential strategy to sensitize colon cancer cells to the cytotoxic effects of doxorubicin, promoting cell death [42].

3. Summary

Tumors adeptly regulate their protein folding capabilities through the ERS response pathway, flourishing even in adverse conditions such as hypoxia, nutrient deprivation, and oxidative stress. Activation of multiple ERS sensors has been identified as a driver for the proliferation, metastasis, and drug resistance of malignant tumors. Notably, tumor drug resistance poses a significant challenge, limiting the efficacy of chemotherapy drugs in tumor treatment. Integrating anti-tumor drugs with regulatory factors and effectors targeting ERS can significantly enhance the sensitivity of tumor cells to drugs, leading to more effective treatment outcomes.

Current research underscores the distinct biological functions of the three UPR pathways – PERK, IRE1, and AT6 – in regulating cell survival or apoptosis. These pathways, in turn, exert downstream effects on abnormal DNA repair, apoptosis control, and autophagy, each playing a unique role in influencing biological functions [25]. Despite the incomplete understanding of ERS and its related anti-cancer mechanisms, delving into the anti-cancer activity triggered by UPR and the intricate interactions between them is essential. This in-depth exploration is crucial for identifying more effective anti-cancer solutions and developing novel drugs, fostering the advancement of translational medicine.

In conclusion, a heightened comprehension of drug resistance mechanisms holds the key to reversing drug resistance in solid tumor cells, paving the way for innovative clinical drug treatments for solid tumors.

Disclosure statement

The authors declare no conflict of interest.

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Assessing the Clinical Efficacy and Effectiveness of Sentinel Lymph Node Biopsy Combined with Breast-Conserving Surgery for Early-Stage Breast Cancer

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Abstract: *Objective:* To analyze the impact of sentinel lymph node biopsy (SLNB) combined with breast-conserving surgery in the clinical treatment of early-stage breast cancer. *Methods:* 80 patients with early-stage breast cancer admitted to the Second Department of Breast Surgery at Dezhou Second People's Hospital from September 2020 to September 2022 were selected and randomly divided into a control group and an observation group using the random number table method, with 40 cases in each group. The control group underwent a modified radical mastectomy, while the observation group underwent SLNB combined with breast-conserving surgery. The surgical efficacy and prognosis between the two groups were compared. *Results:* The observation group exhibited shorter operation, hospitalization, and extubation times, as well as less intraoperative blood loss and drainage volume, all of which were significantly better than those in the control group ($P < 0.05$). Additionally, the observation group demonstrated a higher rate of excellent breast cosmetology and quality of life, with lower complication incidence, significantly outperforming the control group ($P < 0.05$). There was no statistical difference in the metastasis rate and recurrence rate between the two groups ($P > 0.05$). *Conclusion:* The combination of SLNB and breast-conserving surgery proves highly effective for patients with early-stage breast cancer, presenting fewer complications and enhancing both breast cosmetic outcomes and quality of life.

Keywords: Early breast cancer; Sentinel lymph node biopsy; Breast-conserving surgery; Clinical efficacy

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1. Introduction

Breast cancer stands as the predominant malignancy affecting women, causing considerable detriment to both their physical health and life safety. The condition of axillary lymph nodes holds paramount importance in the staging of breast cancer. Therefore, assessing axillary lymph node metastasis is crucial to delineate the necessity of axillary lymph node dissection (ALND) [1]. Sentinel lymph node biopsy (SLNB) serves as a valuable tool in determining metastasis in axillary lymph nodes associated with the primary tumor. It plays a supportive role in

both disease treatment and prognosis assessment, acting as a deterrent against the spread of tumor cells through lymphatic channels. The significance of SLNB in diagnosing and treating malignant tumors is substantial.

Breast-conserving surgery boasts advantages such as minimal surgical trauma, favorable breast cosmetic outcomes, and heightened postoperative patient satisfaction [2]. The combination of SLNB and breast-conserving surgery has demonstrated its ability to enhance the prognosis and quality of life for patients grappling with early-stage breast cancer. Consequently, this approach has found widespread application in clinical settings [3].

This study specifically focused on 80 patients diagnosed with early-stage breast cancer, all of whom underwent treatment at Dezhou Second People's Hospital between September 2020 and September 2022. The primary objective was to observe and analyze the effects of SLNB combined with breast-conserving surgery on these patients.

2. Materials and methods

2.1. General information

Eighty patients with early-stage breast cancer were carefully selected from admissions to the Second Department of Breast Department of Dezhou Second People's Hospital between September 2020 to September 2022. The patients were meticulously grouped using the random number table method, with 40 cases allocated to each group.

For the observation group, the age range of patients was 28 to 70 years, with an average of 47.12 ± 12.18 years. Tumor locations included 23 cases in the left breast and 17 cases in the right breast. Tumor diameter distribution was as follows: ≤ 2 cm in 29 cases and 2–3 cm in 11 cases. American Joint Committee on Cancer (AJCC) staging comprised 27 cases in Stage I and 13 cases in Stage II. Pathological types encompassed 37 cases of invasive ductal carcinoma and 3 cases of lobular carcinoma.

For the control group, the age range of patients was 30 to 72 years, with an average of 47.25 ± 12.21 years. Tumor locations included 25 cases in the left breast and 15 cases in the right breast. Tumor diameter distribution was as follows: ≤ 2 cm in 28 cases and 2–3 cm in 12 cases. AJCC staging comprised 26 cases in Stage I and 14 cases in Stage II. Pathological types encompassed 36 cases of invasive ductal carcinoma and 4 cases of lobular carcinoma. There was no statistical difference between the data of the two groups ($P > 0.05$).

Inclusion criteria included patients diagnosed with early-stage breast cancer confirmed through imaging and needle biopsy, expressing a clear desire to breastfeed, classified as AJCC Stages I~II, with a single tumor and a diameter ≤ 3.0 cm, meeting relevant surgery indications, and providing consent for participation in the study.

Exclusion criteria included patients with axillary lymph node enlargement or multicenter lesions, those who have undergone preoperative chemoradiotherapy or have a history of axillary surgery, those diagnosed with secondary breast cancer, and those with concomitant other malignant tumors or significant organ lesions.

2.2. Methods

The control group underwent modified radical resection with general anesthesia in a supine position. The incision size was meticulously determined based on the patient's breast shape, size, and lesion location. An incision, positioned 3 cm away from the tumor's edge, took a horizontal or vertical fusiform shape. The surgical approach involved undermining while preserving both the pectoralis major and minor muscles. Lymph nodes situated between the pectoralis major muscles and the axilla were dissected, followed by postoperative chest bandaging and the placement of a drainage tube under the armpit.

The observation group underwent SLNB combined with breast-conserving surgery.

(1) SLNB surgery: After ensuring successful anesthesia, 2–4 mL of a 1% methylene blue solution was injected into the parenchyma surrounding the tumor. A 5 cm incision was made at the lower edge of the axillary hair area, and the skin flap was freed toward the axilla. Lymph nodes in the axilla were systematically searched from top to bottom and from inside to outside. The presence of stained lymphatic vessels outside the pectoralis major muscle was detected, and sentinel lymph nodes were identified, promptly removed, and sent for pathological examination. Positive results prompted ALND, while negative results led to standard surgical incision closure.

(2) Breast-conserving surgery: After successful general anesthesia, the surgical range was precisely marked, and an arc-shaped incision was made. Tumor tissue was removed 2 cm from the outer edge, ensuring complete excision. Resection specimens were promptly sent for pathological examination. Positive results prompted an expanded resection scope, with specimens submitted for examination again. Patients with positive results underwent a total mastectomy, while those with negative results had their incisions closed using cosmetic sutures.

2.3. Observation indicators

(1) Perioperative indicators: Perioperative data, including operation time, hospitalization duration, and extubation time, were meticulously recorded for both groups. Additionally, measurements were taken for intraoperative blood loss and postoperative drainage volume.

(2) Breast cosmetic effect: The evaluation of breast cosmetic outcomes took place six months post-surgery. The criteria were as follows: Symmetrical breasts with a normal appearance and skin color, and a nipple gap < 2cm were denoted as “excellent”; Symmetrical breasts with a generally normal appearance, light and bright skin, and a nipple gap between 2–3 cm were denoted as “good”; Not meeting the above criteria were denoted as “poor” [4]. The excellent rate was calculated as (number of “excellent” + “good” cases) / total number of cases × 100%.

(3) Quality of life: The quality of life for breast cancer patients was assessed using the FACT-B scale during a 6-month follow-up period after surgery [5]. Evaluation encompassed social, emotional, physiological, functional, and additional dimensions. Corresponding scores were assigned as 28 points, 24 points, 28 points, 28 points, and 36 points, respectively. These scores demonstrated a positive correlation with the quality of life.

(4) Prognostic indicators: postoperative complications, including hypoaesthesia, subcutaneous effusion, skin flap necrosis, swelling, and numbness were statistically documented for both groups. Additionally, the metastasis rate and recurrence rate six months post-surgery were recorded to assess prognostic outcomes.

2.4. Statistical analysis

Data analysis was conducted using SPSS 27.0 software. Measurement data were presented as mean ± standard deviation (SD), and a *t*-test was employed for comparison. Count data were expressed as *n* (%), and the χ^2 test was applied. Significance was set at $P < 0.05$ to indicate statistical significance.

3. Results

3.1. Comparison of perioperative indicators between the two groups

Table 1 shows that the observation group exhibited significantly shorter operation, hospitalization, and extubation times, accompanied by reduced intraoperative blood loss and drainage volume, all of which were

notably superior to those in the control group ($P < 0.05$).

Table 1. Comparison of perioperative indicators between the two groups (mean ± SD)

Group	Operation time (min)	Intraoperative blood loss (mL)	Length of stay (d)	Extubation time (d)	Postoperative drainage volume (mL)
Observation group ($n = 40$)	74.21 ± 9.48	32.42 ± 7.19	9.98 ± 1.22	7.52 ± 2.21	42.86 ± 6.74
Control group ($n = 40$)	80.72 ± 9.25	70.81 ± 8.45	11.05 ± 1.72	9.08 ± 2.75	112.63 ± 24.85
t	3.109	3.094	3.209	2.797	17.138
P	0.003	0.003	0.002	0.007	0.000

3.2. Comparison of breast cosmetic effects between the two groups

The observation group demonstrated a higher rate of "excellent" and "good" in breast aesthetics compared to the control group ($P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of breast cosmetic effects between two groups [n (%)]

Group	Excellent	Good	Poor	Excellent rate
Observation group ($n = 40$)	27 (67.50)	11 (27.50)	2 (5.00)	38 (95.00)
Control group ($n = 40$)	21 (52.50)	9 (22.50)	10 (20.00)	30 (75.00)
χ^2	-	-	-	6.275
P	-	-	-	0.012

3.3. Comparison of quality of life between the two groups

Table 3 shows that the FACT-B score in the observation group surpassed that of the control group ($P < 0.05$).

Table 3. Comparison of quality of life between the two groups (mean ± SD, points)

Group	Social state	Emotional state	Physiological state	Functional state	Other aspect
Observation group ($n = 40$)	21.38 ± 5.39	19.32 ± 4.08	22.25 ± 4.95	21.45 ± 6.36	24.92 ± 5.28
Control group ($n = 40$)	17.95 ± 4.88	17.02 ± 3.43	18.56 ± 5.47	18.28 ± 5.62	21.55 ± 5.04
t	2.984	2.729	3.163	2.362	2.920
P	0.004	0.008	0.002	0.021	0.005

3.4. Comparison of postoperative complication rates between the two groups

The observation group exhibited a significantly lower incidence of complications in comparison to the control group ($P < 0.05$), as presented in **Table 4**.

Table 4. Comparison of postoperative complication rates between the two groups [n (%)]

Group	Decreased sensation	Subcutaneous effusion	Flap necrosis	Swelling and numbness	Overall incidence
Observation group ($n = 40$)	0 (0.00)	1(2.50)	0 (0.00)	1(2.50)	2 (5.00)
Control group ($n = 40$)	2 (5.00)	2 (5.00)	1(2.50)	3 (7.50)	8 (20.00)
χ^2	-	-	-	-	4.114
P	-	-	-	-	0.043

3.5. Comparison of metastasis rate and recurrence rate between the two groups

Table 5 shows that there was no statistical difference observed in the metastasis rate and recurrence rate between the two groups ($P > 0.05$).

Table 5. Comparison of metastasis rate and recurrence rate between two groups [*n* (%)]

Group	Metastasis rate	Recurrence rate
Observation group ($n = 40$)	1 (2.50)	1 (2.50)
Control group ($n = 40$)	3 (7.50)	4 (10.00)
χ^2	1.053	1.920
P	0.305	0.166

4. Discussion

The majority of early-stage breast cancer patients do not present with axillary lymph node metastasis. Extensive ALND often results in disrupted lymphatic reflux, leading to postoperative complications such as pain, numbness, edema, and restricted upper limb movement, significantly impacting patients' quality of life.

Clinically, modified radical mastectomy is frequently employed to treat early-stage breast cancer. However, this approach is highly invasive, removing the affected breast and ipsilateral axillary lymph nodes, with potential nerve damage and a higher incidence of complications [6]. In contrast, breast-conserving surgery allows for faster postoperative recovery, preserving normal glandular tissue and breast shape, thus enhancing treatment efficacy, breast aesthetics, and patient satisfaction [7]. SLNB is a minimally invasive procedure that accurately determines tumor metastasis, allowing for the avoidance of lymph node dissection in patients with negative results and reducing the risk of recurrence in positive cases [8]. This approach contributes to the overall improvement of patient treatment outcomes, mental health, and quality of life, particularly for those with negative results who can undergo breast-conserving surgery without the emotional burden of breast loss [9].

This study results indicate that the observation group, subjected to SLNB combined with breast-conserving surgery, exhibited shorter operation, hospitalization, and extubation times, along with reduced intraoperative blood loss and drainage volume, compared to the control group ($P < 0.05$). This suggests that this combined approach provides advantages such as minimal bleeding, high surgical efficiency, and swift postoperative recovery, demonstrating significant therapeutic efficacy. Furthermore, the excellent rate of breast cosmetology and quality of life in the observation group surpassed that of the control group ($P < 0.05$). This suggests that SLNB combined with breast-conserving surgery meets the aesthetic needs of early-stage breast cancer patients, enhancing their overall quality of life. While modified radical surgery can preserve the pectoralis major muscles, breast-conserving surgery, guided by SLNB, maximally retains non-lesional breast tissue, utilizing the healthy side nipple as a reference standard. This approach effectively controls the height difference between both sides post-surgery, addressing women's aesthetic needs and improving their quality of life. The lower incidence of complications in the observation group compared to the control group ($P < 0.05$) emphasizes the accuracy of SLNB results. Monitoring cancer cell metastasis and evaluating lymph node involvement enables the avoidance of unnecessary ALND in negative patients, preserving normal tissue and lymph nodes, minimizing removal scope, and reducing surgical trauma and complications. Therefore, SLNB combined with breast-conserving surgery achieves optimal efficacy with high safety and a low complication rate, with no significant differences observed in metastasis and recurrence rates compared to modified radical mastectomy [10].

In summary, SLNB combined with breast-conserving surgery for early-stage breast cancer patients offers

advantages such as reduced intraoperative trauma, minimized bleeding, shorter operation times, and faster postoperative recovery. It effectively decreases complication rates while enhancing breast aesthetics and overall quality of life.

Disclosure statement

The author declares no conflict of interest.

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Evaluation of Postoperative Psychological Distress and Its Driving Factors in Patients with Oral and Maxillofacial Malignant Tumors

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Abstract: *Objective:* To explore and analyze the evaluation and driving factors of postoperative psychological pain inpatients with oral and maxillofacial malignant tumors. *Methods:* Relevant data were collected from 80 patients with oral and maxillofacial malignant tumors who attended the outpatient clinic for follow-up consultations between May 2021 to May 2023. The patients used the psychological distress thermometer (DT) to circle words that best described their experiences in the past week, assigning a numerical value (0–10) to indicate their pain level on each day. The scoring results were employed to assess the psychological pain in these patients. A self-developed patient basic information questionnaire was utilized to record demographic details. Logistic regression analysis was employed to evaluate patients two weeks after surgery, focusing on the assessment of psychological distress and the identification and location of driving factors. *Results:* Following evaluation, the results revealed that the average postoperative DT score for the 80 patients with oral and maxillofacial malignant tumors was 4.53 ± 1.98 points. Scores < 4 points indicated no psychological pain (Group N) in 48 cases, while scores ≥ 4 points indicated psychological pain (Group Y) in 32 cases. The differences in postoperative DT scores among patients with varying educational levels, fears and worries about disease progression, economic problems, sleep problems, level of hope, and oral pain were statistically significant ($P < 0.05$). Multiple linear regression analysis results indicated that education level, fear and worry about disease progression, economic problems, sleep problems, level of hope, and oral pain are driving factors of postoperative psychological pain in patients with oral and maxillofacial malignant tumors ($P < 0.05$). *Conclusion:* The postoperative psychological pain level in patients with oral and maxillofacial malignant tumors is at a moderate level. Educational level, fear and worry about disease progression, economic problems, sleep problems, level of hope, and oral pain were identified as driving factors for postoperative psychological pain in these patients.

Keywords: Oral and maxillofacial malignant tumors; Psychological pain; Driving factors; Regression analysis

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1. Introduction

Many patients with malignancies endure pain, significantly impacting their quality of life and the effectiveness

of malignancy treatment. Despite its controllability, pain in these patients is often overlooked and underreported. It can manifest at any stage of malignancy treatment, contributing to depression, anxiety, missed appointments, and unfavorable outcomes [1]. In 1999, the National Comprehensive Cancer Network (NCCN) recommended routine distress screening for all cancer patients. The Psychological Distress Thermometer (DT) is a simple yet effective tool for screening anxiety symptoms. Utilizing a self-report instrument on a 0 to 10 rating scale, it prompts patients to identify sources of distress through a list of questions. The DT has demonstrated reliability and has been translated into numerous languages. Its ease of administration empowers clinicians to facilitate appropriate psychosocial support and referrals.

Oral and maxillofacial tumors constitute a significant aspect of head and neck tumors, encompassing cysts, benign tumors, tumor-like lesions, and malignant tumors. Alongside evident local tumors, patients may experience pain, local skin bleeding, ulcers, and other symptoms, with common types including tongue cancer, gum cancer, buccal malignant tumors, palate cancer, and floor of mouth cancer. [1]. Studies indicate that the primary treatment for oral and maxillofacial malignant tumors remains surgical resection, with radical surgical resection recommended for patients in early, middle, and advanced stages [2]. When combined with other treatments, this approach significantly increases the chances of curing the disease. However, due to the influence of certain driving factors, patients may experience postoperative psychological pain, subsequently affecting the postoperative recovery of those with oral and maxillofacial malignant tumors.

Postoperative oral pain represents the subjective experience of patients with neurological reactions. While it can alleviate mental stress and mitigate negative emotions such as depression, anxiety, and sadness, it also has the potential to induce psychological pain in patients [3]. This study collected relevant data from 80 patients with oral and maxillofacial malignant tumors who attended The First Affiliated Hospital of Sun Yat-sen University for follow-up consultation between May 2021 and May 2023. The aim was to explore the evaluation and driving factors of postoperative psychological pain in patients with oral and maxillofacial malignant tumors.

2. Materials and methods

2.1. General information

Data from 80 patients with oral and maxillofacial malignant tumors who attended the hospital for follow-up consultation between May 2021 and May 2023 were collected. The cohort comprised 47 male and 33 female patients, with an average age of 53.27 ± 4.06 years. All participants were well-informed about the study details and had a clear understanding of its key points. Ethical approval was obtained from the Ethics Committee of the hospital. Pathological types included gingival cancer, malignant tumors of the lower soft palate, tongue cancer, floor of mouth cancer, facial skin malignant tumors, maxillary and palate tumors, fibrosarcoma, buccal malignant tumors, etc.

Inclusion criteria included patients who were pathologically diagnosed with oral and maxillofacial malignant tumors post-surgery, met surgical indications, possessed normal communication and communication skills, and demonstrated good compliance with complete information. Exclusion criteria included patients with other severe malignant tumors, recent severe internal trauma, or mental disorders.

2.2. Method

The psychological distress level of patients was assessed using the DT, recommended by NCCN as a screening tool for investigating patients' psychological status [4]. The scale covered psychological, social, spiritual, and other essentially unpleasant emotional experiences, including practical problems, communication problems, emotional problems, physical problems, and faith/religious problems. The DT is a visual analog scale ranging

from 0 to 10 points, where 0 indicates no pain and 10 indicates extreme pain. Higher scores indicate more severe psychological pain, with a score of ≥ 4 points generally considered indicative of psychological pain.

The patient's basic information questionnaire included details on gender, age, education level, fears and worries about disease progression, financial problems, sleep problems, level of hope, and severity of oral pain.

2.3. Statistical analysis

Data analysis was conducted using SPSS 26.0 software. Count data were expressed as rates using the χ^2 test. Measurement data were represented as mean ± standard deviation (SD), and the *t*-test was employed. Driving factors of postoperative psychological distress in patients with oral and maxillofacial malignant tumors were examined through multiple linear regression analysis. A significance level of $P < 0.05$ was considered statistically significant.

3. Results

3.1. Assessment of the current status of postoperative psychological distress in patients with oral and maxillofacial malignant tumors

Upon evaluation, the average postoperative DT score of 80 patients with oral and maxillofacial malignant tumors was 4.53 ± 1.98 points. A score < 4 points indicated no psychological pain (N group), with 48 cases (60%), while a score ≥ 4 points indicated psychological pain (Group Y), with 32 cases (40%), and the difference between the two groups was statistically significant ($P < 0.05$; **Table 1**).

Table 1. Postoperative psychological distress level of patients with oral and maxillofacial malignant tumors (mean ± SD, points)

Group	*n*	DT score
Group N	48	2.85 ± 0.96
Group Y	32	6.07 ± 1.34
t value		8.953
P value		0.002

3.2. Assessment of postoperative psychological distress in patients with oral and maxillofacial malignant tumors with different characteristics

DT scores among patients with oral and maxillofacial malignant tumors varied based on different characteristics, including educational levels, fears and worries about disease progression, economic problems, sleep problems, level of hope, and oral pain. Specifically, patients with high school education and below exhibited higher DT scores than college graduates and above. Those with fear and worry about disease progression, financial problems, and sleep problems had higher DT scores than those without such concerns. Patients with lower levels of hope demonstrated higher DT scores than those with optimistic hope levels. Furthermore, individuals experiencing moderate to severe oral pain had higher DT scores than those with mild pain. The differences were statistically significant ($P < 0.05$; **Table 2**).

3.3. Regression analysis of driving factors of postoperative psychological pain in patients with oral and maxillofacial malignant tumors

Using the status of postoperative psychological pain as the dependent variable, further multiple linear regression analysis revealed that education level, fear and worry about disease progression, economic problems, sleep

problems, level of hope, and oral pain were significant factors influencing postoperative psychological pains in patients with oral and maxillofacial malignant tumors ($P < 0.05$; **Table 3**).

Table 2. Evaluation of postoperative psychological distress in patients with oral and maxillofacial malignant tumors with different characteristics (mean ± SD, points)

Index	*n*	DT score	*t* value	*P* value
Gender			1.162	0.783
Male	47	4.56 ± 1.92		
Female	33	4.51 ± 1.93		
Age			1.953	0.476
≥ 60 years old	29	4.46 ± 2.01		
< 60 years old	51	4.58 ± 1.97		
Education level			7.382	0.004
High school and below	41	5.04 ± 2.07		
College degree and above	39	4.12 ± 1.76		
Fear and worry about disease progression			9.475	0.000
Have	34	5.89 ± 1.95		
None	46	4.26 ± 1.83		
Economic issues			7.813	0.003
Have	38	5.12 ± 2.09		
None	42	4.06 ± 1.91		
Sleep problems			9.085	0.001
Have	40	5.38 ± 1.96		
None	40	3.97 ± 1.72		
Hope level			10.154	0.000
Low	39	5.59 ± 2.05		
Good	41	3.75 ± 1.82		
Mouth pain			15.926	0.000
Moderate to severe	35	6.06 ± 1.67		
Mild	45	3.68 ± 1.85		

Table 3. Regression analysis of driving factors of postoperative psychological distress in patients with oral and maxillofacial malignant tumors

Variable	*β* value	SE value	Wald χ^2 value	*P* value	OR value	95% CI value
Education level	-1.116	0.534	5.159	0.004	0.291	0.106–0.485
Fear and worry about disease progression	0.114	0.053	4.708	0.000	0.831	0.432–0.986
Economic issues	0.197	0.482	8.224	0.003	0.359	0.118–0.625
Sleep problems	0.131	0.067	4.025	0.001	0.302	0.109–0.496
Hope level	0.185	0.574	5.769	0.000	0.325	0.112–0.607
Mouth pain	0.128	0.227	6.509	0.000	0.583	0.271–0.789

4. Discussions

The postoperative pain experienced by patients with oral and maxillofacial malignant tumors transcends the physical realm, encompassing psychological and spiritual dimensions. This multifaceted pain profoundly influences the patient's life and post-surgery rehabilitation outcomes. Hence, early assessment and intervention regarding postoperative psychological pain and its driving factors in these patients are imperative.

Among the 80 patients in this study, 48 cases (60%) exhibited no psychological pain, while 32 cases (40%) reported its presence. In analyzing specific driving factors, educational level, fear and worry about disease progression, economic problems, sleep problems, level of hope, and oral pain emerged as key contributors to postoperative psychological pain in patients with oral and maxillofacial malignant tumors. Research indicated that individuals with a high school education or below tend to have higher DT scores than their counterparts with a college education or above. Patients experiencing fear and worry about disease progression, economic problems, and sleep problems exhibited higher DT scores compared to those without such concerns. Additionally, individuals with lower levels of hope or experiencing moderate to severe oral pain demonstrated higher DT scores than those with good hope levels or mild pain. These differences were statistically significant.

Understanding the preoperative discussions, patients with oral and maxillofacial tumors anticipate the upcoming surgery's trauma and stimulation, leading to physical pain and discomfort. Concerns about changes in facial appearance, recovery of basic functions, prognosis, and economic issues contribute to preoperative tension and panic. Severe cases may lead to psychological changes such as anxiety and fear [5,6]. Oral and maxillofacial malignant tumor surgeries often involve a larger scope and greater trauma, resulting in more severe postoperative pain compared to benign tumor surgeries. Persistent postoperative pain can have physical and mental repercussions, interfering with organ functions and inducing symptoms such as hallucinations, delusions, anxiety, and sleep disorders [7]. Perioperative fear and worry about disease progression are crucial risk factors for postoperative psychological pain. Economic concerns directly impact patients' psychological pain, leading to worry and anxiety about medical expenses and the ability to afford treatment [8]. Sleep problems further affect postoperative mood, causing psychological pain. A low level of hope contributes to psychological fluctuations, loss of motivation for treatment, and inner conflict [9]. Postoperative oral pain exacerbates psychological pain, manifesting in unpleasant thoughts, low mood, irritability, insomnia, nightmares, and heightened sensitivity. Severe cases may display external manifestations such as numbness, confusion, speech difficulties, and fear. Psychological counseling, including cognitive-behavioral therapy and psychodynamic therapy, can help alleviate negative emotions in patients experiencing severe psychological pain [10].

This study indicates that the psychological pain level of postoperative patients with oral and maxillofacial malignant tumors is at a moderate level. Educational level, fear and worry about disease progression, economic problems, sleep problems, level of hope, and oral pain are identified as driving factors for postoperative psychological distress. Therefore, personalized preoperative counseling, informed by patients' personality types and assessments, is crucial. Providing comprehensive information about their condition, potential complications, and unpredictable outcomes enhances patients' understanding, facilitates appropriate psychological counseling, and adjusts their preoperative mental state. This approach proves beneficial for postoperative recovery and pain reduction [11].

Disclosure statement

The authors declare no conflict of interest.

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Examining the Pathological Diagnostic Impact of Frozen Sections in Breast Cancer

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Abstract: *Objective:* To analyze the diagnostic value of frozen section pathology in the diagnosis of breast cancer. *Methods:* A total of 50 patients with breast tumors treated between July 2021 and February 2023 were randomly selected as samples. Both paraffin section and frozen section diagnoses were conducted. The paraffin section results served as the gold standard for evaluating the value of frozen section examination. *Results:* Among the frozen section diagnoses, 48 cases (96.00%) were confirmed, 1 case was misdiagnosed (2.00%), and 1 case was delayed (2.00%). Among the confirmed patients, 45 cases (90.00%) were entirely consistent, and 3 cases (6.00%) were basically consistent. The diagnostic rate of the frozen section was 96.00%, compared with 100.00% for the paraffin section ($P > 0.05$). The diagnostic time of the frozen section (35.25 ± 2.11 min) was significantly shorter than that for the paraffin section (6911.36 ± 58.36 min; $P < 0.05$). *Conclusion:* Frozen section diagnosis is rapid and demonstrates relatively high diagnostic accuracy. It can guide doctors in determining whether to pursue breast-conserving treatment and aid in selecting appropriate surgical methods. This is beneficial for preventing unnecessary medical interventions and reducing the need for secondary surgeries in breast cancer patients.

Keywords: Frozen section diagnosis; Pathological diagnosis; Diagnostic results

Online publication: November 22, 2023

1. Introduction

Breast cancer constitutes a significant portion of female malignant tumors and poses a threat to the lives of female patients. In recent years, the age of onset of breast cancer has been decreasing, making it a growing social and public health concern. Clinical treatments for breast cancer typically encompass surgery, chemotherapy, radiotherapy, and endocrine regulation. Often, breast cancer patients undergo adjuvant radiotherapy or chemotherapy after surgery to reduce the risk of recurrence. Relevant literature suggests that early diagnosis and timely surgical intervention play a pivotal role in improving the prognosis of breast cancer [1].

While breast MRI examinations exhibit high sensitivity, they may yield false positives and can be mistaken for benign breast tumors, making it challenging for doctors to devise accurate surgical plans. Conventional needle biopsy techniques are employed to perform preoperative pathological diagnoses, enabling the initial

differentiation between benign and malignant breast cancers and helping avoid unnecessary surgeries. However, these techniques are influenced by factors such as the quantity of tissue cells obtained, scattered calcifications, and the skill of the performing physician, leading to issues with false positives and false negatives. This hinders their clinical applicability. Intraoperative frozen pathology, on the other hand, assists doctors in clarifying the nature of tumors and making initial assessments of tissue grade and type, thereby offering valuable guidance for the precise selection of surgical plans. This study investigates the diagnostic value of intraoperative frozen sections, using a sample of 50 patients with breast tumors randomly selected from those treated between July 2021 and February 2023.

2. Materials and methods

2.1. General information

A total of 50 patients with breast tumors treated between July 2021 and February 2023 were randomly selected as samples. The age of the patients ranged from 16 to 81 years, with an average age of 50.11 ± 7.33 years. The breast tumors had appeared within the range of 2 to 12 months before examination, and the size of the breast tissue specimens submitted for examination varied from 0.5×0.5×0.5 cm to 4.0×4.0×4.0 cm. In terms of lesion location, 24 cases were on the left side, 12 cases were bilateral, and 14 cases were on the right side. Tumor tissue samples were obtained from patients with breast disease. Frozen sections and routine paraffin sections of tumor tissue samples were prepared for corresponding pathological examinations. Inclusion criteria included patients with imaging examinations showing breast masses and normal liver and heart functions. Exclusion criteria included patients with other malignant tumors, immune system disorders, a history of radiotherapy or chemotherapy before enrollment, or abnormal organ function.

2.2. Methods

All patients with breast tumors who received surgical treatment underwent preoperative frozen examination, and various examination equipment and items were prepared. After obtaining breast tissue specimens, freezing tests were performed. The test environment temperature was maintained between -30°C and -18°C to ensure test accuracy. The slices were sealed with ordinary adhesive, and the pathological slices were cut to a controlled thickness of 4 μm. Fixative was used to secure the slices. After completing the fixation process, the slices were stained and sealed. The sealed specimens were first observed with the naked eye, followed by microscopic observation, and diagnostic results were evaluated based on histological diagnostic criteria. In addition, clinical data, such as X-ray mammography calcium results and clinical diagnoses, were comprehensively analyzed.

2.3. Observation indicators

Patient data for breast tumors were analyzed. The frozen section examinations and paraffin section examinations were evaluated. After obtaining the paraffin section examination results, comparative analysis results of the frozen section examinations could be categorized as follows:

(1) Frozen section results were completely/basically consistent with the paraffin section results (indicating similar tissue properties but different disease types), recorded as “diagnosed.”

(2) Cases where malignant tumors were incorrectly identified as benign tumors (false negative) or benign tumors were incorrectly identified as malignant tumors (false positive), recorded as “misdiagnosed.”

(3) Cases where the frozen section was providing inconclusive results and paraffin section results were needed to confirm benign or malignant status and formulate a treatment plan, recorded as “delayed diagnosis.”

2.4. Statistical research

The patient data for breast tumors were processed with SPSS 21.0. Count data were recorded as % (using the χ^2 test), and measurement data were presented as mean ± standard deviation (using the *t*-test). A statistical difference was considered significant if $P < 0.05$.

3. Results

3.1. Comparison of frozen section diagnostic results and paraffin section diagnostic results

The frozen section pathological examination revealed that among the 50 patients who underwent examination for breast masses, 12 had malignant tumors, constituting 24.00% of the intraoperative breast disease rate. Of these, 10 were diagnosed with cancerous lesions, accounting for 83.33% of intraoperative malignant breast tumors, while 1 case was diagnosed with lymphatic tumors, making up 8.33% of malignant breast tumors during surgery. One case of malignant tumor awaited routine paraffin diagnosis. Additionally, there were 9 cases of intraductal papilloma, 17 cases of fibroadenomas, 4 cases of cystic breast lesions, 4 cases of inflammatory breast lesions, 1 case of breast adenosis, and 3 cases of benign breast hyperplasia, each accounting for 18.00%, 34.00%, 8.00%, 8.00%, 2.00%, and 6.00% of the intraoperative breast diseases, respectively.

Upon comparing the results of intraoperative frozen section diagnosis with postoperative paraffin section diagnosis (**Table 1**), it was found that 48 cases were confirmed by intraoperative frozen section diagnosis, resulting in a diagnosis rate of 96.00%. There was one case of misdiagnosis (false negative), leading to a misdiagnosis rate of 2.00%, and one case of delayed diagnosis, with a delay rate of 2.00%. Among the confirmed patients, 45 cases (90.00%) exhibited complete consistency, while 3 cases (6.00%) showed basic consistency. Routine paraffin sections diagnosed all 50 cases, achieving a diagnosis rate of 100.00%.

Table 1. Comparison of intraoperative frozen section diagnostic results and postoperative paraffin section diagnostic [*n* (%)]

Frozen section diagnostic results		*n* (%)	Diagnosed		Misdiagnosed (false negative)	Delayed diagnosis
			Completely consistent	Basically consistent		
Malignant tumor	Breast cancer	10 (20.00)	10 (20.00)	1 (2.00)	0 (0.00)	1 (2.00)
	Lymphoma	1 (2.00)				
	Other	1 (2.00)				
Benign and borderline tumors	Intraductal papilloma	9 (18.00)	25 (50.00)	0 (0.00)	1 (2.00)	0 (0.00)
	Fibroadenoma	17 (34.00)				
Non-neoplastic diseases	Cystic lesions	4 (8.00)	10 (20.00)	2 (4.00)	0 (0.00)	0 (0.00)
	Inflammatory lesions	4 (8.00)				
	Breast adenosis	1 (2.00)				
	Benign hyperplasia	3 (6.00)				
Total		50 (100.00)	45 (90.00)	3 (6.00)	1 (2.00)	1 (2.00)

3.2. Comparison of accuracy and inspection time between frozen sections and paraffin sections

The diagnosis rate of the frozen section was 96.00%, compared to 100.00% for the paraffin section ($P > 0.05$). The diagnostic time of the frozen section was 35.25 ± 2.11 min, including the time for multiple submissions of bilateral breasts and unilateral breasts, which was significantly shorter than that for the paraffin section (6,911.36 ± 58.36 min; $P < 0.05$), as shown in **Table 2**.

Table 2. Comparison of accuracy and inspection time between frozen sections and paraffin sections

Group	Diagnosis rate (%)	Diagnosis time (min)
Frozen sections (n = 50)	48 (96.00)	35.25 ± 2.11
Paraffin sections (n = 50)	50 (100.00)	6,911.36 ± 58.36
χ^2 / t	2.0408	832.5856
P	0.1531	0.0000

4. Discussion

Breast cancer poses a significant threat to the physical and mental well-being of women. It is a disease characterized by the infiltration of multiple carcinogens, which stimulate breast epithelial cells and lead to uncontrolled breast hyperplasia [2]. After the onset of breast cancer, female patients may exhibit the following symptoms:

(1) Mass: The earliest sign of breast cancer is the presence of a mass. These masses are often located in the outer upper region of the breast, typically have a firm texture, are unilateral, solitary, and exhibit limited mobility. Additionally, most breast tumors are painless, though some may cause mild discomfort or a dull ache.

(2) Local skin abnormalities: As cancer progresses and invades adjacent skin, patients may develop specific signs. For instance, mass invasion can lead to dimple-like depressions in the breast, block lymphatic vessels causing lymphedema, or result in hard nodules when they invade the skin.

(3) Areola lesions: Cancer lesions that invade the areola area can cause the nipple to retract inward. In severe cases, the nipple may shrink toward the nipple base and behind the areola.

(4) Nipple discharge: Breast cancer patients may experience nipple discharge outside of pregnancy and lactation periods, with unilateral nipple discharge being common. The nature of the discharge is usually serous or bloody.

(5) Swollen lymph nodes: As breast cancer progresses, cancer cells can detach and enter local lymphatic vessels, causing signs of swollen lymph nodes. These local lymph nodes may exhibit mobility upon touch [3].

Surgical treatment is currently the primary approach for breast cancer, often involving mastectomy combined with axillary lymph node dissection. However, this approach can result in substantial trauma, prolonged operation times, increased risk of postoperative complications, and changes in breast shape, impacting the aesthetics and the physical and mental health of patients. Therefore, some patients prefer breast-conserving surgery to improve breast aesthetics. To enhance the prognosis of breast cancer patients and their postoperative quality of life, early surgical intervention and appropriate surgical plans are essential.

In the treatment of breast cancer patients, doctors frequently select surgical methods based on tumor histology, pathohistology, and other indicators to minimize surgical trauma while ensuring effectiveness. In the preoperative diagnosis of breast cancer, frozen diagnosis is a commonly employed pathological examination. Compared to conventional pathological examination techniques, frozen diagnosis offers speed and efficiency, aiding breast cancer patients in choosing a more efficient and reasonable surgical plan [4].

During a frozen section pathological examination, tissues are rapidly cooled, leading to increased tissue hardness, after which local sections are taken for qualitative diagnosis of the mass tissue. Frozen section examinations are less challenging and offer various techniques, such as the cryostat section, CO_2 frozen section,

and methanol cycle section. Among these, cryostat sectioning technology is widely utilized based on clinical practice analysis [5]. Compared to conventional fine needle aspiration cell protocols, frozen sections are less complex and exhibit a lower misdiagnosis rate. They swiftly clarify the pathological characteristics of breast cancer tissue, offering speed, accuracy, and efficiency, making them widely used in clinical diagnosis [6].

Based on the data analysis in this study, frozen section diagnosis achieved a confirmation rate of 96.00%, with one case of misdiagnosis (false negative) and one case of delayed diagnosis, while paraffin section diagnosis had a 100.00% confirmation rate. The diagnostic time for the frozen sections was significantly shorter (35.25 ± 2.11 min, including multiple examinations of bilateral and unilateral breasts) than that of the paraffin sections (6,911.36 ± 58.36 min) These results suggest that frozen section diagnosis offers high diagnostic efficiency and high concordance with paraffin sections, though it still presents a misdiagnosis risk.

To ensure the accuracy of frozen section diagnosis, several factors must be considered during the actual examination:

(1) Medical history: A thorough review of the patient's medical history and pathology submission form is crucial. Understanding the patient's background, evaluating tumor invasiveness, and controlling the spread of tumor cells is vital. Collecting tumor tissue correctly, obtaining adjacent tissues to prevent cancer cell infiltration into healthy areas, and maintaining diagnostic quality is also important.

(2) Tissue selection: When conducting frozen section examination on patients with small breast tumors, care should be taken to avoid local tissue destruction and loss, which can increase the rate of missed or misdiagnosis. Therefore, selecting larger tissue samples for examination is recommended to prevent bias in diagnostic results.

(3) Quality control: High-quality frozen sections should be produced to enhance the accuracy of identifying benign and malignant breast tissues. Varying section depths should be utilized, and multiple microscopic examinations should be performed on specimens to ensure diagnostic accuracy [7].

For cases involving borderline tissue or highly suspected cancerous tissue, paraffin section technology is more suitable for diagnosis, as frozen sections may not yield accurate data [8].

Considering the diagnostic time, frozen section examinations are notably faster, taking only 6–41 minutes (including multiple breast examinations) compared to the 4–5 days required for paraffin section examinations. This is because the tissues submitted for frozen section examinations do not need to be dehydrated or wax-immersed, hence preserving their original appearance and shortening the diagnosis time. While frozen section examinations are invaluable in guiding doctors and selecting surgical techniques [9], in cases of misdiagnosis or missed diagnosis, clinical experience often helps to evaluate the tumor's nature and select the appropriate treatment plan. In situations where the surgical method remains uncertain, surgery may be postponed until paraffin section results are obtained, ensuring the best diagnostic and treatment outcomes and enhancing the prognosis of breast disease patients [10].

In summary, frozen section examination in breast disease diagnosis offers the advantages of rapid examination and high accuracy. It guides doctors in making flexible decisions regarding breast-conserving treatment and serves as a foundation for selecting appropriate surgical procedures, ultimately preventing unnecessary medical intervention and reducing the need for secondary surgeries, thus providing substantial value.

Disclosure statement

The author declares no conflict of interest.

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Enhancing Infection Control: A Comprehensive Analysis of Microbial Testing and Clinical Accuracy Assessment

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Abstract: *Objective:* To analyze the value of microbiological testing in the treatment of urinary tract infections. *Methods:* A total of 552 patients with urinary tract infections, diagnosed and treated between January and December 2021, were selected for this study. They were divided into observation and control groups, each consisting of 276 cases, using the random number table method. The observation group underwent microbial testing, while the control group underwent routine examinations to compare the diagnosis rate, overall treatment effectiveness, and infection status between the two groups. *Results:* The observation group exhibited significantly improved diagnosis rate, treatment effectiveness, and infection status compared to the control group ($P < 0.05$). *Conclusion:* The application of microbial testing in the treatment of urinary tract infections demonstrates high clinical applicability.

Keywords: Urinary tract infection; Microbial testing; Application effect

Online publication: November 22, 2023

1. Introduction

Urinary tract infections are common clinical diseases. When bacteria invade the patient's urothelium, an inflammatory reaction occurs, which may be complicated by bacteriuria and pyuria. Relevant literature mentions that urinary tract infections can lead to infections in both the lower and upper urinary tract [1]. According to the correlation, it can be classified into sporadic and recurrent infections, with the latter further divided into reinfection or persistent infection. In recent years, clinical medical testing technology has rapidly advanced for detecting various infections. Relevant studies have confirmed that methods such as disinfection, sterilization, physical testing, and ultraviolet rays can help clarify the condition of infectious patients and play a specific role. However, when compared to microbial testing, their detection accuracy might be higher.

Clinical research involving microbial testing can be used to diagnose, prevent, and treat infectious diseases [2]. It is a laboratory monitoring method. Through microbial testing, infectious diseases can be accurately diagnosed and controlled, thereby preventing further development of the infection. Without effective detection and control

knowledge, urinary tract infections could significantly threaten the patient's quality of life and prognosis. Therefore, with the rapid development of clinical medical biology, the application of medical microbial testing technology in clinical practice, which holds higher value, has been proposed. In this study, 552 patients were selected to investigate the value of microbiological testing in the treatment of urinary tract infections.

2. Materials and methods

2.1. Clinical data

The diagnosis and treatment period was from January to December 2021. A total of 552 patients with urinary tract infections were included in this experimental group. They were randomly divided into two groups, each consisting of 276 cases. The observation group had 136 men and 140 women, with an age range of 24 to 72 years old and an average age of 48.5 years old. The control group had 138 cases of men and 138 cases of women, with an age range of 25 to 71 years old and an average age of 48.0 years old. Comparing the data above, the statistical results of the two groups were $P > 0.05$.

Inclusion criteria for this study included patients with symptoms of urinary tract infection, such as frequent urination, urgency, and dysuria; urinalysis revealing white blood cells or red blood cells; abnormal renal function, such as elevated urea nitrogen and creatinine; and imaging examinations showing urinary tract stones, obstruction, or other urinary tract infection-related lesions.

Exclusion criteria for this study included patients with other serious diseases, such as malignant tumors and renal failure; patients with factors that affect the treatment effect, such as long-term use of immunosuppressants; patients with drug allergies as per the treatment plan; and pregnant or lactating women.

2.2. Methods

The control group underwent routine examinations, following the recommendations of clinicians. This included targeted diagnosis for patients, guidance on increasing fluid intake, environmental ultraviolet disinfection and sterilization, without performing microbial testing.

The observation group employed microbial testing and administered corresponding antibiotic treatment based on the test results. Urine samples were collected from the patient after cleansing, pathogenic bacteria were isolated from the urine, and drug susceptibility testing and bacterial identification were conducted. The Gram-negative bacteria card was used for identifying Gram-negative bacteria in the patient's urine. This information aided in identifying pathogenic bacteria associated with Gram-negative bacteria and checking bacterial resistance. The KB method was used to determine the drug resistance of the pathogenic bacteria, and treatment strategies were formulated based on the microbial test results.

2.3. Effect analysis

After treatment, if symptoms such as frequent urination entirely disappeared and the infectious bacteria became negative, it was considered markedly effective. If symptoms improved, and most infectious bacteria disappeared, it was considered effective. In all other cases, it was considered ineffective. The total effectiveness rate was calculated as the sum of the markedly effective and effective rates.

2.4. Statistical methods

The SPSS 25.0 statistical software package was used for performing the χ^2 and *t*-tests. Count data and measurement data were expressed as % and mean ± standard deviation (SD), respectively. A *P* value of less than 0.05 indicated significant statistical differences.

3. Results

The diagnosis rate, overall treatment effectiveness, and infection status of the observation group were significantly improved as compared to the control group ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of diagnosis rate, overall treatment effectiveness, and infection status between the two groups (%)

Group	Diagnosis rate	Markedly effective	Effective	Ineffective	Total effective rate
Observation group ($n = 276$)	265 (96.01)	212	53	11	96.01
Control group ($n = 276$)	201 (72.83)	107	95	74	73.19
χ^2	5.3182	-	-	-	5.3182
P	< 0.05	-	-	-	< 0.05

4. Discussion

4.1. Application of microbial testing in infection control

Microbial testing plays a vital role in infection control, and its applications primarily include the following aspects [3-8]:

(1) Epidemiological investigation: Through microbiological examination of infected cases, the source of infection, transmission routes, and susceptible groups can be traced, providing a scientific basis for formulating prevention and control measures.

(2) Hospital infection control: Microbial testing can be used to monitor the outbreak and spread of infections in hospitals, evaluate the effectiveness of disinfection and sterilization measures, and guide the rational use of antibiotics in clinical settings.

(3) Pathogen identification: Microbial testing helps identify and diagnose different infectious diseases, such as bacterial pneumonia and viral pneumonia, by detecting pathogen antigens and antibodies.

(4) Drug resistance monitoring: Microbial testing can detect bacterial drug resistance and its genotype, predict drug resistance trends, and guide doctors in selecting antibiotics rationally.

4.2. Analysis of the clinical accuracy of microbiological testing

The clinical accuracy of microbiological testing is critical for diagnosing and treating infections. Researchers focus on improving the accuracy of microbial testing, and the following factors affect its accuracy [9-13]:

(1) Quality control: Establishing a strict quality control system, including sample collection, transportation, processing, testing, and result reporting, is the key to improving the accuracy of microbial testing.

(2) Experimental technology: Experimental technology with high sensitivity and specificity, such as molecular biology methods, can enhance the accuracy of microbial testing.

(3) Data analysis: Correct data analysis methods are crucial for improving the accuracy of microbial testing. For example, pathogens can be identified more accurately by comparing the genetic sequences of clinical samples with those of standard strains.

4.3. Practical applications and challenges

Despite the vital role of microbial testing in infection control and clinical applications, there are still challenges in practical application:

(1) Sample selection: The timing, location, and quantity of sample collection can affect microbial testing

results. Choosing the proper sample is crucial for improving test accuracy.

(2) Technical sensitivity: Different experimental techniques exhibit variations in sensitivity and specificity, which may impact the accuracy of microbial testing. Enhancing technical sensitivity is key to improving accuracy.

(3) Data interpretation: Correct data interpretation methods are crucial for improving the accuracy of microbial testing. Clinicians need to have solid professional knowledge and experience to accurately interpret microbiological test data.

(4) Cost-effectiveness: The cost-effectiveness of microbial testing is an important consideration in practical applications. While high-precision inspection technology can improve accuracy, it comes with higher costs. Therefore, maximizing cost-effectiveness while ensuring accuracy is necessary.

4.4. Microbiological testing and urinary tract infection

Common clinical urinary tract inflammatory diseases, including urinary tract infections, can impact a patient's physical health and increase their psychological pressure. Effective and timely diagnosis is crucial for the patient and can significantly improve the treatment outcome. Analyzing the symptoms of urinary tract infection, including urinary urgency, painful urination, urethral burning sensation, and frequent urination, is essential for enhancing the patient's quality of life. Clinically, it is proposed that effective prevention and control of urinary tract infections can have a positive impact. In the diagnosis of urinary tract infection, microbial testing is typically employed. This method offers high diagnostic accuracy, simplicity of operation, and the ability to identify the causative bacteria, susceptible groups, and transmission routes of pathogenic bacteria [13]. Clinical infections can be monitored effectively. Clinical practice has demonstrated that microbial testing can accurately identify pathogenic bacteria. This information supports the implementation of appropriate treatments for patients, contributing to clinical treatment evidence and significantly reducing drug resistance. A practical method of sterilization is biological indicators, which can verify the elimination of bacteria and block transmission routes of pathogenic bacteria, ensuring patient health and significantly reducing the incidence of other infections. When treating patients with urinary tract infections, it is necessary to regularly disinfect the ward environment and medical equipment while monitoring the microorganisms in the environment in real time. This approach allows for the timely discovery of infection sources as well as prompt control and prevention of infections. Therefore, it is imperative to utilize microbial testing in the treatment of urinary tract infections. Testing can markedly improve the accuracy of clinical diagnosis, alleviate patients' clinical symptoms, and facilitate a quicker recovery.

(1) Symptoms: Patients with urinary tract infections typically experience symptoms of bladder irritation such as frequent urination, urgency, and painful urination, as well as difficulty urinating and lower abdominal pain. Some patients may also experience systemic symptoms such as fever and chills.

(2) Urine analysis: Urine sample analysis is essential for diagnosing urinary tract infections. Through physical examination, chemical examination, and microscopic examination of urine samples, abnormalities such as the presence of white blood cells, red blood cells, bacteria, and other substances in the patient's urine can be identified, indicating the presence of a urinary tract infection.

(3) Imaging examination: Imaging examinations can help doctors understand the patient's urinary tract shape and structure and rule out the possibility of other diseases, such as urinary tract stones and obstruction. Commonly used imaging examinations include ultrasound, X-ray, and computed tomography (CT) examinations.

(4) Bacteriological examination: Collecting urine samples from patients for bacteriological examination

can help doctors determine the types of causative bacteria responsible for urinary tract infections, providing a basis for subsequent treatment. Common bacteriological tests include bacterial culture and antigen detection.

Through microbial testing, pathogenic bacteria can be effectively detected [14], and transmission routes can be predicted. During the control of hospital infections, information such as the types of pathogenic microorganisms in patients can be summarized, and statistics can be used to guide patients in the rational use of antibiotics. Simultaneously, microbial testing can be applied to monitor the patient's infection in real-time and integrate with drug sensitivity tests to enable the rational selection of antibiotics, effectively preventing infections and significantly improving the patient's prognosis. Extensive sample data support the application of medical microbiology testing in clinical infection diagnosis and treatment [15], as it has a positive effect. Clinical practice confirms that microbial testing should be used to treat urinary tract infections and is clinically recognized.

4.5. Future development direction

With the continuous development of science and technology, the future development directions of microbial testing in infection control and clinical applications primarily include the following aspects:

(1) Application of new technologies: With the continuous advancement of biotechnology, new detection technologies, such as quantum dot immunofluorescence technology and liquid-phase chip technology, will be applied to microbial testing to improve testing accuracy and sensitivity.

(2) Automation and intelligence: The efficiency, accuracy, and repeatability of microbial testing can be enhanced by applying automation and intelligent equipment. For example, automated bacterial identification systems can rapidly and accurately identify bacteria through image recognition technology.

(3) Multi-drug resistance detection: The detection of multi-drug resistance is an important focus for future microbial testing. Through multi-drug resistance testing, a better understanding of the current status and trends in bacterial resistance can be achieved, guiding the rational use of antibiotics in clinical practice.

(4) Individualized treatment: Microbial testing can provide more personalized treatment plans based on the specific conditions of different patients, enhancing treatment effects and improving patients' quality of life.

5. Conclusion

Microbiological testing holds great significance in infection control and clinical applications. By continuously enhancing the accuracy of microbial testing, the diagnosis and treatment of clinical infections can be better guided, thereby reducing infection morbidity and mortality, and improving patients' quality of life. With the application of new technologies, the development of automation and intelligence, and the promotion of multi-drug resistance testing, the prospects for the development of microbial testing in infection control and clinical applications will be even broader. Experimental data have demonstrated that the observation group's diagnosis rate, overall treatment efficiency, and infection status significantly improved. It can be concluded that the clinical application value of microbial testing during the treatment of urinary tract infections is high. The patient's diagnosis rate, overall treatment efficiency, and infection status have all seen significant improvements, making it a valuable choice for clinical application.

Disclosure statement

The author declares no conflict of interest.

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Addressing Nursing Safety Hazards and Mitigation Strategies for Elderly Endocrinology Patients in Hospital Care

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Abstracts: *Objective:* To investigate the safety hazards in nursing and explore mitigation strategies for elderly patients in the endocrinology department. *Methods:* A total of 240 bedridden elderly patients from February 2021 to January 2023 were recruited and divided into two groups using the random number table method. The control group (n = 120) received conventional nursing care, and the observation group (n = 120) received personalized nursing care. Patients' quality of life, the incidence rate of pressure sores, and patient satisfaction with nursing care were observed and analyzed. *Results:* The incidence of pressure ulcers in the observation group was significantly lower at 17.50% compared to 30.00% in the control group ($P < 0.05$). Quality of life in the observation group was significantly higher than that in the control group ($P < 0.05$). The satisfaction rate in the observation group was significantly higher at 93.33% compared to 84.17% in the control group ($P < 0.05$). *Conclusion:* These findings emphasize that only through the implementation of scientific and rational nursing measures can effectively reduce nursing risks, enhance therapeutic outcomes, and improve the quality of life for elderly patients.

Keywords: Endocrinology; Elderly patients; Nursing safety; Safety hazards; Mitigation strategies

Online publication: November 22, 2023

1. Introduction

With the aging of the population, the medical demands and challenges associated with caring for elderly patients are steadily increasing. This trend is particularly pronounced in the field of endocrinology, where elderly hospitalized patients frequently encounter a range of unique issues. These issues encompass physical function decline, cognitive impairment, psychological stress, the presence of multiple concurrent diseases, inappropriate medication use or medication refusal, reduced vascular elasticity, and compromised resistance [1-10]. These challenges not only intensify the complexity of nursing care but also present significant hurdles for healthcare

professionals. In this paper, personalized nursing methods were employed to investigate the impact on quality of life, the occurrence of pressure ulcers, and overall nursing satisfaction.

2. General information and methods

2.1. General information

A total of 240 bedridden elderly patients in the endocrinology department of the Affiliated Hospital of Hebei University from February 2021 to January 2023 were selected and divided into two groups using the random number table method, with 120 patients in each group. The age range of patients was from 50 to 90 years old, with an average age of 69.36 ± 6.36 years. The occurrence of pressure ulcers among the patients was observed and analyzed.

2.2. Methods

The control group received conventional nursing care, while the observation group received personalized nursing care as follows:

(1) Dietary care: Dietary care is of paramount importance for elderly endocrinology inpatients. Healthcare professionals should select appropriate foods for patients based on their physical condition and illnesses, and encourage healthy eating habits. Recommended diets should be rich in vitamins, minerals, and dietary fiber while avoiding foods high in sugar, fat, and salt. Adequate daily water intake, around 1,500–2,000 mL, is also recommended.

(2) Psychological care: Elderly hospitalized patients in the endocrinology department often experience psychological issues such as anxiety and depression. Healthcare personnel need to monitor the psychological well-being of patients and provide psychological guidance through communication, care, and support. Simultaneously, educating patients and their families about their conditions can help them better understand their situation and cooperate with treatment and care.

(3) Pain management: Pain is a common symptom in elderly hospitalized endocrinology patients. Healthcare professionals should administer appropriate analgesic drugs according to the patient's pain level. They should closely monitor the patient's response to the medication and adjust the dosage as needed to ensure pain relief while avoiding adverse drug reactions.

(4) Medication guidance: For elderly endocrinology hospitalized patients, healthcare personnel must select medications suitable for their physical condition and illness. When administering medications, patients and their families should receive comprehensive information about usage, precautions, and possible adverse reactions to ensure proper use and close observation of adverse reactions.

(5) Sleep care: Good sleep is essential for the recovery of elderly endocrinology inpatients. Healthcare professionals should create a quiet and comfortable sleeping environment and help patients establish a regular sleep routine. Patients should avoid consuming large meals, drinking coffee, or engaging in intense physical activity before bedtime. For patients with insomnia, appropriate medications can be administered to assist with sleep.

(6) Mobility and activity assistance: Healthcare professionals should provide assistance to elderly endocrinology inpatients with limited mobility to ensure appropriate movement. The selection and proper use of walking aids, wheelchairs, and other assistive devices should be based on the patient's individual needs. Additionally, targeted rehabilitation training should be provided to promote the recovery of the patient's physical function as their condition allows.

(7) Skin and wound care: Maintaining clean, dry skin is vital for elderly endocrinology hospitalized

patients. Medical staff should regularly bathe patients, change clothes and bed linens, and keep the bedding clean and dry. For patients with wounds, dressings should be changed regularly to prevent infections. Patients should also be educated on appropriate skin care to prevent complications such as pressure ulcers.

(8) Complication prevention and response: Elderly hospitalized endocrinology patients may experience various complications, including infections, pressure ulcers, and deep vein thrombosis, among others. Healthcare professionals should take measures to prevent these complications, such as maintaining clean skin and regular repositioning. In cases where complications have already arisen, healthcare workers should actively address them, providing appropriate treatment and nursing care to alleviate patient discomfort.

(9) Family and social support: Elderly hospitalized endocrinology patients often require care and support from their families and society. Healthcare professionals should maintain close communication with patients' families to ensure they understand the patient's condition and treatment plan, providing targeted health advice and guidance. Patients should also be encouraged to participate in social activities to enhance their quality of life during rehabilitation.

2.3. Observation indicators

The quality of life, the incidence of pressure ulcers, and nursing satisfaction were observed and analyzed in this study.

2.4. Statistical methods

The SPSS 18.0 statistical software was used to analyze and process the data. Measurement data were expressed as mean ± standard deviation (SD) and analyzed using the *t*-test. Count data were expressed as % and analyzed using the χ^2 test, with a significance level set at $P < 0.05$.

3. Results

3.1. Comparison of the incidence rate of pressure ulcers and quality of life between the two patient groups

The incidence rate of pressure ulcers in the observation group was significantly lower at 17.50% compared to 30.00% in the control group ($P < 0.05$). Additionally, the quality of life in the observation group was significantly higher than that in the control group ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of the incidence rate of pressure ulcers and quality of life between the two patient groups

Group	Incidence rate of pressure ulcers	Quality of life
Observation group ($n = 120$)	21 (17.50%)	60.36 ± 2.36
Control group ($n = 120$)	36 (30.00%)	42.11 ± 2.45
χ^2 / t	5.1769	5.6354
P	0.0229	0.0000

3.2. Comparison of nursing satisfaction between the two groups

The satisfaction rate in the observation group was significantly higher at 93.33% compared to the control group's rate of 84.17% ($P < 0.05$), as illustrated in **Table 2**.

Table 2. Comparison of satisfaction rate between the two groups

Group	Very satisfied	Satisfied	Dissatisfied	Overall satisfaction
Observation group (n = 120)	96 (80.00)	16 (33.33)	8 (6.67)	112 (93.33)
Control group (n = 120)	38 (31.67)	63 (52.50)	19 (15.83)	101 (84.17)
χ^2				5.0496
P				0.0246

4. Discussion

As the global population ages, the healthcare needs of elderly patients continue to rise. Elderly patients admitted to endocrinology departments face a multitude of potential safety hazards stemming from their unique physiological and psychological conditions. These include vision, balance, and muscle control problems that may lead to falls and accidental injuries; hearing, vision, and speech impairments resulting in communication difficulties; memory loss and decreased mobility contributing to a decline in self-care; and the prevalence of various concurrent diseases such as diabetes and hypertension, requiring multiple medications. Prolonged bed rest and decreased immunity can lead to venous thrombosis and infections in elderly endocrine patients, while issues such as decreased appetite and malnutrition need attention. Furthermore, urinary incontinence, defecation difficulties, geriatric syndromes, delirium, decreased mobility, and social isolation can pose additional challenges. Additionally, strict blood glucose control is often necessary for elderly endocrinology patients [11-20].

Elderly patients hospitalized in endocrinology departments are susceptible to accidents and injuries, such as falls and choking, due to their declining physical functions. To mitigate such accidents, several measures should be implemented: regular patient safety education to enhance awareness; provision of adequate handrails, chairs, and facilities to maintain dry ward floors and eliminate potential safety hazards; routine equipment checks, including wheelchairs and bedside tables, to ensure they remain in good condition; personalized care plans tailored to individual patient conditions and physical statuses, along with increased inspection intensity to promptly identify and address safety hazards.

Elderly patients hospitalized in endocrinology departments often require long-term medication, emphasizing the importance of medication safety. To ensure the safety of medication, the following steps should be taken: in-depth understanding of the patient's condition and the proper use of medications, strict adherence to physician instructions, and accurate use of drugs; rigorous implementation of a drug management system, including regular quality checks and timely disposal of expired, damaged, or non-compliant drugs; close monitoring of the patient's response to medications, prompt reporting of any anomalies to the physician, and appropriate action taken; education of patients and their family members regarding medication use to improve compliance and safety awareness.

Elderly patients hospitalized in endocrinology departments may also experience skin issues such as diabetic foot and skin infections. Preventive measures should be taken to avoid skin damage: regular skin condition assessments, especially for diabetic patients' feet and perineum; maintenance of clean and dry skin to prevent infections; timely and appropriate nursing care for existing skin problems, such as the use of pressure-reducing pads and ensuring local areas remain dry; enhanced preventive nursing care for high-risk patients, including foot protection and pressure ulcer prevention.

Elderly patients hospitalized in endocrinology departments may need to disclose private information, making it essential to safeguard patient privacy. To protect privacy, healthcare personnel should: undergo

professional ethics education to ensure patient privacy is respected and protected; create private spaces in wards to facilitate patient-staff communication; educate patients on privacy protection to enhance their self-protection awareness; maintain strict confidentiality of information related to patients' privacy to prevent information leakage.

Effective glycemic control is a crucial therapeutic goal for elderly patients hospitalized in endocrinology departments. To achieve this goal, the following measures should be taken: development of a reasonable glycemic control program for patients, including diet, exercise, and medication; regular monitoring of patient's blood glucose levels and timely adjustments to the treatment plan; instruction of patients and their families in glycemic monitoring methods and related precautions; provision of psychological guidance and lifestyle support for patients with poor glycemic control to enhance their compliance and cooperation.

Elderly endocrinology hospitalized patients often have compromised immune systems and are prone to infections. To prevent infections, the following steps should be taken: strict adherence to hospital infection management systems, enhanced ward cleaning and disinfection; the implementation of nursing care measures for patients at risk of infections, including keeping their skin dry and preventing cross-infections; rational antibiotic use and avoidance of antibiotic misuse; the timely isolation of infected patients, along with corresponding nursing care based on the type of infection.

Elderly endocrinology hospitalized patients often face issues related to limb dysfunction, and rehabilitation exercises play a vital role in improving their quality of life. To ensure effective rehabilitation, the following measures should be taken: creation of personalized rehabilitation exercise programs based on the patient's condition and physical status; gradual progression of exercise intensity and time, following the principle of gradual progress; education and training of accompanying staff to assist patients correctly with rehabilitation exercises; prompt adjustments and improvements to address issues that arise during the rehabilitation exercise process.

In summary, addressing the nursing safety hazards of elderly endocrinology inpatients requires the implementation of a comprehensive response strategy to safeguard patient safety and treatment effectiveness. Close attention and support are essential for physical function, cognitive ability, psychological condition, concurrent diseases, drug use, vascular health, and resistance. Only through the application of scientific and reasonable nursing measures can nursing risks be effectively reduced and the therapeutic effects and quality of life of elderly patients improved.

Disclosure statement

The authors declare no conflict of interest.

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Detection and Clinical Significance of Th17/Treg Cell-Related Factors in Patients with Gestational Diabetes Mellitus

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Abstract: *Objective:* To investigate the detection of Th17/Treg cell-related factors in patients with gestational diabetes mellitus (GDM) and its clinical significance. *Methods:* In this study, a retrospective cohort research method was used to collect the clinical data of 42 patients who were hospitalized in the Affiliated Hospital of Hebei University and received the diagnosis of GDM from January 2018 to December 2022, as well as 42 patients with normal pregnancies during the same period. The Th17/Treg expression levels and metabolism-related indexes in the peripheral blood of patients were detected by radioimmunoassay. *Results:* The relative expression of Th17 in the serum of patients in the GDM group was significantly higher than that of the control group, and the level of Treg was significantly lower than that of the control group ($P < 0.05$); the levels of FBG, FINS, 2hBG, TC, TG and HOMA-IR of the patients in the GDM group were significantly higher than that of the control group, and the level of HOMA-β was significantly lower than that of the control group ($P < 0.05$). *Conclusion:* The imbalance of the Th17/Treg cell ratio in patients with GDM may be related to their disease progression and prognosis, providing new ideas and strategies for the clinical treatment of GDM.

Keywords: Gestational diabetes mellitus; Th17/Treg cells; Cytokines; Clinical significance

Online publication: November 22, 2023

1. Introduction

Gestational diabetes mellitus (GDM) is a form of diabetes mellitus that develops during pregnancy in individuals without prior diabetes mellitus and becomes more prevalent as blood glucose levels rise during pregnancy. Current understanding suggests that GDM results from a combination of genetic and environmental factors. In recent years, research has revealed that cytokines associated with the development of GDM primarily encompass Th17 cytokines, inflammatory factors, and chemokines. Some studies have demonstrated the involvement of Th17 cells in the development and maintenance of insulin resistance, while Treg cells play a crucial immunosuppressive role in maintaining the body's immune homeostasis. Evidence indicates that Th17/Treg cell-associated factors contribute to the pathogenesis of GDM [1].

The development of GDM is influenced by various factors, including genetics, environment, and

immunology. Recently, the study of Th17/Treg cells and their related cytokines has garnered significant attention in the fields of autoimmunity and diabetes. Th17 and Treg cells are vital regulatory components of the immune system, each secreting distinct cytokines to modulate immune responses and inflammatory processes. Therefore, the assessment of the expression of Th17 and Treg cell-related factors in patients with GDM holds importance in comprehending the pathogenesis of GDM and identifying potential therapeutic targets.

2. Information and Methods

2.1. General information

In this study, a retrospective cohort research method was employed to gather clinical data from 42 patients who were hospitalized and diagnosed with GDM between January 2018 and December 2022. Additionally, data were collected from 42 patients with normal pregnancies during the same period. Information was collected regarding the patient's age, BMI, height, waist circumference, body mass index (BMI), and microRNA (miRNA) gene test results. The inclusion criteria for study subjects were as follows: (1) confirmed diagnosis of GDM; (2) BMI ≥ 30 kg/m; (3) GDM diagnosed before 28 weeks of gestation; (4) absence of other conditions such as type 1 diabetes mellitus, other autoimmune diseases, or a family history of diabetes mellitus. All enrolled cases underwent pre-pregnancy fasting blood glucose examinations.

2.2. Methods

Peripheral venous blood was collected within 24 hours of hospitalization and placed in sterile vacuum blood collection tubes. The content of Th17/Treg cells in peripheral blood was determined using radioimmunoassay. All tests were conducted using enzyme-linked immunosorbent assay (ELISA), with the kits sourced from Nanjing Jianjian Bioengineering Research Institute. The ELISA procedure adhered strictly to the kit instructions, and the total RNA content in the samples was assessed using a centrifuge at the conclusion of the experiments.

2.3. Statistical methods

The SPSS 24.0 statistical software was employed for data analysis. Measured data were expressed as mean ± standard deviation (SD), and a *t*-test was performed. Count data were expressed as %, and a χ^2 test was conducted, with $P < 0.05$ considered indicative of a statistically significant difference.

3. Results

3.1. Comparison of Th17 relative expression and Treg level in serum of study subjects

The relative expression of Th17 in the serum of patients in the GDM group was significantly higher than that in the control group, while the level of Treg was significantly lower than that in the control group. These differences were statistically significant ($P < 0.05$), as illustrated in **Table 1**.

Table 1. Comparison of relative expression of Th17 and Treg levels in serum of study subjects

Group	Th17 (%)	Treg (%)
Control group ($n = 42$)	1.24 ± 0.33	3.26 ± 1.62
GDM group ($n = 42$)	3.38 ± 0.69	1.47 ± 0.51
t	8.961	3.694
P	< 0.05	< 0.05

3.2. Comparison of metabolism-related indexes in both groups

Patients in the GDM group exhibited significantly higher levels of fasting blood glucose (FBG), fasting insulin (FINS), two-hour blood glucose (2hBG), total cholesterol (TC), triglycerides (TG), and homeostatic model assessment of insulin resistance (HOMA-IR) compared to those in the control group. Conversely, the homeostatic model assessment of β cell function (HOMA-β) was significantly lower in the GDM group compared to the control group. These differences were statistically significant ($P < 0.05$), as indicated in **Table 2**.

Table 2. Comparison of metabolism-related indexes in both groups

Index	Control group ($n = 42$)	GDM group ($n = 42$)	t	P
FBG	4.52 ± 0.50	6.34 ± 0.89	6.398	< 0.05
FINS	7.87 ± 1.64	13.41 ± 2.37	4.256	< 0.05
2hBG	6.03 ± 1.35	8.33 ± 1.09	5.362	< 0.05
TC	4.31 ± 1.02	5.94 ± 1.71	4.369	< 0.05
TG	1.00 ± 0.32	2.21 ± 0.60	3.568	< 0.05
HOMA-IR	2.52 ± 0.87	3.99 ± 0.96	6.982	< 0.05
HOMA-β	1.91 ± 0.60	1.13 ± 0.22	4.699	< 0.05

4. Discussion

GDM is a distinct condition that develops during pregnancy, and its incidence rate increases with rising blood glucose levels during pregnancy. Its pathogenesis may be associated with impaired β-cell function in the pancreatic islets of affected individuals, leading to increased insulin resistance. In recent years, both domestic and international scholars have conducted extensive research on the pathogenesis of GDM, uncovering various cytokines related to GDM, such as interleukin-17 (IL-17) and tumor necrosis factor-alpha (TNF-α). These cytokines are thought to be involved in the pathogenesis of GDM [2,3]. Research indicates that IL-17 can activate the JAK-STAT pathway and promote the release of cytokines such as IL-1, IL-6, and TNF-α, which in turn, activate various immune cells such as monocytes, neutrophils, and eosinophils, participating in inflammatory reactions. Furthermore, TNF-α can be activated through the NF-κB pathway, promoting the secretion of IL-10 and TNF-α. IL-17 and TNF-α may also contribute to cell apoptosis through the co-activation of the PI3K/Akt signaling pathway [4-8]. Th17 cells are believed to secrete IL-17 and TNF-α, playing a significant role in the pathogenesis of GDM. Research has shown that the levels of Th17 cells and Treg cell-related factors in the peripheral blood of GDM patients are notably elevated [9-11].

Th17 cells are pivotal in inflammatory and autoimmune responses, with their characteristic cytokine being IL-17. In contrast to other T-cell subtypes, Th17 cells play a vital role in processes such as embryo implantation, placental development, and perinatal immunoregulation. In a normal pregnancy, Th17 cells regulate the immune response during uterine metamorphosis and embryo implantation, contributing to a successful pregnancy. However, in GDM patients, abnormal Th17 cell activation can disrupt the immune balance, leading to an inflammatory response and insulin resistance, ultimately precipitating diabetes mellitus. The relationship between GDM and Th17 cells is observed in several aspects. First, GDM patients exhibit an abnormal increase in the frequency and function of Th17 cells, which can directly contribute to insulin resistance and diabetes. Second, serum levels of Th17 cell-related cytokines, such as IL-17, are significantly elevated in GDM patients, indicating the immune response characteristics associated with Th17 cells in GDM. Finally, Th17 cells may further stimulate inflammatory responses and exacerbate insulin resistance through

the action of certain cytokines such as IL-23, creating a harmful feedback loop. The regulation of Th17 cells involves specific cytokines (e.g., IL-4, IL-10, etc.) that can inhibit the differentiation and activation of Th17 cells and serve in immunomodulation. Alterations in the expression of these cytokines may affect Th17 cell differentiation and activation in GDM [12-15], offering potential avenues for prevention and treatment. The impact of GDM on the health of mothers and infants should not be underestimated. Abnormal activation of Th17 cells in GDM may affect placental stability, increasing the risk of miscarriage and preterm delivery. Additionally, maternal inflammatory response and insulin resistance can influence fetal development, increasing the risk of macrosomia and fetal malformations. Therefore, an in-depth study of the role of Th17 cells in GDM may provide insights into the pathogenesis of GDM and suggest new strategies for prevention and treatment.

Treg cells are a subpopulation of T lymphocytes with immunosuppressive functions that play a crucial role in maintaining immune homeostasis and preventing autoimmune diseases. Treg cells can be categorized into natural Treg cells, which differentiate naturally in the thymus, and induced Treg cells, which differentiate from other T cells under specific conditions. Treg cells regulate the body's immune response by secreting inhibitory cytokines (e.g., IL-10 and TGF-β) and by exerting cell-contact-dependent inhibitory effects.

Treg cells and pro-inflammatory cytokines (e.g., IL-17 and IL-23) interact in the inflammatory response. It has been observed that IL-17 promotes insulin resistance, while Treg cells, through the secretion of IL-10, inhibit the inflammatory response, reducing insulin resistance. In GDM patients, the inflammatory response is heightened, pro-inflammatory cytokine levels are increased, and the number and function of Treg cells are impaired. This results in an amplification of the inflammatory response and exacerbation of insulin resistance, contributing to the development of GDM.

The development of GDM is closely linked to metabolic disorders. Studies have indicated that Treg cells influence energy metabolism by regulating the differentiation of adipocytes, the expression of adipose synthase, and insulin signaling. In GDM, a decrease in the number or dysfunction of Treg cells leads to abnormal adipocyte differentiation, increased fat synthesis, and decreased fat breakdown, causing an imbalance in energy metabolism and worsening the condition of GDM.

Research suggests that Treg cells protect pancreatic islet cells by inhibiting inflammatory and autoimmune reactions. In GDM, an enhanced inflammatory response results in damage to pancreatic β-cells and reduced insulin secretion. Conversely, Treg cells mitigate the inflammatory response in pancreatic islet cells by secreting inhibitory cytokines, protecting them from harm. Treg cells have a significant regulatory effect on the immune system. In GDM, a reduced number or dysfunction of Treg cells leads to immune system imbalance, increased pro-inflammatory cytokines, aggravated insulin resistance, and metabolic disorders. Effective alleviation of the inflammatory response and insulin resistance in GDM can be achieved by regulating the number and function of Treg cells.

5. Conclusion

Th17/Treg cell-related factors are implicated in the pathogenesis of GDM, with Th17 cells promoting the production and maintenance of autoantibodies while inhibiting the production of Treg cells through the secretion of IL-17. Furthermore, it was observed that the expression level of Th17-related factors in the peripheral blood of GDM patients was significantly higher than that in normal pregnant women ($P < 0.05$). This suggests that Th17-related factors are closely associated with the severity of the disease in GDM patients and may serve as indicators of disease severity. However, this study has some limitations, such as a small sample size and incomplete clinical data for some GDM patients. Consequently, future research should expand the

sample size and conduct statistical analyses to mitigate the influence of other factors.

In summary, Th17/Treg cells play a pivotal role in the onset and progression of GDM. Yet, numerous research gaps remain regarding the relationship between Treg cells and GDM. These include questions concerning the origin and specific phenotype of Th17/Treg cells in the context of GDM, how Th17/Treg cells impact the pathogenesis of GDM by regulating immune and metabolic pathways, and the potential therapeutic approaches involving the modulation of Th17/Treg cells. Subsequent studies should delve into these aspects more deeply to offer fresh insights into the prevention and treatment of GDM.

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Disclosure statement

The authors declare no conflict of interest.

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Prognostic Value of Semi-Quantitative 18F-FDG PET/CT Parameters in Hodgkin's Lymphoma

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Abstract: *Objective:* To assess the prognostic value of maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) determined by 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) imaging in Hodgkin's lymphoma patients. *Methods:* A total of 148 Hodgkin's lymphoma patients diagnosed with lymph node biopsy from October 2014 to October 2015 were retrospectively analyzed followed by categorizing into good (125 cases) and poor (23 cases) prognosis groups. The chi-squared test was used to analyze the clinicopathological characteristics of Hodgkin's lymphoma patients with the semi-quantitative 18F-FDG PET/CT parameters; the Spearman method was used to analyze the correlation between the semi-quantitative parameters and clinicopathological features of Hodgkin's lymphoma; receiver operating characteristic curve was used to analyze the predictive value of the semi-quantitative parameters for poor prognosis of Hodgkin's lymphoma patients. *Results:* Mean SUV_{max}, MTV, and TLG of the 148 cases of Hodgkin's lymphoma were 7.26 ± 2.38, 12.46 ± 3.14 cm^3, and 76.83 ± 18.56 g, respectively. Significant variations in the Ann Arbor stage and clinical classification were observed with different levels of semi-quantitative parameters ($P < 0.05$). The semi-quantitative parameters were not correlated with age and gender ($P > 0.05$) but positively correlated with Ann Arbor stage and clinical classification ($P < 0.05$). These parameters in the poor prognosis group were higher than those in the good prognosis group ($P < 0.05$). The area under the curve (AUC) of SUV_{max}, MTV, and TLG in predicting the poor prognosis group was 0.881, 0.875, and 0.838, with cut-off values of 7.264, 12.898 cm^3, and 74.580g, as well as specificity of 88.8%, 84.0%, and 78.4%, and sensitivity of 87.0%, 87.0%, and 78.3%, respectively; the AUC of the combined prediction was 0.986, with a specificity of 97.6% and sensitivity of 86.3%. *Conclusion:* The semi-quantitative 18F-FDG PET/CT parameters provide valuable insights for Hodgkin's lymphoma prognosis assessment.

Keywords: Hodgkin's lymphoma; 18F-fluorodeoxyglucose positron emission tomography-computed tomography; Maximum standardized uptake value; Metabolic tumor volume; Total lesion glycolysis; Prognosis

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1. Introduction

Lymphoma is primarily classified into Hodgkin's and non-Hodgkin's lymphoma, representing malignant tumors affecting lymph nodes or lymphoid tissue [1]. Hodgkin's lymphoma constitutes a group of severe blood system diseases. Currently, its diagnosis mainly relies on pathological findings, laboratory tests, and imaging studies [2]. While comprehensive treatments, including chemotherapy and radiotherapy, have led to high long-term remission rates for Hodgkin's lymphoma patients, some patients remain susceptible to relapse, eventually resulting in fatal outcomes [3]. Therefore, it is necessary to identify effective indicators and parameters for guiding treatment decisions and determining prognosis.

Among the diagnostic tools available, 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET/CT) imaging stands out as a common molecular functional imaging technique that has been applied in various diseases, including lymphoma. It plays a pivotal role in diagnosing and assessing the prognosis of different malignant tumors and has significant implications for clinical staging [4,5]. The semi-quantitative parameters of 18F-FDG PET/CT imaging lesions mainly encompass maximum standardized uptake value (SUV_{max}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) [6]. Nevertheless, the current utility of SUV_{max}, MTV, and TLG values obtained through 18F-FDG PET/CT imaging in predicting the prognosis of Hodgkin's lymphoma patients warrants further investigation.

Hence, this study aims to explore the correlation between SUV_{max}, MTV, and TLG values and the clinicopathological characteristics of Hodgkin's lymphoma patients, as well as their predictive value in assessing the prognosis of these patients. The objective is to provide valuable insights into the prediction of Hodgkin's lymphoma patients' prognosis through the development of reliable new metrics.

2. Materials and Methods

2.1. General information

A retrospective analysis of 18F-FDG PET/CT scans was conducted from October 2014 to October 2015. During this period, 148 patients were diagnosed with Hodgkin's lymphoma through PET/CT imaging and lymph node biopsy. These patients had an age range of 19–56 years, with an average age of 44.84 ± 8.72 years. Of the total, 91 were male, and 57 were female.

Inclusion criteria:

(1) Patients who met the diagnostic criteria and were clinically diagnosed with Hodgkin's lymphoma [7].
(2) Patients were newly diagnosed, and their case data were complete.
(3) No radiotherapy or chemotherapy had been administered before the 18F-FDG PET/CT imaging examination.
(4) This study received approval from the hospital's clinical research ethics committee, and all research subjects participated voluntarily.

Exclusion criteria:

(1) Individuals with infectious diseases and other tumors.
(2) The time interval between 18F-FDG PET/CT imaging examination and biopsy exceeded 2 hours.
(3) Pregnant or lactating women.

Patient data were collected and organized, primarily including gender, age, Ann Arbor stage, and clinical classification.

2.2. 18F-FDG PET/CT imaging and image analysis

The VCT64 PET/CT scanner produced by GE Company of the United States was employed for imaging

analysis. The imaging agent, 18F-FDG, was supplied by the PET Center of the Department of Nuclear Medicine at the First Affiliated Hospital of Xinjiang Medical University, with a radiochemical purity exceeding 95%. To prepare for the examination, subjects refrained from eating or drinking for at least 6 hours and ensured fasting blood sugar was below 7.8 mmol/L. 18F-FDG was administered intravenously through the cubital vein based on body weight. Following the injection, patients rested in a dark, warm, and quiet environment for 50 minutes.

A standard PET/CT scan (from the middle of the femur to the top of the skull) was conducted after emptying the bladder. If necessary, lower limbs or sole scans were added. The CT slice thickness was 3.75 mm, with an acquisition voltage of 140 kV. PET imaging was performed in 3D, collecting a total of 5 to 7 beds, with each bed scanned for 3 to 4 minutes. Two experienced imaging physicians jointly analyzed PET/CT images to assess lesion size, location, density, shape, and FDG metabolism. The densest accumulation area among the largest lymph nodes in the body was selected, and an appropriate area of interest was placed to avoid adjacent blood vessels, necrotic areas, and lesion edges, followed by measuring its SUV_{max}, mean standardized uptake value (SUV_{mean}), MTV value, and TLG were calculated using the equation $TLG = SUV_{mean} \times MTV$.

2.3. Treatment and follow-up

All patients underwent 6 courses of first-line BEACOPP regimen (bleomycin + etoposide + doxorubicin/adriamycin + cyclophosphamide + vincristine/oncovin + procarbazine + prednisone) or ABVD regimen (doxorubicin/adriamycin + bleomycin + vinblastine + dacarbazine/DTIC) chemotherapy, and 29 cases received radiotherapy following chemotherapy. Patients with Hodgkin's lymphoma were followed up for 5 years through telephone, home visits, and outpatient visits, with the follow-up period ending in October 2020. Tumor recurrence or death was determined based on imaging examinations, histopathological examinations, and follow-up results. Based on the prognosis, 148 Hodgkin's lymphoma patients were categorized into a good prognosis group (125 cases) and a poor prognosis group (23 cases).

2.4. Statistical analysis

Statistical analysis was performed using SPSS 23.0. Measurement data, following a normal distribution, were expressed as mean ± standard deviation (SD). The *t*-test compared data between two groups. Count data were expressed as [*n* (%)] and compared using the χ^2 test. Spearman's method analyzed the correlation between SUV_{max}, MTV, TLG, and clinical pathological characteristics in Hodgkin's lymphoma patients. Receiver operator characteristic (ROC) curves assessed the predictive value of SUV_{max}, MTV, and TLG for poor prognosis in Hodgkin's lymphoma patients. A *P*-value less than 0.05 indicated statistical significance.

3. Results

3.1. 18F-FDG PET/CT manifestations in patients with Hodgkin's lymphoma

Patients with Hodgkin's lymphoma exhibited increased FDG metabolism in the enlarged lymph nodes at the corresponding site, as shown in **Figure 1**.

3.2. Comparison of clinicopathological characteristics in Hodgkin's lymphoma patients with different SUV_{max}, MTV, and TLG levels

The SUV_{max}, MTV, and TLG of the 148 Hodgkin's lymphoma patients were 7.26 ± 2.38, 12.46 ± 3.14 cm^3, and 76.83 ± 18.56 g, respectively. There were 76 patients with high SUV_{max} levels and 72 patients with low SUV_{max} levels. Additionally, there were 74 patients with high MTV levels and 74 patients with low MTV levels, as well as 73 patients with high TLG levels and 75 patients with low TLG levels. The clinicopathological

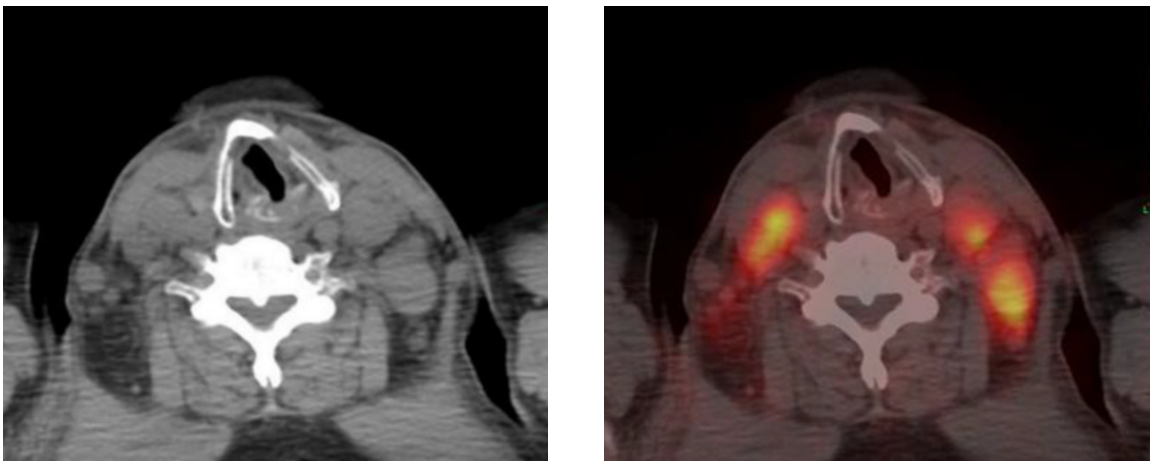


Figure 1. 18F-FDG PET/CT performance of patients with Hodgkin's lymphoma (**left**: CT imaging; **right**: PET imaging)

characteristics of Hodgkin's lymphoma patients with different SUV_{max}, MTV, and TLG levels were analyzed and compared. The results revealed no statistically significant differences in age and gender among Hodgkin's lymphoma patients with varying SUV_{max}, MTV, and TLG levels ($P > 0.05$). However, when comparing Ann Arbor staging and clinical classification of Hodgkin's lymphoma patients with different SUV_{max}, MTV, and TLG levels, statistically significant differences were observed ($P < 0.05$), as shown in **Table 1**.

Table 1. Comparison of clinicopathological characteristics in Hodgkin's lymphoma patients with different SUV_{max}, MTV, and TLG levels [*n* (%)]

Group	*n*	Age		Gender		Ann Arbor staging		Clinical classification	
		≤ 45 (*n* = 86)	> 45 (*n* = 62)	Male (*n* = 91)	Female (*n* = 57)	I/IIA (*n* = 94)	IIB/IVB (*n* = 54)	Classic type (*n* = 119)	Nodular lymphocyte-predominant type (*n* = 29)
SUV_{max} high level	76	48 (63.16)	28 (36.84)	50 (65.79)	26 (34.21)	28 (36.84)	48 (63.16)	70 (92.11)	6 (7.89)
SUV_{max} low level	72	38 (52.78)	34 (47.22)	41 (56.94)	31 (43.06)	66 (91.67)	6 (8.33)	49 (68.06)	23 (31.94)
χ^2	-	1.637		1.221		47.955		13.573	
P	-	0.201		0.269		0.000		0.000	
MTV high level	74	44 (59.46)	30 (40.54)	45 (60.81)	29 (39.19)	28 (37.84)	46 (62.16)	68 (91.89)	6 (8.11)
MTV low level	74	42 (56.76)	32 (43.24)	46 (62.16)	28 (37.84)	66 (89.19)	8 (10.81)	51 (68.92)	23 (31.08)
χ^2	-	0.111		0.029		42.102		12.394	
P	-	0.739		0.866		0.000		0.000	
TLG high level	73	45 (61.64)	28 (38.36)	41 (56.16)	32 (43.94)	26 (35.62)	47 (64.38)	69 (94.52)	4 (5.48)
TLG low level	75	41 (54.67)	34 (45.33)	50 (66.67)	25 (33.33)	68 (90.67)	7 (9.33)	50 (66.67)	25(33.33)
χ^2	-	0.740		1.723		48.377		18.217	
P	-	0.390		0.189		0.000		0.000	

3.3. Correlation between SUV_{max}, MTV, TLG, and clinicopathological characteristics in Hodgkin's lymphoma patients

Analysis using the Spearman method (**Table 2**) indicated that SUV_{max}, MTV, and TLG had no correlation with age and gender ($P > 0.05$), but were positively correlated with Ann Arbor stage and clinical classification ($P < 0.05$).

Table 2. Correlation between SUV_{max}, MTV, TLG, and clinicopathological characteristics in Hodgkin's lymphoma patients

Index		Age	Gender	Ann Arbor staging	Clinical classification
SUV_{max}	*r*	0.105	0.091	0.569	0.303
	P	0.203	0.272	0.000	0.000
MTV	*r*	0.027	0.014	0.533	0.289
	P	0.741	0.867	0.000	0.000
TLG	*r*	0.071	0.108	0.572	0.351
	P	0.393	0.192	0.000	0.000

3.4. Comparison of SUV_{max}, MTV, and TLG values in different prognostic groups of Hodgkin's lymphoma

Table 3 shows that SUV_{max}, MTV, and TLG values in the poor prognosis group were significantly higher than those in the good prognosis group ($P < 0.05$).

Table 3. Comparison of SUV_{max}, MTV, and TLG values in different prognostic groups of Hodgkin's lymphoma (mean ± SD)

Group	Number of examples	SUV_{max}	MTV (cm^3)	TLG (g)
Good prognosis group	125	6.24 ± 1.28	9.78 ± 2.82	60.22 ± 19.75
Poor prognosis group	23	8.05 ± 1.63	14.97 ± 4.71	92.54 ± 23.68
t		5.960	7.199	6.986
P		0.000	0.000	0.000

3.5. Predictive value of SUV_{max}, MTV, and TLG for poor prognosis in Hodgkin's lymphoma patients

ROC curves were plotted using SUV_{max}, MTV, and TLG as test variables for Hodgkin's lymphoma patients (**Figure 2**). The results indicated that SUV_{max}, MTV, and TLG had an area under the curve (AUC) of 0.881 (95% CI: 0.778–0.985), 0.875 (95% CI: 0.791–0.959), and 0.838 (95% CI: 0.743–0.933), respectively. The null hypothesis (AUC = 0.5) was rejected with a significance level of $P = 0.000$. The cutoff values of SUV_{max}, MTV, and TLG were 7.264, 12.898 cm^3, and 74.580 g, with specificities of 88.8%, 84.0%, and 78.4%, and sensitivities of 87.0%, 87.0%, and 78.3%, respectively. When the three variables were combined, the AUC reached 0.986 (95% CI: 0.965–1.000), with a specificity of 97.6% and a sensitivity of 86.3%.

4. Discussions

Hodgkin's lymphoma is characterized by atypical cell morphology in the bone marrow and lymph nodes, typically manifesting as painless lymphadenopathy [8]. It frequently occurs in cervical and mediastinal lymph nodes and can extend to other regional lymph nodes. In advanced stages, it may affect the liver, bone marrow, spleen, and more [9]. While advancements in diagnostic and treatment technologies, including targeted therapies, new chemotherapy drugs, radiotherapy, and liver cell transplantation, have significantly improved the 5-year survival rate of Hodgkin's lymphoma patients, some individuals still face poor prognoses [10]. Therefore, accurately assessing prognosis, developing personalized treatment plans, and reducing treatment risks remain

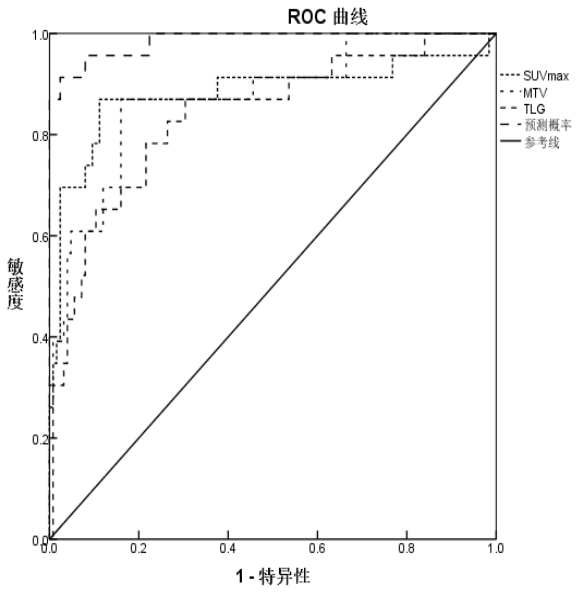


Figure 2. Predictive value of SUV_{max}, MTV, and TLG for poor prognosis in Hodgkin's lymphoma patients

challenges in Hodgkin's lymphoma diagnosis and treatment.

In comparison to traditional imaging methods, PET/CT is a cutting-edge molecular imaging technology that combines anatomy and function. During the examination, CT offers structural and anatomical information about lesions, while PET provides details about their metabolic and functional characteristics. These aspects complement each other [11]. The commonly used glucose metabolism imaging agent, 18F-FDG, leverages variations in glucose metabolism levels between normal and tumor cells. Tumor cells, being more metabolically active, accumulate larger amounts of 18-FDG. PET/CT scans provide clear visualization of tumor location, size, shape, and radioactive distribution [12,13]. Research has shown that SUV_{max}, a metabolic parameter derived from PET/CT imaging, can indirectly indicate tumor cell proliferation based on FDG metabolism levels. MTV represents the tumor volume with higher glucose metabolism, and TLG reflects the tumor load [14].

In this study, SUV_{max}, MTV, and TLG were all significantly correlated with the Ann Arbor stage and clinical classification of Hodgkin's lymphoma. These findings suggest that higher levels of FDG metabolism and tumor cell volume correspond to increased tumor cell proliferation activity, resulting in accelerated growth and a higher likelihood of distant metastasis. This is consistent with the study by Li *et al.* [15], which found similar relationships between these parameters and pathological features such as the Ann Arbor stage and maximum length diameter of primary mediastinal large B-cell lymphoma. Moreover, the results of this study indicated that patients with poor prognosis in Hodgkin's lymphoma tend to exhibit higher levels of SUV_{max}, MTV, and TLG. This reinforces the notion that elevated SUV_{max}, MTV, and TLG correspond to accelerated sugar metabolism, cell division, and an increased degree of malignancy, all of which are unfavorable for patient prognosis. This study further shows that all three parameters detected by 18F-FDG PET/CT imaging hold predictive value for the prognosis of Hodgkin's lymphoma, with SUV_{max} exhibiting the highest predictive value (AUC = 0.881). Notably, combining all three parameters significantly improves specificity.

Wang *et al*. similarly emphasized the importance of 18F-FDG PET/CT in evaluating and predicting the prognosis of Hodgkin's lymphoma patients before autologous stem cell transplantation [16], aligning with

the findings of this study. This suggests that SUV_{max}, MTV, and TLG can be used collectively as reference indicators to predict the poor prognosis of Hodgkin's lymphoma patients. When clinical 18F-FDG PET/CT imaging reveals $SUV_{max} > 7.264$, MTV > 12.898 cm^3, and TLG > 74.580 g, it may indicate a poor prognosis for the patient.

In conclusion, the semi-quantitative parameters, SUV_{max}, MTV, and TLG, derived from 18F-FDG PET/CT imaging, exhibit significant correlations with Ann Arbor staging and clinical classification in Hodgkin's lymphoma patients. Elevated SUV_{max}, MTV, and TLG values are associated with poor prognosis. These parameters hold promise for predicting and evaluating the prognosis of Hodgkin's lymphoma patients. Clinically, they can serve as valuable reference indicators for identifying patients at risk of a poor prognosis. However, it is important to note that this study is retrospective and based on a relatively small number of cases. Additionally, the application of 18F-FDG PET/CT in Hodgkin's lymphoma may have certain limitations due to inconsistent evaluation standards, thus necessitating further research to determine its clinical value.

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A Study on Enhancing Pancreatic Islet Function in Type 2 Diabetes and Coronary Heart Disease Patients with Liraglutide and Metformin Combination Therapy

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Abstract: *Objective:* To investigate the impact of combining liraglutide with metformin on the enhancement of pancreatic islet function in patients with type 2 diabetes and coronary heart disease. *Methods:* 60 patients with type 2 diabetes and coronary heart disease admitted from February 2022 to August 2023 were selected as research subjects. They were randomly assigned to either control or treatment groups, with 30 patients in each. The control group received metformin alone, while the treatment group received liraglutide in combination with metformin. Various indicators, including blood sugar levels, pancreatic islet function, and cardiac function between the two groups were compared. *Results:* The results of FPG, 2hPG, HbA1c, HOMA-IR, NT-proBNP, and LVEDD in the treatment group were lower than those in the control group, whereas the values of FINS, HOMA-β, E/A, and LVEF in the treatment group were higher than those in the control group ($P < 0.05$). *Conclusion:* The use of liraglutide in combination with metformin significantly benefits patients with type 2 diabetes and coronary heart disease. It leads to improved pancreatic islet function, better blood sugar control, and enhanced cardiac function. This combination therapy is recommended for clinical adoption.

Keywords: Liraglutide; Metformin; Type 2 diabetes; Coronary heart disease; Pancreatic islet function

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1. Introduction

Type 2 diabetes affects approximately 95% of diabetic patients. Prolonged high blood sugar levels can lead to chronic damage to the cardiovascular system and further complicate coronary heart disease [1,2]. The combination of type 2 diabetes and coronary heart disease is prevalent in clinical practice, hastening the progression of the patient's condition and posing a serious threat to their health. Therefore, timely and effective clinical treatment is crucial to delay the disease's advancement.

Metformin is currently the primary clinical treatment for type 2 diabetes, mainly working by regulating glucose processing in various systems [3-5]. However, its effectiveness as a standalone treatment is often

unsatisfactory, necessitating combination therapy with other drugs. Liraglutide, a human glucagon-like peptide-1 (GLP-1) analog, can enhance the glucose concentration-dependent secretion of insulin from pancreatic β cells, thereby improving pancreatic islet function [6]. This study aims to analyze the impact of liraglutide in combination with metformin on islet function in patients with type 2 diabetes and coronary heart disease. To achieve this, 80 patients were observed as part of the study.

2. Materials and methods

2.1. General information

A total of 60 patients with type 2 diabetes and coronary heart disease admitted from February 2022 to August 2023 were included as the research subjects of this study. The random number table method was employed to divide the patients into control and treatment groups, with 30 cases in each. In the control group, there were 18 males and 12 females, aged 46–75 (mean age 58.13 ± 3.09) years, with disease duration of 2–11 (mean duration 6.32 ± 0.60) years; in the treatment group, there were 17 males and 13 females, aged 47–76 (mean age 58.20 ± 3.11) years, with disease duration 2–10 (mean duration 6.29 ± 0.58) years. A comparison of the baseline data between the two groups showed no significant differences ($P > 0.05$), indicating comparability.

Inclusion criteria included patients meeting the diagnostic criteria for type 2 diabetes and coronary heart disease [7,8], confirmed by various auxiliary examinations, aged 40–80 years, with complete clinical data. Exclusion criteria included patients with type 1 diabetes, complications such as ketoacidosis, secondary hyperlipidemia, and others, patients with the presence of organic heart disease, severe liver, or kidney insufficiency, patients who are unable to communicate effectively with medical staff, pregnant or lactating women, patients who have taken drugs or hormones that affect weight during menstruation, and patients who are allergic to the drugs used in the study.

2.2. Method

All patients received standard treatment for coronary heart disease, including anti-thrombotic, antihypertensive, and lipid-lowering treatments, as well as a low-salt, low-fat diet, and refrained from smoking or alcohol consumption while engaging in appropriate exercise.

The control group received metformin alone, in the form of metformin hydrochloride tablets (Sino-American Shanghai Bristol-Myers Squibb Pharmaceutical Co., Ltd., national drug approval number H20023370, 0.5 g × 20 tablets). This was taken orally three times a day, before breakfast, lunch, and dinner, at a dosage of 0.5 g per time.

The treatment group received liraglutide in combination with metformin, with the same manufacturer, usage, and dosage of metformin as in the control group. Liraglutide injection (Novo Nordisk, Denmark, national drug approval number J20160037, 3 mL:18 mg) was administered subcutaneously once a day, starting at 0.6 mg and adjusted according to the patient's tolerance, not exceeding 1.8 mg. Both groups continued their treatment for three months, with close monitoring of clinical symptoms and immediate medical attention in case of discomfort.

2.3. Observation indicators

The following indicators between the two groups were compared:

(1) Blood glucose indicators: Fasting blood glucose (FPG), two hours postprandial blood glucose (2hPG), and glycated hemoglobin (HbA1c). FPG and 2hPG were measured using the glucose oxidase method, while HbA1c was analyzed with a glycosylated hemoglobin analyzer using high-performance liquid

chromatography (HPLC).

(2) Pancreatic islet function indicators: Fasting insulin (FINS), insulin resistance index (HOMA-IR), and pancreatic islet β-cell function index (HOMA-β). These were determined using an immunoenzyme-linked adsorption method. HOMA-IR was calculated using the formula FPG × FINS ÷ 22.5, and HOMA-β was calculated as 20 × FINS ÷ (FPG - 3.5).

(3) Cardiac function indicators: Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), left ventricular early/late diastolic peak velocity ratio (E/A ratio), left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD). NT-proBNP was measured using a fully automatic chemiluminescence immunoassay analyzer with the chemiluminescence method. Other indicators were assessed using echocardiography.

2.4. Statistical processing

SPSS 20.0 was used for data analysis. All results followed a normal distribution. Measurement results were expressed as mean ± standard deviation (SD), and a *t*-test was conducted. Counting results were described as %, and a χ^2 test was applied. When the result was $P < 0.05$, it indicated a statistically significant difference.

3. Results

3.1. Comparison of blood glucose indicators between the two groups

Before treatment, there was no significant difference in the levels of FPG, 2hPG, and HbA1c between the two groups ($P > 0.05$); after treatment, the levels of the above indicators in the treatment group were at a lower level than those in the control group ($P < 0.05$). See **Table 1** for details.

Table 1. Comparison of blood glucose indicators between the two groups before and after treatment (mean ± SD)

Group	*n*	FPG (mmol/L)		2hPG (mmol/L)		HbA1c (%)	
		Before	After	Before	After	Before	After
Treatment group	30	8.41 ± 0.82	5.28 ± 0.49	12.59 ± 1.02	7.76 ± 0.74	9.21 ± 0.89	7.39 ± 0.70
Control group	30	8.37 ± 0.79	6.06 ± 0.57	12.52 ± 1.00	8.58 ± 0.82	9.18 ± 0.87	8.04 ± 0.77
t	-	0.192	5.684	0.268	4.066	0.132	3.421
P	-	0.848	0.000	0.789	0.000	0.895	0.001

3.2. Comparison of pancreatic islet function indicators between the two groups

Before treatment, there was no significant difference in the levels of FINS, HOMA-IR, and HOMA-β between the two groups ($P > 0.05$); after treatment, the FINS and HOMA-β values in the treatment group were higher than those in the control group, and the levels of HOMA-IR were lower than those of the control group ($P < 0.05$). See **Table 2** for details.

3.3. Comparison of cardiac function indicators between the two groups

Table 3 shows that the NT-proBNP level, E/A reaction, LVEF, and LVEDD for both the treatment group and the control group had no significant differences before treatment. However, NT-proBNP and LVEDD of the treatment group were lower than the control group, whereas E/A and LVEF were higher than the control group ($P < 0.05$).

Table 2. Comparison of pancreatic islet function indicators between the two groups before and after treatment (mean ± SD)

Group	*n*	FINS (pmol/L)		HOMA-IR		HOMA-β	
		Before	After	Before	After	Before	After
Treatment Group	30	4.61 ± 0.43	9.58 ± 0.92	4.16 ± 0.38	2.82 ± 0.25	16.48 ± 1.31	38.57 ± 3.52
Control group	30	4.66 ± 0.45	6.94 ± 0.66	4.21 ± 0.40	3.47 ± 0.31	16.52 ± 1.33	32.16 ± 2.98
t	-	0.440	12.771	0.496	8.940	0.117	7.612
P	-	0.662	0.000	0.622	0.000	0.907	0.000

Table 3.

Group	*n*	NT-proBNP (mmol/L)		E/A ratio		LVEF (%)		LVEDD (mm)	
		Before	After	Before	After	Before	After	Before	After
Treatment Group	30	583.15 ± 52.02	404.67 ± 35.13	1.42 ± 0.11	0.98 ± 0.09	47.62 ± 4.43	68.05 ± 6.47	62.04 ± 5.97	51.83 ± 4.85
Control group	30	584.07 ± 52.26	441.50 ± 35.82	1.40 ± 0.10	0.83 ± 0.07	47.70 ± 4.45	60.49 ± 5.71	62.10 ± 5.99	56.34 ± 5.30
t	-	0.068	4.021	0.737	7.206	0.070	4.799	0.039	3.438
P	-	0.946	0.000	0.464	0.000	0.945	0.000	0.969	0.001

4. Discussions

Diabetes is a chronic disease characterized by hyperglycemia, with the majority of cases being type 2 diabetes. The incidence of the disease is increasing annually, and the age of onset is progressively advancing. It not only affects the health of patients but also places a substantial burden on society [9]. One of the main pathogenic mechanisms of type 2 diabetes is pancreatic β-cell dysfunction, leading to inadequate insulin secretion. The continuous elevation of blood sugar levels results in metabolic dysfunction, affecting vascular permeability and, in turn, contributing to the development of coronary heart disease [10]. Maintaining blood sugar within a reasonable range can reduce damage to the vascular endothelium and support the overall function of the heart [11]. Therefore, clinical treatment should prioritize blood sugar control.

Metformin is a widely used hypoglycemic drug in clinical practice. Its primary mode of action involves increasing the glucose utilization rate by tissue cells and inhibiting hepatic glycogen generation production and intestinal wall cell glucose uptake [12]. While it has a specific effect, it may not be as effective for some patients, necessitating a combination with other medications.

This study demonstrated that the treatment group had lower values for FPG, 2hPG, HbA1c, HOMA-IR, NT-proBNP, and LVEDD compared to the control group, while the treatment group exhibited higher levels of FINS, HOMA-β, E/A ratio, and LVEF ($P < 0.05$). This suggests that the combination of liraglutide and metformin is effective in controlling blood sugar levels and improving pancreatic islet function. Liraglutide, an endogenous incretin hormone, increases the number and function of pancreatic beta cells, promoting insulin release and enhancing blood sugar control. It also prolongs gastric emptying time, contributing to blood sugar stability [13]. Studies have indicated that liraglutide can enhance cardiac function in patients [14]. Liraglutide, when combined with metformin, exhibits a synergistic effect in patients with type 2 diabetes and coronary heart disease. This combination helps regulate blood sugar levels and protects vascular endothelial function, ultimately reducing damage to myocardial cells and improving metabolism and cardiac function in patients [15].

In summary, the use of liraglutide in combination with metformin for treating patients with type 2 diabetes and coronary heart disease has a significant and positive effect. It effectively enhances pancreatic islet function, leading to better control of blood sugar levels and improved cardiac function. Thus, it is recommended for clinical adoption.

Disclosure statement

The author declares no conflict of interest.

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The Effect of Partial Gastrectomy in the Treatment of Early Gastric Cancer and Its Impact on the Gastrointestinal Function of Patients

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Abstract: *Objective:* To investigate the impact of partial gastrectomy on gastrointestinal function in the treatment of patients with early gastric cancer. *Methods:* A sample of 20 patients with early-stage gastric cancer treated from January 2022 to January 2023 was randomly divided into two groups. Group A underwent partial gastrectomy, while Group B underwent distal subtotal gastrectomy. Surgical outcomes, complication rates, BMI indices, and quality of life were compared. *Result:* All surgical outcomes of patients with early gastric cancer in group A were better than those in group B ($P < 0.05$); the postoperative complication rate for early gastric cancer in group A was lower than that in group B ($P < 0.05$); the BMI index for patients with early gastric cancer in group A was higher than that in group B at different times ($P < 0.05$); the postoperative quality of life (SF-36) score of group A for early gastric cancer was higher than that of group B ($P < 0.05$). *Conclusion:* Partial gastrectomy for patients with early gastric cancer can increase BMI, optimize surgical outcomes, improve gastric function, and enhance the quality of life for gastric cancer patients.

Keywords: Early gastric cancer; Partial gastrectomy; Gastrointestinal function

Online publication: November 22, 2023

1. Introduction

The incidence of gastric cancer is high among digestive system tumor diseases. In patients with early-stage gastric cancer, the disease is confined to the mucosal and submucosal layers, and no invasive metastasis occurs. Clinical analysis indicates that patients with early gastric cancer often experience atypical symptoms, such as abdominal distension, abdominal pain, and reduced appetite [1]. As diagnostic technology continues to advance, the early detection rate of gastric cancer has been increasing yearly. Therefore, it is essential to explore efficient diagnosis and treatment options for early gastric cancer to extend the survival period of gastric cancer patients.

Radical gastrectomy is a clinical approach for treating early gastric cancer, and it has yielded a 5-year postoperative survival rate of 80%–90% [2]. However, there are safety concerns associated with implementing radical resection treatment. Gastric cancer patients may have gastrointestinal-related conditions, and as their

gastrointestinal function deteriorates, it may affect food absorption, leading to secondary malnutrition and weight loss, ultimately reducing postoperative survival rates for gastric cancer patients. Some scholars suggest optimizing and refining radical gastrectomy by minimizing the resection range of gastric cancer lesions to enhance the recovery outcomes of gastric cancer patients. This study employs a sample of 20 cases of early-stage gastric cancer treated from January 2022 to January 2023 to explore the effectiveness of partial gastrectomy.

2. Materials and methods

2.1. General information

Twenty cases of early-stage gastric cancer treated from January 2022 to January 2023 were selected as samples and randomly divided into two groups. There was no difference in the data of early gastric cancer patients in group A and group B ($P > 0.05$), as shown in **Table 1**.

Table 1. Early gastric cancer data analysis

Group	*n*	Gender (%)		Age (years)		Tumor diameter (cm)	
		Male	Female	Range	Mean	Range	Mean
Group A	10	6 (60.00)	4 (40.00)	47–80	64.11 ± 2.85	1–7	4.31 ± 1.22
Group B	10	5 (50.00)	5 (50.00)	47–81	64.13 ± 2.83	1–8	4.29 ± 1.21
χ^2 / *t*		0.2020		0.0157		0.0368	
P		0.6531		0.9876		0.9710	

2.2. Inclusion and exclusion standards

Inclusion criteria included patients diagnosed with gastric cancer using gastroscopy and CT, patients with indications for gastric cancer resection, stage II–III gastric cancer according to Tumor, Node, Metastasis (TNM) staging system, and informed consent.

Exclusion criteria included patients with coagulation disorder, severe complications of gastric cancer, and other malignant tumors.

2.3. Treatment methods

Group A patients underwent partial gastrectomy. Patients were placed in a supine position, and tracheal intubation was performed. An abdominal midline incision was made to access the stomach and identify the location and extent of the gastric tumor. Resection began 5 cm above the tumor and extended to a point 3 cm from the pylorus. This procedure involved complete lesion removal and lymph node dissection. Notably, the operation prioritized the preservation of the pyloric branch, hepatic branch, celiac branch, and other vagus nerves. After the partial resection, the gastric pyloric vestibule and the remaining greater curvature of the stomach were anastomosed end-to-end. The suturing was completed, and a drainage tube was placed before closing the abdominal cavity. Postoperative prophylactic anti-infective drugs were administered.

Group B underwent distal subtotal gastrectomy. Patients were placed in a supine position, and tracheal intubation was performed. An abdominal midline incision was made to access the stomach and abdominal cavity. The precise location and extent of the tumor were determined, along with an assessment of tumor tissue infiltration into adjacent tissues and adhesion conditions. Resection was performed in the distal area more than 5 cm above the tumor, involving the removal of most of the distal stomach and thorough lymph node dissection.

Gastrointestinal tract reconstruction was carried out, suturing was completed, a drainage tube was left in place, and the abdominal cavity was closed. Postoperative prophylactic anti-infective drugs were administered.

2.4. Observation indicators

The observation indicators in this study include:

(1) Surgical outcomes: Operation time, first time out of bed, first flatulence, length of hospital stay, and intraoperative bleeding.
(2) Complication rates: Gastric retention, venous thrombosis, dumping syndrome, reflux esophagitis.
(3) BMI indices: Recorded at two weeks, four weeks, eight weeks, and 16 weeks after surgery.
(4) Quality of life: SF-36 score positively correlates with quality of life in patients with early gastric cancer.

2.5. Statistical research

The data of patients with early gastric cancer were processed with SPSS 21.0. Count data were recorded as % and the χ^2 test was performed. Measurement data were recorded as mean ± standard deviation (SD), and the *t*-test was performed. There is statistical significance when $P < 0.05$.

3. Results

3.1. Surgical outcomes

Table 2 shows that all surgical outcomes of patients with early gastric cancer in group A were better than those in group B ($P < 0.05$).

Table 2. Comparison of surgical outcomes for patients with early gastric cancer (mean ± SD)

Group	Operation time (min)	Getting out of bed for the first time (d)	First exhaust (h)	Length of stay (d)	Intraoperative blood loss (mL)
Group A (n = 10)	108.84 ± 11.85	2.84 ± 0.61	17.24 ± 1.58	7.21 ± 1.52	275.36 ± 22.61
Group B (n = 10)	120.49 ± 14.88	3.92 ± 0.82	21.88 ± 1.96	9.33 ± 1.69	336.25 ± 28.36
t	1.9367	3.3417	5.8283	2.9494	5.3088
P	0.0686	0.0036	0.0000	0.0086	0.0000

3.2. Complication rates

The postoperative complication rate of patients with early gastric cancer in group A was lower than in group B ($P < 0.05$), as shown in **Table 3**.

Table 3. Comparison of complication rates in patients with early gastric cancer [n (%)]

Group	Gastric retention	Venous thrombosis	Dumping syndrome	Reflux esophagitis	Incidence
Group A (n = 10)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Group B (n = 10)	1 (10.00)	1 (10.00)	1 (10.00)	1 (10.00)	4 (40.00)
χ^2	-	-	-	-	5.0000
P	-	-	-	-	0.0253

3.3. BMI indices at different postoperative periods

Table 4 shows that Group A's BMI indices were higher than Group B's at different postoperative periods ($P < 0.05$).

Table 4. Comparison of BMI indices at different postoperative periods (mean ± SD)

Group	2 weeks after surgery (kg/m^2)	4 weeks after surgery (kg/m^2)	8 weeks after surgery (kg/m^2)	16 weeks after surgery (kg/m^2)
Group A (n = 10)	18.42 ± 1.02	19.33 ± 1.09	20.35 ± 1.25	21.84 ± 1.85
Group B (n = 10)	14.61 ± 0.98	15.86 ± 1.07	17.23 ± 1.11	19.18 ± 1.13
t	8.5177	7.1841	5.9019	3.8803
P	0.0000	0.0000	0.0000	0.0011

3.4. Quality of life

After surgery, the SF-36 score in group A was higher than in group B ($P < 0.05$), as indicated in **Table 5**.

Table 5. Comparison of quality of life among patients with early gastric cancer before and after treatment (mean ± SD)

Group	Good health (points)		Mental health (points)		Body functions (points)		Social functions (points)	
	Before	After	Before	After	Before	After	Before	After
Group A (n = 10)	52.84 ± 2.15	79.61 ± 3.28	51.94 ± 2.54	78.28 ± 3.36	53.16 ± 2.42	79.36 ± 3.42	54.11 ± 2.82	80.36 ± 3.58
Group B (n = 10)	52.81 ± 2.19	71.88 ± 2.94	51.88 ± 2.55	71.79 ± 2.96	53.19 ± 2.39	72.81 ± 3.18	54.13 ± 2.81	72.96 ± 3.29
t	0.0309	5.5495	0.0527	4.5833	0.0279	4.4353	0.0159	4.8129
P	0.9757	0.0000	0.9585	0.0002	0.9781	0.0003	0.9875	0.0001

4. Discussion

In the context of increasing life and work-related pressures, the annual incidence rate of gastric cancer is on the rise, leading to shorter survival periods for patients. A summary analysis reveals that gastric cancer is associated with various factors:

(1) Dietary habits: Regional variations in the incidence of gastric cancer are evident, with high occurrences in eastern coastal and northwest regions, and lower numbers in the south. Individuals who consume pickled, smoked, and grilled foods are exposed to fungi and nitrites, increasing their risk of developing gastric cancer.

(2) *Helicobacter pylori* infection: Over 60% of patients with gastric cancer tested positive for *H. pylori* infection. *H. pylori* can promote the conversion of nitrates into nitrite and other substances, potentially leading to cancer. Infection with *H. pylori* can also cause mucosal epithelial proliferation, further raising the risk of cancer.

(3) Stomach diseases: Individuals with a history of gastritis and gastric polyps are at a higher risk of developing gastric cancer.

(4) Heredity: The incidence rate of gastric cancer is higher in direct relatives compared to the general population [3].

In the early stages of gastric cancer, patients often display no specific signs. Only a small fraction of patients may experience symptoms such as nausea, vomiting, or upper gastrointestinal ulcers, resulting in

delayed treatment [4]. As gastric cancer progresses, patients may develop symptoms such as weight loss, stomach pain, fullness, and abdominal discomfort. Severe cases can lead to fatigue, anemia, weight loss, and malnutrition. Advances in microscopy technology have significantly increased the detection rate of gastric cancer, thereby increasing the number of early gastric cancer surgeries.

During standard gastric cancer surgical treatment, a substantial portion of the gastric body is removed, often exceeding 2/3 of the organ, with thorough lymph node dissection to improve the 5-year survival rate of early gastric cancer patients [5]. However, distal subtotal gastrectomy may impair gastric emptying function, primarily due to resection of the gastric antrum and pylorus during the operation. The procedure involves resection of the distal stomach, mobilization of the duodenal bulb, dissection of the lymph nodes in adjacent stomach areas (including the left gastric artery, duodenal ligament, and common hepatic artery), and potential damage to adjacent nerve plexuses, which can affect blood supply and lead to gastric emptying disorders; resection of most of the distal gastric body can affect gastric peristalsis and gastric contraction, causing gastric dysfunction. In addition, poor intraoperative gastrointestinal decompression can cause long-term high tension in the residual stomach, leaving contractile atony and aggravating gastric emptying disorders.

In recent years, distal partial gastrectomy has gained popularity in the treatment of early gastric cancer. The procedure minimizes the impact on gastrointestinal function, preserves gastric structure, reduces complications, and is associated with better long-term outcomes. After surgery, food does not enter the duodenum and directly reaches the cavity area, thereby reducing gastrointestinal hormone secretion and myenteric plexus stimulation caused by eating, leading to the inhibition of acetylcholine secretion and the protection of gastric emptying function [6]. Relevant literature reports that partial gastrectomy is highly feasible in treating early gastric cancer, optimizing gastric emptying function, and reducing the risk of gastric cancer recurrence [7].

Based on the data analysis in this study, the operation time of patients with early gastric cancer in Group A was 108.84 ± 11.85 minutes, the first time out of bed was 2.84 ± 0.61 days after the operation, the first flatus was 17.24 ± 1.58 hours, total hospitalization time was 7.21 ± 1.52 days, and intraoperative blood loss was 275.36 ± 22.61 mL, which were better than those in group B ($P < 0.05$). Partial gastrectomy involves the removal of only a small portion of the gastric body, resulting in minor surgical trauma, less bleeding during the operation, short postoperative recovery times, and improved surgical indicators. Another set of data showed that the postoperative complication rate of patients with early gastric cancer in group A was 0.00%, which was lower than that in group B (40.00%, $P < 0.05$), which indicates that patients who undergo partial gastrectomy experience significantly lower postoperative complication rates compared to those undergoing distal subtotal gastrectomy. Partial gastrectomy reduces the extent of resection, preserves the typical structure of the stomach, and simultaneously restores gastrointestinal function, leading to little impact on the normal physiological functions of the gastrointestinal tract. Therefore, the operation is recommended as it is safer [8]. Additionally, patients who undergo partial gastrectomy exhibited higher postoperative BMI values as compared to distal subtotal gastrectomy ($P < 0.05$), which persist in the long term. The preservation of normal gastric function in partial gastrectomy helps restore appetite and allows for better nutrient absorption, leading to improved BMI indices [9]. Furthermore, patients who undergo partial gastrectomy also report higher postoperative SF-36 scores ($P < 0.05$), indicating better overall health and quality of life. The preservation of some gastric functions minimizes the impact on digestive function, resulting in improved patient well-being after surgery [10].

In summary, partial gastrectomy for early-stage gastric cancer patients can lead to shorter recovery times, improved gastrointestinal function, and overall better outcomes. It is a valuable approach in the management of early gastric cancer.

Disclosure statement

The authors declare no conflict of interest.

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Assessing the Effectiveness of Montelukast Sodium in Managing Pulmonary Infections in Lung Cancer Patients

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Abstract: *Objective:* To investigate the efficacy of montelukast sodium in the treatment of lung cancer patients with pulmonary infections. *Methods:* A total of 330 patients diagnosed with lung cancer and pulmonary infection, who were admitted to the First Affiliated Hospital of Xi'an Medical University from 2020 to 2022, were selected as research subjects. They were randomly divided into two groups: a control group receiving conventional treatment and an observation group receiving conventional treatment combined with montelukast sodium. Each group consisted of 165 cases. The time required for clinical symptom improvement, the resolution of lung infection signs, and the levels of serum inflammatory factors before and after treatment were compared between the two groups. *Results:* The observation group exhibited significantly faster improvement in clinical symptoms compared to the control group ($P < 0.001$). ELISA assays were conducted to detect the expression levels of IL-1β, IL-6, IL-8, and TNF-α in the serum of both groups at 1 week and 2 weeks into the treatment. The results indicated that, as the treatment progressed, the observation group displayed significantly lower levels of the four serum inflammatory factors compared to the control group ($P < 0.001$). *Conclusion:* Montelukast sodium demonstrates efficacy in the treatment of patients with lung cancer complicated by pulmonary infections. These findings suggest its potential for further verification and clinical application.

Keywords: Lung cancer; Pulmonary infections; Montelukast sodium; Clinical symptoms; Inflammatory factors

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1. Introduction

Lung cancer stands as a prevalent malignancy within the respiratory system. Factors such as smoking, air pollution, occupational exposure, a history of chronic obstructive pulmonary disease (COPD), and family medical history have contributed to a continuous increase in lung cancer incidence year by year [1]. Clinical case data statistics reveal a rising trend in the occurrence of lung infections among lung cancer patients in recent years. It is well-known that infections typically trigger a prominent inflammatory response within the body, leading to the release of various serum inflammatory factors. These, in turn, cause damage to the vascular endothelium and exacerbate the patient's condition.

The advent of emerging targeted therapies and immunotherapy has substantially improved the overall survival of lung cancer patients. However, a significant number of patients eventually experience relapse and develop drug resistance. In this context, researchers have been increasingly uncovering new anti-tumor properties in some older medications. Montelukast sodium, for instance, has demonstrated notable anti-tumor effects in prostate cancer and colon cancer [2,3]. Nevertheless, there is limited research pertaining to its effect on lung cancer.

Therefore, this study endeavors to explore the potential of montelukast sodium in treating patients afflicted with both lung cancer and pulmonary infections. By examining the levels of serum inflammatory factors, this study aims to gain insights into its therapeutic efficacy. This research may offer a novel avenue for the treatment of patients dealing with the dual challenges of lung cancer and pulmonary infections.

2. Materials and methods

2.1. General information

A total of 330 patients diagnosed with lung cancer and concurrent pulmonary infections, who were admitted to the First Affiliated Hospital of Xi'an Medical University between 2020 to 2022, were chosen as the study subjects. These patients were randomly divided into two groups: an observation group and a control group, each comprising 165 cases. The observation group consisted of 92 males and 73 females, with ages ranging from 45 to 90 years old and an average age of 65.03 ± 0.52 years. The control group consisted of 85 males and 80 females, with ages ranging from 39 to 82 years old and an average age of 62.05 ± 0.08 years. General information of the patients are shown in **Table 1**.

Patients in both groups had one or more underlying conditions, primarily including hypertension, COPD, diabetes, and coronary heart disease, among others. There was no statistically significant difference between the two groups regarding lung cancer staging and type ($P > 0.05$). Additionally, all patient data were reviewed and approved by the hospital's ethics committee.

Inclusion criteria encompassed:

(1) Compliance with the diagnostic criteria for lung cancer as defined by the 8th edition of the "International TNM Staging Criteria for Lung Cancer" issued by the International Society for the Study of Lung Cancer in 2015 [4].
(2) Chest CT scans indicate lung lesions characterized by nodules, infiltrates, honeycombing, or reticular patterns, suggesting inflammatory changes.
(3) Clear indications of a lung infection through a combination of pulmonary function tests, blood tests, clinical symptoms, and physical signs.

Exclusion criteria included:

(1) Coexistence with other malignancies.
(2) Concomitant severe heart, liver, kidney, or other organ dysfunction.
(3) Presence of other primary infectious diseases or immune disorders.
(4) Use of targeted drugs or new immune preparations during the study.
(5) Inability to cooperate with clinical treatment or incomplete clinical data.

Table 1. Patients general information

General information	Observation group (n = 165)	Control group (n = 165)	χ^2 value	P value
Gender			0.587	0.44
Male	92	85		
Female	73	80		
Age (years)			1.673	0.196
< 60	59	48		
≥ 60	106	117		
Lung cancer staging			3.68	0.298
I	11	15		
II	32	28		
III	6 1	48		
IV	6 1	74		
Tumor type			8.373	0.38
Adenocarcinoma	6 7	52		
Squamous cell carcinoma	45	7 0		
Small cell lung cancer	30	24		
Other	23	19		

2.2. Research methods

The control group received conventional treatments such as standard chemotherapy, radiotherapy, and anti-infective treatment. The observation group received conventional treatments as well as montelukast sodium (Merck; trade name Singulair; National Drug Approval No. J20130047) at a dosage of 10 mg orally each night before bedtime. The treatment course for both groups extended over a period of 2 weeks.

2.3. Serum inflammatory factors assessment

After 1 and 2 weeks of treatment, 5 mL of fasting median cubital venous blood was collected from both patient groups and serum samples were extracted. Enzyme-linked immunosorbent assay (ELISA) was used to assess interleukins IL-1β, IL-6, and IL-8 levels in the serum as well as tumor necrosis factor-alpha (TNF-α) expression of the patients. The ELISA kit was procured from Beijing Jingmei Bioengineering Co, Ltd., and procedures were conducted following the kit instructions.

2.4. Statistical processing

Data analysis was performed using SPSS 21.0 software. Measurement data were expressed as mean ± standard deviation (SD). The t-test was used for comparisons between the two groups. Count data were expressed as %. The χ^2 test was used for intergroup comparisons. A P value of less than 0.05 was considered a statistically significant difference.

3. Results

3.1. Time for improvement of clinical symptoms

After 2 weeks of treatment, the time required for improvement in clinical symptoms and physical signs in

both patient groups was observed. Specifically, the resolution time of symptoms such as fever, cough and expectoration, asthma, and the presence of pulmonary rales was focused on. **Table 2** shows the time for improvement of clinical symptoms in both groups.

Table 2. Time for improvement of clinical symptoms in both patient groups (mean ± SD)

Group	*n*	Fever	Cough and expectoration	Asthma	Pulmonary rales
Observation group	165	3.28 ± 0.32	12.72 ± 4.05	4.46 ± 1.02	5.16 ± 1.41
Control group	165	4.36 ± 0.51	17.36 ± 4.64	5.12 ± 1.15	7.24 ± 1.48
t		23.042	9.752	5.515	13.071
P		< 0.001	< 0.001	< 0.001	< 0.001

3.2. Determination of serum inflammatory factor levels

Serum samples from both patient groups were collected, and the ELISA method was utilized to assess the levels of IL-1β, IL-6, IL-8, and TNF-α in the serum of both the observation group and the control group. Initially, all four serum inflammatory factors in both groups were maintained at elevated levels before treatment, with no statistical difference between them ($P > 0.05$). As the treatment progressed, the levels of these inflammatory factors in the serum of both groups exhibited significant reductions after 1 week and 2 weeks of treatment ($P < 0.001$). **Table 3** shows the comparison of serum inflammatory factor levels between the two groups before, 1-week, and 2-week after treatment.

Table 3. Comparison of serum inflammatory factor levels between the two patient groups (mean ± SD)

Index	Group	Before treatment	1-week after treatment	2-week after treatment
IL-1β (pg/mL)	Observation group	6.16 ± 0.55	3.34 ± 0.32	2.45 ± 0.21
	Control group	6.12 ± 0.58	4.28 ± 0.41	3.82 ± 0.35
	t	0.6248	23.2159	43.1147
	P	> 0.05	< 0.001	< 0.001
IL-6 (pg/mL)	Observation group	17.56 ± 1.60	10.06 ± 0.71	8.21 ± 0.22
	Control group	17.53 ± 1.64	12.15 ± 0.93	7.15 ± 0.43
	t	0.1682	82.0089	28.1897
	P	> 0.05	< 0.001	< 0.001
IL-8 (pg/mL)	Observation group	19.47 ± 3.08	8.63 ± 0.81	8.35 ± 0.62
	Control group	19.45 ± 2.93	15.25 ± 1.39	12.45 ± 0.79
	t	0.0604	52.8568	52.4430
	P	> 0.05	< 0.001	< 0.001
TNF-α (ng/mL)	Observation group	6.25 ± 0.71	2.27 ± 0.33	1.57 ± 0.24
	Control group	6.23 ± 0.69	4.16 ± 0.48	2.87 ± 0.39
	t	0.2595	41.6785	34.4658
	P	> 0.05	< 0.001	< 0.001

4. Discussion

Lung cancer ranks among the most prevalent clinical malignancies. Statistics from the American Cancer Society in 2022 revealed that lung cancer remains the leading cause of cancer-related fatalities, with a low 5-year survival rate of only 20% [5]. Due to environmental pollution and shifts in lifestyle, its incidence and mortality continue to rise yearly [6]. Recent data from the National Cancer Center indicates that, with an aging population, China's cancer incidence exceeds that of the United States, making lung cancer the most prevalent cancer and the foremost cause of cancer-related death in China [7]. Owing to the subtle early symptoms of the disease, most patients are already grappling with pulmonary infections upon diagnosis. Combined with factors such as resistance to radiotherapy and chemotherapy, patient outcomes are often suboptimal, and the prognosis is grim [8-10]. The 5-year survival rate for patients remains dishearteningly low. Discovering novel treatments is an imperative trend in the management of malignant tumors, including lung cancer.

Montelukast sodium, marketed under the trade name Singulair, serves as a leukotriene receptor antagonist with a distinct inhibitory impact on cysteinyl leukotriene receptors (CYSLTRs). It suppresses the release of crucial inflammatory factors in various cells, including mast cells and eosinophils [11]. This drug has been widely used to prevent and treat asthma-related conditions, as it relaxes bronchial smooth muscle and diminishes airway hyperresponsiveness [12-13]. Recent years have unveiled the potential of montelukast sodium in tumor treatment. Tsai *et al*. found that administering montelukast sodium to mice with lung cancer significantly delayed tumor growth, inhibited lung cancer cell proliferation and colony formation, and induced lung cancer cell apoptosis [14]. By limiting hypoxia-inducible factor 1-alpha (HIF-1α) protein translation, montelukast sodium demonstrates tumor-suppressing effects, leading to the belief that it may serve as a novel treatment for prostate cancer [2]. In the realm of lung cancer research, it was discovered that montelukast sodium can inhibit the expression of cysteinyl leukotriene receptor 1 (CYSLTR1) in lung cancer cells and prevent lung cancer cell migration [6]. Bellamkonda *et al*. demonstrated that montelukast sodium can impede tumor cell growth in a nude mouse model of colon cancer. Additionally, *in vitro* studies showcased its ability to inhibit tumor cell proliferation, and adhesion, and induce cell cycle arrest and apoptosis in a dose-dependent manner [3]. As of now, there is a dearth of reports on the effectiveness of montelukast sodium in lung cancer treatment in China. This study observed that, after the administration of oral montelukast sodium treatment to the observation group, compared to patients not receiving montelukast sodium, their symptoms demonstrated significant improvement ($P < 0.001$), suggesting that montelukast sodium may play a clinical role in the treatment of lung cancer patients dealing with concurrent pulmonary infections.

Serum inflammatory factors serve as objective indicators for identifying and diagnosing infectious diseases while also playing a role in the onset and progression of pulmonary infections [15]. Research has indicated that IL-6, TNF-α, IL-1β, and others exhibited significant elevation in patients with pulmonary infections [16]. IL-1β, a pleiotropic cytokine, serves as a key mediator in immune response regulation and inflammation. Recent studies have highlighted IL-1β's involvement in tumorigenesis, angiogenesis, tumor invasion, and tumor metastasis, influencing the tumor microenvironment and affecting drug responsiveness through various pathways [17]. IL-6, a multifunctional cytokine, also acts as an inflammatory chemokine. Elevated IL-6 concentrations have been linked to immune response suppression, vascular endothelial cell damage, and lung injury [18]. Initially considered a factor in inflammation, IL-8 has progressively been associated with cancer initiation. An increasing amount of research found that certain chemotherapy drugs combined with radiotherapy can reduce IL-8 expression in tumors [19]. TNF-α, produced by activated macrophages and various tumor cells, functions as a pro-inflammatory factor with multiple biological roles. It serves as a crucial factor in cell activation, differentiation, proliferation, and apoptosis signaling, with TNF-α protein secreted by macrophages and tumor

cells potentially accelerating tumor progression through autocrine mechanisms [20].

The influence of these serum inflammatory factors underscores their close association with tumor development and lung infections. There have been no reports domestically and internationally on serum inflammatory factor levels in patients with lung cancer complicated by pulmonary infections who have undergone montelukast sodium treatment. This study results indicate that, prior to administering montelukast sodium to the observation group, serum expression levels of IL-8, IL-1β, IL-6, and TNF-α were essentially identical to those in the control group, with no statistical difference ($P > 0.05$). However, following 1 and 2 weeks of montelukast sodium treatment in the observation group, serum inflammatory factor levels were assessed, revealing that the observation group exhibited significantly lower levels compared to the control group ($P < 0.001$). These findings indicate that montelukast sodium may reduce the expression of IL-8, IL-1β, IL-6, and TNF-α in the serum of patients with pulmonary infections. Li and colleagues have reported that serum levels of IL-1β, IL-6, and TNF-α gradually rise in patients with stage I-IV lung cancer [21]. While this study has yet to establish a refined link between lung cancer stages and inflammatory factor levels, the treatment course has led to the conclusion that serum inflammatory factor levels in the observation group substantially decreased over time following montelukast sodium application. Some scholars believe that lung cancer patients with pulmonary infections experience an inflammatory stress state, which impacts immune function, triggers immune system activation, and raises the risk of lung infection [22-24]. This study further illustrates that, while effectively managing pulmonary infections, attention to tumor treatment should not be disregarded. Montelukast sodium may offer effective treatment for lung cancer accompanied by pulmonary infections.

In conclusion, this study demonstrates that, following treatment with montelukast sodium in patients with lung cancer and concurrent pulmonary infections, clinical symptoms such as cough, fever, asthma, and signs of pulmonary rales were significantly improved. Moreover, serum pro-inflammatory factors TNF-α, IL-8, IL-1β, and IL-6 exhibited marked decreases. These findings underscore the importance of evaluating patient conditions and enhancing treatment effectiveness, particularly when addressing pulmonary infections in these patients, by considering symptoms, signs, and the body's inflammatory stress state.

Disclosure statement

The authors declare no conflict of interest.

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In-service Doctors





Foreign Researchers





Hospital



University



Scientific institutions

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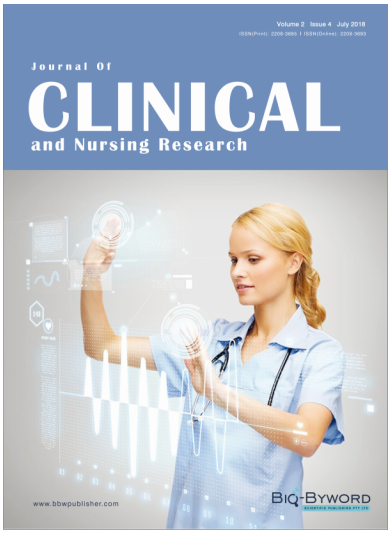
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