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Effects of respiratory muscle training on psychological status and physical health of depression with sleep disorders in radiotherapy for lung cancer

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CITATION

Zhang Y, Xu Y. Effects of respiratory muscle training on psychological status and physical health of depression with sleep disorders in radiotherapy for lung cancer. *Psycho-Oncologie*. 2025; 19(3): 3682. <https://doi.org/10.18282/po3682>

ARTICLE INFO

Received: 20 December 2024

Revised: 20 January 2025

Accepted: 25 February 2025

Available online: 13 August 2025

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Abstract: Recent years have seen a growing incidence of lung cancer (LC). This study explored the effect of respiratory muscle training (RMT) combined with vitamin B6 on patients with depression combined with sleep disorders (DSD). By comparing the Pittsburgh sleep quality index (PSQI), self-rating anxiety scale (SAS)/self-rating depression scale (SDS) of the three groups of DSD patients who received conventional rehabilitation training ($n = 54$), the control group who received conventional rehabilitation training combined with vitamin B6 ($n = 47$), and the combined group who received RMT combined with vitamin B6 ($n = 65$), we found that the Pittsburgh sleep quality index (PSQI), the self-rating anxiety scale (SAS)/self-rating depression scale (SDS) of the combined group were significantly lower than the PSQI, scale (SAS)/self-rating depression scale (SDS) and Clinical frailty scale (CFS) in the three groups of DSD patients, and we found that the sleep disorder, psychological status and cancer-related fatigue in the combined group were more significantly improved ($P < 0.05$). Meanwhile, the nutritional status of the combined group after treatment was also more favorable than the other two groups ($P < 0.05$). Finally, through one-year prognostic follow-up, we found that although there was no difference in prognostic survival rate and tumor recurrence rate among the three groups ($P > 0.05$), the Mandarin Chinese version of the Leicester Cough Questionnaire (LCQ-MC) score was higher in the combined group ($P < 0.05$). These results suggest that RMT combined with vitamin B6 can lay a more reliable foundation for the prognosis and rehabilitation of patients with DSD.

Keywords: breathing exercises; depression; lung neoplasms; radiotherapy; sleep wake disorders

1. Introduction

Lung cancer (LC) is the most common lung malignancy originating from the trachea, bronchial mucosa, or glands. It is non-contagious, with certain familial clustering and genetic susceptibility, and is often accompanied by symptoms such as cough, bloody sputum or hemoptysis, wheezing, and chest pain [1]. According to the statistics of the World Health Organization in 2022, about 51 out of every 100,000 people suffer from LC globally, and it is also the malignant tumor with the highest mortality rate [2]. Surgery is still the mainstay of treatment for LC at present. Radiation therapy (RT), on the other hand, is an excellent adjuvant therapeutic option, which eliminates and eradicates the primary or metastatic foci of local tumors by radiation, improves the therapeutic efficacy of surgery, and improves the prognostic survival rate of patients [3]. However, RT is usually accompanied by very serious side effects such as nausea, vomiting, skin damage, and bone marrow suppression [4]. It is also because of these negative effects that patients often experience insomnia and difficulty sleeping during RT [5]. Statistics show that about 32% of LC patients have depression

combined with sleep disorders (DSD) during radiotherapy, and the occurrence of DSD is not only unfavorable to the treatment of patients but also very easy to lead to cardiopulmonary complications, which seriously affects patients' postoperative rehabilitation [6]. In this regard, it is proposed in the clinic that the pulmonary rehabilitation training of DSD patients must be strengthened.

Respiratory muscle training (RMT) is a new type of pulmonary rehabilitation training that enhances the strength and endurance of the respiratory muscles, improves respiratory and lung functions, and promotes the recovery of the patient's pulmonary function [7]. RMT is also a common adjunctive therapy for LC and has been shown to be effective [8]. On the other hand, B vitamins are vitamins in the human body that are mainly responsible for regulating nerve function, and are often used as adjuvant drugs in the treatment of neurological diseases such as insomnia and depression [9,10]. In a study by Paulin FV et al, they found that the use of RMT in combination with vitamin B was effective in improving the recovery of patients with advanced chronic obstructive pulmonary disease (COPD) [11], which inspired us to think that RMT in combination with vitamin B could likewise contribute to the recovery of patients with LC combined with DSD. However, there are no studies to confirm our view.

Therefore, this study will comprehensively explore the effects of RMT in combination with vitamin B6 on the body function and nutritional status of patients with DSD to provide a more reliable guarantee for the treatment and postoperative rehabilitation of LC patients in the future.

2. Materials and methods

2.1. Study population

A retrospective analysis was performed on 166 patients with DSD at Affiliated Hospital of Nantong University from January 2022 to September 2023. Among them, 65 cases received RMT combined with vitamin B6, which was regarded as the combined group; 47 cases received routine rehabilitation training combined with vitamin B6 and were regarded as the control group; and 54 cases received routine

Table 1. Comparison of clinical data.

		Routine (n = 54)	Control (n = 47)	Combined (n = 65)	F (c²)	P
Age (years)		64.67 ± 12.02	64.66 ± 7.81	64.92 ± 10.38	0.013	0.988
Sex	Male/female	22 (40.74)/25 (59.26)	20 (42.55)/34 (57.45)	21 (32.31)/44 (67.69)	1.48	0.477
Smoking	Yes/no	10 (18.52)/44 (81.48)	11 (23.40)/36 (76.60)	8 (12.31)/57 (87.69)	2.391	0.303
Pathological staging	I-II/III-IV	40 (74.07)/14 (25.93)	37 (78.72)/10 (21.28)	50 (76.92)/15 (23.08)	0.313	0.855
Scope of surgery	Lung wedge resection/segmental resection/lobar resection/radical lung cancer surgery/others	10 (18.52)/2 (3.70)/3 (5.56)/30 (55.56)/9 (16.67)	6 (12.77)/1 (2.13)/1 (2.13)/24 (51.06)/15 (31.91)	15 (23.08)/4 (6.15)/5 (7.69)/31 (47.69)/10 (15.38)	8.777	0.361

rehabilitation training and were regarded as the routine group. The study involving human subjects complied with the Declaration of Helsinki and was approved by the ethical committee of the Affiliated Hospital of Nantong University, and all participants provided written informed consent. The baseline data of the patients in the two groups

are shown in **Table 1**, and the differences in age and gender were not statistically significant ($P > 0.05$) and were comparable between the two groups.

2.2. Eligibility and exclusion criteria

Inclusion criteria: Confirmed diagnosis of LC by pathological biopsy, with tumor node metastasis (TNM) stage of II-III [12]; the presence of sleep disorders after thoracoscopic surgery in our hospital, with symptoms lasting for more than 3 days; normal coagulation function; no distant metastasis. Exclusion criteria: Preoperative presence of pulmonary infection; estimated survival > 3 months; previous history of thoracotomy; myocardial infarction episode within the last month; active pulmonary tuberculosis, obvious liver and kidney dysfunction, severe pulmonary arterial hypertension, or severe thoracic adhesions; psychiatric disorders; patients with coronavirus infection disease (COVID).

2.3. Methods

Three groups of patients underwent thoracoscopic LC radical resection by the same physician in our hospital; RT was performed 3–4 weeks after surgery using X-rays of 6 MV at a dose of 2 Gy/dose, 5 times/week for 4 weeks. Targeted therapy with amitinib (Jiangsu Hausen Pharmaceutical Group Co., Ltd., China) was given concurrently during the RT period, 110 mg/dose, 1 time/d, at the end of each RT. Postoperative pain management was consistent.

Control group: Patients were given oral vitamin B6 (Tianjin Huajin Pharmaceutical Co., Ltd., China), 50 mg/dose, for 2 months. On this basis, patients were given routine education and were instructed to carry out cough and expectorate training after admission, 15 min per session, 4 times/day.

Combined group: Oral vitamin B6 was administered as in the control group and RMT was performed. Training was conducted 1–2 h after meals. The patient was assisted in taking a sitting position, with the head in a neutral position and the body relaxed. The training instrument (Shanghai Rui Jiong Medical Equipment Co., Ltd., RJ-8001) was placed in front of the patient, and the patient was asked to bite the mouthpiece of the instrument when the breathing was stable, after which the nose clip was clamped to measure the maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) in strict accordance with the operating requirements of the instrument. The measurement was repeated 3 times to take the maximum value. During training, the initial resistance was set at 30% MIP and MEP, which was gradually increased in the later stage according to the patient's tolerance (increased by 1% every 1 d as tolerated by the patient). (1) Inspiratory muscle resistance training: The patient sits, tries to exhale all the gas in the lungs, will be with resistance to the mouthpiece tightly clasped in the mouth, through the mouthpiece to maximize the use of the mouth inhalation, exhaling through the nose, cycle, 2 min/group, rest 1 min between groups, a total of 5 groups. (2) Expiratory muscle resistance training: The patient sits, the mouthpiece with resistance is tightly fastened to the mouth, inhale deeply through the nose, exhale through the mouth, exhale all the gases as quickly as possible, maximize nasal inhalation and oral exhalation, and then cycle through the process, 2 min/group, with a rest of 1 min in between the groups, for a total of 5 groups.

In both groups, training was started 3 days before surgery, rested for 7 days after surgery, and then continued until RT was completed. The patients' RMTs were completed with the assistance and guidance of our rehabilitation physicians.

Routine group: Patients were given routine education and were instructed to carry out cough and expectorate training after admission, 15 min per session, 4 times/day, which lasts until the end of RT.

2.4. Prognostic follow-up

A 12-month follow-up survey was conducted after patients completed RT. The frequency of follow-up visits was monthly for months 1–6 and bimonthly for months 7–12. The follow-up visit was by hospital review.

2.5. Endpoints

(1) We used the Pittsburgh Sleep Quality Index (PSQI) [13] and the Self-Rating Anxiety Scale (SAS)/Self-Rating Depression Scale (SDS) [14] to evaluate the sleep quality and psychological state of patients, respectively. The scores of both scales are proportional to the severity of sleep disorders and anxiety. (2) We used the CFS scale [15] for assessment from somatic, emotional, and cognitive dimensions, with a higher score indicating more obvious CRF. (3) Nutritional proteins, including albumin (ALB), transferrin (TRF), hemoglobin (HGB), and total protein (TP), were detected. (4) Visual Analogue Scale (VAS; 0–10 points) [16] was used to investigate patients' pain perception (0–10 points) after surgery (T0), at the first radiotherapy (T1), and at the time of 2 weeks of radiotherapy (T2), with higher scores indicating more pronounced pain. (5) Patients' recovery at 1 year of prognosis, including overall survival and tumor recurrence, was recorded. At the last follow-up, the rehabilitation quality of patients was evaluated by using the Mandarin Chinese version of the Leicester Cough Questionnaire (LCQ-MC) [17] from physical, psychological, and social domains; the score is positively associated with the rehabilitation quality.

2.6. Statistical processing

Statistical Package for the Social Sciences (SPSS) software v22.0 was used for statistical analysis of the data. Count data were represented by [*n* (%)], and the Chi-square test was used for comparisons. Measurement data were first subjected to the Shapiro-Wilk test; normally distributed data were recorded as ($\pm$ s) and compared using repeated measures. Analysis of variance (ANOVA) and Least-Significant Difference (LSD) within-groups test; non-normally distributed data were recorded as median (interquartile spacing) and compared using Kruskal-Wallis H analysis and Mann-Whitney U within-groups test. Survival and recurrence rates were calculated using the Kaplan-Meier method, and comparisons were made using the log-rank test. A minimum significance threshold of $P < 0.05$ was used.

3. Results

3.1. Comparison of sleep quality and psychological state

The three groups were not statistically different in pre-treatment PSQI, SAS and

SDS scores ($P > 0.05$). The combined group had lower scores of PSQI, SAS and SDS than the control and routine groups after treatment ($P < 0.05$), while the PSQI, SAS, and SDS scores of the control group were lower than those of the routine group ($P < 0.05$). Furthermore, the intra-group comparison showed reduced PSQI, SAS and SDS scores after treatment compared with the values before treatment in three groups ($P < 0.05$, **Table 2**).

Table 2. Comparison of sleep quality and psychological state.

		Routine (n = 54)	Control (n = 47)	Combined (n = 65)	F	P
PSQI	Before	15.98 ± 2.62	15.72 ± 3.30	15.74 ± 2.80	0.135	0.874
	After	11.46 ± 2.03*	9.21 ± 1.85**	7.60 ± 2.09*#&	54.73	< 0.001
SAS	Before	58.20 ± 5.88	58.04 ± 4.94	57.94 ± 3.71	0.043	0.958
	After	49.96 ± 7.00*	43.68 ± 7.33**	35.60 ± 6.29*#&	66.1	< 0.001
SDS	Before	57.13 ± 5.25	55.96 ± 6.39	56.65 ± 6.35	0.465	0.629
	After	49.46 ± 7.46*	42.33 ± 5.66**	37.92 ± 4.79*#&	54.57	< 0.001

Note: * denotes $P < 0.05$ compared with before treatment, # denotes $P < 0.05$ compared with the routine group, & denotes $P < 0.05$ compared with the control group. Pittsburgh Sleep Quality Index (PSQI); Self-Rating Anxiety Scale (SAS).

3.2. Comparison of CRF

The CFS scores were similar between groups before treatment ($P > 0.05$); while lower CFS scores from the somatic, emotional, and cognitive dimensions were determined in the combined group compared with the routine and control groups ($P < 0.05$), there was no difference between the somatic domain scores of the control group and the routine group ($P > 0.05$), but the results of the emotional and cognitive domain scores were lower than those of the routine group ($P < 0.05$). The CFS scores of three groups decreased after treatment compared to the values before treatment ($P < 0.05$, **Table 3**).

Table 3. Comparison of CRF.

		Routine (n = 54)	Control (n = 47)	Combined (n = 65)	F	P
Somatic domain score	Before	22.72 ± 4.55	22.43 ± 5.06	22.89 ± 2.93	0.167	0.846
	After	15.52 ± 2.81*	15.60 ± 4.69**	12.83 ± 4.35*#&	9.081	< 0.001
Emotional domain score	Before	20.35 ± 3.43	20.32 ± 4.22	20.54 ± 3.44	0.062	0.940
	After	17.76 ± 1.75*	14.91 ± 2.91**	11.25 ± 3.82*#&	69.490	< 0.001
Cognitive domain score	Before	15.56 ± 2.60	15.55 ± 2.82	15.82 ± 4.17	0.123	0.884
	After	13.30 ± 1.69*	10.96 ± 2.40**	8.58 ± 1.56*#&	93.890	< 0.001

Note: * denotes $P < 0.05$ compared with before treatment, # denotes $P < 0.05$ compared with the routine group, & denotes $P < 0.05$ compared with the control group. Clinical Frailty Scale, CFS.

3.3. Comparison of nutritional proteins

The three groups did not differ in pre-treatment ALB, TRF, HGB, and TP levels ($P > 0.05$); the combined and control groups had higher ALB, TRF, HGB, and TP levels than the routine group after treatment ($P < 0.05$). Compared with before treatment, the nutritional proteins of the combined and control groups increased ($P < 0.05$), while those of the routine group remained unchanged ($P > 0.05$, **Table 4**).

Table 4. Comparison of nutritional proteins.

		Routine (n = 54)	Control (n = 47)	Combined (n = 65)	F	P
TRF (g/L)	Before	2.81 ± 0.56	2.91 ± 0.45	2.81 ± 0.71	0.472	0.625
	After	2.90 ± 0.50	3.29 ± 0.35*	3.41 ± 0.67*&	13.85	< 0.001
HGB (g/L)	Before	109.40 ± 11.02	110.13 ± 10.18	111.70 ± 17.16	0.449	0.639
	After	112.63 ± 11.97	120.46 ± 10.78*	124.67 ± 18.06*&	10.43	< 0.001
TP (g/L)	Before	58.49 ± 9.59	57.24 ± 8.34	58.00 ± 7.58	0.275	0.76
	After	57.58 ± 8.01	64.28 ± 8.44*	65.20 ± 9.09*&	13.14	< 0.001

Note: * denotes $P < 0.05$ compared with before treatment, & denotes $P < 0.05$ compared with the control group. Transferrin, TRF; Hemoglobin, HGB; Total protein, TP.

3.4. Comparison of pain conditions

At T0, there was no statistically significant difference in VAS scores among the three groups ($P > 0.05$). At T1, the VAS scores of the combined group and the control group were lower than that of the routine group ($P < 0.05$). At T2, the VAS score of the combined group was (1.74 ± 0.59), which was lower than that of the control and routine group ($P < 0.05$). The VAS score at T2 in the control group was (2.23 ± 0.73), which was also lower than that of the route group ($P < 0.05$). The VAS score in all three groups was lower than that of T0 at T1, and lower than that of T1 at T2 ($P < 0.05$, **Table 5**).

Table 5. Comparison of pain conditions.

Groups	Routine (n = 54)	Control (n = 47)	Combined (n = 65)	F	P
T0	5.41 ± 1.73	5.30 ± 1.98	5.00 ± 1.62	0.856	0.427
T1	3.93 ± 0.93*	3.34 ± 0.87*#	3.14 ± 0.70*#	13.9	< 0.001
T2	3.37 ± 0.90*#@#	2.23 ± 0.73*#@#	1.74 ± 0.59*#@#&	73.31	< 0.001

Note: * denotes $P < 0.05$ compared with T1, @ denotes $P < 0.05$ compared with T2, # denotes $P < 0.05$ compared with the routine group, & denotes $P < 0.05$ compared with the control group.

3.5. Comparison of prognosis and rehabilitation

Finally, the prognostic follow-up results showed that there was no difference in the comparison of prognostic tumor recurrence rate and mortality rate among the three groups ($P > 0.05$). The LCQ-MC scoring results revealed that the physical, psychological, and social fields, as well as the total score of the combined group were (2.05 ± 0.57), (1.89 ± 0.62), (2.15 ± 0.80), and (6.09 ± 1.06), all of which were higher compared to the routine and control groups ($P < 0.05$), while the control group had higher physical and psychological domains and total scores than the routine group ($P < 0.05$, **Figure 1**).

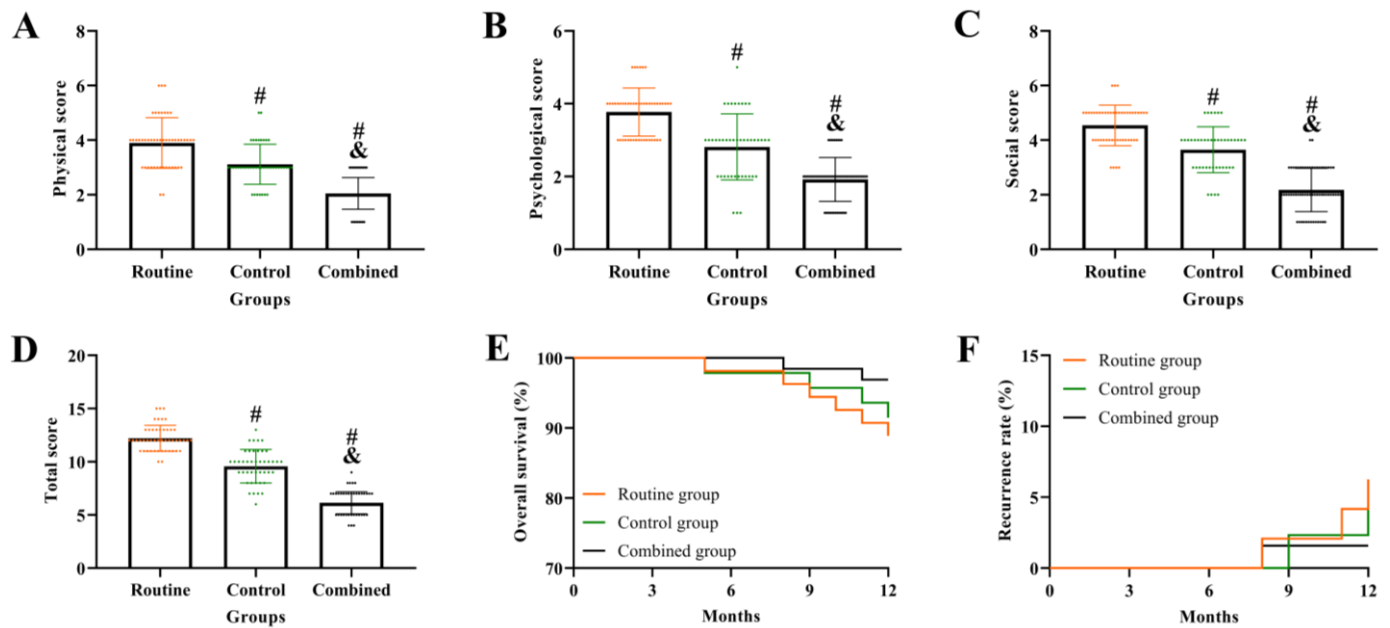


Figure 1. Comparison of prognosis and rehabilitation: **(A)** comparison of physical score; **(B)** comparison of psychological score; **(C)** comparison of social score; **(D)** comparison of total score; **(E)** comparison of prognostic survival; **(F)** comparison of prognostic recurrence.

Note: # denotes $P < 0.05$ compared with the routine group, & denotes $P < 0.05$ compared with the control group.

4. Discussion

In recent years, the incidence of LC has been increasing year by year, and improving the quality of clinical treatment is of great significance to ensure patient outcomes [18]. DSD is a typical adverse reaction and an important factor affecting patient recovery [19]. In this study, we found that RMT combined with vitamin B6 is of great help in improving the rehabilitation and nutritional status of patients with DSD, which has great clinical implications.

As we all know, sleep disorders are mental and psychological disorders, which are mainly caused by various psychological burdens during the perioperative period [20]. Vitamin B6 is a water-soluble vitamin, which exists in the form of phosphate in the body. As an essential substance for human fat and sugar metabolism, vitamin B6 has an important positive effect on nerves, participating in neurotransmitter reactions and alleviating insomnia and neurasthenia [21]. This also, to some extent, alleviates the patient's abnormal neural excitement, thus ameliorating sleep disorders. Similarly, Lemoine P et al. found that the combination of melatonin and vitamin B6 was effective in the treatment of mild/moderate insomnia [22]. Therefore, the post-treatment PSQI, SAS, and SDS were seen to be lower in the control group in this study. In addition to this, the combined group showed better improvement in SAS, SDS and PSQI than the control group, which we believe is due to the important role of RMT in this. Traditional lung rehabilitation training is generally based on balloon blowing, lip-constriction breathing, abdominal breathing, etc., which is limited despite certain rehabilitation effects [23]. Through RMT, the patient's muscle strength is enhanced, the tolerance of respiratory muscle fatigue is improved, the imbalance of the ventilation/blood flow ratio is ameliorated, and the symptoms such as postoperative

hypoxia are alleviated. Meanwhile, increased muscle strength can enhance cough intensity, facilitate the clearance of tracheal mucosal secretions, and promote lung recruitment. This improves the RT experience of patients from a pathological perspective and reduces their psychological burden. As a result, PSQI, SAS, and SDS were further reduced in the combined group compared to the control group, which shows that RMT combined with vitamin B6 is effective in improving sleep disorders as well as alleviating anxiety in DSD patients. In a self-management study by Lee et al. on a South Asian population, they also found that the use of RMT helped to improve the negative mood of patients with anxiety and depression [24], similar to our results. The CFS score investigation also showed a more evident decrease in the post-treatment score in the combined group, which can once again support the positive effect of RMT combined with vitamin B6 on improving the overall recovery status of DSD.

In the comparison of nutritional status, the combined and control groups had significantly higher levels of nutritional proteins, which is also closely related to the positive impact of vitamin B6 on the nutritional status of patients. Vitamin B6 can participate in the metabolism of amino acids, fat, one-carbon units, and homocysteine, facilitate the synthesis of nicotinic acid in the body, and promote the absorption of vitamin B12, iron, zinc, and other elements, thus playing a role in promoting metabolism in the body and maintaining the normal function of the body [25]. Therefore, the overall nutritional status of the combined and control groups was obviously better than that of the routine group. Similarly, in a study by Gea et al., it was mentioned that in patients with respiratory diseases, there is a direct relationship between their nutritional status and muscle function [26]. Therefore, we believe that the enhancement of muscle strength in patients by RMT also contributes to the improvement of their nutritional status.

In terms of pain, the combined group also showed more significant alleviation in pain compared to the routine and control groups. The reason for this is that RMT increases resistance in the abdomen, which can promote greater contraction of expiratory and inspiratory muscles, activate respiratory auxiliary muscle groups such as transverse abdominis and external oblique abdominis, and enhance the strength of respiratory muscle groups; moreover, resistance abdominal breathing training can correct incorrect breathing patterns, ameliorate rapid and superficial breathing methods, increase diaphragmatic activity, and help relieve dyspnea caused by pulmonary capacity reduction [27]. The study mentions that the positive effects of RMT on lung function are mainly in the following 3 areas: (1) Improvement of lung capacity. RMT helps to expand lung capacity by increasing the depth and frequency of respiration, thus improving lung capacity. This allows the lungs to exchange gases more efficiently and provide sufficient oxygen to the body [28]. (2) Enhancement of respiratory muscle strength. Through specific breathing exercises, the diaphragm and other respiratory muscles can be strengthened to improve respiratory muscle power. This not only helps to improve breathing efficiency but also reduces breathing difficulties caused by respiratory muscle fatigue [29]. (3) Improvement of breathing pattern. RMT can help people learn how to use their lungs more efficiently and reduce shortness of breath and shortness of air by improving breathing patterns [30]. Combining these effects, the rehabilitation of all functions in the combined group was

therefore the best of the 3 groups.

Finally, the prognosis and rehabilitation survey results showed a more significant improvement in the LCQ-MC score of the combined group compared to the routine and control groups. This is also due to the fact that RMT combined with vitamin B6 facilitates the RT e rehabilitation of patients, alleviates their sleep disorders, and improves their psychological state and nutritional status, laying a more reliable foundation for their prognosis and health. However, there was no difference in tumor recurrence rate and survival rate among the three groups, which may be related to the fact that the cases included in this study were mainly patients in the early and middle stages, and the treatment was timelier, so the prognosis was generally better. Of course, it may also be due to the short follow-up time caused by chance. Besides, given the small number of cases in this study, more cases need to be included to improve the reliability of the research results. It is also necessary to increase objective clinical indicators to evaluate the overall effect of RMT combined with vitamin B6 on patients with DSD so as to provide a more reliable reference for clinical practice.

5. Conclusion

RMT combined with vitamin B6 can effectively relieve negative psychological states in patients with DSD, alleviate their sleep disturbances, and improve their nutritional status to provide a more reliable guarantee for their prognosis and health, which is recommended for clinical use.

Author contributions: Conceptualization, YZ and YX; methodology, YZ; formal analysis, YX; investigation, YZ; data curation, YX; writing—original draft preparation, YZ; writing—review and editing, YZ; project administration, YX. All authors have read and agreed to the published version of the manuscript.

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and was approved by the ethical committee of the Affiliated Hospital of Nantong University (NO. l2024021, 18 February 2024), and all participants provided written informed consent.

Availability of data and materials: The data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest: The authors declare no conflict of interest.

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