World Journal of Psychiatry

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World J Psychiatry 2024 July 19; 14(7): 1009-1016

DOI: 10.5498/wjp.v14.i7.1009

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Impact of comorbid subthreshold depressive symptoms on cancer-related fatigue and complications in adults with leukemia

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Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade A

Scientific Significance: Grade B

P-Reviewer: Fenoy A

Received: March 21, 2024

Revised: May 13, 2024

Accepted: June 18, 2024

Published online: July 19, 2024

Processing time: 112 Days and 18 Hours

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Abstract

BACKGROUND

Patients not only experience symptoms caused by cancer but also suffer from the accompanying psychological pain. Therefore, these patients do not have high quality of life. According to the World Health Organization, the incidence of leukemia in China in 2020 was 5.1/100000, the mortality rate was 3.3/100000, and the prevalence rate was 16.7/100000. Therefore, it is important to examine the influence of comorbid subthreshold depressive symptoms on leukemia patients.

AIM

To determine the impact of comorbid subthreshold depressive symptoms on cancer-related fatigue and complications in leukemia patients, thereby providing a basis for early diagnosis and treatment in clinical practice.

METHODS

A questionnaire survey was conducted among leukemia patients admitted to a tertiary hospital in Xi'an, Shaanxi Province, China, from August 2022 to December 2023. Patients with a score > 16 on the Chinese Classification of Mental Disorders (CCMD-3) and a Hamilton Depression Rating Scale score of 8-17 were classified as the subthreshold depressive group (n = 95), while 100 leukemia patients admitted during the same period were classified as the control group. Data were collected using Epidata 3.1 software, and comparisons were made between the two groups regarding general clinical data, the Piper Fatigue Scale (PFS), the Pittsburgh Sleep Quality Index (PSQI), the Numeric Rating Scale for pain assessment, laboratory indicators, and the occurrence of complications.

RESULTS

In this survey, 120 leukemia patients with depression were preliminarily screened, 95 patients with subthreshold depression were ultimately selected as the subthreshold depression group, and 100 leukemia patients admitted during the same period were enrolled as the normal group. Comparison of basic clinical data between the two groups revealed no significant differences in age, sex, body mass index, cognitive function, or comorbidity with other chronic diseases. However, there were statistically significant differences in the use of radiotherapy and regular exercise between the two groups (P < 0.05). Comparisons of scales and laboratory indicators revealed no significant differences in albumin or PSQI scores between the two groups, but there were statistically significant differences in pain scores, PSQI scores, PFS scores, hemoglobin levels, and C-reactive protein levels (P < 0.05). Spearman's correlation analysis indicated that cancer-related fatigue was correlated with age, hemoglobin levels, C-reactive protein levels, pain, and regular exercise among leukemia patients with subthreshold depression. Multivariate regression analysis revealed that advanced age, combined radiotherapy, pain, and low hemoglobin levels were risk factors for cancer-related fatigue in leukemia patients with comorbid subthreshold depression, while regular exercise was a protective factor against cancer-related fatigue. Follow-up comparisons revealed a significantly lower overall incidence of complications in the control group (4%) than in the depressive group (24.21%; P < 0.001).

CONCLUSION

Leukemia patients with comorbid subthreshold depressive symptoms experience more severe cancer-related fatigue and a higher incidence of complications. These findings may be related to advanced age, combined radiotherapy, pain, and low hemoglobin levels, while regular exercise may effectively alleviate symptoms.

Key Words: Subthreshold depression; Leukemia; Cancer-related fatigue; Complications; Minor depression

Core Tip: In this randomized controlled trial, leukemia patients with subthreshold depression were compared with leukemia patients without subthreshold depression. Multiple regression analysis revealed that advanced age, combined radiotherapy, pain, and low hemoglobin were risk factors for cancer-related fatigue in leukemia patients with subthreshold depression, and regular exercise was a protective factor against cancer-related fatigue. The total incidence of leukemia complications in the control group (4%) was significantly lower than that in the depressive group (24.21%).

Citation: Liu YX, Wang J. Impact of comorbid subthreshold depressive symptoms on cancer-related fatigue and complications in adults with leukemia. *World J Psychiatry* 2024; 14(7): 1009-1016

URL: https://www.wjgnet.com/2220-3206/full/v14/i7/1009.htm

DOI: https://dx.doi.org/10.5498/wjp.v14.i7.1009

INTRODUCTION

Subthreshold depression, also known as minor depression, refers to a suboptimal health state or a subgroup of individuals who exhibit depressive mood manifestations but do not meet the diagnostic criteria for major depressive disorder in terms of clinical symptoms, quantity, or nature[1]. Epidemiological surveys have shown that subthreshold depression is prevalent in the general population, with a prevalence ranging from 5% to 24%[2], which is significantly greater than that of major depressive disorder. The symptoms of subthreshold depression are subtle and often go unnoticed, with patients often becoming aware of them due to incidental factors and attributing them to specific stages or adverse events. Underdiagnosis or misdiagnosis is common in this condition. If left uncorrected and untreated, subthreshold depression symptoms can worsen, leading to major depressive disorder. Compared to the general population, individuals with subthreshold depression have a greater likelihood of developing major depression within one year, and this relationship is even stronger among cancer patients[3]. In recent years, both domestic and international scholars have conducted extensive research on subthreshold depression in cancer patients with the aim of increasing knowledge regarding this condition and finding appropriate ways to correct patients' adverse psychological states, thereby improving their quality of life[4]. The current study aimed to explore the impact of comorbid subthreshold depression on cancer-related fatigue and complications among leukemia patients. The findings are reported as follows.

MATERIALS AND METHODS

General information

This study employed a randomized controlled design to examine leukemia patients who sought treatment for depressive symptoms at Central Hospital Affiliated with Shandong First Medical University from August 2022 to December 2023.

The sample size for this study was estimated based on the requirements of the prevalence rate: n =, α = 0.05, two-sided $Z_{a/2}$ = 1.96. P represents the overall occurrence rate of the investigated phenomenon in the target population, which, in this study, is the occurrence rate of cancer-related fatigue in leukemia patients. Through preliminary investigations, P was determined to be 78%, and δ represents the allowable error, which can be taken as 0.1 P, 0.15 P, or 0.2 P. In this study, δ was set as 0.1 P. The calculated sample size was 100 patients.

Inclusion and exclusion criteria

The inclusion criteria for patients were as follows: (1) Had a clear cytological or pathological diagnosis of leukemia[5]; (2) Met the diagnostic criteria for subthreshold depression, with a Chinese Classification of Mental Disorders (CCMD-3) score > 16 and a Hamilton Depression Rating Scale (HAMD) score between 8 and 17[6]; (3) Males or females aged between 18 and 80 years; (4) Had an estimated life expectancy of at least 6 months; (5) Had no cognitive impairment or ability to comprehend the nature of the study; and (6) Were willing to participate in the study, underwent relevant follow-ups, and signed an informed consent form.

The exclusion criteria were as follows: (1) Age less than 18 years; pregnant or lactating individuals; (2) Had comorbid severe mania, depression, anxiety disorders, or schizophrenia; and (3) Were deemed unsuitable for participation by the researchers.

Study design

Data from preadmission interviews or admission records of leukemia patients were collected and organized using Epidata 3.1 software. The data were double-recorded and cross-checked and then provided to the research team for further analysis.

Clinical information was recorded for evaluation, investigating the current status and influencing factors of cancer-related fatigue in leukemia patients. The evaluation included four aspects: (1) Sociodemographic characteristics, including age, sex, body mass index (BMI), marital status (married or in a relationship, single, widowed, separated, or divorced), and employment status (unemployed, employed); (2) Recording of comorbid chronic diseases prior to admission; and (3) Observational scales, including the 22-item Piper Fatigue Scale (PFS), the 18-item Pittsburgh Sleep Quality Index, and the Numeric Rating Scale (NRS). The PFS includes four dimensions (emotional, cognitive, behavioral, and sensory). Each item is rated on a scale of 0-10, representing the degree of impairment. A higher cumulative score indicates more severe fatigue (0, no fatigue; 1-3, mild fatigue; 4-6, medium fatigue; 7-10, severe fatigue). The items on the PSQI are grouped into seven different dimensions, with scores ranging from 0 to 3 and a total score of 21. A lower total score indicates better sleep quality. The NRS is used to assess the intensity pain on a scale from 0 to 10 (0 represented no pain, 1-3 indicated mild pain without sleep disturbance, 4-6 represented moderate pain with mild sleep disturbance, 7-9 indicated severe pain causing difficulty falling asleep or awakening during sleep, and 10 represented excruciating pain). Additionally, laboratory data, including complete blood count, C-reactive protein, *etc.*, were collected.

Statistical analysis

Statistical analysis was performed using SPSS 27.0 software, and image processing was conducted using GraphPad 8.0 software. For continuous variables, *t* tests were used for comparisons. For categorical variables, χ^2 or Fisher's exact tests were employed for comparisons. Spearman's correlation analysis was performed. Multiple linear regression analysis was also performed to identify risk factors for cancer-related fatigue. A statistical significance level of $P < 0.05$ was considered significant.

RESULTS

Basic clinical characteristics

A total of 120 leukemia patients with depressive symptoms were preliminarily screened in this study, with 10 patients scoring < 16 on the CCMD-3 scale, 8 patients scoring < 8 on the HAMD scale, and 5 patients excluded due to major depressive disorder. Ultimately, 97 individuals with subthreshold depression were selected. A questionnaire survey was conducted among these subthreshold depression patients, with 95 responses collected, resulting in a response rate of 99%. There were 95 valid questionnaires, yielding an effective response rate of 99%. One hundred leukemia patients without depression who were admitted during the same period composed the control group. A comparison of the basic clinical characteristics between the two groups revealed no significant differences in age, sex, BMI, cognitive function, or comorbid chronic diseases. However, there were statistically significant differences between the two groups in terms of combined radiotherapy and regular exercise ($P < 0.05$), as shown in Table 1.

Comparison of observational indicators

Comparisons of the scales and laboratory indicators between the two groups revealed no significant differences in albumin levels or PSQI scores. However, there were statistically significant differences between the two groups in terms of pain scores, PFS scores, hemoglobin levels, and C-reactive protein levels ($P < 0.05$), as shown in Table 2 and Figure 1.

Correlation analysis of PFS scores in leukemia patients with subthreshold depression

Spearman's correlation analysis was conducted to examine the correlation between subthreshold depression in leukemia patients and PFS score, as well as the correlations between cancer-related fatigue and age, hemoglobin levels, C-reactive protein levels, pain, and regular exercise. The results revealed a positive correlation between age and the total PFS score ($r = 0.741$, $P = 0.013$), a positive correlation between regular exercise and the total PFS score ($r = 0.602$, $P = 0.029$), a negative

Table 1 Comparison of basic clinical characteristics

	Subthreshold depression (*n* = 95)	Control (*n* = 100)	Statistic	*P* value
Age (years, mean ± SD)	65.3 ± 10.22	63.6 ± 12.4	0.585	0.561
Gender			χ^2 = 1.60	0.45
Male, *n* (%)	56 (58.94)	52 (52.00)		
Female, *n* (%)	39 (41.05)	48 (48.00)		
Marriage, *n* (%)			Fisher's exact test	0.307
Married	63 (66.32)	50 (50.00)		
Single	10 (10.52)	8 (8.00)		
Bereft	10 (10.52)	12 (12.00)		
Devoice	12 (12.65)	25 (25.00)		
Work status, *n* (%)			χ^2 = 0.804	0.423
Unemployed	79 (0.84)	80 (80.00)		
Employed	16 (0.17)	20 (20.00)		
Comorbid chronic disease, *n* (%)			χ^2 = 0.795	0.428
Yes	12 (12.65)	10 (10.00)		
No	83 (87.36)	90 (90.00)		
BMI (kg/m^2, mean ± SD)	24.23 ± 9.29	23.91 ± 10.22	0.868	0.386
Combined radiotherapy, *n* (%)			χ^2 = 2.227	0.028
Yes	33 (35.76)	7 (7.00)		
No	62 (65.26)	93 (93.00)		
Regular exercise, *n* (%)			χ^2 = 2.609	0.010
Yes	12 (12.82)	54 (54.00)		
No	83 (87.87)	46 (46.00)		

Table 2 Comparison of observational indicators between the two groups

	Subthreshold depression (*n* = 95)	Control (*n* = 100)	Statistic	*P* value
Pain score (score, mean ± SD)	3.98 ± 2.43	1.34 ± 0.2	35.918	0.000
PSQI (score, mean ± SD)	11.0 ± 3.1	9.8 ± 1.8	1.841	0.070
Piper Fatigue Scale score (score, mean ± SD)	7.2 ± 1.6	4.5 ± 1.4	4.410	0.000
Hemoglobin (g/L, mean ± SD)	60.24 ± 12.45	71.19 ± 15.34	1.011	0.000
Albumin (g/L, mean ± SD)	33.98 ± 15.66	34.45 ± 19.46	1.534	0.128
CRP (mg/L, mean ± SD)	8.13 ± 1.55	4.24 ± 1.42	2.832	0.005

PSQI: Pittsburgh Sleep Quality Index; CRP: C-reactive protein.

correlation between hemoglobin levels and the total PFS score (r = -0.667, P = 0.034), a positive correlation between C-reactive protein levels and PFS score (r = 0.463, P = 0.004), and no correlation between pain and the total PFS score (P > 0.05). The correlations between each factor and the total PFS score and the scores of each dimension are shown in Table 3.

Multivariate regression analysis of PFS scores in leukemia patients with subthreshold depression

Multivariate linear regression analysis was conducted with subthreshold depression as the dependent variable and age, concurrent radiotherapy, regular exercise, pain score, PFS score, hemoglobin level, albumin level, and C-reactive protein level as the independent variables. Variables including age, concurrent radiotherapy, regular exercise, depression score, and hemoglobin level were entered into the equation (P < 0.05). The multivariate linear regression equation was as follows: subthreshold depression (Y) = -497.82+ 6.662 × age + 153.09 × concurrent radiotherapy - 236.85 × regular exercise + 2.017 × depression score + 2.826 × hemoglobin level. The regression equation revealed that advanced age, concurrent

Table 3 Correlation analysis of Piper Fatigue Scale scores in leukemia patients

	PFS score	Emotion	Recognition	Behavior	Sensation
Age	0.741[a]	0.791[a]	0.753[a]	0.745[a]	0.736[a]
Pain	0.321	0.561	0.176	0.264	0.146
Hemoglobin	-0.667[a]	-0.447	-0.453	-0.681[a]	-0.636[a]
CRP	0.463[a]	0.328[a]	0.285	0.339	0.642[a]
Regular exercise	0.602[a]	0.561[a]	0.453	0.456	0.636[a]

[a]$P < 0.05$.

PFS: Piper Fatigue Scale; CRP: C-reactive protein.

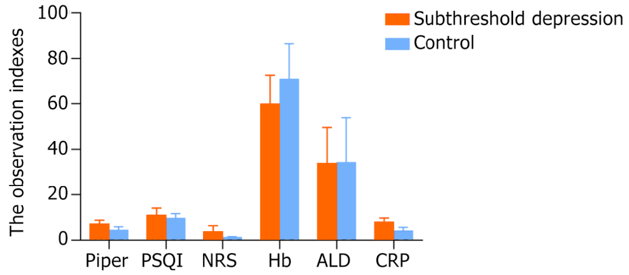

Figure 1 Comparison of observational indicators between the two groups. PSQI: Pittsburgh Sleep Quality Index; NRS: Numeric Rating Scale; Hb: Hemoglobin; ALD: Aldolase; CRP: C-reactive protein.

radiotherapy, pain, and low hemoglobin levels were risk factors for cancer-related fatigue, while regular exercise served as a protective factor against cancer-related fatigue (Table 4).

Comparison of leukemia complications between the two groups

After conducting follow-up comparisons in this study, it was found that the overall incidence of leukemia complications in the control group was significantly lower (4%) than that in the depressive group, which had an overall incidence of 24.21% ($P < 0.001$; Figure 2).

DISCUSSION

Previous studies have shown that the incidence of cancer-related fatigue in patients with malignant tumors ranges from 75% to 99%[7]. Patients with different types of malignant hematological diseases have high rates of cancer-related fatigue, but there are variations in the severity of cancer-related fatigue, suggesting that the type of hematological disease may influence the degree of cancer-related fatigue. Research has indicated that patients with depression experience dysregulation of autonomic nervous system function and neurotransmitter secretion in the brain[8]. This leads to decreased secretion of neurotransmitters such as dopamine and serotonin; increased levels of inflammatory mediators such as IL-1, IL-6, and TNF-α; and the induction of physical fatigue symptoms and various physiological discomforts. When the body experiences fatigue, negative emotions such as low mood, decreased interest, and even loss of interest are more likely to occur, causing leukemia patients to lose motivation for medical activities and daily life, thereby exacerbating fatigue. Depression and fatigue interact with each other, forming a vicious cycle. Studies have shown that psychological interventions such as mindful breathing, integrated psychological care, and diverse nursing can increase patients' potential, improve their compliance with medical advice and treatment, alleviate depression and anxiety, and reduce the severity of fatigue[9]. Therefore, in the clinical nursing process, it is necessary to detect patients' negative emotions early, assess their depressive state, and provide effective nursing interventions to alleviate depression and improve cancer-related fatigue in patients with malignant hematological diseases.

Based on the research in this article and the analysis of domestic and global studies, advanced age, concurrent radiotherapy, pain, and low hemoglobin levels are risk factors for cancer-related fatigue, while regular exercise acts as a protective factor. As elderly patients age, they experience organ aging, reduced stress tolerance, decreased immune function, and gradual physical weakness and are more susceptible to adverse symptoms caused by primary blood disorders and chemotherapy. Compared to younger individuals, their self-regulation abilities are weaker, resulting in more severe and longer-lasting cancer-related fatigue. Uslu and Canbolat[10] conducted a survey of 228 elderly cancer patients using the Edmonton Symptom Assessment System and the Cancer Fatigue Scale, recognizing age as a key risk factor influencing cancer-related fatigue. Therefore, it is crucial in nursing practice to have a real-time understanding of

Table 4 Multivariate regression analysis of piper fatigue scale scores in patients with malignant hematological diseases

	Value	B	SE	β	*t* value	*P* value
Age (years)		6.660	2.331	0.062	2.821	0.002[a]
Concurrent radiotherapy	(No = 1, Yes = 2)	123.09	69.894	0.042	2.021	0.033[a]
Regular exercise	(No = 1, Yes = 2)	-236.85	75.913	-0.068	-3.120	0.002[a]
Pain	Score	2.014	0.421	0.102	4.420	< 0.001[a]
Hemoglobin		2.825	1.333	0.043	2.081	0.031[a]

[a]$P < 0.05$.

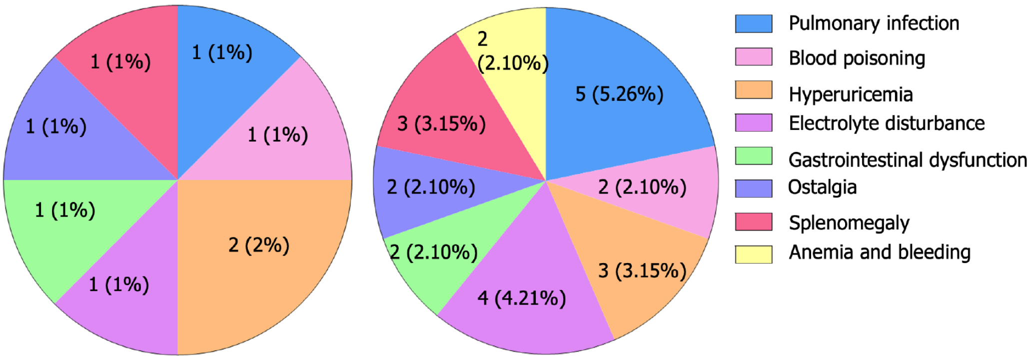

Figure 2 Comparison of leukemia complications between the two groups.

the physical condition of elderly patients, promptly identify their weakness and fatigue, and take proactive and effective intervention measures.

During the process of radiotherapy, all cells in the irradiated area are typically affected. Sensitive blood cells and tissue cells may undergo rapid division, leading to significant metabolic changes and stress responses in the body. This can cause adverse reactions in the surrounding tissues or throughout the body, such as ulcers, radiation dermatitis, and fatigue. It is crucial to address the negative emotions of radiotherapy patients and provide targeted psychological care to alleviate cancer-related fatigue symptoms and improve their quality of life[11].

Additionally, low hemoglobin levels are a risk factor for the severity of cancer-related fatigue. Hemoglobin is a functional protein in the blood that transports oxygen throughout the body. When hemoglobin levels decrease, the oxygen content in the blood also decreases, resulting in tissue hypoxia and subsequent fatigue symptoms[12]. Due to severe impairment of hematopoietic function in patients with hematologic malignancies, the number of red blood cells decreases, leading to reduced oxygen content in the blood and more pronounced fatigue. Therefore, in clinical interventions, it is necessary to improve the diagnosis and treatment of the underlying disease and improve the patient's hemoglobin levels. Under the guidance of doctors, health care professionals can provide patients with scientific dietary recommendations, increase their intake of iron, folate, vitamin B12, and other nutrients, and avoid consuming coffee, tea, and other substances that may hinder nutrient absorption. These measures can help improve a patient's nutritional status, alleviate cancer-related anemia, and relieve cancer-related fatigue[13].

Furthermore, subthreshold depressive states can exacerbate a patient's perception of pain. Previous research[14] has shown that depressive states increase sensitivity to pain and intensify the experience of pain. Leukemia patients often experience physical discomfort and pain. In this study, multivariate regression analysis with the inclusion of subthreshold depressive patients revealed pain as a risk factor for cancer-related fatigue, especially in later follow-up investigations where the incidence of bone pain complications was significantly higher in the depressive group than in the control group. Depressive states may make it more challenging for patients to tolerate pain, leading to increased fatigue and decreased quality of life.

This study indicated that regular exercise acts as a protective factor against cancer-related fatigue in patients with subthreshold depression. There is a strong correlation between exercise and the severity of cancer-related fatigue, and exercise is a crucial factor in determining the occurrence rate and severity of cancer-related fatigue. Regular exercise can alleviate cancer-related fatigue. Numerous intervention studies and meta-analyses have confirmed that aerobic exercise can reduce pain, tension, and depression caused by chemotherapy, improve cardiorespiratory endurance, enhance muscle strength, and improve overall health[15]. Multiple cancer-related guidelines recommend that patients with malignant tumors, under appropriate physical conditions, engage in moderate-intensity aerobic exercise or resistance training to alleviate cancer-related fatigue[16-18]. Therefore, it is suggested that health care professionals, in collaboration with patients' family members, provide guidance and supervision for leukemia patients to engage in personalized exercise choices such as running, fitness classes, swimming, and resistance training to prevent and alleviate cancer-related fatigue. Furthermore, a follow-up survey conducted after discharge revealed that the overall complication rate in the control group was 4%, which was significantly lower than the 24.21% rate in the depressive group ($P < 0.001$). The occurrence of depression not only affects the symptoms of cancer-related fatigue but also has a significant impact on the prognosis and complications of patients.

CONCLUSION

In summary, the incidence of cancer-related fatigue in leukemia patients with comorbid subthreshold depression is as high as 92%. Age, concurrent radiotherapy, regular exercise, depression, and hemoglobin levels are factors influencing cancer-related fatigue. In clinical practice, it is crucial to pay close attention to the symptoms of cancer-related fatigue in advanced-aged patients, those receiving concurrent radiotherapy, patients with depression, and those with low hemoglobin levels. Early implementation of personalized intervention measures is highly important for preventing and alleviating the occurrence and development of cancer-related fatigue in patients with hematological malignancies.

FOOTNOTES

Author contributions: Liu YX initiated the project, designed the experiment and conducted clinical data collection, and performed postoperative follow-up and recorded data; Wang J conducted a number of collation and statistical analysis, and wrote the original manuscript; both authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Central Hospital Affiliated to Shandong First Medical University.

Informed consent statement: This study obtained informed consent forms.

Conflict-of-interest statement: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data sharing statement: All data generated or analyzed during this study are included in this published article.

Country of origin: China

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S-Editor: Lin C
L-Editor: A
P-Editor: Zhang XD

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