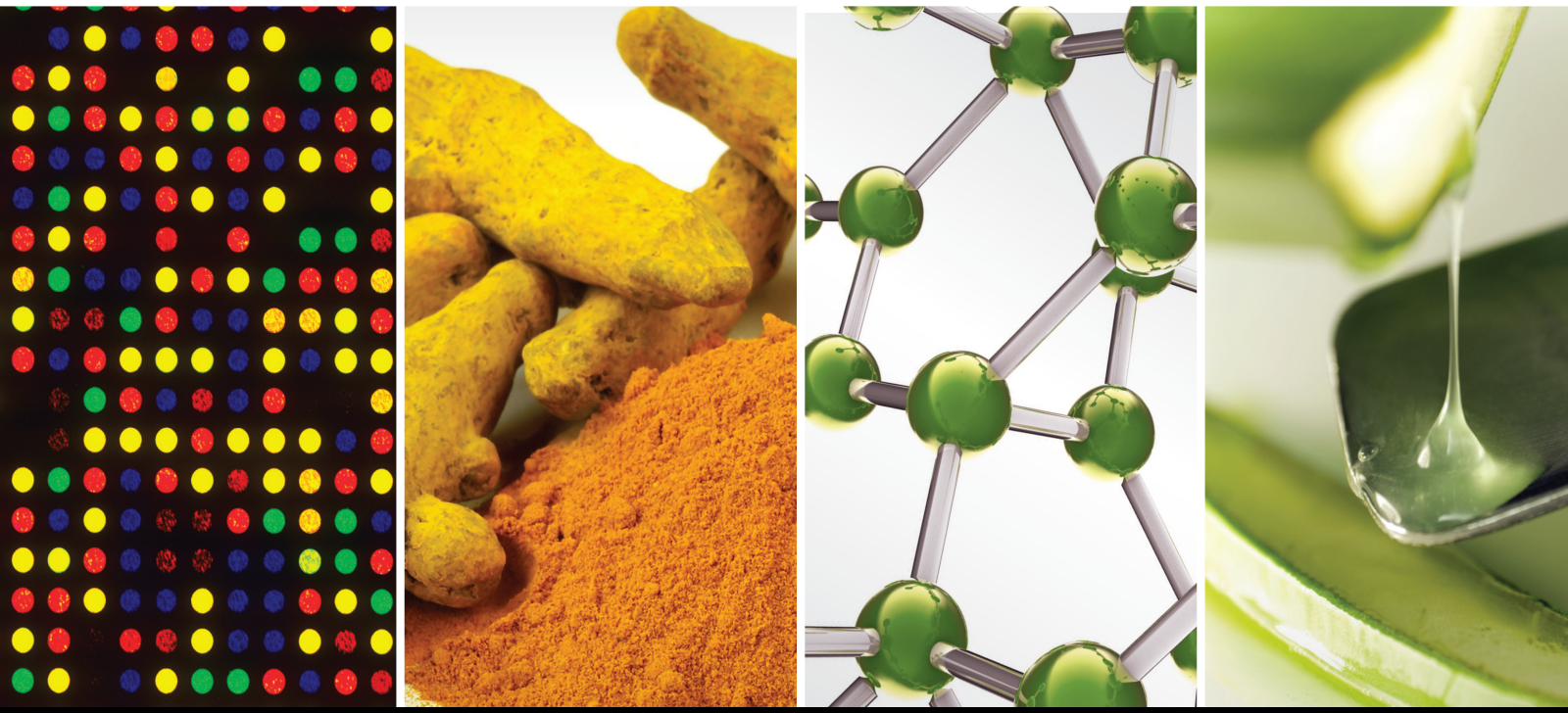
Evidence-Based Complementary and Alternative Medicine

Marine Natural Products Against Aging-Associated Diseases

Lead Guest Editor: Atul Kabra
Guest Editors: Gokhan Zengin and Jelena Zivkovic



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Chief Editor

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Retraction

Retracted: Analysis of Early Warning Diagnostic Indexes and Influencing Factors of Anxiety and Depression in Patients with Arrhythmia

Evidence-Based Complementary and Alternative Medicine

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] H. Yu, Y. Zhao, and Y. Li, "Analysis of Early Warning Diagnostic Indexes and Influencing Factors of Anxiety and Depression in Patients with Arrhythmia," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 2061340, 7 pages, 2022.

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Retraction

Retracted: MicroRNA-641 Inhibits Endometrial Cancer Progression via Targeting AP1G1

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[1] Y. Dong, H. Yang, and H. Hua, "MicroRNA-641 Inhibits Endometrial Cancer Progression via Targeting AP1G1," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7918596, 9 pages, 2022.

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Retraction

Retracted: Correlation of Presacral Tumour Recurrence with Tumour Metastasis and Long-Term Tumour Recurrence Risk in Patients with Rectal Cancer

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[1] L. Wang, H. Wu, R. Wang, H. Zhang, and J. Chen, "Correlation of Presacral Tumour Recurrence with Tumour Metastasis and Long-Term Tumour Recurrence Risk in Patients with Rectal Cancer," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 6202457, 9 pages, 2022.

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Research Article

Analysis of Early Warning Diagnostic Indexes and Influencing Factors of Anxiety and Depression in Patients with Arrhythmia

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Objective. Arrhythmia patients complicated with psychological problems are very common in clinics. The imbalance of autonomic nervous regulation of the heart caused by anxiety and depression will further promote the occurrence and development of arrhythmia. For nonorganic heart disease, β receptor blockers combined with antianxiety drugs have a good effect. Therefore, it is necessary to analyze the influencing factors of anxiety and depression in patients with arrhythmias. *Methods*. We included 150 patients with arrhythmia and divided them into observation groups (80 patients with anxiety and depression) and control groups (70 patients without anxiety and depression). All patients were monitored by Holter, and the detection of arrhythmia was compared between the two groups. We took the general situation and quality of life of the investigated patients as independent variables and the anxiety and depression status of the patients as dependent variables. *Results*. The detection rates of atrioventricular premature beats, ventricular premature beats, atrial fibrillation, short bursts of atrial tachycardia, and atrioventricular block in the observation group were all higher than those in the control group by dynamic electrocardiogram. Multivariate logistic stepwise regression analysis showed that age, years of education, obsessive-compulsive score, somatization score and alcohol consumption were the main influencing factors for anxiety and depression. *Conclusions*. The detection rate of arrhythmia in patients with anxiety/depression status was higher than in those without abnormal psychophylaxis. We should need to pay close attention to the risk factors of age, education years, obsessive-compulsive score, somatization score, and alcohol consumption, so as to prevent and timely detect anxiety and depression symptoms in patients with arrhythmias.

1. Introduction

Arrhythmia refers to any abnormality in the origin of cardiac impulses, heartbeat frequency, and rhythm, and impulse conduction. It can be caused by various organic cardiovascular diseases, drug poisoning, electrolyte and acid-base imbalance, and some arrhythmias can also be caused by autonomic nerve dysfunction [1, 2]. Arrhythmia complicated with anxiety or depression is very common in clinic. The latest data shows that the incidence of depression and anxiety among outpatients with arrhythmia is 20–30% [3]. The incidence in hospitalized patients can reach 40–60%. Anxiety and depression can activate hypothalamus-pituitary-adrenal system, promote sympathetic hypertonia, affect the coordination of autonomic nerves on cardiac regulation, and lead to the occurrence or aggravation of arrhythmia [4]. Research shows that both organic heart disease and nonorganic heart disease patients will produce obvious anxiety and depression symptoms, which will further aggravate the occurrence and development of arrhythmias and even lead to an increase in the mortality of organic heart disease patients [5, 6].

Anxiety in the field of psychology often refers to an inner uneasiness or groundless fear aroused by the lack of obvious and objective reasons [7, 8]. In fact, it does not happen in reality, but it is a kind of nervous, worried, and fearful emotion caused by my expectation that I will face bad or even dangerous situations. It is mainly manifested as continuous tension, uneasiness, worry, accompanied by mental tension, restlessness, excessive small movements, and excessive emotion and crying, and even panics [9]. At the same time, most patients will also be complicated with symptoms

of autonomic nervous dysfunction such as chest tightness, dry mouth, palpitation, tremors of both hands, cold sweat, anorexia, and constipation [10]. Contrary to the common people's understanding, an appropriate sense of anxiety will not bring negative effects to mankind, but rather the positive factors of human life can provide positive life motivation [11]. However, excessive anxiety will have a significant negative impact on people, not only as a manifestation of mental illness but also when accompanied by physical illness. If the heart rate accelerates and the blood pressure rises, and then the ventricular fibrillation threshold are lowered, the risk of sudden death from coronary heart disease is greatly increased [12]. Similar to anxiety, depression is also a common bad mood, which refers to the mental state dominated by a low mood. It often occurs together with bad emotions such as anxiety, helplessness, and agitation, and physical discomfort such as insomnia. There are various causes of depression, but only about 35% of depressed patients are caused by simple stress events, and about 65% of patients are related to somatic diseases [13]. Some studies have confirmed that depression can cause cortisol hyperfunction, improve sympathetic sensitivity, increase the corresponding hormone level in plasma, and then, cause insulin resistance, pancreatic islet secretion defect, lipid metabolism disorder, and other endocrine disorders, increase the incidence of obesity, and further aggravate the severity of arrhythmia [14, 15].

The prognosis of arrhythmia is related to the etiology, inducement, evolution trend and whether it leads to serious hemodynamic disorder [16]. It can suddenly attack and cause sudden death, and can also continue to involve the heart and cause failure. The poor prognosis and sudden death rate of cardiovascular diseases are increasing, which are related to bad psychology, disease cognition, and emotional reactions, especially anxiety and depression [17]. Emotions play an important role in the occurrence, development, and outcome of arrhythmia patients, especially the common bad emotions such as anxiety and depression [18]. Therefore, the identification and diagnosis of anxiety and depression disorders are directly related to the therapeutic effect and prognosis of arrhythmias [19].

Anxiety and depression can induce and promote arrhythmias in patients with cardiovascular diseases, and Holter can effectively reflect the relationship between them. Holter is one of the most convenient methods for arrhythmia detection and evaluation [20]. Various arrhythmias can be detected by Holter. Holter is a method that can continuously record and compile ECG changes of the human heart in an active and quiet state for a long time [21]. This technology was first applied to the study of monitoring cardiac electrical activity by Holter in 1947, so it is also called the Holter monitoring electrocardiograph, and it has become one of the important diagnostic methods of nontraumatic examination in the clinical cardiovascular field. Compared with ordinary ECG, Holter can continuously record up to 100,000 ECG signals within 24 hours, which can improve the detection rate of nonsustained arrhythmias, especially transient arrhythmias and transient myocardial ischemia attacks [22]. Holter is widely used, mainly for capturing paroxysmal arrhythmias, such as paroxysmal tachycardia and premature beats, and recording their occurrence time, quantity, and distribution; whether there is transient angina pectoris, myocardial ischemia, and the inducement and time of attack. Anxiety and depression patients often seek medical treatment for cardiovascular symptoms such as palpitation, chest tightness, fatigue, etc. ventricular or atrial arrhythmia often occurs in 24 h Holter [23]. Depression and anxiety can lead to a series of physiological and pathological changes by causing dysfunction of autonomic nervous system and enhancement of sympathetic nerve activity in vivo, thus, increasing the activity of catecholamine system, thus, inducing coronary artery spasm, exacerbating myocardial ischemia, and causing the formation of abnormal autonomy of the original nonautonomic cardiomyocytes under the effect of excessive catecholamine secretion [24]. The release of procoagulant substances and angiotensin II makes the sympathetic nerve excited, the heart rate accelerates, the blood pressure increases, the perceptual domain decreases, the HRV decreases, and the QT dispersion increases, which leads to an increase in cardiac load and a decrease in the threshold of ventricular ectopic activation, thus causing malignant ventricular arrhythmias with poor prognosis [25]. The comparison of the detection rates of arrhythmias in anxiety and depression patients by Holter ECG showed that the detection rates of atrial premature beats, ventricular premature beats, and short bursts of atrial tachycardia, atrial fibrillation, and atrioventricular block were significantly increased [26]. Therefore, Holter may be used as an early diagnosis and an early warning index of anxiety and depression in patients with arrhythmia.

With the rapid development of social economy, fast-paced lifestyle, social loneliness, excessive Internet use, overeating, or excessive dieting, as well as various life stress events have caused huge psychological and physiological burdens, of which anxiety and depression accompanied by arrhythmias are the most common [27, 28]. The novelty of this study was to detect the rate of arrhythmia in patients with anxiety status was higher than those without abnormal psychophylaxis.

2. Materials and Methods

We consecutively included 150 patients hospitalized in our hospital due to arrhythmia from January 2021 to April 2022 in our hospital. Inclusion criteria: Meeting the diagnostic criteria of arrhythmia; all have basic reading and writing ability and clear consciousness. Exclusion criteria: Patients with physical or mental diseases other than feelings of anxiety and depression; history of cardiac intervention and surgery; blind and deaf; pregnant or lactating women. There were 134 males and 16 females. The average age was (46.43 ± 5.12) years old. Disease types were as follows: 88 cases of paroxysmal supraventricular tachycardia, 30 cases of preexcitation syndrome, 18 cases of frequent ventricular premature beats, and 14 cases of atrial fibrillation. The study was approved by the ethics committee of our hospital, and all patients signed informed consent.

General information of all selected patients, including treatment mode, life behavior, body mass index, hospitalization time before treatment. Anxiety and depression were assessed by self-assessment of depression and self-assessment of anxiety. Both self-assessment of depression and self-assessment of anxiety had 20 self-assessment items. The higher the score, the higher the degree of anxiety and depression. The median value was 40 points. The Self-rating Depression Scale (SDS) and Self-rating Anxiety Scale (SAS) questionnaires were used to assess the anxiety and depression of the patients. If the SDS score was ≥50, the patients would be assessed as depresssion, and if the SAS score was ≥50, the patients would be assessed as anxiety. The patients' self-assessment and the professional doctors of our hospital would conduct blind assessment. The quality of life was investigated with the Chinese version of Symptom Checklist 90 (SCL-90) scale. The 70 items included in the scale can be summarized into 7 symptom groups, including somatization Compulsion, interpersonal sensitivity, hostility, terror, paranoia, psychosis. The higher the score, the worse the quality of life.

All patients were monitored by Holter monitoring (CV3000 12 lead Holter recording and analysis system, Beijing gushanfeng company). Holter was recorded continuously for 24 hours. The occurrence of arrhythmia was determined manually and automatically by computer system. The detection of arrhythmia in the two groups was statistically analyzed. The influencing factors of anxiety and depression in patients with arrhythmia were investigated and analyzed by professionals according to the above three scales. The evaluation was completed within 15–20 minutes. The questionnaire was collected and checked on-site to ensure that the effective rate of the survey was 100%.

2.1. Statistical Analysis. SPSS 25.00 statistical software was used, *t*-test was used for measurement data, and (%) was used for counting data $\chi 2$ inspection. For multiple comparisons, data were analyzed via analysis of variance (ANOVA) with the Tukey–Kramer multiple comparisons test. The influencing factors were analyzed by dichotomous logistic stepwise regression, and $P < 0.05$ means that the difference is statistically significant.

3. Results

3.1. Baseline Demographic Data. The smoking rate of the patients in the observation group was higher and the number of years of education decreased was lower than that of the control group ($P < 0.05$), but there were no statistical difference in alcohol consumption, disease course, body mass index (BMI), and hospitalization time ($P > 0.05$) (Table 1).

3.2. The Type of Arrhythmia in Patients with/without Anxiety and Depression Status. The detection rates of atrial premature beats, ventricular premature beats, and short bursts of atrial tachycardia, atrial fibrillation, and atrioventricular block in the observation group were significantly higher than those in the control group. Data analysis found that the difference was statistically significant ($P < 0.05$, Table 2).

3.3. The Quality of Life Scores of the Two Groups. The scores of somatization, compulsion, interpersonal sensitivity, hostility, terror, paranoia and psychosis in the observation group were significantly increased ($P < 0.05$), which are shown in Table 3.

Binary logistic stepwise regression analysis of the influencing factors of anxiety and depression in patients with arrhythmia.

We took the general situation and quality of life from the survey as independent variables and the anxiety and depression status of the patients as dependent variables, and included them in the binary logistic stepwise regression analysis. The results showed that age, years of education, obsessive-compulsive score, somatization score, and alcohol consumption were the main influencing factors leading to anxiety and depression ($P < 0.05$), which are shown in Table 4.

4. Discussion

The most common arrhythmia is premature cardiac beats, including atrial premature beats and ventricular premature beats. Patients often have chest tightness, palpitations, heartbeat or shortness of breath, and an individual cough. Premature beats often occur in patients with nonorganic heart disease, and are often related to mental tension, excitement, drinking, strong tea, and coffee [29]. Through 24-hour ECG dynamic monitoring, it was found that the incidence of premature contraction in nervous workers was twice as high as that in general workers. Palpitation, chest tightness, and other symptoms of patients with premature beats are not necessarily related to premature beats but can also be caused by anxiety and depression. Anxiety and depression can also increase the incidence of premature beats [30]. When premature beats are combined with anxiety and depression, the activation of the hypothalamus-pituitary adrenal system, the promotion of sympathetic hypertonia, and the release of too many catecholamines lead to abnormal myocardial autonomy and the posterior depolarization of increased Ca influx, thus leading to an increase in the incidence of premature beats [31]. In this study, 150 patients with premature cardiac beats were scored by the Hamilton scale, which showed that all the included cases were accompanied by obvious anxiety and depression. All patients were randomly divided into antianxiety and depression treatment group and the control group. The results showed that the incidence of premature cardiac beats in the fluocinonide treatment group was significantly reduced compared with the control group, and the cardiac-related symptoms were also significantly reduced. Arrhythmias associated with common nonorganic heart diseases include idiopathic ventricular tachycardia, idiopathic atrial fibrillation, atrial flutter, and atrial tachycardia. The symptoms of chest tightness and palpitation are more obvious during the attack, and because the attacks are repeated and without any

Table 1: Baseline demographic characteristics.

Index	Observation group	Control group	*P*-value
Age (years)	55.43 ± 5.53	48.26 ± 6.75	0.015*
Drinking (*n*)	21 (26.25)	7 (10.00)	0.012*
Smoking (*n*)	17 (21.25)	15 (20.14)	0.925
Course of disease (months)	4.33 ± 1.30	4.39 ± 0.97	0.202
Years of education (years)	9.20 ± 4.31	14.29 ± 4.24	0.015*
Body mass index (BMI, kg/m^2)	21.76 ± 4.11	21.76 ± 4.18	0.313
Hospitalization time (days)	14.44 ± 0.67	14.40 ± 0.66	0.472

Table 2: Type of arrhythmia in patients with/without anxiety and depression status.

Type	Observation group	Control group	*P* value
Atrioventricular premature beats	48 (60.00)	21 (30.00)	0.006
Ventricular premature beats	32 (40.00)	13 (18.57)	0.003
Atrial tachycardia	21 (26.25)	7 (10.00)	0.002
Atrial fibrillation	17 (21.25)	5 (7.14)	0.005
Atrioventricular block	13 (16.25)	2 (2.86)	0.012

Table 3: The quality-of-life scores in patients with/without anxiety and depression status.

Index	Observation group	Control group	*P -value*
Somatization	1.65 ± 0.45	1.38 ± 0.41	0.010
Forced scoring	1.55 ± 0.59	1.46 ± 0.42	0.013
Sensitivity to human nature	1.50 ± 0.44	1.34 ± 0.35	0.016
Hostile	1.54 ± 0.47	1.32 ± 0.33	0.018
Terror	1.69 ± 0.51	1.50 ± 0.36	0.019
Paranoia	1.49 ± 0.35	1.36 ± 0.34	0.025
Psychosis score	1.35 ± 0.31	1.22 ± 0.22	0.028

Table 4: Analysis of the influencing factors of anxiety and depression in patients with arrhythmia.

Variable	*B-value*	*P value*	*OR-value*
Age	1.398	0.013	5.231
Years of education	1.690	0.004	4.872
Forced scoring	1.701	0.006	4.982
Somatization score	1.600	0.015	0.203
Drinking	1.573	0.007	0.502

incentive, patients are often more prone to anxiety and depression. Premature beats, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, conduction block and other arrhythmias can occur in various heart diseases, such as coronary heart disease, hypertension, heart failure, cardiomyopathy and so on. The occurrence of arrhythmias often predicts the aggravation of the original heart diseases, makes the conditions and symptoms more complex and diverse, and aggravates the anxiety or depression of patients. This change of mood can further accelerate the deterioration of the disease [32]. Studies have shown that arrhythmia patients with anxiety and depression have more serious dysfunction of the autonomic nerve in regulating the heart, which usually leads to increased sympathetic activity and decreased parasympathetic activity [33, 34]. A large number of studies have shown that the prevalence of anxiety in patients with coronary heart disease is as high as 40%~70%. When depression and anxiety occur in patients with coronary heart disease, it can cause a large amount of catecholamines to be secreted in the body, leading to an accelerated heart rate [35]. Studies have shown that anxiety and depression in patients with coronary heart disease can not only increase the incidence of arrhythmia but also greatly increase mortality. A very important factor in the pathophysiological mechanism of chronic heart failure is the activation of the renin-angiotensin-aldosterone system, which in turn aggravates the process of heart failure. Moreover, it is easy to promote rapid ventricular arrhythmia, and anxiety and depression will promote the activation of sympathetic nerves, which will further aggravate heart failure and increase the incidence of malignant arrhythmia and sudden death in patients with chronic heart failure [36].

Electrocardiograms are often used to monitor patients with cardiovascular diseases, which have different characteristics at different periods of time [37]. Through dynamic electrocardiogram monitoring, it was found that the detection rate of arrhythmia accompanied by anxiety and depression in the observation group was significantly higher than that in the control group, and the difference was statistically significant ($P < 0.05$), suggesting that anxiety and depression were closely related to the occurrence of arrhythmia. This study believes that anxiety and depression can trigger autonomic nervous disorders in the body and further increase the cardiac load with the release of procoagulant substances and angiotensin II, reducing the threshold of ventricular ectopic activation and triggering malignant ventricular arrhythmia. Arrhythmia is complicated by anxiety and depression, which is closely related to arrhythmia. The detection rate of arrhythmia in patients monitored by Holter is high, which has clinical application value.

Anxiety and depression are common mental disorders in the clinic. Studies have shown that anxiety and depression are common psychological disorders in patients undergoing

interventional treatment, and about 6.0% of patients suffer from anxiety and depression symptoms. The results showed that the education level, regional distribution, marital status, and nature of work of patients with arteriosclerosis were related to their accompanying emotional disorders. The level of the patient's education determines a person's ability to acquire knowledge and broaden their vision to another level. Because of their remote families, rural patients are inconvenient to seek medical treatment, and their economic conditions are generally worse than those of urban patients, with large emotional fluctuations. Moreover, rural patients have more contact with their neighbors and friends and are more susceptible to the attitude of the surrounding people. For those with a high educational level, for various reasons, they often sit for a long time, exercise less, stay up late, smoke and drink too much for entertainment, or surf the Internet too much, which will lead to obesity, endocrine disorders, immune system disorders, and other harmful cardiovascular and cerebrovascular elasticity [38]. People with low education generally engage in more physical labor, relatively more exercise, good spirits, reduced physical pressure, and less vascular damage. At the same time, exercise is conducive to emotional relief. Therefore, people with low education have a higher rate of arteriosclerosis than those with high education, especially those with mental skills. Those who have social support, especially those who have family members and caregivers, will have a less psychological burden than those who are alone. Even if they are ill, because their families accompany and support them, their morale is relatively stable.

If these influencing factors were given timely and appropriate health education, the prevention of primary diseases could be effectively improved. Health education shall be given to medical staff and inpatients, and targeted health education shall be given to different types of arteriosclerosis diseases. We should widely publicize the knowledge about psychological snow and arteriosclerosis, explain to patients or their families the importance of long-term exercise and health care, pay attention to weight control, and adhere to a low salt and low fat diet; pay attention to emotional adjustment and keep a happy mind; stick to physical exercise. At the same time, it is necessary to explain the general knowledge of psychology and general physical diseases, especially arteriosclerosis, to the patients' families in a targeted way, so that the families can have a general understanding of the diagnosis and treatment of the disease, support and care for the patients. On the other hand, patients should constantly learn, understand themselves, adapt to the environment, control their emotions, vent appropriately, and reduce psychological pressure. People who worry about and fear diseases should know that these are controllable diseases, and they should persist in taking drugs when necessary. When side effects of drugs occur, they can be identified and dealt with in time, so as to avoid aggravating side effects and causing greater pain and affecting patients' emotions [38].

Antianxiety and depression treatment is effective and meaningful in both chronic diseases and acute stress events. Therefore, in the prevention of anxiety and depression, health education, purpose, related complications, and other information are conveyed to patients, and targeted psychological intervention is carried out for patients, which can significantly improve their psychological coping ability and promote their physical and mental recovery. The limitation of the study was that the number of patients is not so large. Also, the mechanism was not clarified. Further studies are needed to study the mechanism.

In conclusion, the detection rate of arrhythmias in elderly patients with cardiovascular disease combined with anxiety and depression under Holter monitoring is high, and anxiety and depression are closely related to the occurrence of arrhythmias in elderly patients with cardiovascular disease. We need to pay close attention to the risk factors of age, education years, obsessive-compulsive rating, somatization rating, and alcohol consumption so as to prevent and timely detect anxiety and depression in patients with arrhythmias.

Data Availability

The data used to support this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Retraction

Retracted: MicroRNA-641 Inhibits Endometrial Cancer Progression via Targeting AP1G1

Evidence-Based Complementary and Alternative Medicine

Received 11 July 2023; Accepted 11 July 2023; Published 12 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] Y. Dong, H. Yang, and H. Hua, "MicroRNA-641 Inhibits Endometrial Cancer Progression via Targeting AP1G1," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 7918596, 9 pages, 2022.

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Research Article

MicroRNA-641 Inhibits Endometrial Cancer Progression via Targeting AP1G1

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MicroRNA-641 (miR-641) was significantly decreased in various cancers, but its roles in endometrial cancer (EC) remain unclear. We explored the influences of miR-641 on the EC cells. In our study, the miR-641 expression was reduced in EC cells. Overexpression of miR-641 inhibited viability and proliferation of HEC-1A and HECCL-1 cells by CCK-8 and colony formation assays. Additionally, flow cytometry revealed that overexpression of miR-641 could remarkably promote apoptosis and arrest the cell cycle at the G1 phase of HEC-1A and HECCL-1 cells. Besides, forced expression of miR-641 suppressed the migration and invasion of HEC-1A and HECCL-1 cells as evidenced by wound healing and transwell assay. Moreover, AP1G1 was confirmed as a target gene of miR-641 by StarBase prediction and DLR assay and their expressions were negatively correlated. Overexpression of AP1G1 neutralized the roles of miR-641 mimic on the viability, proliferation, apoptosis, and migration of HEC-1A and HECCL-1 cells. Our findings illustrated that miR-641 was reduced in the EC cells and AP1G1 antagonized the miR-641 mimic-induced inhibition of the EC progression *in vitro*. Therefore, miR-641 may emerge as an effective molecule for EC treatment.

1. Introduction

Endometrial cancer (EC) is a reproductive system tumor in females and ranks fourth in developed countries. Furthermore, in developing countries, the incidence rate of EC is also in the seventh place in female tumors. EC often occurs in postmenopausal women, but in recent years, clinical research shows that EC has a significant trend in youth [1, 2]. After standardized treatment, the 5-year survival rate rises year by year. The late prognosis of late, poorly differentiated EC or special types is an important factor leading to death. Therefore, to improve the prognosis of EC, it is necessary to investigate the pathogenesis and effective targets of EC [3].

At present, most studies show that EC is related to obesity, hypertension, diabetes, or long-term exposure to estrogen without progesterone antagonists [4–6]. However, at the molecular level, the mechanism of EC is not clear and the abnormal gene regulation, such as the imbalance of oncogenes, tumor suppressor genes, and polymorphism, cannot fully explain the pathogenesis of EC [7, 8]. It has been shown that microRNAs (miRNAs), noncoding single strand small molecules with 19–25 nucleotides in length could mediate the progression of EC [9, 10]. For example, miR-135a was upregulated in the EC cells and the overexpression of miR-135a could increase proliferation and metastasis while inducing chemoresistance of the EC cells [11]. Additionally, miR-214-3p was impoverished in EC tissues and cell lines. Upregulation of miR-214-3p suppressed metastasis of the EC cells through inhibition of EMT via targeting TWIST1 [12]. Therefore, miRNAs may be effective targets for EC therapy.

miRNA-641 (miR-641) exhibited an essential role in lung cancer, cervical carcinoma, and glioblastoma [13–15]. However, its mechanism in the EC cells remain unknown. Herein, we evaluated miR-641 expression in the EC cells, the detailed role, and possible mechanisms were determined.

2. Materials and Methods

2.1. Cells. HEC-251 and EC cell lines HEC-1A, RF952, HECCL-1, and BMDC1 were bought from the Chinese Academy of Science and incubated with DMEM (Gibco, USA) plus 10% FBS (Gibco, USA) and antibiotics in a humidified 5% CO_2 incubator at 37°C.

2.2. Transfection. miR-641 mimic/mimic NC and specific siRNAs against AP1G1, the pcDNA3.1 vector targeting AP1G1 and the empty vector (Genechem, China) were transfected into the EC cell lines via Lipofectamine 3000 (Thermo Fisher, USA).

2.3. CCK-8 Assay. The transfected HEC-1A and HECCL-1 cells (1×10^4 cells/well) were kept in 96-well plates and incubated for indicated times. The viability was tested by a CCK-8 kit (Beyotime, China). OD was recorded at 450 nm by Tecan Infinite M200 (LabX, Switzerland).

2.4. Colony Formation Assay. HEC-1A and HECCL-1 cells (1×10^3/well) were cultured in 6-well plates with a refreshing medium every 3 days for 14 days. Then, the cells were stained with 10% crystal violet to determine the proliferative ability.

2.5. Flow Cytometry. 1×10^6/mL transfected HEC-1A and HECCL-1 cells were fixed with 70% ethanol at 4°C overnight. After washing, 100 μL of RNase A was administrated for 30 min at 37°C and 400 μL of PI dye solution and was applied and incubated for 0.5 h at 4°C. The cell cycle was checked using a flow cytometer (BD, USA).

The transfected HEC-1A and HECCL-1 cells were harvested and resuspended. Then, the cells were treated with Annexin V-FITC (5 μL) and PI (10 μL). The apoptosis was measured.

2.6. Wound Healing Assay. HEC-1A and HECCL-1 cells (5×10^5 cells/well) were kept in 6-well plates. After the confluence reached 80%, a 10 μL pipette tip wound of the monolayer and the cells were cultured continuously. The cells were photographed at 48 h with inverted microscopy (Tokyo, Japan).

2.7. Transwell Assay. The transfected HEC-1A and HECCL-1 (1×10^6 cells/well) were seeded into the upper chamber of the transwell equipment (Corning, USA) with serum-free DMEM medium. The lower chamber had DMEM with 20% FBS. To check the invasion of cells, Matrigel (Becton-Dickinson, USA) was transferred to the upper chambers. After 48 h, the cells were stained with 0.5% crystal violet and observed with inverted microscopy (Tokyo, Japan).

2.8. Dual-Luciferase Reporter (DLR) Assay. Wild type and mutant AP1G1 3'-UTR vectors were synthesized by subcloning AP1G1 3'-UTR and mutant 3'-UTR sequences into the plasmids (Promega, USA). Then, HEC-1A and HECCL-1 were co-transfected with reporter vectors (80 ng) and miR-641 mimic/NC mimic using Lipofectamine 3000 (Thermo Fisher, USA). After 48 h, luciferase activities were recorded.

2.9. RT-qPCR Assay. RNA was separated by Trizol (Invitrogen, USA) and synthesized to cDNA with a TaqMan Reverse Transcription Kit (AB, USA). RT-qPCR was implemented using ABI 7300 (AB, USA) with a SYBR Green PCR Kit (Qiagen, USA). Relative expression was evaluated by the $2^{-\Delta\Delta Ct}$ method. The primers were as follows: miR-641 forward, 5′-TTATACTCTCACCATTTGGATC-3′, reverse, 5′-TGACAAGATTTTACATCAAG AA-3′. U6 forward, 5′-CTCGCTTCGGCAGCACATA-3′, reverse, 5′-AACGCTTCACGAATTT GCGT-3′.

2.10. Western Blot. Protein was isolated and quantified via a BCA kit (Beyotime, China), separated through 12% SDS-PAGE, shifted into PVDF membranes (Millipore, USA) and sealed with 5% non-fat milk. Then, the samples were treated with the primary antibodies, probed with a HRP-conjugated secondary antibody (1 : 2,000, ab6728), observed with an ECL kit (Millipore, USA) and analyzed via Image J. The primary antibodies were as follows: anti-Cyclin D1 (1 : 1, 000, ab16663), anti-CDK2 (1 : 1000, ab32147), anti-PCNA (1 : 1000, ab92552), anti-COX2 (1 : 1000, ab15191), anti-MMP-2 (1 : 1000, ab97779), anti-MMP-9 (1 : 1000, ab38898), anti-APP1G1 (1 : 1000, ab167153), and anti-β-actin (1 : 2, 000, ab8227) (Abcam, USA).

2.11. Statistical Analysis. Data were processed by the GraphPad Prism 5.0 and exhibited as the mean ± SD. ANOVA followed by Tukey's POC host calculated the differences between the groups. $P < 0.05$ indicated a statistical significance.

3. Results

3.1. miR-641 Is Downregulated in the EC Cells and miR-641 Mimics Suppresses Viability and Proliferation of the EC Cells. First, RT-qPCR was employed to evaluate the miR-641 expression in HEC-251 and the EC cell lines HEC-1A, RF952, HECCL-1, and BMDC1. Figure 1(a) demonstrates that miR-641 was lessened in the EC cells compared with HEC-251 cells, especially in HEC-1A and HECCL-1 cells. Moreover, miR-641 mimic and miR-641 mimic NC were transfected into HEC-1A and HECCL-1 cells and the efficiency was evaluated by RT-qPCR assay. Figure 1(b) reports that miR-641 in HEC-1A and HECCL-1 cells transfected with miR-641 mimic was increased relatively to the miR-641 mimic NC group. In addition, Figure 1(c) displays that overexpression of miR-641 diminished the viabilities of HEC-1A and HECCL-1 cells. Furthermore, the proliferation of HEC-1A and HECCL-1 cells was detected and miR-641 mimic inhibited the proliferation of HEC-1A and HECCL-1 cells relative to miR-641 mimic NC (Figure 1(d)). These suggested that the EC cells has a low level of miR-641 and its overexpression inhibited cell viability and proliferation.

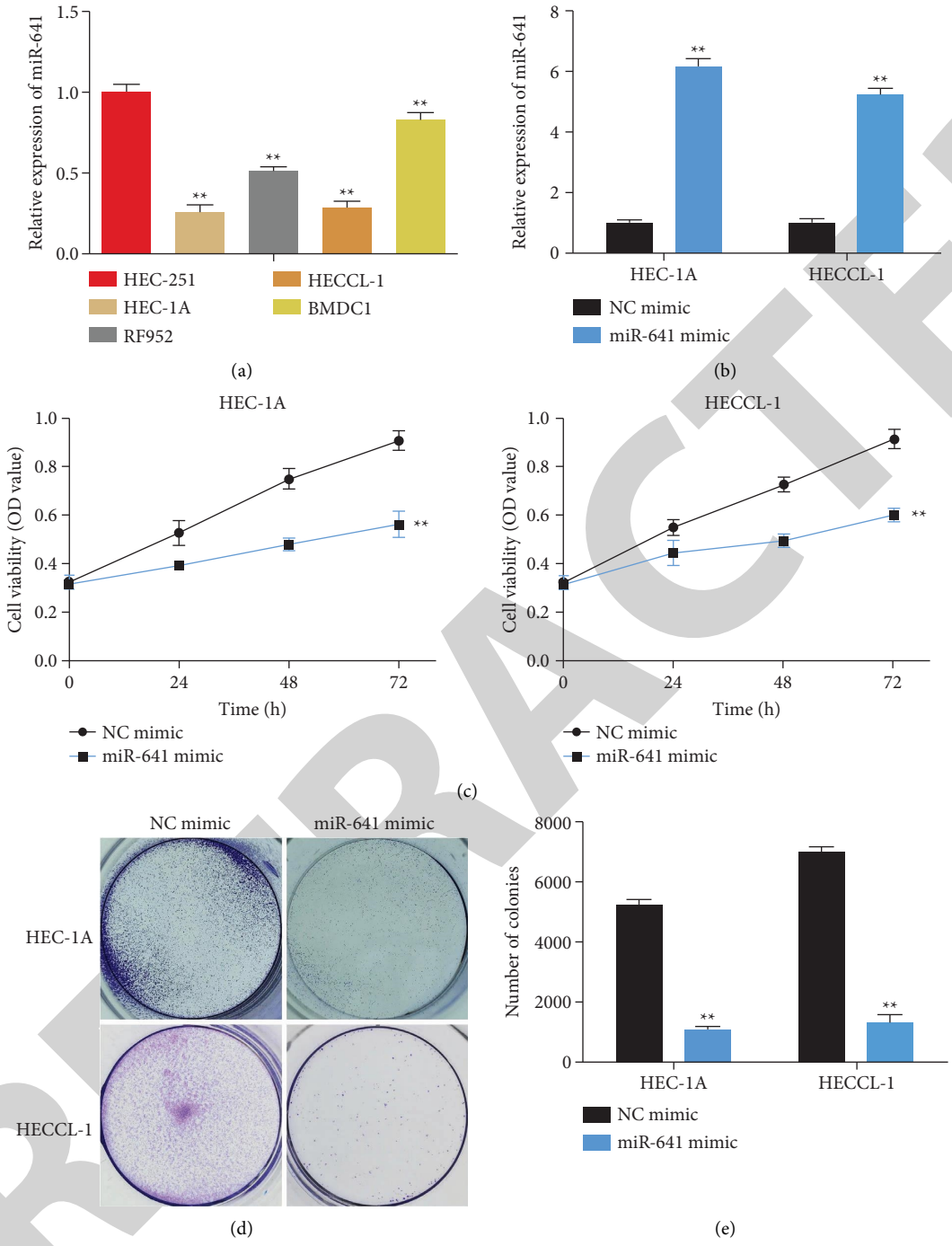

Figure 1: miR-641 is downregulated in the EC cells and upregulation of miR-641 inhibits viability and proliferation of the EC cells. (a) The expression level of miR-641 in the EC cells was detected by RT-qPCR assay. (b) The expression level of miR-641 in HEC-1A and HECCL-1 cells transfected with miR-641 mimic was evaluated by RT-qPCR assay. (c) The viability of HEC-1A and HECCL-1 cells transfected with miR-641 mimic was assessed by CCK-8 assay at indicated times. (d) The proliferation of HEC-1A and HECCL-1 cells transfected with miR-641 mimic was evaluated by colony formation assay. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. miR-641 mimic NC.

3.2. Upregulation of miR-641 Accelerates Apoptosis and Induces the G1 Phase Arrest of the EC Cells. Flow cytometry was performed and the data showed that the miR-641 mimic caused the apoptosis of HEC-1A and HECCL-1 cells compared to the miR-641 mimic NC group (Figure 2(a)). Additionally, it was found that miR-641 mimic triggered cell cycle arrest in the G1 phase of HEC-1A and HECCL-1 cells compared to the miR-641 mimic NC group (Figure 2(b)). Furthermore, the results of the Western blot in Figure 2(c) indicate that upregulation of miR-641 inhibited the protein levels of Cyclin D1 and CDK2, whereas the P21 expression was promoted in HEC-1A and HECCL-1 cells. These evinced that cell apoptosis and cell cycle arrest in the G1 phase are triggered by upregulation of miR-641.

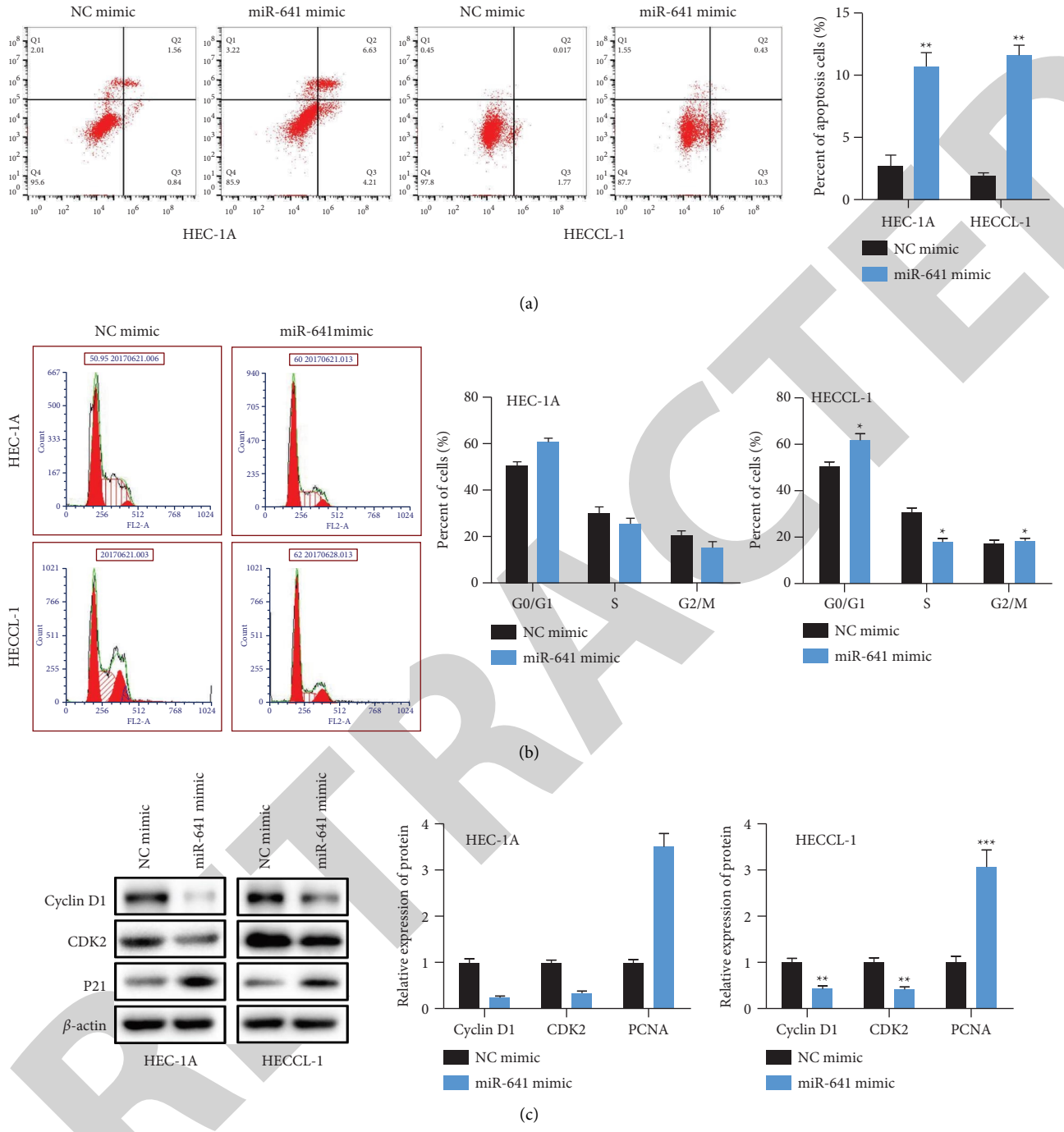

Figure 2: Upregulation of miR-641 promotes apoptosis and induces G1 phase arrest of the EC cells. (a) The apoptotic rate of HEC-1A and HECCL-1 cells transfected with miR-641 mimic was determined by flow cytometry assay. (b) The cell cycle of HEC-1A and HECCL-1 cells transfected with miR-641 mimic was determined by flow cytometry assay. (c) The expression levels of proteins, including Cyclin D1, CDK2, and P21, were evaluated by western blot assay. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. miR-641 mimic NC.

3.3. Upregulation of miR-641 Retards Metastasis of the EC Cells. Wound healing and transwell assays determined the role of miR-641 in the EC cell migration and invasion. Figure 3(a) illustrates that the miR-641 mimic suppressed the migration of HEC-1A and HECCL-1 cells compared to the miR-641 mimic NC group. In addition, Figure 3(b) reports that miR-641 mimic reduced the metastasis of both the cell lines. Furthermore, the levels of metastasis-associated proteins were checked and the data in Figure 3(c) reveal that the levels of Cox-2, MMP-2, and MMP-9 were reduced in the cells transfected with miR-641 mimic. These summarized that metastasis of the EC cells is caused by the upregulation of miR-641.

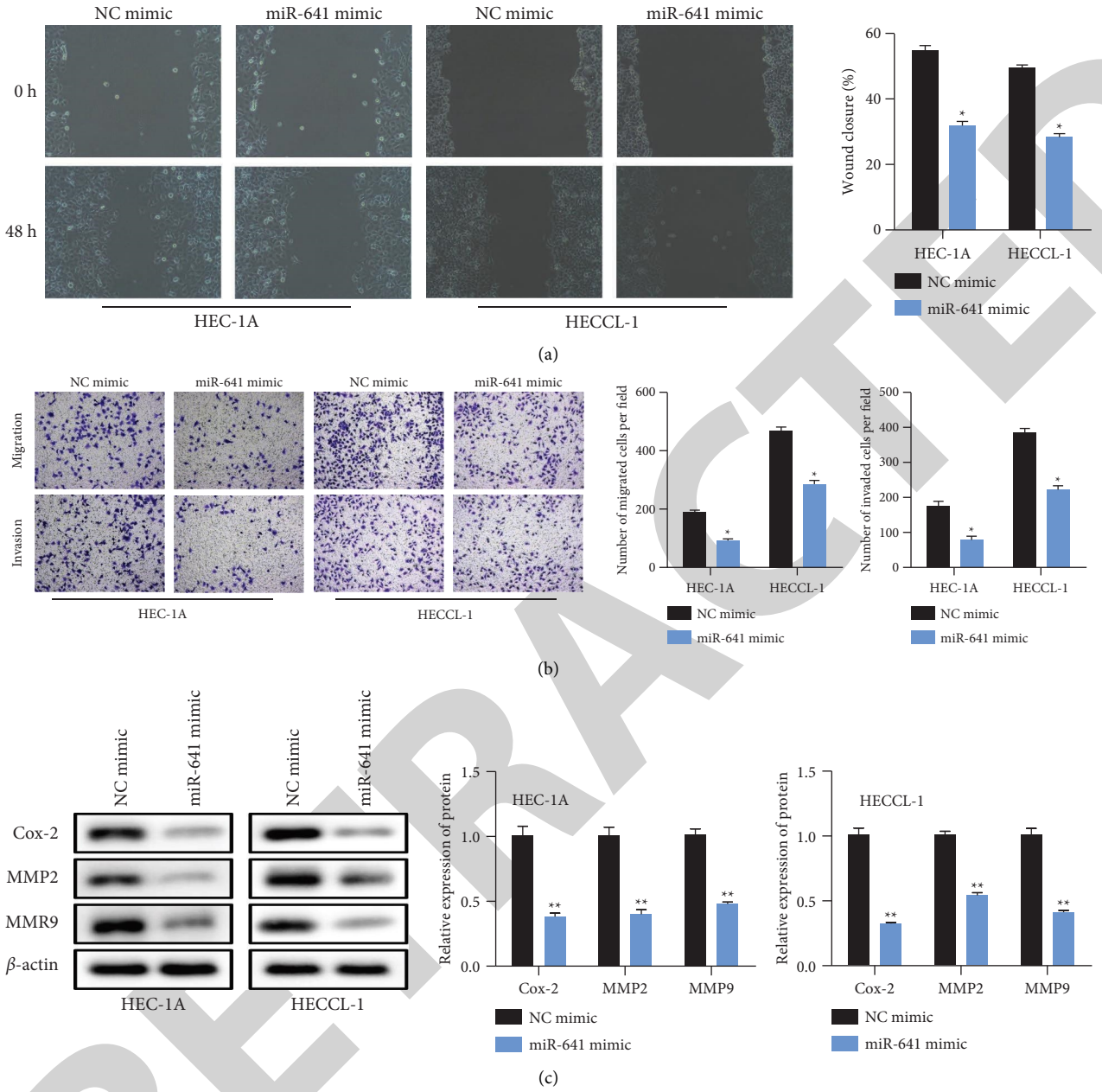

Figure 3: Upregulation of miR-641 inhibits migration and invasion of the EC cells. (a) The migration of HEC-1A and HECCL-1 cells transfected with miR-641 mimic was determined by wound healing assay. (b) The migration and invasion of HEC-1A and HECCL-1 cells transfected with miR-641 mimic were determined by the transwell migration and invasion assays. (c) The expression levels of proteins, including Cox-2, MMP-2, and MMP-9, were evaluated by western blot assay. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. miR-641 mimic NC.

3.4. AP1G1 Is Sponged by miR-641 in the EC Cells. miRNAs function as oncogenes or antioncogenes via sponging downstream target genes. In Figure 4(a), using StarBase, AP1G1 was predicted as a possible target of miR-641 and it was proved to manage the development of colon cancer and breast cancer [16–18]. Furthermore, it was detected by DLR assay that miR-641 weakened the luciferase activity of 3'UTR of AP1G1 mRNA, whereas the suppressive effect was terminated by the mutation on the binding sites (Figure 4(b)). Moreover, the AP1G1 expression in the miR-641 mimic-transfected HEC-1A and HECCL-1 cells were assessed. In Figures 4(c) and 4(d), the levels of AP1G1 were dropped in miR-641 mimic-transfected cells. These results proved that AP1G1 was sponged by miR-641 in EC.

3.5. AP1G1 Affects the Roles of miR-641 on the EC Cells. The cells were infected with Lv-AP1G1, and the efficacy was determined by RT-qPCR assay and the data are given in Figure 5(a). Functionally, the result of the CCK-8 assay emerged that overexpression of AP1G1 eliminated the prominent reduction in proliferation of HEC-1A and HECCL-1 cells transfected with miR-641 mimic

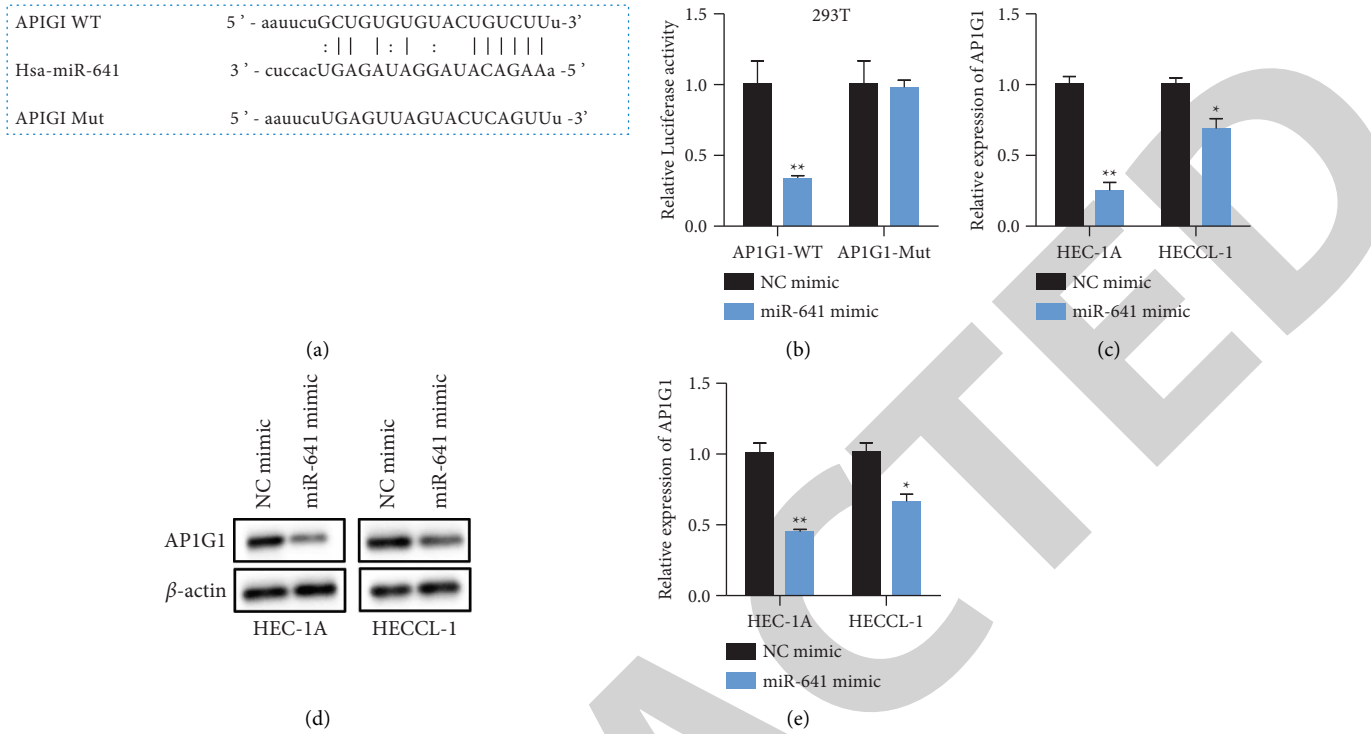

Figure 4: AP1G1 is a direct target of miR-641 in the EC cells. (a) The target gene of miR-641 was predicted with StarBase. (b) Dual luciferase reporter analysis was employed to validate the coactions between AP1G1 and miR-641. (c) The mRNA expression of AP1G1 in HEC-1A and HECCL-1 cells transfected with miR-641 mimic was evaluated by RT-qPCR assay. (d) The protein expression of AP1G1 in HEC-1A and HECCL-1 cells transfected with miR-641 mimic was evaluated by western blot assay. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. miR-641 mimic NC.

(Figure 5(b)). Colony formation assay also unveiled that the overexpression of AP1G1 altered the impaired proliferative ability of cells transfected with miR-641 mimic (Figure 5(c)). Correspondingly, the promotive impacts of miR-641 mimic on cell apoptosis cells were ameliorated by AP1G1 overexpression (Figure 5(d)). Moreover, the transwell assay manifested that overexpression of AP1G1 compensated inhibitory influence of miR-641 mimic on the metastasis of both the cell lines (Figure 5(e)). These data summarized that AP1G1 took part in the function of miR-641 in EC.

4. Discussion

EC is a heterogeneous tumor derived from endometrium with different histological types and is a common malignancy with a 53% survival rate within 5 years [19]. The mortality rate of EC has gradually risen and tends to be younger [20]. Hence, the development of new biomarkers has become the main means of diagnosis and therapy of EC.

miRNAs, as a group of short sequence RNAs, do not encode proteins with a length of about 19–25 nt and are widely distributed in eukaryotes. In addition, their synthesis is an extremely complex biological process, mainly in the cytoplasm and nucleus [21]. miRNAs can regulate cell survival, differentiation, and response to the external environment through degrading target gene miRNAs or inhibiting the expression of regulatory genes in the translation process via the incomplete complementary pairing of their "seed" sequence with the 3'-UTR region of target gene miRNAs [22]. MicroRNAs control EC at different stages of development, and their abnormal expression in tumors plays a dual role in promoting or inhibiting cancer. For example, miR-125b was upregulated in EC and the silence of miR-125b retard the proliferation and enhance apoptosis of the EC cells by directly suppressing TP53INP1 [23]. A high level of miR-106b was reported in EC and it enhanced the proliferation but inhibited apoptosis by suppressing p21 and Bim [24]. miR-204 was decreased in EC and further targeted FOXC1. Meanwhile, high expression of miR-204 in EC boosted the metastasis and infiltration of the EC cell HEC-1-A [25]. It can be seen that the detection of miRNA expressions in EC can help to evaluate the role of miRNAs. miR-641 has been found in various types of tumors acting as a tumor suppressor. For instance, Kong et al. found that miR-641 was dropped in lung cancer tissues and overexpression of miR-641 blocked the proliferation and induced apoptosis of lung cancer cells via sponging MDM2 [26]. Yao et al. manifested that upregulation of miR-641 deterred the proliferation of cervical cancer cells [27]. Hinske et al. found a low level of miR-641 in glioblastoma and it regulated the activation of AKT2 [15]. However, the possible mechanisms of miR-641 on EC remained unclarified. Here, we found that the miR-641 expression was low in the EC cells and its overexpression weakened proliferation and metastasis, reinforced apoptosis, and induced cell cycle arrest in the G1 phase. These results were consistent with previous research which verified that miR-641 acted as a tumor suppressor miRNA in EC.

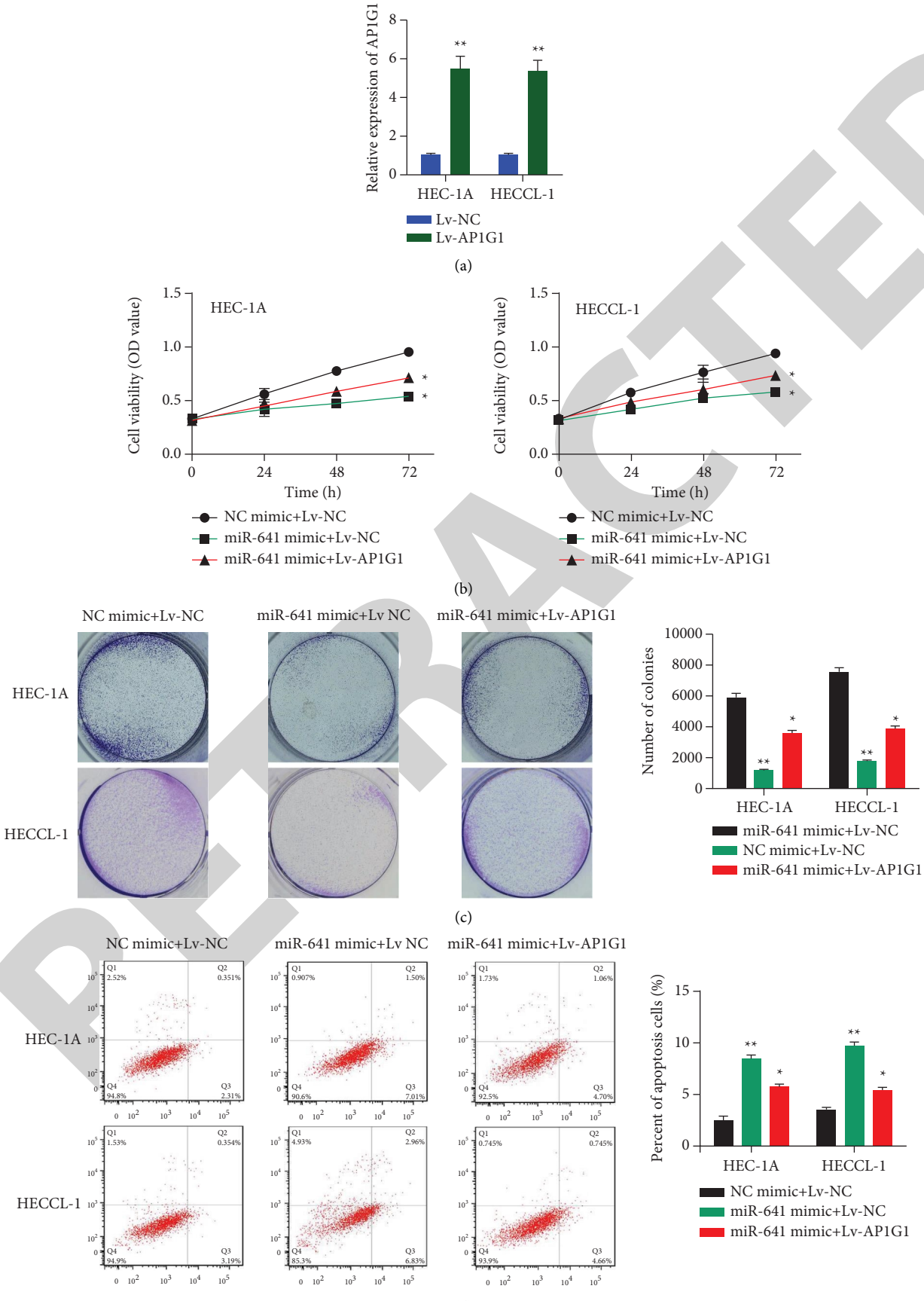

Figure 5: Continued.

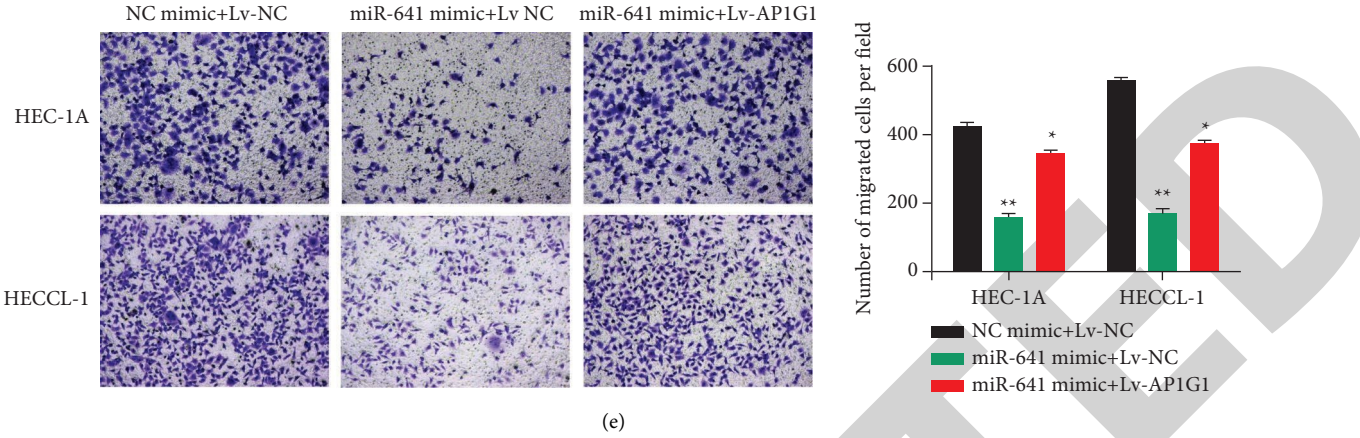

Figure 5: AP1G1 mediates the effect of miR-641 on the EC cells. (a) The expression of AP1G1 in HEC-1A and HECCL-1 cells infected with Lv-AP1G1 was evaluated by RT-qPCR assay. (b) The viability of HEC-1A and HECCL-1 cells infected with Lv-AP1G1 was assessed by CCK-8 assay at indicated times. (c) The proliferation of HEC-1A and HECCL-1 cells infected with Lv-AP1G1 was evaluated by colony formation assay. (d) The apoptotic rate of HEC-1A and HECCL-1 cells infected with Lv-AP1G1 was determined by flow cytometry assay. (e) The migration of HEC-1A and HECCL-1 cells infected with Lv-AP1G1 was determined by the transwell migration assay. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. NC mimic + Lv-NC. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ vs. miR-641 mimic + Lv-NC.

miRNAs can promote or inhibit cancer progression by binding with their targets. Thus, the aim to study the mechanisms of miRNAs is to find their downstream targets [28, 29]. Because miRNA functioned by binding to 3'-UTR of target genes [30], AP1G1 was selected as a possible target of miR-641 via StarBase [31]. Furthermore, DLR assay proved that AP1G1 was sponged by miR-641. It has also been found that AP1G1 was highly expressed in several cancers and it was diminished in colon cancer tissues and cell lines, and silencing AP1G1 restored the role of HCP5 to slow down colon cancer progression [16]. Besides, the overexpression of AP1G1 reversed the promotive effect of lowly expressed MEG3 on the attack of liver cancer [17]. Moreover, AP1G1 was closely related to ASCT2-EGFR mediated with cetuximab and sensitization of head and neck squamous cell carcinoma cells [18]. Thus, our study found that AP1G1 was overexpressed in the EC cells, and overexpression of AP1G1 counteracted the functions of miR-641 on viability, proliferation, apoptosis, and metastasis of the EC cells.

Taken together, we presented that the miR-641 expression was tarnished in the EC cells. The upregulation of miR-641 inhibited viability, proliferation, migration and invasion, accelerated apoptosis, and triggered cell cycle arrest in the G1 phase of the EC cells via targeting AP1G1. This study provides strong evidence that miR-641 might be an effective target for the treatment of EC.

Data Availability

The datasets generated/analyzed during the current study are available.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

All authors give their consent for publication.

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Retraction

Retracted: Correlation of Presacral Tumour Recurrence with Tumour Metastasis and Long-Term Tumour Recurrence Risk in Patients with Rectal Cancer

Evidence-Based Complementary and Alternative Medicine

Received 11 July 2023; Accepted 11 July 2023; Published 12 July 2023

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] L. Wang, H. Wu, R. Wang, H. Zhang, and J. Chen, "Correlation of Presacral Tumour Recurrence with Tumour Metastasis and Long-Term Tumour Recurrence Risk in Patients with Rectal Cancer," *Evidence-Based Complementary and Alternative Medicine*, vol. 2022, Article ID 6202457, 9 pages, 2022.

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Research Article

Correlation of Presacral Tumour Recurrence with Tumour Metastasis and Long-Term Tumour Recurrence Risk in Patients with Rectal Cancer

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Objective. To explore the risk factors that affect long-term presacral tumour recurrence in patients with rectal cancer (RC) after radical rectal cancer resection. *Methods*. In our study, a total of 50 patients with presacral tumour recurrence after radical resection of RC in our hospital between May 2017 and May 2018 were enrolled in the observation group, and the other 50 patients without presacral tumour recurrence after the resection over the same span were enrolled in the control group. The two groups were compared in distant metastatic rate and long-term recurrence, and corresponding K-M curves were drawn. Additionally, the quality of life of the two groups was also compared. Patients in both groups were assigned to a long-term recurrence group or a non-long-term recurrence group based on their long-term recurrence, and a multivariate logistic regression analysis was carried out for analysis of risk factors of long-term recurrence. *Results*. The two groups were not greatly different in clinical data ($P > 0.05$). The observation group was higher than the control group in terms of distant metastasis and long-term recurrence ($P < 0.05$). In addition, the MOS 36-Item Short-Form Health Survey (SF-36) scores of the observation group were all lower than those of the control group in the eight dimensions ($P < 0.05$). Moreover, tumour diameter (OR: 0.315, 95% CI: 0.118–0.835), differentiation (OR: 2.652, 95% CI: 1.086–6.852), and presacral recurrence (OR: 2.370, 95% CI: 1.263–4.447) were all independent risk factors for long-term recurrence of patients undergoing radical resection of RC. *Conclusions*. Patients undergoing radical resection of RC face greatly higher risks of presacral tumour distant metastasis and long-term tumour recurrence, and tumour diameter ≥ 5 cm, low-differentiation degree, and presacral recurrence are independent risk factors for long-term recurrence of patients undergoing radical resection of RC. In the future, when performing radical resection of rectal cancer, it is necessary to pay attention to the changes in the above indicators in patients so as to prevent tumour recurrence.

1. Introduction

Digestive system-related cancers have always been knotty in clinical practice, and gastric cancer, colorectal cancer (CRC), liver cancer, and pancreatic cancer are common ones among them [1, 2]. CRC is a malignant tumour produced by the colon or rectal mucosal epithelium under many factors [3], with an incidence ranking third among all malignant tumours and a mortality ranking fourth among them [4]. At the current stage, patients with CRC in China mainly include patients with rectal cancer (RC), about 60–70% of all CRCs [5]. RC is difficult to diagnose due to the lack of clinical symptoms, and most patients have entered the middle or late stage at diagnosis when they show clinical symptoms and have manifested metastasis of tumour cells [6, 7]. Thus, it is imperative to analyze factors affecting the recurrence of RC to find a better treatment for cancer.

For patients meeting the surgical indications, surgical treatment is the main choice, and radical resection of RC is the only radical treatment for patients with RC at present [8, 9]. However, according to the previous statistics, patients with RC still face the risk of local recurrence after surgery. Studies have shown that the probability of recurrence in patients with RC has reached about 8–20% [10]. Especially, local recurrence will involve soft tissue and bony structure in front of the sacrum backward, which is presacral tumour

recurrence. The proportion of patients with presacral tumour recurrence accounts for 15.63%–41.67% of patients with local recurrence after surgery, and the recurrence rate of presacral tumour after surgery is 2.8%–4.8% [11, 12]. Patients with presacral tumour recurrence will not only suffer unbearable pain due to the influence on bone structure but also face higher treatment difficulty, which seriously compromise their quality of life [13]. Local recurrence of RC always increases the difficulty of treatment for patients, and recurrence in different parts often causes different tumour metastasis, long-term recurrence, and prognosis [14, 15].

However, at present, there is no reliable assessment method for the prognosis and recurrence of CR, and corresponding preventive measures are lacking. This has also caused more and more patients with CR prognosis and recurrence, which has caused a great burden on the clinic. Therefore, this study probed into the correlation of presacral tumour recurrence with tumour metastasis and long-term tumour recurrence risk in patients with RC, with the aim of providing a basis and direction for clinical research.

2. Materials and Methods

2.1. Clinical Data. Totally, 50 patients with presacral tumour recurrence after radical resection of RC in our hospital between May 2017 to May 2018 were enrolled in the observation group, including 31 males and 19 females, with a mean age of 57.0 ± 9.4 years. Additionally, other 50 patients without presacral tumour recurrence after the resection over the same span were enrolled in the control group, including 29 males and 21 females, with a mean age of 56.4 ± 10.2 years. This study was carried out with permission from the ethics committee of our hospital and informed consent forms signed by all participants.

2.2. Inclusion and Exclusion Criteria

2.2.1. The Inclusion Criteria. Patients confirmed with RC by pathology, patients meeting the oncology clinical practice guideline released by the National Comprehensive Cancer Network (NCCN) [16], patients who underwent radical resection of RC, patients confirmed with presacral tumour recurrence based on CT, MRI, and pathological biopsy, and those with detailed clinical data were included.

2.2.2. The Exclusion Criteria. Patients with familial adenomatous polyposis, patients with a history of gastrointestinal diseases, patients comorbid with hypertension, diabetes, severe liver or kidney diseases, infectious diseases, or other malignant tumours, and those with mental disorders or communication disorders were excluded.

2.3. Follow-Up. All patients who underwent radical resection of RC were followed up by telephone, home visit, and reexamination for 36 months; the follow-up was ended in the case of recurrence or distant metastasis.

2.4. Outcome Measures. The observation group and control group were compared with baseline data, distant metastasis, total recurrence, and long-term recurrence, and K-M curves were drawn. Additionally, the MOS 36-Item Short-Form Health Survey (SF-36) [17] scores of the two groups were evaluated to understand their quality of life. SF-36 is a concise health questionnaire developed by the Boston Health Research Institute, which includes eight dimensions: physical function, role-physical, bodily pain, general health, vitality, social function, role emotional, and mental health. The higher the score for each dimension, the better the patient's quality of life. A multivariate logistic regression analysis (MLRA) was carried out to analyze the risk factors of long-term recurrence after radical resection of RC.

2.5. Statistical Analyses. In this study, the collected data were statistically analyzed using SPSS20.0 (Chicago SPSS Company, the United States) and visualized into figures using GraphPad Prism 7 (San Diego GraphPad Software Co., Ltd., the United States). The utilization rate of enumeration data (%) was analyzed using the chi-square test and expressed by X^2. Measurement data were presented as the mean ± SD. All the measurement data were in the normal distribution. The intergroup comparison was performed using the independent samples t test. In addition, MLRA was conducted for analysis of the long-term recurrence of patients with RC after radical resection, and K-M survival analysis was conducted for analysis of the distant metastasis, recurrence, and long-term recurrence of patients. Moreover, the log-rank test was used for analysis. $P < 0.05$ suggests a notable difference.

3. Results

3.1. Summary of Results. The observation group was higher than the control group in terms of distant metastasis and long-term recurrence ($P < 0.05$). Additionally, the SF-36 scores of the observation group were all lower than those of the control group in the eight dimensions ($P < 0.05$). Tumour diameter, differentiation, and presacral recurrence were all independent risk factors for long-term recurrence in patients undergoing radical resection of RC.

3.2. Baseline Data of Patients. We compared the baseline data of the two groups and found no notable differences between them in gender, age, body mass index (BMI), place of residence, pathological stage, operation mode, experience in neoadjuvant therapy or adjuvant therapy, tumour diameter, and differentiation ($P > 0.05$, Table 1). It indicated that the two groups of patients were comparable.

3.3. Correlation of Presacral Recurrence with Distant Metastasis and Tumour Recurrence. During the prognostic follow-up, we successfully tracked all study subjects. According to comparison results of the two groups in distant metastatic

Table 1: Baseline data.

		Observation group	Control group	χ^2/t	P
Gender	Male	31 (62.00)	29 (58.00)	0.167	0.683
	Female	19 (38.00)	21 (42.00)		
Age		57.0 ± 9.4	56.4 ± 10.2		
BMI (kg/m^2)		22.84 ± 2.15	22.42 ± 1.71		
Place of residence	Town	41 (82.00)	36 (72.00)	1.412	0.235
	Countryside	9 (18.00)	14 (28.00)		
Pathological stage	I-II	32 (64.00)	38 (76.00)	1.714	0.190
	III	18 (36.00)	12 (24.00)		
Surgical approach	Prelow contact	33 (66.00)	36 (72.00)	0.421	0.517
	Abdomen and perineum removed together	17 (34.00)	14 (28.00)		
Experience in neoadjuvant therapy or adjuvant therapy	Yes	39 (78.00)	34 (68.00)	1.268	0.260
	No	11 (22.00)	16 (32.00)		
Tumour diameter	<5 cm	30 (60.00)	39 (78.00)	3.787	0.052
	≥5 cm	20 (40.00)	11 (22.00)		
Differentiation	Highly differentiation	18 (36.00)	12 (24.00)	5.857	0.054
	Moderate differentiation	16 (32.00)	28 (56.00)		
	Low-differentiation	16 (32.00)	10 (20.00)		
Recurrence site	Presacral soft tissue	27 (54.00)			
	Lower sacrum	21 (42.00)			
	High sacrum	2 (4.00)			

rate and long-term recurrence rate, the two items in the observation group were notably higher than those in the control group ($P < 0.05$, Table 2).

3.4. Comparison of Patients' Surgical Conditions. Comparing the postoperative conditions of the two groups of patients, the operation time of the observation group was not different from that of the control group ($P > 0.05$, Figure 1(a)). However, the intraoperative blood loss of the observation group was (149.12 ± 35.23 mL), which was higher than that of the control group (128.14 ± 23.26 mL) ($P > 0.05$, Figure 1(b)). The hospitalization time of the observation group was (14.72 ± 3.53 d), which was higher than that of the control group ($P < 0.05$, Figure 2(c)).

3.5. Comparison of Patients' Life Quality. The life quality of the two groups was evaluated based on their SF-36 scores, the results show that the physiological function score of the observation group was (51.37 ± 22.15), which was lower than that of the control group ($P < 0.05$, Figure 2(a)). The body pain score of the observation group was (64.64 ± 15.36), which was also lower than that of the control group ($P < 0.05$, Figure 2(b)). The state of health score of the observation group was (54.33 ± 12.85), which was lower than the state of health score of the control group (65.40 ± 9.25) ($P < 0.05$, Figure 2(c)). Comparing the energy scores of the two groups, the observation group was lower ($P < 0.05$, Figure 2(d)). The social function score of the observation group was significantly lower than that of the control group ($P < 0.05$, Figure 2(e)). The emotion score of the observation group was (63.45 ± 14.85), which was also lower than that of the control group ($P < 0.05$, Figure 2(f)). Finally, the mental health scores of the two groups were compared, the observation group was (51.27 ± 15.92), the control group was (67.94 ± 17.15), and the observation group was lower than the control group ($P < 0.05$, Figure 2(g)).

3.6. Univariate Analysis of Risk Factors for Long-Term Tumour Recurrence. According to the occurrence of long-term recurrence, the patients were assigned to a long-term recurrence group ($n = 11$) or a non-long-term recurrence group ($n = 89$). We carried out a univariate analysis of their clinical data and found that the two groups were greatly different in pathological stage, experience in neoadjuvant treatment or adjuvant treatment, tumour diameter, differentiation, and presacral recurrence (all $P < 0.05$, Table 3).

3.7. Multivariate Analysis. We included the indicators with differences in univariate analysis into the assignment (Table 4), and then chose to go forward: MLRA based on LR showed that pathological stage and experience in neoadjuvant therapy or adjuvant therapy were not independent risk factors for patients' long-term recurrence, but tumour diameter (OR: 0.315, 95% CI: 0.118–0.835), differentiation (OR: 2.652, 95% CI: 1.086–6.852), and presacral recurrence (OR: 2.370, 95% CI: 1.263–4.447) were all independent risk factors for long-term recurrence of patients undergoing radical resection of RC (Table 5).

Table 2: Correlation of presacral recurrence with distant metastasis and tumour recurrence.

	Observation group	Control group	χ^2	P
Distant metastatic	18 (36.00)	5 (10.00)	9.543	0.002
Long-term recurrence	9 (18.00)	2 (4.00)	5.005	0.025

4. Discussion

Laparoscopic radical resection is a common operation for early CRC, which can help complete cancer tissue resection and digestive tract reconstruction by puncture directly to the focus of the cancer with the help of laparoscopic vision. It features with simple operation and advantages in bringing less trauma, less complications, and quick recovery, and its efficacy receives gradual recognition [18–20]. However, according to relevant studies in recent years, patients with CRC still suffer recurrence and metastasis after surgery because of the complicated colorectal lymphatic drainage, abundant blood supply, interconnection and densely distribution of CRC cells, difficulty in inhibiting the cells, and their inclination to metastasis. Therefore, we should pay attention to the postoperative situation of patients with RC and prevent the deterioration of the disease in time, thus improving the life quality and long-term prognosis of patients [21, 22]. Presacral tumour recurrence is a subtype of locally recurrent RC. Because of the involvement of the presacral fascia or bone, the tumour is fixed behind the pelvis, which greatly increases the treatment difficulty. There are many difficulties in the diagnosis and therapy of presacral recurrence, and there is not much consensus on a unified diagnosis and therapy. At present, its diagnosis is based on clinical symptoms, imaging, endoscopy, tumour marker detection, pathological biopsy, and surgery, chemotherapy, or radiotherapy is selected as the specific treatment method according to the patient's condition [23–25]. The feasibility and specific measures of operation depend on the anatomical characteristics of recurrent tumours, but there is still a lot of controversy about the adoption of surgical methods. One study by Guo et al. [26] mentioned the effect of different surgical methods on the efficacy of RC patients with presacral tumour recurrence. Specifically, the incidence of dysfunction after sacrectomy was 50%, significantly higher than the other two groups, but there was no difference in postoperative survival rate, and the 1-year survival rate of patients was about 85% regardless of the surgical method. Local recurrence is common after radical resection of RC, and surgery is one of the optimal treatment options. However, extensive pelvic organ resection is usually needed to obtain a negative margin, which leads to a high incidence of postoperative complications, and serious complications will compromise the prognosis of patients. One study by Paku et al. [27] has revealed that low preoperative nutritional prognosis index and excessive

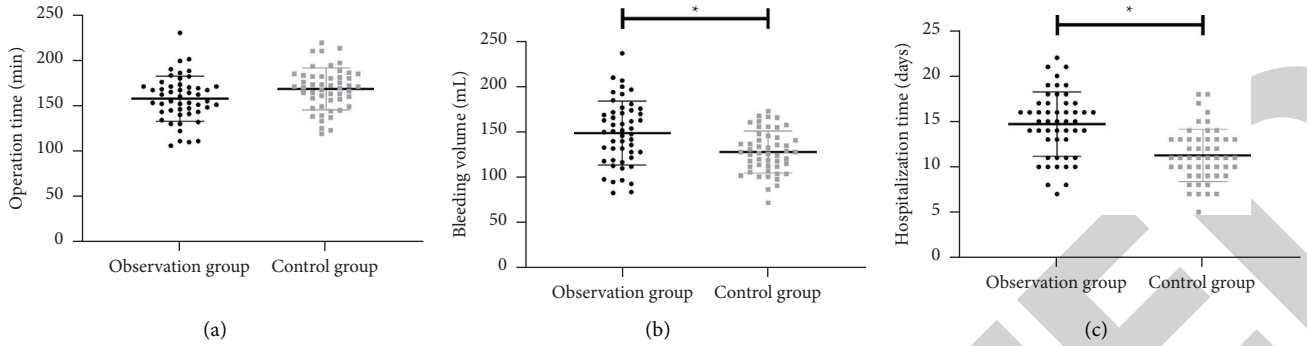

Figure 1: Comparison of surgical conditions between the two groups. (a) Comparison of operation time. (b) Comparison of intraoperative blood loss. (c) Comparison of length of hospital stay. $^{*}P < 0.05$.

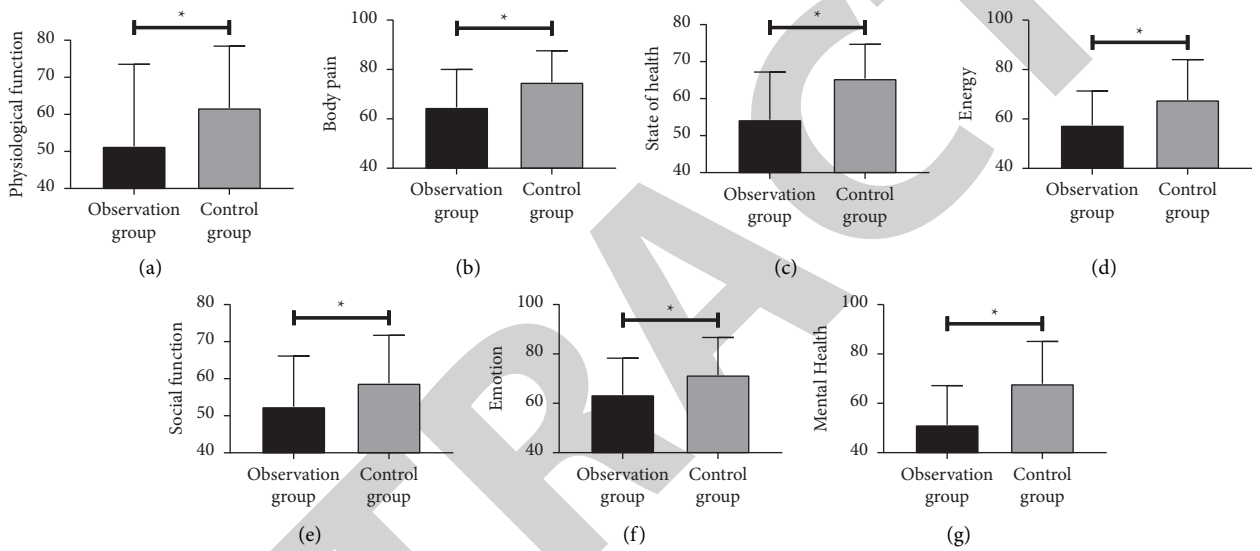

Figure 2: Comparison of SF-36 scores between the two groups. (a) Comparison of physiological function score. (b) Comparison of body pain score. (c) Comparison of state of health score. (d) Comparison of energy score. (e) Comparison of social function score. (f) Comparison of emotion score. (g) Comparison of mental health score. $^{*}P < 0.05$.

intraoperative blood loss are risk factors for severe postoperative complications of locally recurrent RC, which can improve the prevention of severe postoperative complications of locally recurrent RC to a certain extent.

In our present study, after radical resection of RC, patients with presacral tumour recurrence showed a notably higher tumour metastasis rate and a notably higher long-term tumour recurrence rate than those without presacral tumour recurrence. According to the K-M curves, patients with presacral tumour recurrence had worse distant metastasis, total recurrence, and long-term recurrence than those without it. We also studied the influence of presacral tumour recurrence on patients' quality of life. The life quality of patients undergoing radical resection of RC has always needed to be improved because the resection may cause pelvic autonomic nerve injury, urinary, and sexual dysfunction, which are the most common complications after RC surgery. At present, there are some solutions. For instance, one study by Wei and Fang [28] has pointed out that total mesorectal resection with preservation of anterior rectal fascia can effectively reduce the incidence of postoperative urination and sexual dysfunction in male patients with middle or low RC, and most importantly, it will not compromise the curative effect on and prognosis of patients. In one study by Cao et al. [29], radiotherapy, and chemotherapy in the perioperative period have strongly reduced local recurrence and improved long-term survival rates, but despite the fact that they can improve patients' prognosis, they would greatly increase the incidence of adverse reactions such as defecation, urination, and sexual dysfunction, and further lower the quality of life of patients. According to the results of our study, patients with presacral tumour recurrence got notably lower SF-36 scores in the 8 dimensions than those without it. Patients with presacral recurrence are often accompanied by unbearable pain. If the recurrence is not controlled immediately by surgery, the patients often need multiple courses of chemotherapy or radiotherapy for disease control. During these courses, analgesics are also needed for pain alleviation [30], which will undoubtedly lower the scores of patients' physical pain,

Table 3: Univariate analysis.

		Long-term recurrence group	Non-long-term recurrence group	χ^2/t	P
Gender	Male	6 (54.55)	54 (60.67)	0.153	0.696
	Female	5 (45.45)	35 (39.33)		
Age		57.6 ± 8.2	56.1 ± 9.2	0.516	0.607
BMI (kg/m^2)		22.35 ± 2.15	22.00 ± 1.71	0.622	0.535
Place of residence	Town	8 (72.73)	68 (77.27)	0.113	0.736
	Countryside	3 (27.27)	20 (22.73)		
Pathological stage	I-II	4 (36.36)	68 (74.73)	6.956	0.008
	III	7 (63.64)	23 (25.27)		
Surgical approach	Prelow contact	6 (54.55)	63 (70.79)	1.207	0.272
	Abdomen and perineum removed together	5 (45.45)	26 (29.21)		
Experience in neoadjuvant therapy or adjuvant therapy	Yes	4 (36.36)	69 (77.53)	8.417	0.004
	No	7 (63.64)	20 (22.47)		
Tumour diameter	<5 cm	2 (18.18)	67 (75.28)	14.920	0.001
	≥5 cm	9 (81.82)	22 (24.72)		
Differentiation	Highly differentiation	1 (11.11)	29 (32.58)	9.321	0.010
	Moderate differentiation	3 (22.22)	41 (46.07)		
	Low differentiation	7 (66.67)	19 (21.35)		
Presacral recurrence	Yes	9 (81.82)	41 (46.07)	5.005	0.025
	No	2 (18.18)	48 (53.93)		

Table 4: Assignment.

Factors	Assignment
Pathological stage	III = 1, I-II = 0
Experience in neoadjuvant therapy or adjuvant therapy	No = 0, yes = 1
Tumour diameter	<5 cm = 0, ≥5 cm = 1
Differentiation	Highly differentiation = 1, moderate differentiation = 2, and low differentiation = 3
Presacral recurrence	Yes = 1, no = 0
Long-term recurrence	Long-term recurrence = 1, survival = 0

Table 5: Multivariate analysis.

Factors	B	S.E.	Wals	P	Exp (B)	95% CI of Exp (B).	
						Lower limit	Upper limit
Pathological stage	0.903	0.482	3.762	0.056	2.934	1.186	6.851
Experience in neoadjuvant therapy or adjuvant therapy	1.171	0.483	10.876	0.065	3.310	1.120	6.799
Tumour diameter	1.156	0.498	5.387	0.020	0.315	0.118	0.835
Differentiation	1.022	0.475	4.824	0.036	2.652	1.086	6.852
Presacral recurrence	0.865	0.338	7.228	0.007	2.370	1.263	4.447

health status, energy, and mental health. Therefore, psychological treatment is also required to improve their psychological status. At the end of the study, we analyzed the risk factors for long-term recurrence of patients undergoing radical resection of RC via MLRA. Long-term recurrence refers to a recurrence 5 years after the operation. Short-term local recurrence is common after radical resection of RC, but long-term recurrence also needs attention. The study of long-term recurrence needs a long-run follow-up, so corresponding studies are rare. Wang et al. [31] have studied the 3-year recurrence-free survival rate (RFSR) patients undergoing radical resection of RC by the K-M method. In their study, no obvious difference was found between patients with RC who showed a complete clinical response to neoadjuvant chemotherapy and those who received radical resection of RC in 3-year RFSR. Therefore, neoadjuvant chemotherapy might be a promising conservative choice for aggressive radical surgery, but they have not conducted a longer-term follow-up study, so the tumour metastasis and recurrence after more than 5 years are unclear. According to our MLRA, tumour diameter ≥ 5 cm, low-differentiation degree, and presacral recurrence were all independent risk factors for long-term recurrence of patients undergoing radical resection of RC. The results suggest that tumour diameter, differentiation degree, and presacral recurrence can be used as predictive indicators of long-term recurrence of patients.

At present, there is no reliable assessment method for the prognosis and recurrence of CR in clinical practice, so there is also a lack of corresponding preventive measures. Through the results of this study, we can form a preliminary concept for preventing the recurrence of CR prognosis, which is of great significance for ensuring the safety of patients' lives. However, this study still has some limitations. First, the samples included in this study are patients undergoing radical resection of RC, and those treated by other methods, such as radiotherapy and chemotherapy, are not included. Second, we have not deeply studied the influence of various treatment methods on patients with presacral recurrence. Finally, we have not carried out *in vitro* cell studies or animal experiments. Therefore, we hope to explore the mechanism of presacral recurrence more in future studies.

To sum up, patients undergoing radical resection of RC face greatly higher risks of presacral tumour distant metastasis and long-term tumour recurrence, and tumour diameter ≥ 5 cm, low-differentiation degree and presacral recurrence are independent risk factors for long-term recurrence of patients undergoing radical resection of RC.

Data Availability

The datasets used during the present study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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