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Advances in Obstetrics and Gynecology Research

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Effectiveness and Safety of Low-flow Sevoflurane Combined with Remifentanyl on Anaesthesia of Patients Undergoing Gynaecological Laparoscopic Surgery

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Abstract: *Objective:* To evaluate the advantages of sevoflurane (low-flow) + remifentanyl for patients undergoing gynaecological laparoscopic surgery. *Methods:* 300 patients admitted for gynaecological laparoscopic surgery between July 2020 and July 2023 were selected and divided equally by random number table, 150 cases were counted in the observation group, and sevoflurane (low-flow) + remifentanyl was chosen for maintenance anaesthesia; 150 cases were counted in the reference group, and anaesthesia was maintained only with remifentanyl. The anaesthesia indexes, haemodynamics, stress reaction indexes, and adverse reaction rate of the two groups were compared. *Results:* The anaesthesia indexes of the observation group were better than those of the reference group ($P < 0.05$). Before 5 min of anaesthesia (T1), there was no difference between the haemodynamics and stress reaction indexes of the two groups ($P > 0.05$). After 30 min of pneumoperitoneum (T2) and immediately after the end of surgery (T3), the hemodynamic and stress indicators of the observation group were lower than those of the reference group ($P < 0.05$). The adverse reaction rate of the observation group was lower than that of the reference group ($P < 0.05$). *Conclusion:* Sevoflurane (low-flow) + remifentanyl can improve the anaesthesia indexes of gynecological laparoscopic surgery patients, stabilize intraoperative haemodynamics, reduce the stress reaction, and the safety of medication is high.

Keywords: Low-flow; Sevoflurane; Remifentanyl; Gynaecological laparoscopic surgery; Anaesthesia effects

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1. Introduction

Laparoscopic surgery is a more commonly used surgical procedure in clinical gynaecology, which has the advantages of minimal invasiveness, safety, and a high surgical success rate. However, the creation of an artificial pneumoperitoneum in laparoscopic surgery increases intrathoracic pressure, which decreases the

diastolic function of the heart and leads to intraoperative stress ^[1,2]. For this reason, attention needs to be paid to the induction and maintenance of anaesthesia for this procedure to ensure the effectiveness of anaesthesia while minimizing the negative effects on the circulatory system, so that the patient can complete the surgical treatment smoothly and safely. Currently, remifentanyl is a commonly used anaesthetic drug for laparoscopic surgery, which can maintain haemodynamic stability. Combined with sevoflurane (low-flow) inhalation, anaesthesia can reduce the adverse stress caused by carbon dioxide pneumoperitoneum and enhance the analgesic effect ^[3]. For this reason, 300 gynaecological laparoscopic surgery patients were selected in this study to evaluate the anaesthetic effect of sevoflurane (low-flow) + remifentanyl.

2. Information and methods

2.1. General information

The study period was from July 2020 to July 2023, and 300 laparoscopic surgery patients admitted to the gynaecology department were selected. Random number table grouping, observation group 150 cases, age in 24–68 years old, mean (44.28 ± 5.91) years old; body mass in 41–79 kg, mean (58.94 ± 6.37) kg; lesion site: uterus 41 cases, ovary 68 cases, fallopian tube 41 cases. In the reference group, there were 150 cases with ages ranging from 23 to 66 years, with a mean of (44.71 ± 5.67) years old; body mass ranging from 42 to 78 kg, with a mean of (58.60 ± 6.72) kg; and lesion sites: uterus in 38 cases, ovary in 72 cases, and fallopian tube in 40 cases. Compared with the basic data of the two groups, $P > 0.05$, that is, comparable.

Inclusion criteria: (1) meet the indications for laparoscopic surgery; (2) meet the indications for anaesthesia; (3) normal mental status; (4) normal communication and audio-visual ability; (5) complete clinical data.

Exclusion criteria: (1) combined with liver and kidney diseases; (2) accompanied by mental disorders; (3) combined with malignant tumours and other serious diseases; (4) allergic to the study drugs; (5) transit open surgery; and (6) withdrawing from the study in the middle of the study.

2.2. Methods

Both groups of patients were fasted and abstained from food and drink before surgery, and atropine was injected intramuscularly at a dose of 0.5 mg, 30 min before surgery, and intravenous access was created after admission to the room, and the patients were monitored for signs and treated with oxygen. The anaesthesia method was the same in both groups, which was general anaesthesia by tracheal intubation, and anaesthesia was induced by intravenous infusion of fentanyl ($6 \mu\text{g/kg}$) + atracurium (0.5 mg/kg) + midazolam (0.1 to 0.8 mg/kg) + etomidate (0.1 mg/kg). The ventilation frequency level of mechanical ventilation was maintained at 15–20 times per minute, and the respiratory parameters were reasonably adjusted in the light of the patient's specific situation. The pneumoperitoneal pressure level of carbon dioxide was 10–15 mmHg, and low-flow air intake treatment was also given.

The anaesthesia maintenance method of the reference group was: remifentanyl micro-pumping, and its pumping volume was 0.5 mg/kg per minute, and it was continuously pumped until the pneumoperitoneum stopped. In the observation group, based on the reference group, sevoflurane was inhaled at a concentration between 1.5% and 3.0%, and the end-expiratory concentration was maintained at 2.0%. The depth of anaesthesia was moderately adjusted according to the patient's condition, and sevoflurane was discontinued

when the pneumoperitoneum stopped.

The two groups were given continuous oxygen therapy during the operation, with the oxygen flow rate set at 4.5–6.5 L/min, and atracurium was added intermittently according to the intraoperative situation, with an additional amount of 0.5 mg/kg.

2.3. Observation indexes

- (1) Anaesthesia indexes: Observe the time of conscious wakefulness, the time of spontaneous respiratory resumption, the time of orientation resumption, the time of eye-opening and the time of extubation.
- (2) Haemodynamics: Heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (SpO₂) data from cardiac monitor were recorded from T1 to T3 time points.
- (3) Indicators of stress response: At T1 to T3 time points, levels of cortisol (COR), norepinephrine (NE) and epinephrine (E) were measured by radioimmunoassay.
- (4) Adverse reactions: Observe the adverse reactions such as laryngospasm, hypotension, agitation with nausea and vomiting.

2.4. Statistical analysis

The data were processed by SPSS 28.0 software, and the measurement data were expressed as mean \pm standard deviation (SD), using *t* value comparison and test, and the count data were expressed as (*n*/%), using χ^2 value comparison and test, and the statistical significance was $P < 0.05$.

3. Results

3.1. Comparison of anaesthesia indexes between the two groups

All anaesthesia indexes of the observation group were better than those of the reference group ($P < 0.05$) (Table 1).

Table 1. Comparison of anaesthesia indexes between the two groups (mean \pm SD, min)

Grouping	Time to consciousness	Time to return to spontaneous respiration	Time to return to directional force	Eye opening time	Extubation time
Observation group (<i>n</i> = 150)	9.42 \pm 1.82	4.60 \pm 0.53	7.26 \pm 1.63	6.65 \pm 1.30	5.44 \pm 0.64
Reference group (<i>n</i> = 150)	12.73 \pm 1.95	5.38 \pm 0.67	9.47 \pm 1.68	8.42 \pm 1.37	10.53 \pm 1.49
<i>t</i>	15.198	11.182	11.563	11.478	38.442
<i>P</i>	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

3.2. Comparison of haemodynamic indexes between the two groups

At T1, there was no difference in the haemodynamics of the two groups ($P > 0.05$). At T2 and T3, the haemodynamics of the observation group was lower than that of the reference group ($P < 0.05$) (Table 2).

Table 2. Comparison of haemodynamic indexes between the two groups (mean \pm SD)

Grouping	HR (cycles/min)			MAP (mmHg)			SpO ₂ (%)		
	T ₁	T ₂	T ₃	T ₁	T ₂	T ₃	T ₁	T ₂	T ₃
Observation group (<i>n</i> = 150)	81.29 \pm 7.61	84.25 \pm 6.71	82.43 \pm 6.50	64.15 \pm 6.54	70.52 \pm 8.91	66.27 \pm 6.17	97.55 \pm 1.53	96.74 \pm 1.03	95.66 \pm 1.12
Reference group (<i>n</i> = 150)	81.38 \pm 7.50	90.33 \pm 6.53	87.19 \pm 6.37	65.02 \pm 6.73	78.33 \pm 8.19	73.02 \pm 6.84	97.54 \pm 1.46	94.03 \pm 1.01	93.87 \pm 1.15
<i>t</i>	0.103	7.953	6.406	1.135	7.904	8.975	0.058	23.008	13.657
<i>P</i>	0.918	< 0.001	< 0.001	0.257	< 0.001	< 0.001	0.954	< 0.001	< 0.001

3.3. Comparison of stress reaction indexes between the two groups

At T₁, there was no difference in the stress reaction indexes of the two groups ($P > 0.05$). At T₂ and T₃, the stress reaction indexes of the observation group were lower than those of the reference group ($P < 0.05$) (Table 3).

Table 3. Comparison of stress reaction indexes of the two groups (mean \pm SD, ng/L)

Group	COR			NE			E		
	T ₁	T ₂	T ₃	T ₁	T ₂	T ₃	T ₁	T ₂	T ₃
Observation group (<i>n</i> = 150)	127.54 \pm 15.36	135.66 \pm 18.92	130.57 \pm 16.99	231.68 \pm 24.61	255.83 \pm 27.92	245.91 \pm 22.05	187.64 \pm 15.71	197.53 \pm 20.30	190.55 \pm 18.07
Reference group (<i>n</i> = 150)	126.92 \pm 15.24	207.91 \pm 19.82	183.67 \pm 17.58	230.21 \pm 23.94	340.72 \pm 28.61	310.24 \pm 23.17	188.77 \pm 15.93	234.61 \pm 24.63	207.15 \pm 20.47
<i>t</i>	0.351	32.294	26.601	0.524	26.008	24.633	0.619	14.228	7.446
<i>P</i>	0.726	< 0.001	< 0.001	0.600	< 0.001	< 0.001	0.537	< 0.001	< 0.001

3.4. Comparison of adverse reaction rates between the two groups

The adverse reaction rate of the observation group was lower than that of the reference group ($P < 0.05$) (Table 4).

Table 4. Comparison of adverse reaction rates between the two groups (*n*/%)

Group	Laryngospasm	Hypotension	Agitation	Nausea and vomiting	Incidence
Observation group (<i>n</i> = 150)	0	1 (0.67)	0	1 (0.67)	1.33 (2/150)
Reference group (<i>n</i> = 150)	2 (1.33)	3 (2.00)	1 (0.67)	3 (2.00)	6.00 (9/150)
χ^2	-	-	-	-	4.624
<i>P</i>	-	-	-	-	0.032

4. Discussion

Gynaecological laparoscopic surgery is a minimally invasive procedure, which can reduce the patient's organic damage and shorten the postoperative recovery cycle ^[4,5]. However, the need to create an artificial pneumoperitoneum during surgery, coupled with the exogenous stimulation of special positions, laparoscopes

and other surgical instruments, can easily lead to intraoperative stress, which in turn affects the patient's nervous system as well as the circulatory system, and reduces their surgical tolerance. Previous studies have found that carbon dioxide artificial pneumoperitoneum will elevate the diaphragm due to the increase in abdominal pressure during the creation process, which will compress the lungs, reduce lung compliance, affect pulmonary ventilation, and then change the SpO₂ level ^[6]. Laparoscopic surgery requires patients to maintain a head-down position, which is prone to hemodynamic fluctuations. In order to improve the smoothness of surgery, the anaesthesia protocol needs to be optimized ^[7].

Remifentanyl is a short-duration anaesthetic drug, with a fast onset of action and a small distribution volume in the body, which is not easy to lead to drug accumulation reactions and basically has no respiratory depression ^[8,9]. In the anaesthesia process of laparoscopic surgery, the anaesthesia depth of remifentanyl is controllable, and the target-controlled infusion can maintain a more ideal blood concentration and continuously exert anaesthesia effect. Combined with sevoflurane can enhance the anaesthetic effect, the drug's blood gas partition coefficient is small, inhalation anaesthesia does not stimulate the respiratory tract. The fast induction speed and postoperative wakefulness play a synergistic mechanism with remifentanyl and thus improve the anaesthesia index ^[10]. In this study, the anaesthesia indexes of patients in the observation group were better than those of the reference group ($P < 0.05$).

Remifentanyl can reasonably regulate the depth of anaesthesia during anaesthesia for laparoscopic surgery, and stabilize its blood concentration by target-controlled infusion so that it can continuously play an analgesic role and reduce intraoperative stress reactions. Remifentanyl can achieve blood-brain equilibrium within 1 min of administration, and within 10 min of stopping the drug after surgery, patients can breathe on their own without significant interference in haemodynamics ^[11]. Sevoflurane is an inhaled drug, which has little negative impact on circulatory function, and the drug can be metabolized rapidly, relaxing muscles and exerting strong analgesic effects in a short time, so the intraoperative haemodynamics are more stable and the stress reaction is less. In addition, the drug component of sevoflurane is sevoflurane, which has a more aromatic odour and is highly accepted by patients ^[12]. Inhalation anaesthesia can flexibly control the depth of anaesthesia, maximize the advantages of the combination of drugs, and enable patients to successfully complete surgical treatment. In this study, the hemodynamic indexes of T2 to T3 in the observation group were lower than those of the reference group, and the stress response indexes were lower than those of the reference group ($P < 0.05$). The results were basically consistent with the findings of Han Menghe *et al.* (2021) ^[13].

Remifentanyl basically does not affect the liver and kidney functions during metabolism, and its bioavailability is high ^[14]. While sevoflurane is administered by inhalation, it does not significantly affect circulatory function, can reasonably control the concentration of anaesthetic drugs. The drug metabolism rate is high with no drug accumulation, and it is not easy to lead to adverse reactions after using the drug. The combination of drugs can exert anaesthetic efficacy in multiple targets and mechanisms, increase the anaesthetic effectiveness of remifentanyl, and reduce the specific dosage of remifentanyl, so there are fewer side effects after anaesthesia ^[15]. In this study, the adverse reaction rate of the observation group was lower than that of the reference group ($P < 0.05$).

5. Conclusion

In conclusion, sevoflurane (low-flow) + remifentanyl can be used as a common anaesthetic maintenance

regimen for gynaecological laparoscopic surgery, which can shorten the post-anaesthetic awakening time, restore the autonomic respiratory function and orienting force as soon as possible. It can stabilize intraoperative haemodynamics, prevent intraoperative stress reactions, and has high anaesthetic safety.

Disclosure statement

The authors declare no conflict of interest.

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Investigation of Female Menopausal Syndrome and Cognition of Hormone Replacement Therapy

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Abstract: *Objective:* To investigate the incidence of female menopausal syndrome and the cognition of hormone replacement therapy (HRT), providing a basis for interventions for menopausal syndrome in women. *Methods:* From October 2021 to June 2023, a survey was conducted mainly in Guangzhou's Huangpu District, using a cluster random sampling method to select 3,000 women who voluntarily participated. A questionnaire was used to collect general information about the participants and their awareness of HRT. *Results:* All 3,000 participants completed the questionnaire. The majority were aged 46–50 (51.90%), most were workers (24.40%), had a high school education (40.17%), and were married (91.20%). The most common symptoms of menopausal syndrome were insomnia, fatigue, and joint/muscle pain, with prevalence rates of 71.23%, 66.57%, and 63.57%, respectively, significantly higher than other symptoms ($P < 0.05$). Other symptoms included depression, mood swings, palpitations, hot flashes, and sweating. Among the participants, 64.93% were unaware of HRT, 11.63% had heard of it, 9.40% were very familiar with it, and 14.03% had used it. Healthcare professionals were the main source of HRT knowledge for the participants, with other sources including the internet, friends, media, and lectures. The moderate and severe symptom groups included 1,832 and 1,168 participants, respectively. In the severe group, follicle-stimulating hormone and luteinizing hormone levels were significantly higher than in the moderate group ($P < 0.05$), and estradiol levels were significantly lower than in the moderate group ($P < 0.05$). *Conclusion:* The incidence of menopausal syndrome is high among middle-aged women, with common symptoms including insomnia, fatigue, and joint/muscle pain. These symptoms may be related to hormone levels. Many women lack awareness of HRT for the menopausal syndrome, with healthcare professionals being the primary source of information. To ensure women's physical and mental health, it is necessary to strengthen education and raise awareness of health care, emphasizing early prevention and intervention to improve the quality of life for middle-aged and elderly women.

Keywords: Perimenopausal syndrome; Perimenopause; Hormone therapy; Women's health

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1. Introduction

Menopause is a traditional term referring to the perimenopausal period. Most women entering menopause

experience a range of symptoms due to their inability to regulate through their neuroendocrine-immune system. The sudden decrease in estrogen disrupts the body's balance, leading to typical menopausal symptoms such as mood swings, hot flashes, sweating, and urogenital atrophy, seriously impacting women's physical and mental health ^[1]. Perimenopausal syndrome patients are often influenced by traditional beliefs, and the lack of widespread knowledge about health care during the menopausal transition in China, combined with the fact that perimenopausal issues affect other systems, makes it difficult for patients to determine which medical department to consult ^[2]. Although research on the menopausal transition is progressing internationally, the acceptance rate among Chinese women remains low, and there is limited understanding of the significance of HRT. Therefore, understanding the symptoms of perimenopausal syndrome and awareness of HRT is important for improving postmenopausal quality of life and advancing health care for menopausal women ^[3]. Based on this, the current study was conducted in Guangzhou's Huangpu District from October 2021 to June 2023. Using a cluster random sampling method, 3,000 women who voluntarily participated were surveyed to investigate the incidence of menopausal syndrome and the cognition of HRT, providing a basis for interventions for menopausal syndrome in women.

2. Materials and methods

2.1. General information

From October 2021 to June 2023, a survey was primarily conducted in the Huangpu District of Guangzhou, selecting 3,000 women who voluntarily participated in the survey, following the principle of cluster random sampling. The inclusion criteria were: (1) holding household registration in the Huangpu District of Guangzhou or having lived in the district for more than one year; (2) aged between 40 and 60; (3) having a uterus and at least one ovary; (4) being conscious, able to communicate normally, and without motor disabilities affecting writing; (5) being informed about the study and voluntarily participating in the survey. The exclusion criteria were: (1) having serious neurological disorders such as intracranial tumors or severe Parkinson's disease; (2) having been previously diagnosed with drug, alcohol, or substance dependence; (3) having used steroid hormone therapy recently (within the past three months); (4) having atypical endometrial hyperplasia or being diagnosed with endometrial cancer or breast cancer.

2.2. Methods

A self-made questionnaire was used for the survey, in a self-administered format. The participants filled out the questionnaire independently, and any doubts were clarified by the investigators. The survey content included basic information such as age, occupation, education, economic status, menstrual history, and medical history, as well as the participants' knowledge and use of hormone replacement therapy. Menopausal syndrome symptoms were evaluated using a modified Kupperman score. Based on the severity of symptoms, the participants were categorized into a moderate group and a severe group, with a score of 16–30 considered moderate and > 30 considered severe. The serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) were measured and compared between different groups.

2.3. Statistical analysis

The study was analyzed using the SPSS 22.0 statistical software package. Measurement data were expressed as mean \pm standard deviation (SD), and inter-group comparisons were conducted using the *t*-test. Count data were

expressed as [*n* (%)], and inter-group comparisons were conducted using the chi-squared (χ^2) test. A *P*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Basic information of the participants

All 3,000 participants completed the questionnaire. The majority were aged 46–50 years (51.90%), most worked as laborers (24.40%), and most had a high school education (40.17%). The majority were married women (91.20%). See **Table 1**.

Table 1. Basic information

Item	Number of people	Proportion (%)
Age (years)		
40–45	777	25.90
46–50	1,557	51.90
51–55	288	9.60
56–60	378	12.60
Occupation		
Laborer	732	24.40
Science and technology	288	9.60
Administrative staff	141	4.70
Finance and accounting	45	1.50
Business services	303	10.10
Teacher	309	10.30
Medical staff	282	9.40
Retired	327	10.9
Other	573	19.10
Education level		
Undergraduate and above	210	7.00
Junior college	302	10.07
Technical school	735	24.50
High school	1,205	40.17
Middle school	867	28.90
Below middle school	548	18.27
Marital status		
Married	2,736	91.20
Divorced	138	4.6
Widowed	75	2.5
Others	51	1.7

3.2. Occurrence of menopausal syndrome symptoms

The most common symptoms of menopausal syndrome among the participants were insomnia, fatigue, and joint and muscle pain, with proportions of 71.23%, 66.57%, and 63.57%, respectively, which were significantly higher than other symptoms ($P < 0.05$). Other symptoms included depression, mood swings, palpitations, hot flashes, and sweating. See **Table 2**.

Table 2. Occurrence of menopausal syndrome symptoms

Symptom	Number of people	Proportion (%)
Hot flashes and sweating	1,753	58.43
Paresthesia	1,095	36.50
Insomnia	2,137	71.23
Irritability	1,689	56.30
Dyspareunia and vaginal dryness	264	8.80
Urgency and frequent urination	1,054	35.13
Depression and mood swings	1,799	59.97
Dizziness	1,542	51.40
Fatigue	1,997	66.57
Joint and muscle pain	1,907	63.57
Headache	878	29.27
Palpitations	1,792	59.75
Skin crawling sensation	556	18.53

3.3. Awareness of hormone replacement therapy

Among the participants, 64.93% were unaware of HRT, 11.63% had heard of it, and 9.40% were very familiar with it. Additionally, 14.03% had used HRT. See **Table 3**.

Table 3. Awareness of hormone replacement therapy

Awareness of HRT	Number of people	Proportion (%)
Very familiar	282	9.40
Heard about it	349	11.63
Unaware	1,948	64.93
Used it	412	14.03

3.4. Sources of information on hormone replacement therapy

Medical professionals were the primary source of information about hormone replacement therapy for the participants, followed by the internet, friends, and media or lectures. See **Table 4**.

Table 4. Sources of information on hormone replacement therapy

Source of information	Number of people	Proportion (%)
Medical professionals	2,426	80.87
Internet	270	9.00
Friends	189	6.30
Media and lectures	115	3.83

3.5. Comparison of serum sex hormone levels between the two groups

There were 1,832 participants in the moderate group and 1,168 in the severe group. The levels of FSH and LH in the severe group were significantly higher than in the moderate group ($P < 0.05$), while the level of E2 was significantly lower in the severe group ($P < 0.05$). See **Table 5**.

Table 5. Comparison of serum sex hormone levels between the two groups (mean \pm SD)

Group	<i>n</i>	FSH (mIU/mL)	LH (mIU/mL)	E2 (pmol/L)
Moderate group	1,832	16.78 \pm 3.45	19.43 \pm 2.83	40.43 \pm 5.22
Severe group	1,168	20.43 \pm 3.43	22.24 \pm 2.84	32.43 \pm 5.24
<i>t</i>		28.319	26.482	40.869
<i>P</i>		< 0.001	< 0.001	< 0.001

4. Discussion

Perimenopause refers to the period from the onset of biological, endocrine, and clinical characteristics associated with menopause to one year after menopause. The incidence of perimenopausal syndrome is relatively high, and the symptoms it causes have a serious impact on the quality of life of women^[4]. The results of this survey show that the majority of the participants were aged 46–50 years (51.90%), with most working as laborers (24.40%) and having a high school education (40.17%). The majority were married women (91.20%), suggesting that perimenopausal syndrome is related to the occupational environment, education level, and other factors. Studies have shown that the incidence rate is highest among those with a moderate level of education^[5]. Other researchers have pointed out that the incidence of menopausal syndrome is positively correlated with education level, with women with lower education levels having a higher incidence compared to those with higher education levels^[6]. Women with higher education tend to have broader and more complex knowledge exposure and pay more attention to their health. They are more likely to seek medical intervention when symptoms of perimenopause appear. In contrast, women with lower education levels may have limited access to health knowledge and lack health awareness, potentially viewing menopause and perimenopausal symptoms as natural physiological phenomena and therefore not paying much attention to them^[6]. Compared to people engaged in physical labor, those engaged in intellectual work tend to have a higher level of education and a better understanding of perimenopause, which leads them to place more importance on health care during this stage. They may use various methods to alleviate their symptoms^[7]. Additionally, the perimenopausal syndrome is also affected by family and social environments, income levels, and other factors^[8].

The main reason for emotional changes and psychological disorders in perimenopausal women is that aging of the reproductive endocrine system reduces the body's ability to respond to external stress. The decrease in estrogen is the primary cause of physiological and psychological dysfunction in women ^[9]. The results of this survey show that the most common symptoms of menopausal syndrome among the participants were insomnia, fatigue, and joint and muscle pain, with proportions of 71.23%, 66.57%, and 63.57%, respectively, which were significantly higher than other symptoms ($P < 0.05$). Other symptoms included depression, mood swings, palpitations, hot flashes, and sweating. Insomnia is the most common perimenopausal symptom among Chinese women, significantly higher than hot flashes and sweating in Western women ^[10]. Long-term sleep disorders can lead to various diseases, so psychological intervention for perimenopausal women should be emphasized. The results also show that the levels of FSH and LH in the severe group were significantly higher than those in the moderate group ($P < 0.05$), while E2 levels were significantly lower than those in the moderate group ($P < 0.05$), indicating that the symptoms may be related to hormone levels. Testing hormone levels in patients can provide a basis for intervention and evaluation of treatment efficacy. Studies have shown that hormone therapy for perimenopausal women can reduce the risk of insomnia, suggesting that hormone therapy can prevent insomnia ^[11]. The perimenopausal syndrome can be prevented and treated with HRT, which can also prevent the accelerated progression of diseases like coronary heart disease, osteoporosis, and cognitive decline that occur after menopause ^[12]. Studies have shown that hormone therapy can alleviate menopausal symptoms and help maintain bone density in women ^[13]. Other reports have pointed out that HRT can alleviate mood changes, joint and muscle pain, insomnia, and other symptoms associated with menopause ^[14]. However, many perimenopausal women in China are unaware of hormone replacement therapy. In this study, 64.93% of the participants did not know about HRT, 11.63% had heard of it, 9.40% were very familiar with it, and 14.03% had used it. The main source of information about hormone replacement therapy was medical professionals, indicating that there is a need to strengthen education about hormone therapy.

5. Conclusion

In conclusion, the symptoms of perimenopausal syndrome, such as insomnia, fatigue, and joint and muscle pain, have a high incidence rate and are related to factors such as education level and occupation. Many women with menopausal syndrome are not well-informed about hormone replacement therapy. To ensure women's physical and mental health, it is necessary to strengthen education and awareness about health care and to implement early preventive interventions.

Disclosure statement

The authors declare no conflict of interest.

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Exploring the Role of Cuproptosis-Associated Genes in Cancer Progression and Therapy Resistance: A Comprehensive Analysis Across Multiple Cancer Types

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Abstract: This review provides a comprehensive overview of the role of cuproptosis-associated genes across various cancer types, emphasizing their importance in tumor progression and therapy resistance. In breast cancer and colorectal cancer, the dysregulation of genes related to mitochondrial function and copper metabolism, such as *FDX1*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, and *PDHA1/PDHB*, promotes metabolic reprogramming and enhances cancer cell survival. Ovarian cancer exhibits unique dysregulations in genes like *ATP7B*, *CCS*, and *COMMD1*, which influence copper metabolism and redox signaling pathways, thereby contributing to chemoresistance and tumor growth. In head and neck cancer, the upregulation of *MTIX*, *ATP7A*, and *CCS* potentially aids cancer cell survival under oxidative stress conditions. Lung cancer is characterized by distinct dysregulation of genes such as *SLC31A1*, *ATOX1*, and *COMMD1*, modulating copper homeostasis and redox signaling to support tumor proliferation. Liver cancer and kidney cancer present unique sets of dysregulated cuproptosis-associated genes, such as *SLC39A4*, *SCO2*, and *ATP7A*, suggesting novel therapeutic targets specific to these cancer types. Pathway analysis reveals enrichment in mineral absorption pathways, highlighting the importance of these genes in maintaining cellular mineral homeostasis. Understanding the complex interplay between cuproptosis-associated genes and cancer biology offers insights into potential therapeutic strategies targeting copper metabolism for improved treatment outcomes across various cancer types.

Keywords: Cuproptosis; Cancer; Dysregulation; Therapeutic

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1. Introduction

Cancer remains one of the most formidable health challenges worldwide, accounting for millions of deaths each year ^[1]. Despite significant advances in early detection and treatment, the complexity and heterogeneity of

cancer continue to hinder effective management. A critical aspect of cancer biology that has garnered substantial attention in recent years is the regulation of cell death ^[1]. While apoptosis, necrosis, and ferroptosis have been extensively studied ^[2,3], a novel form of regulated cell death, known as cuproptosis, has emerged as a potential key player in cancer progression and treatment resistance ^[4,5].

Cuproptosis is a copper-dependent form of cell death that is fundamentally distinct from other cell death mechanisms ^[4]. It is characterized by the disruption of mitochondrial function due to copper accumulation, leading to protein aggregation and the loss of mitochondrial iron-sulfur (Fe-S) cluster proteins ^[6]. These disruptions ultimately result in cell death. The discovery of cuproptosis underscores the dual role of copper as both an essential trace element and a potential cytotoxic agent when dysregulated ^[7].

Copper is indispensable for various biological processes, including mitochondrial respiration, antioxidant defense, and iron metabolism ^[8]. Under normal physiological conditions, copper homeostasis is tightly regulated to prevent toxicity ^[9]. However, cancer cells often exhibit altered copper metabolism, leading to increased copper levels that can contribute to tumorigenesis and metastasis ^[10]. Understanding the molecular pathways involved in copper-induced cell death has, therefore, become a crucial area of research in cancer biology.

Central to the process of cuproptosis are several key genes that regulate mitochondrial function and copper metabolism ^[11]. These include *Ferredoxin 1 (FDX1)*, *Lipoic Acid Synthetase (LIAS)*, *Lipoyltransferase 1 (LIPT1)*, *Dihydrolipoamide Dehydrogenase (DLD)*, *Dihydrolipoamide S-Acetyltransferase (DLAT)*, and the *Pyruvate Dehydrogenase E1* subunits Alpha and Beta (*PDHA1* and *PDHB*) ^[12]. These genes play vital roles in maintaining mitochondrial integrity and metabolic homeostasis. Their dysregulation can lead to enhanced tumorigenicity, resistance to apoptosis, and altered cellular metabolism—hallmarks of cancer.

2. Copper metabolism in cancer

Copper's role in cancer is multifaceted. On one hand, copper is essential for the activity of several enzymes involved in oxidative stress response and cellular respiration, which are crucial for rapidly proliferating cancer cells ^[13]. On the other hand, excessive copper can be toxic, leading to oxidative damage and cell death ^[14]. This paradoxical nature of copper makes it a double-edged sword in cancer biology.

Cancer cells often exhibit increased copper uptake and accumulation. For instance, elevated levels of copper have been detected in various malignancies, including breast, lung, colorectal, and liver cancers ^[15]. This heightened copper accumulation can support the metabolic demands of cancer cells but also predispose them to copper-induced cytotoxicity, which can be therapeutically exploited.

3. The mechanism of cuproptosis

Cuproptosis is triggered by the intracellular accumulation of copper, which interferes with normal mitochondrial function. The primary mechanism involves copper binding to lipoylated components of the tricarboxylic acid (TCA) cycle within mitochondria. This binding leads to protein aggregation and the subsequent loss of Fe-S cluster proteins, which are essential for mitochondrial electron transport and metabolic function ^[16]. The resulting mitochondrial dysfunction precipitates a cascade of events that culminate in cell death ^[17].

The genes associated with cuproptosis are integral to this process. For example, *FDX1* is involved in electron transfer within mitochondria and the biogenesis of Fe-S clusters ^[18]. *LIAS* is critical for the synthesis of lipoic acid, a cofactor for key mitochondrial enzyme complexes ^[19]. *LIPT1* facilitates the attachment of lipoic

acid to these enzymes ^[19], while *DLD* and *DLAT* are components of the pyruvate dehydrogenase complex, which links glycolysis to the TCA cycle ^[20]. *PDHA1* and *PDHB* are also crucial for this metabolic link ^[20]. Dysregulation of any of these genes can disrupt mitochondrial function and increase sensitivity to copper-induced cell death ^[11].

4. Clinical implications

The discovery of cuproptosis and its associated genes opens new avenues for cancer therapy. By targeting copper metabolism and cuproptosis pathways, novel treatments may be developed to selectively induce cell death in cancer cells while sparing normal tissues. Therapeutic strategies such as copper chelation, gene modulation, and combination therapies are being explored to exploit the vulnerabilities of cancer cells with dysregulated copper metabolism.

This review aims to provide a comprehensive overview of the role of cuproptosis-associated genes in various cancers. By elucidating the mechanisms through which these genes influence tumor progression and resistance, we seek to highlight their potential as therapeutic targets and contribute to the development of more effective cancer treatments.

5. The role of cuproptosis-associated genes in cancer

5.1. The role of cuproptosis-associated genes in breast cancer

In breast cancer, cuproptosis-associated genes play critical roles in tumor progression and therapy resistance by regulating mitochondrial function and copper metabolism. Elevated levels of *FDXI*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, and the pyruvate dehydrogenase complex subunits *PDHA1* and *PDHB* have been observed in breast cancer tissues, indicating their involvement in enhancing mitochondrial respiration, metabolic reprogramming, and energy production ^[21]. For instance, *FDXI* and *LIAS* contribute to mitochondrial electron transport and lipoic acid synthesis, respectively, supporting the high energy demands of proliferating cancer cells ^[22,23]. *LIPT1* and *DLD* are critical for maintaining mitochondrial enzyme complex functions, promoting metabolic flexibility and survival ^[24]. Additionally, *DLAT* and the *PDHA1*/*PDHB* subunits facilitate the conversion of pyruvate to acetyl-CoA, which is essential for linking glycolysis to the tricarboxylic acid (TCA) cycle ^[25,26]. These metabolic adaptations enable cancer cells to thrive in diverse microenvironments and resist therapeutic stress ^[27].

5.2. The role of cuproptosis-associated genes in colorectal cancer

Cuproptosis-associated genes play crucial roles in the progression and therapy resistance of colorectal cancer (CRC) by regulating mitochondrial function and copper metabolism. Similar to breast cancer, genes such as *FDXI*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, and the *PDHA1*/*PDHB* subunits are often dysregulated in CRC, enhancing mitochondrial respiration and metabolic reprogramming to meet the high energy demands of tumor cells ^[28]. For instance, *FDXI* enhances mitochondrial electron transport and Fe-S cluster biogenesis ^[29,30]. ***DLD* and *DLAT*, key components of the pyruvate dehydrogenase complex, facilitate the conversion of pyruvate to acetyl-CoA,** which is crucial for energy production and biosynthesis ^[31,32]. *PDHA1* and *PDHB* further promote mitochondrial respiration and anabolic processes ^[33]. These metabolic adaptations help CRC cells survive under various conditions and resist therapeutic stress ^[34]. Consequently, targeting these genes could disrupt cancer cell metabolism, reduce tumor growth, and enhance sensitivity to treatments ^[35].

5.3. The role of cuproptosis-associated genes in ovarian cancer

In ovarian cancer, specific cuproptosis-associated genes exhibit unique patterns of dysregulation not commonly observed in breast cancer and CRC, highlighting distinct pathways of metabolic reprogramming and therapeutic resistance. One such gene is *ATP7B*, a copper-transporting ATPase that plays a crucial role in regulating intracellular copper levels. In ovarian cancer, *ATP7B* is frequently overexpressed, facilitating increased copper efflux and protecting cancer cells from copper-induced toxicity. This overexpression contributes to chemoresistance, particularly to platinum-based drugs, by enhancing the efflux of platinum compounds, thereby reducing their intracellular accumulation and cytotoxicity ^[36].

Another unique gene is *Copper Chaperone for Superoxide Dismutase (CCS)*, which is involved in delivering copper to the antioxidant enzyme superoxide dismutase 1 (SOD1). In ovarian cancer, elevated levels of *CCS* enhance the activity of SOD1, thereby increasing the antioxidant capacity of cancer cells and promoting their survival under oxidative stress conditions commonly induced by the tumor microenvironment and chemotherapy ^[37].

Additionally, the gene *Copper Metabolism Domain Containing 1 (COMMD1)* plays a distinct role in ovarian cancer. *COMMD1* is involved in the regulation of NF- κ B signaling and copper homeostasis. In ovarian cancer, aberrant expression of *COMMD1* has been linked to altered NF- κ B activity, promoting inflammation, cell proliferation, and resistance to apoptosis. By influencing these pathways, *COMMD1* supports tumor growth and survival, making it a potential target for therapeutic intervention ^[38].

These unique dysregulations in *ATP7B*, *CCS*, and *COMMD1* underscore the complex interplay between copper metabolism and cancer cell survival in ovarian cancer, presenting novel opportunities for targeted therapies that could disrupt these specific pathways and enhance treatment efficacy. Further research into the precise mechanisms by which these genes contribute to ovarian cancer progression and resistance will be essential for developing effective therapeutic strategies ^[39,40].

5.4. The role of cuproptosis-associated genes in head and neck cancer

Among the important dysregulated cuproptosis-associated genes in head and neck cancer, *Metallothionein 1X (MT1X)* stands out. Metallothioneins (MTs) are a family of low molecular weight, cysteine-rich proteins that play critical roles in metal homeostasis and detoxification. *MT1X*, in particular, has been implicated in copper metabolism and redox regulation. In head and neck cancer, *MT1X* expression is often upregulated, possibly as a cellular response to increased copper levels within the tumor microenvironment. This upregulation may provide a survival advantage to cancer cells by mitigating the cytotoxic effects of copper overload, thereby promoting tumor progression and resistance to therapy ^[41].

Another notable gene is *ATP7A*, which encodes a copper-transporting P-type ATPase involved in copper efflux from cells. While *ATP7A* dysregulation has been implicated in various cancers, including breast and ovarian cancer, its role in head and neck cancer appears to be distinct. In head and neck cancer, *ATP7A* expression levels may be finely tuned to balance the copper requirements for cell proliferation and survival, without tipping over into cytotoxic cuproptosis. This nuanced regulation of *ATP7A* highlights its importance as a potential therapeutic target in head and neck cancer ^[42].

Furthermore, the *CCS* gene stands out as a key player in head and neck cancer. *CCS* plays a crucial role in delivering copper to SOD, an antioxidant enzyme that neutralizes reactive oxygen species (ROS) ^[43].

5.5. The role of cuproptosis-associated genes in lung cancer

In lung cancer, one of the significantly dysregulated cuproptosis-associated genes is *SLC31A1*, which encodes the copper transporter protein CTR1. While CTR1 dysregulation has been implicated in several cancers, its role in lung cancer appears to be distinct. CTR1 is responsible for copper uptake into cells, a crucial step in maintaining cellular copper homeostasis and regulating cuproptosis. In lung cancer, CTR1 expression levels may be finely regulated to support the heightened metabolic demands and proliferation of cancer cells, while avoiding excessive cuproptosis. This nuanced regulation of CTR1 highlights its importance as a potential therapeutic target in lung cancer, differing from its roles in other cancer types ^[44].

Another notable gene is *ATOX1*, which encodes a copper chaperone protein involved in delivering copper to ATP7A, a copper-transporting ATPase. Although *ATOX1* dysregulation has been observed in various cancers, its role in lung cancer is particularly significant. *ATOX1* may modulate copper homeostasis and redox signaling pathways to support cancer cell survival and proliferation. Targeting *ATOX1*-mediated copper trafficking could offer a novel therapeutic approach in lung cancer, distinct from its roles in other cancer types ^[45].

Additionally, *COMMD1* stands out as a unique player in lung cancer. *COMMD1* regulates copper homeostasis and cuproptosis by interacting with various copper transporters and signaling molecules. Its dysregulation may disrupt copper homeostasis and redox signaling pathways, contributing to lung cancer progression through mechanisms distinct from those in breast, colorectal, ovarian, and head and neck cancers ^[46].

5.6. The role of cuproptosis-associated genes in liver cancer

In liver cancer, a distinct set of cuproptosis-related genes is implicated in tumorigenesis, presenting unique molecular targets not shared with other cancers, such as breast, colorectal, ovarian, head and neck, and lung cancers. These genes are critical for copper homeostasis, redox regulation, and cell survival in the context of liver cancer. One such gene is *SLC39A4*, which encodes the zinc transporter ZIP4. While primarily involved in zinc transport, ZIP4 also plays a role in copper uptake. Dysregulation of ZIP4 in liver cancer may affect copper homeostasis and redox signaling pathways, promoting tumor growth and progression. Targeting ZIP4-mediated copper transport could offer a novel therapeutic approach specific to liver cancer ^[47].

Another key gene is the *Synthesis of Cytochrome c Oxidase 2 (SCO2)*, which is involved in assembling cytochrome c oxidase, a crucial component of the mitochondrial electron transport chain. Dysregulation of *SCO2* in liver cancer may impair mitochondrial function and disrupt redox balance, contributing to tumorigenesis through mechanisms different from those observed in other cancers. Targeting *SCO2*-mediated mitochondrial pathways could provide a promising therapeutic strategy for liver cancer ^[48].

Additionally, *CCS* plays a critical role in liver cancer. *CCS* facilitates the delivery of copper to SOD, an antioxidant enzyme that neutralizes ROS. Dysregulation of *CCS* in liver cancer may impair copper homeostasis and redox signaling, promoting tumor growth and metastasis through mechanisms that differ from those in other cancers ^[49].

5.7. The role of cuproptosis-associated genes in kidney cancer

In the complex landscape of kidney cancer, certain cuproptosis-associated genes play pivotal roles, distinct from those observed in other common cancer types, such as breast, colorectal, ovarian, head and neck, lung, and liver cancers. One such gene is *ATP7A*, which encodes a copper-transporting ATPase involved in copper efflux from cells. While dysregulation of *ATP7A* has been implicated in various cancers, its role in kidney cancer appears to be unique. *ATP7A* may modulate copper homeostasis and redox signaling pathways in kidney tumorigenesis,

potentially promoting cancer cell survival and proliferation through mechanisms independent of those seen in other cancer types [50,51].

Furthermore, *ATOX1*, which encodes a copper chaperone protein involved in delivering copper to the ATP7A transporter, is another key player in kidney cancer. *ATOX1*-mediated copper trafficking pathways may play a distinct role in kidney tumorigenesis, potentially influencing copper homeostasis and redox signaling to promote cancer cell proliferation and survival [52,53].

6. Cuproptosis-associated genes dysregulated pathways

Figure 1 presents a comprehensive analysis of pathway enrichment related to cuproptosis-associated genes. **Figure 1A** highlights various metabolic pathways with their respective fold enrichment, showing “Mineral absorption” as the most significantly enriched pathway, supported by its high fold enrichment and the large number of cuproptosis-associated genes involved (**Figure 1A**). The color gradient of the dots indicates statistical significance, with redder dots representing higher significance levels. Additionally, **Figure 1B** provides a detailed KEGG pathway map of “Mineral absorption,” where key components such as DMT1, TF, and ATP7A are marked in red, underscoring their crucial role in this process. These cuproptosis-associated genes participate in the transcellular and paracellular transport of minerals like Ca²⁺, Mg²⁺, Fe²⁺, and Zn²⁺ through the intestinal epithelium into the bloodstream.

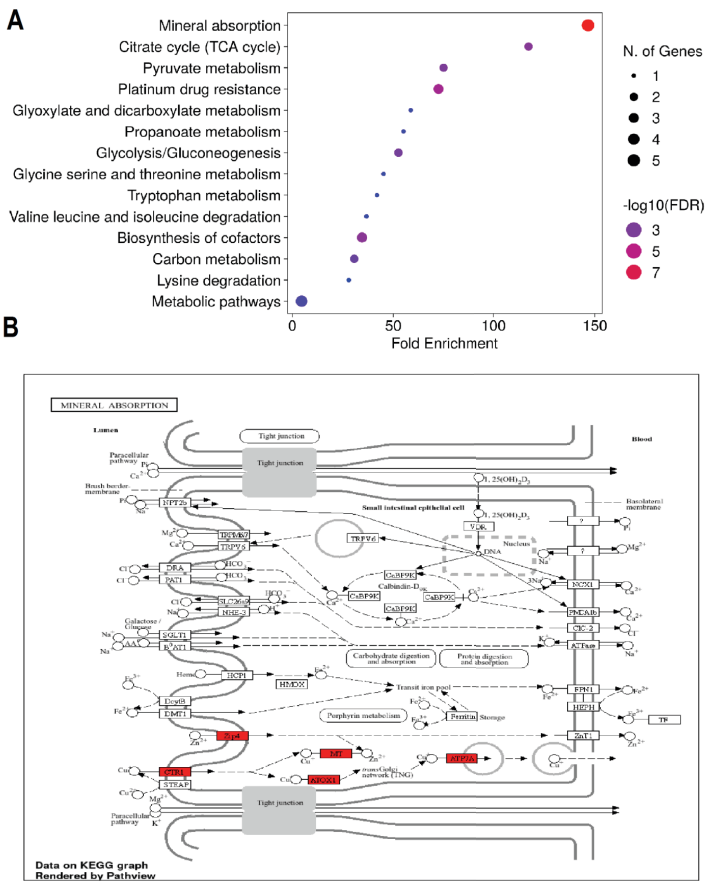


Figure 1. Cuproptosis-associated genes and related pathways. (A) A bubble graph illustrating cuproptosis-associated genes and related pathways. (B) KEGG map of the most significantly associated pathway.

7. Conclusion

From this comprehensive review of the literature, several conclusions can be drawn:

First, cuproptosis-associated genes exhibit tissue-specific dysregulation patterns, indicating unique molecular pathways driving tumorigenesis in each cancer type. For example, *ATP7B* overexpression is prominent in ovarian cancer, while *ATP7A* dysregulation is notable in kidney cancer. These genes play different roles—or may not be dysregulated at all—in other cancer types, such as breast, colorectal, head and neck, lung, and liver cancers. This highlights the importance of considering tissue-specific contexts when studying the role of cuproptosis-associated genes in cancer.

Second, cuproptosis-associated genes contribute to various aspects of cancer progression, including metabolic reprogramming, therapy resistance, and redox signaling modulation. For instance, in breast and colorectal cancers, dysregulated genes such as *FDX1*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, *PDHA1*, and *PDHB* enhance mitochondrial respiration and metabolic flexibility, promoting tumor growth and survival. In contrast, in liver cancer, dysregulated genes like *SLC39A4*, *SCO2*, and *CCS* play crucial roles in copper homeostasis and redox regulation, influencing tumor progression and metastasis.

Third, targeting dysregulated cuproptosis-associated genes presents promising opportunities for cancer therapy. By disrupting specific pathways involved in copper metabolism, mitochondrial function, and redox signaling, novel therapeutic strategies could be developed to selectively target cancer cells while sparing normal tissues. For example, targeting *ATP7B*-mediated copper efflux in ovarian cancer or *SCO2*-mediated mitochondrial pathways in liver cancer could represent effective therapeutic approaches tailored to the unique biology of each cancer type.

Overall, the comprehensive understanding of the role of cuproptosis-associated genes in cancer underscores the intricate interplay between copper metabolism, mitochondrial function, and redox signaling in tumorigenesis. Further research into the precise mechanisms underlying dysregulated cuproptosis-associated genes and their tissue-specific effects is essential for developing targeted therapies with improved efficacy and reduced toxicity for cancer patients.

Disclosure statement

The author declares no conflict of interest.

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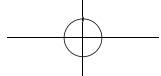
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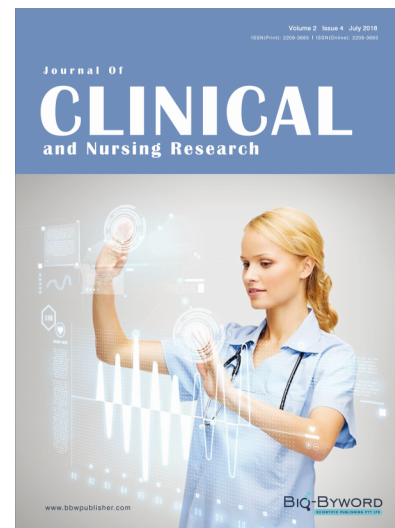
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