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Pregnancy Complicated with Acute Promyelocytic Leukemia: A Case Report and a Literature Review

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Abstract

Acute promyelocytic leukemia (APL) is a special subgroup of acute myeloid leukemia (AML). About 95% of the patients have specific chromosome translocation t (15 ≤ 17) (q22, q12). APL progresses rapidly and is characterized by extensive and severe bleeding and disseminated intravascular coagulation (DIC). Patients may present with severe clinical manifestation which is often caused by the occurrence of DIC in the early stages of the disease. Pregnancy complicated with APL is rare in the clinical setting. They have many complications, high mortality and are difficult to manage clinically. This case report describes a case of a primary pregnancy complicated with APL, in order to better understand how to manage such complex cases.

Keywords

Gestational APL, ATRA, Leukemia, Bleeding

1. Introduction

Acute promyelocytic leukemia is a special subtype of acute myeloid leukemia, accounting for about 10% of AML. Pregnancy combined with APL is clinically rare. It has been reported in the literature, its incidence is about 1 in 75,000 to 1 in 100,000 pregnant women [1] [2]. Combined with acute blood cell abnormalities and coagulation dysfunction, acute promyelocytic leukemia is extremely harmful to mothers and children. On the one hand, it can cause abortion, premature delivery, intrauterine growth restriction, fetal and maternal death. On the other hand, its treatment is very challenging for clinicians. Chemotherapy is controversial during pregnancy due to its potential teratogenic risks. In addition, complications associated with treatment of APL, including retinoic acid syn-

drome, increase the complexity of the treatment. Therefore, timely diagnosis and treatment to avoid complications and related deaths are particularly important. In this report, we present a case of a 28-year female who was diagnosed with acute promyelocytic leukemia in her second trimester of pregnancy and successfully treated in the First Affiliated Hospital of Dali University. We will report and discuss the patient's medical history, clinical data, treatment methods and results, in order to improve the clinician's understanding of pregnancy with acute promyelocytic leukemia, and improve the outcome of such patients.

2. Case Report

A 28 years G1P0 female in her 28 + weeks of gestation, presented to our hospital with complaints of skin freckles on the whole body for half a month and gum bleeding for about 10 days. She was found to be mildly anemic with bleeding gums and slightly cleft lip. An ecchymosis of about 6*7 cm size was visible on the posterior part of the right lower limb. Multiple ecchymoses of varying sizes, biggest being 1*2 cm size, were also visible on the anterior part of the lower limb and upper limbs. There was no lymphadenopathy, no tenderness in the sternum. Respiratory and Cardiovascular examinations were normal. An abdominal examination was also normal except for distended abdomen suggestive of 28 weeks of pregnancy. Baseline laboratory investigations revealed pancytopenia with white blood cell (WBC) count of $1.44*10^9$/L (Normal value range $(4 - 10)*10^9$/L), neutrophil (NEUT) of $0.58*10^9$/L, red blood cell (RBC) count of $2.76*10^{12}$/L (Normal value range $(3.5 - 5)*10^{12}$/L), hemoglobin (HGB) of 83 g/L (110 - 150 g/L), platelet (PLT) of $25*10^9$/L ($(100 - 300)*10^9$/L), and naive cells 0.35. Coagulation function revealed PT 13.6 seconds (Normal value range 10.5 - 14.5 seconds), APTT 29.8 seconds (Normal value range 31 - 44 seconds), TT 22.9 seconds (Normal value range 14 - 20 seconds), FIB 0.5 g/L (Normal value range 2 - 4 g/L), D-2 polymer 5.81 ug/ml (Normal value range 0 - 500 ug/ml). Bone marrow examination revealed extremely active bone marrow hyperplasia with about 35% abnormal promyelocytes. Bone marrow pathology suggestion: acute myeloid leukemia, tilt M3, bone marrow report picture as shown below (Figure 1 and Figure 2). She was admitted with the diagnosis of acute promyelocytic leukemia with intrauterine pregnancy 28+ weeks with coagulation dysfunction. The decision to continue the pregnancy with leukemia treatment was made as per the wishes of the patient and the family after active communication regarding the risk of mortality and fetal teratogenicity. In a bid to induce differentiation, she was treated with 20 mg all-tans-retinoic acid (ATRA) twice a day starting on the day of admission. She was also managed with infusion of suspended red blood cells to correct anemia along with infusion of platelet and cryoprecipitate to improve coagulation function. Dynamic fetal heart rate monitoring was carried out throughout this period. Fusion gene investigation detected PML/RARA (bcr1) fusion gene following which "arsenic trioxide (ATO) 8 mg once a day" chemotherapy was added. During this period the patient developed
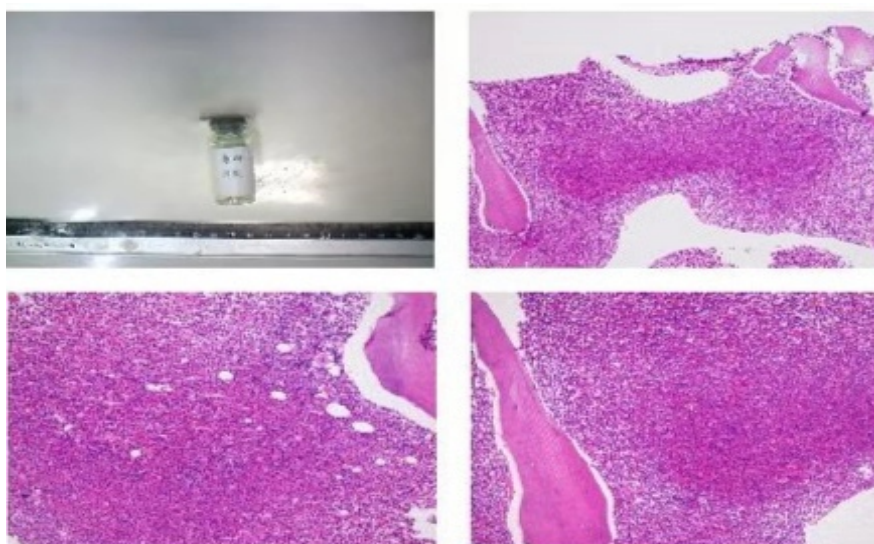
Figure 1. Suggestion: Myeloid hyperplasia is extremely active, only a small number of erythroid and megakaryocytes [CD235a (+erythroid), CD61 (+megakaryosystem)]; monomorphic abnormalities of promyelocytic cells diffuse hyperplasia, IHC showed: MPO (+granule), CD68 (+granule), Ki + 67 (+5%), CD34 (−). Special staining results of bone marrow showed: collagen fiber (−), reticular fiber (MF-1 grade).
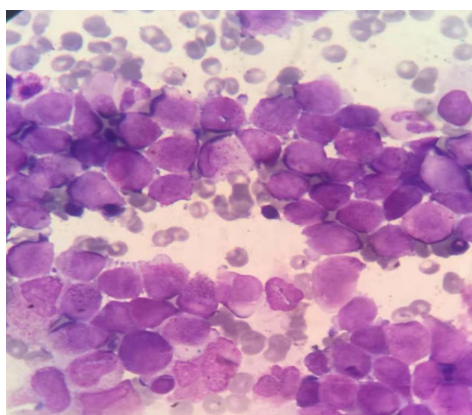
Figure 2. Acute promyelocytic leukemia in peripheral blood smear. Abnormal promyelocytes showed "Austenite body" nuclei and abundant cytoplasmic granules.

lower limb edema and chest tightness. Blood routine investigation (about 2 weeks following admission) during this time was as follows: WBC $26.26*10^9$/L, RBC $2.43*10^{12}$/L, HGB 74g/L, PLT $59*10^9$/L, naive cells 0.34. Considering the retinoic acid syndrome, "daunorubicin 40 mg, dexamethasone 10 mg, furosemide 20 mg" was added to the treatment and the dose of ATRA was adjusted to 20 mg once a day. However, the chest tightness still persisted even after adjusting the treatment plan. Thus, ATRA and ATO were discontinued. Her symptoms relieved after 2 days and the dose of ATRA was adjusted again to 20 mg once a day. Following consultation with obstetrician and request of the patient and her family, it was decided to continue the pregnancy as far as possible. On May 27th, the obstetrics color ultrasound: 1) Intrauterine single live birth, the size of the

fetus is equivalent to about 32 weeks of pregnancy +, head position; 2) Amniotic fluid is less than the sound image. Initial screening for six fatal malformations: no brain, severe brain swelling, severe open spina bifida, single-chamber heart, severe chest and abdominal wall defects, visceral eversion, fatal cartilage hypoplasia and other abnormalities. About 1 month after admission, the blood routine was reviewed and it revealed WBC $2.67*10^{-9}$/L, RBC $2.47*10^{-12}$/L, HGB 82 g/L and PLT$258*10^{-9}$/L. The coagulation function had returned to normal. Repeat bone marrow report suggested that she had achieved complete remission. The patient was regularly examined during the entire chemotherapy period and no abnormalities were observed in the fetus. Regular examination of blood routines and abnormal examinations outside the hospital was performed. At 39 + 5 weeks of pregnancy, she delivered a healthy 3.05 kg male baby with normal delivery. Apgar scored 1 minute 5 minutes, 5 minutes 9 minutes, 10 minutes 10 minutes. No abnormalities were found in the examination. Blood routine: WBC $12.99*10^{-9}$/L, NEUT% 73.3%, LYMP% 18.7%, MONO% 4.2%, RBC $5.7*10^{-12}$/L, HGB 222g/L, PLT $118*10^{-9}$/L, RET% 5.08%, late RBC% 10%, liver function: BI 66.7 umol/L, IBI 56.2 umol/L. Myocardialzymogram showed: CK 862 U/L (Normal value range 24 - 195 U/L), CK-MB 94 U/L (Normal value range 0 - 24 U/L); no abnormalities in cardiac color Doppler ultrasound, comprehensive consideration of the presence of 1) mild asphyxia; 2) myocardial damage, staying in neonatology, after symptomatic treatment, improved and discharged. The baby had no congenital abnormalities. The delivery was smooth and there were no complications. After the delivery, the patient did not continue hospitalization and she was followed up by telephone. She had no complaints and both she and the child are doing well.

3. Discussion

3.1. General Treatment of APL in Adults

At present, treatment of adult APL is divided into two parts: induction therapy and post-remission treatment. Induction therapy is based on the dual induction of ATRA + ATO, for a total of about 4 weeks. An anthracycline or cytarabine and hydroxyurea may be added as appropriate. After remission is achieved, treatment is divided into consolidation therapy and maintenance therapy. Consolidation therapy mainly consists of the use of ATRA + ATO combination therapy. The latest guidelines recommend the use of ATRA + ATO or compound Huang Qi tablets for a total of about 7 months. Maintenance therapy is critical to improving the cure rate in patients with APL. The current recommendation for maintenance treatment regimen is ATRA combined with 6-mercaptopurine and methotrexate for a total of 2 years [3]. The above treatment regimen is seen to be effective in more than 80% of patients [4].

3.2. Adverse Effects of Chemotherapy in APL

In the past few decades, the use of ATRA and arsenic has made considerable

progress in the treatment of APL. This has greatly improved the cure rate. As a member of the retinoid family, ATRA is considered to have high teratogenicity. The use of ATRA during early pregnancy may cause fetal retinal damage [5]. Other complications that can result from the use of ATRA during the first trimester of pregnancy include craniofacial alterations, neural tube defects, cardiovascular malformations, thymic aplasia, psychological impairments, and kidney alterations. It is also toxic to the fetal heart during the middle and late pregnancy. So ATRA is not recommended for use in early pregnancy. ATRA can be used in the middle and late pregnancy, but due to its cardiotoxicity, fetal heart rate monitoring should be performed frequently [5]. However, Valappil *et al.* reviewed 27 cases where ATRA was used during pregnancy. No congenital malformations were reported in the newborn in this study, which provided evidence for the use of ATRA during pregnancy. The author will make a corresponding report on the pregnancy from acute promyelocytic leukemia in pregnancy from 2010 to now, see Table 1 for details. All patients were treated with ATRA-induced differentiation, and some patients were treated with doxorubicin, and none of them had teratogenicity, which further proves the above point. Moreover, the ATRA treatment dose for pregnant patients with APL is about 40 - 45 mg/m^2/day, which is no different from that of non-pregnant APL patients, and the dose of doxorubicin is currently inconclusive. Compared with ATRA, anthracyclines are relatively less toxic and can be used in the first trimester. Among anthracyclines, idarubicin is more likely to cross the placental barrier due to the lipophilicity of anthracyclines. Tetramycin is more suitable for early pregnancy than edababicin. ATO has also been reported to have strong embryo toxicity and

Table 1. Case reports of treatment of acute promyelocytic leukemia during pregnancy.

Mother's Age	Gestational Age (wks)		Chemotherapy Regimen	Fetal Outcome	Maternal Outcome
	At diagnosis	At delivery			
27	7	Termination of pregnancy	Planed for ATRA, then Termination of pregnancy, ATRA plus idarubicin	Termination of pregnancy	CR
23	26	27	ATRA 45 mg/m^2/day	Death	CR
40	26	30	TRA 45 mg/m^2/twice day, idarubicin 12 mg/m^2/every other day	A healthy baby	CR
30	34	35	Not treated during pregnancy, After pregnancy ATO + ATRA	2450 g Preterm healthy	CR
30	23^{+3}	30	ATRA 80 mg/day, Idarubicin (20 mg/day) was concomitantly administered on days 2, 4, and 5	Fetal death (Hemorrhage)	CR
41	24^{+4}	35	ATRA 45 mg/m^2/day	2950 g preterm healthy baby	CR
two woman 24[1st] 27[2nd]	24[1st] 34[2nd]	25[1st] 36[2nd]	ATRA 45 mg/m^2/day	Death[1st] A healthy 3200 g female infant[2nd]	Death[1st] CR[2nd]
23	26	26	ATRA 45 mg/m^2/twice	Death	CR

is not recommended for use during the entire pregnancy [6]. At present, there are few reports on its use in pregnant APL. Domestic NiuJunjie *et al.* [7] reported that ATRA combined with ATO was used to treat APL in late pregnancy. Cesarean section was terminated after 20 days of medication. There were no pregnancy complications. Fetal development was normal during follow-up 13 months. It is suggested that ATO may be safe for late pregnancy, but more clinical data are needed to prove it. In this case, the patient used ATO at a dose of 8 mg/day, and the fetus did not have malformations. In addition, other chemotherapeutic drugs, such as methotrexate, cytarabine and sputum analogs, may increase the risk of cardiotoxicity and should be avoided in early pregnancy.

Another issue is that is important to take into consideration during treatment with ATRA is retinoic acid syndrome. This is a fatal complication of acute promyelocytic leukemia during induction chemotherapy. It is also known as differentiation syndrome (DS). Patients receiving ATRA for APL are at risk of developing this syndrome within 1 - 3 weeks of initiation of induction chemotherapy. There are differences in the incidence of this syndrome in the literature. A review of recent literature indicates that the incidence rate is probably from 2% to 27%. Its pathogenesis has not been clearly understood. The currently recognized mechanisms are mainly related to adhesion factors, cytokines and chemokines. There are no definite diagnostic criteria for its diagnostic criteria, but most scholars believe that its clinical manifestations include unexplained fever, weight gain, peripheral edema, dyspnea due to pulmonary interstitial infiltration, pleural and pericardial effusion, intermittent hypotension, acute renal failure, and so on. In recent years, some scholars think that it should also include the following aspects: ocular manifestations (bilateral visual acuity decline), skin lesions (granulosercoma suppurative transformation), ET syndrome (acute febrile neutrophil dermatosis), edematous pancreatitis, bradycardia, pericardial tamponade, and pulmonary hemorrhage, etc.). The occurrence of differentiation syndrome can increase the mortality of APL and seriously affect the therapeutic effect of ATRA. Therefore, early understanding and timely treatment of DS is the best way to prevent its progress and reduce its harm to patients. A review of the relevant literature indicates the following points as now recognized in the management:

1) Dexamethasone: Many studies at home and abroad have found that dexamethasone can effectively reduce the secretion of inflammatory cytokines in alveolar epithelial cells, thereby controlling the occurrence of DS. Therefore, dexamethasone 10 - 20 mg /d was applied early, until the symptoms disappeared, which is clearly pointed out in the guidelines at home and abroad. However, there is controversy about whether the prophylactic use of glucocorticoids is needed. Studies have shown that patients with high white blood cell count during diagnosis are at higher risk of developing DS. Such patients can benefit from prophylactic use of glucocorticoids. The development of DS can be prevented by using it which can reduce DS incidence and mortality [8].

2) Regarding the reduction or discontinuation of ATRA or ATO, various studies have differing opinions. The author believes that if DS is severe and chemotherapy and glucocorticoids are not able to relieve the symptoms, ATRA and ATO should be stopped to ensure the safety of patients.

3) Add other chemotherapy drugs: At present, hydroxyurea, combined chemotherapy, etc. can be used. Combination chemotherapy includes mostly daunorubicin, nordaxin, homoharringtonine and cytarabine. Most studies have shown that DS can be avoided.

4) Other supportive treatments such as oxygen inhalation, diuretics, blood transfusion, platelet transfusion, mechanical ventilation, and other supportive treatments.

In this case, the patient developed retinoic acid syndrome on the 19th day of initiation of induction therapy. "Daunorubicin 40 mg, dexamethasone 10 mg, furosemide 20 mg", was added to the treatment regimen while adjusting the ATRA dose to 20 mg once a day from twice a day. As her symptoms persisted despite adjusting the treatment plan, both ATO and ATRA were discontinued. Her symptoms were relieved after 2 days of discontinuing ATRA and ATO. The clinical manifestations observed and treatment applied in this case are consistent with the literature reports. However, this case raises some serious questions. Was the patient more susceptible to develop DS due to her pregnancy? Is there any reproductive toxicity associated with the use of glucocorticoids? Thus, the treatment of differentiation syndrome induced by use of ATRA induction chemotherapy in APL during pregnancy remains to be further studied.

4. Management

Reasonable selection of chemotherapy drugs can avoid fetal congenital malformation to a certain extent, but the risk of abortion, premature birth, low birth weight neonatal, neonatal neutropenia and sepsis will still increase. However, based on the lack of clinical and epidemiological evidence, the choice of chemotherapy drugs and the timing of chemotherapy still remain as clinical challenges. Most scholars recommend immediate termination of pregnancy and active anti-leukemia treatment in early pregnancy. In special circumstances, if APL is diagnosed in early pregnancy and the patient is eager to continue the pregnancy, treatment can be actively supported. Chemotherapy can be started after 8 - 10 weeks of pregnancy. The 10th week of pregnancy is the most active period of fetal growth and development. The use of cytotoxic drugs during this period has a 10% - 20% risk of teratogenicity and is prone to abnormal embryonic development. However, if diagnosis is made in the middle or later stages of pregnancy, chemotherapy should be started immediately and strived to achieve complete remission within a short period. If the condition is critical, chemotherapy should be started at the same time as symptomatic supportive treatment. When the condition becomes stable, the pregnancy should be terminated. Most scholars believe that pregnancy should be as much as possible after 36 weeks. If prema-

ture birth occurs, it is recommended to use cortisol appropriately to reduce the labor.

The mode of delivery of APL patients is another area that requires careful assessment of the patient's general condition. Normal delivery is preferable to cesarean section as it has a lower risk of bleeding than cesarean delivery. However, cesarean section is the best choice when patients cannot withstand the pressure of normal vaginal delivery. In patients with stable disease, chemotherapy drugs can be suspended for a short time before labor and can be continued after delivery continue [9] [10]. In patients who are diagnosed later during pregnancy, near the time of delivery, chemotherapy can be delayed after delivery.

Pregnancy with APL is extremely challenging and requires the active participation of patients, family members, hematologists, obstetricians and neonatal doctors in decision-making to achieve good outcomes for both patient and fetus. In this case, the patient was diagnosed with APL at 28 weeks of gestation and immediately achieved hematologic remission after receiving induction chemotherapy with ATRA + arsenic trioxide. After chemotherapy, she gave birth to a healthy male baby at 39 weeks + 5 days of pregnancy.

5. Outlook

As mentioned above, ATO has also been reported to have some embryonic toxicity and is not recommended for use during pregnancy. However, in this case, ATO was used during pregnancy. Nevertheless, no deformity was seen in the baby after the delivery. Successful delivery of normal infants after ATO treatment has been reported by some other studies. Whether arsenic trioxide has dose-dependent toxicity due to its accumulation in the body or it does not have any toxicity during pregnancy remains to be considered. As previously stated, no extensive studies have been performed regarding this issue. Data are limited to a few studies conducted in populations exposed to arsenic from drinkable water or from working at or living near smelters. At the same time, there is no clear evidence that leukemia cells can pass through the placental barrier. Some scholars believe that because the placental barrier can prevent leukemia cells from entering the fetus, it is rare for leukemia to pass through the placenta to the fetus. But the author believes that it is not possible to come to this conclusion as only a few cases of leukemia in pregnancy have been studied. A lot of extensive research and studies still need to be performed regarding leukemia in the later stages of pregnancy.

6. Conclusions

APL during pregnancy is a rare occurrence. The literature and research on the outcomes of these patients are also scarce. As discussed above, both ATRA and ATO have been reported to have embryonic toxicity and are not recommended to be used during pregnancy. Nevertheless, successful outcome has been documented in pregnant females who have been treated with ATRA in some studies.

The case described in this report was diagnosed with APL in last trimester of pregnancy and there was further complication of differentiation syndrome. Despite receiving the combination of ATRA and ATO and developing differentiation syndrome, she gave birth to a healthy infant with no abnormalities.

Whether the toxicity of ATO is dose-dependent or it does not have any toxicity during pregnancy remains to be considered. No studies have been performed about this and there is still room for more extensive research and placental pathological examination after pregnancy [11].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Analysis of the Status Quo and Influencing Factors of Readiness for Hospital Discharge of Patients Undergoing Hysteromyomectomy

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Abstract

Objective: To evaluate the status quo and influencing factors of readiness for hospital discharge of patients undergoing hysteromyomectomy. **Methods:** A total of 240 patients with uterine fibroid undergoing hysteromyomectomy from 2 hospitals in Jingzhou were investigated using a self-designed general information questionnaire, the Readiness for Hospital Discharge Scale and the Quality of Discharge Teaching Scale. **Results:** The total score of readiness for hospital discharge was (91.36 ± 18.46), the multiple linear regression analysis showed that the quality of discharge guidance, the scope of myomectomy, pain degree of incision and the average monthly income per family were the main influencing factors of readiness for hospital discharge. **Conclusion:** The readiness for hospital discharge was at a medium level in patients with uterine fibroid undergoing hysteromyomectomy, medical personnel should give specific discharge guidance according to the specific conditions of patients to ensure the safety of patients after discharge.

Keywords

Uterine Fibroid, Readiness for Discharge, Discharge Teaching, Influencing Factors

1. Introduction

The readiness for hospital discharge was first proposed by Fenwick [1] in 1976, it refers to the ability of patients to cope in the community after transitioning from an acute care hospital, it's a kind of self-perception of whether patients are ready for discharge. As a mediation variable in the transition period from discharge to return home, the readiness for hospital discharge is closely related to the effect of rehabilitation, quality of life and outcome after discharge [2]. Surgical treatment

is the main treatment for symptomatic uterine fibroid, but the current treatment is more or less accompanied by trauma and postoperative complications. Some studies have shown that the risk of postoperative recurrence of uterine fibroid is 4% - 30%, among which 10% patients still need further intervention after hysteromyomectomy, some patients performed high stress response due to surgery: anxiety, depression, fear, etc., so there will still be different degrees of health problems after discharge from hospital and there is a high demand for health care [3] [4] [5] [6]. The readiness of hospital discharge is related to patients' self-care ability, and has a significant impact on improving patients' self-efficacy and quality of life after discharge. To investigate the level of readiness for hospital discharge level of patients after hysteromyoma operation, 240 patients were investigated, and the influencing factors were analyzed, so as to provide scientific basis for improving the self-care ability of patients and developing standardized discharge guidance in clinical.

2. Materials and Methods

2.1. Patients

240 patients with uterine fibroid undergoing hysteromyomectomy from December 2018 to June 2019 in the work were included. Inclusion criteria: it conforms to the diagnostic standards of uterine fibroid by "Chinese Journal of obstetrics and gynecology" [7], accepted the surgical treatment; hospital stay ≥ 3 days; discharge with medical advice; voluntarily participated in the study. Exclusion criteria: with communication barriers, unclear consciousness or mental disorder; with other important organ function damage. This study has been approved by the head nurses of the nursing departments.

2.2. Research Tools

1) A general information questionnaire was designed by the researchers according to the research purpose, including 15 basic information such as general demographic data (age, residence, education level, marital status, working status and mode of payment), disease-related data (reason for medical consultations, operation method, scope of myomectomy and so on).

2) The Readiness for hospital discharge scale (RHDS) was developed by Marianne *et al.* [8] in 2006. In this study, the Chinese version of RHDS translated and revised by Lin Youhua *et al.* [1], a Taiwan scholar of China, was used. After translation and reliability and validity test, the scale only contains 12 items based on the original scale. The items from 3 sub-scales: personal status, coping ability and expected support, scored on a 10-point scale (0 - 10). Higher scores indicate greater readiness. The Cronbach's *α* coefficient of the Chinese scale is 0.89, the content validity index is 0.88, and the content validity index of each item is 0.80 - 1, which is highly correlated with the original scale.

3) The quality of discharge teaching scale (QDTS) was developed by Weiss *et al.* [2]. In this study, the Chinese version of QDTS translated and revised by

Wang Binghua *et al.* [9] was used. The scale retained all the items and structures of the original scale, including 24 items, 3 sub-scales: the amount of "content needed", "content received" and "teaching skills". The total scale score is calculated by adding the content received and the delivery sub-scale scores. The content validity index was 0.98, the Cronbach's *α* coefficients of the total scale and 3 factors were 0.924, and 0.882 - 0.935. The Chinese version of QDTS is reliable and valid and can be used for assessment and measurement of the quality of discharge teaching in Chinese settings.

2.3. Data Collection

In this study, relevant data were collected by sending questionnaires to discharged patients who met the inclusion criteria. The questionnaire survey was carried out on the day before the patient discharged from the hospital. 260 questionnaires were issued and 240 effective questionnaires were recovered, the effective recovery rate was 92.31%.

2.4. Statistical Analysis

SPSS22.0 software was used for statistical analysis. The general data of patients are expressed by frequency and percentage, and the scores of each scale are analyzed by Mean ± SD. The results of single factor analysis are compared by *t*-test or variance analysis, *Pearson* correlation analysis is carried out between the two scales. 95% CI was calculated for all analyses ($α = 0.05$).

3. Results

3.1. Comparison of Readiness of Hospital Discharge Scores of Patients with Different Demographic Characteristics

The results of single factor analysis show that in demographic data, the education level and monthly income of family are the influencing factors of readiness of hospital discharge ($P < 0.05$). The difference of readiness of hospital discharge scores of patients with different reasons for medical consultations, scope of myomectomy, operative method, pain degree of incision and day after operation was statistically significant ($P < 0.05$) (Table 1).

3.2. The Status Quo of Readiness for Hospital Discharge

The mean total score of RHDS in this study was (91.36 ± 18.46), in a Medium level. The standardized scores in the three subscales were: personal status (7.48 ± 1.87), coping ability (7.67 ± 1.84), and expected support (7.70 ± 2.04) (Table 2).

3.3. The Status of the Quality of Discharge Teaching

In the study, the mean total score of QDTs was (136.94 ± 26.50), while the standardized scores were higher for the received subscale (6.23 ± 2.26) than for the Content needed subscale (5.75 ± 2.55), indicated that the patient's care needs were met (Table 3).

Table 1. Comparison of readiness of hospital discharge scores of patients (n = 240).

Characteristic	Grade	Number (%)	Readiness ($\bar{X} \pm S$)	Statistic value	P-value
Residence	Urban	61 (25.42)	92.67 ± 17.79	0.407[1]	0.666
	Town	68 (28.33)	92.04 ± 17.02		
	Countryside	111 (46.25)	90.23 ± 19.80		
Age (years)	≤35	62 (25.83)	95.98 ± 16.82	2.427[1]	0.066
	36 - 45	81 (33.75)	89.78 ± 20.77		
	46 - 55	74 (30.83)	91.19 ± 17.21		
	≥56	23 (9.58)	85.04 ± 16.52		
Education	Primary or below	38 (15.83)	85.69 ± 18.32	2.683[1]	0.032
	Junior middle school	108 (45.00)	89.82 ± 19.79		
	Secondary/High school	34 (14.17)	93.24 ± 19.03		
	College	37 (15.42)	95.54 ± 16.26		
	Bachelor degree or above	22 (9.17)	99.05 ± 10.00		
Marital status	Single	12 (5.00)	91.58 ± 16.96	0.365[1]	0.694
	Married	215 (89.58)	91.09 ± 18.74		
	Divorce/Widowhood	13 (5.42)	95.62 ± 16.46		
Working state	Incumbency	118 (49.17)	94.03 ± 17.85	2.267[1]	0.081
	Retired	23 (9.58)	87.35 ± 11.91		
	Unemployed	98 (40.83)	88.87 ± 20.08		
Mode of payment	All voluntary spends	16 (6.67)	96.56 ± 15.66	1.564[1]	0.185
	Public expense	2 (0.83)	100.50 ± 3.54		
	New rural cooperative medical insurance	119 (49.58)	89.19 ± 19.30		
	Other medical insurance	95 (38.58)	93.65 ± 16.41		
	Poverty seeking help	8 (3.33)	83.75 ± 31.07		
Reasons for medical	Physical examination	117 (48.75)	93.97 ± 17.03	4.850[2]	0.029
	Clinical feature	123 (51.25)	88.98 ± 19.63		
Scope of myomectomy	Total hysterectomy	60 (25.00)	84.37 ± 18.73	5.374[1]	0.001
	Partial hysterectomy	153 (63.75)	93.54 ± 17.74		
	Myomectomy	21 (8.75)	90.86 ± 19.57		
	Others	6 (2.50)	107.50 ± 8.87		
Operative method	Laparotomy	64 (26.67)	84.69 ± 18.37	5.182[1]	0.002
	Laparoscope	24 (10.00)	93.21 ± 19.27		
	Hysteroscopy	146 (60.83)	93.32 ± 17.92		
	Ultrasonic focusing	6 (2.50)	107.50 ± 8.87		
Pain degree of incision	0	61 (25.42)	98.59 ± 14.49	7.368[1]	<0.001
	1	75 (31.25)	94.92 ± 16.98		

Continued

	2	77 (32.08)	87.17 ± 19.28		
	3	20 (8.33)	78.35 ± 20.07		
	4	6 (2.50)	74.50 ± 13.10		
	5	1 (0.42)	68.00		
Day after operation	≤3	36 (15.00)	90.69 ± 20.53	4.736[1]	0.010
	4 - 7	161 (67.08)	93.50 ± 17.40		
	≥8	43 (17.92)	83.91 ± 19.21		
Admission times	1	197 (82.08)	92.03 ± 18.34	2.754[1]	0.066
	2	34 (14.17)	91.24 ± 19.74		
	>2	9 (3.75)	77.33 ± 11.97		
Chronic disease	No	209 (87.08)	92.24 ± 18.16	2.360[1]	0.097
	1	24 (10.00)	87.21 ± 22.13		
	≥2	7 (2.92)	79.29 ± 7.39		
Monthly income (RMB)	≤2000	50 (20.83)	88.56 ± 19.58	6.512[1]	<0.001
	2000 - 4000	78 (32.50)	85.14 ± 19.47		
	4000 - 6000	67 (27.92)	94.72 ± 17.34		
	6000 - 9000	28 (11.67)	97.86 ± 11.30		
	≥9000	17 (7.08)	104.24 ± 12.18		
Primary caregiver	Children/Husband	186 (77.50)	91.33 ± 18.75	2.012[1]	0.136
	Self	32 (13.33)	87.31 ± 18.88		
	Others	22 (9.17)	97.55 ± 14.40		

[1]*F*-value, [2]*t*-value.

Table 2. Readiness for hospital discharge of patients after hysteromyoma (n = 240, $\bar{X}$ ± S).

Sub-scales	Number of items	Full score	Actual score	Standardized score
Personal status	4	40	29.92 ± 7.46	7.48 ± 1.87
Coping ability	4	40	30.67 ± 7.35	7.67 ± 1.84
Expected support	4	40	30.78 ± 8.14	7.70 ± 2.04
Total score	12	120	91.36 ± 18.46	7.61 ± 1.54

Table 3. The quality of discharge teaching of patients after hysteromyoma (n = 240, $\bar{X}$ ± S).

Sub-scales	Number of items	Full score	Actual score	Standardized score
Content needed	6	60	34.48 ± 15.28	5.75 ± 2.55
Content received	6	60	37.38 ± 13.57	6.23 ± 2.26
Guidance skills and effect	12	120	99.56 ± 18.25	8.30 ± 1.52
Total score	18	180	136.94 ± 26.50	7.61 ± 1.47

3.4. Correlation Analysis of Readiness for Hospital Discharge and the Quality of Discharge Teaching of Patients

The scores of QDTS and its correlation with RHDS: in the study, there were statistically significant relativity between RHDS score and both total scale score and most subscales scores of QDTS ($P < 0.05$) (Table 4).

3.5. Analysis of the Influencing Factors of Readiness for Hospital Discharge of Patients

Taking the total score of readiness for hospital discharge of patients as the dependent variable, 7 variables with statistical significance in single factor analysis were used as independent variables for multiple linear regression analysis. Variable assignments were as follows: 1) Education: Primary or below = 1, Junior middle school = 2, Secondary specialized or high school = 3, College = 4, University = 5; 2) Reasons for medical consultations: physical examination = 1, clinical features = 2; 3) Scope of myomectomy: Total hysterectomy = 1, Partial hysterectomy = 2, Myomectomy = 3, Others = 4; 4) Operative method: Laparotomy = 1, Laparoscope = 2, Hysteroscopy = 3, Ultrasonic focusing = 4; 5) Pain degree of incision:0 = 1, 1 = 2, 2 = 3, 3 = 4, 4 = 5; 6) Day after operation: ≤3 days = 1, 4 - 7 days = 2, ≥8 days = 3; 7) Monthly income of family: ≤2000 = 1, 2000 - 4000 = 2, 4000 - 6000 = 3, 6000 - 9000 = 4, ≥9000 = 5. The results showed that monthly income of family, pain degree of incision, uterine fibroid resection and the quality of discharge teaching were the main influencing factors of readiness for hospital discharge (Table 5).

Table 4. Correlation analysis of two scales (n = 240, *r*-value).

	Total score of discharge readiness	Personal status	Coping ability	Expected support
Content needed	−0.113	−0.140	−0.168*	0.015
Content received	0.387*	0.273*	0.348*	0.323*
Guidance skills and effect	0.464*	0.390*	0.432*	0.322*
Total score of discharge guidance quality	0.491*	0.397*	0.450*	0.361*

*$P < 0.05$.

Table 5. Multiple linear regression analysis of readiness for hospital discharge (n = 240).

	Regression coefficient	Standardized regression coefficient	*t*-value	*P*-value
Constant term	41.278	-	4.745	0.000
Scope of myomectomy	3.901	0.189	2.729	0.007
Pain degree of incision	−3.701	−0.202	−2.759	0.006
Monthly income of family	3.134	0.159	2.394	0.018
Total of the quality of discharge teaching	0.280	0.412	5.880	<0.001

$F = 5.730$, $P < 0.05$, $R^2 = 0.363$, adjusted $R^2 = 0.345$.

4. Discussion

4.1. The Readiness for Hospital Discharge of Patients with Hysteromyoma Is at a Medium Level

Item 1 of the readiness for hospital discharge scale is true or false, 93.75% (225 cases) of patients think they are prepared for discharge. However, only 68.75% of the patients have an average score of more than 7, according to Weiss *et al.* [10], the standardized score of readiness for hospital discharge is less than 7, which is a low-level threshold, probably because the patient's worry about hospital expenses. Even if they are not ready for discharge, they still answer that they are prepared, or some patients have cognitive bias and overestimate their preparation for discharge [11]. In this study, the total score of the readiness for hospital discharge of patients with hysteromyoma was (91.36 ± 18.46), and the average score of items was (7.61 ± 1.54), in a middle level. The results were similar to those of patients after radical operation of cervical cancer [12] (7.70 ± 1.03) and hepatobiliary surgery [13] (7.28 ± 1.64). The scores of 3 dimensions from high to low were expected support, coping ability and personal status, which may be related to the following factors: 1) The overall education level of the patients included in this study was low (60.83% were junior middle school or below), and about 46% of the patients lived in rural areas, so many of them lack the knowledge of disease rehabilitation, compared with cities and towns, rural areas have a narrow access to information platform and less social support. Study [14] shown that 70.9% of women have poor overall understanding of hysteromyoma and its treatment, with an average score of less than 60%. 2) The recovery of hysteromyoma after operation is a long-term process, some patients are damaged in physical integrity, and they have insufficient understanding or psychological preparation on how to deal with the disease recovery after discharge. It is suggested that medical staff should pay attention to the difference of patients' needs in health education for patients with hysteromyoma after operation, especially the patients with low education level and living in rural areas, and implement individualized health education programs to meet their needs.

4.2. The Readiness for Hospital Discharge of Patients with Hysteromyoma Is Affected by Various Factors

1) The readiness for hospital discharge of patients with hysteromyoma after operation is affected by the reasons for medical consultations, and monthly income of the family.

The results of this study show that the score of the readiness for hospital discharge of patients who seek for medical treatment for physical examination is higher than those who seek medical treatment due to clinical symptoms. The reason may be that the patients who find medical treatment due to physical examination have no or less clinical manifestations, and have higher awareness of their own health care. The monthly income of the family is significantly related to their personal status and coping ability ($P < 0.001$), the higher the monthly

income of the patients, the higher the level of the discharge preparation. The reasons may be that the patients with good economic conditions can actively seek medical help, have better medical security method and less economic burden, can focus on postoperative rehabilitation after discharge quickly. Higher monthly income is a protect factor for discharge readiness, which can better meet the health needs of the patients [15].

2) The readiness for hospital discharge of patients with hysteromyoma after operation is affected by scope of myomectomy, operative method and pain degree of incision.

The results of this study show that the score of readiness for hospital discharge of patients with hysteromyoma treated by high-intensity focused ultrasound therapy is higher, and that of patients treated with hysteromyoma or laparoscopy is the second, and that of patients with open total hysterectomy is the lowest. On the day of discharge, the patients with lower incision pain degree have higher discharge readiness level. As an extracorporeal therapy, high intensity focused ultrasound therapy is simple and has no damage or wound to normal tissues, and patients can quick recovery postoperatively [16]. Patients undergoing laparotomy recovery slowly, their self-care ability is reduced, so most of them have lower readiness for hospital discharge level. Operative method and pain degree of incision were also the main influencing factors of patients' personal status and coping ability ($P < 0.05$). Giving nursing intervention to patients can relieve the pain of incision and keep patients in a best state of mind and body, and promote the recovery [17].

3) The readiness for hospital discharge of patients with hysteromyoma after operation is closely related to the quality of discharge teaching.

The results of this study showed that the quality of discharge teaching for patients with hysteromyoma after operation was at a medium level (136.94 ± 26.50) and positively correlated with the readiness for hospital discharge ($r = 0.491$, $P < 0.05$). The score of the guidance skills and effect is highest, it may be that the investigation department of the institutes teach the health knowledge to patients and their families in one day of a week. In the other two dimensions, the score of the content needed and actual received were relatively low. The reason for the analysis may be that the discharge teaching scale is evaluated by the patient subjectively, which need them to fill in by connecting the expectation with practice, however some patients have cognitive bias and so it is easy to make a wrong judgment if they do not understand their own situation. In addition, this study also found that operative method and whether there are other chronic diseases have a significant impact on the content of patients' needs (all $P < 0.05$). Patients who undergoing laparotomy or total hysterectomy or have other chronic diseases have a higher demand for related health knowledge. Compared with patients themselves, medical staffs have a more comprehensive understanding and objective evaluation about patients, suggesting that medical staff should give targeted discharge guidance, not only to meet the functional needs of patients, but also to pay attention to their acceptance and utilization of informa-

tion. The complete readiness for hospital discharge includes physical stability, sufficient support, psychological ability and enough information and knowledge. It suggests that medical staff should strengthen communication with patients and their families, provide them with high-quality discharge guidance services, and ensure that patients understand and master relevant contents of discharge guidance [18].

4.3. Limitations

1) If regarded this study as a descriptive cross-sectional study, the sample size is small and limited to a certain city, which cannot replace the situation of large areas, resulting in a decline in the persuasiveness of the results. 2) The questionnaire is collected in the hospital, and most of it is issued and recovered by the patient's responsible nurses, so there may be some inaccuracies of the data, which may bias the results.

5. Conclusion

The readiness for hospital discharge of patients with hysteromyoma after operation is at a medium level, which needs to be improved. Monthly income of family, scope of myomectomy, pain degree of incision and the quality of discharge teaching quality are the main influencing factors. For patients with poor economic status, received laparotomy or hysterectomy, we should pay more attention to them and strengthen the guidance. We can learn from Taiwan and foreign hospitals to try to carry out discharge preparation services to help patients prepare for discharge. At the same time, family members should be encouraged to give support to patients, mobilize their subjective initiative, and ensure the safety of patients after discharge. In the future study, we can understand the common problems through qualitative interviews that hinder patients' perception of discharge readiness, and formulate corresponding nursing interventions based on the problems. Through interviews with patients, combined with relevant literature and guidelines, we can develop standard discharge guidance process and content.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Current Status and Influencing Factors of the Quality of Work Life of Nurses in Intensive Care Unit

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Abstract

Objective: To investigate the current status and influencing factors of the quality of work life of nurses in Intensive Care Unit (ICU). **Methods:** A total of 243 ICU nurses from 6 general hospitals in Jingzhou were selected by convenient sampling method. Questionnaires were conducted with the general information questionnaire, Connor-Davidson Resilience Scale (CD-RISC) and Work-Related Quality of Life Scale-2 (WRQoL-2). **Results:** The total average score of the quality of work life of ICU nurses was (3.35 ± 0.44), which was at a medium level. Department, professional title, frequency of night shift, experience of workplace violence and psychological resilience were the influencing factors of the quality of work life of nurses in ICU, accounting for 39.4% of the variance. **Conclusion:** The quality of work life of ICU nurses needs to be improved. Nursing managers should pay attention to the work environment of ICU nurses, rationally allocate manpower, and improve the status of psychological resilience of nurses, so as to improve their quality of work life.

Keywords

ICU, Nurse, Quality of Work Life, Psychological Resilience, Influencing Factors

1. Introduction

The National Nursing Career Development Plan (2016-2020) pointed out that one of the main tasks of the development of nursing industry during the 13th Five-Year Plan period was to improve the quality of nursing services and pro-

mote high-quality nursing [1]. The quality of work life of nurses is directly proportional to the quality of care services. Having a good quality of work and life is a prerequisite for nurses to carry out high-quality nursing and contribute to the sustainable development of health service systems [2]. The Intensive Care Unit (ICU) is a department that treats all kinds of severe illness and multi-systemic failure patients. Its nursing work has the characteristics of high risk, high tension and high labor intensity. ICU nurses have higher work pressure, long-term stress, and poor quality of work life [3] [4] [5]. At present, domestic research on the quality of nursing work life focuses on the emergency department and pediatrics department. There are few studies on the quality of work life of ICU nurses, and it is limited to the top three hospitals. It is extremely urgent to carry out research on the quality of work life of ICU nurses. Therefore, this study aims to investigate the current status and influencing factors of the quality of work life of ICU nurses in different grades of hospitals, and provide reference for the intervention study to improve the quality of work life of ICU nurses.

2. Object and Method

2.1. Research Object

From January to April of 2019, the ICU nurses in 6 general hospitals (3 tertiary general hospitals and 3 secondary general hospitals) in Jingzhou were selected as research objects by convenient sampling method. Inclusion criteria: work in clinical care in ICU; work experience in ICU ≥ 1 year; volunteer to participate in this survey. Exclusion criteria: those who are unable to complete the questionnaire for various reasons; non-unit nurses, such as training nurses.

2.2. Research Tools

2.2.1. General Information Questionnaire
The general information questionnaire was designed by consulting domestic and foreign related literatures [2] [6] [7], and reviewed by 5 nursing management experts, and revised with expert opinions. Including gender, age, hospital grade, department, working years, working years in ICU, marital status, education level, professional title, position, frequency of night shift, monthly income, and experience of workplace violence.

2.2.2. Work-Related Quality of Life Scale
Based on Van Laar *et al.* [8], Shao Ya *et al.* [9] translated and revised the Work-Related Quality of Life Scale-2 (WRQoL-2), including 7 factors, 33 items. Using the Likert 5 rating (1 = very disagree, 2 = disagree, 3 = no opinion, 4 = agree, 5 = very agree), convert the score of the reverse items and then calculate the score. The scores of the scale range from 33 to 165. The higher the score of the scale, the higher the quality of work life. The content validity CVI of the scale is 0.91; the total Cronbach's α coefficient is 0.939, and the factors are between 0.652 and 0.859.

2.2.3. Psychological Resilience Scale

Based on Connor *et al.* [10], Li Yameng *et al.* [11] translated and revised the Connor-Davidson Resilience Scale (CD-RISC), including 3 factors (adaptability, toughness, goal achievement), 23 items. Using the Likert 5 rating (0 = never, 1 = rarely, 2 = sometimes, 3 = often, 4 = always), the scores of the scale range from 0 to 92.The higher the score, the better the psychological resilience. The total Cronbach's *a* coefficient of the scale is 0.940, and the factors are between 0.803 and 0.903.

2.3. Survey Method

This study was approved by the hospital ethics committee. The questionnaire of this study included 7 factors of WRQoL-2 and 3 factors of CD-RISC. The estimation formula of the sample size was [Max (dimension number)*(15 - 20)]*[1 + (15% - 20%)]. It was calculated that the sample size of this study needed 173 - 240. Under the coordination of the nursing department and the head nurses of each hospital, the nursing staff would be concentrated in the department. After obtaining the consent of the respondents, the anonymous survey was adopted. The purpose, significance and filling method of the investigation would be explained to the respondents before the investigation. After the questionnaire was filled out, checked it on the spot. A total of 260 questionnaires were distributed in this study. After eliminating the response absence rate of >10% or selecting the same option, 243 valid questionnaires were collected, with an effective rate of 93.5%.

2.4. Statistical Method

SPSS22.0 software was used for statistical analysis. The general data and the scores of each scale were described by Mean ± SD, frequency, and percentage. The *t*-test or *F*-test was used to compare the scores of the quality of work life of ICU nurses with different demographic characteristics. The analysis of the factors influencing the quality of work life of ICU nurses was performed by multiple linear regression analysis. The difference was statistically significant ($P < 0.05$).

3. Results

3.1. The Scores of the Quality of Work Life and Psychological Resilience of ICU Nurses

The total score of the quality of work life of 243 ICU nurses was (110.60 ± 14.61), and the total average score was (3.35 ± 0.44). The factors divided into low to high were work pressure (2.82 ± 0.51), work conditions (3.25 ± 0.62), general well-being (3.34 ± 0.59), work evaluation (3.47 ± 0.56), work-family balance (3.53 ± 0.75), work control (3.59 ± 0.52), career satisfaction (3.64 ± 0.50). The score of psychological resilience was (55.83 ± 12.23), and the total average score was (2.43 ± 0.53). The score of adaptability dimension was (2.21 ± 0.49), followed by toughness (2.51 ± 0.60) and goal achievement (2.71 ± 0.62).

3.2. Comparison of the Scores of the Quality of Work Life of ICU Nurses with Different Demographic Characteristics

There were significant differences in scores of the quality of work life of ICU nurses in different departments, titles, professional positions, frequencies of night shift, and experiences of workplace violence ($P < 0.05$). These were shown in Table 1.

3.3. Multiple Linear Regression Analysis on the Influencing Factors of the Quality of Work Life of ICU Nurses

Taking the total average score of the quality of work life of ICU nurses as the dependent variable, and the department, professional title, position, frequency of night shift, experience of workplace violence and the total score of psychological resilience as the independent variable, the multiple linear regression analysis was carried out. The assignment of the independent variable was shown in Table 2. The results of multiple regression analysis showed that department, professional title, frequency of night shift, experience of workplace violence and psychological resilience were the influencing factors of the quality of work life of ICU nurses, accounting for 39.4% of the variance. The results were shown in Table 3.

4. Discussion

4.1. The Importance of Investigating the Quality of Work Life of ICU Nurses

Lee *et al.* found that as many as 720 nurses (56.1%) had a turnover intention through a survey of 1283 hospital nurses in Taiwan [12]. The score of work stressor of ICU nurses was higher than that of other department nurses [4], and the turnover intention of ICU nurses was higher than that of general outpatient nurses [13]. As the core department of the hospital, the stability of ICU nursing team is the key point that hospital managers need to pay attention to [14]. Studies have shown that the lower the quality of work life of nurses, the stronger their tendency to leave [15]. Through the investigation of the status quo of the quality of work life of ICU nurses, the hospital nursing management system can be prospectively reviewed, the weak links can be found, and nursing managers can take corresponding measures to improve the quality of work life of ICU nurses and prevent ICU nurses from losing. At the same time, the improvement of the quality of work life of nurses will improve the well-being and satisfaction of nurses, leading to beneficial outcomes for hospitals and patients, such as higher patient satisfaction [16] [17].

4.2. The Quality of Work Life of ICU Nurses Needs to Be Improved

In this study, the total average score of the quality of work life of ICU nurses was (3.35 ± 0.44), which was at a medium level, and the situation was not optimistic. Among them, the two factors of work pressure and work conditions had the lowest score, which may be related to the following reasons: 1) ICU was a

Table 1. Comparison of the scores of the quality of work life of ICU nurses with different demographic characteristics (n = 243).

Characteristics	Cases (%)	Average score (X ± S)	*t*/*F*-value	*P*-value
Gender			−0.678#	0.502
Meal	28 (11.5)	3.29 ± 0.49		
Female	215 (88.5)	3.36 ± 0.44		
Age			2.191	0.071
21 - 25 years old	53 (21.8)	3.47 ± 0.36		
26 - 30 years old	101 (41.6)	3.31 ± 0.46		
31 - 35 years old	50 (20.6)	3.24 ± 0.46		
36 - 40 years old	22 (9.1)	3.43 ± 0.35		
≥41 years old	17 (7.0)	3.45 ± 0.56		
Hospital grade			−0.692#	0.491
Tertiary hospital	192 (79.0)	3.28 ± 0.43		
Second-class hospital	51 (21.0)	3.32 ± 0.39		
Department			−2.371#	0.019*
Comprehensive ICU	105 (43.2)	3.28 ± 0.43		
Specialist ICU	138 (56.8)	3.41 ± 0.44		
Working years			2.092	0.082
1 - 5 years	102 (42.0)	3.40 ± 0.42		
6 - 10 years	79 (32.5)	3.25 ± 0.47		
11 - 15 years	41 (16.9)	3.35 ± 0.39		
16 - 20 years	7 (2.9)	3.63 ± 0.60		
≥21 years	14 (5.8)	3.39 ± 0.46		
Working years in ICU			1.336	0.257
1 - 5 years	119 (49.0)	3.40 ± 0.41		
6 - 10 years	84 (34.6)	3.27 ± 0.49		
11 - 15 years	28 (11.5)	3.35 ± 0.39		
16 - 20 years	5 (2.1)	3.44 ± 0.34		
≥21 years	7 (2.9)	3.44 ± 0.64		
Marital status			1.571#	0.118
Unmarried	87 (35.8)	3.41 ± 0.46		
Married	156 (64.2)	3.32 ± 0.43		
Education level			0.351	0.704
Associate degree	35 (14.4)	3.41 ± 0.38		
Bachelor	204 (84.0)	3.34 ± 0.45		
Postgraduate	4 (1.6)	3.28 ± 0.54		
Professional title			2.924	0.035*
Nurse	76 (31.3)	3.44 ± 0.40		
Nurse practitioner	96 (39.5)	3.34 ± 0.42		
Supervisor	64 (26.3)	3.28 ± 0.51		
Deputy chief nurse and above	7 (2.9)	3.63 ± 0.33		

Continued

Position			4.677	0.010*
Nurse	186 (76.5)	3.36 ± 0.44		
Nursing/Teaching team leader	44 (18.1)	3.24 ± 0.44		
Head nurse	13 (5.3)	3.66 ± 0.39		
Frequency of night shift			3.745	0.012*
None	40 (16.5)	3.45 ± 0.36		
1 - 4 times/month	58 (23.9)	3.43 ± 0.47		
5 - 8 times/month	83 (34.2)	3.35 ± 0.44		
Over 8 times/month	62 (25.5)	3.21 ± 0.44		
Monthly income			0.749	0.560
<3000 yuan	9 (3.7)	3.31 ± 0.29		
3000 - 4999 yuan	67 (27.6)	3.43 ± 0.35		
5000 - 6999 yuan	116 (47.7)	3.33 ± 0.44		
7000 - 8999 yuan	43 (17.7)	3.30 ± 0.58		
>9000 yuan	8 (3.3)	3.34 ± 0.54		
Experience of workplace violence			−3.952[#]	<0.001**
Yes	107 (44.0)	3.23 ± 0.41		
No	136 (56.0)	3.45 ± 0.45		

*: $P < 0.05$; **: $P < 0.01$; #: t-value.

Table 2. Assignment of the independent variable.

Variable	Assignment
Department	Comprehensive ICU = 1; Specialist ICU = 2
Professional title	Nurse = 1; Nurse practitioner = 2; Supervisor = 3; Deputy chief nurse and above = 4
Position	Nurse = 1; Nursing/Teaching team leader = 2; Head nurse = 3
Frequency of night shift	None = 1; 1 - 4 times/month = 2; 5 - 8 times/month = 3; over 8 times/month = 4
Experience of workplace violence	No = 1; Yes = 2
Score of psychological resilience	Substitution of original value

Table 3. Multiple linear regression analysis of factors influencing the quality of work life of ICU nurses (n = 243).

Variable	B	SE	β	t	P
Constant term	2.105	0.185		11.370	<0.001
Score of psychological resilience	0.020	0.002	0.547	10.724	<0.001
Experience of workplace violence	0.146	0.046	0.164	3.145	0.002
Department	0.118	0.047	0.132	2.531	0.012
Professional title	−0.067	0.028	−0.126	−2.401	0.017
Frequency of night shift	−0.052	0.023	−0.120	−2.243	0.026

$R^2 = 0.394$, $F = 32.490$, $P < 0.001$.

department for treating critical patients, most of patients can't take care of themselves, so nurses had a large amount of nursing work. 2) Heavy workload, sudden emergencies, frequent night shifts, easy to lead to lower physical fitness and energy loss; 3) The special nature of ICU nursing work required the nurses to have a higher level of knowledge and skills, and to be proficient in the use and maintenance of various types of monitoring equipment. 4) The working environment of the ICU was closed and noisy, and various monitoring instruments had frequent alarms, which may lead to anxiety and fatigue of the nurses. At the same time, the ICU nurses in this study generally had lower scores of general well-being, work evaluation, and work-family balance, which may be related to the following reasons: 1) 62.2% of respondents were 26 - 35 years old, except the heavy workload of ICU nursing, they had be responsible for teaching, scientific research, etc., easily led to imbalance between work and family life. 2) ICU nurses with a working experience of less than 10 years accounted for 74.5%, showing obvious rejuvenation, lack of clinical experience, unable to effectively deal with emergencies, and reduced work evaluation. 3) 44% of ICU nurses in this study experienced workplace violence, and there were concerns about work environment, career development and their own safety, resulting in a decrease in general well-being.

4.3. Factors Influencing the Quality of Work Life of ICU Nurses

4.3.1. The Influence of Demographic Characteristics on the Quality of Work Life of ICU Nurses

The results of this study showed that department, professional title, frequency of night shift, and experience of workplace violence were the influencing factors of the quality of worklife of ICU nurses, and the scores were statistically significant ($P < 0.05$). The quality of work life of nurses in specialist ICU was higher than that of comprehensive ICU nurses. It may be due to the relatively single disease of specialist ICU patients, and most of them were postoperative patients, the condition was relatively stable, and the nursing workload was relatively lighter [18]. The ICU nurses with deputy chief nurses and above titles had higher scores of the quality of work life, and the scores of the quality of work life of head nurses were higher than those of ordinary nurses. It may be due to the rich clinical experience of this group of people, which can arrange working hours reasonably, and they were mainly engaged in nursing management and scientific research and had lower work pressure. ICU nurses with frequent night shifts had lower scores of the quality of work life. It may be due to frequent night shifts, resulting in irregular sleep, reduced the quality of sleep, prone to anxiety and depression, and nurses may face emergencies such as rescue at any time, the state of mental stress was high and the body load was too heavy [19] [20]. ICU nurses who had experienced workplace violence had lower scores of the quality of work life, which may be due to the fact that workplace violence had a certain degree of impact on their physical and mental health, and work pressure was increasing. It is suggested that nursing managers should pay attention to the con-

struction of ICU work environment, create a positive and healthy work atmosphere for nurses, and increase the intensity of introducing and retaining talents. At the same time, according to the age and ability of nurses, the labor and frequency of night shift can be reasonably allocated to reduce the workload of nurses.

4.3.2. The Influence of Psychological Resilience on the Quality of Work Life of ICU Nurses

The results of this study showed that the score of ICU nurses' psychological resilience was (55.83 ± 12.23), which was at a medium level. The results of regression analysis showed that psychological resilience was the main influencing factor of the quality of work life. Mainly manifested in: 1) Psychological resilience emphasized the ability of individuals to effectively cope and actively adapt to adverse conditions [14], high professional expectations and fast-paced work environment would make ICU nurses face the risk of high-intensity fatigue and stress-related diseases [21], low psychological resilience may lead to maladaptation, showing mental illness such as anxiety and depression [22]; it was likely to lead to the occurrence of an error event and a reduction in job evaluation; 2) ICU nurses were repeatedly faced with the end of life, prolonging life through artificial support measures, providing end-of-life care, etc., due to lack of reaction time and experience in dealing with similar incidents, it would cause tension, panic and psychological burden. However, psychological resilience can improve the individual's ability to face and adapt to trauma, tragedy, threats or major stressors [23]; 3) The results of Hudgins *et al.* [24] showed that psychological resilience played a vital role in improving nurses' work satisfaction. Low level of psychological resilience can lead to negative factors in nurses' negative coping work. Therefore, nursing managers should strengthen the intervention of ICU nurses' psychological resilience, actively carry out psychological counseling for nurses, and provide psychological assistance when necessary. At the same time, outdoor group activities can be properly carried out to foster a harmonious organizational atmosphere, to create a place for ICU nurses to vent their emotions and stress, and to alleviate work pressure.

5. Conclusion

In summary, the quality of work life and psychological resilience of ICU nurses were at a medium level, and the situation was not optimistic. Department, professional title, frequency of night shift, experience of workplace violence and psychological resilience were the influencing factors of the quality of work life of ICU nurses. Nursing managers should allocate manpower rationally and take appropriate measures to improve the psychological resilience of ICU nurses, thus improving their quality of work life. In this study, only 243 ICU nurses from 6 general hospitals in Jingzhou were investigated, and the number of samples was limited to some extent, and the results only represented the status quo of ICU nurses within the scope of investigation. After that, it plans to carry out

large sample survey, and carry out intervention research on the quality of work life of ICU nurses, so as to formulate feasible measures for improving the quality of work life of ICU nurses, and lay a good foundation for promoting the quality of ICU nursing service and promoting high-quality nursing.

Funding Projects

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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PLK1 Is Implicated in the Poor Prognosis of Hepatocellular Carcinoma

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Abstract

We aimed to identify if PLK1 could be used as a new diagnostic and therapeutic biomarker in hepatocellular carcinoma (HCC) patient. Expression of PLK1 in HCC was analyzed by using GEPIA (Gene Expression Profiling Interactive Analysis) and UALCAN databases. GEPIA and CBioPortal tools were applied to determine patients' survival and PLK1 mutations, respectively. PPI (Protein-Protein Interaction) networks were further built by STRING (Search Tool for the Retrieval of Interacting Genes) and Metascape Web portals. The data demonstrated that the expression of PLK1 in HCC was significantly enhanced when compared to normal liver tissues (P < 0.001). A higher PLK1 expression resulted in a remarkably shorter disease-free survival as well as overall survival. Moreover, the expression of PLK1 in HCC was related to HCC patients' grade and race, but not gender. The data also suggested that expression of PLK1 elevated gradually from stage 1 to 3 but decreased in stage 4. Three specific gene mutations K146R, S335Afs*120 and D429H of PLK1 occurred in HCC and these unique mutations were not seen in any other tumor tissues. Finally, PPI networks and GO enrichment analysis suggested that PLK1 might be associated with cell cycle and p53 signaling pathway etc. Taken together, our novel findings suggest that PLK1 is implicated in the poor prognosis of hepatocellular carcinoma.

Keywords

PLK1, HCC, TCGA, Biomarker, Cancer Therapy

1. Introduction

Clinical data showed that hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide due to its frequent metastasis

and lack of curative treatment [1]. More than 580,000 new cases of liver cancer occur in Asia every year [2]. Progressive accumulation of alterations in cancer drives genes and dysregulation of their associated signaling pathways, causing the occurrence and progression of HCC [3]. HCC is insensitive to radiotherapy and chemotherapy, and there is no uniform standard for the optimal dose of radiotherapy [4]. Although liver transplantation is a potential therapy for HCC, its application is limited by the liver donor supply. For targeted therapy, it can block the effect of key molecules in the formation and progression of liver cancer. Targeted drugs affect liver cancer cells more than normal cells. However, only a few drugs are currently available for patients with advanced liver cancer. Therefore, it is significant to investigate the novel key genes and major signal pathways involving in the development of HCC. To date, serum alpha-fetoprotein (AFP) and PIVKA-II (protein induced by vitamin K absence or antagonist-II) are two best used biomarker for HCC in clinical screening [5]-[10]. The combination use of the both biomarkers has significantly improved HCC sensitivity detection despite that their sensitivity and specificity are far from satisfactory [11] [12] [13] [14]. However, numerous recent studies have shown that the cut-off value of PIVKA-II and AFP, the tumor size and etiology did not have significant effects on the liver cancer heterogeneity. Therefore, it is necessary to find new genes that are useful for screening, diagnosis and monitoring of HCC.

PLK1 (Polo-like kinase 1), a serine/threonine-protein kinase that belongs to the polo-like kinase family, participates in various biological processes, including cell cycle and RNA processing [15] [16]. At present, five polo-like kinsey family members (PLL1-5) have been identified in humans [17]. Bu *et al.* [18] tested high expression of PLK1 in the HCC tissues, and showed significantly worse effect in the hematological type. Study suggested that PLK1 promotes the degradation of SUZ12 and ZNF198 by protea-some, which is a major factor in liver cancer [19]. PLK1 phosphorylation of PTEN also caused a tumor promoting metabolic state [20]. Moreover, PLK1 is over expressed in many cancers and serves as a significant prognostic factor in cancers, such as small-cell lung cancer, colon cancer and ovarian cancer [21]. In addition, high expression levels of PLK1 in melanoma and breast cancer correlated well with the metastatic potential of these tumors [22] [23]. PLK1 over-expression might also contribute to the deregulation of cell proliferation during oncogenesis by overcoming mitotic checkpoints [24].

Therefore, in order to verify the value of PLK1 in the diagnosis and treatment of HCC, it is very important to analyze the expression and significance of PLK1 in liver cancer tissues.

2. Materials and Methods

2.1. UALCAN Analysis

UALCAN (http://ualcan.path.uab.edu/analysis.html) is a web tool to profile gene expressions between tumor and non-tumor tissues and provides interactive data

analyses [25]. In this study, we utilized this online tool to analyze the expression levels of PLK1 between HCC specimen and normal tissues.

2.2. Survival Analysis

GEPIA (http://gepia.cancer-pku.cn/) is an interactive web resource and database for analyzing cancer transcriptome and patients' survival. In this study, we utilized this online tool to analyze patients' survival. Using GEPIA, overall survival (OS) and disease free survival (DFS) were presented and the hazards ratio was calculate based on Cox PH Model, 95% confidence interval was added as dotted line. The thresholds for high and low expression level cohorts are 50%, respectively.

2.3. Construction of the PPI Networks

The STRING database (http://string-db.org/) and Metascape (http://metascape.org/) tool was used to analyze the PPI networks. In this study, the PPI networks of the PLK1 gene was constructed using STRING and Metascape database. The non-interacting genes were excluded in order to simplify the PPI network. The top 12 genes with the highest degree of connection to the others were presented.

2.4. GO and KEGG Analysis

The STRING database (http://string-db.org/) is an online tool for high-throughput functional analysis of genes. In this study, the potential associations between the 12 core genes and PLK1 were assessed through the GO annotation analysis and KEGG pathway enrichment analysis [26] [27]. P-values < 0.05 were considered as statistically significance.

2.5. Analysis of Genetic Alterations

cBioPortal (https://www.cbioportal.org/) is a database with integrated genetic data, including DNA mutations, gene amplifications and protein alterations. In our study, the cBioPortal database was used to analyze the association between genetic mutations and the development of HCC. The top 12 genes which are related to PLK1 were analyzed by using cBioPortal database. And we performed PLK1 gene mutations analysis across all tumor samples from the TCGA-HCC database.

3. Results

3.1. The Expression Levels of PLK1 in HCC Patients

To verify PLK1 expression levels in HCC tissues and the value to the diagnosis and surveillance of HCC, GEPIA database was applied. As shown in Figure 1(a), the data showed that the expression level of PLK1 in the HCC group is significant higher than normal liver group (P < 0.001). Moreover, the relationship between PLK1 expression levels and HCC patients' clinicopathological parameters were further analyzed by UALCAN databases. The result demonstrated that
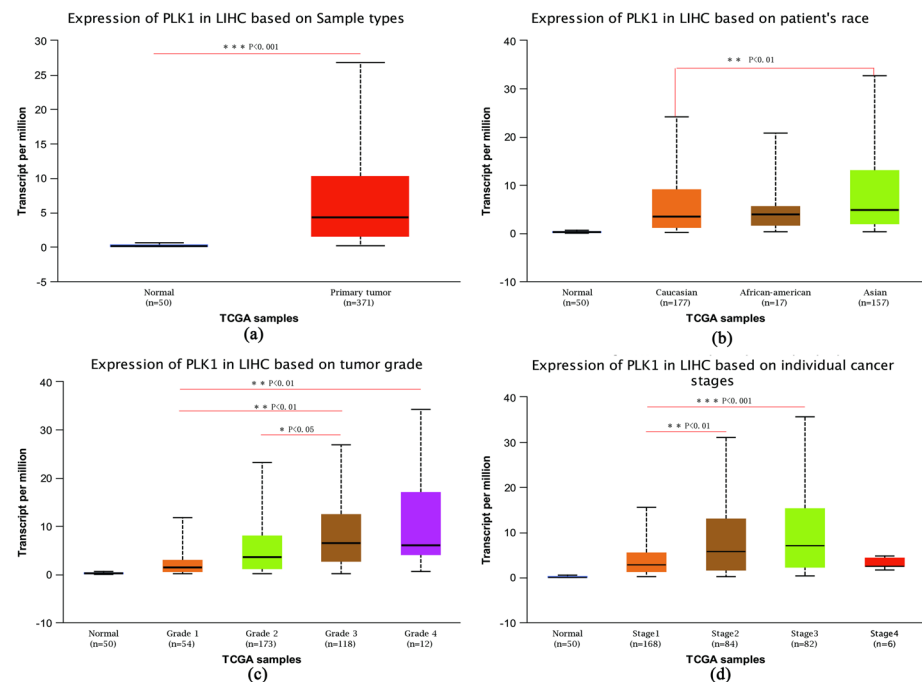
Figure 1. Over-expression of PLK is associated with malignancy of HCC. (a) PLK1 expression in normal and HCC tissues from TCGA data-sets; (b) The expressions of PLK1 was partially related to patients race; (c) The high expression of PLK1 was significantly related to cancer grade; (d) The expressions of PLK1 was partially related to cancer stages. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

expression of PLK1 was higher in Asian HCC patients than Caucasian patients ($P < 0.01$, **Figure 1(b)**). The expression of PLK1 increased from grade 1 to grade 4 of HCC, suggesting PLK1 was remarkably correlated with HCC patients' grade (**Figure 1(c)**) (grade 1 vs grade 3, $P < 0.01$; grade 1 vs grade 4, $P < 0.01$; grade 2 vs grade 3, $P < 0.05$). As shown in **Figure 1(d)**. we also found there are gradually increased expression of PLK1 from stage 1 to stage 3 but obviously declined in stage 4 (stage 1 vs stage 2, $P < 0.01$ and stage 1 vs stage 3, $P < 0.001$).

3.2. Survival Analysis of HCC Patients Based on PLK1 Expression

Here, PLK1 expression of HCC patients was divided into low-expression group and high-expression group (cutoff-high is 50%, cutoff-low is 50%). As shown in **Figure 2**, the overall survival (**Figure 2(a)**) and disease free survival (**Figure 2(b)**) were significant better in low PLK1 expression group than high PLK1 expression group ($P < 0.001$). Survival curves analysis showed that PLK1 was suitable for predicting liver cancer patients' prognosis.

3.3. PPI Networks and GO Enrichment Analysis of PLK1

The functional interactions between proteins can provide us some information in molecular mechanism. In this study, PPI network was constructed by the Metascape database. PPI network analysis indicated that PLK1 has more interactions with other 12 proteins, including CDC20, ERCC6L, CCNB1, CCNB2,
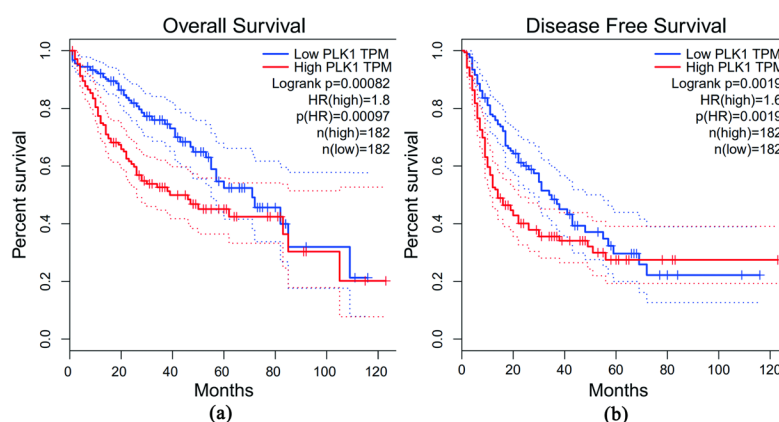
Figure 2. Prognostic value of PLK1 in liver cancer patients. Higher expressions of PLK1 was associated with poorer OS (a) and DFS (b) in HCC patients.

KIF2C, BUB1, MAD2L1, CENPE, INCENP, CDK1, CDCA8 and NDC80 (**Figure 3(a)**). To predict the biological functions and signaling pathways in which PLK1 were involved in HCC, GO enrichment and KEGG pathway analyse were further performed (**Figure 3(b)** and **Table 1**). The results showed that those proteins were biologically closely associated with cell cycle, p53 signaling pathway, oocyte meiosis and progesterone-mediated oocyte maturation etc.

3.4. Specific Mutations of PLK1 Genes in HCC Patients

In order to analyze the mutations of PLK1 gene in HCC patient's tissues, the CBioPortal database analysis was employed. As shown in **Figure 4**, we performed PLK1 gene mutations analysis across all tumor samples from the TCGA-HCC database (https://www.cbioportal.org/). Intriguingly, there were three specific mutations K146R, S335Afs*120 and D429H (**Figure 4(a)** and **Figure 4(b)**) in the HCC samples that were not present in any other tumor samples. These particular mutations of PLK1 in HCC patients might contribute greatly to HCC clinical diagnosis and monitoring. Moreover, the mutations between PLK1 and its interacted genes (CDC20, ERCC6L, CCNB1, CCNB2, KIF2C, BUB1, MAD2L1, CENPE, INCENP, CDK1, CDCA8 and NDC80) were analyzed through the cBioPortal dataset. The alteration statuses of 12 key genes were analyzed using TCGA HCC patients' data of cBioPortal database. The genetic alteration of PLK1 genes was altered in 52 (13%) of 377 HCC patients (**Figure 4(c)**).

3.5. Prediction of Relevance Genes to PLK1

To predict the biological functions and signaling pathways in which PLK1 were involved in HCC, we found that the 12 genes were considered to be relevant genes and the scatter plots were shown in **Figures 5(a)-(l)**.

4. Discussion

Bioinformatics methods can provide us with gene expression levels and predict
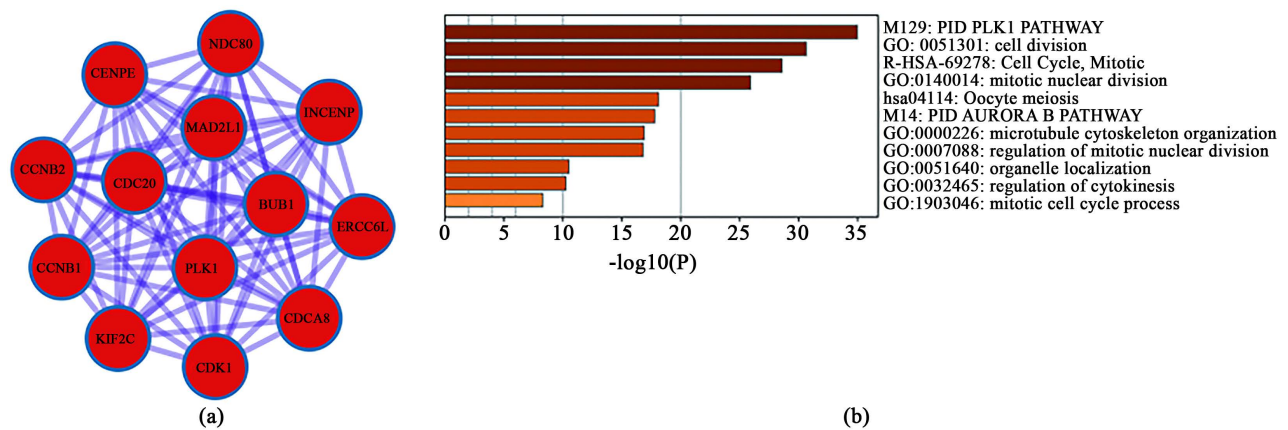
Figure 3. PPI network and GO enrichment analysis of twelve hub genes related to PLK1. (a) PPI network and MCODE components identified in the gene lists; (b) GO enrichment analysis of the 12 PLK1 related genes.
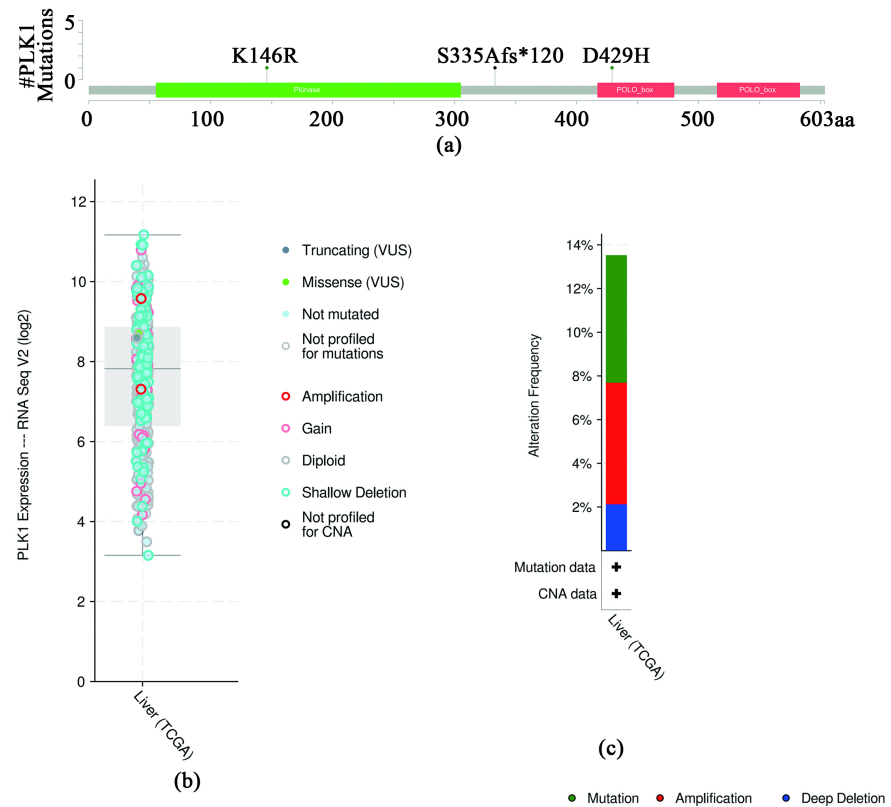
Figure 4. (a) and (b) The particular mutations (K146R, S335Afs*120 and D429H) of PLK1 in HCC patients. (c) A visual summary of genetic alterations (data from HCC in TCGA) shows the genetic alteration of PLK1 genes which were altered in 52 (13%) of 377 HCC patients.

potential therapeutic targets. A large number of clinical data showed that the death rate of liver cancer is very high. One of the best ways to reduce mortality is to detect accurately and treat successfully. Identifying key genes associated with the development and the progression of HCC is crucial for its diagnosis and treatment.

Table 1. Significantly enriched GO terms and KEGG pathways of PLK1.

Category	Terms	Count	P-Value
GOTERM_BP_DIRECT	cell division	21	2.35E−31
GOTERM_BP_DIRECT	mitotic cell cycle process	19	6.36E−25
GOTERM_BP_DIRECT	cell cycle	21	2.57E−23
GOTERM_BP_DIRECT	nuclear division	14	1.80E−19
GOTERM_BP_DIRECT	sister chromatid segregation	12	2.37E−19
GOTERM_BP_DIRECT	chromosome segregation	13	6.97E−18
GOTERM_BP_DIRECT	regulation of cell cycle process	16	8.80E−18
GOTERM_BP_DIRECT	regulation of nuclear division	12	1.51E−17
GOTERM_BP_DIRECT	mitotic nuclear division	11	6.31E−17
GOTERM_BP_DIRECT	regulation of cell cycle	17	2.87E−16
GOTERM_BP_DIRECT	mitotic sister chromatid segregation	10	4.30E−16
GOTERM_BP_DIRECT	anaphase-promoting complex-dependent catabolic process	8	2.87E−15
GOTERM_BP_DIRECT	regulation of mitotic nuclear division	10	3.03E−14
GOTERM_BP_DIRECT	microtubule cytoskeleton organization	12	6.12E−14
GOTERM_BP_DIRECT	regulation of cell cycle phase transition	11	2.65E−12
GOTERM_BP_DIRECT	chromosome organization	14	3.17E−12
GOTERM_BP_DIRECT	regulation of chromosome segregation	8	4.06E−12
GOTERM_BP_DIRECT	negative regulation of cell cycle process	10	4.06E−12
GOTERM_BP_DIRECT	regulation of mitotic metaphase/anaphase transition	7	4.42E−12
GOTERM_BP_DIRECT	negative regulation of cell cycle phase transition	9	4.89E−12
GOTERM_MF_DIRECT	anaphase-promoting complex binding	3	9.51E−6
GOTERM_MF_DIRECT	protein serine/threonine kinase activity	7	1.24E−5
GOTERM_MF_DIRECT	micro-tubule binding	6	1.24E−5
GOTERM_MF_DIRECT	ATP binding	10	2.44E−5
GOTERM_MF_DIRECT	protein kinase binding	7	2.44E−5
GOTERM_MF_DIRECT	histone kinase activity	3	2.44E−5
GOTERM_MF_DIRECT	ubiquitin-protein transferase regulator activity	3	2.44E−5
GOTERM_MF_DIRECT	microtubule motor activity	4	4.46E−5
GOTERM_MF_DIRECT	cyclin-dependent protein serine/threonine kinase activity	3	4.96E−5
GOTERM_MF_DIRECT	ATPase activity	5	0.0002
GOTERM_MF_DIRECT	ubiquitin-protein transferase activator activity	2	0.0002
GOTERM_MF_DIRECT	catalytic activity, acting on a protein	8	0.004

Continued

GOTERM_MF_DIRECT	enzyme binding	8	0.004
GOTERM_MF_DIRECT	catalytic activity	13	0.004
GOTERM_MF_DIRECT	protein binding	14	0.005
GOTERM_MF_DIRECT	binding	18	0.03
GOTERM_MF_DIRECT	protein-containing complex binding	4	0.04
GOTERM_CC_DIRECT	spindle	14	2.13E−18
GOTERM_CC_DIRECT	chromosome, centromeric region	11	1.40E−17
GOTERM_CC_DIRECT	condensed chromosome, centromeric region	12	1.40E−17
GOTERM_CC_DIRECT	microtubule cytoskeleton	17	1.40E−16
GOTERM_CC_DIRECT	condensed chromosome kinetochore	10	2.79E−16
GOTERM_CC_DIRECT	cytoskeletal part	17	1.37E−14
GOTERM_CC_DIRECT	mid-body	9	1.05E−12
GOTERM_CC_DIRECT	condensed nuclear chromosome, centromeric region	6	3.00E−12
GOTERM_CC_DIRECT	condensed chromosome outer kinetochore	5	3.96E−11
GOTERM_CC_DIRECT	condensed nuclear chromosome kinetochore	5	6.72E−11
GOTERM_CC_DIRECT	condensed nuclear chromosome	7	8.66E−11
GOTERM_CC_DIRECT	intracellular non-membrane-bounded organelle	19	9.47E−11
GOTERM_CC_DIRECT	cytosol	20	1.44E−10
GOTERM_CC_DIRECT	condensed nuclear chromosome outer kinetochore	4	4.54E−10
GOTERM_CC_DIRECT	spindle midzone	5	1.99E−9
GOTERM_CC_DIRECT	microtubule	8	2.41E−8
GOTERM_CC_DIRECT	nuclear lumen	17	3.27E−8
GOTERM_CC_DIRECT	nucleoplasm	16	4.07E−8
GOTERM_CC_DIRECT	microtubule associated complex	6	4.85E−8
GOTERM_CC_DIRECT	spindle pole	6	5.91E−8
KEGG_PATHWAY	cell cycle	10	3.64E−16
KEGG_PATHWAY	oocyte meiosis	10	3.64E−16
KEGG_PATHWAY	progesterone-mediated oocyte maturation	9	2.60E−15
KEGG_PATHWAY	p53 signaling pathway	3	0.00019
KEGG_PATHWAY	HTLV-I infection	4	0.00036
KEGG_PATHWAY	foxo signaling pathway	3	0.00081
KEGG_PATHWAY	cellular senescence	3	0.0012
KEGG_PATHWAY	ubiquitin mediated proteolysis	2	0.0150
KEGG_PATHWAY	microRNAs in cancer	2	0.0163
KEGG_PATHWAY	viral carcinogenesis	2	0.0215

(a)

(b)

(c)

(d)

(e)

(f)

(g)

(h)
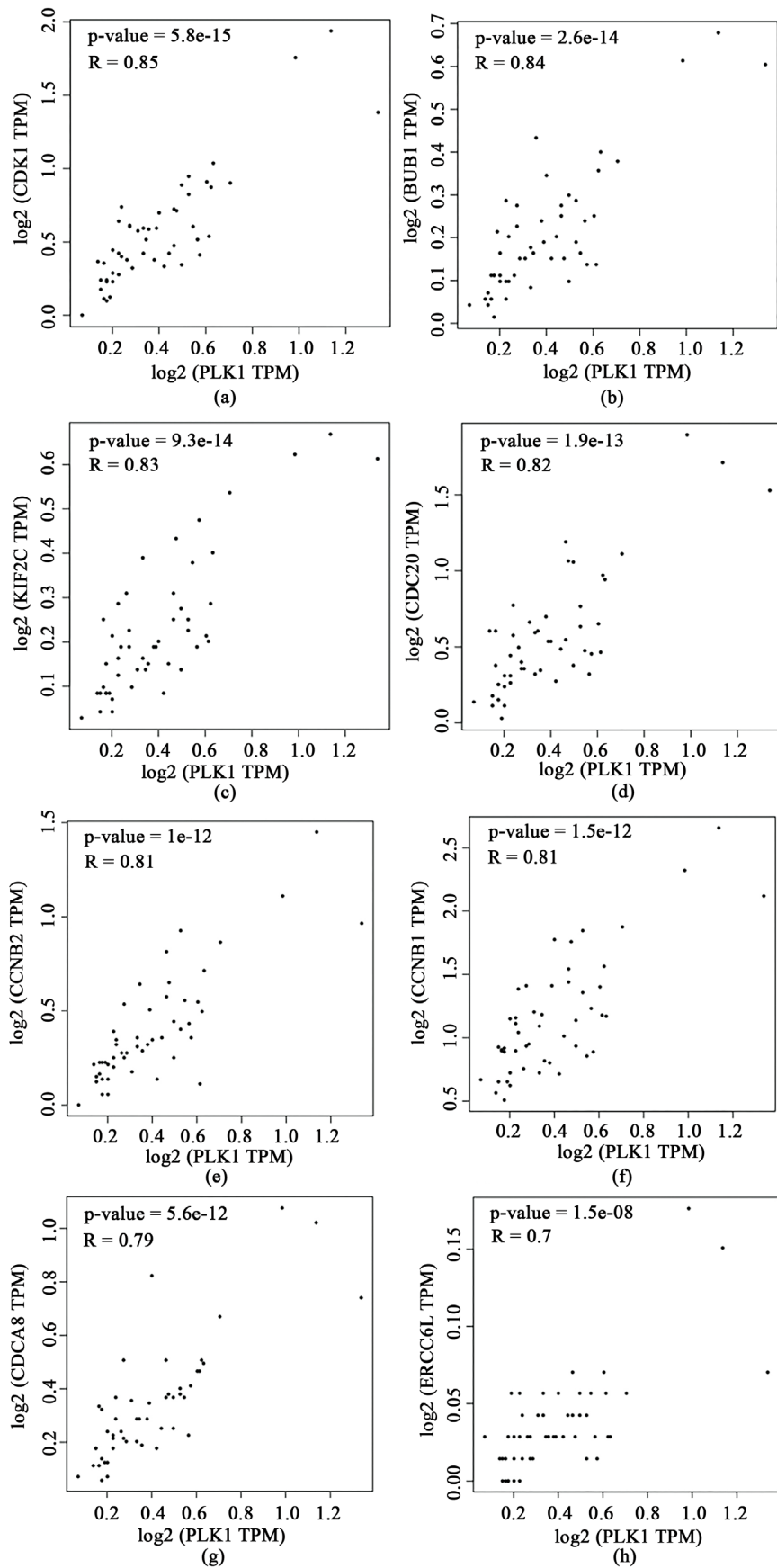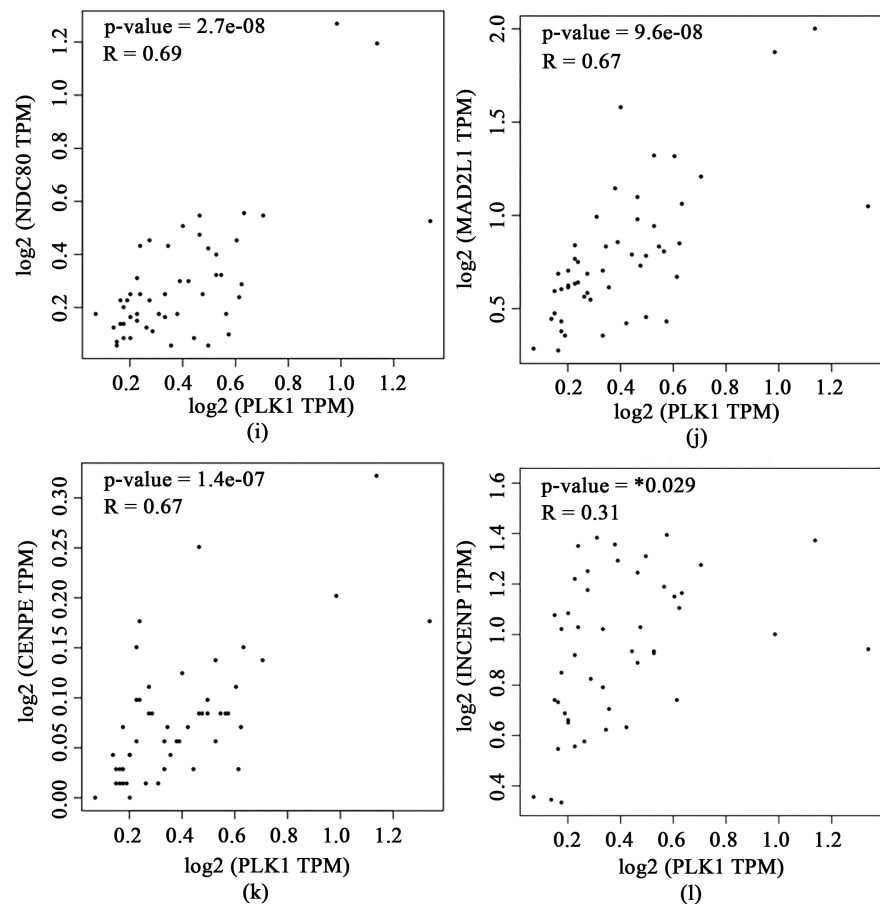
Figure 5. The plots of 12 pair-wise correlation genes. (a) PLK1 and CDK1; (b) PLK1 and BUB1; (c) PLK1 and KIF2C; (d) PLK1 and CDC20; (e) PLK1 and CCNB2; (f) PLK1 and CCNB1; (g) PLK1 and CDCA8; (h) PLK1 and ERCC6L; (i) PLK1 and NDC80; (j) PLK1 and MAD2L1; (k) PLK1 and CENPE; (l) PLK1 and INCENP.

In this study, our data showed that PLK1 expression was higher in HCC patients than that in normal tissues. PLK1 expression was remarkably correlated with HCC patients' grade. The results demonstrated that PLK1 expression enhanced gradually from stage 1 to stage 3 but decreased in stage 4. A higher PLK1 expression resulted in a significant shorter disease free survival as well as overall survival in HCC patients, suggesting that PLK1 may play an important role in the prognosis of HCC. By mutation analysis, CBioPortal tool unveiled three specific mutations (K146R, S335Afs*120 and D429H) unique presented in the HCC samples that were not occurred in any other tumor types. These characteristic mutations of PLK1 in HCC patients might facilitate to HCC clinical diagnosis and monitoring.

To determine the probably pathogenic mechanism of PLK1 in HCC, PPI networks were further applied. The twelve interacted proteins were identified by using PPI network analysis. Go enrichment analysis suggested these genes are enriched in cell cycle and p53 signaling pathway etc. Recent study indicated that cell cycle dysregulation plays an important role in the liver tumorigenesis [1].

It's been reported that disruption of the cell cycle pathway can result in cell cycle arrest and has previously been related to the prognosis of human cancers [28]. Furthermore, cell cycle arrest has been confirmed to be an effective approach in controlling tumor growth [29] [30]. Boxuan Li *et al.* [31] found that PLK1 plays a crucial role in the disruption of the cell cycle pathway by dramatically induced apoptosis. Shen, L.Y. found that PLK1 could arrest cell cycle in G2/M phase and then block cell cycle pathway [32]. High expression level of PLK1 was also identified in HCC tissues [33]. Taken together, our novel findings suggest that PLK1 might play a crucial role in regulating the middle of cell cycle pathway.

Recently, new findings have pointed that PLK1 is able to inhibit apoptosis in a p53-dependent manner in a variety of carcinomas [34]. Wei Sun [35] reported that the p53 tumor-suppressor protein is phosphorylated by PLK1, which can inhibit the proapoptotic function of p53.The inhibition of PLK1 leads to a failure to complete mitosis, eventually resulting in cell death [36]. PLK1 could interact with the DNA binding domain of p53, thereby decreasing its stability and transcriptional activity [37]. Thus, p53 is a major target for PLK1 controlling the growth of carcinoma cells. PLK1 is a cell cycle protein that plays multiple roles in promoting cell cycle progression. Among the many roles, the most prominent role of PLK1 is to regulate the mitotic spindle formation checkpoint at the M-phase [38]. Robert D. Van Horn [39] thought that CDK1 and PLK1 are likely to act in a positive feedback activation loop for CDK1 activation through CDC25-mediated dephosphorylation during G2/M transition. CDK1 and PLK1 could form a positive feedback activation loop in human cells. Activation of CDK1 initiates the entry into mitosis and activation of PLK1. PLK1 then further feedback-activate CDK1 to promote rapid and timely entry into mitosis and coordinately regulate various aspects of mitosis, such as bipolar mitotic spindle formation and checkpoint response [40].

Sharon I. King *et al.* have demonstrated a striking association between cancer and K146R mutation of PLK1 by immunohistochemical analysis and DNA sequencing analysis of 215 primary breast tumours [41]. Targeting PLK1 mutant at K146R site breast cancer might offer therapeutic opportunities. Although no related mutations have been reported in HCC tissues, we suggest that these particular mutations of PLK1 in HCC patients might contribute greatly to HCC clinical diagnosis and monitoring.

5. Conclusion

In summary, this study has novelly identified the elevated expression of PLK1in HCC patients when compared to that in normal tissue, and it is negatively correlated with patients' survival time. The results from this study may push forward the mechanism underlying PLK1 progression, and provide the high prognostic value of HCC. However, further studies are needed to intensively disclose the molecular mechanism and implication of PLK1 in HCC tumorigenesis and therapy.

Acknowledgements

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Caveolin-1 Polymorphism (rs7804372) and Cancer Risk: A Meta-Analysis of 15 Case-Control Studies

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Abstract

Purpose: Epidemiological studies have assessed the association between Caveolin-1 polymorphism and cancer risk. However, published data are still inconclusive. To clarify this inconsistency, we conducted a meta-analysis to evaluate the relationship between Caveolin-1 polymorphism (rs7804372) and cancer susceptibility. **Methods:** We conducted a comprehensive literature search, using PubMed, Embase, Medline, Web of Science, CNKI, and Wanfang database, which included English and Chinese literatures. The latest updated date was January 2018. The following search terms were performed to retrieve the relevant articles: ((CAV1) OR (Caveolin-1) OR (rs7804372)) AND (cancer OR tumor OR carcinoma OR neoplasms OR malignancy) AND (polymorphism OR mutation OR variant OR genotype). Odds ratio (OR) with 95% confidence interval (CI) was used to estimate the pooled effect. **Results:** In the overall analysis, this kind of polymorphism showed a significant association with increased risk of cancer: allelic model (T/A; OR = 1.33, 95% CI: 1.19 - 1.49; $P < 0.0001$), homozygous (TT/AA; OR = 1.73, 95% CI: 1.37 - 2.18; $P < 0.0001$), and heterozygous genetic models (TT/TA; OR = 1.23, 95% CI: 1.14 - 1.33; $P < 0.0001$), the dominant genetic model (TT + TA/AA; OR = 1.58, 95% CI: 1.28 - 1.96; $P < 0.0001$), and the recessive genetic model (TT/TA + AA; OR = 1.34, 95% CI: 1.20 - 1.50; $P < 0.0001$). In addition, the stratified analysis of the results was carried out by ethnicity, HWE status, and cancer types. The outcome indicated that Caveolin-1 rs7804372 polymorphism was associated with an increased risk of cancer. **Conclusion:** The present study demonstrated that the allele T of Caveolin-1 (rs7804372) polymorphism might associate with increased susceptibility to cancer, and might predict worse survival in patients with various types of cancer. However, further well-designed studies are required to evaluate this association.

Keywords

Caveolin-1, Polymorphism, Cancer, Susceptibility

1. Introduction

As is well known, cancer is one of the leading causes of death in the world [1], neoplasia refers to the complex situation of the organism in various genetic and environmental factors, in which gene mutation plays an important role in genetic factor [2]. Most mutations cause changes in the body, but minor mutations may cause large malignancies. The genetic variants are capable of enhancing cancer development and could be helpful for the early diagnosis, and help in the design of targeted treatment and prevention strategies.

Caveolin-1 (encoded by the CAV-1 gene) is an oncogenic membrane protein associated with endocytosis, extracellular matrix organisation, cholesterol distribution, cell migration and signaling [3]. Caveolin-1 is considered to play a key role in the cell apoptosis and tumor formation [4] [5] [6], and is even considered a tumor suppressor [7] or suppressor depending on tumour type and stage [8].

For the past decade, Cav-1 has been considered a potential biomarker for cancer prognosis, because its expression is upregulated in numerous types of cancer, including breast cancer [9] [10] [11], gastrointestinal tumor [12] [13] [14] [15], urinary neoplasms [16] [17] [18] [19], and other cancers [20] [21] [22]. Available studies show that significant association was found in CAV-1 rs3807987, or rs7804372 gene polymorphism was associated with cancer risk [9]-[22], a recent meta-analysis by Tang *et al.* showed that CAV-1 rs3807987 polymorphisms may modify the risk of cancer, especially digestive system cancer [23]. But, results for the association of Caveolin-1 polymorphism (rs7804372) and cancer risk were contradictory and inconclusive. In order to solve the problem of the inconsistent results, our study continuously analyzed Caveolin-1 gene rs7804372 for more detailed information between gene polymorphism and cancer susceptibility.

2. Materials and Methods

2.1. Identification and Eligibility of Relevant Studies

The following databases were searched: PubMed (2000-April, 2018) and Chinese biomedicine literature database (1978-April, 2018) using the following search terms: (Caveolin-1 or CAV-1) and "polymorphism, Genetic" to identify all relevant articles on the subject. Other potential omitted studies were identified by hand screening. The inclusion criteria of studies were as following: 1) studies that evaluated the association between Caveolin-1 polymorphism (rs7804372) and cancer risk, 2) Study provided sufficient data to calculate the odds ratios (ORs) and 95% confidence intervals (CIs), 3) Case-control study.

2.2. Data Extraction

Using the above criteria for inclusion and exclusion, two independent researchers extracted the information from the included studies. The information mainly included: first author, year of publication, country, ethnicity, tumor type, design of experiment (population-or hospital-based controls) number of genotyped cases and controls, genotypic methods, the characteristics of the controls and quality control. Disagreements were resolved in consultation with the third reviewer. The study quality was assessed according to the NOS [24].

2.3. Statistical Methods

The crude ORs and their corresponding 95% CIs were used to assess the strength of associations between Caveolin-1 polymorphism (rs7804372) and cancer risk. 5 genetic model were used to calculate ORs, including: allelic model (T vs A), homozygous (TT vs AA), and heterozygous genetic models (TT vs TA), the dominant genetic model (TT + TA vs AA), and the recessive genetic model (TT vs TA + AA). I^2-test (range, 0% - 100%) and chi-square-based Q test were used for assessment of heterogeneity across all selected studies [25]; If $P < 0.1$ or $I^2 > 50\%$, the outcome indicated significant heterogeneity and the random-effects model was used to calculate the pooled OR [25]; otherwise, the fixed-effects model was applied [25]. Hardy-Weinberg equilibrium (HWE) was tested by comparing the observed and expected genotype frequencies of the controls (Chi-square test). Stratified analysis was also conducted according to the type of cancer, ethnicity and HWE (Hardy-Weinberg equilibrium). Publication bias was estimated using Begg's funnel plot [26]. Meta-analysis was performed using Software STATA version 12.0 (STATA Corporation, College Station, TX, USA). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of Studies

A total of 15 studies investigating the polymorphism of Caveolin-1 (rs7804372) met our inclusion criteria, including 5893 cases and 6522 controls. These studies were published from 2010 to 2017. In all 15 studies, there were 13 studies of Chinese, remaining two studies were Japanese and Iranians respectively. The all studies included 3 studies on breast cancer, 2 studies on prostate cancer, 4 studies on urinary system neoplasms, 2 studies on gastric cancer, 1 studies on renal cell carcinoma, 1 studies on nasopharyngeal carcinoma, 1 studies on leukemia, 1 studies on oral cancer, 1 studies on hepatocellular carcinoma, 1 studies on esophageal squamous cell carcinoma, 1 studies on upper genitourinary cancer, 1 studies on colorectal cancer, 1 studies on bladder cancer. The distributions of the genotypes in control groups in 6 studies were not in HWE. The Newcastle-Ottawa Scale (NOS) scores of all included studies ranged from 5 to 8 scores (Stang). The characteristics of each study are summarized in Table 1.

Table 1. Characteristics of included studies.

Auther	Year	Country	Genotype method	SOC	Ethnicity	Cancer type	Case			Control			HWE	NOS
							TT	AT	AA	TT	AT	AA	P-value	
Wang [9]	2017	China	PCR	HB	Chinese	BC	317	207	36	338	202	42	0.13	8
Fard [10]	2018	Iran	RFLP-PCR	PB	Iranian	BC	96	65	42	106	74	23	0.08	6
Chang [17]	2014	china	PCR	HB	Chinese	RCC	29	48	15	285	191	104	<0.01	5
Bau [20]	2011	china	RFLP-PCR	HB	Chinese	OC	363	193	64	306	206	108	<0.01	8
Hsu [12]	2013	china	RT-PCR	HB	Chinese	HCC	166	93	39	152	98	48	<0.01	5
lin [13]	2014	china	RFLP-PCR	HB	Chinese	GC	188	135	35	192	133	33	0.16	5
liu [11]	2011	China	RFLP-PCR	HB	Chinese	BC	745	410	77	694	472	111	0.02	5
Sugie [16]	2013	japan	RFLP-PCR	HB	Japanese	PC	60	63	11	25	42	19	0.86	6
Wang [27]	2014	China	RFLP-PCR	HB	Chinese	ESCC	259	143	25	221	166	40	0.28	5
chang [17]	2013	China	RFLP-PCR	HB	Chinese	UUTC	140	65	13	303	224	53	0.21	5
Yang [14]	2010	China	RFLP-PCR	HB	Chinese	CRC	216	117	29	179	120	63	<0.01	7
Tsou [21]	2011	China	RFLP-PCR	HB	Chinese	NPC	109	55	12	86	57	33	<0.01	5
Zhang [15]	2014	chian	RFLP-PCR	HB	Chinese	GC	239	134	39	210	136	66	<0.01	6
bau [18]	2011	chian	RFLP-PCR	HB	Chinese	bladder cancer	231	122	22	198	142	35	0.2	6
wu [19]	2011	chian	RFLP-PCR	HB	Chinese	PC	163	75	12	254	196	50	0.18	6
Wang [22]	2013	chian	RFLP-PCR	HB	Chinese	leukemia	167	86	13	140	99	27	0.14	6

SOC: Source Of Controls; PB: Population-Based Controls; HB: Hospital-Based Controls; HWE: Hardy-Weinberg Equilibrium; NOS: Newcastle-Ottawa Scale; RFLP-PCR: Polymerase Chain Reaction Restriction Fragment Length Polymorphism; BC: Breast Cancer; RCC: Renal Cell Carcinoma; OC: Oral Cancer; HCC: Hepatocellular carcinoma; GC: Gastric Cancer; PC: Prostate Cancer; ESCC: Esophageal Squamous Cell Carcinoma; UUTC: Upper Urothelial Tract Cancer; CRC: Colorectal Cancer; NPC: Nasopharyngeal Carcinoma.

3.2. Meta-Analysis Results

The main meta-analysis results and the heterogeneities are shown in Table 2 and Table 3. As shown in the Table 2, all 5 comparisons revealed the association between Caveolin-1 rs7804372 polymorphism and cancer risk after meta-analysis with fixed- or random-effects models. In the overall analysis, this kind of polymorphism showed a significant association with increased risk of cancer: allelic model (T/A; OR = 1.33, 95% CI: 1.20 - 1.49; P < 0.0001), homozygous (TT/AA; OR = 1.73, 95% CI: 1.37 - 2.18; P < 0.0001), and heterozygous genetic models (TT/TA; OR = 1.23, 95% CI: 1.14 - 1.33; P < 0.0001), the dominant genetic model (TT + TA/AA; OR = 1.58, 95% CI: 1.28 - 1.96; P < 0.0001), and the recessive genetic model (TT/TA + AA; OR = 1.34, 95% CI: 1.20 - 1.50; P < 0.0001). In addition, the stratified analysis of the results was carried out by Ethnicity, HWE status, and Cancer types. The outcome indicated that Caveolin-1 rs7804372 polymorphism was associated with an increased risk of cancer (Table 3).

3.3. Sensitivity Analysis and Publication Bias

We checked the inclusion criteria of this meta-analysis by a sensitivity analysis. Pooled estimates for all genetic models were insensitive to the removal of individual studies, and the corresponding pooled ORs were not substantially altered (Figure 1), suggesting that our results were stable and reliable.

Begg's funnel plot and Egger's test were performed to assess publication bias (Figure 2). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results did not show any evidence of publication bias.

Table 2. Meta-analysis of association between caveolin-1 rs7804372 polymorphisms and cancer risk.

Genetic models	P for heterogeneity	I^2 (%)	Model	OR (95% CI)	P-value
Caveolin-1 rs7804372					
T vs A	<0.0001	72.90%	Random	1.33 (1.19, 1.49)	<0.0001
TT vs AA	<0.0001	67.20%	Random	1.73 (1.37, 2.18)	<0.0001
TT vs AT	0.29	14.60%	Fix	1.23 (1.14, 1.33)	<0.0001
TT vs AT + AA	0.007	54.10%	Random	1.34 (1.20, 1.50)	<0.0001
TT + AT vs AA	0.001	63.00%	Random	1.58 (1.28, 1.96)	<0.0001

**Table 3.** Summary of the subgroup analysis in this meta-analysis.

Comparison	Category	Category	Studies	OR (95% CI)	P-value
T vs A	Ethnicity	Chinese	13	1.36 (1.23, 1.50)	<0.0001
		other	2	1.15 (0.45, 2.93)	0.77
	HWE	Y	9	1.27 (1.05, 1.53)	0.01
		N	6	1.41 (1.26, 1.57)	<0.0001
	Cancer type	breast cancer	3	0.99 (0.74, 1.32)	0.93
		Gastrointestinal tumor	5	1.29 (1.09, 1.53)	0.003
		Urinary neoplasms	4	1.56 (1.36, 1.78)	<0.0001
		other cancer	3	1.54 (1.35, 1.77)	<0.0001
TT vs AA	Ethnicity	Chinese	13	1.79 (1.49, 2.15)	<0.0001
		other	2	1.40 (0.17, 11.18)	0.75
	HWE	Y	9	1.58 (1.07, 2.34)	0.02
		N	6	1.88 (1.59, 2.22)	<0.0001
	Cancer type	breast cancer	3	0.98 (0.53, 1.82)	0.95
		Gastrointestinal tumor	5	1.65 (1.17, 2.32)	0.004
		Urinary neoplasms	4	2.28 (1.64, 3.18)	<0.0001
		other cancer	3	2.27 (1.71, 3.02)	<0.0001
TT vs AT + AA	Ethnicity	Chinese	13	1.24 (1.14, 1.34)	<0.0001
		other	2	1.20 (0.84, 1.70)	0.317
	HWE	Y	9	1.26 (1.08, 1.48)	0.004
		N	6	1.23 (1.10, 1.37)	<0.0001
	Cancer type	breast cancer	3	1.08 (0.87, 1.33)	0.49
		Gastrointestinal tumor	5	1.17 (1.02, 1.35)	0.03
		Urinary neoplasms	4	1.53 (1.28, 1.84)	<0.0001
		other cancer	3	1.30 (1.08, 1.57)	0.006
TT vs AT	Ethnicity	Chinese	13	1.35 (1.22, 1.50)	<0.0001
		other	2	1.24 (0.53, 2.93)	0.62

Continued

	HWE	Y	9	1.31 (1.08, 1.60)	0.006
		N	6	1.32 (1.23, 1.42)	<0.0001
TT vs AT		breast cancer	3	1.03 (0.79, 1.36)	0.81
	Cancer type	Gastrointestinal tumor	5	1.28 (1.13, 1.46)	<0.0001
		Urinary neoplasms	4	1.64 (1.39, 1.95)	<0.0001
		other cancer	3	1.51 (1.27, 1.79)	<0.0001
	Ethnicity	Chinese	13	1.63 (1.44, 1.86)	<0.0001
		other	2	1.22 (0.20, 7.59)	0.83
	HWE	Y	9	1.43 (1.01, 2.01)	0.04
		N	6	1.74 (1.48, 2.05)	<0.0001
TT + AT vs AA		breast cancer	3	0.96 (0.53, 1.72)	0.89
	Cancer type	Gastrointestinal tumor	5	1.56 (1.14, 2.12)	0.005
		Urinary neoplasms	4	1.57 (1.27, 1.94)	<0.0001
		other cancer	3	1.95 (1.41, 2.68)	<0.0001
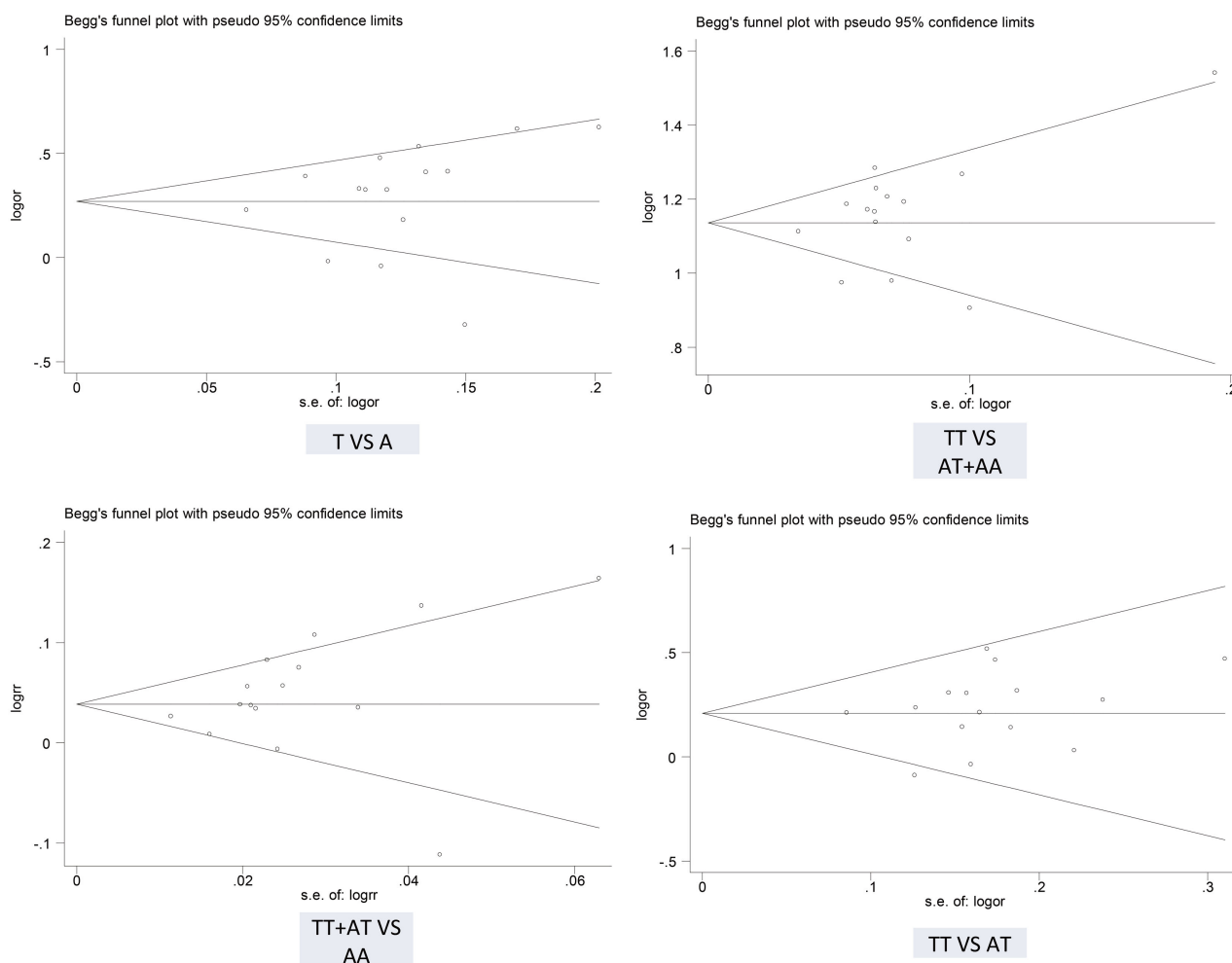
Figure 1. Sensitivity analysis results of the association between caveolin-1 rs7804372 polymorphism and overall cancer risk. Abbreviations: CI, confidence interval; OR, odds ratio.
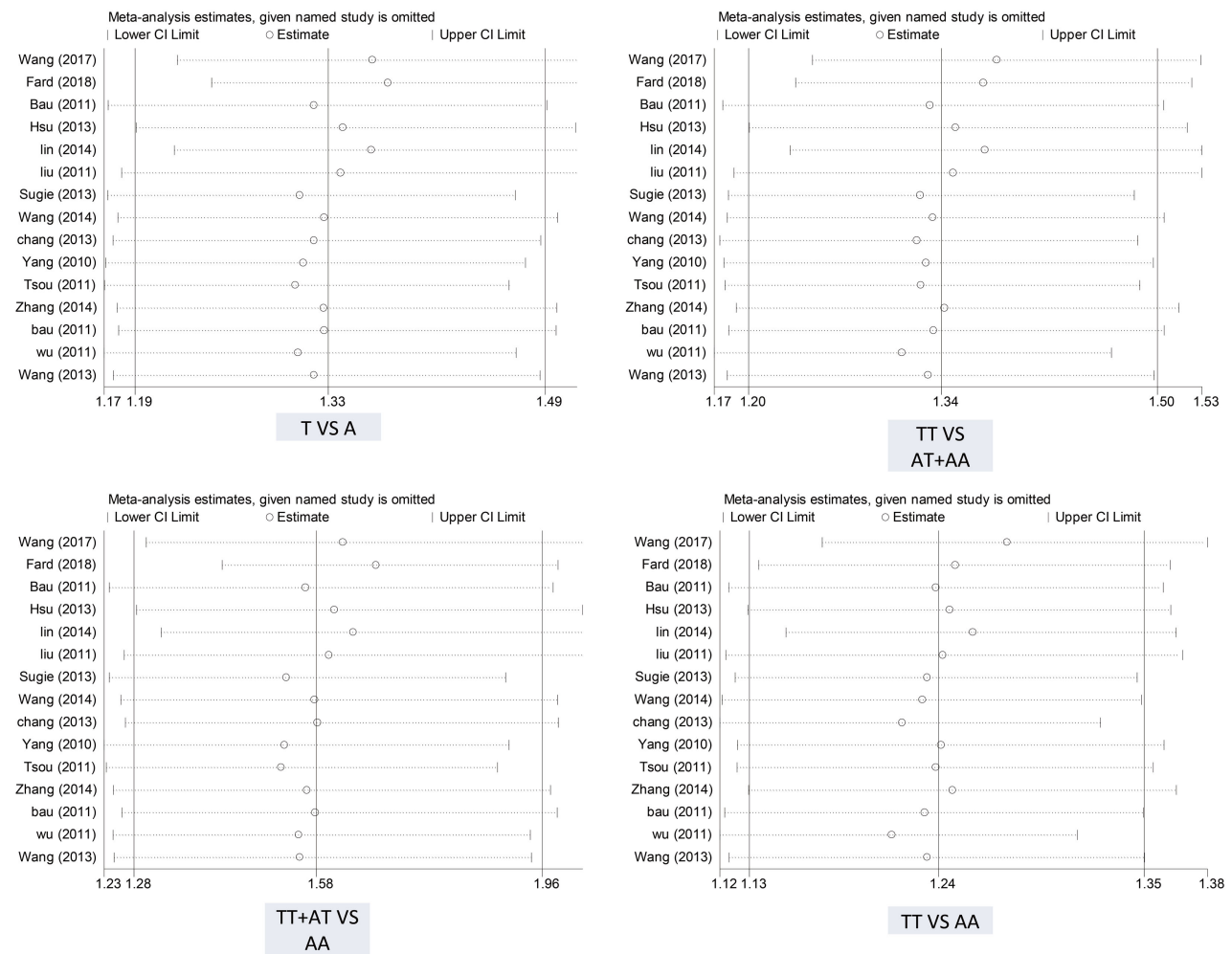
Figure 2. Begg's funnel plots of the association between Caveolin-1 rs7804372 polymorphism and Overall cancer risk. Abbreviations: SE, standard error of the logOR; logOR, natural logarithm of the OR; OR, odds ratio.

4. Discussion

Located on human chromosome 7 (7q31.1) and contains 3 exons, Caveolin-1 gene can encode the protein of Caveolin-1. CAV-1 is the major structural protein in Caveolin and consists of 178 amino acids, which plays an important role in many signaling pathways, molecular transport, and cellular proliferation and differentiation, potentially involved in the development and metastasis of tumors. In order to figure out controversial results from previous reports, we collected all available published studies and performed a meta-analysis to confirm the association between caveolin-1 (rs7804372) and cancer.

Based on a 15 case-control study, the meta-analysis focuses on the relationship between Asian polymorphism of Caveolin-1 (rs7804372) polymorphism and tumor correlation, and is analyzed by 5 kinds of comparison models. Our study demonstrated caveolin-1 (rs7804372) polymorphism increased the risk of cancer in all five comparison models.

Our meta-analysis had some advantages. For instance, we strictly obeyed the

inclusion and exclusion criteria to reduce selection bias. We confirmed stratification analysis and sensitivity analysis to seek the sources of high heterogeneity. Stratification analysis was conducted according to ethnicity, HWE status, and Cancer type. Our data indicated Caveolin-1 rs7804372 polymorphism was significantly associated with an increased risk of cancer among Chinese studies. Meantime, statistically significantly increased risks were found among HWE status, and cancer type studies also. However, there were not significantly increased risks of breast cancer in all genetic models. Owing to induce cellular transformation, activate MAPK signaling pathway and alter act in networks, Caveolin-1 rs7804372 polymorphism associates with a higher ER, Her-2 positive rate and tumors size among BC patients (Wangmeng 2017).

Despite the fact that we strictly obeyed the inclusion and exclusion criteria, this meta-analysis may have some limitations. First, publication bias may be present, base of only including data of published studies. Second, All included literatures were case-control studies and have not enough data, we did not perform stratification analysis to clear heterogeneity. Third, some studies do not meet the Hardy-Weinberg equilibrium and cannot fully represent the frequency of genes in the local population. Finally, This meta-analysis mainly based on the Asian population. Therefore, the results can be promoted and applicable to other groups remains unclear.

5. Conclusion

The present study demonstrated that the allele T of Caveolin-1 (rs7804372) polymorphism might associate with increased susceptibility to cancer, and might predict worse survival in patients with various types of cancer. However, further well-designed studies are required to evaluate this association.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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The Emerging Roles of Non-Coding RNAs in Cataract

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Abstract

Non-coding RNAs (ncRNAs) are a large class of transcripts lacking evident protein coding potential, and play versatile roles in a diverse range of physiological and pathological processes. Mounting evidences have indicated that ncRNAs are aberrantly expressed in a wealth of diseases such as cataract. Cataract is a cloudy lens caused by radiation, age, drugs and other factors. NcRNAs, including microRNAs, long non-coding RNAs, circular RNAs, have been identified to regulate the occurrence and development of cataract. Current studies indicate that ncRNAs exert the multifaceted functions in the lens of cataract patients and have been proved as potential diagnostic biomarkers or therapeutic targets for cataracts. This review summarizes the study of relationship between the lens and ncRNAs, which can provide a novel insight into the pathogenesis of cataract.

Keywords

Cataract, PCO, microRNAs, Long Non-Coding RNAs, Circular RNAs

1. Introduction

In the coming decades, cataract and cataract blindness will continue being a leading public health issue in China due to the aging population [1]. Cataract is one of the main causes of blindness around the world. Many factors can increase the incidence of cataracts, such as inheritance, aging, radiation, injury, diabetes mellitus and medication [2] [3] [4]. Lens Opacification Classification System III (LOCS) is the most commonly used for evaluating. Cataract is divided into cortical cataract, nuclear cataract and posterior sub-capsular cataract. Phacoemulsification is a satisfactory method for the treatment of cataract, but there are also

many postoperative complications [5] [6] [7]. Posterior capsular opacification (PCO) is the most common complication after a few years of surgery [8]. Therefore, the prevention and treatment of cataract has become particularly important. It is necessary to study the mechanism of age-related cataract (ARC), diabetic cataract (DC) and PCO objective to explore a new therapeutic target for cataract.

In the entire human genome, about 70 percent of the DNA are transcribed into RNA, but only 2 percent can be used to encode proteins. Although non-coding RNA does not encode a protein, such RNAs do contain information and function. These non-coding RNAs mainly include microRNAs, tsRNA (tRNA-derived small RNA), circular RNAs, long coding RNAs and pseudogene [9]. The main function of non-coding RNA include: to participate in the stability of mRNA and the regulation of translation level; to participate in the transport of protein; to participate in the procession and modification of RNA and to affect the structure of chromosomes [10]. Most of those definite functions are still unknown in cataract, so non-coding RNAs have been the focus of researchers. Researches have shown that the abnormal expression of non-coding RNAs (miRNA, lncRNA, circRNA) can lead to the disorder of normal lens development, apoptosis of lens epithelial cells, the disorder of fiber cells and the transparency of the lens decreases, which leads to the mechanism of cataract [11] [12] [13].

In this review, we summarize the deregulations and discuss the pathological implications of miRNAs, lncRNAs and circRNAs in ophthalmology. We highlight the biological functions of non-coding RNAs and their targets, pathways in ARC, DC or PCO. Finally, we discuss the potential roles of ncRNAs as diagnostic tools and therapeutic targets in cataract.

2. The Role of microRNAs in Cataract

2.1. The Function of microRNAs

MicroRNAs (miRNAs) are type of highly conserved and small, single-stranded non-coding RNAs about 20 - 22 nucleotides, that regulate the expression of target genes at post-transcriptional level. Primary miRNAs (pri-miRNAs) processed sequentially via two ribonucleases Drosha and Dicer, which belongs the RNase III family, and transcribed from miRNA genes. Mature miRNA is packed into the RNA induced silencing complex (RISC) which can directs the complex to target mRNAs, giving rise to translational repression and target mRNA degradation, by binding to the 3'untranslated region (3'UTR) of mRNA in complementary sequences [14]. MiRNAs play an important regulatory role in physiological and pathological processes, which is widely found in animals, plants and viruses. Mounting studies have shown that miRNA dysregulation plays key roles in a plethora of diseases, including cataract. Certain well-known miRNAs (such as miR-31, miR-21, and miR-224-5p) have identified as master regulators of cell proliferation, differentiation, apoptosis, cell growth, stress response and autophagy [15] [16] [17]. Ample evidence has indicated that miRNA dysregulation

impact the procession of cataract. In particular, miRNAs are involved in the regulation of function of lens epithelial cell [18].

## 2.2. The Expression and Function of miRNA in the Cataract

Current studies indicated miRNAs have identified as a group of regulators affect the cataract formation. The dysregulation of miRNAs has discovered in a diverse range of the lens, retina and other ocular tissues, and has related with poor prognosis in a wealth of clinical cases. Most studies compared differential miRNA expression in cataract human lenses between cataract patients and normal subjects [11] [19] [20] [21] (Table 1).

The expression of miRNAs was upregulated or downregulated to induce the epithelial-to-mesenchymal transition (EMT), apoptosis, autophagy, proliferation of LECs via different signaling pathways [11] [18] [25]. Here, we summarize several relatively clear mechanisms of microRNA. For instance, miR-26a/b suppressed LEC-EMT by directly targeting Jagged-1 and controlling Jagged-1/Notch signaling pathway [11]. MiR-204-5p regulates lens epithelial cell–EMT via targeting SMAD4 during in human PCO [24]. MiRNA-181a regulates the expression of c-Met, slug, and cox-2 thereby inhibits the migration, proliferation, and EMT of lens epithelial cells [18]. Those downregulated kind of miRNA regulate the LEC-EMT through different ways, resulting in PCO. In ARC, miRNA-34a was upregulated and acted on Notch2, Bcl-2 and SIRT1 and causes apoptosis of HLECs [20] [25]. In DC, miRNA-30a was downregulated and regulated the EMT and autophagy by different pathways [22] [23].

Taken together, miRNAs could repression of those targeted protein via combine the 3'untranslated region (3'UTR) of mRNA and regulation of the different function of lens epithelium cells, and then participate in the occurrence and development of cataract (Figure 1).

Table 1. The expression and the role of miRNAs in the lens.

miRNA	Expression	Target	Cataract type	Function	reference
miR-26a/b	down	Jagged-1/Notch	ASC and PCO	suppress LEC proliferation, migration and EMT	[11]
miR-30a	down	BECN-1	DC	regulation of autophagy and apoptosis in LECs	[22]
miR-30a	down	SNAI1	DC	inhibit EMT	[23]
miRNA-204-5p	down	TGFβ/SMAD4	PCO	inhibit EMT	[24]
miR-181a	down	c-Met, slug, COX-2	PCO	suppress the migration, proliferation, and EMT of LECs	[18]
miR-34a	up	Notch2	ARC	promote LECs apoptosis	[25]
miR-34a	up	Bcl-2, SIRT-1	ARC	promote LECs apoptosis	[20]
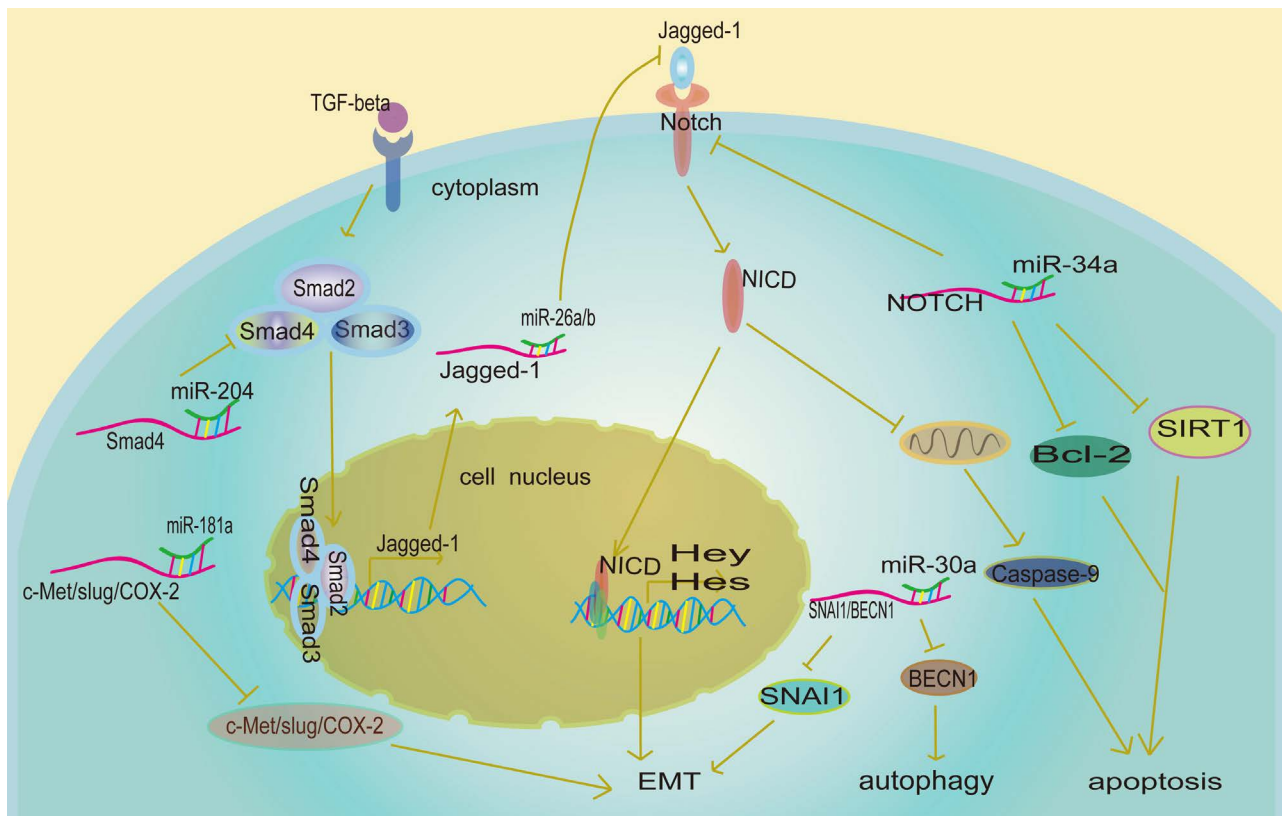
Figure 1. The role of microRNAs in cataract. MiRNAs reduce the expression of related proteins by binding to the mRNA to control the rate of translation or RNA degradation and result in EMT, autophagy, and apoptosis of HLECs.

3. The Role of lncRNAs in Cataract

3.1. The Structure and Function of lncRNAs

Long non-coding RNAs (LncRNAs) are bigger than 200 nucleotide-long RNA molecules, which lack or have limited protein-coding potential [26]. Most of lncRNAs are RNA polymerase II, whose transcription has polyA tail and 5'cap, mainly concentrated in the nucleus, which exhibit the level of evolutionary protection or expression is lower than that of mRNAs. LncRNAs regulate various aspects of gene expression via interacting with DNA, RNA or protein [27], and involved in the transcription, post-transcription of gene expression and epigenetic regulation [28]. LncRNAs play a vital role in cell differentiation regulation and many other life activities, as well as many diseases. LncRNAs are involved in regulating the ageing process, a large number of lncRNA have found to be involved in cell cycle, such as senescence proliferation and differentiation, as well as the regulation of important senescence related signaling pathways [29] [30], thereby contributing to the development of age-related diseases such as cataract.

3.2. The Expression and Function of lncRNAs in the Cataract

Emerging studies reveal that the dysregulation of lncRNAs are impact the development and progression of cataract [31] [32] [33] [34] [35]. Compared with transparent lenses, KCNQ1OT1, TUG1, and H19 has identified to have signifi-

cantly increased expression in age-related cataract [36] [37] [38]. The significant differential expression of lncRNAs in age-related cataract human lenses indicates that lncRNAs might play a crucial role in cataract formation (Table 2).

Current researches have indicated lncRNAs exert multifaceted roles in various biological processes and disorders of cataract. Cytoplasmic lncRNAs regulate expression at the post-transcriptional level by "sponging" miRNA or interacting with RNA-binding proteins. Jin et al. demonstrated that miR-214 has a potential binding site for both KCNQ1OT1 and caspase-1 3'-UTR, KCNQ1OT1 acted as endogenous miRNA "sponge" to degrade the transcription of target genes and bind miR-214 to suppressed the miR-214 expression, consequently the HLECs impact pyroptosis, which is a type of programmed cell death by caspase-1 mediated via inflammatory cytokines [12]. LncRNA MIAT acts as a competing endogenous RNA (ceRNA) to sponge miR-150-5p and accelerates the proliferation and migration of HLECs [34]. LncH19 was up-regulated in ARC and act as ceRNA via H19/miR-29a/TDG pathway, which may be a promising target for the treatment [36]. Another study discovered that H19/miR-675 axis may affected CRYAA expression involved in the pathogenesis of nuclear ARC [33]. CRYAA encodes the predominant structural protein participate in refractive properties and the maintenance of lens clarity. The imbalanced expression of alpha-crystallin could accumulate damage and cripple its protective effect to the lens. Therefore, H19 could be a useful marker in ARC. LncPLCD3-OT1 may act as a ceRNA to regulate the expression of PLCD3 by combining with mi-224-5p

Table 2. The expression and the role of lncRNAs in the lens.

LncRNA	Target gene	Major methods and subject	Role or function	Cataract classification	reference
KCNQ1OT1 ↑	SMAD4	TGF-β2 induced SRA01/02 *in vitro*	HLECs proliferation and EMT	ASC and PCO	[31]
KCNQ1OT1 ↑	MiR-214/caspase-1	induced SRA01/04 cell *in vitro*	Promote HLECs Pyroptosis,	ARC	[12]
FEZF1-AS1 ↑	FEZF1	induced SRA01/04 cell *in vitro*	Promote HLECs proliferation	PCO	[39]
MIAT ↑	MiRNA-150-5p/Akt	SRA01/04 cell *in vitro*	Increase HLECs proliferation and viability; decrease HLECs dead or dying	PCO	[34]
H19 ↑	miRNA-675-5p	HECs *in vitro*	Increase HLECs proliferation and migration, decrease HLECs dead or dying	Nuclear cataract	[33]
H19 ↑	miR-29	HECs *in vitro*	Increase HLECs proliferation and migration, decrease HLECs apoptosis	ARC	[36]
TUG1 ↑	MiRNA-214	HECs *in vitro*	Promote HLECs apoptosis,	cataract	[37]
MALAT1 ↑	P38	HECs *in vitro*	Promote HLECs apoptosis	Diabetic cataract	[32]
PLCD3-OT1 ↓	MiR-224-5P	induced SRA01/04 cell *in vitro*	Inhibit HLECs apoptosis	ARC	[38]

and also plays a protective role in ARC [38]. Highly expressed TUG1 promotes lens epithelial cell apoptosis via sponging miR-421 [37]. LncRNAs also shown to regulate gene expression by interacting with a diverse range of proteins. As an example, the elevated KCNQ1OT1 positively regulated SMAD4 expression to promote LEC proliferation and EMT in PCO [31]. LncFEZF1-AS1 promoted the proliferation and migration via upregulating FEZF1 expression in PCO [39]. Upregulated MALAT1 can activate p38, a component of mitogen-activated protein kinases (MAPKs) pathway, resulting in HLECs apoptosis in DC. Collectively, aberrant expression of lncRNAs contribute to cataract via different regulatory mechanisms and signaling pathways (**Figure 2**).
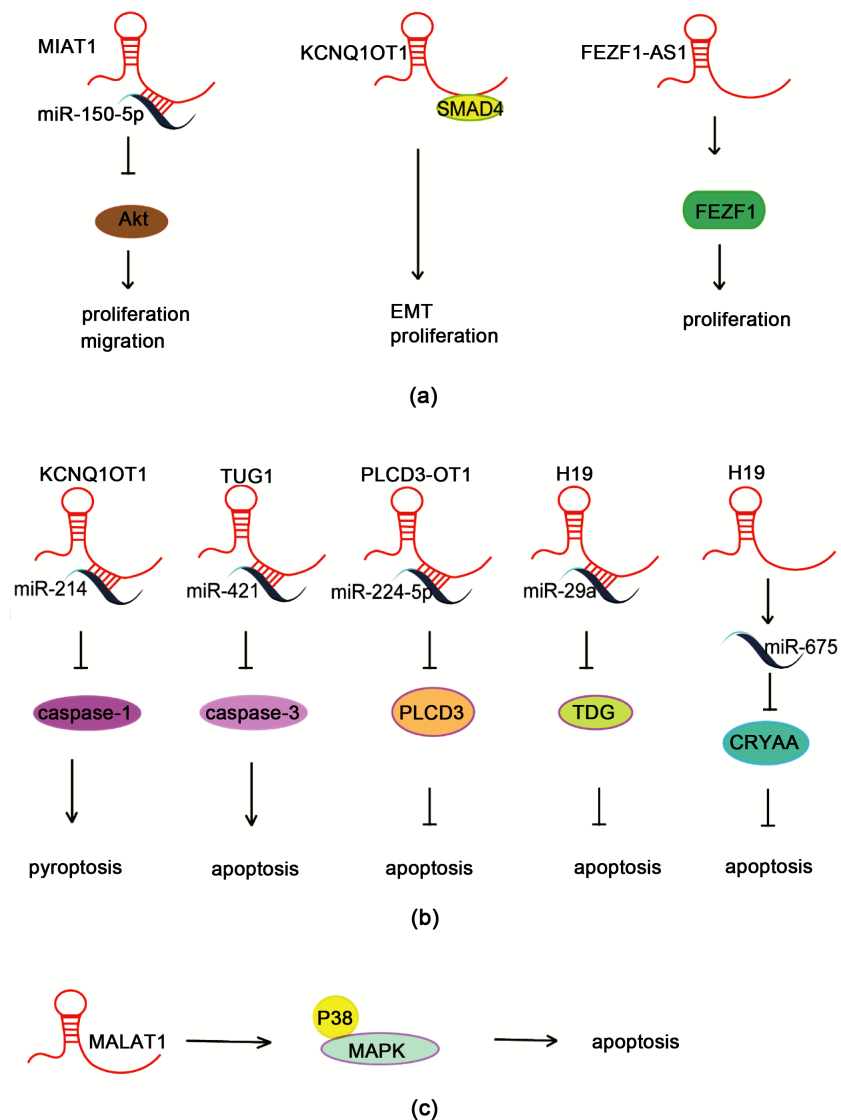
Figure 2. The role of lncRNAs in the lens. LncRNAs regulates the proliferation an EMT contribute to PCO via different pathways (a); LncRNAs regulates the pyroptosis and apoptosis contribute to age-related cataract via different pathways (b); lncRNAs regulatory mechanism in DC (c). (a) LncRNAs in ARC; (b) LncRNAs in PCO; (c) LncRNA in DC.

4. The Role of circRNAs in Cataract

### 4.1. The Structure and Function of circRNAs

Circular RNAs (circRNAs) are a novel class of non-coding RNAs generated from back splicing and the covalently closed loop structure linking the 3' and 5' ends. CircRNAs are commonly classified into three types: exonic circRNA, exon-intronic circRNA, and circular intronic RNA [40]. The pre-mRNA was changed from a chain structure to a ring structure, and then the introns in the ring were further cut to form circRNA which has broadly studied in recent years also can serve as useful markers in many cancers [41]. Although circRNA can't achieve biological function by encoding functional protein and have a low expression level, it revealed its work by combining with miRNA as molecule sponges [42]. The miRNA sponge effect of circRNA is only the unique function of some circRNAs, rather than the general characteristics of circRNAs. Some circRNAs molecules can also bind to RNA binding protein as protein sponges [43].

4.2. CircRNAs in the Cataract

Circular RNAs stably expressed in a variety of biological cells, and have tissue specificity and other characteristics. Circular RNAs participate in a wide range of developmental and physiological processes, including cell apoptosis, proliferation and differentiation. Accumulating evidence have proved their crucial regulation in respective biological processes and ocular diseases. Recently, the studies on circRNAs have shown that many circRNAs play roles as microRNA sponges, RNA-binding protein sponges, transcription regulators [44]. These roles give circRNA a great potential in biological applications. CircKMT2E acted as a sponge molecule of miR-204-5p and involved in the pathogenesis of DC [45]. Liu *et al.* reported that CircHIPK3 are the potential regulators to regulate HLECs function in cataractogenesis through miR-193a-mediated CRYAA expression [13]. CircHIPK3 acted as a molecular sponge to adsorb miRNA-193a to inhibit the production of crystalline proteins-CRYAA. CRYAA is a protein that keeps the crystal clearly. CircHIPK3 could regulate HLECs function provide a novel insight into ARC (**Figure 3**).

5. Conclusions and Future Perspectives

In conclusion, this review mainly summarized and analyzed the physiological and pathological effects of these non-coding RNAs in the lens. The expression of non-coding RNAs modulated the diverse proteins, RNAs and signaling pathways to impair the proliferation, migration, apoptosis, pyroptosis, autophagy and abnormal EMT of HLECs. ARC is commonly caused by apoptosis, pyroptosis, autophagy of the lens epithelial cell or unbalanced expression of crystalline proteins. However, PCO is commonly caused by proliferation, metastasis, and EMT of the lens epithelial cell. In DC, non-coding RNAs may be the etiology and inducing factors to trigger the cataract, resulting in its earlier occurrence
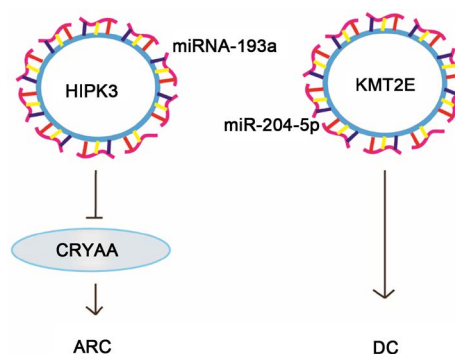
Figure 3. The mechanism of circular RNA in cataract. Circular RNA HIPK3 regulates human lens epithelial cells apoptosis by targeting the miR-193a/CRYAA axis. CircKMT2E acted as a sponge molecule of miR-204-5p and involved in the pathogenesis of DC.

and faster progress. With a growing number of ncRNAs being identified and characterized in human diseases, the emerging researches in the pre-clinical setting have shown the promise of ncRNAs as diagnostic and prognostic biomarkers. However, targeting ncRNAs in ophthalmology is still in its infancy, and improved techniques and approaches are expected in this field. In future efforts, focus should be put on a comprehensive molecular mechanism of ncRNA networks to decipher the precise roles of ncRNAs in cataract.

Acknowledgements

Conflicts of Interest

The authors declare no conflicts of interest.

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Hybrid Knife Technology in Endoscopic Therapy

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Abstract

Hybrid knife as a multi-function endoscopic instrument provides an effective model for endoscopic diagnosis and treatment of diseases. Hybrid knife does not need exchange of instrument during endoscopic operation. It can effectively reduce the potential risk of perforation and hemorrhage so that improving quality of life for patients. The technology has been widely used in clinic, especially in the treatment of digestive internal medicine, and in the course of respiratory intervention. Researchers have started to use the hybrid knife technique and have obtained good surgical results. In this review, we introduced the advantages of hybrid knife and summarized the clinic application, including the tumor excision and the tissue collection for pathology. Furthermore, the application of hybrid knife has significant implication to gastrointestinal and urinary diseases, and airway tumors, and we also explored the possibility of application of hybrid knife system in more diseases. Hybrid knife system has important clinical significance and is worth further study and exploration.

Keywords

Hybrid Knife, Endoscopy, Clinical Application, Risk Management

1. Introduction

Endoscopic submucosal dissection (ESD) is an important therapy technology that removed en bloc lesion of gastrointestinal mucosal neoplasia. The normal ESD steps are followed: marking, elevation, incision, dissection and coagulation. In some cases, chromoendoscopy was also used to stain lesions by methylene blue or other stains before marking. The lesion was marked around in a circle, and the separation medium was injected in the mucous layer and selectively

generated a fluid cushion in the mucosa [1]. Lesion was shifted up by the fluid cushion and this elevation has benefits for incision and dissection. Incision was made from the marked line near the edge of fluid cushion. Endoscopic knife was applied to dissect the submucosa beneath the lesion and kept the lesion intact. If the fluid cushion was diminished or lost, the process was repeated among injection and dissection. Repeating the elevation provides a good presentation of the cut level (beneath the tumor) and contributes towards achieving the desired tumor resection. Vessels or seeping bleeding was avoided, if occurred, coagulation was necessary. At the beginning of ESD development, four steps were involved in the different endoscopic instruments. No-knife change is the aim of ESD improvement to decrease the operation time with the low risk of bleeding and perforation.

Multi-function probe of hybrid knife realized the same device for submucosal injection, circular cutting, focus dissection and electrocoagulation hemostasis [2] (Figure 1). Hybrid knife combined the waterjet system and electrosurgical tip together and carried out the marking, injection and incision in one probe. Waterjet system of hybrid knife was a sophisticated control fluid system which performed medium injection and lesion elevation.

Injection fluid was not limited to normal saline and other media were also used to keep the pad shape longer [3]. It is possible for hybrid knife to replenish fluid immediately during endoscopic surgery. Good fluid cushion boarded surgical sites, exposed lesions and compressed blood vessels.

The broad surgical site provided a window to cut and peel around the mucosa of the lesion more safely [4]. The hybrid knife can shorten ESD operation time and reduce the bleeding and perforation in clinic surgery [5].

Hybrid knife was used to en bloc resection of bladder tumors and other fields, because of the advantages of hybrid's cutting tool such as cutting-edge fluid injection and no-change instruments during operation. The application of hybrid knife to en bloc resection has extended from superficial gastrointestinal tumors to non-invasive bladder tumors [6] [7]. With the rapid development of endoscopic technologies and instruments, hybrid knife was also applied to treat achalasia [8]. Beside on this, hybrid knife was carried out in clinical detection and
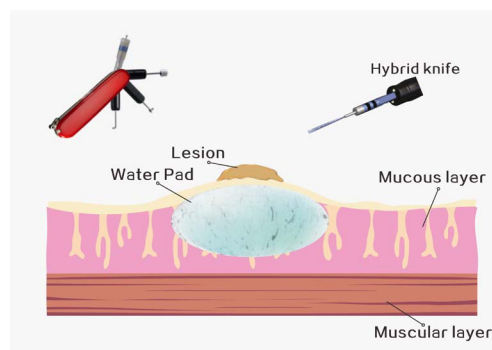
Figure 1. Comparison of cutting superficial tumor with traditional endoscopic knife and hybrid knife. Notes: According to the characteristics and functions of Hybrid knife, we draw this picture (Figure 1).

diagnosis, such as pathological tissue collection and pleural biopsy of early bladder cancer [9] [10].

In this article, we reviewed the application of hybrid knife system in endoscopic surgery. At first, we introduced the clinical research of the surgical treatment of bladder cancer, early gastric and cancer colorectal cancer by using hybrid knife under endoscope, and then discussed the application of hybrid knife in the collection of pathological tissues of early bladder cancer and the collection of biopsy specimens from pleural diseases. Finally, we introduced the research of Hybrid knife in related animal experiments, and discussed the feasibility of Hybrid knife in more clinical diseases in the future.

2. Traditional High-Frequency Electric Knife Used in Clinic

In endoscopic surgery, there are many traditional instruments, high-frequency electric knife is widely used in clinic. With the development of domestic medicine and the maturity of applied medical devices, domestic medical devices are becoming more mature. As early as 1995, the clinical doctors compared the domestic instruments with the imported instruments. The results showed that the performance of the domestic high-frequency electric knife could fully meet the requirements of the operation. The main performance of the domestic high-frequency electric knife system had reached the level of the same as imported product, and the price was lower than that of the foreign products [11] [12] (**Table 1**). Experts believed that domestic high-frequency electric knife is worth popularizing and suitable for clinic. However, due to the high current intensity of high-frequency electric knife, if it is used improperly, it is easy to cause serious harm to patients. Therefore, on the basis of these traditional instruments, combined with their advantages and disadvantages, new endoscopic instruments have been developed and used in clinic, and the hybrid knife is one of the new endoscopic treatment systems in nowadays.

3. The Application of Hybrid Knife in Endoscopic Surgery
3.1. Non-Muscle Invasive Bladder Cancer (NMIBC)

Among the 81,190 estimated newly diagnosed bladder cancer in the US in 2018,

Table 1. Comparison between domestic high-frequency electric knife and imported products.

Country	Model	Price	Power	Operation effectiveness
USA	Valleylab (SSE4)	expensive	1 - 300 w	100% success
USA	Force GSU	expensive	1 - 250 w	100% success
Germany	ERBE (T400)	expensive	1 - 400 w	100% success
China	GPD	1/5 of Valleylab (SSE4) products	1 - 350 w	100% success
China	ZARS	1/4 of Force GSU products	1 - 350 w	100% success

nearly 75% were non-muscle-invasive bladder cancer (NMIBC) [13]. 5-year survival rate of NMIBC reached 94% [14]. Transurethral resection of bladder tumor (TUEBRT) was the first choice of treatment NMIBC based on transurethral electrotomy [14].

In 2013, Dr. Mundhenk *et al.* Firstly reported the use of Hybrid knife to perform TUEBRT on 16 NMIBC patients [15]. The average resection time was 27 minutes without significantly decrease of hemoglobin and other major complications [15]. Another study about the methods and postoperative effects of Hybrid knife in NMIBC surgery showed that the operation time was 35 minutes, without replacement of the surgical instrument in the four working stages: marking, elevation, incision/dissection and coagulation [7]. Therefore, four working stages were not disrupted by the instrument change and the operation time sharply decreased.

The researchers showed that Hybrid knife expanded the benefits of submucosal water cushion. Hybrid knife has been standard technique to keep the submucosal water pad intact during the dissection and focal resection and inject additional fluid according to the necessary [1] [2]. Animal research showed that the fluid cushion formed a selective edema in the submucosal to protect the mucosal layers. This protection was not limited to the separation mucosal layers from the focus, increased operation window but also included prevention of thermal damage. Meanwhile the fluid cushion increased the pressure of mucosal layers and compressed the blood vessels to decrease bleeding. So that Hybrid knife removed the en-block tumor without fragments and maximized the prognosis without bladder perforation or tumor implants [7]. Through the Hybrid knife technique, the tumor can be cut off by the whole piece, safe and effective postoperative results and curative effects can be obtained.

3.2. Early Gastric Cancer (EGC)

Endoscopic submucosal dissection (ESD) is a mature endoscopic technique for the treatment of early gastrointestinal epithelioma [16] [17]. ESD has become a treatment option for early EGC and is increasingly used in early esophagus and colorectal cancer. Many foreign researchers made a comparative study, it is about application of traditional knife and hybrid knife in endoscopic submucosal dissection, and compared the characteristics of hybrid knife and traditional incision knife in the treatment of gastric lesions. It shows that using hybrid knife technology can effectively shorten operation time and improve operation efficiency. Some researchers carried out a prospective study on 30 patients with early gastric cancer, the results show that ESD can obtain 100% complete resection rate and 90% overall resection rate of endoscope by using hybrid knife [6]. Research display [18], after the use of the hybrid knife, the performance of endoscopic submucosal stripping was increased by 28.9%, and the improvement was more significant in technically simpler parts, such as lesions under the stomach or less than 4 cm.

3.3. Colorectal Polyps and Superficial Tumors

The treatment strategy for colorectal polyps and superficial tumors has gradually turned from surgery to endoscopic resection. Compared with surgery, endoscopic resection was less invasive, which made patients recover faster and maintain normal intestinal function. ESD was a wide spread technique for the treatment of early superficial gastrointestinal tumors. ESD was operated in almost any location of the gastrointestinal tract [19] [20]. But whole resection of large superficial colorectal tumors was difficult by ESD because of the thin wall of the colon, the poor flexibility and elongation of the colon [21]. During endoscopic resection of lesions, colon circulation, intestinal motility, folding anatomy and surgical field of vision were major factors to impact the prognosis. In order to prevent complications such as perforation and uncontrollable bleeding, it was important to maintain a good image of the submucosal anatomical layer [21] [22]. Hybrid knife provided a good surgical exposure area to improve ESD safety and effectiveness. High-pressure injection liquid of Hybrid knife separates the focus from the muscular layer quickly and safely, and made the submucosal space visible. At the same time, the water pad remains the colon muscular layer intact and the water beam had little damage to it. Hybrid knife was very effective and safe in treating large superficial colorectal lesions that were not suitable for endoscopic mucosal resection (EMR) or endoscopic polypectomy [23]. There are clinical trials show that the combined use of water-jet hydrodissection, saline solution immersion, and the pocket-creation method to perform ESD can be an effective technique to remove colorectal polyps. The hybrid knife "probe mode" can be used safely and effectively in saline solution immersion. The resected specimen size was 120 × 80 mm, and the procedure time was 241 minutes. There was no perforation or bleeding either during or after the procedure [24].

3.4. Achalasia of Cardia (AC)

Achalasia is a primary esophageal dyskinesia functional disease. At present, the treatment methods included muscle relaxants, endoscopic botulinum toxin injection, balloon dilation and surgical myotomy [25]. Endoscopic esophageal sphincterotomy (POEM) is a new minimally invasive technique for the treatment of esophageal achalasia [26]. However, it is reported that gas-related complications after surgery, such as mediastinal emphysema and pneumothorax, with mucosal perforation up to 20%. At the same time, the average operation time was 68 - 114 minutes [27] [28].

Evidence from prospective randomized trials indicated that Hybrid knife technology significantly reduced the surgical processing time of POEM, also reduced the bleeding rate [8]. In this prospective randomized, 100 patients with achalasia were randomly divided into two groups: hybrid knife group, conventional group [8]. The experimental results showed that the average time of operation in the hybrid knife group was about 22.9 minutes, the operation time of the conventional group was 35.9 minutes, the hemostatic rate of the convention-

al group and the usage rate of the hemostatic clamp were higher than the hybrid knife group, and 96.5% of the patients had successful treatment. There are a lot of literature to describe conventional knife and hybrid knife used in clinical and animal experiments (Table 2), and the application of hybrid knife technology in some surgeries (Table 3).

3.5. Respiratory Diseases

Currently, more clinical workers begin to learn the hybrid knife technology, and apply it in clinical research. Hybrid knife is widely used in the treatment of digestive diseases. For example, it is used in early gastric cancer, achalasia of cardia, rectal polyps diseases [18] [25] [29] [30]. However, at present, some researchers have applied this technology to respiratory diseases, such as the diagnosis and treatment of bronchial mucosal tumors. Clinical workers have used hybrid knife to treat and diagnosis primary bronchial mucosa-associated lymphoid tissue (MALT) [33]. In this study, they applied a water-jet hybrid knife in biopsy excision of intracheal broad-based lesions. This is the first time that hybrid knife has used in bronchoscopy, and it has been successful. In addition, there were researchers used hybrid knife technology in the bronchial cyst and

Table 2. Comparison of the features of conventional knife and hybrid knife in surgeries.

Classification	Operation	Conventional knife				Hybrid knife				References
		Cases	Average time (min)	Hemorrhage (%)	Perforation (%)	cases	Average time (min)	Hemorrhage (%)	Perforation (%)	
Clinical trial	ESD	34	57.2	2.94	5.88	49	41.3	0	4.08	[29]
	ESD	59	35.0	4.85	3.39	58	27.5	1.64	1.72	[3]
	ESD	39	44.0	7.70	5.13	39	27.0	7.70	2.56	[18]
	STER	15	78.7	40.67	0	16	50.5	22.69	0	[30]
	POEM	50	35.9	0	0.02	50	22.9	0	0	[8]
Animal experiment	ESD	6	58.32	58.33	22.17	6	47.18	47.17	2.84	[31]
	ESD	20	68.7	20	10	30	44.6	13	13	[4]
	ESD	13	9.5	23.08	0	14	8.0	14.29	7.14	[32]

Notes: STER: submucosal tunnel endoscopic resection; ESD: Endoscopic submucosa dissection; POME: Peroral endoscopic myotomy.

Table 3. The application of hybrid knife technology in some surgeries.

Disease	Operation	Cases	Average time (min)	Perforation	References
NMIBC	TUR-BT	16	27	0	[15]
Giant rectal polyp	ESD	1	241	0	[24]
Achalasia of cardia	POEM	11	100.7	0	[27]
Achalasia of cardia	POEM	16	114	0	[8]

Notes: NMIBC: Non-muscle invasive bladder cancer; TUR-BT: Transurethral resection of bladder tumor; ESD: Endoscopic submucosa dissection; POME: Peroral endoscopic myotomy.

deep benign fibrous histiocytoma [34] [35]. They think the common complications in the treatment of tumors of the membranous trachea are bleeding and perforation. The combination of lelctrrocautery and electrocoagulation may decrease the risk of bleeding. The hybrid knife can create an adequate submucosal cushion, and the direction of dissection can be targeted tangentially to the surface of the lesion at the submucosal layer to minimize the risk of perforation. At present, hybrid knife technology plays a key role in the clinic. The researchers have more in-depth study of it, and the field of application is become more extensive, and they have got good results in clinical diagnosis and treatment. In the future, hybrid knife technology is likely to be applied to radical surgery of airway tumor.

4. Disease Detection

4.1. Pathological Tissue Collection of Early Bladder Cancer

For early bladder cancer diagnosis, Hybrid knife technique also has a good function of tumor pathological tissue collection. Because of high 5-year survival rate of early bladder cancer, fine diagnosis completely improved the life quality of patients. Preservation ordered structure and prevention disordered deformation are the key of pathological tissue collection for early bladder cancer diagnosis. Some traditional methods may have disordered cutting directions, disorganized and broken tissues, which were not conducive to detection, leading to erroneous reports of anatomical and pathological detection, thus making uncertainty in the final diagnosis of patients and delaying in treatment [9]. Hybrid knife did not need to change the instrument or perform transverse tumor resection during the operation, so that Hybrid knife preserved the integrity of the tissue and made the accurate detection of histopathology. And the pathological examination department believed that the positive degree of tumor process, vascular invasion and bladder muscle invasion were easily determined both macroscopically and microscopically by using the Hybrid knife technique to obtain pathological tissues [7]. It was helpful to determine the depth of invasion, degree of differentiation, vascular and lymphatic invasion of the lesion and to evaluate the prognosis of the patient.

4.2. Biopsy Specimens Obtained from Pleural Diseases

Hybrid knife was applied to the definite diagnosis of pleural diseases and sufficient samples were obtained from the thickened pleura [10]. Yan Yin *et al.* described three patients with pleural effusion of unknown cause and performed pleural biopsy using high pressure water jet [36]. The cases showed that Hybrid knife was more effective in pleural biopsy when encountering malignant or benign fibrous thorax. Hybrid knife took biopsy in no more than 15 minutes, and its function of high-pressure water jet makes submucosal injection easier than conventional injection. The size of biopsy specimen obtained with Hybrid knife is significantly larger than that obtained with traditional methods, such as injec-

tion needle and triangular sharp knife [37]. Therefore, the Hybrid knife system is a time-saving, convenient, safe and effective technology in the application of video-assisted thoracoscopic biopsy specimens. The effectiveness and optimal indications of this technique need further research to explore and prove.

5. Conclusion and Prospect

As a new type of endoscopic treatment instrument, hybrid knife is widely used in clinic, especially in the treatment of gastrointestinal diseases and urinary diseases. The water jet hybrid knife performed endoscopic liver wedge resection through the natural opening of the pig model. This technique still has a long way to go to reach the same level as the commonly used segmental keratectomy [38]. Some researchers have performed transumbilical endoscopic cholecystectomy in a pig non-survival model using the water jet hybrid knife technique. The operation had achieved some results, they believed that this technique still need further research before it can be applied in clinic treatment [39]. Although these animal experimental research results are still in the preliminary exploration stage and have not been applied to clinical, these studies suggest a new direction for the application of hybrid knife technology and provide a new scheme for minimally invasive surgical treatment.

The hybrid knife system technology under endoscope can be applied to the treatment of various diseases, which has important clinical significance and was worth further study and exploration. In-depth study and discussion of hybrid knife technology, its diagnosis and treatment of diseases have theoretical significance and clinical value. At present, hybrid knife technology is mainly used in digestive system. To explore the application of hybrid knife system technology in other diseases or surgeries, it will be a new choice for ESD development to provide clinical diagnosis and treatment of diseases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation Note List

Abbreviation	Full Name in English
ESD	Endoscopic Submucosal Dissection
NMIBC	Non-Muscle Invasive Bladder Cancer
TUEBRT	Transurethral Resection of Bladder Tumor
EGC	Early Gastric Cancer
EMR	Endoscopic Mucosal Resection
AC	Achalasia of Cardia
POEM	Endoscopic Esophageal Sphincterotomy
STER	Submucosal Tunnel Endoscopic Resection
TUR-BT	Transurethral Resection of Bladder Tumor
MALT	Mucosa-Associated Lymphoid Tissue

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