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Expression of miR-19b-3p and its relationship with cognitive function before and after lung cancer resection under thoracic epidural anesthesia combined with intravenous anesthesia

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Abstract:
Objective: To investigate the expression of miR-19b-3p and its relationship with cognitive function before and after lung cancer resection under thoracic epidural anesthesia combined with intravenous anesthesia. **Methods:** Altogether 194 patients undergoing lung cancer resection in our hospital were selected as research objects and randomly divided into two groups. Patients in the intervention group was given thoracic epidural anesthesia combined with intravenous anesthesia, while patients in the control group was given intravenous anesthesia alone. The anesthetic effect (operation time, awakening time, extubation time, recovery time) of the two groups of patients was observed and recorded. Ramsay sedation score, VAS score, MMSE score and incidence of postoperative cognitive dysfunction (POCD) in different time periods were compared. The expression level of serum miR-19b-3p before and after operation was observed. Cox regression analysis was applied to analyze postoperative prognostic factors in lung cancer patients. **Results:** The anesthesia effect of patients in the intervention group was notably better than that of the control group ($p<0.05$). There was no difference in t1 in terms of Ramsay sedation score and VAS score between the two groups, while Ramsay sedation score and VAS score in t2 and t3 of patients in the intervention group were remarkably better than those in the control group ($p<0.05$). MMSE score at 1 d and 3 d after operation of patients in the intervention group was notably better than that in the control group ($p<0.05$). The incidence of POCD in the intervention group was notably lower than that in the control group ($p<0.05$) at 1 d and 3 d after operation. Age, high miR-19b-3p expression, intravenous anesthesia, awakening time and recovery time were all important related factors when POCD occurred. **Conclusion:** Thoracic epidural anesthesia combined with intravenous anesthesia has good curative effect and response in lung cancer resection patients. It can produce great sedative and analgesic effects, reduce the incidence of POCD, and decrease the expression of miR-19b-3p in serum of lung cancer patients.
Keywords: thoracic epidural anesthesia combined with intravenous anesthesia, lung cancer resection, miR-19b-3p, cognitive function

Introduction

Lung cancer is a common clinical malignant tumor with high morbidity and mortality (Zhao et al., 2019; Torre et al., 2016). Some research have reported that surgical resection is one of the main treatment methods for lung cancer, which brings potential cure opportunities for patients (Chai et al., 2019; Yamanashi et al., 2017). But the recurrence and metastasis of the disease are factors affecting the survival rate. Perioperative anesthetic management is not only related to postoperative rehabilitation, but also correlated with the long-term prognosis of tumors (Sen et al., 2019). Other studies have shown that different anesthesia methods for patients will affect the prognosis of patients (Xu et al., 2017).

General anesthesia often causes neurological degeneration and long-term behavioral deficits in patients (Warner et al., 2018). Due to anesthesia and analgesia during operation, patients often suffer from cognitive impairment and severe agitation during anesthesia recovery, thus impairing patients' cognitive and memory abilities (Cao et al., 2019).

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Thoracic epidural anesthesia can reduce the recurrence rate of cancer, reduce respiratory failure after anesthesia, and prolong the survival time of patients (Li et al., 2019). There is also a study showing that thoracic epidural anesthesia can not only reduce the requirements of general anesthesia, but also effectively relieve the pain degree during perioperative period (Do et al., 2017). miRNA is a small non-coding RNA, which can guide mRNA transcription by binding with 3'-UTR to control the progression and metastasis of cancer (Wang et al., 2019; Zhang et al., 2018). Studies have shown that miRNA has been used as a biomarker for diagnosis and detection of therapeutic effects of various cancers including non-small cell lung cancer (Zhou et al., 2017). In the study of team of Bulgakova O (Bulgakova et al., 2018), miR-19b-3p can be used as a serious non-invasive method for the diagnosis of lung cancer.

In this study, thoracic epidural anesthesia combined with intravenous anesthesia is used to study the expression of serum miR-19b-3p, cognitive impairment and influencing factors in patients undergoing lung cancer resection.

Data and methods

General Data

Altogether 194 patients who underwent lung cancer resection in our hospital were selected as the research object and randomly divided into two groups. Among them, 107 patients were enrolled in the intervention group, including 55 males and 52 females, with an average age of (60.34±9.02) years. Another 87 cases of patients were in the control group, including 47 males and 40 females, with an average age of (60.74±9.18) years. Inclusion criteria were as follows: All patients were diagnosed as lung cancer by pathological examination (Luo et al., 2017). Patients did not receive any radiotherapy, chemotherapy or immunotherapy before operation. Patients whose expected survival time was ≥ 1 year. Patients whose clinical general data were complete. This study was conducted with the approval of the ethics committee of our hospital, and all the subjects and their families were informed and signed a fully informed consent form. Exclusion criteria were as follows: Patients transferred to other hospital or withdrew from the experiment. Patients who had disorders in hearing, vision and communication, hemopoietic disorders, or neurological diseases.

Drugs and instruments

Midazolam (Yichang Humanwell Pharmaceutical Co., Ltd., SFDA approval number: H20067040), propofol (Guangdong Jiabo Pharmaceutical Co., Ltd., SFDA approval number: H20051842), fentanyl (Yichang Humanwell Pharmaceutical Co., Ltd., SFDA approval number: H20050580), vecuronium (Cisen Pharmaceutical Co., Ltd., SFDA approval number: H20067458), lidocaine (Beijing Yookon Pharmaceutical Co., Ltd., SFDA approval number: H11020558), ropivacaine hydrochloride (Guangdong Jiabo Pharmaceutical Co., Ltd., SFDA approval number: H20133178), TRIzol kit (Hangzhou Qiannuo Biotechnology Co., Ltd., TR1026), UV spectrophotometer (Wuhan Chundu Biotechnology Co., Ltd., CD-11239-ML).

Operative method

Patients in the control group were given intravenous anesthesia. They were injected with midazolam 0.04 mg/kg, propofol 2.0 mg/kg, fentanyl 4 g/kg and vecuronium 0.1mg/kg for general anesthesia induction. Propofol was given to maintain anesthesia depth. Patients in the intervention group was given thoracic epidural anesthesia combined with intravenous anesthesia. Before operation, puncture and catheterization were performed in the T8-9 space of the patient, followed by injection of 5 mL 1% lidocaine. Five minutes later, whether the catheter was located in the epidural space was confirmed. After confirmation, 10 mL of 0.3% ropivacaine hydrochloride was injected. After 5 minutes, 6 mL of 0.3% ropivacaine hydrochloride was injected again. After that, anesthetic could be added appropriately according to the operation time and emergency situation.

Outcome measures

The operation time, postoperative recovery time, postoperative extubation time and postoperative recovery time of the two groups of patients were observed and recorded.

At the time of awakening (t1), 3 hours after awakening (t2) and 6 hours after awakening (t3), Ramsay sedation scale was used to evaluate the sedation status of the patients, VAS pain scale was used to evaluate the postoperative pain status, and mini-mental state examination (MMSE) was used to evaluate the mental state of the patients before, 1 day and 3 days after the operation.

(3) POCD evaluation was performed at 1 d and 3 d after operation.

Experimental method

Five ml of venous blood from two groups were drawn on an empty stomach and placed in EDTA-K2 anticoagulation tube, centrifuged at 3000r/min for 20 min. Upper serum (500 μl) was drawn and stored in EP tube for later use. The total RNA in serum was extracted according to the manual of TRIzol serum extraction kit. The absorbance of RNA was measured by UV-Vis spectrophotometer, and the concentration was calculated. Two μl of total RNA was taken to prepare cDNA according to the instruction manual of the kit. Reverse transcription reaction system was as follows: 42 for 60 min and 95 for 5min. The synthesized cDNA sample was stored at -20 for later use. U6 was regarded as the internal reference gene. The total volume of the reaction system was 20 μl: PCR Premix 10 μl, upstream primer (10×) 2 μl, downstream primer (10×) 2 μl, dd water (Rnase and Dnase free) 5 μl L. PCR amplification cycle conditions were as follows: 90 for 5 min, 90 for 5 s, 60 for 30 s, 72 for 5 s, with a total of 40 cycle. Amplification data were analyzed by ABI PRISM 7500 fluorescence quantitative PCR, and the results were expressed by $2^{-\triangle CT}$.

Statistical methods

SPSS20.0 (IBM Corp, Armonk, NY, USA) was utilized for statistical analysis. GraphPad Prism 7 was used to draw the data picture. The counting data were expressed by [n(%)]. Chi-square test was used to compare the counting data between groups. When the theoretical frequency in Chi-square test was less than 5, Chi-square test was used for continuity correction. The measurement data was expressed by mean standard deviation (x±sd). The measurement data between groups were compared by independent sample t-test, and paired t-test was used for intra-group comparison before and after. The prognostic factors of lung cancer patients were analyzed by univariate and multivariate Cox regression. When $p<0.05$, the difference was statistically significant.

Results

General Data

There was no significant difference between the two groups in clinical baseline data such as gender, average age, body mass index (BMI), residence, nation, educational background, smoking history, drinking history, diabetes history, hypertension history, work history, glucose (mmol/L), and tumor diameter ($p>0.05$), as shown in Table 1.

Table 1 Comparison of general data of patients in the two groups [n(%)](x±sd)

Classification	Intervention group (n=107)	Control group (n=87)	t/χ^2 value	P value
Gender			0.132	0.716
Male	55(51.40)	47(54.02)		
Female	52(48.60)	40(45.98)		
Average age (years)			0.305	0.761
	60.34±9.02	60.74±9.18		
BMI(kg/m^2)			0.246	0.806
	22.14±3.08	22.25±3.11		
Residence			3.16	0.075
City	58(54.21)	36(41.38)		
Countryside	49(45.79)	51(58.62)		
Nation			0.042	0.838
Han	52(48.60)	41(47.13)		
Minority	55(51.40)	46(52.87)		
Education background			0.033	0.855
≥ high school	37(34.58)	29(33.33)		
＜ high school	70(65.42)	58(66.67)		

Smoking history			3.470	0.063
With	83(77.57)	57(65.52)		
Without	24(22.43)	30(34.48)		
Drinking history			1.338	0.247
With	53(58.88)	44(50.57)		
Without	44(41.12)	43(49.43)		
History of diabetes			0.042	0.838
With	55(51.40)	46(52.87)		
Without	52(48.60)	41(47.13)		
History of hypertension			0.225	0.635
With	59(55.41)	45(51.72)		
Without	48(44.86)	42(48.28)		
Work history			0.379	0.538
With	44(41.12)	32(36.78)		
Without	63(58.88)	55(63.22)		
Glucose(mmol/L)			1.218	0.225
	5.98±0.57	6.07±0.43		
Diameter of tumor (cm)			0.231	0.818
	2.87±1.35	2.82±1.67		

Comparison of anesthesia effect between two groups of patients after operation

There was no difference in operation time between the two groups (p>0.05), while the awakening time, extubation time and recovery time of patients in the intervention group were shorter than those in the control group (p<0.05). As shown in Table 2.

Table 2 Comparison of anesthesia-induced intubation operation time between the two groups ($\bar{x}$±sd, min)

	Intervention group(n=107)	Control group (n=87)	t	P
Operation time (min)	180.32±10.13	182.22±10.17	1.297	0.196
Awakening time	20.56±6.19	25.19±6.18	5.185	＜0.001
Extubation time	25.83±6.16	32.64±6.17	7.652	＜0.001

Recovery time	10.79±2.67	13.82±2.62	7.927	＜0.001

Ramsay score of two groups of patients in different time periods

The Ramsay scores of t2 and t3 in both groups were higher than those of t1 (p<0.05), while the Ramsay scores of t3 were notably lower than those of t2 (p<0.05), and the Ramsay scores of t2 and t3 in the intervention group were notably lower than those in the control group (p<0.05). As shown in Table 3.

Table 3 Comparison of Ramsay score of two groups of patients in different time periods ($\bar{x}$±sd, points)

Group	t1	t2	t3	F	P
Intervention group (n=107)	3.07±0.41	4.23±1.55*	3.28±1.12*	32.060	＜0.001
Control group (n=87)	3.12±0.42	4.74±1.53*#	4.25±1.23*#	44.700	＜0.001
t	0.836	2.292	5.740	-	-
P	0.404	0.023	＜0.001	-	-

VAS scores of two groups of patients in different time periods

The VAS scores of patients in t2 and t3 in both groups were higher than those in t1 (p<0.05), while those in t3 period were remarkably lower than those in t2 (p<0.05), and those in intervention group were considerably lower than those in control group (p<0.05). As shown in Table 4.

Table 4 Comparison of VAS score of two groups of patients in different time periods ($\bar{x}$±sd, points)

Group	t1	t2	t3	F	P
Intervention group(n=107)	2.13±0.31	3.61±0.33*	2.31±0.40*	650.900	＜0.001
Control group (n=87)	2.16±0.32	3.79±0.38*#	2.99±0.43*#	408.500	＜0.001
t	0.661	3.530	11.390	-	-
P	0.509	＜0.001	＜0.001	-	-

MMSE scores of two groups of patients in different time periods

The MMSE scores of the two groups were significantly lower on 1 d and 3 d after operation than before operation (p<0.05), and it in the 3 d after operation was remarkably higher than 1 d after operation (p<0.05). The MMSE scores of the intervention group were remarkably better than those of the control group (p<0.05). As shown in Figure 1.

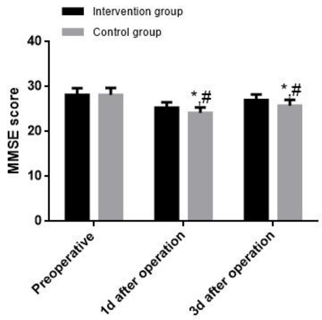

Figure 1: MMSE scores of two groups of patients in different time periods
There was no difference in MMSE scores between the two groups before operation. MMSE scores of patients in the intervention group were remarkably higher than those in the control group at 1 d and 3 d after operation. Notes: Comparison with before operation * < 0.05, comparison with postoperative control group # < 0.05.

Incidence of POCD in different time periods after operation

There were 7 cases (6.54%) of POCD in the intervention group 1 d after operation and 14 cases (16.09%) in the control group, which was remarkably lower in the intervention group than the control group ($p<0.05$). We counted the patients who had POCD 3 d after operation and found that there was 1 case (0.93%) in the intervention group and 6 cases (6.90%) in the control group. The POCD patient in the intervention group 3 d after operation was notably lower than those in the control group ($p<0.05$). As shown in Table 5.

Table 5 Incidence of POCD in two groups of patients [n(%)]

Group	n	1 d after operation	3 d after operation
Intervention group	107	7(6.54)	1(0.93)
Control group	87	14(16.09)	6(6.90)
χ^2	-	4.534	4.904
p	-	0.033	0.027

Expression of miR-19b-3p before and after operation in the two groups

The expression of serum miR-19b-3p of patients in the intervention group and control group was (1.21±0.18) and (1.18±0.17) before operation, with no significant difference ($p>0.05$), while it of patients in the intervention group and control group was (0.53±0.12) and (0.79±0.15) after operation. The results showed that the expression of miR-19b-3p in the intervention group was notably lower than that in the control group ($p<0.05$). As shown in Figure 2.

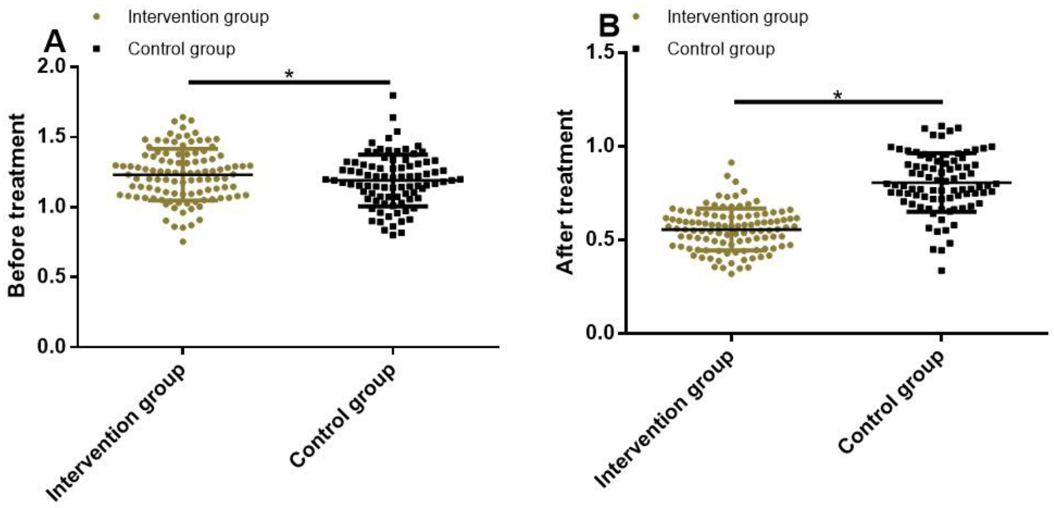

Figure 2: Expression of miR-19b-3p before and after operation in the two groups
A, Expression of miR-19b-3p in serum of lung cancer patients before operation. B, Expression of miR-19b-3p in serum of lung cancer patients after operation. Note: *＜0.05.

Prognostic analysis of POCD

Univariate analysis was carried out on the clinical general data of patients with postoperative POCD and non-POCD patients. The results showed that age, tumor diameter, miR-19b-3p expression, anesthesia method, awakening time and recovery time were the influencing factors of POCD. Then multivariate Cox regression analysis was carried out on the different indexes, whose results indicated that age, tumor diameter, high miR-19b-3p expression, intravenous anesthesia, awakening time and recovery time were the important related factors when POCD occurred ($p<0.05$), as shown in Table 6-8.

Table 6 The relationship between clinical parameters and the therapeutic effect of lung cancer resection [N (%)] (X SD)

Classification	POCD group(n=28)	non-POCD group(n=166)	t/χ^2 value	P value
Gender			2.319	0.128
Male	11(39.29)	91(54.82)		
Female	17(60.71)	75(45.18)		
Average age (years)			2.590	0.010
	65.34±9.02	60.54±9.08		
Smoking history			0.243	0.622
With	16(57.14)	103(62.05)		
Without	12(42.86)	63(37.95)		
Drinking history			2.395	0.122
With	12(42.86)	47(28.31)		
Without	16(57.14)	119(71.69)		

History of diabetes			2.756	0.097
With	16(57.14)	67(40.36)		
Without	12(42.86)	99(59.64)		
History of hypertension			1.453	0.228
With	14(50.00)	63(37.95)		
Without	14(50.00)	103(62.05)		
Diameter of tumor (cm)			6.501	0.011
≤5	10(35.71)	102(61.45)		
＞5	18(64.29)	54(38.55)		
miR-19b-3p			8.039	0.005
High expression	19(67.86)	65(39.16)		
Low expression	9(32.14)	101(60.84)		
Anesthesia method			9.349	0.002
Joint	8(28.57)	99(59.64)		
Single	20(71.43)	67(40.36)		
Awakening time			4.151	＜0.001
	26.52±6.22	21.23±6.24		
Pulling time			0.489	0.628
	25.83±6.12	26.44±6.11		
recovery time			6.678	＜0.001
	14.31±2.42	11.02±2.41		

Table 7 Logistic Multivariate Regression Analysis Assignment

Factors	Variable	Assignment
Age	X1	No=0, Yes=1
Diameter of tumor (cm)	X2	≤5cm=0，＞5cm=1
miR-19b-3p	X3	High expression=0, low expression=1

Anesthesia method	X4	Chest epidural anesthesia combined with intravenous anesthesia=0, intravenous anesthesia=1
Awakening time	X5	≤1 h=0，＞1 h=1
Recovery time	X6	≤10 min=0，＞10 min=1

Table 8 Multivariate Cox regression analysis

Index	β value	P value	X^2 value	OR value	95%CI
Age	0.974	0.035	2.051	0.510	0.255-1.020
Diameter of tumor (cm)	-0.651	0.047	2.054	0.521	0.214-1.271
miR-19b-3p	1.378	0.002	9.506	3.968	1.652-9.529
Anesthesia method	1.159	0.010	6.673	3.188	1.323-7.685
Awakening time	0.927	0.042	4.127	2.527	1.033-6.180
recovery time	1.042	0.030	4.732	2.835	1.109-7.249

Discussion

In this study, combined anesthesia and single anesthesia were used to observe the curative effect on lung cancer resection patients. We found that the postoperative pain score and cognitive function of patients in the intervention group were notably better than those in the control group, and the expression of miR-19b-3p after operation was remarkably lower than that in the control group, indicating that thoracic epidural anesthesia combined with intravenous anesthesia can effectively reduce the stress response of patients after operation.

Thoracic epidural anesthesia is commonly used in clinical abdominal or thoracic surgery (Twardowski et al., 2014). In the study of team of Mahajan A (Mahajan et al., 2017), epidural anesthesia can inhibit electrical storm in patients with heart rate variability and enhance the high-frequency components to regulate heart rate variability through the parasympathetic. In Hong J M's research (Hong et al., 2017), the combination of thoracic epidural anesthesia and intravenous anesthesia has been used in clinical large-scale upper abdominal surgery, which can effectively relieve pain, reduce metabolism and reduce postoperative recovery time. The results of this study showed that there was no difference in the operation time between the two groups, while the postoperative awakening time, extubation time and recovery time in the intervention group were significantly lower than those in the control group. This shows that epidural anesthesia combined with intravenous anesthesia can accelerate the recovery rate of patients after lung cancer resection. Studies have shown that postoperative pain is a common problem that troubles patients, and postoperative pain will affect the patients' early activities and hinder the patients' postoperative recovery speed (Hao et al., 2016; Zhu et al., 2019). The results of this study showed that Ramsay score and VAS score in t2 and t3 of the two groups of patients were higher than t1, and changed with the extension of awakening time. Ramsay score and VAS score in t3 of the two groups of patients were lower than t2, and Ramsay score and VAS score in t2 and t3 of patients in the intervention group were notably lower than those in the control group. This suggests that thoracic epidural anesthesia combined with intravenous anesthesia can effectively inhibit the stimulation of pain and the conduction to the center. The combination of the two can produce better postoperative analgesic and sedative effects, thus reducing the occurrence of stress response during the awakening of lung cancer patients. The mechanism may be related to the synergistic effect of the combined application of two anesthetic drugs. Studies have shown that surgery can remove the primary and metastatic lesions of lung cancer patients and lay the foundation for subsequent treatment. However, due to the effects of anesthesia and analgesia, numerous patients will experience severe cognitive impairment and agitation during the recovery from anesthesia (Tian et al., 2017; Huang et al., 2018). The results of this study showed that the MMSE scores of the two groups of patients on the 1 d and 3 d after operation were remarkably lower than those before operation, and the MMSE scores of the patients in the intervention group on the 1 d and 3 d after operation were remarkably better than those in the control group. This indicates that thoracic epidural anesthesia combined with intravenous anesthesia can effectively reduce the incidence of postoperative cognitive impairment.

miRNA distortion contributes to the canceration of diseases, which also shows that miR-19b-3p can be used as a circulating immune biomarker for non-small cell lung cancer, and has higher sensitivity and specificity (Su et al., 2018). This study showed that miR-19b-3p increased in serum of lung cancer patients, while it in intervention group was significantly lower than that in control group after operation. This indicates that thoracic epidural anesthesia combined with intravenous anesthesia can effectively reduce the expression of miR-19b-3p. Studies have shown that (Li et al., 2015) POCD is one of the most important complications of postoperative anesthesia, and age and intraoperative adverse reactions are revealed to be risk factors for POCD. According to Hou R et al., (Hou et al., 2018), different anesthesia methods may reduce the incidence of POCD for complete analgesia during surgery. In the end, we found through Cox regression analysis that age, high miR-19b-3p expression, intravenous anesthesia, awakening time, recovery time were all important related factors when POCD occurred.

Although this study confirmed that thoracic epidural anesthesia combined with intravenous anesthesia is more effective than intravenous anesthesia alone, there is still room for improvement. First, effects of miR-19b-3p expression on lung cancer patients can be added, and the relationship between miR-19b-3p and toxic and side effects during treatment can be observed. The results of this study need to be further supported.

In conclusion, thoracic epidural anesthesia combined with intravenous anesthesia has good curative effect and response in lung cancer resection patients. It can produce great sedative and analgesic effects, reduce the incidence of POCD, and decrease the expression of miR-19b-3p in serum of lung cancer patients.

References

Bulgakova O, Zhabayeva D, Kussainova A. (2018). miR-19 in blood plasma reflects lung cancer occurrence but is not specifically associated with radon exposure. Oncology Letters, 15(6): 8816.

Cao Q, Tian X, Dong C. (2019). Effects of different doses of cisatracurium besilate on hemodynamics and postoperative cognitive function in patients undergoing radical resection of lung cancer. Oncology Letters, 18(2): 1761.

Chai T, Lin Y, Shen Z. (2019). Comparison between video-assisted thoracoscopic lung cancer resection and robot-assisted lung cancer resection: Protocol for a systematic review and meta-analysis. Medicine, 98(11).

Do D H, Bradfield J, Ajijola O A. (2017). Thoracic Epidural Anesthesia Can Be Effective for the Short-Term Management of Ventricular Tachycardia Storm. Journal of the American Heart Association: Cardiovascular and Cerebrovascular Disease, 6(11).

Hao Z, Cai Y, Fu S. (2016). Comparison Study of Post-operative Pain and Short-term Quality of Life between Uniportal and Three Portal Video-assisted Thoracic Surgery for Radical Lung Cancer Resection. Zhongguo fei ai za zhi= Chinese journal of lung cancer, 19(3): 122.

Hong J M, Lee H J, Oh Y J. (2017). Observations on significant hemodynamic changes caused by a high concentration of epidurally administered ropivacaine: correlation and prediction study of stroke volume variation and central venous pressure in thoracic epidural anesthesia. BMC Anesthesiology, 17.

Hou R, Wang H, Chen L. (2018). POCD in patients receiving total knee replacement under deep vs light anesthesia: A randomized controlled trial. Brain and Behavior, 8(2).

Huang Z, Wang N, Suo L. (2018). Single or multiple encounters of general anaesthesia do not cause any cognitive dysfunction: Findings from a retrospective population-based, case-control study. Pakistan journal of pharmaceutical sciences, 31(4 (Supplementary)): 1571.

Li X, Li F, Liu Z. (2015). Investigation of one-lung ventilation postoperative cognitive dysfunction and regional cerebral oxygen saturation relations. Journal of Zhejiang University. Science. B, 16(12): 1042.

Li Y, Dong H, Tan S. (2019). Effects of thoracic epidural anesthesia/analgesia on the stress response, pain relief, hospital stay, and treatment costs of patients with esophageal carcinoma undergoing thoracic surgery: A single-center, randomized controlled trial. Medicine, 98(7).

Luo X, Zang X, Yang L. (2017). Comprehensive Computational Pathological Image Analysis

Predicts Lung Cancer Prognosis. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer, 12(3): 501

Mahajan A, Takamiya T, Benharash P. (2017). Effect of thoracic epidural anesthesia on heart rate variability in a porcine model. Physiological Reports, 5(7).

Sen Y, Xiyang H, Yu H. (2019). Effect of thoracic paraspinal block-propofol intravenous general anesthesia on VEGF and TGF-β in patients receiving radical resection of lung cancer. Medicine, 98(47): e18088.

Su J, Leng Q, Lin Y. (2018). Integrating Circulating Immunological and Sputum Biomarkers for the Early Detection of Lung Cancer. Biomarkers in Cancer, 10.

Tian H T, Duan X H, Yang Y F. (2017). Effects of propofol or sevoflurane anesthesia on the perioperative inflammatory response, pulmonary function and cognitive function in patients receiving lung cancer resection. European review for medical and pharmacological sciences, 21(23): 5515.

Torre 3rd P, Zeldow B, Yao T J. (2016). Newborn Hearing Screenings in Human Immunodeficiency Virus-Exposed Uninfected Infants. Journal of AIDS and immune research, 1(1).

Twardowski P, Owczuk R, Wujtewicz M A. (2014). The influence of epidural anesthesia on the electrical activity of heart atria. Kardiochirurgia i torakochirurgia polska= Polish journal of cardio-thoracic surgery, 11(2): 156.

Wang L, Yang G, Zhao D. (2019). CD103-positive CSC exosome promotes EMT of clear cell renal cell carcinoma: role of remote MiR-19b-3p. Molecular Cancer, 18.

Warner D O, Zaccariello M J, Katusic S K. (2018). Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: The MASK study. Anesthesiology, 129(1): 89.

Xu Q, Shi N J, Zhang H. (2017). Effects of combined general-epidural anesthesia and total intravenous anesthesia on cellular immunity and prognosis in patients with non-small cell lung cancer: A comparative study. Molecular Medicine Reports, 16(4): 4445.

Yamanashi K, Okumura N, Takahashi A. (2017). Surgical and survival outcomes of lung cancer patients with intratumoral lung abscesses. Journal of Cardiothoracic Surgery, 12.

Zhang Q, Wang W, Xu W. (2018). Genetic Variations in the 3'-untranslated Regions of Genes Involved in the Cell Cycle and Apoptosis Pathways Affect Bladder Cancer Risk. Cancer genomics & proteomics, 15(1): 67.

Zhao Z, Lv B, Zhao X. (2019). Effects of OPRM1 and ABCB1 gene polymorphisms on the analgesic effect and dose of sufentanil after thoracoscopic-assisted radical resection of lung cancer. Bioscience Reports, 39(1).

Zhou X, Wen W, Shan X. (2017). A six-microRNA panel in plasma was identified as a potential biomarker for lung adenocarcinoma diagnosis. Oncotarget, 8(4): 6513.

Zhu J, Xu Q, Zou R. (2019). Distal acupoint stimulation versus peri-incisional stimulation for postoperative pain in open abdominal surgery: a systematic review and implications for clinical practice. BMC Complementary and Alternative Medicine, 19.