The Potential Diagnostic Accuracy of Let-7 Family for Cancer: A Meta-Analysis

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Abstract

Background: Cancer is a global public health problem affecting human health. Early stage of cancer diagnosis, when it is not too large and has not spread is important for successful treatment. Many researchers have proposed that the let-7 microRNA family can be used as a biomarker for cancer diagnosis. The aim of this meta-analysis is to evaluate whether let-7 family can be used as a diagnostic tool for cancer patients. **Methods:** We conducted a comprehensive literature search on PubMed, EMBASE, Web of Science, Cochrane Library, Google Scholar, China National Knowledge Infrastructure (CNKI) and Wanfang database, updated to October 23, 2020. A random effects model was used to pool the sensitivity and specificity. Besides, we measured the diagnostic value using positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR) and area under the curve (AUC) were pooled. In addition, meta-regression and subgroup analysis were performed to explore the possible sources of heterogeneity, and Deeks' funnel chart was used to assess whether there was publication bias. **Results:** 31 studies from 15 articles were included in the current meta-analysis. The overall sensitivity, specificity, PLR, NLR, DOR and AUC were 0.80 (95% CI: 0.75-0.85), 0.81 (95% CI: 0.74-0.86), 4.2 (95% CI: 2.9-5.9), 0.24 (95% CI: 0.19-0.32), 17 (95% CI: 10-29) and 0.87 (95% CI: 0.84-0.90), respectively. Subgroup analysis shows that the let-7 family cluster of serum type showed a better diagnostic accuracy of cancer, especially the breast cancer. Although there is no publication bias, it still has some limitations. **Conclusions:** let-7 family can be considered as a promising non-invasive diagnostic biomarker for cancer.

Keywords

let-7 family, cancer, diagnosis, meta-analysis

Introduction

Cancer is a global public health problem threatening human health and survival. According to the latest data from the World Health Organization's Global Cancer Observatory, there were approximately 18.08 million new cancers worldwide in 2018.[1] Among all cancer types, the top ones with the highest annual incidence are lung cancer (11.6%) and breast cancer (11.6%), followed by colorectal cancer (10.2%), prostate cancer (7.1%) and gastric cancer (5.7%), and finally liver cancer (4.7%) and esophageal cancer (3.2%).[2] It is estimated that by 2030, the number of new cancer cases worldwide will reach 24.11 million, with most cases occurring in low and middle-income countries.[3] Cancer is the second leading cause of death in the world, causing 9.6 million deaths in 2018.[4] It is estimated that by 2030, the global number of cancer deaths will reach 13.03 million.[3] Approximately 70% of cancer deaths occur in low and middle-income countries.[4]

The impact of cancer on the family and society is huge, its early and accurate diagnosis is very important because it can lead to effective therapeutic intervention, reduce treatment costs, significantly improve prognosis and overall survival.[5] The current main strategy for cancer diagnosis is to extract solid tissue from the affected area for tissue biopsy, which is the gold standard for identifying tumor molecular properties, such as cancer type, gene and mutation expression and screening.[6] However, the tissues extraction process is invasive and complicated, which could cause discomfort, increases the pain, risk and the economic burden of patients. In addition, this

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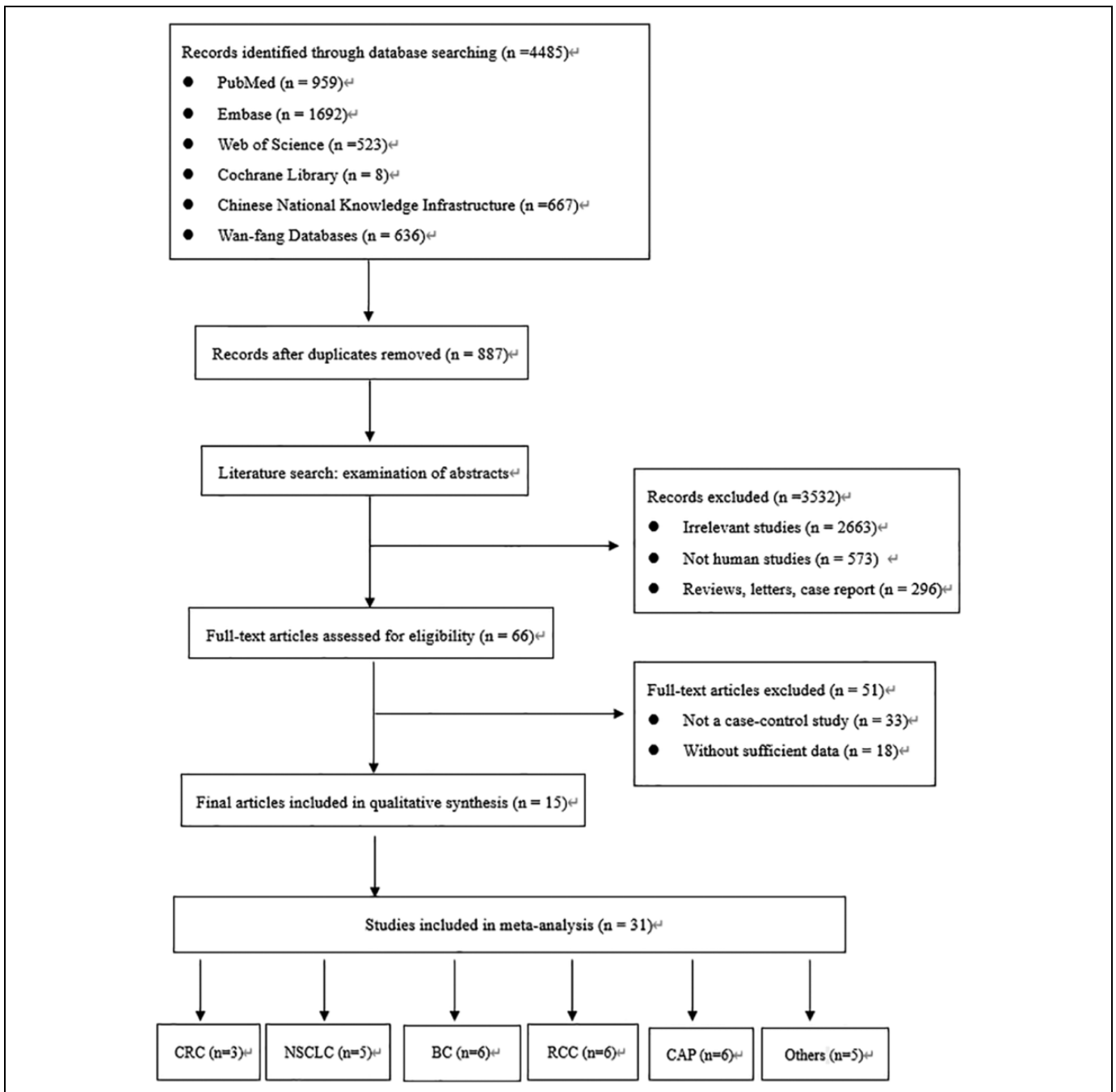Email: 631192403@qq.com

Figure 1. The flow chart of this meta-analysis to identify inclusion studies.

procedure has some clinical risks and the possibility of surgical complications. Moreover, some tumors are difficult to access in certain anatomical locations and are inaccessible for biopsy, and in some cases, extracting them may increase the risk of metastatic disease.[6] Imaging tests are also widely used (such as X-ray examinations and computed tomography), however excessive levels of radiation may bring health risks to patients. Non-radiation method, such as magnetic resonance imaging (MRI), is inconclusive and inefficient for minimum residual disease detection, and also provide limited information.[7] Although several potential cancer biomarkers have been discovered, such as carbohydrate antigen 19-9 (CA 19-9), prostate specific antigen (PSA) or carcinoembryonic antigen (CEA), some studies have shown that the above biomarkers showed a low sensitivity and specificity in the early diagnosis of certain cancers.[8] Therefore, finding a low-risk, high-precision and

Table 1. Characteristics of the Included Studies.

Author	Year	Country	microRNAs	Regulation mode	Case	No.	Control	No.	Specimen	Sen (%)	Spe (%)	AUC
Heneghan, H. M. [22]	2010	Ireland.	let-7a	Up	BC	83	Healthy	63	Plasma	0.78	1.00	0.92
Jeong, H. C. [15]	2011	Korea	let-7a	Down	NSCLC	35	Healthy	30	Plasma	0.90	0.90	0.95
Mahn, R. [23]	2011	Germany	let-7i	Up	CAP	35	BPH	7	Serum	0.83	0.86	0.91
Mahn, R. [23]	2011	Germany	let-7i	Up	CAP	37	BPH	18	Serum	0.81	0.61	0.70
Chen, Z. H. [24]	2012	China	let-7e	Down	CAP	80	Healthy	54	Plasma	0.78	0.75	0.80
Chen, Z. H. [24]	2012	China	let-7c	Down	CAP	80	Healthy	54	Plasma	0.69	0.70	0.78
Chen, Z. H. [24]	2012	China	let-7e	Down	CAP	80	BPH	44	Plasma	0.77	0.73	0.81
Chen, Z. H. [24]	2012	China	let-7c	Down	CAP	80	BPH	44	Plasma	0.75	0.71	0.78
Maclellan, S. A [25]	2012	Canada	let-7b	Up	OSCC	30	Healthy	26	Serum	0.81	0.80	0.82
Lee, CH. [17]	2013	China	let-7c	Down	BC	101	Healthy	15	Tissue	0.82	1.00	0.95
Zheng, H. [26]	2013	China	let-7f	Down	EOC	134	Healthy	70	Plasma	0.67	0.84	0.78
Liu, S. S. [27]	2014	China	let-7e	Up	RB	65	Healthy	65	Plasma	0.76	0.42	0.59
Fedorko, M. [18]	2017	Czech Republic	let-7g	Up	RCC	69	Healthy	36	Urine	0.70	0.60	0.69
Fedorko, M. [18]	2017	Czech Republic	let-7e	Up	RCC	69	Healthy	36	Urine	0.62	0.61	0.65
Fedorko, M. [18]	2017	Czech Republic	let-7d	Up	RCC	69	Healthy	36	Urine	0.66	0.61	0.66
Fedorko, M. [18]	2017	Czech Republic	let-7c	Up	RCC	69	Healthy	36	Urine	0.65	0.62	0.67
Fedorko, M. [18]	2017	Czech Republic	let-7b	Up	RCC	69	Healthy	36	Urine	0.73	0.67	0.75
Fedorko, M. [18]	2017	Czech Republic	let-7a	Up	RCC	69	Healthy	36	Urine	0.71	0.81	0.83
Huang, S. K. [28]	2018	China	let-7a	Down	BC	128	Healthy	77	Serum	0.98	0.39	0.68
Huang, S. K. [28]	2018	China	let-7a	Down	BC	30	Healthy	30	Serum	0.97	0.60	0.78
Gunel, T. [29]	2019	Turkey	let-7d-3p	Down	EOC	8	Healthy	8	Serum	0.60	0.61	0.70
Aly, D. M. [30]	2020	Egypt	let-7a-1	Down	HCC	40	LC	20	Serum	0.70	0.82	0.74
Chen, J. L. [16]	2020	China	let-7	Down	NSCLC	30	Healthy	30	EBC	0.67	0.77	0.75
Chen, J. L. [16]	2020	China	let-7	Down	NSCLC	30	Healthy	30	Serum	0.60	0.87	0.77
Chen, J. L. [16]	2020	China	let-7	Down	NSCLC	30	Healthy	30	Tissue	0.93	0.90	0.89
Noha G. [31]	2020	Egypt	let-7c	Up	CRC	84	Healthy	45	Serum	0.78	0.96	0.86
Jin, X. C. [32]	2017	China	let-7b-5p +l et-7e-5p + miR-24-5p + miR-21-5p	Up	NSCLC	47	Healthy	13	exosome	0.80	0.92	0.90
Huang, S. K. [28]	2018	China	let-7a + miR-155 + miR-574-5p + MALAT1	Up	BC	128	Healthy	77	Serum	0.99	0.90	0.97
Huang, S. K. [28]	2018	China	let-7a + miR-155 + miR-574-5p + MALAT1	Up	BC	30	Healthy	30	Serum	0.97	0.93	0.96
Noha G. [31]	2020	Egypt	let-7c + miR-146a + miR-21 + miR-26a	Up	CRC	84	Healthy	45	Serum	0.82	1.00	0.95
Noha G. [31]	2020	Egypt	let-7c + miR-146a	Up	CRC	84	Healthy	45	Serum	0.85	0.88	0.89

Abbreviations: CRC, colorectal cancer; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; LC, liver cirrhosis; EOC, epithelial ovarian cancer; BC, breast cancer; RCC, renal cell carcinoma; RB, retinoblastoma; OSCC, oral squamous cell carcinoma; CAP, prostate cancer; BPH, benign prostate hyperplasia; Up, up-regulated; Down, down-regulated; No., number; Sen, Sensitivity; Spe, Specificity; AUC, area under the curve; EBC, exhaled breath condensate; MALAT1, metastasis-associated lung adenocarcinoma transcript 1.

non-invasive biomarker to compensate for the shortcomings in the existing cancer detection methods are desperately needed.

Cancer is a genetic disease involving multi-step changes in the genome. The emergence of microRNA (miRNA) has attracted the attention of many experts because it is involved in key biological processes, including cell development, differentiation, apoptosis and proliferation.[9] MicroRNA is a group of small endogenous non-coding RNAs, 18-25 nucleotides in length, which perform key regulatory functions of gene expression by binding to target mRNA.[10] Moreover, miRNA may function as tumor suppressor or oncogene in tumor progression and metastasis.[11] In recent years, microRNA as a biomarker of cancer or tumor has been widely used in early diagnosis of disease, progress monitoring, prognostic evaluation and response to treatment,[12] because of its strong specificity, repeatability and accuracy.[13] More and more miRNAs have been discovered, among which the let-7 family is one of the most widely studied, which is considered as a biomarker, prognostic indicator and therapy for cancer precision medicine.[14] Subsequently, more and more studies have verified the possibility of let-7 family as

effective non-invasive biomarkers for cancer. Jeong *et al*[15] proposed that let-7a can be used as a high-efficiency biomarker for non-small cell lung cancer (NSCLC) with a sensitivity of 90% and a specificity of 90%. However, Chen *et al*[16] found that let-7 has low diagnostic efficiency for NSCLC with a sensitivity of 67% and a specificity of 77%. In addition, Lee *et al*[17] found that let-7c has a higher diagnostic value for breast cancer (BC), with a sensitivity of 82% and a specificity of 100%. Whereas Fedorko *et al*[18] got a result of 65% sensitivity and 62% specificity when let-7c was used for detection of renal cell carcinoma (RCC). The diagnostic efficacy of let-7 family for various cancers is satisfactory but inconsistent. The reason may be due to different test method standards, small number of clinical samples, and lack of multi-center data demonstration.[13] Therefore, we conducted this meta-analysis to evaluate whether let-7 family can be used as a diagnostic tool for cancer patients.

Materials and Methods

Search Strategy

We conducted a comprehensive search for related articles published up to October 23, 2020 in PubMed, EMBASE, Web of Science, Cochrane Library, Google Scholar, Wanfang Database and China National Knowledge Infrastructure (CNKI) according to the PRISMA statement.[19] Without language restrictions and limited to publications with human subjects, the medical subject headlines (MeSH) terms and keywords were used as follows: "let-7 microRNA" or "miR-let-7" or "let-7" or "hsa-let-7" and "cancer" or "cancers" or "neoplasm" or "neoplasms." In addition, in order to make article retrieval more comprehensive, we manually searched the reference list of related comments to obtain additional articles.

Inclusion and Exclusion Criteria

Two independent investigators screened literatures based on the inclusion criteria: (1) studies aim to evaluated the diagnostic capacity of let-7 family for cancers detection; (2) all cancer patients have been diagnosed through the gold standard test (namely by histopathology examinations); (3) all cancer patients have not received any treatment; (4) healthy people or benign hyperplasia were used as the control; (5) studies contained sufficient data on sensitivity, specificity and sample size to construct a diagnostic two-by-two table. In contrast, the exclusion criteria were: (1) duplicate reports or publications with incomplete information; (2) studies focused on survival or prognosis of cancers; (3) patients who have received treatment (surgery, chemotherapy, radiotherapy); (4) microRNA let-7 obtained from cell lines or animals and (5) comments, reviews, case reports, letters to the editors and systematic reviews or meta-analysis.

Data Extraction and Quality Assessment

The data of the included studies were extracted independently by 2 investigators, which included the first author's name,
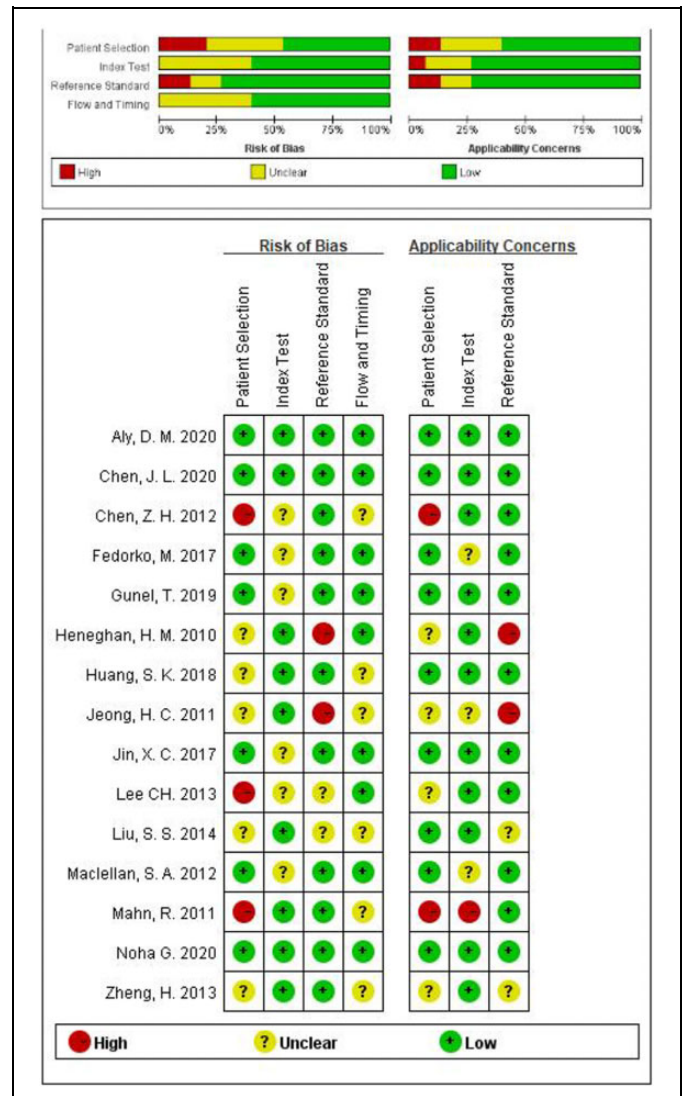

Figure 2. Quality evaluation according to the QUADAS-2 criteria.

publication year, country, let-7 family number, differentiated expression (up or downregulated), cancer types, sample size, specimen source, relevant statistical data required and methodological quality information. Two investigators independently assessed the quality of the included studies using the Quality Assessment for Diagnostic Accuracy Studies-2 (QUADAS-2) tool.[20] Any disagreements were resolved by a third investigator. The protocol for this systematic review was registered on INPLASY (202130013) and is available in full on the inplasy.com (https://doi.org/10.37766/inplasy2021.3.0013).

Statistical Analysis

All statistical analyses were performed using Review Manager 5.2 and STATA version 13.0. The number of true positives, false positives, false negatives, and true negatives in patients from each study was extracted to estimate the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and we generated the
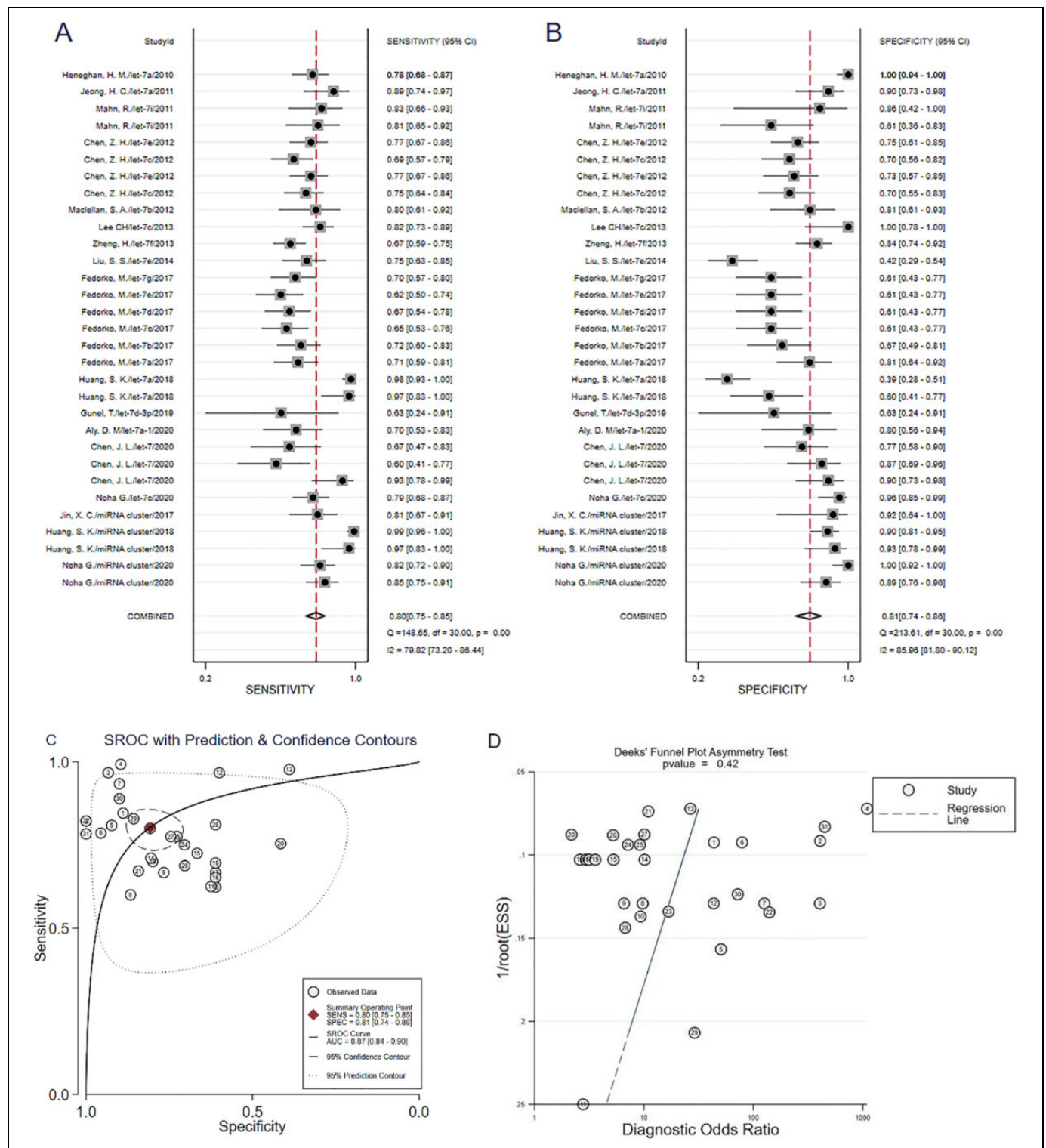
Figure 3. Forest plots of sensitivity (A), specificity (B), AUC (C), and funnel plot (D) of let-7 for diagnosing cancer patients.

summary receiver operating characteristics (SROC) curve and calculated the value of area under the curve (AUC). AUC were used to evaluate the diagnostic efficacy: AUC = 1.00 is perfect, AUC > 0.90 is excellent, AUC > 0.80 is good, AUC < 0.80 is

medium.[21] The heterogeneity was estimated based on I^2 statistic. It indicated significant heterogeneity if I^2 value is greater than 50%, and then a random effects model is performed. The potential sources of heterogeneity were explored by regression
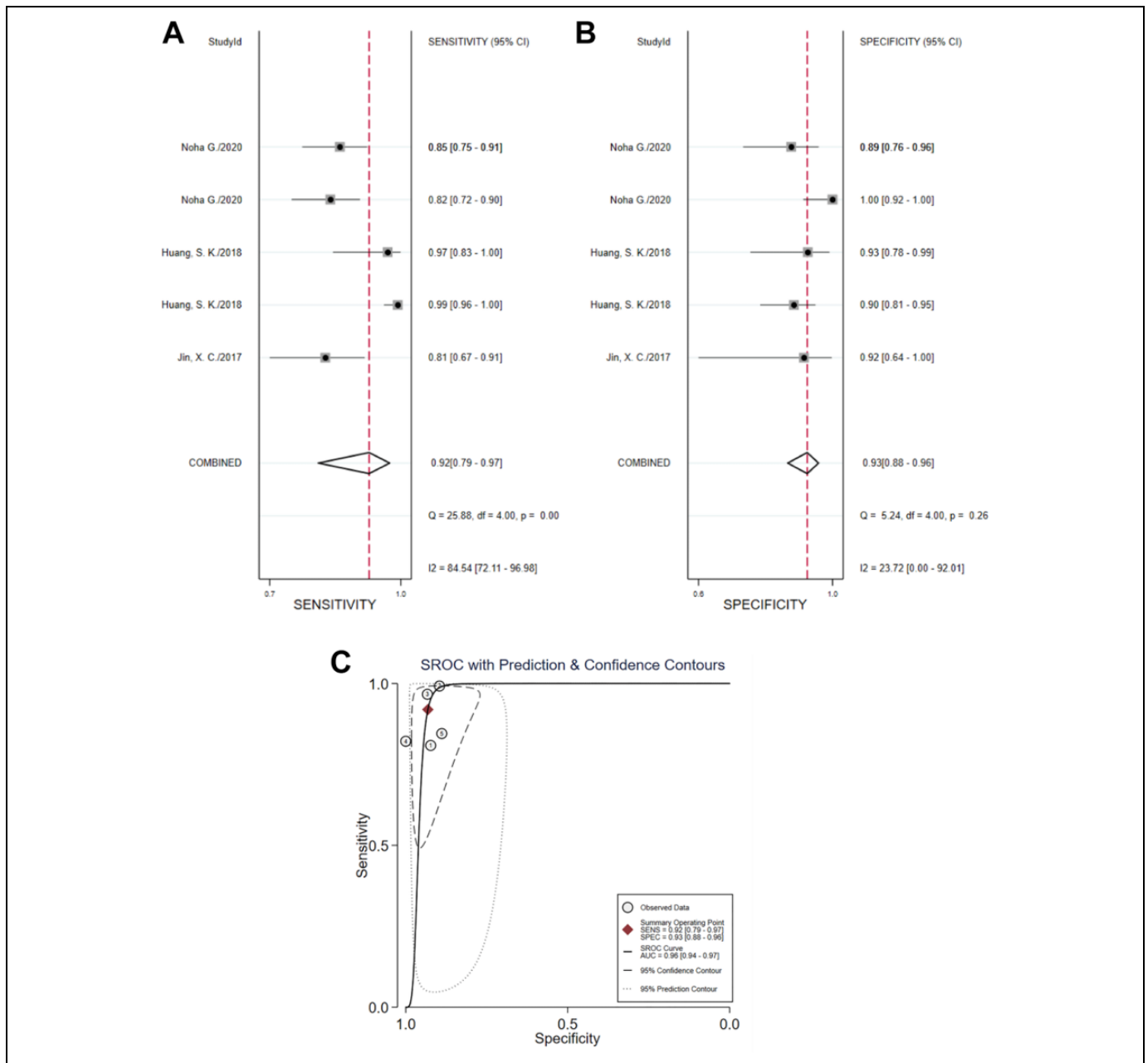
Figure 4. Forest plots of sensitivity (A), specificity (B), and AUC (C) of let-7 cluster for diagnosing cancer.

analysis and subgroup analysis. Finally, the publication bias was analyzed using the Deek's funnel plot, in which bias was considered to be significant if *P*-value was less than 0.05.

Results

Literature Screening

A total of 6645 articles were initially identified from PubMed, Embase, Web of Science, Cochrane Library, Google Scholar,

China National Knowledge Infrastructure (CNKI) and Wanfang database, and 2654 duplicate records were excluded. After reviewing titles and abstracts manually, 3898 studies were excluded because they were animal experiments or linear cell studies, irrelevant studies, review articles or letters. After reading the full text carefully, 78 articles were excluded due to no case-control studies or insufficient data. Finally, 31 studies from 15 articles were included in the current meta-analysis, of which, 3 colorectal cancer (CRC), 5 non-small cell lung cancer (NSCLC), 6 breast cancer (BC), 6 renal cell carcinoma

(RCC), 6 prostate cancer (CAP), 1 hepatocellular carcinoma (HCC), 2 epithelial ovarian cancer (EOC), 1 retinoblastoma (RB), and 1 oral squamous cell carcinoma (OSCC). The literature screening flowchart is shown in Figure 1.

Study Characteristics and Quality Assessments

The basic characteristics of 31 studies included are shown in Table 1, in order of publication year, from 2010 to 2020. In total included 2008 cancer patients and 1187 controls. The cancer types included colorectal cancer, non-small cell lung cancer, breast cancer, renal cell carcinoma, prostate cancer, hepatocellular carcinoma, epithelial ovarian cancer, retinoblastoma, and oral squamous cell carcinoma. A total of 26 miRNA studies involved a single miRNA, and 5 studies focused on miRNA cluster. Quantitative real-time reverse transcription PCR (qRT-PCR) was used to measure the expression of let-7 family in cancer patients. The study population came from China, Korea, Ireland, Germany, the Czech Republic, Turkey, Egypt and Canada, with Asian and European races predominantly. The methodological quality assessment graph shown in Figure 2.

Diagnostic Accuracy of Let-7 Family for Cancer

According to the heterogeneity analysis, the sensitivity and specificity of let-7 family in screening various cancers have I^2 values of 79.82% and 85.96%, indicating that statistical heterogeneity existed between studies, so a random effects model was used in our meta-analysis. The pooled sensitivity was 0.80 (95% CI: 0.75-0.85), specificity was 0.81 (95% CI: 0.74-0.86), PLR was 4.2 (95% CI: 2.9-5.9), NLR was 0.24 (95% CI: 0.19-0.32) and DOR was 17 (95% CI: 10-29) (Figure 3A and B). We also draw the ROC curve and calculate the AUC value to further explore the predictive ability. The AUC value was 0.87 (95% CI: 0.84-0.90), which indicated that let-7 has good diagnostic accuracy for cancer and can distinguish cancer patients from control groups (Figure 3C).

Diagnostic Value of Let-7 Family Cluster for Cancer

There were 5 studies focused on let-7 family cluster. The pooled sensitivity was 0.92 (95% CI: 0.79-0.97), specificity was 0.93 (95% CI: 0.88-0.96), PLR was 13.5 (95% CI: 7.7-23.7), NLR was 0.17 (95% CI: 0.03-0.24), DOR was 156 (95% CI: 54-455), and AUC was 0.97 (95% CI: 0.96-0.98) (Figure 4). The results showed that let-7 family cluster has excellent diagnostic accuracy in the diagnosis of cancer.

Meta-Regression Analysis and Subgroup Analysis

In order to explore the potential sources of between-study heterogeneity in sensitivity and specificity, we conducted a meta-regression analysis. As shown in Figure 5, the results of meta-regression analysis indicated that the country, regulation mode and sample size contributed to the main source of heterogeneity in sensitivity ($P < 0.01$), regulation mode and sample size might explain heterogeneity in specificity ($P < 0.05$).
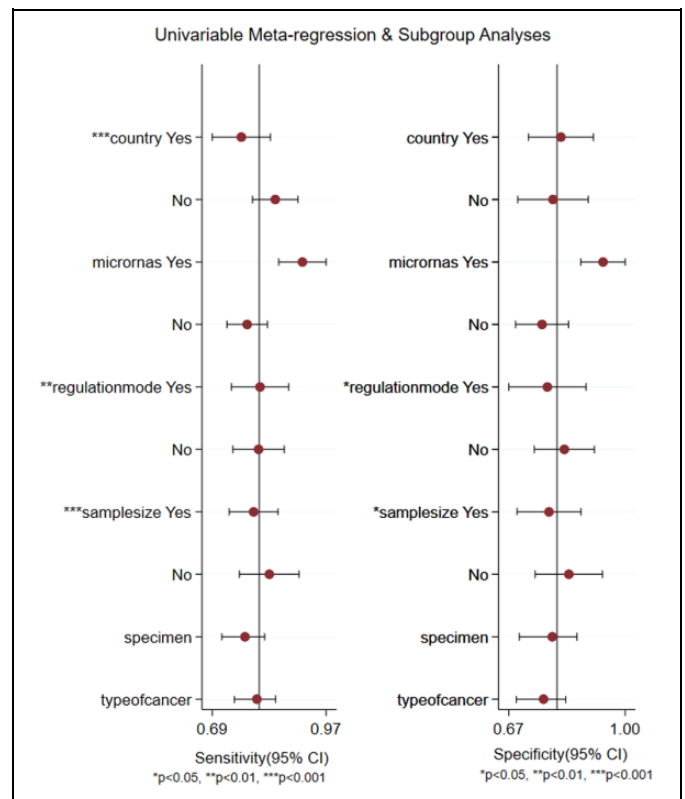

Figure 5. Forest plots of multivariable meta-regression for sensitivity and specificity.

Subsequently, we conducted a subgroup analysis to find probable sources of heterogeneity, which included the country, miRNA profiling, regulation mode, sample size, specimen types, and types of cancer. We found that the let-7 miRNA cluster showed a better diagnostic accuracy than single ones, with a sensitivity (0.92 vs. 0.77), specificity (0.93 vs. 0.77), PLR (13.5 vs. 3.3), NLR (0.09 vs. 0.30), DOR (156 vs. 11), and AUC (0.96 vs. 0.83). Moreover, the diagnostic accuracy of let-7 family for breast cancer is much higher than other cancers (such as colorectal cancer, non-small cell lung cancer, renal cell carcinoma, and prostate cancer), with a sensitivity, specificity, PLR, NLR, DOR, AUC being 0.95, 0.86, 6.8, 0.06, 115, 0.96, respectively. In addition, serum types had a higher diagnostic value than plasma types: sensitivity (0.88 vs. 0.75), specificity (0.80 vs. 0.81), PLR (4.4 vs. 3.9), NLR (0.16 vs. 0.31), DOR (28 vs. 12) and AUC (0.91 vs. 0.78). Finally, studies of let-7 yield a better diagnosis accuracy in the Asian race populations than other populations. The regulation mode and sample size had no influence on the diagnosis. The results of all subgroup analysis in detail were summarized in Table 2.

Publication Bias

Deeks' funnel plot test assessed the potential publication bias in this meta-analysis. As demonstrated in Figure 3D, the pooled Deeks' test result of the overall study was $P = 0.42$, which suggested no significant publication bias among those studies.

Table 2. Summary Estimates of Diagnostic Power and Their 95% Confidence Intervals.

Subgroup	Se (95% CI)	Sp (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	AUC (95% CI)
Country						
Asian	0.85 [0.76-0.92]	0.79 [0.69-0.87]	4.1 [2.6-6.5]	0.18 [0.11-0.31]	23 [10-51]	0.89 [0.86-0.92]
Non-Asian	0.75 [0.71-0.83]	0.82 [0.71-0.90]	4.3 [2.4-7.4]	0.31 [0.24-0.39]	14 [6-30]	0.80 [0.76-0.83]
miRNA profiling						
Single miRNA	0.77 [0.72-0.81]	0.77 [0.69-0.83]	3.3 [2.4-4.5]	0.30 [0.24-0.37]	11 [7-17]	0.83 [0.80-0.86]
miRNA clusters	0.92 [0.79-0.97]	0.93 [0.88-0.96]	13.5 [7.7-23.7]	0.09 [0.03-0.24]	156 [54-455]	0.96 [0.94-0.97]
Regulation mode						
Up- regulated	0.80 [0.73-0.85]	0.84 [0.71-0.91]	4.9 [2.6-9.3]	0.24 [0.17-0.34]	21 [8-51]	0.87 [0.84-0.90]
Down-regulated	0.81 [0.72-0.87]	0.76 [0.68-0.83]	3.4 [2.6-4.5]	0.25 [0.18-0.36]	13 [8-21]	0.85 [0.82-0.88]
Sample size						
<100	0.82 [0.74-0.88]	0.83 [0.75-0.90]	5.0 [3.2-7.8]	0.21 [0.14-0.32]	23 [11-50]	0.90 [0.87-0.92]
≥100	0.79 [0.72-0.84]	0.79 [0.67-0.88]	3.9 [2.3-6.5]	0.26 [0.19-0.37]	15 [7-31]	0.86 [0.82-0.88]
Specimen type						
Serum	0.88 [0.78-0.93]	0.80 [0.61-0.91]	4.4 [2.1-9.1]	0.16 [0.09-0.28]	28 [10-81]	0.91 [0.88-0.93]
Plasma	0.75 [0.70-0.79]	0.81 [0.63-0.91]	3.9 [1.9-8.0]	0.31 [0.24-0.41]	12 [5-32]	0.78 [0.74-0.81]
Types of cancer						
CRC	0.82 [0.76-0.86]	0.96 [0.66-1.00]	21.7 [1.8-255.0]	0.19 [0.15-0.25]	114 [9-1439]	0.83 [0.80-0.86]
NSCLC	0.80 [0.66-0.89]	0.71 [0.25-0.95]	2.8 [0.7-11.7]	0.18 [0.12-0.64]	10 [1-86]	0.83 [0.79-0.86]
BC	0.95 [0.85-0.98]	0.86 [0.08-1.00]	6.8 [0.2-254.4]	0.06 [0.03-0.12]	115 [4-3493]	0.96 [0.94-0.98]
RCC	0.68 [0.63-0.72]	0.65 [0.59-0.71]	2.0 [1.6-2.4]	0.49 [0.41-0.58]	4 [3-6]	0.72 [0.68-0.75]
CAP	0.76 [0.72-0.80]	0.72 [0.65-0.77]	2.7 [2.2-3.3]	0.33 [0.28-0.41]	8 [6-12]	0.80 [0.77-0.84]

Abbreviations: Se, sensitivity; Sp specificity; PLR, positive likelihood ratios; NLR, negative likelihood ratios; DOR, diagnostic odds ratio; AUC, area under the curve; CI, confidence interval; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; BC, breast cancer; RCC, renal cell carcinoma; CAP, prostate cancer.

Discussion

With the development of society, tumors have become one of the serious diseases threatening human health. Cancer that is diagnosed at an early stage, when it is not too large and has not spread widely, is more likely to be treated, thus making early diagnosis important. The current gold standard for cancer diagnosis is histopathological biopsy, which cannot be accepted by all patients due to its invasive process and possible risks. Many scholars have proposed that the let-7 family of miRNAs can be used as novel non-invasive biomarkers, which brings hope for cancer diagnosis. In mammals, let-7 is known as the maintainer of differentiation, and its abnormal regulation and expression are related to the occurrence and development of cancer.[14] The human genome contains 13 let-7 family members, which encode 9 mature miRNAs, due to sequence similarity, it is generally considered that the functions of all members overlap.[33] The let-7 family plays a complex regulatory function in many diseases. In addition to being a diagnostic marker for cancer, it is more likely to be a screening factor or a prognostic evaluation indicator. Let-7 is still a promising cancer treatment, and tumor let-7 levels can be used to choose the best treatment for everyone.[14] Many scholars have conducted research on

whether let-7 family can be used as a cancer diagnostic biomarker, the results are generally satisfactory, but inconsistent. Therefore, we conducted this meta-analysis to evaluate the potential diagnostic accuracy of let-7 family for early diagnosis of cancer.

We searched multiple databases and finally included 31 studies on the value of let-7 family for cancer diagnosis. The overall pooled sensitivity, specificity, PLR, NLR and DOR were 0.80 (95% CI: 0.75-0.85), 0.81 (95% CI: 0.74-0.86), 4.2 (95% CI: 2.9-5.9), 0.24 (95% CI: 0.19-0.32) and 17 (95% CI: 10-29), respectively. We also drew the ROC curve and calculate the corresponding AUC to evaluated the overall diagnostic accuracy. The AUC value was 0.87, which meaning that let-7 has good diagnostic accuracy for cancer.[21]

Subsequently, we conducted regression analysis and subgroup analysis to explore possible sources of heterogeneity, according to country, miRNA profiling, regulation mode, sample size, specimen types, and types of cancer. We found that let-7 miRNA clusters show better diagnostic accuracy than single one in the early diagnosis of cancer. The miRNA cluster has a complex molecular mechanism, which participates in the occurrence and development of tumors from multiple pathways, and finally forms a stable and reliable network diagnostic

structure.[13] However, a single miRNA has poor specificity and is not only expressed in cancer, but also differentially expressed in other diseases.[12] In addition, the diagnostic accuracy of let-7 family for breast cancer is much higher than other cancers, with a sensitivity of 95%, a specificity of 86%, and an AUC value of 0.96. Breast cancer is the most frequently diagnosed cancer and remains one of the main reasons of cancer-related mortality in women worldwide.[34] At present, let-7 family has been proved to be involved in involved in mammary gland development, proliferation, creation and metastasis of breast cancer.[35] Besides, previous studies believe that plasma retains more proteins to isolate miRNA together,[36] so it has a higher diagnostic value, this is inconsistent with our research results. We found that serum types have a higher diagnostic value in cancer than plasma types. Therefore, multi-sample, multi-center research results are needed to verify our findings. Finally, the regulation mode and sample size had no influence on the diagnosis.

This is a comprehensive meta-analysis on the evaluation of the diagnostic accuracy of let-7 family for cancer, which contains the latest published research. We set up strict inclusion and exclusion criteria, and 2 researchers independently screened the studies that met the criteria. We make every effort to avoid publication bias, but we acknowledge that this meta-analysis still has some limitations. First, although we have adopted a comprehensive literature search strategy, some valuable research may be lost. Secondly, there are some deviations in the selection of the control group. Most control groups are healthy people, and only 5 control groups are in a benign state of disease. Therefore, we should expand the scope of let-7 clinical research. Third, the number of samples in some studies is small, so in the subgroup analysis, some cancer clinical data are relatively small without subgroup analysis, which may limit the strength of our conclusions. Finally, we did not extract the cut-of value, which may lead to inconsistent conclusions.

Conclusion

In summary, our current meta-analysis results indicate the let-7 family can be considered as a promising non-invasive diagnostic biomarker for cancer. Especially, the Let-7 family has high sensitivity and specificity in breast cancer diagnosis. In addition, the use of let-7 miRNA clusters and serum specimens can improve diagnostic accuracy. This result is encouraging and exciting. In the future, large-scale multi-center clinical studies are still needed to verify our conclusions, so as to provide new ideas for early diagnosis of cancer patients.

Abbreviations

AUC, Area under the curve; BC, Breast cancer; BPH, Benign prostate hyperplasia; CA 19-9, Carbohydrate antigen 19-9; CAP, Prostate cancer; CEA, Carcinoembryonic antigen; CI, confidence interval; CNKI, China National Knowledge Infrastructure; CRC, Colorectal cancer; DOR, Diagnostic odds ratio; EBC, Exhaled breath condensate; EOC, Epithelial ovarian cancer; HCC, Hepatocellular carcinoma; MALAT1, Metastasis-associated lung adenocarcinoma transcript 1;

MeSH, medical subject headlines; miRNA, microRNA; MRI, Magnetic resonance imaging; NLR, Negative likelihood ratio; NSCLC, Non-small cell lung cancer; OSCC, Oral squamous cell carcinoma; PLR, Positive likelihood ratio; PSA, Prostate specific antigen; qRT-PCR, Quantitative reverse transcription PCR; QUADAS-2, Quality Assessment of Diagnostic Accuracy Study 2; RB, Retinoblastoma; RCC, Renal cell carcinoma; SE, Sensitivity; SP, Specificity.

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