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The role of circular RNAs (circRNAs) as a prognostic factor in lung cancer: a meta-analysis

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Abstract

Background Lung cancer is a leading cause of cancer-related death worldwide. Among various histological types of lung cancer, majority are non-small cell lung cancer (NSCLC) which account for > 80%. Circular RNAs (circRNAs) are widely expressed in various cancers including lung cancer and implicated in tumourigenesis and cancer progression. This study aimed to systematically evaluate the prognostic values of circRNAs in lung cancer.

Methods A systematic literature search was done in PubMed, Embase, and MEDLINE databases to select the eligible studies which reported the association between the expression of circRNAs and overall survival (OS) or disease-free survival (DFS) in histopathologically diagnosed lung cancer patients. The pooled hazard ratio (HR) and 95% confidence interval (CI) were assessed to determine the prognostic significance of circRNAs.

Results A total of 43 studies were eligible for this meta-analysis (MA). 39 different types of circRNAs were reported: 28 showing upregulating and 11 showing downregulating action in lung cancer. High expression of circRNAs with upregulating action in lung cancer was associated with worse prognosis and poor OS (HR 1.93, 95% CI [1.61–2.33], $p < 0.00001$). High expression of circRNAs with downregulating action in lung cancer was associated with favorable OS and prognosis (HR 0.73, 95% CI [0.58–0.94], $p = 0.01$). However, there was no statistically significant association between high and low expression of both upregulating and downregulating circRNAs and DFS (HR 1.44, 95% CI [0.92–2.24], $p = 0.11$).

Conclusions This MA confirmed the pivotal role of circRNAs as important prognostic biomarkers for lung cancer, especially NSCLC. High expression of upregulating circRNAs is associated with poor prognosis; however, high expression of downregulating circRNAs is associated with favorable prognosis. Therefore, downregulatory action of circRNAs should be considered a promising treatment in the management of lung cancer, especially NSCLC.

Keywords Circular RNA, Non-small cell lung cancer, Survival, Prognosis, Meta-analysis

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Introduction

Lung cancer is a leading cause of cancer-related death in both men and women [1]. >80% of lung cancers are non-small cell lung cancer (NSCLC) and only 13% are small cell lung cancer (SCLC) [2]. Generally, the prognosis of lung cancer especially NSCLC is mainly based on the tumor-node-metastasis (TNM) staging [2], histopathological types [2], and predictive biomarker analyses, such as epidermal growth factor (EGFR) mutation [3], anaplastic lymphoma kinase (ALK) translocations [4] and *BRAF* mutation [5]. However, the prognosis varies significantly even among the patients with the same TNM staging, histomorphological characteristics, and mutation status [6].

In cancer management, diagnostic and prognostic biomarkers with high sensitivity and specificity play a crucial role in preventing or treating cancer. Circular RNAs (circRNAs) which are abundant in serum, plasma, and other body fluids with stable property and high specificity has been described as molecular marker in the initiation and development of cancer [7, 8].

In recent years, circRNAs have been recognized as a new sensitive, non-invasive biomarker for diagnosis, prognosis and even prediction to therapeutic responses in many types of cancer including lung cancer [9]. Few meta-analyses (MAs) were done to assess the role of circRNAs in lung cancer. However, they were only focused on NSCLC and not on different histopathological types of lung cancer [10, 11]. Therefore, we aimed to conduct this updated MA which includes the latest primary studies to synthesize the evidence on the role of circRNAs as a prognostic factor in all histopathological types of lung cancer.

Materials and methods

The systematic review (SR) and MA were done according to the updated guideline of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement [12].

Identification of eligible studies

The systematic literature search was carried out in health-related electronic databases such as PubMed, Embase and MEDLINE. The search terms used were "circular RNAs/circRNAs, lung cancer, non-small cell lung cancer, small cell lung cancer and prognosis". The search was limited to original articles published in the English language up to July 2023. To find additional studies, reference lists of the original articles were also screened.

Inclusion and exclusion criteria

Studies selection was based on criteria of PICOTS format: (1) Participants (P): All patients who have been histopathologically diagnosed with non-small cell and small cell lung cancer; (2) Index prognostic factor (I): circRNAs; (3) Comparisons (C): Not applicable to this review; (4) Outcomes (O): Outcomes were overall survival (OS) which is defined as the length of time that patients remained alive after diagnosis of cancer; and disease progression-free survival (DFS) which is defined as the length of time that patients remained disease-free/cancer-free; (5) Setting (S): Hospital/Pathology laboratory [13]. Review articles, case reports, editorials, letters, commentaries, and articles in non-English languages were excluded from this MA.

Literature search and study selection

Two researchers (TTW, SA) conducted an independent literature search in healthcare electronic databases (PubMed, Embase and MEDLINE). Any disagreements between both researchers were initially discussed between two researchers. If an agreement was not reached, two researchers discussed with a third researcher (SNA) to finalize. The articles were screened according to the PRISMA flowchart as displayed in Fig. 1. The articles that did not fit the inclusion criteria based on abstract and title alone were excluded. Finally, full-text articles were examined to obtain the included studies required for MA.

Assessment of study quality

The quality of eligible studies was assessed by the Newcastle-Ottawa Quality Assessment Scale (NOS) [14]. Studies were assessed using three categories, selection of study groups (0–4 points), comparability (0–2 points), and exposure (0–3 points). A total score ≤ of 3 was considered low quality, scores between 4 and 6 were moderate quality and scores ≥ 7 were high quality. These scores were used only to facilitate the interpretation of the MA results, but not used as a criterion for inclusion or exclusion of the studies. During these processes, any discrepancy or disagreement was resolved by discussion among authors to arrive at a consensus.

Data extraction

Two researchers (TTW, SA) independently extracted the relevant data from the included studies using a piloted data extraction sheet. Discrepancies were discussed thoroughly and finalized with a third researcher (SNA). The data that were extracted included study title, first author with year of publication, country of publication, histopathological type of lung cancer, type of circRNA, OS and DFS with hazard ratio (HR), [95% confidence interval (CI)], and p-value.

Statistical analysis

The outcome analyses of OS and PFS were estimated as HR for the prognostic value of circRNAs in patients with

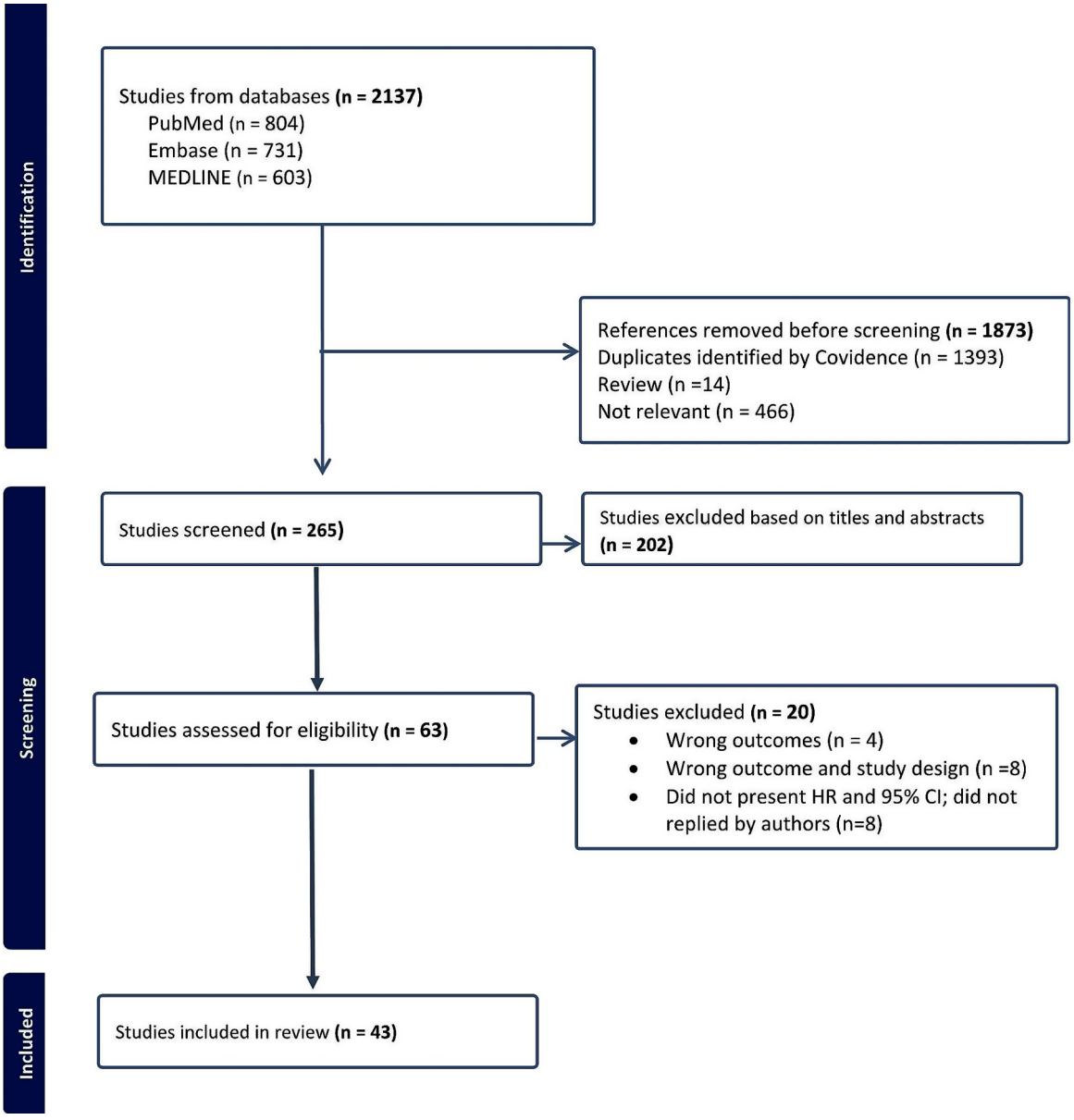

Fig. 1 PRISMA flowchart summarizing the process to identify the eligible studies

lung cancers. From the statistical analysis, heterogeneities were assessed using I^2 statistics. To avoid heterogeneity, if the I^2 statistic is more than 50%, a random effects model was used; and if the I^2 statistic is less than 50%, a fixed effect model was used. A two-tailed p-value of less than 0.05 was considered statistically significant. The corresponding 95% CI was used to quantify the precision of the estimated HR. MA was performed with Review Manager (RevMan 5.4) software.

Results

Literature search results

A total of 2137 potential studies were identified using the preliminary search strategy; 804 were from PubMed, 731 were from EMBASE, and 603 were from MEDLINE. A total of 1873 studies which included duplicates, review articles and irrelevant studies were removed in the screening stage. Based on the title and abstracts, 202 studies were removed. After that, the full texts of 63 studies were reviewed. 20 studies were excluded due to wrong outcomes, wrong study design, or no reported HR and 95% CI. Finally, 43 studies were included for SR and MA. A three-phase flow chart of the study selection process based on the updated PRISMA statement 2020 is illustrated in Fig. 1.

Characteristics of the included studies

The characteristics of the 43 included studies are shown in Table 1. All the included studies were carried out in China. There were 39 different types of circRNAs. Among them, Cirs-7 was reported by 3 studies [34, 39, 41], Circ_0020123 was reported by 2 studies [33, 35] and Circ_0067934 was reported by 2 studies [36, 46]. 28 different types of cirRNAs (Circ_0003645, CircUSP7, Circ_001569, Circ_0128332, Circ_0074027, Circ-BANP, Circ-RAD23B, CircATXN7, CircRARS, Circ_000984, Circ_0016760, Circ-FOXM1, CircRNA_103809, Circ-SWT1, Circ_0001715, Circ_0007534, CircPVT1, CircPRKCI, Circ_0020123, CiRS-7, Circ_0067934, CircVANGL1, Circ-PRMT5, Circ_0001946, Circ_0023179, Circ_101237, CircFADS2 and Circ_102231) showed upregulating action in the lung cancer and 11 different types of circRNAs (Circ_100395, Circ_0065214, CESRP1, Circ-ITCH, Circ_0001649, Circ_11780, Circ-SMARCA5, CircCRIM1, Circ_0046264, Circ_0006427 and Circ_007230) showed downregulating action in the lung cancer. 32 studies [15–44] reported that high expression of circRNAs was associated with unfavorable prognosis and facilitated the tumour progression (upregulation). The remaining 11 studies [47–57] reported that high expression of circRNAs was associated with favorable prognosis by inhibiting tumour progression (downregulation) in lung cancer. Among 43 studies, a majority of the studies reported on NSCLC; 32 studies [15–17, 19, 21–28, 30, 31, 33–36, 38, 39, 41–44, 46–48, 50–53, 57] on NSCLC, 2 studies [20, 55] on just lung cancer without specific histopathological types, 8 studies on adenocarcinoma [18, 29, 32, 37, 40, 45, 54, 56], and only one study on SCLC [49]. All 43 studies reported OS with HR and 95% CI. Only 5 studies [24, 28, 39, 43, 53] reported DFS with HR and 95% CI.

Methodological quality of the included studies and publication bias

Based on the NOS assessment of the methodological quality of the included studies, the scores of all 43 included studies ranged from 6 to 9. Therefore, all included studies in this MA showed high quality. Publication bias was assessed for all included studies. Funnel plots of Begg's and Egger's tests for the publication bias of upregulated and downregulated circRNAs are shown in Figures S1 and S2.

Prognostic value of circRNAs on OS and DFS in lung cancers

As 32 studies [15–46] reported circRNAs that were upregulating in lung cancer and only 11 studies [47–57] reported circRNAs that were downregulating in lung cancer, we meta-analyzed these two groups of circRNAs separately. MA of upregulating circRNAs showed a favorable OS with low expression compared to high expression (HR 1.93, 95% CI [1.61–2.33], $p<0.00001$); and heterogeneity I^2 was 76% (Fig. 2). MA of downregulating circRNAs showed a favorable OS with high expression compared to low expression (HR 0.73, 95% CI [0.58–0.94], $p=0.01$); and heterogeneity I^2 was 54% (Fig. 3).

As only 4 studies [24, 28, 39, 43] reported DFS in association with expression of upregulating and only one study [53] reported downregulating cirRNAs respectively, MA was done all together for those 5 studies. There was no significant association between DFS and expression of circRNAs (HR 1.44, 95% CI [0.92–2.24], $p=0.11$); heterogeneity I^2 was 90% (Fig. 4).

Discussion

CircRNAs are known to have a diverse array of functions. They act as miRNA sponges, interact with RNA-binding proteins (RBPs), regulate alternative splicing and transcription, facilitate translation, generate pseudogenes, transport molecules, and mediate cell-to-cell communication [58, 59]. Characterized by their unique covalently closed loop structures, circRNAs are involved in the regulation of gene expression and are emerging as key players in the oncogenic process [60]. They have also emerged as a large class of primarily non-coding RNA molecules, many of which have key roles in cancer development and progression through diverse mechanisms of action [61]. Thus, they were reported as promising biomarkers for cancer diagnosis and prognostication as well as for early cancer detection and therapeutic targets or agents to inhibit oncogenic microRNAs or proteins [59, 62]. In recent years, an increasing number of studies have shown that some circRNAs have a significant association with the prognosis and progression of cancer; and they are aberrantly expressed in lung cancer, especially NSCLC [63, 64]. In the oncogenic process of NSCLC, circRNAs contribute to cancer proliferation and invasion by sponging specific miRNAs, impacting crucial oncogenic pathways [63, 65].

Upregulating circRNAs play roles in proliferation, migration, invasion, apoptosis, cell cycle, stemness of lung cancer stem cells, chemotherapy resistance, tumor metabolism, tumor microenvironment (TME), and immune evasion of lung cancer cells [66]. Most of the upregulating circRNAs promoted the activation of nuclear factor kappa-B (NF-kB) regulatory signaling, epidermal growth factor receptor (EGFR), cyclin E1 (CCNE1) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (PIK3CD); and thus, exerted remarkable effects through sponging miR-7 [34, 39, 41]. Therefore, cancers that highly express those upregulating circRNAs are associated with a poor

Table 1 Characteristics of the included studies

No	Author, Year [Reference]	Country	Histological type	High/Low expression	Type of CircRNA	OS (HR [95% CI], *p* value)	DFS (HR [95% CI], *p* value)	Action of CircRNA to lung cancer	NOS
1	An, 2019 [15]	China	NSCLC	32/27	Circ_0003645	2.486 (1.354 to 4.566)	-	Upregulated	8
2	Chen, 2021 [16]	China	NSCLC	63/63	CircUSP7	3.090(1.552–6.151)0.037	-	upregulated	7
3	Ding, 2018 [17]	China	NSCLC	29/27	Circ_001569	HR:2.02, p: 0.001	-	upregulated	6
4	Du, 2019 [18]	China	LAC	29/29	Circ_0128332	3.941 (2.124–7.864)0.007	-	upregulated	7
5	Gao, 2020 [19]	China	NSCLC	26/26	Circ_0074027	2.248 (1.053 to 4.799)	-	upregulated	7
6	Han, 2018 [20]	China	LC	28/31	Circ-BANP	2.740 (1.740 to 6.620)	-	upregulated	7
7	Han, 2019 [21]	China	NSCLC	20/20	Circ-RAD23B	1.900 (0.900 to 4.020)	-	upregulated	8
8	Huang, 2019 [22]	China	NSCLC	45/12	CircATXN7	0.540 (0.120 to 2.320)	-	upregulated	6
9	Li, 2023 [23]	China	NSCLC	90/90	CircRARS (-0001551)	1.36(0.697–2.65)0.367	-	upregulated	8
10	Li, 2019 [24]	China	NSCLC	80/75	Circ_000984	2.985 (1.342 to 4.231)0.008	3.138 (1.224–4.427) 0.004	Upregulated	7
11	Li, 2018 [25]	China	NSCLC	45/38	Circ_0016760	1.910 (1.119 to 3.259)	-	upregulated	6
12	Liu, 2019 [26]	China	NSCLC	44/36	Circ-FOXM1	1.747 (1.014 to 3.009)	-	upregulated	7
13	Liu, 2018 [27]	China	NSCLC	22/22	CircRNA_103809	1.100 (0.320 to 3.760)	-	upregulated	7
14	Long, 2023 [28]	China	NSCLC	48/48	Circ_0004689 (CircSWT1)	2.104(1.154–3.836)0.015	1.776 (1.081–2.917) 0.023	Upregulated	8
15	Lu, 2020 [29]	China	LAC	NA	Circ_0001715	0.807(0.663–0.982)0.032	-	upregulated	7
16	Qi, 2018 [30]	China	NSCLC	56/42	Circ_0007534	1.969 (1.177 to 3.293)	-	upregulated	7
17	Qin, 2019 [31]	China	NSCLC	43/47	CircPVT1	1.830 (0.920 to 3.660)	-	upregulated	6
18	Qiu, 2018 [32]	China	LAC	55/34	CircPRKCI	2.664 (1.327 to 5.347)0.006	-	upregulated	7
19	Qu, 2018 [33]	China	NSCLC	40/40	Circ_0020123	2.120 (1.000 to 4.520)	-	upregulated	7
20	Su, 2018 [34]	China	NSCLC	77/51	CiRS-7	1.705 (1.020 to 2.860)	-	upregulated	7
21	Wan, 2019 [35]	China	NSCLC	28/27	Circ_0020123	2.061 (1.069 to 3.972)	-	upregulated	6
22	Wang, 2018 [36]	China	NSCLC	79/80	Circ_0067934	3.198 (1.293 to 5.673)	-	upregulated	7
23	Wang, 2019 [37]	China	LAC	49/46	CircVANGL1	1.680 (0.860 to 3.25)	-	upregulated	8
24	Wang, 2019 [38]	China	NSCLC	45/45	Circ-PRMT5	4.331 (1.896 to 9.774)	-	upregulated	6
25	Yan, 2018 [39]	china	NSCLC	NA	CiRS-7	1.575 (1.016 to 2.440) 0.042	1.774 (1.185–2.655) 0.005	upregulated	6
26	Yao, 2019 [40]	China	LAC	34/38	Circ_0001946	1.870 (1.070 to 3.260)	-	upregulated	8
27	Zhang, 2018 [41]	China	NSCLC	41/19	CiRS-7	6.132 (2.923 to 7.556)	-	upregulated	8
28	Zhang, 2023 [42]	China	NSCLC	63/63	Circ_0023179	0.53 (0.32–0.88)	-	upregulated	8
29	Zhang, 2020 [43]	China	NSCLC	153/150	Circ_101237	1.311(1.121–2.269)0.042	1.436(1.266–2.107) 0.046	upregulated	7
30	Zhao, 2018 [44]	China	NSCLC	22/21	CircFADS2	3.210 (1.250 to 7.730)	-	upregulated	7
31	Zong, 2018 [45]	China	LAC	29/28	Circ_102231	1.520 (0.760 to 3.050)	-	upregulated	8
32	Zou, 2018 [46]	China	NSCLC	41/38	Circ_0067934	2.133 (1.677 to 3.251)	-	upregulated	8
33	Chen, 2018 [47]	China	NSCLC	35/34	Circ_100395	0.560 (0.24 to 1.30)	-	down regulated	6
34	Chen, 2022 [48]	China	NSCLC	110/63	Circ_0065214	0.636 (0.380–0.984) 0.048	-	down regulated	7
35	Huang, 2020 [49]	China	SCLC	52/54	CESRP1	0.660 (0.440 to 0.990)	-	down regulated	6
36	Li, 2019 [50]	China	NSCLC	95/95	Circ-ITCH	0.560 (0.280 to 1.120)	-	down regulated	7
37	Liu, 2018 [51]	China	NSCLC	22/31	Circ_0001649	0.41 (0.22–0.77)	-	down regulated	7
38	Liu, 2020 [52]	China	NSCLC	46/47	Circ_11780	0.640 (0.320 to 1.290)	-	down regulated	6
39	Tong, 2020 [53]	China	NSCLC	230/230	Circ-SMARCA5	0.678 (0.534 to 0.861)	0.684 (0.549–0.852) 0.001	down regulated	9
40	Wang, 2019 [54]	China	LAC	46/46	CircCRIM1	0.590 (0.365 to 0.953)	-	down regulated	7

Table 1 (continued)

No	Author, Year [Reference]	Country	Histological type	High/Low expression	Type of CircRNA	OS (HR [95% CI], *p* value)	DFS (HR [95% CI], *p* value)	Action of CircRNA to lung cancer	NOS
41	Yang, 2018 [55]	China	LC	55/44	Circ_0046264	1.89 (0.97–3.67)	-	down regulated	7
42	Yao, 2019 [56]	China	LAC	54/40	Circ_0006427	0.550 (0.290 to 1.070)	-	down regulated	7
43	Zhou, 2022 [57]	China	NSCLC	23/23	Circ_0072309	2.219(1.104–4.460)0.025	-	down regulated	7

OS: Overall survival; DFS: Disease free survival; NSCLC: Non-small cell lung carcinoma; SCLC: Small cell lung carcinoma; LAC: Lung adenocarcinoma; NOS: NEWCASTLE – OTTAWA scale

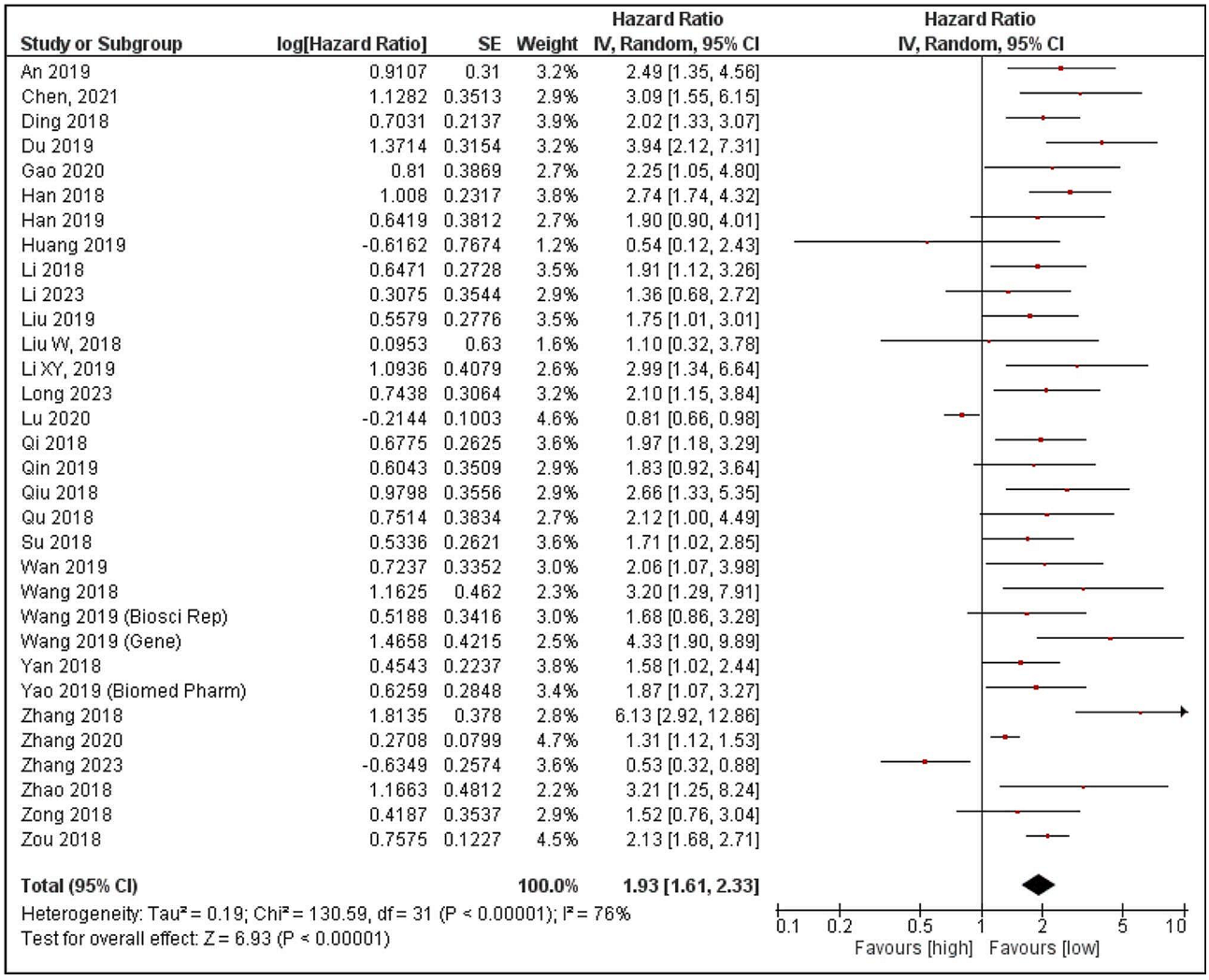

Fig. 2 Forest plot of the association between high and low expression of upregulating CircRNAs and overall survival of lung cancer

prognosis due to rapid tumour invasion, tumour proliferation and chemoresistance.

Some researchers have reported MA on the prognosis of NSCLC in association with various types of circRNAs. The first MA was done in 2019 and it was found that both upregulating and downregulating circRNAs are associated with a poor prognosis of lung cancer [67]. Later, another MA reported that expression of upregulating circRNAs was significantly associated with a poor prognosis for NSCLC [68].

In our MA, we collected 43 primary studies that reported an association between the expression of 39 different types of circRNAs and the survival outcomes of lung cancer. Based on our best literature search, our MA included the highest number of prognostic factor studies, and it included primary studies published in 2023. All the studies were conducted in China, and all

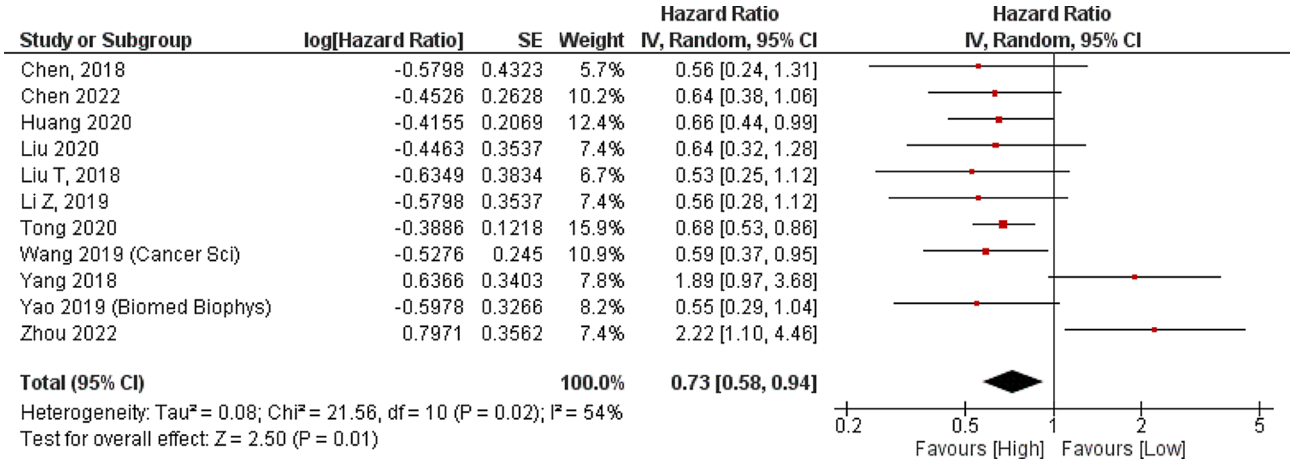

Fig. 3 Forest plot of the association between high and low expression of downregulating CircRNAs and overall survival of lung cancer

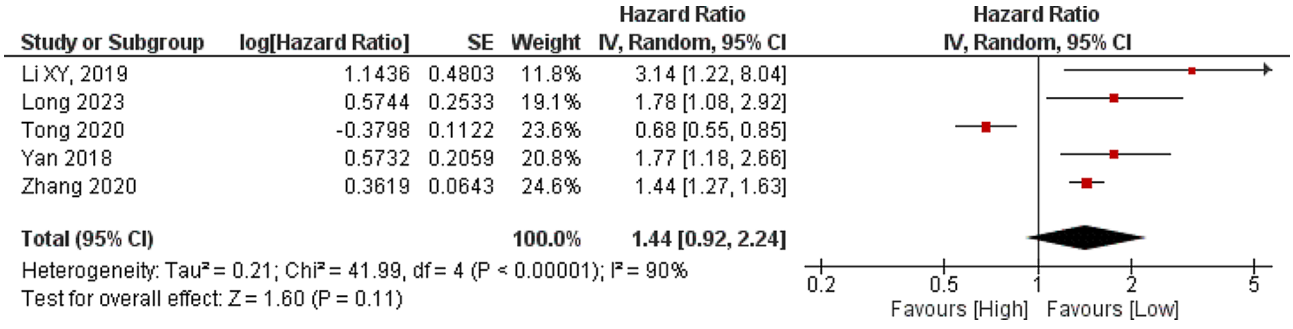

Fig. 4 Forest plot of the association between high and low expression of CircRNAs and disease-free survival of NSCLC

the participants in the studies are Chinese. Among them, 40 (32 NSCLC+8 Adenocarcinoma) studies reported on NSCLC, 2 were just lung cancer and only one study reported on SCLC. Regarding the actions of circRNAs on lung cancer, 32 studies reported an association between upregulating circRNAs and lung tumours; and 11 studies reported an association between downregulating circRNAs and lung tumours. In those 32 studies, it was reported that high expression of circRNAs was associated with an unfavorable prognosis by facilitating tumour progression, inducing resistance to immune checkpoint inhibitor therapy, enhancing metastasis etc. 11 studies reported that high expression of circRNAs was associated with a favorable prognosis, as those cirRNAs have downregulating action on cancer cells by inhibiting cancer cell proliferation and enhancing chemosensitivity.

Although we planned to conduct a MA on the association of circRNAs and prognosis in both NSCLC and SCLC, we can only conduct it for NSCLC as only one study reported prognosis for SCLC. This study reported that circRNA cESRP1 expression had downregulating effect in SCLC tissues, playing a crucial role in chemosensitivity by sponging miR-93-5p to inhibit the TGF-β pathway, and it was associated with survival [49].

The results of our MA were comparable with other published MAs. A MA on the association of expression of downregulating circRNAs and OS in NSCLC showed that high expression of downregulating circRNAs was correlated with favorable OS in both NSCLC and SCLC. Pooled results of those MAs indicated that the expression of upregulating circRNAs was significantly associated with the worse prognosis in NSCLC [67, 68]. A MA on the diagnostic and prognostic value of circRNAs in lung cancer also reported a significant association between circRNAs expression and diagnostic and prognostic values in lung cancer patients [69]. Many types of circRNAs are also correlated with tumour size, lymph node metastasis, distant metastasis, TNM staging, and differentiation, by promoting lung cancer invasion and migration [11]. Most of the prognostic role of circRNAs was based on the mechanism of microRNA (miRNA) molecular sponge by adsorbing miRNA, regulating the transcription of parental genes, interacting with RNA-binding proteins to play biological roles, and translating proteins [70–72].

In our MA, three studies reported on ciRS-7 and they reported that high expression of ciRS-7 was associated with a poor prognosis of NSCLC [34, 39, 41]. CiRS-7 was described as associated not only with the poor

prognosis of NSCLC, but also with the poor prognosis of other malignancies such as hepatocellular carcinoma and renal cell carcinoma [73, 74]. Previously, ciRS-7 was reported to act as a tumour promoter by regulating the miR-139-3p/TAGLN axis and activating the PI3K/AKT signaling pathway to promote tumour progression and metastasis [74]. A study on lung adenocarcinoma reported that high expression of this circRNA was associated with TNM staging and lymphatic metastasis [75].

In our MA, circ-100,395, circ-0065214, cESRP1, circ-ITCH, circ-0001649, circ-11,780, circSMARCA5, circ-CRIM1, circ-0046264, circ-0006427 and circ-0072309 had downregulating effect in NSCLC by playing an important role in NSCLC cell proliferation, cell migration, and apoptosis. Regarding the downregulating action of circRNAs in lung cancer, those circRNAs inhibit the growth and invasion of lung cancer cells for example through the miR-558/TNFAIP1 and TPM1 pathways [76]. Considering the effect of individual circRNAs, cESRP1 circRNA acted on the chemoresistant cells and augmented chemosensitivity by sponging miR-93-5p in SCLC to inhibit the TGF-β pathway [49]. Circ-0065214 (circSCAP) directly binds to the SF3A3 protein, facilitating the reduction of SF3A3 by promoting its ubiquitin–proteasome-mediated degradation, which enhances the expression of MDM4-S to finally activate its downstream p53 signaling [48]. Circ_100395 inhibits the malignancy of NSCLC by targeting miR-141-3p and upregulating LATS2; these can in turn increase phosphorylation of YAP and inactivate the Hippo/YAP pathway [47]. Moreover, it significantly decreases the tumour volume and weight in vivo [77]. These downregulating actions of enhancing chemosensitivity and inhibiting tumour invasion can be considered in the management of lung cancer. Accumulated evidence to date highlights the multifaceted role of circRNAs in cancer, especially their regulatory functions across various signaling pathways underscore their potential as biomarkers and therapeutic targets in the field of oncology [59]. Therefore, regulating the expression level of circRNAs is of great significance to the malignant biological behavior of lung cancer [63].

There were a few limitations in conducting this MA. Although we aimed to conduct MA on both NSCLC and SCLC, this MA was mainly on NSCLC as only one study on SCLC was included. Although we planned to conduct subgroup analysis on different types of circRNAs, all 43 included studies reported different diverse types of circRNAs and it was not possible to perform subgroup analysis. Subgroup analysis on histopathological types was not able to perform, as most of the studies reported on NSCLC or lung cancer. Subgroup analysis on prognostic association in different treatment regimens was also not performed, as most of the included studies did not report the types of treatment. Another limitation was that all 43 included studies are from China with a Chinese population. If primary studies from other parts of the world could be included, it would be an epidemiologically more informative report.

Conclusion

Our MA confirmed that circRNAs serve as important biomarkers for the prognostic value of lung cancer, especially NSCLC. The findings supported that high expression of upregulating circRNAs is associated with poor OS and poor prognosis; on the other hand, downregulating action of circRNAs are associated with favorable OS and better prognosis. CircRNAs act as tumour-promoting or tumour-suppressing factors to regulate the biological behaviours of lung cancer, such as proliferation, metastasis, and apoptosis, regulate the sensitivity of chemotherapy or targeted drugs and the efficacy of immunotherapy, and provide a preliminary theoretical basis for adjuvant clinical treatment. Moreover, circRNA can be considered a promising novel biomarker for the prognosis of lung cancer, especially NSCLC. The downregulatory action of circRNAs should be considered a promising treatment in the management of lung cancer, especially NSCLC. More translational research should be explored to understand the downregulatory action of circRNAs to be used as a promising treatment in the management of lung cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12704-w.

Supplementary Material 1

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Author contributions

Research design: TTW, SNA; Data collection and extraction: TTW, SA, SNA; Statistical analysis: TTW, SA; Drafting manuscript: SA, TTW, SNA, NNT; Final approval of manuscript: SA, TTW, SNA, NNT.

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Data availability

Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as supplementary information. The data used to support the findings of this study are included within the manuscript and supplementary files.

Declarations

Ethical approval

This research work has been approved by IMU Joint-Committee on Research & Ethics with project ID: BMS I/2022 (04).

Consent to participants
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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