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Prognostic Value of Circular RNAs in Digestive System Malignancies: Evidence From a Systematic Review and Meta-analysis

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ABSTRACT

Dysregulation of circular RNAs (circRNAs) has been implicated in the development and progression of various cancers. However, their clinicopathological and prognostic value in digestive system malignancies remains unclear. This meta-analysis was performed to investigate the potential prognostic role of circRNAs in these cancers, classifying them as oncogenic or tumor-suppressor based on original study findings, while noting context-dependent roles. A comprehensive electronic literature search was conducted to identify eligible studies evaluating the prognostic significance of circRNAs in digestive cancers. Pooled hazard ratios (HRs), odds ratios (ORs), and 95% confidence intervals (CIs) were calculated to assess the associations between circRNA expression and overall survival (OS), as well as clinicopathological parameters. A total of 111 eligible studies were included in this meta-analysis. High expression of oncogenic circRNAs was significantly associated with worse OS (HR = 1.90, 96% CI: 1.72–2.22; P < 0.001), while elevated tumor-suppressor circRNAs showed a non-significant protective trend (HR = 0.74, 95% CI: 0.54–1.03; P > 0.05). Upregulated circRNAs were also significantly correlated with advanced TNM stage (OR = 2.68, 95% CI: 2.09–3.45) and larger tumor size (OR = 1.52, 95% CI: 1.16–1.98). Conversely, downregulated circRNAs showed an inverse association with advanced TNM stage (OR = 0.44, 95% CI: 0.25–0.79) and tumor size (OR = 0.51, 95% CI: 0.34–0.77). High heterogeneity (I^2 > 50%) was observed, likely due to diverse cancer types and detection methods, but sensitivity analyses confirmed the result robustness. Egger's test indicated potential publication bias (P < 0.05). Mechanistically, circRNAs influence prognosis via miRNA sponging, RNA-binding protein interactions, and transcriptional regulation. This meta-analysis provides robust evidence that aberrant circRNA expression is associated with aggressive tumor characteristics and poor prognosis in digestive system cancers. However, clinical translation is limited by non-standardized detection methods and reliance on tissue-based assays. Large-scale, multicenter studies with standardized detection protocols and liquid biopsy validation are required to establish circRNAs as non-invasive prognostic biomarkers.

Keywords: Circular RNA, Digestive System Neoplasms, Meta-analysis, Prognosis, Biomarkers

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1. Introduction

Circular RNAs (circRNAs) are a class of endogenous non-coding RNAs characterized by covalently closed loop structures without free 5′ or 3′ ends, generated through back-splicing of canonical spliceosomes (1). Unlike linear RNAs, circRNAs lack a polyadenylated tail and are therefore less susceptible to exonucleases degradation (2, 3). Their abundance, evolutionary conservation, stability, and diverse regulatory functions position circRNAs as promising molecular indicators and therapeutic targets in human cancers (4, 5).

CircRNAs may exhibit tissue- or cell-type-specific expression patterns (6, 7) and participate in various biological processes, including regulation of transcription and splicing, acting as microRNA (miRNA) sponges, interacting with RNA-binding proteins (RBPs), and even facilitating protein translation (8, 9). Given these regulatory capacities, circRNAs have gained increasing attention in cancer pathogenesis, including malignancies of digestive system. Nevertheless, the clinical utility of most circRNAs remains to be elucidated.

Digestive system malignancies, with approximately 3.4 million newly diagnosed cancer cases and 1.5 million deaths annually, are among the most common malignancies worldwide (10). Despite recent advances in clinical oncology, a large proportion of patients are diagnosed at advanced stages, highlighting the need for clinically applicable biomarkers with high sensitivity and specificity for early detection. Recent evidence indicates that circRNAs can influence cancer progression through various mechanisms, such as sponging oncogenic miRNAs (e.g., miR-21 in gastric cancer) or activating the oncogenic pathways like Wnt/β-catenin in colorectal cancer (CRC) (11). Differential expression patterns have been observed in digestive tumors such as hepatocellular carcinoma (HCC), GC, and pancreatic ductal adenocarcinoma (PDAC) compared to normal human digestive system tissues (12-17). For example, certain circRNAs like circFNDC3B are downregulated in CRC, while others like circHIPK3 are overexpressed, indicating context-dependent roles in tumor biology (18, 19).

Individual studies investigating the prognostic implications of circRNAs in digestive cancers are often limited by small sample sizes, heterogeneous methodologies, and conflicting results. A meta-analysis provides an opportunity to quantitatively synthesize this evidence, assess heterogeneity, and derive more robust estimates of their prognostic value.

The present meta-analysis systematically evaluates the clinical significance of circRNAs as prognostic and clinicopathological biomarkers across all digestive system cancers, with the aim of identifying reliable molecular markers that can aid in patient stratification and personalized treatment. Unlike previous reviews limited to single tumor types, this study integrates data across all digestive malignancies. Furthermore, it incorporates rigorous bias assessments and highlights key challenges, such as assay standardization, that must be addressed for clinical implementation.

2. Materials and Methods

2.1 Search Strategy and Study Selection

A comprehensive literature search was conducted across PubMed, Web of Science, EMBASE, Scopus, and Cochrane Library databases up to July 31, 2025, to identify the studies assessing the clinical utility of circRNAs as prognostic biomarkers in digestive system malignancies. Keywords and MeSH terms including "circRNAs", "circular RNAs", "Digestive System Neoplasms", "liver", "hepatocellular", "colon", "colorectal", "rectal", "esophageal", "gastric", "pancreatic", "cancer", "tumor", "malignant", "neoplasm", "carcinoma", "prognosis", "prognostic", "prognostic biomarker", and "survival analysis" were used individually or/and in various combinations. Titles and abstracts were screened independently by two authors (HMM and EZ), with disagreements resolved by consensus. Reference lists of all relevant papers and eligible studies were manually searched to identify additional articles. Attempts were made to contact the study when key data were not available. An updated search was performed prior to manuscript revision to include recently published studies.

2.2 Inclusion and Exclusion Criteria

Studies were included if they: 1) involved patients diagnosed with digestive system malignancies; 2) investigated the clinicopathological and prognostic significance of circRNAs; 3) used quantitative methods for circRNA detection, including RT-PCR and other validated approaches; and 4) reported hazard ratios (HRs) or risk ratios (RR) with 95% confidence intervals (CI) for overall survival (OS) and/or disease-free survival (DFS), or provided sufficient data to calculate the aforementioned factors. Studies were excluded if they: 1) did not focus on circRNA or digestive cancers; 2) contained duplicate data; 3) were letters, reviews, or non-English articles; 4) lacked available data and author contact was unsuccessful; 5) involved animal models, single case reports, or expert opinions; 6) combined mixed cancer types without separate analyses. Studies with mixed cancers were included only if subgroup analyses or stratified results were presented.

2.3 Data Extraction and Quality Assessment

Two trained authors (HMM and EZ) independently extracted the data and assessed the study quality according to the Newcastle-Ottawa Scale (NOS). Discrepancies were resolved through discussion with a third investigator. The NOS checklists for cohort and case-control studies were applied accordingly, with distinct criteria addressing selection, comparability, and outcome/exposure domains tailored for each study design. Key extracted data included author, publication year, country, ethnicity, sample size, circRNA type, expression levels, tumor type, TNM stage, distant metastasis (DM), treatment data, study design, detection methods, and HRs or RRs for survival outcomes. Cutoff values for categorizing "high" versus "low" circRNA expression were applied as reported in the original studies, most commonly using the median expression level or other statistical criteria defined by the authors. Studies lacking necessary data for a given outcome were excluded from that analysis.

2.4 Statistical Analysis

Pooled HRs or ORs with 95% CIs were directly extracted from the published data to evaluate the prognostic value of circRNAs in digestive system malignancies. For studies lacking direct HRs, Kaplan-

Meier curves were digitized and HRs estimated using the method described by Tierney, Stewart (20). Log HRs and standard errors were then used to summarize OS outcomes. Statistical heterogeneity among studies was assessed using the chi-square-based Cochran's-Q test and I-squared (I^2) statistic, with $I^2 > 50\%$ and $P < 0.05$ indicating significant heterogeneity. Depending on the presence or absence of heterogeneity, either random-effects or fixed-effects models were applied. Heterogeneity refers to differences in study results beyond what would be expected by chance alone. It assesses whether the variability among included studies is due to true clinical differences or methodological inconsistencies (21). To further explore potential sources of heterogeneity, subgroup analyses based on cancer type, circRNA function, and other clinical variables were planned and performed. Furthermore, sensitivity analyses were performed to evaluate the effect of each individual study on pooled results (22). Publication bias was assessed by Egger's linear regression test and Begg's funnel plots (23, 24). All the statistical analyses were conducted using the OpenMetaAnalyst, an open-source software, and Comprehensive Meta-Analysis Software 3 (Version 3.3.070) (25). A $P < 0.05$ was considered statistically significant.

3. Result

3.1 Literature Search

As described in Figure 1, a total of 335 relevant articles were initially identified during the database search, of which 140 were excluded as duplicates. By screening the titles and abstracts, 74 studies were categorized as conference abstracts, letters, editorials, or reviews and were excluded. Consequently, 142 articles were subjected to full-text review. Of these, 32 studied were excluded due to insufficient data for analysis, and 7 studies were excluded because they did not report relevant outcomes. Therefore, 103 articles encompassing 111 studies were ultimately eligible for data extraction and meta-analysis. The majority of the investigated circRNAs were found to be up-regulated, whereas, the expression levels of 20 circRNA decreased in digestive system cancers. A flowchart demonstrating the study selection process is summarized in Figure 1.

3.2 Study Characteristics

Baseline characteristics of the included studies are summarized in Supplementary-1. All eligible studies were published between 2016 and 2023, with sample sizes ranging from 30 to 380 participants. Cancer types in the studies included gastric cancer (GC, n=38), hepatocellular carcinoma (HCC, n=32), colorectal cancer (CRC, n=18), pancreatic ductal adenocarcinoma (PDAC, n=18), and esophageal cancer (ESCO, n=5). Most studies measured circRNA expression using quantitative real-time PCR (qRT-PCR). As indicated in Supplementary-1, 83 circRNAs types were identified as oncogenic, while 26 acted as tumor suppressors. Specimen sources were predominantly tissues and plasma samples; 92.2% of studies (95 articles) utilized tissue samples, whereas 7.8% (8 articles) utilized plasma, serum, or a combination of tissue and plasma/serum samples for circRNA expression analysis.

Patient ages spanned a wide range, with median ages generally between 45 and 68 years. Gender distribution was generally balanced, though some studies showed a slight predominance of one gender. Tumor sizes were often categorized around clinically relevant cut-offs (e.g., 3 cm, 5 cm). TNM staging varied, covering early (I/II) to advanced (III/IV) stages, enabling evaluation of circRNA expression across disease severity. According to the Newcastle-Ottawa Scale (NOS), the quality of the included studies ranged from 6 to 8, indicating a high quality.

3.3 Meta-analysis for Overall Survival

A total of 111 studies investigating five types of gastrointestinal cancers evaluated the association between circRNA expression levels and OS. All studies reported univariate and multivariate analyses. Significant heterogeneity was observed in the univariate analysis for up-regulated circRNAs (I^2=69.19%, P<0.05) and down-regulated circRNAs (I^2=90.69%, P<0.001). Accordingly, random-effects models were applied.

Pooled results from both univariate and multivariate models showed that high expression of oncogenic circRNAs was significantly associated with poorer prognosis, with a HR of 1.96 (95% Cl: 1.72-2.22, $P < 0.001$) in the univariate analysis, and a HR of 1.92 (95% Cl: 1.62-2.28, $P < 0.001$) in the multivariate analysis (Figure 2A, Supplementary-2).

In contrast, regarding the tumor-suppressor circRNAs, no significant association was observed in either analysis, with HRs of 0.74 (95% CI: 0.54-1.03, $P > 0.05$) in the univariate model and 0.59 (95% CI: 0.18–1.93, $P > 0.05$) in the multivariate model (Figure 2B, Supplementary-2). High heterogeneity was also detected in the multivariate analysis of down-regulated circRNAs ($I^2 = 90.43\%$, $P < 0.001$), leading to the application of random-effects models.

To further explore potential sources of heterogeneity, subgroup analyses were performed based on cancer type and other clinical variables, with results presented in Supplementary-2. In subgroup analysis based on cancer types high circRNA expression was significantly associated with shorter OS in HCC (pooled HR=2.08; 95% CI, 1.75-2.48; $P < 0.05$), GC (pooled HR=2.36; 95% CI, 1.92-2.91; $P < 0.05$) and PDAC (pooled HR=1.76; 95% CI, 1.27-2.45; $P < 0.05$). However, no significant correlation was found for CRC (pooled HR=1.50; 95% CI, 0.99-2.30; $P > 0.05$) and EsoC (pooled HR=3.12; 95% CI, 0.92-10.58; P>0.05).

Additionally, sensitivity analyses were conducted by sequentially excluding individual studies to assess the robustness of the results, confirming that no single study significantly influenced the overall pooled estimates,

thereby indicating the stability and reliability of the pooled findings (Figures 2C).

3.4 Meta-analysis for Clinicopathological Parameters

In order to evaluate the relationship between circRNAs and clinicopathological features of digestive system cancers further meta-analysis was conducted (Supplementary-2). A significant association was found between high expression of circRNAs and poorer clinical outcomes, including tumor size (OR = 1.52, 95%Cl: 1.16-1.98), TNM stage (OR = 2.68, 95%Cl: 2.09-3.45) and DM (OR = 2.73, 95%Cl: 1.67-4.45) (Supplementary-2). Conversely, overexpression of tumor-suppressor circRNAs was significantly associated with favorable clinicopathological parameters, such as smaller tumor size (OR = 0.51, 95%Cl: 0.34-0.77), lower TNM stage (OR = 0.44, 95%Cl: 0.25-0.79) and reduced DM (OR = 0.22, 95%Cl: 0.10-0.40) (Supplementary-2). Among the clinicopathological factors assessed, high circRNA expression was strongly associated with advanced TNM stage (OR = 2.68) and presence of distant metastasis (OR = 2.73), which are established strong predictors of poor prognosis in digestive system cancers. Pooled analysis showed no significant relationship between high tumor-suppressor circRNAs expression and other clinicopathological parameters including age and gender.

3.5 Publication Bias and Sensitivity Analysis

To evaluate the potential publication bias, we quantitatively performed both Begg's rank correlation test and Egger's linear regression test (26). The results of egger's test indicated a statistically significant publication bias for studies evaluating both up and down-regulated circRNAs (P<0.05). These findings were also visually supported by the funnel plots, which showed asymmetry in both subgroups (Figure 3A and 3B). The presence of publication bias suggests that studies with negative or null results may be underrepresented in the literature. To mitigate this bias, a trim-and-fill analysis was conducted, which demonstrated that the overall conclusions remained robust despite potential publication bias. Moreover, to explain the heterogeneity of individual studies, the sensitivity analysis was performed and the main outcomes of our study did not alter the overall pooled ORs or HRs when deleting studies one by one (Figure 2D).

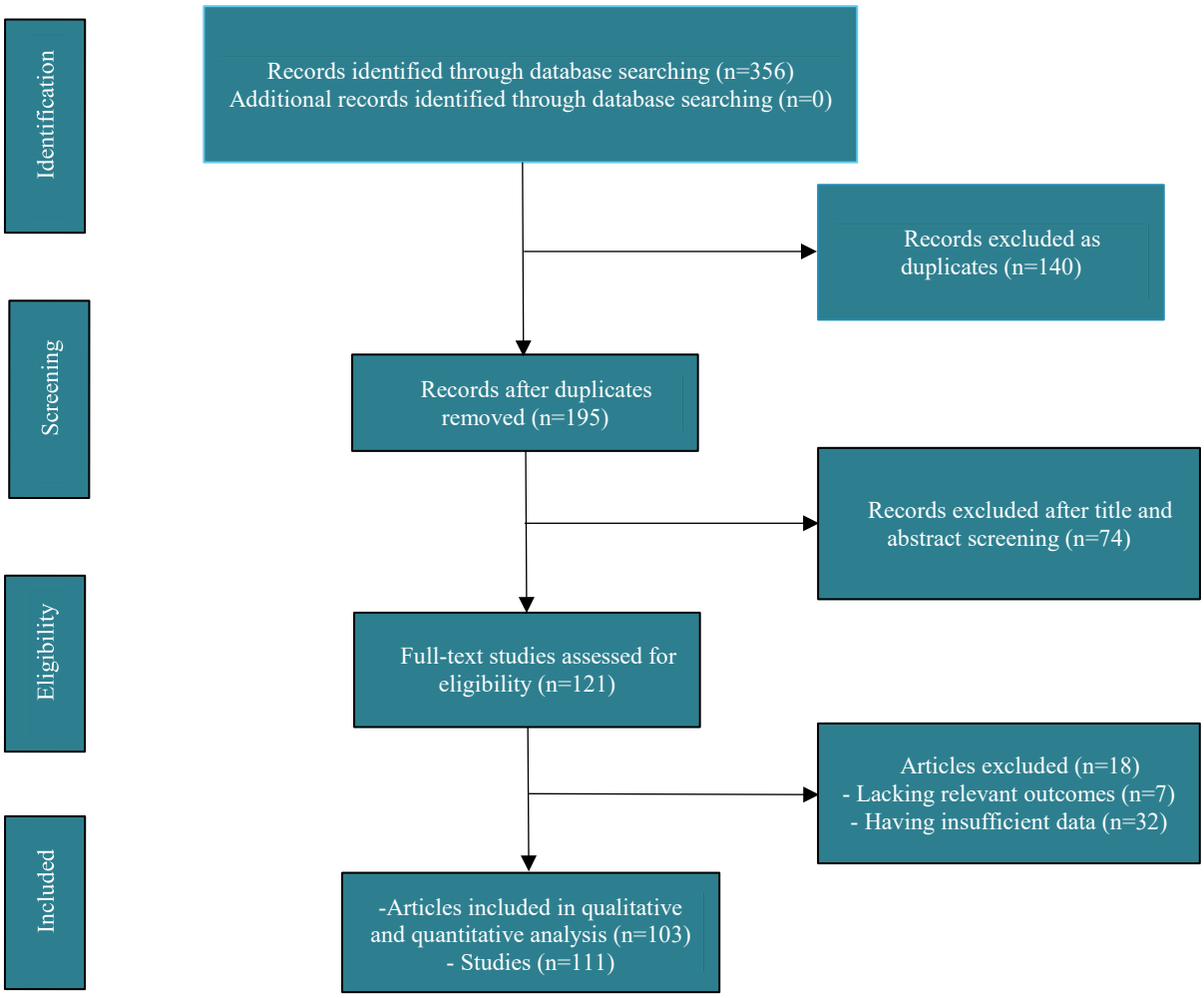
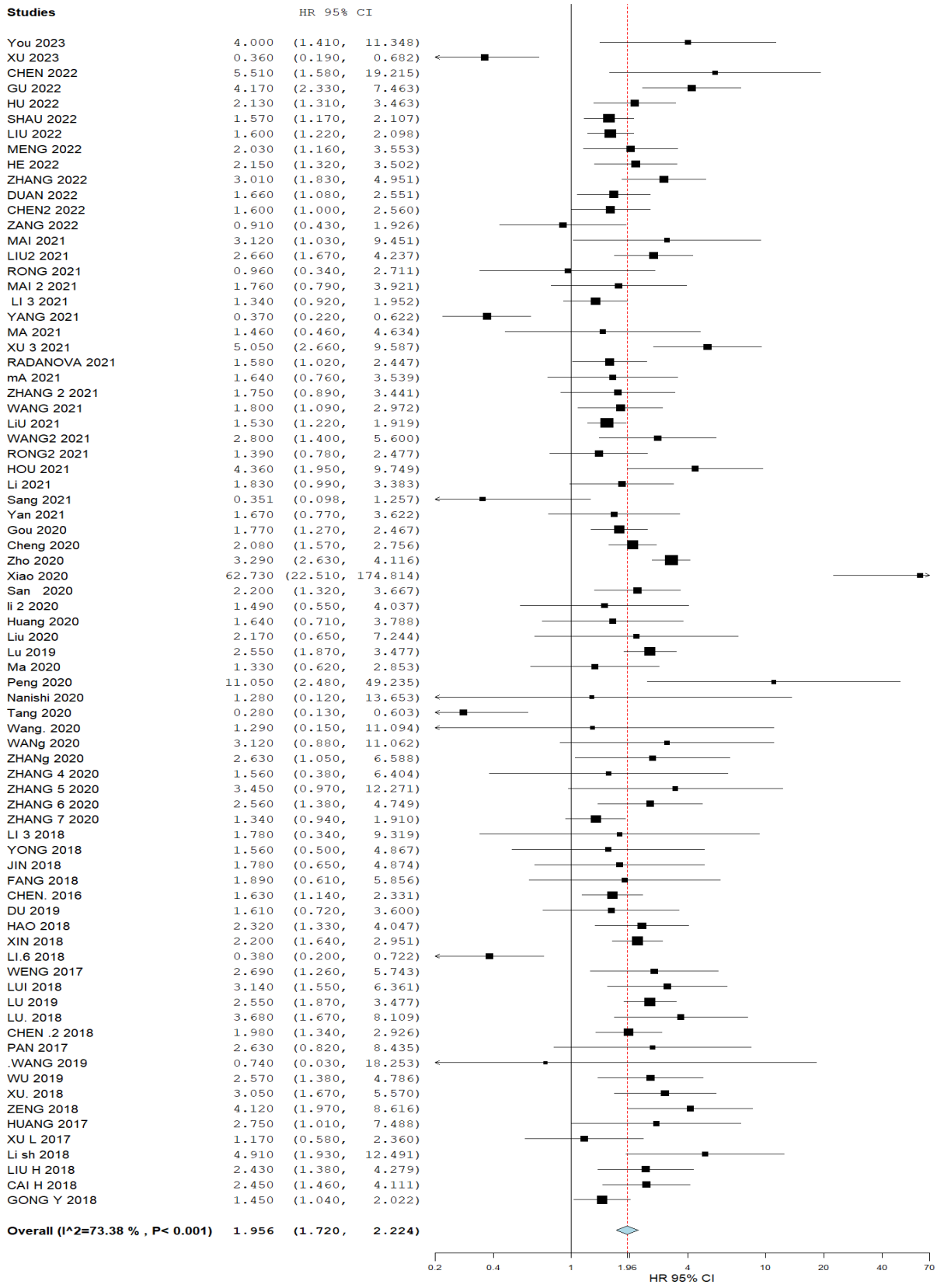
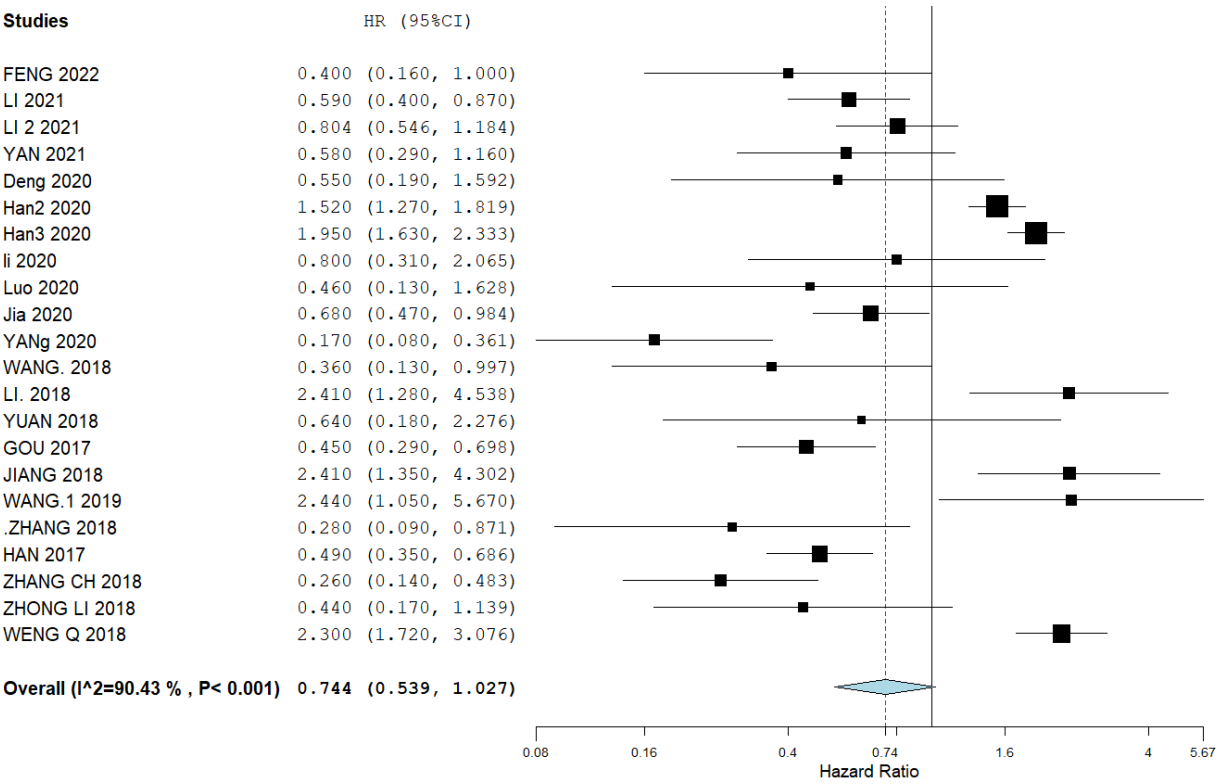


Figure 1. Flow diagram of the study selection (**Designed by Authors, 2025**).

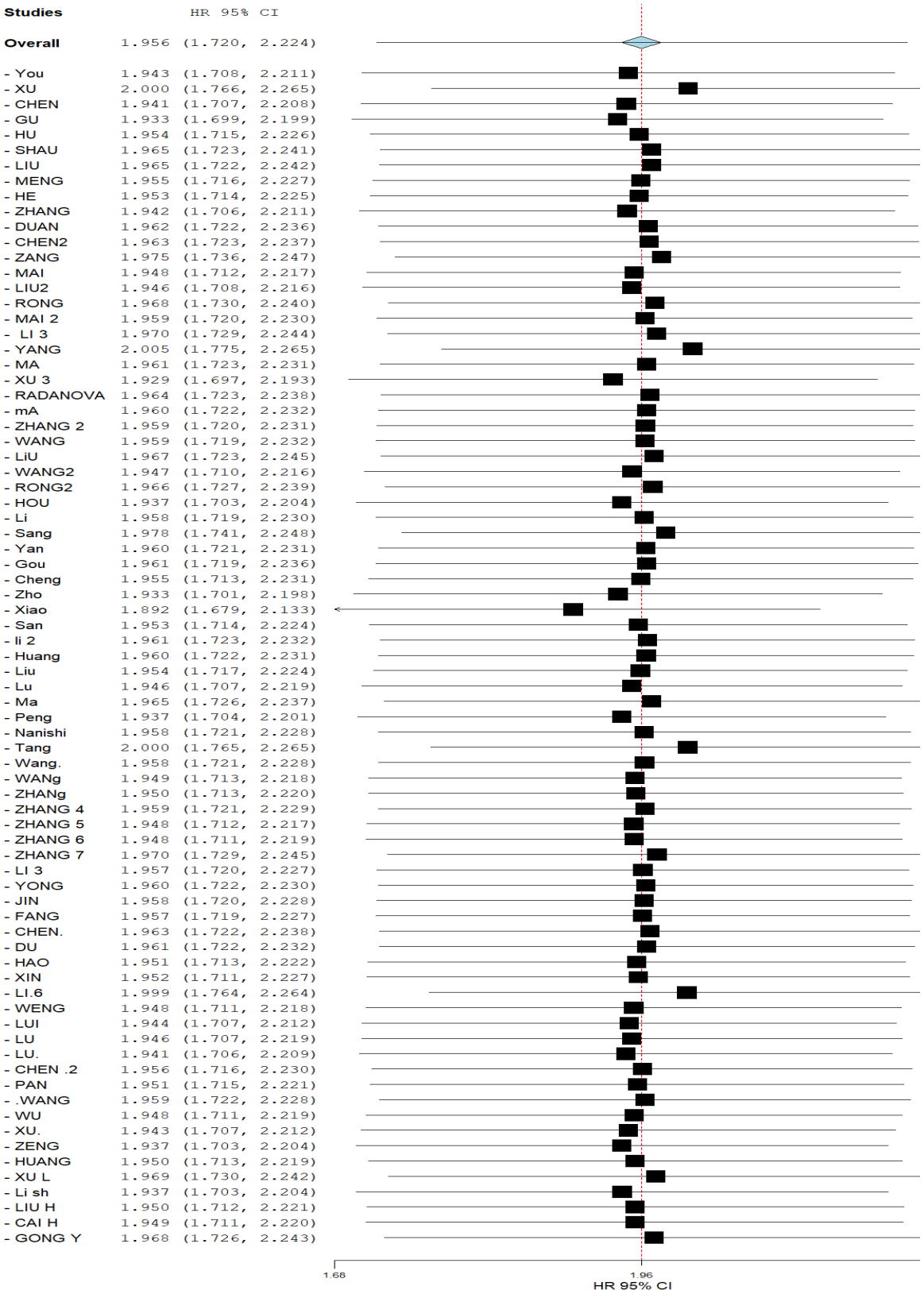
A:


Studies
HR 95% CI
You 2023 4.000 (1.410, 11.348)
XU 2023 0.360 (0.190, 0.682)
CHEN 2022 5.510 (1.580, 19.215)
GU 2022 4.170 (2.330, 7.463)
HU 2022 2.130 (1.310, 3.463)
SHAU 2022 1.570 (1.170, 2.107)
LIU 2022 1.600 (1.220, 2.098)
MENG 2022 2.030 (1.160, 3.553)
HE 2022 2.150 (1.320, 3.502)
ZHANG 2022 3.010 (1.830, 4.951)
DUAN 2022 1.660 (1.080, 2.551)
CHEN2 2022 1.600 (1.000, 2.560)
ZANG 2022 0.910 (0.430, 1.926)
MAI 2021 3.120 (1.030, 9.451)
LIU2 2021 2.660 (1.670, 4.237)
RONG 2021 0.960 (0.340, 2.711)
MAI 2 2021 1.760 (0.790, 3.921)
LI 3 2021 1.340 (0.920, 1.952)
YANG 2021 0.370 (0.220, 0.622)
MA 2021 1.460 (0.460, 4.634)
XU 3 2021 5.050 (2.660, 9.587)
RADANOVA 2021 1.580 (1.020, 2.447)
mA 2021 1.640 (0.760, 3.539)
ZHANG 2 2021 1.750 (0.890, 3.441)
WANG 2021 1.800 (1.090, 2.972)
LiU 2021 1.530 (1.220, 1.919)
WANG2 2021 2.800 (1.400, 5.600)
RONG2 2021 1.390 (0.780, 2.477)
HOU 2021 4.360 (1.950, 9.749)
Li 2021 1.830 (0.990, 3.383)
Sang 2021 0.351 (0.098, 1.257)
Yan 2021 1.670 (0.770, 3.622)
Gou 2020 1.770 (1.270, 2.467)
Cheng 2020 2.080 (1.570, 2.756)
Zho 2020 3.290 (2.630, 4.116)
Xiao 2020 62.730 (22.510, 174.814)
San 2020 2.200 (1.320, 3.667)
li 2 2020 1.490 (0.550, 4.037)
Huang 2020 1.640 (0.710, 3.788)
Liu 2020 2.170 (0.650, 7.244)
Lu 2019 2.550 (1.870, 3.477)
Ma 2020 1.330 (0.620, 2.853)
Peng 2020 11.050 (2.480, 49.235)
Nanishi 2020 1.280 (0.120, 13.653)
Tang 2020 0.280 (0.130, 0.603)
Wang. 2020 1.290 (0.150, 11.094)
WANg 2020 3.120 (0.880, 11.062)
ZHANg 2020 2.630 (1.050, 6.588)
ZHANG 4 2020 1.560 (0.380, 6.404)
ZHANG 5 2020 3.450 (0.970, 12.271)
ZHANG 6 2020 2.560 (1.380, 4.749)
ZHANG 7 2020 1.340 (0.940, 1.910)
LI 3 2018 1.780 (0.340, 9.319)
YONG 2018 1.560 (0.500, 4.867)
JIN 2018 1.780 (0.650, 4.874)
FANG 2018 1.890 (0.610, 5.856)
CHEN. 2016 1.630 (1.140, 2.331)
DU 2019 1.610 (0.720, 3.600)
HAO 2018 2.320 (1.330, 4.047)
XIN 2018 2.200 (1.640, 2.951)
LI.6 2018 0.380 (0.200, 0.722)
WENG 2017 2.690 (1.260, 5.743)
LUI 2018 3.140 (1.550, 6.361)
LU 2019 2.550 (1.870, 3.477)
LU. 2018 3.680 (1.670, 8.109)
CHEN .2 2018 1.980 (1.340, 2.926)
PAN 2017 2.630 (0.820, 8.435)
.WANG 2019 0.740 (0.030, 18.253)
WU 2019 2.570 (1.380, 4.786)
XU. 2018 3.050 (1.670, 5.570)
ZENG 2018 4.120 (1.970, 8.616)
HUANG 2017 2.750 (1.010, 7.488)
XU L 2017 1.170 (0.580, 2.360)
Li sh 2018 4.910 (1.930, 12.491)
LIU H 2018 2.430 (1.380, 4.279)
CAI H 2018 2.450 (1.460, 4.111)
GONG Y 2018 1.450 (1.040, 2.022)
Overall (I^2=73.38 % , P< 0.001) 1.956 (1.720, 2.224)
0.2
0.4
1
1.96
4
10
20
40
70
HR 95% CI

B:


Studies
HR (95%CI)
FENG 2022 0.400 (0.160, 1.000)
LI 2021 0.590 (0.400, 0.870)
LI 2 2021 0.804 (0.546, 1.184)
YAN 2021 0.580 (0.290, 1.160)
Deng 2020 0.550 (0.190, 1.592)
Han2 2020 1.520 (1.270, 1.819)
Han3 2020 1.950 (1.630, 2.333)
li 2020 0.800 (0.310, 2.065)
Luo 2020 0.460 (0.130, 1.628)
Jia 2020 0.680 (0.470, 0.984)
YANg 2020 0.170 (0.080, 0.361)
WANG. 2018 0.360 (0.130, 0.997)
LI. 2018 2.410 (1.280, 4.538)
YUAN 2018 0.640 (0.180, 2.276)
GOU 2017 0.450 (0.290, 0.698)
JIANG 2018 2.410 (1.350, 4.302)
WANG.1 2019 2.440 (1.050, 5.670)
.ZHANG 2018 0.280 (0.090, 0.871)
HAN 2017 0.490 (0.350, 0.686)
ZHANG CH 2018 0.260 (0.140, 0.483)
ZHONG LI 2018 0.440 (0.170, 1.139)
WENG Q 2018 2.300 (1.720, 3.076)
Overall (I^2=90.43 % , P< 0.001) 0.744 (0.539, 1.027)
0.08
0.16
0.4
0.74
1.6
4
5.67
Hazard Ratio

C:


Studies HR 95% CI
Overall 1.956 (1.720, 2.224)
- You 1.943 (1.708, 2.211)
- XU 2.000 (1.766, 2.265)
- CHEN 1.941 (1.707, 2.208)
- GU 1.933 (1.699, 2.199)
- HU 1.954 (1.715, 2.226)
- SHAU 1.965 (1.723, 2.241)
- LIU 1.965 (1.722, 2.242)
- MENG 1.955 (1.716, 2.227)
- HE 1.953 (1.714, 2.225)
- ZHANG 1.942 (1.706, 2.211)
- DUAN 1.962 (1.722, 2.236)
- CHEN2 1.963 (1.723, 2.237)
- ZANG 1.975 (1.736, 2.247)
- MAI 1.948 (1.712, 2.217)
- LIU2 1.946 (1.708, 2.216)
- RONG 1.968 (1.730, 2.240)
- MAI 2 1.959 (1.720, 2.230)
- LI 3 1.970 (1.729, 2.244)
- YANG 2.005 (1.775, 2.265)
- MA 1.961 (1.723, 2.231)
- XU 3 1.929 (1.697, 2.193)
- RADANOVA 1.964 (1.723, 2.238)
- mA 1.960 (1.722, 2.232)
- ZHANG 2 1.959 (1.720, 2.231)
- WANG 1.959 (1.719, 2.232)
- LiU 1.967 (1.723, 2.245)
- WANG2 1.947 (1.710, 2.216)
- RONG2 1.966 (1.727, 2.239)
- HOU 1.937 (1.703, 2.204)
- Li 1.958 (1.719, 2.230)
- Sang 1.978 (1.741, 2.248)
- Yan 1.960 (1.721, 2.231)
- Gou 1.961 (1.719, 2.236)
- Cheng 1.955 (1.713, 2.231)
- Zho 1.933 (1.701, 2.198)
- Xiao 1.892 (1.679, 2.133)
- San 1.953 (1.714, 2.224)
- li 2 1.961 (1.723, 2.232)
- Huang 1.960 (1.722, 2.231)
- Liu 1.954 (1.717, 2.224)
- Lu 1.946 (1.707, 2.219)
- Ma 1.965 (1.726, 2.237)
- Peng 1.937 (1.704, 2.201)
- Nanishi 1.958 (1.721, 2.228)
- Tang 2.000 (1.765, 2.265)
- Wang. 1.958 (1.721, 2.228)
- WANg 1.949 (1.713, 2.218)
- ZHANg 1.950 (1.713, 2.220)
- ZHANG 4 1.959 (1.721, 2.229)
- ZHANG 5 1.948 (1.712, 2.217)
- ZHANG 6 1.948 (1.711, 2.219)
- ZHANG 7 1.970 (1.729, 2.245)
- LI 3 1.957 (1.720, 2.227)
- YONG 1.960 (1.722, 2.230)
- JIN 1.958 (1.720, 2.228)
- FANG 1.957 (1.719, 2.227)
- CHEN. 1.963 (1.722, 2.238)
- DU 1.961 (1.722, 2.232)
- HAO 1.951 (1.713, 2.222)
- XIN 1.952 (1.711, 2.227)
- LI.6 1.999 (1.764, 2.264)
- WENG 1.948 (1.711, 2.218)
- LUI 1.944 (1.707, 2.212)
- LU 1.946 (1.707, 2.219)
- LU. 1.941 (1.706, 2.209)
- CHEN .2 1.956 (1.716, 2.230)
- PAN 1.951 (1.715, 2.221)
- .WANG 1.959 (1.722, 2.228)
- WU 1.948 (1.711, 2.219)
- XU. 1.943 (1.707, 2.212)
- ZENG 1.937 (1.703, 2.204)
- HUANG 1.950 (1.713, 2.219)
- XU L 1.969 (1.730, 2.242)
- Li sh 1.937 (1.703, 2.204)
- LIU H 1.950 (1.712, 2.221)
- CAI H 1.949 (1.711, 2.220)
- GONG Y 1.968 (1.726, 2.243)
1.68
1.96
HR 95% CI

D:

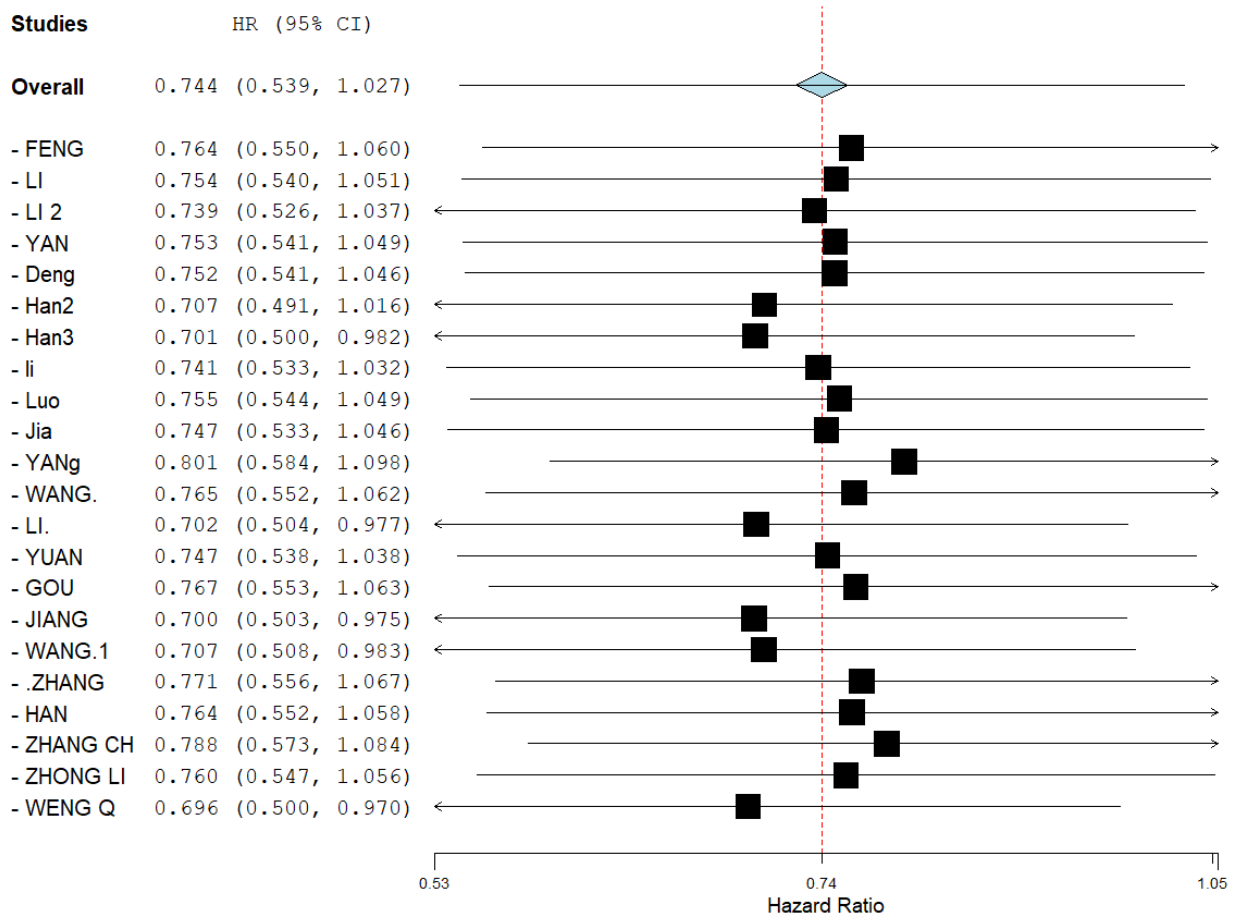
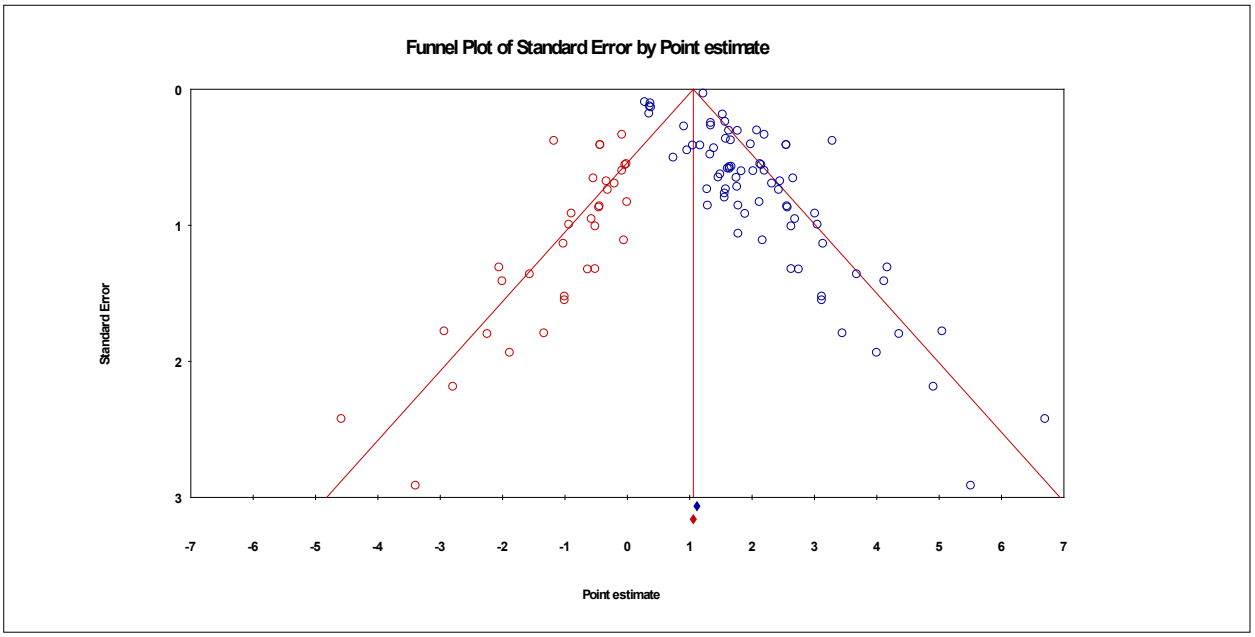


Figure 2. Forest plot showing the association of circular RNAs and cancer risk in pooling HR for overall survival in (A) oncogenic and (B) tumor-suppressor circRNAs. Sensitivity analysis on the relationship between circular RNAs level and digestive system malignancies risk for (C) up-regulated and (D) down-regulated circRNAs. (**Designed by Authors, 2025**).

A:



B:

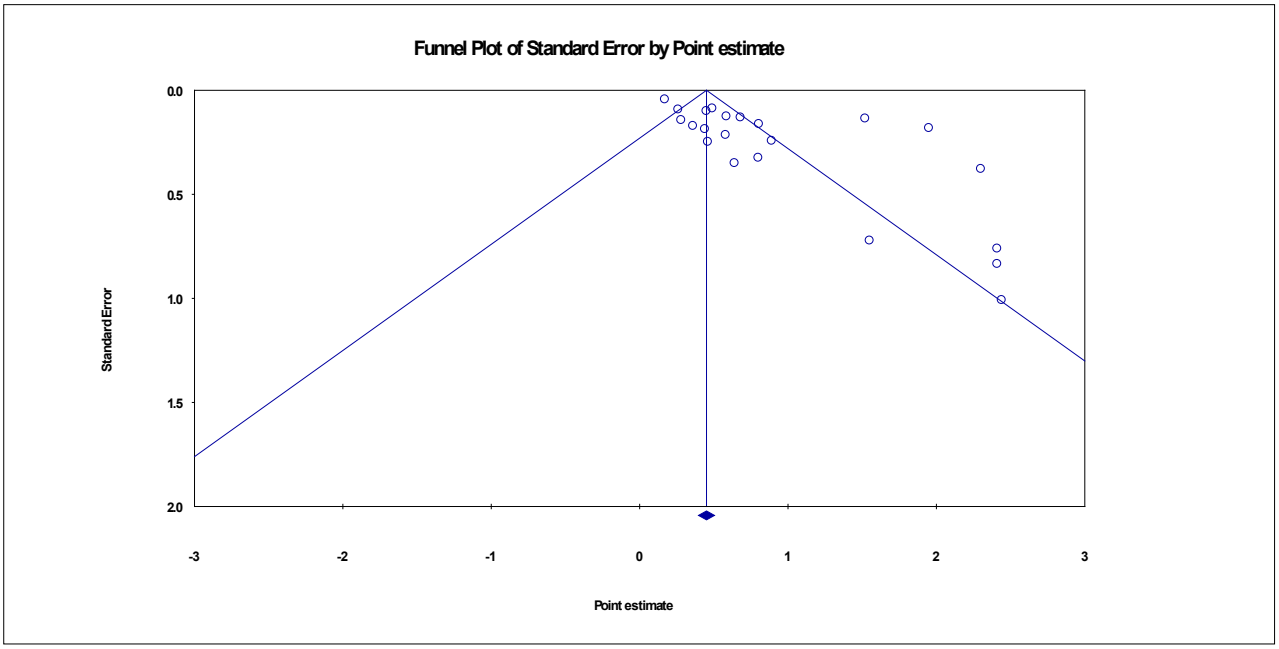


Figure 3. Funnel plot of the publication bias on the association of circular RNAs and different cancers in pooling ORs analysis for (A) up-regulated and (B) down-regulated circRNAs. (**Designed by Authors, 2025**).

4. Discussions

Digestive system malignancies represent a significant global health burden with often poor prognosis. CircRNAs, a novel class of endogenous non-coding RNAs, have recently emerged as important regulators in cancer biology due to their stability and functional versatility. However, despite increasing individual studies investigating circRNAs in digestive cancers, a comprehensive evaluation of their prognostic significance remains lacking. This meta-analysis integrates current evidence to systematically assess the relationship between circRNA expression and clinical outcomes in digestive system tumors, providing a clearer understanding of their potential utility as prognostic biomarkers.

In the present study, a total of 111 prognosis-related circRNAs were assessed from tumor tissues across various types of digestive system malignancies. Our findings indicated that high expression of oncogenic circRNAs is significantly associated with advanced tumor stage, larger tumor size, and worse overall survival, nearly doubling mortality risk (HR=1.96, 95% CI: 1.72–2.22). Conversely, higher levels of tumor-suppressor circRNAs were correlated with favorable clinical outcomes, though the protective effect was not statistically significant (HR=0.74, 95% CI: 0.54–1.03). Notably, TNM stage (OR=2.68) and metastasis (OR=2.73) exhibited the strongest associations with circRNA dysregulation, underscoring their role as key predictors of prognosis. However, in CRC no significant correlation with OS was observed despite the high circRNA dysregulation, likely due to molecular heterogeneity, including diverse circRNA isoforms and varying interactions with the tumor microenvironment across CRC subtypes. These results suggest that circRNAs may serve as promising biomarkers for predicting prognosis in digestive system cancers.

Importantly, researchers are increasingly exploring the biological mechanisms through which circRNAs influence tumor progression and prognosis. CircRNAs can act as competing endogenous RNAs, serving as miRNA sponges to inhibit miRNA activity and regulate downstream gene expression. For example, oncogenic circRNAs such as circ-PVT1 in gastric cancer function as a miRNA sponge by sequestering miR-124-3p, leading to the upregulation of ZEB1 and promoting chemoresistance, proliferation, and malignancy **(27)**. Similarly, circ-BFAR in PDAC acts as a sponge for miR-34b-5p, activating the MET/Akt signaling pathway to enhance tumor growth and metastasis **(28)**. However, the role of circ-PVT1 is controversial, as some studies report a protective effect in specific contexts, potentially due to tissue-specificity or isoform differences. For instance, circ-PVT1 may suppress CRC progression by downregulating miR-216a-5p, which in turn modulates YBX1 expression, inhibiting tumor growth and metastasis **(29)**. This protective effect in CRC likely arises from tissue-specific interactions with the tumor microenvironment or distinct molecular pathways, contrasting with its oncogenic role in other cancers, like GC. These discrepancies may also arise from differences in sample types (e.g., tissue vs. plasma) or detection methods across studies.

Conversely, tumor-suppressor circRNAs can hinder tumor growth by absorbing oncogenic miRNAs or modulating key pathways. For instance, circ-ITCH in CRC suppresses the Wnt/β-catenin signaling pathway, inhibiting cell proliferation and invasion, potentially through interactions with miRNAs like miR-7 and miR-214 (30). Moreover, certain circRNAs have been found to directly interact with RNA-binding proteins or even modulate transcription and splicing processes, thereby playing a role in carcinogenesis. These various mechanisms offer a plausible biological explanation for the observed link between circRNA expression and cancer outcomes in the present meta-analysis.

Previous studies have demonstrated dysregulation of circRNAs in various digestive system cancers, including HCC, ESOC, GC, PDAC, and CRC (19, 28, 31, 32). However, conflicting results exist regarding the precise role of individual circRNAs in tumorigenesis. Some studies have identified circRNAs with tumor-suppressor roles, where low expression was associated with poor prognosis in patients with HCC (33-41), CRC (42-45), GC (31, 46-48) and PDAC (49). On the other hand, other studies have shown an oncogenic role for circRNAs in promoting tumorigenesis in various types of cancer, where up-regulated circRNAs were correlated with advanced tumor progression in HCC (32, 39, 41, 50-60), GC (33, 52, 61-76), PDAC (28, 55, 77-79), ESOC (80, 81), and CRC (80, 82-90).

However, it remains controversial whether circRNAs might serve as prognostic markers for OS or DFS/RFS. In our stratified analysis, the pooled HRs with 95% CI for up and down-regulated circRNAs were 1.90 (1.67–2.16) and 0.78 (0.50–1.07), respectively. This indicates that overexpression of oncogenic circRNAs is associated with poor prognosis, while tumor-suppressor circRNAs may be predictor of better outcomes.

Limitations

One notable limitation of our meta-analysis was the high heterogeneity detected among included studies. This heterogeneity likely arises from several sources. First, the diverse biological functions of circRNAs across different cancer types may result in variable prognostic impacts. Second, methodological differences, including patient selection criteria, sample sizes, qRT-PCR protocols, threshold definitions for circRNA expression, and statistical analyses contribute to variability in findings. Third, clinical heterogeneity such as differences in tumor stages, treatment regimens, and follow-up durations further complicate the interpretation. This justified the use of random-effects models in our analyses to account for such variability. Addressing this heterogeneity through larger, well-designed, and standardized studies will be crucial to validate and refine the prognostic value of circRNAs. Despite these findings, several limitations should be noted. First, approximately 98% of included studies were conducted in China, with only one study from Japan, which limits generalizability across diverse populations. Second, all included studies used qRT-PCR for detection, and lack of standardization across protocols could introduce methodological heterogeneity. Third, due to limited sample sizes and reporting inconsistencies, subgroup analysis by individual circRNAs was not feasible. Fourth, potential confounding factors such as age, sex, and tumor subtype were not consistently reported. Fifth, selection bias may have existed in the exclusion of studies due to lack of HR outcomes in some articles, as well as language restrictions. Finally, most studies analyzed tissue samples, with only a few assessing plasma or serum circRNA levels, which limits the assessment of non-invasive biomarkers.

5. Conclusion

In conclusion, this meta-analysis demonstrated that circRNAs dysregulation is associated with key clinicopathological features and may serve as a prognostic biomarker in digestive system malignancies. Their potential biological roles, supported by emerging mechanistic evidence, further underscore their relevance in cancer biology. Nevertheless, larger, multi-center studies with standardized methods are required to validate these findings and clarify the clinical utility of circRNAs. Future research should prioritize multicenter trials to validate top candidate circRNAs, such as circ-PVT1 and circ-ITCH, as clinical biomarkers, and employ functional studies, such as CRISPR-based screens to confirm their roles in processes like metastasis. Additionally, comparative studies evaluating the additive prognostic value of circRNAs relative to established biomarkers, such as CEA in CRC and CA19-9 in PDAC are needed to enhance their clinical translation.

6. Declarations

6.1 Acknowledgments

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6.2 Ethical Considerations

Although ethical approval is generally not required for meta-analyses, this study was conducted based on a previously approved research protocol with the ethical approval code: IR.MUMS.MEDICAL.REC.1398.848.

6.3 Authors' Contributions

Fatemeh shams: formal analysis, software, validation. Mohammad Hassan Arjmand: conceptualization, investigation, methodology, writing the original draft. Elnaz Zahiri: project administration, writing, review and editing. Hasan Mehrad-Majd: project administration, supervision, writing and editing. All authors approved the final version of the manuscript and agreed to be accountable for the accuracy and integrity of the work.

6.4 Conflict of Interest

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

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6.6 Using Artificial Intelligence Tools (AI Tools)

The authors were not utilized AI Tools.

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Supplementary

Supplementary 1. Baseline characteristics of eligible studies for prognosis analysis.

Study year	Age (High/Low)	Country	Tumor type	Tumor size (High/Low)	Sample size	Male (High/Low) Female (High/Low)	TNM Stage of tumor (High/Low)	Expression						Expression status	Survival Analysis	HR (CI)	Method	Circ RNA name	Sample type	NOS Score
								High (n)			Low (n)									
								total	LNM	DM	total	LNM	DM							
You 2023	<50 17/11 ≥50 18/24	China	GC	≥3 cm 21/15 <3cm 14/20	70	22/19 13/16	I/II 13/23 III/IV 22/12	35	-	16	35	-	8	UP	OS	4.0 (1.41-11.11)	qRT-PCR	Circular RNA 0001789	Tissue	7
Xu 2023	NR	China	ESCC	NR	53	NR	NR	25	-	-	28	-	-	UP	OS	U: 0.36 (0.19-0.70) M: 0.32 (0.14-0.69)	qRT-PCR	circ-TNRC6B	Tissue	6
Chen 2022	≤60 39/38 >60 9/10	China	CRC	≤5 20/18 >5 28/30	96	27/20 21/28	I/II 8/21 III/IV 40/27	48	38	20	48	27	11	UP	OS	U: 5.51 (1.58–19.21) M: 3.84 (1.09–13.56)	qRT-PCR	hsa_circ_0084927	Tissue	7
Gu 2022	≤60 24/9 >60 60/21	China	ESCC	NR	114	65/19 19/11	I/II 35/12 III/IV 49/15	84	50	-	30	11	-	UP	OS	U: 4.17 (2.33-7.47) M: 3.70 (2.15-7.52)	qRT-PCR	circCYP24A1	Tissue	7
Hu 2022	NR	China	PDAC	NR	82	NR	NR	-	-	-	-	-	-	UP	PFS	2.13 (1.31-3.48)	qRT-PCR	circFARP1	Tissue	
Shao 2022	NR	China	GC	NR	96	NR	NR	-	-	-	-	-	-	UP	OS DFS	1.57 (1.17-2.10) 1.48 (1.13-1.94)	qRT-PCR	hsa_circ_0086720	Tissue	6
Feng 2022	>50 15/15 ≤50	China	HCC	>5 9/13 ≤5 16/12	56	18/19 7/6	I/II 15/9 III/IV 10/16	25	-	-	25	-		Down	OS	0.40 (0.16-0.9)	qRT-PCR	CircFGGY	Tissue	7

	10/10																		
Liu 2022	>65 21/17 ≤65 7/5	China	GC	>4 20/9 ≤4 8/13	50	20/15 8/7	I/II 11/14 III/IV 17/8	28	-	-	22	-	-	UP	OS	1.6 (1.22-2.09)	qRT-PCR	circPGD	Tissue	6
Meng 2022	<60 10/12 ≥60 38/37	China	PDAC	NR	97	31/32 17/17	I/II 27/22 III/IV 21/27	-	-	-	-	-	-	UP	OS	U: 2.03 (1.16–3.53) M: 3.01 (1.66–5.49)	qRT-PCR	circSTX6	Tissue	7
Chen2022	≥60 26/27 <60 22/21	China	PDAC	NR	96	27/28 21/20	I/II 9/10 III/IV 39/38	48	-	-	48	-	-	Up	OS	U:1.60 (1.00-2.50)	qRT-PCR	circ-MTHFD1L	Tissue	6
He 2022	≤50 9/5 >50 37/41	China	PADC	≤2 25/36 >2 21/10	92	28/24 18/22	I/II 32/28 III/IV 14/18	46	35	5	46	24	2	UP	OS	2.15 (1.32-3.51)	qRT-PCR	circATG7	Tissue	6
Zheng 2022	NR	China	GC	NR	60	NR	NR	-	-	-	-	-	-	UP	OS	NOT DETERMINED	qRT-PCR	hsa_circ_0015286	Tissue	6
Zhang 2022	≥60 46/48 <60 55/53	China	HCC	NR	202	53/59 48/42	I/II 59/22 III/IV 43/78	101	**47**	-	101	71	-	UP	OS PFS	U: 3.01 (1.83–4.93) M: 2.84 (1.32–4.57) U: 3.26 (1.56–5.52) M: 3.16 (1.43–4.92)	qRT-PCR	circ_0000615	Tissue	7
Duan 2022	≤50 33/24 >50 27/28	China	HCC	≤5 14/21 >5 46/31	112	53/45 7/7	NR	60	-	-	52			UP	OS DFS	1.66 (1.08-2.55) 1.73 (1.13-2.66)	qRT-PCR	circMAP3K4	Tissue	7
Zang 2022	≥60 21/61	China	GC	≥5 11/27 <5	120	20/47 8/29	I/II 3/11	28	-	-	76	-	-	UP	OS	0.91 (0.43-1.91)	qRT-PCR	EIF4G3	Tissue/serum	6

	< 60 7/14			18/45			III/IV 33/61												
Mai 2021	≤ 55 52/40 > 55 32/22	China	CRC	≤5 55/58 >5 31/4	148	39/284 7/45	I/II 17/45 III/IV 59/17	86	68	-	62	19	-	UP	OS	3.12 (1.03-9.45)	qRT-PCR	circ_PVT1	Serum	7
Liu 2021	> 50 27/25 ≤ 50 36/22	China	HCC	>5 36/24 ≤5 27/23	110	55/378/10	I/II 24/30 III/IV 39/17	63	-	-	47	-	-	UP	OS RFS	U:2.67 (1.68-4.25) U:2.433 (1.49-3.98 M: 2.67 (1.68-4.25) M: 2.43 (1.49-3.98)	qRT-PCR	circDLC1	Tissue	7
Rong 2021	≥ 60 15/5 < 60 18/8	china	HCC	≥ 5 25/0 <5 18/13	46	29/104/3	I/II 16/12 III/IV 17/1	33	-	-	13	-	-	UP	OS	0.96 (0.34-2.70)	qRT–PCR	circHPS5	Tissue	6
Mai 2021	≤ 55 49/43 > 55 31/25	China	CRC	≤5 49/64 >5 31/4	148	35/324 5/36	I/II 11/51 III/IV 69/17	91	64	-	57	41	-	UP	OS	1.76 (0.79-3.89)	qRT-PCR	circ_001569	Serum	7
Yu 2021	NR	China	PADC	NR	40	NR	NR	-	-	-	-	-	-	Down	OS	NOT DETERMINED	qRT-PCR	Circ_0092367	Tissue	6
Xu 2021	NR	China	PADC	NR	30	NR	NR	-	-	-	-	-	-	Down	OS	NOT DETERMINED	qRT-PCR	Circ_0013587	Tissue	6
Li 2021	≤ 60 31/41 > 60 44/34	china	HCC	≥5 cm 30/46 <5 45/29	150	67/618/14	NR	75	-		75	-	-	Down	OS	0.59 (0.40-0.89)	qRT-PCR	Circ_0004913 expression	Tissue	7
Li 2021	≤ 60 34/38 > 60	China	HCC	≥5 36/40 <5 39/35	150	65/631 0/12	NR	75	-	-	75	-	-	Down	OS	0.80 (0.55-1.18)	qRT-PCR	Circ_0008160	Tissue	7

	41/37																		
Li 2021	≤60 36/36 >60 39/39	China	HCC	≥5 43/33 <5 32/42	150	67/618/14	NR	75	-	-	75	-	-	UP	OS	1.34 (0.92-1.97)	qRT-PCR	Circ_0000517	Tissue	7
Yang 2021	NR	China	PADC	NR	110	NR	NR	55	-	-	55	-	-	UP	OS	0.37 (0.61-0.22)	qRT-PCR	circRHOBTB3	Tissue	6
Ma 2021	NR	China	PADC	NR	95	NR	NR	38	-	-	37	-	-	UP	OS DFS	OS: 1.46 (0.46-4.68) DFS : 1.25 (0.73-2.13)	qRT-PCR	Circ-0005105	Tissue	6
Shen 2021	NR	China	PADC	NR	?	NR	NR	-	-	-	-	-	-	UP	OS	NOT DETRMINED	qRT-PCR	Circ_0092314	Tissue	6
Xu 2021	≥60 33/29 <60 15/19	China	GC	<3.5 30/23 ≥3.5 18/25	96	46/242 6/24	I/II 11/32 III/IV 37/16	66	35	-	30	17	-	UP	OS	U: 5.051(2.66–9.60) M: 2.690(1.19–6.09)	qRT-PCR	CircTMC5	Tissue	7
Radanova 2021	NR	Bulgaria	CRC	NR	122	NR	NR-	-	-	-	-	-	-	UP	OS	U: 1.58 (1.02–2.45) M: 1.59 (1.02–2.47)	qRT-PCR	hsa_circ_0001445	Tissue	7
Ma 2021	<60 18/25 ≥60 42/35	China	GC	<5 27/45 ≥5 33/15	120	34/382 6/22	I/II 15/37 III/IV 45/23	60	24	-	60	51	-	UP	OS	1.64 (0.76-3.53)	RT-qPCR	circPTPN22	Serum/tissue	7
Zhang 2021	≥60 13/10 <60 10/12	China	PADC	≥5 13/9 <5 10/13	45	12/131 1/9	NR	23	15	-	22	6	-	UP	OS	1.75 (0.89-3.44)	RT-qPCR	RNA circ_0066147	Tissue	7
Wang 2021	≤60 27/23	China	CRC	≤5 16/29 >5	84	24/221 8/20	I/II 12/23 III/IV	42	-	6	42	-	41	UP	OS	1.80 (1.09-2.80)	qRT-PCR	circSPARC	Tissue	7

	>60 15/19			26/13			30/19												
Liu 2021	≤60 73/88 >60 78/64	China	GC	≤5 cm 80/73 >5 cm 71/79	313	111/111 40/41	I/II 40/35 III/IV 111/117	151	-	-	152	-	-	UP	OS DSF	U: 1.53 (1.22–1.92) M: 1.784 (1.26–2.53)	qRT-PCR	circ_0005092	Tissue	7
Yan 2021	>60 23/37 ≤60 25/27	China	GC	≤6 31/29 >6 17/35	112	38/85 10/12	I/II 15/14 III/IV 33/50	84	33	-	28	13	-	Down	OS	0.58 (0.29-01.13)	qRT-PCR	circEVI5 (hsa_circ_0013162)	Tissue	7
Liu 2021	NR	China	ESCC	NR	160	NR	NR	87	-	-	73	-	-	UP	PFS	1.40 (0.62-3.16)	RT-qPCR	CircRNA_141539	Tissue	7
Wang 2021	NR	China	GC	NR	40	NR	NR	20	-	-	20	-	-	UP	OS	2.8 (1.40-5.50)	qRT-PCR	Circ_SMAD4	Tissue	7
Rong 2021	≤60 64/30 >60 74/41	China	PADC	NR	209	75/306 3/41	I/II 96/68 III/IV 42/3	71	-	-	138	-	-	UP	OS	1.39 (0.78-2.22)	qRT-PCR	circEYA3	Tissue	7
Hou 2021	≥50 10/12 <50 5/3	China	PADC	≥4 3/7 <4 12/8	30	9/76/8	I/II 3/10 III/IV 12/5	15	13	-	15	7	-	UP	OS	U: 4.36 (1.95-7.77) M: 2.94 (1.85-6.16)	qRT-PCR	CircCCT3	Tissue	7
Li 2021	≤60 19/12 >60 84/13	China	GC	≤5 cm 49/13 >5cm 54/12	128	71/153 2/10	I/II 55/21 III/IV 49/3	-	-	-	-	-	-	UP	OS DFS	1.83 (0.99-3.48) 1.26 (1.11-1.82)	qRT-PCR	Circ-PTPDC1	Tissue	7
Song 2021	≥60 20/22 <60	China	CRC	<5 26/42 ≥5 25/9	102	33/291 8/22	I/II 18/36 III/IV 33/15	-	-	-	-	-	-	UP	OS	M:0.35 (0.09–0.97) U: 0.46 (0.18–1.12)	qRT-PCR	circ_0001821	Tissue	7

	31/29																		
Yan 2021	NR	China	GC	NR	63	NR	NR	-	-	-	-	-	-	UP	OS DFS	U: 1.67 (0.77-3.65) U: 1.99 (0.91-4.37)	qRT-PCR	Hsa_circ_0001020	Tissue	7
Han 2021	NR	China	GC	NR	375	NR	NR	-	-	-	-	-	-	-	-	-	-	-	-	-
Deng 2020	<60 20/11 ≥60 11/17	China	GC	≤5cm 25/22 >5cm 6/6	59	20/21 11/7	I/II 5/13 III/IV 26/15	31	-	0	28	-	-	Down	OS	0.55 (0.19-1.57)	qRT-PCR	circ-RHOBTB3	Tissue	7
Han 2020	≥65 (10/28) <65 (6/26)	China	GC	≥5 cm (5/35) <5 cm (11/19)	70	8/35 8/19	I/II (8/25) III/IV (8/29)	16	11	-	54	40	-	Down	OS	1.52 (1.27-1.80)	qRT-PCR	circ-0002108 7	Tissue	7
Han 2020	≥65 (11/27) <65 (10/22)	China	GC	≥5cm (10/30) <5 cm (11/19)	70	14/29 7/20	I/II (14/19) III/IV (7/30)	21	13	-	49	38	-	Down	OS	1.95 (1.63-2.34)	qRT-PCR	circ-0005051	Tissue	7
Guo 2020	>60 (68/62) ≤60 (36/42)	China	PDAC	NR	208	58/66 46/38	I/II (67/83) III (37/21)	104	68	-	104	60	-	Up	OS DFS	U:1.77 (1.27-2.47) M: 1.72 (1.23-2.40) U:1.66 (1.21-2.27) M: 1.62 (1.18-2.21)	qRT-PCR	circ-BFAR	Tissue	7
Cheng 2020	NR	China	HCC	NR	278	NR	NR	-	-	-	-	-	-	Up	OS	U: 2.08 (1.57-2.75) M: 1.63 (1.11-2.41)	qRT-PCR	circ-0016788	Tissue	6
Zhou 2020	≥50 (60/30) <50	China	HCC	≥3cm (100/26) <3cm (48/60)	234	96/64 52/22	I/II (55/54) III/IV (93/32)	148	87	88	86	34	29	Up	OS	U: 3.29 (2.63-8.5) M: 3.42 (2.21-6.5)	qRT-PCR	circ-101237	serum	6

	(88/56)																		
Li 2020	≥60 (10/7) <60 (28/32)	China	HCC	≥5cm (14/24) <5cm (24/15)	77	30/358/4	I/II (29/22) III (9/17)	38	-	-	39	-	-	Down	OS	0.80 (0.31-2.08)	qRT-PCR	circ-102,166	Tissue	5
Xiao 2020	-	China	CRC	-	200	-	-	-	-	-	-	-	-	Up	OS	U: 62.73 (22.51-174.85) M: 6.23 (1.29-30.13)	qRT-PCR	circ-FADS2	Tissue	8
Sun 2020	≥60 (25/21) <60 (16/20)	China	HCC	>5cm (23/11) ≤5cm (18/30)	82	29/26 12/15	I/II (17/30) III/IV (24/11)	41	-	-	41	-	-	Up	OS	U: 2.20 (1.32-3.69) M: 1.81 (1.03-3.19)	qRT-PCR	circ-0005394	Tissue	7
Li 2020	≥50 (9/9) <50 (11/11)	China	HCC	≥5cm (12/15) <5cm (8/5)	40	13/11 7/9	I/II (9/6) III/IV (11/14)	20	13	-	20	11	-	Up	OS	1.49 (0.55-4.00)	qRT-PCR	circ-FBXO11	Tissue	7
Huang 2020	NR	China	GC	NR	60	NR	NR	-	-	-	-	-	-	Up	OS	1.64 (0.71-3.85)	qRT-PCR	circ-103809	Tissue	7
Luo 2020	≥60 (7/25) <60 (2/14)	China	GC	≥5 cm (1/27) <5 cm (8/12)	48	5/27 4/12	I/II (7/11) III/IV (2/28)	9	4	-	39	33	-	Down	OS	0.46 (0.13-1.58)	qRT-PCR/IHC	circ-CCDC9	Tissue	7
Liu 2020	>60 (35/37) ≤60 (25/23)	China	GC	>5 cm (35/16) ≤5 cm (25/44)	120	50/48 10/12	I/II (18/32) III/IV (42/28)	60	40	-	60	26	-	Up	OS/DFS	2.17 (0.65-7.14) 2.08 (0.79-5.55)	qRT-PCR	circ-MAT2B	Tissue	6

Jia 2020	≥ 50 (26/38) < 50 (16/44)	China	HCC	>5cm (16/39) ≤ 5 cm (26/43)	124	37/78 5/4	I/II 23/38 III/IV 19/44	42	-	-	82	-	-	Down	OS	0.68 (0.47-0.98)	qRT-PCR	circ-NFATC3	Tissue	7
Lu 2019	≥ 65 (33/17) < 65 (37/10)	China	GC	≥5 cm (29/14) <5 cm (31/13)	97	48/21 22/6	I/II (29/16) III (41/11)	58	46	-	-	12	-	Up	OS	U: 2.55 (1.87-3.81) M: 1.43 (1.05-2.27)	qRT-PCR	circ-RanGAP1	Tissue	7
Ma 2020	> 60 (36/40) ≤ 60 (13/10)	China	CRC	NR	99	34/25 15/25	I/II (28/39) III/IV (21/11)	49	-	-	50	-	-	Up	OS	1.33 (0.62-2.77)	qRT-PCR	circ-5615	Tissue	7
Peng 2020	≥ 60 (13/16) < 60 (20/17)	China	GC	≥ 4 cm (25/14) <4 cm (8/19)	66	26/28 5/7	I/II (9/17) III/IV (24/16)	33	-	-	33	-	-	Up	OS	U: 11.05 (2.48-49.23) M: 5.13 (1.06-24.75)	qRT-PCR	circ-0010882	Plasma	6
Nanishi 2020	< 70 (18/12) ≥ 70 (19/21)	Japan	GC	<5 cm (13/10) ≥5cm (24/23)	70	30/20 7/13	NR	37	-	-	33	-	-	Up	RFS /OS	1.28 (0.12-13.11)	qRT-PCR	circ-ERBB2	Plasma	8
Tang 2020	> 60 (38/36) ≤ 60 (40/55)	China	CRC	>5 cm (48/64) ≤ 5cm (30/27)	169	57/59 21/32	I/II (22/51) III/IV (56/40)	78	-	11	91	-	3	Up	OS	U: 0.28 (0.13-0.61) M: 0.44 (0.19-1.00)	qRT-PCR	circ-MBOAT2	Tissue	7
Wang 2020	> 60 (13/10) ≤ 60	China	CRC	>3 cm (14/6) ≤ 3cm (9/17)	46	13/12 10/11	I/II (5/15) III/IV (18/8)	23	17	13	23	7	6	Up	OS	1.29 (0.15-11.11)	qRT-PCR	circ-NOX4	Tissue	7

	(10/13)																		
Wang 2020	>60 (17/21) ≤60 (22/18)	China	EsoC	NR	78	19/232 0/16	I/II (17/31) III/IV (22/8)	39	-	-	39	-	-	Up	OS	3.12 (0.88-11.11)	qRT-PCR	circ-LRP6	Tissue	7
Zhang 2020	≥60 (6/14) <60 (6/14)	China	GC	≥3.5 cm (8/16) <3.5cm (4/12)	40	7/195/9	I/II (4/11) III (8/17)	12	10	-	28	17	-	Up	OS	M: 2.63 (1.05-8.36)	qRT-PCR	circ-DUSP16	Tissue	6
Yang 2020	NR	China	CRC	NR	50	NR	NR	26	-	-	24	-	-	Down	OS	U: 0.17 (0.08-0.38) M: 0.16 (0.07-0.39)	qRT-PCR	circ-0002320	Plasma	6
Zhang 2020	≥60 (7/9) <60 (8/6)	China	GC	NR	30	8/107/5	I/II (1/11) III/IV (14/4)	15	6	-	15	8	-	Up	OS	1.56 (0.38-6.25)	qRT-PCR/IHC	circ-ATXN7	Tissue	7
Zhang 2020	NR	China	GC	NR	55	NR	NR	28	-	-	27	-	-	Up	OS	3.45 (0.97-12.5)	qRT-PCR	circ-0026359	Tissue	7
Zhang 2020	≥60 (22/23) <60 (14/13)	China	GC	≥5 cm (25/10) <5 cm (11/26)	72	18/151 8/21	I/II (9/19) III/IV (27/17)	36	33	-	36	23	-	Up	OS	U: 2.56 (1.38-4.73) M: 2.04 (1.01-4.11)	qRT-PCR	circ-ATAD1	Tissue	7
Zhang 2020	>50 (63/68) ≤50 (57/52)	China	HCC	>5cm (82/55) ≤5cm (38/65)	240	83/793 7/41	I/II (52/44) III/IV (68/76)	120	-	-	120	-	-	Up	OS	1.34 (0.94-2.05)	qRT-PCR	circ-UHRF1	Tissue	6
Li 2018	NR	China	GC	NR	32	NR	NR	-	-	-	-	-	-	Up	OS	1.78 (0.34-9.09)	qRT-PCR	circ-0056618	Tissue	6

Cai 2018	<60 9/12 ≥60 21/18	China	GC	<5cm 23/18 ≥5cm 7/12	60	20/241 0/6	I/II 17/7 III 13/23	30	14	10	30	24	21	Down	OS/DFS	OS (M): 0.38 (0.15-0.95) DFS(M): 0.35 (0.15-0.82)	qRT-PCR	circ-SMARCA5	Tissue	7
Yong 2018	≤60 9/8 >60 11/12	China	CRC	NR	40	9/13 8/10	I/II 7/14 III/IV 13/6	20	-	-	20	-	-	Up	OS	1.56 (0.50-4.76)	qRT-PCR	circ-0071589	Tissue	7
Wang 2018	<60 13/10 ≥60 10/13	China	CRC	<5cm 14/8 ≥5cm 9/15	46	13/17 1 0/6	I/II 13/4 III/IV 10/19	23	-	3	23	-	11	Down	OS	0.36 (0.13-1.04)	qRT-PCR	circ-0014717	Tissue	6
Li 2018	NR	China	CRC	NR	101	NR	NR	-	-	-	-	-	-	Down	OS	2.41 (1.28-4.55)	qRT-PCR	circ-0000711	Tissue	7
Jin 2018	NR	China	CRC	NR	52	NR	NR	-	-	-	-	-	-	Up	OS	1.78 (0.65-5.00)	qRT-PCR	circ-0136666	Tissue	6
Fang 2018	NR	China	CRC	NR	44	NR	NR	24	-	-	20	-	-	Up	OS	1.89 (0.61-5.88)	qRT-PCR	circ-100290	Tissue	7
Cai 2019	<60 7/13 ≥60 18/12	China	GC	<5cm 8/15 ≥5cm 17/10	50	15/191 0/6	I/II 6/16 III 19/9	25	20	-	25	12	-	Up	OS	M: 3.33 (1.34-8.28)	qRT-PCR	circ-HECTD1	Tissue	6
Chen 2016	<60 48/36 ≥60 59/44	China	GC	≤5cm 66/43 >5cm 41/37	187	86/582 1/22	I/II 24/13 III/IV 83/67	107	93	16	80	70	11	Up	OS/DFS	OS (U):1.63 (1.14-2.34) OS (M): 1.45 (1.00-2.10) DFS (U): 1.52 (1.07-2.17) DFS (M): 1.43 (0.99-2.06)	qRT-PCR	circ-PVT1	Tissue	7
Yuan 2018	NR	China	CRC	NR	32	NR	NR	15	-	-	17	-	-	Down	OS	0.64 (0.18-2.25)	qRT-PCR	circ-0026344	Tissue	7

Du 2019	≤60 22/30 >60 23/15	China	GC	-	90	32/24 13/21	I/II (16/31) III/IV (29/14)	45	30	28	45	12	11	Up	OS	1.61 (0.72- 3.57)	qRT-PCR	circ-PRMT5	Tissue	7
Guo 2017	≥55 1102 <506 98	China	HCC	NR	288	117063 0	NR	-	-	-	-	-	-	Down	OS	0.45 (0.29-0.68)	qRT-PCR	circ-ITCH	Tissue	6
Hao 2018	≥60 17/14 <60 13/16	China	PDAC	NR	60	12/15 18/15	I/II 13/23 III/IV 17/7	30	26	-	30	17	-	Up	OS	U: 2.32 (1.33-4.06) M: 2.13 (1.22-3.74)	qRT-PCR	circ-0007534	Tissue	7
Xin 2018	-	China	HCC	NR	380	NR	NR	-	-	-	-	-	-	Up	OS	U: 2.2 (1.64-3.01) M: 2.07 (1.52-2.83)	qRT-PCR	circ-ASAP1	Tissue	6
Jiang 2018	≥60 14/20 <60 11/13	China	PDAC	NR	58	14/17 11/16	I/II 17/13 III/IV 8/20	25	14	-	33	23	-	Down	OS	U: 2.41 (1.35-4.33) M: 1.99 (1.03-3.84)	qRT-PCR	circ-0001649	Tissue	7
Jin 2019	>60 40/38 ≤60 32/35	China	CRC	>5cm 30/21 ≤5cm 42/52	145	45/50 27/23	I/II 42/55 III/IV 30/18	-	-	-	-	-	-	Up	OS/ DFD	OS (M): 3.24 (1.48-5.16) DFS (M): 3.45 (1.64-5.44)	qRT-PCR	circ-0005075	Tissue	6
Li 2018	≤60 20/26 >60 22/17	China	PDAC	≤2cm 12/16 >2cm 30/27	85	31/35 11/8	I/IIa 18/29 IIb/III/IV 24/14	42	19	10	43	11	2	Up	OS	M: 1.75 (1.05-2.92)	qRT-PCR	circ-IARS	Tissue	6
Li 2018	≤50 8/15	China	Esophageal	<5cm 51/52	62	50/49 11/13	I/II 25/37 III	-	-	-	-	-	-	Up	OS/ DFS	0.38 (0.20-0.74)	qRT-PCR	circ-ciRS-7	Tissue	7

	> 50 5 3/47		(ESO C)	≥5c m 10/1 0			36/ 25												
We ng 2017	≤ 71 4 6/39 > 71 4 3/37	C hina	C RC	-	1 65	4 1/28 4 8/48	I/II (29/4 9) III/ IV(60 /27)	8 9	5 5	2 7	7 6	2 3	1 1	Up	OS	U: 2.69 (1.26-5.74) M: 2.73 (1.09-6.8)	q RT- PCR	circ- ciRS-7	Tiss ues	6
Liu 2018	≤ 61 3 6/30 > 61 3 0/33	C hina	G C	≤3c m 35/4 2 >3c m 31/2 1	1 29	4 0/41 2 6/22	I/II 36/ 49 III/ IV 30/ 14	-	-	2 4	-	-	1 2	Up	OS	U: 3.14 (1.55-4.57) M: 2.3 (1.67-3.78)	q RT- PCR	circ- 0009910	Tiss ue	7
Lu 2019	< 65 3 7/10 ≥ 65 3 3/17	C hina	G C	<5c m 31/1 3 ≥5c m 29/1 4	9 7	4 8/21 2 2/6	I/II 29/ 16 III 41/ 11	7 0	4 6	-	2 7	1 2	-	Up	OS	U: 2.55 (1.87-3.81) M: 1.43 (1.05-2.27)	q RT- PCR	circ- RanGAP 1	Tiss ue plas ma	7
Lu 2018	< 60 9/ 5 ≥ 60 2 3/14	C hina	G C	<5c m 10/6 ≥5c m 22/1 3	5 1	2 4/14 8/ 5	I (7/8) II (12/6) III(13/5)	3 2	1 5	-	1 9	3	-	Up	OS	3.68 (1.67-5.33) 2.68 (1.42-4.80)	q RT- PCR	circ- 0000467	Tiss ue	7
Wa ng 2019	< 60 1 6/18 ≥ 60 1 4/12	C hina	H CC	<3c m 12/3 ≥3c m 18/2 7	6 0	2 3/25 7/ 5	I/II 13/ 3 III/ IV 17/ 27	3 0	-	-	3 0	-	-	Do wn	OS	2.44 (1.05-5.88)	q RT- PCR	circ- 0091570	Tiss ue	7
Li 2018	≤ 60 2 4/26 > 60 2 2/21	C hina	P DAC	≤2c m 16/1 5 >2c m 30/3 2	9 3	3 4/38 1 2/9	I/II a 19/ 33 IIb /IV 27/ 14	4 6	2 2	9	4 7	1 1	3	UP	OS	M: 1.76 (1.06-2.93)	q RT- PCR	circ- PDE8A	Tiss ue	6
Che n 2018	≥ 55 2 2/15	C hina	H CC	NR	7 8	3 4/36 5/ 3	N R	3 9	1 4	6	3 9	5	1	Up	OS	U: 1.98 (1.34-3.02) M: 6.66 (2.66-8.42)	q RT- PCR	circ- 0128298	Tiss ue	6

	< 55 17/24																		
Pan 2017	≤ 65 41/42 > 65 35/36	China	GC	NR	154	36/454 1/32	I/II (38/46) III/IV (43/27)	83	28	5	71	29	0	Up	OS	2.63 (0.82-4.50)	qRT-PCR	circ-ciRS-7	Tissue	7
Wang 2019	< 60 24/22 ≥ 60 37/37	China	GC	<5cm 24/30 ≥5cm 37/29	120	35/32 26/27	I/II 20/36 III/IV 41/23	61	39	8	59	25	3	Up	OS	U: 0.74 (0.03-1.33) M: 0.83 (0.35-1.01)	qRT-PCR	circ-LMTK2	Tissue	7
Wu 2019	< 60 16/12 ≥ 60 17/17	China	GC	<5cm 11/14 ≥5cm 22/15	62	15/18 18/11	I/II 8/15 III/IV 25/14	33	30	-	29	19	-	Up	OS	U: 2.57 (1.38-4.78) M: 2.06 (1.06-4.01)	qRT-PCR	circ-DCAF6	Tissue	6
Xu 2018	< 60 14/16 ≥ 60 18/14	China	PDAC	NR	62	14/15 18/15	I/II 12/24 III/IV 20/6	32	27	-	30	16	-	Up	OS	U: 3.05 (1.67-5.58) M: 2.63 (1.26-5.45)	qRT-PCR	circ-0030235	Tissue	6
Zeng 2018	≤ 65 38/41 > 65 51/48	China	CRC	≤5cm 50/57 >5cm 39/32	178	53/49 36/40	I/II 51/70 III/IV 38/19	89	46	18	89	30	5	Up	OS	U: 4.12 (1.97-7.96) M: 2.75 (1.74-6.51)	qRT-PCR	circ-HIPK3	Tissue	6
Zhang X 2018	< 54 38 ≥ 54 39	China	HCC	<5cm 20 ≥5cm 57	77	67 1	I/II 34 III/IV 43	-	-	-	-	-	-	Down	OS	U: 0.28 (0.09-0.83) M: 0.19 (0.05-0.68)	qRT-PCR	circ-0001649	Tissue	7
Han 2017	NR	China	HCC	NR	116	NR	NR	-	-	-	-	-	-	Down	OS	0.49 (0.35-0.69)		circ-MTO1	Tissue	7

Zhang Ch 2018	NR	China	HCC	NR	75	NR	NR	38	-	-	37	-	-	Down	OS	0.26 (0.14-0.50)	qRT-PCR	circ-0091579	Tissue	6
Zhong Li 2018	<60 10/11 ≥60 14/12	China	HCC	<3cm 14/6 ≥3cm 10/17	47	19/155/18	I/II 15/7 III/IV 9/16	24	4	-	23	11	-	Down	OS	0.44 (0.17 - 2.42)	qRT-PCR	circ-C3P1	Tissue	7
Huang 2017	≤55 16/27 >55 13/24	China	HCC	-	80	21/418/10	I/II 11/32 III/IV 18/19	29	23	9	51	26	3	Up	OS	2.75 (1.01-7.25)	qRT-PCR	circ-100338	Tissue	6
Yu J 2018	≤50 44/45 >50 34/40	China	HCC	≤5cm 43/32 >5cm 35/53	163	62/741 6/11	I 38/24 II/III 40/61	78	19	-	85	39	-	Down	OS DFS	M: 2.47 (1.459-4.182) M: 1.673 (1.08-2.591)	qRT-PCR	circ-cSMARCA5	Tissue	6
Xu L 2017	<40 26 ≥40 82	China	HCC	-	95	96 12	-	48	-	-	47	-	-	Up	DFS	1.17 (0.58 - 2.38)	qRT-PCR	circ-ciRS-7	Tissue	7
Li Sh 2018	<50 10/12 ≥50 16/13	China	HCC	<5cm 19/9 ≥5cm 7/16	51	19/187/7	I/II 8/16 III/IV 18/9	26		12	25	-	5	Up	OS	U: 4.91 (1.93–12.48) M: 3.25 (1.10-9.59)	qRT-PCR	circ-101368	Tissue	7
Liu H 2018	<60 22/20 ≥60 18/10	China	HCC	≤5cm 8/14 >5cm 32/16	70	32/268/4	I/II 13/21 III/IV 27/9	40	-	-	30	-	-	Up	OS	U: 2.43 (1.38-4.24) M: 2.29 (1.06-4.95)	qRT-PCR	circ-001569	Tissue	6
Weng Q 2018	<60 48/47	China	HCC	≤5cm 25/44	120	54/516/9	I/II 26/48 III	60	12	-	60	6	-	Down	OS	2.3 (1.72-4.58)	qRT-PCR	circ-0064428	Tissue	6

	≥ 60 1 2/13			>5cm 35/16			34/12													
Cai H 2018	-	China	HCC	-	78	-	-	56	-	-	22	-	-	Up	OS	2.45 (1.46-4.19)	qRT-PCR	circ-0103809	Tissue	7
Gong Y 2018	-	China	HCC	-	64	-	-	32	-	-	32	-	-	Up	OS	1.45 (1.04-2.32)	qRT-PCR	circ-ZEB1.33	Tissue	6

Note. HCC: hepatocellular carcinoma; PDAC: pancreatic ductal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; CRC: colorectal cancer; GC: gastric cancer; OS: overall survival; DFS: disease free survival; Uni: Univariate analysis; Multi: Multivariate analysis; LNM: lymph node metastasis; DM: distant metastasis; Note: the dashes represent no data.

Supplementary-2. Association between serum levels of down (A) and upregulated (B) CircRNAs and characteristics of patients with digestive system.

Down regulated (A)						
Variable	**Number of study**	**Model**	**Heterogeneity**		**Test of association**	
			I^2 (%)	**P value**	**Pooled OR/HR**	**95% CI**
Tumor size (Large vs Small)	**16**	**Random**	**56.76**	**0.006**	**0.51**	**0.34-0.77**
Subgroup analysis						
HCC	9	Random	74.34	0.001	0.53	0.27-1.04
GC	**6**	**Random**	**69.87**	**0.001**	**0.26**	**0.10-0.65**
CRC	1	Fixed	NA	NA	0.34	0.13-1.13
Gender (Male vs female)	17	Fixed	25.14	0.57	0.85	0.65-1.11
Subgroup analysis						
HCC	9	Fixed	16.23	0.28	0.95	0.66-1.36
GC	6	Fixed	49.61	0.79	0.73	0.46-1.15
CRC	1	Fixed	NA	NA	0.45	0.13-1.59
PDAC	1	Fixed	NA	NA	1.19	0.42-3.40
Age (High vs Low)	17	Random	53.68	<0.001	0.93	0.66-1.20
Subgroup analysis						
HCC	9	Fixed	0.00	0.91	1.22	0.93-1.60
GC	4	Fixed	0.00	0.40	1.15	0.63-2.09
CRC	1	Fixed	NA	NA	0.59	0.18-1.89
PDAC	1	Fixed	NA	NA	0.82	0.28-2.37
Distance Metastasis (Yes vs No)	**2**	**Fixed**	**NA**	**0.84**	**0.22**	**0.10-0.40**
TNM Stage (III/IV vs I/II)	**14**	**Random**	**78.73**	**0.00**	**0.44**	**0.25-0.79**
Subgroup analysis						

HCC		7	Random	83.14	<0.001	0.54	0.23-1.27
GC		6	Random	73.46	<0.001	0.53	0.22-1.26
CRC		**1**	**Fixed**	**NA**	**NA**	**0.16**	**0.04-0.62**
PDAC		**1**	**Fixed**	**NA**	**NA**	**0.07**	**0.01-0.30**
Overall survival	Univariate	22	Random	90.43	<0.001	0.74	0.54-1.03
	Multivariate	4	Random	90.96	<0.001	0.59	0.18-1.93
Subgroup analysis of univariate							
HCC		12	Random	89.77	<0.001	0.67	0.43-1.05
GC		5	Random	82.32	<0.001	1.16	0.80-1.69
CRC		4	Random	89.95	<0.001	0.56	0.14-2.21
PDAC		1	Fixed	NA	NA	2.41	1.35-4.30
Subgroup analysis of multivariate							
CRC		1	Random	NA	NA	0.16	0.07-0.36
GC		1	Random	NA	NA	0.38	0.15-0.96
PDAC		**1**	**Random**	**NA**	**NA**	**1.99**	**1.03-3.84**
HCC		2	Random	91.83	<0.001	0.73	0.06-9.08

Up regulated (B)						
Variable	**Number of study**	**Model**	**Heterogeneity**		**Test of association**	
			I^2 (%)	**P value**	**Pooled OR/HR**	**95% CI**
Tumor size (Large vs Small)	44	Random	74.23	0.00	1.52	1.69-1.98
Subgroup analysis						
GC	**18**	**Random**	**73.16**	**0.00**	**1.51**	**1.01-2.24**
CRC	7	Random	81.80	0.00	1.64	0.72-3.87
HCC	12	Random	77.58	0.00	1.57	0.96-2.56
PDAC	5	Fixed	48.80	0.09	1.38	0.89-2.15
Gender (Male vs Female)	54	Fixed	NA	0.31	0.99	0.88-1.11
Subgroup analysis						
GC	21	Fixed	50.00	0.00	0.81	0.61-1.07
CRC	9	Fixed	40.69	0.09	1.16	0.90-1.49
ESCC	1	Fixed	NA	NA	1.98	0.80-4.87
PDAC	10	Fixed	0.00	0.58	0.96	0.73-1.24
HCC	12	Fixed	0.00	0.58	1.04	0.80-1.36
ESOC	1	Fixed	NA	0.31	0.99	0.88-1.11
Age (High vs Low)	54	Fixed	NA	0.08	1.07	0.96-1.19
Subgroup analysis						
PDAC	11	Random	50.02	0.02	1.41	0.98-2.03
GC	18	Fixed	0.00	0.48	0.95	0.78-1.16
CRC	9	Fixed	0.00	0.74	0.96	0.74-1.24
ESCC	1	Fixed	NA	NA	1.07	0.43-2.67

HCC		14	Fixed	0.00	0.67	0.98	0.81-1.19
ESOC		1	Fixed	NA	NA	0.66	0.27-1.61
Distance metastasis		**17**	**Random**	**66.31**	**0.00**	**2.73**	**1.67-4.45**
Subgroup analysis							
GC		**5**	**Fixed**	**43.33**	**0.16**	**2.51**	**1.60-3.93**
CRC		5	Random	88.47	0.00	1.11	0.24-5.01
PDAC		**3**	**Fixed**	**0.00**	**0.79**	**3.50**	**1.66-7.40**
HCC		**4**	**Fixed**	**0.00**	**0.57**	**3.82**	**2.24-5.10**
TNM stage (III/IV vs I/II)		**50**	**Random**	**73.75**	**0.00**	**2.68**	**2.09-3.45**
Subgroup analysis							
GC		**18**	**Random**	**55.84**	**0.00**	**2.41**	**1.72-3.39**
CRC		**9**	**Fixed**	**9.17**	**0.41**	**4.13**	**3.20-5.34**
ESCC		1	Fixed	NA	NA	1.40	0.60-3.23
PDAC		**9**	**Random**	**64.15**	**0.00**	**2.88**	**1.67-4.98**
HCC		**11**	**Random**	**86.80**	**0.00**	**1.98**	**1.009-3.91**
ESOC		**1**	**Fixed**	**NA**	**NA**	**5.01**	**1.84-13.66**
Overall survival	**Uni variant**	**77**	**Random**	**73.38**	**<0.001**	**1.96**	**1.72-2.22**
	Multi variant	**40**	**Random**	**73.57**	**<0.001**	**1.92**	**1.62-2.28**
Subgroup analysis of univariate							
GC		**29**	Random	**68.14**	**<0.001**	**2.36**	**1.92-2.91**
ESCC		3	Random	**95.18**	**<0.001**	0.83	0.16-4.26
CRC		13	Random	**63.18**	**<0.001**	1.50	0.99 -2.23
PDAC		**12**	**Fixed**	**76.03**	**0.358**	**1.76**	**1.27-2.45**
HCC		**19**	**Random**	**63.05**	**<0.001**	**2.08**	**1.75-2.48**
ESOC		1	Fixed	NA	NA	3.12	0.88-11.06
Subgroup analysis of multivariate							
CRC		**4**	**Fixed**	**0.00**	**0.13**	**2.34**	**1.74-3.14**
ESCC		**1**	**Fixed**	**NA**	**NA**	**3.70**	**1.82-7.51**
GC		**14**	**Fixed**	**0.00**	**0.28**	**1.76**	**1.53-2.01**
PDAC		**7**	**Fixed**	**0.00**	**0.56**	**2.00**	**1.64-2.44**
HCC		**9**	**Fixed**	**0.00**	**0.52**	**2.23**	**1.88-2.64**

Note: OS: overall survival; DFS: disease free survival; F: Fixed effects model; R: random effects model; DM: distant metastasis.