Prognostic Role of Circular RNAs Expression in Bladder Carcinoma: A Meta-Analysis

Siyuan Wang, Shengqiang Fu, Qiang Chen, Yutang Liu, Zhilong Li, and Ting Sun

Background: Circular RNAs (circRNAs), a type of noncoding RNA, are associated with the occurrence and development of cancers. In recent years, their potential as biomarkers for bladder cancer (BC) has attracted increased attention.

Aims: To reveal the value of circRNAs in the prognosis of BC.

Methods: Relevant studies were collected to extract the clinicopathological data and overall survival (OS) of patients with BC. We then evaluated their tumor-related clinicopathological indicators using pooled odds ratio (OR) and 95% confidence interval (CI). Hazard ratio (HR) and 95% CI were used to estimate the OS of BC patients who expressed abnormal circRNAs.

Results: The results indicate that seven circRNAs (circMYLK, circASXL1, hsa_circ_0000144, circ-VANGL1, circGprc5a, circZFR, and circ-cTFRC) whose expression was upregulated in tumor tissues, are associated with poor clinicopathological features (tumor/node/metastasis [TNM] stage: OR=4.86, 95% CI: 2.53–9.34; histological grade: OR=3.71, 95% CI: 2.37–5.79; lymph node metastasis: OR=3.23; 95% CI: 2.15–4.88; recurrence: OR=5.33; 95% CI: 2.27–12.52) and poor prognoses (OS: HR=1.69; 95% CI: 1.17–2.44). We also found that seven circRNAs (circMTO1, circ-ITCH, circUBXN7, circFNDC3B, circ-ZKSCAN1, circPICALM, and circACVR2A) that were downregulated in tumors were associated with better clinicopathological indicators (TNM stage: OR=0.23, 95% CI: 0.14–0.38; histological grade: OR=0.21, 95% CI: 0.13–0.33; lymph node metastasis: OR=0.26; 95% CI: 0.15–0.47) and better prognoses (OS: HR=0.42; 95% CI: 0.30–0.58).

Conclusion: Our results suggest that certain circRNAs are related to the clinicopathological characteristics and prognosis of BC patients, and may potentially be used as biomarkers.

Keywords: circular RNA, bladder cancer, prognosis, meta-analysis

Introduction

BLADDER CANCER (BC) was ranked the ninth-most prevalent cancer in the world (Antoni *et al.*, 2017). In 2012, a total of 429,793 patients were diagnosed with BC, and 165,084 deaths occurred globally (Siegel *et al.*, 2017). BC cases are classified according to the depth of tumor infiltration (Burger *et al.*, 2013). Newly diagnosed BC cases comprised 75% nonmuscle invasive bladder cancer (MIBC) and 25% MIBC. MIBC patients typically present with local or distant metastases and poor prognoses. Therefore, it is urgent to find useful molecular biomarkers for the diagnosis and prognosis of newly identified BC cases.

Noncoding RNAs (ncRNAs), include several classes of transcripts, are encoded by the genome, but are not translated into proteins. Recently, with the development of next-

generation RNA sequencing technologies, many cancer-related ncRNAs have been discovered (Slack and Chinnaiyan, 2019). Among them, microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs) have been associated with clinical outcomes. miRNAs are short ncRNAs (~22 nt) that regulate the expression of other RNAs via binding with complementary sequences in target mRNAs (Gebert and MacRae, 2019). lncRNAs, sequence length >200 bp, have been shown to play important roles in cancer through chromatin modification and transcriptional and post-transcriptional regulation of mRNAs (Yao *et al.*, 2019). circRNAs are primarily produced by the splicing process for the production of mature mRNAs and are characterized by a covalent closed-loop structure that has neither a 5' cap end nor a 3' polyadenylation tail (Salzman, 2016). Studies have confirmed that some abnormally expressed circRNAs can affect

the development of tumors by regulating the expression of target genes and might be suitable as cancer biomarkers (Meng *et al.*, 2017; Wang *et al.*, 2018b). Salmena *et al.* (2011) proposed the competitive endogenous RNA (ceRNAs) hypothesis linking the expression of mRNAs, miRNAs, lncRNAs, and circRNAs together into a complex network. This theory proposes that lncRNAs or circRNAs can serve as “molecular sponges” of miRNAs to decrease the latter’s activity, thereby upregulating miRNA target gene expression. In support of this theory, an ever-increasing number of circRNAs have been shown to regulate gene expression via such ceRNA networks in numerous tumors (Wang *et al.*, 2018a; Cong *et al.*, 2019). For example, circ-tau tubulin kinase 2 (TTBK2) competitively binds miRNA-217 and upregulates the expression of the oncogene HNF1 homeobox B (HNF1 β) to promote proliferation, invasion, and migration of glioma cells (Zheng *et al.*, 2017). In lung adenocarcinoma, circ-mitochondrial TRNA translation optimization 1 (circMTO1) serves as a sponge of oncogenic miRNA-17 to increase the expression of the RNA-binding protein QKI-5, leading to the inactivation of the Notch signaling pathway, thereby restraining the growth of lung adenocarcinomas (Zhang *et al.*, 2019a). In BC, circ-myosin light chain kinase (circMYLK) binds to miRNA-29a to activate the VEGFA/VEGFR and downstream Ras/ERK signaling pathways to promote the proliferation, migration, and vascularization of BC cells (Zhong *et al.*, 2017). Although there are multiple studies that have been undertaken at the cell and organismal level (Cong *et al.*, 2019; Li *et al.*, 2019b), it is unclear whether the abnormally expressed circRNAs are related to the clinicopathology of BC patients and whether they have a clear diagnostic and prognostic value. Due to the fact that the data provided by individual studies of circRNAs in BC were insufficient to analyze their diagnostic and prognostic roles, we conducted a meta-analysis.

Materials and Methods

Study selection

We searched for the following search terms: (“circRNA” OR “circular RNA”) AND (“bladder cancer” OR “bladder

tumor” OR “bladder carcinoma” OR “bladder neoplasm”) in PubMed, EMBASE, Web of Science, and Cochrane Library before November 21, 2019. We selected studies using the following inclusion criteria: (1) literature findings that included data on abnormally expressed circRNAs and survival outcomes in BC patients; (2) the study that indicated that the included patients were pathologically diagnosed as having BC; and (3) the studies that investigated the clinicopathological features of circRNAs in BC. Exclusion criteria were as follows: (1) results of the literature studies were not published in English; (2) similar studies from the same author reusing clinical specimens; and (3) reviews, meta-analyses, and case reports.

Data extraction

First, S.W. and S.F. rigorously evaluated the eligibility of the included studies, and then extracted data from each study including the following: (1) the first author, the year of publication, the circRNA that was abnormally expressed, the related miRNA(s), detection methods, and the presumptive regulatory role of the circRNA; (2) clinicopathological information regarding circRNA expression, age, gender, tumor size, tumor/node/metastasis (TNM) stage, histological grade, lymphatic metastasis, vascular invasion, and recurrence; (3) prognostic data including follow-up time, hazard ratio (HR), and 95% confidence interval (CI) of BC patients.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to determine the quality of the literature included in this meta-analysis (Stang, 2010).

Statistical analyses

We used pooled odds ratios (OR) and 95% CI to evaluate BC clinicopathological indicators; we used the HR and 95% CIs to evaluate overall survival (OS) of BC. Heterogeneity among the included studies was tested using I^2 tests. When $I^2 < 50\%$, there was considered to be no significant heterogeneity, a fixed effect model was used for this analysis.

FIG. 1. Flowchart of the research selection process.

Otherwise, a random-effect model was used (Egger *et al.*, 1997). Sensitivity analysis was used to check the consistency of the overall effect assessment, and Begg’s test was used to analyze the publication bias of the study. A *p*-value <0.05 was considered statistically significant.

Results

Search results

As shown in Figure 1, the process of selecting the included literature was as follows: 172 records of circRNA expression and BC were found: PubMed (56), EMBASE (74), Web of Science (41), and Cochrane databases (1). Among them, 91 duplicate publications were deleted. After filtering through titles and abstracts, 34 records were excluded. The remaining 47 articles were evaluated for eligibility via reading of the full text; 33 were excluded due to insufficient data. A total of 14 studies were included in the final meta-analysis.

Study characteristics and study quality

The baseline data from the 14 included studies are shown in Table 1. These studies covered a total of 14 circRNAs spread among 1430 patients who were pathologically diagnosed as suffering from BC in Asia. Seven of these circRNAs were associated with poor clinicopathological outcomes (Tang *et al.*, 2017; Zhong *et al.*, 2017; Gu *et al.*, 2018; Huang *et al.*, 2018; Su *et al.*, 2019; Zeng *et al.*, 2019; Zhang *et al.*, 2019c); and the remaining seven were associated with better clinicopathological outcomes (Liu *et al.*, 2018a, 2018b; Yang *et al.*, 2018; Bi *et al.*, 2019; Dong *et al.*, 2019; Li *et al.*, 2019a; Yan *et al.*, 2019). In addition, our baseline data also included the miRNA levels reported in the primary studies that are thought to be part of a ceRNA network that regulates the expression of tumor genes. Follow-up times ranged from 44 to 84 months. The NOS was used to evaluate the quality of the included studies. All 14 of the included studies received scores that were >7 points, indicating that the quality of the studies included in this meta-analysis is high, and likely ensuring the reliability of the overall results (Fig. 2).

Meta-analysis for clinicopathological features

The relationships between the circRNA levels and the BC clinicopathological characteristics are shown in Table 2. We observed that higher levels of seven circRNAs (circMYLK, circASXL1, hsa_circ_0000144, Circ-VANGL1, circGprc5a, circZFR, and circ-cTFRC) were associated with poor clinicopathological outcomes (TNM stage: OR = 4.86, 95% CI: 2.53–9.34; histological grade: OR = 3.71, 95% CI: 2.37–5.79; lymph node metastasis: OR = 3.23; 95% CI: 2.15–4.88; recurrence: OR = 5.33; 95% CI: 2.27–12.52, all *p* < 0.05). Furthermore, the results also showed that seven circRNAs (circMTO1, circ-ITCH, circUBXN7, circFNDC3B, circ-ZKSCAN1, circPICALM, and circACVR2A) with lower expression levels were associated with better clinicopathological results (TNM stage: OR = 0.23, 95% CI: 0.14–0.38; histological grade: OR = 0.21, 95% CI: 0.13–0.33; lymph node metastasis: OR = 0.26; 95% CI: 0.15–0.47, all *p* < 0.05). In contrast, we did not observe significant correlations for age, gender, tumor size, and vascular invasion (*p* > 0.05).

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDIES INCLUDED IN THIS META-ANALYSIS

Study	Year	circRNA	miRNA	Sample	circRNA expression		Detection method	Expression status	Survival follow-up analysis (months)
					High	Low			
Zhong <i>et al.</i>	2017	circMYLK	miR-29a	Tumor tissue	16	16	qRT-PCR	Upregulated	OS
Tang <i>et al.</i>	2017	circASXL1	NA	Tumor tissue	27	34	qRT-PCR	Upregulated	OS
Huang <i>et al.</i>	2018	hsa_circ_0000144	miR-217	Tumor tissue	34	35	qRT-PCR	Upregulated	OS
Zeng <i>et al.</i>	2019	Circ-VANGL1	miR-605-3p	Tumor tissue	44	43	qRT-PCR	Upregulated	OS
Gu <i>et al.</i>	2018	circGprc5a	NA	Tumor tissue	29	30	qRT-PCR	Upregulated	OS
Zhang <i>et al.</i>	2019c	circZFR	miR-377	Tumor tissue	52	52	qRT-PCR	Upregulated	OS
Su <i>et al.</i>	2019	circ-cTFRC	miRNA-107	Tumor tissue	110	110	qRT-PCR	Upregulated	OS
Li <i>et al.</i>	2019a	circMTO1	miR-221	Tumor tissue	53	64	qRT-PCR	Downregulated	OS
Yang <i>et al.</i>	2018	circ-ITCH	miR-17	Tumor tissue	25	45	qRT-PCR	Downregulated	OS
Liu <i>et al.</i>	2018a	circUBXN7	miR-1247-3p	Tumor tissue	42	42	qRT-PCR	Downregulated	OS
Liu <i>et al.</i>	2018b	circFNDC3B	miR-1178-3p	Tumor tissue	22	60	qRT-PCR	Downregulated	OS
Bi <i>et al.</i>	2019	circ-ZKSCAN1	miR-1178-3p	Tumor tissue	66	71	qRT-PCR	Downregulated	OS
Yan <i>et al.</i>	2019	circPICALM	miR-1265	Tumor tissue	118	50	qRT-PCR	Downregulated	OS
Dong <i>et al.</i>	2019	circACVR2A	miR-626	Tumor tissue	102	38	qRT-PCR	Downregulated	OS

circMTO1, circ-mitochondrial TRNA translation optimization 1; circMYLK, circmyosin light chain kinase; circRNA, circular RNA; miRNA, microRNA; NA, not available; OS, overall survival; qRT-PCR, quantitative real-time polymerase chain reaction.

	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that Outcome of Interest Was Not Present at Start of Study	Comparability of Cases and Controls on the Basis of the Design or Analysis (1)	Comparability of Cases and Controls on the Basis of the Design or Analysis (2)	Assessment of Outcome	Was Follow-Up Long Enough for Outcomes to Occur	Adequacy of Follow Up of Cohorts
Chaohui Gu 2018	+	+	+	+	+	?	+	+	●
Chengdi Yang 2018	+	+	+	+	+	?	+	+	?
Dong Yan 2019	+	+	+	+	+	?	+	+	?
Gang Tang 2017	+	+	+	+	+	?	+	+	?
Hongwei Liu 2018 (1)	+	+	+	+	+	?	+	+	+
Hongwei Liu 2018 (2)	+	+	+	+	?	?	+	+	+
Hongwei Su 2019	+	+	+	+	+	?	+	+	?
Junming Bi 2019	+	+	+	+	+	?	+	+	?
Wei Dong 2019	+	+	+	+	+	?	+	+	?
Weiping Huang 2018	+	+	+	+	+	?	+	+	?
Wen-Yuan Zhang 2019	+	+	+	+	+	?	+	+	?
Yixiao Li 2018	+	+	+	+	+	?	+	+	?
Zhenyu Zhong 2017	+	+	+	+	+	+	+	●	?
Zhihua Zeng 2018	+	+	+	+	+	+	+	●	?

+ Yes (low risk)
 ? Unclear
 ● No (high risk)

FIG. 2. The Newcastle-Ottawa Scale assesses the quality of studies included.

Meta-analysis for OS

Our results show that the circRNAs that are abnormally expressed in BC patients have significant prognostic value. One such value is that seven of the circRNA (circMYLK, circASXL1, hsa_circ_0000144, Circ-VANGL1, circGprc5a, circZFR, and circ-CTFRC) expression levels were inversely related to OS of BC patients (HR = 1.69; 95% CI: 1.17–2.44; $p = 0.005$) (Fig. 3A). Another is that seven different circRNA (circMTO1, circ-ITCH, circUBXN7, circFNDC3B, circ-ZKSCAN1, circPICALM, and circACVR2A) expression

levels were positively correlated with the OS of BC patients (HR = 0.42; 95% CI: 0.30–0.58; $p < 0.001$) (Fig. 3B). The statistical results show that the various circRNAs had no significant heterogeneity ($I^2 = 0.0\%$, $p = 0.945$; $I^2 = 45.1\%$, $p = 0.091$), and thus, we used a fixed-effect model for the analysis.

Sensitivity analysis and publication bias

As shown in Figure 4 when the included studies were deleted one by one, our sensitivity analysis results showed that

TABLE 2. CLINICAL CHARACTERISTICS OF CIRCULAR RNAs IN BLADDER CANCER

	<i>Tumor promoter</i>			<i>Tumor suppressor</i>		
	<i>OR</i>	<i>95% CI</i>	<i>p</i>	<i>OR</i>	<i>95% CI</i>	<i>p</i>
Age	1.49	0.88–2.50	0.14	0.83	0.57–1.20	0.32
Gender (male/female)	1.25	0.80–1.95	0.32	1.37	0.94–2.00	0.10
Tumor size (≥ 3 / < 3)	0.59	0.33–1.06	0.08	0.99	0.59–1.68	0.98
TNM stage pT2–pT4/pTa–pT1	4.86	2.53–9.34	0.000	0.23	0.14–0.38	0.000
Histological grade	3.71	2.37–5.79	0.000	0.21	0.13–0.33	0.000
Lymph node metastasis (Y/N)	3.23	2.15–4.88	0.000	0.26	0.15–0.47	0.000
Vascular invasion (Y/N)	0.88	0.32–2.38	0.80	0.58	0.19–1.77	0.33
Recurrence (Y/N)	5.33	2.27–12.52	0.000	1.23	0.40–3.75	0.71

CI, confidence interval; N, no; OR, odds ratio; TNM, tumor/node/metastasis; Y, yes.

FIG. 3. Forest plot of circRNA expression and OS in BC patients. (A) Forest plot of tumor-promoting circRNAs. (B) Forest plot of tumor-inhibiting circRNAs. BC, bladder carcinoma; CI, confidence interval; circRNA, circular RNA; HR, hazard ratio; OS, overall survival.

FIG. 4. Sensitivity analysis of circRNAs in predicting OS outliers in BC patients. (A) Tumor-promoting circRNAs; (B) tumor-inhibiting circRNAs.

the pooled HR results from the remaining studies for OS did not change. Results based on Begg's funnel plots show that there was no significant publication bias (Fig. 5A, B, $p > 0.05$).

Discussion

BC is characterized by both high morbidity and mortality (Martinez Rodriguez *et al.*, 2017). It remains a leading cause of cancer-related deaths because of distant metastases and high recurrence rates (Di Meo *et al.*, 2017). Surgery and postoperative chemotherapy are the primary treatments. Although the treatment of BC has improved somewhat due to surgical techniques and second-generation chemotherapy

drugs, the overall treatment effect has not significantly improved due to its biological characteristics (Martinez Rodriguez *et al.*, 2017). This highlights the urgent need for novel biomarkers to more accurately predict its recurrence and to aid in the choice of treatment regimens.

circRNAs were discovered in 1976 and were originally thought to be by-products of splicing precursor mRNAs (Sanger *et al.*, 1976). With the development of high-throughput and bioinformatic technologies, circRNAs have been proven to be widely expressed in various organisms, and to have tissue and cell specificity (Patop *et al.*, 2019). High-throughput sequencing of oral squamous cell carcinoma RNAs has shown that circRNAs are widely expressed in both cancerous tissues and the normal oral mucosa tissues. Chen

FIG. 5. The Begg's test evaluated the publication bias of this meta-analysis. **(A)** Tumor-promoting circRNAs; **(B)** tumor-inhibiting circRNAs.

et al. (2017) identified that 280 circRNAs were differentially expressed (Chen *et al.*, 2017). In BC, there are tens of thousands of circRNAs, among which thousands have differential expressions (Li *et al.*, 2017).

Zhong *et al.* identified the abnormal expression of 469 circRNAs in BC by comparing their expression with normal tissues using microarray chips. Among these circRNAs, 285 were upregulated and 184 were downregulated. They confirmed six of these circRNAs as being significantly differently expressed using quantitative real-time polymerase chain reaction (qRT-PCR). Subsequently, *in vivo* and *in vitro* experiments confirmed that overexpression of one of these, circTCF25, could downregulate miR-103a-3p and miR-107, thereby increasing the expression of cyclin dependent kinase 6 (CDK6) and promoting BC cell proliferation and migration (Wang *et al.*, 2017). In this meta-analysis, 14 studies were included in a total of 1,430 BC cases, revealing the relationship between the expression of different types of circRNA and the clinicopathological and prognostic significance of BC. As different circRNAs play different

roles in BC, 7 of the 14 studies we included associated with better clinicopathological features and the remaining 7 are opposite. We divided them into two groups for analysis. We found that BC patients with high expression of circRNA (circMYLK, circASXL1, hsa_circ_0000144, Circ-VANGL1, circGprc5a, circZFR, and circ-cTFRC) associated with poor clinicopathological features showed inferior OS (OS: HR=1.69; 95% CI: 1.17–2.44). circRNA (circMTO1, circ-ITCH, circUBXN7, circFNDC3B, circ-ZKSCAN1, circPICALM, and circACVR2A) with a high expression that associated with better clinicopathological features has a more favorable OS (OS: HR=0.42; 95% CI: 0.30–0.58). These results suggest that certain circRNAs in BC patients may have a significant prognostic value in OS. Our results further show that some circRNAs (circMYLK, circASXL1, hsa_circ_0000144, Circ-VANGL1, circGprc5a, circZFR, and circ-cTFRC) associated with poorer TNM staging, histological grading, lymph node metastasis, and recurrence in BC, while other circRNAs (circMTO1, circ-ITCH, circUBXN7, circFNDC3B, circ-ZKSCAN1, circPICALM, and circACVR2A)

are related to clinical tumor characteristics such as better TNM staging, histological grade, and lymph node metastasis. However, we found that no matter which type of circRNAs are highly expressed, they are not related to the clinicopathological characteristics of age, sex, tumor size, and vascular invasion. All these results suggest that the abnormally expressed circRNAs may be related to the clinical prognosis of BC patients.

In our research, circZFR was identified as one of the highly expressed circRNAs related to tumor recurrence and poor prognoses in multiple cancers. In nonsmall-cell lung carcinoma (NSCLC), Zhang *et al.* (2019b) showed that expression was significantly upregulated in cancer tissues and cell lines. The knock down of circZFR significantly inhibited cell proliferation, migration, and invasion of NSCLC cells *in vitro*. Moreover, it was demonstrated that circZFR acted as a sponge to absorb miRNA-101-3p and to promote cullin 4B expression. Similarly, Tan *et al.* (2019) found that circZFR is highly expressed in hepatocellular carcinoma (HCC) tissues, and their knockdown of circZFR significantly inhibited the proliferation and epithelial/mesenchymal transition of HCC cells. Kaplan/Meier analyses and log-rank tests showed that elevated expression of circZFR was related to poor prognoses of HCC patients. In terms of mechanism, they found that circZFR enhanced the expression of catenin beta 1 (CTNNB1) by sponging miR-3619-5p, thereby activating the Wnt/ β -catenin pathway, which is known to promote the carcinogenic effect in HCC. In BC, Zhang *et al.* (2019c) found that the expression of circZFR was increased, and that its expression levels were positively correlated with patients' TNM stage, lymphatic metastases, recurrence, and poor OS. They showed that circZFR could promote BC cell growth, migration, and invasion by binding to miR-377 and acting as a sponge to promote zinc finger E-box binding homeobox 2 (ZEB2) expression. These results indicate that circZFR may be a biomarker of BC and that ZEB2 may become a target for the treatment of BC.

Although we made every effort to ensure the authenticity and reliability of our research, this meta-analysis is not without its limitations. First, due to the limited amount of literature collected, the number of cases that were ultimately included was relatively small. Second, when the original literature that was included did not directly indicate the HR value, we calculated HRs from the Kaplan/Meier curve (Parmar *et al.*, 1998), which may also introduce potential biases. Therefore, it is important that additional primary research on these circRNAs be conducted through larger BC patient cohort studies.

Conclusions

In conclusion, our research shows that abnormally expressed circRNAs are related to the clinicopathological features of BC and could serve as prognostic biomarkers for BC patients.

Author Disclosure Statement

No competing financial interests exist.

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Address correspondence to:

Ting Sun, MD

Department of Urology

The First Affiliated Hospital of Nanchang University

No. 17, Yongwai Center Street

Donghu District

Nanchang 330006

Jiangxi

China

E-mail: journal_123@163.com