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ORIGINAL ARTICLE

Evaluation of prognostic value of lncRNA BANCR in tumor patients: A systematic review and meta-analysis

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Summary

Purpose: *Long non-coding RNA (lncRNA) BANCR is reported to be upregulated in many tumors. Nevertheless, the potential value of BANCR in tumor prognosis is unclear, which is mainly explored in this study.*

Methods: *Articles published before January 1, 2019 on the correlation between BANCR and prognosis, lymph node metastasis and distant metastasis were searched for in PubMed, Embase, Cochrane Library and Web of Science and relevant data were extracted. The correlation between the expression of BANCR and tumor prognosis using four survival indicators, including overall survival (OS), disease-free survival (DFS), relapse-free survival (RFS) and progression-free survival (PFS)), lymph node metastasis and distant metastasis was analyzed by calculating hazard ratio (HR), odds ratio (OR) and 95%CI. A heterogeneity test was performed on the selected articles, and the combined effect size, HR, OR and 95%CI were calculated using STATA 12.0 software.*

Results: *A total of 11 articles including 1240 tumor patients were included in this meta-analysis. OS was shorter in tumor patients with high BANCR expression (HR=1.58, 95%CI:1.10-2.26), whereas RFS, DFS and PFS were not shorter compared with low BANCR expression (HR=1.26, 95%CI: 0.50-3.18). Moreover, regression analysis revealed that a high level of BANCR was correlated with lymph node metastasis (OR=1.61, 95%CI: 1.24-2.10) and distant metastasis (OR=2.22, 95%CI: 1.35-3.65).*

Conclusions: *BANCR overexpression was closely correlated with poor overall survival, lymph node metastasis and distant metastasis. Our conclusion still needs to be further verified in a multi-hospital trial using a large sample size.*

Key words: *LncRNA BANCR, prognosis, tumor, meta-analysis*

Introduction

The latest World Cancer Report (2018) published by the WHO reported that there are 14.7 million tumor patients worldwide and 8.2 million tumor deaths in 2018, with a mortality rate of 58.2% [1-3]. Cancer morbidity and mortality are increasing and nearly half of cancer cases occur in Asia. China ranks first in the world in terms of new cancer cases [4,5]. In particular, morbidity and mortality from liver, esophageal, gastric and lung cancer in China are responsible for this situation [6,7]. It is estimated that there will be 19 million tumor cases in 2025 and 24 million in 2035 [1, 6-8]. Cancer is a great threat to human health and its incidence has increased in recent years [8].

A tumor is a newly formed body tissue owing to dysregulated cell growth and abnormal proliferation in the presence of tumorigenic factors, generally manifesting as local masses [9,10]. A single cell undergoing neoplastic transformation repeatedly proliferates into daughter cells, which

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in turn form into a subgroup of tumor cells [4,10]. Therefore, tumor proliferation is generally clonal. Tumor growth lacks the differentiation ability, thus allowing proliferation even in the absence of tumorigenic stimuli [11,12]. This is the essential difference between tumor growth and cell proliferation under physiological conditions or inflammatory stimulation. Nowadays, there are effective targeted cancer therapies. Corresponding drugs developed for specific tumor sites (proteins or gene fragments) specifically kill tumor cells, while more importantly, adjacent normal cells are not influenced [13].

The Human Genome Project identified that at least 70-90% of gene sequences could be transcribed into RNA, but they could not translate proteins, namely non-coding RNAs [14,15]. Long non-coding RNA (lncRNA) is a vital part of non-coding RNA, which lacks the protein-encoding function due to the deficiency of an open reading frame [16]. LncRNAs are extensively expressed in different types of tumors and participate in tumor occurrence, progression and prognosis [16,17]. It is reported that lncRNA BANCR is upregulated in multiple malignant tumors and is closely correlated with tumor grade, lymph node metastasis and distant metastasis [18-20]. The expression level of BANCR in tumor patients may contribute to the early diagnosis and prognosis of tumors. Research on the correlation between BANCR and tumor prognosis has been widely conducted. However, conclusions may not be highly reliable owing to small sample sizes and few tumor types. This study analyzed the prognostic value of BANCR in different types of tumors and provided references for BANCR as a biomarker.

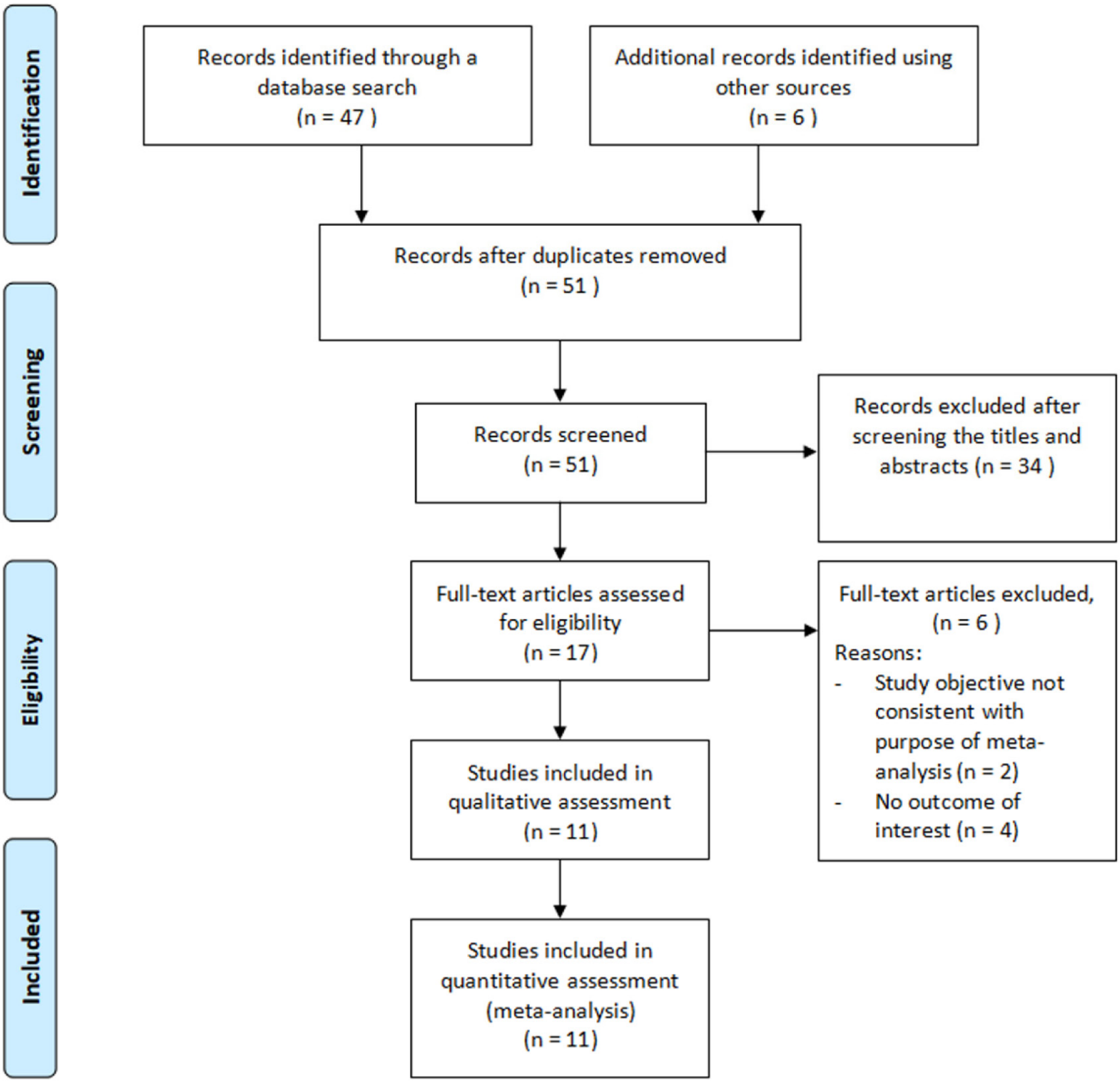

Figure 1. Flow diagram of literature search and selection process.

Table 1. Main characteristics of studies included in the meta-analysis

Publication year	*First author*	*Nationality*	*Dominant ethnicity*	*Study design*	*Malignant disease*	*Detected sample*	*Method*	*Sample size*	*Source of HR*	*Survival analysis*	*Outcome*
2018	Xue	China	Asian	R	RCC	Plasma	qRT-PCR	62	Estimated	Multivariate	OS
2018	Jiang	China	Asian	R	BC	Plasma	qRT-PCR	216	Estimated	Multivariate	OS, RFS
2018	Lou	China	Asian	R	BC	Plasma	qRT-PCR	65	Estimated	Multivariate	OS, DFS
2018	Shen	China	Asian	R	CRC	Plasma	qRT-PCR	106	Estimated	Multivariate	OS
2016	Liu	China	Asian	R	ESCC	Plasma	qRT-PCR	142	Estimated	Multivariate	OS, DFS
2016	Zhou	China	Asian	R	HCC	Plasma	qRT-PCR	109	Estimated	Multivariate	OS
2016	Peng	China	Asian	R	OSC	Plasma	qRT-PCR	84	Estimated	Multivariate	OS
2015	Li	China	Asian	R	GC	Plasma	qRT-PCR	184	Estimated	Multivariate	OS
2015	Su	China	Asian	R	RB	Plasma	qRT-PCR	60	Estimated	Multivariate	OS
2014	Sun	China	Asian	R	NSCLC	Plasma	qRT-PCR	109	Estimated	Multivariate	OS, PFS
2013	Li	China	Asian	R	MM	Plasma	qRT-PCR	103	Estimated	Multivariate	OS

Study design is described as prospective (P) or retrospective (R); OS: overall survival, DFS: disease-free survival, RFS: relapse-free survival, PFS: progression-free survival, MM: Malignant melanoma, CRC: colorectal cancer, BC: Bladder cancer, GC: gastric cancer, RCC: Renal cell carcinoma, HCC: hepatocellular carcinoma, ESCC: esophageal squamous cell carcinoma, OSC: osteosarcoma, RB: retinoblastoma, NSCLC: non-small cell lung cancer

Table 2. Characteristics of lymph node metastasis and distant metastasis in the meta-analysis

Publication year	*First author*	*Nationality*	*Dominant ethnicity*	*Malignant disease*	*Sample size*	*High BANCR expression*			*Low BANCR expression*		
						Total	*LMN*	*DM*	*Total*	*LMN*	*DM*
2018	Xue	China	Asian	RCC	62	-	-	-	-	-	-
2018	Jiang	China	Asian	BC	216	125	63	-	91	17	-
2018	Lou	China	Asian	BC	65	31	13	-	34	24	-
2018	Shen	China	Asian	CRC	106	53	32	-	53	17	-
2016	Liu	China	Asian	ESCC	142	71	57	30	71	33	19
2016	Zhou	China	Asian	HCC	109	54	-	-	55	-	-
2016	Peng	China	Asian	OSC	84	42	-	20	42	-	10
2015	Li	China	Asian	GC	184	92	60	12	92	43	0
2015	Su	China	Asian	RB	60	30	-	-	30	-	-
2014	Sun	China	Asian	NSCLC	109	54	-	-	55	-	-
2013	Li	China	Asian	MM	103	-	-	-	-	-	-

CRC: colorectal cancer, BC: Bladder cancer, GC: gastric cancer, RCC: Renal cell carcinoma, OSC: osteosarcoma, RB: retinoblastoma, ESCC: esophageal squamous cell carcinoma, HCC: hepatocellular carcinoma, MM: Malignant melanoma, NSCLC: non-small cell lung cancer, LNM: lymph node metastasis, DM: distant metastasis

Methods

Literature search

Case-control and cohort studies on the correlation between BANCR and tumor prognosis, lymph node metastasis and distant metastasis published before January 1, 2019 were searched for in PubMed, Embase, Cochrane Library and Web of Science. The key words were as follows: "lncRNA BANCR" and "cancer", "tumor" and "prognosis". Citations of eligible articles were fully searched. There were no limitations on publication areas and study populations. The most recent and complete research was chosen in the case of overlapping data.

Inclusion and exclusion criteria

Published research on the correlation between BANCR and tumor prognosis was selected. Inclusion criteria were applied as follows: (1) Case-control or cohort studies; (2) Studies on the correlation between BANCR and tumor prognosis; and (3) HR, OR and 95%CI or relative data that could be used to calculate these parameters were provided.

Exclusion criteria were applied as follows: (1) Non-case-control studies; (2) Retrospective studies; (3) Raw data on the correlation between BANCR and tumor prognosis were not provided; (4) Repeatedly published, low-quality articles. Reviews or abstracts were excluded.

Data extraction

Data acquisition was independently carried out by two reviewers, and a third reviewer was responsible for re-evaluating disagreements. Baseline data acquisition included: first author, study type, sample size, year of publication, region, confounding factors, HR (hazard ratios), OR and 95%CI. HR was extracted with two methods: (1) Direct extraction from the article; (2) Calculated by Kaplan-Meier curves.

Statistics

HR, OR and 95%CI were calculated to assess the correlation strength between BANCR and tumor prognosis. A fixed-effect model (Mantel-Haenszel method) was used when $p<0.05$; Otherwise, the random-effects model (Dersimonian-Laird method) was used. Begg's test and Egger's test were utilized for evaluating publication bias.

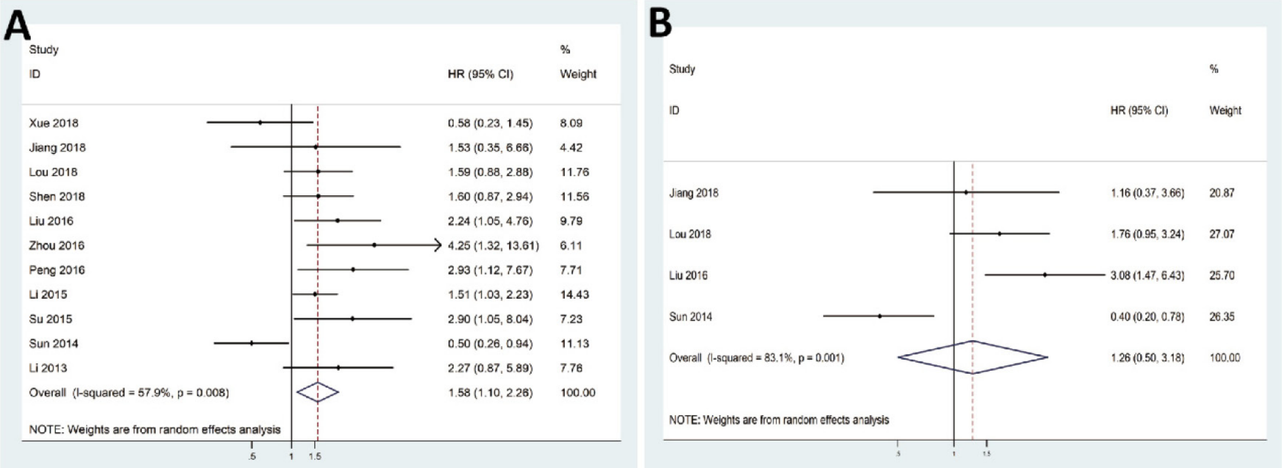

Figure 2. Forest plots of the prognosis of lncRNA BANCR and cancer in random-effects model. **(A):** OS; **(B):** RFS/DFS/PFS.

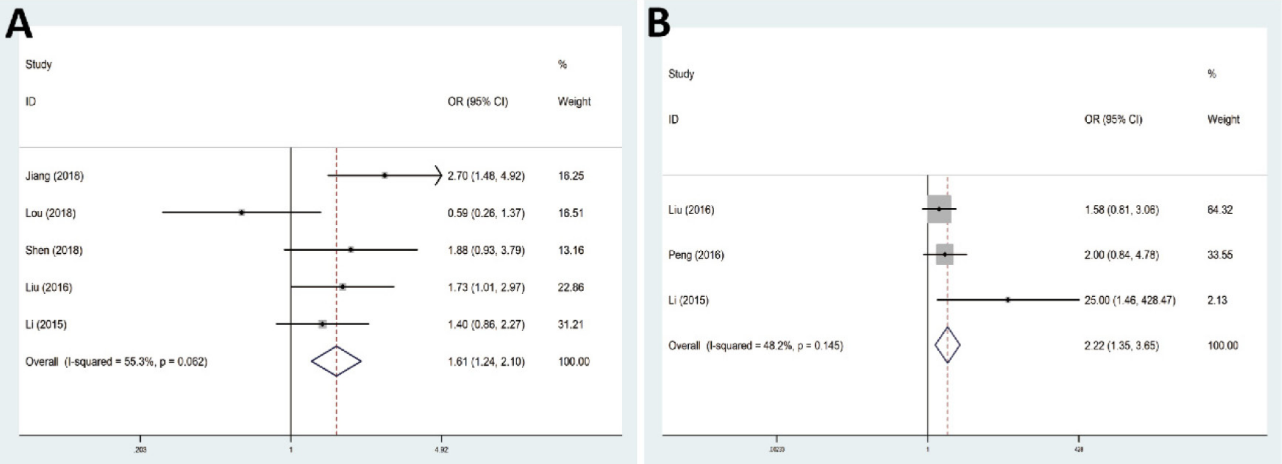

Figure 3. Forest plots of the association between lncRNA BANCR and lymph node metastasis and distant metastasis susceptibility in fixed-effects model. **(A):** lymph node metastasis; **(B):** distant metastasis.

Statistical analysis was performed using Stata software (version 12.0, Stata Corporation, College Station, TX, USA). P<0.05 was considered as statistically significant.

Results

Characteristics of the studies

Our study included 11 articles that analyzed the correlation strength between BANCR level and tumor prognosis in 1240 tumor patients [18-28]. Baseline characteristics and prognostic parameters are presented in Table 1. The literature search and selection process are depicted in Figure 1.

Quantitative synthesis results

Firstly, we evaluated the potential correlation between the BANCR level and tumor prognosis. A total of four survival-related indicators were assessed, including OS (overall survival), RFS (relapse-free survival), DFS (disease-free survival) and PFS (progression-free survival). OS was shorter in tumor patients with high BANCR expression (HR=1.58, 95%CI:1.10-2.26, Figure 2A), whereas RFS, DFS and PFS were not shorter compared with those with low BANCR expression (HR=1.26, 95%CI:0.50-3.18, Figure 2B).

Secondly, the correlation between BANCR level, lymph node metastasis and distant metastasis was also assessed. Table 2 illustrates the correlation strength between the BANCR level and tumor metastasis. A high level of BANCR was correlated with lymph node metastasis (OR=1.61, 95%CI: 1.24-2.10, Figure 3A) and distant metastasis (OR=2.22, 95%CI: 1.35-3.65, Figure 3B).

Publication bias

Publication bias in this study was assessed using Begg's test and Egger's test. The systematic shape of the funnel diagram indicated no significant publication bias (Figures 4,5).

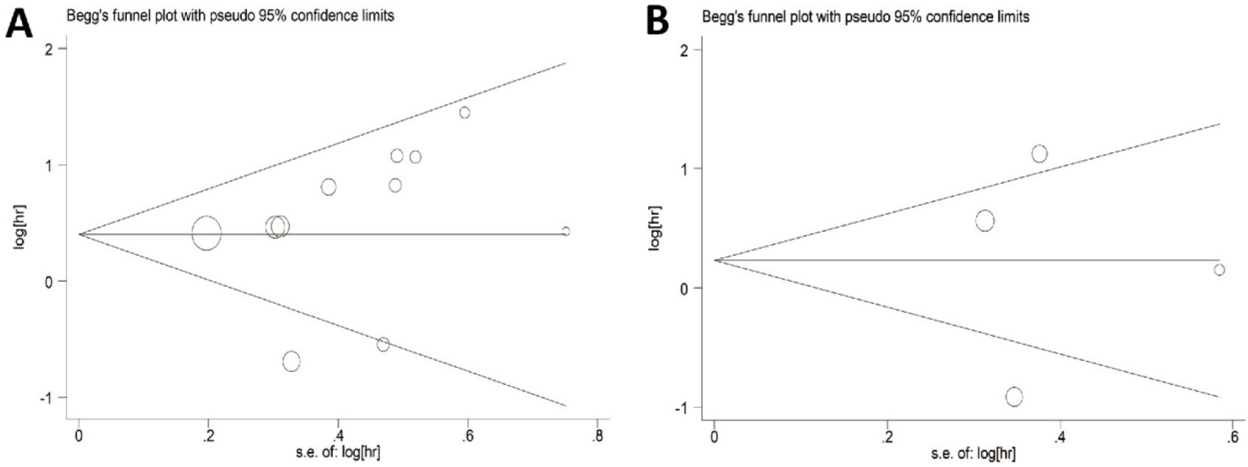

Figure 4. Begg's funnel plot of publication bias test about the prognosis of lncRNA BANCR and cancer. **(A):** OS; **(B):** RFS/DFS/PFS.

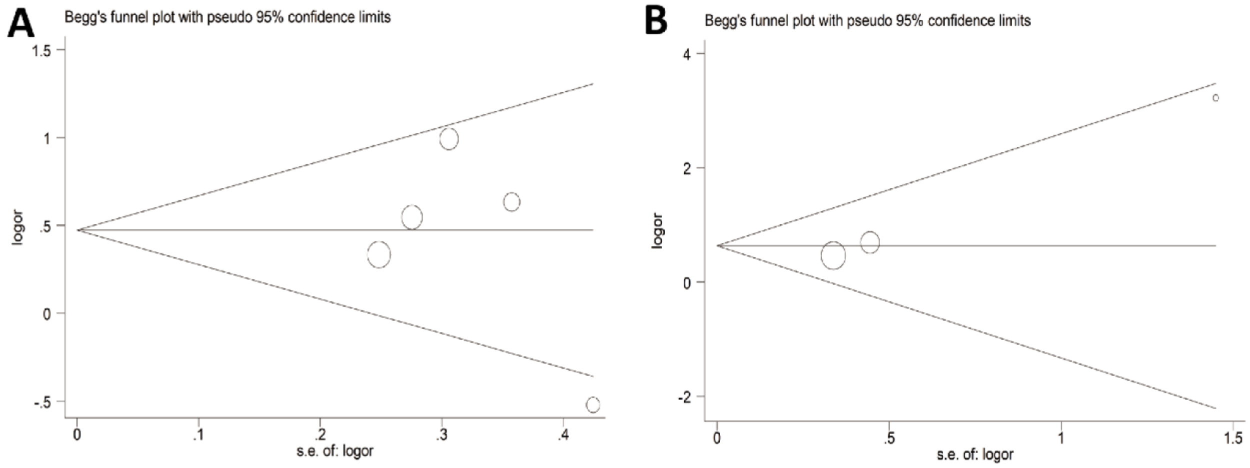

Figure 5. Begg's funnel plot of publication bias test about the association between lncRNA BANCR and lymph node metastasis and distant metastasis susceptibility. **(A):** lymph node metastasis; **(B):** distant metastasis.

Discussion

LncRNA has been extensively investigated as a newly discovered regulator. LncRNA BANCR has been identified to exert a vital role in the occurrence and progression of tumors [14,18-20]. This study aims to clarify the prognostic value of BANCR in tumors. Based on 11 articles included in this study, a high level of BANCR indicated a shorter OS. It is noteworthy that BANCR overexpression shortened the tumor survival in Asian patients, suggesting that gene-environment factors are of great significance in tumor progression. Because of the few overlaps in prognosis-related lncRNAs, most of them need to be further explored. We did not screen overlapping lncRNAs since the sample size was relatively small in this study. Nevertheless, we could still speculate that lncRNAs with a high repetition rate were more likely to be cancer prognostic markers. In the 11 articles studied, tumor tissues were fixed with different methods. Owing to the stable characteristics of lncRNAs, fixation methods would not influence our results. LncRNA is also spread through the blood circulation, but we did not assess the blood level of lncRNA as a hallmark for tumor prognosis since such samples were missing from the articles included in the study. Therefore, we were uncertain whether lncRNAs in tissues or blood samples were more suitable as cancer prognostic markers [17].

There are many limitations in the use of lncRNA-based prognostic markers. Well-known lncRNAs account for only a small part of all lncRNAs, and their viability was unclear [16,17]. The current study analyzed a single lncRNA in one type of tumor [17]. This study demonstrated that OS was shorter in tumor patients with high BANCR expression (HR=1.58, 95%CI:1.10-2.26), whereas RFS, DFS and PFS were not shorter compared with low BANCR expression (HR=1.26, 95%CI:0.50-3.18). A high level of BANCR was correlated with lymph node metastasis (OR=1.61, 95%CI:1.24-2.10) and distant metastasis (OR=2.22, 95%CI:1.35-3.65). Tumor prognosis could be influenced by tumor stage and therapeutic strategies. Therefore, large-scale and high-quality research is needed for further validation.

A powerful meta-analysis leads to more reliable conclusions than individual research, especially in case of unexplained correlations [29]. This study could only prove the correlation between BANCR and OS and not between BANCR and other prognostic markers, which may be explained by sample size differences, genotyping methods, research designs and statistical methods.

This study has several shortcomings. Firstly, tumor occurrence and metastasis is influenced by multiple factors. We did not control intrinsic confounding factors because of the limited information avalaible. Secondly, the etiology of tumors involves a complex gene-environment network. In-depth research is required for analyzing the potential genetic and environmental factors involved in tumorigenesis. Thirdly, a comprehensive analysis of research populations of different ages and ethnicities may result in certain biases. Therefore, this prognostic factor may lead to some heterogeneity. Additionally, tumor incidence varies a lot in different ethnicities. This study only explored the correlation in the Asian population, which may result in selection bias. Fourthly, different detection methods and definitions of the BANCR expression may have influenced the conclusions. Finally, the HR calculated based on survival curve may have errors in some articles. Therefore, this conclusion should be further validated in a large-scale population of different ethnicities, while genetic factors should also be explored.

Conclusions

BANCR overexpression was closely correlated with poor overall survival, lymph node metastasis and distant metastasis. Our conclusion still needs to be further verified in a multi-hospital study using a large sample size.

Conflict of interests

The authors declare no conflict of interests.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
2. Yang B, Zheng D, Zeng U, Qin A, Gao J, Yu G. Circulating tumor cells predict prognosis following secondline AZD 9291 treatment in EGFR-T790M mutant non-small cell lung cancer patients. JBUON 2018;23:1077-81.
3. Pe M, Dorme L, Coens C et al. Statistical analysis of patient-reported outcome data in randomised controlled trials of locally advanced and metastatic breast cancer: a systematic review. Lancet Oncol 2018;19:e459-e469.

4. Pan RY, Chung WH, Chu MT et al. Recent Development and Clinical Application of Cancer Vaccine: Targeting Neoantigens. J Immunol Res 2018;2018:4325874.
5. Liu Z, Jiang L, Zhang G, Li S, Jiang X. MiR-24 promotes migration and invasion of non-small cell lung cancer by targeting ZNF367. JBUON 2018;23:1413-9.
6. Chen W, Zheng R, Baade PD et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
7. Vahidnia F, Hirschler NV, Agapova M, Chinn A, Busch MP, Custer B. Cancer Incidence and Mortality in a Cohort of US Blood Donors: A 20-Year Study. J Cancer Epidemiol 2013;2013:814842.
8. Smith RA, Andrews KS, Brooks D et al. Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2017;67:100-21.
9. Pahle J, Walther W. Vectors and strategies for nonviral cancer gene therapy. Expert Opin Biol Ther 2016;16:443-61.
10. Rizou T, Perlikos F, Lagiou M et al. Development of novel real-time RT-qPCR methodologies for quantification of the COL11A1 mRNA general and C transcripts and evaluation in non-small cell lung cancer specimens. JBUON 2018;23:1699-1710.
11. Tsimberidou AM. Targeted therapy in cancer. Cancer Chemother Pharmacol 2015;76:1113-32.
12. Gotwals P, Cameron S, Cipolletta D et al. Prospects for combining targeted and conventional cancer therapy with immunotherapy. Nat Rev Cancer 2017;17:286-301.
13. Belgioia L, Desideri I, Errico A et al. Safety and efficacy of combined radiotherapy, immunotherapy and targeted agents in elderly patients: A literature review. Crit Rev Oncol Hematol 2019;133:163-70.
14. Yu X, Zhao J, He Y. Long non-coding RNA PVT1 functions as an oncogene in human colon cancer through miR-30d-5p/RUNX2 axis. JBUON 2018;23;48-54.
15. Ayers D, Scerri C. Non-coding RNA influences in dementia. Noncoding RNA Res 2018;3:188-94.
16. Wang P, Xu J, Wang Y, Cao X. An interferon-independent lncRNA promotes viral replication by modulating cellular metabolism. Science 2017;358:1051-5.
17. Cao M, Zhao J, Hu G. Genome-wide methods for investigating long noncoding RNAs. Biomed Pharmacother 2019;111:395-401.
18. Xue S, Jiang SQ, Li QW et al. Decreased expression of BRAF-activated long non-coding RNA is associated with the proliferation of clear cell renal cell carcinoma. BMC Urol 2018;18:79.
19. Jiang J, Shi SH, Li XJ et al. Long non-coding RNA BRAF-regulated lncRNA 1 promotes lymph node invasion, metastasis and proliferation, and predicts poor prognosis in breast cancer. Oncol Lett 2018;15:9543-52.
20. Lou KX, Li ZH, Wang P et al. Long non-coding RNA BANCR indicates poor prognosis for breast cancer and promotes cell proliferation and invasion. Eur Rev Med Pharmacol Sci 2018;22:1358-65.
21. Shen X, Bai Y, Luo B, Zhou X. Upregulation of lncRNA BANCR associated with the lymph node metastasis and poor prognosis in colorectal cancer. Biol Res 2017;50:32.
22. Liu Z, Yang T, Xu Z, Cao X. Upregulation of the long non-coding RNA BANCR correlates with tumor progression and poor prognosis in esophageal squamous cell carcinoma. Biomed Pharmacother 2016;82:406-12.
23. Zhou T, Gao Y. Increased expression of LncRNA BANCR and its prognostic significance in human hepatocellular carcinoma. World J Surg Oncol 2016;14:8.
24. Li L, Zhang L, Zhang Y, Zhou F. Increased expression of LncRNA BANCR is associated with clinical progression and poor prognosis in gastric cancer. Biomed Pharmacother 2015;72:109-12.
25. Su S, Gao J, Wang T, Wang J, Li H, Wang Z. Long non-coding RNA BANCR regulates growth and metastasis and is associated with poor prognosis in retinoblastoma. Tumour Biol 2015;36:7205-11.
26. Sun M, Liu XH, Wang KM et al. Downregulation of BRAF activated non-coding RNA is associated with poor prognosis for non-small cell lung cancer and promotes metastasis by affecting epithelial-mesenchymal transition. Mol Cancer 2014;13:68.
27. Li R, Zhang L, Jia L et al. Long non-coding RNA BANCR promotes proliferation in malignant melanoma by regulating MAPK pathway activation. PLoS One 2014;9:e100893.
28. Yang L, Liu G. LncRNA BANCR suppresses cell viability and invasion and promotes apoptosis in non-small-cell lung cancer cells in vitro and in vivo. Cancer Manage Res 2019;11:3565-74.
29. Nakagawa S, Noble DW, Senior AM, Lagisz M. Meta-evaluation of meta-analysis: ten appraisal questions for biologists. BMC Biol 2017;15:18.