Review Article

Clinicopathological Significance and Prognostic Values of Long Noncoding RNA BCYRN1 in Cancer Patients: A Meta-Analysis and Bioinformatics Analysis

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Received 15 February 2022; Accepted 14 June 2022; Published 14 July 2022

Academic Editor: Raluca-Ioana Stefan-Van Staden

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Background. Although combination therapies have substantially improved the clinical outcomes of cancer patients, the prognosis and early diagnosis remain unsatisfactory. As a result, it is critical to look for novel indicators linked to cancer. Despite a number of recent studies indicating that the IncRNA brain cytoplasmic RNA1 (BCYRN1) may be a potential predictive biomarker in cancer patients, BCYRN1’s prognostic value is still being debated.

Methods. We utilized PubMed, Embase, Web of Science, and the Cochrane Library to search for studies related to BCYRN1 until October 2021. Valid data were extracted after determining the articles according to the inclusion and exclusion criteria, and forest plots were made using Stata software. We used hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals to evaluate the relationship between abnormal BCYRN1 expression and patient prognosis and clinicopathological characteristics. Results. Meta-analysis revealed that increased BCYRN1 expression was associated with both overall tumor survival (OS; HR = 1.84, 95% CI 1.51−2.25, p < 0.0001) and disease-free survival (DFS; HR = 1.65, 95% CI 1.20−2.26, p = 0.002). Furthermore, a strong association was discovered between increased BCYRN1 expression and tumor invasion depth (OR = 2.11, 95% CI 1.49−2.99, p = 0.000), clinical stage (OR = 2.52, 95% CI 1.18−5.37, p = 0.017), and distant tumor metastasis (OR = 4.19, 95% CI 1.45−12.05, p = 0.008). Conclusions. We found that high BCYRN1 expression was associated with poor survival prognosis and aggressive clinicopathological characteristics in various cancers, indicating that it is a potential prognostic indicator as well as a therapeutic target. Further research is needed on pan-cancer cohorts to determine the clinical relevance of BCYRN1 in distinct cancer types.

1. Introduction

Since the turn of the new century, cancer incidence and mortality have gradually exceeded that of other chronic diseases [1]. According to the most recent CA, a cancer journal, estimates, 1.9 million new cases of cancer were diagnosed in the United States in 2021, with an estimated 610,000 deaths [2]. Although combination therapies, such as surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy, have substantially improved the clinical outcomes of cancer patients, the prognosis and early diagnosis remain unsatisfactory [3]. In recent years, advances in screening techniques, targeted therapies, immunotherapies, bioinformatics, and cancer biology have
identified novel biomarkers for early diagnosis and prognosis prediction [4], and novel tumor marker detection techniques are important [5–8].

Long non-coding RNAs (lncRNAs) have gained considerable interest as cancer biomarkers in recent years with the advent of next-generation sequencing technologies [9]. The lncRNAs have a length of more than 200 nucleotides and lack any protein-coding activity [10]. They regulate gene expression at the transcriptional level through chromatin remodeling and miRNA sponging, at the post-transcriptional level by affecting RNA splicing and stability and at the translational level by controlling signal transmission [11, 12]. Studies increasingly show that aberrant lncRNA expression is linked to biological processes such as tumor growth, angiogenesis, metastasis, and invasion, and lncRNAs can be exploited as tumor suppressor genes or oncogenes for cancer therapy and prevention [12, 13].

The lncRNA brain cytoplasmic 200 (BC200), also known as brain cytoplasmic RNA1 (BCYRN1), is normally expressed in neurons and is implicated in cancer and neurological diseases [14]. Studies show that BCYRN1 is overexpressed in non-small-cell lung cancer [15–17], hepatocellular carcinoma [18–20], colorectal cancer [21–24], bladder cancer [25, 26], esophageal squamous cell carcinoma [27, 28], gastric cancer [29, 30], cervical cancer [31], ovarian cancer [32], and breast cancer [33] tissues compared to matched normal tissues. However, no systematic review has been conducted so far on the pan-cancer data of BCYRN1. To this end, we performed a meta-analysis of the relevant studies to further evaluate whether BCYRN1 is a reliable prognostic biomarker and therapeutic target for different cancers by evaluating the correlation between BCYRN1 expression levels and cancer-related clinicopathological features and patient prognosis. Finally, the clinicopathological and prognostic value of BCYRN1 in cancer patients was validated by bioinformatics analysis of cancer databases.

2. Materials and Methods

2.1. Search Strategy for Literature. All procedures mentioned below were performed in accordance with PRISMA Checklist protocols [34]. Prior to October 1, 2021, PubMed, Web of Science, Embase, and the Cochrane Library were used to search for relevant papers studying the association between lncRNA BCYRN1 expression and clinical outcomes in cancer patients. Medical Subject Headings (MeSH) keywords and free terms were merged in this search. Our search keywords are as follows: (“lncRNA” OR “long non-coding RNA”) AND (“BCYRN1” OR “BC200” OR “BC200a” OR “LINC00004” OR “nCRNA00004” OR “brain cytoplasmic RNA1”) AND (“neoplasm” OR “carcinoma” OR “tumor” OR “cancer”). To guarantee accuracy and consistency, two writers independently assessed the database search approach and discussed the results.

2.2. Inclusion and Exclusion Criteria. The duplicate articles were first eliminated, and the titles and abstracts of the remaining studies were screened on the basis of the following inclusion criteria: (1) patients with histopathologically proven cancer; (2) analysis of cancer tissues and adjacent normal tissues; (3) detection of BCYRN1 levels by qRT-PCR; (4) the paper included clinical factors such as age, gender, tumor size, TNM stage, clinical stage, lymph node metastasis, or distant metastases, as well as prognostic markers such as overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS); (5) demarcation of patients into BCYRN1 low and BCYRN1 high expression groups based on the cut-off value, with the number of patients in each group explicitly specified; (6) survival hazard ratios (HRs) and 95% confidence interval (CI) by multivariate analysis or Kaplan–Meier (K-M) curves; and (7) published in the English language. Exclusion criteria are as follows: (1) studies describing other lncRNAs or lncRNAs unrelated to cancer; (2) duplicate articles; (3) other types of literature, such as reviews, letters, conference abstracts, meta-analyses, case reports, and so on; (4) articles focusing on biological functions and related mechanisms; and (5) a lack of sufficient HR and 95% CI to extract data.

2.3. Data Extraction and Quality Evaluation. The following information should be extracted from eligible literature: first author, publication year, country, tumor type, sample type, sample size (high/low), cutoff of BCYRN1 expression, analysis method, survival (OS/RFS/PFS), HR availability, HR (95%CI) with p value, month of follow-up, and Newcastle–Ottawa Scale score (NOS). Survival HRs (95% CI) were retrieved indirectly from K-M curves using the Engauge Digitizer tool in case multivariate analysis had not been performed. The NOS scoring criteria (scores from 0 to 9) were used to assess the quality of the included studies, and those with scores >6 were included in the meta-analysis.

2.4. Statistical Analysis. We used log HR and SE to summarize survival outcomes, while OR and corresponding 95% CI were applied to summarize clinicopathological parameters. In addition, between-study heterogeneity was assessed by the x2 test and I2 statistic. Q test (P<0.05 and I2>50%) indicated that there was statistical heterogeneity among studies, and a random-effects model was used to analyze the results. In other cases, a fixed-effects model was employed. We used forest plots to present the meta-analysis results and used the Begg test to assess any prospective bias in the publications. Sensitivity analyses were performed by sequentially removing individual included studies to test whether the overall pooled estimate was stable. Analyses were performed using Stata 12.0 for Windows (Stata, College Station, TX, USA), and p<0.05 was considered statistically significant.

2.5. To Identify the Differential Expression of BCYRN1 Gene in Human Cancers. UCSC Xena (https://xena.ucsc.edu/) originated from TCGA database) was used to retrieve RNA sequences, somatic mutations (SNPs and short INDELS), clinicopathologic, and survival data for 33 malignancies. We picked the ONCOMINE database (http://www.oncomine.org/) to acquire a complete knowledge of BCYRN1
3.2. Characteristics of Included Research Projects. All in-
nalysis.,fl_he procedure is outlined in Figure 1. Finally, 12 studies with sufficient data on
nary analysis due to lack of significant data or unsatisfactory
downloaded, of which 31 were rejected following prelimi-
unrelated findings. Forty-three full-text articles were
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2.6. Association between BCYRN1 Expression and TMB or MSI in Pan-Cancer. Tumor mutational burden (TMB) was
computed using the Perl script and divided by the entire
length of the exons to count the number of mutations in each
tumor sample (i.e., 33 tumors using somatic mutation data
and corrected to a number of mutated bases per 1 million
bases). The microsatellite instability (MSI) score came from
the TCGA website. The "cor. test" command was used to do
Spearman’s method correlation study between cancer gene
expression and TMB or MSI. A radar map was created using
the R-package "fmsb" to view both indications.

2.7. Verification of Survival Outcomes in the GEPIA Database. Gene expression profiling interaction analysis (GEPIA)
was performed according to the Cancer Genome Atlas (TCGA)
data set to further validate the prognostic relevance of
BCYRN1 overexpression in tumor tissues. TCGA and GTEx
data were matched in various tumors, with a cutoff of
p < 0.01. OS and DFS of BCYRN1 in pan-cancer were plotted
using the Kaplan–Meier method.

3. Results

3.1. Screening Process for Eligible Literatures. The cancer-
related gene BCYRN1 was thoroughly searched in four major
English databases: PubMed (n = 53), Web of Science
(n = 93), Embase (n = 73), and Cochrane Library (n = 0).
After deleting duplicates (n = 106), the remaining papers’
titles and abstracts (n = 113) were examined and appraised.
Sixty-three articles were rejected owing to the aims, article
type (reviews, case studies, or conference abstracts), or
unrelated findings. Forty-three full-text articles were
downloaded, of which 31 were rejected following prelimi-
nary analysis due to lack of significant data or unsatisfactory
quality of the data. Finally, 12 studies with sufficient data on
survival and clinical features were included in the meta-
analysis. The procedure is outlined in Figure 1.

3.2. Characteristics of Included Research Projects. All in-
ncluded studies had been conducted in China and comprised
1,284 patients. The articles were published between 2016 and
2021. Two studies looked into hepatocellular carcinoma; two
looked into colorectal cancer; and the remaining studies
looked into bladder cancer, extranodal NK/T-cell lymphoma, glioblastoma, gastric cancer, prostate cancer, colon
cancer, cancer, and esophageal squamous cell carcinoma. BCYRN1 expression in cancer and para-cancer tissues was
detected by qRT-PCR. The patients were demarcated into the
BCYRN1 low and BCYRN1 high groups, and the cutoff
was the median expression level in five studies and mean
expression in three studies. No cutoff value was indicated in
the remaining four studies. Only two studies included the
DFS and one PFS, whereas 8 studies provided OS. The HR
and 95% CI of three studies were obtained directly from the
multivariate regression analysis, and that for the remaining
six were extracted from the K-M survival curves using
Engauge Digitizer software. The duration of follow-up
ranged from 40 to 96 months. The NOS scores of the studies
were 6 to 8. The data are summarized in Table 1.

3.3. Association of BCYRN1 Level with Survival Outcome. Eight studies including 1,028 cancer patients investigated the
link between BCYRN1 levels and OS. Since no significant
heterogeneity was found (I² = 0.0%, p = 0.964), we per-
formed a pooled analysis using a fixed-effect model. Pooled
HRs indicated that high BCYRN1 levels were strongly as-
associated with worse OS (HR = 1.84, 95% CI 1.51–2.25,
p < 0.001; Figure 2(a)). In addition, only two studies (280
patients) were included to assess the association of BCYRN1
expression with DFS. Consistent with the OS results, in-
creased BCYRN1 expression was found to be associated with
unfavorable DFS (HR = 1.65, 95% CI 1.20–2.26, p = 0.002;
Figure 2(b)). Furthermore, we conducted subgroup analyses
to look into the relationship between BCYRN1 expression
levels and OS based on the cancer type (digestive or other
systems; Figure 2(c)), sample size (≥100 or <100 tissues;
Figure 2(d)), follow-up time (≥80 or <80 months;
Figure 2(e)), and article quality (NOS score ≥8 or ≤7;
Figure 2(f)). There was no evidence of considerable het-
erogeneity within groups, and the findings of the subgroup
analysis had no effect on BCYRN1’s ability to predict OS in
these malignancies.

3.4. Association of BCYRN1 Expression with Clinicopathologic Parameters. The results showed that overexpression of
BCYRN1 was associated with age (≥60 vs. <60, OR = 1.12,
95% CI 0.82–1.15, p = 0.475; Figure 3(a)), gender (male vs.
female, OR = 0.89, 95% CI 0.63–1.24, p = 0.568; Figure 3(b)),
tumor size (large vs. small, OR = 1.61, 95% CI 0.82–3.15,
p = 0.166; Figure 3(c)), lymph node metastasis (positive vs.
negative, OR = 2.09, 95% CI 0.79–5.31, p = 0.135;
Figure 3(d)), and tumor differentiation (poor vs. good,
OR = 1.10, 95% CI 0.59–2.05, p = 0.774; Figure 3(e)) that
were not significantly associated, and the results were not
found to be statistically significant. However, high expres-
sion of BCYRN1 was observed to be significantly associated
with some advanced clinical features, including TNM stage
(III-IV vs. I-II, OR = 2.52, 95% CI 1.18–5.37, p = 0.017;
Figure 3(f)), T stage of the tumor (III-IV vs. I-II, OR = 2.11,
95% CI 1.49–2.99, p = 0.000; Figure 3(g)), and tumor distant
metastasis (positive vs. negative, OR = 4.19, 95% CI

Table 1: Characteristics of the included studies.

| Author          | Year | Country | Cancer type | Sample size (high/low) | Sample | Survival analysis | Detection method | Cutoff value | Extract method of HR | Follow-up time | NOS score |
|-----------------|------|---------|-------------|------------------------|--------|-------------------|-----------------|--------------|----------------------|----------------|-----------|
| Zheng et al. [25] | 2021 | China   | BLC         | 210 (105/105)          | Tissue | OS                | qRT-PCR         | Median       | Data in paper Survival curves | 96 months        | 8         |
| Wang et al. [36]  | 2021 | China   | ENKTCL      | 40 (20/20)            | Tissue | PFS               | qRT-PCR         | Median       | Survival curves         | 40 months        | 7         |
| Su et al. [37]   | 2020 | China/Taiwan | GB        | 48 (25/23)            | Tissue | NR                | qRT-PCR         | NR           | NR                   | NR             | 6         |
| Huo et al. [26]  | 2020 | China   | PRCA        | 72 (36/36)            | Tissue | NR                | qRT-PCR         | NR           | Data in paper Survival curves | 90 months        | 7         |
| Zhai and Li [29] | 2019 | China   | GC          | 127 (63/64)           | Tissue | OS                | qRT-PCR         | Median       | Survival curves         | 60 months        | 8         |
| Yu and Chen [23] | 2019 | China   | CRC         | 150 (79/71)           | Tissue | OS                | qRT-PCR         | Mean         | Survival curves         | 50 months        | 8         |
| Ming et al. [20] | 2019 | China   | HCC         | 73 (37/36)            | Tissue | OS                | qRT-PCR         | Median       | Survival curves         | 70 months        | 8         |
| Gao and Wang [16] | 2019 | China   | NSLC        | 76 (32/44)            | Tissue | OS                | qRT-PCR         | Mean         | Survival curves         | 80 months        | 7         |
| Lin [38]         | 2018 | China   | HCC         | 240                   | Tissue | OS                | qRT-PCR         | Mean         | Survival curves         | 80 months        | 8         |
| Wu et al. [21]   | 2018 | China   | CC          | 82                    | Tissue | OS                | qRT-PCR         | Mean         | Survival curves         | 80 months        | 7         |
| Gu et al. [24]   | 2018 | China   | CRC         | 96 (63/33)            | Tissue | NR                | qRT-PCR         | NR           | NR                   | NR             | 6         |
| Zhao et al. [28] | 2016 | China   | ESCC        | 70 (35/35)            | Tissue | OS                | qRT-PCR         | Median       | Data in paper Survival curves | 50 months        | 8         |

Note. BLC: bladder cancer, ENKTCL: extranodal NK/T-cell lymphoma, GB: glioblastoma, PRCA: prostate cancer, GC: gastric cancer, CRC: colorectal cancer, HCC: hepatocellular carcinoma, NSLC: non-small-cell lung cancer, CC: colon cancer, ESCC: esophageal squamous cell carcinoma, qRT-PCR: quantitative real-time polymerase chain reaction, and NR: not reported.
1.45–12.05, \( p = 0.008 \); Figure 3(h)). A fixed-effects model was used for low heterogeneity (0–50%), while a random-effects model was used for large heterogeneity (>50%). Data pertaining to the forest plot of survival prognosis and clinical pathology are recorded in Table 2.

3.5. Publication Bias and Sensitivity Analysis. Begg’s test was used to analyze potential publication bias. For OS, the funnel plot appeared asymmetric, and the Begg test (\( p > |t| = 0.019 \); Figure 4(a)) indicated some publication bias. Using the scissors method, after filling out three imaginary unpublished papers, the funnel plot became symmetrical, and the pooled HR and 95% CI remained stable (HR = 1.768, 95% CI 1.473–2.123, \( p < 0.001 \); Figure 4(b)) [39]. For pathological parameters with significant differences in pooled ORs, Begg plot data showed TNM stage (\( p > |t| = 0.231 \); Figure 4(c)), distant metastasis (\( p > |t| = 0.237 \); Figure 4(d)), and tumor T
stage \((p > |t| = 0.605; \text{Figure 4(e)})\), indicating no significant publication bias. A sensitivity analysis was performed for OS (Figure 5(a)) and tumor T stage (Figure 5(b)), and the pooled HR and OR changed within a limited range without significant change after deletion of each study, indicating that our results were stable. From this, it can be seen that the relevant conclusions we draw are stable and reliable.

3.6. Expression of BCYRN1 in Pan-Cancers. We used R software to examine RNA sequencing data in the TCGA database to further investigate the differential expression of BCYRN1 in pan-cancers. According to our findings, BCYRN1 is significantly expressed in multiple cancer types, including CHOL, COAD, KIRP, LIHC, LUAD, LUSC, PRAD, and READ. However, low BCYRN1 expression was observed in BRCA, CESC, GBM, and THCA (Figure 6(a)). Using the cBioPortal database, we observed the variation of BCYRN1 in various types of cancer. The correlation results showed that the variation was mainly significant amplification, followed by deep deletion. Among all malignancies, cervical adenocarcinoma had the highest frequency of variants, followed by sarcoma (Figure 6(b)).

![Figure 3: Forest plots for the association of BCYRN1 expression with clinicopathological features: (a) age, (b) gender, (c) TNM stage, (d) lymph node metastasis, (e) distant metastasis, (f) tumor T stage, (g) tumor size, and (h) differentiation grade.](image-url)
3.7. Association of BCYRN1 Expression with TMB and MSI in Pan-Cancer. High TMB is a newly identified class of biomarkers related to sensitivity to immune checkpoint inhibitors, including PD-1/PD-L1 inhibition, which can assess the efficacy of immunotherapy in cancer patients [40, 41]. Therefore, it is interesting to investigate the relationship between TMB and BCYRN1 expression in different types of cancer. The results indicate that BCYRN1 expression correlates with TMB in a significant number of cancers. BCYRN1 expression was positively correlated with TMB in six cancer types, including BLCA, BRCA, HNSC, LUAD, LUSC, and THYM. In contrast, BCYRN1 expression was inversely correlated with TMB in six other cancer types, which included COAD, GBM, LGG, LIHC, STAD, and UCEC (Figure 7(a)).

Recently, it has been found that MSI can be detected in numerous tumors (such as colorectal cancer) and has the potential to be a marker of PD-1 blockade [42, 43]. Therefore, further verification of whether BCYRN1 expression is associated with MSI in different types of cancer is warranted. The results showed that BCYRN1 expression was significantly correlated with MSI in 14 cancer types. BCYRN1 expression was positively correlated with MSI in 8 of the cancer types (DLBC, HNSC, LGG, LIHC, LUAD, LUSC, TGCT, and THCA). In addition, BCYRN1 expression was inversely correlated with MSI in six other cancer types (ACC, CESC, COAD, KIRC, SARC, and UCEC; Figure 7(b)).

3.8. Correlation Analysis between BCYRN1 Expression and TNM Staging of Pan-Cancer. BCYRN1 expression was associated with the clinical stage in several cancers (Figure 8). For LIHC (p = 0.0023; Figure 8(a)), TGCT (p = 0.025; Figure 8(b)), and COAD (p = 0.0093; Figure 8(c)), BCYRN1 was highly expressed in stage III-IV, but lowly expressed in stage I-II. From this, it can be seen that in the above cancers, high expression of BCYRN1 is associated with clinical stage progression of cancer and has the potential to be a predictor of tumor prognosis and progression.

3.9. Verification of Survival Outcomes in the GEPIA Database. Regarding the relationship between BCYRN1 expression and prognosis, in the GEPIA cohort, 33 malignancies in 4,740 patients were divided into high and low expression groups according to the median value, and the survival curve showed that upregulation of BCYRN1 expression was associated with deterioration of OS ((HR = 1.3, log rank p < 0.05)) and DFS (HR = 1.2, log rank p < 0.05; Figure 9), which confirmed the results of our meta-analysis. These results support our conclusion and suggest that BCYRN1 may become a novel prognostic biomarker in multiple cancers.

4. Discussion

Given the steady increase in the annual rates of cancer incidence and mortality throughout the world, it is estimated that cancer will overtake chronic diseases as the primary cause of death and a major impediment to increasing life expectancy [44]. Despite the recent advances in cancer therapies, most cancer patients have a poor prognosis. Therefore, early diagnosis and treatment are critical to improving patient prognosis. However, the biomarkers currently used in clinical practice lack sensitivity and specificity, thereby necessitating the identification of novel tumor markers [45]. LncRNAs are transcribed by RNA polymerase II, and their expression levels vary significantly between tumors and the corresponding normal tissues. Studies show that lncRNAs regulate gene expression through X chromosome silencing, chromatin modification, transcriptional interference, and activation, which in turn regulate various physiological and pathological processes [46]. The lncRNA BCYRN1 is upregulated in multiple cancers and is therefore a potential diagnostic biomarker and therapeutic target. In addition, aberrant BCYRN1 expression is also related to the neurodegeneration underlying Alzheimer’s disease [47]. We conducted a meta-analysis of 12 studies including 1,284 cancer patients and 10 distinct cancer types and found that BCYRN1 overexpression in the tumors correlated significantly to poor survival, worse clinical stage, distant tumor metastasis, and advanced tumor T stage with greater invasiveness. Our findings are in line with previous reports indicating the prognostic relevance of BCYRN1 in cancer. Finally, we further evaluated the prognostic and pathological value of BCYRN1 by downloading relevant data using public databases, and the results were consistent with our meta-analysis.

Table 2: Association of BCYRN1 expression with clinicopathological features and survival prognosis.

| Outcome | Studies (n) | OR/HR | 95% CI  | p value | Model | Heterogeneity |
|---------|-------------|-------|---------|---------|-------|--------------|
| Age (≥60 vs.<60) | 8 | 1.12 | 0.82–1.15 | 0.475 | Fixed | 6.09 | 0.0% | 0.529 |
| Gender (male vs. female) | 7 | 0.89 | 0.63–1.24 | 0.568 | Fixed | 4.81 | 0.0% | 0.568 |
| Tumor size (large vs. small) | 2 | 1.61 | 0.82–3.15 | 0.166 | Fixed | 1.64 | 39% | 0.200 |
| Lymph node metastasis (positive vs. negative) | 4 | 2.09 | 0.79–5.51 | 0.135 | Random | 14.55 | 79.4 | 0.002 |
| Tumor differentiation (bad vs. well) | 5 | 1.10 | 0.59–2.05 | 0.774 | Random | 10.61 | 62.3% | 0.031 |
| TNM stage (III-IV vs. I-II) | 4 | 2.52 | 1.18–5.37 | 0.017 | Random | 9.79 | 67.3% | 0.020 |
| Tumor T stage (III-IV vs. I-II) | 6 | 2.11 | 1.49–2.99 | 0.000 | Fixed | 4.94 | 0.0% | 0.423 |
| Distant metastasis (positive vs. negative) | 4 | 4.19 | 1.45–12.05 | 0.008 | Random | 8.19 | 63.4% | 0.042 |
| Overall survival (OS) | 8 | 1.84 | 1.51–2.25 | 0.000 | Fixed | 1.91 | 0.0% | 0.964 |
| Disease-free survival (DFS) | 2 | 1.65 | 1.20–2.26 | 0.002 | Fixed | 0.86 | 0.0% | 0.353 |

For LIHC (p = 0.0023; Figure 8(a)), TGCT (p = 0.025; Figure 8(b)), and COAD (p = 0.0093; Figure 8(c)), BCYRN1 was highly expressed in stage III-IV, but lowly expressed in stage I-II. From this, it can be seen that in the above cancers, high expression of BCYRN1 is associated with clinical stage progression of cancer and has the potential to be a predictor of tumor prognosis and progression.
Three studies included in the meta-analysis reported increased expression of BCYRN1 in lung cancers, which correlated with poor outcomes. Wang et al. showed that BCYRN1 promoted the proliferation and metastasis of NSCLC cells by activating the Wnt/β-catenin signaling pathway [15]. Another study reported an association between BCYRN1 and advanced tumor stage and metastasis in NSCLC patients. BCYRN1 augmented the malignant development by targeting H1299/DDP-induced apoptosis [16]. Furthermore, Hu and Lu found that c-myc-activated BCYRN1 controlled NSCLC cell metastasis by upregulating MMP9 and MMP13 [17]. Three studies analyzed the relationship between BCYRN1 and liver cancer and reported upregulation of BCYRN1 in the tumor tissues. Ding et al. identified the BCYRN1/miR-490-3p/POU3F2 ceRNA regulatory network mediating reduced survival and increased tumor cell proliferation and metastasis in HCC patients [18]. Tan et al. found that BCYRN1 influences hepatoma cell proliferation and migration by modulating the expression of the c-Myc protein [19], and Ming et al. showed that BCYRN1

Figure 4: Begg’s publication bias plots: (a) OS, (b) OS after clipping, (c) TNM stage, (d) distant metastasis, and (e) tumor T stage.
regulates tumor-associated pathways and promotes hepatocarcinogenesis via IncRNA-miRNA-mRNA networks [20]. The upregulation of BCYRN1 in colorectal cancer was reported in four studies. Wu et al. found that knocking down BC200 decreased invasion and epithelial-mesenchymal transition (EMT) in HCT-116 and HT29 cells via the downregulation of MMP-2 and MMP-9 [21]. Yang et al. showed that BCYRN1 functioned as an oncogene in colorectal cancer via the miR-204-3p/KRAS axis [22]. In addition, Yu and Chen reported that the aberrantly high expression of BCYRN1 in colorectal cancer tissues increased metastasis and worsened patient prognosis [23]. Likewise, BCYRN1 overexpression was linked to larger tumors and advanced pathological stages in colorectal cancer patients [24]. Two studies so far have analyzed the relationship between BCYRN1 expression and prostate cancer. Zheng et al. showed that the high expression of BCYRN1 in prostate cancer tissues induced BCA lymphatic metastasis by activating VEGF-C/VEGFR3 signaling [25]. Huo et al. found that BCYRN1 enhanced HDAC11 levels and promoted

Figure 5: Sensitivity analysis for studies about OS and tumor T stage by omitting each study sequentially: (a) OS and (b) tumor T stage.
**Figure 6:** BCYRN1 gene expression levels and alteration in different cancer types from TCGA: (a) the alteration frequency of the BCYRN1 gene in different cancers obtained from the cBioPortal and (b) BCYRN1 gene expression levels in different cancer types from TCGA data. The red fusiform represents tumor tissue, and the blue fusiform represents normal tissue. *FDR < 0.05, **FDR < 0.01, and ***FDR < 0.001.
prostate cancer cell proliferation, glucose metabolism, and survival by targeting miR-939-3p [26]. Two studies showed a link between BCYRN1 expression and gliomas. Mu et al. showed that BCYRN1 is downregulated in gliomas and controls CUEDC2 expression and the PTEN/AKT/p21 pathway to suppress tumor progression by competitively binding to miR-619-5p [48]. Su et al. on the other hand reported overexpression of BCYRN1 in gliomas and found that it targets the BC200/miR218-5p signaling axis to overcome TMZolamide resistance and inhibit tumor growth [37]. Here are two reports investigating the link between BCYRN1 expression and ESCC. Zhao et al. showed that BC200 enhances esophageal cancer cell metastasis and controls the expression of ATF4 and its downstream genes [27] and that patients with high BC200 expression exhibited worse disease-free and overall survival [28]. There are two reports investigating the link between BCYRN1 expression and stomach cancer. Zhai and Li found that BCYRN1 is highly expressed in stomach cancer tissues and controls gastric cancer cell proliferation, cell cycle, migration, and invasion by targeting miR-204-5p [29]. Ren et al. reported similar findings [30]. Peng et al. discovered that BCYRN1 was highly expressed in cervical cancer and that miR-138 inhibition increased cervical cancer proliferation and invasion [31]. In
Logrank $p = 1.2 \times 10^{-14}$
HR (high) $= 1.3$
$p (HR) = 1.5 \times 10^{-14}$
n (high) $= 4664$
n (low) $= 4740$

**Overall Survival**

| Months | Percent survival |
|--------|-----------------|
| 0      | 100             |
| 100    | 90              |
| 200    | 80              |
| 300    | 70              |

**Disease Free Survival**

| Months | Percent survival |
|--------|-----------------|
| 0      | 100             |
| 100    | 90              |
| 200    | 80              |
| 300    | 70              |

**Figure 9:** The relationship between BCYRN1 expression and cancer patient prognosis in the GEPIA cohort: (a) OS plots based on BCYRN1 expression in 33 types of cancer ($n$ (low) = 4,740 vs. $n$ (high) = 4,664) and (b) DFS plots based on BCYRN1 expression in 33 types of cancer ($n$ (low) = 4,740 vs. $n$ (high) = 4,664).

| Cancer types | Expression | Potential targets | Pathways and mechanisms | Related microRNAs | References |
|--------------|------------|-------------------|-------------------------|-------------------|------------|
| NSCLC        | Up β-Catenin/c-Myc/cyclin D1 | Cell proliferation and migration; Wnt/β-catenin signaling | | NR | [15] |
|              |            |                   |                         |                   |------------|
|              | Up PI3K/AKT/STAT3 | Cell proliferation, invasion, and migration; PI3K/AKT pathway | | NR | [16] |
|              | Up c-MYC   | Cell metastasis; promoting the expressions of MMP9 and MMP13 | | NR | [17] |
| HCC          | Up POU3F2  | Cells growth, clone formation, and movement abilities; affected the proliferation and migration of HepG2 cells; reduced the expression of Bcl-xL protein | | miR-490-3p | [18] |
| Colon cancer | Up STAT3/β-catenin | Proliferation; apoptosis; reduction of the phosphorylation of STAT3 | | NR | [19] |
| CRC.         | Up KRAS    | Proliferation, migration, and invasion; apoptosis | | miR-204-3p | [20] |
|              | CCA T2     | CCA T2; miR-320a axis proliferation; apoptosis | | miR-320a | [21] |
|              | NPR3       | | | NR | [22] |
| BLC          | Up WNT5A/VEGF-C/VEGFR3 | Activates WNT5A/vegf-c/vegfr3 feedforward loop to drive lymphatic metastasis | | | [23] |
| Glioma       | Up HDAC11  | Sponged miR939-3p to upregulate histone deacetylase 11 (HDAC11) expression | | miR-939-3p | [24] |
| ESCC         | Down CUEDC2| Regulate CUEDC2 expression and the PTEN/akt/p21 pathway | | miR-619-3p | [25] |
| GC           | Up ATP4    | Cell invasion and migration | | NR | [26] |
|              | Up NR      | Cell proliferation, cell cycle, migration, and invasion; cell proliferation and metastasis; apoptosis | | miR-204-5p | [27] |
| Cervical cancer | Up EpCAM  | | | NR | [28] |
| ENKTCL       | Up PI3K/AKT/mTOR/p53 | PI3K/AKT/mTOR/p53 pathways | | NR | [29] |
| Breast cancer | Up Bcl-xL  | Apoptosis | | NR | [30] |

**Note.** NSCLC: non-small-cell lung cancer, HCC: hepatocellular carcinoma, CRC: colorectal cancer, BLC: bladder cancer, ESCC: esophageal squamous cell carcinoma, ENKTCL: extranodal NK/T-cell lymphoma, NR: not reported, ↑: promote, and ↓: inhibit.
addition, BCYRN1 is upregulated in extranodal lymphomas and may enhance ASP resistance by activating autophagy [36]. BC200 is expressed at low levels in ovarian cancer and may inhibit tumor cell proliferation [32]. Singh et al. found that BC200 is upregulated in breast cancer and is a potential target for estrogen-dependent breast cancer [33]. Except for gliomas and ovarian cancer, BCYRN1 is highly expressed in most malignancies, and the oncogenic mechanisms need future investigation. The mechanism and research progress of BCYRN1 in various types of cancer are shown in Table 3.

There are several limitations to our study that ought to be considered. Since all studies had been conducted in China, our findings may only apply to Asian patients. Second, only a tiny percentage of cases were included, and several cancer types had limited sample sizes. To overcome these restrictions, we analyzed the gene in an existing public database to validate and increase the reliability of the results. Third, manually deriving HRs for OS and PFS from Kaplan–Meier curves might lead to operational mistakes. Fourth, we did not have a uniform threshold value for high and low BCYRN1 expression, since some studies used median and others used mean. Fifth, this study used meta-analysis and bioinformatics analysis to make a preliminary summary and judgment of the prognosis and expression of BCYRN1 in tumors, providing a theoretical basis for future research in this area, but the lack of specific laboratory validation is a great regret. Sixth, this paper is an analysis of pan-cancer, but there is heterogeneity between each cancer, and BCYRN1 can be specifically analyzed in separate cancer types in the future. Finally, all studies were published in English, which may have led to selection bias.

5. Conclusion

Elevated BCYRN1 expression is correlated to worse prognosis and clinicopathological features (including T stage, clinical stage, and distant tumor metastasis) in cancer patients. There was no significant relationship between high BCYRN1 expression and patient age, gender, tumor differentiation, lymphatic metastasis, or tumor size. Thus, BCYRN1 is a potential diagnostic biomarker and therapeutic target in various cancers, although the underlying mechanisms and clinical significance have to be corroborated further with large-scale, multicenter cohort studies.

Abbreviation

ACC: adrenocortical carcinoma  
BCYRN1: brain cytoplasmic RNA 1  
BLCA: Bladder urothelial carcinoma  
BRCA: Breast invasive carcinoma  
CESC: Cervical squamous cell carcinoma and endocervical adenocarcinoma  
CHOL: Cholangio carcinoma  
CI: Confidence interval  
COAD: Colon adenocarcinoma  
DFI: Disease-free interval  
DFS: Disease-free survival  
DLBC: Lymphoid neoplasm diffuse large B-cell lymphoma  
DSS: Disease-specific survival  
ESCA: Esophageal carcinoma  
GBM: Glioblastoma multiforme  
GEPIA: Gene expression profiling interactive analysis  
GTEX: The genotype-tissue expression  
HCC: Hepatocellular carcinoma  
HNSC: Head and neck squamous cell carcinoma  
HR: Hazard ratio  
KICH: Kidney chromophobe  
KIRC: Kidney renal clear cell carcinoma  
KIRP: Kidney renal papillary cell carcinoma  
LAML: Acute myeloid leukemia  
LGG: Brain lower-grade glioma  
LIHC: Liver hepatocellular carcinoma  
LncRNA: Long non-coding RNA  
LNM: Lymph node metastasis  
LUAD: Lung adenocarcinoma  
LUSC: Lung squamous cell carcinoma  
MESO: Mesothelioma  
mRNA: MicroRNA  
mRNA: Messenger RNA  
MSI: Microsatellite instability  
NOS: Newcastle–Ottawa scale  
NSCLC: Non-small-cell lung cancer  
OR: Odds ratio  
OS: Overall survival  
OV: Ovarian serous cystadenocarcinoma  
PAAD: Pancreatic adenocarcinoma  
PCPG: Pheochromocytoma and paraganglioma  
PFI: Progression-free interval  
PRAD: Prostate adenocarcinoma  
READ: Rectum adenocarcinoma  
RFS: Recurrence-free survival  
SARC: Sarcoma  
SKCM: Skin cutaneous melanoma  
STAD: Stomach adenocarcinoma  
TCGA: The cancer genome atlas  
TGCT: Testicular germ cell tumors  
THCA: Thyroid carcinoma  
THYM: Thymoma  
TMB: Tumor mutational burden  
TME: Tumor immune microenvironment  
UCEC: Uterine corpus endometrial carcinoma  
UCS: Uterine carcinosarcoma  
UVM: Uveal melanoma.

Data Availability

The analyzed data sets generated during the study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.
Authors’ Contributions

Yongfeng Wang and Xiaoyong Han conceived the study; Guangming Zhang and Liangyin Fu performed the literature search; Haojie Jin and Xianglai Jiang extracted the required data; Ranyin Zhao and Chenhui Qin performed the statistical analyses; Xiaoyong Han wrote a draft; and Kehu Yang and Hui Cai reviewed the paper. Xiaoyong Han and Yongfeng Wang contributed equally to this work.

Acknowledgments

This study was supported by grants from the Central to Guide Local Scientific and Technological Development (ZYYD21FFZJ-1), Key Talent Project of Gansu Province of the Organization Department of Gansu Provincial Party Committee (2020RCXM076), Key Laboratory of Gastrointestinal Cancer Diagnosis and Treatment of National Health Commission (2019PT320005), Gansu Provincial Youth Science and Technology Fund Program (21JR7RA642), Gansu Key Laboratory of Molecular Diagnosis and Precision Treatment of Surgical Tumors (18JR2RA033), Guiding Plan for Scientific and Technological Development of Lanzhou (2019-ZD-102), and Natural Science Foundation of Gansu Province (21JR11RA186).

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