Review Article

Prognostic Value of Long Noncoding RNAs in Patients with Gastrointestinal Cancer: A Systematic Review and Meta-Analysis

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Received 22 June 2018; Revised 10 September 2018; Accepted 20 September 2018; Published 26 November 2018

Academic Editor: Giuseppe Biondi-Zoccai

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Gastrointestinal cancers (GICs) are a huge threat to human health, which mainly include esophageal, gastric, and colorectal cancers. The purpose of this study was to clarify the prognostic value of long noncoding RNAs (lncRNAs) in GICs. A total of 111 articles were included, and 13103 patients (3123 with esophageal cancer, 4972 with gastric cancer, and 5008 with colorectal cancer) were enrolled in this study. The pooled hazard ratio (HR) values and corresponding 95% confidence interval (95% CI) of overall survival (OS) related to different lncRNA expressions in esophageal, gastric, colorectal, and gastrointestinal cancer patients were 1.92 (1.70–2.16), 1.96 (1.77–2.16), 2.10 (1.87–2.36), and 2.00 (1.87–2.13), respectively. We have identified 74 lncRNAs which were associated closely with poor prognosis of GIC patients, including 58 significantly upregulated lncRNA expression and 16 significantly downregulated lncRNA expression. In addition, 47 of the included studies revealed relative mechanisms and 12 of them investigated the correlation between lncRNAs and microRNAs. Taken together, this meta-analysis supports that specific lncRNAs are significantly related to the prognosis of GIC patients and may serve as novel markers for predicting the prognosis of GIC patients. Furthermore, lncRNAs may have a promising contribution to lncRNA-based targeted therapy and clinical decision-making in the future.

1. Introduction

Gastrointestinal cancers (GICs) are one of the most common causes of cancer-related deaths with a high mortality worldwide, which mainly include esophageal, gastric, and colorectal cancers (EC, GC, and CRC). In addition to aging and expansion of world population, cancer-causing behaviors play a key role in the increasing largely global burden of GIC, such as smoking and changes in dietary patterns [1]. There are many therapy strategies applicable to GIC patients, such as surgery, neoadjuvant chemoradiotherapy, and adjuvant chemoradiotherapy [2], and GIC patients at early stage could be curable by receiving suitable treatment with a 90% five-year overall survival. However, five-year overall survivals are still poor for patients with advanced stages [3, 4]. Consequently, early diagnosis and selection of high-risk individuals with poor prognosis are important in the recovery of patients. However, effective methods to evaluate prognosis of GIC patients are still lacking nowadays. Currently, mounting reports have reported that noncoding RNA could be used to predict the prognosis of GIC patients. For example, microRNAs are potentially eligible for predicting the survival of GIC patients [5]. Many studies indicated that long noncoding RNAs (lncRNAs) could competitively suppress microRNAs by acting as molecular sponges recently [6]. Besides, aberrant expression of specific lncRNAs as molecular biomarkers was associated closely with prognosis of GIC patients and involved in targeted therapy, which might promote the development of novel prevention strategies and advanced therapies [7–12].

lncRNA is a long (more than 200 nucleotides) class of noncoding RNA that is often expressed in a disease-, tissue-, or stage-specific manner [13]. According to recent estimate, more than 28000 distinct lncRNAs are encoded by
human genome and they regulate gene expression by means of different mechanisms, including chromatin modification, transcription, and posttranscriptional processing, which are becoming attractive therapeutic targets of cancers [14, 15]. Such upregulated lncRNA HOXA11-AS expression promotes tumor proliferation and invasion by scaffolding the chromatin modification factors PRC2, LSD1, and DNMT1 [16]. lncRNA FEZF1-AS1 recruits and bounds to LSD1 to epigenetically repress downstream gene p21, thereby promoting proliferation [17], and lncRNA GHET1 promotes gastric carcinoma cell proliferation by increasing c-Myc mRNA stability [18]. Furthermore, lncRNA plays crucial roles in the diverse biological processes such as development, differentiation, and carcinogenesis [19]. In addition, lncRNA may induce resistance of an anticancer drug. For example, upregulated lncRNA MALAT1 induces chemoresistance of CRC cells [20].

Recently, mounting evidences have indicated that various lncRNAs can function as oncogenes or tumor suppressor genes and the dysregulation of lncRNA expression as molecular biomarkers presented promising huge prognostic values in GIC patients [21–26]. However, the ability of evaluating relationship between multiple lncRNA expression and prognosis of GIC patients was limited due to monocentric, small samples and various experimental methods and criteria from different research departments. Therefore, the purpose of the study was to elaborate the relationship between multiple lncRNA expression and prognosis of GIC patients so that further understanding of prognostic values of lncRNAs might promote lncRNA-based target therapeutic development and make a clinical decision that is suitable for the individual quickly.

2. Materials and Methods

2.1. Search Strategy. To obtain the relevant studies for this meta-analysis, two authors (Weiibao Kang and Qiang Zheng) searched a wide range of database (PubMed, Web of Science, and Embase) independently up to August 27, 2018. Search terms are as follows: “LncRNA”, “Long non-coding RNAs”, “IncRNAs”, “lncRNA”, “Long ncRNAs”, “lncRNA”, “LINC RNA”, “Long ncRNAs”, “cancer”, “tumor”, “malignancy”, “carcinoma”, “neoplasia”, “neoplasm”, “gastrointestinal”, “gastroenteric”, “colon”, “colorectal”, “rectum”, “intestinal”, “gastric”, “esophageal”, “esophagus”, “follow up studies”, “prognosis”, “prediction”, “survival”, “hazard ratio”, “incidence”, and “mortality”, which were combined with AND/OR.

2.2. Selection Criteria. All eligible studies were assessed and extracted data by the same two investigators independently based on the selection criteria. Inclusion criteria are the following: (1) patients who were diagnosed as having gastrointestinal cancer by pathologists and did not receive any preoperative chemotherapy or radiotherapy before obtaining samples; (2) predicting prognosis of full stage (I–IV) patients on the basis of the expression levels of lncRNAs; (3) the expression levels of lncRNAs were divided into high and low levels; (4) we could obtain overall survival (OS), disease-free survival (DFS), hazard ratio (HR), and 95%
Table 1: Characteristics of studies and lncRNA expression related to OS in GIC patients.

| References | IncRNAs (n = 105) | Year | Nations | Number (n = 12178) | OS 95% CI | Cut-off value | Detection methods | Sample types | Follow-up |
|------------|-------------------|------|---------|---------------------|-----------|---------------|-----------------|--------------|-----------|
| Sun et al. [13] | RNAGASS1 | 2014 | China | 89 GC | 2.43* | 1.29–4.59 | Median | RT-PCR | Tissue | <40 |
| Li et al. [29] | SNHG201 | 2016 | China | 107 CRC | 2.97* | 1.51–5.82 | YI | RT-PCR | Tissue | <40 |
| Kong et al. [15] | PVT11 | 2015 | China | 80 GC | 2.09* | 1.07–4.10 | Median | RT-PCR | Tissue | <40 |
| Qi et al. [31] | AGAP2-AS11 | 2017 | China | 50 GC | 2.67* | 1.45–4.93 | Median | RT-PCR | Tissue | 6–36 |
| Chen et al. [32] | XIST1 | 2016 | China | 106 GC | 3.11 | 1.67–3.78 | Median | RT-PCR | Tissue | <120 |
| Ye et al. [33] | Inc-GNAT1-1 | 2016 | China | 68 CRC | 2.16* | 1.01–4.63 | Median | RT-PCR | Tissue | <20 |
| Saito et al. [21] | ATB1 | 2015 | Japan | 183 GC | 3.50* | 1.73–7.44 | Median | RT-PCR | Tissue | 0.192–134.4 |
| Yuan et al. [35] | PVT11 | 2016 | China | 111 GC | 2.28* | 1.05–4.93 | Median | RT-PCR | Tissue | 20–48 |
| Ye et al. [36] | CLMAT31 | 2015 | China | 90 CRC | 2.05* | 1.10–3.82 | Dichotomize | RT-PCR | Tissue | <45 |
| Zheng et al. [37] | UCA11 | 2015 | China | 112 GC | 2.35* | 1.22–4.52 | Dichotomize | RT-PCR | Tissue | <92 |
| Chen et al. [38] | NEAT11 | 2015 | China | 96 EC | 1.92* | 1.40–6.49 | YI | RT-PCR | Tissue | <80 |
| Wang et al. [39] | CCAT21 | 2016 | China | 108 GC | 2.11* | 1.44–3.20 | Median | RT-PCR | Tissue | <70 |
| Zhao et al. [22] | HOTAIR1 | 2015 | China | 168 GC | 1.47* | 1.04–2.06 | Median | RT-PCR | Tissue | <70 |
| Zhang et al. [40] | Sox20t1 | 2016 | China | 132 GC | 2.05* | 1.28–3.30 | Median | RT-PCR | Tissue | <96 |
| Chen et al. [41] | HIF1A-AS21 | 2015 | China | 83 GC | 1.72* | 1.00–2.96 | Median | RT-PCR | Tissue | <60 |
| Li et al. [10] | HOTAIR1 | 2013 | China | 100 EC | 1.91 | 1.06–4.00 | 125-fold | RT-PCR | Tissue | <60 |
| Yue et al. [42] | FERL41 | 2015 | China | 70 CC | 3.99* | 1.67–9.01 | Median | RT-PCR | Tissue | <80 |
| He et al. [43] | CCAT11 | 2014 | China | 48 CC | 2.09* | 1.42–3.06 | Median | RT-PCR | Tissue | 24–37 |
| Yin et al. [44] | MEG31 | 2015 | China | 62 CRC | 0.13* | 0.02–0.99 | Mean | RT-PCR | Tissue | <60 |
| Nie et al. [45] | MIR31HG1 | 2016 | China | 48 CC | 2.35* | 1.15–4.79 | Median | RT-PCR | Tissue | 3–36 |
| Park et al. [46] | BM742401 | 2013 | Korea | 113 GC | 1.03* | 0.57–1.88 | Median | RT-PCR | Tissue | <80 |
| Liu et al. [23] | CRNDE-h1 | 2016 | China | 148 CRC | 2.39* | 1.30–4.39 | Median | RT-PCR | Serum | 1–65 |
| Li et al. [47] | PANDAR1 | 2017 | China | 102 CRC | 3.08* | 0.84–7.89 | Median | RT-PCR | Tissue | <60 |
| Chen et al. [48] | H191 | 2016 | China | 128 GC | 1.96* | 0.97–3.97 | Median | RT-PCR | Tissue | 20–48 |
| Zou et al. [49] | Sox20t1 | 2016 | China | 155 GC | 3.24* | 1.24–6.43 | Median | RT-PCR | Tissue | <70 |
| Jiang et al. [50] | TUG11 | 2016 | China | 218 EC | 1.40* | 1.01–1.95 | NR | RT-PCR | Tissue | 12–72 |
| Svoboda et al. [51] | HOTAIR1 | 2014 | Czech | 84 CRC | 5.9 | 1.34–26.1 | Median | RT-PCR | Blood | 12–54 |
| Wang et al. [52] | OTUB1-isofrom 21 | 2016 | China | 156 GC | 1.54 | 1.04–2.27 | Median | RT-PCR | Tissue | <80 |
| Guo et al. [53] | FTX1 | 2015 | China | 187 CRC | 2.37 | 1.42–2.74 | Median | RT-PCR | Tissue | <60 |
| Pan et al. [54] | FOXCUT1 | 2014 | China | 82 EC | 2.13* | 1.38–3.29 | Mean | RT-PCR | Tissue | 1–72 |
| Zhou et al. [55] | LET1 | 2014 | China | 93 GC | 2.28 | 1.30–5.18 | Mean | RT-PCR | Tissue | <60 |
| Hu et al. [56] | linc-UBC11 | 2015 | China | 85 GC | 3.56* | 1.71–7.39 | Median | RT-PCR | Tissue | <100 |
| Wang et al. [57] | CCAT21 | 2015 | China | 86 GC | 2.41 | 1.19–5.42 | Mean | RT-PCR | Tissue | <60 |
| Ren et al. [58] | HOTTIP1 | 2015 | China | 156 CRC | 2.15 | 1.31–3.42 | Median | RT-PCR | Tissue | 33–65 |
| Liu et al. [59] | DANCRI1 | 2015 | China | 104 CRC | 2.13* | 1.16–7.06 | Median | RT-PCR | Tissue | <60 |
| Wang et al. [60] | ZEB1-AS11 | 2015 | China | 87 EC | 2.37 | 1.28–6.12 | Median | RT-PCR | Tissue | <61 |
| Li et al. [61] | BANCRI1 | 2015 | China | 184 GC | 1.51* | 1.03–2.23 | Median | RT-PCR | Tissue | 5–93 |
| Ma [62] | PANDAR1 | 2016 | China | 100 GC | 3.68 | 1.13–12.06 | NR | RT-PCR | Tissue | 2–36 |
| Huang et al. [63] | MALAT11 | 2016 | China | 132 EC | 6.64 | 2.95–14.95 | NR | RT-PCR | Tissue | <60 |
| Ni et al. [64] | UCA11 | 2015 | China | 54 CRC | 3.11* | 0.59–16.39 | Median | RT-PCR | Tissue | 9–51 |
| Wu et al. [25] | uc002y2u21 | 2014 | China | 684 EC | 2.61 | 1.50–3.78 | NR | RT-PCR | Tissue | <140 |
| Sun et al. [16] | HOXA11-AS11 | 2016 | China | 85 GC | 2.85* | 1.65–4.91 | Median | ISH | Tissue | 9–36 |
| Peng et al. [65] | NEAT11 | 2016 | China | 56 CRC | 1.70* | 1.04–2.80 | NR | RT-PCR | Tissue | <60 |
| Jiao et al. [66] | UCA11 | 2016 | China | 66 EC | 2.24* | 1.17–4.29 | Median | RT-PCR | Tissue | 5–30 |
| References | IncRNAs  
(n = 105) | Year | Nations  
(n = 12178) | Number | OS  
95% CI | Cut-off value | Detection methods | Sample types | Follow-up |
|------------|-----------|------|-------------|--------|---------|-------------|----------------|-------------|-----------|
| Liu and Shangguan [67] | CARLo-5↑ | 2017 | China | 240 GC | 2.41* | 1.13–5.94 | 0.041 | RT-PCR | Tissue | <60 |
| Ma et al. [11] | CCAL↑ | 2016 | China | 252 CRC | 2.25* | 1.35–3.74 | Median | RT-PCR | Tissue | <100 |
| Yang et al. [18] | GHETI↑ | 2014 | China | 42 GC | 1.90↑ | 0.53–6.85 | Median | RT-PCR | Tissue | 7–40 |
| Wu et al. [68] | HOTAIR↑ | 2014 | China | 120 CC | 3.92↑ | 1.23–12.50 | 5-fold | RT-PCR | Tissue | 10–72 |
| Zhou et al. [69] | ROR↑ | 2016 | China | 60 CC | 7.22↑ | 2.43–17.43 | Median | RT-PCR | Tissue | <80 |
| Yang et al. [70] | Loc554202↑ | 2016 | China | 178 CRC | 2.45 | 1.34–7.74 | Median | RT-PCR | Tissue | <70 |
| Lü et al. [71] | BC032469↑ | 2016 | China | 58 GC | 2.78↑ | 0.95–8.09 | Mean | RT-PCR | Tissue | <23 |
| Su et al. [72] | BLACAT1↑ | 2017 | China | 48 CRC | 1.50* | 1.32–1.70 | Mean | RT-PCR | Tissue | <60 |
| Hu et al. [12] | GAPLINC↑ | 2014 | China | 90 GC | 1.54* | 1.22–1.94 | Median | ISH | Tissue | <80 |
| Fu et al. [73] | NEAT1↑ | 2016 | China | 140 GC | 1.61 | 1.03–2.53 | Median | RT-PCR | Tissue | <96 |
| Yao et al. [26] | RP11-766N7.4↑ | 2017 | China | 50 EC | 2.14↑ | 1.10–4.15 | Median | RT-PCR | Tissue | 32–60 |
| Xie et al. [74] | SPRY4-IT1↑ | 2014 | China | 92 EC | 2.05 | 1.04–4.03 | Median | RT-PCR | Tissue | 3–60 |
| Peng [75]↑ | SPRY4-IT1↑ | 2015 | China | 175 GC | 0.82↑ | 0.31–1.57 | Median | RT-PCR | Tissue | <60 |
| Nie et al. [76] | ZFAS1↑ | 2016 | China | 54 GC | 2.08↑ | 1.11–3.93 | Median | RT-PCR | Tissue | 3–36 |
| Ohtsuka et al. [77] | H19↑ | 2016 | USA | 117 CC | 1.28↑ | 1.08–1.50 | 0.64 | RT-PCR | Tissue | <90 |
| Li et al. [20] | MALAT1↑ | 2017 | China | 68 CRC | 2.17↑ | 1.32–3.55 | Median | RT-PCR | Tissue | 1–51 |
| Zhou et al. [78] | AFAP1-AS1↑ | 2016 | China | 162 EC | 1.89↑ | 1.22–2.92 | Median | RT-PCR | Tissue | 6–72 |
| Sun et al. [80]↑ | RP11-119F7.4↑ | 2015 | China | 96 GC | 1.20↑ | 0.84–1.71 | Median | RT-PCR | Tissue | <100 |
| Zhang et al. [81]↑ | ANRIL↑ | 2014 | China | 120 GC | 1.74↑ | 1.04–2.93 | 3-fold | RT-PCR | Tissue | <60 |
| Li et al. [82]↑ | NEAT1↑ | 2015 | China | 239 CRC | 1.70↑ | 1.18–2.45 | 2-fold | RT-PCR | Tissue | <60 |
| Chen et al. [83] | LINCO0152↑ | 2016 | China | 97 GC | 1.66↑ | 1.01–2.73 | Median | RT-PCR | Tissue | <60 |
| Chen et al. [19] | FEZF1-AS1↑ | 2016 | China | 153 CRC | 2.40↑ | 1.07–5.41 | Median | RT-PCR | Tissue | <60 |
| Han et al. [84]↑ | H19↑ | 2016 | China | 83 CRC | 1.43↑ | 1.24–1.79 | 3-fold | RT-PCR | Tissue | <50 |
| Yang et al. [85]↑ | GAPLINC↑ | 2016 | China | 180 CRC | 2.21↑ | 1.38–3.57 | Median | RT-PCR | Tissue | <100 |
| Jin et al. [86]↑ | HULC↑ | 2016 | China | 54 GC | 1.92↑ | 1.00–3.67 | 2-fold | RT-PCR | Serum | 11–32 |
| Cao et al. [87]↑ | BC200↑ | 2016 | China | 70 EC | 2.24↑ | 1.12–4.49 | Median | RT-PCR | Tissue | <50 |
| Cao et al. [88]↑ | SPRY4-IT1↑ | 2016 | China | 84 CRC | 3.21↑ | 1.55–6.67 | 2.87-fold | RT-PCR | Tissue | 3–36 |
| Gao et al. [89]↑ | linc-UBC1↑ | 2017 | China | 96 CRC | 2.43↑ | 1.09–5.42 | Median | RT-PCR | Tissue | <60 |
| Wang et al. [90]↑ | AFAP1-AS1↑ | 2016 | China | 52 CRC | 2.36 | 1.11–5.01 | Median | RT-PCR | Tissue | <50 |
| Ge et al. [91]↑ | PCAT-1↑ | 2013 | China | 108 CRC | 3.12 | 1.36–7.19 | Median | RT-PCR | Tissue | <100 |
| Deng et al. [92]↑ | 91H↑ | 2014 | China | 72 CRC | 3.66 | 1.66–8.10 | 2.86-fold | RT-PCR | Tissue | 2–36 |
| Sun et al. [93]↑ | AK098081↑ | 2016 | China | 84 CRC | 1.90↑ | 1.39–2.58 | Median | RT-PCR | Tissue | 1–118 |
| Xu et al. [94]↑ | FENDRR↑ | 2014 | China | 158 GC | 1.76 | 1.04–3.12 | Median | RT-PCR | Tissue | 20–48 |
| Bian et al. [96]↑ | UCA1↑ | 2016 | China | 90 CRC | 2.40↑ | 1.04–5.50 | Median | RT-PCR | Tissue | <100 |
| Zuo et al. [97]↑ | UCA1↑ | 2017 | China | 37 GC | 2.92↑ | 1.07–7.96 | Median | RT-PCR | Tissue | <40 |
| Lu et al. [98]↑ | PANDAR↑ | 2017 | China | 124 CRC | 3.53↑ | 1.41–4.45 | Median | RT-PCR | Tissue | <60 |
| Lv et al. [99]↑ | MEG3↑ | 2016 | China | 96 EC | 2.12 | 1.05–4.27 | Median | RT-PCR | Tissue | <120 |
| Xu et al. [100]↑ | TUSC7↑ | 2017 | China | 63 CRC | 2.92 | 1.03–8.33 | Median | RT-PCR | Tissue | <120 |
| Ma et al. [101]↑ | DUXAP8↑ | 2016 | China | 72 GC | 2.37↑ | 1.39–4.05 | Median | RT-PCR | Tissue | 5–36 |
| Fei et al. [103]↑ | LINCO0982↑ | 2016 | China | 106 GC | 2.87↑ | 1.34–6.17 | Median | RT-PCR | Tissue | 20–48 |
| Chen et al. [104]↑ | SNHG15↑ | 2016 | China | 106 GC | 2.93↑ | 1.30–6.58 | Median | RT-PCR | Tissue | 20–48 |
| Tan et al. [105]↑ | SPRY4-IT1↑ | 2017 | China | 106 CRC | 2.34↑ | 1.14–4.83 | Median | RT-PCR | Tissue | <70 |
| Wang and Xing [106]↑ | ZFAS1↑ | 2016 | China | 159 CRC | 1.88↑ | 1.01–3.53 | Median | RT-PCR | Tissue | <101 |

* Table 1: Continued. 
** Year, Nations, Number, OS 95% CI, Cut-off value, Detection methods, Sample types, Follow-up are specific values related to the table entries. **
Table 1: Continued.

| References         | IncRNAs (n = 105) | Year | Nations | Number (n = 12178) | HR  | OS 95% CI | Cut-off value | Detection methods | Sample types | Follow-up |
|--------------------|-------------------|------|---------|---------------------|-----|-----------|---------------|------------------|--------------|-----------|
| Yao et al. [107]   | MALAT-1[1]        | 2016 | China   | 137 EC              | 1.27 | 0.90–1.80 | 0.5-fold      | RT-PCR          | Tissue       | 3–36²    |
| Liu et al. [108]²  | BANCR[1]          | 2016 | China   | 142 EC              | 0.95 | 0.21–0.95 | Median        | RT-PCR          | Tissue       | 1–60²    |
| Chen et al. [109]  | HOTAIR[1]         | 2013 | China   | 78 EC               | 2.40 | 1.35–4.28 | Mean          | RT-PCR          | Tissue       | 2–60     |
| Hu et al. [102]²  | POU3F3[1]         | 2016 | China   | 205 EC              | 1.89 | 1.22–2.58 | Upper 95%    | RT-PCR          | Plasma       | <60      |
| Yu et al. [110]    | s05535[1]         | 2018 | China   | 98CRC               | 4.01 | 1.06–15.14| NR            | RT-PCR          | Tissue       | <60      |
| Jiang et al. [111] | CRNDE[1]          | 2017 | China   | 251CRC              | 1.69 | 1.05–2.74 | NR            | ISH             | Tissue       | 1–117    |
| Cui et al. [112]   | HEIH[1]           | 2018 | China   | 84CRC               | 1.46 | 1.02–2.08 | Median        | RT-PCR          | Tissue       | <60      |
| Wu et al. [113]¹  | GHRLOS[1]         | 2017 | China   | 366CRC              | 1.96 | 1.34–2.86 | 1/2-fold      | RT-PCR          | Tissue       | 5–85     |
| Li et al. [115]    | ZEB1-AS1[1]       | 2017 | China   | 24GC                | 2.36 | 1.41–3.96 | Median        | RT-PCR          | Tissue       | 72       |
| Huang et al. [116] | LINC00673[1]     | 2017 | China   | 73GC                | 2.38 | 1.12–5.06 | 2-fold        | RT-PCR          | Tissue       | <20      |
| Li et al. [117]    | PVT1[1]           | 2017 | China   | 104ESCC             | 2.75 | 1.35–5.59 | Median        | RT-PCR          | Tissue       | <80      |
| Shi et al. [118]   | ZFAS1[1]          | 2017 | China   | 246ESCC             | 1.59 | 1.07–2.36 | Median        | RT-PCR          | Tissue       | 114      |
| Wu et al. [119]    | XIST[1]           | 2017 | China   | 127ESCC             | 2.4  | 1.44–4.01 | Median        | RT-PCR          | Tissue       | <80      |
| Ba et al. [120]    | LINC00673[1]      | 2017 | China   | 79GC                | 2.56 | 1.01–4.54 | Median        | RT-PCR          | Tissue       | <50      |
| Zhu et al. [121]   | SNHG1[1]          | 2017 | China   | 108CRC              | 3.17 | 1.55–6.21 | Median        | RT-PCR          | Tissue       | <50      |
| Yang et al. [122]  | LINC01133[1]      | 2018 | China   | 149ESCC             | 2.18 | 1.23–3.85 | Median        | RT-PCR          | Tissue       | <60      |

¹One study involved IncRNA Linc00152, IncRNA POU3F3, and IncRNA CFLAR. * indicates adjusted HR; # indicates calculated HR of OS and follow-up time; † indicates studies included OS and DFS; ↑ or ↓ indicates upregulated or downregulated with poor prognosis. OS: overall survival; DFS: disease-free survival; HR: hazard ratio; CI: confidence interval; EC: esophageal cancer; GC: gastric cancer; CRC: colorectal cancer; GIC: gastrointestinal cancer; NR: no report; YI: Youden index; RT-PCR: reverse transcription PCR; ISH: in situ hybridization.

2.3. Data Extraction and Quality Assessment. The two authors (Weibiao Kang and Qiang Zheng) extracted data independently and got consensus finally. The characteristics collected of individual articles were as follows: author, year of publication, nation of population enrolled, number of patients, HR and 95% CI (OS/DFS), cut-off value, method, sample type, and follow-up. We assessed the quality of each study by using the guidelines for meta-analysis of observation studies in epidemiology (MOOSE) [27].

2.4. Statistical Analysis. Statistical analysis was conducted by Review Manager 5.2 (provided by Cochrane collaboration). \( P < 0.01 \) was considered statistically significant. The heterogeneity among studies was calculated by Q and \( I^2 \) tests. \( P > 0.10 \) in combination with \( I^2 < 50\% \) indicated low heterogeneity; fixed-effect models should be used. Otherwise, random-effect model would be used finally. For some studies from which we could not extract HR and corresponding 95% CI (OS/DFS) directly, Engauge Digitizer 4.1 software was applied to obtain the necessary points from Kaplan-Meier survival curves, then HR and corresponding 95% CI were calculated by published methods proposed by Tierney et al. [28]. Additionally, forest plots of the pooled HR values and funnel plots used to analyse qualitatively publication bias were presented. Furthermore, we also applied sensitivity analysis for this meta-analysis.

3. Results

3.1. Study Identification and Characteristics. According to the selection criteria, a total of 111 articles (21 EC, 47 GC, and 44 CRC; one study involved GC and CRC) involving 13103 patients (3123 with EC, 4972 with GC, and 5008 with CRC) were identified and included in the meta-analysis; specific steps were showed in Figure 1 [10–13, 15–26, 29–123]. Most of the studies taken into account refer to Asian population, especially China. Cut-off values of high or low lncRNA expression were mostly median or mean. Detection methods of lncRNA expression were mainly RT-PCR (reverse transcription PCR) or ISH (in situ hybridization). Sample types were almost from tissues. As for clinical outcome indicators, 74 studies [10–13, 16, 18–23, 25, 26, 29, 31–33, 36, 38, 40, 41,
Table 2: Characteristics of studies and lncRNAs expression related to DFS in GIC patients.

| References          | lncRNAs (n = 37) | Year | Nations | Number (n = 4360) | DFS 95% CI HR | Cut-off value | Detection methods | Sample types | Follow-up |
|---------------------|------------------|------|---------|-------------------|----------------|--------------|------------------|--------------|-----------|
| Kong et al. [15]    | PVT1†            | 2015 | China   | 80GC              | 2.22* 1.13–4.44 | Median        | RT-PCR          | Tissue       | <40       |
| Liu et al. [17]     | FEZF1-AS1†       | 2017 | China   | 82GC              | 1.52* 0.88–2.63 | 2-fold        | RT-PCR          | Tissue       | 1–43^     |
| Fan et al. [30]     | LINC00261†       | 2016 | China   | 138GC             | 1.81* 1.06–3.10 | Median        | RT-PCR          | Tissue       | 20–48     |
| Xu et al. [34]      | PVT1†            | 2017 | China   | 190GC             | 1.75 1.25–2.56  | Mean          | RT-PCR          | Tissue       | 1–85      |
| Yuan et al. [35]    | PVT1†            | 2016 | China   | 111GC             | 2.21* 1.11–4.40 | Median        | RT-PCR          | Tissue       | 20–48     |
| Zheng et al. [37]   | UCA1†            | 2015 | China   | 112GC             | 2.55* 1.33–4.97 | Dichotomize   | RT-PCR          | Tissue       | <92       |
| Wang et al. [39]    | CCAT2†           | 2016 | China   | 108GC             | 2.31* 1.55–3.42 | Median        | RT-PCR          | Tissue       | <70       |
| Yue et al. [42]     | FERI-L4†         | 2015 | China   | 70CC              | 4.51* 1.99–9.02 | Median        | RT-PCR          | Tissue       | <80       |
| Chen et al. [48]    | H19†             | 2016 | China   | 128GC             | 1.29* 1.00–1.65 | Median        | RT-PCR          | Tissue       | 20–48     |
| Zou et al. [49]     | Sox20†           | 2016 | China   | 155GC             | 3.84* 1.87–7.33 | Median        | RT-PCR          | Tissue       | <70       |
| Wang et al. [24]    | NR_034119†       | 2016 | China   | 107CRC            | 1.93* 1.04–3.61 | NR            | RT-PCR          | Serum        | 11–74     |
| Wang et al. [52]    | OTUB1-isofrom 2† | 2016 | China   | 156GC             | 1.50* 1.02–2.20 | Median        | RT-PCR          | Tissue       | <80       |
| Liu et al. [59]     | DANCR†           | 2015 | China   | 104CRC            | 2.40* 1.39–7.28 | Median        | RT-PCR          | Tissue       | <60       |
| Wang et al. [60]    | ZEB1-AS1†        | 2015 | China   | 87EC              | 2.7 1.38–8.35  | Median        | RT-PCR          | Tissue       | <61       |
| Ma et al. [62]      | PANDAR†          | 2016 | China   | 100GC             | 2.36 1.15–4.83  | NR            | RT-PCR          | Tissue       | 2–36      |
| Peng et al. [65]    | NEAT1†           | 2016 | China   | 56CRC             | 2.39* 1.37–4.19 | NR            | RT-PCR          | Tissue       | <60       |
| Zhou et al. [69]    | ROR†             | 2016 | China   | 60CC              | 5.64* 1.92–16.58| Median        | RT-PCR          | Tissue       | <80       |
| Yang et al. [70]    | Loc554202†       | 2016 | China   | 178CRC            | 2.75 1.55–7.93  | Median        | RT-PCR          | Tissue       | <70       |
| Peng et al. [75]    | SPRY4-IT1†       | 2015 | China   | 175GC             | 1.74* 1.32–2.48 | Median        | RT-PCR          | Tissue       | <60       |
| Nie et al. [76]     | ZFAS1†           | 2016 | China   | 54GC              | 1.83* 1.07–3.15 | Median        | RT-PCR          | Tissue       | 3–36*     |
| Xu et al. [79]      | LSINCT5†         | 2014 | China   | 71GC              | 1.08* 1.29–3.56 | Mean          | RT-PCR          | Tissue       | <72       |
| Sun et al. [80]     | RP11-119F7.4†    | 2015 | China   | 96GC              | 1.16* 0.81–1.65 | Median        | RT-PCR          | Tissue       | <100      |
| Zhang et al. [81]   | ANRIL†           | 2014 | China   | 120GC             | 1.72* 1.04–2.84 | 3-fold        | RT-PCR          | Tissue       | <60       |
| Li et al. [82]      | NEAT1†           | 2015 | China   | 239CRC            | 1.80* 1.27–2.55 | 2-fold        | RT-PCR          | Tissue       | <60       |
| Han et al. [84]     | H19†             | 2016 | China   | 83CRC             | 1.52* 1.30–1.90 | 3-fold        | RT-PCR          | Tissue       | <50       |
| Cao et al. [87]     | BC200†           | 2016 | China   | 70EC              | 2.17* 1.12–4.19 | Median        | RT-PCR          | Tissue       | <50       |
| Wang et al. [90]    | AFAp1-AS1†       | 2016 | China   | 52CRC             | 2.12 1.03–4.35  | Median        | RT-PCR          | Tissue       | <50       |
| Sun et al. [93]     | AK0980801†       | 2016 | China   | 84CRC             | 1.40* 0.86–2.28 | Mean          | RT-PCR          | Tissue       | 1–118*    |
| Xu et al. [94]      | FENDRR†          | 2014 | China   | 158GC             | 1.8 1.11–2.91  | Median        | RT-PCR          | Tissue       | 20–48     |
| Shang et al. [95]   | UCA1†            | 2016 | China   | 77GC              | 2.54 1.09–5.92  | NR            | RT-PCR          | Tissue       | <60       |
| Fei et al. [103]    | LINC00982†       | 2016 | China   | 106GC             | 2.40* 1.19–4.81 | Median        | RT-PCR          | Tissue       | 20–48     |
| Chen et al. [104]   | SNHG15†          | 2016 | China   | 106GC             | 2.40* 1.38–4.18 | Median        | RT-PCR          | Tissue       | 20–48     |
| Liu et al. [108]    | BANCR†           | 2016 | China   | 142EC             | 3.42* 2.29–5.10 | Median        | RT-PCR          | Tissue       | 1–60*     |
| Wu et al. [113]     | GHRLOS†          | 2017 | China   | 366CRC            | 2.02* 1.42–2.88 | 1/2-fold      | RT-PCR          | Tissue       | 5–85      |
| Yu et al. [114]     | linc00261†       | 2017 | China   | 80GC              | 2.57* 1.39–4.20 | NR            | RT-PCR          | Tissue       | <30       |
| Ba et al. [120]     | LINC00673†       | 2017 | China   | 79GC              | 2.94* 1.23–4.21 | Median        | RT-PCR          | Tissue       | <50       |
| Xu et al. [123]     | FOXD2-AS1†       | 2018 | China   | 106GC             | 1.75* 1.04–2.97 | Median        | RT-PCR          | Tissue       | 20–48     |

*One study involved GC and CRC. † indicates adjusted HR; ^ indicates calculated HR of DFS and follow-up time; ! indicates studies included OS and DFS; ‡ or § indicates upregulated or downregulated with poor prognosis. OS: overall survival; DFS: disease-free survival; HR: hazard ratio; CI: confidence interval; EC: esophageal cancer; GC: gastric cancer; CRC: colorectal cancer; GIC: gastrointestinal cancer; NR: no report; RT-PCR: reverse transcription PCR.
Table 3: lncRNAs and relevant targets in gastrointestinal cancer.

| lncRNAs (n = 37) | Poor prognosis | Role | Relevant targets | Function | Reference |
|------------------|----------------|------|------------------|----------|-----------|
| SNHG20↑          | Upregulated    | Oncogene | Cyclin A1, p21 | Proliferation/invasion/metastasis | [29] |
| PVTI↑            | Upregulated    | Oncogene | EZH2, p15, p16, FOXM1 | Proliferation/metastasis | [15, 34] |
| FEZF1-AS1↑       | Upregulated    | Oncogene | LSD1, P21, FEZF1 | Proliferation/invasion/metastasis | [17, 19] |
| AGAP2-AS1↑       | Upregulated    | Oncogene | LSD1, EZH2, P21, E-cadherin | Proliferation/metastasis | [31] |
| XIST↑            | Upregulated    | Oncogene | miR-101, EZH2 | Proliferation/metastasis | [32] |
| ATB↑             | Upregulated    | Oncogene | miR-200s, ZEB1, ZEB2 | Invasion/EMT | [21] |
| UCA1↑            | Upregulated    | Oncogene | Ets-2, Sox4, miR-204, miR-204-5p, TGFβ1 | Migration/apoptosis/chemoresistance/EMT | [64, 66, 96, 97] |
| NEAT1↑           | Upregulated    | Oncogene | Akt, vimentin, N-cadherin, Zo-1, E-cadherin | Pro/progression/EMT | [65, 73] |
| CCAT2↑           | Upregulated    | Oncogene | EZH2, E-cadherin, LAT52 | Progression | [39] |
| CCAT1↑           | Upregulated    | Oncogene | c-Myc | Proliferation/invasion/migration | [43] |
| PANDAR↑          | Upregulated    | Oncogene | N-cadherin, vimentin, β-catenin, Snail, Twist, E-cadherin | EMT/growth/metastasis | [98] |
| H19↑             | Upregulated    | Oncogene | E-cadherin, Rb-E2F, CDK8, β-catenin, elf4A3 | Migration/proliferation | [48, 77, 84] |
| FOXCUT↑          | Upregulated    | Oncogene | FOXC1 (mRNA) | Proliferation/metastasis | [54] |
| MALAT1↑          | Upregulated    | Oncogene | EZH2, miR-218 | Chemoresponse/EMT | [20] |
| uc002yug.2↑      | Upregulated    | Oncogene | RUNX1 | Proliferation/metastasis | [25] |
| HOXA11-AS↑       | Upregulated    | Oncogene | EZH2, LSD1, miR-1297 | Growth/metastasis | [16] |
| CCAL↑            | Upregulated    | Oncogene | AP-2α | Progression/multidrug resistance | [11] |
| GETH1↑           | Upregulated    | Oncogene | c-Myc (mRNA) | Proliferation | [18] |
| ROR↑             | Upregulated    | Oncogene | miR-145 | Proliferation/metastasis | [69] |
| BC032469↑        | Upregulated    | Oncogene | miR-1207-5p | Proliferation | [71] |
| BLACAT1↑         | Upregulated    | Oncogene | EZH2, p15 | Proliferation | [72] |
| GAPLINC↑         | Upregulated    | Oncogene | miR211-3p, CD44, PSF, NONO, SNAI2 | Invasion | [12, 85] |
| SPRY4-IT↑        | Upregulated    | Oncogene | Cyclin D1, MMP2, MMP9, E-cadherin, vimentin | Proliferation/metastasis | [75, 88] |
| ZFAS1↑           | Upregulated    | Oncogene | EZH2, LSD1, CoREST, KLF2, NDK2 | Proliferation | [76] |
| ANRIL↑           | Upregulated    | Oncogene | PRC2, miR-99a, miR-449a | Proliferation | [81] |
| LINCO0152↑       | Upregulated    | Oncogene | EZH2, p15, p21 | Proliferation | [83] |
| DUXAP8↑          | Upregulated    | Oncogene | EZH2, SUZ12, PLEKHO1 | Proliferation | [101] |
| SNHG15↑          | Upregulated    | Oncogene | MMP2, MMP9 | Proliferation/metastasis | [104] |
| GAS5↑            | Downregulated  | Suppressor | E2F1, P21 | Proliferation | [13] |
| Inc-GNAT1-1-1↑   | Downregulated  | Suppressor | RKIP-NF-xB-Snail | Proliferation/metastasis | [33] |
| FER1L4↓          | Downregulated  | Suppressor | miR-106a-5p | Proliferation/metastasis | [42] |
| MEG3↓            | Downregulated  | Suppressor | p53 | Proliferation/apoptosis | [99] |
| MIR31HG↓         | Downregulated  | Suppressor | E2F1, P21 | Proliferation | [45] |
| RP11-766N7.4↓    | Downregulated  | Suppressor | Vimentin, N-cadherin, E-cadherin | Migration/EMT | [26] |
| FENDRR↓          | Downregulated  | Suppressor | FN1, MMP2, MMP9 | Migration | [94] |
| TUSC7↓           | Downregulated  | Suppressor | miR-211-3p | Proliferation | [100] |
| LINCO0982↓       | Downregulated  | Suppressor | P15, P16 | Proliferation | [103] |

108, 113, 120] included both OS and DFS. We have identified 74 lncRNAs which were associated closely with poor prognosis of GIC patients, including 58 significantly upregulated lncRNA expression and 16 significantly downregulated lncRNA expression (Tables 1 and 2). Moreover, 47 of the included studies revealed relative mechanisms, and 12 of
them investigated the correlation between lncRNAs and microRNAs (Table 3).

3.2. Meta-Analysis Findings. Random-effect and fixed-effect models were applied to evaluate the pooled hazard ratio (HR) and its corresponding 95% confidence interval (CI) of OS or DFS based on the heterogeneity level. The pooled HR value (95% CI) of OS which correlated with the expression of lncRNA-UCA1 [37, 64, 66, 96, 97] was 2.42 (1.68–3.49) with low heterogeneity \((P = 0.99, I^2 = 0\%)\) and statistically significant \((P < 0.00001)\) (Figure 2). For all included studies, the pooled HR values (95% CI) of OS related to different lncRNA expressions in EC, GC, and CRC patients were 1.92 (1.70–2.16), 1.96 (1.77–2.16), and 2.10 (1.87–2.36), respectively. And the pooled HR value (95% CI) of OS related to different lncRNA expressions was 2.00 (1.87–2.13) in GIC with moderate heterogeneity \((P = 0.0001, I^2 = 37\%)\) and statistically significant \((P < 0.00001)\) (Figure 3). Besides, the pooled HR value (95% CI) of DFS related to different lncRNA expressions was 1.92 (1.73–2.14) in GIC patients with moderate heterogeneity \((P = 0.006, I^2 = 41\%)\) and statistically significant \((P < 0.00001)\) (Figure 4). Furthermore, funnel plots of included studies related to lncRNA-UCA1, OS, and DFS in GIC patients were presented in Figures 5, 6, and 7, respectively. These figures are approximately symmetrical, and we can think that there is no obvious publication bias.

| Study or subgroup | Log[hazard ratio] | SE | Weight | Hazard ratio IV, fixed, 95% CI | Hazard ratio IV, fixed, 95% CI |
|-------------------|------------------|----|--------|------------------------------|------------------------------|
| Jiao 2016/UCA1 †  | 0.80648          | 0.33145 | 31.6%   | 2.24 [1.17, 4.29]             |                               |
| Zheng 2015/UCA1 † | 0.85442          | 0.3341   | 31.1%   | 2.35 [1.22, 4.52]             |                               |
| Zuo 2017/UCA1 †   | 1.07158          | 0.51193  | 13.2%   | 2.92 [1.07, 7.96]             |                               |
| Ni 2015/UCA1 †    | 1.13462          | 0.48404  | 4.8%    | 3.11 [0.59, 16.39]            |                               |
| Bian 2016/UCA1 †  | 0.87547          | 0.42488  | 19.2%   | 2.40 [1.04, 5.52]             |                               |

Total (95% CI) 100.0% 2.42 [1.68, 3.49]

Heterogeneity: \(\chi^2 = 0.28, df = 4 (P = 0.99); I^2 = 0\%\)

Test for overall effect: \(Z = 4.75 (P < 0.000001)\)

4. Discussion

GIC is still a huge threat to human health in spite of ongoing emergence of new anticancer drugs because of chemotherapy resistance and metastasis inducing poor prognosis. In the last decade, more and more studies focused on the clinical roles of lncRNAs and many reports indicated that lncRNA can be a molecular biomarker in gastrointestinal cancer patients for predicting prognosis. However, the prognostic value of lncRNAs that need to be clarified, verified, and summarized was limited by various research centers and small samples.

The purpose of this study was to elucidate the relationship between multiple lncRNA expressions and prognosis of GIC patients. Through big data meta-analysis, we provided evidence to illustrate the prognostic value of aberrantly expressed lncRNAs in GIC patients. The results from this meta-analysis showed that the pooled HR values (95% CI) of OS and DFS related to different lncRNA expressions in GIC patients were 2.00 (1.87–2.13) and 1.92 (1.73–2.14), respectively, which implied that aberrantly expressed lncRNAs may serve as cancer biomarkers in GIC patients. By detecting expression levels of specific lncRNAs in tissue or other body fluids, we cannot only make appropriate clinical decisions based on different prognoses but also monitor the therapeutic efficacy of GIC patients receiving different treatments. In addition, lncRNAs may be used to screen patients at high risk at the early stage based on abnormal expression. Moreover, elevated lncRNA-UCA1 expression promoted tumor cell migration, invasion, EMT, proliferation, and chemoresistance and inhibited its apoptosis by different target genes, which was associated with poor prognosis. For example, Jiao et al. [66] reported that lncRNA-UCA1 as a competing endogenous RNA (ceRNA) of Sox4 enhanced tumor cell proliferation by targeting miR-204 and Sox4 and Bian et al. [96] demonstrated that lncRNA-UCA1 promoted tumor cell proliferation and 5-fluorouracil resistance by functioning as a ceRNA of miR-204-5p. The pooled HR value (95% CI) of OS which correlated with the expression of lncRNA-UCA1 was 2.42 (1.68–3.49) with low heterogeneity \((P = 0.99, I^2 = 0\%)\) and statistically significant \((P < 0.00001)\). Therefore, lncRNA-UCA1 as a molecular biomarker can be applied in predicting the prognosis of GIC patients. Generally, predicting prognosis of patients and exploring mechanisms of lncRNAs play pivotal roles in clinical decision-making and development of novel targeted gene therapies. Therefore, we summarized the researches involved in mechanisms of lncRNAs; we found that 37 lncRNAs had explicit targets and 11 lncRNAs as ceRNAs regulated cancer progression by sponging corresponding microRNAs. These studies demonstrated that the potential relationship between lncRNAs and microRNAs plays a key role in tumor pathogenesis and promoted carcinogenic study and development of gene therapy. Many studies focusing on the same lncRNA revealed different targets, and the underlying correlation between lncRNAs and microRNAs was still unclear. In the future, we should focus on the interrelationship between lncRNA and microRNA or other types of RNA, in achieving targeted treatment by simultaneous intervention of multiple types of RNA.
Figure 3: Forest plot showing the pooled HR (95% CI) of OS related to the expression level of different lncRNAs in gastrointestinal cancer patients. (1.1.1) Specific lncRNA expression in EC (esophageal cancer); (1.1.2) specific lncRNA expression in GC (gastric cancer); (1.1.3) specific lncRNA expression in CRC (colorectal cancer). HR: hazard ratio; CI: confidence interval; OS: overall survival.
Several limitations should not be ignored. First, most of included patients were from East Asia, especially China, which makes our conclusions may just be suitable for Chinese patients. Second, the cut-off values and detection methods in evaluating different IncRNA expressions were various in different included studies, which may lead to heterogeneity between studies. Third, language bias was also one of the limitations, because we only enrolled English papers in the meta-analysis. Fourth, the majority of authors were generally more inclined to report positive results so that the pooled effect values calculated might overestimated the predictive significance of IncRNAs in prognosis of GIC patients; the publication bias have reached a consensus. Fifth, we calculated the HR estimates from the Kaplan-Meier survival curves because of some studies from which we could not extract HR and 95% CI directly. Sixth, the confounding factors in some included studies without the adjusted HR values would lead to high heterogeneity.

In summary, this meta-analysis supports the fact that different IncRNAs are significantly related to the prognosis of GIC patients and may serve as novel markers for predicting the prognosis in GIC patients. In addition, IncRNAs may have a promising contribution to IncRNA-based targeted therapy and clinical decision-making in the future.

![Figure 4](image-url)
Conflicts of Interest

The authors have declared that they have no conflict of interest.

Authors’ Contributions

Weibiao Kang and Qiang Zheng contributed equally.

Acknowledgments

The authors thank all authors of the included studies. This work was supported by the Natural Science Research Projects at Higher Institutions in Anhui Province (KJ2018ZD017).

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