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ORIGINAL RESEARCH

Prognostic value of long noncoding RNAs in gastric cancer: a meta-analysis

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Background: In the last few years, accumulating evidence has indicated that numerous long noncoding RNAs (lncRNAs) are abnormally expressed in gastric cancer (GC) and are associated with the survival of GC patients. This study aimed to conduct a meta-analysis on 19 lncRNAs (AFAP1 antisense RNA 1 [AFAP1-AS1], CDKN2B antisense RNA 1 [ANRIL], cancer susceptibility 15 [CASC15], colon cancer associated transcript 2 [CCAT2], gastric adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA [GAPLINC], H19, imprinted maternally expressed transcript [H19], HOX transcript antisense RNA [HOTAIR], HOXA distal transcript antisense RNA [HOTTIP], long intergenic non-protein coding RNA 673 [LINC00673], metastasis-associated lung adenocarcinoma transcript 1 [MALAT1], maternally expressed 3 [MEG3], promoter of CDKN1A antisense DNA damage activated RNA [PANDAR], Pvt1 oncogene [PVT1], SOX2 overlapping transcript [Sox2ot], SPRY4 intronic transcript 1 [SPRY4-IT1], urothelial cancer associated 1 [UCA1], X inactive specific transcript [XIST], ZEB1 antisense RNA 1 [ZEB1-AS1] and ZNFX1 antisense RNA 1 [ZFAS1]) to systematically estimate their prognostic value in GC.

Methods: The qualified literature was systematically searched in PubMed, Web of Science, Embase and Cochrane Database of Systematic Reviews (up to March 16, 2018), and one meta-analysis relating to the relationship between lncRNA expression and overall survival (OS) of GC patients was performed. The only evaluation criterion of survival results was OS.

Results: A total of 6,095 GC patients and 19 lncRNAs from 51 articles were included in the present study. Among the listed 19 lncRNAs, 18 lncRNAs (other than SPRY4-IT1) showed a significantly prognostic value ($P<0.05$).

Conclusion: This meta-analysis suggested that the abnormally expressed lncRNAs (AFAP1-AS1, ANRIL, CASC15, CCAT2, GAPLINC, H19, HOTAIR, HOTTIP, LINC00673, MALAT1, MEG3, PANDAR, PVT1, Sox2ot, UCA1, XIST, ZEB1-AS1 and ZFAS1) were significantly associated with the survival of GC patients, among which AFAP1-AS1, CCAT2, LINC00673, PANDAR, PVT1, Sox2ot, ZEB1-AS1 and ZFAS1 were strong candidates in predicting the prognosis of GC patients.

Keywords: long noncoding RNA, gastric cancer, prognosis, meta-analysis

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Introduction

In the last few years, accumulating evidence has indicated that numerous long noncoding RNAs (lncRNAs) are abnormally expressed in gastric cancer (GC) and are associated with the survival of GC patients.[1–113] GC is the fourth most diagnosed tumor type and the third most common origin of tumor-related death all over the world.[114,115] Although the incidence and mortality of GC are declining, >24,590 individuals are diagnosed with GC per year, of which 10,720 die from GC in the USA.[116] Although diagnosis and treatment strategies have been improved, the number of surviving cases remains low, since diagnosis

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often occurs in the late stages.[116,117] Thus, the molecular characteristics about the carcinogenesis of GC and the recognition of new biomarkers for GC are urgently needed.

lncRNA is a new type of noncoding RNA that has a length of >200 nucleotides (nt) and lacks important open reading frameworks and can be divided into five main categories (sense, antisense, bidirectional, intronic and intergenic).[118] Abundant evidence has demonstrated that lncRNAs play significant regulatory roles in tumor biology via various mechanisms affecting transcriptional and posttranscriptional levels.[118–120] Currently, for both cell behavior and clinicopathological factors, significant advances with respect to lncRNA effects on GC have been discovered.[121]

On account of the obvious expression differences between normal and malignant tissues as well as causal roles of lncRNAs in cancer development, lncRNAs are now attracting increasing attention, which has led to numerous investigations of the correlation between lncRNA states and clinical results in GC. Nevertheless, most of these studies were performed with small samples, and there were inconsistently observed connections. Consequently, we conducted a meta-analysis to determine the accurate role of lncRNAs in the prognosis of GC patients, which possibly supplied us with new insights into the clinical value of combined detection in forecasting prognostic results and determining promising biomarkers in GC treatment strategies.

Methods

Literature search strategy

We basically performed a systematic selection of papers published in English from four databases (PubMed, Web of Science, Embase and Cochrane Database of Systematic Reviews). A comprehensive search was conducted using the subject term: lncRNA and gastric cancer. Two authors (Song Gao and Zhi-Ying Zhao) checked the titles and abstracts of the retrieved papers, and Yue Zhang reevaluated uncertain data. Figure 1 shows the flow diagram of the literature search and selection.

Inclusion criteria

We set up inclusion criteria for qualified papers, which were analyzed using our full-text assessment: 1) articles

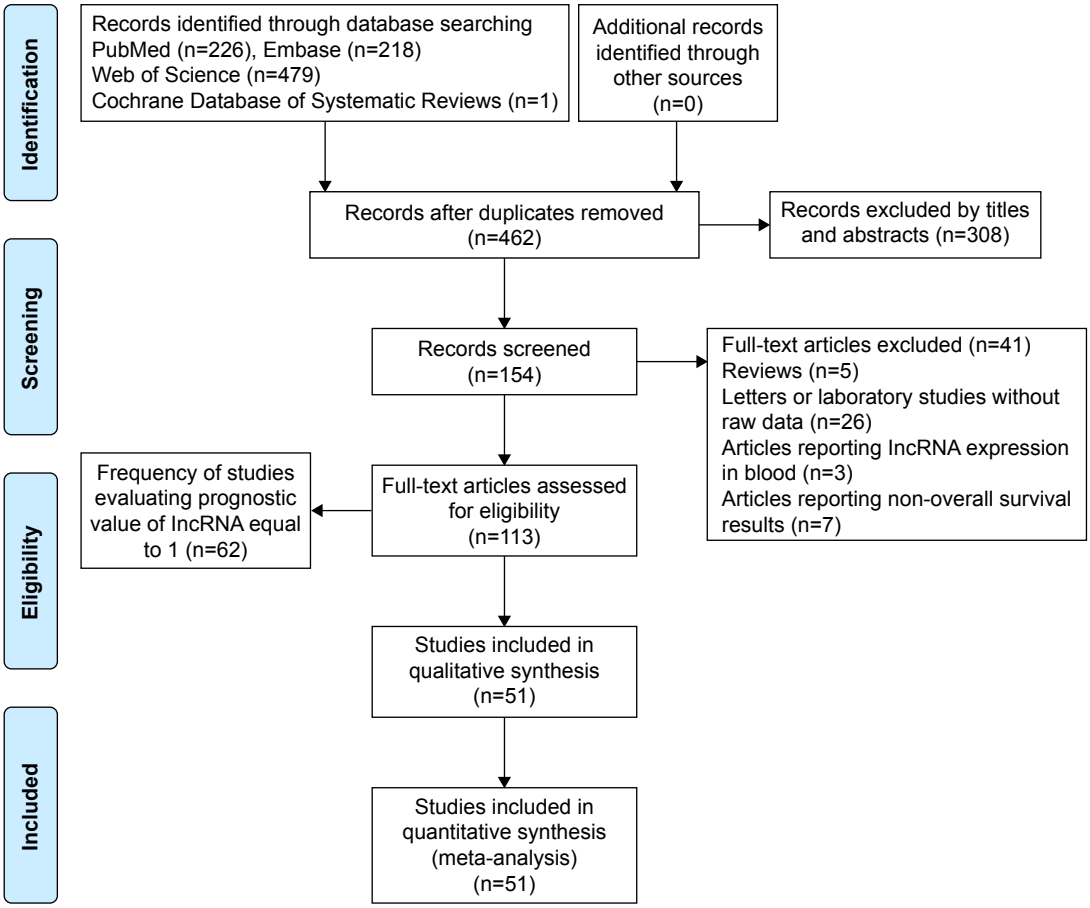

Figure 1 Flow diagram of the literature search and selection.
Abbreviation: lncRNA, long noncoding RNA.

concerning the pertinence between lncRNA level in cancer tissues and prognosis of GC patients; 2) the survival results were estimated using overall survival (OS) and 3) full-text papers published in English.

Exclusion criteria

Articles that did not meet the abovementioned inclusion criteria, reviews, letters and laboratory studies without raw data were excluded. Articles of non-dichotomous lncRNA expression levels and frequency of studies evaluating prognostic value of lncRNAs equal to 1 were also excluded. If more than one paper had been published on the identical study cohort, only the most well-rounded investigation was selected for this research. In addition, if both of the univariate and multivariate outcomes were covered, only the latter were chosen, since they were adjusted for confounding factors.

Research frequency

Table 1 gives the frequency of investigations reporting prognosis of GC patients, which included the lncRNA name, frequency of researched lncRNA and reference.

Data extraction

The survival data were recovered from qualified articles independently by two authors (Song Gao and Zhi-Ying Zhao). Data extracted from them are as follows: researched lncRNA,

Table 1 Research frequency of lncRNAs in GC

lncRNA	n	R	lncRNA	n	R	lncRNA	n	R
AC027119.1	1	1	H19	4	29, 36–38	NEAT1	1	83
AC138128.1	1	2	HAGLROS	1	39	NR_003573	1	7
ADAMTS9-AS2	1	1	HIF1A-AS2	1	40	OR3A4	1	84
AFAP1-AS1	2	3, 4	HOTAIR	9	41–59	OTUB1-isoform 2	1	85
AGAP2-AS1	1	5	HOTTIP	3	50–52	PANDAR	2	86, 87
AK023391	1	6	HOXA-AS2	1	53	PCAT1	1	88
AK093735	1	7	HXA11-AS	1	54	PVT1	2	89, 90
AK123072	1	8	KRTI8P55	1	55	RP11-119F7.4	1	91
ANRIL	2	9, 10	LET	1	56	RP11-120K18.2	1	1
ATB	1	11	LINC00052	1	57	RP11-389G6.3	1	1
BANCR	1	12	LINC00152	1	58	RP11-499F3.2	1	1
BC005927	1	13	LINC00628	1	59	RP11-789C1.1	1	92
BC032469	1	14	LINC00668	1	60	RPLPOP2	1	29
BC041951	1	15	LINC00673	2	61, 62	SLC26A4	1	29
BCAR4	1	16	LINC00675	1	63	SMIM10L2A	1	29
CASC2	1	17	LINC00982	1	64	SMIM10L2B	1	29
CASC15	2	18, 19	LINC01018	1	65	SNHG1	1	93
CCAT1	1	20	LINC01234	1	66	SNHG6	1	94
CCAT2	2	21, 22	LINC01296	1	67	SNHG12	1	95
CHRDL1	1	23	LINC-ROR	1	68	SNORD116-4	1	29
CTD-2147F2.1	1	1	LINC-UBC1	1	69	Sox2ot	2	96, 97
DANCR	1	24	LOC100130476	1	70	SPRY4-IT1	2	98, 99
DLX6-AS1	1	1	LOC553137	1	65	TINCR	1	29
E2F1	1	25	MACC1	1	71	TTTY14	1	65
EGOT	1	26	MACC1-AS1	1	71	TUG1	1	100
FENDRR	1	27	MALAT1	4	43, 72–74	UCA1	4	101–104
FEZF1-AS1	1	28	MANCR	1	75	VPS9D1-AS1	1	105
FOXD2-AS1	1	29	MEG3	2	76, 77	XIAP-AS1	1	106
FRLnc1	1	30	MIR31HG	1	78	XIST	2	107, 108
GACAT3	1	31	MIR4435-2HG	1	65	XLOC_010235	1	92
GAPLINC	2	32, 33	MLK7-AS1	1	79	ZEB1-AS1	2	109, 110
GAS5	1	34	MLLT4-AS1	1	80	ZFAS1	2	111, 112
GBET1	1	35	MRUL	1	81	ZMAT1	1	113
GClnc1	1	15	MTM	1	82			

Notes: Highlighted lncRNAs were included in the meta-analysis. n, number of research frequency; R, reference.

Abbreviations: AFAP1-AS1, AFAP1 antisense RNA 1; ANRIL, CDKN2B antisense RNA 1; CASC15, cancer susceptibility 15; CCAT2, colon cancer associated transcript 2; GAPLINC, gastric adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA; GC, gastric cancer; H19, H19, imprinted maternally expressed transcript; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA distal transcript antisense RNA; LINC00673, long intergenic non-protein coding RNA 673; lncRNA, long noncoding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed 3; PANDAR, promoter of CDKN1A antisense DNA damage activated RNA; PVT1, Pvt1 oncogene; Sox2ot, SOX2 overlapping transcript; SPRY4-IT1, SPRY4 intronic transcript 1; UCA1, urothelial cancer associated 1; XIST, X inactive specific transcript; ZEB1-AS1, ZEB1 antisense RNA 1; ZFAS1, ZNFX1 antisense RNA 1.

first author's name, paper publication year, reference, patient's nationality, study design, histological type, patient number, neoplasm staging, cutoff value, detected method, follow-up period, survival analysis type, HRs and 95% CIs. The detailed data are shown in Table 2. If HR and 95% CI were not directly shown in the paper, data from survival curve were extracted. Disagreements were discussed with the third investigator (Yue Zhang).

Statistical analysis

Stata version 13.0 (StataCorp LP, College Station, TX, USA) was used for the whole meta-analysis. HR and 95% CI from GC patients were calculated on the basis of survival curve and patient number using Engauge Digitizer version 4.1 and Tierney's method.[122] The random-effect model was used in the whole article because different histological type (frozen, formalin-fixed paraffin-embedded or undefined) from GC patients at different neoplasm staging, cutoff value and lncRNA detected method was used in the single study. The HR was considered significant if its *P*-value was <0.05 and 95% CI did not contain the value 1. Furthermore, the lncRNA was considered as a strong biomarker of prognosis, if its HR was >2. The Begg's funnel plot was used to estimate publication bias, and a two-tailed *P*-value <0.05 was considered as significant. The sensitivity analysis was performed to examine how sensitive the merged HR was if the single study was removed, and if the point of evaluation was outside the 95% CI after it was removed from the whole analysis, a single research was considered as excessive influence.

Results

Meta-analysis

Table 3 gives the basic information of the merged meta-analysis for researched lncRNAs.

AFAP1 antisense RNA 1 (AFAP1-AS1), CDKN2B antisense RNA 1 (ANRIL), cancer susceptibility 15 (CASC15), colon cancer-associated transcript 2 (CCAT2), gastric adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA (GAPLINC) and H19, imprinted maternally expressed transcript (H19) demonstrated significantly prognostic value

Two articles[3,4] reported the relationship between high AFAP1-AS1 expression and OS, indicating that GC patients with its high expression had significantly worse OS than those with its low expression (HR=2.47, 95% CI=1.41–4.30, $P<0.01$).

Table 2 Basic information of included articles

lncRNA	Study	Country/source	Study design	Sample	Number	Stage	Cutoff	Method	Follow-up (months)	OS	HR (L/H)	HR (H/L)	95% CI
AFAP1-AS1	Feng et al[3]	China	R	Frozen	91	I–IV	None	qRT-PCR	66	Multivariate		3.32	1.55–5.90
AFAP1-AS1	Qiao et al[4]	China	R	Frozen	87	I–IV	Median	qRT-PCR	60	Univariate		1.88	1.01–3.52
ANRIL	Zhang et al[9]	China	R	Tissue	120	I–IV	3	qRT-PCR	60	Multivariate		1.74	1.04–2.93
ANRIL	Deng et al[10]	China	R	Tissue	100	I–IV	None	qRT-PCR	>60	Univariate		1.61	0.95–2.74
CASC15	Yao et al[18]	China	R	Tissue	60	I–IV	None	qRT-PCR	60	Univariate		2.33	1.15–4.72
CASC15	Wu et al[19]	China	R	Tissue	88	I–IV	Mean	qRT-PCR	60	Univariate		1.70	0.84–3.47
CCAT2	Wang et al[21]	China	R	Frozen	85	I–IV	Mean	qRT-PCR	60	Multivariate		2.41	1.19–5.42
CCAT2	Wang et al[22]	China	R	Frozen	108	I–IV	Median	qRT-PCR	66	Multivariate		2.11	1.44–3.20
GAPLINC	Hu et al[32]	China	R	Tissue	90	I–IV	Median	RT-qPCR	>60	Multivariate		1.48	1.16–1.89
GAPLINC	Liu et al[33]	China	R	Frozen	33	None	2.03	qRT-PCR	60	Univariate		1.77	0.57–5.52
H19	Li et al[36]	China	R	Frozen	74	I–IV	Mean	qRT-PCR	53	Univariate		2.26	0.58–8.86
H19	Zhang et al[37]	China	R	Frozen	80	I–IV	Mean	qRT-PCR	60	Multivariate		1.14	1.01–1.29
H19	Chen et al[38]	China	R	Tissue	128	I–IV	4.615	qRT-PCR	48	Multivariate		1.96	0.97–3.97
H19	Li et al[29]	TCGA	R	Tissue	361	I–IV	None	Downloaded	>50	Univariate		1.79	1.26–2.53
HOTAIR	Endo et al[41]	China I	R	Frozen	36	I–IV	1.0	qRT-PCR	>60	Univariate		0.95	0.21–4.31
		China II			32							5.12	0.96–27.18
HOTAIR	Xu et al[42]	China	R	Frozen	83	I–IV	None	RT-qPCR	>72	Multivariate		2.13	1.00–4.50
HOTAIR	Okugawa et al[43]	Japan	R	Frozen	150	III–IV	0.239	RT-qPCR	60	Multivariate		1.77	1.06–2.95

HOTAIR	Liu et al[44]	China	R	Both	78	II–IV	Median	qRT-PCR	>40	Multivariate		4.08	2.07–8.04
HOTAIR	Zhang et al[45]	China	R	Both	50	II–IV	Median	qRT-PCR	>45	Univariate		2.86	1.16–7.03
HOTAIR	Zhao et al[46]	China	R	Tissue	168	III–IV	Median	qRT-PCR	>60	Multivariate		1.47	1.04–2.06
HOTAIR	Chen et al[47]	China	R	Frozen	65	I–IV	2.35	qRT-PCR	>60	Multivariate		2.00	1.06–3.77
HOTAIR	Feng and Huang[48]	China	R	Tissue	32	None	None	qRT-PCR	>120	Univariate		1.52	0.45–5.14
HOTAIR	Li et al[49]	China	R	FFPE	100	I–IV	Mean	qRT-PCR	90	Univariate		1.83	0.82–4.05
HOTTIP	Ye et al[50]	China	R	Frozen	98	I–III	Median	qRT-PCR	60	Univariate		2.06	0.97–4.38
HOTTIP	Yang et al[51]	China	R	Frozen	94	I–III	Median	RT-qPCR	54	Univariate		1.03	0.52–2.05
HOTTIP	Zhao et al[52]	GEO	R	Tissue	348	I–IV	None	Downloaded	>150	Univariate		1.63	1.19–2.23
LINC00673	Ba et al[61]	China	R	Frozen	79	I–IV	Median	qRT-PCR	66	Multivariate		2.56	1.01–4.54
LINC00673	Huang et al[62]	China	R	Tissue	73	I–IV	2	qRT-PCR	>40	Multivariate		2.38	1.12–5.06
MALAT1	Qi et al[72]	TCGA	R	Tissue	118	III–IV	None	RT-qPCR	>50	Univariate		1.98	1.38–2.83
MALAT1	Li et al[73]	China	R	Tissue	78	I–IV	None	qRT-PCR	>60	Univariate		2.52	1.35–4.68
MALAT1	Li et al[74]	China	R	FFPE	150	I–IV	None	RT-qPCR	>150	Univariate		1.38	1.03–1.85
MALAT1	Okugawa et al[43]	Japan	R	Frozen	150	III–IV	0.985	RT-qPCR	60	Univariate		1.54	0.92–2.58
MEG3	Sun et al[76]	China	R	Frozen	72	II–IV	Median	RT-qPCR	48	Univariate	1.93		0.99–3.75
MEG3	Guo et al[77]	China	R	Frozen	134	I–IV	None	qRT-PCR	>60	Univariate	2.00		0.88–4.54
PANDAR	Ma et al[86]	China	R	Tissue	100	I–IV	None	qRT-PCR	36	Multivariate		3.68	1.13–12.06
PANDAR	Liu et al[87]	China	R	Tissue	146	I–IV	Mean	qRT-PCR	84	Multivariate		3.10	2.70–3.54
PVT1	Kong et al[89]	China	R	Tissue	80	I–IV	Median	qRT-PCR	36	Multivariate		2.09	1.07–4.10
PVT1	Yuan et al[90]	China	R	Tissue	111	I–IV	Median	qRT-PCR	48	Multivariate		2.28	1.05–4.93
Sox2ot	Zhang et al[96]	China	R	Frozen	132	I–IV	Median	qRT-PCR	>84	Multivariate		2.05	1.28–3.30
Sox2ot	Zou et al[97]	China	R	Tissue	155	None	Median	qRT-PCR	>60	Univariate		3.24	1.24–6.43
SPRY4-IT1	Peng et al[98]	China	R	Frozen	175	I–IV	Median	qRT-PCR	60	Multivariate	0.82		0.31–1.57
SPRY4-IT1	Xie et al[99]	China	R	Frozen	61	I–IV	Median	qRT-PCR	36	Univariate	2.49		1.08–5.75
UCA1	Zheng et al[101]	China	R	Frozen	112	I–IV	Median	RT-qPCR	60	Multivariate		2.35	1.22–4.52
UCA1	Nasrollahzadeh-Khakiani et al[102]	TCGA	R	Tissue	188	I–IV	Median	Downloaded	>116	Univariate		1.11	0.72–1.73
UCA1	Zuo et al[103]	China	R	Frozen	37	I–IV	Median	qRT-PCR	36	Multivariate		2.92	1.07–7.96
UCA1	Gu et al[104]	China	R	Frozen	62	I–IV	None	qRT-PCR	60	Univariate		1.80	0.95–3.38
XIST	Chen et al[107]	China	R	Frozen	106	I–IV	Median	qRT-PCR	>90	Multivariate		1.72	1.32–2.26
XIST	Ma et al[108]	China	R	FFPE	98	I–IV	None	qRT-PCR	54	Univariate		2.49	1.40–4.42
ZEB1-AS1	Li et al[109]	China	R	Tissue	124	I–IV	Median	qRT-PCR	72	Multivariate		2.36	1.41–3.96
ZEB1-AS1	Zhang et al[110]	China	R	Frozen	76	I–IV	Median	qRT-PCR	90	Univariate		2.72	1.27–5.84
		KM	R	Tissue	631	I–IV	None	Downloaded	>150	Univariate		1.95	1.52–2.49
ZFAS1	Zhang et al[111]	China	R	Frozen	104	I–IV	Median	qRT-PCR	60	Multivariate		2.57	1.25–6.84
ZFAS1	Nie et al[112]	China	R	Tissue	54	I–IV	Median	qRT-PCR	36	Univariate		2.43	0.96–6.17

Abbreviations: AFAP1-AS1, AFAP1 antisense RNA 1; ANRIL, CDKN2B antisense RNA 1; Both, frozen and formalin-fixed paraffin-embedded tissues; CASC15, cancer susceptibility 15; CCAT2, colon cancer associated transcript 2; FFPE, formalin-fixed paraffin-embedded; GAPLINC, gastric adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA; GEO, Gene Expression Omnibus; H19, H19, imprinted maternally expressed transcript; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA distal transcript antisense RNA; HR (H/L), hazard ratios of high expression versus low expression of lncRNAs; HR (L/H), hazard ratios of low expression versus high expression of lncRNAs; KM, Kaplan–Meier plotter; LINC00673, long intergenic non-protein coding RNA 673; lncRNA, long noncoding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed 3; OS, overall survival; PANDAR, promoter of CDKN1A antisense DNA damage activated RNA; PVT1, Pvt1 oncogene; qRT-PCR, quantitative real-time polymerase chain reaction; R, retrospective; RT-qPCR, reverse transcription quantitative real-time polymerase chain reaction; Sox2ot, SOX2 overlapping transcript; SPRY4-IT1, SPRY4 intronic transcript 1; TCGA, The Cancer Genome Atlas; UCA1, urothelial cancer associated 1; XIST, X inactive specific transcript; ZEB1-AS1, ZEB1 antisense RNA 1; ZFAS1, ZNFX1 antisense RNA 1.

Table 3 HR with 95% CI of lncRNA expression in GC

lncRNA	Number of articles	Included articles	HR	95% CI	Figure	*P*-value	Heterogeneity (Higgins I^2 statistic)	Total patients
High AFAP1-AS1	2	3, 4	2.47	1.41–4.30	2	<0.01	I^2=32.7%, *P*=0.22	178
High ANRIL	2	9, 10	1.68	1.16–2.43	2	<0.01	I^2=0.0%, *P*=0.84	220
High CASC15	2	18, 19	1.99	1.21–3.28	2	<0.01	I^2=0.0%, *P*=0.54	148
High CCAT2	2	21, 22	2.17	1.53–3.09	2	<0.01	I^2=0.0%, *P*=0.76	193
High GAPLINC	2	32, 33	1.49	1.18–1.89	2	<0.01	I^2=0.0%, *P*=0.76	123
High H19	4	29, 36–38	1.51	1.05–2.17	2	0.03	I^2=64.1%, *P*=0.04	643
High HOTAIR	9	41–49	1.93	1.53–2.43	3	<0.01	I^2=14.0%, *P*=0.31	794
High HOTTIP	3	50–52	1.57	1.20–2.05	6	<0.01	I^2=0.2%, *P*=0.37	540
High LINC00673	2	61, 62	2.47	1.45–4.20	6	<0.01	I^2=0.0%, *P*=0.89	152
High MALAT1	4	43, 72–74	1.70	1.33–2.18	6	<0.01	I^2=29.7%, *P*=0.23	496
Low MEG3	2	76, 77	1.96	1.17–3.28	6	0.01	I^2=0.0%, *P*=0.95	206
High PANDAR	2	86, 87	3.11	2.72–3.55	6	<0.01	I^2=0.0%, *P*=0.79	246
High PVT1	2	89, 90	2.17	1.31–3.60	6	<0.01	I^2=0.0%, *P*=0.87	191
High Sox2ot	2	96, 97	2.30	1.52–3.46	7	<0.01	I^2=0.0%, *P*=0.35	287
Low SPRY4-IT1	2	98, 99	1.42	0.48–4.22	7	0.53	I^2=71.4%, *P*=0.06	236
High UCA1	4	101–104	1.73	1.12–2.68	7	0.01	I^2=45.5%, *P*=0.14	399
High XIST	2	107, 108	1.89	1.38–2.59	7	<0.01	I^2=23.4%, *P*=0.25	204
High ZEB1-AS1	2	109, 110	2.07	1.67–2.56	7	<0.01	I^2=0.0%, *P*=0.62	831
High ZFAS1	2	111, 112	2.51	1.34–4.69	7	<0.01	I^2=0.0%, *P*=0.93	158

Abbreviations: AFAP1-AS1, AFAP1 antisense RNA 1; ANRIL, CDKN2B antisense RNA 1; CASC15, cancer susceptibility 15; CCAT2, colon cancer associated transcript 2; GAPLINC, gastric adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA; GC, gastric cancer; H19, H19, imprinted maternally expressed transcript; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA distal transcript antisense RNA; LINC00673, long intergenic non-protein coding RNA 673; lncRNA, long noncoding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed 3; PANDAR, promoter of CDKN1A antisense DNA damage activated RNA; PVT1, Pvt1 oncogene; Sox2ot, SOX2 overlapping transcript; SPRY4-IT1, SPRY4 intronic transcript 1; UCA1, urothelial cancer associated 1; XIST, X inactive specific transcript; ZEB1-AS1, ZEB1 antisense RNA 1; ZFAS1, ZNFX1 antisense RNA 1.

Two researches[9,10] covered the connections between high ANRIL expression and OS, suggesting that GC patients with its high expression had significantly poorer OS than those with its low expression (HR=1.68, 95% CI=1.16–2.43, $P<0.01$).

Two investigations[18,19] analyzed the associations between high CASC15 expression and OS, showing that GC patients with its high expression had significantly shorter OS than those with its low expression (HR=1.99, 95% CI=1.21–3.28, $P<0.01$).

Two studies[21,22] focused on the correlation between high CCAT2 expression and OS, manifesting that GC patients with its high expression had significantly worse OS than those with its low expression (HR=2.17, 95% CI=1.53–3.09, $P<0.01$).

Two papers[32,33] paid attention to the pertinence between high GAPLINC expression and OS, demonstrating that GC patients with its high expression had significantly poorer OS than those with its low expression (HR=1.49, 95% CI=1.18–1.89, $P<0.01$).

Four literature[29,36–38] described the relativity between high H19 expression and OS, proving that GC patients with its high expression had significantly shorter OS than those with its low expression (HR=1.51, 95% CI=1.05–2.17, $P=0.03$; Figure 2).

HOX transcript antisense RNA (HOTAIR) demonstrated significantly prognostic value

Nine essays[41–49] discussed the relation between high HOTAIR expression and OS, illuminating that GC patients with its high expression had significantly worse OS than those with its low expression (HR=1.93, 95% CI=1.53–2.43, $P<0.01$; Figure 3).

Publication bias

The Begg's funnel plot was used to estimate publication bias, and its *P*-value was 0.20, so there was no significant publication bias in the pooled analysis of OS about high HOTAIR expression (Figure 4).

Sensitivity analysis

The sensitivity analysis was performed to examine how sensitive the merged HR was if the single study was removed.

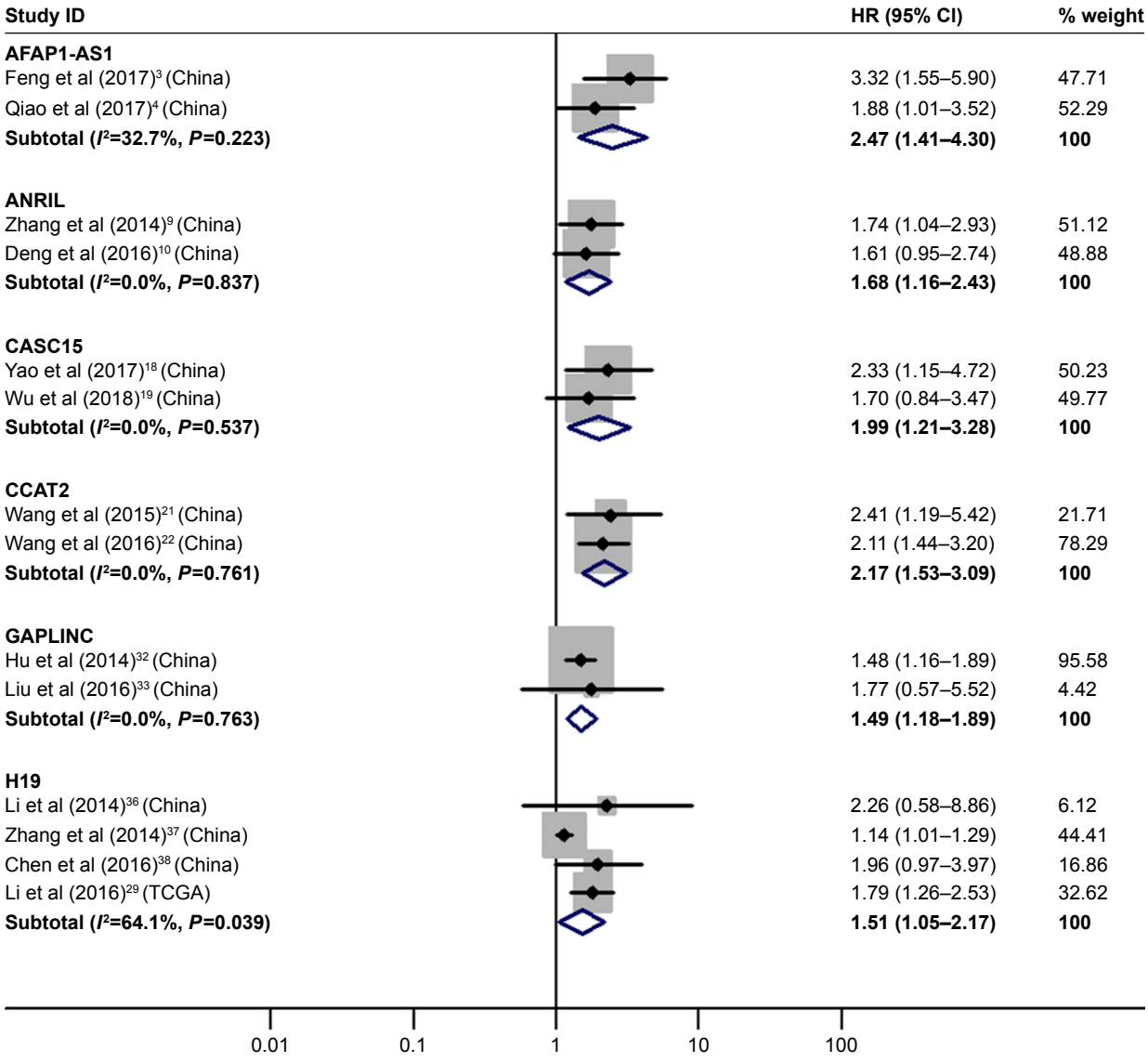

Figure 2 Forest plot of pooled analyses of OS in association with high AFAP1-AS1, ANRIL, CASC15, CCAT2, GAPLINC and H19 expression levels.
Note: Weights are from random-effects analysis.
Abbreviations: AFAP1-AS1, AFAP1 antisense RNA 1; ANRIL, CDKN2B antisense RNA 1; CASC15, cancer susceptibility 15; CCAT2, colon cancer associated transcript 2; GAPLINC, gastric adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA; H19, H19, imprinted maternally expressed transcript. OS, overall survival.

After this process, no individual study significantly affected the combined HR with 95% CI (Figure 5).

HOXA distal transcript antisense RNA (HOTTIP), long intergenic non-protein coding RNA 673 (LINC00673), metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), maternally expressed 3 (MEG3), promoter of CDKN1A antisense DNA damage activated RNA (PANDAR) and Pvt1 oncogene (PVT1) demonstrated significantly prognostic value

The details are shown in Table 3 and Figure 6.

SOX2 overlapping transcript (Sox2ot), urothelial cancer-associated 1 (UCA1), X inactive specific transcript (XIST), ZEB1 antisense RNA 1 (ZEB1-AS1) and ZNFX1 antisense RNA 1 (ZFAS1) demonstrated significantly prognostic value

The details are shown in Table 3 and Figure 7.

Discussion

Current situation

So far, the clinical treatment of GC remains limited. In the past score years, there has been little progress in both traditional

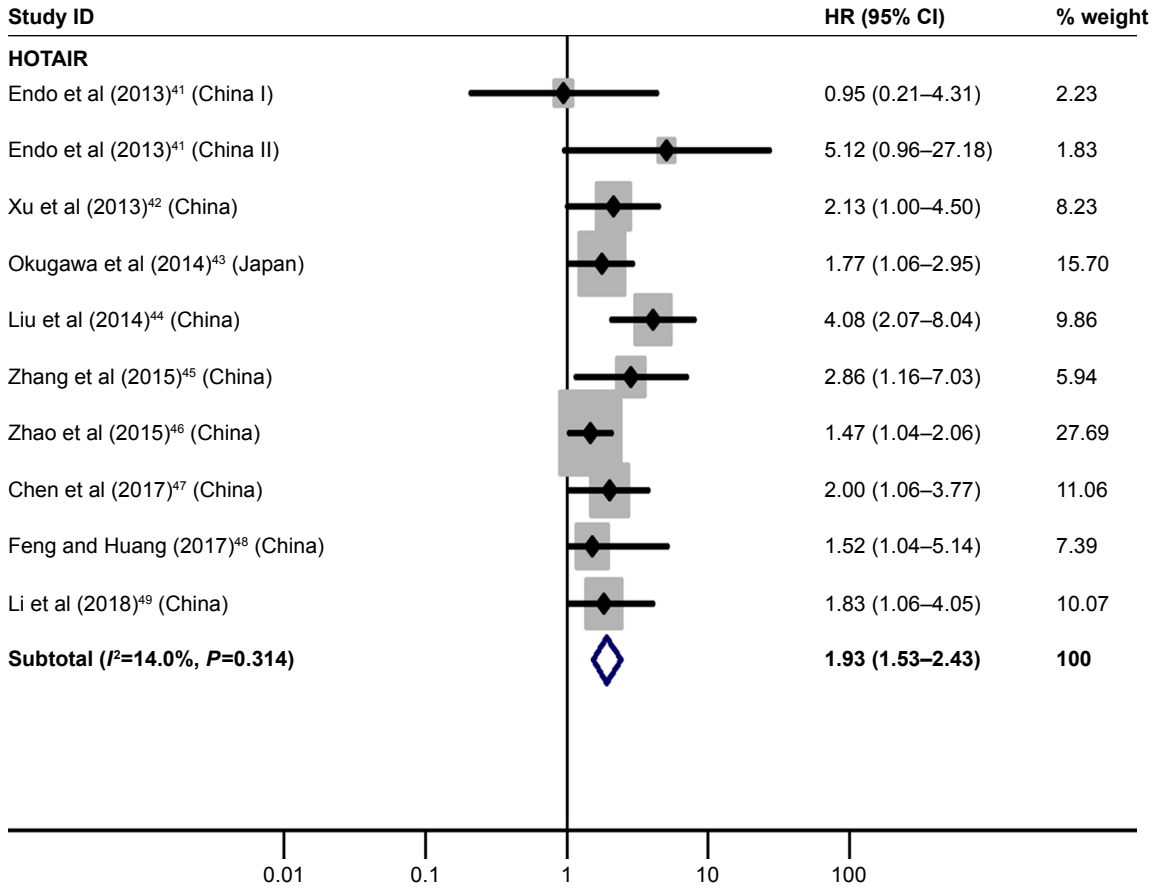

Figure 3 Forest plot of pooled analysis of OS in association with high HOTAIR expression levels.
Note: Weights are from random-effects analysis.
Abbreviations: HOTAIR, HOX transcript antisense RNA; OS, overall survival.

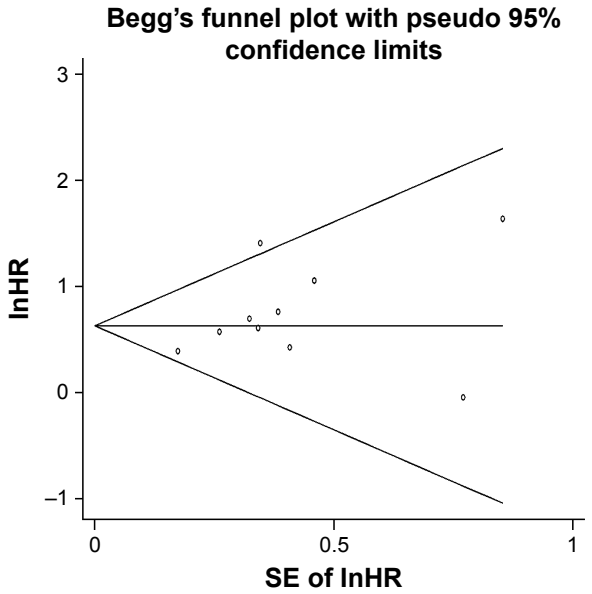

Figure 4 Beggs's funnel plot of publication bias for pooled analysis of OS in association with high HOTAIR expression levels.
Abbreviations: HOTAIR, HOX transcript antisense RNA; OS, overall survival; SE, standard error.

and new treatment methods. Therefore, novel biomarkers that can improve the prognosis of GC patients are in need. Recently, there is an increasing evidence that lncRNAs can hinder the growth and metastasis of cancer. For example, Xu et al[123] reported that upregulating long stress-induced noncoding 5 (LSINCT5) significantly promoted the growth of the GC cell, while downregulating LSINCT5 suppressed its growth. Dan et al[124] conducted the cancer model experiments using mice, proving that MEG3 overexpression could suppress GC growth and metastasis in vivo by suppressing miR-21 expression. More importantly, several abnormally expressed lncRNAs have been discovered to touch upon the development of GC and perhaps possess prognostic potency in this illness. In view of the above consequences, we conducted this meta-analysis about the prognostic value of lncRNAs in GC.

Research finding

In the present research, a total of 51 articles reporting 19 lncRNAs, which were latent prognostic biomarkers and

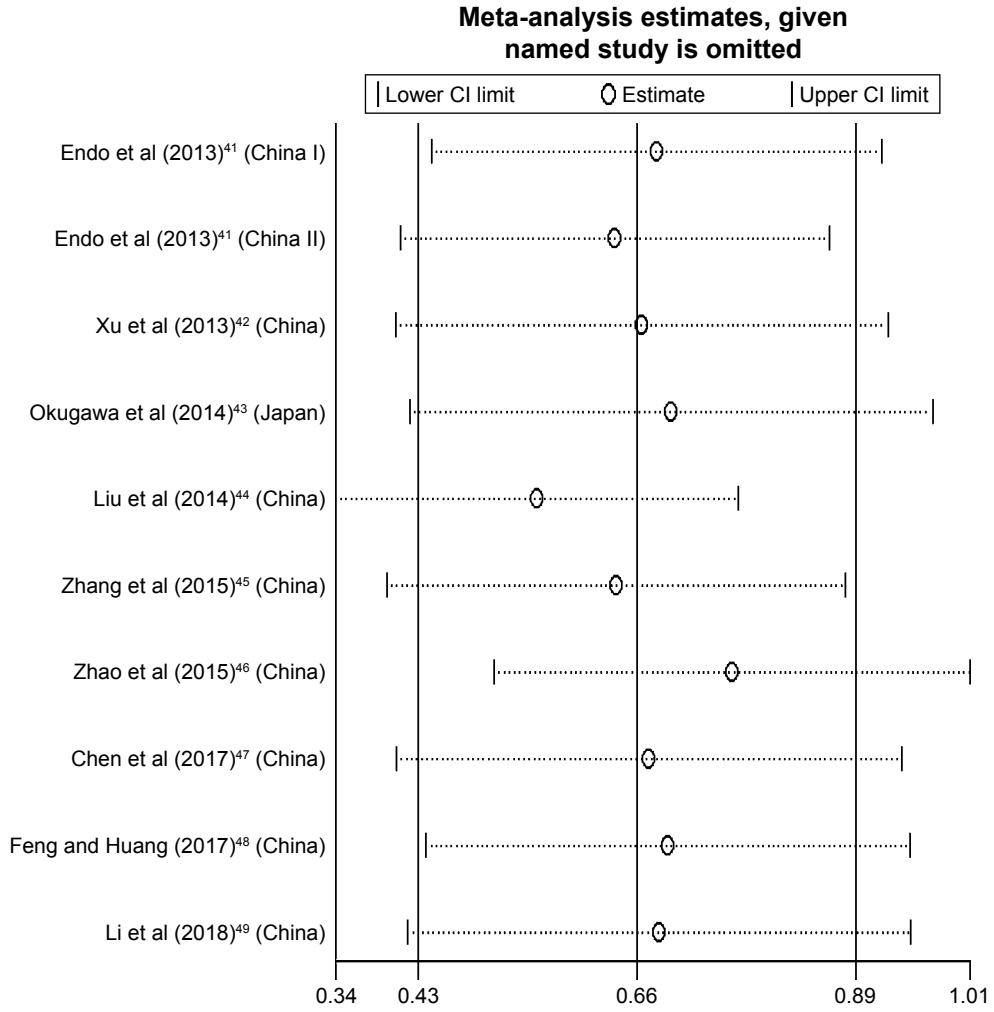

Figure 5 Sensitivity analysis of pooled analysis of OS in association with high HOTAIR expression levels.
Abbreviations: HOTAIR, HOX transcript antisense RNA; OS, overall survival.

6,095 GC patients were included, among which 18 lncRNAs (except SPRY4 intronic transcript 1 [SPRY4-IT1]) manifested a significantly prognostic value. Meanwhile, strong heterogeneity was only shown in two (H19 and SPRY4-IT1) analyses about lncRNAs, during which there was no significant associations between SPRY4-IT1 expression and OS. Further analysis suggested that AFAP1-AS1, CCAT2, LINC00673, PANDAR, PVT1, Sox2ot, ZEB1-AS1 and ZFAS1 were strong candidates in predicting prognosis of GC patients.

Molecular mechanisms

Figure 8 shows the summary of lncRNAs with aberrant expression, potential targets and pathways included in this study. It is noteworthy that there existed inconsistent outcomes about expression of HOTTIP and SPRY4-IT1 compared with normal controls, so these two lncRNAs were not shown to be up or down expressed. Unexpected results were findings that CDKN1A was target of both CASC15 and PANDAR and KLF2 was target of both LINC00673 and ZFAS1. In addition, cell proliferation was the most related cell function of these lncRNAs.

Merits

The current study had several merits: 1) nearly all articles appraising the associations between OS of GC patients and lncRNA expression were searched and are clearly shown in Table 1; 2) most of our meta-analyses revealed no or low heterogeneity ($I^2 \leq 50.0\%$), indicating relatively consistent results of the meta-analyses and 3) all the included studies had a relatively large sample size (≥ 30), decreasing the error of low sample size to some degree.

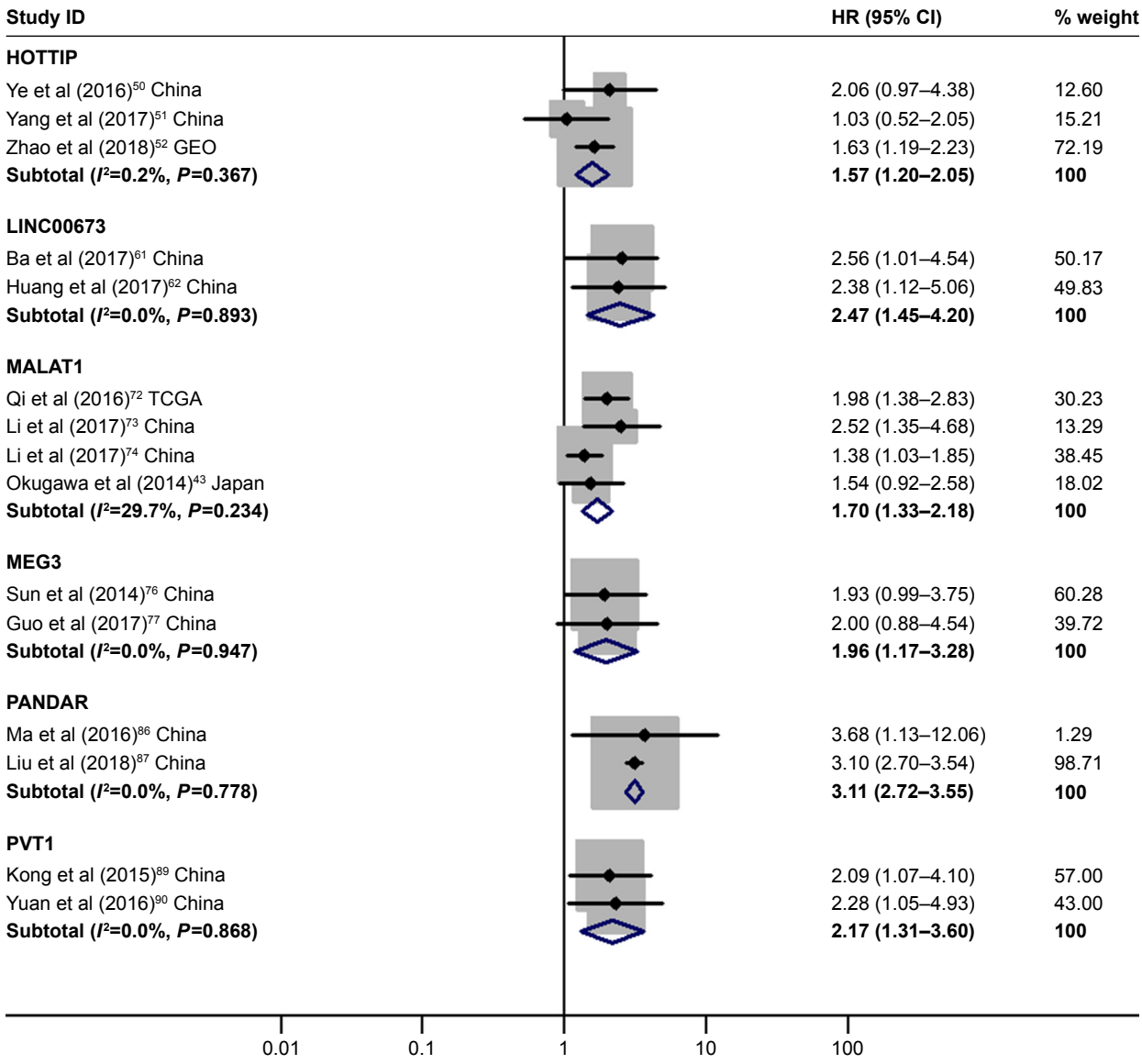

Figure 6 Forest plot of pooled analyses of OS in association with high HOTTIP, LINC00673, MALAT1, PANDAR, PVT1 expression levels, or low MEG3 expression levels.
Note: Weights are from random-effects analysis.
Abbreviations: GEO, Gene Expression Omnibus; HOTTIP, HOXA distal transcript antisense RNA; LINC00673, long intergenic non-protein coding RNA 673; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed 3; OS, overall survival; PANDAR, promoter of CDKN1A antisense DNA damage activated RNA; PVT1, Pvt1 oncogene; TCGA, The Cancer Genome Atlas.

Limitations

However, the limitations of this work could not be ignored: 1) only English papers were included in the present research, which may exclude potentially relevant articles; 2) most of the patients were from China, which cannot adequately represent the prognosis of global patients; 3) only the meta-analysis of HOTAIR was composed of nine articles,[41–49] and other merged analyses about lncRNAs were from relatively small article number (two to four) and 4) the papers omitted due to no mention of OS may provide a lot of information on which lncRNAs hold promise for a prognostic value.

Inspirations

This study left several inspirations for us: 1) lncRNAs were arranged in an alphabetical order as shown in Table 1, via which the recently research frequency could be distinctly seen by clinical workers and scientific researchers; 2) the detailed outcomes of OS from the pooled analyses are shown in Table 3, through which combined detection of lncRNAs might better predict the survival time of GC patients and 3) for the molecular mechanisms of the included lncRNAs, their connections are shown in Figure 8, which might play enlightening roles in future basic experiments on lncRNAs in GC.

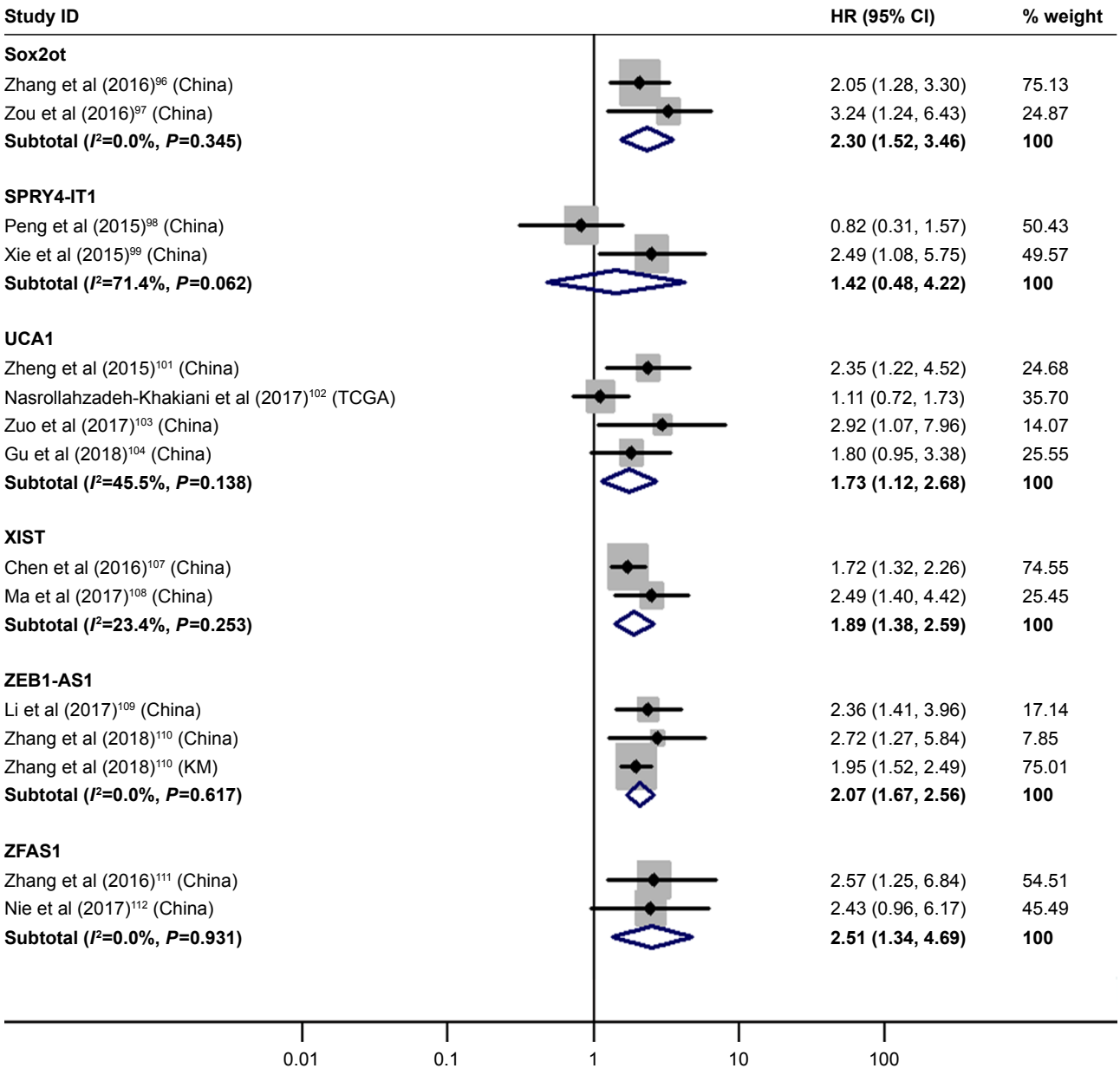

Figure 7 Forest plot of pooled analyses of OS in association with high Sox2ot, UCA1, XIST, ZEB1-AS1, ZFAS1 expression levels, or low SPRY4-IT1 expression levels.
Note: Weights are from random-effects analysis.
Abbreviations: OS, overall survival; Sox2ot, SOX2 overlapping transcript; SPRY4-IT1, SPRY4 intronic transcript 1; UCA1, urothelial cancer associated 1; XIST, X inactive specific transcript; ZEB1-AS1, ZEB1 antisense RNA 1; ZFAS1, ZNFX1 antisense RNA 1.

Conclusion

This meta-analysis suggested that the abnormally expressed lncRNAs (AFAP1-AS1, ANRIL, CASC15, CCAT2, GAPLINC, H19, HOTAIR, HOTTIP, LINC00673, MALAT1, MEG3, PANDAR, PVT1, Sox2ot, UCA1, XIST, ZEB1-AS1 and ZFAS1) were significantly associated with the survival of GC patients, among which AFAP1-AS1, CCAT2, LINC00673, PANDAR, PVT1, Sox2ot, ZEB1-AS1 and ZFAS1 were strong candidates in predicting prognosis of GC patients.

Author contributions

Yue Zhang contributed toward study concept and design. Song Gao and Zhi-Ying Zhao were involved in acquisition of data. Song Gao, Zhi-Ying Zhao and Rong Wu carried out analysis and interpretation of data. Yue Zhang performed drafting of the manuscript. Song Gao, Zhi-Ying Zhao, Rong Wu, Yue Zhang and Zhen-Yong Zhang assisted with revision of manuscript. Yue Zhang and Zhen-Yong Zhang helped in supervision of work. All authors read and approved the final manuscript. All authors contributed toward data analysis,

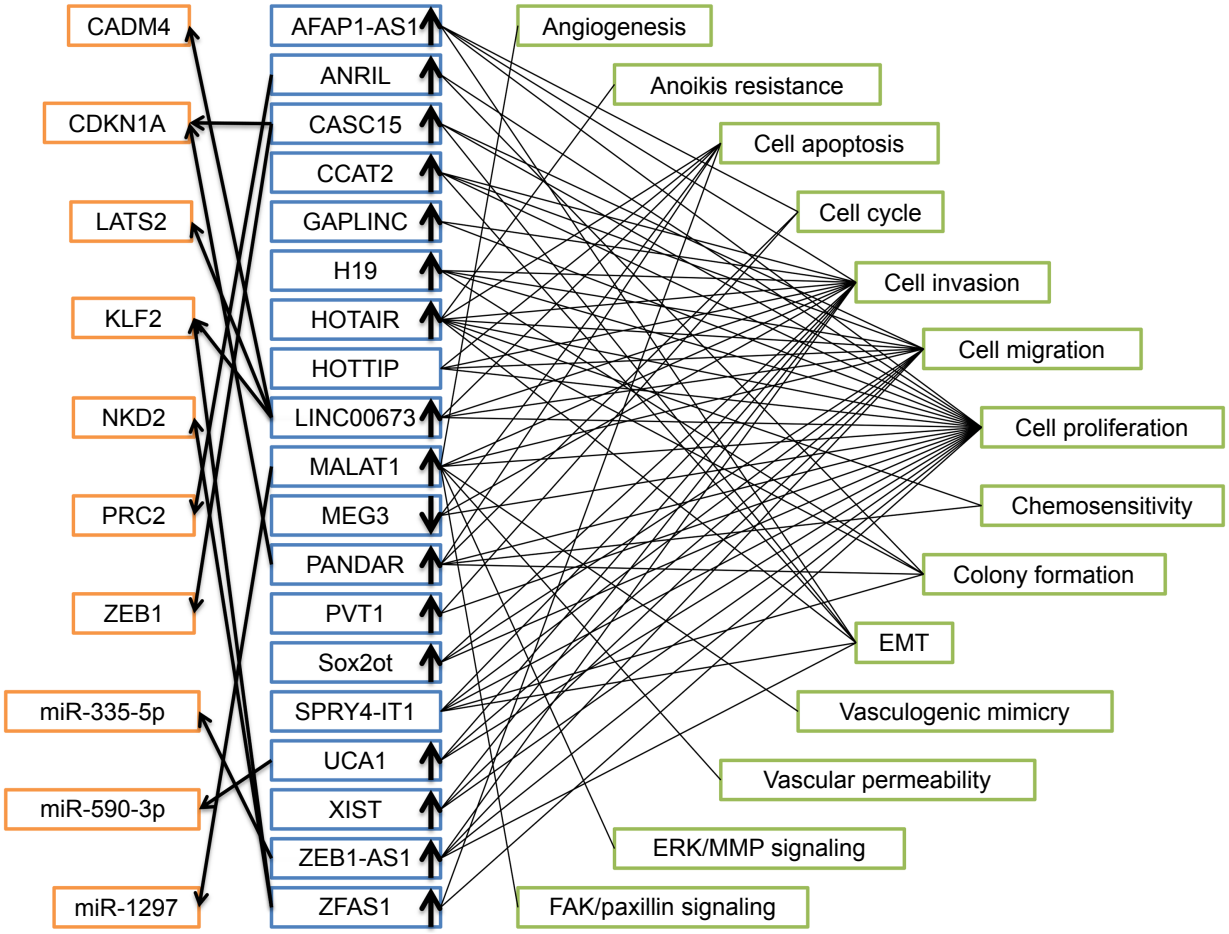

Figure 8 Summary of lncRNAs with altered expression, potential targets and pathways entered in this study.
Abbreviations: AFAP1-AS1, AFAP1 antisense RNA 1; ANRIL, CDKN2B antisense RNA 1; CASC15, cancer susceptibility 15; CCAT2, colon cancer associated transcript 2; EMT, epithelial–mesenchymal transition; GAPLINC, gastric adenocarcinoma associated, positive CD44 regulator, long intergenic noncoding RNA; H19, H19, imprinted maternally expressed transcript; HOTAIR, HOX transcript antisense RNA; HOTTIP, HOXA distal transcript antisense RNA; LINC00673, long intergenic non-protein coding RNA 673; lncRNA, long noncoding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MEG3, maternally expressed 3; PANDAR, promoter of CDKN1A antisense DNA damage activated RNA; PVT1, Pvt1 oncogene; Sox2ot, SOX2 overlapping transcript; SPRY4-IT1, SPRY4 intronic transcript 1; UCA1, urothelial cancer associated 1; XIST, X inactive specific transcript; ZEB1-AS1, ZEB1 antisense RNA 1; ZFAS1, ZNFX1 antisense RNA 1.

drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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