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REVIEW ARTICLE

Abnormally expressed lncRNAs in the prognosis and clinicopathology of oesophageal cancer: a systematic review and meta-analysis

PENG QIAN[1]*, ZHIYIN XU[1], HUI CHEN[1], SUYANG YUE[2] and YONGJIAN LV[2]

[1]*Departments of Gastroenterology, Taizhou People's Hospital, Taizhou, Jiangsu 225300, People's Republic of China*
[2]*Departments of Gastroenterology, Huaian Second People's Hospital, Huaian, Jiangsu 223001, People's Republic of China*
*For correspondence. E-mail: 758497482@qq.com.

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Abstract. The relationship between the long noncoding RNA (lncRNA) expression and oesophageal cancer prognosis has been widely studied, but less consensus has been reached. We conducted this study to evaluate the relationship between the expression of lncRNAs and the prognosis and clinical pathology of oesophageal cancer. We conducted a systematic search of PubMed, EMBASE and Cochrane Library until 25 January 2019. Studies that evaluated the associations of a specific lncRNA with survival and/or clinicopathology of oesophageal cancer were included. Pooled hazard ratios (HRs), odds ratios (ORs), and corresponding 95% confidence intervals (CIs) were calculated using fixed or random-effect models. Sensitivity analysis was used to verify the stability of results. Publication bias was detected using Begg tests and adjusted utilizing the trim-and-fill method if a bias existed. A total of 51 studies comprising 6510 patients and regarding 41 lncRNAs were included in the present systematic review and meta-analysis. The results showed that dysregulation of lncRNAs was associated with overall survival, disease-free survival, and progression-free survival. The expression of lncRNAs was related to some certain clinicopathological parameters of oesophageal cancer, including tumour size, T classification, lymph node metastasis, tumour node metastasis (TNM) stage and differentiation. Among these findings, lncRNA AK001796, CASC9, HOTAIR, MALAT1 and UCA1 were identified and were expected to be ideal biomarkers for the prognosis and clinicopathology of oesophageal cancer. Although significant publication bias was observed in some studies, the results were not changed after adjustment using the trim-and-fill method. Abnormal lncRNA-expression profiles could serve as a promising indicator for prognostic evaluation of patients with oesophageal cancer. The combination of these lncRNAs will contribute to clinical decision-making in the future.

Keywords. lncRNAs; oesophageal cancer; prognosis; clinicopathological feature; meta-analysis.

Introduction

Oesophageal cancer is the eighth most common type of cancer and the sixth leading cause of cancer-associated mortality worldwide (Siegel *et al*. 2017). Oesophageal squamous cell carcinoma (ESCC) is the predominant subtype, accounting for 80–90% of cases, especially in China (Li *et al*. 2016). Traditionally, we use clinicopathological features—such as tumour size, lymph node status and tumour node metastasis (TNM) stage—to predict the prognosis of patients (Navin *et al*. 2011). However, even for patients with similar status and treatment, their survival outcomes can still be different. As research in this field has progressed, we have realized that a better understanding of carcinogenic mechanisms and utilizing ideal biomarkers of cancer can facilitate in the diagnoses and prognoses of oesophageal cancer (Su *et al*. 2018).

Long non-coding RNAs (lncRNAs) are defined as RNA transcripts longer than 200 nucleotides and have been reported to lack protein-coding abilities previously (Gupta *et al*. 2010). In recent years, lncRNAs have attracted increasing scientific interest. Large numbers of studies have shown that specific lncRNAs are involved in the development and progression of cancer. Mechanistically, lncRNAs

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can regulate gene expression at different levels: transcriptional regulations, post-transcriptional regulations, epigenetic modifications or single-nucleotide polymorphisms (SNPs) (Huang *et al*. 2015a). For instance, Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) can act as a competitive endogenous RNA (ceRNA) to sponge microRNAs, thereby regulating cell metastasis, progression and invasion through their targets (Wang *et al*. 2015). Maternally expressed gene 3 (MEG3) can also serve as ceRNA to regulate Bcl-2 and inhibit cell proliferation through competitive binding microRNA-181a (Peng *et al*. 2015). Hence, different lncRNAs are identified as key players in the role of carcinogenesis or tumour suppression in a variety of cancer types (Gibb *et al*. 2011; Cheetham *et al*. 2013). Further, accumulating studies have also indicated that lncRNAs could offer great promise in the diagnosis, prognosis and treatment of cancers (Dong *et al*. 2015; Liu *et al*. 2019).

In oesophageal cancer, the abnormal regulation of lncRNA plays important roles in proliferation, invasion, metastasis, apoptosis, angiogenesis, resistance to radiotherapy, which suggests potential clinical significance (Fanelli *et al*. 2018). Up to now, there has been no specific meta-analysis of lncRNA on oesophageal cancer due to small sample size. It is suggested that the findings of these studies should be combined and that the potential clinical value of lncRNAs in oesophageal cancer be systematically analysed. Thus, we performed this systematic review and meta-analysis to assess the relationship of lncRNA expression with the prognosis and clinicopathology of oesophageal cancer patients.

Materials and methods

This systematic review and meta-analysis was conducted according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Moher *et al*. 2009). We registered this study at the International Prospective Register of Systematic Reviews (no. CRD42019124145).

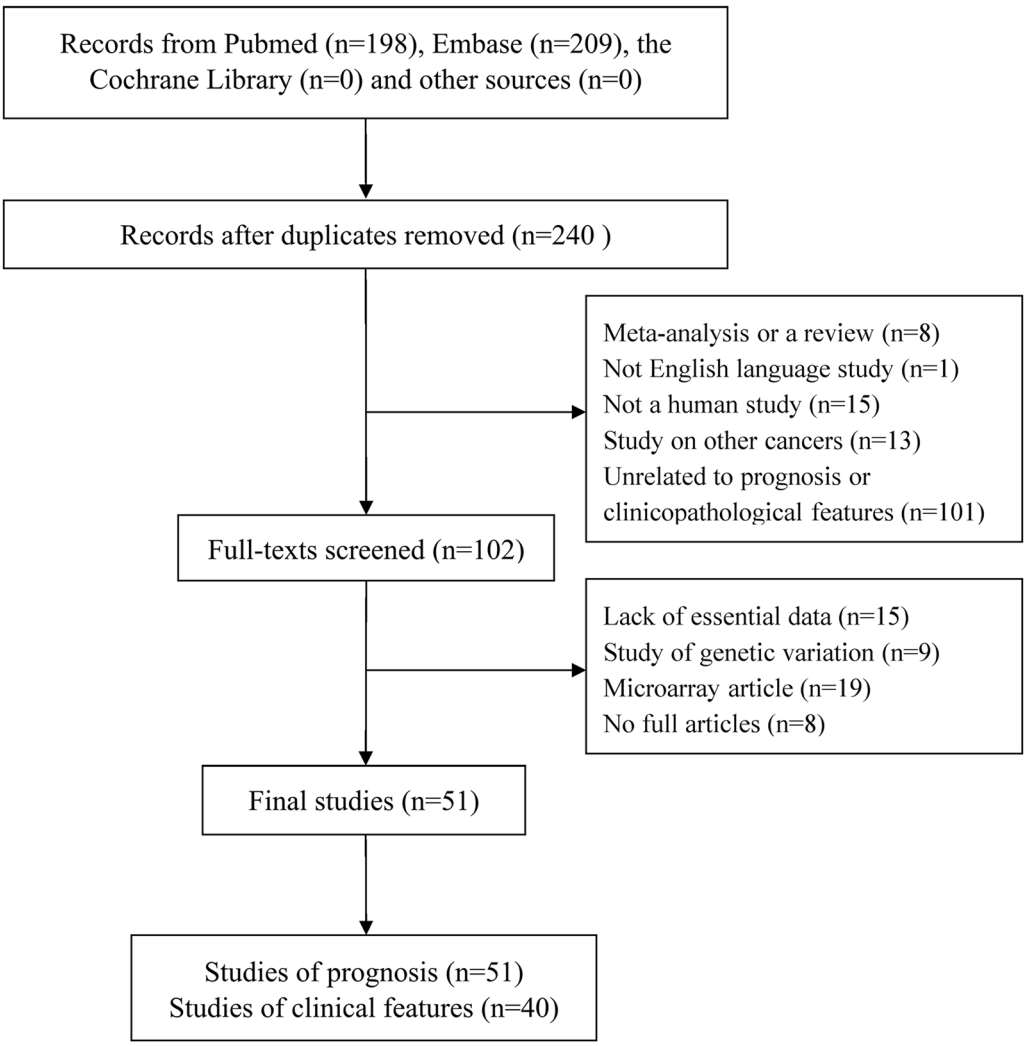

Figure 1. Flow diagram of the literature search and selection.

Table 1. Characteristics of studies included in this meta-analysis.

Studies	Region	LncRNA	Expression	Case number (high/low)	Tumor type	Sample type	Detective method	Cut-off	Follow-up (month)	Outcome	NOS
Bao (2018)	China	FOXD2-AS1	Upregulated	147(73/74)	ESCC	Tissue	qRT-PCR	Median	90	OS/DFS	7
Cao (2018)	China	ANRIL	Upregulated	50(21/29)	ESCC	Tissue	qRT-PCR	Median	60	OS/DFS	8
Chen (2013)	China	HOTAIR	Upregulated	78(27/51)	ESCC	Tissue	qRT-PCR	Mean	60	OS	8
Chen (2015)	China	NEAT1	Upregulated	96(54/42)	ESCC	Tissue	qRT-PCR	YI	< 80	OS	7
Dong (2017)	China	MEG3	Downregulated	143(26/117)	ESCC	Tissue	qRT-PCR	FC	70	OS	7
Gao (2018)	China	CASC9	Upregulated	128(66/62)	ESCC	Tissue	qRT-PCR	Median	60	OS/DFS	8
Ge (2013)	China	HOTAIR	Upregulated	137(103/34)	ESCC	Tissue	qRT-PCR	RC	60	OS	5
Han (2018)	China	SNHG16	Upregulated	128(65/63)	ESCC	Tissue	qRT-PCR	Median	60	OS	8
Hu (2016)	China	CFLAR-AS1	Upregulated	205(114/91)	ESCC	Plasma	qRT-PCR	FC	60	OS	6
		LINC00152	Upregulated	205(131/74)	ESCC	Plasma	qRT-PCR	FC	60	OS	6
		POU3F3	Upregulated	205()118/87	ESCC	Plasma	qRT-PCR	FC	60	OS	6
Huang (2018)	China	AC093850.2	Upregulated	77(10/67)	ESCC	Tissue	qRT-PCR	NO	< 100	OS/DFS	6
		LINC00460	Upregulated	77(8/69)	ESCC	Tissue	qRT-PCR	NO	< 100	OS/DFS	6
		RP11-366H4.1.1	Upregulated	77(60/17)	ESCC	Tissue	qRT-PCR	NO	< 100	OS/DFS	6
Huang (2016)	China	MALAT1	Upregulated	133(99/34)	EC	Tissue	qRT-PCR	NO	60	OS	7
Jiang (2016)	China	TUG1	Upregulated	218(109/109)	ESCC	Tissue	qRT-PCR	NO	12–72	OS	6
Jiao (2016)	China	UCA1	Upregulated	66(33/33)	EC	Tissue	qRT-PCR	Median	5–30	OS	6
Kang (2018)	China	MALAT1	Upregulated	100(50/50)	ESCC	Tissue	qRT-PCR	Mean	100	OS/DFS	8
		UCA1	Upregulated	100(49/51)	ESCC	Tissue	qRT-PCR	Mean	100	OS/DFS	8
Ke (2018)	China	NKILA	Downregulated	137(68/69)	ESCC	Tissue	qRT-PCR	Median	< 100	OS/DFS	7
Li (2013)	China	HOTAIR	Upregulated	100(30/70)	ESCC	Tissue	qRT-PCR	FC	< 60	OS	7
Li (2016)	China	PVT1	Upregulated	104(52/52)	ESCC	Tissue	qRT-PCR	Median	< 100	OS/DFS	8
Li (2014)	China	UCA1	Upregulated	90(41/49)	ESCC	Tissue	qRT-PCR	Mean	60	OS	8
Liang (2018)	China	CASC9	Upregulated	69(34/35)	ESCC	Tissue	qRT-PCR	NO	60	OS	5
Liang (2017)	China	LINC00460	Upregulated	65(32/33)	ESCC	Tissue	qRT-PCR	FC	65	OS	6
Lin (2018)	China	TTN-AS1	Upregulated	80(50/30)	ESCC	Tissue	qRT-PCR	NO	100	OS	6
Liu (2018a)	China	AK001796	Upregulated	50(25/25)	ESCC	Tissue	qRT-PCR	NO	60	OS	5
Liu (2016)	China	BANCR	Upregulated	142(71/71)	ESCC	Tissue	qRT-PCR	Median	60	OS/DFS	8
Lu (2016)	China	BC032469	Upregulated	45(35/10)	ESCC	Tissue	qRT-PCR	NO	50	OS	6
Lv (2013)	China	HOTAIR	Upregulated	93(48/45)	ESCC	Tissue	qRT-PCR	NO	70	OS	5
Lv (2016)	China	MEG3	Downregulated	96(48/48)	ESCC	Tissue	qRT-PCR	NO	120	OS	5
Niu (2018)	China	LINC-UBC1	Upregulated	50(26/24)	ESCC	Tissue	qRT-PCR	NO	60	OS	5
Pan (2014)	China	FOXCUT	Upregulated	82(45/37)	ESCC	Tissue	qRT-PCR	Mean	72	OS	7
Qin (2016)	China	PCAT-1	Upregulated	321(250/71)	ESCC	Tissue	qRT-PCR	RC	60	OS	7
Ren (2017)	China	MIR31HG	Downregulated	185(95/90)	ESCC	Tissue	qRT-PCR	Median	60	OS	8
Shi (2015)	China	PCAT-1	Upregulated	130(65/65)	ESCC	Tissue	qRT-PCR	Median	60	OS	8
Wang (2018a)	China	LINC01296	Upregulated	221(114/107)	ESCC	Tissue	qRT-PCR	Mean	60	OS/DFS	8
Wang (2018b)	China	GAS5	Downregulated	112(56/56)	ESCC	Plasma	qRT-PCR	Median	60	OS	6
Wang (2018c)	China	DUXAP10	Upregulated	96(36/60)	ESCC	Tissue	qRT-PCR	Mean	60	OS	8
Wang (2016)	China	MALAT1	Upregulated	106(46/60)	ESCC	Tissue	qRT-PCR	NO	60	OS	6
Wang (2015b)	China	ZEB1-AS1	Upregulated	87(44/43)	ESCC	Tissue	qRT-PCR	Median	60	OS/DFS	8
Wu (2017a)	China	XIST	Upregulated	127(64/63)	ESCC	Tissue	qRT-PCR	Median	< 100	OS/DFS	8
Wu (2017b)	China	CASC9	Upregulated	91(45/46)	ESCC	Tissue	qRT-PCR	NO	50	OS	7
Xiao (2018)	China	ATB	Upregulated	218(109/109)	ESCC	Tissue	qRT-PCR	NO	80	OS	5

Table 1 (*contd*)

Studies	Region	LncRNA	Expression	Case number (high/low)	Tumor type	Sample type	Detective method	Cut-off	Follow-up (month)	Outcome	NOS
Xie (2018)	China	LINC01503	Upregulated	113(39/74)	ESCC	Tissue	qRT-PCR	NO	50	OS/DFS	5
Xie (2014)	China	SPRY4-IT1	Upregulated	92(46/46)	ESCC	Tissue	qRT-PCR	Median	60	OS	6
Yang (2018)	China	LINC01133	Downregulated	149(74/75)	ESCC	Tissue	qRT-PCR	Median	60	OS/PFS	7
Yao (2016)	China	MALAT1	Upregulated	137(103/34)	ESCC	Tissue	qRT-PCR	FC	40	OS	7
Yao (2017)	China	RP11-766N7.4	Downregulated	50(29/21)	ESCC	Tissue	qRT-PCR	Median	60	OS	7
Yi (2018)	China	XIST	Upregulated	140(70/70)	ESCC	Tissue	qRT-PCR	NO	< 150	OS	7
Yoon *et al.* (2017)	Korea	LUCAT1	Upregulated	24(7/17)	ESCC	Tissue	qRT-PCR	Median	40	OS	5
Zhang (2018)	China	NEF	Downregulated	78(39/39)	ESCC	Plasma	qRT-PCR	Median	60	OS	7
Zhang (2017)	China	SNHG1	Upregulated	72(38/34)	ESCC	Tissue	qRT-PCR	NO	70	OS	6
Zhao (2016)	China	BC200	Upregulated	70(35/35)	ESCC	Tissue	qRT-PCR	Median	50	OS/DFS	8
Zhong (2018)	China	LINC00675	Downregulated	143(70/73)	ESCC	Tissue	qRT-PCR	Median	60	OS	8
Zong (2019)	China	AK001796	Upregulated	175(87/88)	ESCC	Tissue	qRT-PCR	Median	60	OS	8

RC, ROC curve; Fc, fold change; YI, Youden-index; NO; no report; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; ESCC, oesophageal squamous cell carcinoma; EC, oesophageal carcinoma.

Search strategy

Two independent reviewers searched several databases, including PubMed, EMBASE and the Cochrane Library, for studies of lncRNAs and oesophageal cancer. The publication dates used to search the literature were from inception to 25 January 2019. The following search terms were used: lncRNA OR long noncoding RNA OR lincRNA OR long intergenic non-protein coding RNA OR long non-protein-coding RNA OR long untranslated RNA; and oesophageal carcinoma OR oesophageal neoplasm OR oesophageal tumor OR oesophageal squamous cell carcinoma OR ESCC OR oesophageal adenocarcinoma OR EAC.

Inclusion and exclusion criteria

The criteria for inclusion of studies were as follows: (i) clinical study of the expression of lncRNA in oesophageal cancer; (ii) patients who were diagnosed with oesophageal cancer by pathologists did not receive any preoperative chemotherapy or radiotherapy before obtaining samples; (iii) the study investigated the relationship between lncRNA expression and survival or clinicopathological features of oesophageal cancer; (iv) the study provided sufficient information for extraction or calculation of the individual hazard ratio (HR) or odds ratio (OR) and associated 95% confidence intervals (CI); (v) the expression level of lncRNAs in each study was divided into two levels based on cut-off value: high and low; and (vi) full text was available and published in English. The criteria for exclusion of studies were as follows: (i) lack of appropriate data that could be extracted or calculated, (ii) reprocessed data from public databases, and (iii) reviews, meta-analysis, letters, case reports and conference abstracts.

Quality assessment and data extraction

Two reviewers independently reviewed articles for inclusion/exclusion qualifications and to assess the quality of each study, for which the Newcastle–Ottawa Scale (NOS) was used (Lo *et al*. 2014). The following data were extracted: (i) basic information, including first author's name, publication year, region, type of lncRNAs and expression, case number, tumour type, sample type, detection method, cut-off value, follow-up duration, and outcome; (ii) prognostic outcome (HR and 95% CI) and clinicopathological parameters; (iii) if the raw data could not provide HRs directly, Kaplan–Meier survival curves were read using the Engauge Digitizer (version 4.1) to obtain data (Tierney *et al*. 2007); and (iv) if a study reported the data via multivariate analysis and/or univariate analysis for survival rates, the former was directly applied. Any disagreements were reviewed and resolved by consensus.

Statistical analysis

HRs with the corresponding 95% CI were used to estimate the association of lncRNA with survival rates of oesophageal cancer. As for clinical features, ORs and associated 95% CI were used.

According to the inclusion criteria, the expression of lncRNA in oesophageal cancer sample was divided into two levels (high and low) by the cut-off value for each study. In our systematic review and meta-analysis, whether the lncRNA was carcinogenic or anticarcinogenic, we calculated all of the HRs and ORs for high expression of lncRNAs.

Hence, the analysis of oncogenic lncRNAs and tumour-suppressor lncRNAs were each performed. The heterogeneity among the eligible studies was calculated by the I^2 statistic. If $I^2 < 50\%$ indicated low heterogeneity, fixed-effect models were used. Otherwise, random-effect models would ultimately be used. Stata 12.0 (StataCorp, College Station, USA) was used to perform all analyses and to construct the forest plot. A value of $P < 0.05$ was considered statistically significant. To verify the stability of the pooled results, we undertook sensitivity analysis. Publication bias was evaluated using Begg tests and defined significantly at a $P < 0.05$. In addition, the trim-and-fill method was conducted if a bias existed (Weinhandl *et al*. 2012).

Results

Included literature

As shown in the flow diagram (figure 1), 407 articles were originally retrieved from PubMed, EMBASE and the Cochrane Library, and 240 articles were left after removing duplications. After screening titles and abstracts, 102 full-text articles remained for further assessment, and 51 articles were excluded based on the inclusion criteria. Finally, a total of 51 studies—including 51 on prognosis (Chen *et al*. 2013, 2015; Ge *et al*. 2013; Pan *et al*. 2014; Hu *et al*. 2016; Huang *et al*. 2016, 2018; Jiang *et al*. 2016; Jiao *et al*. 2016; Dong *et al*. 2017; Bao *et al*. 2018; Cao *et al*. 2018; Gao *et al*. 2018; Han *et al*. 2018; Kang *et al*. 2018; Ke *et al*. 2018; Li *et al*. 2013, 2014, 2017; Liang *et al*. 2017, 2018; Lin *et al*. 2018; Liu *et al*. 2016, 2018a; Lu *et al*. 2016; Lv *et al*. 2013, 2016; Niu *et al*. 2018; Qin *et al*. 2016; Shi *et al*. 2015; Ren *et al*. 2017; Wang *et al*. 2015b, 2016, 2018a, b, c; Wu *et al*. 2017a, b; Xiao *et al*. 2018; Xie *et al*. 2014, 2018; Yao *et al*. 2016; Yao *et al*. 2017; Yi *et al*. 2018; Yang *et al*. 2018; Yoon *et al*. 2017; Zhang *et al*. 2018; Zhang *et al*. 2017; Zhao *et al*. 2016; Zhong *et al*. 2018; Zong *et al*. 2019) and 40 on clinicopathological features (Chen *et al*. 2013; Ge *et al*. 2013; Li *et al*. 2013; Li *et al*. 2014; Pan *et al*. 2014; Xie *et al*. 2014; Chen *et al*. 2015; Shi *et al*. 2015; Wang *et al*. 2015b; Huang *et al*. 2016; Jiang *et al*. 2016; Jiao *et al*. 2016; Liu *et al*. 2016; Lu *et al*. 2016; Zhao *et al*. 2016; Li *et al*. 2017; Liang *et al*. 2017; Ren *et al*. 2017; Yao *et al*. 2016, 2017; Zhang *et al*. 2017; Bao *et al*. 2018; Cao *et al*. 2018; Gao *et al*. 2018; Han *et al*. 2018; Kang *et al*. 2018; Ke *et al*. 2018; Liang *et al*. 2018; Liu *et al*. 2018a; Niu *et al*. 2018; Wang *et al*. 2018a, c; Wu *et al*. 2017a, b; Xiao *et al*. 2018; Yang *et al*. 2018; Yi *et al*. 2018; Zhang *et al*. 2018; Zhong *et al*. 2018; Zong *et al*. 2019)—were eligible for this systematic review and meta-analysis.

Characteristics of the enrolled studies

After screening, 51 articles involving 6510 patients with oesophageal cancer were enrolled in this systematic review and meta-analysis. All articles were published between 2013 and 2019. Fifty studies were carried out in China and one was carried out in Korea. A total of 41 different lncRNAs were linked with survival outcomes in oesophageal cancer. Among them, lncRNA AC093850.2, AK001796, ANRIL, ATB, BANCR, BC032469, BC200, CASC9, CFLAR-AS1, DUXAP10, FOXCUT, FOXD2-AS1, HOTAIR, LINC00152, LINC00460, LINC01296, LINC01503, LINC-UBC1, LUCAT1, MALAT1, NEAT1, PCAT-1, POU3F3, PVT1, RP11-366H4.1.1, SNHG1, SNHG16, SPRY4-IT1, TTN-AS1, TUG1, UCA1, XIST and ZEB1-AS1 were oncogenic lncRNAs in 42 studies and lncRNA GAS5, LINC00675, LINC01133, MEG3, MIR31HG, NEF, NKILA, and RP11-766N7.4 were tumour-suppressor lncRNAs in nine studies. Except for the studies of Huang *et al.* (2016) and Jiao *et al.* (2016), which did not specifically describe the pathological type of oesophageal cancer, the pathology type of the other studies were referred to ESCC. Specimens were composed of tissue (n = 48) and plasma (n = 3). LncRNA expression for all studies was detected by reverse transcription-polymerase chain reaction (RT-PCR). The follow-up time varied from 30 to 150 months. The eligible articles consisted of the following: 51 on overall survival (OS), 14 on disease-free survival (DFS), one on progression-free survival (PFS) and 40 on clinicopathological features. The NOS scores ranged from 5 to 8 stars and were all regarded as high quality. The detailed characteristics of the eligible articles are presented in table 1.

Prognostic value of lncRNA expression for oesophageal cancer survival

All of the eligible studies reported the OS of oesophageal cancer. Since all of the HRs were calculated for high expression of lncRNAs in this meta-analysis, we conducted the analysis of oncogenic lncRNAs and tumour-suppressor lncRNAs. Thus, for the group of oncogenic lncRNAs, an observed HR > 1 indicated a worse survival. On the contrary, for the group of tumour -suppressor lncRNAs, an observed HR < 1 meant a poorer survival. The HRs extracted or calculated were merged to evaluate the prognostic value of lncRNA sequentially. The heterogeneity of

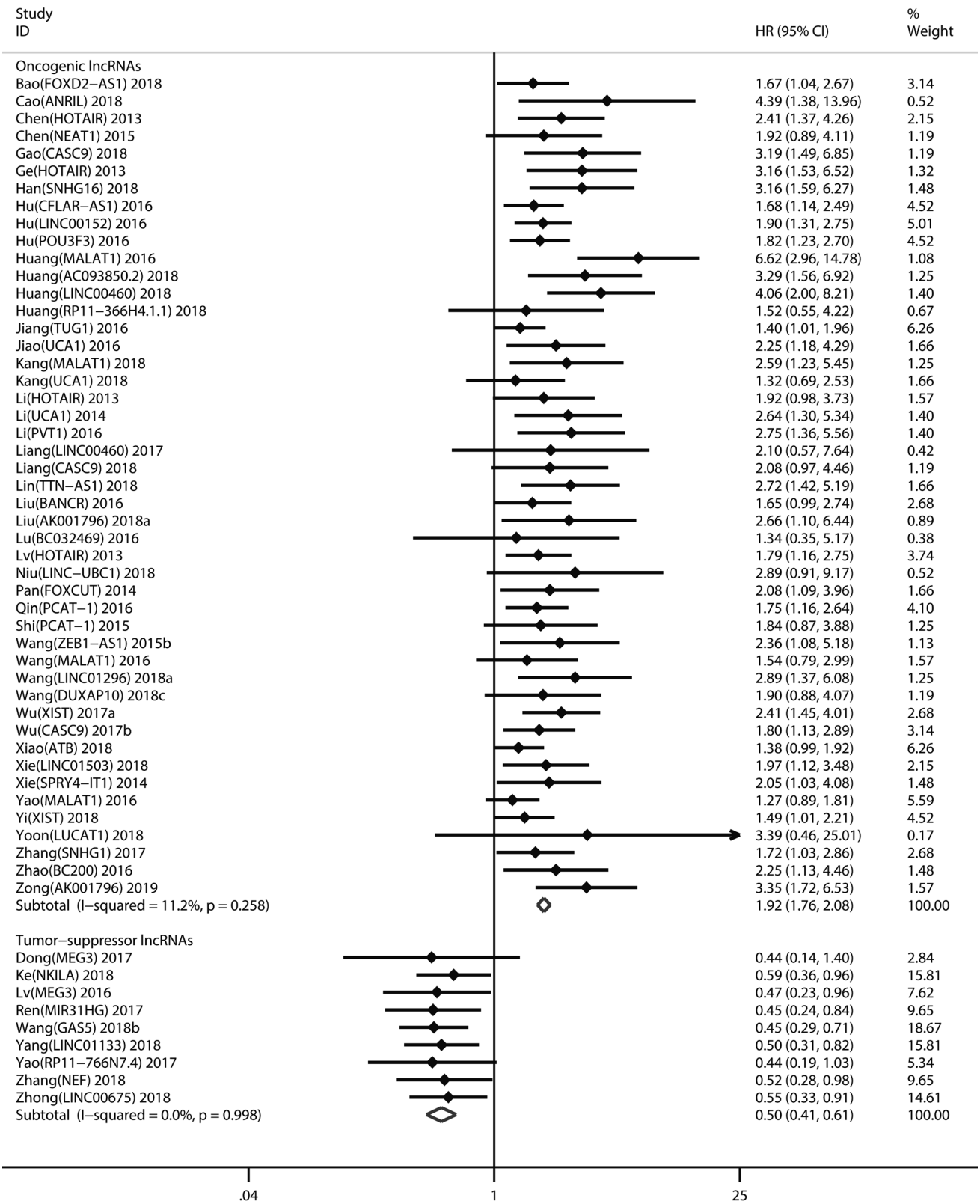

Figure 2. Forest plots of studies evaluating HRs of different types lncRNAs (oncogenic lncRNAs and tumour-suppressor lncRNAs) and OS of oesophageal cancer patients. HR, hazard ratio; OS, overall survival.

the two sets of analyses were not significant (oncogenic lncRNAs : I^2 = 11.2%, P = 0.26 and tumour-suppressor lncRNA : I^2 = 0.0%, P = 0.99). Thus, we applied the fixed-effects model, which revealed that high expression of

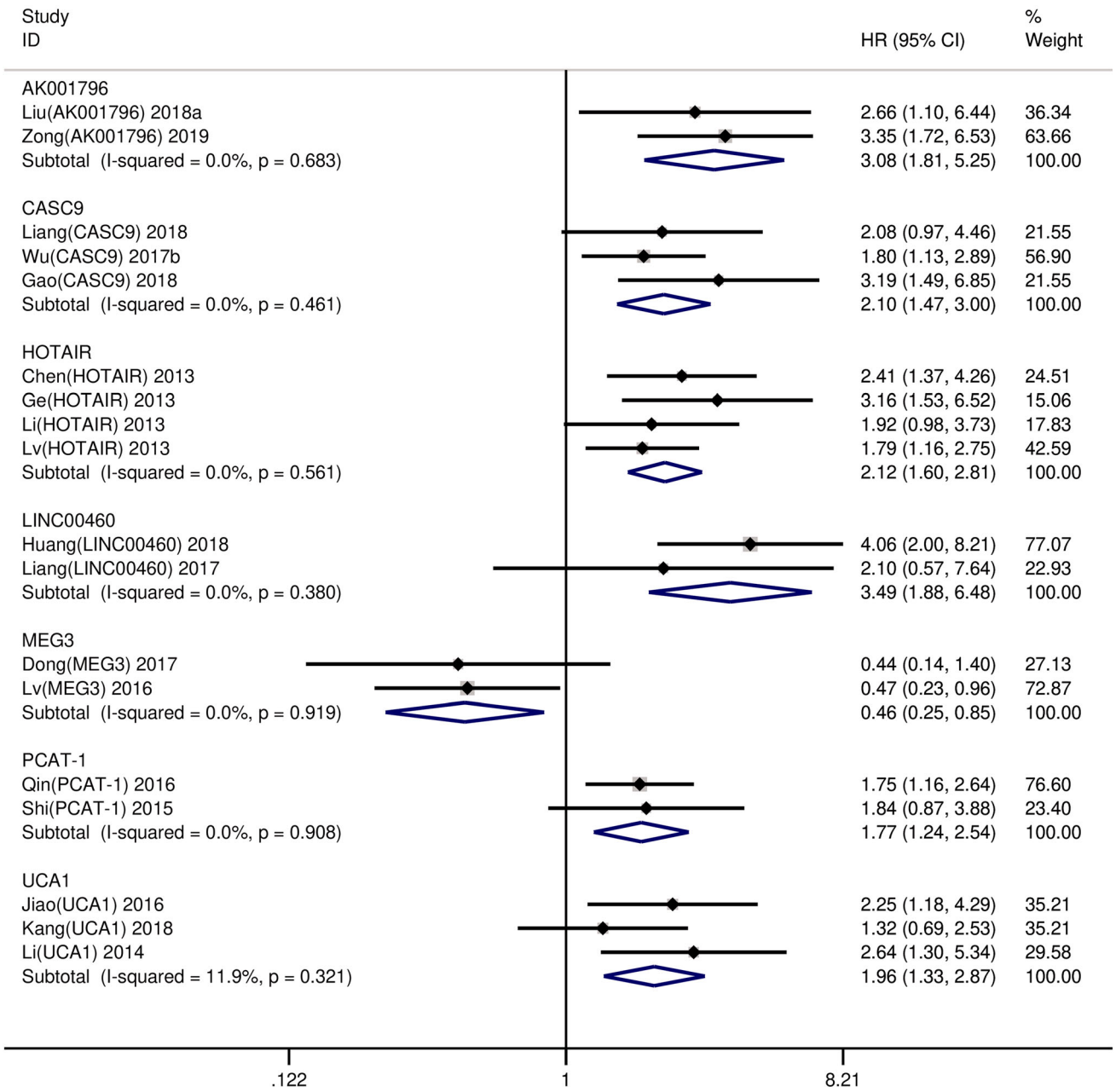

Figure 3. Forest plots of studies evaluating HRs of lncRNAs (AK001796, CASC9, HOTAIR, LINC00460, MEG3, PCAT-1, UCA1) and OS of oesophageal cancer patients with fixed-effects model. HR, hazard ratio; OS, overall survival.

oncogenic lncRNAs was associated with poor OS (pooled HR: 1.92, 95% CI: 1.77–2.09, $P < 0.01$). Additionally, we found that the downregulation of tumour-suppressor lncRNAs was predictive of a short OS (pooled HR: 0.50, 95% CI: 0.41–0.61, $P < 0.01$) (figure 2).

Of the 41 total lncRNAs for OS, the following nine were repeatedly reported: AK001796, CASC9, HOTAIR, LINC00460, MEG3, PCAT-1, UCA1, MALAT1 and XIST. Among them, their reported frequencies were as follows: HOTAIR and MALAT1 were detected in four articles; CASC9 and UCA1 were detected in three articles; and AK001796, LINC00460, MEG3, PCAT-1 and XIST were investigated in two articles. Therefore, we subsequently carried out corresponding meta-analysis to assess the relationships between the same type of lncRNA expression and OS. Since the heterogeneity tests of AK001796, CASC9, HOTAIR, LINC00460, MEG3, PCAT-1 and UCA1 were less than 50%, the fixed-effects model was applied. On the contrary, we used the random-effects model for aggregated MALAT1 and XIST because their heterogeneity was obvious. As shown in figure 3, patients with high expression of AK001796, CASC9, HOTAIR, LINC00460, PCAT-1 and UCA1 had shorter OS (pooled HR = 3.09, 95% CI: 1.81–5.25, $P < 0.01$; pooled HR = 2.10, 95% CI: 1.47–3.00,

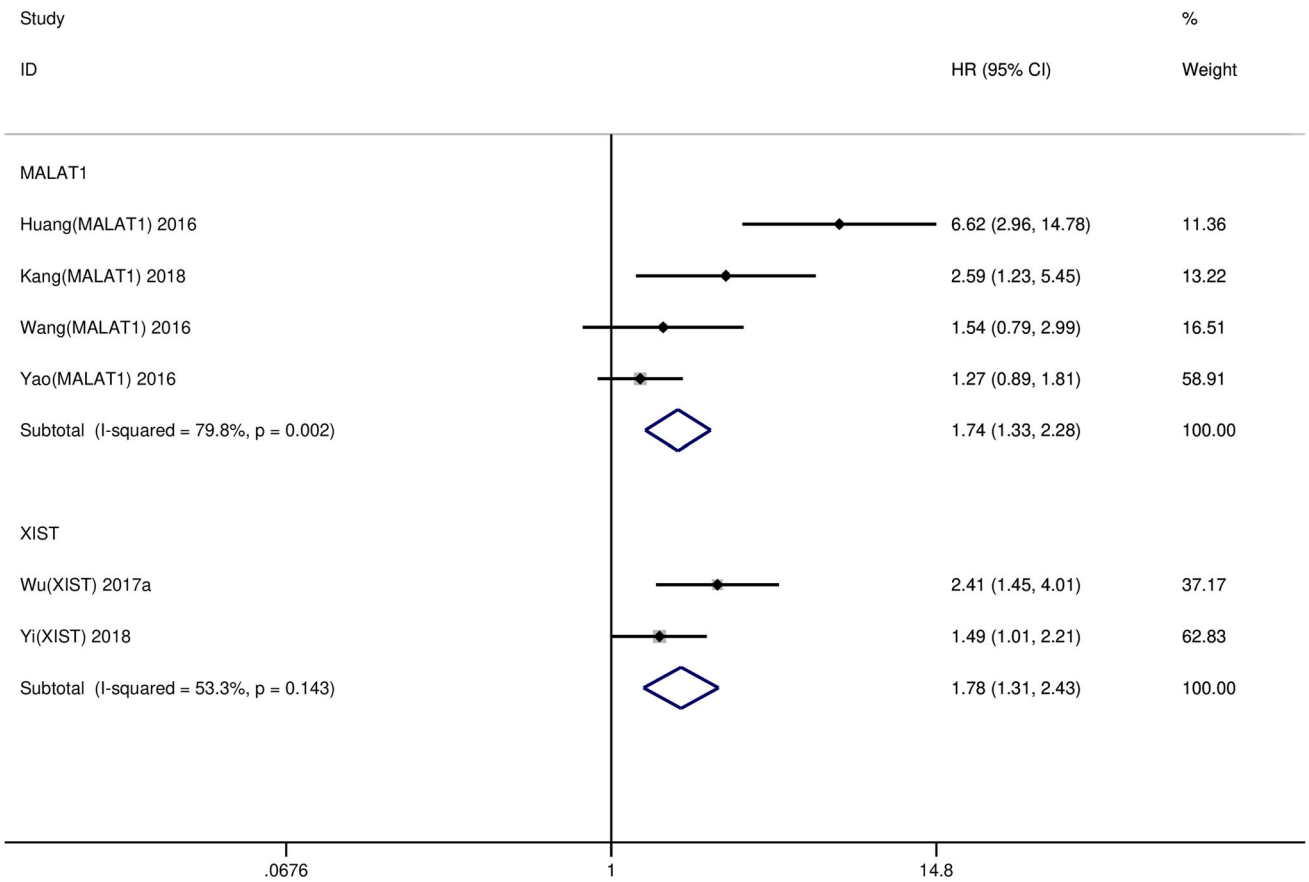

Figure 4. Forest plots of studies evaluating HRs of lncRNAs (MALAT1, XIST) and OS of oesophageal cancer patients with random-effects model. HR, hazard ratio; OS, overall survival.

$P < 0.01$; pooled HR = 2.12, 95% CI: 1.60–2.81, $P < 0.01$; pooled HR = 3.49, 95% CI: 1.88–6.48, $P < 0.01$; pooled HR = 1.77, 95% CI: 1.24–2.54, $P < 0.01$; pooled HR = 1.96, 95% CI: 1.33–2.87, $P < 0.01$, respectively), while an increased level of MEG was associated with better OS (pooled HR = 0.46, 95% CI: 0.25–0.85, $P = 0.01$). In figure 4, the higher expressions of lncRNA MALAT1 (pooled HR = 2.27, 95% CI: 1.14–4.51, $P = 0.02$) and XIST (pooled HR = 1.84, 95% CI: 1.16–2.94, $P = 0.01$) were associated with poor OS.

A total of 14 articles investigated the correlation between 17 different lncRNAs and DFS. Similar to the merge of HRs for OS, as shown in figure 5, the pooled HR of oncogenic lncRNAs indicated that elevated expression of lncRNAs AC093850.2, AK001796, ANRIL, BANCR, BC200, CASC9, FOXD2-AS1, LINC00460, LINC01296, LINC01503, MALAT1, PVT1, RP11-366H4.1.1, UCA1, XIST and, ZEB1-AS1 were associated with decreased DFS (pooled HR: 2.62, 95% CI: 2.23–3.08, $P < 0.01$, $I^2 = 9.2\%$, fixed model). We were not able to conduct a corresponding meta-analysis due to only one study investigating the association between downregulated lncRNA signature and OS. In the study by Ke *et al.* (2018), the lncRNA NKILA was a tumour-suppressor lncRNA in oesophageal cancer and was correlated with a worse prognosis DFS (HR: 0.48, 95% CI: 0.28–0.83, $P = 0.03$).

As only one article investigated the association between lncRNA signature and PFS, we were unable to perform a corresponding meta-analysis. In the study by Yang *et al.* (2018), the lncRNA LINC01133 was upregulated in oesophageal cancer and was associated with a poor outcome of PFS (HR: 2.00, 95% CI: 1.23–3.26, $P < 0.01$).

Clinicopathological characteristics

A total of 31 lncRNAs were investigated in the 40 included studies on clinicopathological features. The oncogenic lncRNAs in this part of meta-analysis were as follows: AK001796, ANRIL, ATB, BANCR, BC032469, BC200, CASC9, DUXAP10, FOXCUT, FOXD2-AS1, HOTAIR, LINC00460, LINC01296, LINC-UBC1, MALAT1, NEAT1, PCAT-1, PVT1, SNHG1, SNHG16, SPRY4-IT1, TUG1, UCA1, XIST and ZEB1-AS1. Additionally, tumour-suppressor lncRNAs were as follows: LINC00675, LINC01133, MIR31HG, NEF, NKILA and RP11-766N7.4. We evaluated the association between lncRNA expression and clinicopathological features of oesophageal cancer, and corresponding OR values were determined. Similar to the meta-analysis of survival rate, we divided lncRNA into two groups: oncogenic lncRNAs and tumour-suppressor

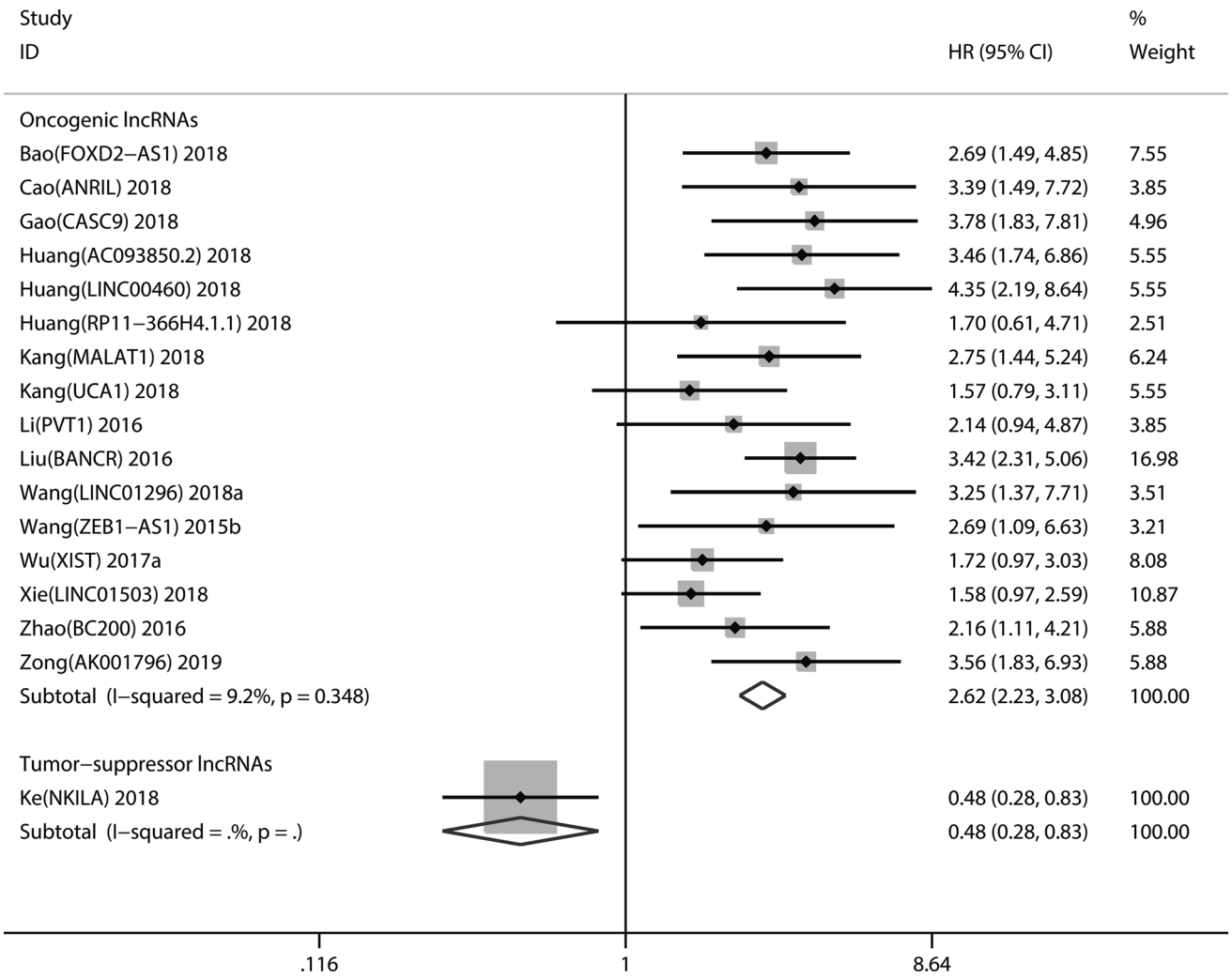

Figure 5. Forest plots of studies evaluating HRs of different types lncRNAs (oncogenic lncRNAs and tumour-suppressor lncRNAs) and DFS of oesophageal cancer patients. HR, hazard ratio; OS, DFS, disease-free survival.

lncRNAs. In this part of the meta-analysis, for the group of oncogenic lncRNAs, OR > 1 implied that the high lncRNA expression was associated with a particular parameter; on the contrary, for the group of tumour-suppressor lncRNAs, OR < 1 reflected that the low expression of lncRNA was correlated with a certain indicator. We summarized the relationship between the two types of lncRNAs and clinicopathologic characteristics such as age, gender, smoking history, drinking status, tumour location, tumour size, T stage, lymph node metastasis, and TNM stage and differentiation. We found that high expression of oncogenic lncRNAs was associated with poorer pathological parameters, such as the following: size (cm) (> 4 vs ≤ 4) (pooled OR = 2.01, 95% CI: 1.59–2.55, $P < 0.01$); T classification (T3/4 vs T1/2) (pooled OR = 2.21, 95% CI: 1.53–2.55, $P < 0.01$); lymph node metastasis (yes vs no) (pooled OR = 2.27, 95% CI: 1.61–3.20, $P < 0.01$); TNM stage (III/IV vs I/II) (pooled OR = 2.78, 95% CI: 2.25–3.45, $P < 0.01$); differentiation (poor/moderate vs well) (pooled OR = 1.58, 95% CI: 1.06–2.35, $P < 0.01$); For the group of tumour-suppressor lncRNAs, we found that high expression of tumour-suppressor lncRNAs were significantly correlated with gender (male vs female) (pooled OR = 0.70, 95% CI: 0.51–0.95, $P = 0.02$); size (cm) (> 5 vs ≤ 5) (pooled OR = 0.41, 95% CI: 0.23–0.72, $P < 0.01$); T classification (T3/4 vs T1/2) (pooled OR = 0.33, 95% CI: 0.16–0.69, $P < 0.01$); lymph node metastasis (pooled OR = 0.30, 95% CI: 0.19–0.48, $P < 0.01$); TNM stage (III/IV vs I/II) (pooled OR = 0.35, 95% CI: 0.21–0.60, $P < 0.01$). However, none of these studies reported whether the relationship between lncRNAs and age, smoking, drinking or location was significant. The details of the relationship between lncRNA expression and clinicopathological characteristics are summarized in table 2.

Six lncRNAs: AK001796, CASC9, HOTAIR, MALAT1, UCA1 and XIST, were investigated several times. We subsequently merged data from similar lncRNAs to assess their association with clinical features. The significant associations are summarized in table 3 and are as follows:

Table 2. Association between different types of lncRNAs and clinical characteristics.

Characteristic	Oncogenic lncRNAs					Tumour-suppressor lncRNAs				
	Studies	OR 95% CI	*P*	I^2(%)	P(H)	Studies	OR 95%CI	*P*	I^2(%)	P(H)
Age (> 45 vs ≤ 45)	3	0.90 (0.56,1.42)	0.64	< 0.01	0.41	–	–	–	–	–
(> 50 vs ≤ 50)	1	0.66 (0.27,1.62)	0.36	–	–	–	–	–	–	–
(> 55 vs ≤ 55)	4	0.87 (0.54,1.39)	0.56	< 0.01	0.81	1	1.23 (0.69,2.19)	0.49	–	–
(> 60 vs ≤ 60)	27	1.11 (0.96,1.30)	0.16	< 0.01	0.77	4	1.17 (0.82,1.68)	0.38	31.6	0.22
(> 65 vs ≤ 65)	–	–	–	–	—	2	1.44 (0.99,2.11)	0.06	< 0.01	0.44
Gender (male vs female)	34	1.02 (0.89,1.17)	0.77	< 0.01	0.91	6	0.70 (0.51,0.95)	0.02	< 0.01	0.86
Smoking (yes vs no)	15	1.07 (0.86,1.33)	0.53	< 0.01	0.69	3	0.78 (0.38,1.60)	0.50	63.1	0.07
Drinking (yes vs no)	13	1.19 (0.95,1.51)	0.13	< 0.01	0.86	3	0.68 (0.32,1.47)	0.33	67.5	0.05
Location (lower/middle vs upper)	13	0.92 (0.70,1.21)	0.56	< 0.01	0.61	1	1.14 (0.47,2.75)	0.77	–	–
Size (cm) (> 3 vs ≤ 3)	1	1.73 (0.62,4.89)	0.30	–	–	1	0.21 (0.08,0.56)	< 0.01	–	–
(> 4 vs ≤ 4)	11	2.01 (1.59,2.55)	< 0.01	36	0.11	1	0.37 (0.18,0.78)	0.01	–	–
(> 5 vs ≤ 5)	4	1.03 (0.72,1.45)	0.89	45	0.14	2	0.41 (0.23,0.72)	< 0.01	< 0.01	0.43
T classification (T3/4 vs T1/2)	16	2.21 (1.53,3.17)	< 0.01	61.2	< 0.01	2	0.33 (0.16,0.69)	< 0.01	< 0.01	0.63
Lymph node metastasis (yes vs no)	30	2.27 (1.61,3.20)	< 0.01	79.4	< 0.01	5	0.30 (0.19,0.48)	< 0.01	41	0.15
TNM stage (III/IV vs I/II)	29	2.78 (2.25,3.45)	< 0.01	42.9	0.01	4	0.35 (0.21, 0.60)	< 0.01	59.7	0.06
Differentiation (poor/moderate vs well)	17	1.58 (1.06,2.35)	0.02	67	< 0.01	–	–	–	–	–

P(H), the *P* value of heterogeneity; OR: odds ratio.

AK001796 was associated with lymph node metastasis (pooled OR = 2.00, 95% CI: 1.14–3.50, $P = 0.02$) and TNM stage (pooled OR = 2.46, 95% CI: 1.41–4.29, $P < 0.01$). CASC9 had a strong impact on tumour size (cm) (> 4 vs ≤ 4) (pooled OR = 2.15, 95% CI: 1.07–4.30, $P = 0.03$), T classification (pooled OR = 2.63, 95% CI: 1.55–4.46, $P < 0.01$) and TNM stage (pooled OR = 2.80, 95% CI: 1.72–4.56, $P < 0.01$). HOTAIR was significantly correlated to TNM stage (pooled OR = 6.93, 95% CI: 2.79-17.18, $P < 0.01$). MALAT1 was significantly related to lymph node metastasis (pooled OR = 2.02, 95% CI: 1.14–3.60, $P = 0.02$). Finally, UCA1 had a relationship with TNM stage (pooled OR = 4.35, 95% CI: 2.43–7.78, $P < 0.01$).

Sensitivity analysis and publication bias

Sensitivity analyses were conducted to estimate the stability of oncogenic lncRNAs for OS, DFS, T classification, lymph node metastasis, TNM stage, differentiation and tumour-suppressor lncRNAs for OS and TNM stage. From the results of the sensitivity analyses, no noteworthy influence was detected after removing any single study, which indicated that our conclusions were reliable (figures 6–8). Other pooled results did not conduct sensitivity analysis owing to a small number ($n < 10$) of included articles or owing to low heterogeneity.

We performed analyses of publication bias when the analysis of the enrolled articles was greater than 10. As shown in figure 9, publication bias was detected by the Begg test. The test of oncogenic lncRNAs for OS, as well as lymph node metastasis and TNM stage revealed significant publication bias. Subsequently, the trim-and-fill method was performed. After adjustments, pooled HR for OS (HR = 1.69, 95% CI: 1.57–1.82, $P < 0.01$), pooled OR for TNM stage (OR = 2.15, 95% CI: 1.86–2.49, $P < 0.01$) and pooled OR for lymph node metastasis (OR = 1.45, 95% CI: 1.02–2.07, $P = 0.04$) showed that the recalculated HRs and ORs did not change significantly. The remaining analyses did not show significant publication bias, and the details are provided in figure 10.

Table 3. Summary of certain lncRNAs related to clinicopathological features.

lncRNAs	Clinicopathological feature
AK001796	Lymph node metastasis (pooled OR = 2.00, 95% CI: 1.14-3.50, $P = 0.02$), TNM stage (pooled OR = 2.46, 95% CI: 1.41–4.29, $P < 0.01$)
CASC9	Size (cm) (> 4 vs ≤ 4) (pooled OR = 2.15, 95% CI: 1.07–4.30, $P = 0.03$), T classification (pooled OR = 2.63, 95% CI: 1.55-4.46, $P < 0.01$), TNM stage (pooled OR = 2.80, 95% CI: 1.72-4.56, $P < 0.01$)
HOTAIR	TNM stage (pooled OR = 6.93, 95% CI: 2.79–17.18, $P < 0.01$)
MALAT1	Lymph node metastasis (pooled OR = 2.02, 95% CI: 1.14–3.60, $P = 0.02$)
UCA1	TNM stage (pooled OR = 4.35, 95% CI: 2.43–7.78, $P < 0.01$
XIST	–

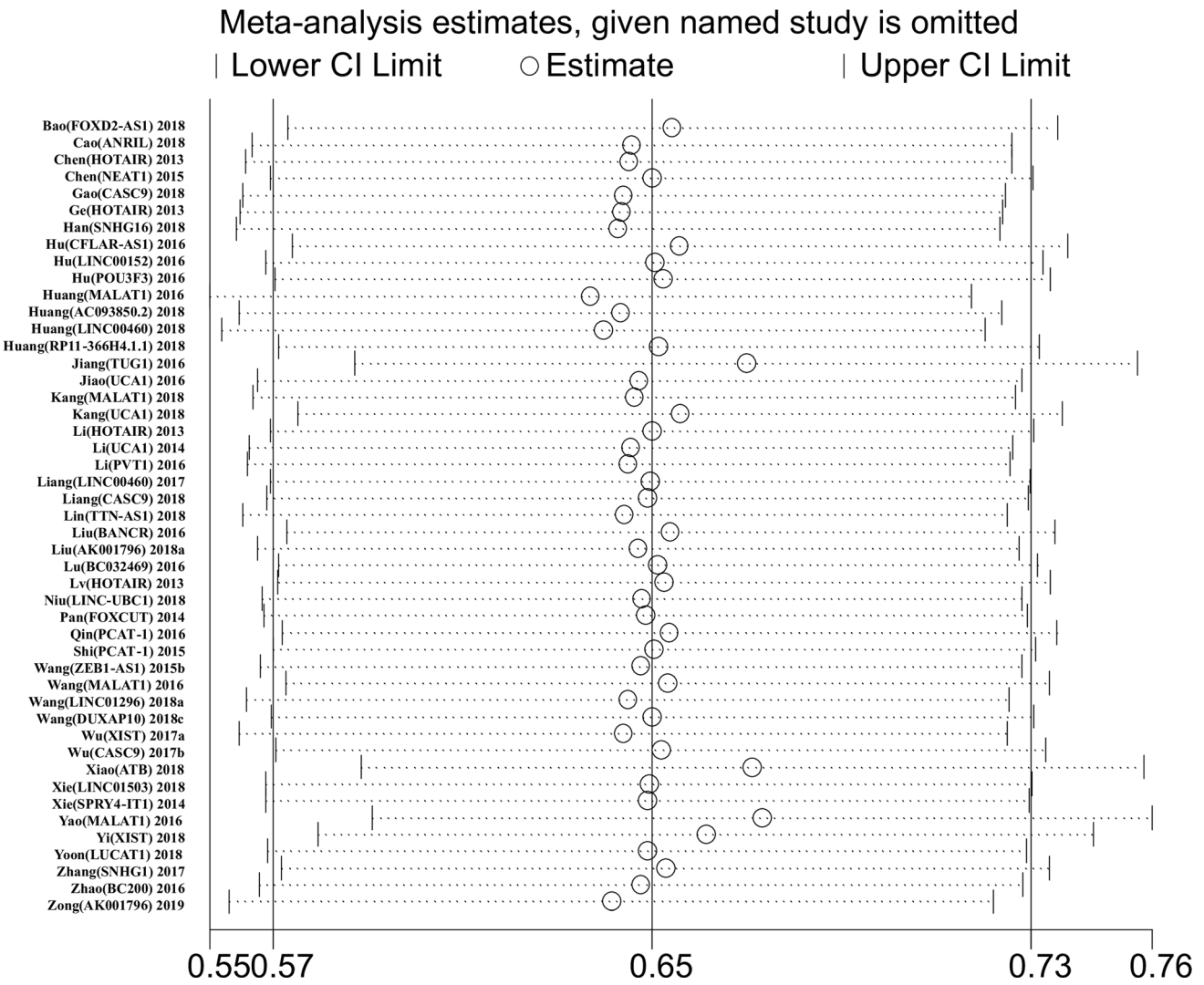

Figure 6. Sensitivity analyses of the association between the expression of oncogenic lncRNAs and the OS of oesophageal cancer patients. HR, hazard ratio; OS, overall survival.

Discussion

Over the past decade, accumulating studies have shown that lncRNAs are closely related to many diseases, especially tumours. The upregulation or downregulation of lncRNA affects many biological cell processes and ultimately affects the occurrence and development of tumours (Ma *et al*. 2013). There is increasing evidence that abnormal expression of lncRNAs is associated with clinical features of cancer patients. Recently, several meta-analyses have shown that lncRNAs have the potential to be diagnostic or prognostic markers in various cancers, such as lung, colorectal and ovarian cancers (Wang *et al*. 2017; Ning *et al*. 2018; Xiong *et al*. 2018). Concerning oesophageal cancer, Song *et al.* (2016) have shown that elevated HOTAIR lncRNA is indicative of a poor prognosis for patients with ESCC.

Additionally, Liu *et al.* (2018b) have demonstrated that high expression of PCAT-1 is related to poor prognosis in gastrointestinal cancers. In the review of Fanelli *et al.* (2018) they propose that lncRNAs could represent reliable biomarkers in gastroesophageal cancers. However, no study has conducted quantitative analyses to specifically assess the correlations among the expressions of multiple lncRNAs and oesophageal cancer. Based on several studies finding that dysregulation of lncRNAs may have an impact on the prognosis or clinical features of oesophageal cancer, we performed this systematic review and meta-analysis to assess the relationship of lncRNA expression with the prognosis and clinicopathology of oesophageal cancer patients.

In this systematic review and meta-analysis, a total of 51 articles comprising 41 lncRNAs were included in the final analysis. According to the precise expression patterns of lncRNAs in oesophageal cancer specimens, compared with those in normal controls, we divided lncRNAs into two groups: oncogenic lncRNAs and tumour-suppressor lncRNAs. Hence, we performed meta-analysis for these two

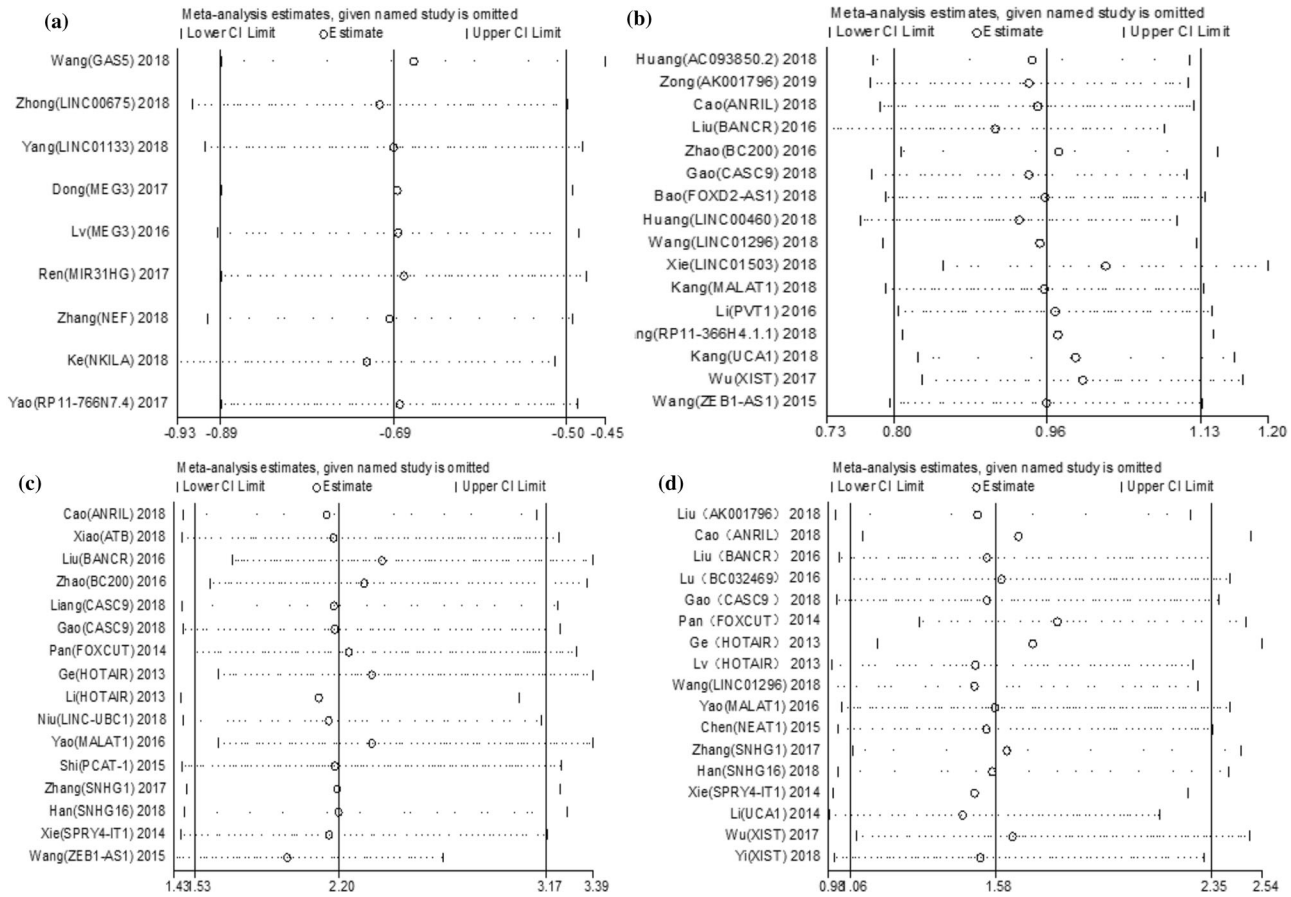

Figure 7. Sensitivity analyses of the studies: (a) the expression of tumour-suppressor lncRNAs and OS, (b) the expression of oncogenic lncRNAs and DFS, (c) the expression of oncogenic lncRNAs and T classification, and (d) the expression of oncogenic lncRNAs and differentiation. OS, overall survival; DFS, disease-free survival.

groups of lncRNAs to estimate the relationship between their expression and survival or clinical features.

Regarding the prognostic value, the results implied that high expression of oncogenic lncRNAs and downregulated tumour-suppressor lncRNAs exhibited a significant risk factor for OS and DFS, which suggested that aberrantly expressed lncRNAs may act as cancer prognostic biomarkers in oesophageal cancer. In the studies for OS, the most frequently evaluated lncRNAs included AK001796, CASC9, HOTAIR, LINC00460, MEG3, PCAT-1, UCA1, MALAT1 and XIST, which were considered independent risk factors for poor prognoses in oesophageal cancer patients. Among these lncRNAs, HOTAIR was reported in four studies and exhibited a favourable association with OS, which is in accordance with the previous study of Song *et al.* (2016). In addition, we observed that elevated MALAT1 and XIST were significantly associated with low OS. However, there were obvious heterogeneities in their analyses, which we may attribute to the differences in methodology, such as cut-off value, sample selection, and data-extraction method. Since this could confound our conclusion, further research is needed to verify the findings of our research.

Regarding the clinicopathological features, we found that oncogenic lncRNAs were significantly associated with tumour size, T classification, lymph node metastasis, TNM stage, and differentiation. Additionally, tumour-suppressor lncRNAs were significantly correlated with gender, T classification, lymph node metastasis, and TNM stage. Moreover, we then identified several relevant lncRNAs, which have often been studied. The assessment of similar lncRNAs with clinical features revealed that lncRNAs, especially AK001796, CASC9, HOTAIR, MALAT1, and UCA1 were reliable biomarkers for tumour size, T classification, lymph node metastasis, and TNM stage. However, this conclusion should be further verified due to the existence of heterogeneity in some of the included studies of our meta-analyses.

Through the above analysis, we demonstrated that the prognostic values of lncRNAs in oesophageal cancer, and altered lncRNAs were significantly associated with some clinicopathological parameters. Since most of the literature have been included from Chinese ESCC samples, this

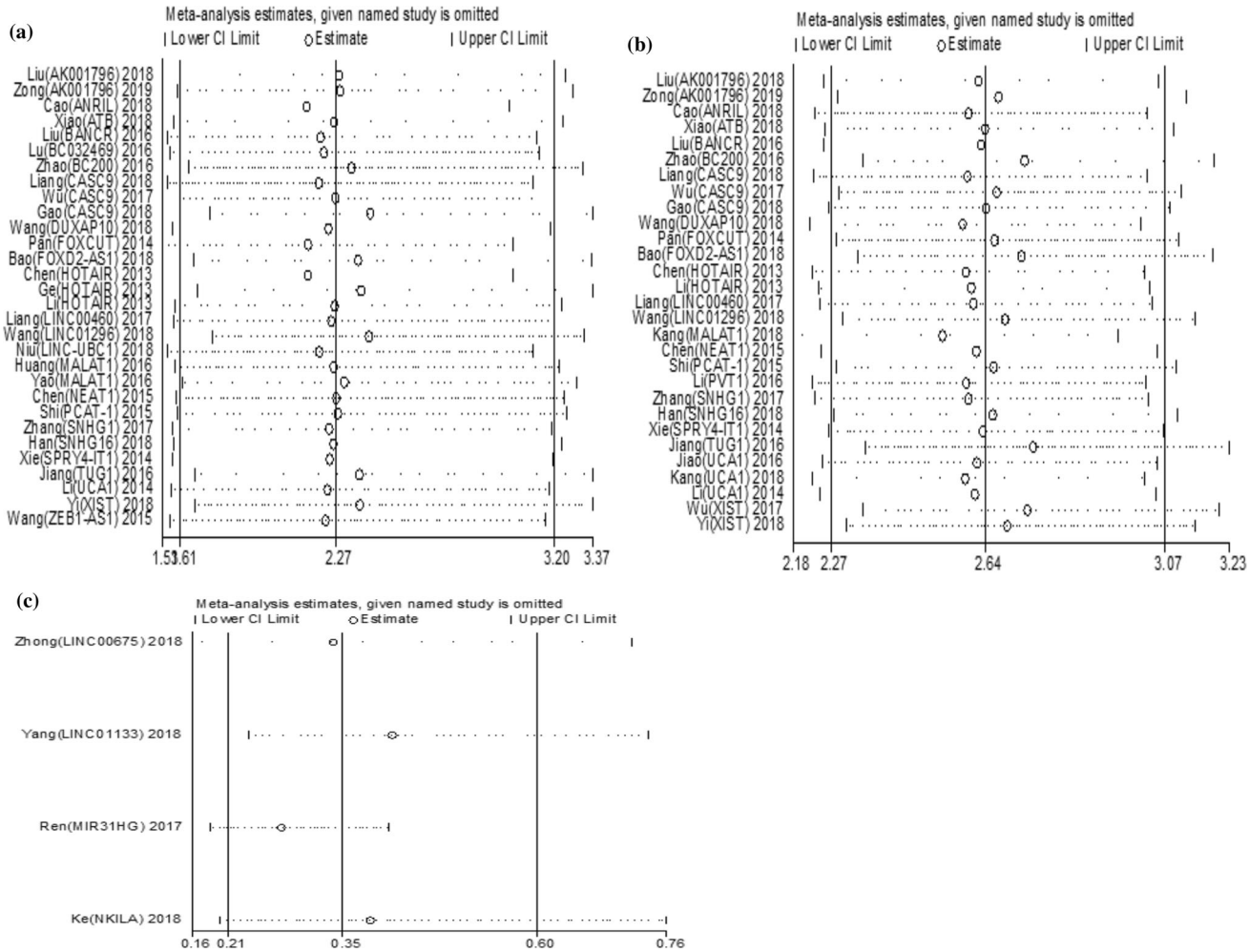

Figure 8. Sensitivity analyses of the studies: (a) the expression of oncogenic lncRNAs and lymph node metastasis, (b) the expression of oncogenic lncRNAs and TNM stage, (c) the expression of tumour-suppressor lncRNAs and TNM stage. TNM, tumour node metastasis.

systematic review and meta-analysis gets a good guiding significance for this part of the population. Among them, AK001796, CASC9, HOTAIR, MALAT1 and UCA1 were the most studied and were correlated not only with prognosis but also with clinicopathological features of oesophageal cancer. Numerous molecular mechanisms could account for this relationship. Liu *et al.* (2018a) confirmed AK001796 as an oncogenic lncRNA in ESCC due to its knockdown, inhibiting ESCC cell growth by regulating the expression of murine double minute 2 (MDM2)/p53 signalling on cell cycle and cell proliferation. LncRNA CASC9 promotes ESCC metastasis through upregulating laminin gamma 2 (LAMC2) expression by interacting with the CREB-binding protein (CBP) (Liang *et al*. 2018). The study by Ge *et al.* (2013) shown that HOTAIR facilitated the migration and invasion of ESCC cells; along with Polycomb Repressive Complex2 (PRC2), HOTAIR directly inhibited WNT inhibitory factor 1 (WIF-1) expression via promoting its histone H3 lysine-27 (H3K27) methylation in the promoter region and subsequently activating the Wnt/β-catenin signalling pathway. MALAT1 acts as an oncogene by post-transcriptional regulatory mechanisms and promotes malignant development of ESCC by targeting β-catenin via enhancer of zeste homolog 2 (Ezh2) (Wang *et al*. 2016). Additionally, UCA1 affects the stage of tumour cells through the PI3K/Akt signalling pathway to exert cancer-promoting effects on proliferation and apoptosis in various cancer types (Huang *et al*. 2014). Therefore, AK001796, CASC9, HOTAIR, MALAT1 and UCA1 were identified and were expected to be ideal biomarkers to diagnose and determine the prognosis of oesophageal cancer. Similar studies also revealed that HOTAIR, MALAT1 and UCA1 may serve as indicators for poor prognosis in digestive system malignancies, respectively (Sun *et al*. 2016; Abdeahad *et al*. 2019; Wang *et al*. 2019). Despite heterogeneity and publication bias in some studies, the sensitivity analysis and trim-and-fill method were used to evaluate the included studies. The conclusions did not

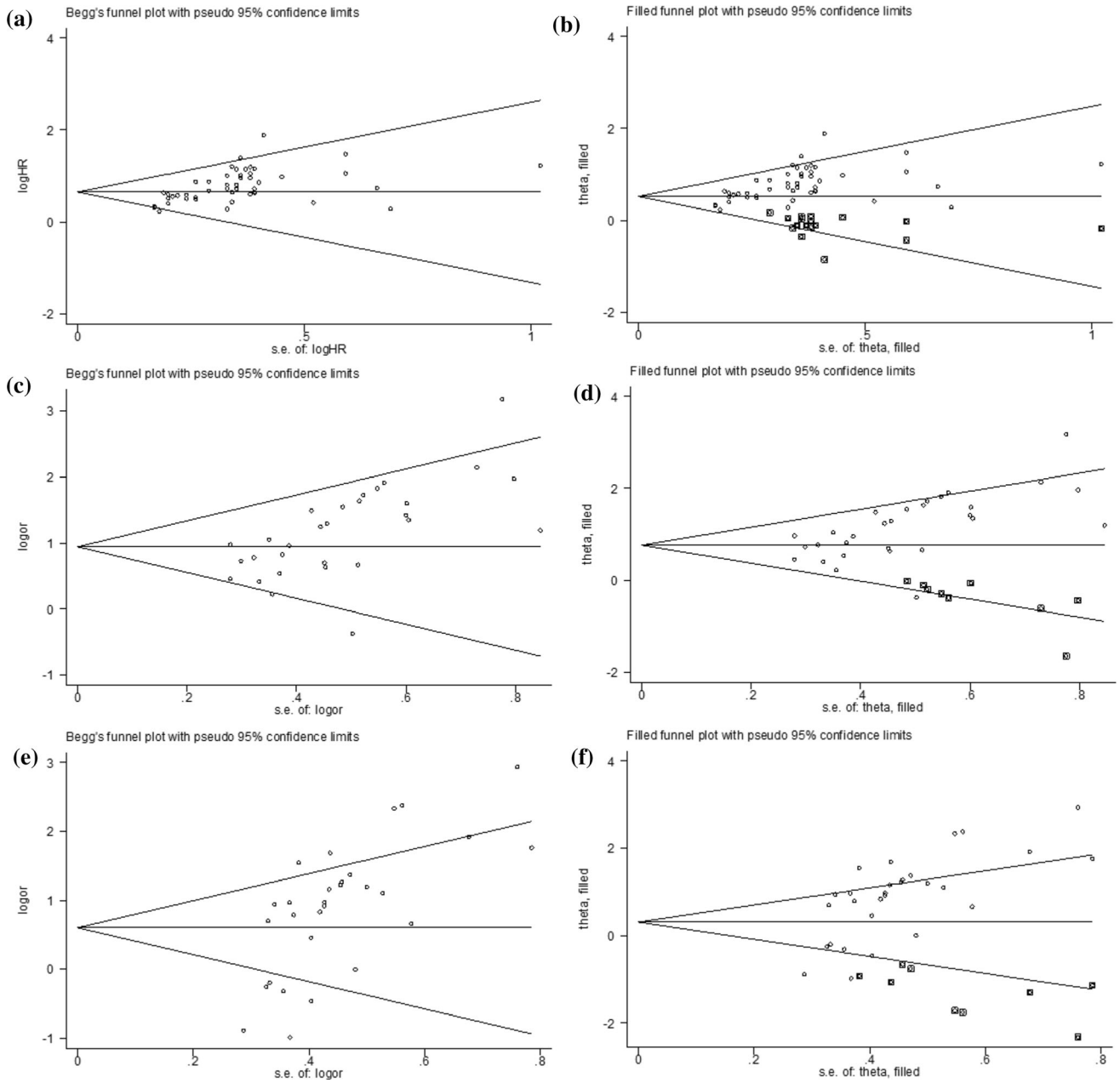

Figure 9. Begg funnel plot for publication bias and the corresponding filled funnel plot using the 'trim-and-fill' method. (a) Begg funnel plot for OS of oncogenic lncRNAs, (b) Trim-and-fill method for OS of oncogenic lncRNAs, (c) Begg funnel plot for TNM stage of oncogenic lncRNAs, (d) Trim-and-fill method for TNM stage of oncogenic lncRNAs, (e) Begg funnel plot for lymph node metastasis of oncogenic lncRNAs, and (f) Trim-and-fill method for lymph node metastasis of oncogenic lncRNAs. OS, overall survival; TNM, tumour node metastasis.

change significantly, which suggests that the outcomes of our analyses are credible.

Through our analysis, we demonstrate the prognostic value of lncRNAs in oesophageal cancer. Due to the complex interacting network of lncRNA and their diversity, the mechanism of lncRNA is not yet fully clarified, thus large-scale and high-quality studies should be carried out to select the most predictable lncRNA. Currently, it is suggested that the combination of several lncRNAs could obtain a more reliable prognostic value, which will contribute to clinical decision-making in the future (Fanelli *et al*. 2018). However, some limitations of this study should be considered. First, our conclusions could be influenced by heterogeneity in part of the results of this meta-analysis, as well as from unknown mechanisms in carcinogenesis. Second, part of the HRs and 95% CIs could not be directly obtained and were estimated

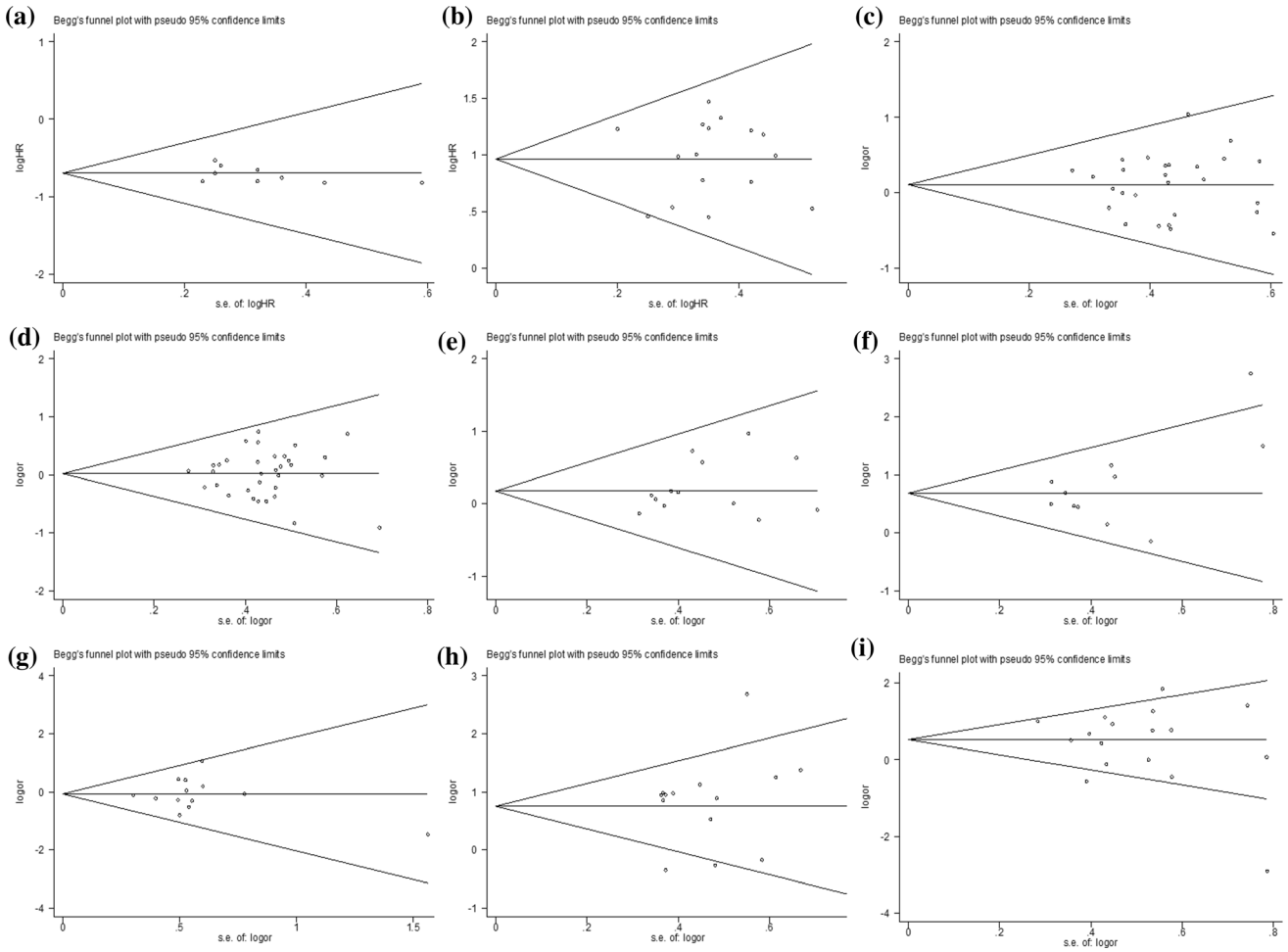

Figure 10. Begg funnel plot for publication bias. (a) OS of tumour-suppressor lncRNAs. (b) DFS of oncogenic lncRNAs. (c) Age (> 60 vs ≤ 60) of oncogenic lncRNAs. (d) Gender of oncogenic lncRNAs. (e) Smoking of oncogenic lncRNAs. (f) Size (cm) (> 4 vs ≤ 4) of oncogenic lncRNAs. (g) Location (lower/middle vs upper) of oncogenic lncRNAs. (h) T classification (T3/4 vs T1/2) of oncogenic lncRNAs and (i) differentiation (poor/moderate vs well) of oncogenic lncRNAs. OS, overall survival; DFS, disease-free survival.

by software, which may reduce the overall accuracy of the combined results. Third, most of the included studies were carried out in China, with only one study being performed in Korea. Hence, it is possible that our findings may not extend to other populations across the world. Finally, since there was just one study for each lncRNA for most cases, the prognostic value of each lncRNA may be overestimated.

Conclusions

In summary, our analysis showed that abnormal lncRNA expression profiles may serve as a promising indicator for prognostic evaluation of patients with oesophageal cancer, especially for Chinese. Among them, AK001796, CASC9, HOTAIR, MALAT1 and UCA1 were well candidates. The combination of these lncRNAs will contribute to clinical decision-making in the future.

The data used to support the findings of this study are included within the article.

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