The role of *Livin* expression in the clinicopathological features and prognosis of lung cancer: a meta-analysis

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Background: While the impact of *Livin* expression on patients with lung cancer was evaluated in previous studies, the results remained debatable. The relationship between *Livin* expression and clinicopathological features and prognosis in lung cancer was assessed in the present meta-analysis.

Methods: Web of Science, PubMed, Embase, Springer, Cochrane Library, China National Knowledge Internet database (CNKI), Wanfang database, Chinese VIP database and Chinese Biological Medical Database (CBM) were searched for relevant publications analyzing the role of *Livin* in prognosis and clinicopathological features of lung cancer before September 2020. The results were evaluated using pooled odds ratio (OR) and 95% confidence intervals (CIs) calculated by STATA 12.0 software.

Results: Twenty studies with a total of 1,395 patients were enrolled in this meta-analysis based on inclusion and exclusion criteria. *Livin* expression was significantly associated with smoking status (OR =2.51, 95% CI: 1.70–3.72, P<0.05), lung adenocarcinomas (LAC) (OR =2.16, 95% CI: 1.60–2.92, P<0.05), TNM stage (OR =2.49, 95% CI: 1.63–3.69, P<0.05) and poor differentiation (OR =2.04, 95% CI: 1.35–3.08, P<0.05). *Livin* expression was significantly related to metastasis (OR =4.22, 95% CI: 2.68–6.64, P<0.05) and lower 5-year overall survival (OR =4.23, 95% CI: 2.60–6.88, P<0.05) of patients with lung cancer.

Conclusions: The results of our study manifested that *Livin* expression was significantly related to smoking status, LAC, high TNM stage, poor differentiation, metastasis and 5-year overall survival rate, which indicated that *Livin* may be a potential biomarker for prognosis of lung cancer.

Keywords: Meta-analysis; *Livin*; lung cancer; overall survival; clinicopathological features

Introduction

As one of the most commonly diagnosed malignancies worldwide (1) that accounts for 33.3% of overall cancer mortality, lung cancer is the leading cause of cancer-related deaths (2). Despite recent advancements in treatment interventions, the prognosis of lung cancer patients has not been improved significantly (3). Therefore, it is important to understand the prognosis mechanism of lung cancer.

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Livin is located on human chromosome 20q13.3 and contains a BIR domain and a RING finger domain. It is part of the group of inhibitory apoptotic proteins (IAP) and was discovered in 2000/2001. Like other IAP members, the N-terminus of *Livin* comprises one or more tandem baculovirus IAP repeated sequence with anti-apoptotic effects (4). Specifically distributed in a variety of tumor tissues, *Livin* plays a role in the regulation of cell apoptosis through a variety of pathways. Apoptosis is known to be regulated by the following caspase-mediated pathways: the death receptor pathway, the mitochondrial pathway and the endoplasmic reticulum pathway (5). It has been reported that *Livin* is overexpressed in tumor tissues, and that the overexpression of *Livin* is closely related to tumor invasion, metastasis and treatment resistance (6,7). In recent years, many studies focusing on the correlation between *Livin* expression and various tumors, such as melanoma (8), breast cancer (9), colorectal cancer (10), gastric cancer (11), hepatocellular carcinoma (12) and osteosarcoma (13) have shown that high *Livin* expression is a predictive biomarker of tumor progression and that *Livin* expression profile is useful for providing prognostic information. Consistently, *Livin* expression in lung cancer tissues has been found to be significantly higher than that in adjacent normal lung tissues and lung benign lesions (14-16). Although many studies have reported that *Livin* expression is associated with poor prognosis of lung cancer, the prognostic value of *Livin* expression in lung cancer patients remains controversial. For example, Wu and colleagues (15) have demonstrated that *Livin* expression is associated with tumor size, differentiation, TNM stage and metastasis. However, Zhang and colleagues (16) have verified that *Livin* expression is correlated with metastasis, but not with gender, age, smoking status, tumor size, differentiation and TNM stage. In this meta-analysis, all available literature was systematically evaluated to explore the prognostic value of *Livin* expression in patients with lung cancer. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2835).

Methods

Search strategy and study selection

All relevant published papers before September 2020 were retrieved with no language restrictions from Web of Science, PubMed, Embase, Springer, Cochrane Library, China National Knowledge Internet database (CNKI), Wanfang database, Chinese VIP database and Chinese Biological Medical Database (CBM) by utilizing keywords "lung cancer, *Livin* and Inhibition apoptosis Protein (IAP)". Literature searching was conducted in detail by two investigators (Min Fei and Yingquan Luo).

Inclusion and exclusion criteria

Articles fulfilling the following criteria were included in our analysis:
  (I)   Patients being studied had lung cancer confirmed by pathological diagnosis;
  (II) Contained sufficient prognostic and clinicopathological parameters for analysis, including age, gender, tumor size, smoking status, pathological classification, TNM stage, differentiation, metastasis or overall survival;
  (III) Patients being studied had no preoperative treatments.
Articles with the following conditions were excluded:
  (I)   Not published as an original article or review, such as cell and animal experiments, case reports, communications, expert opinions, letters and editorials;
  (II) Contained no cut-off value;
  (III) Similar studies by the same author;
  (IV) Studies based on blood specimens;
  (V)   Patients being studied had lung cancer not diagnosed by a biopsy.

Data extraction

The eligibility of all retrieved documents was assessed and relevant information was independently recorded the relevant information by Min Fei and Qian Yan. To eliminate discrepancy, the extracted data, which included authors, publication year, *Livin* detection method, cut-off definition, age, sex, TNM stage, differentiation, metastasis, smoking status and 5-year overall survival, were checked by Jian Zhou. The corresponding authors were consulted for further information when required.

Quality evaluation

The quality of the included literature was assessed using Newcastle-Ottawa Scale (NOS) (17). All included studies had a quality assessment score of ≥7 stars. Quality
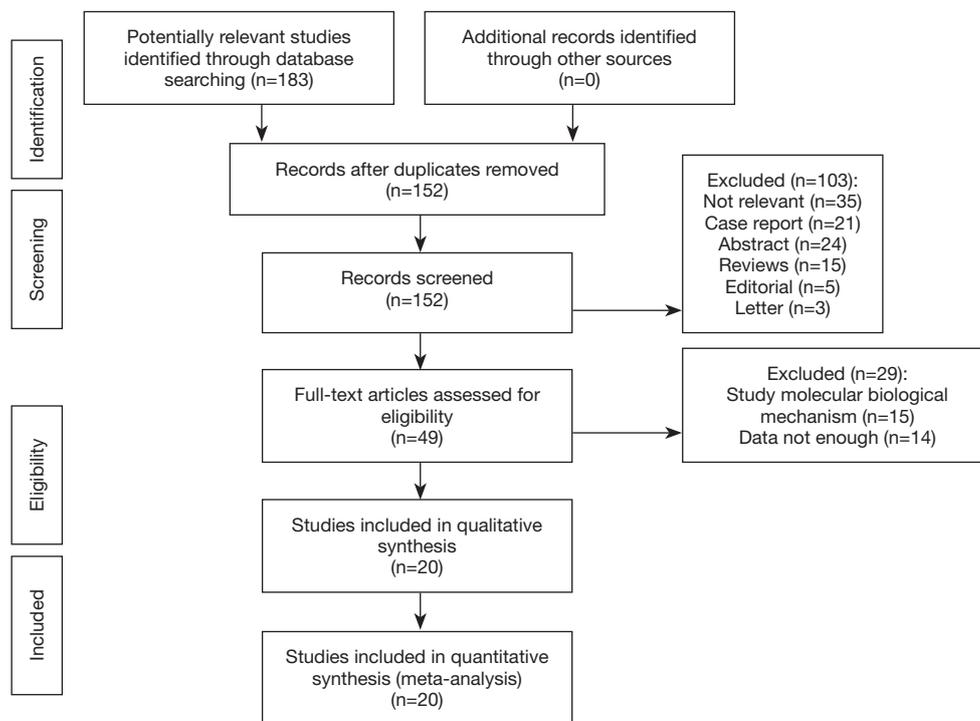
Figure 1 The flow diagram of literature screening. From: Moher D, Liberati A, Tetzlaff J, *et al.* Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009;6:e1000097.

evaluation was independently conducted by Min Fei and Qian Yan. Discrepancies were resolved through discussion.

Statistical analyses

Statistical analyses were performed using STATA 12.0 software (Stata Corp LP, College Station, TX, USA) with P<0.05 considered to be statistically significant. Heterogeneity evaluation of included studies was conducted. In the absence of significant heterogeneity, the fixed-effect model (FEM) was selected for analysis (18). Otherwise, the random-effects model (REM) was used to lower the effect of heterogeneity (19). To analyze the prognostic value of *Livin* on lung cancer, OR with corresponding 95% confidence interval (95% CI) was calculated. The results presented in the form of forest plots were considered to be relevant when the overall 95% CI horizontal line of all enrolled studies did not intersect the invalid vertical line, but fell on the right side of the invalid line instead.

In addition, the stability of conclusion was appraised using sensitivity analysis through sequential removal of individual studies. To identify publication bias, Egger and Begg funnel plots were used. Symmetrical funnel plots or P>0.05 (Egger test) suggest the absence of publication

bias, while asymmetric funnel plots or P<0.05 (Egger test) indicate the presence of publication bias (20).

Results

Basic information of studies

A total of 183 articles were initially retrieved from various databases. There were still 151 articles after the removal of duplicating studies, following which 49 studies remained after the elimination of comments, case reports, meta-analyses and unrelated studies. Next, with further review, 15 studies that were limited to molecular biological mechanism investigation, and another 14 studies that did not offer sufficient data (OR and 95% CI) were excluded. Finally, 20 studies (14-16,21-37) with a total of 1,395 patients were incorporated in this meta-analysis (*Figure 1*). The basic information of studies was shown in *Table 1* and *Table 2*. Number of included patients in each study ranged from 30 to 216 (median 123). The expression of *Livin* was detected using immunohistochemistry (IHC) in 19 studies, and western blot (WB) in 1 study. Most of these eligible articles selected Asian populations as the research object.

Table 1 The basic characteristics of the included literature.

Ref	Study	Year	Cases	Livin expression (P/N)	Age (median)	Method	NOS	Inclusion period	Preoperative treatment	Livin cut-off
(14)	Chai et al.	2019	108	56/52	NR	SP	8	2011–2017	No	A1*B>3
(15)	Wu et al.	2017	70	41/29	64.3	IHC	8	2012–2014	No	A2+B≥2
(21)	Liang et al.	2017	90	52/38	NR	IHC	8	2004–2009	No	(A3+B)/2≥4
(22)	Chai et al.	2017	152	45/107	NR	SP	7	2008–2016	No	A1*B>3
(23)	Zhang et al.	2017	86	53/33	61.5	IHC	7	2006–2011	No	A4*B≥6
(16)	Zhang et al.	2016	45	31/14	58.5	SP	7	2013–2014	No	A3*B>1
(24)	Su et al.	2016	216	137/79	60	SP	8	2007–2014	No	A5*B>3
(25)	Wang et al.	2014	88	51/37	NR	IHC	7	2007–2008	No	A3*B≥3
(26)	Wang et al.	2013	40	32/8	NR	SP	7	2010–2011	No	B≥1
(27)	Chen et al.	2012	50	38/12	59	WB	7	2010–2012	No	C
(28)	Xiang et al.	2012	54	36/18	NR	SP	7	2010–2011	No	A3*B≥1
(29)	Han et al.	2012	40	26/14	62	IHC	7	2006–2008	No	A3*B≥2
(30)	Yang et al.	2012	52	24/28	NR	SP	7	2004–2006	No	A1*B>3
(31)	Zhang et al.	2012	50	44/6	62	IHC	7	2001–2005	No	A3*B≥1
(32)	Zhuang et al.	2012	46	31/15	59	IHC	8	2010–2011	No	A3≥1
(33)	Yan et al.	2011	40	28/12	NR	IHC	7	2009–2011	No	A1≥2
(34)	Li et al.	2010	43	29/14	56.3	SP	7	2007–2009	No	A1≥2
(35)	Sun et al.	2008	30	17/13	54.5	SP	7	2003–2006	No	A3+B≥1
(36)	Gao et al.	2008	48	15/33	56	SABC	7	2006–2007	No	A1≥2
(37)	Tao et al.	2007	40	19/21	58	SABC	7	2003–2004	No	A1≥2

A, positive cell percentage; A1, scored 1 (≤10%), 2 (10–50%), 3 (50–75%), 4 (>75%); A2 scored 1 (≤25%), 2 (26–50%), 3 (51–75%), 4 (>75%); A3, scored 1 (≤5%), 2 (6–25%), 3 (25–50%), 4 (>51%); A4, scored 1 (≤70%), 2 (71–80%), 3 (81–90%), 4 (>90%); A5, scored 1 (≤10%), 2 (10-30%), 3 (30–70%), 4 (>70%); B, staining intensity; scored 0 (absence of staining), 1 (weak staining), 2 (moderate staining), 3 (strong staining); C, Gray value of Livin protein expression divided by gray value of GAPDH in Western blot >0.01. IHC, immunohistochemistry; SP, streptavidin peroxidase; SABC, streptavidin-biotin complex; WB, Western Blot; NR, no report; P, positive; N, negative.

The NOS scores of included studies were ≥7 (with a mean value of 7.25).

Correlation between Livin expression and clinicopathological features

As indicated in *Figure 2*, there was no significant heterogeneity detected all included studies ($I^2 \leq 50\%$). Consequently, fixed effect model was used to assess the association between *Livin* expression and lung cancer clinicopathological features. Our meta-analysis revealed that *Livin* expression was found to be unrelated to age (OR =0.99, 95% CI: 0.73–1.34, P> 0.05; *Figure 2A*), gender (OR =0.97, 95% CI: 0.64–1.47, P>0.05; *Figure 2B*) and tumor size (OR =0.94, 95% CI: 0.50–1.78, P>0.05; *Figure 2C*). Conversely, *Livin* expression was found to be significantly associated statistically with smoking status (OR =2.51, 95% CI: 1.70–3.72, P<0.05; *Figure 2D*), LAC (OR =2.16, 95% CI: 1.60–2.92, P<0.05; *Figure 2E*), high TNM stage (OR =2.49, 95% CI: 1.69–3.69, P<0.05; *Figure 2F*) and poor differentiation (OR =2.04, 95% CI: 1.35–3.08, P<0.05; *Figure 2G*). In particular, *Livin* expression was revealed to be significantly correlated with metastasis (OR =4.22, 95% CI: 2.68–6.64, P<0.05; *Figure 2H*) and reduced 5-year overall

Table 2 The included items from the enrolled studies

Ref	Study	Age (years)		Gender		Tumor size (cm)		Smoking		Pathological classification		TNM stage		Differentiation degree		Metastasis		Overall survival	
		>60	<60	Male	Female	>3	<3	Yes	No	LAC	SqCLC	I+II	III+IV	Poor	Good	Yes	No	Death	Survival
(14)	Chai et al.	60	48	–	–	–	–	60	48	34	74	–	–	–	–	–	–	–	–
(15)	Wu et al.	–	–	–	–	–	–	–	–	–	–	38	32	27	43	29	41	57	13
(21)	Liang et al.	49	41	49	41	–	–	–	–	–	–	55	35	8	82	–	–	63	27
(22)	Chai et al.	80	72	–	–	–	–	64	88	–	–	–	–	–	–	–	–	–	–
(23)	Zhang et al.	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
(16)	Zhang et al.	21	24	28	17	34	11	25	20	–	–	28	17	11	34	26	19	28	17
(24)	Su et al.	–	–	–	–	–	–	–	–	113	103	–	–	–	–	–	–	–	–
(25)	Wang et al.	28	60	–	–	–	–	–	–	–	–	48	40	–	–	–	–	34	54
(26)	Wang et al.	21	19	–	–	–	–	–	–	27	13	–	–	–	–	–	–	–	–
(27)	Chen et al.	12	38	31	19	26	24	–	–	32	18	–	–	14	36	–	–	–	–
(28)	Xiang et al.	29	25	33	21	–	–	–	–	24	30	27	27	29	25	36	18	–	–
(29)	Han et al.	21	19	–	–	29	11	30	10	–	–	–	–	–	–	21	19	–	–
(30)	Yang et al.	–	–	–	–	–	–	28	24	22	30	–	–	15	37	19	33	–	–
(31)	Zhang et al.	29	21	36	14	–	–	31	19	31	19	–	–	22	28	–	–	–	–
(32)	Zhuang et al.	–	–	–	–	–	–	–	–	25	21	–	–	–	–	32	14	–	–
(33)	Yan et al.	32	8	25	15	25	15	–	–	10	30	–	–	11	29	21	19	–	–
(34)	Li et al.	24	19	26	17	–	–	–	–	23	20	27	16	13	30	–	–	–	–
(35)	Sun et al.	11	19	22	8	19	11	–	–	–	–	22	8	–	–	–	–	–	–
(36)	Gao et al.	–	–	–	–	–	–	–	–	26	22	37	11	18	30	–	–	–	–
(37)	Tao et al.	–	–	24	16	–	–	–	–	–	–	–	–	–	–	25	15	–	–

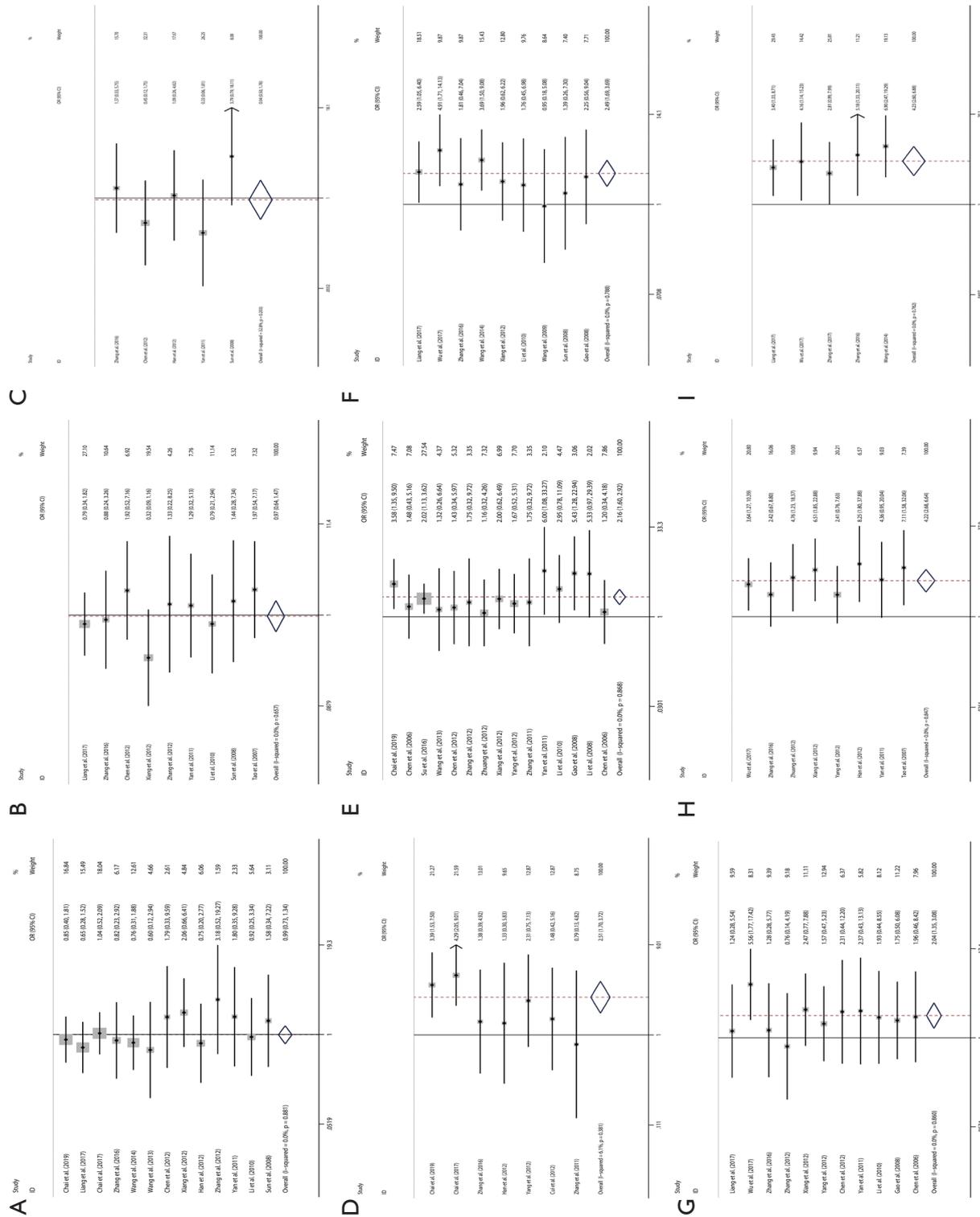LAC, lung adenocarcinomas; SqCLC, squamous-cell lung carcinoma.

Figure 2 Forest plots showing the association between Livin expression and lung cancer. (A) Age; (B) gender; (C) tumor size; (D) smoking status; (E) pathological classification; (F) TNM stage; (G) differentiation; (H) metastasis; (I) overall survival.
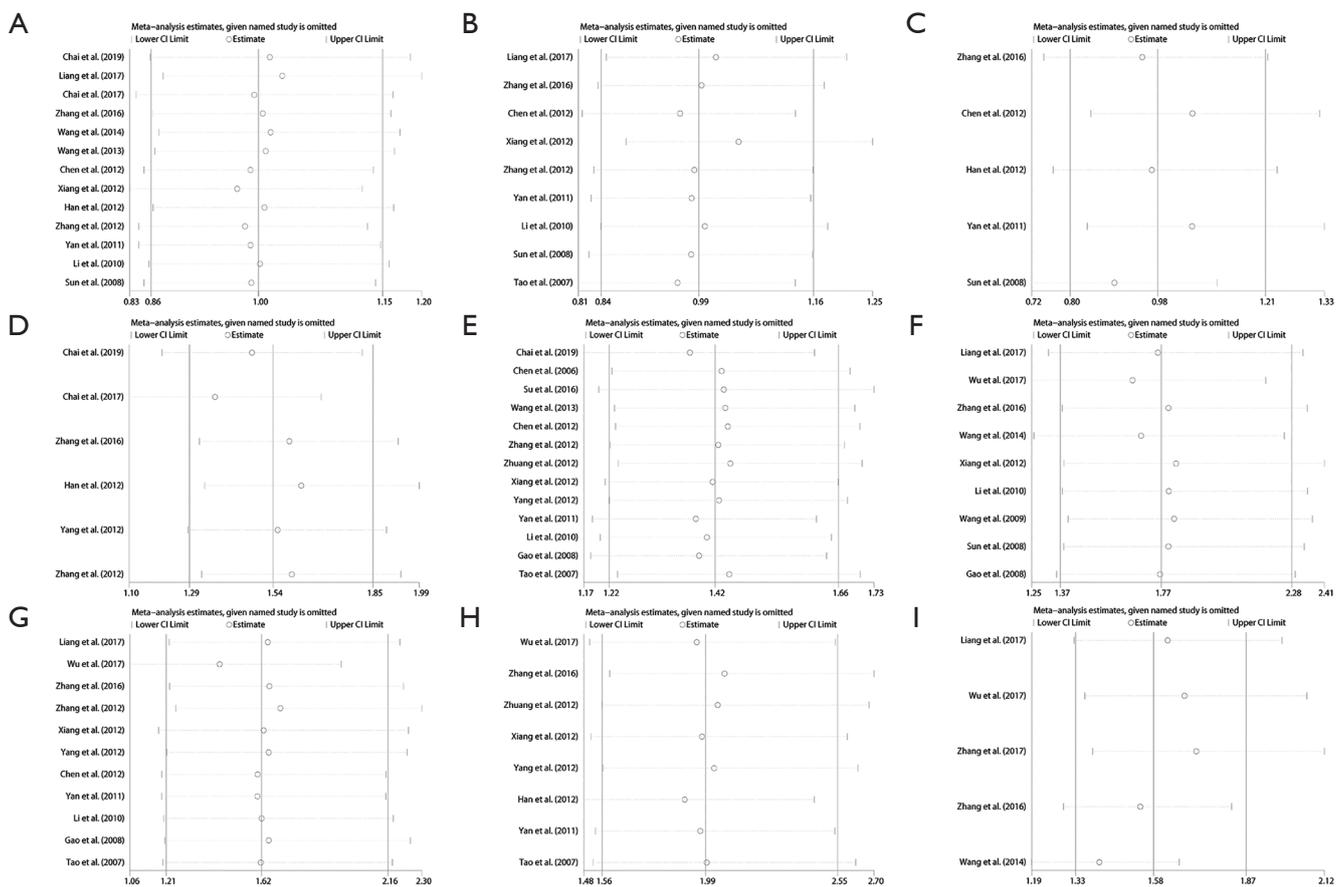
Figure 3 Sensitivity analysis on the association of Livin expression in lung cancer patients. (A) Age; (B) gender; (C) tumor size; (D) smoking status; (E) pathological classification; (F) TNM stage; (G) differentiation; (H) metastasis; (I) overall survival.

survival (OR =4.23, 95% CI: 2.60–6.88, P<0.05; *Figure 2I*). The combined OR suggested that *Livin* expression was significantly associated with metastasis and overall survival in lung cancer patients.

Sensitivity analyses

The stability of our results was estimated by sensitivity analysis by excluding one study after another. Our analysis showed that there were no significant changes in OR and heterogeneity, and that our findings were not impacted by any study, which was an indication of the credibility of our conclusion (*Figure 3*).

Publication bias

As shown in *Figure 4*, substantially symmetrical funnel plots (A,B,C,E,F,G,H,I) indicated the absence of significant

publication bias (P>0.05) in the association between *Livin* expression and age, gender, tumor size, pathological classification, TNM stage, differentiation, metastasis and overall survival. However, asymmetrical funnel plot (D) indicated the presence of publication bias (P<0.05) in the association between *Livin* positive expression and smoking status. In order to make sure that all included articles conformed to the inclusion criteria and were eligible, the association between smoking status and lung cancer outlined in the included studies was carefully reviewed. Studies with desired results that were published more easily may contribute to publication bias, so the conclusion from these studies should be treated with caution.

Discussion

Lung cancer is a disease with poor prognosis characterized by the highest rates of mortality and morbidity among
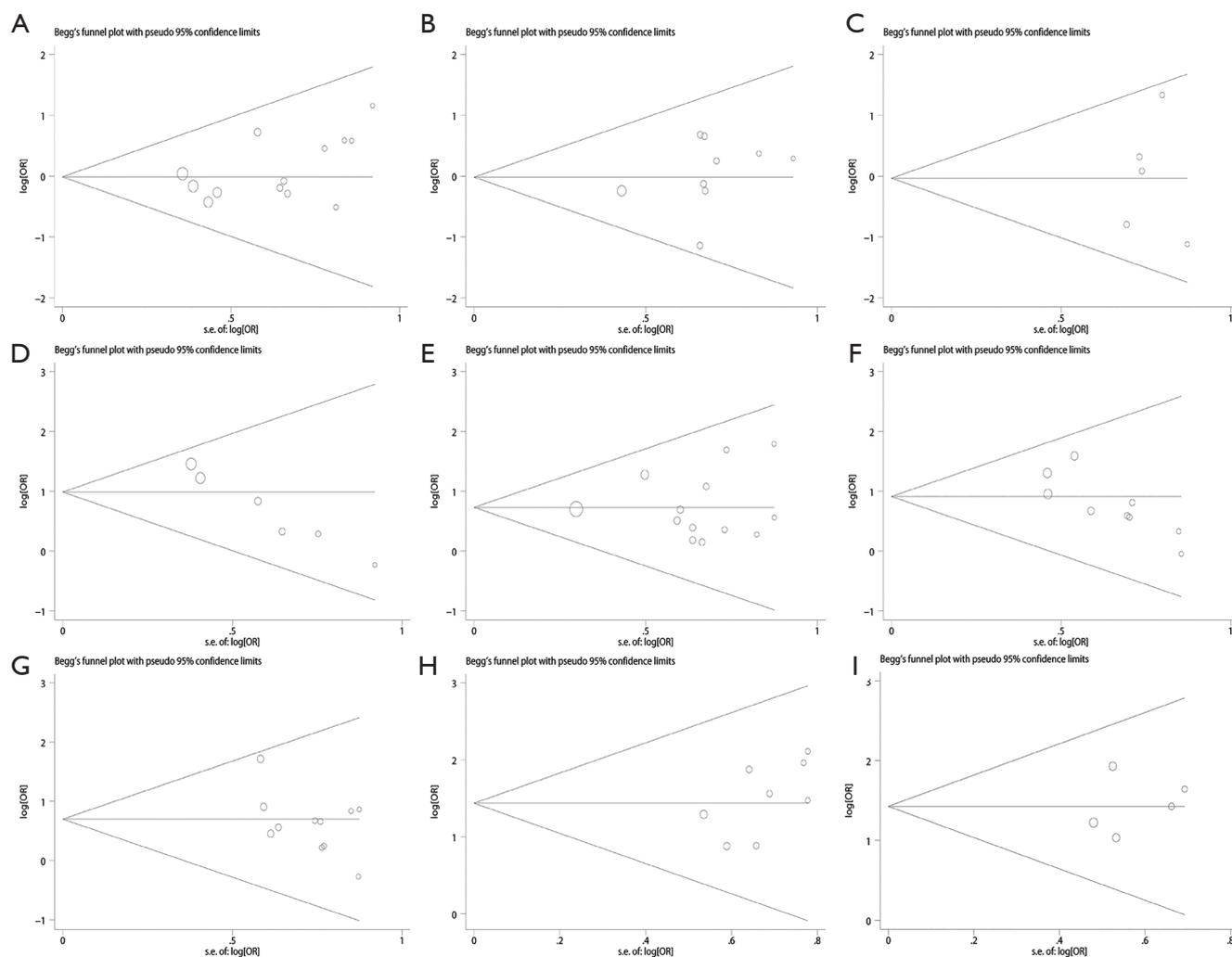
Figure 4 Funnel plots assessing possible publication bias for the relation between Livin and lung cancer. (A) Age; (B) gender; (C) tumor size; (D) smoking status; (E) pathological classification; (F) TNM stage; (G) differentiation; (H) metastasis; (I) overall survival.

other cancer types (38,39), and represents a significant clinical challenge. The efficacy of traditional lung cancer treatment interventions, including surgery, radiotherapy and chemotherapy has been unsatisfactory (40). Accordingly, in order to improve the life quality of patients, effective treatment strategies that can decrease tumor recurrence and treatment resistance have gained much research attention in recent years, especially targeted therapy and immunotherapy (41,42). Nevertheless, the mortality rate has not been improved significantly (43). Hence, the discovery of novel prognostic biomarkers and targets is urgently in need to improve treatment efficacy.

Similar to other solid tumors, lung cancer is resistant to

apoptosis (44). Therefore, targeting of apoptotic pathway represents a promising method in the identification of normal cells and in the selective killing of cancer cells. Highly expressed IAP in malignant tumors has been shown to tightly control the level of cell apoptosis (45). As a member of the IAP family, *Livin* inhibits tumor cells from undergoing apoptosis, leading to infinite cell proliferation and metastasis (46). *Livin* plays an apoptotic role by binding with caspases (5) or by activating the TAK1/JNK1 pathway (47). Previous studies have found that *Livin* is overexpressed in lung cancer, and that overexpression of *Livin* is strongly associated with lung cancer prognosis and diagnosis. This meta-analysis systematically evaluated the

effect of *Livin* on the prognostic outcome of lung cancer patients.

Here, we demonstrated significant association between *Livin* expression and smoking status (OR =2.51, 95% CI: 1.70–3.72, P<0.05), LAC (OR =2.16, 95% CI: 1.60–2.92, P<0.05), high TNM stage (OR =2.49, 95% CI: 1.69–3.69, P<0.05), and poor differentiation (OR =2.04, 95% CI: 1.35–3.08, P<0.05). Furthermore, *Livin* expression was found to be associated with tumor metastasis (OR =4.22, 95% CI: 2.68–6.64, P<0.05), and 5-year survival rate (OR =4.23, 95% CI: 2.60–6.88, P<0.05). However, *Livin* was shown to be unrelated to age, gender and tumor size. In our assessment of outcome stability by sensitivity analyses, when a single study was removed, there were no significant changes of pooled OR, indicating that the results were consolidated. Significant association between *Livin* expression and lung cancer prognosis may be attributed to the binding between the BIR domain of *Livin* and caspase-3, 7 and 9, a process which inhibits caspase activity and blocks the apoptosis signal transduction of tumor cells (48). Alternatively, *Livin* may bind TAB1 to mediate the activation of JNK1 through TAB1 activation, a process which inhibits cell apoptosis (49) and subsequently causes tumor cell to metastasis and invasiveness. Clearly, *Livin* is a promising biomarker of lung cancer clinicopathologic features.

This study has a number of limitations. Firstly, the cut-off values for *Livin* expression were based on positive cell percentage and staining intensity. The cut-off values were not exactly the same, which may contribute to study bias. According to previous studies, although different cut-off values may not affect the final conclusion (50,51), the conclusion should be treated with caution. Secondly, studies with desired results were more easily released, and publication bias was found for the association between *Livin* expression and smoking status. Thirdly, most subjects in all eligible literature were from Asia. Therefore, a detailed study with larger sample size is essential to comprehensively appraise the prognostic value of *Livin* in lung cancer.

Conclusions

Taken together, for the first time, we discuss the association between *Livin* expression and lung cancer. Our meta-analysis suggests that *Livin* expression is significantly associated with smoking status and LAC (P<0.05), indicating that *Livin* may be a potential diagnostic biomarker of LAC.

Moreover, our results show that *Livin* expression is associated with high TNM stage, poor differentiation,

metastasis and low 5-year overall survival of lung cancer (P<0.05), suggesting that *Livin* may be a candidate prognostic biomarker for lung cancer. Due to the limitations, more rigorous and well-designed investigations are necessary to better estimate the prognostic role of *Livin* in lung cancer.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2835

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2835). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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