The impact of LncRNA dysregulation on clinicopathology and survival of pancreatic cancer: a systematic review and meta-analysis (PRISMA compliant)

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Abstract

Purpose: An increasing number of studies have reported a significant association between long non-coding RNAs (lncRNAs) dysregulation and pancreatic cancers. In the present study, we aimed to gather articles to evaluate the prognostic value of long non-coding RNA in pancreatic cancer.

Experimental design: We systematically searched all eligible articles from databases of PubMed, Web of Science, and Scopus to meta-analysis of published articles and screen association of multiple lncRNAs expression with clinicopathology and/or survival of pancreatic cancer. The pooled hazard ratios (HRs) and their 95% confidence intervals (95% CIs) were used to analysis of overall survival, disease-free survival and progression-free survival were measured with a fixed or random effects model.

Results: A total of 39 articles were included in the present meta-analysis. Our results showed that dysregulation of lncRNAs were linked to overall survival (39 studies, 4736 patients HR = 0.41, 95% CI 0.25 ± 0.58, random-effects in pancreatic cancer. Moreover, altered lncRNAs were also contributed to progression-free survival (8 studies, 1180 patients HR: 1.88, 95% CI (1.35–2.62) and disease-free survival (2 studies, 285 patients, HR: 6.07, 95% CI 1.28–28.78). In addition, our findings revealed the association between dysregulated RNAs and clinicopathological features in this type of cancer.

Conclusions: In conclusion, dysregulated lncRNAs could be served as promising biomarkers for diagnosis and prognosis of pancreatic cancer.

Keywords: Pancreatic cancer, LncRNAs, Overall survival, Disease-free survival, Progression-free survival, Clinicopathological features

Introduction

Pancreatic cancer (PC) is a worldwide challenging cancer characterized by poor prognosis, ranking as one of the most lethal human malignancy. The 5-year overall survival (OS) of PC patients is less than 5%, with median survival time between 3–6 months. However, progresses in early detection, surgical techniques and treatments strategies including chemotherapy and targeted therapy...
have resulted in better improvements in management of PC patients, dismal prognosis of the disease has not improved over years [1].

So, it is an urgent need to identify novel diagnostic and prognostic biomarkers associated with pancreatic cancer. In recently decades Long noncoding RNAs (lncRNAs) as type of RNA that do not encode proteins with a length of >200 nt and crucial role in several different biological processes in diverse human diseases such as development and progression of various cancers [2, 3]. Also lncRNAs play a critical physiological role in apoptosis, metastasis, invasion, migration and cell proliferation in different cancers [4, 5]. The dysregulation of different IncRNAs is reported to be potential prognostic indicators in multiple human cancers [6–9].

Previous meta-analysis has showed that high lncRNAs expression could be used as potential prognostic markers among Asian bladder cancer patients [10]. Also dysregulation of IncRNAs expression were significantly associated with clinicopathology and survival of breast cancer patients [11]. Also similar results have been reported in ovarian, cervical and prostate cancer [12–14]. In pancreatic cancer lncRNAs are identified in body fluids and are extensively found in the blood, saliva, urine, even pancreatic fluid and exosomes from tumors. And were done analysis about effect of potential of IncRNAs in the diagnosis and treatment of PC but it is not comprehensive and complete. Due to absence comprehensive article that summarize and conclude information in this field, in this study we systematically update analysis of related articles to confirm the potential prognostic value of IncRNAs in patients with pancreatic cancer. Furthermore, the association between IncRNAs and clinicopathological characteristics from published articles was investigated to update analysis rather than 2017 [15].

Materials and methods
This systematic review and meta-analysis was done based on the standard guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (S1 Checklist) [16, 17].

Statistical analysis
HRs and 95% CIs were obtained from studies or calculated from Kaplan–Meier survival curves using Engauge Digitizer version 4.1 [19] to calculated the overall pooled HR and 95% CI for the association between lncRNAs and survival in PC. The pooled HR was calculated using fixed-effect model, or random-effect model in cases of
high between-study heterogeneity. Heterogeneity was assessed by the Cochrane Q-test, using I^2 statistic. Heterogeneity was considered significant as P < 0.1 or I^2 ≥ 50%. Due to high heterogeneity in results, we also were done subgroup analysis based on molecular mechanisms, ethnicity and the expression level of lncRNAs in PC. The funnel plot asymmetry test as well as the Eggers’ regression test were used to assess publication bias. Stata version 13.0 (StataCorp LP, College Station, TX, USA) was applied for the whole meta-analysis.

Results
As shown in Fig. 1, 336 articles were found in initial searches from PubMed, Web of Science and Scopus databases. After removing duplicate articles and screening by the title and abstracts, 191 full-text articles remained for further review. Of these, 152 studies were excluded due to insufficient data. Finally, a total of 39 studies which met our eligibility criteria were included in the current meta-analysis.

Study characteristics
A total of 39 eligible studies involving 4736 patients diagnosed with pancreatic cancer were included in this meta-analysis. These studies were published between 2014 and 2020. Of these, 38 studies were conducted in China [20–54], and only one study in Turkey [55]. Samples were collected from tumor tissues in most studies, except three studies extracted them from blood [49], plasma [26] and serum [56]. All of these articles showed association of dysregulation of lncRNAs expression with different survival outcomes in PC. Overall survival (OS) [22–32, 34–37, 39–49, 52–59], progression free survival (PFS) [39, 56], disease specific survival (DSS) [33], and disease free survival (DFS) [36] were investigated to evaluate survival outcomes. Expression of the lncRNAs was measured by use of quantitative real-time polymerase chain reaction (qRT-PCR) using GAPDH [21, 24, 26–29, 32–35, 37, 39, 40, 42, 43, 48, 50–53, 55, 57], β-actin [23, 29–31, 45–47], RNU6B [25, 38, 41, 44], U6 [20, 22, 56] and U7 as reference genes for endogenous normalization [51].
We assessed quality of included studies using the NOS tool. Given values ranged from 4 to 8 stars based of the number of parameter that analyzed in articles: 3 study was poor quality score and awarded 4 stars [40, 57, 58], 5 study achieved 6 stars and medium quality [25, 35, 45, 46, 48], 13 studies gained 7 stars [22, 24, 30, 32, 36–38, 44, 50, 55, 59–61] and 18 articles awarded 8 stars with high quality [21, 23, 26–29, 31, 33, 34, 36, 39, 41, 43, 49, 51–53, 56, 62]. The characteristics of the included studies are summarized in Table 1.

**Association between lncRNAs expression and OS**
We conducted the present meta-analysis to figure out the value of aberrantly expressed lncRNAs in OS of 4691 PC patients from 39 studies. Statistical analyses represented significant association between the expression level of dysregulated lncRNAs and poor OS of PC patients in the relevant studies (HR = 0.41, 95% CI 0.25 ± 0.58, I² = 80.5%, P = 0.000, random-effects) as well as this effect in these studies analyzed by univariate analysis (HR = 0.19, 95% CI – 0.156 ± 0.535, I² = 0.0% P = 0.457) and multivariate analysis (HR = 0.262, 95% CI 0.207 ± 0.317, I² = 81.7% P = 0.000) (Fig. 2), while a significant heterogeneity existed between studies (I² = 80.5%, P = 0.000). Due to the presence of obvious heterogeneity, we performed subgroup analyses based on the ethnicity, molecular mechanisms and the expression level of lncRNAs in PC patients but similarly, heterogeneity was also assessed in our stratified analyses and there did not significant changes in heterogeneity after our subgrouping (Table 2).

**Association between lncRNAs expression and DFS**
The prognostic value of lncRNAs in DFS was explored in two studies including 260 patients. LncRNAs expression were significantly linked with DFS (HR = 0.51, 95% CI 0.19 ± 0.83, P = 0.00, fixed-effects; Fig. 3), while no significant heterogeneity was observed in these studies.

**Correlation of lncRNAs with clinicopathological characteristics of pancreatic cancer**
Further stratified study grouped by clinicopathologic features exhibited that OS of patients with PC was markedly associated with gender (univariate analysis: HR = 0.04, 95% CI – 0.07 to 0.16, P = 0.344; multivariate analysis: HR = 0.01, 95% CI – 0.14 to 0.17, P = 0.868), Distance metastasis (univariate analysis: HR = 0.02, 95% CI – 0.53 to 0.57, P = 0; multivariate analysis: HR = 0.08, 95% CI 0.02 to 0.13, P = 0.0) Node metastasis (univariate analysis: HR = – 0.12, 95% CI – 0.34 to 0.11, P = 0; multivariate analysis: HR = 0.20, 95% CI 0.12 to 0.28, P = 0.0) and other clinicopathologic factors demonstrated in Table 3.

**Publication bias**
The Funnel plot analysis was used to display asymmetry among the OS, DFS, distant metastasis, differentiation, gender, neural and prineural invasion, LNM, TNM and Stage (Fig. 4). Besides, no evidence of statistically significant publication bias observed by applying the Bigger tests and the Funnel plot analysis in combined prognostic studies.

**Sensitivity analysis**
Sensitivity analysis was performed to discover the influence of the individual study on the pooled results by removing one single study from the overall pooled analysis. The results depicted that no individual study significantly changed the pooled HRs (Fig. 5) demonstrating that our analysis was relatively stable and reliable. Also sensitivity analysis showed that no individual study had great influence on final results of our meta-analysis.

**Discussion**
Despite many advances in cancer research and treatment, the insidious onset of symptoms and extremely poor diagnosis of PC has still remained a controversial issue. The 5-year survival rate was estimated lower than 25% resulting in worse clinical outcomes in PC [63]. Imaging methods including, computed tomography, magnetic resonance imaging and endoscopic ultrasound are currently available methods used in the diagnosis and prognosis of PC. Moreover, a number of serum biomarkers, such as circulating tumor DNA and certain microRNAs are used in these regard [64, 65]. However, clinical application oh these methods in pancreatic cancer has been limited by their low specificity and sensitivity. Therefore, finding novel biomarkers are of most importance for early detection and more accurate treatment of this disease [66].

Over two past decades, numerous studies have focused on the potential roles of lncRNAs as contributors in various cell biological processes including gene and protein expression patterns. A growing body of evidence has verified the association between aberrant expressions of multiple lncRNAs with clinical outcomes for cancer patients. Notably, diagnostic significance of different lncRNAs profiling in digestive system tumors has been proved in numerous publications [67, 68]. So, in order to investigate the promising prognostic biomarkers for PC, as a high-degree malignancy of digestive system, the present systematic meta- analysis was performed to provide evidences to confirm potential association between altered lncRNAs and poor survival outcomes in PC. In this study, the information of 4736 PC patients was extracted from 39 studies conducted between 2014–2020. Our results represented altered lncRNAs is significantly linked with...
Table 1  Main features of all included studies for diagnosis and prognosis

| Id | lncRNAs     | Author           | Year | Country | Duration of research | Number of Patients (high/low) | Sum of Patients | Expression in Tumor | Internal reference | Method       | Cut-off Quality Score | Follow-up (Month) | Sample | Outcome |
|----|-------------|------------------|------|---------|----------------------|------------------------------|-----------------|---------------------|-------------------|--------------|---------------------|-------------------|--------|---------|
| 1  | TMED11P     | Zhenfei Zhu      | 2016 | China   | 2007–2013            | 21/57                        | 78              | Down-regulation     | U6                | qRT-PCR      | Median 7           | 60                | Tissue | OS      |
| 2  | LOC389641   | Shangyou Zheng   | 2015 | China   | 2008–2015            | 53/53                        | 106             | Up-regulation       | GAPDH             | qRT-PCR      | Median 8           | 72                | Tissue | OS      |
| 6  | HMlincRNA717| X.L.SUN          | 2016 | China   | 2005–2011            | 74/76                        | 150             | Down-regulation     | U6                | qRT-PCR      | Median 7           | 70                | Tissue | OS      |
| 7  | ATB         | Shihbin Qu       | 2015 | China   | No                   | 75/75                        | 150             | Down-regulation     | β-Actin           | qRT-PCR      | Median 8           | 60                | Tissue | OS      |
| 8  | CCDC26      | Wei Peng         | 2016 | China   | 2011–2015            | 20/20                        | 40              | Up-regulation       | GAPDH             | qRT-PCR      | Median 7           | 60                | Tissue | OS      |
| 9  | uc.345      | Chao Liu         | 2016 | China   | 2011–2013            | 68/35                        | 103             | Up-regulation       | RNU6B             | qRT-PCR      | Median 6           | 50                | Tissue | OS      |
| 11 | Linc-pint   | Le Li            | 2016 | China   | 2008–2011            | 28/23                        | 51              | Down-regulation     | GAPDH             | qRT-PCR      | Median 8           | 60                | Plasma | OS      |
| 17 | AFAP1-AS1   | Xue-Liang Fu     | 2016 | China   | 2012–2014            | 40/40                        | 80              | Up-regulation       | GAPDH             | qRT-PCR      | Median 8           | 50–60             | Tissue | OS      |
| 17 | UCA1        | Xue-Liang Fu     | 2016 | China   | 2012–2014            | 40/40                        | 80              | Down-regulation     | GAPDH             | qRT-PCR      | Median 8           | 50–60             | Tissue | OS      |
| 17 | ENSG00000218510| Xue-Liang Fu   | 2016 | China   | 2012–2014            | 40/40                        | 80              | Down-regulation     | GAPDH             | qRT-PCR      | Median 8           | 50–60             | Tissue | OS      |
| 17 | CRNDE       | Xue-Liang Fu     | 2016 | China   | 2012–2014            | 40/40                        | 80              | Up-regulation       | GAPDH             | qRT-PCR      | Median 8           | 50–60             | Tissue | OS      |
| 17 | NR_036488   | Xue-Liang Fu     | 2016 | China   | 2012–2014            | 40/40                        | 80              | Up-regulation       | GAPDH             | qRT-PCR      | Median 8           | 50–60             | Tissue | OS      |
| 17 | ENSG00000244649| Xue-Liang Fu   | 2016 | China   | 2012–2014            | 40/40                        | 80              | Up-regulation       | GAPDH             | qRT-PCR      | Median 8           | 50–60             | Tissue | OS      |
| 18 | UCA1        | Ping Chen        | 2016 | China   | 2006–2009            | 64/64                        | 128             | Up-regulation       | GAPDH             | qRT-PCR      | Mean 8            | 60                | Tissue | OS      |
| 23 | HOTTIP-005  | Yingxue Wang     | 2015 | China   | 2006–2014            | 118/26                       | 144             | Up-regulation       | GAPDH & β-Actin  | qRT-PCR      | Median 8           | 60                | Tissue | OS      |
| 23 | XLOC_006390 | Yingxue Wang     | 2015 | China   | 2006–2014            | 110/34                       | 144             | Up-regulation       | GAPDH & β-Actin  | qRT-PCR      | Median 8           | 60                | Tissue | OS      |
| 23 | RP11-567G11.1| Yingxue Wang     | 2015 | China   | 2006–2014            | 96/48                        | 144             | Up-regulation       | GAPDH & β-Actin  | qRT-PCR      | Median 8           | 60                | Tissue | OS      |
| 24 | MALAT1      | Er-Jun Pang      | 2014 | China   | No                   | 63/63                        | 126             | Up-regulation       | β-Actin           | qRT-PCR      | Median 7           | 60                | Tissue | OS      |
| 38 | ENST00000480739| Y-W Sun         | 2014 | China   | No                   | 20/15                        | 35              | Down-regulation     | β-Actin           | qRT-PCR      | Median 8           | 30                | Tissue | OS      |
| Id | lncRNAs   | Author          | Year   | Country | Duration of research | Number of Patients (high/low) | Sum of Patients | Expression in Tumor | Internal reference | Method       | Cut-off Quality | Follow-up (Month) | Sample | Outcome |
|----|-----------|-----------------|--------|---------|----------------------|-------------------------------|-----------------|---------------------|-------------------|--------------|-----------------|-----------------|---------|---------|
| 39 | HULC      | Wei Peng        | 2014   | China   | 2006–2010            | 212/92                        | 304             | Up-regulation       | GAPDH             | qRT-PCR      | No              | 7               | 60      | Tissue OS |
| 40 | MALAT1    | Jiang-Hua Liu   | 2014   | China   | 2010–2011            | 26/19                         | 45              | Up-regulation       | GAPDH             | qRT-PCR      | Mean            | 8               | 40      | Tissue DSS |
| 41 | BC008363  | Jiao Li         | 2014   | China   | 2009–2010            | 17/13                         | 30              | Down-regulation     | GAPDH             | qRT-PCR      | Median          | 8               | 30      | Tissue OS |
| 42 | LOC285194 | Yue-Chao Ding   | 2014   | China   | 2004–2009            | 45/40                         | 85              | Down-regulation     | GAPDH             | qRT-PCR      | Mean            | 6               | 60      | Tissue    |
| 50 | C/EBPb    | Chen-Song Huang | 2017   | China   | 2008–2013            | 54/29                         | 83              | Up-regulation       | NO                | qRT-PCR      | Mean            | 7               | 100     | Tissue OS |
| 50 | LINC01133 | Chen-Song Huang | 2018   | China   | 2015–2017            | 88/89                         | 177             | Up-regulation       | NO                | qRT-PCR      | Mean            | 8               | 100     | Tissue OS |
| 59 | DUXAP8    | Yifan Lian      | 2018   | China   | 2007–2012            | 29/29                         | 58              | Down-regulation     | GAPDH             | qRT-PCR      | Median          | 7               | 60      | Tissue OS |
| 67 | CASC2     | Yaquen Yu       | 2017   | China   | No                   | 56/54                         | 110             | Down-regulated      | RNU6B             | qRT-PCR      | Median          | 7               | 48      | Tissue OS |
| 76 | DANC2     | Lei Chen        | 2018   | China   | No                   | 86/120                        | 206             | Up-regulation       | GAPDH             | qRT-PCR      | Mean            | 8               | 72      | Tissue OS |
| 83 | LINC00946 | Wan-Xin Peng    | 2019   | China   | No                   | 46/131                        | 177             | Up-regulation       | GAPDH             | qRT-PCR      | No              | 4               | 80      | Tissue OS |
| 103| XIST      | Wei Wei         | 2017   | China   | No                   | 32/32                         | 64              | Up-regulation       | RNU6B             | qRT-PCR      | Median          | 8               | 30      | Tissue OS |
| 109| ABHD11-AS1| X. QIAO         | 2018   | China   | 2010–2013            | 72/75                         | 147             | Up-regulation       | GAPDH             | qRT-PCR      | No              | 8               | 60      | Tissue OS |
| 112| DLEU1     | Song Gao        | 2018   | China   | 2012–2017            | 39/23                         | 62              | Up-regulation       | GAPDH             | qRT-PCR      | Median          | 8               | 60      | Tissue OS |
| 114| FEZF1-AS1 | Zheng-Lin Ou    | 2019   | China   | No                   | 28/28                         | 56              | Up-regulation       | RNU6B             | qRT-PCR      | Median          | 7               | 60      | Tissue OS |
| 125| Inc-PCTST | Yandong Wang    | 2018   | China   | 2015–2016            | 24/24                         | 48              | Down-regulated      | β-Actin           | qRT-PCR      | Median          | 6               | 20      | Tissue OS |
| 126| MACC1-AS1 | Chen Qi         | 2019   | China   | No                   | 49/49                         | 98              | Up-regulation       | β-Actin           | qRT-PCR      | No              | 6               | 100     | Tissue OS |
| 136| XLOC_000647| Hao Hu          | 2018   | China   | 2015–2016            | 24/24                         | 48              | Down-regulated      | β-Actin           | qRT-PCR      | Median          | 7               | 20      | Tissue OS |
| 144| HOTTIP    | Ozkan Balcin    | 2018   | Turkey  | 2006–2014            | 61/39                         | 100             | Up-regulation       | GAPDH             | Q.qRT-PCR     | No              | 7               | 46      | Tissue OS |
### Table 1 (continued)

| Id  | IncRNAs     | Author             | Year | Country | Duration of research | Number of Patients (high/low) | Sum of Patients | Expression in Tumor | Internal reference | Method | Cut-off | Quality Score | Follow-up (Month) | Sample | Outcome |
|-----|-------------|--------------------|------|---------|----------------------|------------------------------|-----------------|---------------------|-------------------|--------|---------|--------------|------------------|--------|----------|
| 152 | MSC-AS1     | Yunpeng Sun        | 2019 | China   | No                   | 23/22                        | 45              | Up-regulation       | GAPDH             | qRT-PCR | Median 6 | 36   | Tissue OS |
| 159 | Sox2ot      | Zhonghu Li         | 2018 | China   | 2012–2016            | 31/30                        | 61              | Up-regulation       | NO                | qRT-PCR | Median 8 | 50   | Blood OS |
| 162 | SPRY4-IT1   | Yue Yao            | 2018 | China   | 2011–2012            | 26/20                        | 46              | Up-regulation       | GAPDH             | qRT-PCR | No      | 7    | Tissue OS |
| 169 | GSTM3TV2    | Guangbing Xiong    | 2019 | China   | No                   | 100/80                       | 180             | Up-regulation       | GAPDH & U7        | qRT-PCR | No      | 8    | Tissue OS |
| 172 | SNHG15      | X.-B. GUO          | 2018 | China   | No                   | 82/89                        | 171             | Up-regulation       | GAPDH             | qRT-PCR | Median 8 | 60   | Tissue OS |
| 185 | HULC        | Zheng-Lin Ou       | 2019 | China   | 2012–2014            | NO                           | 60              | Up-regulation       | GAPDH             | qRT-PCR | Median 8 | 40   | Tissue OS |
| 186 | IncRNA-UFC1 | Peng Liu           | 2019 | China   | 2012–2015            | 19/29                        | 48              | Up-regulation       | U6                | qRT-PCR | Mean    | 8    | Serum OS  |
| 187 | FOKP4-AS1   | Xiao-Guang Liu     | 2019 | China   | No                   | NO                           | 112             | Up-regulation       | NO                | NO      | Median 4 | 50   | Tissue OS |
| 188 | PLACT1      | Xiaofan Ren        | 2020 | China   | 2008–2018            | 83/83                        | 166             | Up-regulation       | NO                | NO      | Median 7 | 60   | Tissue OS |
| 189 | ENSG00000254041.1 | Bo Chen             | 2020 | China   | 2013–2014            | 35/35                        | 70              | Up-regulation       | GAPDH             | qRT-PCR | Median 4 | 50   | Tissue OS |

OS overall survival, RFS recurrence-free survival, DFS disease free survival, DSS disease specific survival, PFS prognosis free survival, TMED11P trafficking protein 11, pseudogene, IncRNA-ATB long non-coding RNA-activated by transforming growth factor β, AFAP1-AS1 actin filament-associated protein 1 antisense RNA 1, UCA1 urothelial carcinoma associated 1 RNA, CRNDE Colorectal neoplasia differentially expressed, HOT1P HOXA transcript at the distal tip, Miat1 metastasis associated lung adenocarcinoma transcript 1, CASC2 Cancer susceptibility candidate 2, DANCR Differentiation antagonizing non-protein coding RNA, XIST X-inactive specific transcript, SNHG16 small nucleolar RNA host gene 16, HULC Highly up-regulated in liver cancer, qRT-PCR quantitative real-time polymerase chain reaction, NA not applicable
OS decline. Notably, we updated and augmented the reported results of meta-analysis carried out in 2017 with regard to the association between dysregulated lncRNAs and survival outcomes in PC [15].

In the current study, we assessed the prognostic role of different lncRNAs and their association with clinicopathological characteristics of PC. We found significant relation between altered expression of lncRNAs with poor OS period of PC (HR = 1.52, with 95% CI 1.04–2.22, and P = 0.031 in univariate analysis; HR = 1.55, with 95% CI 1.19–2.02, and P = 0.001 in multivariate analysis), suggesting that lncRNAs expression profile can be a prognostic biomarker of PC [14, 63, 69]. Correspondingly, our stratified analysis evidenced that the clinicopathological factors as Gender, distance metastasis, node metastasis, differentiation, neural and prineural invasion, vascular invasion, TNM, Stage were remarkably contributed with OS of PC.
Moreover, large degree of heterogeneities among included studies were observed inspiring us to search its main causes from different aspects [70]. In this regard, we did subgroup analyses based on the ethnicity, molecular mechanisms and the expression level of lncRNAs in PC patients, however heterogeneity was also showed in our stratified analyses without any significant effect on heterogeneity.

Totally it could be concluded that lncRNAs expression profiling may serve as a helpful diagnostic and prognostic biomarker in of PC. So investigating the suitable single or panel of lncRNAs should be the focus of future studies [71–73].

However, it should be noted that there are several limitations in our meta-analysis including (1) The small sample sizes of the diagnostic meta-analysis as well as the limited clinical relevance of our results; (2) large heterogeneity in our analyses; (3) The HRs and 95% CIs from some of articles could not be directly obtained and were estimated by software, which may decline the accuracy of our results.
### Table 3  Summary of the subgroup analyses of the association between OS and clinicopathological features in PC

|                               | Included studies | HR (95% CI) | P value | I2 (%) | Effect model | Included studies | HR (95% CI) | P value | I2 (%) | Effect model |
|-------------------------------|------------------|-------------|---------|--------|--------------|------------------|-------------|---------|--------|--------------|
| Gender                        | 23               | 0.01 (−0.14, 0.17) | 0.868 | 0.0% | Fixed | 10 | 0.04 (−0.07, 0.16) | 0.344 | 8.5% | Fixed |
| Distance metastasis           | 20               | 0.08 (0.02, 0.13) | 0.000 | 74.7% | Random | 1 | 0.02 (−0.53, 0.57) | 0.000 | 0% | – |
| Node metastasis               | 29               | 0.20 (0.12, 0.28) | 0.000 | 65.9% | Random | 5 | −0.12 (−0.34, 0.11) | 0.000 | 83.0% | Random |
| Differentiation               | 20               | 0.34 (0.22, 0.46) | 0.145 | 25.4% | Fixed | 12 | 0.15 (0.01, 0.29) | 0.921 | 0% | Fixed |
| Neural and prineural invasion | 13               | 0.24 (0.11, 0.36) | 0.002 | 61.1% | Random | 11 | 0.01 (−0.01, 0.02) | 0.178 | 28.0% | Fixed |
| Vascular invasion             | 9                | 0.36 (0.17, 0.56) | 0.047 | 50.9% | Random | 2 | 0.24 (−0.14, 0.62) | 0.339 | 0% | Fixed |
| TNM                           | 30               | 0.07 (−0.15, 0.29) | 0.000 | 76.4% | Random | – | – | – | – |
| Stage                         | 15               | 0.10 (−0.00, 0.19) | 0.000 | 69.8% | Random | 4 | 0.48 (0.26, 0.70) | 0.004 | 77.9% | Random |

HR hazard ratio, 95% CI confidence intervals
overall accuracy of the pooled effects. Totally, results from our study did not fully show the real clinical significance of lncRNA signature in PC, and in order to obtain a decisive conclusion, further comprehensive meta-analyses are needed to confirm the strong
association between the expression pattern of lncRNAs and outcome of PC patients.

Conclusion
Altogether, our meta-analysis was updated and completed pervious reports to survey the prognostic value of lncRNAs and their association with clinical features of PC patients. Despite some above mentioned limitations, the present study revealed that lncRNAs could be used as potential prognostic markers for PC. However, more high quality and large-scale studies are still needed to validate the clinical utilities of lncRNAs in management of PC.

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Authors' contributions
ESH, HHK and MAZ provided direction and guidance throughout the preparation of this manuscript. AS and AN conducted the literature and drafted the manuscript. HN and FI reviewed the manuscript and made significant revisions on the drafts. All authors read and approved the final manuscript.

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Declarations
Ethics approval and consent to participate
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Consent for publication
Not applicable.

Competing interests
The authors declared that they have no competing interests.

Fig. 5 Sensitivity analysis of the effect of individual studies on the pooled HRs for lncRNAs expression and OS of PC patients
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