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Prognostic value of pretreatment serum lactate dehydrogenase level in pancreatic cancer patients

A meta-analysis of 18 observational studies

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Abstract

Background: Several studies were conducted to investigate the prognostic value of pretreatment serum lactate dehydrogenase (LDH) level in pancreatic cancer (PC), but the results were inconsistent. This study aims to comprehensively assess the prognostic value of pretreatment serum LDH level in PC patients by combining the data of the published literatures on this topic.

Methods: Embase, PubMed, and Web of Science were completely retrieved until June, 2018. The observational studies focusing on the prognostic value of pretreatment serum LDH level in PC patients were eligible. STATA version 12.0 was used to undertake the statistical analysis.

Results: Eighteen studies with a total of 3345 patients were included in this meta-analysis. The meta-analysis was conducted to generate pooled hazard ratios (HRs) and 95% confidence interval (CI) for overall survival (OS). Our analysis results suggested that high serum LDH level predicted worse OS (HR 1.57, 95% CI 1.30–1.90, $P < .001$) in PC patients. Moreover, for patients with advanced PC, the prognostic relevance of pretreatment serum LDH level not only existed in those receiving palliative chemotherapy (HR 1.72, 95% CI 1.35–2.18, $P < .001$), but also in those who were precluded from chemotherapy (HR 1.91, 95% CI 1.4219–2.58, $P < .001$).

Conclusion: The meta-analysis results demonstrated that pretreatment serum LDH level is closely associated with OS, and it may be a useful biomarker for assessing the prognosis of PC patients.

Abbreviations: ATP = adenosine triphosphate, CCR = colorectal cancer, CI = confidence interval, HR = hazard ratio, LDH = lactate dehydrogenase, NA = not available, NOS = Newcastle-Ottawa Scale, OS = overall survival, PC = pancreatic cancer, PFS = progression-free survival, TKIs = tyrosine kinase inhibitors.

Keywords: chemotherapy, lactate dehydrogenase, meta-analysis, overall survival, pancreatic cancer

1. Introduction

Pancreatic cancer (PC) is 1 of the most fatal malignant tumors, still ranked as the fourth leading cause of cancer-associated deaths.[1] Most of the patients are diagnosed with advanced status due to lacking of specific symptoms at the early stage of disease, and thereby these patients have a poor median overall survival (OS) less than 1 year, and their 5-year survival is just around 5%.[2] More disappointing thing is that, even in patients with curatively resectable PC, the overall 5-year survival rate remains unfavorable, ranging from 18% to 24%.[3] Therefore, it is essential and urgent to identify novel biomarkers for predicting prognosis of PC patients, which provide more precise guidance to individualized treatment.

The transformation of normal cells into cancer cells and abnormal proliferation of cancer cells always result in aberrant serum enzyme synthesis, and this phenomenon even could be detected before the changes in tumor morphology, or the appearance of clinical manifestations.[4] Hence, the roles of abnormal serum enzymes in cancers are sparking growing interest and concern recently. Lactate dehydrogenase (LDH)—a common serum enzyme—participates in the conversion of pyruvate into lactate, and plays a critical role in maintaining the continued glycolysis, which is closely associated with tumor initiation and progression.[5–7] It has been considered that LDH may act as an indicator for tumor burden and aggressiveness because it is required for tumor maintenance.[5,6] Moreover, there is evidence supporting that serum LDH levels increased in many cancers and was associated with prognosis of various cancer patients, including PC.[8–18]

Although numerous researchers have also investigated the prognostic value of the pretreatment serum LDH level in PC, a consensus conclusion is still pending, and this may partially be attributed to a limited number of cases in individual studies, which is related to low statistical power. Therefore, to avoid the bias caused by small sample size-associated weak statistical power, herein, we conducted this meta-analysis of the published literatures to systematically evaluate the value of pretreatment serum LDH level as prognostic predictor in patients with PC.

2. Methods

2.1. Identification of eligible studies

We searched PubMed, EMBASE, and Web of science for eligible articles published from inception to June, 2018. The following searching terms were used: (LDH OR lactate dehydrogenase OR lactic dehydrogenase) AND (pancreatic cancer OR pancreatic

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Table 1

Main characteristics and results of the eligible studies for evaluation of overall survival.

Study	Country	Median age	Sample size	Disease status	Treatment	Cut-off (U/L)	Follow-up (mos)	HR (95% CI)	NOS
Faloppi et al, 2016[10]	Italy	NR	132	Initial metastatic/locally advanced	Chemotherapy	NR	12	1.77 (1.20–2.62), K	7
Faloppi et al, 2016[10]	Italy	NR	71	Initial metastatic/locally advanced	Chemotherapy	NR	NA	2.26 (1.34–3.79), K	6
Gao et al, 2018[19]	China	65 (41–87)	136	Initial metastatic/locally advanced	Chemotherapy	245	NA	0.69 (0.30–1.58), M	7
Hashimoto et al, 2009[20]	Japan	NR	326	Initial metastatic/recurrence	Chemotherapy	220	NA	1.82 (1.37–2.38), M	7
Ji et al, 2016[21]	China	61 (26–81)	185	Curatively resectable	Resection	240	NA	1.64 (1.12–2.39), M	7
Ouyang et al, 2017[22]	China	NR	189	Initial metastatic	Palliative care	250	35.2	2.02 (1.44–2.84), K	6
Park et al, 2016[23]	Korea	65 (34–83)	88	Initial metastatic/recurrence	Chemotherapy	NA	44.32	1.96 (1.07–3.58), M	8
Pu et al, 2017[24]	China	62	220	Curatively resectable	Resection	245	15	0.89 (0.33–1.31), U	7
Pu et al, 2017[24]	China	62	134	Curatively resectable	Resection	245	15	0.85 (0.57–1.27), U	6
Ren et al, 2014[25]	China	68 (42–86)	44	Initial metastatic/locally advanced	NA	NA	8	1.46 (0.76–2.78), M	6
Stocken et al, 2008[26]	UK	63 (29–89)	653	Initial metastatic/locally advanced	Chemotherapy	NA	20.7	2.08 (1.50, 2.88), U	6
Wang et al, 2018[27]	China	61 (34–86)	94	Initial metastatic/locally advanced	Chemotherapy	NA	NA	3.18 (1.74–5.83), M	6
Xiao et al, 2017[28]	China	65	105	Initial metastatic/locally advanced	Chemotherapy	250	NA	2.47 (1.28–4.77), M	6
Xiao et al, 2017[28]	China	67	30	Initial metastatic/locally advanced	Palliative care	250	NA	1.57 (0.83–2.96), M	7
Xue et al, 2014[29]	China	NR	269	Initial metastatic/recurrence	Chemotherapy	250	NA	1.67 (1.12–2.44), M	7
Yu et al, 2017[17]	China	NR	139	Initial metastatic/locally advanced	Chemotherapy	185	78	1.98 (1.23–3.20), M	7
Yu et al, 2017[17]	China	NR	225	Initial metastatic/locally advanced	Chemotherapy	185	78	0.75 (0.55–1.01), M	8
Zhang et al, 2012[30]	China	63 (28–89)	302	Mix	Mix	NA	NA	1.31 (0.94–1.82), M	6

K = Kaplan–Meier method, M = multivariate analysis, NA = not available, NOS = Newcastle-Ottawa Scale, U = univariate analysis.

carcinoma OR pancreatic tumor OR pancreatic malignancy OR pancreatic malignant tumor OR pancreatic ductal adenocarcinoma). In addition, potentially pertinent studies were also identified by reviewing reference lists of the relevant articles.

The inclusion criteria were as follows: studies provided sufficient information to estimate the hazard ratio (HR) and 95% confidence interval (CI) of OS; the eligible studies had to investigate the association of pretreatment serum LDH level with OS; and when multiple studies enrolled the same population or subpopulation, we included the most recent study or the one with the most cases. The exclusion criteria included: lack of sufficient information to estimate the HR and 95% CI of OS; case reports, review articles, conference abstracts, letters, and no-clinical studies; and not reporting the relationship of serum LDH level with OS.

2.2. Data extraction

Two reviewers independently extracted relevant data, and disagreements were removed by consensus. The extracted data for each study included the name of the first author, publication year, country, age, case number, disease status, cut-offs of high serum LDH level, follow-up duration, survival analysis method, and estimated HRs (95% CIs). If the included studies did not directly provide HR and 95% CI, Kaplan–Meier survival curves were used to calculate the estimates for the association of LDH with OS. If data from any of the above categories were not provided in the included studies, items were defined as "not available" (NA) (Table 1).

2.3. Quality assessment

The quality of eligible studies was assessed based on the Newcastle-Ottawa Scale (NOS),[31] which comprises 8 points with 3 aspects: selection, comparability, and exposure. The scores of NOS system vary from 0 to 9, and studies with 6 scores or more are defined as high quality

2.4. Statistical analysis

We measured the effects of high serum LDH level on OS using HR and 95% CI. By convention, an observed HR of >1 indicates poorer OS for the group with a high LDH level. The effect of LDH on OS was thought to be statistically substantial if the pooled HR was >1 and 95% CI did not overlap 1. Statistical heterogeneity among the included studies was evaluated with Cochran Q and I^2 statistics. The random-effects model was applied for the pooling analysis when a substantial heterogeneity existed among the included studies ($I^2 > 50\%$), whereas the fixed-effects model was applied to pool data when no significant heterogeneity was detected across the included studies ($I^2 < 50\%$). Forrest plots were undertaken to assess the pooled HR for OS. The Begg[32] and Egger tests[33] were used to quantitatively assess publication bias, in which P value and the funnel plot generated from these tests were used to determine the presence of publication bias. When funnel plot is asymmetrical, it indicates that significant publication bias existed.

To investigate potential heterogeneity, 3 subgroup meta-analyses were conducted based on study region (Asian and non-Asian), median sample size (<186 and >186), disease status (curatively resectable and unresectable), survival analysis method (Kaplan–Meier method, univariate and multivariate), and treatment (chemotherapy, palliative care, and resection). STATA version 12.0 was applied to analyze all of the data. All statistical tests were 2-sided, and a P value of $<.05$ was considered significant. Sensitivity analyses were performed to assess the robustness of the pooled HRs by sequentially omitting 1 study.

3. Results

3.1. Literature search

A total of 412 literatures were retrieved via the initial search. After excluding136 duplicated articles, 276 records were left for the screening of titles, abstracts, and publication types. Then, 231 publications were excluded because of irrelevant topics, conference abstracts, reviews, and letters and comments. After discreetly reviewing the rest of the publications, 10 were further excluded due to lacking available data and nonclinical studies. Finally, a total of 14 publications with 18 studies were included in this meta-analysis.[10,17,19–30] The detailed process of literature search and selection is presented in Fig. 1.

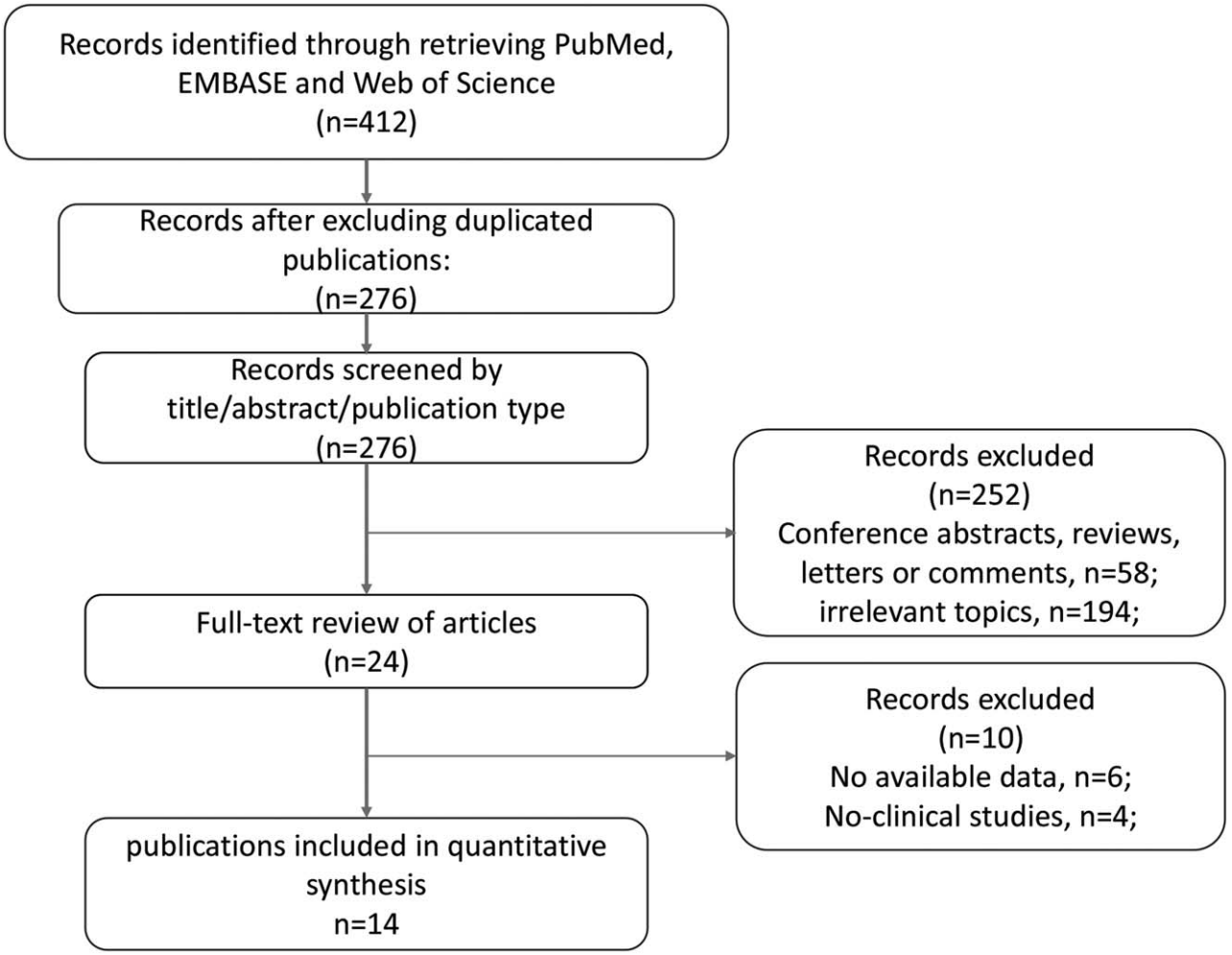

Figure 1. The flow diagram of literature selection process.

3.2. The main characteristics of eligible studies

The main characteristics of all eligible studies were summarized in Table 1. A total of 14 publications with 18 studies enrolling 3345 patients were included into the present meta-analysis.[10,17,19–30] Among these studies, 13 studies were from China,[17,19,21,22,24,25,27–30] 1 from Japan,[20] 1 from Korea,[23] 2 from Italy,[10] and 1 from UK.[26] The sample sizes of the included studies ranged from 44 to 653, with a median of 186 cases. Three studies enrolled patients with curatively resectable PC,[21,24] and 14 studies focused on PC patients with initial metastatic, locally advanced or recurrence,[10,17,19,20,22,23,25–29] and 1 study referred to a mixed group of patients, including curatively resectable PC or initial metastatic, and locally advanced or recurrence.[30]

3.3. Quality assessment

The quality of each study included in this meta-analysis was assessed according the NOS. The quality of all enrolled studies varied from 6 to 8 (Table 1), suggesting that the quality of the included literatures were medium to high level, and it was acceptable to include all of them into our meta-analysis.

3.4. Meta-analysis

3.4.1. Correlation between pretreatment serum LDH level and OS. A total of 18 studies with 3345 patients analyzed the correlation between pretreatment serum LDH level and OS of PC patients.[10,17,19–30] Because of the significant heterogeneity among the 18 studies (I^2=69.7.9%, P=.001; Fig. 2), we calculated the pooled HR and 95% CI with random-effects model. As shown in Fig. 2, high serum LDH level was significantly associated with worse OS (HR 1.57, 95% CI 1.30–1.90, P<.001).

3.4.2. Subgroup analysis. We performed subgroup analyses based on 4 stratifying factors, including ethnicity, sample size, disease status, and survival analysis method and treatment type, to explore the potential source of heterogeneity and check the robustness of the pooled results in different clinical backgrounds. The subgroup analysis based on ethnicity showed that high serum LDH level was significantly related to worse OS in both Asian patients (HR 1.48, 95% CI 1.19–1.85, P<.001; Fig. 3) and non-Asian patients (HR 2.00, 95% CI 1.60–2.51, P<.01; Fig. 3), and also in subgroups of <186 (HR 1.68, 95% CI 1.31–1.14, P=.010; Fig. 4) and >186 (HR 1.44, 95% CI 1.06–1.96, P<.001; Fig. 4). For disease status, subgroup analysis

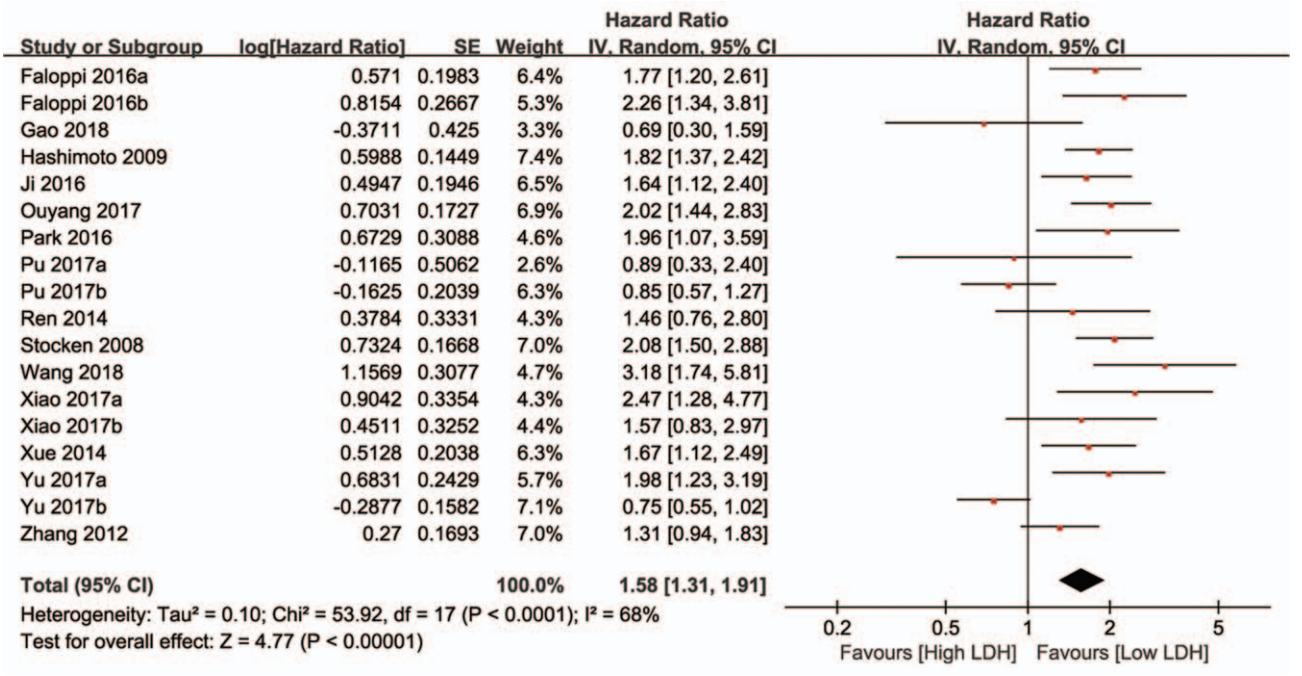

Figure 2. Meta-analysis of correlation between pretreatment serum LDH level and OS of PC patients. LDH = lactate dehydrogenase, OS = overall survival, PC = pancreatic cancer.

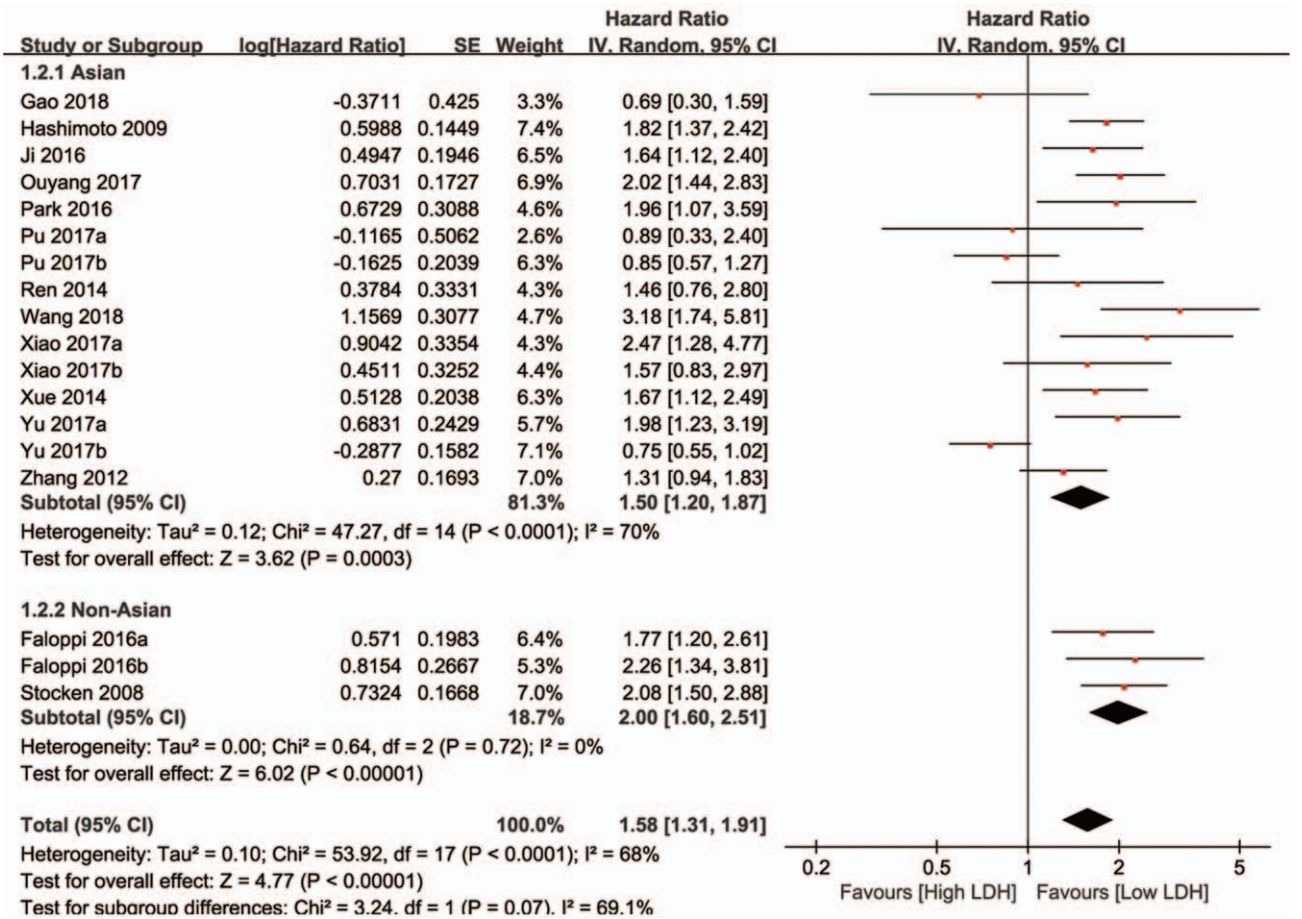

Figure 3. The pooled HR for OS of PC patients in subgroups stratified by ethnicity (Asian and non-Asian). HR = hazard ratio, OS = overall survival, PC = pancreatic cancer.

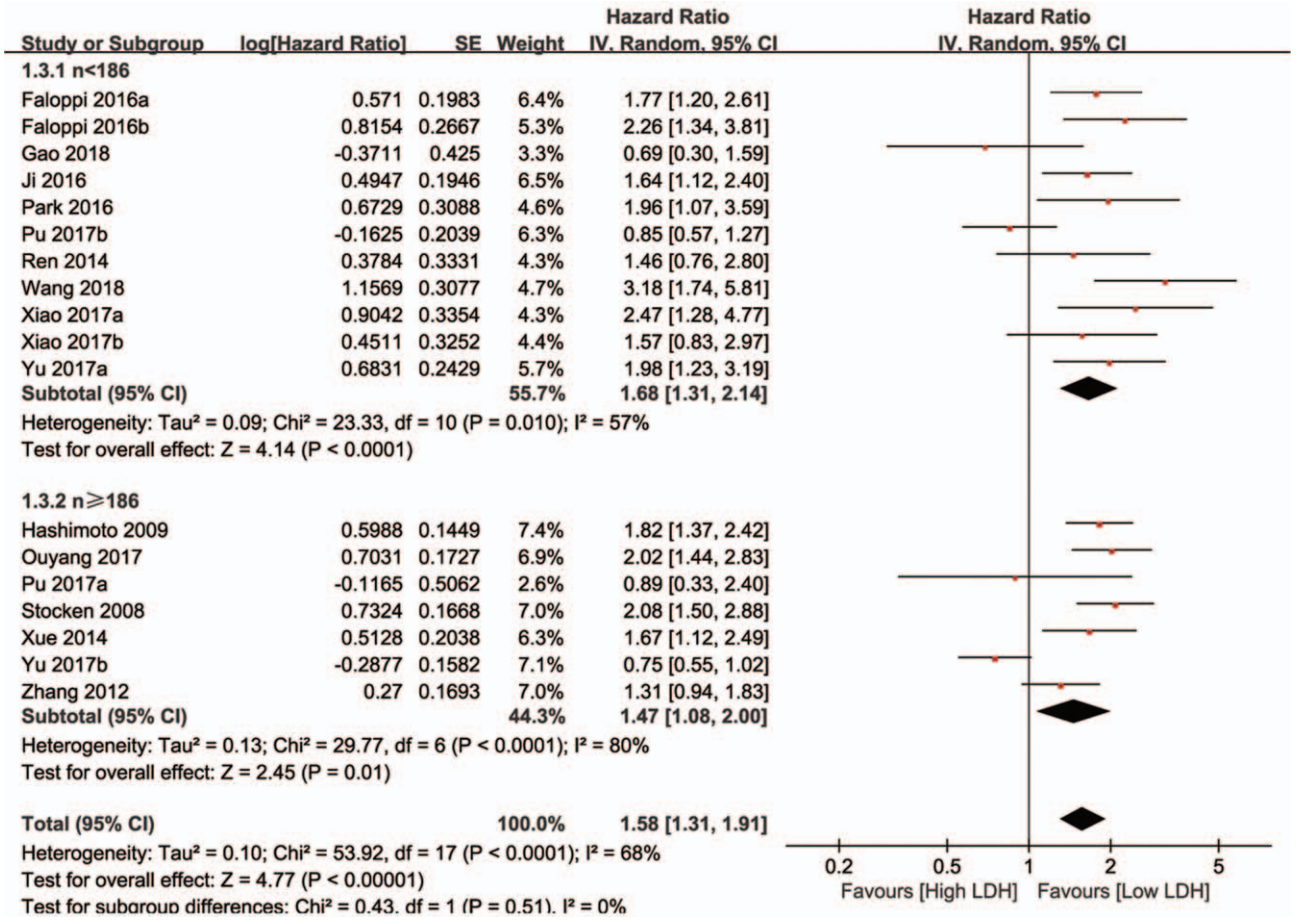

Figure 4. The pooled HR for OS of PC patients in subgroups stratified by median sample size (<186 and >186). HR = hazard ratio, OS = overall survival, PC = pancreatic cancer.

demonstrated that there was an obvious association between high serum LDH level and unfavorable OS in patients with unresectable PC (HR 1.72, 95% CI 1.38–2.14, $P < .001$; Fig. 5). Nevertheless, no significant association between high serum LDH level and poor OS was observed in patients with resectable PC (HR 1.11, 95% CI 0.69–1.77, $P = 0.06$; Fig. 5). Subgroup analysis by survival analysis method showed that high serum LDH level was significantly associated with worse OS in the subgroups of multivariate analysis (HR 1.57, 95% CI 1.23–1.99, $P < .001$; Fig. 6) and Kaplan–Meier method (HR 1.97, 95% CI 1.57–2.48, $P < .001$; Fig. 6), whereas no significant relationship between high serum LDH level and poor OS was found in univariate analysis group (HR 1.20, 95% CI 0.62–2.32, $P = .08$; Fig. 6). With respect to treatment, the subgroup analysis showed that the prognostic relevance of pretreatment serum LDH level existed in advanced pancreatic cancer patients who received chemotherapy (HR 1.73, 95% CI 1.32–2.25, $P < .001$; Fig. 7), and in patients precluded from chemotherapy (HR 1.91, 95% CI 1.42–2.58, $P < .001$; Fig. 7). However, no significant association between pretreatment serum LDH and OS in patients with curatively resectable PC was observed any more (HR 1.11, 95% CI 0.69–1.77, $P = .048$; Fig. 7).

However, the significant heterogeneity did not completely disappear in all the 4 subgroups mentioned above, suggesting that ethnicity, sample size, disease status, and survival analysis method and treatment might not the source of the heterogeneity in this meta-analysis. Thus, meta-regression was performed to further determine whether these factors were the source of the heterogeneity. As shown in Table 2, in accordance with the results of subgroup analyses, our meta-regression validated that these factors surely did not contribute to the heterogeneity. Anyway, although we failed to identify the sources of heterogeneity, by these subgroup analyses, we further verified the prognostic value of serum LDH level in PC patients.

3.4.3. Sensitivity analysis and publication bias assessment.

Sensitivity analysis was performed to assess the robustness of the pooled HR assessing the association between LDH and OS by sequentially omitting single study. The result showed that the pooled HR did not altered significantly after removing any study (Fig. 8A). In addition, the *P* values of the Begg and Egger tests for the association between LDH and OS were 0.967 and 0.402, respectively, and the Begg funnel plot for the association between LDH and OS was close to symmetry, which demonstrated that there was no significant publication bias (Fig. 8B). Collectively, the results of sensitivity analysis and publication bias assessment confirmed that our pooled HR was stable and reliable.

4. Discussion

To the best of our knowledge, this is the first comprehensive meta-analysis of the prognostic value of pretreatment serum LDH level in PC. The present meta-analysis demonstrated that PC patients with high serum LDH level have worse OS, and the

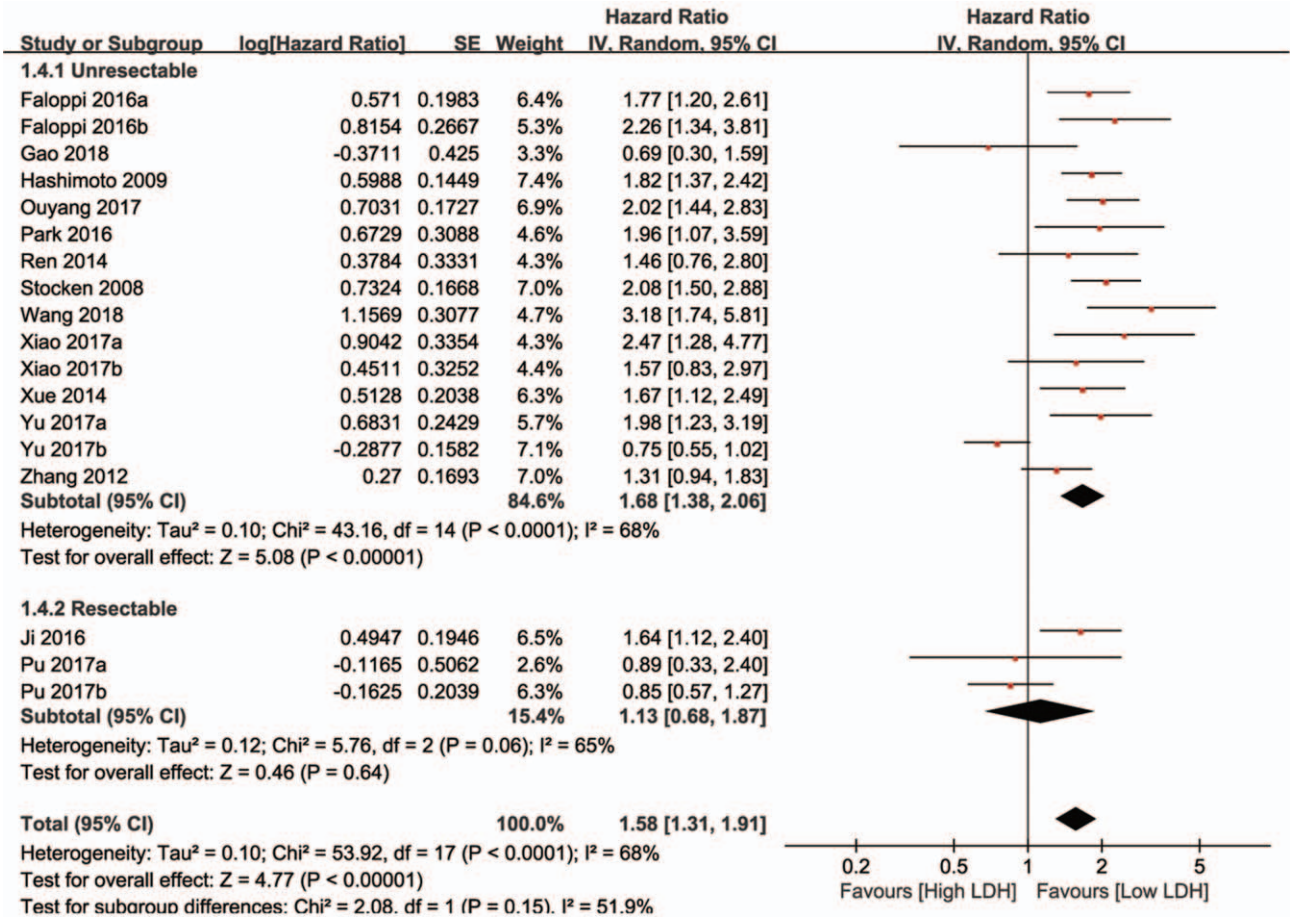

Figure 5. The pooled HR for OS of PC patients in subgroups stratified by disease status (curatively resectable and unresectable). HR = hazard ratio, OS = overall survival, PC = pancreatic cancer.

robustness of the pooled result was verified by the results of sensitivity analysis and publication bias. Additionally, we observed a consistent association between high serum LDH and worse OS in the subgroups of unresectable PC, multivariate analysis, and Kaplan–Meier analysis. However, we failed to find a significant association between serum LDH and OS in the subgroups of resectable PC and univariate analysis. Considering that only a few of the included studies with a limited number of cases provided available data for the pooled analysis of the association between serum LDH level and OS in patients resectable PC, we speculated that low statistical power might hide the inverse link between serum LDH level and OS in patients with resectable PC. Therefore, in future, more well-designed studies with large samples are required to further evaluate the prognostic value of serum LDH level in patients with curatively resectable PC. Similarly, only 2 studies with small sample size were included into the subgroup of univariate analysis, which might also conceal the relationship between serum LDH level and OS in PC patients due to the weak statistical power. Additionally, several potential confounding factors might also affect the pooled analysis of the data from univariate analysis.

There are several mechanisms explaining the positive correlations of high serum LDH level and worse OS in PC patients. Cancer cells exhibit an increased glycolysis capacity in comparison with normal cells, and this phenomenon even occurs under the condition of adequate oxygen supply, which is called as the Warburg effect.[34] In recent years, an increasing evidence demonstrated that abnormally enhanced aerobic glycolysis plays a critical role in cancer initiation and proliferation. Particularly, LDH is a key participant in the Warburg effect, in the final process of which it converts pyruvate to lactate, providing NAD+ for continued glycolysis and thereby promoting tumor progression. Moreover, it has been demonstrated that a high concentration of lactate could contribute to tumor progression and metastasis by directly enhancing cellular motility or through up-regulating several tumor growth factors, such as hypoxia-inducible factor 1α and vascular endothelial growth factor.[35] A tight association between LDH and cellular-myelocytomatos oncogene has been validated, and silencing LDH could substantially inhibit tumor growth in a mouse model.[36] More importantly, it has also been demonstrated that LDH could directly promote the growth of pancreatic cancer cells.[37] In addition, a study by Yu et al[17] indicated that serum LDH level was closely associated with the systemic inflammatory response in patients with advanced PC who received chemotherapy, and meanwhile, cancer-associated inflammation has been considered to be capable of affecting chemotherapeutic response and survival in patients with cancers,[38] implicating that the positive relationship between serum LDH level and systemic inflammation may also interpret the value of pretreatment serum LDH

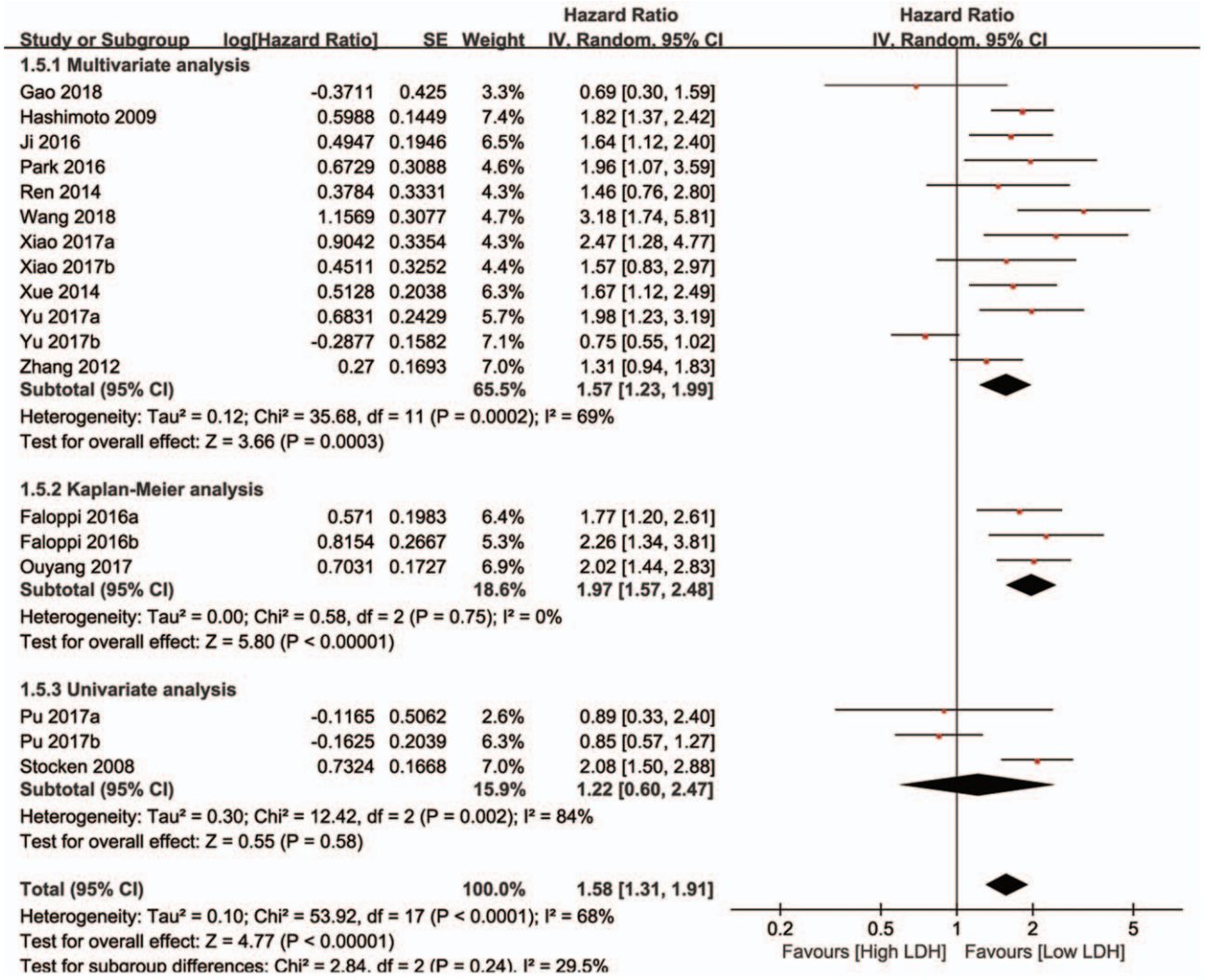

Figure 6. The pooled HR for OS of PC patients in subgroups stratified by survival analysis method (Kaplan–Meier method, univariate and multivariate). HR = hazard ratio, OS = overall survival, PC = pancreatic cancer.

level as a prognostic factor in PC patients. Collectively, these mechanisms support the conclusion of this meta-analysis that high serum LDH level predicted worse OS in PC patients.

This meta-analysis has some inspiration on clinical implications. On one hand, the present meta-analysis showed that high serum LDH level was closely associated with poor OS, suggesting that LDH may be an efficient biomarker for identifying cancer patients with high or low-risk, which would assist doctors in formulating individualized treatment and intensified follow-up plan. It has been suggested that high serum LDH level was related to stronger resistance to chemotherapy in many cancers.[39–41] Consistently, the subgroup analysis stratified by chemotherapy also demonstrated that advance PC patients with high serum LDH level had worse OS compared with low serum LDH level. Therefore, tackling high serum LDH level before starting chemotherapy might be a promising strategy for improving OS of patients with advanced PC. Additionally, although it was not analyzed in this meta-analysis for unavailable data, there was evidence demonstrating that serum LDH level was associated with response to targeted therapies in cancer patients. For instance, Scartozzi et al and Passardi et al reported that the addition of bevacizumab, an antiangiogenic monoclonal antibody, to chemotherapy caused a decrease in the rate of progressive disease and a prolonged progression-free survival (PFS) in colorectal cancer (CCR) patients with high serum LDH, but not low LDH, and they speculated that the underlying mechanism might be that high concentration LDH could contribute to angiogenesis in cancers.[42,43] Thus, CCR patients with high serum LDH may be ideal candidates for bevacizumab therapy. However, there is a totally inverse situation regarding the predictive value of serum LDH, when it comes to the application of tyrosine kinase inhibitors (TKIs), including sorafenib, to cancer patients. For instance, Faloppi et al found that sorafenib exhibited a substantial advantage in improving OS and PFS in PC patients with low LDH serum level, suggesting that patients with low serum LDH may be suitable for sorafenib therapy. These clinical findings are favored by an in vitro experiment, in which it was certified that inhibiting LDH production with oxamic acid in cancer cells enhanced the antiproliferative activity of TKIs, including sorafenib,[44] in turn, suggesting that high LDH concentration could reduce the activity of TKI. It has been demonstrated that TKI exhibits its activity

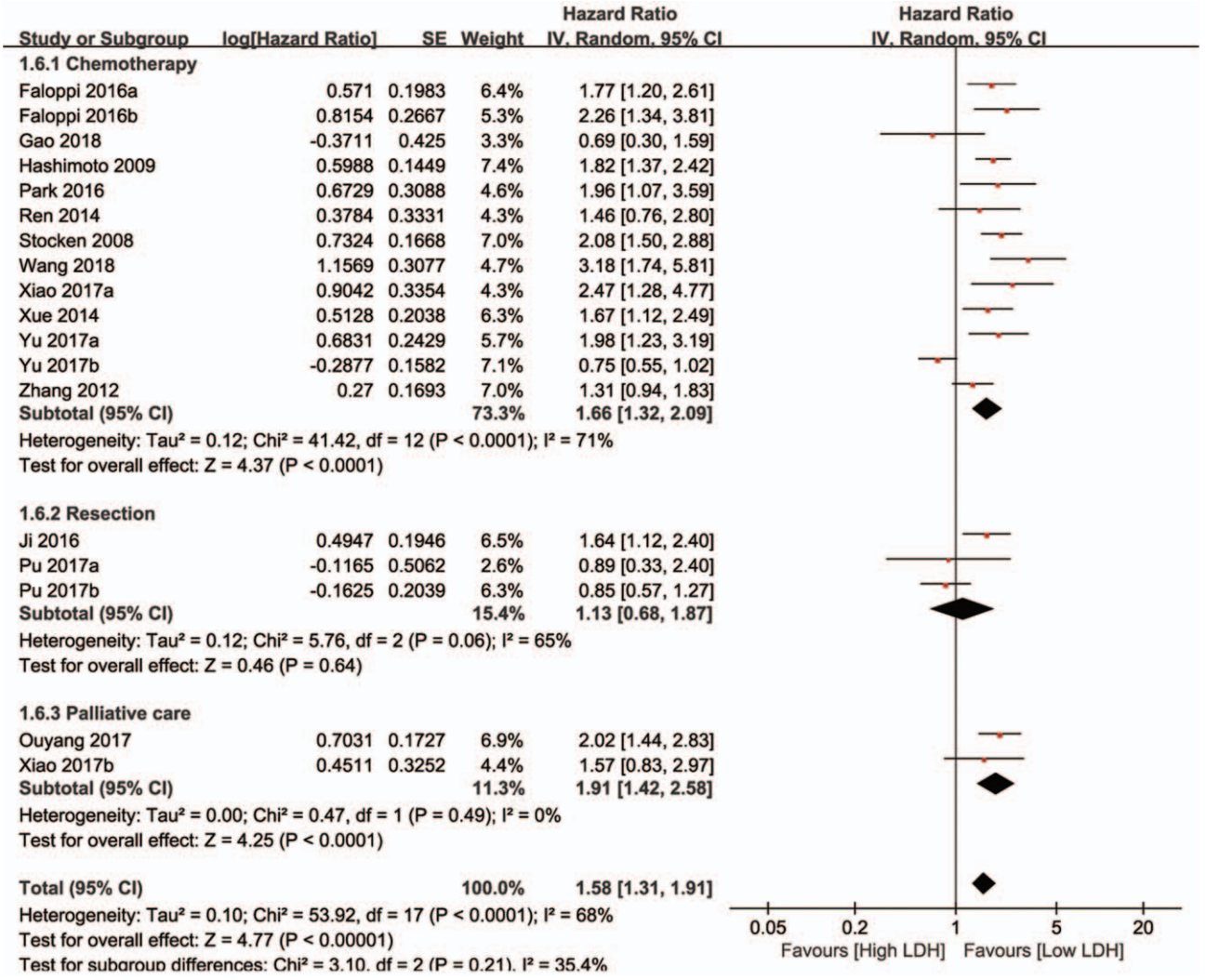

Figure 7. The pooled HR for OS of PC patients in subgroups stratified by treatment (chemotherapy, palliative care, and resection). HR = hazard ratio, OS = overall survival, PC = pancreatic cancer.

mainly by competing with adenosine triphosphate (ATP) for the kinase ATP binding site that is a key switch for the activation of tyrosine kinases.[45] Cancer cells are usually exposed to hypoxic condition, in which their energy request mainly rely on anaerobic glycolysis, and LDH participates in converting pyruvate and NADH into lactate and NAD+ in the final step of anaerobic glycolysis, consequently promoting ATP production. Thus, inhibiting LDH could interfere with anaerobic glycolysis of cancer cells, ultimately reducing ATP production and then alleviating the competition of ATP against TKIs, which may partly explain the inhibitory effects of high serum LDH level on the activity of TKIs. Therefore, the predictive value of a pretreatment serum LDH level in therapeutic response may vary by the effector mechanisms of drugs, and further work is required to further confirm the predictive value of serum LDH in pancreatic cancer.

On the other hand, there is evidence favoring that the inverse association between high pretreatment serum LDH level and poor OS may reflect heavy tumor burden or tumor aggressiveness.[5,6] Therefore, dynamically monitoring changes of post-therapy serum LDH level may also help to predict the therapeutic response and prognosis in patients with pancreatic cancer. For instance, a study by Xiao et al[46] found that postoperative high serum LDH was significantly correlated with worse OS in patients with early-stage PC.

However, this meta-analysis has some limitations. First of all, significant heterogeneity existed among the included studies. Although subgroup analyses and sensitivity analysis were performed, we failed to identify the origin of heterogeneity.

Table 2

The potential resource of heterogeneity evaluated by meta-regression.

Variable	Std. Err.	*t*-value	Regression coefficient (95% CI)	*P*
Ethnicity	0.33	1.27	1.35 (0.81–2.26)	.22
Sample size	0.23	0.75	1.15 (0.77–1.75)	.47
Survival analysis method	0.20	1.54	1.27 (0.91–1.76)	.14
Treatment	0.14	−0.67	0.90 (0.65–1.25)	.51
Disease status	0.39	1.75	1.55 (0.91–2.65)	.10

CI = confidence interval, Std. Err. = standard error.

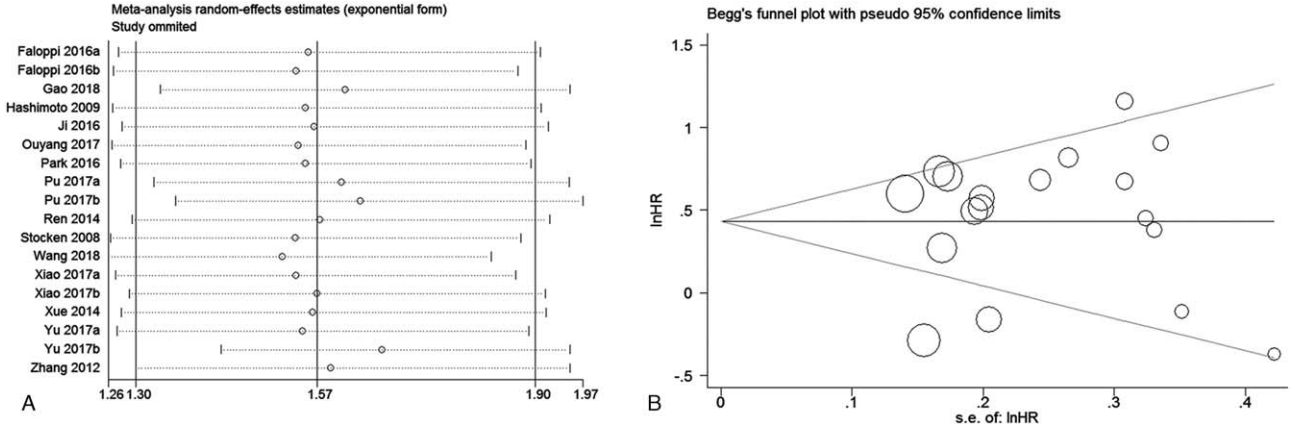

Figure 8. Sensitivity analysis (A) and funnel plot for publication bias (B) of OS. OS = overall survival.

Thus, more homogeneous studies are required to further confirm our findings. Second, we only included articles that provided the HR and the 95% CI, whereas other articles were not be considered because they only reported odds ratios and relative risk for survival. This may introduce bias into this meta-analysis. Additionally, the present meta-analysis was restricted to articles published in English, considering that other languages may not be accessible for the readers, and thus publication language may also have added additional bias. Furthermore, some of the included studies did not provided the HR and the 95% CI for OS directly, so we calculated the HR and the 95% CI from the Kaplan–Meier survival curve using Engauge software, to a degree which may lead to some statistical errors and introduce bias as well. Third, the cut-off values for high serum LDH level were different, which might also be potential source of heterogeneity of this meta-analysis. Thus, an optimized cut-off value should be determined in future studies, thereby enhancing the utility of LDH as prognostic predictor. Last, but not the least, only a limited number of eligible studies were included into the subgroups of resectable PC patients, recurrent PC patients, and unresectable PC patients not receiving chemotherapy for analyzing the prognostic value of LDH. Therefore, more studies are required to explore the prognostic value of serum LDH level in these patients. Regardless, this meta-analysis demonstrated that pretreatment serum LDH level is a useful biomarker for assessing the prognosis of PC patients.

Author contributions

The meta-analysis was designed by Gan JX, Wang WH, and Yin LN. Gan JX and Wang WH performed the systemic review and data summary. Gan JX, Wang WH, Yang ZX, Pan JP, and Zheng L were responsible for the analysis of pooled data. The manuscript was written and modified by Gan JX, Zheng L and Yin LN. ALL authors read and approved the final manuscript.

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Supervision: Zengxi Yang, Jiebin Pan.
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Visualization: Jianxin Gan, Zengxi Yang, Jiebin Pan, Liang Zheng.
Writing – original draft: Jianxin Gan.
Writing – review & editing: Liang Zheng, Lanning Yin.

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