

Pooled analysis of prognostic value and clinical significance of Rab1A expression in human solid tumors

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Abstract

Background: This study aims to assess the relationship between Rab1A expression and clinicopathological parameters and prognosis of patients with human solid cancer by summarizing the studies included.

Methods: PubMed, EMBASE, The Cochrane Library, and other sources were searched for relative studies. The risk ratios (RRs) and confidence interval (CI) were used to assess association between Rab1A expression and clinical parameters and prognosis in solid cancer patients.

Results: Eight studies were included in the final analysis with 800 patients. The results revealed that expression of Rab1A was significantly related with differentiation (RR=0.883, 95%CI=0.782–0.997, $P=.044$), lymph node metastasis (RR=0.835, 95%CI=0.753–0.926, $P=.001$), tumor-lymph node-metastasis (TNM) stage (RR=1.190, 95%CI=1.071–1.322, $P<.001$) and tumor size (RR=0.818, 95%CI=0.730–0.915, $P<.001$). What is more, no significant difference was seen in 1-year survival between high and low expression of Rab1A in multiple malignancies (RR=0.855, 95%CI=0.697–1.050, $P=.136$). However, increased Rab1A revealed poorer prognosis with 2-year survival (RR=0.760, 95%CI=0.701–0.824, $P<.001$), 3-year survival (RR=0.669, 95%CI=0.604–0.742, $P<.001$), 4-year survival (RR=0.622, 95%CI=0.554–0.698, $P<.001$) and 5-year survival (RR=0.525, 95%CI=0.458–0.698, $P<.001$). Expression of Rab1A was increased obviously in solid cancer tissues compared with the adjacent normal tissue (RR=4.78, 95%CI 4.05–5.63, $P=.015$).

Conclusion: This study revealed Rab1A expression links closely with tumor size, differentiation, lymph node metastasis, TNM stage and poor prognosis of human solid cancer patients. It may act as a biomarker of prognosis and a novel therapeutic target in solid cancer.

Abbreviations: CI = confidence interval, OR = odds ratio, OS = overall survival, RR = risk ratio, TNM = tumor-lymph node-metastasis.

Keywords: clinicopathological parameters, neoplasm, prognosis, Rab1A

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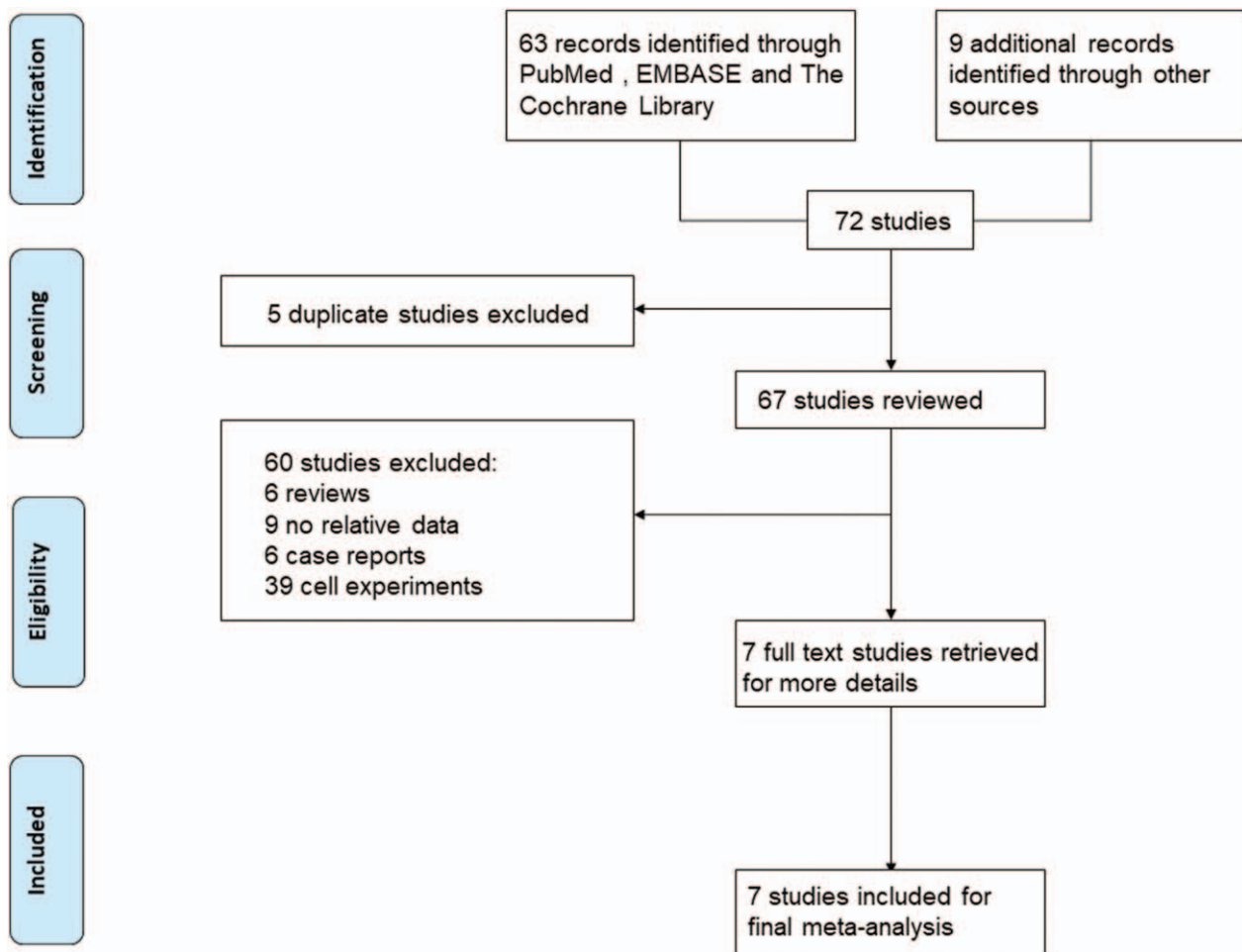


Figure 1. Flow diagram of study selection.

1. Introduction

Due to the high rate of incidence and mortality, Cancer is today one of the most serious problems and costly health problems and causes more deaths than cardiovascular disease does worldwide.^[1] In USA, about 1.68 million new cancer cases and 60 thousand new cancer deaths have been estimated to occur in 2017.^[2] Although the complex therapies including surgery, chemotherapy and molecular targeted therapy in some cancers have made significant progress, the prognosis of patients with cancer remained relatively poor mainly due to the metastasis of distant organs.^[3] Thus, it is significantly urgent to identify novel therapeutic targets to improve the survival of the patients with cancer especially with advanced or metastatic stages.

Rab1A is a member of the RAB family, a small guanosine triphosphatase (GTPase), has been well established to mediate vesicular trafficking from the endoplasmic reticulum (ER) to the Golgi apparatus.^[4] Previous researches revealed Rab1A is involved in mediating signal transduction,^[5] cell migration^[6] and regulation of autophagy.^[7] What is more, overexpression of Rab1A has been linked to several diseases, such as Parkinson disease, aspirin-exacerbated respiratory disease and cardiomyopathy.^[8–10] Recently, Aberrant activation of Rab1A is closely involved in tumorigenesis and progression of several kinds of

malignancies, including cervical cancer, breast cancer, prostate cancer, hepatocellular carcinomas.^[11–16]

However, there is no large sample report to explore relationship between the expression level of Rab1A and clinicopathological parameters and prognosis of patients with solid cancers. Herein, we assessed the association of Rab1A expression with patient survival and clinicopathological characteristics by comprehensively pooling data from published publications. Consequently, we report the first meta-analysis to clarify the prognostic implication of Rab1A expression among solid cancer patients.

2. Materials and methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. This study was approved by the Independent Ethics Committee of the Affiliated Suzhou Hospital of Nanjing Medical University.

2.1. Search strategy

In order to obtain the related studies, PubMed, EMBASE, Cochrane Library, Elsevier, Web of Science, Google Scholar, Chinese Biological Medical Literature database (CBM) were

Table 1

Characteristics of included studies.

| Reference | Year | Country | No. | Male/Female | TNM stage | Follow-up months | Rab1A (-/+ No. | 5-year OS (-/+)% |
|-----------|----------|---------|-----|-------------|-----------|------------------|----------------|------------------|
| Wang XX | 2016 | China | 60 | 45/15 | I-IV | NA | 3/57 | NA |
| Xu BH | 2015 (1) | China | 143 | 121/22 | I-IV | 96 | 47/96 | 90/47 |
| Hou PZ | 2018 | China | 69 | 23/46 | I-IV | 36 | 31/38 | NA |
| Shimada K | 2005 | China | 54 | 35/18 | I-IV | NA | 1/53 | NA |
| Xu BH | 2018 | China | 280 | 172/108 | I-IV | 72 | 90/190 | 80/44 |
| Thomas JD | 2014 | USA | 90 | 47/43 | I-IV | 60 | 16/74 | 82/40 |
| Megger DA | 2016 | Germany | 14 | NA | NA | NA | 2/12 | NA |
| Xu BH | 2015 (2) | China | 90 | 81/9 | I-IV | 60 | 30/60 | 60/27 |

NA=not available, TNM=tumor-lymph node-metastasis.

searched for the key words “Rab1A or rab1A GTP-Binding Protein or GTP-Binding Protein, rab1A or rab1A GTP Binding Protein or rab1A Protein” and “cancer or carcinoma or tumor or tumor or neoplasm or malignancy”. These key words were searched alone or in combination without limitation for language. The selected studies were also identified by scanning all pertinent studies and their references. The latest search was done on January 29, 2018.

2.2. Selection criteria

Inclusion criteria for the meta-analysis were:

- (1) the study investigated any type of human solid tumors;
- (2) the association between expression of Rab1A and Clinicopathological features and clinical prognosis of patients with solid cancer;

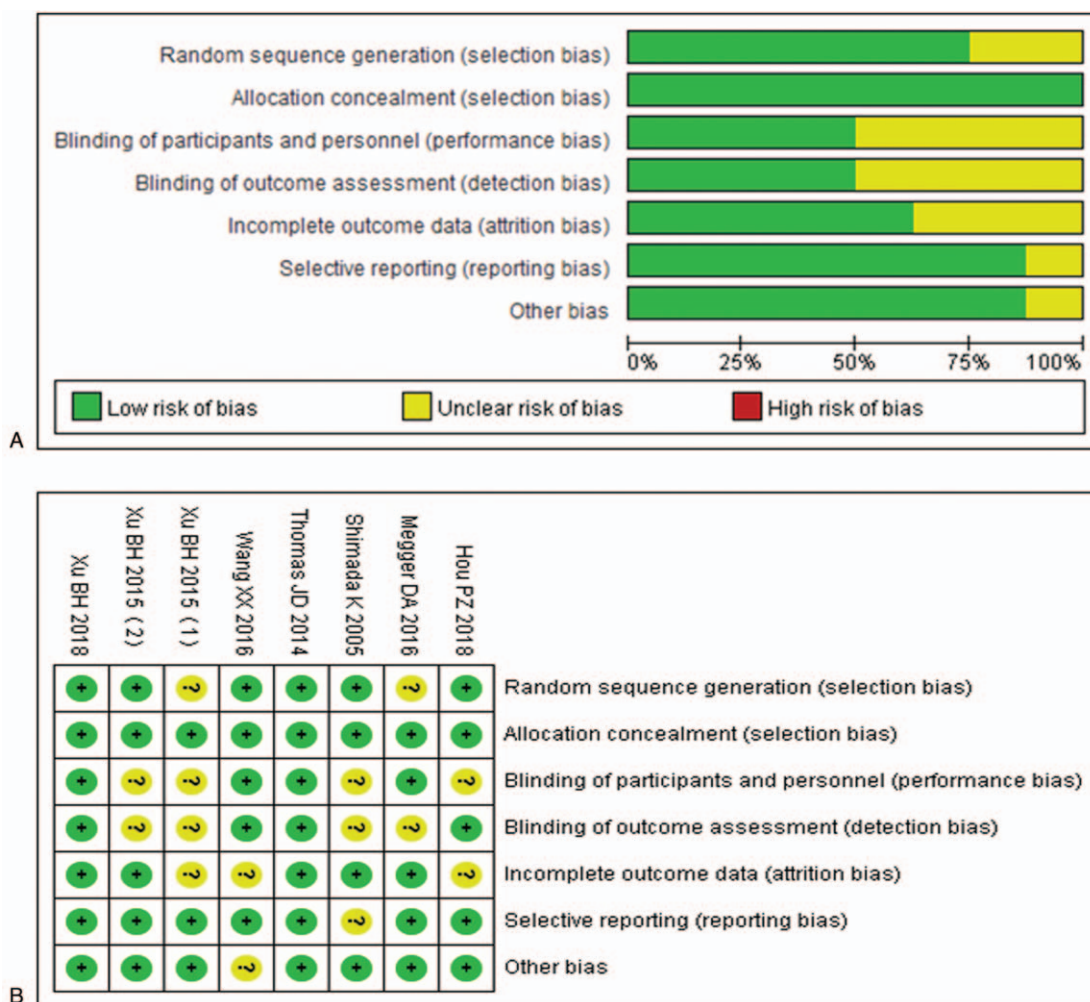


Figure 2. Assessment of risk of bias. A. Methodological quality graph: authors’ judgment about each methodological quality item presented as percentages across all included studies; B. Methodological quality summary: authors’ judgment about each methodological quality item for each included study, “+” low risk of bias; “?” unclear risk of bias; “-” high risk of bias.

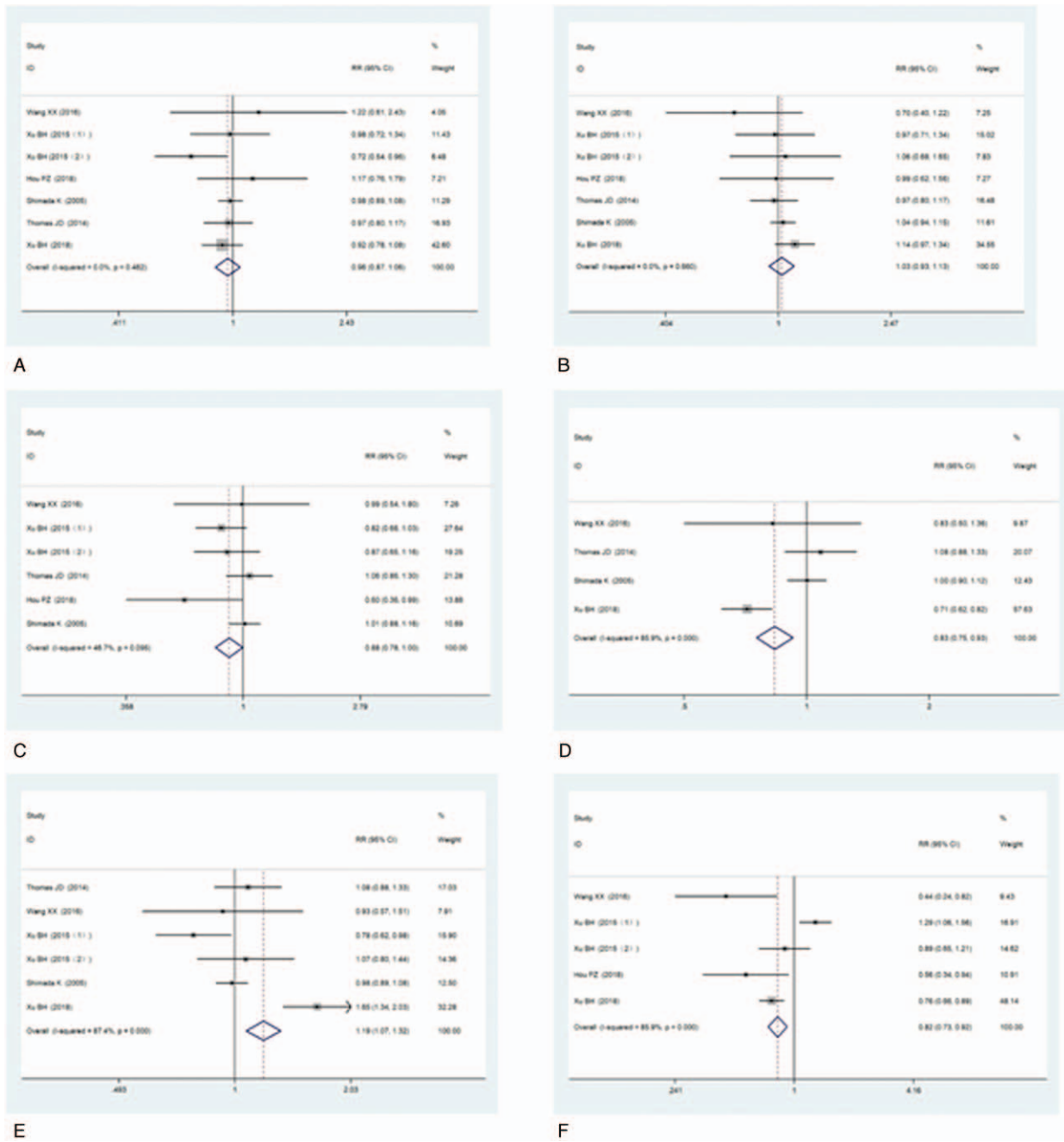


Figure 3. The forest plot of RRs for the association between Rab1A expression and the A. gender, B. age, C. differentiation, D. lymph node metastasis, E. TNM stage, F. Tumor size.

Table 2
Main results for meta-analysis between Rab1A and clinicopathological factors.

| | No. of studies | pooled RR (95%CI) | Z, P _{RR/HR} | Heterogeneity test (I ² , P _{bias}) | Egger test (t, P _{publication bias}) | Begg test (Z, P _{publication bias}) |
|---|----------------|----------------------|-----------------------|--|--|---|
| Gender (male vs female) | 7 | 0.960 (0.871, 1.058) | 0.83, 0.406 | 0%, 0.462 | 0.00, 0.997 | 0.60, 0.548 |
| Age (younger vs older) | 7 | 1.026 (0.928, 1.134) | 0.50, 0.619 | 0%, 0.660 | -1.26, 0.262 | 0.90, 0.368 |
| Differentiation (poor/moderate vs well) | 6 | 0.883 (0.782, 0.997) | 2.01, 0.044 | 46.7%, 0.095 | -1.55, 0.197 | 1.13, 0.260 |
| Lymph node metastasis (absent vs present) | 4 | 0.835 (0.753, 0.926) | 3.42, 0.001 | 86%, 0.000 | -0.12, 0.917 | 0.34, 0.734 |
| TNM stage (I/II vs III/IV) | 6 | 1.190 (1.071, 1.322) | 3.24, 0.001 | 87.4%, 0.000 | 0.28, 0.791 | 0.00, 1.000 |
| Tumor size (small vs large) | 5 | 0.818 (0.730, 0.915) | 3.50, 0.000 | 86%, 0.000 | -0.75, 0.507 | 0.24, 0.806 |

CI = confidence interval, RR = risk ratios, TNM = tumor-lymph node-metastasis.

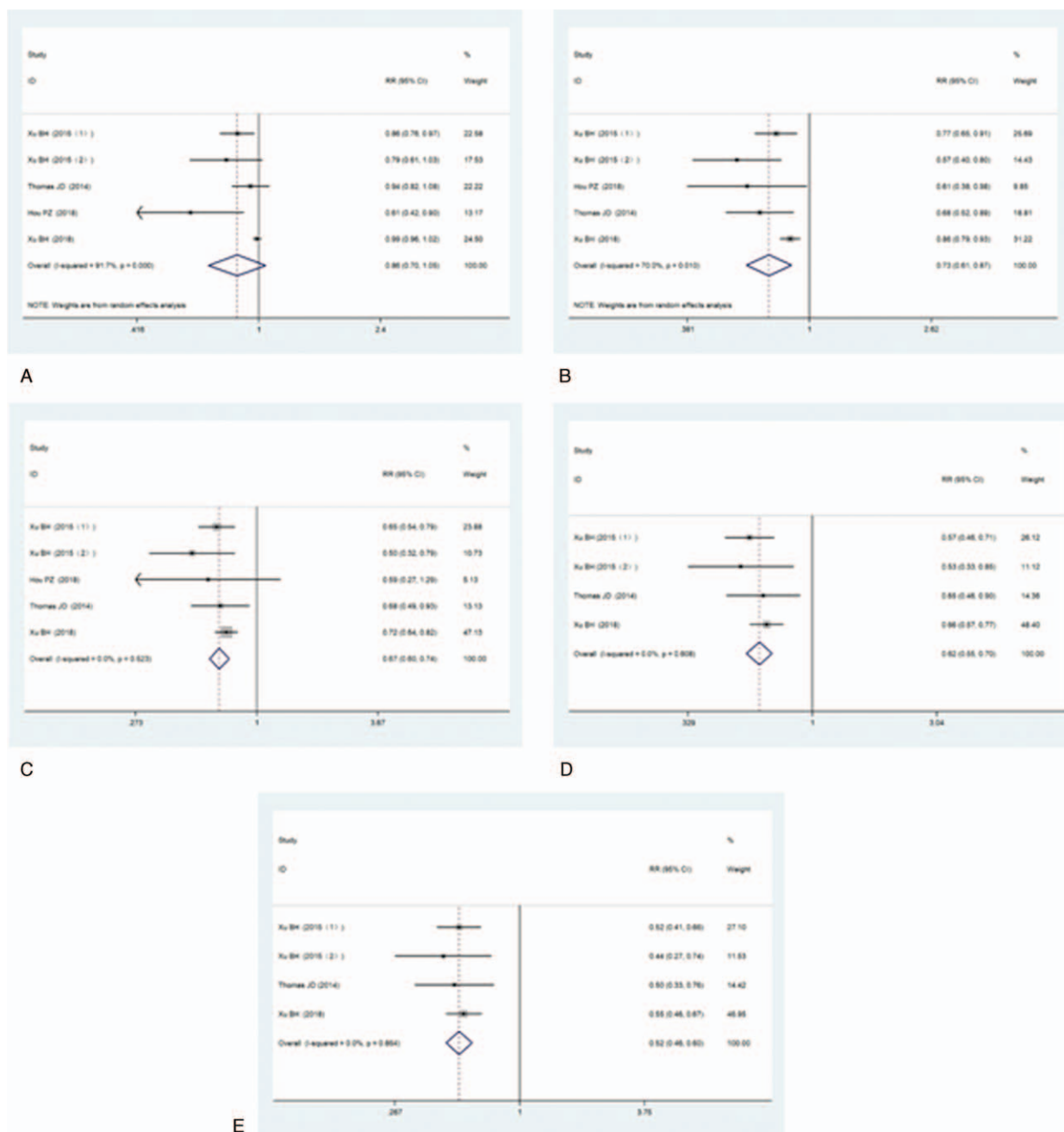


Figure 4. The forest plot of RRs for the association between Rab1A expression and the A. 1-year survival, B. 2-year survival, C. 3-year survival, D. 4-year survival, E. 5-year survival.

Table 3
Main results for meta-analysis between Rab1A expression and survival.

| | No. of studies | Overall RR/HR (95%CI) | Z, P _{RR/HR} | Heterogeneity test (I ² , P _{bias}) | Egger test (t, P _{publication bias}) | Begg test (Z, P _{publication bias}) |
|-----------------|----------------|-----------------------|-----------------------|--|--|---|
| 1-year survival | 5 | 0.855 (0.697, 1.050) | 1.49, 0.136 | 91.7%, 0.000 | -4.46, 0.019 | 1.22, 0.221 |
| 2-year survival | 5 | 0.76 (0.701, 0.824) | 6.69, 0.000 | 70%, 0.01 | -6.80, 0.007 | 1.22, 0.221 |
| 3-year survival | 5 | 0.669 (0.604, 0.742) | 7.64, 0.000 | 0%, 0.523 | -2.23, 0.113 | 0.73, 0.462 |
| 4-year survival | 4 | 0.622 (0.554, 0.698) | 8.06, 0.000 | 0%, 0.608 | -1.19, 0.355 | 0.34, 0.734 |
| 5-year survival | 4 | 0.525 (0.458, 0.602) | 9.19, 0.000 | 0%, 0.864 | -4.15, 0.053 | 1.70, 0.089 |

CI=confidence interval, HR=hazard ratios, RR=risk ratios.

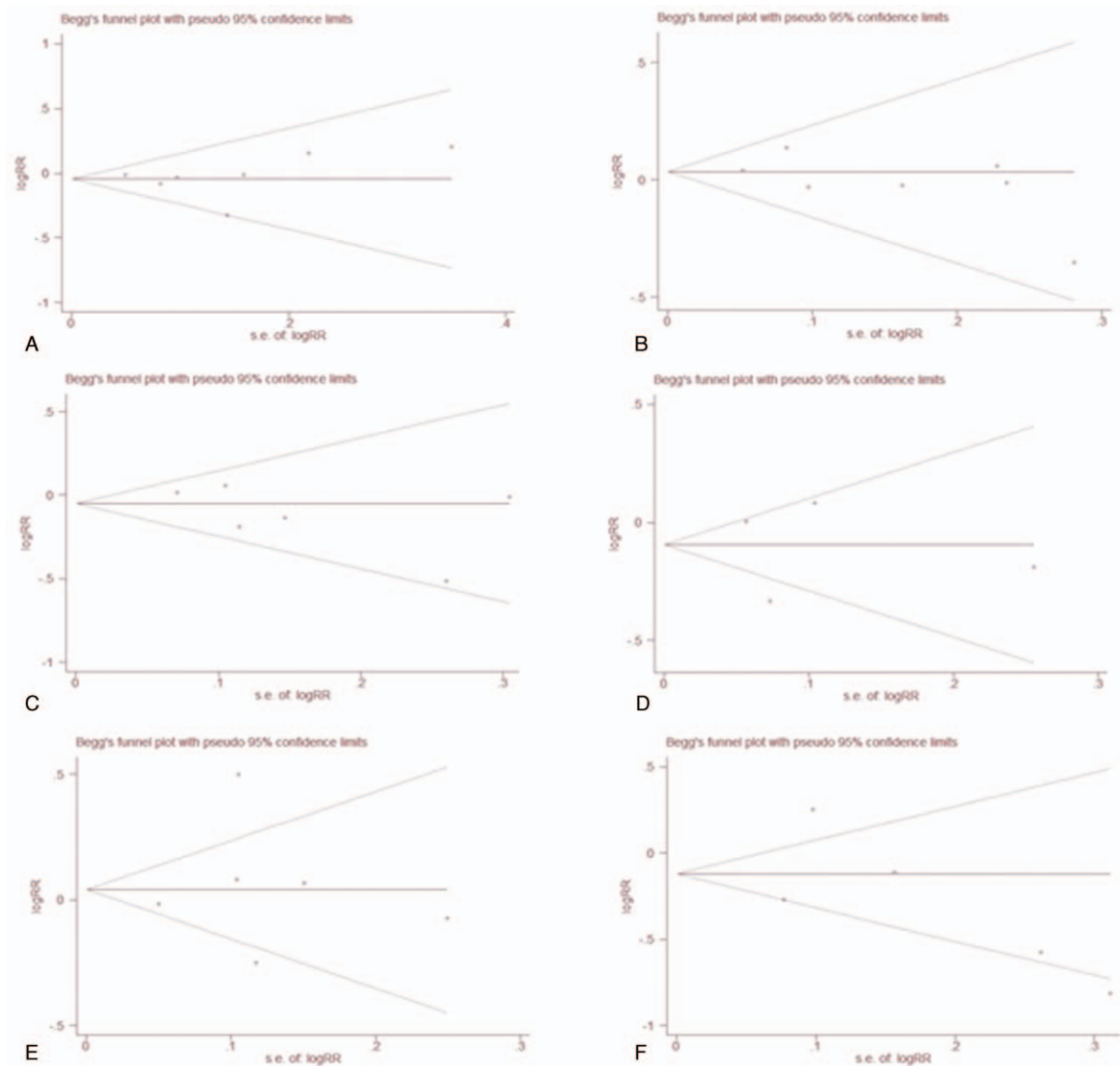


Figure 5. Funnel plots for publication bias. A. gender, B. age, C. differentiation, D. lymph node metastasis, E. TNM stage, F. Tumor size.

- (3) original research;
- (4) only studies assessed identical target factors included.

The exclusion criteria for articles included:

- (1) non-solid tumors;
- (2) animal research, case reports and review articles;
- (3) the literatures without complete research data
- (4) repeated studies or the same database or patients.

2.3. Data extraction

Titles and abstracts of potentially related studies were screened by 2 independent authors (CZW and SXY) and whole manuscripts meeting inclusion criteria were obtained. In addition, 2 researchers (CZW and XML) independently research the data of the first author, publication date, research design, patients (number, characteristics), study period, sample size, gender, differentiation of cancer, tumor size, lymph node metastasis, TNM stage and

overall survival (OS). Any discrepancies proposed were discussed by a third investigator (XML) to reach a consensus by analyzing the original data again. The Cochrane Collaboration Risk of Bias Tool was used to assess quality of the included studies.

2.4. Statistical analysis

The meta-analysis was performed by the software of Review Manager 5.3 (Cochrane Collaboration) and the software of Stata 14.0 (STATA, College Station, TX). RR with 95% CI were used to analyze the relationship of Rab1A expression with clinicopathological characteristics and clinical prognosis of the solid cancer patients. A chi-squared test of $P < .10$ or $I^2 > 50\%$ indicated heterogeneity among the studies. If the heterogeneity was not significant, a fixed effect model was used. Otherwise, a random effects model was used for further analysis. $P < .05$ for both tests was considered statistically significant.

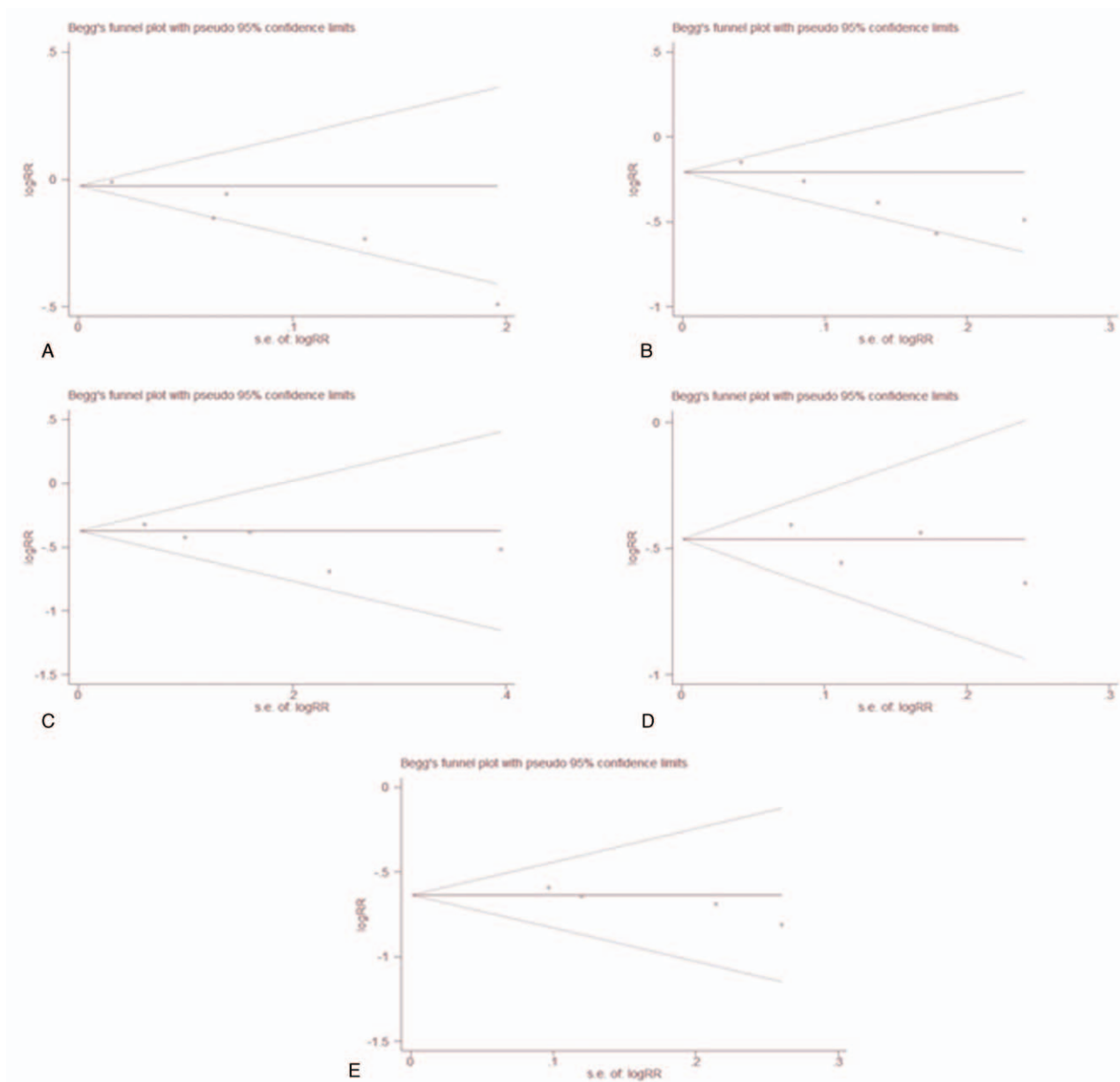


Figure 6. Funnel plots for publication bias. A. 1-year survival, B. 2-year survival, C. 3-year survival, D. 4-year survival, E. 5-year survival.

3. Results

3.1. Literature search and study characteristics

The search strategy retrieved 72 potentially related references. According to the selection criteria, 8 final trials (seven references included since 1 reference included 2 final trials) were included in the meta-analysis.^[17–23] A total of 800 patients were included in this meta-analysis. The flow diagram of study selection was concluded and shown in Figure 1. Study characteristics of these eight studies were summarized in Table 1. Most studies were published in recent 4 years, indicating the prognostic value of Rab1A is a potentially novel field of research. There were seven studies for clinicopathological parameters, 5 for OS. The maximum and minimum sample size were 280 and 14, respectively. The follow up time ranged from 36 to 96 months.

Quality assessment indicated that allocation concealment was low in all the included studies. Two studies carried out by Xu et al^[20] and Thomas et al^[18] had a significantly high quality (Fig. 2A, B).

3.2. Correlations between Rab1A and clinicopathological features

A total of 7 studies explored the correlation between Rab1A expression and clinicopathological Characteristics of human solid tumors. As shown in Figure 3 and Table 2, the results indicated that Rab1A expression was not significantly related with the gender (RR=0.960, 95%CI=0.871–1.058, $P=.406$), age (RR=1.026, 95%CI=0.928–1.134, $P=.619$) in human solid cancer patients (Fig. 3A–B, Table 2). However, significant relationships between Rab1A expression and differentiation

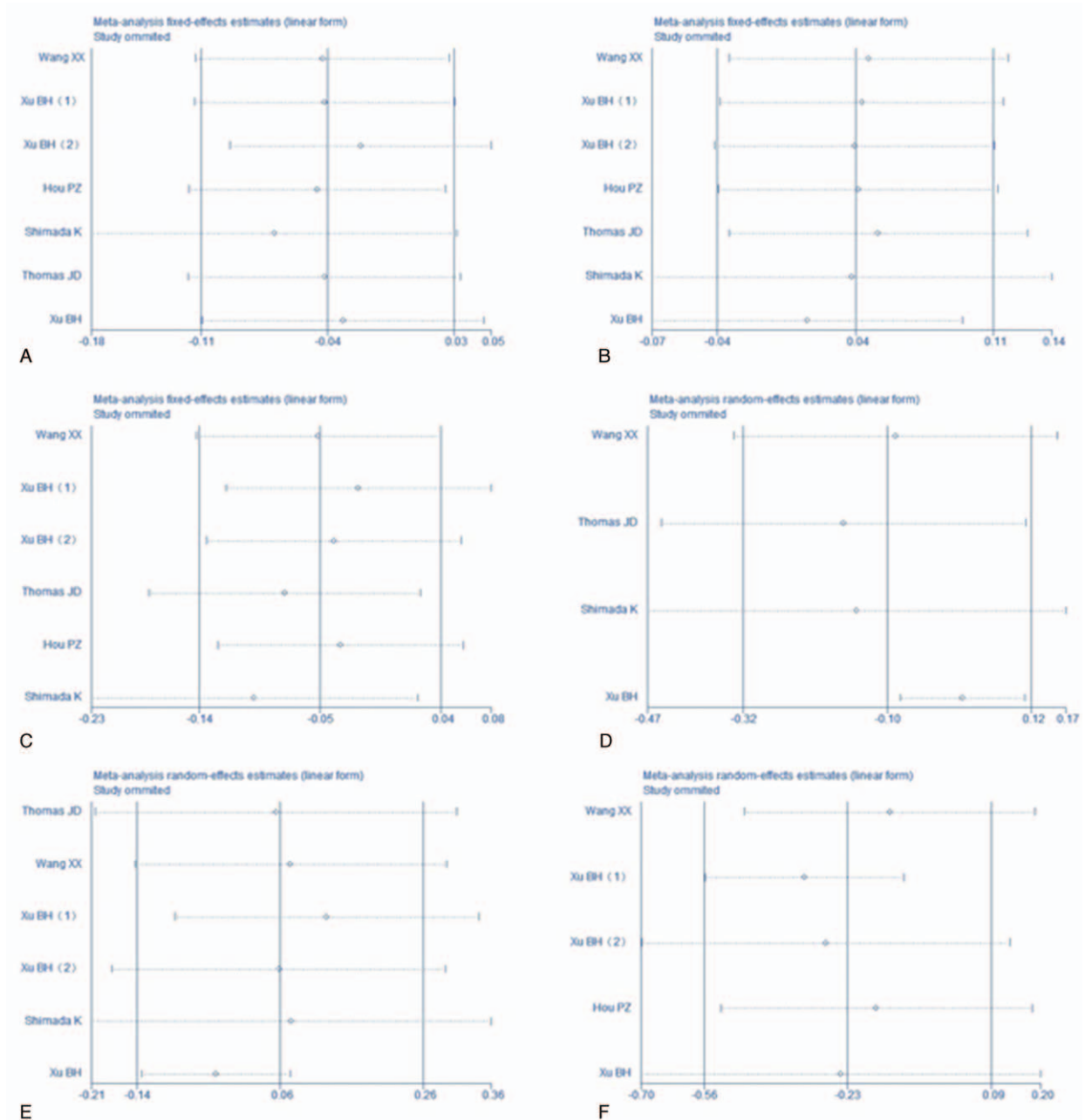


Figure 7. Sensitivity analysis. A. gender, B. age, C. differentiation, D. lymph node metastasis, E. TNM stage, F. Tumor size.

(RR=0.883, 95%CI=0.782–0.997, $P=.044$), lymph node metastasis (RR=0.835, 95%CI=0.753–0.926, $P=.001$), TNM stage (RR=1.190, 95%CI=1.071–1.322, $P<.001$) and tumor size (RR=0.818, 95%CI=0.730–0.915, $P<.001$) were observed (Fig. 3C–F, Table 2).

3.3. Association of Rab1A expression with OS

To investigate the relationship between the expression of Rab1A and prognosis in human solid cancer, we first analyzed 6 studies selected and obtained a significant difference between the expression of Rab1A in human solid cancer tissue and paired adjacent normal tissue (OR=20.30, 95%CI 15.56–

26.48, $P<.001$). Second, we get the related data from five selected studies directly or extracted from the Kaplan–Meier survival curve to explore the association between Rab1A expression and prognosis. The results revealed there was no significant difference in 1-year survival between high and low expression of Rab1A in multiple malignancies (RR=0.855, 95%CI=0.697–1.050, $P=.136$, random effect) (Fig. 4A, Table 3). However, a significant correlation between Rab1A overexpression and a poor OS was detected in 2-year survival (RR=0.760, 95%CI=0.701–0.824, $P<.001$, random effect) (Fig. 4B, Table 3), so as in 3-year survival (RR=0.669, 95%CI=0.604–0.742, $P<.001$, fixed effect), 4-year survival (RR=0.622, 95%CI=0.554–0.698, $P<.001$, fixed effect) and 5-year

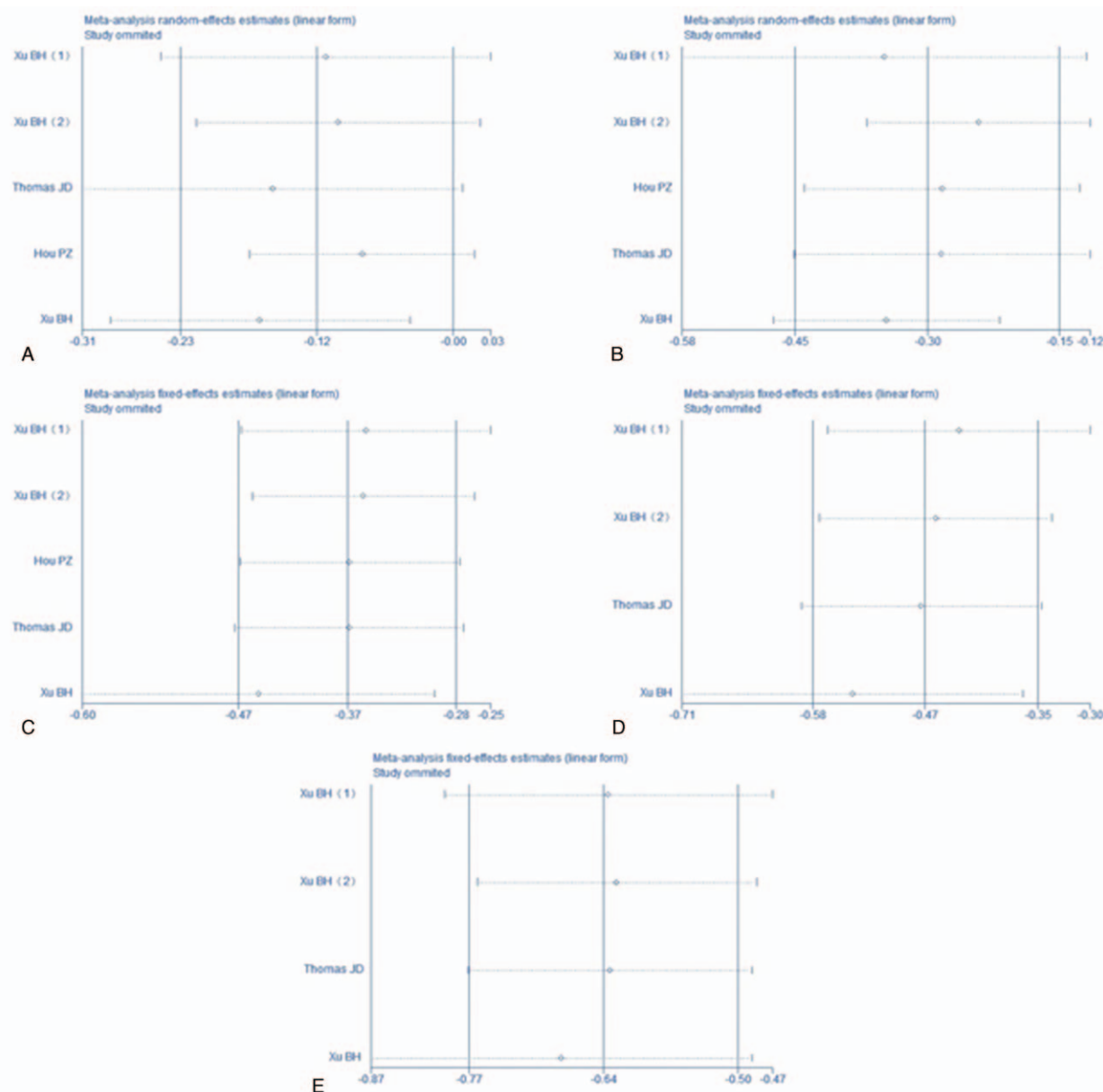


Figure 8. Sensitivity analysis. A. 1-year survival, B. 2-year survival, C. 3-year survival, D. 4-year survival, E. 5-year survival.

survival (RR=0.525, 95%CI=0.458–0.698, $P < .001$, fixed effect) (Fig. 4C–E, Table 3).

3.4. Publication bias and sensitivity analysis

Begg or Egger test was performed to assess the potential bias in the selected literatures. None of the significant publication bias was indicated in clinicopathological characteristics (Fig. 5A–F, Table 2) and 1-year to 5-year survival analysis (Fig. 6A–E). Sensitivity analyses were also performed, it indicated that no significant changed in clinicopathological characteristics (Fig. 7A–F) and pooled RR of 1-year to 5-year survival (Fig. 8A–E).

4. Discussion

Recent genome studies have demonstrated that Rab1A acts as an oncogene and plays a significant role in various biological

processes, including carcinogenesis and tumor metastasis.^[18,24] And aberrant expression of Rab1A is closely associated with clinicopathological features of human solid cancers.^[19,20] They may also provide us new molecular biomarkers for diagnosis and prognosis of cancers. Nowadays, Rab1A has been proved to be overexpressed in various of human solid cancers, such as tongue squamous carcinoma,^[17] breast cancer,^[15] prostate cancer,^[14] hepatocellular carcinomas,^[22,23] lung cancer^[19] and so on. Systematic analysis of the relationship between Rab1A and cancer prognosis has not been explored yet. Therefore, a meta-analysis is urgently needed to investigate the association between overexpression of Rab1A and clinicopathological characteristics and prognosis in human solid cancers.

Several studies have reported that the association between overexpression of Rab1A and various clinicopathological factors in several human malignancies, such as gender, age, differentiation, lymph node metastasis and TNM stage and so on.^[17–20,23]

However, the results remain unfavorable and inconsistent. Thus, a pooled analysis about the expression of Rab1A and clinicopathological factors is necessary. In our analysis, a total of eight studies comprising 800 patients were enrolled. The result revealed that Rab1A expression was not significantly related with the gender and age in human malignancies patients. However, the pooled analysis showed an obvious correlation between Rab1A expression and differentiation, lymph node metastasis, TNM stage and tumor size.

In several human malignancies, increased expression of Rab1A led to a poor survival.^[21–23,25] In our meta-analysis, we systematically evaluated survival data from 1-year to 5-year OS. Our study demonstrated that increased Rab1A modestly led to a poor 1-year survival, but it does not reach a significant difference. Thomas et al^[18] and Xu et al^[20] revealed overexpression of Rab1A did not significantly reduce the 1-year survival. In contrast, the left studies suggested increased Rab1A expression level caused a poorer 1-year survival significantly. In addition, we observed that high expression of Rab1A led to a poor prognosis from 2-year to 5-year survival. In conclusion, high expression of Rab1A played a crucial role in long-term survival rather than short-term survival. What is more, we also analyzed the expression of Rab1A in human malignancies tissue and paired adjacent normal tissue. The result showed that the expression level of Rab1A increased obviously in malignancies tissue.

Despite our efforts to make a comprehensive analysis, this meta-analysis had several limitations. First, the sample size is relatively small and the number of eligible studies is relatively limited, making us unable to perform a subgroup analysis of OS. Second, we cannot obtain the original data of the selected patients to verify the accuracy. For example, we get the survival information from the Kaplan–Meier survival curve indirectly. Third, most patients selected come from China, which means our results might not be applied to different ethnicities and regions. Therefore, more large-scale studies are urgently needed to further analyze the prognostic value of Rab1A in different ethnicities. Fourth, the data collection may be incomplete due to only retrieving literature from Chinese and English databases, a potential language bias might exist. Thus, more studies were needed to explore the relationship between Rab1A expression and clinicopathological parameters and survival in human malignancies patients.

5. Conclusions

Together with, our results demonstrated that the expression of Rab1A is related with tumor size, differentiation, lymph node metastasis, TNM stage. In addition, overexpression of Rab1A also leads to a poorer prognosis. More clinical studies with larger sample size are needed to further investigate the role of Rab1A in the prognosis of different solid tumors.

Author contributions

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Project administration: Zhengwu Cheng.

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Software: Xinyu Shao, Menglin Xu.

Writing – original draft: Junfeng Wang, Chunli Zhou.

Writing – review & editing: Zhengwu Cheng, Junfeng Wang, Ling Gao.

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