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Clinicopathological and prognostic role of ROC1 in neoplasms

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Regulator of cullins 1 (ROC1) is frequently overexpressed in multiple tumors, and many pieces of research demonstrate that ROC1 is associated with the prognosis and development of a diversity of neoplasms and it is able to serve as a promising prognostic biomarker. Here we performed this meta-analysis to evaluate the prognostic and clinicopathological significance of ROC1 in patients suffering from cancer.

Methods: We searched Pubmed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and WanFang database. The role of ROC1 in cancers was evaluated by pooled hazard ratios (HRs), odd ratios (ORs) and 95% confidence intervals (CIs).

Results: In total, 9 studies including 1002 patients were enrolled in this analysis. The pooled results showed that patients with high expression of ROC1 had poor overall survival (OS) (HR: 2.04, 95% CI: 1.48–2.60, $P < 0.001$) and recurrence-free survival (RFS) (HR: 1.727, 95% CI: 0.965–2.488, $P < 0.001$). Additionally, elevated expression of ROC1 was significantly correlated with advanced clinical Tumor Node Metastasis stage (OR: 2.708, 95% CI: 1.856–3.951, $P < 0.001$), positive lymph node metastasis (OR: 1.968; 95% CI: 1.294–2.993, $P = .002$), large tumor size (OR: 1.522, 95% CI: 1.079–2.149, $P = .017$) and poor tumor differentiation (OR: 2.448, 95% CI: 1.793–3.344, $P < 0.001$).

Conclusions: Elevated ROC1 expression predicted worse prognosis and advanced pathological parameters in various cancers. ROC1 was a significant prognostic biomarker for poor survival in human cancers.

Abbreviations: BLCA = bladder cancer, CIs = confidence intervals, DFS = disease-free survival, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, HRs = hazard ratios, IHC = immunohistochemistry, KM = Kaplan–Meier, LNM = lymph node metastasis, NOS = Newcastle–Ottawa scale, NSCLC = non-small cell lung cancer, ORs = odd ratios, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival, RBX1 = RING box protein 1, ROC1 = regulator of cullins 1, TNM = tumor node metastasis.

Keywords: biomarker, clinicopathological features, meta-analysis, neoplasms, prognosis, ROC1

1. Introduction

Cancer plays an important cause of morbidity and mortality worldwide, around 28.4 million new cancer cases are predicted to come about in 2040, a 47% rise from 19.3 million cases in 2020, according to International Agency for Research on Cancer research.[1] Studies have demonstrated that many biomarkers play significant roles in neoplasms but <1% of markers have been used for clinical practice.[2] Therefore, it is meaningful to investigate ideal prognostic predictor to offer valuable information in early detection and prediction of clinical parameters in cancer patients, guiding suitable treatment.[3]

Regulator of cullins 1 (ROC1) coded by oncogene ROC1, also known as RING box protein 1 (RBX1), a small molecule protein with a highly conserved framework and function, is a member of RING finger family. ROC1 is a key component of the E3 ubiquitin ligase SCF protein complex, which targeting in degrading numerous active proteins then adjusting a large amount of crucial biological process such as signal transduction, transcription and cell cycle procedure, regulating cell growth and apoptosis. ROC1 has attracted great interest in recent years because of its abnormal expression in a diversity of cancer.[4,5] Aberrant expression of ROC1 has been detected in various tumors, including breast cancer, bladder cancer, liver cancer, gastric cancer and

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nonsmall lung cancer.[5] Previous studies have demonstrated that high levels of ROC1 are intimately related to poor 5-year overall survival (OS) in gastric cancer, non-small cell lung cancer, esophageal cancer and liver cancer patients.[6–9] In bladder cancer, esophageal squamous cell carcinoma and gastric cancer, ROC1 acts as an independent prognostic biomarker of recurrence-free survival (RFS).[6, 10, 11] Overall, ROC1 promotes malignant progression of cancer and elevated ROC1 expression is positively associated with poor prognosis in tumors. On the other hand, increased ROC1 expression is associated with large tumor size, lymph node metastasis (LNM) and Tumor Node Metastasis (TNM) stage in a diversity of neoplasms.[6, 8, 10, 12–15] So elevated expression of ROC1 could be a potential biomarker for identifying patients with poor prognostic factors and advanced clinical features, serving as a potential target for cancer therapy.[9, 11, 16] Due to the limited sample size in present studies, we carried out this meta-analysis to elucidate the association of ROC1 between the prognosis and clinicopathologic characteristics in cancer patients, thus estimating the potential value of ROC1 as a promising prognostic predictor in human tumors.

2. Materials and methods

2.1. Literature searching strategies

We searched literature in Pubmed, Embase, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and WanFang database. The keywords were as follows: "RBX1 protein" OR "ring-box 1 protein" OR "ROC1 protein" AND "cancer" OR "carcinoma" OR "neoplasm" OR "tumor" AND "prognosis" OR "survival" OR "diagnosis". The latest search ended on November 1, 2021. We followed the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (see Supplementary PRISMA_2020_checklist.docx http://links.lww.com/MD/G847).

3. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies assessing the association between ROC1 levels with prognosis or clinicopathological parameters in humans; (2) studies classifying patients with high and low expression of ROC1 in tumor tissues; (3) research providing available data for extraction or calculation of hazard ratios (HRs) and 95% confidence intervals (CIs) for OS or RFS, or ORs for clinical parameters; (4) ROC1 protein expression was detected in cancer tissues by immunohistochemistry stain, immunoreactivity score (IRS) score or percentage of positive cells and categorized into "high" and "low" groups. The exclusion criteria were the following: (1) reviews, letters, conference reports and animal studies; (2) studies lacking enough data to obtain HRs and 95% CIs.

4. Data extraction and quality assessment

Two investigators (Nirui Shen and Qingting Wang) independently examined all literature based on the inclusion and exclusion criteria. The following data were carefully extracted from each included publication: (1) the family name of the first author, publication year, cancer type, sample size, follow-up time, detection method, outcome measures; (2) TNM stage, lymphatic node metastasis, tumor differentiation and tumor size; (3) HRs and 95% CIs for OS or RFS in each study. If HRs and 95% CIs were analyzed by multivariate and univariate analysis, the former was the priority. If studies solely provided Kaplan–Meier curves, Engauge Digitizer Version application was used to extract survival data.[17] Study quality was evaluated by the Newcastle-Ottawa quality assessment Scale (NOS) and the quality of the study was considered as high if the score ≥ 7.[18]

5. Statistical analysis

We used pooled HRs and 95% CIs to assess the association between ROC1 levels and prognosis in different tumors. Heterogeneity was performed by Chi-squared based Q test and I^2 statistics. A fixed-effect model was used if the heterogeneity was not significant ($P > 0.05$ for Chi-squared test or $I^2 < 50\%$) or the random-effect model was applied. Pooled odds ratios (ORs) and 95% CIs were used to evaluate the relationship between ROC1 levels and clinicopathological parameters. Subgroup analyses were classified by cancer type, sample size, follow-up months and HR estimation methods to analyze sources of heterogeneity. Sensitivity analysis was applied to examine the stability of the results, and the publication bias was evaluated by Funnel plots ($P < 0.05$ was considered significant). STATA software version 15.1 was used to perform all accessible data.

5.1. Ethical consideration

The institutional review board approval was not necessary because all the data in the study were retrieved from public databases.

6. Results

6.1. Study identification and characteristics

A total of 9 studies including 1002 patients were eligible in this analysis ultimately.[6–10, 16, 19–21] The flow diagram was shown in Figure 1. All researches were published from June 2013 to October 2021. Patients were classified into high and low groups according to ROC1 expression levels. There were 5 cancer types containing bladder cancer, non-small cell lung cancer, liver cancer, gastric cancer, and esophageal cancer. OS was used to evaluate the prognostic value of ROC1 in 8 studies and RFS was used in 3 research. The major information of included studies was summarized in Table 1.

6.2. Association between ROC1 expression levels and OS

HRs for OS was accessible in 8 studies involving 912 patients for this analysis. No significant heterogeneity was found in studies ($I^2 = 0.0\%$, $P = .864$), so pooled HRs and their 95% CIs were computed via a fixed model. As shown in Figure 2, patients with high expression of ROC1 had a poor OS in various carcinomas (HR: 2.04, 95% CI: 1.48–2.60, $P < 0.001$). Then we performed subgroup analyses by cancer type, sample size, follow-up time and HR obtained measurements (Fig. 3). Subgroup analysis showed overexpression of ROC1 could predict a poor 5-year survival rate both in digestive system malignancy (HR: 2.012, 95% CI = 1.407–2.618, $P < 0.001$; $I^2 = 0.0\%$, $P = .576$) and non-digestive system malignancy (HR: 2.211, 95% CI: 0.666–3.756, $P = .005$; $I^2 = 0.0\%$, $P = .871$) (Fig. 3A). After stratified by sample size, the prognostic value of ROC1 was not altered in <100 people group (HR: 1.690, 95% CI: 0.901–2.479, $P < 0.001$; $I^2 = 0.0\%$, $P = 0.864$) and >100 people group (HR: 2.403, 95% CI: 1.597–3.209, $P < 0.001$; $I^2 = 0.0\%$, $P = .815$) (Fig. 3B).

In addition, there was a notable association between increased ROC1 expression and poor OS in studies when follow-up time was < 90 months (HR: 2.078, 95% CI: 1.124-3.032, $P < 0.001$; $I^2 = 0.0\%$, $P = .959$) and > 90 months (HR: 2.018, 95% CI: 1.319–2.716, $P < 0.001$; $I^2 = 0.0\%$, $P = .406$) (Fig. 3C). HR estimation approach did not alter the association between ROC1 levels and OS in direct method subgroup (HR: 2.355, 95% CI: 1.441–3.268, $P < 0.001$; $I^2 = 0.0\%$, $P = .824$) and indirect method subgroup (HR: 1.845, 95% CI: 1.129-2.561, $P < 0.001$; $I^2 = 0.0\%$, $P = .666$) (Fig. 3D).

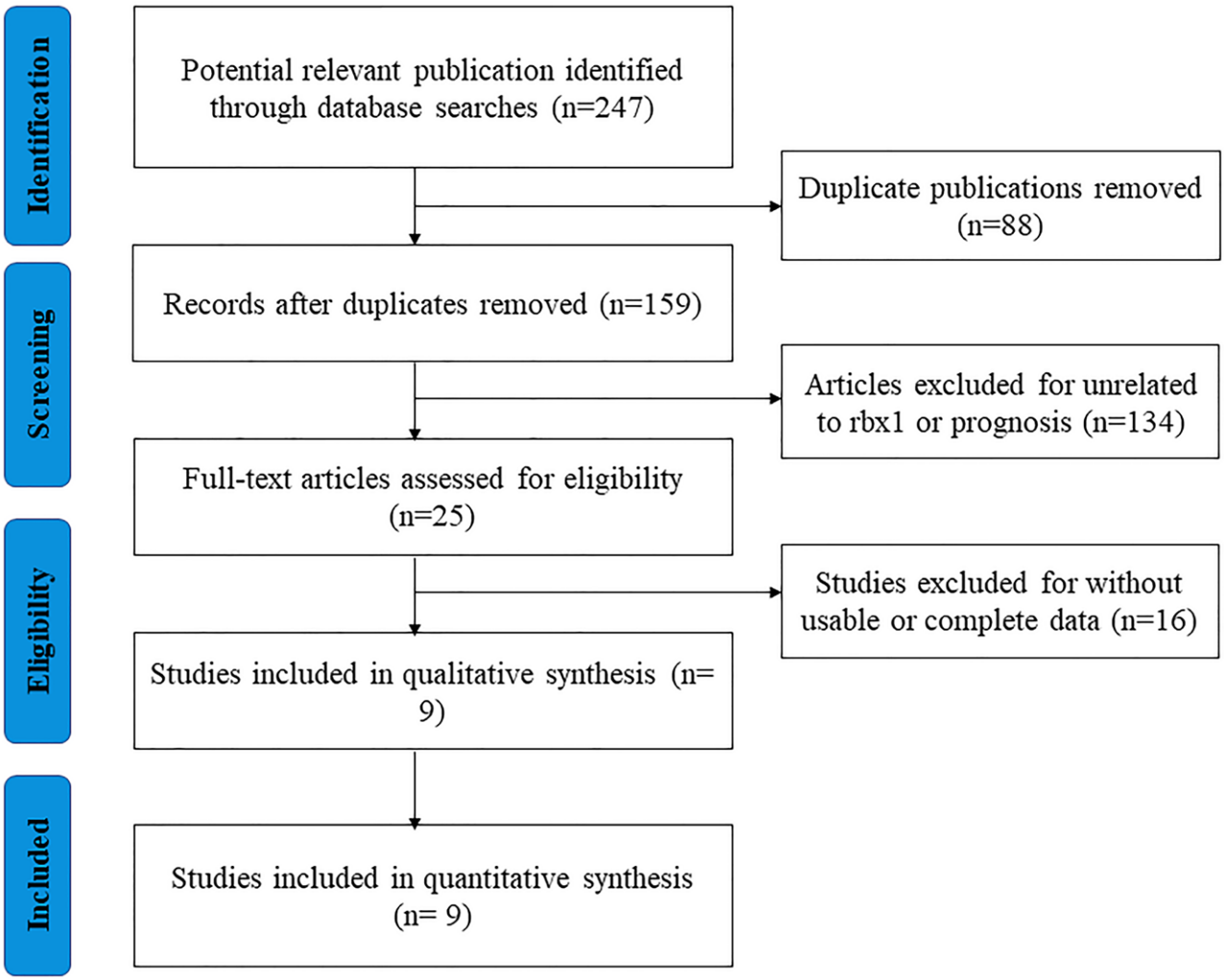

Figure 1. Flow chart of the studies identified in this meta-analysis.

6.3. Correlation between ROC1 expression levels and RFS

Three studies including 335 patients described HRs for RFS which contains bladder cancer, gastric cancer and esophageal squamous cell cancer. No significant heterogeneity was found among studies (I^2 = 0.0%, P = .795), so we used a fixed-effect model. The pooled HR for RFS was 1.727 (95% CI: 0.965–2.488, P < 0.001) (Fig. 4), indicating a remarkable association between high ROC1 expression levels and worse RFS.

6.4. Correlation between ROC1 and clinicopathologic parameters

Seven articles demonstrated the association between ROC1 expression and clinical pathological parameters in bladder cancer, esophageal squamous cell carcinoma, gastric cancer, hepatocellular carcinoma and non-small cell lung cancer. High ROC1 expression level was significantly related to poor differentiation (OR: 2.448, 95% CI: 1.793–3.344, P < 0.001) via a fixed effect model (I^2 = 36.7%, P = .148) (Fig. 5A), advanced TNM stage (OR: 2.708, 95% CI: 1.856–3.951, P < 0.001) via a fixed effect model (I^2 = 11.8%, P = .339) (Fig. 5B), large tumor size (OR: 1.522, 95% CI: 1.079–2.149, P = .017) via a fixed effect model (I^2 = 37.5%, P = .156) (Fig. 5C) and positive LNM (OR: 1.968, 95% CI: 1.294–2.993, P = .002) via a fixed effect model (I^2 = 0.0%, P = .438) (Fig. 5D).

6.5. Sensitivity analysis and publication bias

To test the stability of this meta-analysis, after removing each study, the pooled HR was not notably changed, indicating that the results were stable (Fig. 6). Also, Egger test showed no obvious evidence for publication bias (P = .719, 95% CI: -1.799-2.424) (Fig. 7).

7. Discussion

Regulator of cullins 1 (ROC1), encoded by the oncogene ROC1, is a highly conservative member of RING finger family.[22, 23] ROC1 protein, which serving as a cyclin-dependent kinase inhibitor, promotes cell proliferation and against apoptosis under both physiological and pathological states. It plays an indispensable role in cell proliferation through preventing p27 accumulation in the embryonic development.[4, 24] Importantly, ROC1 participates in tumorigenesis and tumor progression as an essential subunit of E3 ubiquitin-ligase SCF protein which degrades multiple proteins such as cell cycle proteins and transcription factors subsequently regulating cell growth and apoptosis.[5] ROC1 is reported to be overexpressed in a variety of neoplasms, including liver cancer, gastric cancer, esophageal cancer, bladder cancer, non-small cell lung cancer, renal cell carcinoma (RCC), prostate cancer, ovarian cancer and melanoma.[5, 12, 15, 25, 26] Thereby we conducted this meta-analysis to explore the potential connection between ROC1 expression and its

Table 1.

Main characteristics of 9 studies included in this meta-analysis.

Study	Cancer type	Test method	Sample size	Tumor size (large/small)	Tumor stage (I–II/ III–IV)	Lymphatic metastasis(yes/ no)	Tumor differentiation (poor/well-moderate)	Follow-up	Outcome measure	Hazards ratios	HR (95% CI)	NOS	ROC-1 high
Wang 2013	BLCA	IHC	70	15/15/26/14	NA	NA	22/6/19/23	85 mo	OS, RFS	KM	OS: 1.23 (0.06–25.08) RFS: 2.688 (1.048–6.892)	7	9–12
Yang 2013	HCC	IHC	151	54/33/28/36	NA	NA	36/20/46/49	90 mo	OS	KM	OS: 2.62 (1.55–4.42)	7	+++ to ++++
Migita 2014	GC	IHC	145	NA	NA	NA	NA	107 mo	OS, RFS	Direct	OS: 3.272 (1.544–6.886)RFS: 1.73 (0.78–3.84)	8	48%
Xing 2016	NSCLC	IHC	192	76/56/29/31	32/39/73/48	26/34/79/53	80/53/25/34	5.5 yr	OS	Direct	OS: 2.66 (1.22–5.82)	7	5–12
Celik 2017	BLCA	IHC	90	NA	NA	NA	40/8/17/25	NA	NA	NA	NA	6	6–9
Zhang 2017	ESCC	IHC	95	48/26/11/6	NA	33/16/26/19	43/22/16/14	100 mo	OS	KM	OS: 1.54 (0.88–2.68)	7	+++ to ++++
Chen 2018	GC	IHC	83	37/32/4/10	20/34/20/9	32/29/9/13	27/25/13/17	80 mo	OS	Direct	OS: 2.735 (1.162–6.442)	7	+++ to ++++
Kunishige 2020	ESCC	IHC	120	NA	NA	NA	NA	65 mo	OS, RFS	Direct	OS: 2.023 (1.165–3.513) RFS: 1.63 (0.95–2.79)	8	> 76.6%
Wu 2021	BLCA	IHC	56	10/4/19/23	8/14/21/13	12/3/17/24	21/11/8/16	82 mo	OS	KM	OS: 1.86 (0.70–4.93)	8	+++ to ++++

BLCA = Bladder cancer; DFS = Disease-free survival; ESCC = Esophageal squamous cell carcinoma; C = Gastric cancer; HCC = Hepatocellular carcinoma; HR = Hazard ratio; IHC = Immunohistochemistry; IRC = immunoreactivity score; KM = Kaplan–Meier; NA = Not available; NOS = Newcastle–Ottawa scale; NSCLC = non-small cell lung cancer; OS = Overall survival; PFS = progression-free survival; RFS = Recurrence-free survival; Staining intensity = + to ++++.

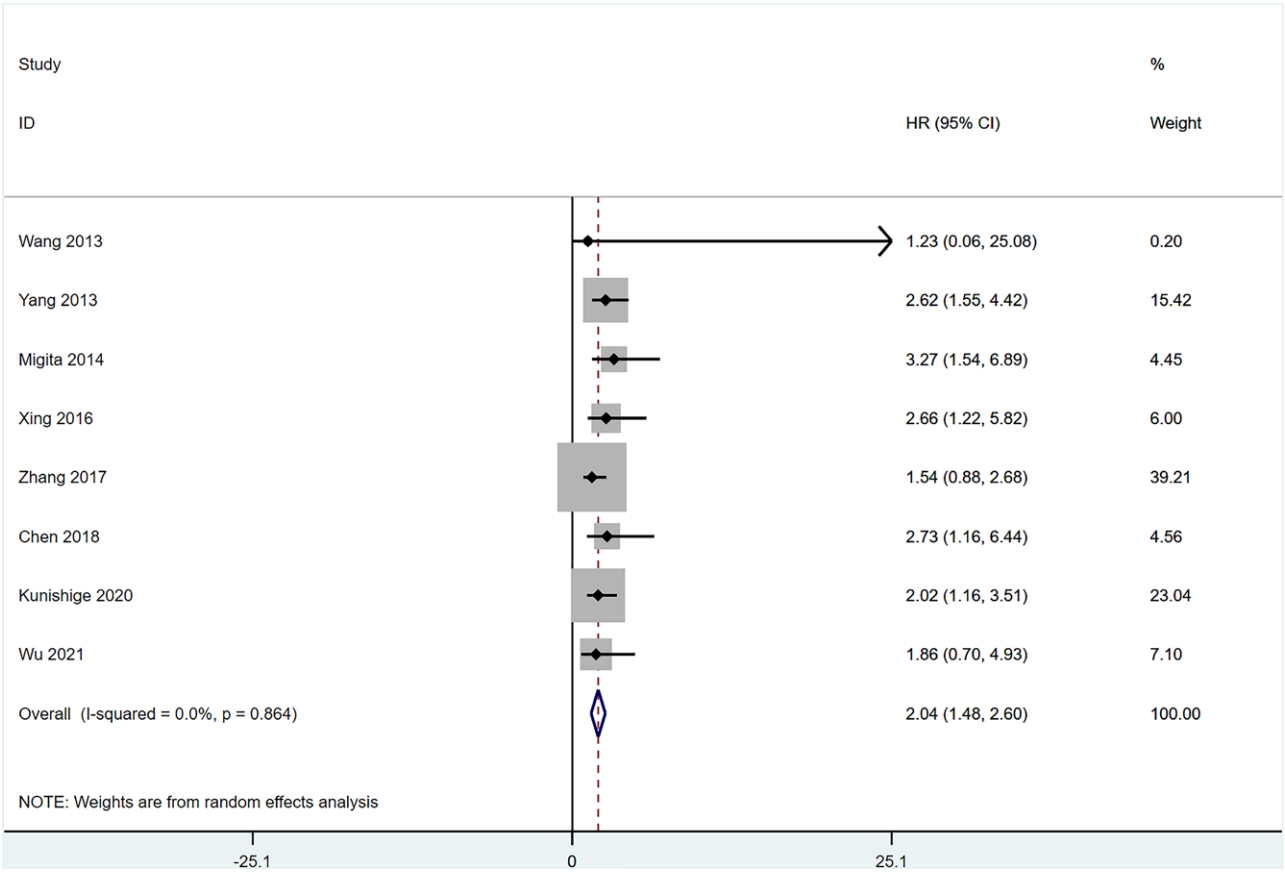

Figure 2. Forest plot to assess ROC1 expression and overall survival (OS). CI = confidence interval; HR = hazard ratio.

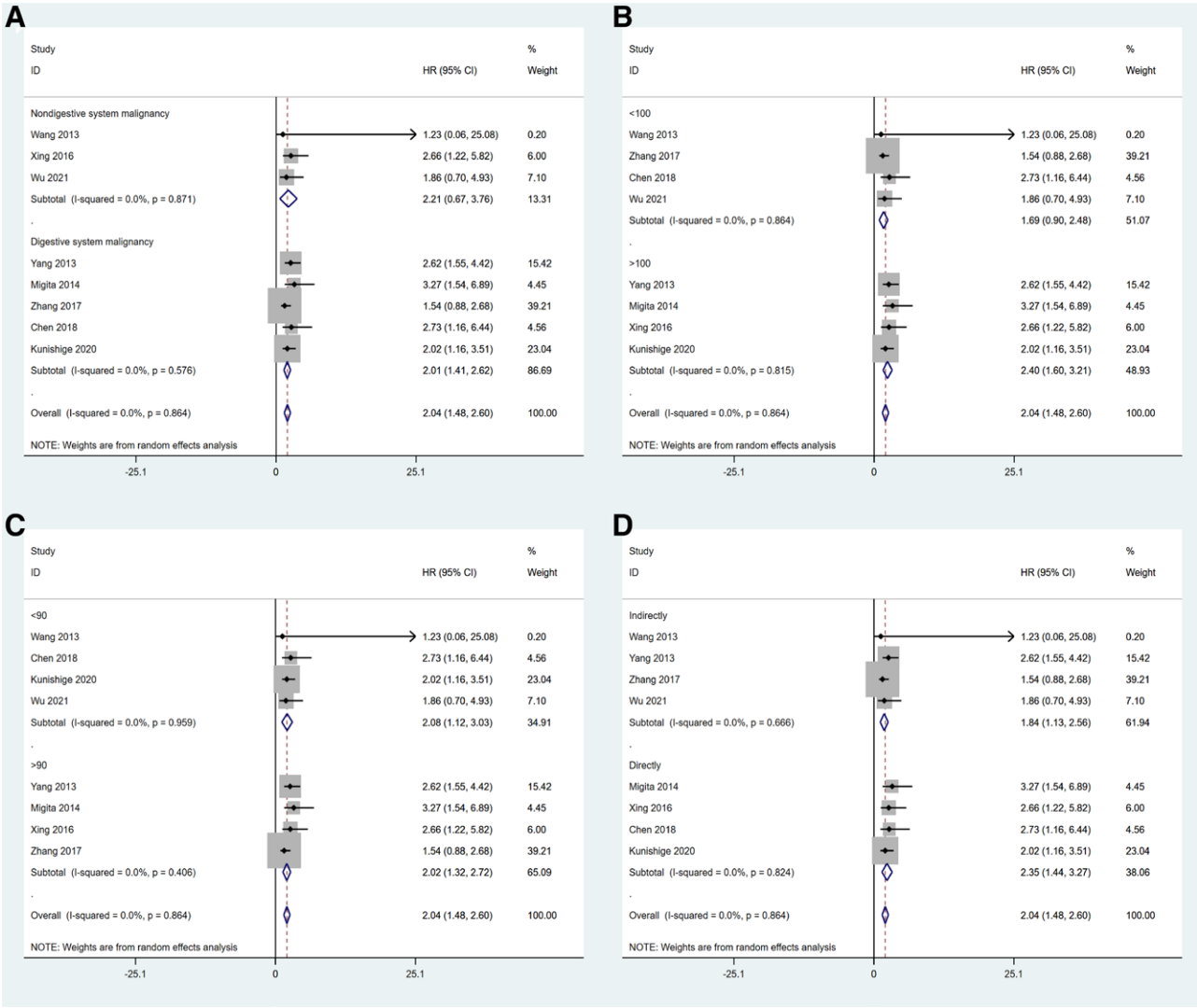

Figure 3. Stratified analyses to assess ROC1 expression and overall survival (OS). (A) subgroup analysis of HR of OS by cancer type; (B) subgroup analysis of HR of OS by sample size; (C) subgroup analysis of HR of OS by follow-up time; (D) subgroup analysis of HR of OS by HR obtained measurements.

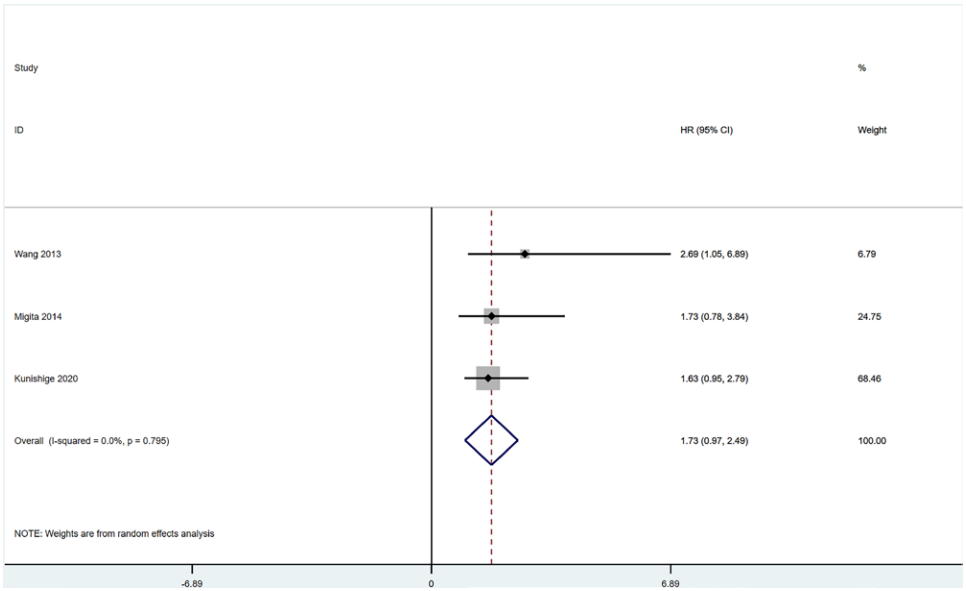

Figure 4. Forest plot to assess ROC1 expression and recurrence-free survival (RFS).

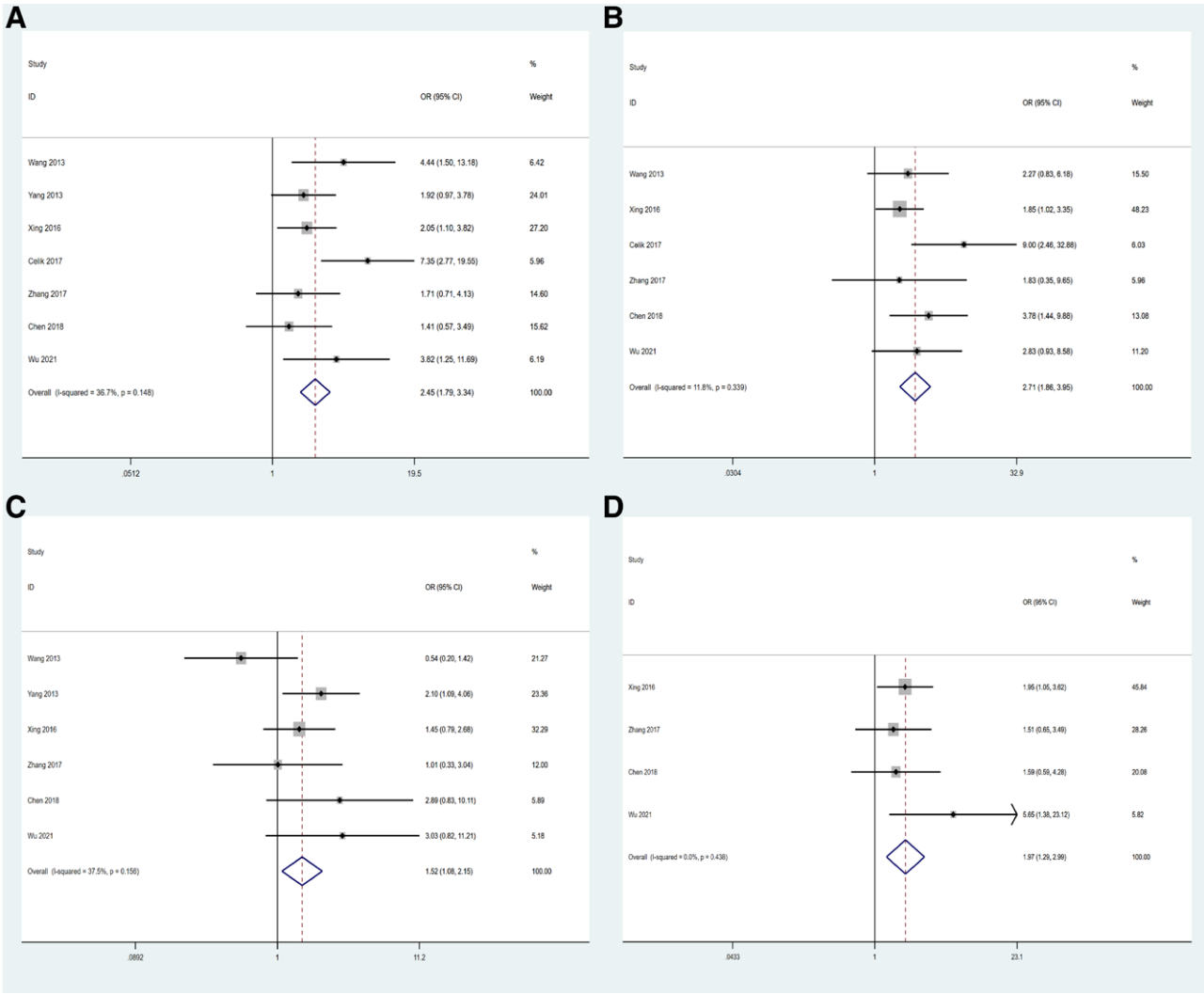

Figure 5. Forest plots to assess ROC1 expression and clinicopathological features. (A) differentiation; (B) tumor node metastasis (TNM) stage; (C) tumor size; (D) LNM.

prognostic values in cancers. Our results showed that ROC1 was able to serve as a potential prognostic biomarker in multiple tumors.

This was the first meta-analysis comprehensively reviewed the prognostic value of ROC1 in various cancers. A total of 9 studies including 1002 patients within 5 cancer types were included in our analysis. We demonstrated that aberrant high levels of ROC1 was notably associated with worse overall survival, poor tumor differentiation, advanced clinical TNM stage, large tumor size and positive LNM in neoplasms, indicating that increased ROC1 was a promising prognostic biomarker in clinicopathologic parameters in a diversity of cancers. In addition, we discovered that high levels of ROC1 was associated with poor RFS in bladder cancer, gastric cancer and esophageal squamous cell cancer. Collectively, our study concluded that ROC1 could serve as a novel prognostic biomarker with poor tumor progression.

ROC1 regulates cell survival, apoptosis and cellular senescence through multiple signal pathways thus promotes carcinogenesis in various human cancer cells.[23] Jia et al have found that silencing of ROC1 remarkably inhibits cancer cells growth via induction of G2/M arrest, apoptosis, and senescence through accumulation of cyclin B1 and Cdc2, collection of Puma, and p53/p21 and p16/pRB independent ways.[27] In liver neoplasms, Yang et al have discovered that knockdown of ROC1 significantly inhibits the growth of cancer cells through inducing p21-dependent cell senescence, and stimulates autophagy by inhibiting of DEPTOR-mTOR (mammalian target of rapamycin) axis. A study by Zhang et al indicates that slowing ROC1 activity with siRNA inhibition significantly curbs the growth of liver cancer through regulation of apoptosis factor ATF4, DNA damage factor P-H2AX and Neddylation pathway which is a novel modulator of the tumor microenvironment.[9, 28–30] In bladder cancer, aberrant ROC1 expression excessively degrade some cyclin dependent kinase inhibitors (e.g., p21, p27) and participates in ROC1-SUFU-GUI2 axis, boosting cancer cell growth.[31, 32] Wu et al have showed that ROC1 controls p-IκBα ubiquitination and regulates NF-κB signaling, stimulating p65 expression and activating several crucial genes subsequently promoting bladder cancer cell growth.[10, 16] In gastric cancer, Chen et al have demonstrated that depletion of ROC1 expressively impedes the growth of gastric cancer cells via p21-mediated cellular senescence and mitochondrial-dependent apoptosis, and ROC1 suppression can notably inhibit proliferation and invasion of gastric cancer cells.[7, 13] Kunishige et al have concluded that downregulation of ROC1 significantly disrupt the proliferation of esophageal cancer cells through regulation of p21.[6] Celik et al have demonstrated that overexpression of ROC1 is associated with advanced clinical stage and high prostate specific antigen (PSA) levels in prostate cancer patients

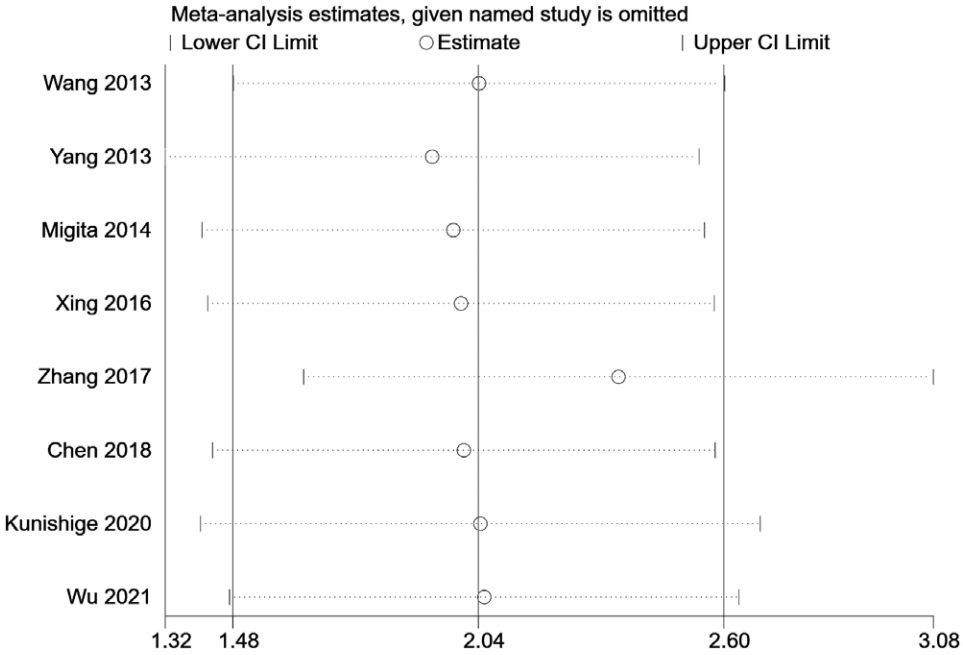

Figure 6. Sensitivity analysis of the correlation between ROC1 and prognosis.

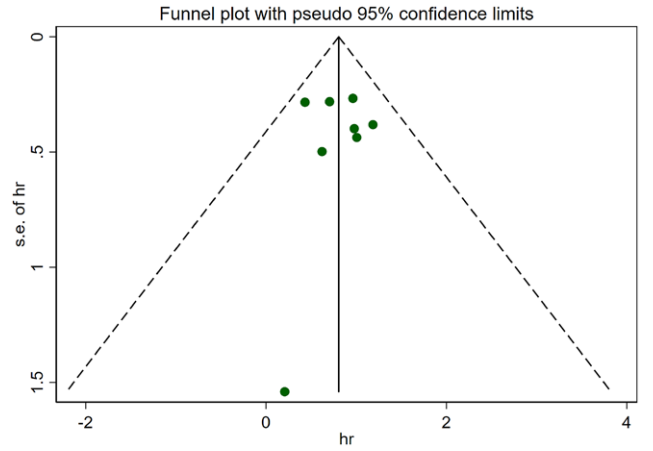

Figure 7. Funnel plot about the publication bias for overall survival (OS).

and depletion of ROC1 crucially induces apoptosis, senescence, autophagy and G2/M arrest in prostate cancer cells.[12] Several studies have indicated that overexpression of ROC1 is connected with higher Fuhrman grade and ROC1silencing remarkably hinders cancer cells growth and survival through G2/M arrest, senescence and apoptosis by accumulation of WEE1, p21, p27, NOXA, and BIM in renal cell carcinoma (RCC).[14, 25] Elevated ROC1 expression is associated with poor clinical features in ovarian cancer and reduced expression of ROC1 can inhibit ovarian cancer cells proliferation via ubiquitination of TP53 through the miR-194-5p/ROC1 pathway, finally blocking cancer cells growth and invasion. Additionally, ROC1 is found to be associated with chromosome instability in ovarian cancer cells.[15, 33] In skin cancer, Zhang et al have investigated that downregulation of ROC1 significantly impeded the progression of malignant melanoma through miR-135b/ROC1 axis.[34] Therefore, those positive proof indicate that ROC1 plays principle roles in tumor progression and can act as a promising prognostic maker for human cancers.

Nevertheless, our analysis had some limitations. Firstly, only 9 studies including 1002 patients were involved in this analysis and fewer studies about RFS were enrolled in the analysis, which prevented us from obtaining adequate evidence. Secondly, some survival data were extracted from Kaplan–Meier curves which may affect the pooled HR. To minimize the inaccuracy, 2 researchers independently extracted data from survival curves. Thirdly, the cutoff values defining high/low ROC1 expression were not uniform, which may influence the pooled outcomes. Fourthly, this meta-analysis included some retrospective studies. Therefore, more multicenter, large sample size trials are required to get more accurate conclusions.

8. Conclusions

In conclusion, we demonstrated that ROC1 had a noticeable prognostic value in numerous tumors. Increased ROC1 can act as a promising prognostic biomarker for poor OS and RFS, advanced TNM stage, poor differentiation, large tumor size and positive LNM in human neoplasms.

Author contributions

NRS, QTW, and MXL are responsible for the study design, definition of intellectual content, data analysis, manuscript preparation and editing; YJQ and YW performed the searches and screened the potential studies, extracted data and assess the risk of bias. NRS and DYL arbitrated any disagreements during the review. All review authors critically reviewed, revised and approved the final version of this manuscript.
Conceptualization: Nirui Shen, Qingting Wang, Manxiang Li.
Methodology: Yuanjie Qiu, Yan Wang.
Software: Danyang Li, Nirui Shen.
Writing original draft: Nirui Shen, Qingting Wang.
Writing revision & editing: Nirui Shen, Manxiang Li.

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