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The prognostic value of proliferating cell nuclear antigen expression in colorectal cancer

A meta-analysis

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Abstract

Background: A number of studies have attempted to determine the prognostic significance of proliferating cell nuclear antigen (PCNA) in patients with colorectal cancer (CRC), but the reports are controversial and inconsistent. Thus, we conducted a meta-analysis to clarify the value of PCNA in CRC prognosis.

Methods: A systematic search of relevant studies was performed in 4 electronic databases including PubMed, Cochrane Library, Embase, and Web of Science until February 2018. Hazard ratios (HRs) combined with 95% confidence intervals (95% CIs) were used to evaluate the relationship of PCNA expression with overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS).

Results: A total of 1372 CRC patients in 14 studies were identified eventually in our meta-analysis. The pooled HRs demonstrated that CRC patients with high PCNA expression was significantly correlated with poor OS (HR = 1.81; 95% CI: 1.51–2.17; $P = .000$), CSS (HR = 1.99; 95% CI: 1.04–3.79; $P = .037$); but not significantly with DFS (HR = 2.48; 95% CI: 0.98–6.26; $P = .055$). Sensitivity analysis showed the pooled HRs for OS, CSS, and DFS were stable when the included studies were removed one by one.

Conclusion: Our meta-analysis suggested that high PCNA expression was associated with poor prognosis, and it could serve as a reliable and prognostic biomarker in CRC patients. More large-scale studies are needed to further support the conclusion.

Abbreviations: CI = confidence interval, CSS = cancer-specific survival, DFS = disease-free survival, HR = hazard ratio, NOS = Newcastle-Ottawa Scale, OS = overall survival, PCNA = proliferating cell nuclear antigen.

Keywords: colorectal cancer, meta-analysis, proliferating cell nuclear antigen, survival outcome

1. Introduction

Colorectal cancer (CRC) is a common and lethal type of malignant tumor with high morbidity.[1] At present, CRC is the third leading cause of death in developed countries.[2] In China, CRC remains the fifth highest incidence and the fourth highest mortality among all cancers in both men and women.[3] In the last one decade, CRC has been considered as a highly invasive disease and its incidence has steadily increased. Although novel target therapies of CRC have been greatly developed, the prognosis of clinical patients is still not ideal. Thus, it is needed to seek an effective predictive measure to identify those CRC patients with poor prognosis, thereby allowing them to be benefit from early systemic treatment. Up to now, it is widely recognized that the prognosis is highly decided by clinical tumor-node-metastasis (TNM) stage[4];however, the clinical outcome of CRC patients in the same TNM stage is markedly different.[5] Therefore, valuable biomarkers for CRC prognosis prediction should be identified to improve clinical treatment.

Proliferating cell nuclear antigen (PCNA), a protein with 36 kDa length, which was identified as a cyclin or auxiliary protein for DNA polymerase delta.[6,7] PCNA expression showed a periodic change periodically with the replication of DNA, which plays an important role in the cell proliferation. In addition, its co-expression with other widely recognized markers suggests a key role in cell division. A series of studies have demonstrated that PCNA over expression is correlated with poor prognosis in several types of cancer including CRC. However, it still remains controversial for the prognosis prediction of PCNA expression in CRC. High PCNA expression was considered an unfavorable prognostic marker in CRC in many studies,[8–13] but some other studies suggested that it had no significance and even revealed a favorable prognosis.[14,15] In order to evaluate the value of PCNA in the prognosis of CRC more precisely, we conducted a meta-analysis to further investigate the correlation between PCNA expression and prognosis in CRC patients.

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HZ and TH have contributed equally to this work.

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2. Materials and methods

2.1. Search strategy

Several electronic databases, including PubMed, Web of Science, Embase, and Cochrane Library, were systematically searched from September 1991 to February 2018. The search strategy with terms was used as follows: ("cancer" or "tumor" or "neoplasm" or "carcinoma" or "malignancy") and ("colorectal" or "colonic" or "colon" or "rectal" or "rectum") and ("PCNA" or "proliferating cell nuclear antigen") and ("prognosis" or "survival" or "outcome" or "mortality" or "prognostic"). Moreover, we further screened the reference lists of the included articles carefully to search additional eligible publications.

2.2. Selection criteria

Study selection was conducted by 2 investigators independently and all included studies meet the following criteria: the research objects must be human beings rather than animals; the association of PCNA with the prognostic value in CRC should be described; studies detected PCNA protein expression by immunohistochemistry (IHC); hazard ratio (HR) and 95% confidence interval (CI) for overall survival (OS), cancer-specific survival (CSS), disease-free survival (DFS) were provided directly or could be calculated through the sufficient survival data. Exclusion criteria were as follows: non-human studies; non-English papers; review articles, case reports, letters, or meeting records; the study did not report HR and 95% CI or lacked sufficient data for calculating.

2.3. Data extraction

Data were retrieved from included studies by 2 independent reviewers (YX and LP), using a predesigned standardized form and any inconsistence was resolved by conversation with a third investigator (RW). These valuable data were extracted as follows: surname of the first author, publication year, inclusion period, country, cancer type, number of patients, sex, age, method of evaluating PCNA, PCNA cut-off of staining, follow-up time, and effect estimates, as well as, HR of PCNA expression for OS, CSS, or DFS, and their 95% CI (Table 1). If the HRs and 95% CIs were not directly available, we calculated them according to the methods reported by Tierney et al[16] or estimated them on the basis of the Kaplan–Meier survival curves using Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/).[17]

2.4. Quality assessment

Two independent reviewers (YX and LP) assessed the quality of the included studies using the Newcastle–Ottawa scale (NOS), which was recommended by the Cochrane Non-Randomized Studies Methods Working Group.[18] Three broad perspectives containing 8 methodology items were used to assess each included study. The score of NOS is ranging from 0 to 9. A high-quality study was regarded as a score ≥6. To ensure the reliability of this meta-analysis, we only included high-quality studies for further analysis.

2.5. Statistical analysis

Pooled HR with its 95% CI was applied to assess the association between PCNA expression and prognostic outcomes. An observed HR >1 indicated unfavorable prognosis for patients with high PCNA expression, and the effect of PCNA expression on survival would be considered statistical significance when the 95% CI corresponding to the HR did not overlap 1. The heterogeneity of between-study in this meta-analysis was evaluated using Cochran Q test and Higgins I-squared (I^2) statistic. Heterogeneity was considered high, medium or low if I^2 ≥75%, 50%–75%, or <50%, respectively.[19] When the heterogeneity was low ($I^2 < 50\%$), a fixed-effect model (Mantel–Haenszel method) was applied. Otherwise, a random-effect mode (DerSimonian and Laird method) was chosen. In addition, subgroup analyses were performed to investigate the potential factors of heterogeneity based on ethnicity, staining cutoff, analysis method, and sample size. If heterogeneity was observed, sensitivity analysis was performed to assess the influence of each study on the robustness of pooled results. Publication bias was estimated by Egger test and Begg funnel plot, with $P > .05$ indicating no potential publication bias.[20] To ensure the accuracy of the evaluation, we only performed Egger test and Begg funnel plot on overall survival (OS) which had sufficient included studies (n ≥ 10).[21] All statistical analyses were performed by STATA version 12.0 software (Stata Corporation, College Station, TX), and $P < .05$ was considered statistically significant.

Table 1

Characteristics of included studies in the meta-analysis.

Study	Year	Study period	Country	Cancer type	Case number	Gender (M/F)	Age, y	Detection method	Cutoff staining	Follow up, mo	Survival analysis	Analysis method	Quality score*
Ho	2017	NR	China	CC	59	44/15	52/7[a] (≥50 y/<50 y)	IHC	50%	NR	OS	Multivariate analysis	6
Li	2016	2011–2014	China	RC	329	207/122	62 (mean)	IHC	10%	1–58 (range)	OS	Multivariate analysis	8
Ye	2016	2005–2007	China	CRC	117	55/62	36/25 (≥65 y/<65 y)	IHC	10%	63.5 (mean)	OS, DFS	Multivariate analysis	7
Huh	2009	2001–2004	Korea	RC	135	80/55	66/69 (≥65 y/<65 y)	IHC	45%	60 (mean)	OS, DFS	Multivariate analysis	8
Chen	2009	1998–2000	China	CRC	88	50/38	62.2 (mean)	IHC	50%	60 (mean)	OS	Multivariate analysis	8
Hu	2008	1986–2006	China	RC	49	25/24	59.2 (mean)	IHC	75.50%	62.3 (mean)	CSS, DFS	Univariate analysis	8
Kunihiro	1998	NR	Japan	CRC	59	39/20	64.1 (mean)	IHC	47%	NR	OS	Survival curve	7
Kawamoto	1998	1989–1995	Japan	CRC	92	48/44	58/34 (>60 y/≤60 y)	IHC	42.30%	NR	OS	Survival curve	7
Nakae	1998	1991–1993	Japan	CRC	52	NR	28/24 (≥65 y/<65 y)	IHC	48.80%	NR	OS	Survival curve	7
Hiraga	1998	1983–1993	Japan	CRC	100	64/36	62.7 (mean)	IHC	48%	65.7 (mean)	CSS	Survival curve	8
Choi	1997	1990–1992	Korea	CRC	86	49/37	57.4 (mean)	IHC	46.50%	NR	CSS	Survival curve	8
Tatsuta	1997	1983–1991	Japan	CRC	58	NR	NR	IHC	47%	NR	OS	Survival curve	7
Neoptolemos	1996	1967–1976	UK	CRC	91	46/45	65 (mean)	IHC	50%	NR	OS	Survival curve	8
Nakamura	1995	1991–1994	Japan	CRC	57	38/19	64.7 (mean)	IHC	49.40%	36 (mean)	OS	Survival curve	6

CC = colon cancer, CRC = colorectal cancer, CSS = cancer-specific survival, DFS = disease-free survival, IHC = immunohistochemistry, NR = not reported, OS = overall survival, RC = rectal cancer.

[a] 52 patients ≥50 years, and other 7 patients <50years.

* The quality assessment of included studies using the Newcastle-Ottawa Scale (NOS).

2.6. Ethical statement

This meta-analysis conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[22] This meta-analysis based on previous published studies. Consequently, no ethical approval or patient consent was required.

3. Results

3.1. Search results

In total, 699 relevant articles were incorporated into our initial study after primary retrieval, including 188 in Pubmed, 202 in Embase, 304 in Web of Science, 5 in Cochrane Library. Among these studies, 280 were excluded for duplicate publication. Three hundred eighty articles were further excluded by screening the titles and abstracts. The remaining 45 potentially relevant articles were evaluated carefully through reading the full text. Twenty-five articles were further removed with the following reasons: such as no IHC evaluation, no sufficient survival data available (hazard ratio [HR] and 95% confidence interval [CI]), and low-quality studies. Finally, 14 articles published from 1995 to 2017 with 1372 patients is in line with the criteria for meta-analysis.[8–14,23–29] The detailed process of study selection is presented as a flowchart in Fig. 1.

3.2. Characteristics of studies

In total, 6 studies originated from Japan, 5 were from China, 2 were from Korea, and 1 was from the United Kingdom. Among these studies, 11 studies were performed to analyze overall survival (OS), 3 studies reported the data of cancer-specific survival (CSS), and 3 studies were conducted to investigate disease-free survival (DFS). Based on the NOS score, 7 studies got a score of 8, 5 studies achieved a score of 7, and 2 studies had a score of 6. The mean NOS score for these studies was 7.357 (range 6–8). All studies conducted IHC staining to investigate PCNA expression. The main characteristics of the 14 included studies are summarized in Table 1.

3.3. Meta-analysis

In total, 11 studies in our meta-analysis investigated the correlation between PCNA expression and OS. The result showed that CRC patients with high PCNA expression had a poor OS (HR = 1.81; 95% CI: 1.51–2.17; $P = .000$; Fig. 2). The data was pooled by fixed-effect model and no obvious between-study heterogeneity was observed ($I^2 = 40.1\%$, $P = .081$). Three studies explored the association of PCNA expression with CSS and DFS, respectively. Meta-analysis of these studies demonstrated that PCNA overexpression in CRC patients correlated with a poor CSS (HR = 1.99; 95% CI: 1.04–3.79; $P = .037$; Fig. 3), but no statistical association with DFS (HR = 2.48; 95% CI: 0.98–6.26; $P = .055$; Fig. 4). We conducted fixed-effect model and random-effect model to pool the data and no obvious heterogeneity for CSS ($I^2 = 47.3\%$, $P = .150$) was observed, but a medium heterogeneity existed in DFS ($I^2 = 65.6\%$, $P = .054$).

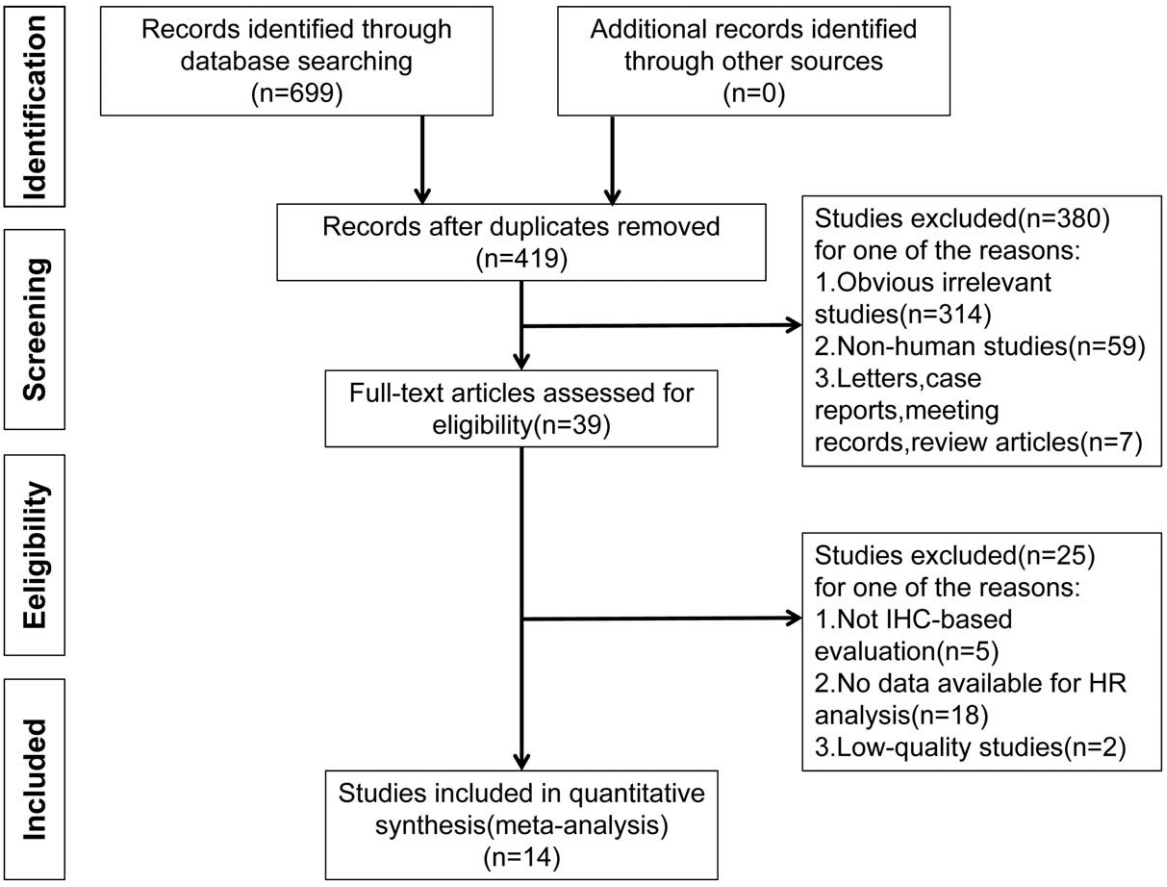

Figure 1. Flowchart of study selection.

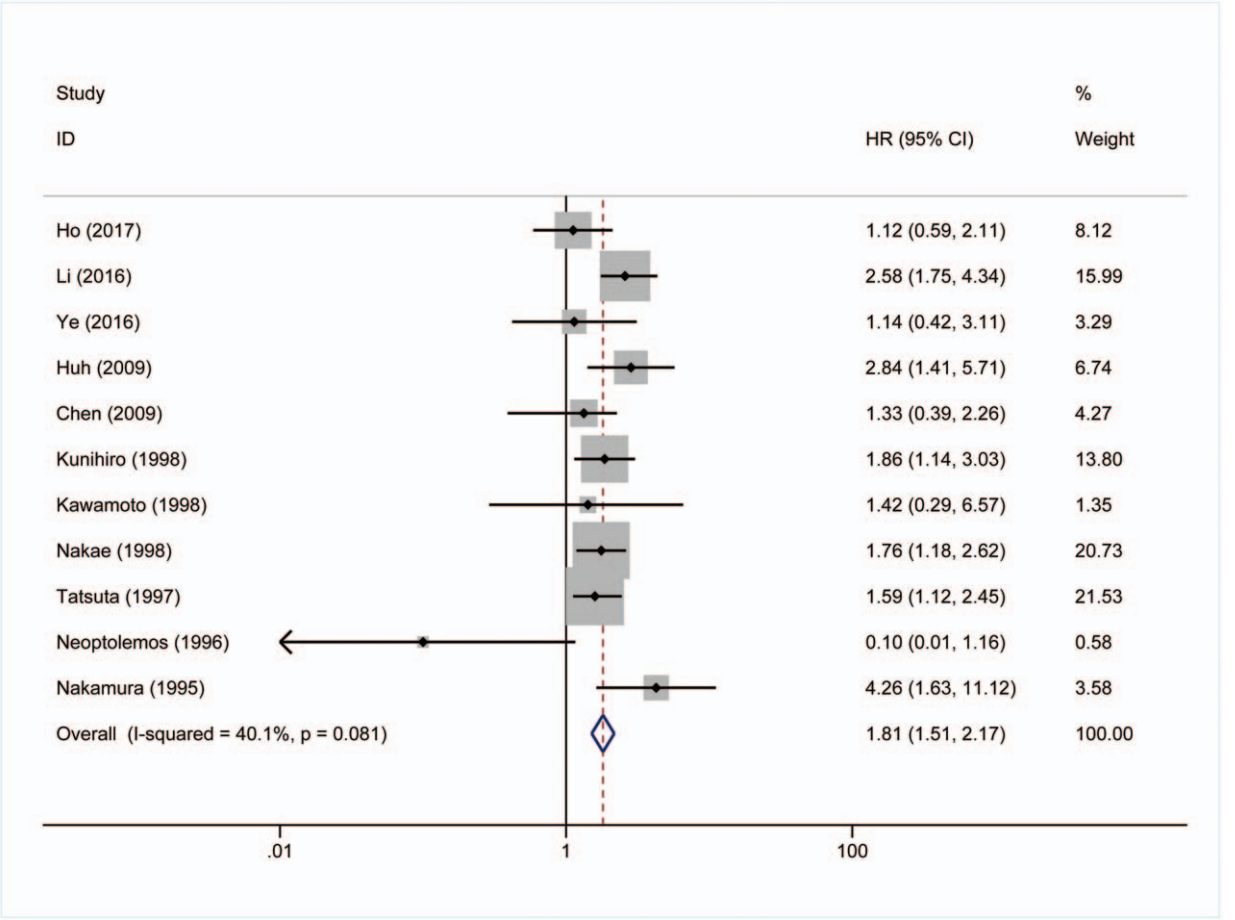

Figure 2. Forest plot diagrams of hazard ratios for correlations between PCNA expression and overall survival (OS). A HR > 1 implies a worse OS for the group with increased PCNA. The center of the lozenge gives the combined HR for the meta-analysis, and its extremities give the 95% CI. CI = confidence interval, HR = hazard ratio, PCNA = proliferating cell nuclear antigen.

3.4. Subgroup analysis

In addition, we conducted subgroup analysis based on ethnicity, cut-off value, analysis method, and sample size.

3.4.1. Subgroup analysis based on ethnicity. In the ethnicity subgroup, high PCNA expression was correlated with poor OS (HR = 1.84; 95% CI: 1.53–2.21; $P = .000$), CSS (HR = 1.99; 95% CI: 1.04–3.79; $P = .037$), but not with DFS (HR = 2.48; 95% CI: 0.98–6.26; $P = .055$) in Asian patients, as well as not with OS (HR = 0.10; 95% CI: 0.01–1.08; $P = .058$) in Non-Asian patients (Table 2).

3.4.2. Subgroup analysis based on different cut-off value. In the cut-off of staining subgroup analysis, high PCNA expression was correlated with poor OS (HR = 1.96; 95% CI: 1.61–2.38; $P = .000$), DFS (HR = 1.88; 95% CI: 1.10–3.23; $P = .022$) but not with CSS (HR = 1.61; 95% CI: 0.81–3.17; $P = .171$) when the cut-off value <50%. Studies with a cut-off value ≥50% showed that high PCNA expression was associated with poor DFS (HR = 7.35; 95% CI: 2.14–25.20; $P = .002$) and CSS (HR = 13.20; 95% CI: 1.75–101; $P = .013$) but not with OS (HR = 0.92; 95% CI: 0.39–2.16; $P = .854$).

3.4.3. Subgroup analysis based on analysis method. With respect to analysis method, high PCNA expression was correlated with poor OS (HR = 1.70; 95% CI: 1.08–2.69; $P = .022$) and DFS (HR = 1.88; 95% CI: 1.10–3.23; $P = .022$) for multivariate analysis, and poor DFS (HR = 7.35; 95% CI: 2.14–25.20; $P = .002$) for univariate analysis, as well as with poor OS (HR = 1.63; 95% CI: 1.17–2.26; $P = .004$) but not with CSS (HR = 1.61; 95% CI: 0.81–3.17; $P = .171$) for survival curve group.

3.4.4. Subgroup analysis based on sample size. For sample size subtype, high PCNA expression was associated with poor OS (HR = 2.39; 95% CI: 1.67–3.41; $P = .000$) and DFS (HR = 1.88; 95% CI: 1.10–3.23; $P = .022$) in study with sample numbers ≥100; as well as with poor OS (HR = 1.64; 95% CI: 1.33–2.03; $P = .000$) and DFS (HR = 7.35; 95% CI: 2.14–25.20; $P = .002$) in study with sample numbers <100 but not with CSS (HR = 3.80; 95% CI: 0.41–35.49; $P = .241$).

3.5. Sensitivity analysis

Sensitivity analysis was performed by removing all included studies sequentially to detect the influence of each study on the pooled HR. The pooled HR of OS, DFS, and CSS were not significantly changed, suggesting the results were stable (Tables 3–5).

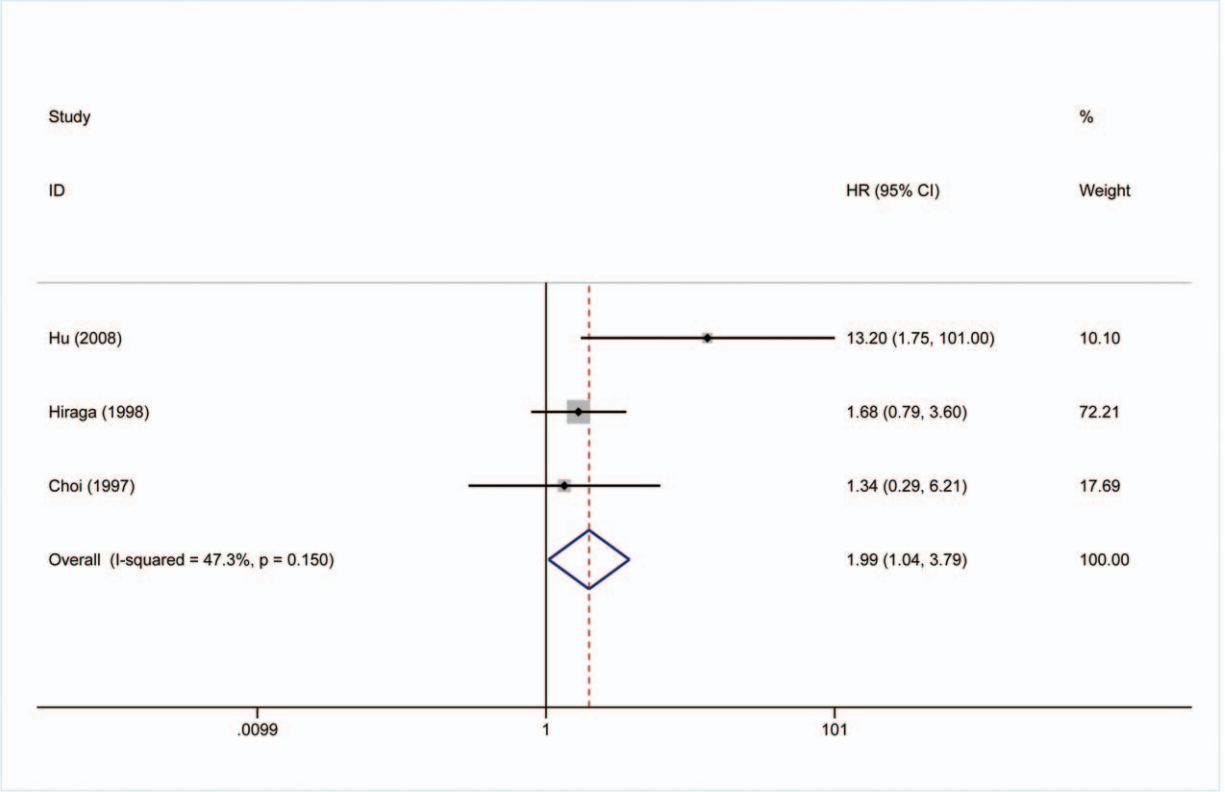

Figure 3. Forest plot diagrams of hazard ratios for correlations between PCNA expression and cancer-specific survival (CSS). A HR > 1 implies a worse CSS for the group with increased PCNA. The center of the lozenge gives the combined HR for the meta-analysis, and its extremities give the 95% CI. CI = confidence interval, HR = hazard ratio, PCNA = proliferating cell nuclear antigen.

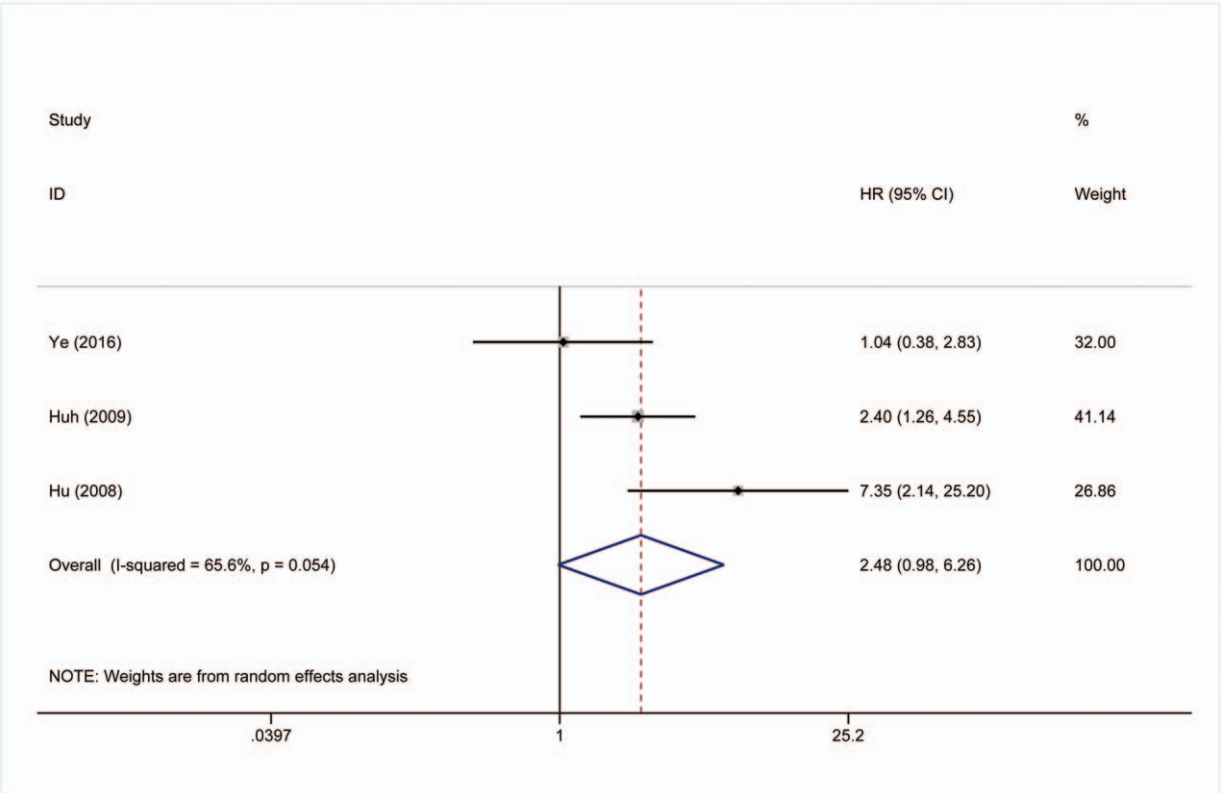

Figure 4. Forest plot diagrams of hazard ratios for correlations between PCNA expression and disease-free survival (DFS). No association was found between PCNA and DFS, and the 95% CI for the overall HR did overlap 1. The center of the lozenge gives the combined HR for the meta-analysis, and its extremities give the 95% CI. CI = confidence interval, HR = hazard ratio, PCNA = proliferating cell nuclear antigen.

Table 2

Subgroup analysis of the associations between PCNA overexpression and prognostic outcomes.

Groups	Number of studies	Pooled HR	95% CI)	*P* value	Model	Heterogeneity	
						I^2 (%)	*P* value
OS							
Ethnicity							
Asians	10	1.84	1.53–2.21	.000	Fixed	18.0	.278
Non-Asians	1	0.10	0.01–1.08	.058	-	-	-
Cutoff of staining							
<50%	8	1.96	1.61–2.38	.000	Fixed	9.2	.359
≥50%	3	0.92	0.39–2.16	.854	Random	50.9	.130
Analysis method							
Multivariate analysis	5	1.70	1.08–2.69	.022	Random	53.0	.075
Survival curve	6	1.63	1.17–2.26	.004	Fixed	9.0	.359
Univariate analysis	0	-	-	-	-	-	-
Sample size							
≥100	3	2.39	1.67–3.41	.000	Fixed	18.1	.295
<100	8	1.64	1.33–2.03	.000	Fixed	37.2	.132
CSS							
Ethnicity							
Asians	3	1.99	1.04–3.79	.037	Fixed	47.3	.150
Non-Asians	0	-	-	-	-	-	-
Cutoff of staining							
<50%	2	1.61	0.81–3.17	.171	Fixed	0.0	.795
≥50%	1	13.20	1.75–101	.013	-	-	-
Analysis method							
Univariate analysis	1	13.20	1.75–101	.013	-	-	-
Survival curve	2	1.61	0.81–3.17	.171	Fixed	0.0	.795
Multivariate analysis	0	-	-	-	-	-	-
Sample size							
≥100	1	1.68	0.79–3.59	.180	-	-	-
<100	2	3.80	0.41–35.49	.241	Random	67.9	.078
DFS							
Ethnicity							
Asians	3	2.48	0.98–6.26	.055	Random	65.6	.054
Non-Asians	0	-	-	-	-	-	-
Cutoff of staining							
<50%	2	1.88	1.10–3.23	.022	Fixed	47.1	.169
≥50%	1	7.35	2.14–25.20	.002	-	-	-
Analysis method							
Multivariate analysis	2	1.88	1.10–3.23	.022	Fixed	47.1	.169
Univariate analysis	1	7.35	2.14–25.20	.002	-	-	-
Survival curve	0	-	-	-	-	-	-
Sample size							
≥100	2	1.88	1.10–3.23	.022	Fixed	47.1	.169
<100	1	7.35	2.14–25.20	.002	-	-	-

CI = confidence interval, CSS = cancer-specific survival, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, PCNA = proliferating cell nuclear antigen.

Table 3

Pooled HRs of sensitivity analysis for the effect of PCNA expression on overall survival.

Study omitted	Estimate HR	95%CI	
		Lower	Upper
Ho (2017)	1.89	1.56	2.28
Li (2016)	1.69	1.39	2.06
Ye (2016)	1.84	1.53	2.21
Huh (2009)	1.75	1.45	2.11
Chen (2009)	1.84	1.52	2.21
Kunihiro (1998)	1.80	1.48	2.19
Kawamoto (1998)	1.82	1.51	2.18
Nakae (1998)	1.82	1.49	2.24
Tatsuta (1997)	1.88	1.53	2.30
Neoptolemos (1996)	1.84	1.53	2.21
Nakamura (1995)	1.75	1.46	2.11
Combined	1.81	1.51	2.17

CI = confidence interval, HR = hazard ratio, PCNA = proliferating cell nuclear antigen.

3.6. Publication bias

Publication bias was evaluated by Begg and Egger tests in the present meta-analysis. As shown in Fig. 5, there is no apparent asymmetry exists in the funnel plots. The Begg *P* value was .533

Table 4

Pooled HRs of sensitivity analysis for the effect of PCNA expression on cancer-specific survival.

Study omitted	Estimate HR	95%CI	
		Lower	Upper
Ye (2016)	3.69	1.27	10.74
Huh (2009)	2.67	0.39	18.14
Hu (2008)	1.73	0.78	3.85
Combined	1.99	1.04	3.79

CI = confidence interval, HR = hazard ratio, PCNA = proliferating cell nuclear antigen.

Table 5

Pooled HRs of sensitivity analysis for the effect of PCNA expression on disease-free survival.

Study omitted	Estimate HR	95%CI	
		Lower	Upper
Hu (2008)	1.61	0.81	3.17
Hiraga (1998)	3.08	0.91	10.45
Choi (1197)	2.16	1.06	4.40
Combined	2.48	0.98	6.26

CI = confidence interval, HR = hazard ratio, PCNA = proliferating cell nuclear antigen.

and Egger *P* value was .318 suggested that no obvious publication bias was discovered in our meta-analysis. (Figs. 5 and 6)

4. Discussion

PCNA, a highly conserved acid nuclear protein, whose expression shows a periodic change with the DNA replication phase.[30] Moreover, PCNA plays an important part in the DNA repair pathways including base excision repair, nucleotide excision repair, and mismatch repair, and it can directly interacted with several proteins of these pathways to exerts the DNA repair role.[31] In addition to the DNA replication and

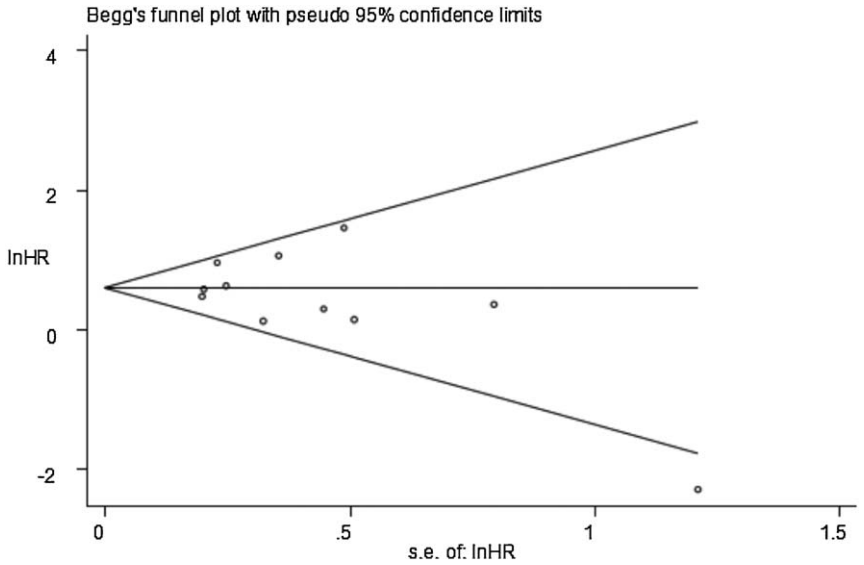

Figure 5. Begg funnel plot detect the potential publication bias of the prognostic value of PCNA for overall survival in colorectal cancer (*P* = .533). PCNA = proliferating cell nuclear antigen.

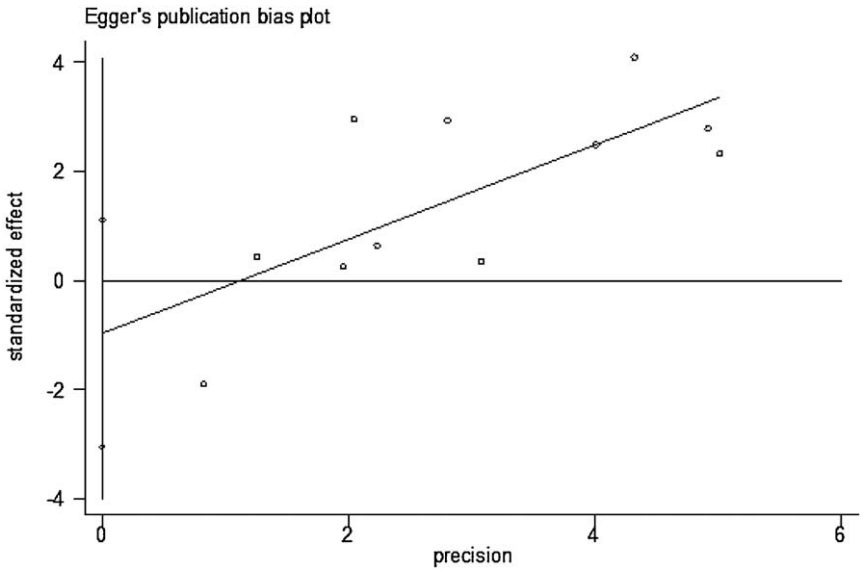

Figure 6. Egger publication bias plot detect the potential publication bias of the prognostic value of PCNA for overall survival in colorectal cancer (*P* = .318). PCNA = proliferating cell nuclear antigen.

repair, PCNA has also identified as a central regulator of cell cycle which mediate the accurate transition of the cell by controlling the cell cycle process from G1 to M phase.[32] More importantly, it has been well demonstrated that PCNA is associated with tumor progression and its expression is significantly altered in various tumor tissues. Hence, PCNA has been considered as an effect marker to detect cancer cell proliferation.

A series of researches have investigated the prognostic role of PCNA expression in several malignancies such as non-small cell lung carcinoma (NSCLC),[33] osteosarcoma,[34] breast cancer,[35] cervical cancer,[36] hepatocellular carcinoma,[37] renal cell carcinoma,[38] and nasopharyngeal carcinoma.[39] However, the prognostic and clinicopathological values of PCNA remains ambiguous in CRC. For example, Lavezzi et al[40] demonstrated that PCNA is a valid biomarker to predict the prognosis of CRC and its overexpression is closely associated with tumor aggressive progression. A study conducted by Al-Sheneber et al[41] suggested PCNA also significantly associated with several clinicopathological factors such as clinical stage, histological grade, and distant metastasis, which could evaluate tumor biological behavior and prognosis. However, Neoptolemos et al[14] reported that higher PCNA expression was independently associated with favorable survival outcome. Therefore, the purpose of this meta-analysis was to resolve the remaining controversy and reach a reasonable conclusion.

In our study, we exclusively investigated the PCNA IHC expression, and the correlation between PCNA expression level and CRC patients prognosis was also evaluated. The conclusion of our meta-analysis was that high PCNA expression could predict unfavorable prognosis in CRC patients. Especially, CRC patients with PCNA overexpression exhibited poor OS, CSS. However, no significant correlation between PCNA expression and DFS. In addition, no obvious between-study heterogeneity was observed for OS (I^2=40.1%, P for heterogeneity=.081) and CSS (I^2=47.3%, P for heterogeneity =.150) but not for DFS (I^2=65.6%, P for heterogeneity =.054). Several subgroup analyses were further performed based on ethnicity, cut-off staining, analysis method, and sample size. The analysis results showed that the following factors may caused hererogeneity. Firstly, there is no consistent standard to define the PCNA positive expression, so it is difficult to avoid the heterogeneity caused by different threshold value. Secondly, in the sample size subgroup, the pooled results showed that the number of patients might be a cause of heterogeneity. Furthermore, some other factors might also be potential sources of heterogeneity, such as ethnicity and analysis method. We further conducted a sensitivity analysis, the pooled HR demonstrated that the results were stable and did not change upon omitting each study.

As far as we know, our study is the first to analyze the associations between PCNA expression and prognosis in CRC patients by pooling the survival data. However, several limitations exist in our meta-analysis should be acknowledged. First of all, few studies were included and their sample sizes were relatively small. Some subgroup analyses with only 2 studies in the meta-analysis may make conclusions less reliable. Secondly, all included studies measured PCNA expression via IHC, but the positive expression of PCNA in most studies based on different cut-off values. The inconsistent criteria to define the threshold value of PCNA positive expression may potentially contribute to heterogeneity. Therefore, a consistent standard should be defined in the future. Thirdly, it is well accepted that the survival information can be extracted from survival curve using; however, the source of inaccuracy for survival data can not be completely eliminated during the extracting process.

5. Conclusion

Despite the limitations listed above, this study indicated the prognostic importance of PCNA expression in CRC. According to our meta-analysis, the results demonstrated that PCNA overexpression predicted poor prognosis in patients with CRC for OS and CSS. It might be used as an index to assess the risk of stratification in patients with CRC, and even be the marker of targeted therapy. However, more large-scale prospective studies are needed to further support our results.

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