The Impact of KPNA2 on Prognosis of Colorectal Cancer Patients: A Meta-Analysis

Zhangzhe Yan
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Science

Mingang He
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Science

Haoxin Shi
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Science

Haipeng Wang
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Science

Miao Qin
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Science

Zengjun Li (zjli@sdfmu.edu.cn)
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Science

Yanlai Sun
Shandong Cancer Hospital and Institute, Shandong First Medical University, Shandong Academy of Medical Science

---

Research Article

Keywords: Colorectal cancer, Karyopherin alpha 2, Meta-analysis, Prognosis

Posted Date: January 12th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1235315/v1

Abstract

Background and purpose: Colorectal cancer (CRC) is one of the most common malignant tumors with the highest mortality globally. At present, there is no exact biomarker to predict the prognosis and clinicopathological monitoring of CRC patients. Recent studies on the relationship of Karyopherin α 2 (KPNA2) expression and the prognosis of CRC has gradually become a hot spot while the results are still controversial. The aim of this study was to analyze and assess the prognostic role of KPNA2 in CRC patients.

Methods: PubMed, Web of Science, Medline, EMBASE, CNKI, Wanfang, VIP, and Chinese Medical Database were systematically searched. The cohort study of high-level expression of KNPA2 and low-level expression of KPNA2 in CRC patients was included, the relevant data were extracted and the literature quality was evaluated. At the same time, the relationship between KPNA2 expression level and the overall survival (OS), the clinicopathological stage of CRC patients was studied. Meta-analysis was carried out by Stata MP 17.0 (Stata Corporation, College Station, TX, USA) software.

Results: A total of 7 cohort studies involving 1166 patients were included. The analysis results showed that higher KPNA2 expression was significantly associated with higher tumor stage (OR=1.90, 95% CI 1.42–2.54), higher degree of tumor invasion (OR=2.14，95% CI 1.55-2.94), more lymph node metastasis (OR=2.20, 95% CI 1.68-2.88) and more distant metastasis (OR=3.66，95% CI 1.81-7.40). Moreover, higher KPNA2 expression was significantly associated with the shorter OS (HR=2.31, 95%CI 1.46-3.68).

Conclusion: KPNA2 overexpression is an unfavorable prognostic factor for CRC patients. It could serve as a prognostic biomarker and as a potential therapeutic target for CRC.

Background

CRC ranks third in terms of incidence of cancer (1.9 million cases) and the second-largest cause of cancer-related death (925000 deaths) in the world [1]. Although earlier diagnosis and the earlier clinical treatment are beneficial to the CRC patients, the prognosis of CRC patients with distant metastasis is still poor. Trying to find biomarkers that could be served as the prognostic and therapeutic targets for CRC will help to improve the patients' quality of life and reduce mortality.

There are 7 known members of the Karyopherin α family. KPNA2 is one of the most important members [2], and its degree of evolution is very conservative [3, 4]. The dysfunction of karyopherin led to a variety of diseases, including tumors. Therefore, the study of nucleocytoplasmic transport mechanism is of great significance for the diagnosis, treatment and prognosis of tumors [5]. In recent years, more and more studies have shown that the expression of KNNA2 is abnormal in various tumors, and its expression level is closely related to the malignant degree and prognosis of tumors. Therefore, we speculated that KPNA2 might play crucial roles in tumors occurrence and progression [6]. From the published literatures, the relationship between KPNA2 expression and prognosis of CRC remains controversial. This meta-analysis

then aimed to study the relationship between KPNA2 expression and tumor prognosis and clinicopathological stage in CRC patients.

Materials And Methods

1.1. Literature search and selection

PubMed, web of science, MEDLINE, EMBASE, CNKI, Wanfang, VIP and Chinese Medical Database were searched to select the potential articles related to CRC and KPNA2 up to November 30, 2021. The search of published literatures was undertaken using the following search words: "KPNA2", "karyopherin alpha 2", "rch1", "rag cohort protein 1", "colorectal cancer", "colon cancer", "rectal cancer".

1.2. Inclusion and exclusion criteria of literature

Only literatures published in English or Chinese were selected. The references and other similar articles related to the retrieved articles were also screened.

1.2.1. Inclusion criteria: (1) The patients were diagnosed as CRC; (2) The expression level of KPNA2 was detected; (3) The association of KPNA2 expression with tumor clinicopathological stage or OS was evaluated; (4) The sufficient data were provided to estimate the hazard ratios (HRs) or odds ratios (ORs) and their 95% confidence intervals (95% CIs); (5) The papers are published in English or Chinese. (6) For articles with the same or duplicate data, only those with the largest sample size or the latest sample size were selected.

1.2.2. Exclusion criteria: (1) The relationship between KPNA2 expression and CRC was not reported; (2) Meeting summaries, case reports, summaries, editorial letters and comments; (3) Animal research.

1.3. Data extraction and Quality Assessment

Data extraction and literature quality evaluation were performed by 2 independent well-trained researchers. If there was any disagreement, it was discussed and resolved with reference to the original literature on the basis of the participation of the third researcher. The author's name, year of publication, number of patients, detection method, sample source, tumor stage, survival rate, KPNA2 expression levels and cutoff value were extracted from the original literature (Table 1). If there was missing data, it was supplemented by contacting the literature author. Table 2 showed the modified Newcastle-Ottawa scale (NOS) [7], which evaluated the quality of the included literatures through three dimensions: patient selection, comparability and outcome. Studies with NOS scores ≥5 were regarded as high quality.

Table 1 The basic characteristics of the included literatures

Study/Year (Reference)	Tumor site	Sample size	KPNA2 Detection method	Cut-off level of 'high' KPNA2 expression	No. of patients with 'high' KPNA2	Survival analysis		Pathological stage (0-Ⅱ/Ⅲ-Ⅳ)		TNM Stage						Study quality (Points)
										Tis-T2/T3-T4		N0/N1-N2		M0/M1		
						HR	CI	Low KPNA2	High KPNA2	Low KPNA2	High KPNA2	Low KPNA2	High KPNA2	Low KPNA2	High KPNA2	
Rachidi SM 2013	colon	54	IHC	IRS≥3	14	2.39	0.54, 10.63	NR	NR	NR	NR	NR	NR	NR	NR	5/9
Zhang Y 2015	colon	195	IHC	IRS≥3	136	2.77	1.31, 5.84	37/22	64/72	14/46	14/121	40/20	64/71	58/1	119/17	8/9
Takada T 2016	colorectal	122	IHC	IRS≥2	91	4.25	1.44, 12.60	14/17	37/54	9/22	19/72	15/16	46/45	NR	NR	8/9
Yu L 2017	colorectal	300	IHC	IRS≥4	182	1.15	0.70, 1.88	89/29	102/80	29/89	23/155	97/21	102/80	NR	NR	7/9
Jeong D 2017	colorectal	293	IHC	IRS≥4	204	3.17	2.06, 4.89	123/81	41/48	45/159	14/75	126/78	41/48	195/9	85/4	8/9
Xie M 2019	colorectal	110	IHC	IRS≥6	79	1.99	0.69, 5.72	NR	NR	11/20	13/66	23/8	38/41	29/2	60/19	8/9
Ma CY 2020	colorectal	92	IHC	IRS≥6	67	NR	NR	NR	NR	13/12	15/52	18/7	41/26	24/1	48/19	6/9

Note: IHC, immunohistochemistry; IRS: immunoreactive score, NR: not reported.

Table 2 Revised Newcastle-Ottawa scale

Newcastle–Ottawa quality assessment scale
Selection
(1) Representativeness of the exposed cohort
(a) Truly representative of the average patients with colorectal cancers in the community*
(b) Somewhat representative of the average patients with colorectal cancers in the community*
(c) Selected group of users (e.g., nurses, volunteers)
(d) No description of the derivation of the cohort
(2) Selection of the non exposed cohort
(a) Drawn from the same community as the exposed cohort*
(b) Drawn from a different source
(c) No description of the derivation of the non exposed cohort
(3) Ascertainment of exposure (Proof of colorectal cancers and KPNA2 measurement)
(a) Secure record (e.g., surgical records)*
(b) Structured interview*
(c) Written self report
(d) No description
(4) Demonstration that outcome of interest was not present at start of study
(a) Yes*
(b) No
Comparability
(1) Comparability of cohorts on the basis of the design or analysis
(a) Study controls for recurrence or metastasis*
(b) Study controls for any additional factor (Age, gender, grade, KPS score, etc.)*
Outcome
(1) Assessment of outcome
(a) Independent blind assessment*
(b) Record linkage*
(c) Self report
(d) No description
(2) Was follow-up long enough for outcomes to occur? (Death or recurrence)
(a) Yes (60 months)*
(b) No
(3) Adequacy of follow up of cohorts
(a) Complete follow up- all subjects accounted for*
(b) Subjects lost to follow up unlikely to introduce bias-small number lost- (25%) follow up, or description provided of those lost)*
(c) Follow up rate (<75%) and no description of those lost
(d) No statement

Note: A maximum of one star (*) can be given for each numbered item within the ‘Selection’ and ‘Outcome’ categories. While a maximum of two stars (**) can be given for ‘Comparability’

1.4. Statistical analysis

Odds ratios (ORs) with 95% confidence interval (CI) were utilized to evaluate the association of KPNA2 expression levels with clinical parameters, and the risk ratios (HRs) of 95% CI were used to analyze the

association between KPNA2 expression levels and OS. Cochrane's Q test and I^2 measurements were used to assess the heterogeneity of the pooled results. P > 0.10 or I^2 < 50% were considered as the heterogeneity without statistical significance, and then the fixed-effect model should be used, otherwise the random effect model should be used. The validity and reliability of the data were evaluated by sensitivity analysis. The risk of publication bias was assessed using the Begg' s funnel plot. All statistical analyses were performed using STATA version 17.0 (STATA Corporation, College Station, TX, USA).

Results

2.1. Studies selection and the characteristics of the included studies

Using the above strategy, a total of 103 studies were identified. After further screening stepwise, 7 eligible cohort studies (Fig. 1) were finally included [8-14]. A total of 1166 CRC patients, of which 773 (66.3%) with 'high' KPNA2. The basic characteristics of the included studies are shown in Table 1.

2.2. KPNA2 expression and OS of CRC Patients

The analysis of the relationship between KPNA2 expression and OS in CRC patients showed that high expression of KPNA2 was significantly correlated with the shortening of OS in CRC patients (Fig. 2A, HR = 2.31, 95% CI 1.46-3.68), but there existed heterogeneity (I^2= 55.4%, P=0.047); The results of sensitivity analysis showed that the overall trend did not change when each study was deleted item by item (Fig. 2B); Begg' s funnel analysis of literature publication bias showed that no publication bias was found (Fig. 2C, PR > |z| = 1.000).

2.3. KPNA2 expression and clinicopathological features

Six studies reported the association between the degree of tumor invasion and KPNA2 expression. The results showed that CRC patients with higher expression of KPNA2 had a higher degree of tumor invasion (Fig. 3A, OR = 2.14, 95% CI = 1.55-2.94), and there was no significant heterogeneity between the results (I^2 = 0.0%, P = 0.645); Six studies demonstrated the association between KPNA2 expression and lymph node metastasis. The combined data of the included studies showed that the expression of KPNA2 in CRC patients was positively correlated with the degree of lymph node metastasis (Fig. 3B, OR = 2.20, 95% CI = 1.68-2.88), and the heterogeneity was not obvious (I^2 = 42.9%, P = 0.199); Four studies reported the association between KPNA2 expression and tumor distant metastasis. The analysis results showed that CRC patients with higher KPNA2 expression were more prone to distant metastasis (Fig. 3C, OR = 3.66, 95% CI = 1.81-7.40), and there was no significant heterogeneity among these studies (I^2 = 48.6%, P = 0.120).

Sensitivity analysis was performed after deleting each study one by one, and the overall trend did not change (Figure 4A-C). The results of Begg' s funnel plot showed that there was no significant publication bias (Fig. 5A-C, Pr > | z | = 0.133; Pr > | z | = 1.000; Pr > | z | = 0.089).

The pooled data from four studies showed that the expression of KPNA2 was positively correlated with the tumor stage of CRC patients (OR = 1.90, 95% CI = 1.42 – 2.54), and no significant heterogeneity was observed between studies (Fig. 6A, I^2 = 0.0%, P = 0.555). The results of sensitivity analysis show that excluding any study does not change the overall trend, indicating that the results are statistically significant (Fig. 6B). Begg' s funnel plot shows that there is no significant publication bias (Fig. 6C, PR > |z| = 0.734).

2.4. Subgroup analysis based on different cut-off values of KPNA2 expression

Since different cutoff values were used in each study to define the high expression of KPNA2, we further performed subgroup analysis according to different cutoff values to evaluate whether the correlation between KPNA2 expression and OS or tumor stage was statistically significant when different cutoff values were used. Subgroup analysis showed that when IRS ≥ 3 was used as the cut-off value, the higher the expression level of KPNA2, the shorter the OS, and this result was statistically significant (Fig. 7A, HR 2.69, 95% CI 1.38-5.24). When IRS ≥ 4 or ≥ 6 was used as the cut-off value, the higher the expression level of KPNA2, the deeper the depth of tumor invasion (Fig. 7B-C, OR 1.84, 95% CI 1.17-2.88; OR 3.23, 95% CI 1.64-6.25) and the more lymph node metastases (OR 2.58, 95% CI 1.78-3.72; OR 2.32, 95% CI 1.18-4.55) and the result was statistically significant. When IRS ≥ 6 was defined as the cut-off value, the higher the expression level of KPNA2, the greater the possibility of distant metastasis of CRC (Fig. 7D, OR 6.18, 95% CI 1.83-20.91). When IRS ≥ 4 was defined as the cut-off value, the higher the expression level of KPNA2, the lower the degree of tumor differentiation (Fig. 7E, OR 1.90, 95% CI 1.42-2.54), and the result was statistically significant.

Discussion

CRC is one of the most common cancers in the world. In recent years, the promotion of early screening has significantly reduced the mortality rate of CRC, but the prognosis of patients with advanced CRC still remains very poor [15]. Tumor biomarkers such as carcinoembryonic antigen (CEA) and CA19-9 have been used in the screening and monitoring of CRC [16, 17], and the sensitivity of these markers to the monitoring of prognosis and pathological staging of CRC patients is still controversial. Therefore, new biomarkers should be determined. It is necessary to predict the prognosis and progression of tumors in CRC patients and for clinical targeted therapy.

Studies have shown that the high expression of KPNA2 is positively correlated with tumor staging and progression, suggesting that KPNA2 may be involved in the process of tumor progression [6]. A meta-analysis conducted by Zhou LN et al [18] confirmed that KPNA2 overexpression is associated with the poor prognosis of 15 types of malignant tumors, including breast cancer, prostate cancer, endometrial cancer, ovarian cancer, and non-small cell lung cancer. It is expected to become a biological indicator to monitor the prognosis of malignant tumors in the future. Many studies have reported the relationship between KPNA2 expression and CRC progression and prognosis, but there is no systematic elaboration on the association between the high expression of KPNA2 and the prognosis and clinicopathological

stage of CRC patients [8-14]. This study comprehensively reviewed the value of KPNA2 expression in the prognosis and clinicopathological staging of CRC patients.

This meta-analysis includes 7 studies with 1166 CRC patients, of which 773 (66.3%) with 'high' KPNA2. Firstly, the association between high KPNA2 expressions and the OS was analyzed, the results showed that OS was shortened in CRC patients with high KPNA2 expression. Secondly, we analyzed the relationship between the expression of KPNA2 and the depth of tumor invasion, the results showed that the higher the expression level of KPNA2, the deeper tumor invasion. The results of this meta-analysis also showed that CRC patients with high expression of KPNA2 tended to have a higher degree of lymph node metastasis and distant metastasis. The results of pooled analysis on the relationship of KPNA2 expression with CRC tumor stage showed that the higher the expression level of KPNA2, the higher the tumor stage. In conclusion, the analysis results showed that KPNA2 could promote CRC invasion and metastasis, resulting in poor prognosis of CRC patients. Subgroup analysis of high-level expression of KPNA2 defined by different cutoff values showed that when the cutoff value was IRS $\geq$ 3, its correlation with OS shortening in CRC patients was statistically significant. When the cut-off value is IRS $\geq$ 4 or $\geq$ 6, the high level of KPNA2 expression is associated with deeper infiltration depth and higher degree of lymph node metastasis in CRC patients, and the results are statistically significant. When the cutoff value is IRS $\geq$ 6, the correlation between high expression of KPNA2 and distant metastasis of CRC is statistically significant. When the cut-off value is IRS $\geq$ 4, it is significantly correlated with a higher degree of tumor stage in CRC patients, and the results are statistically significant. These results show that selecting an appropriate cutoff value to define the high expression of KPNA2 is essential for the accurate monitoring of the prognosis or clinicopathology of CRC patients.

This meta-analysis still has some possible limitations. First, the sample size of the included studies is relatively small. Only 7 studies were included in this meta-analysis, the first published in 2013, and 5 studies in recent 5 years. At present, there are still few cohort studies on the relationship between KPNA2 and CRC prognosis and clinicopathological stage. Secondly, the difference in the cutoff value of KPNA2 high expression between different studies may affect the accurate evaluation of CRC prognosis. Although relevant subgroup analysis has been performed in this study, the final conclusion remains to be discussed due to the limited number of subgroup studies. Large multicenter studies using the same detection method and cut-off value may help to obtain more accurate results in the future. Thirdly, there is heterogeneity in the analysis results of the relationship between KPNA2 expression and OS in CRC patients in this meta-analysis. Although the exclusion of each study one by one in the sensitivity analysis does not change the overall trend, if the sample of Yu L et al [11] is excluded for this meta-analysis, the heterogeneity will be significantly reduced. It is not difficult to find that in the study of Yu L et al., the HR of overall survival is significantly lower than that of other studies, the reason is that in the survival analysis in the original literature, the overall survival rate of the low expression group of KPNA2 is lower than others. In fact, there are differences in molecular carcinogenesis, pathology, surgical topography and procedures, and multimodal treatment of colon cancer and rectal cancer [19]. Li M et al [20] retrospectively evaluated 230 CRC patients and found that the prognosis of colon cancer was significantly better than

that of rectal cancer (70.6% vs. 57.0%; p=0.017). However, there are only two studies included in this meta-analysis focused on colon cancer [8, 9], the other five studies [10-14], including Yu L et al, were not stratified by tumor sites, and this may be the source of heterogeneity.

In conclusion, the results of this meta-analysis demonstrated that KPNA2 expression may be significantly correlated with tumor stage, invasion, metastasis, and survival of CRC patients. To accurately evaluate the prognosis and clinical stage of CRC through the expression of KPNA2, we should further explore and define the appropriate cut-off value of KPNA2 high expression. KPNA2 can be used to evaluate the clinicopathological stage of tumor in preoperative, monitor the recurrence in postoperative, and as a target for targeted therapy. However, this conclusion still needs to be confirmed by more large-scale prospective studies.

Abbreviations

KPNA2: Karyopherin α 2

CRC: Colorectal Cancer

OS: Overall Survival

OR: Odds Ratio

HR: Hazard Ratios

CI: Confidence Interval

NOS: Newcastle-Ottawa Scale

IHC: Immunohistochemistry

IRS: Immunoreactive score

NR: Not Reported

CEA: Carcinoembryonic Antigen

Declarations

Acknowledgements

We thank Xiaoli Zhang and Jing Liu from Shandong University for valuable discussion.

Authors' contributions

ZZY, ZJL, and YLS performed the experiment conception and design. ZZY, MGH, and HXS did the literature search. ZZY, MQ and HPW performed the data analysis. ZZY and ZJL did the paper writing. All authors read and approved the final manuscript.

Funding

This work was supported by the grant from the National Key R&D Program of China (2018YFC0114707), and the Key R&D Program of Shandong Province, China (2018GSF118047).

Availability of data and materials

All the data used in this study can be obtained from the original articles.

Ethics approval and consent to participate

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

Consent for publication

None.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. doi:10.3322/caac.21660
2. Kelley JB, Talley AM, Spencer A, Gioeli D, Paschal BM. Karyopherin alpha7 (KPNA7), a divergent member of the importin alpha family of nuclear import receptors. BMC Cell Biol. 2010; 11: 63. Published 2010 Aug 11. doi:10.1186/1471-2121-11-63
3. D.S. Goldfarb, A.H. Corbett, D.A. Mason, M.T. Harreman, S.A. Adam, Importin alpha: a multipurpose nuclear-transport receptor, Trends Cell Biol. 14 (2004) 505–514.
4. D.A. Mason, D.E. Stage, D.S. Goldfarb, Evolution of the metazoan-specific importin alpha gene family, J. Mol. Evol. 68 (2009) 351–365
5. Kau TR, Way JC, Silver PA. Nuclear transport and cancer: from mechanism to intervention. Nat Rev Cancer. 2004;4(2):106-117. doi:10.1038/nrc1274
6. Christiansen A, Dyrskjøt L. The functional role of the novel biomarker karyopherin α 2 (KPNA2) in cancer. Cancer Lett. 2013;331(1):18-23. doi: 10. 1016/j. canlet. 2012. 12. 013

7. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-605. doi:10.1007/s10654-010-9491-z
8. Rachidi SM, Qin T, Sun S, Zheng WJ, Li Z. Molecular profiling of multiple human cancers defines an inflammatory cancer-associated molecular pattern and uncovers KPNA2 as a uniform poor prognostic cancer marker. PLoS One. 2013;8(3): e57911. doi: 10. 1371/journal.pone.0057911
9. Zhang Y, Zhang M, Yu F, et al. Karyopherin alpha 2 is a novel prognostic marker and a potential therapeutic target for colon cancer. J Exp Clin Cancer Res. 2015; 34: 145. Published 2015 Dec 1. doi:10.1186/s13046-015-0261-3
10. Takada T, Tsutsumi S, Takahashi R, et al. KPNA2 over-expression is a potential marker of prognosis and therapeutic sensitivity in colorectal cancer patients. J Surg Oncol. 2016;113(2):213-217. doi:10.1002/jso.24114
11. Yu L, Wang G, Zhang Q, et al. Karyopherin alpha 2 expression is a novel diagnostic and prognostic factor for colorectal cancer. Oncol Lett. 2017;13(3):1194-1200. doi:10.3892/ol.2017.5579
12. Jeong D, Kim H, Ban S, et al. Karyopherin α-2 is a reliable marker for identification of patients with high-risk stage II colorectal cancer. J Cancer Res Clin Oncol. 2017;143(12):2493-2503. doi:10.1007/s00432-017-2512-5
13. Xie M, Zhong HL, Lei GW, et al. Expression of KPNA2 in colorectal carcinoma and its clinical significance. Chinese J of Diagn Pathol. 2019,26(01):34-37. doi: CNKI: SUN: ZDBL.0.2019-01-010.
14. Ma CY Expression of Nuclear Transporter Protein KPNA2 in Colorectal Cancer Tissues and Its Relationship with Clinicopathological Features of Colorectal Cancer. Hebei Medicine. 2020,26(02):197-201. doi: CNKI: SUN: HCYX.0.2020-02-006.
15. Ratto C, Sofo L, Ippoliti M, Merico M, Doglietto GB, Crucitti F. Prognostic factors in colorectal cancer. Literature review for clinical application. Dis Colon Rectum. 1998;41(8):1033-1049. doi:10.1007/BF02237397
16. Lee IK, Kim DH, Gorden DL, et al. Prognostic value of CEA and CA 19-9 tumor markers combined with cytology from peritoneal fluid in colorectal cancer. Ann Surg Oncol. 2009;16(4):861-870. doi:10.1245/s10434-008-0294-3
17. Cardella J, Coburn NG, Gagliardi A, et al. Compliance, attitudes and barriers to post-operative colorectal cancer follow-up. J Eval Clin Pract. 2008;14(3):407-415. doi:10.1111/j.1365-2753.2007. 00880. x
18. Zhou LN, Tan Y, Li P, et al. Prognostic value of increased KPNA2 expression in some solid tumors: A systematic review and meta-analysis. Oncotarget. 2017;8(1):303-314. doi:10.18632/oncotarget.13863
19. Paschke S, Jafarov S, Staib L, et al. Are Colon and Rectal Cancer Two Different Tumor Entities? A Proposal to Abandon the Term Colorectal Cancer. Int J Mol Sci. 2018;19(9):2577. Published 2018 Aug 30. doi:10.3390/ijms19092577

20. Li M, Li JY, Zhao AL, Gu J. Colorectal cancer or colon and rectal cancer? Clinicopathological comparison between colonic and rectal carcinomas. Oncology. 2007;73(1-2):52-57. doi:10.1159/000120628

Figures

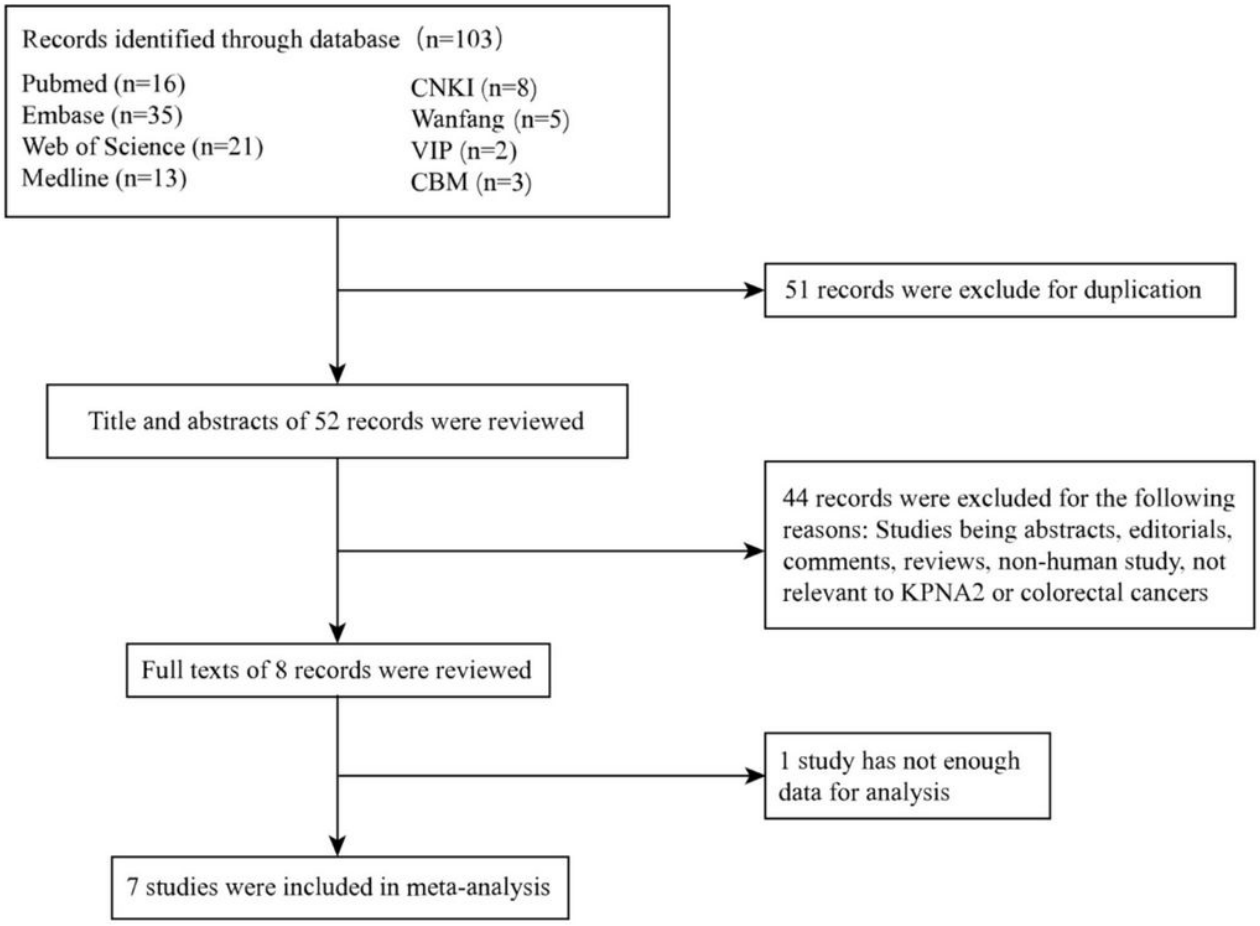

Figure 1

Flow chart of study selection procedure

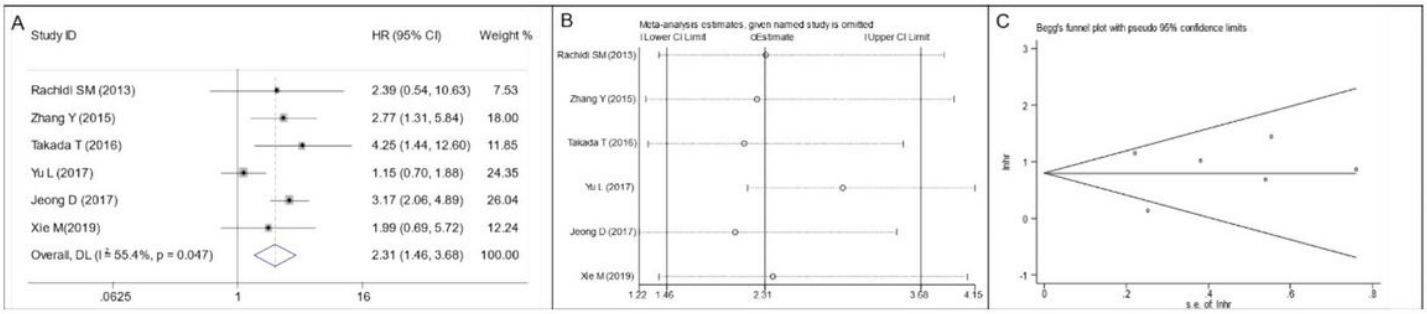

Figure 2

Analysis results of the relationship between KPNA2 expression and OS in CRC patients. A. Forest plot for the association between KPNA2 expression and OS; B. Sensitivity analysis of the relationship between KPNA2 expression and OS; C. Funnel plot of publication bias for OS

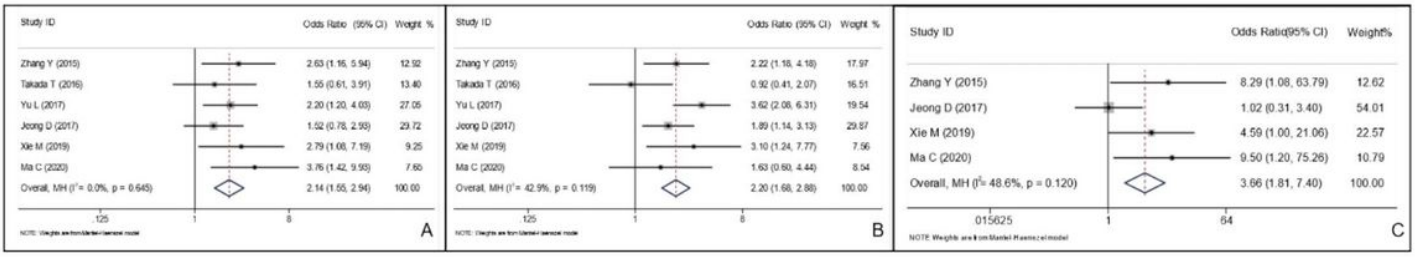

Figure 3

Forest plot for the relationships between KPNA2 expression and the tumor stage of CRC patients. A shows the relationship between KPNA2 expression and the depth of tumor invasion. B shows the relationship between KPNA2 expression and the lymph node metastasis. C shows the relationship between KPNA2 expression and the distant metastasis.

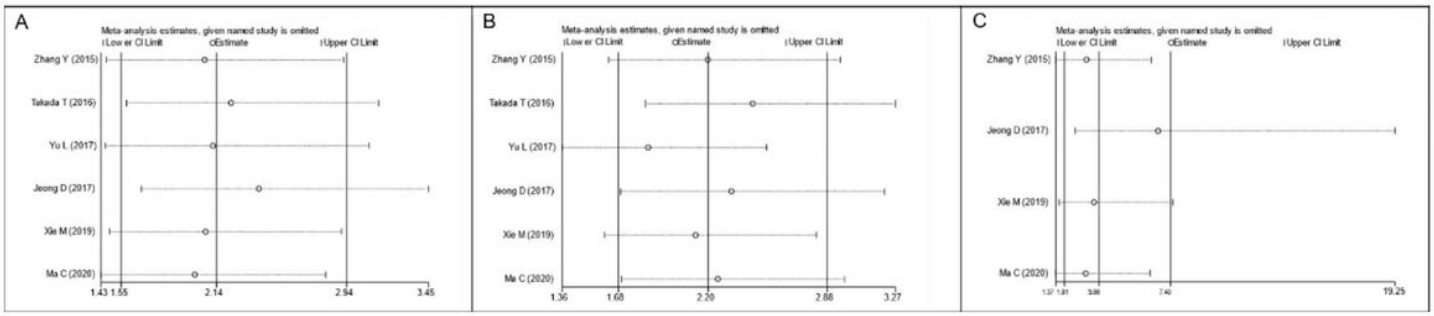

Figure 4

Sensitivity analysis results for meta-analysis of the relationship between KPNA2 expression and the clinicopathologic stage of CRC patients. A. the depth of tumor invasion; B. the lymph node metastasis; C.

the distant metastasis.

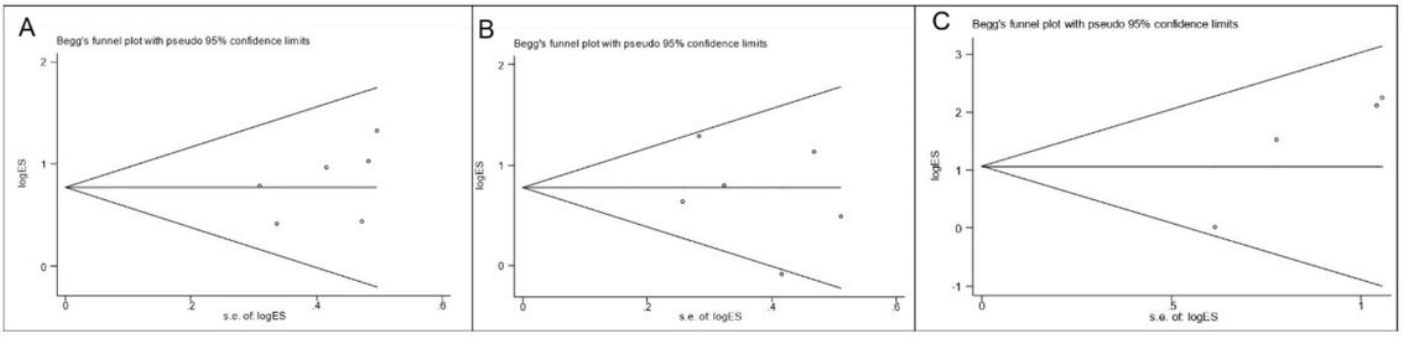

Figure 5

Begg's funnel plots of publication bias for meta-analysis of the relationship between KPNA2 expression and the clinicopathologic stage of CRC patients: A. the depth of tumor invasion; B. the lymph node metastasis; C. the distant metastasis

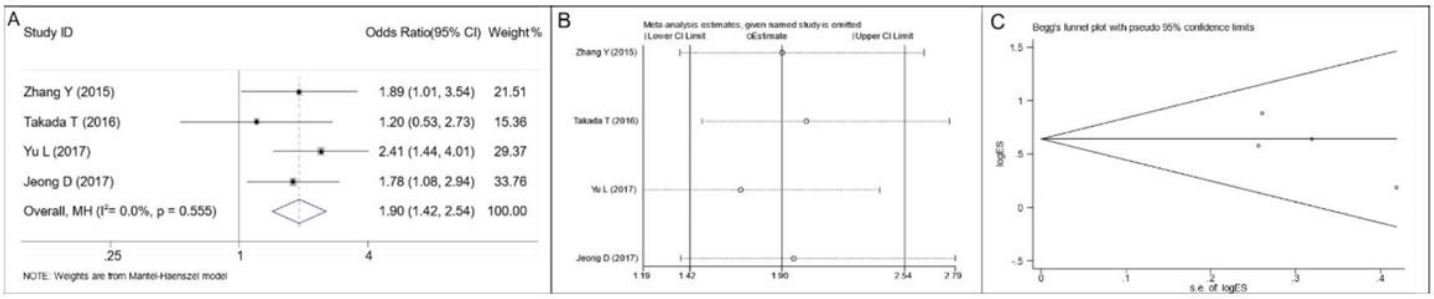

Figure 6

Analysis results of relationship between KPNA2 expression and tumor stage in CRC patients. A. Forest plot for the association between KPNA2 expression and tumor stage; B. Sensitivity analysis of the relationship between KPNA2 expression and tumor stage; C. Funnel plot of publication bias for tumor stage

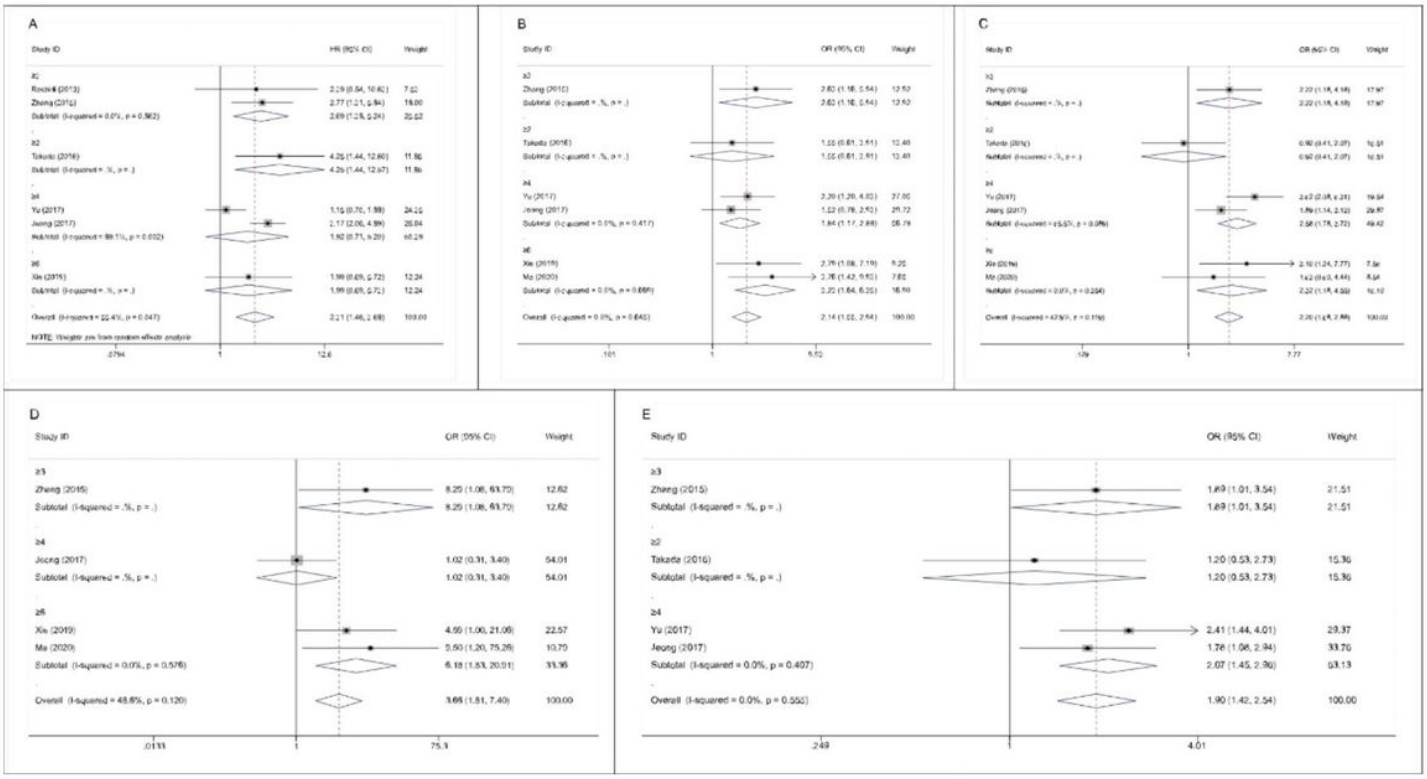

Figure 7

Forest plot for subgroup analysis based on different cut-off values. A. The relationship between KPNA2 expression and OS; B. The relationship between KPNA2 expression and the depth of tumor invasion; C. The relationship between KPNA2 expression and the lymph node metastasis; D. The relationship between KPNA2 expression and the distant metastasis; E. The relationship between KPNA2 expression and tumor stage