Prognostic Role of Preoperative C-Reactive Protein in Upper Tract Urothelial Carcinoma after Radical Nephroureterectomy - An Updated Meta-Analysis

XIAOYUAN QIAN
Huazhong University of Science and Technology https://orcid.org/0000-0003-3616-5520
CAN QIAN
Southwest Hospital
JIAQIAO ZHANG
Huazhong University of Science and Technology Tongji Medical College
YUCHAO LU
Huazhong University of Science and Technology Tongji Medical College
ZHIXIAN WANG
Huazhong University of Science and Technology Tongji Medical College
QING WANG
Huazhong University of Science and Technology Tongji Medical College
YANG XUN
Huazhong University of Science and Technology Tongji Medical College
PENG ZHOU
Huazhong University of Science and Technology Tongji Medical College
YUANYUAN YANG
Huazhong University of Science and Technology Tongji Medical College
SHAOGANG WANG (sgwangtjm@163.com)
https://orcid.org/0000-0002-3206-1495

Primary research

Keywords: Upper urinary tract carcinoma, C-reactive protein, Prognostic role, Meta-analysis

Posted Date: July 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-41004/v1

Abstract

Background: C-reactive protein (CRP) is an acute-phase protein that is mainly stimulated by the inflammation-associated cytokines and high concentrations of CRP have been detected in many tumors. Many studies have shown that there is a close correlation between CRP and the prognosis of upper urinary tract carcinoma (UTUC). However, the prognosis significance of CRP in UTUC is still controversial. Our study aims to perform an updated systematic review and meta-analysis to investigate the association between CRP and the prognostic value for UTUC undergoing radical nephroureterectomy (RNU).

Methods: A comprehensive electronic database search, using PubMed, EMBASE, and Web of Science, was performed to identify relevant research articles published before April 2020. Strict inclusion and exclusion criteria were established to extract data. Newcastle-Ottawa Scale was used to assess the quality of all candidate studies. The pooled hazard ratios (HR) and 95% confidence intervals (CIs) for recurrence-free survival (RFS), cancer-specific survival (CCS), and overall survival (OS) were calculated to evaluate the intensity of association. And heterogeneity and publication bias were assessed. Moreover, to ensure the stability of the analysis results, a sensitivity analysis was tested. All data were analyzed by Stata 15.0 and Review Manager 5.3.

Results: Thirteen studies including a total of 2801 patients were eligible for meta-analysis. Our results verified that elevated CRP predicted poorer FRS (pooled HR=1.38, 95%CIs：1.12-1.71, P=0.003), CCS (pooled HR=1.64, 95%CI：1.38-1.94, P<0.001), OS (pooled HR=1.35, 95%CIs: 1.03-1.79 ,P=0.03) in patients with UTUC after RNU. Besides, elevated CRP was overtly correlated with tumor pathological stage (T3/T4 vs. ≤T2: OR=3.40, 95% CIs 2.39-4.84, P<0.001), tumor grade ((1/2 vs. 3: OR=1.68, 95% CIs 1.24-2.28, P<0.001), lymph node involvement (LNI) (+ vs. -: OR=2.73, 95% CIs 1.80-4.14, P<0.001), lymphovascular invasion (LVI) (+ vs. -: OR=4.1, 95% CIs 2.26-7.44, P<0.001). And these results got after using sensitivity analysis were verified to be stable and reliable. Furthermore, Begg's test result (RFS: P=0.089, CCS: P=0.592, and OS: P=0.089) showed no significant publication bias in the procedure.

Conclusion: Elevated CRP indicates a poor prognosis for patients with UTUC undergoing RNU. Elevated CRP plays a significant role in reasonable risk stratification and individualized treatment.

Background

UTUCs are uncommon and account for only 5–10% of all urothelial carcinoma,[1] which is one of the most common tumors. About sixty percent of UTUCs are in the invasive stage at the time of diagnosis and patients aged 70–90 years have a peak incidence which can be observed.[1, 2] Although a small number of low-grade patients with small lesions can be treated by endoscopic tumor ablation, for most patients, radical nephroureterectomy (RNU) with excision of an ipsilateral bladder cuff, including or not including retroperitoneal LN dissection, is the gold-standard treatment strategy for UTUCs. However, patients have a high rate of recurrence, including urinary bladder recurrence, local retroperitoneal recurrence and contralateral UTU, and poor prognosis after surgery. [1, 3, 4]

CRP is an acute-phase protein that is mainly stimulated by the inflammation-associated cytokines, IL-6, during the acute-phase responses. Numerous causes can result in the changes in the plasma concentrations of CRP, including infectious and non-infectious factors, such as infection, trauma, surgery, burns, tissue infarction *etc*.[5] Moreover, many studies have found a strong association between elevated CRP and risk of cancers, such as hepatocarcinoma, lung cancer, skin cancer, renal cell carcinoma, bladder tumor, and lymphoma.[6–8] And preoperative CRP levels can predict disease characteristics, the extent of disease, and prognosticate survival in urologic cancers.[7] However, the exact effect of preoperative CRP in patients with UTUC is inconsistent in different studies. Although a previous meta-analysis study [9] has summarized that elevated CRP levels had an adverse prognostic value in UTUC after surgery, owing to a few enrolled studies, the accuracy of their results needed to be further confirmed. Therefore, we performed an updated systematic review and meta-analysis including more studies to perfect their research. At the same time, we got a dramatically different result that patients in an elevated CRP group had a poorer OS, which could predict worse outcomes in UTUC. And associations between abnormal CRP and clinicopathological features were also demonstrated.

In this study, we aimed to explore the prognostic value of elevated CRP levels for RFS, CCS, and OS in patients with UTUC by the method of pooling outcomes (HR and 95%CIs) from available data and associations between elevated preoperative CRP and part of clinicopathological features.

Methods

Literature search strategy

According to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, a comprehensive electronic databases search by employing PubMed, EMBASE, and Web of Science was performed to identify relevant research articles which were published before April 2020. To ensure comprehensive retrieval, Medical Subject Headings with free words in the title/abstract were combined to perform the research strategy. Our research terms included："Upper urinary tract" OR "Upper tract" OR "Kidney Pelvis" OR "Ureter" AND "Carcinoma, Transitional Cell" OR "Urothelial carcinoma" AND "CRP" OR "Protein, C-Reactive" AND "Prognosis" OR "Predictor" OR "Cohort studies". All studies written in English were included.

Study inclusion criteria and relevant definitions

All studies meet the following restrict inclusion criteria: (1) the diagnosis of UTUC must be verified by postoperative pathological examination; (2) all UTUC patients had undergone RNU; (3) preoperative measurement of serum CRP was routinely performed up to a week prior to RNU; (4) studies reported HRs and 95% CIs for preoperative serum CRP level in RFS, and(or) CCS, and(or) OS or raw data contained in articles, from which outcomes can be calculated; (5) the study design belonged to a prospective or retrospective cohort study.

When disease recurrence was defined as local recurrence in the operative site, regional lymph nodes, or distant metastasis, RFS was calculated from the time of curative treatment to tumor recurrence. And CSS was defined as the time from the date of diagnosis to the date of death caused by UTUC. In addition, OS was measured from the date of definite diagnosis to death or last follow-up of patients.

Exclusion Criteria

Exclusion criteria were deemed as the following: (1) duplicate studies; (2) case reports, conference abstracts, letters, reviews, systematic reviews or commentary; (3) animal studies; (4) articles shared an identical study population with others;(5) non-English works; (6) studies without full-text.

Data extraction

The retrieved studies were carefully screened and meaningful data were extracted by two independent researchers(XY Qian and ZX Wang). If there were different opinions about relevant information, they discussed them with the third researcher (C Qian) to come to an agreement. By browsing the title and abstract, the irrelevant studies were excluded. The full texts were then read to enroll qualified studies, according to the set inclusion and exclusion criteria of our meta-analysis. The data we extracted include (1) basic characteristics for research including first author's surname, year of publication, study region, sample size; (2) patients' information including gender, age, follow-up time; (3) data of UTUC including size, stage, tumor grade, LN (lymph node) status, LVI (lymphovascular invasion) status, and the cut-off value of preoperative serum CRP; (4) outcomes of interest including HR and 95% CIs for RFS, CSS, and OS. For studies sharing an identical population, we only chose the most informative or recent study for further analyses. Only multivariate outcomes were extracted if univariate and multivariate outcomes were provided. However, univariate outcomes were not acceptable if multivariate results weren't obtained in our study.

Quality assessment

Quality assessment of enrolled studies was evaluated by two independent researchers(XY Qian and ZX Wang), using the Newcastle-Ottawa quality assessment scale (NOS) [10] which ranges from 0 to 9 stars. Only if the study score was greater than or equal to 6 stars, could this study be graded as high quality, which was included in this meta-analysis.

Statistical analysis

Outcomes of interest with HR along with 95%CIs were pooled to evaluate the influence of preoperative serum CRP on RFS, CSS, and OS. Statistic heterogeneity among included studies was assessed by the Cochrane Q statistic and I^2 statistic. And $P_{heterogeneity}$ <0.1 or I^2 >50% meant that heterogeneity existed among studies and that we should use the random-effects model to pool outcomes of interest. However, if heterogeneity didn't exist, the fixed-effects model would be chosen. And sensitivity analysis was performed to assess the robustness of the results by eliminating study one by one. Furthermore, publication bias was also examined by a funnel plot and Begg's test. The whole process of the meta-analysis was performed with Stata 15.0 and Review Manager 5.3. And all statistical tests were two-sided and the statistical significance level was set at P<0.05.

Results

Search results

A total of 392 publications were retrieved by using our initial search algorithm we had developed. There were 312 records left after removing duplicate articles. And 262 articles were excluded by screening the title and abstract. The remaining 50 articles were read in full text, and it is 13 studies [11-23] that satisfied the inclusion criteria and were analyzed in our meta-analysis. The specific literature screening process was displayed in Figure 1.

Study characteristics

The clinical characteristics of all 13 eligible publications were summarized in Table1. All cohorts enrolled about 2801 patients with median or mean age ranging from 65.7 to 74 years and belonged to a retrospective study, which had the median duration of follow-up varying from 15.1 to 56.4 months. Of the 13 studies, 9 were reported in Japan, 2 in German, 1 in Korea, and 1 in multi-centers which was conducted in Japan. And the serum CRP cut off ranged from 0.13mg/dl to 1.0mg/dl, which were mainly at 0.3 and 0.5 mg/dl. All patients didn't find distant metastasis before surgery. The enrolled patients all were treated by RNU, and the main pathologic features of the included patients are shown in Table 2. Rates of the high pathological stage (3/4), high tumor grade (3), and positive LNI, LVI achieved at 21.22%-84.44%, 32.93%-77.78%, 5.36%-100%, 6.67%-68.93%, respectively. There were 5 cohorts containing outcomes for pretreatment CRP in RFS, 12 in CCS, and 4 in OS. For quality assessed by the NOS, all included studies were deemed as high quality, of which all had 7 or 8 stars (See table 1).

Elevated preoperative CRP and FRS in UTUC

There were 5 cohorts extracted the data of preoperative CRP and FRS in patients with UTUC. Meta-analysis results of the association between elevated CRP and RFS of UTUC pointed out that the significant heterogeneity (I^2 = 68%; $P_{heterogeneity}$= 0.01) between enrolled cohorts was detected. Therefore, a sensitivity analysis was conducted, whose result suggested that Obata J and his colleagues' study [19] was the main reason causing the heterogeneity. Deleting this study, we performed the meta-analysis again by using the fixed-effect model and got perfect results that there was no significant heterogeneity(I^2 = 0%; $P_{heterogeneity}$= 0.85) between remaining 4 studies and that elevated CRP was strongly correlated with short FRS (HR=1.38; 95%CIs: 1.12-1.71; P=0.003)(Figure 2a).

Elevated preoperative CRP and CCS in UTUC

After the data of 12 cohorts about HR and 95%CIs for CCS was dealt with by the random-effect model, there was a significant heterogeneity presented (I^2=74%; $P_{heterogeneity}$ <0.001). By performing sensitivity-analysis, we confirmed that Inamoto T *et al.* 2012[13] and Stein B *et al.* 2013[23] were the main sources

of this heterogeneity. Removing two studies, non- significant heterogeneity (I^2 = 0%; $P_{heterogeneity}$= 0.45) were found and we chose the fixed-effects model to pooled the HR and 95%CIs of left 10 articles. Besides, the pooled results indicated that the more adverse CCS occurred in patients with UTUC, accompanying elevated CRP (HR=1.64; 95%CIs: 1.38-1.94; P<0.001) (Figure 2b). What's more, although all included studies used inconsistent cut-off values for CRP, it wasn't a source causing significant heterogeneity, which was demonstrated by a sensitivity analysis.

Preoperative CRP and OS in UTUC

When the association between preoperative CRP and OS was explored, the data of 4 (Total:4) cohorts were calculated. The significant heterogeneity wasn't found and the fixed effect model was considered (I^2=9%; $P_{heterogeneity}$ =0.35). That patients, who were diagnosed with UTUC, with elevated preoperative CRP had a poorer OS was seen (HR=1.35; 95%CI: 1.03-1.79; P=0.03) (Figure 2c).

Preoperative CRP and clinicopathological features in UTUC

The above procedures were repeated to merge the relevant results. And the final meta-analysis findings were that elevated preoperative CRP was overtly correlated with tumor pathological stage (III/IV vs. I/II: OR=3.40, 95% CIs 2.39-4.84, P<0.001), tumor grade ((1/2 vs. 3: OR=1.68, 95% CIs 1.24-2.28, P<0.001), lymph node involvement(LNI) (+ vs. -: OR=2.73, 95% CIs 1.80-4.14, P<0.001), and lymphovascular invasion (LVI) (+ vs. -: OR=4.1, 95% CIs 2.26-7.44, P<0.001). All pooled results were presented in Figure 3.

Publication bias

To investigate whether publication bias existed in results, the funnel plots were depicted respectively(Figure 4). There was no significant publication bias that existed in FRS, CCS, and OS by Begg's test (P =0.089, P =0.592, P = 0.089, respectively).

Discussion

Our study aimed to explore the prognostic value of preoperative elevated CRP levels for patients with UTUC after RNU. In our analysis, 13 cohort studies including 2801 UTUC patients were included to pool the outcomes and our results displayed the associations between abnormal CRP and prognosis of UTUCs. Data we calculated shown that, in patients with UTUC receiving RNU, high preoperative CRP predicted poorer FRS (pooled HR = 1.38, 95%CIs: 1.12–1.71, P = 0.003), CCS (pooled HR = 1.64, 95%CIs 1.38–1.94, P < 0.001), and OS (pooled HR = 1.35, 95%CIs:1.03–1.79, P = 0.03). And there was no significant publication bias which existed in FRS, CCS and OS, respectively (Begg's test: P = 0.089, P = 0.592, P = 0.089). Compared with You L and his colleagues' study [9], we reconfirmed that elevated preoperative CRP had a poor impact on RFS and CCS of patients with UTUC and found elevated CRP also played a significant adverse effect on OS in patients with UTUC treated by RNU, which greatly differed from theirs. On the basis of their research, in which there were 2 studies [3, 24] only containing outcomes in the univariate analysis, we retrieved another 8 relevant studies [12–19] including sound results in multivariate analysis, and, since then, 1233 cases were added to our studies. What's more, we found that authors neglecting the heterogeneity between all studies used a random-effects model to pool all outcomes of interest in their analysis, which may have a certain influence on the accuracy of the final results. Therefore, this updated meta-analysis increased the number of UTUC cases up to 2801 and incorporated more reliable multivariate analysis results. And we made up for their improper method used in their procedure and perfected their relevant research.

Except for other causes, increased serum CRP levels as a biomarker often associated with malignancy in cancer patients. In UTUCs, a high CRP value (> 0.5 mg/dl or 0.9 > mg/dl) was significantly associated with progressive tumor characteristics, including muscle-invasive disease (pT ≥ 2), high tumor stage, high grade, lymph node metastasis, positive LVI, distant metastasis, poor tumor differentiation, etc[3, 11, 19, 20], which was consistent with what we pooled. And detecting serum CRP concentration is objective and reproducible measurement before the operation. Therefore, it may easily be implemented as a prognostic factor for the degree of malignancy and to more accurately stratify patients with UTUC before surgery, which could guide treatment strategy, but more prospective and retrospective studies are needed to confirm this result.

Although the molecular mechanism of abnormally elevated CRP in patients diagnosed with cancer in various studies remains unclear, there were several plausible explanations why CRP could be elevated. One of these possible mechanisms is that the increasing serum CRP as one of many acute-phase proteins which were mainly induced by inflammation-associated cytokines[5] - interleukin-6, interleukin-1β, tumor necrosis factor α, interferon-γ, transforming growth factor β, and interleukin-8 - reflects the inflammatory state of the body caused by tumors, which may contribute to tumor cell more rapid growth[25, 26]. Alternatively, immune suppression caused by changes in tumor microenvironment resulted in sustaining tumor cell growth and activating the capability for tumor invasion and metastasis. [27] Generally speaking, proinflammatory cytokines and immune dysfunction significantly affect the serum CRP levels and indirectly display the growth capacity of tumors. And elevated CRP levels has great reference value for the prognosis of cancer patients. According to our pooled data, it was RFS, CCS, and OS that elevated CRP had a great influence on. And in our study, that patients with UTUC undergoing RNU had a poor OS in the elevated CRP groups shown statistical significance, which also demonstrated more adverse prognosis in patients diagnosed with UTUC.

While our meta-analysis offers plenty of evidence that increased preoperative CRP is closely bound up with more adverse prognosis of patients with UTUC treated by RNU, some limitations in our study can be detected, which should be acknowledged. Firstly, significant heterogeneity existed for RFS and CCS. After heterogeneity in studies was determined and sensitivity analyses were conducted, there was some mild heterogeneity in included studies. Secondly, limited databases (Web of Science, PubMed, and EMBASE) were searched, which might make some valid articles missed and have the estimating power limited. Thirdly, all of the enrolled studies were retrospective and published in English, most of which published by Japanese scholars. Therefore, information and selection biases may exist in studies. And publication bias is more inclined to be discovery, owing to the fact that present studies including positive results are more easily to be published in English journals.

Conclusion

The present meta-analysis shows that elevated preoperative CRP is associated with poorer survival outcomes and aggressive clinicopathological features in UTUC after RNU. And the measurement of serum CRP levels is objective and reproducible. Hence, the test of preoperative CRP may be beneficial for the treatment and prognostic evaluation of patients with UTUC. However, our results need more large-scale case-control studies and well-designed prospective studies to be confirmed.

List of abbreviations

CRP, C-reactive protein; UTUC, upper urinary tract carcinoma; RNU, radical nephroureterectomy; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; LNI, lymph node involvement; LVI, lymphovascular invasion; HR, hazard ratios; CIs, intervals; NOS, Newcastle-Ottawa Scale.

Declarations

Abbreviations

CRP, C-reactive protein; UTUC, upper urinary tract carcinoma; RNU, radical nephroureterectomy; CSS, cancer-specific survival; OS, overall survival; RFS, recurrence-free survival; LNI, lymph node involvement; LVI, lymphovascular invasion; HR, hazard ratios; CIs, intervals; NOS, Newcastle-Ottawa Scale.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

Conceptualization: Jiaqiao Zhang, Yuchao Lu; Literature search: Yuanyuan Yang, Yang Xu; Data analysis: Xiaoyuan Qian, Zhixian wang. Writing—original draft: Xiaoyuan Qian; Writing— review, and editing: Peng zhou and Can Qian. All authors approved the final manuscript.

Acknowledgments

Not applicable.

References

1. Roupret M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. Eur Urol. 2018;73(1):111–22.
2. Shariat SF, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol. 2010;29(4):481–6.
3. Fang D, et al. Pattern and risk factors of intravesical recurrence after nephroureterectomy for upper tract urothelial carcinoma: a large Chinese center experience. J Formos Med Assoc. 2014;113(11):820–7.
4. Margulis V, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009;115(6):1224–33.
5. Gabay C, Kushner I. *Acute-phase proteins and other systemic responses to inflammation [published correction appears in N Engl J Med 1999 Apr 29;340(17):1376]. N Engl J Med.* 1999;*340(6):448-454.*.
6. Chaturvedi AK, et al. C-reactive protein and risk of lung cancer. J Clin Oncol. 2010;28(16):2719–26.
7. Huang J, et al. C-reactive protein in urologic cancers. Mol Aspects Med. 2015;45:28–36.
8. Trichopoulos D, et al. Plasma C-reactive protein and risk of cancer: a prospective study from Greece. Cancer Epidemiol Biomarkers Prev. 2006;15(2):381–4.

9. Luo Y, et al. Preoperative C-reactive protein as a prognostic predictor for upper tract urothelial carcinoma: A systematic review and meta-analysis. Mol Clin Oncol. 2015;3(4):924–8.
10. Stang A *Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25, 603–605 (*2010*)*..
11. Aziz A, et al. Preoperative C-reactive protein in the serum: a prognostic biomarker for upper urinary tract urothelial carcinoma treated with radical nephroureterectomy. Urol Int. 2014;93(3):352–60.
12. Fujita K, et al. Role of adjuvant chemotherapy for lymph node-positive upper tract urothelial carcinoma and the prognostic significance of C-reactive protein: A multi-institutional, retrospective study. Int J Urol. 2015;22(11):1006–12.
13. Inamoto T, et al. Specific body mass index cut-off value in relation to survival of patients with upper urinary tract urothelial carcinomas. International Journal of Clinical Oncology. 2012;17(3):256–62.
14. Ishihara H, et al., *Preoperative controlling nutritional status (CONUT) score as a novel predictive biomarker of survival in patients with localized urothelial carcinoma of the upper urinary tract treated with radical nephroureterectomy.* Urol Oncol, 2017. **35**(9): p. 539.e9-539.e16.
15. Ku JH, et al. Preoperative serum albumin as a prognostic factor in patients with upper urinary tract urothelial carcinoma. Int Braz J Urol. 2014;40(6):753–62.
16. Morizane S, et al. Risk stratification model, including preoperative serum C-reactive protein and estimated glomerular filtration rate levels, in patients with upper urinary tract urothelial carcinoma undergoing radical nephroureterectomy. Int Urol Nephrol. 2015;47(8):1335–41.
17. Nishihara K, et al. High postoperative neutrophil-to-lymphocyte ratio as a poor prognostic marker in patients with upper tract urothelial carcinoma. Oncology Letters. 2019;17(6):5241–50.
18. Nishikawa M, et al. Significance of multiple preoperative laboratory abnormalities as prognostic indicators in patients with urothelial carcinoma of the upper urinary tract following radical nephroureterectomy. Int J Clin Oncol. 2018;23(1):151–7.
19. Obata J, et al. C-reactive protein: a biomarker of survival in patients with localized upper tract urothelial carcinoma treated with radical nephroureterectomy. Urol Oncol. 2013;31(8):1725–30.
20. Saito K, et al. The impact of preoperative serum C-reactive protein on the prognosis of patients with upper urinary tract urothelial carcinoma treated surgically. BJU Int. 2007;100(2):269–73.
21. Sakano S, et al. Risk group stratification based on preoperative factors to predict survival after nephroureterectomy in patients with upper urinary tract urothelial carcinoma. Ann Surg Oncol. 2013;20(13):4389–96.
22. Tanaka N, et al. The predictive value of C-reactive protein for prognosis in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy: a multi-institutional study. Eur Urol. 2014;65(1):227–34.
23. Stein B, et al. Preoperative serum C- reactive protein: a prognostic marker in patients with upper urinary tract urothelial carcinoma. BMC Cancer. 2013;13:101.
24. Azuma T, et al. Preoperative neutrophil-lymphocyte ratio as an independent prognostic marker for patients with upper urinary tract urothelial carcinoma. Clin Genitourin Cancer. 2013;11(3):337–41.
25. Kinoshita T, et al. Serum interleukin-6 level reflects the tumor proliferative activity in patients with colorectal carcinoma. Cancer. 1999;85(12):2526–31.
26. Jee SH, et al., *Overexpression of interleukin-6 in human basal cell carcinoma cell lines increases anti-apoptotic activity and tumorigenic potency. Oncogene*. 2001;*20(2):198-208*..
27. Hanahan D, et al. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell. 2012;21(3):309–22.

Tables

No.	Author	Year	Study region	Recruitment period	No. of patients	Age(years)	Gender(m/f)	Follow-up(months)	CRP cut off(mg/dl)	Study design	Surv anal
1	Aziz A, et al.	2014	German	1990–2012	265	NA	169/96	Median(IQR) 37(9–48)	0.9	Retrospective	RFS, CCS
2	Fujita K, et al.	2015	Japan	1998–2013	45	Median(range) 67 (50–81)	29/16	Median(range) 20(1–113)	0.3	Retrospective	CCS
3	Inamoto T,et al.	2012	Japan	1996–2009	103	Median(range) 69 (23–91)	71/32	Median(IQR) 29(14–63)	0.3	Retrospective	CCS
4	Ishihara H,et al.	2017	Japan	2003–2014	107	NA	68/39	NA	0.5	Retrospective	RFS, CCS
5	Ku JH,et al.	2014	Korea	1999–2010	181	Median(IQR) 65.7(59.4–72.6)	144/37	Median(range) 56.4(0.1–158)	1.0	Retrospective	OS
6	Morizane S,et al.	2015	Japan	1993–2005	345	Median(range) 74 (38–95)	234/111	Median(range) 39.9 (6.1–190)	0.5	Retrospective	CCS
7	Nishihara K,et al.	2019	Japan	2004–2015	134	Median(range) 70 (64–76)	88/46	Median(range) 40.4(20.8–71.3)	0.3	Retrospective	CCS
8	Nishikawa M,et al.	2017	Japan	2005–2015	135	Median(range) 69 (52–86)	106/29	NA	0.5	Retrospective	CCS
9	Obata J,et al.	2012	Japan	1993–2009	183	Median(range) 70(40 – 92)	138/45	Median(range) 39(3-201)	0.5	Retrospective	RFS, CCS
10	Saito K,et al.	2007	Japan	1990–2005	130	NA	88/42	Median(range) 47 (3–190)	0.5	Retrospective	RFS, CCS
11	Sakano S,et al.	2013	Multi-center	1995–2009	536	Median(range) 71(32–92)	370/166	Median(range) 40.9(3–200)	0.13	Retrospective	CCS
12	Stein B, et al.	2013	Germany	1981–2011	115	Median(range) 66.8(34–90))	83/32	Median(IQR) 15.1(7.2–37.7)	0.5	Retrospective	CCS
13	Tanaka N,et al.	2014	Japan	1993–2010	522	NA	382/140	Median(IQR) 32(15–62)	0.5	Retrospective	RFS, CCS

m/f: male/female; IQR: interquartile range; NA: data not applicable; NOS: Newcastle-Ottawa Scale; CSS: cancer-specifc survival; OS: overall survival; RFS: recu survival.

No.	Author	Staging system	Grading system	Stage 1–2/3–4	Grade1-2/3	LNI+/LNI-	LVI+/LVI-	Distant metastasis
1	Aziz A, et al.	2010AJCC	1998 WHO/ISUP	158/110	103/162	59/206	52/209	None
2	Fujita K, et al.	NA	NA	7/38	10/35	45/0	3/42	None
3	Inamoto T,et al.	2002 TNM	1998 WHO/ISUP	56/47	48/55	17/86	71/32	None
4	Ishihara H,et al.	2009 TNM	NA	46/61	30/77	NA	54/53	None
5	Ku JH,et al.	2004 UICC/AJCC	1973 WHO	101/80	121/60	8/26	31/150	None
6	Morizane S,et al.	2002 TNM	1973 WHO/ISUP	188/152	222/109	21/119	102/227	None
7	Nishihara K,et al.	2009 TNM	1999 WHO	80/54	89/45	17/117	48/83	None
8	Nishikawa M,et al.	2009 AJCC	NA	65/70	42/93	28/107	44/91	None
9	Obata J,et al.	NA	NA	88/95	43/140	NA	74/109	None
10	Saito K,et al.	2002 TNM	1998 WHO	63/67	67/63	24/106	64/66	None
11	Sakano S,et al.	2010 AJCC	1998 WHO	375/101	NA	40/477	NA	None
12	Stein B, et al.	2002 TNM	1997 UICC	NA	61/54	NA	NA	None
13	Tanaka N,et al.	2002 UICC/AJCC	1973 WHO	258/264	203/319	28/494	196/326	None

NA: not available; LNI: lymph node involvement; LVI: lymphovascular invasion; AJCC: American Joint Committee on Cancer classifcation; UICC: Union Internationale Contre le Cancer; WHO/ISUP World Health Organiza tion/International Society of Urological Pathology classifcation

Figures

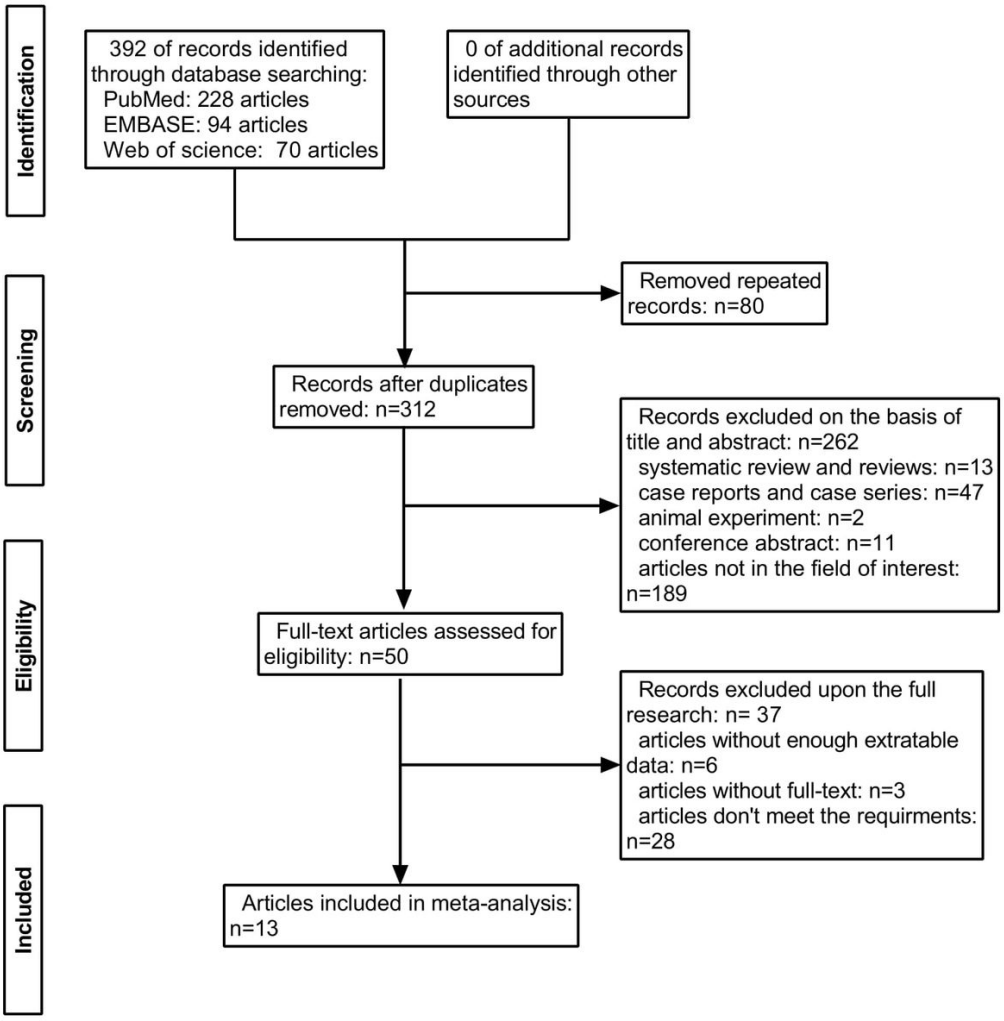

Figure 1

Flowchart of the search and selection process in this meta-analysis.

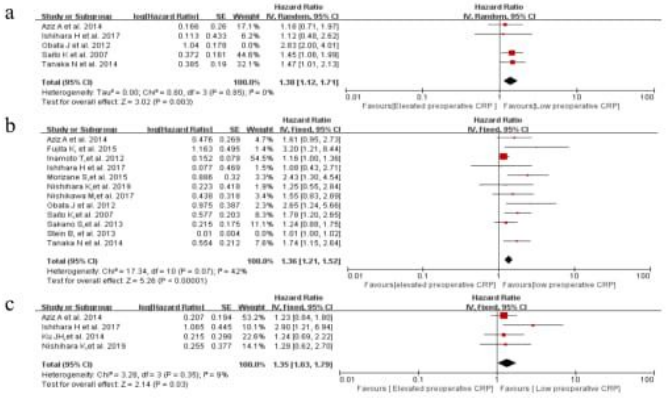

Figure 2

Forest plots of studies assessing the association between elevated CRP and (a)RFS, (b)CCS, and (c)OS, respectively. (CRP, C-reactive protein; CI, confidence intervals; RFS, recurrence-free survival; CCS, cancer-specific survival; OS, overall survival)

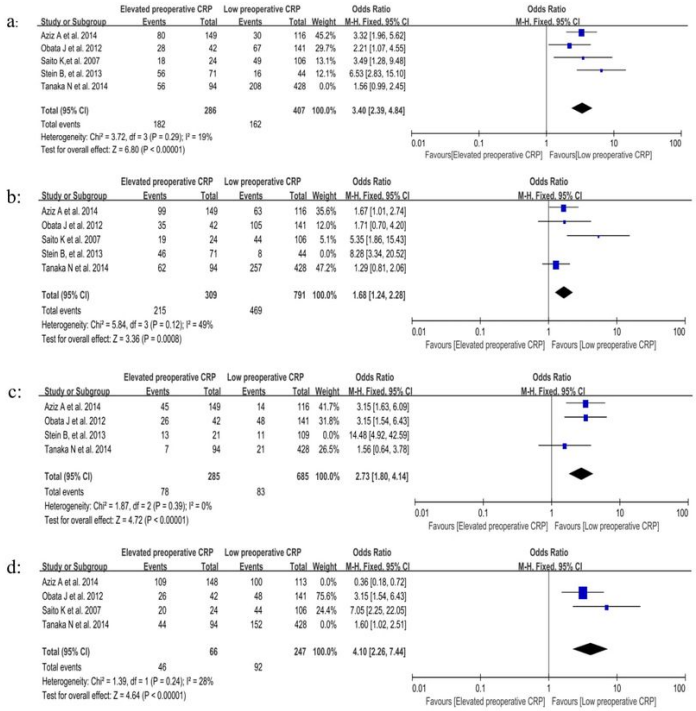

Figure 3

A meta-analyses of CRP and clinicopathological features in UTUC (a is for stage(3/4 vs. 1/2), b for grade (1/2 vs. 3), c for LNI(+ vs. -), and d for LVI(+ vs. -)).

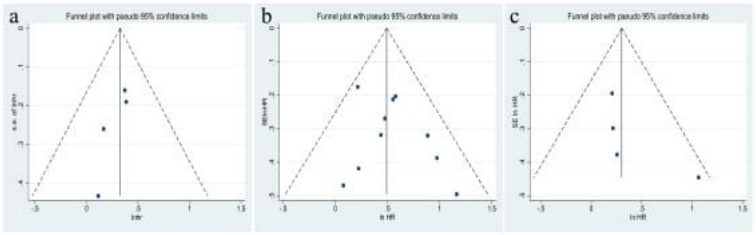

Figure 4

Funnel plots for publication bias of the hazard ratios (HRs) of (b) RFS, (b) CSS, and (c) OS.