

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2022 June 15; 14(6): 1067-1217



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ABOUT COVER

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INDEXING/ABSTRACTING

The WJGO is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, PubMed Central, and Scopus. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for WJGO as 3.393; IF without journal self cites: 3.333; 5-year IF: 3.519; Journal Citation Indicator: 0.5; Ranking: 163 among 242 journals in oncology; Quartile category: Q3; Ranking: 60 among 92 journals in gastroenterology and hepatology; and Quartile category: Q3. The WJGO's CiteScore for 2020 is 3.3 and Scopus CiteScore rank 2020: Gastroenterology is 70/136.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Ying-Yi Yuan*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma*.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed, Florin Burada

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

June 15, 2022

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Does chronic kidney disease affect the complications and prognosis of patients after primary colorectal cancer surgery?

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Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ekine-Afolabi B, United Kingdom; Matsumoto T, Japan; Rathnaswami A, India

A-Editor: Liu X, China

Received: December 27, 2021

Peer-review started: December 27, 2021

First decision: March 13, 2022

Revised: March 26, 2022

Accepted: May 27, 2022

Article in press: May 27, 2022

Published online: June 15, 2022



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Abstract

BACKGROUND

The effect of chronic kidney disease (CKD) on the outcomes of colorectal cancer (CRC) patients after primary CRC surgery is controversial.

AIM

To analyze whether CKD had specific effect on the outcomes after CRC surgery.

METHODS

We searched the PubMed, Embase, Cochrane Library databases and CNKI, from inception to March 14, 2022. Newcastle-Ottawa Scale was used for the quality assessment in this meta-analysis, and we used RevMan 5.3 was used for data analysis.

RESULTS

A total of nine studies including 47771 patients were eligible for this meta-analysis. No significant difference was found in terms of overall postoperative complications [odds ratio (OR) = 1.78, 95%CI: 0.64-4.94, $P = 0.27$]. We analyzed the specific complications and found that the CKD group had higher rates of pulmonary infection (OR = 2.70, 95%CI: 1.82-4.00, $P < 0.01$), cardiovascular complications (OR = 3.39, 95%CI: 2.34-4.91, $P < 0.01$) and short-term death (OR = 3.01, 95%CI: 2.20-4.11, $P < 0.01$). After pooling the hazard ratio (HR), the CKD group had worse overall survival (OS) (HR = 1.51, 95%CI: 1.04-2.20, $P = 0.03$). We performed subgroup analyses of the dialysis and non-dialysis groups, and no significant difference was found in the non-dialysis group (HR = 1.20, 95%CI: 0.98-1.47, $P = 0.08$). The dialysis group had worse OS (HR = 3.36, 95%CI: 1.92-5.50, $P < 0.01$) than the non-dialysis group. The CKD group had worse disease-free survival (DFS) (HR = 1.41, 95%CI: 1.12-1.78, $P < 0.01$), and in the subgroup analysis of the dialysis and non-dialysis groups, no significant difference was found in the non-dialysis group (HR = 1.27, 95%CI: 0.97-1.66, $P = 0.08$). The dialysis group had worse OS (HR = 1.95, 95%CI: 1.23-3.10, $P < 0.01$) than the non-

dialysis group.

CONCLUSION

Preexisting CKD was associated with higher rates of pulmonary infection, higher rates of short-term death, and worse OS and poorer DFS following CRC surgery.

Key Words: Chronic kidney disease; Colorectal cancer; Outcome; Prognosis; Meta-analysis

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Core Tip: Previous studies have shown that patients with chronic kidney disease might have an increased risk of colorectal cancer, however, the impact of chronic kidney disease on complications and prognosis after colorectal cancer surgery is controversial. Furthermore, the prognosis remained unclear as well. Therefore, this study aimed to analyze whether chronic kidney disease had specific effect on the outcomes after colorectal cancer surgery. In conclusion, preexisting chronic kidney disease was associated with higher rates of pulmonary infection, higher rates of short-term death, poorer overall survival rates, and poorer disease-free survival rates following colorectal cancer surgery.

Citation: Liu XY, Zhang B, Cheng YX, Tao W, Yuan C, Wei ZQ, Peng D. Does chronic kidney disease affect the complications and prognosis of patients after primary colorectal cancer surgery? *World J Gastrointest Oncol* 2022; 14(6): 1199-1209

URL: <https://www.wjgnet.com/1948-5204/full/v14/i6/1199.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v14.i6.1199>

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignant tumor and ranks the second leading cause of cancer-related deaths around the world. Nearly 1.8 million new CRC patients and 0.7 million cancer-related deaths occur each year[1]. Radical resection is the only curative treatment for early-stage CRC[2, 3], and comprehensive therapy (such as immune therapy, radiotherapy, chemotherapy and surgery) is recommended for advanced-stage CRC[4-8].

It is estimated that approximately 500 million adults worldwide are diagnosed with chronic kidney disease (CKD), but the prevalence varies greatly among different countries[9,10]. CKD can increase mortality and morbidity, and it involves an economic burden as well[11,12]. Some key pathophysiological causes of CKD may contribute to increased postoperative morbidity (including excessive arterial calcification, endothelial dysfunction and increased levels of inflammatory factors)[13].

As previous studies reported, patients with CKD might increase the risk of CRC[14]; however, the effect of CKD on complications and prognosis after CRC surgery remains controversial. Some studies held the view that CKD had no effect on surgical complications[15,16]. Moreover, other studies believed that CKD increased postoperative complications[17,18]. Furthermore, the prognosis remained unclear as well. Therefore, our study aimed to analyze whether CKD had an effect on the complications and prognosis of CRC patients who underwent primary CRC surgery.

MATERIALS AND METHODS

This meta-analysis conformed to the Preferred Reporting method for Systematic Reviews and Meta-Analyses (PRISMA) statement[19]. The register number of this meta-analysis was CRD42021266160.

Literature search strategy

We searched the PubMed, Embase, Cochrane Library databases and CNKI from inception to March 14, 2022. There were two key items in this search strategy: chronic kidney disease and colorectal cancer. To expand the search scope, in terms of chronic kidney disease, we used "kidney" OR "dialysis" OR "hemodialysis" OR "estimated glomerular filtration rate". Colorectal cancer was searched as follows: "rectal cancer" OR "colorectal cancer" OR "colon cancer" OR "rectal neoplasm" OR "colorectal neoplasm" OR "colon neoplasm" OR "rectal tumor" OR "colorectal tumor" OR "colon tumor". Then, two key items were combined with "AND". We restricted the search language to Chinese and English, and we limited the searching scope to titles and abstracts. In addition, we use Reference Citation Analysis (<https://www.referencecitationanalysis.com>) to retrieve relevant literature.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) Studies that included patients undergoing colorectal surgery; (2) Studies that compared the CKD group and the non-CKD group of CRC patients; and (3) Study outcomes included the complications or prognosis. The exclusion criteria were as follows: (1) Studies with insufficient data on complications or prognosis; and (2) Case reports, comments, letter to editor, conferences and reviews. The procedures of inclusion and exclusion criteria were carried out by two reviewers separately, and if there was a disagreement, it was settled by discussion with another reviewer.

Study selection

Two reviewers searched the databases separately. The titles and abstracts were screened after removing duplicates, after which full texts were evaluated for eligibility. Disagreement was settled by another reviewer.

Data extraction

Two reviewers extracted and cross-checked the data. The data which were extracted were: (1) Publication year, first author, country, sample size, study design, Newcastle-Ottawa Scale (NOS) score and the definition of the CKD group and the non-CKD group; (2) The baseline information included age, sex, comorbidities, American Society of Anesthesiologists (ASA) score and tumor stage; (3) The surgery-related information included surgery type and surgery method; (4) Postoperative complications included anastomotic leakage (divided into three groups: grade A, grade B and grade C. Grade A needed no active intervention, grade B needed active intervention and grade C needed reoperation)[20], pulmonary complications, intestinal obstruction, surgical site infection, postoperative bleeding and short-term death; and (5) Overall survival (OS) and disease-free survival (DFS).

Outcomes

The primary outcome referred to the short-term outcome, which was equal to postoperative complications (including anastomotic leakage, intestinal obstruction, surgical site infection, postoperative bleeding, pulmonary complications and short-term death during the hospital stay). The second outcome was the long-term prognosis of OS and DFS.

Quality assessment

The assessment of the included studies was according to the Newcastle-Ottawa Scale (NOS)[21]. Nine points represented high-quality studies, seven to eight points represented medium-quality studies and scores less than seven points represented low-quality studies.

Statistical analysis

In the current meta-analysis, the pooled prognosis (OS and DFS) used hazard ratios (HRs) and 95% CIs, and the HRs were extracted from COX analyses. If no available data reported the HRs from COX analyses, then we extracted the HRs from Kaplan-Meier survival curves[22]. The mean \pm SD was used for continuous variables, and proportions were used for categorical variables. Mean differences (MDs)/odds ratios (ORs) plus 95% CIs were calculated for continuous and dichotomous variables. Statistical heterogeneity was analyzed using the I^2 and the chi-square test[23,24]. When $I^2 > 50\%$, we used the random effects model, in this model, $P < 0.1$ was considered to be statistically significant. We used the fixed effects model, in this model, when $I^2 \leq 50\%$, and $P < 0.05$ was considered to be statistically significant. All the statistical analysis was performed using RevMan 5.3 (The Cochrane Collaboration, London, United Kingdom).

RESULTS

Study selection

We identified 903 studies (266 studies were obtained from PubMed, 509 studies were obtained from Embase, 103 studies were obtained from the Cochrane Library and 25 studies were obtained from CNKI). A total of 903 studies were included after removed duplicate, 671 studies were left for initial evaluation. After titles and abstracts were screened, 9 studies were left for full-text screening. Finally, nine studies[15-18,25-29] were included (Figure 1).

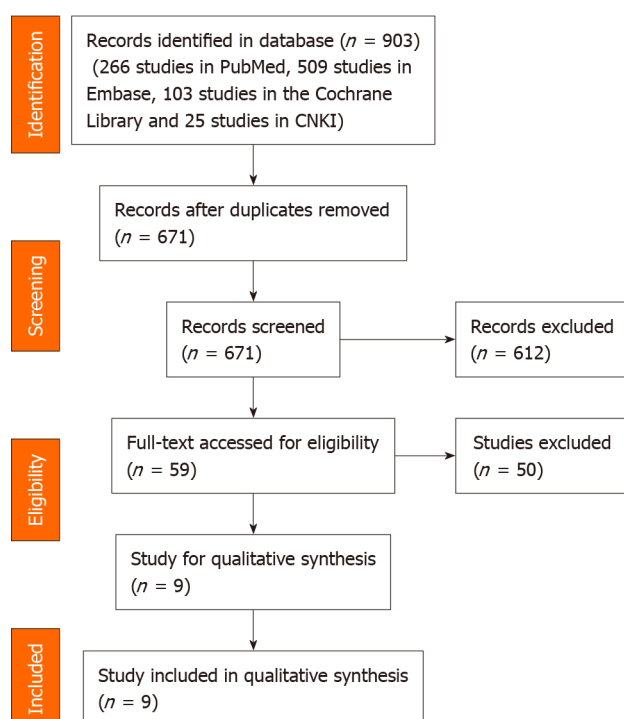
Patient characteristics and quality assessment

A total of nine studies[15-18,25-29] including 47771 patients, were enrolled in the current meta-analysis. As for publishing countries, five of nine studies were conducted in Japan, and the other studies were in the United States, the United Kingdom, Canada and China. The publication years were from 2012 to 2022, eight studies were retrospective studies, only one study was a prospective study. The study dates were from 2001 to 2020. The NOS score and definitions of the CKD group and the non-CKD group are

Table 1 Characteristics of the studies included in the meta-analysis

Ref.	Country	Study design	Study date	Sample size		Total	Definition of CKD and non-CKD		NOS
				CKD group	Non-CKD group		CKD group	Non-CKD group	
Currie <i>et al</i> [15], 2014	United Kingdom	Prospective	2006-2011	126	582	708	15 < eGFR < 60	eGFR ≥ 60	7
Nozawa <i>et al</i> [17], 2012	Japan	Retrospective	2001-2010	245	882	1127	eGFR < 60	eGFR ≥ 60	8
Higashino <i>et al</i> [16], 2020	Japan	Retrospective	2008-2015	14	567	581	Dialysis	Non-dialysis	7
Hu <i>et al</i> [18], 2015	United States	Retrospective	2009-2013	265	42138	42401	Dialysis	Non-dialysis	8
Chen <i>et al</i> [26], 2016	China	Retrospective	2012-2015	5	10	15	eGFR < 60	eGFR > 60	6
Obara <i>et al</i> [25], 2021	Japan	Retrospective	2007-2016	24	24	48	Dialysis	Non-dialysis	8
Obara <i>et al</i> [27], 2022	Japan	Retrospective	2011-2015	59	204	263	eGFR < 55	eGFR ≥ 55	7
Shiraishi <i>et al</i> [28], 2022	Japan	Retrospective	2016-2020	78	1294	1372	eGFR < 60	eGFR ≥ 60	8
Dudani <i>et al</i> [29], 2021	Canada	Retrospective	2005-2013	136	1118	1254	eGFR < 60	eGFR > 60	8

CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rates (mL/min/1.73 m²); NOS: Newcastle-Ottawa Scale.



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Figure 1 Flowchart of study selection.

shown in Table 1. Six studies reported that the modification of diet in renal disease equation was used to estimate the estimated glomerular filtration rates (eGFR)[16,18,25,27-29]; however, the method used in the other studies was unclear[15,17,26] (see Table 1).

Baseline information

Sex, age, ASA score, T staging and N staging were included for baseline information analysis. The CKD group had an older age (OR = 8.67, 95%CI: 5.73-11.61, $P < 0.01$) and a higher proportion of ASA 3-4 grade (OR = 10.27, 95%CI: 2.98-35.35, $P < 0.01$) after pooling the baseline information. As for other baseline information, no significant difference was found between the two groups ($P > 0.05$) (Table 2).

Table 2 Summary of characteristics between chronic kidney disease group and Non-chronic kidney disease group

Characteristics	Studies	Participants (CKD/non-CKD)	Mean difference/odds ratio (95%CI)	Heterogeneity
Baseline information				
Male	9	952/46819	0.92 (0.63, 1.35); $P = 0.67$	$I^2 = 82\%$; $P < 0.01$
Age, yr	3	190/796	8.67 (5.73, 11.61); $P < 0.01$	$I^2 = 60\%$; $P = 0.08$
ASA1-ASA2	3	218/2443	0.10 (0.03, 0.34); $P < 0.01$	$I^2 = 88\%$; $P < 0.01$
ASA3-ASA4	3	218/2443	10.27 (2.98, 35.35); $P < 0.01$	$I^2 = 88\%$; $P < 0.01$
T0-T2	4	508/2962	0.71 (0.46, 1.08); $P = 0.11$	$I^2 = 55\%$; $P = 0.08$
T3-T4	4	508/2962	1.41 (0.92, 2.16); $P = 0.11$	$I^2 = 55\%$; $P = 0.08$
N0	4	508/2962	1.09 (0.89, 1.33); $P = 0.42$	$I^2 = 0\%$; $P = 0.40$
N1-N3	4	508/2962	0.92 (0.75, 1.33); $P = 0.42$	$I^2 = 0\%$; $P = 0.40$
Surgery-related information				
Colon cancer	4	409/2055	2.10 (0.91, 4.85); $P = 0.08$	$I^2 = 80\%$; $P < 0.01$
Rectal cancer	4	409/2055	0.48 (0.21, 1.10); $P = 0.08$	$I^2 = 80\%$; $P < 0.01$
Laparoscopy surgery	6	566/44809	0.88 (0.54, 1.42); $P = 0.59$	$I^2 = 72\%$; $P < 0.01$
Open surgery	6	566/44809	1.14 (0.70, 1.86); $P = 0.59$	$I^2 = 72\%$; $P < 0.01$
Emergency operation	2	324/42342	1.31 (0.84, 2.05); $P = 0.23$	$I^2 = 0\%$; $P = 0.49$
Operative time	3	309/1096	-3.58 (-18.95, 11.79); $P = 0.65$	$I^2 = 60\%$; $P = 0.08$
Intraoperative blood loss	3	309/1096	1.40 (-30.34, 33.15); $P = 0.93$	$I^2 = 0\%$; $P = 0.96$
Postoperative complications				
Overall complication	7	738/44407	1.78 (0.64, 4.94); $P = 0.27$	$I^2 = 95\%$; $P < 0.01$
Specific complications				
Cardiovascular	4	641/43612	3.39 (2.34, 4.91); $P < 0.01$	$I^2 = 36\%$; $P = 0.20$
Anastomotic leakage	4	508/2962	1.44 (0.89, 2.32); $P = 0.14$	$I^2 = 35\%$; $P = 0.21$
Pulmonary infection	5	607/44891	2.70 (1.82, 4.00); $P < 0.01$	$I^2 = 0\%$; $P = 0.84$
Intestinal obstruction	5	420/2971	0.89 (0.58, 1.37); $P = 0.60$	$I^2 = 6\%$; $P = 0.37$
Surgical site infection	6	685/45109	1.29 (1.00, 1.65); $P = 0.05$	$I^2 = 0\%$; $P = 0.86$
Other site infection	3	515/43030	1.07 (0.64, 1.80); $P = 0.79$	$I^2 = 0\%$; $P = 0.60$
Postoperative bleeding	3	347/2200	0.63 (0.17, 2.36); $P = 0.49$	$I^2 = 0\%$; $P = 0.50$
Short-term death	4	650/44169	3.01 (2.20, 4.11); $P < 0.01$	$I^2 = 0\%$; $P = 0.50$

CKD: Chronic kidney disease; ASA: American Society of Anesthesiologists; T: Tumor; N: Node.

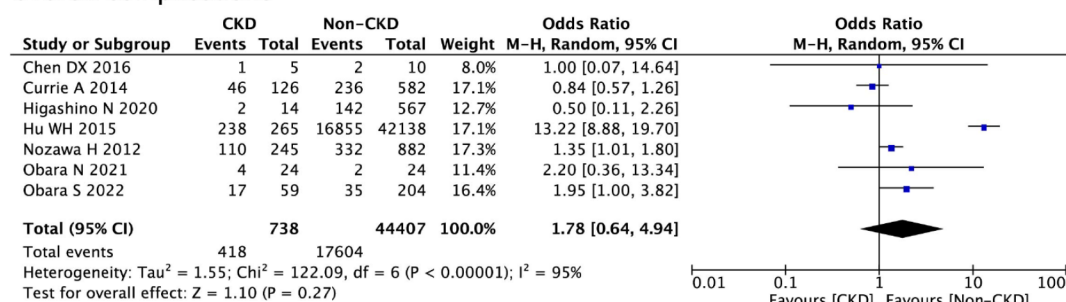
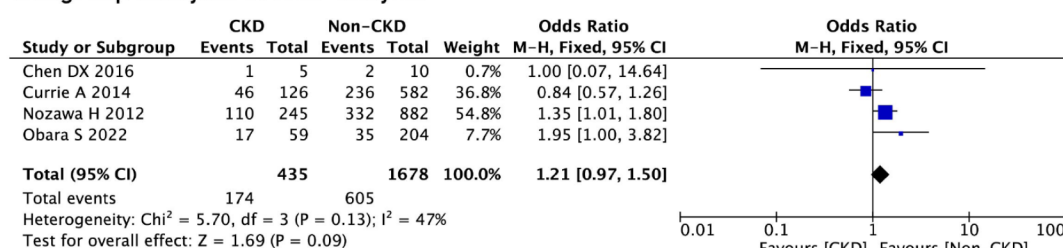
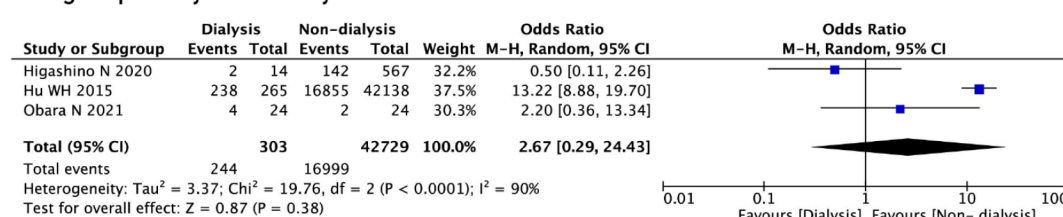
Surgery-related information

We compared the surgery-related information between the two groups, and it was found no significant difference in terms of laparoscopic surgery, open surgery, emergency operation, intraoperative blood loss or operation time ($P > 0.05$). But, the CKD group had higher proportion of patients who underwent colon cancer surgery (OR = 2.10, 95%CI: 0.91-4.85, $P = 0.08$) (Table 2).

Postoperative complications

There was no significant difference in terms of overall postoperative complications (OR = 1.78, 95%CI: 0.64-4.94, $P = 0.27$). We performed subgroup analyses of the dialysis and non-dialysis groups and no significant difference was found between the non-dialysis group (OR = 1.21, 95%CI: 0.97-1.50, $P = 0.09$) and the dialysis group (OR = 2.67, 95%CI: 0.29-24.23, $P = 0.38$) (Figure 2).

We conducted the analysis of specific complications, and we found that the CKD group had higher rates of pulmonary infections (OR = 2.70, 95%CI: 1.82-4.00, $P < 0.01$), cardiovascular complications (OR = 3.39, 95%CI: 2.34-4.91, $P < 0.01$) and short-term death (OR = 3.01, 95%CI: 2.20-4.11, $P < 0.01$) (Table 2).

A**Overall complications****B****Subgroup analysis of Non-dialysis****C****Subgroup analysis of dialysis**

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Figure 2 Complications. A: Overall complications between the chronic kidney disease (CKD) group and the non-CKD group; B: Subgroup analysis of the non-dialysis groups; C: Subgroup analysis of the dialysis groups.**OS and DFS**

The CKD group had worse OS (HR = 1.51, 95%CI: 1.04-2.20, $P = 0.03$) after pooling up the HRs. We performed subgroup analyses of the dialysis and non-dialysis groups and no significant difference was found in the non-dialysis group (HR = 1.20, 95%CI: 0.98-1.47, $P = 0.08$). The dialysis group had worse OS (HR = 3.36, 95%CI: 1.92-5.90, $P < 0.01$) than the non-dialysis group (Figure 3).

The CKD group had worse DFS (HR = 1.41, 95%CI: 1.12-1.78, $P < 0.01$). We performed subgroup analyses of the dialysis and non-dialysis groups, and no significant difference was found in the non-dialysis group (HR = 1.27, 95%CI: 0.97-1.66, $P = 0.08$). The dialysis group had worse OS (HR = 1.95, 95%CI: 1.23-3.10, $P < 0.01$) than the non-dialysis group (Figure 4).

Sensitivity analysis

We performed repeated meta-analysis by omitting each study at a time, in our meta-analysis, the exclusion of any one of the included studies did not alter the results.

DISCUSSION

A total of nine studies were included in this meta-analysis. There was no significant difference in terms of overall postoperative complications after pooling all of the data. As for prognosis, the CKD group had worse OS and DFS. We performed subgroup analysis of the dialysis and non-dialysis groups. Dialysis was associated with a worse OS and DFS as well.

The classification of renal function is mainly based on the eGFR[30] and different renal function classifications might have an impact on surgery outcomes. As previous studies have reported, CKD could increase postoperative complications after gastric cancer surgery and hepatocellular carcinoma surgery, and the complications included anastomotic leakage and short-term postoperative death[31-

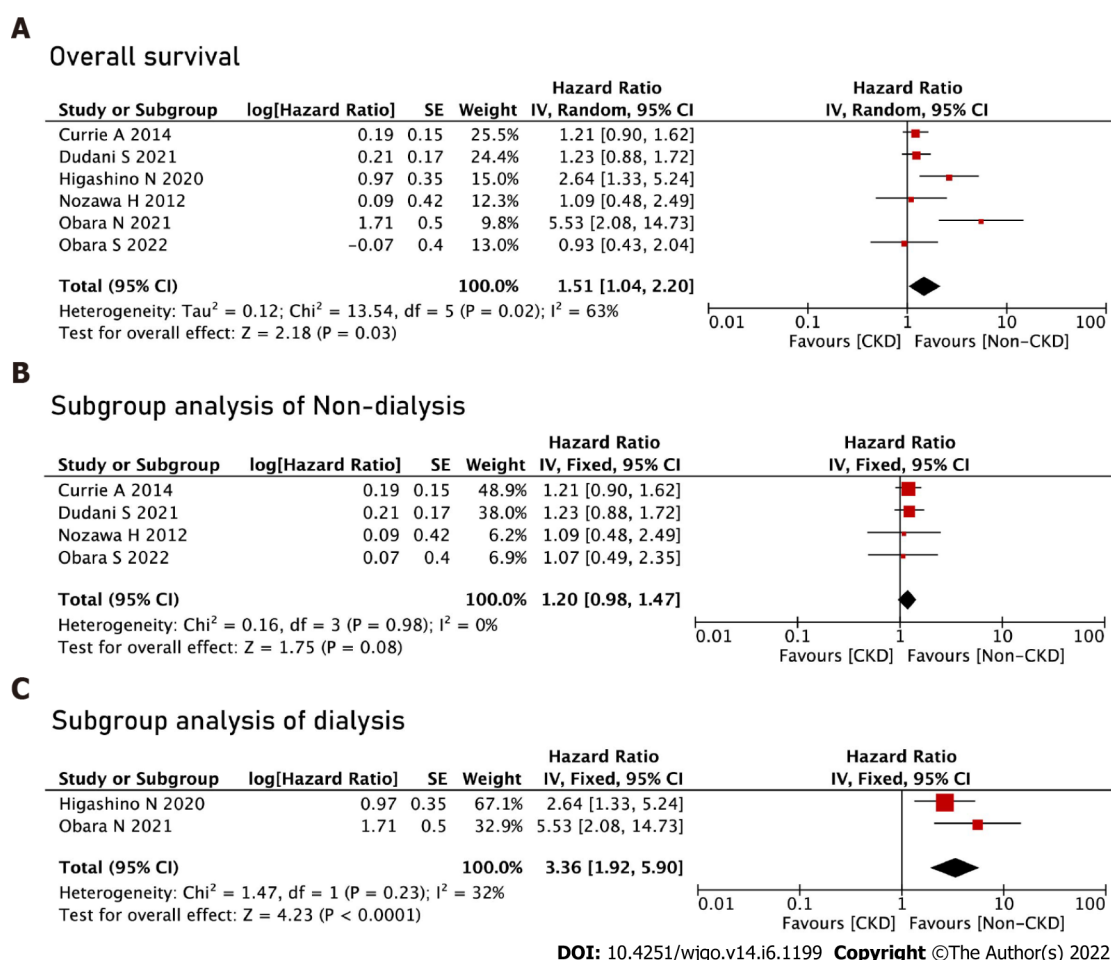


Figure 3 Overall survival. A: Overall survival between the chronic kidney disease (CKD) group and the non-CKD group; B: Subgroup analysis of the non-dialysis groups; C: Subgroup analysis of the dialysis groups.

33]. In addition, patients with concurrent CKD and cancer have a poor prognosis[32]. In terms of CRC, although an impact of renal function on postoperative complications and prognosis has been reported, it remains controversial.

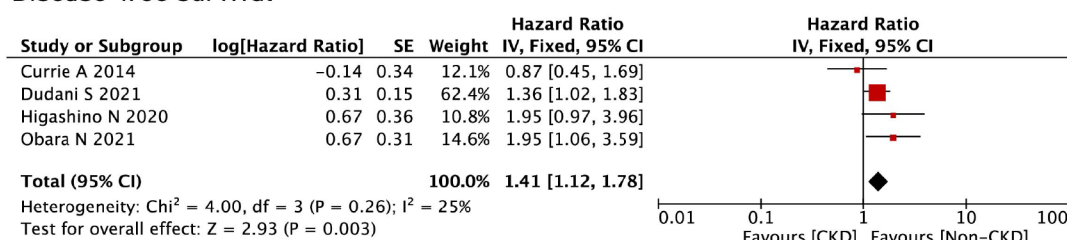
In this study, there was no significant difference in terms of overall postoperative complications, and we chose the random effect model to conduct the analysis because of the high heterogeneity among studies. We conducted the analysis of specific complications, and we found that the CKD group had higher rates of pulmonary infection, cardiovascular complications and short-term death. The possible reason was that patients undergoing colorectal surgery might experience fluid overload due to nutritional support during non-oral periods. Therefore, these events might increase the risk of lung-related complications[18]. Cardiovascular complications might be associated with endothelial dysfunction in CKD patients[16,34]. Furthermore, patients with CKD are in a relatively immunosuppressive state due to nutritional deficiencies, the lymphocyte suppression and the loss of serum immune system components, which might result in an increase in infectious diseases and short-term deaths after surgery[35].

The CKD group had worse OS rates DFS rates. The probable reason was that CKD was associated with endothelial dysfunction, malnutrition, volume overload or changes in calcium and phosphorus metabolism, and the dysfunction would cause higher rates of cardiovascular events[13,36]. In addition, an association between postoperative complications and cancer-related poor prognosis has been reported in esophageal, gastric and colorectal cancer; therefore, higher rates of postoperative complications might result in a poor prognosis[37,38]. Moreover, postoperative complications and perioperative blood loss can suppress immune function, which might be a factor for promoting cancer recurrence[39,40]. We performed subgroup analyses of the dialysis and non-dialysis groups. Dialysis was associated with worse OS and DFS. Therefore, the distinction in OS and DFS between the two groups might be mainly determined by dialysis.

Some parameters that were insufficient for meta-analysis included cancer-related death, blood transfusion, reoperation rate, adjuvant chemotherapy and the R0 resection rate. However, attention should be given to these parameters. In addition to OS and DFS, cancer-specific survival (CSS) could reflect tumor-related deaths. Obara *et al*[25] reported that CSS was a negative parameter between the

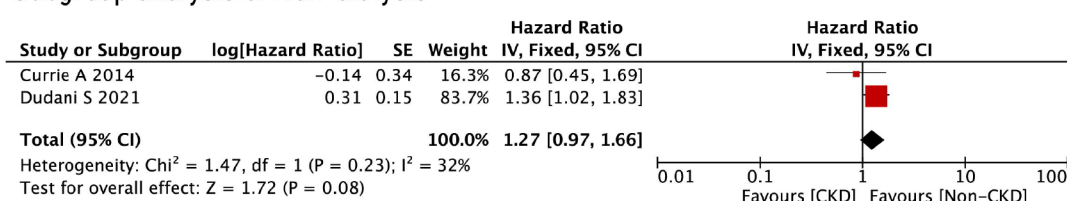
A

Disease-free survival



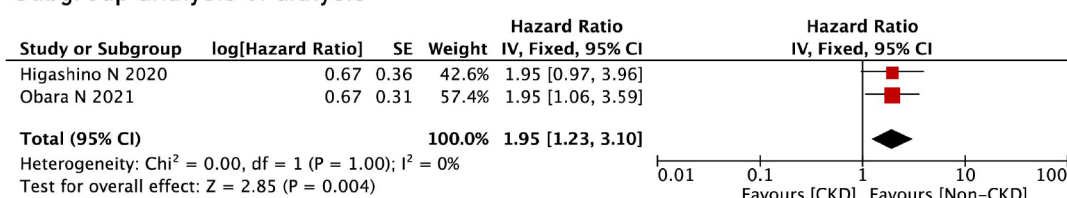
B

Subgroup analysis of Non-dialysis



C

Subgroup analysis of dialysis



DOI: 10.4251/wjgo.v14.i6.1199 Copyright ©The Author(s) 2022.

Figure 4 Disease-free survival. A: Disease-free survival between the chronic kidney disease (CKD) group and the non-CKD group; B: Subgroup analysis of the non-dialysis groups; C: Subgroup analysis of the dialysis groups.

two groups, and the major long-term cause of death in CKD patients might be cardiovascular death. Blood transfusion, a factor that influences the prognosis, might have been more common in the CKD group. Therefore, for surgeons, careful control during the operation and perioperative management of CKD are necessary to reduce blood transfusion.

Some limitations were existing. First, only nine studies were included, and the sample size was relatively small. Second, the cutoff for CKD differed among the included study. Five studies reported that the cutoff eGFR was 60 mL/min/1.73 m², one study reported that the cutoff value was 55 mL/min/1.73 m² and the remaining three studies used hemodialysis as the cutoff. Obvious heterogeneity was seen after pooling the data in terms of complications, OS and DFS, therefore, we performed a subgroup analysis, and heterogeneity was reduced. Third, we extracted all of the data that could be analyzed in this study, however, some information was lacking, such as postoperative hospital stay, cancer-related death, blood transfusion, reoperation rate, adjuvant chemotherapy, R0 resection rate, perioperative chemo-radiotherapy and completion of the schedule of chemo-radiotherapy. Fourth, some of the survival data were extracted from the Kaplan-Meier survival curves, which might result in inaccuracies. Finally, among the specific postoperative complications, it was found that pulmonary infection, cardiovascular complications and short-term death were significantly different between the groups; however, this conclusion was based on only four studies, including two CKD studies and two dialysis studies, which would result in heterogeneity. Therefore, multicenter, high-quality and well-controlled prospective studies including comprehensive baseline information comparing the complications, OS, DFS and CSS should be conducted.

CONCLUSION

In conclusion, preexisting CKD was associated with higher rates of pulmonary infection, higher rates of short-term death, and worse OS and DFS following CRC surgery.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer (CRC) is the third most common malignant tumor and the second leading cause of cancer deaths worldwide. Several key pathophysiological causes of chronic kidney disease (CKD) may lead to increased postoperative morbidity, including excessive arterial calcification, endothelial dysfunction and increased levels of inflammatory factors. Previous studies have shown that patients with CKD might have an increased risk of CRC; however, the impact of CKD on complications and prognosis after CRC surgery is controversial.

Research motivation

The aim of this study was to conduct meta-analysis of current studies and to analyze whether CKD had specific effect on the outcomes after CRC surgery.

Research objectives

The aim of this study is to provide some recommendations for clinical work by investigating the impact of CKD on postoperative complications and prognosis in colorectal cancer.

Research methods

We searched the PubMed, Embase, Cochrane Library databases and CNKI, from inception to March 14, 2022. Newcastle-Ottawa Scale was used for the quality assessment in this meta-analysis, and we used RevMan 5.3 was used for data analysis.

Research results

A total of nine studies including 47771 patients were included in this meta-analysis. No significant difference was found in terms of overall postoperative complications. We analyzed the specific complications and found that the CKD group had higher rates of pulmonary infection, cardiovascular complications and short-term death. After pooling the hazard ratios, the CKD group had worse overall survival (OS).

Research conclusions

Preexisting CKD was associated with higher rates of pulmonary infection, higher rates of short-term death, and worse OS and poorer disease-free survival (DFS) following CRC surgery.

Research perspectives

Based on the results and limitations of this research, multicenter, high-quality and well-controlled prospective studies including comprehensive baseline information comparing the complications, OS, DFS and CSS should be performed in the future.

ACKNOWLEDGEMENTS

We thank the Department of Gastrointestinal Surgery, of The First Affiliated Hospital of Chongqing Medical University for their contributions.

FOOTNOTES

Author contributions: Liu XY and Bin Zhang are co-first authors; Liu XY and Zhang B contributed to data extraction; Peng D contributed to quality assessments and writing-origin draft; Peng D and Liu XY contributed to data analysis; Peng D, Liu XY, Zhang B, Cheng YX, Tao W, Yuan C, and Wei ZQ contributed to writing-review and editing; The final manuscript was read and approved by all of our authors.

Conflict-of-interest statement: The authors declare that they have no competing interests.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Zhang H

L-Editor: A

P-Editor: Zhang H

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