Effects of Antihypertensive Drugs Use on Risk and Prognosis of Colorectal Cancer: A Meta-Analysis of 37 Observational Studies

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Background: Antihypertensive drugs might play a key role in the risk and poor prognosis of colorectal cancer. However, current epidemiologic evidence remains inconsistent. The aim of this study is to quantify the association between antihypertensive drugs and colorectal cancer.

Methods: To identify available studies, we systematically searched electronic databases: PubMed, Web of Science, Embase, Cochrane Library. The risk estimates and their corresponding 95% confidence intervals (CIs) were collected and analyzed by using random-effects models. Heterogeneity test and sensitivity analysis were also performed.

Results: Overall, 37 observational studies were included in this analysis (26 studies with cohort design, three studies with nested case-control design, and 8 studies with case-control design). Antihypertensive drugs did not present a significant effect on the risk or overall survival of patients with colorectal cancer [Risk ratio (RR) = 1.00, 95% CI: 0.95–1.04; Hazard ratio (HR) = 0.93, 95% CI: 0.84–1.02]. In the subgroup analysis, diuretics use was significantly associated with a worse overall survival of patients with colorectal cancer (HR = 1.27; 95% CI: 1.14–1.40). However, use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers was associated with improved progression-free survival of patients who suffered from colorectal cancer (HR = 0.83; 95% CI: 0.72–0.95).

Conclusion: Antihypertensive drug usage did not influence the risk and overall survival of patients with colorectal cancer in general. Further investigation reminded us that diuretics use might reduce the overall survival time in colorectal cancer patients, whereas those who took Angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers had a longer progression-free survival.

Keywords: antihypertensive drugs, colorectal cancer, risk, prognosis, meta-analysis

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; BB, beta-blockers; CC, case-control; CCB, calcium-channel blockers; CI, confidence interval; HR, hazard ratio; MIX, male and female; NA, not available; NCC, nest case-control; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RR, risk ratio.
INTRODUCTION

Colorectal cancer is the third most commonly cancer in the world, and the second most deadly cancer globally (Sung et al., 2021). Some risk factors, such as genetic, lifestyle (Deng et al., 2021), obesity, and environmental factors, were reported to be associated with colorectal cancer (Dekker et al., 2019). It is estimated that approximately 47% (16.1 million individuals) U.S. residents aged >18 years suffer from hypertension and consequently use antihypertensive agents (Merai et al., 2016). Antihypertensive drugs including angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), calcium-channel blockers (CCB), beta-blockers (BB) and diuretics are commonly used to lower blood pressure as well as reduce the occurrence and risk of cardiovascular disease (Thomopoulos et al., 2015; Ettehad et al., 2016).

The association between the use of antihypertensive agents and cancer risk have been raised as concerns since 1976. It is reported that the use of Rauwolfia in hypertension patients did not increase the risk of breast cancer (Aromaa et al., 1976). A decade later, a large multicenter screening program consisting of 1,362 cases and 1,250 controls participants, found that long-term usage of Rauwolfia elevated the risk of breast cancer (Stanford et al., 1986). Hallas demonstrated that the long-term use of ACEI increased the risk of colorectal cancer (Hallas et al., 2012), but another study concluded that ARB decreased the risk (Wang et al., 2012). A study of 14,166 patients indicated that long-term diuretics therapy might increase colon cancer-specific mortality (Tenenbaum et al., 2001). A population-based study, with a follow-up time of 6.6 years, supported that pre- or post-diagnostic BB intake was not related with colorectal cancer prognosis (Jansen et al., 2017), but a recent study suggested BB might improve overall survival (OS) (Fiala et al., 2019). In addition, a cohort study from Shanghai proposed that ARB and BB usage were associated with better survival in colorectal cancer patients (Cui et al., 2019). Previous meta-analysis also showed that the usage of ACEI/ARB resulted in a significant improved OS of patients with colorectal cancer (0.90; 95% CI 0.82–0.98; p = 0.021), but this conclusion needs to be further verified because only 5 studies were included (Zhou et al., 2020).

From the above, current evidence on the relationship between antihypertensive drugs and the risk and prognosis of colorectal cancer remains inconsistent. And several types of antihypertensive drugs influence the risk and prognosis of colorectal cancer differently. Therefore, we conducted a systematic review and meta-analysis investigating the risk of developing colorectal cancer and prognosis of colorectal cancer among individuals using antihypertensive drugs.

MATERIALS AND METHODS

Data Sources and Search Strategy

The established criteria followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The PRISMA 2009 checklist was shown in Supplementary Table S1. Utilized electronic databases included PubMed, Web of Science, Embase, Cochrane Library. Two authors independently searched for observational data on colorectal cancer from studies published up to April 17, 2020 without any restriction regarding geographical parameters, publication type or language. The search strategy and terms were based on a combination of MeSH terms, keywords, and substance names which were listed in the Supplementary Table S2. In addition, all reference lists of relevant meta-analysis articles and relevant reviews were analyzed to identify additional articles.

Inclusion and Exclusion Criteria

After excluding duplicate citations, two reviewers independently scanned titles and abstracts to identify initial studies and excluded those which were unrelated. Afterward, full texts of the remaining studies were reviewed for further evaluation. If the two reviewers didn’t agree about inclusion/exclusion of a publication, it was resolved by the adjudicating senior authors (Zhijun Dai), with consensus achieved by discussion.

All studies included fulfilled the following inclusion criteria: (a) studies which were observational study, such as a cohort or case-control design; (b) for risk, patients must not suffer from cancer before using antihypertensive drugs; for prognosis, patients must be diagnosed with colorectal cancer; (c) studies which evaluated the effect of antihypertensive drugs in colorectal cancer risk or prognosis; (d) studies which compared antihypertensive drugs users with not having received any prescription of antihypertensive drugs during the study period; (e) studies which described survival outcomes such as OS, recurrence-free survival (RFS), cancer-specific survival (CSS), progression-free survival (PFS), disease-free survival (DFS); (f) studies that reported effect value such as HR, RR, odds ratio (OR) with their 95% confidence intervals (CIs); (g) the exposure of antihypertensive drugs were clearly defined within the study.

We excluded articles for the following reasons: (a) articles which were meta-analysis, reviews, case reports, experimental laboratory articles, abstracts, animal studies, commentaries, letters; (b) articles which used antihypertensive or other drugs as references.

For studies using the same populations, we included the latest or the longest follow-up study. Two reviewers checked the data of the included studies to prevent duplication.

Data Extraction

Two reviewers extracted the following information independently: the first author’s name, the geographical location, publication year and population gender, the exposure time and follow-up period, number and characteristics of populations, number of cancer case, number of deaths, cancer sites, study design, types of antihypertensive drugs used, outcome indicator, and effect values with their respective 95% CIs.

Quality Assessment

Under the guidance of Newcastle-Ottawa Quality Assessment Scale (NOS), the quality of each article was assessed by two
reviewers independently. Any disagreements were discussed by the group members until an agreement was reached. As Supplementary Table S3 shown, NOS scores of studies included in this meta-analysis varied from six to eight points and 7–8 scores were considered indicative of high quality.

**Statistical Analysis**

Risk estimates with their respective 95% CIs were calculated by using random effect models to estimate the risk and prognosis of colorectal cancer for patients who used antihypertensive drugs, compared with those who did not. The Cochran’s Q test and I² statistic were performed to assess heterogeneity, whereby p values <0.1 or I² values >50% represents significant heterogeneity. Subgroup analyses was conducted through stratifying data by geographical locations, cancer sites, study design types, publish date, and NOS score, to elucidate potential sources of heterogeneity. We investigated the publication bias by funnel plots and Egger’s test (Begg and Mazumdar, 1994; Egger et al., 1997). If p values was greater than 0.05 in the Egger’s test or it was symmetry in the funnel plot, the publication bias was acceptable. In this study, we conducted sensitivity analysis to assess the effect of each study on the meta-analysis model. All statistical tests were two-sided, and the significance level was 0.05. In addition, all data were analyzed using Stata 12.0 software (Markum-mitchell, Torrance, CA, United States).

**RESULTS**

**The Characteristics of Included Study**

While 953 articles were initially identified through online searches, 549 articles were retained for analysis after duplicates were removed. Although we searched the above databases without any language restriction, all studies included were published in English. Studies were retrieved by filtering titles and abstracts, and 39 studies were excluded after full text review, and reasons why studies were excluded were listed in Supplementary Table S4. Ultimately, we included 37 studies for our meta-analysis, including 20 publications concerning cancer risk (Pahor et al., 1996; Michels et al., 1998; Rosenberg et al., 1998; Tenenbaum et al., 2001; Beiderbeck-Noll et al., 2003; Boudreau et al., 2008; van der Knaap et al., 2008; Friedman et al., 2011; Hallas et al., 2012; Jansen et al., 2012; Wang et al., 2012; Mansouri et al., 2013; Makar et al., 2014; Chang et al., 2015; Lin et al., 2015; Numbere et al., 2015; Grimaldi-Bensouda et al., 2016; Dierssen-Sotos...
| Study | Cancer site | Gender | Age | Country | Population | Cancer case | Diagnosis period | Follow-up period | Medicine | Study design | NOS |
|-------|-------------|--------|-----|---------|------------|-------------|-----------------|-----------------|----------|-------------|-----|
| Beiderbeck-Nollet et al. (2003) | Colon-Rectum | MIX | ≥71 | Netherlands | 3204 | 59 | January 1, 1991 and January 1, 1999 | 16,640 person-years (mean 5.2 years) | CCB | cohort | 8 |
| Boudreau et al. (2008) | Colorectum | MIX | 70 (mean) | USA | 665 | 357 | January 1, 2000, and December 31, 2003 | NA | ACEI/CCB/ Diuretics | case-control | 6 |
| Braskey, et al. (2021) | Colorectum | FEMALE | 50–79 | USA | 142,812 | 2,185 | 1993–2020 | 10 years | ACEI/ARB | cohort | 8 |
| Chang, et al. (2015) | Colon | MIX | 53.5 (mean) | China | 24,238 | 68 | January 1, 2000 and December 31, 2011 | 12 years | BB | cohort | 7 |
| Cheung et al. (2020) | Colorectum | MIX | 60.6 (52.3–71.9) | China | 187,897 | 854 | 2005–2017 | 3 years | ACEI/ARB | cohort | 8 |
| Dierssen Sotos et al. (2017) | Colon-Mix | FEMALE | 65.1 (20–85) | Spain | 6077 | NA | January 1st, 2007 and March 31st, 2012 | NA | ACEI/ARB | case-control | 7 |
| Friedman et al. (2011) | Colon | MIX | 61.3 (mean) | UK | 150750 | 14588 | 1996–2009 | at least 2 years | CCB | cohort | 8 |
| Grimaldi-Bensouda et al. (2016) | Colon | MIX | 69.4 (mean) | Denmark | 149, 417 | 30683 | 2000–2005 | 7.8 years | ACEI/ARB | case-control | 7 |
| Jansen et al. (2012) | Colon | MIX | 67.7 (±10.5) | Germany | 3470 | 762 | 2000 and 2010 | 4.93 years, 5.17 years | BB | cohort | 8 |
| Jansen et al. (2012) | Colon | MIX | 68.1 (±9.1) | UK | 2847 | 4316 | 1987–2002 | >1year | ACEI/ARB/B/ CCB/Diuretics | nest case-control | 7 |
| Mansouri et al. (2013) | Colon | MIX | 50–74 | UK | 4188 | 371 | April 2009 to March 2011 | >1year | ACEI | cohort | 7 |
| Michels et al. (1998) | Colon | MIX | 62.8 (±12.8) | China | 13,542 | 70 | 1988–1994 | 6 years, 107,256 person-years | CCB | cohort | 8 |
| Numbere et al. (2015) | Colon | MIX | ≥18 | UK | 208,635 | 18968 | January 1, 1987 and December 31, 2012 | 3.27 years, 15,774 person-years | BB/CCB | case-control | 8 |
| Pahor et al. (1996) | Colon-Rectum | MIX | ≥71 | USA | 5,052 | 88 | 1988–1992 | >1year | CCB | cohort | 7 |
| Rosenberg et al. (1998) | Colon-Rectum | MIX | 46–69 | USA | 9513 | 302 | 1976 to 1996 | 4–7 years (mean 5.6 ± 0.8 years) | ACEI/BB/CCB | case-control | 7 |
| Tenerbaum et al. (2001) | Colon | MIX | 61.8 ± 6.2 | Israel | 1023 | 23 | February 1, 1990, and October 30, 1992 | 6.9 years | Diuretics | cohort | 8 |
| van der Knaap et al. (2008) | Colon | MIX | 70.4 ± 9.7 | Netherlands | 730 | 129 | July 1989 and July 1993 | 9.6 years | ACEI/ARB | cohort | 7 |
| Wang et al. (2012) | Colon | MIX | 62 ± 13 | China | 42921 | 187 | January 1997–December 2009 | 4.8 ± 2.4 years | ARB | cohort | 8 |
| Overall Survival | Rectal | MIX | 72.2 ± 9.3 | Sweden | 11966 | 776 | January 1, 2007–October 31, 2016 | 1 year | BB | cohort | 6 |
| Cardwell et al. (2014) | Colorectum | MIX | NA | UK | 4762 | 2444 | 1998–2006 | 6 years | ACEI/ARB | nest case-control | 7 |
| Cui et al. (2019) | Colorectum | MIX | 40–74 | China | 890 | 383 | 1996–2000, Shanghai Men’s Health Study (2002–2006) | 4 years | ACEI/ARB/B/ CCB/Diuretics | cohort | 8 |
| Fiala et al. (2019) | Colorectum | MIX | 63.2 (28.0–86.1) | Czech Republic | 514 | 345 | 2005–2019 | 519 days | ACEI/ARB/ BB/CCB | cohort | 7 |

(Continued on following page)
| Study                  | Cancer site | Gender | Age     | Country   | Population | Cancer case | Diagnosis period | Follow-up period | Medicine | Study design | NOS |
|------------------------|-------------|--------|---------|-----------|------------|-------------|----------------|----------------|----------|--------------|-----|
| Giampieri et al. (2015)| Colorectum  | MIX 61 | (37–85) | Italy     | 235        | 29          | 2010 and 2013  | 41.3 vs. 25.7 months | BB       | cohort 6      |
| Hicks et al. (2013)   | Colorectum  | MIX NA |         | UK        | 4794       | 1559        | 1998 and 2007  | 6.2 years (range 1–13.9) | BB       | nest case-control cohort 8 |
| Holmes et al. (2013)  | Colorectum  | MIX 70 | ± 13    | Canada    | 3967       | 3824        | 2004 and 2008  | >1 year          | ACEI/ARB/BB/CCB/Diuretics cohort 7 |
| Jansen et al. (2014)  | Colorectum  | MIX 70 | ± 9.1   | Germany   | 1975       | 187         | 2003 and 2007  | 5.0 years         | BB       | cohort 7      |
| Jansen et al. (2017)  | Colon-Rectum| MIX 73 | ± 9     | Germany   | 8100       | 919         | 1998 and 2011  | 6.6 years, 4639 person-years | BB       | cohort 8      |
| Mafiana et al. (2019) | Colorectum  | MIX 55 | ± 15.15 | Arab      | 301        | NA          | 2006–2014      | 5.3 years         | ACEI/ARB cohort 6 |
| Morris et al. (2016)  | Rectal      | MIX 61 | ± 11.5  | USA       | 261        | 74          | January 1, 1999 and July 1, 2012 | 2.2 years (26.7 months) | ARB cohort 7 |
| Osumi et al. (2015)   | Colorectum  | MIX 61 | ± 13 (38–75) | Japan | 181 | 104 | June, 2007 and September, 2010 | 3.2 years | CCB cohort 8 |
| Sorensen et al. (2000) | Colon      | MIX 64 | 9 ± 13.1 | Denmark   | 27788      | 82          | January 1, 1989 and December 31, 1995 | 73,193 person-years | CCB cohort 8 |
| Weberpals et al. (2017)| Colorectum | MIX 71 | ± 8.7   | Netherlands | 3572 | 1553 | April 1, 1998 and December 31, 2011 | 6.3 years | BB cohort 7 |
| Progression-free survival | Colon     | MIX 69 | ± 11.6  | USA       | 2039       | 760         | 1995–2014      | 4.9 years         | ACEI/ARB/BB/CCB/Diuretics cohort 8 |
| Bowles et al. (2019)  | Colorectum  | MIX 63 | ± 13.1  | Czech      | 514        | 296         | 2005–2019      | 519 days          | ACEI/ARB/BB/CCB/Diuretics cohort 7 |
| Fiala et al. (2019)   | Colorectum  | MIX 61 | (28.0–88.1) | Republic | 235 | 29 | 2010 and 2013 | 8.36 vs. 7.13 months | BB/CCB cohort 6 |
| Giampieri et al. (2015)| Colorectum  | MIX 61 | (37–85) | Italy     | 1975       | 91          | 2003 and 2007  | 5.0 years         | BB       | cohort 7      |
| Jansen et al. (2014)  | Colorectum  | MIX 61 | ± 9.1   | Germany   | 261        | 74          | January 1, 1999 and July 1, 2012 | 5.3 years | ACEI/ARB cohort 7 |
| Morris et al. (2016)  | Rectal      | MIX 61 | ± 11.5  | USA       | 181        | 104         | June, 2007 and September, 2010 | 2.2 years (26.7 months) | ARB cohort 7 |
| Osumi et al. (2015)   | Colorectum  | MIX 61 | (38–75) | Japan      | 461        | 94          | 2009–2014      | 57 months        | ACEI/ARB cohort 7 |
| Ozawa et al. (2019)   | Colorectum  | MIX 66 | ± 9     | Canada    | 261        | NA          | 2009–2014      | NA                | BB       | cohort 6      |

Abbreviations: MIX: male and female; NA: not available; NOS: Newcastle-Ottawa quality assessment scale; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CCB: calcium-channel blockers; BB: beta-blockers.
et al., 2017; Cheung et al., 2020; Brasky et al., 2021), 17 regarding cancer prognosis (Sorensen et al., 2000; Hicks et al., 2013; Holmes et al., 2013; Cardwell et al., 2014; Jansen et al., 2014; Giampieri et al., 2015; Osumie et al., 2015; Morris et al., 2016; Jansen et al., 2017; Weberpals et al., 2017; Sud et al., 2018; Bowles et al., 2019; Cui et al., 2019; Fiala et al., 2019; Maffia et al., 2019; Ozawa et al., 2019; Ahl et al., 2020). Of these 37 studies, 26 studies used cohort design, three studies used nested case-control design, and 8 studies used case-control design. Our study selection process is illustrated in a flow chart (Figure 1). The total number of participants included in this analysis was 1,117,991, ranging from 107 to 208,635 participants per study. Data was extracted from 13 countries from three continents including North America (n = 11 studies), Asia (n = 8 studies), and Europe (n = 18 studies). Apart from 3 studies (Boudreau et al., 2008; Numbere et al., 2015; Dierssen-Sotos et al., 2017) that did not specify the follow-up time, the follow-up time of the other 34 articles were more than 1 year. Key characteristics of studies included in the meta-analysis are summarized in Table 1.

**Antihypertensive Drugs and Risk of Colorectal Cancer**

As shown in Figure 2, all antihypertensive drugs were not associated with colorectal cancer risk (RR = 1.00; 95% CI: 0.95–1.04).

There were 11 studies evaluated the link between the risk of colorectal cancer and BB, including two nested case-control studies, two cohort studies and seven case-control studies. As illustrated in Figure 3, no association was shown between BB and the risk of colorectal cancer (RR = 1.03; 95% CI: 0.96–1.10). And the results were robust when the subgroup analysis was stratified by cancer sites or geographical districts. However, the usage of BB significantly increased the risk of colorectal cancer in seven case-control studies (RR = 1.08; 95% CI: 1.03–1.14) and in the high-quality study with NOS score of 8 (RR = 1.13; 95% CI: 1.09–1.18), but not in two cohort studies (RR = 0.80; 95% CI: 0.57–1.11) and two nest-cohort studies (RR = 0.96; 95% CI: 0.76–1.20) (Table 2). In the Supplementary Figure S1, the association between colorectal cancer risk and duration of BB exposure was represented by forest plot. Only one study reported that the risk of colon cancer decreased markedly when the patients used BB for longer than 1,000 days (Chang et al., 2015).
**FIGURE 3** | Forest plot of studies among the risk of colorectal cancer with beta-blockers.

**TABLE 2** | The association between antihypertensive drugs use and risk of colorectal cancer.

| Category          | N   | BB vs. non RR (95% CI) | I² (%) | P   | CCB vs. non RR (95% CI) | I² (%) | P   | ACEI/ARB vs. non RR (95% CI) | I² (%) | P   |
|-------------------|-----|------------------------|--------|-----|-------------------------|--------|-----|-------------------------------|--------|-----|
| Colon             | 6   | 1.01 (0.94–1.10)       | 38.8   | 0.147 | 4 | 0.94 (0.78–1.14)       | 27.5   | 0.247 | 2 | 0.80 (0.55–1.15)       | 67.8   | 0.078 |
| Rectal            | 1   | 1.40 (1.02–1.93)       | NA     | NA   | 3 | 1.07 (0.67–1.70)       | 0.0    | 0.850 | 1 | 1.00 (0.58–1.73)       | NA     | NA   |
| Case-control      | 7   | 1.08 (1.03–1.14)       | 41.9   | 0.111 | 4 | 1.10 (1.06–1.15)       | 0.0    | 0.600 | 7 | 1.06 (0.91–1.23)       | 74.8   | 0.001 |
| Cohort            | 2   | 0.80 (0.57–1.11)       | 46     | 0.174 | 6 | 0.90 (0.82–0.99)       | 0.0    | 0.439 | 5 | 0.82 (0.67–1.00)       | 77.2   | 0.002 |
| NCC               | 2   | 0.96 (0.78–1.20)       | 88.7   | 0.003 | 2 | 0.99 (0.92–1.07)       | 0.0    | 0.900 | 2 | 0.96 (0.88–1.04)       | 0.0    | 0.574 |
| North America     | 5   | 1.05 (1.00–1.11)       | 6.8    | 0.368 | 6 | 1.01 (0.83–1.24)       | 0.0    | 0.607 | 4 | 1.04 (0.92–1.17)       | 0.0    | 0.983 |
| Europe            | 4   | 1.03 (0.91–1.16)       | 85.2   | 0.0   | 6 | 1.00 (0.90–1.11)       | 75.9   | 0.001 | 8 | 0.98 (0.85–1.00)       | 88.2   | 0.000 |
| Asia              | 2   | 0.80 (0.57–1.11)       | 46     | 0.174 | NA | NA                      | NA     | NA   | 2 | 0.73 (0.63–0.84)       | 0.0    | 0.341 |
| 1995–2000         | 2   | 1.21 (0.96–1.52)       | 32.1   | 0.225 | 5 | 1.00 (0.78–1.27)       | 0.0    | 0.472 | 2 | 1.00 (0.73–1.37)       | 0.0    | 1.000 |
| 2000–2010         | NA  | NA                     | NA     | NA   | 3 | 1.09 (0.77–1.55)       | 0.0    | 0.899 | 2 | 0.96 (0.73–1.27)       | 0.0    | 0.883 |
| 2010–2020         | 9   | 1.01 (0.94–1.09)       | 75.5   | 0.000 | 4 | 1.00 (0.90–1.11)       | 85.4   | 0.000 | 10| 0.94 (0.81–1.08)       | 90.0   | 0.000 |
| NOS score         | 6   | 1.04 (0.99–1.10)       | 0.0    | 0.604 | 1 | 1.06 (0.72–1.56)       | NA     | NA   | 1 | 0.98 (0.67–1.43)       | NA     | NA   |
|                  | 7   | 0.99 (0.83–1.18)       | 79.4   | 0.001 | 6 | 0.99 (0.93–1.07)       | 0.0    | 0.628 | 10| 0.98 (0.88–1.13)       | 84.9   | 0.000 |
|                  | 8   | 1.13 (1.09–1.18)       | 0.0    | 0.521 | 5 | 1.00 (0.83–1.21)       | 77.4   | 0.001 | 3 | 0.83 (0.63–0.99)       | 86.1   | 0.001 |

Abbreviations: ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CCB: calcium-channel blockers; BB: beta-blockers; RR: relative risk; CI: confidence intervals; N: number of studies; NCC: nest case-control; NA, not available.

Bold indicates values which are statistically significant.
In total, 12 studies including 399,301 participants were analyzed for the link between CCB use and colorectal cancer risk. After pooled analysis, no significant association was observed between CCB and risk of colorectal cancer (RR = 1.01; 95% CI: 0.92–1.10, Figure 4). Meta-analysis of four case-control studies revealed that the pooled RR was 1.10 (95% CI: 1.06–1.15, I² = 0.0%), while it was 0.90 (95% CI: 0.82–0.99) for six cohort studies. As for different cancer sites, geographical districts subgroup, publish date and NOS score, no significant association was observed (Table 2). The detailed duration exposure data to CCB and the risk of colorectal cancer were shown in Supplementary Figure S2.

Fourteen studies indicated that the usage of ACEI/ARB was not significantly associated with risk of colorectal cancer (RR = 0.94; 95% CI: 0.84–1.07, Figure 5). In subgroup analysis, these results were robust, and were consistent irrespective of study design type, cancer site, publish date or NOS score. However, two cohort study from Asian population found that used ACEI/ARB was related with reduced risk of colorectal cancer (RR = 0.73; 95% CI: 0.63–0.84), but there was no significant association in Europe and North America. In addition, the pooled RR was 0.97 (95% CI: 0.75–1.25) for ACEI users, and 0.92 (95% CI: 0.67–1.27) for ARB users. The detailed duration exposure data to ACEI/ARB and the risk of colorectal cancer were shown in Supplementary Figure S3.

Four studies reported the association between the risk of colorectal cancer and usage of diuretics, and pooled analysis showed a RR value of 1.04 (95% CI: 0.86–1.27, Figure 6). Due to the limited number of studies included, further analysis could not be conducted. The detailed duration exposure data to diuretics and the risk of colorectal cancer were shown in Supplementary Figure S4.

Antihypertensive Drugs and Overall Survival of Colorectal Cancer

As shown in Figure 7, 27 articles focused on association between the usage of antihypertensive drugs and OS of patients with colorectal cancer. Totally, antihypertensive drugs use was not associated with improved OS of patients with colorectal cancer (HR = 0.93; 95% CI: 0.84–1.02). As for the subtype of antihypertensive drugs, usage of diuretics was significantly associated with a worse OS of colorectal cancer patients (HR = 1.27; 95% CI: 1.14–1.40). However, similar effect was not observed in those who used ACEI/ARB, BB or CCB (ACEI/ARB: HR = 0.90, 95% CI: 0.81–1.01; BB: HR = 0.90, 95% CI: 0.93–1.10; CCB: HR = 0.99, 95% CI 0.90–1.09; respectively).

Antihypertensive Drugs and Progression Free Survival of Colorectal Cancer

The pooled estimates of 15 studies which included 3,072 participants, demonstrated that the usage of antihypertensive drugs was related to longer PFS of colorectal cancer patients (HR = 0.85; 95% CI: 0.76–0.94, Figure 8). In the subgroup analysis, ACEI/ARB users were associated with a better PFS compared with non-users (HR = 0.83; 95% CI: 0.72–0.95), but not for BB and CCB users.

Publication Bias

We performed the Begg’s funnel plot and Egger’s test to investigate publication bias (Supplementary Figures S5, S6). No apparent indication of publication bias between colorectal...
FIGURE 5 | Forest plot of studies among the risk of colorectal cancer with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

FIGURE 6 | Forest plot of studies among the risk of colorectal cancer with diuretics.
cancer risk and BB/CCB/diuretics users, except for ACEI/ARB users (Egger’s: \( p = 0.018 \); Begg’s tests: \( p = 0.827 \)). For prognosis of colorectal cancer patients, both Egger’s (OS: \( p = 0.159 \), PFS: \( p = 0.657 \)) and Begg’s tests (OS: \( p = 0.243 \), PFS: \( p = 0.499 \)) showed no significant publication bias.

**Sensitivity Analysis**

Each study was individually eliminated to access the effect of individual studies on the results (Supplementary Figures S7, S8). In the analysis of colorectal cancer risk with CCB users, the pooled RR was statistically significant after deletion of one article (RR = 1.07; 95% CI: 1.03–1.12) (Grimaldi-Bensouda et al., 2016). However, the other results were not influenced significantly when we removed each article.

**DISCUSSION**

This meta-analysis included 37 observational studies involving a large number of participants to quantify the association between usage of antihypertensive drugs and risk as well as prognosis of colorectal cancer. Overall, the usage of antihypertensive drugs was not associated with the risk or OS of colorectal cancer, which is accordant with previous published researches. In 2011, a network analysis rejected the hypothesis that the usage of antihypertensive agents was linked with a relative increase in the occurrence of cancer or cancer-specific death (Bangalore et al., 2011). After that, Ioannidis and colleagues conducted an umbrella review of 74 meta-analysis studies and stated that no medication was proven to increase the risk of cancer (Ioannidis et al., 2014).

Interestingly, our further analysis identified that antihypertensive drugs might improve PFS of colorectal cancer patients, especially for ACEI/ARB users, which is similar to the recent published meta-analysis, which suggested that ACEI/ARB improved OS of colorectal cancer patients (Zhou et al., 2020). Actually, in our pooled analysis with more included studies, the usage of ACEI/ARB was not associated with risk or OS of colorectal cancer, which is consistent with the study of Sipahi et al., which concluded that the usage of ACEI did not affect the risk or survival of patients with cancer through a meta-analysis of 10 RCTs and 59,004 patients (Sipahi et al., 2010). Previous studies indicated that ACEI/ARB affected cancer prognosis by suppressing cancer proliferation and angiogenesis, and
promoting cell apoptosis (Ager et al., 2008; George et al., 2010). A review summarized ACEI/ARB presented a potential effect in colorectal cancer by inhibiting vascular endothelial growth factor and insulin-like growth factor 1, and the usage of ACEI suppressed the development and metastasis of colorectal cancer (Asgharzadeh et al., 2018). In addition, a potential indirect antitumor mechanism of ACEI/ARB was found to enhance the delivery of antitumor drugs into tumor tissues (Maeda et al., 2013). Consistent with our results, McMenamin and colleagues conducted a systematic review and proposed that ACEI or ARB use might improve outcome of colorectal cancer patients (Mc Menamin Ü et al., 2012). Besides, usage of ACEI/ARB significantly increased the rate of pathological complete regression after neoadjuvant treatment in rectal cancer (Morris et al., 2016). Therefore, the ACEI/ARB use for colorectal cancer patients with hypertension might be suggested.

Heterogeneity, though unavoidable, cannot be ignored. In all meta-analysis, the cause of the heterogeneity should be searched for and analyzed. After conducting subgroup analyses by geographical locations, cancer sites, study design, publish date, and NOS score, the heterogeneity was reduced significantly. First, given that most colorectal cancer and hypertensive populations are old people, age is an essential risk factor for colorectal cancer. One study observed a statistically significant protective effect for ACEI users from colorectal cancer, which was restricted to the under 65 years old group (Dierssen-Sotos et al., 2017). In our meta-analysis, the average age of the population in most studies was over 65 and analysis in each study was adjusted on the basis of age, only few studies did not indicate the age distribution or include all people over 18 years old. Therefore, few different distribution of age might cause some heterogeneity. Second, subgroup analyses suggested that different research design can partially explain heterogeneity across the study. For example, the heterogeneity was reduced obviously after subgroup analyses by research design was conducted. In the subgroup of case-control study, the use of CCB was associated with an increased risk of colorectal cancer. However, in the subgroup of cohort study, CCB might play an anti-cancer effect. These two opposite conclusions indicated that the association between CCB use and the risk of colorectal cancer were still controversial, and more research was needed to verify the true connection between them. Third, ethnic variation may explain bias and heterogeneity. According to the Taiwan National Health Insurance and the Hong Kong Hospital Authority research database, two cohort studies found that usage of ACEI/ARB was related with a decrease in the colorectal cancer risk. However, there were not positive association for the included studies from North American and Europe. Several studies also provided evidence that ethnic variation influenced the efficacy of antihypertensive drugs (Gupta et al., 2010; Ogedegbe et al., 2015). In fact, the major of included studies in our analysis were conducted in Europe and North America. To an extent, these cohort studies

![FIGURE 8 | Forest plot of studies among the PFS of colorectal cancer patients with antihypertensive drugs.](image-url)
may provide accurate and consistent baseline data due to their similar geographical conditions. Further large well-conducted prospective studies from Asia are required to confirm our results. In the end, given the very heterogenous nature of studies included (in terms of study years, exposure assessment from different databases, outcomes and covariates assessment and analytical strategies from different studies), may partly account for heterogeneity in our study. Furthermore, we conducted subgroup analyses stratifying on NOS scores, and the heterogeneity was decreased significantly.

Antihypertensive drugs might promote or interfere with tumor cell proliferation, migration and apoptosis, as well as angiogenesis (Grossman et al., 2001; Greene and Amaral, 2002; Kanehira et al., 2005; Tang et al., 2013; Granados et al., 2020). CCB was found to inhibit the spreading of neoplastic cells by regulating cell proliferation and calcium influx (Grossman et al., 2001). Additionally, it could enhance the anti-tumor effects of chemotherapy drugs, and participate in the regulation of cell differentiation, death, and susceptibility to MAPK inhibitors in vitro and in vivo (Granados et al., 2020) The expression of beta-adrenergic receptors were at high level in a large number of cancer cells, which could be activated and promote the process of tumor progression, including anti-apoptosis, proliferation, angiogenesis, invasion, and metastasis (Tang et al., 2013). ACEI/ARB has been proven to inhibit angiogenesis, tumor proliferation and metastasis (Greene and Amaral, 2002; George et al., 2010). However, some animal experiments supported that ACEI/ARB promoted tumor growth by increasing the expression of vascular endothelial growth factor (VEGF), reducing the level of platelet reactive protein 1 in the tissue and transforming growth factor-beta dependent cell growth (Kanehira et al., 2005; Clerc et al., 2010). Currently, the mechanism underlying the possible causal links between antihypertensive drugs and cancer risk are controversial and needs further investigation.

Our investigation was limited by several factors. Firstly, despite using the random effect model, our results should be treated with caution due to significant heterogeneity and limited data. Though most studies we included had adjusted for confounding factors, such as age, BMI, sex, race, outcome value, social background et al., the heterogeneity still exist. Secondly, potential deviations, such as recall deviations, detection deviations, selection deviation and confounding factors, have to be considered in observational studies. Thirdly, mild publication bias was detected when analyzing studies of risk. In addition, our sensitivity analysis showed that the association between colorectal cancer risk and CCB was unstable and controversial. Finally, due to the lack of relevant data, we cannot conduct a dose-response association between duration of antihypertensive drugs exposure and the development of colorectal cancer. It should be noted that all studies included in this analysis included participants who were middle-aged and older, so the results cannot be applied to the general population or children.

In summary, there was no sufficient evidence to prove that antihypertensive drug usage had an impact on the risk and OS of colorectal cancer. Our findings indicated that ARB/ACEI use might improve the PFS of colorectal cancer. More well-designed prospective studies are needed to support our findings.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

**AUTHOR CONTRIBUTIONS**

All authors read, critically reviewed and approved the final manuscript. YD, YX, and MW conducted the database searches, screened titles, abstracts and full-texts for eligibility, PX and BW performed study quality assessments. ZD planned and designed the research; NL, YW, and SY provided methodological support/advice; NL tested the feasibility of the study; SY, YW, LZ, QH, and LL extract data; YD and YX performed the statistical analysis; YD and YX wrote the manuscript.

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**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.670657/full#supplementary-material
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