



# Hypertension and risk of cholangiocarcinoma: a systematic review and meta-analysis

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**Background:** Hypertension has been demonstrated to enhance the risk of cholangiocarcinoma (CCC) by several researches, which, however, still remains controversial. To this end, a systematic review and meta-analysis was performed to further investigate the association between hypertension and CCC risk.

**Methods:** We searched PubMed, EMBASE, ISI Web of Science to collect relevant researches published before November 2017. Afterwards, random effects model proposed by DerSimonian and Laird was employed to determine the correlation between hypertension and CCC risk.

**Results:** Nine articles, comprising 2,016 patients with CCC and 199,812 healthy controls, were finally enrolled in our study. Our findings failed to support the correlation between hypertension and elevated risk of CCC among these heterogeneous studies [summary odds ratio (OR), 0.87; 95% confidence interval (CI), 0.57–1.17;  $I^2=79.5\%$ ]. In subgroup analysis following separation of intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC), hypertension also failed to harbor a correlation with elevated risk of ECC (OR, 0.74; 95% CI, 0.42–1.37) and ICC (OR, 1.07; 95% CI, 0.43–1.71).

**Conclusions:** Hypertension did not harbor any correlation with elevated risk of CCC.

**Keywords:** Hypertension; cholangiocarcinoma (CCC); biliary tract neoplasms; meta-analysis

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## Introduction

Cholangiocarcinoma (CCC), initially described by Durand Fardel in 1840, is a malignant cancer originated from the epithelium of bile duct (1,2). CCC represents the second most common primary hepatic carcinoma, accounting for 3% of all gastrointestinal malignancies as well as 10–25% of liver malignancies (3,4). Moreover, in recent decades, the incidence of CCC is still rising. Intriguingly, the epidemiology of intrahepatic cholangiocarcinoma (ICC)

and extrahepatic cholangiocarcinoma (ECC) are different, with an increasing incidence of the former, but a decreasing incidence of the latter in certain regions worldwide, including the UK and the USA (5). In the past 20 years, the incidence of ICC has been elevated by 165%, while that of ECC has been declined by 14% in the US (6). In addition, the prognosis of CCC is very poor. The relative survival rates of 1, 3 and 5 years have been reported to be 25%, 9.7% and 6.8%, respectively, almost any change in recent decades (7,8). And the cause of CCC is not yet fully

understood, with only several confirmed risk factors of CCC, including gallstones, primary sclerosing cholangitis, parasitic infections as well as bile-duct cysts (9). Recently, additional indicators affecting CCC risks have been determined by multiple meta-analyses, including cirrhosis, alcohol consumption, smoking, and diabetes mellitus (10-14). In recent years, increasing attention has been paid to hypertension for its relationship with endometrial cancer and breast cancer (15,16). Moreover, the association between hypertension and CCC has been documented in case-control studies. However, its association is controversial. To this end, this systematic review with meta-analysis enrolling published observational researches was carried out to obtain a better understanding of the correlation of hypertension with the risk of CCC.

## Methods

This study was performed in accordance with PRISMA statement (17) as well as MOOSE guidelines (18).

### *Data sources and search strategy*

Web of Science, EMBASE as well as PubMed databases were thoroughly searched using the following keywords: (“blood Pressure” OR “hypertension” OR “metabolic syndrome” OR “risk factor”) and (“biliary tract cancer” OR “bile duct cancer” OR “biliary tract neoplasms” OR “cholangiocarcinoma”). Language of article or date of publication was not restricted.

### *Inclusion criteria*

The inclusion criteria were listed in the following: study design (cohort or case control); hypertension as an exposure factor while CCC/biliary tract cancer/bile duct cancer as an outcome; and accessible odds ratio (OR)/risk ratio (RR) values as well as corresponding 95% CIs or adequate data for calculation. In the case of the same outcomes shown by two researches, study with larger sample would be chosen.

### *Data abstraction and quality assessment*

Two investigators (J Lin, J Long) independently collected the demanded data from all enrolled studies in a standard manner. The following data were obtained from each study: study design, sources of controls, first author’s name, country of origin, year of publication, number of subjects,

adjusted confounding variables, duration of follow-up as well as OR/RR values and 95% CIs.

The Newcastle-Ottawa Scale (NOS) (19) was utilized to determine study quality. Quality categories were assigned in line with the scores of each study. The maximal score was 9 points. To be specific, NOS scores of <4, 4–6, and 7–9 suggested low, moderate, and high quality, respectively (20). Discrepancies were resolved by consensus.

### *Statistical analysis*

The OR/RR values and 95% CIs were employed to determine CCC risk in hypertensive patients. Random effects model was used to determine the association of hypertension with CCC risk, which was proposed by DerSimonian and Laird (21).

The  $I^2$  statistic was utilized to determine the heterogeneity between studies, where  $I^2$  value of 25%, 50%, and 75% implicated low, moderate, and high heterogeneity, respectively (22). A P value <0.1 implicated obvious heterogeneity. Meta-regression was used to evaluate the extent to which heterogeneity between the study results was correlated with geographical locations, and confounders adjusted for (smoking status, alcohol use, gallstones). Funnel plot and Begg’s (23) and Egger’s (24) tests were employed to investigate publication bias, where funnel plot asymmetry as well as a P value <0.05 implicated publication bias.

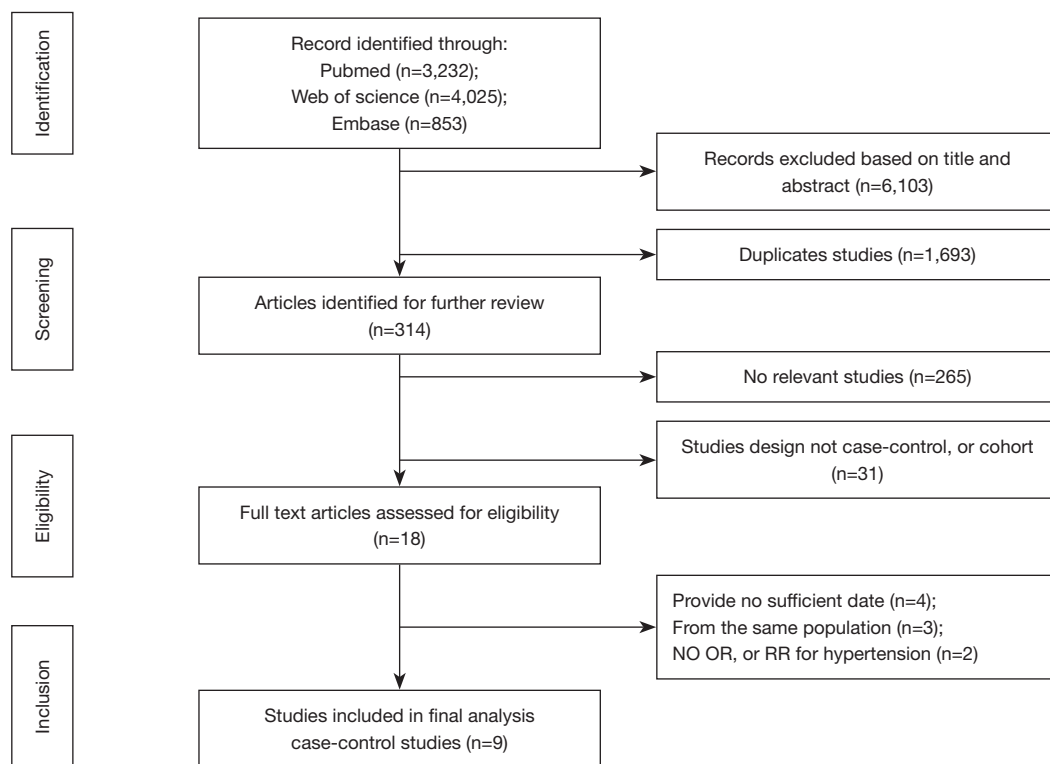
Subgroup analyses were carried out according to subtype of cancer, gallstones, alcohol consumption, geography smoking, and whether liver fluke infestation after adjustment. Sensitivity analysis was carried out to investigate whether the outcomes were stable by sequential omission of each study. Moreover, sensitivity analysis was also conducted by changing the pooling model (fixed-effects model or random-effects model) to eliminate studies with NOS score <7.

STATA version 12.0 was utilized for statistical analysis.

## Results

### *Study selection and study characteristics*

The selection procedure was shown in *Figure 1*. As a result, 8,110 articles were initially obtained (3,232, 4,025, and 853 from PubMed, EMBASE, and Web of Science, respectively), 1,693 of which were duplicates. After eliminating further 6,103 studies on the basis of title and



**Figure 1** The process of study selection for the meta-analysis.

abstract, nine studies were excluded after evaluating the full texts, because they did not meet the inclusion criteria: four studies provided insufficient information (25-28), three articles reported on the same population (29-31), and two studies did not provide OR, or RR for hypertension or sufficient information to calculate these variables (32,33). Thus, nine eligible observational studies were enrolled in this meta-analysis (34-42).

The major features of the enrolled researches were summarized in *Table 1*, all of which were case-control studies, ranging from 1980 to 2013. Five, two, one and one studies were conducted in China, the USA, Korea and Japan, respectively. Specifically, in this study, 2,016 patients with CCC and 199,812 healthy controls were enrolled to probe into the effect of hypertension on the risk of CCC. The NOS scores of nine studies varied from 5 to 8, with six high-quality studies as well as three moderate ones (*Table 2*).

#### ***Association of cholecystectomy with CCC risk***

Nine case-control studies were enrolled to probe into the correlation of hypertension with the risk of CCC (34-42). One study demonstrated that significantly higher risk of

CCC was observed in hypertensive subjects compared to those of healthy controls (35). Another research showed that hypertension was correlated with increased risk of CCC (37). However, the above correlation was not found in the remaining researches (34,36,38-42). The pooled estimate of hypertension influence was insignificant (OR, 0.87; 95% CI, 0.57-1.17), with significantly heterogeneous studies ( $I^2=79.5\%$ ;  $P=0.000$ ) (*Figure 2*). In addition, this correlation was also detected in ECC (OR, 0.74; 95% CI, 0.42-1.37,  $I^2=0\%$ ), instead of ICC (OR, 1.07; 95% CI, 0.43-1.71,  $I^2=83.5\%$ ) (*Table 3*).

#### ***Subgroup and sensitivity analyses***

The outcomes of subgroup analysis as well as sensitivity analysis were shown in *Table 3*. In terms of sensitivity analysis, despite elimination of researches with NOS sources under 7, the correlation of hypertension with the risk of CCC was still stable (*Table 3*). In addition, the overall outcomes for the association of hypertension with CCC was stable despite changed pooling model (fixed-effects model: OR, 0.88; 95% CI, 0.76-1.01; random-effects model: OR, 0.87; 95% CI, 0.57-1.17) (*Table 3*). Moreover, another

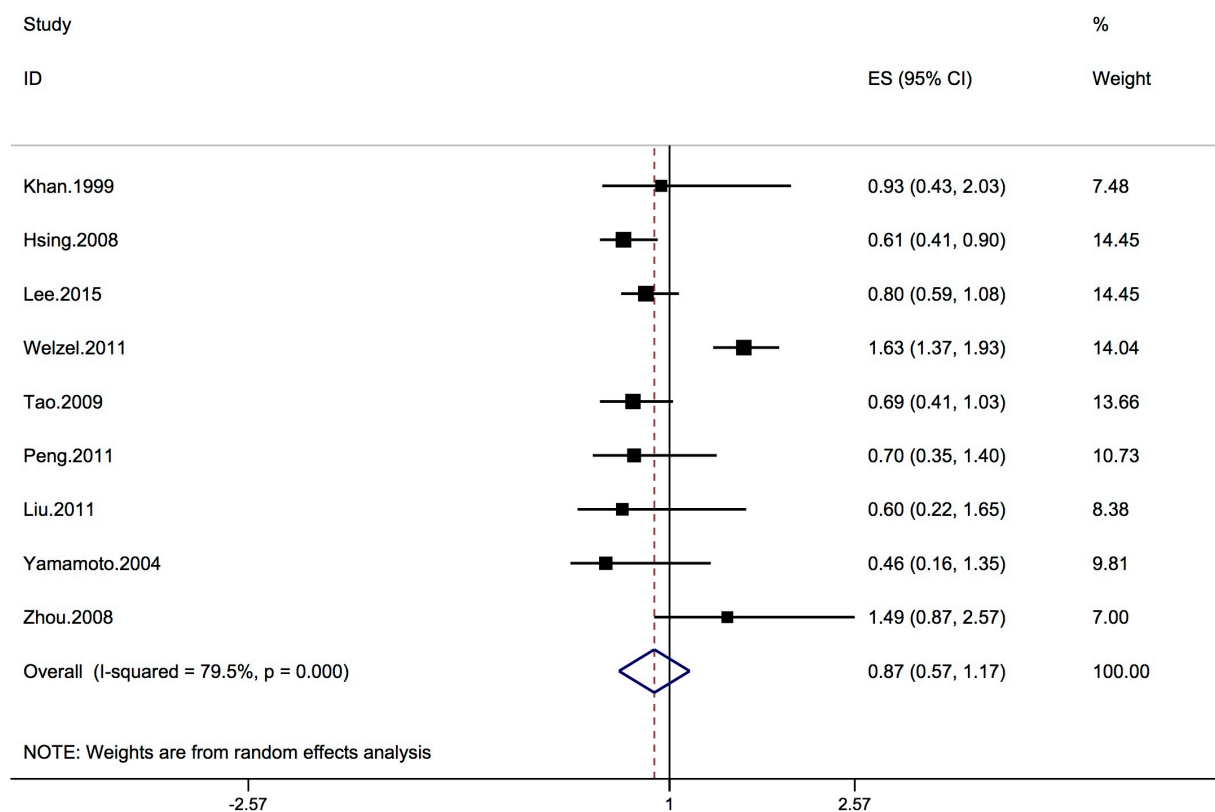
**Table 1** The main characteristics of the included studies

| Author/years of publication   | Country | No. case/control | Follow    | Sources of controls | Subtype of cancer | Subtype of study | Adjusted factors  | Adjusted OR (95% CI) |
|-------------------------------|---------|------------------|-----------|---------------------|-------------------|------------------|---|----------------------|
| Khan <i>et al.</i> , 1999     | USA     | 69/139           | 1980–1994 | Hospital            | ECC               | Case-control     | Age, gender, ethnicity, socioeconomic status, and each other  | 0.93 (0.43, 2.03)    |
| Yamamoto <i>et al.</i> , 2004 | Japan   | 50/205           | 1991–2002 | Hospital            | ICC               | Case-control     | HBV infection, HCV infection, and diabetes mellitus, cholelithiasis, alcohol, smoking, transfusion, family history                                | 0.46 (0.16, 1.35)    |
| Zhou <i>et al.</i> , 2008     | China   | 312/438          | 2004–2006 | Hospital            | ICC               | Case-control     | HBV infection, HCV infection, and diabetes mellitus, hepatolithiasis, alcohol, smoking  | 1.49 (0.87, 2.57)    |
| Hsing <i>et al.</i> , 2008    | China   | 134/762          | 1997–2001 | Population          | ECC               | Case-control     | Age   | 0.61 (0.41, 0.90)    |
| Tao <i>et al.</i> , 2010      | China   | 190/380          | 1998–2008 | Hospital            | CC                | Case-control     | Age, gender   | 0.69 (0.41, 1.03)    |
| Liu <i>et al.</i> , 2011      | China   | 87/228           | 2000–2008 | Hospital            | CC                | Case-control     | HBV infection, HCV infection, and liver fluke infestation, diabetes mellitus, hypertension, alcohol, smoking                                      | 0.60 (0.22, 1.65)    |
| Peng <i>et al.</i> , 2011     | China   | 98/196           | 2002–2009 | Hospital            | ICC               | Case-control     | HBV infection, cirrhosis, hepatolithiasis, choledocholithiasis, cholecystolithiasis, and liver fluke infestation, diabetes mellitus, hypertension | 0.70 (0.35, 1.40)    |
| Welzel <i>et al.</i> , 2011   | USA     | 743/195,953      | 1994–2005 | Population          | ICC               | Case-control     | Age, gender, race, geographic location, and Medicare/Medicaid dual enrollment   | 1.63 (1.37, 1.93)    |
| Lee <i>et al.</i> , 2015      | Korea   | 276/552          | 2007–2013 | Hospital            | CC                | Case-control     | NR  | 0.80 (0.59, 1.08)    |

ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval; NR, not reported.

**Table 2** Scores of the Newcastle-Ottawa scale for case control studies. The asterisks represent a score (number of stars)

| Author/years of publication   | Fully defined cases | Representative cases | Selection of controls | Definition of controls | Controlling the important factors or confounding factors | Determination of exposure | Same method of determination for cases and control | Non-response rate | Total score |
|-------------------------------|---------------------|----------------------|-----------------------|------------------------|--|---------------------------|--|-------------------|-------------|
| Khan <i>et al.</i> , 1999     | *                   | *                    | -                     | *                      | **   | *                         | *  | *                 | 8           |
| Hsing <i>et al.</i> , 2008    | *                   | *                    | -                     | *                      | *  | *                         | *  | *                 | 7           |
| Lee <i>et al.</i> , 2015      | *                   | *                    | *                     | -                      | -  | -                         | *  | *                 | 5           |
| Tao <i>et al.</i> , 2010      | *                   | *                    | -                     | *                      | **   | *                         | *  | *                 | 8           |
| Zhou <i>et al.</i> , 2008     | *                   | *                    | *                     | *                      | **   | *                         | *  | -                 | 8           |
| Welzel <i>et al.</i> , 2011   | *                   | *                    | -                     | *                      | *  | *                         | *  | *                 | 7           |
| Yamamoto <i>et al.</i> , 2004 | *                   | -                    | *                     | *                      | *  | *                         | *  | -                 | 6           |
| Liu <i>et al.</i> , 2011      | *                   | *                    | -                     | *                      | -  | *                         | *  | -                 | 5           |
| Peng <i>et al.</i> , 2011     | *                   | *                    | -                     | *                      | **   | *                         | *  | *                 | 8           |



**Figure 2** Forrest plot showing the relationship between hypertension and the risk of cholangiocarcinoma. Points represent the risk estimates for each individual study. Horizontal lines represent 95% confidence intervals, and diamonds represent the summary risk estimates with 95% confidence intervals. CI, confidence interval; ES, effect size.

**Table 3** Subgroup and sensitivity analyses of the effect of hypertension and the risk of cholangiocarcinoma

| Subgroup                                      | No. of studies | RR (95% CI)       | I <sup>2</sup> value (%) | P value |
|---|----------------|-------------------|--------------------------|---------|
| All studies                                   | 9              | 0.87 (0.57, 1.17) | 79.5                     | 0.001   |
| Subtype of cancer                             |                |                   |                          |         |
| ECC   | 2              | 0.74 (0.42, 1.37) | 0                        | 0.453   |
| ICC   | 4              | 1.07 (0.43, 1.71) | 83.5                     | 0.001   |
| Geographic areas                              |                |                   |                          |         |
| West  | 2              | 1.38 (0.73, 2.04) | 61.8                     | 0.106   |
| East  | 7              | 0.71 (0.57, 1.17) | 0                        | 0.522   |
| Adjustment for confounders                    |                |                   |                          |         |
| Liver fluke infestation                       |                |                   |                          |         |
| Yes   | 2              | 0.66 (0.24, 1.09) | 0                        | 0.825   |
| No  | 7              | 0.92 (0.57, 1.28) | 84.1                     | 0.001   |
| Gallstone                                     |                |                   |                          |         |
| Yes   | 3              | 0.80 (0.29, 1.32) | 48.2                     | 0.145   |
| No  | 6              | 0.89 (0.52, 1.26) | 85.5                     | 0.001   |
| Smoking                                       |                |                   |                          |         |
| Yes   | 3              | 0.79 (0.21, 1.37) | 49.9                     | 0.136   |
| No  | 6              | 0.90 (0.54, 1.26) | 85.5                     | 0.001   |
| Alcohol intake                                |                |                   |                          |         |
| Yes   | 4              | 1.06 (0.39, 1.74) | 0                        | 0.833   |
| No  | 5              | 0.71 (0.57, 0.85) | 82.1                     | 0.001   |
| Sensitive analyses                            |                |                   |                          |         |
| High quality studies                          | 6              | 0.99 (0.55, 1.42) | 85.8                     | 0.001   |
| Fixed-effects vs. random-effects model method |                |                   |                          |         |
| Fixed-effects model                           | 9              | 0.88 (0.76, 1.01) | 79.5                     | 0.001   |
| Random-effects model                          | 9              | 0.87 (0.57, 1.17) | 79.5                     | 0.001   |

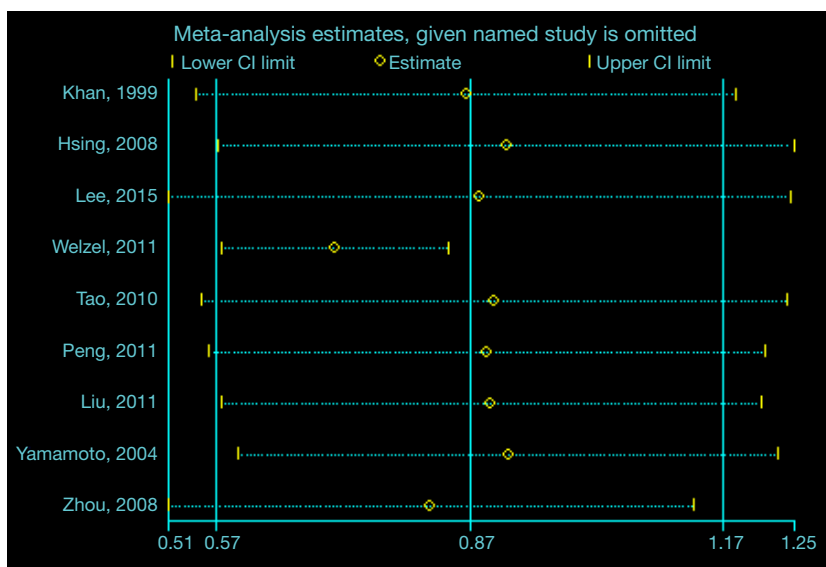
ICC, intrahepatic cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; RR, relative risk; CI, confidence interval.

approach of sensitivity analysis was conducted to explore this heterogeneity, where pooled ORs were calculated by sequential omission of one study every time. The most substantial variation of pooled ORs in sensitivity analysis and the I<sup>2</sup> was observed when Welzel *et al.* [2011] (37) was eliminated. Without Welzel *et al.* [2011] (37), the pooled OR for the effect of hypertension on CCC was 0.58 (95% CI, 0.65–0.82). The I<sup>2</sup> values was 37.4% (P=0.13), demonstrating remarkably declined heterogeneity in comparison to when Welzel *et al.* [2011] (37) was enrolled (Figure 3). Meta-regression analysis was also performed

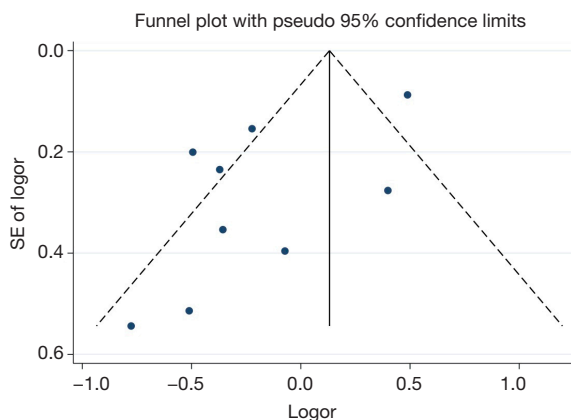
to probe into the potential source of heterogeneity. However, meta-regression models did not indicate that the geographical locations (P=0.910), and confounders adjusted for smoking status (P=0.738), alcohol use (P=0.819), gallstones (P=0.904) were a source of heterogeneity.

#### Publication bias

The funnel plot failed to show substantial asymmetry, neither did Begg's or Egger's tests detect any substantial publication bias (P>0.05) (Figure 4).



**Figure 3** Sensitivity analysis of the association between hypertension and the risk of cholangiocarcinoma.



**Figure 4** Funnel plot of studies included in the meta-analysis of the relationships between hypertension and the risk of cholangiocarcinoma. Logor, log odds ratio; SE, standard error.

**Discussion**

To our knowledge, this meta-analysis is the first to probe into the correlation of hypertension and CCC risk. Nine studies were selected to assess the influence of hypertension on CCC risk, which revealed that hypertension is not significantly correlated with the risk of CCC (OR, 0.87; 95% CI, 0.57–1.17), among significantly heterogeneous studies. In the separation analysis of ICC and ECC, the correlation between hypertension and elevated risk of ECC (OR, 0.74; 95% CI, 0.42–1.37) or ICC (OR, 1.07; 95% CI,

0.43–1.71) was not significant, either.

Our study harbors certain advantages. To begin with, it is the first large-scale meta-analysis (2,016 patients with CCC and 199,812 healthy volunteers) to determine the influence of hypertension on CCC risk. Hence, our results might provide novel insight into the above-described relationship, which is likely to be significant to CCC research. Moreover, subgroup as well as sensitivity analyses were carried out to figure out the influencing factors of the outcomes, which enhances the reliability of our results. Thirdly, a comprehensive search of Web of Science, EMBASE as well as PubMed databases was conducted to select potential studies, aiming at the investigation of the correlation of hypertension with the risk of CCC. Last but not least, the majority of enrolled studies were of high quality. Together, the above factors contribute to the convincingness of this meta-analysis.

There exist certain limitations in the present study. To begin with, all enrolled researches were case-control studies, possibly leading to recall as well as selection biases. In addition, there was significant heterogeneity among studies due to diverse study designs as well as inconsistency of demographic characteristics. Although we were not always able to ascertain the source of heterogeneity, we have performed several sensitivity and meta-regression to address this issue. Secondly, we only assessed CCC risk in hypertensive patients compared to healthy controls. None of the selected studies provided the stages or grades



of hypertension and risk of CCC; hence, we were unable to carry out a dose-response analysis to more accurately evaluate the correlation between these variables. Thirdly, in this study, we only assessed a potential correlation, vulnerable to confounding bias. The established risk factors for CCC include parasitic infections, bile-duct cysts, hepatolithiasis as well as primary sclerosing cholangitis (9), which, however, were only adjusted in a few studies. Moreover, our findings are vulnerable to diagnostic bias. Hypertensive subjects are prone to receive physical examination, which may contribute to the early detection of CCC.

### Conclusions

In summary, available evidence from observational studies indicates that hypertension has no association with elevated risk of CCC. However, more prospective studies as well as basic research are warranted to verify the association of hypertension with CCC risk.

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### Footnotes

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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