Association of Circulating Leptin and Adiponectin with Risk and Prognosis of Hepatocellular carcinoma: A Combination of Traditional, Survival and Dose-response Meta-analysis

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Abstract

**Background:** The association between leptin, adiponectin levels and the risk and prognosis of hepatocellular carcinoma has been investigated by a growing number of studies, but the results were controversial.

**Methods:** We performed the meta-analysis to assess the relationships between leptin, adiponectin levels and the risk and prognosis of hepatocellular carcinoma (CRD42020195882). Through June 14, 2020, PubMed, Cochrane Library, Embase databases, Clinicaltrials, and Opengrey was searched, including references of qualifying articles. Titles, abstracts, and articles were reviewed by at least 2 independent readers. Stata 16.0 was used to calculate statistical data.

**Results:** Thirty studies were included in this meta-analysis and results showed that hepatocellular carcinoma group has significantly higher leptin levels than the cancer-free control group (SMD = 1.83, 95% CI (1.09, 2.58), P = 0.000), the healthy control group (SMD = 4.32, 95% CI (2.41, 6.24), P = 0.000) and the cirrhosis group (SMD = 1.85, 95% CI (0.70, 3.01), P = 0.002). Hepatocellular carcinoma group has significantly higher adiponectin levels than the the healthy control group (SMD = 1.57, 95% CI (0.37, 2.76), P = 0.010), but no statistical difference compared with the cancer-free control group (SMD = 0.24, 95% CI (-0.35, 0.82), P = 0.430) and the cirrhosis group (SMD = -0.51, 95% CI (-1.30, 0.29), P = 0.213). The leptin rs7799039 polymorphism was associated with an increased the risk of hepatocellular carcinoma (G vs A: OR = 1.28, 95% CI (1.10, 1.48), P = 0.002). There were linear relationships between adiponectin levels and the risk of hepatocellular carcinoma (OR = 1.066, 95% CI (1.03, 1.11), P = 0.001). In addition, the results showed that high/positive expression of adiponectin was significantly related to lower overall survival in hepatocellular carcinoma patients (HR = 1.70, 95% CI (1.22, 2.37), P = 0.002); however, there was no significantly association between the leptin levels and overall survival (HR = 0.92, 95% CI (0.53, 1.59), P = 0.766).

**Conclusion:** The study shows that high leptin levels were associated with a higher risk of hepatocellular carcinoma. Adiponectin levels were proportional to hepatocellular carcinoma risk, and were related to the poor prognosis.

1 Introduction

In 2018, hepatocellular carcinoma (HCC) became the sixth most common cancer in the world and the fourth leading cause of cancer death globally [1]. The pathogenesis of HCC is complicated and still unclear, the process is high invasion and aggression, and the prognosis is very poor [2]. HCC is generally secondary to liver cirrhosis or viral hepatitis. Approximately 80% of patients with newly viral infections evolve chronic infections, with about10-20% developing cirrhosis and 1–5% advancing to end-stage HCC over 20–30 years [3]. Studies have further identified obesity, particularly abdominal obesity, as a potential risk factor for HCC. Hence, leptin and adiponectin, as the most plenteous and the best-studied obesity-related adipokines, may play an important role in the development of HCC [4, 5].

Leptin is well known as a regulator of energy expenditure and food intake through Hypothalamic regulation. Research into leptin has revealed that this hormone not only plays a critical part in metabolism, but mediates the development of neoplasm by enhancing tumor angiogenesis, promoting cellular proliferation, migration, invasion, and inhibiting apoptosis of tumor cells [6]. Leptin acts on receptors that are expressed across many tissues (including liver). Adiponectin is also referred to as AdipoQ, initially described by Arita et al., and has hepatoprotective properties and anti-inflammatory [7, 8]. The beneficial effects of AdipoQ have been observed in alcoholic and non-alcoholic liver disease models [9]. Animal studies have also proven a protective role for AdipoQ in HCC and cirrhosis [10, 11], and high AdipoQ levels in patients with cirrhosis and HCC were linked to the progression of disease [12, 13].

In recent years, reports on the correlation between leptin, AdipoQ levels and HCC have gradually increased, and some studies have attempted to clarify the role of both in HCC. However, conflicting associations are reported between leptin, AdipoQ levels and HCC. Therefore, the meta-analysis has been performed to systematically determine the relationship between leptin, AdipoQ levels as well as relevant gene polymorphisms and the risk and prognosis of HCC.

2. Methods

The meta-analysis was performed according to the Meta-Analysis of Observational Studies in Epidemiology recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [14, 15]. The protocol for this meta-analysis is available in PROSPERO (CRD42020195882).

2.1 Literature search strategy

We searched PubMed, Embase, the Cochrane Library, Clinicaltrials (https://clinicaltrials.gov/), and Opengrey (http://www.opengrey.eu/) on June 14, 2020, limited to the English language. The following terms were searched in [Title/Abstract]: Adiponectin [MeSH], AdipoQ, Adipocyte Complement Related Protein 30 kDa, Adipose Most Abundant Gene Transcript 1, apm1 Protein, ACRP30 Protein, Adipocyte, C1q and Collagen Domain Containing Protein, Leptin [MeSH], Obese Protein, Obese Gene Product, Ob Gene Product, Ob Protein, Liver Neoplasms [MeSH], Liver Neoplasm*, Hepatocellular Cancer*, Hepatic Cancer*, Liver Cancer*, Cancer of Liver. Besides, the reference lists of the included articles were manually searched.

2.2 Study selection criteria

Inclusion criteria: studies (1) were focused on the correlation between leptin or AdipoQ levels and HCC risk, and provided full text and complete data in HCC patients and controls, or (2) investigate the correlation between AdipoQ or leptin levels and the prognosis of HCC, and provide sufficient information to get the hazard ratio (HR) and 95% confidence intervals (CIs). Exclusion criteria: conference abstracts, case reports, comments, review, editorials, letters to the editor, and experimental animal studies were excluded. When studies reported on the same or overlapping patient populations, only the study with the most complete data set and the most rigorous methodology was used.
2.3 Data extraction

Extracted the basic information from each study: the first author, year of publication, country, study design, study period, number of subjects and sample source. In addition, Extracted the following information in Table 1: the source of the case group, the source of the cancer-free control (CFC) group, age, gender, body mass index, measured indicators and detected method. Summarized the following information in Table 2: the source of case/control, matching variables, single-nucleotide polymorphisms, genotyping methods, frequency of case and control genotype. Selected the following information in Table 3: follow-up, measured indicators, detected method, cut-off value, survival analysis, source of HR and analytic method. If there was inaccurate or missing information extracted from the original article, we tried to contact the corresponding authors of studies to guarantee data accuracy.
Table 1
Main characteristics of the studies examining the relationship between leptin, AdipoQ levels and the risk of HCC

| Author, Year, Country | Study design | Study period | the source of case group | the source of Cancer-free control group | Number | Mean age | Males | BMI |
|-----------------------|--------------|--------------|--------------------------|----------------------------------------|--------|---------|-------|-----|
| Abouzied, 2017, Egypt  | C            | --           | HCC                      | Healthy controls                       | 25/25  | 57.7/29.2| 18/23 | 21.7/22.2 |
| Aleksandrova, 2014, Europe | N            | 2000–2006    | HCC                      | Healthy controls                       | 125/250| 60.1/60.1| 85/171| 28.1/26.9 |
| Ataseven, 2006, Yurkey | C            | --           | HBV-related HCC          | HBV-related cirrhosis/Healthy controls | 22/23  | 59.8/45.5/37.1| 15/11/11| -- |
| Bakir, 2017, Egypt    | S            | 03/2016–11/2016 | HCV-related cirrhotic HCC | HCV-related cirrhosis                   | 50/40  | 53.2/50.7| 29/25 | 24.5/26.1 |
| Bastard, 2018, France | N            | 03/2006–07/2016 | Viral cirrhotic HCC      | Viral cirrhosis                         | 56/96  | 59.8/58.9| 34/61 | 25.6/25.8 |
| Chen, CL, 2014, Taiwan| N            | 01/1999–12/2004 | HBV-related HCC          | Chronic hepatitis B                     | 187/374| 52.4/52.2| 154/311| -- |
| Chen, MJ, 2012, Taiwan| C            | 01/2009–12/2009 | Viral HCC                | Healthy controls                        | 65/165 | 58.8/47.7| 47/112| 24.7/24.4 |
| Costantini, 2013, Italy| C            | --           | HCV-related HCC          | HCV-related cirrhosis/Chronic hepatitis C/Healthy controls | 26/30/30/20 | 70.0/68/63.4/60.9 | 18/14/15/9 | -- |
| Feder, 2019, Germany  | P            | 05/2012–05/2015 | HCC                     | Healthy controls                        | 32/49  | --      | --   | -- |
| Fukushima, 2010, Japan| P            | 1993–2003    | HCV-related HCC          | Chronic hepatitis C                     | 9/27   | 53.0/51.3| 5/11 | -- |
| Hamdy, 2015, Egypt    | S            | 01/2014–12/2014 | HCV-related cirrhotic HCC | HCV-related cirrhosis                   | 61/29  | 52.3/52.3| 51/21 | 33.7/36.7 |
| Khattab, 2012, Egypt  | C            | 02/2009–01/2010 | HCC                     | Chronic hepatitis C/Healthy controls    | 147/147/320 | 43.9/41.6/42.9 | 114/115/201 | 24.9/25.1/25.3 |
| Kotani, 2009, Japan   | N            | 1990–1999    | HCC                     | Healthy controls                        | 59/334 | 63.5/62.7| --   | -- |
| Liu, CJ, 2009, Taiwan | S            | 01/2002–10/2005 | HBV-related HCC         | HBV-related cirrhosis/Chronic hepatitis B/Healthy controls | 120/40/120/116 | 50.7/50.3/30/53.8 | 100/29/63/67 | -- |
| Liu, ZW, 2005, China  | C            | --           | HCV-related cirrhotic HCC| HCV-related cirrhosis/Chronic hepatitis C/Healthy controls | 2/10/30/30 | 59.5/53.7/41/39.4 | 2/6/17/18 | 23.0/22.7/23.0/23.1 |
| Author, Year, Country | Study design | Study period | the source of case group | the source of Cancer-free control group | Number | Mean age | Males | BMI |
|-----------------------|--------------|--------------|-------------------------|-----------------------------------------|--------|----------|-------|-----|
| Michikawa, 2013, Japan | N            | 1993–2006    | Viral HCC               | Chronic viral hepatitis                  | 90/117 | –        | 62/80 | –   |
| Radwan, 2019, Egypt   | S            | –            | HCC                     | Chronic hepatitis C                      | 48/52  | 53.2/52.5| 26/32 | 25.2/27.7 |
| Sadik, 2012, Egypt    | C            | 01/2008–02/2009 | HCV-related HCC | HCV-related cirrhosis/Healthy controls   | 69/36/21 | 59.1/53.0/55.8 | 43/23/13 | 28.0/27.1/29.1 |
| Sumie, 2011, Japan    | C            | 01/1997–10/2007 | HCV-related HCC | Chronic hepatitis C                      | 97/97  | 67.4/61.2| 67/67 | 22.5/23.1 |
| Voumvouraki, 2011, Greece | C       | –            | Viral cirrhotic HCC    | Viral cirrhosis/Chronic hepatitis C/Healthy controls | 38/34/44/60 | 62.0/60.0/53.0/– | 25/12/8/– | – |
| Wang, 2003, Taiwan    | C            | 01/2000–12/2000 | Viral cirrhotic HCC    | Viral cirrhosis/Healthy controls         | 31/26/25 | 65.0/59.0/65.0 | 31/26/25 | 23.2/23.7/24.4 |

P = Cohort, S = Cross-sectional, C = Case-control, N = Nested Case-control, HCC = Hepatocellular carcinoma, HCV = hepatitis C virus, HBV = hepatitis B virus, ELI = Electro-chemiluminescence immunoassay, RIA = Radioimmunoassay, HMW AdipoQ = High Molecular Weight Adiponectin, BMI = body mass index, NOS = Newcastle-Ottawa Scale

| Author, Year, Country | Study design | Case/control | Number | Matching variables | SNP | Samples source | Genotyping methods | Frequency of case genotype | Frequency of control genotype | NOS score |
|-----------------------|--------------|--------------|--------|--------------------|-----|----------------|----------------------|---------------------------|----------------------------|-----------|
| Amer, 2017, Egypt     | C            | HCC/Healthy controls | 150/100 | age, sex and smoking rate | rs7799039 (leptin gene) | blood | PCR-RFLP technique | AA = 60; AG = 69; GG = 21; G allele = 111; A allele = 189 | AA = 49; AG = 47; GG = 4; G allele = 54; A allele = 146 | 7 |
| Zhang, 2018, China    | C            | HCC/Healthy controls | 575/921 | age and sex | rs7799039 (leptin gene) | blood | SNPscan™ | AA = 295; AG = 221; GG = 59; G allele = 339; A allele = 811 | AA = 505; AG = 360; GG = 56; G allele = 472; A allele = 1370 | 7 |
| Cai, 2013, China      | C            | HCC/Healthy controls | 200/200 | age and sex | rs1501299 (adiponectin gene) | blood | DNA sequencing | TT = 12; TG = 60; GG = 128; G allele = 316; T allele = 84 | TT = 39; TG = 69; GG = 92; G allele = 253; T allele = 147 | 8 |

C = Case-control, SNP = single-nucleotide polymorphisms, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, NOS = Newcastle-Ottawa Scale
relationship between AdipoQ or leptin expression and the prognosis of HCC, and the main characteristics were summarized in Table 2. A total of 30 articles met our inclusion criteria for the meta-analysis of AdipoQ expression and HCC risk.

### 3.4 Quality assessment

The Newcastle-Ottawa Scale (NOS), a risk assessment tool recommended by the Cochrane collaboration, was applied to evaluate the quality of non-randomized controlled studies. The following factors were taken into consideration: patient selection, comparability of the study groups, and assessment of outcome. The maximum score obtained by this scoring system was 9, and studies with scores ≥ 7 were defined as high quality [14]. The above steps were carried out by two researchers (Lilong Zhang, Qihang Yuan) independently and cross-checked, and all disagreements were dealt with by the senior authors (Weixing Wang).

### 3.5 Statistical analysis

All statistical analyses were performed using Stata 16.0. Continuous and dichotomous variables were compared by the standardized mean difference (SMD) and odds ratio (OR), respectively. Hazard ratio (HR) was calculated to assess correlations between AdipoQ or leptin expression and the prognosis of HCC. For studies that presented continuous data as median and range values/ interquartile, the means and standard deviations were calculated using statistical algorithms described by Luo et al. and Wan et al., respectively [16, 17]. In the case of the studies only provided Kaplan-Meier survival curves, Engage Digitizer version 2.11 software was used to extract relevant numerical value from survival curves and calculate the HR (95% CI) [18, 19]. All the effect quantities were represented by the 95% confidence interval (CI). P < 0.05 was considered statistically significant. We used the chi-squared test to evaluate the statistical heterogeneity between different studies. P > 0.1 and I² < 50% indicated low heterogeneity where a fixed-effect model was used; otherwise, the random-effect model was used.

Furthermore, a 2-stage dose-response meta-analysis was performed to explore the association between different categories of leptin, AdipoQ levels and HCC risk [20, 21]. 1) The fixed-effect nonlinear model was constructed based on the restrictive cubic spline function (Knot = 3). 2) According to the results of the heterogeneity test and nonlinear correlation test, the corresponding model is adopted.

Finally, for the indicators with high heterogeneity, we carried out sensitivity analyses for identifying the source of heterogeneity and checking the robustness of the results. The leave-one-out method was employed, which allowed us to determine the implication of each study on the pooled effect size. Besides, meta-regression analysis was performed to explore the potential sources of heterogeneity. For indicators with over 10 included articles, we generated a funnel plot to inspect publication bias visually. Begg’s and Egger’s tests were also conducted for analyzing the publication bias quantitatively, where, P < 0.05 was regarded as statistically significant. We validated the results of publication bias by establishing trim and fill funnel plot if required.

### 3. Results

#### 3.1 Studies Retrieved and Characteristics

In this meta-analysis, we identified 1,068 potentially eligible records, and screened the titles and abstracts of these records for inclusion. On examination of the full text of 78 records, and 30 met our inclusion criteria (Fig. 1). Although Ebrahim’s article met the research topics, it was excluded because the full text was not available [22]. Twenty-one articles [23–44] (10 case-control, 5 nested case-control, 4 cross-sectional and 2 cohort studies) evaluated the relationship between leptin or AdipoQ levels and HCC risk, and main characteristics were summarized in Table 1. Three case-control studies [44–46] assessed the relationship between Leptin or AdipoQ gene polymorphism and HCC risk, and main characteristics were reported in Table 2. Six articles [47–52] analyzed the relationship between AdipoQ or leptin expression and the prognosis of HCC, and the main characteristics were summarized in Table 3.
the included studies using the Newcastle–Ottawa scale is shown in Table 1–3, and the score obtained ranged from 5 to 8. Twenty articles were awarded 7 or 8 points, and considered as high-quality; Six studies were awarded 6 points and four studies were awarded 5 points, which were considered as moderate quality.

3.2 Association between circulating leptin levels and HCC risk

Pooling data of 12 studies [23–28, 30, 32, 37, 40–42] with 1896 participants assessed the association between leptin levels and HCC risk. Heterogeneity analysis showed that the significant heterogeneity was observed among the studies ($I^2 = 97.5\%, \ P = 0.000$), the random-effect model was applied. The results showed that leptin levels were significantly higher in the HCC group than in the CFC group (SMD = 1.83, 95% CI (1.09, 2.58), $P = 0.000$) (Fig. 2). Subgroup analysis, according to the source of CFC group, showed HCC group has significantly higher leptin levels than the healthy control group (SMD = 4.32, 95% CI (2.41, 6.24), $P = 0.000$) and the cirrhosis group (SMD = 1.85, 95% CI (0.70, 3.01), $P = 0.002$), but no statistical difference compared with the chronic hepatitis group (SMD = 0.94, 95% CI (-0.1, 2.03), $P = 0.090$) (Fig. 3 and Table 4). We further conducted subgroup analysis by the source of case group, and the results showed HCV-related cirrhotic HCC has significantly higher leptin levels than HCV-related cirrhosis (SMD = 0.82, 95% CI (0.40, 1.24), $P = 0.000$), whereas there was no difference in other subgroups (Table 4).
In addition, we also performed other subgroup analyses and the results were shown in Table 4. Stratification by ethnicity showed no significant difference in the HCC group and CFC group in Asian (SMD = 0.10, 95% CI (-0.50, 0.70), P = 0.751), Caucasian (SMD = 0.58, 95% CI (-0.06, 1.22), P = 0.077) and African population (SMD = 9.36, 95% CI (1.27, 19.99), P = 0.084). Stratification by sample size showed HCC group has significantly higher leptin levels than CFC group shown in bold.

| Variable                                      | Included studies          | Test of association | Test of heterogeneity |
|-----------------------------------------------|---------------------------|---------------------|-----------------------|
|                                               |                           | SMD  | 95%CI   | Pvalue* | Mod | Pvalue | \( \phi \) |
| HCC vs Healthy controls                       |                           |      |        |        |     |        |          |
| Overall                                       | [23–25, 30, 37, 40–42]    | 4.32 | 2.41–6.24 | 0.000 | RE | 0.000 | 98.4%    |
| HCC(unreported reason) vs Healthy controls    | [23, 24]                  | 5.58 | -5.11–16.26 | 0.306 | RE | 0.000 | 98.8%    |
| Viral cirrhotic HCC vs Healthy controls       | [37, 41, 42]              | 1.02 | -0.78–2.79 | 0.263 | RE | 0.000 | 94.1%    |
| HCV-related HCC vs Healthy controls           | [30, 37, 40]              | 8.87 | -1.08–1.82 | 0.081 | RE | 0.000 | 98.7%    |
| HCC vs Cirrhosis                              |                           |      |        |        |     |        |          |
| Overall                                       | [25–27, 30, 37, 40–42]    | 1.85 | 0.70–3.01 | 0.002 | RE | 0.000 | 97.0%    |
| HCV-related cirrhotic HCC vs HCV-related cirrhosis | [26, 37]                | 0.82 | 0.40–1.24 | 0.000 | FE | 0.145 | 53.0%    |
| HCV-related HCC vs HCV-related cirrhosis      | [30, 40]                  | 8.71 | -3.84–21.25 | 0.174 | RE | 0.000 | 99.2%    |
| Viral cirrhotic HCC vs Viral cirrhosis        | [27, 41, 42]              | 0.13 | -0.11–0.37 | 0.302 | FE | 0.591 | 0        |
| HCC vs Chronic hepatitis                      |                           |      |        |        |     |        |          |
| Overall                                       | [28, 30, 32, 37, 41]      | 0.94 | -0.15–2.03 | 0.090 | RE | 0.000 | 94.9%    |
| HCV-related HCC vs Chronic hepatitis C        | [30, 32, 37]              | 1.63 | -1.39–4.65 | 0.290 | RE | 0.000 | 96.0%    |
| Viral cirrhotic HCC vs Chronic hepatitis C    | [37, 41]                  | -0.10 | -0.51–0.32 | 0.643 | FE | 0.561 | 0        |
| Ethnicity                                     |                           |      |        |        |     |        |          |
| Asian                                         | [25, 28, 32, 37, 42]      | 0.10 | -0.50–0.70 | 0.751 | RE | 0.000 | 85.6%    |
| Caucasian                                     | [24, 27, 30, 41]          | 0.58 | -0.06–1.22 | 0.077 | RE | 0.000 | 93.3%    |
| African                                       | [23, 26, 40]              | 9.36 | -1.27–19.99 | 0.084 | RE | 0.000 | 99.3%    |
| Sample size                                   |                           |      |        |        |     |        |          |
| < 100                                         | [23, 25, 26, 32, 37, 42]  | 1.57 | 0.22–2.91 | 0.022 | RE | 0.000 | 95.8%    |
| \( \geq 100 \)                                | [24, 27, 28, 30, 40, 41]  | 2.23 | 1.21–3.26 | 0.000 | RE | 0.000 | 98.4%    |
| Mean age                                      |                           |      |        |        |     |        |          |
| < 60                                          | [23, 25–27, 28, 32, 37, 40] | 2.87 | 1.57–4.17 | 0.000 | RE | 0.000 | 98.2%    |
| \( \geq 60 \)                                 | [24, 30, 41, 42]          | 0.76 | 0.03–1.49 | 0.040 | RE | 0.000 | 93.7%    |
| Study design                                  |                           |      |        |        |     |        |          |
| Case-control                                  | [23, 25, 30, 37, 40–41]   | 3.81 | 1.83–5.79 | 0.000 | RE | 0.000 | 97.5%    |
| Nested Case-control                           | [24, 27, 28]              | 0.14 | 0.01–0.26 | 0.035 | FE | 0.777 | 0.0%     |
| Assay method                                  |                           |      |        |        |     |        |          |
| ELISA                                         | [23–28, 30, 37, 40, 41]   | 2.13 | 1.27–2.99 | 0.000 | RE | 0.000 | 97.9%    |
| RIA                                           | [32, 42]                  | 0.79 | 0.39–1.19 | 0.000 | FE | 0.570 | 0.0%     |
| Alanine aminotransferase                      |                           |      |        |        |     |        |          |
| < 70 U/L                                      | [23, 26, 28, 32, 37, 40]  | 4.42 | 2.26–6.50 | 0.000 | RE | 0.000 | 98.6%    |
| \( \geq 70 \) U/L                            | [25, 27, 30, 41, 42]      | 0.43 | -0.38–1.23 | 0.296 | RE | 0.000 | 94.4%    |
| Albumin                                       |                           |      |        |        |     |        |          |
| < 3.5 g/dl                                    | [25, 26, 30, 40, 42]      | 3.47 | 1.28–5.66 | 0.002 | RE | 0.000 | 98.7%    |
| \( \geq 3.5 \) g/dl                          | [27, 28, 32, 41]          | 0.12 | -0.02–0.26 | 0.091 | FE | 0.633 | 0.0%     |

RE = Random-effects model, FE = Fixed-effects model, HCC = Hepatocellular carcinoma, HCV = hepatitis C virus. * Statistically significant results were shown in bold.
in both small (n < 100) sample numbers (SMD = 1.57, 95% CI (0.22, 2.91), P = 0.022) and large (n ≥ 100) sample numbers (SMD = 2.23, 95% CI (1.21, 3.26), P = 0.000). Stratification by mean age showed HCC group has significantly higher leptin levels than CFC group in both “< 60” (SMD = 2.87, 95% CI (1.57, 4.17), P = 0.000) and “≥ 60” (SMD = 0.76, 95% CI (0.03, 1.49), P = 0.040). Stratification by study design showed HCC group has significantly higher leptin levels than CFC group in both case-control studies (SMD = 3.81, 95% CI (1.83, 5.79), P = 0.000) and nested case-control studies (SMD = 0.14, 95% CI (0.01, 0.26), P = 0.035). Stratification by assay method revealed the HCC group has significantly higher leptin levels than the CFC group by both “ELISA” (SMD = 2.13, 95% CI (1.27, 2.99), P = 0.000) and “RIA” (SMD = 0.79, 95% CI (0.39, 1.19), P = 0.000). Stratification by Alanine aminotransferase (ALT) levels of HCC patients showed HCC group has significantly higher leptin levels than CFC group in “< 70 U/L” (SMD = 4.42, 95% CI (2.26, 6.50), P = 0.000), but not in the “≥ 70 U/L” (SMD = 0.43, 95% CI (0.38, 1.23), P = 0.296). Stratification by albumin levels of HCC patients showed HCC group has significantly higher leptin levels than CFC group in “< 3.5 g/dl” (SMD = 3.47, 95% CI (1.28, 5.66), P = 0.002), but not in the “≥ 3.5 g/dl” (SMD = 0.12, 95% CI (-0.02, 0.26), P = 0.091).

Meta-regression analysis showed that the ethnicity (P = 0.004), but not the source of control (P = 0.242) and case (P = 0.185), sample size (P = 0.735), mean age (P = 0.420), study design (P = 0.344), assay method (P = 0.606), ALT (P = 0.172) and albumin (P = 0.853) had significant impacts on the heterogeneity in the meta-analysis. To assess the impacts of each study on the overall meta-analysis, we carried out sensitivity analysis using the leave-one-out method. No substantial change of data on leptin levels was observed. Therefore, the results of our meta-analysis were relatively stable and credible (Fig. 4).

Funnel plot representing SMDs of the leptin levels in the HCC group compared to the CFC group were used to evaluate publication bias. Through the visual inspection of the funnel plot, there was obvious asymmetry that indicated a possibility of publication bias (Fig. 5), which were supported by the Begg’s tests (P = 0.034) and Egger’s tests (P = 0.025). Therefore, further verification by trim and fill funnel plot was employed to adjust for the potential publication bias. However, the pooled data regarding leptin that had been significant before the adjustment with the “trim and fill” method remained significant after the adjustment (SMD = 3.486, 95% CI (0.937–6.035), P < 0.05), indicating that this publication bias did not affect the pooled estimates.

### 3.3 Association between circulating AdipoQ levels and HCC risk.

Pooling data of 13 studies [24, 27–29, 31, 33–36, 38–40, 43] with 2092 participants evaluated the association between AdipoQ levels and HCC risk. Heterogeneity analysis showed that the significant heterogeneity was observed among the studies (I² = 98.2%, P = 0.000), the random-effect model was applied. The results showed that AdipoQ levels were no statistical difference in the HCC group than in the CFC group (SMD = 0.24, 95% CI (0.35, 0.82), P = 0.430) (Fig. 6).

Subgroup analysis, according to the source of CFC group, showed HCC group has significantly higher AdipoQ levels than the healthy control group (SMD = 1.57, 95% CI (0.37, 2.76), P = 0.010), but no statistical difference compared with the chronic hepatitis group (SMD = 0.10, 95% CI (0.80, 1.00), P = 0.826) and the cirrhosis group (SMD = -0.51, 95% CI (-1.30, 0.29), P = 0.213) (Fig. 7 and Table 5). We further conducted subgroup analysis by the source of case group, and the results showed viral HCC has significantly higher AdipoQ levels than Healthy controls (SMD = 1.11, 95% CI (0.44, 1.78), P = 0.001), and HCV-related HCC has significantly lower AdipoQ levels than HCV-related cirrhosis (SMD = -1.22, 95% CI (-1.54, -0.90), P = 0.000), whereas there was no difference in other subgroups (Table 5).
### Table 5
Subgroup analysis of the association between adiponectin levels and HCC risk

| Variable | Included studies | Test of association | Test of heterogeneity |
|----------|------------------|---------------------|-----------------------|
|          |                  | SMD | 95%CI | P-value* | Modal | P-value | χ² |
| HCC vs Healthy controls |                  |     |       |          |       |         |     |
| Overall  | [24, 29, 31–36, 40] | 1.57 | 0.37, 2.76 | 0.010 | RE | 0.000 | 99.0% |
| HCC(unreported reason) vs Healthy controls [24, 31, 34, 35] | 1.88 | -0.31, 4.08 | 0.092 | RE | 0.000 | 99.5% |
| Viral HCC vs Healthy controls | [29, 36, 40] | 1.11 | 0.44, 1.78 | 0.001 | RE | 0.000 | 90.8% |
| HCC vs Cirrhosis |                  |     |       |          |       |         |     |
| Overall  | [27, 33, 36, 40] | -0.51 | -1.30, 0.29 | 0.213 | RE | 0.000 | 93.9% |
| Viral cirrhotic HCC vs Viral cirrhosis | [27, 33] | -0.37 | -1.80, 1.05 | 0.607 | RE | 0.000 | 95.9% |
| HCV-related HCC vs HCV-related cirrhosis | [33, 40] | -1.22 | -1.54, -0.90 | 0.000 | FE | 0.531 | 0.0% |
| HCC vs Chronic hepatitis |                  |     |       |          |       |         |     |
| Overall  | [28, 34, 36, 38, 39, 43] | 0.10 | -0.80, 1.00 | 0.826 | RE | 0.000 | 98.4% |
| HCC(unreported causes) vs Chronic hepatitis C | [34, 39] | -0.48 | -5.71, 4.75 | 0.857 | RE | 0.000 | 99.6% |
| HCV-related HCC vs Chronic hepatitis C | [28, 43] | 0.08 | -0.22, 0.38 | 0.599 | RE | 0.068 | 70.0% |
| Viral HCC vs Chronic viral hepatitis | [28, 36, 38, 43] | 0.35 | -0.08, 0.78 | 0.108 | RE | 0.000 | 91.8% |
| Ethnicity |                  |     |       |          |       |         |     |
| Asian    | [28, 29, 35, 36, 38, 43] | 0.31 | 0.02, 0.61 | 0.036 | RE | 0.000 | 88.3% |
| Caucasian | [24, 27, 31] | 0.73 | 0.11, 1.35 | 0.022 | RE | 0.000 | 90.3% |
| African  | [33, 34, 39, 40] | -0.32 | -2.93, 2.29 | 0.811 | RE | 0.000 | 99.5% |
| Sample size |                  |     |       |          |       |         |     |
| < 200    | [27, 31, 33, 39, 40, 43] | 0.76 | 0.03, 1.50 | 0.042 | RE | 0.000 | 98.5% |
| ≥ 200    | [24, 28, 29, 34–36, 38 ] | -0.40 | -1.34, 0.54 | 0.403 | RE | 0.000 | 97.1% |
| Mean age |                  |     |       |          |       |         |     |
| < 60     | [27–29, 33, 34, 36, 39, 40] | 0.10 | -0.85, 1.05 | 0.833 | RE | 0.000 | 98.8% |
| ≥ 60     | [24, 35, 43] | 0.13 | -0.14, 0.39 | 0.362 | RE | 0.037 | 69.7% |
| Study design |                  |     |       |          |       |         |     |
| Nested Case-control | [24, 27, 28, 35, 38] | 0.25 | 0.14, 0.36 | 0.000 | EE | 0.585 | 0.0% |
| Case-control | [29, 34, 40, 43] | 0.84 | -0.74, 2.12 | 0.298 | RE | 0.000 | 99.2% |
| Cross-sectional | [33, 36, 39] | -1.10 | -3.46, 1.26 | 0.361 | RE | 0.000 | 99.0% |
| Sample source |                  |     |       |          |       |         |     |
| Serum    | [24, 27, 29, 31, 33–36, 39, 40, 43] | 0.23 | -0.51, 0.97 | 0.540 | RE | 0.000 | 98.5% |
| Plasma   | [28, 38] | 0.23 | 0.08, 0.38 | 0.003 | FE | 0.795 | 0.0% |
| Assay method |                  |     |       |          |       |         |     |
| ELISA    | [24, 27, 28, 31, 33, 35, 36, 38–40, 43] | -0.03 | -0.45, 0.40 | 0.901 | RE | 0.000 | 95.7% |
| Non-ELISA | [29, 34] | 1.75 | -0.75, 4.26 | 0.170 | RE | 0.000 | 99.4% |
| Alanine aminotransferase |                  |     |       |          |       |         |     |
| < 70 U/L | [28, 33, 36, 40, 43] | 0.00 | -0.53, 0.53 | 0.992 | RE | 0.000 | 94.8% |
| ≥ 70 U/L | [27, 34, 39] | 0.08 | -2.96, 3.12 | 0.958 | RE | 0.000 | 99.5% |
| Albumin  |                  |     |       |          |       |         |     |
| < 3.5 g/dl | [33, 34, 40] | 0.62 | -1.98, 3.22 | 0.639 | RE | 0.000 | 98.5% |
| ≥ 3.5 g/dl | [27, 28] | 0.24 | 0.09, 0.40 | 0.002 | RE | 0.000 | 99.4% |

RE = Random-effects model, FE = Fixed-effects model, HCC = Hepatocellular carcinoma, HCV = hepatitis C virus. *Statistically significant results were shown in bold.
Subgroup analysis, according to the molecular-weight of AdipoQ, showed no significant difference about high-molecular-weight AdipoQ (SMD = -0.01, 95% CI (-0.20, 0.18), P = 0.911) and non-high-molecular-weight AdipoQ (SMD = 0.28, 95% CI (0.06, 0.62), P = 0.103) levels in the HCC group and CFC group (Fig. 8). In addition, we also performed other subgroup analysis and the results were shown in Table 5. Stratification by ethnicity showed HCC group has significantly higher AdipoQ levels than CFC group in Asian (SMD = 0.31, 95% CI (0.02, 0.61), P = 0.036) and Caucasian population (SMD = 0.73, 95% CI (0.11, 1.35), P = 0.022), but not in African population (SMD = -0.32, 95% CI (-2.93, 2.29), P = 0.811). Stratification by sample size showed HCC group has significantly higher AdipoQ levels than CFC group in small (n < 200) sample numbers (SMD = 0.76, 95% CI (0.03, 1.50), P = 0.042), but not in large (n ≥ 200) sample numbers (SMD = -0.40, 95% CI (-1.34, 0.54), P = 0.403). Stratification by mean age showed no significant difference in the HCC group and CFC group in both “< 60” (SMD = 0.10, 95% CI (0.85, 1.05), P = 0.833) and “≥ 60” (SMD = 0.13, 95% CI (0.14, 0.39), P = 0.362). Stratification by study design showed HCC group has significantly higher AdipoQ levels than CFC group in nested case-control studies (SMD = 0.25, 95% CI (0.14, 0.36), P = 0.000), but not in case-control studies (SMD = 0.84, 95% CI (-0.74, 2.12), P = 0.298) and cross-sectional studies (SMD = -1.10, 95% CI (-3.46, 1.26), P = 0.361). Stratification by the sample source revealed HCC group has significantly higher AdipoQ levels than CFC group in the source of plasma (SMD = 0.23, 95% CI (0.08, 0.38), P = 0.003), but not in the source of serum (SMD = 0.23, 95% CI (0.51, 0.97), P = 0.540). Stratification by assay method revealed no significant difference in the HCC group and CFC group by both "ELISA" (SMD = -0.03, 95% CI (0.45, 0.40), P = 0.901) and "Non-ELISA" (SMD = 1.75, 95% CI (0.75, 4.26), P = 0.170). Stratification by ALT levels of HCC patients showed no significant difference in the HCC group and CFC group in both "< 70U/L" (SMD = 0.00, 95% CI (-0.53, 0.53), P = 0.992) and "≥ 70U/L" (SMD = 0.08, 95% CI (2.96, 3.12), P = 0.958). Stratification by albumin levels of HCC patients showed HCC group has significantly higher AdipoQ levels than CFC group in "≥ 3.5 g/dl" (SMD = 0.24, 95% CI (0.09, 0.40), P = 0.002), but not in the "< 3.5 g/dl" (SMD = 0.62, 95% CI (1.98, 3.22), P = 0.639). In addition, we also found that AdipoQ levels in HCC patients was not related to gender (man vs woman: SMD = -0.29, 95% CI (-0.69, 0.11), P = 0.153) and vascular invasion (present vs absent: SMD = 0.19, 95% CI (0.11, 0.49), P = 0.208).

Khattab et al. [34] found that AdipoQ levels in HCC with the size of nodules ≥ 5 cm were significantly greater than 5 cm (24.2 ± 2.1 vs 20.8 ± 3.8, P = 0.009), whereas, AdipoQ levels were not related to TNM stages, number of nodules and lymph node metastasis. Feder et al. [31] discovered that AdipoQ levels were no statistical difference in HCC and colorectal liver metastases patients, and negatively related to steatosis grade, but not correlate with inflammation or fibrosis score. Sadik et al. [40] reported that AdipoQ levels of cirrhotic HCC were significantly higher than the noncirrhotic HCC group, whereas leptin was not.

Meta-regression analysis showed that the source of control (P = 0.150) and case (P = 0.579), ethnicity (P = 0.338), sample size (P = 0.140), mean age (P = 0.540), study design (P = 0.283), assay method (P = 0.092), source of sample (P = 0.993), ALT (P = 0.544) and albumin (P = 0.575) had no significant affects on the heterogeneity in the meta-analysis. We also carried out sensitivity analysis using the leave-one-out method, and no substantial change of data on AdipoQ levels was observed, therefore, the results of our meta-analysis were relatively stable and credible (Fig. 9).

Funnel plot representing SMDs of the AdipoQ levels in the HCC group compared to the CFC group were used to assess publication bias. Through the visual inspection of the funnel plot, there was obvious asymmetry that indicated a possibility of publication bias (Fig. 10), which were not supported by the Begg’s tests (P = 0.300) and Egger’s tests (P = 0.142); therefore, further verification by trim and fill funnel plot was employed to adjust for the potential publication bias. The result of the “trim and fill” method revealed that no trimming was performed and the data was unchanged, suggesting that there was no significant publication bias.

### 3.4 Association between leptin, AdipoQ gene polymorphism and HCC risk

Pooling data from 2 studies [44, 46] with 1746 participants evaluated the association between leptin rs7799039 and HCC risk. In the allele model analysis, the G allele was significantly associated with an increased risk of HCC (G vs A: OR = 1.28, 95% CI (1.10, 1.48), P = 0.002). In the codominant model analysis, the GG genotypes was associated with a 2.03-fold elevated risk in HCC (GG vs AA: OR = 2.03, 95% CI (1.41, 2.93), P = 0.000), whereas the AG genotypes was no (AG vs AA: OR = 1.07, 95% CI (0.87, 1.31), P = 0.505). In the recessive model analysis, the GG genotypes was associated with a 1.97-fold elevated risk for developing HCC (GG vs AA + AG: OR = 1.97, 95% CI (1.38, 2.82), P = 0.000). However, in the overdominant and dominant model analysis, the AG and GG genotypes were no significantly associated with an increased HCC risk (AG vs AA + GG: OR = 0.97, 95% CI (0.80, 1.18), P = 0.770; AG + GG vs AA: OR = 1.19, 95% CI (0.98, 1.44), P = 0.078). There was no significant heterogeneity in the above results (Fig. 11).

As for AdipoQ, Cai et al. [45] found that the AdipoQ rs1501299 was associated with the increased susceptibility to HCC, and the additive model showed that the GT and GG genotypes were significantly associated with an increased HCC risk (GT vs TT: OR = 2.83, 95% CI (1.36, 5.89), P = 0.006; GG vs TT: OR = 4.52, 95% CI (2.25, 9.11), P = 0.001). In the dominant model analysis, the GG + GT genotypes were associated with a 3.8-fold elevated risk in HCC(GG + GT vs TT: OR = 3.795, 95% CI (1.92, 7.49), P = 0.001). However, the rs266729, rs822395, rs822396 and rs2241766 were no significantly associated with HCC. It is a pity that we just retrieved one study that evaluated the association of AdipoQ gene polymorphism with HCC, so that we failed to perform related meta-analysis.

### 3.5 Dose-response of circulating AdipoQ, leptin levels and HCC risk

Pooling data from 4 studies [24, 28, 35, 38] with 1507 participants showed that there was a linear dose-response relationship between AdipoQ levels and HCC risk (Pnon-linearity = 0.233). We defined the increment in 1 µg/ml AdipoQ levels as a unit to show the trend more clearly. The trends were significant for increasing HCC risk per one unit increase of AdipoQ (OR = 1.066, 95% CI (1.03, 1.11), P = 0.001; Fig. 12), without significant heterogeneity (P_heterogeneity = 0.338).

As for leptin, Aleksandrova et al. [24] and Chen et al. [28] both confirmed that leptin was no significant dose-response trend in the development of HCC. Unfortunately, we only found these two studies, and we unable to perform a meta-analysis.

### 3.6 Association between AdipoQ, leptin and survival in HCC
Pooling data of 4 studies [47–49, 51] with 435 participants analyzed the association between AdipoQ expression and survival in HCC. Heterogeneity analysis showed that no significant heterogeneity was observed among the studies ($I^2 = 0\%$, $P = 0.660$), the fixed-effect model was applied. The results showed that high/positive expression of AdipoQ was significantly related to lower overall survival (OS) in HCC patients ($HR = 1.70$, 95% CI (1.22, 2.37), $P = 0.002$; Fig. 13).

Pooling data of 3 studies [47, 50, 52] with 241 participants measured the association between leptin expression and prognosis in HCC. Heterogeneity analysis showed that the significant heterogeneity was observed among the studies ($I^2 = 66.0\%$, $P = 0.053$), the random-effect model was applied. The results showed that high/positive expression of leptin was no significantly associated with prognosis in HCC patients ($HR = 0.92$, 95% CI (0.53, 1.59), $P = 0.766$; Fig. 13).

4. Discussion

Over the last two decades, the abnormal expression of leptin and AdipoQ is correlated with various obesity-related cancers. In 2016, Wei et al. [53] carried out a meta-analysis of 107 articles to investigate AdipoQ levels in various malignancies and found that AdipoQ levels in some cancer cases (including acute leukemia, multiple myeloma, breast cancer, colorectal cancers, endometrial cancer, prostate cancer, thyroid cancer, tongue cancer, gastroesophageal cancer) were significantly lower, and in HCC was significantly higher than in the CFC group. However, only 7 articles regarding HCC were involved in the meta-analysis. Song et al. [54] performed a meta-analysis of 9 Chinese and English studies and also revealed that the AdipoQ levels in HCC patients were significantly higher than those in the CFC group. Our results indicated that HCC patients showed significantly higher AdipoQ levels than the healthy control group, but no significant difference about AdipoQ levels than CFC group. Currently, no meta-analysis on leptin and HCC risk has been carried out, and our results showed that HCC patients showed significantly higher leptin levels than the CFC group, healthy control group and cirrhosis group. Besides, comparing the HCC group and the different sources of the CFC group, the results were different. Thus we can conclude that AdipoQ and leptin levels are altered in patients with chronic hepatitis and cirrhosis compared to healthy controls, which is consistent with Buechler’s conclusion [13].

However, the high heterogeneity was observed in this pooled analysis and the findings should be explained with caution. We conducted meta-regression, subgroup analyses, and carried out sensitivity analyses to determine the source of heterogeneity. In the pooled analysis of leptin, the results of meta-regression indicated that the heterogeneity derived from ethnicity, and subgroup analyses showed that heterogeneity is related to the source of the control group, study design, assay method and baseline levels of albumin. In the pooled analysis of AdipoQ, the source of heterogeneity wasn’t found by the meta-regression, and heterogeneity is linked to the source of the control group, study design, mean age and sample source by the subgroup analyses.

Many single-nucleotide polymorphisms were found in the leptin gene, and the earliest one is the LEP rs7799039 polymorphism, an SNP identified in the 50-untranslated region of the leptin gene [55], which has been studied in various malignant tumors and was suggested it could affect the transcriptional level and leptin expression [56]. Some previous meta-analyses indicated that LEP rs7799039 polymorphism conferred the risk of cancer [57–59]. However, no meta-analysis was conducted to explore the correlation between LEP rs7799039 polymorphism and HCC risk. In this study, we found that LEP rs7799039 polymorphism was involved in the susceptibility to HCC. Unfortunately, the included studies are too few, and the conclusion ought to be further verified by more high-quality studies.

By dose-response, we were able to more clearly explore the association between AdipoQ and leptin and the risk of HCC. In 2019, Yoon et al. [60] found that AdipoQ levels were significantly associated with decreased risk of cancer, such as breast, colorectal, and endometrial cancer, and leptin was significantly associated with increased risk of cancer, such as endometrial and kidney cancer. However, our results showed that the increase of AdipoQ levels was significant for increasing HCC risk. There were just 2 dose-response studies between leptin and HCC risk, so meta-analysis was given up.

Leptin and AdipoQ may have closely associated with not only the occurrence of cancer, but the prognosis of cancer. Our findings that high/positive expression of AdipoQ was significantly correlated with lower OS in HCC patients are similar to the meta-analysis of 10 studies, which revealed that elevated AdipoQ expression was related to poor prognosis in cancer patients (including HCC patients) [61]. It is worth noting that high/positive expression of leptin was no significantly correlated with prognosis in HCC patients in this meta-analysis.

High levels of leptin may play an important role in the promotion of cancer cell migration, proliferation, survival and angiogenesis [62, 63]. This is achieved by the activation of Janus kinase/signal transducer and activator of transcription, phosphatidylinositol 3-kinase, mitogen-activated protein kinase, and extracellular signal-regulated kinase signaling pathways [64, 65], which were thought to be related to oncogenes [66, 67]. Leptin can also promote the development of liver fibrosis, steatosis and proinflammation [4, 68]. Besides, Mittenbuhler et al. revealed leptin signaling as a promoter of HCC in obesity [69].

Many studies have found AdipoQ to have significant anti-proliferative, anti-carcinogenic activity and anti-inflammatory [70]. Nazmy et al. found that AdipoQ’s tumorigenic activity can provide more protection for the body against the HCC by hindering reduction in p53 expression, reactivation of TNF-related apoptosis-inducing ligand signaling and induction of apoptotic pathway [71]. Al-Gayyar et al. revealed that AdipoQ can completely block the increase of sulfatase 2 induced by HCC, ameliorate the expression of tumor invasion markers, matrix metalloproteinase-9, syndecan-1 and fibroblast growth Factor-2 induced by HCC, decrease the expression of nfkb and tumor necrosis factor α (TNF-α) induced by HCC, thus achieve the hepatoprotective [72]. Manieri’s research showed that adipoQ can activate two proteins in liver cells, p38α and AMP-activated protein kinase, which can prevent cell proliferation and impair tumor growth [73]. Our finding that elevated AdipoQ was linked to higher risk and poor prognosis of HCC, which seems paradoxical with the above view. Some mechanisms have been suggested to account for this contradiction. 1) AdipoQ resistance: even if AdipoQ is plentifully expressed, it may not be able to prevent poor prognosis due to the down-regulated of AdipoQ receptor or the dysfunctional of AdipoQ signaling pathway. Many HCC patients have liver cirrhosis or fibrosis, both of which are related to the down-regulation of AdipoQ receptors in the liver and reduction of AdipoQ clearance, leading to AdipoQ resistance status [74]. Also, the expression of AdipoQ originally enhances to compensate for the progression of HCC, but the higher levels of AdipoQ are ineffective due to the overall worsening of the patient’s physical condition [51]. 2) AdipoQ stimulates AKT-mediated activation of cancer cells, which is a significant predictor of poor survival [51, 75].
There are some limitations to this meta-analysis that should be considered. First, the partial results should be interpreted with caution due to the high level of heterogeneity. Second, few studies were conducted to explore the correlation between leptin, AdipoQ gene polymorphism and HCC risk. The results of LEP rs7799039 polymorphism and HCC risk should require more studies to confirm. Third, we extracted partly HR from the survival curve of the original article, which may introduce some small errors. Finally, almost all studies included in the meta-analysis had leptin and AdipoQ levels measured only one time and did not show its long-term changes in the development of HCC.

5. Conclusions
The present study shows that high leptin levels were associated with a higher risk of HCC, which may represent a useful biomarker for early detection of HCC. AdipoQ levels were proportional to HCC risk, with a linear dose-response relationship, and were related to the poor prognosis, which may be a useful biomarker for determining the prognosis of HCC.

Abbreviations
HCC
Hepatocellular carcinoma; HCV:hepatitis C virus; HBV:hepatitis B virus; CFC:Cancer-free control; AdipoQ:Adiponectin; SMD:standardized mean difference; OR:odds ratio; HR:Hazard ratio; CI:confidence interval; NOS:Newcastle-Ottawa Scale; ALT:Alanine aminotransferase; ELISA:Enzyme-linked immunosorbent assay; RIA:Radioimmunoassay; OS:overall survival

Declarations
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Authors’ contributions
ZL and WW conceived and designed the study. ZL, YQ and CD were responsible for the collection and assembly of data, data analysis, and interpretation. ZL was involved in writing the manuscript. LM, and WW revised the manuscript. All the work was performed under WW instruction. All authors read and approved the final manuscript.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Competing interests
The authors declare that they have no competing interests.

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Figures

Figure 1

PRISMA 2009 Flow Diagram

Records identified through database searching (n = 1053)

Additional records identified through other sources (n = 15)

Records after duplicates removed (n = 913)

Records screened (n = 915)

Records excluded (n = 837)

Full-text articles assessed for eligibility (n = 78)

Studies included in qualitative synthesis (n = 30)

Studies included in quantitative synthesis (meta-analysis) (n = 30)

Full-text articles excluded, with reasons (n = 48)

- Conference abstracts: 21
- Not original articles: n=8
- Non-English literature: n=3
- Different topics of current research: n=14
- Unable to access full text: n=1

PRISMA flow diagram of study selection for the meta-analysis.
Figure 2

Forest plot for studies comparing leptin levels between the HCC patients and cancer-free control group. SMD: standardized mean difference; CI: confidence interval

Figure 3

Forest plot of the subgroup analyses concerning leptin levels based on the source of cancer-free control group. SMD: standardized mean difference; CI: confidence interval

Figure 4

Sensitivity analysis for studies comparing leptin levels between the HCC patients and cancer-free control group. CI: confidence interval

Figure 5

Funnel plot for studies comparing leptin levels between the HCC patients and cancer-free control group. SMD: standardized mean difference
Figure 6
Forest plot for studies comparing adiponectin levels between the HCC patients and cancer-free control group. SMD: standardized mean difference; CI: confidence interval.

Figure 7
Forest plot of the subgroup analyses concerning adiponectin levels based on the source of cancer-free control group. SMD: standardized mean difference; CI: confidence interval.

Figure 8
Forest plot of the subgroup analyses based on the the molecular-weight of adiponectin between the HCC patients and cancer-free control group. SMD: standardized mean difference; CI: confidence interval.

Figure 9
Sensitivity analysis for studies comparing adiponectin levels between the HCC patients and cancer-free control group. CI: confidence interval.
Figure 10

Funnel plot for studies comparing adiponectin levels between the HCC patients and cancer-free control group. SMD: standardized mean difference

Figure 11

Forest plot for studies comparing adiponectin leptin gene polymorphism between the HCC patients and cancer-free control group. OR: odds ratio; CI: confidence interval

Figure 12

Dose-response associations of adiponectin levels and the risk of HCC.

Figure 13

Forest plot of the relationship between adiponectin, leptin expression and the survival in HCC. HR: Hazard ratio; CI: confidence interval