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META-ANALYSIS

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Adiponectin as a biomarker in liver cirrhosis—A systematic review and meta-analysis

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Abstract

Introduction: Adiponectin, a key adipokine, shows promise as a non-invasive biomarker for liver cirrhosis by reflecting inflammation and metabolic changes, but conflicting findings highlight the need for a systematic review and meta-analysis to clarify its role. Our study aimed to evaluate adiponectin levels across various stages of liver cirrhosis, compare them with other chronic liver diseases (CLD) and hepatocellular carcinoma (HCC), and assess its potential as a diagnostic and prognostic biomarker.

Methods: Our systematic search was conducted on September 2023 using PubMed, EMBASE and Scopus, searching for observational studies evaluating serum and plasma adiponectin levels in liver cirrhosis. Inclusion and exclusion criteria were applied, and study quality was assessed using the Newcastle-Ottawa Scale. To evaluate the overall effect size, we utilized a random-effects model along with a mean difference (MD) analysis. The principal summary outcome was the MD in adiponectin levels.

Results: We included 16 articles involving 2617 subjects in our qualitative and quantitative synthesis. We found significantly higher adiponectin levels in liver cirrhosis patients (8.181 [95% CI 3.676, 12.686]), especially in Child-Pugh B individuals (13.294 [95% CI 4.955, 21.634]), compared to controls. Child-Pugh A patients did not show significant differences compared to controls. In addition, adiponectin levels were significantly elevated in primary biliary cholangitis (PBC) patients compared to controls (8.669 [95% CI .291, 17.047]), as well as in liver cirrhosis compared to other CLD patients (4.805 [95% CI 1.247, 8.363]), including non-alcoholic fatty liver disease (NAFLD) (8.532 [95% CI 3.422, 13.641]), but not viral hepatitis. No significant MD was observed between liver cirrhosis and HCC patients.

Conclusion: Adiponectin levels are significantly elevated in liver cirrhosis, especially in advanced stages, potentially serving as a biomarker for advanced cirrhosis. Adiponectin also differentiates cirrhosis from other CLD, including NAFLD.

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However, its role in distinguishing cirrhosis from viral hepatitis and HCC is limited.

KEYWORDS
adipokines, adiponectin, Child-Pugh, chronic liver diseases, hepatocellular carcinoma, inflammation, liver cirrhosis

1 | INTRODUCTION

Liver cirrhosis represents a significant global health concern, with its prevalence steadily on the rise in recent years, primarily attributed to the escalating incidence of chronic liver diseases (CLD) worldwide.[1–4] Cirrhosis of the liver is characterized by the progressive replacement of healthy liver tissue with fibrous scar tissue, leading to impaired liver function. Liver cirrhosis can arise from various etiologies, each contributing differently to the progression of the disease. Common causes include chronic viral hepatitis (hepatitis B and C), excessive alcohol consumption, metabolic-dysfunction-associated fatty liver disease (MASLD) and autoimmune conditions such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). Moreover, liver cirrhosis can further complicate with the development of hepatocellular carcinoma (HCC), posing an additional challenge in the clinical management of affected individuals.[4–6]

Consequently, understanding the mechanisms underlying liver cirrhosis and identifying reliable biomarkers for its diagnosis and prognosis have become paramount in clinical research. Moreover, understanding the diverse liver cirrhosis etiologies is crucial for assessing the differential impact of cirrhosis on metabolic and inflammatory biomarkers. In the realm of liver cirrhosis research, the pursuit of non-invasive biomarkers has been driven by the need to reduce the dependence on invasive procedures such as liver biopsies, which are associated with inherent risks and limitations. Non-invasive biomarkers offer a safer and more accessible alternative for early detection, risk assessment and monitoring of liver cirrhosis.[7–9]

Adipokines are closely linked to various inflammatory conditions, such as chronic kidney disease,[10] type 2 diabetes mellitus[11] and pregnancy-related metabolic changes.[12] Adiponectin, a key adipokine, has been associated with inflammation in obesity and metabolic syndrome.[13,14] In the context of liver cirrhosis, elevated serum levels of inflammatory markers like C-reactive protein and soluble urokinase-type plasminogen activator receptor have been observed.[15,16] Among the emerging classes of biomarkers, adipokines have garnered attention due to their roles in metabolic regulation and their potential involvement in liver pathophysiology.[17–19] Given this, exploring the relationship between adiponectin and liver cirrhosis is highly relevant to understanding the inflammatory processes involved.

Adiponectin, an adipokine primarily secreted by adipose tissue, has recently emerged as a promising candidate for liver cirrhosis research.[19] Adiponectin exerts pleiotropic effects on various metabolic pathways and has been implicated in the modulation of inflammation, oxidative stress and insulin resistance.[20] Furthermore, its levels have been reported to be altered in liver cirrhosis, making it a compelling candidate for further investigation.

The potential utility of adiponectin as a biomarker in liver cirrhosis lies in its ability to reflect the complex interplay between adipose tissue dysfunction, inflammation, and metabolic disturbances that are often associated with liver disease.[21] If proven effective, adiponectin could serve as a non-invasive, readily accessible biomarker for the early detection of liver cirrhosis, risk stratification and monitoring of disease progression, thus improving patient outcomes and reducing the need for invasive procedures. The current literature includes several studies evaluating serum and plasma adiponectin levels in liver cirrhosis. However, results remain inconclusive with conflicting results.

In this systematic review and meta-analysis, we aimed to evaluate serum and plasma adiponectin levels in liver cirrhosis patients versus controls, analyse variations across different Child-Pugh stages, and compare these levels with other CLD and HCC. Our goal was to assess adiponectin's diagnostic and prognostic value and provide an overview of its potential as a clinically relevant biomarker in liver cirrhosis.

2 | MATERIALS AND METHODS

We wrote this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020 as outlined in Appendix S1.[22]

2.1 | Data sources and search strategy

We aimed to conduct a comprehensive review of existing evidence available on PubMed, EMBASE and Scopus, focusing on observational studies that investigated the levels of serum and plasma adiponectin in various aspects of liver diseases. These aspects included primarily liver cirrhosis, the presence and severity based on the Child-Pugh classification, in addition to primary biliary cirrhosis (PBC), HCC and CLD, including NAFLD and viral hepatitis. The search strategy applied included the following search string for PubMed ((“Liver Cirrhosis, Experimental”[Mesh]) OR (“Liver Cirrhosis, Experimental”[All Fields]) OR (“Liver Cirrhosis”[Mesh]) OR (“Liver Cirrhosis”[All Fields]) OR (“Liver Cirrhosis, Biliary”[Mesh]) OR (“Liver Cirrhosis, Biliary”[All Fields]) OR (“Liver Cirrhosis, Alcoholic”[Mesh]) OR (“Liver Cirrhosis, Alcoholic”[All Fields])) AND ((“Adiponectin”[Mesh]) OR (“Adiponectin”[All Fields])), as well as a similar one to match EMBASE and Scopus. To minimize potential bias in our results, we performed a manual search to identify any relevant publications that might have been missed by examining the references of included articles. Our search spanned from the inception of relevant databases up to 30 September 2023, and we intentionally avoided applying search filters or restrictions related to duration, country, or language. Nevertheless, we applied filters for articles and articles in press using EMBASE. Following this comprehensive search, we conducted a screening evaluation by reviewing titles and abstracts to determine the appropriateness of each article. Articles that met our inclusion and exclusion criteria underwent a full-text review. Two investigators (V.C. and T.E.) independently evaluated the eligibility of the studies and performed data extraction from the eligible studies. Any discrepancies were resolved through mutual consensus between the two investigators.

2.2 | Eligibility criteria

The inclusion criteria for original articles were as follows: (1) full-text articles including observational cohort designs, population-based/hospital-based studies, cross-sectional studies, or case–control designs that investigated the effects of adiponectin in liver cirrhosis; (2) liver cirrhosis assessment according to each study criteria; (3) human studies exclusively; (4) studies published in English, German, Russian, Italian, Spanish or Romanian languages.

The exclusion criteria were as follows: (1) editorials, letters to the editor, case reports, conference abstracts, literature and systematic reviews, practice guidelines, commentaries and abstracts published without an entire article.

2.3 | Risk of bias assessment in individual studies

We assessed the potential bias in individual studies using the standardized Newcastle-Ottawa Scale (NOS) for cross-sectional studies, which enabled us to evaluate study quality and internal validity. The NOS criteria included sample representativeness, sample size justification, comparability between respondents and non-respondents, ascertainment of the exposure (risk factor) using validated or non-validated measurement tools, control for important factors, outcome assessment methods (independent blink assessment, record linkage or self-report) and appropriate statistical analysis description, including presentation of association measurements with confidence intervals and *p*-values. Two independent investigators (V.C. and M.I.) conducted the assessments, resolving any discrepancies through discussion to reach a consensus when necessary.

2.4 | Summary measures and synthesis of results

The primary outcome measure was the mean difference (MD) of adiponectin levels. The systematic review and meta-analysis data analyses were conducted using R with the Metafor package (OpenMeta [Analyst]).[23,24] Heterogeneity between the studies was assessed using the χ^2-based Q-test and I^2. The random-effects model and MD were employed for the analysis of the estimated total effect size. In studies reporting medians and interquartile ranges, we calculated mean and standard deviation (SD) values. This was performed according to the Cochrane Handbook recommendations.[25] Additionally, we combined groups in studies with multiple subgroups of liver cirrhosis patients or control subjects without an overall group, adhering to recommendations from the Cochrane Handbook.

Subgroup analyses were performed based on the presence of liver cirrhosis classification (Child-Pugh A, B and C), PBC, HCC, CLD, NAFLD, viral hepatitis and controls, utilizing available values from the extracted data in the included studies. The case group consisted of patients diagnosed with liver cirrhosis, while the control group included individuals without liver cirrhosis. The data from each study were reported as the estimated MD with a 95% confidence interval (CI). A p-value less than .05 was considered statistically significant.

For meta-analyses that included more than 10 studies, we checked for publication bias with funnel plots and the Egger test; in the case of high heterogeneity, we did a sensitivity analysis to explore the heterogeneity.[26] The sensitivity analysis assessed the leave-one-out effect on heterogeneity and effect estimate, excluding high-leverage studies or outliers.

3 | RESULTS

3.1 | General results

The initial search identified a total of 405 articles (PubMed = 218 articles, EMBASE = 167 articles, Cochrane Library = 20 articles), as illustrated in Figure 1. Following the removal of 64 duplicate studies, 341 articles underwent evaluation for inclusion and exclusion criteria based on titles and abstracts. The screening process resulted in the following outcomes: (1) irrelevant articles ($n=300$), literature review ($n=7$), experimental studies ($n=6$), systematic review ($n=1$). A total of 314 articles were excluded during the initial screening. A comprehensive review of full texts was performed for further eligibility assessment on the remaining 27 articles. Of these, 11 articles were excluded for the following reasons: (1) no clear adiponectin values ($n=7$), log adiponectin levels ($n=2$), no clear liver cirrhosis group ($n=2$). Consequently, the total number of articles included in the qualitative synthesis was 16, out of which 16 articles were included in the quantitative synthesis.[27–42]

3.2 | Study characteristics

A summary of the main characteristics of the included studies is presented in Table S1. This systematic review and meta-analysis encompassed a total of 2617 individuals. Not all studies reported the sex distribution, hence preventing the calculation of sex distribution accurately. Among the total study sample, 1099 subjects (42%) were identified with liver cirrhosis.

Geographically, seven studies were conducted in Europe (Germany $n=3$, Austria $n=1$, Switzerland $n=1$, Greece $n=1$, Italy $n=1$), three in the Middle East (Egypt $n=3$), six in Asia (Japan $n=1$, China $n=3$, India $n=1$, Taiwan $n=1$).

3.3 | Definition of liver cirrhosis

Liver cirrhosis was assessed using liver biopsy for diagnosing liver cirrhosis in most studies ($n=13$), while the remaining studies used imagistic assessment.

3.4 | Serum and plasma adiponectin levels in liver cirrhosis vs. controls

Serum and plasma adiponectin levels were assessed in a total of thirteen studies comparing patients with liver cirrhosis to control subjects.[27–39] Figure 2 summarizes the obtained meta-analysis results comparing serum and plasma adiponectin levels in liver cirrhosis vs. controls (serum and plasma), as well as subgroups according to the adiponectin sampling source, being serum or plasma separately. The combined analysis of these studies, examining serum and plasma adiponectin levels in liver cirrhosis patients compared to control subjects, revealed an overall MD of 8.181 (95% CI 3.676, 12.686). There was considerable heterogeneity, as indicated by an I^2 of 98.12% and a p-value of $<.001$. Figures S1–S3 outline the funnel plot and leave one-out analysis.

Eleven studies contributed to the pooled analysis involving serum sampling[28–39] yielding an overall MD of 7.342 (95% CI 2.287, 12.398). Heterogeneity was considerable, with an I^2 of 96.68% and a p-value of .069. In the pooled analysis of two studies involving plasma sampling,[27,28] the overall MD was 12.353 (95% CI 1.693, 23.014). There was considerable heterogeneity, as indicated by an I^2 of 98.06% and a p-value of $<.001$.

3.5 | Serum and plasma adiponectin levels according to Child-Pugh classification

Figure 3 summarizes the obtained results evaluating adiponectin levels according to liver cirrhosis patients as per to the Child-Pugh classification (A, B and C) and adiponectin sampling source, either serum or plasma. Moreover, Figure 4 outlines the adiponectin values in liver cirrhosis patients according to the Child-Pugh classification compared to control subjects.

3.5.1 | Serum and plasma adiponectin levels in Child-Pugh A vs. B

Serum and plasma adiponectin levels were assessed in a total of five studies comparing Child-Pugh A to Child-Pugh B patients.[27–29,40,42] The combined analysis of the studies revealed an overall MD of −8.388 (95% CI −14.527, −2.249). Moderate heterogeneity was reported with an $I^2=56.96\%$ and p-value = .117.

Additionally, a subgroup analysis was conducted based on the type of sampling, distinguishing between serum and plasma. Three studies contributed to the pooled analysis involving serum sampling[29,40,42] with an overall MD of −1.509 (95% CI −8.426, 5.408). Heterogeneity was not

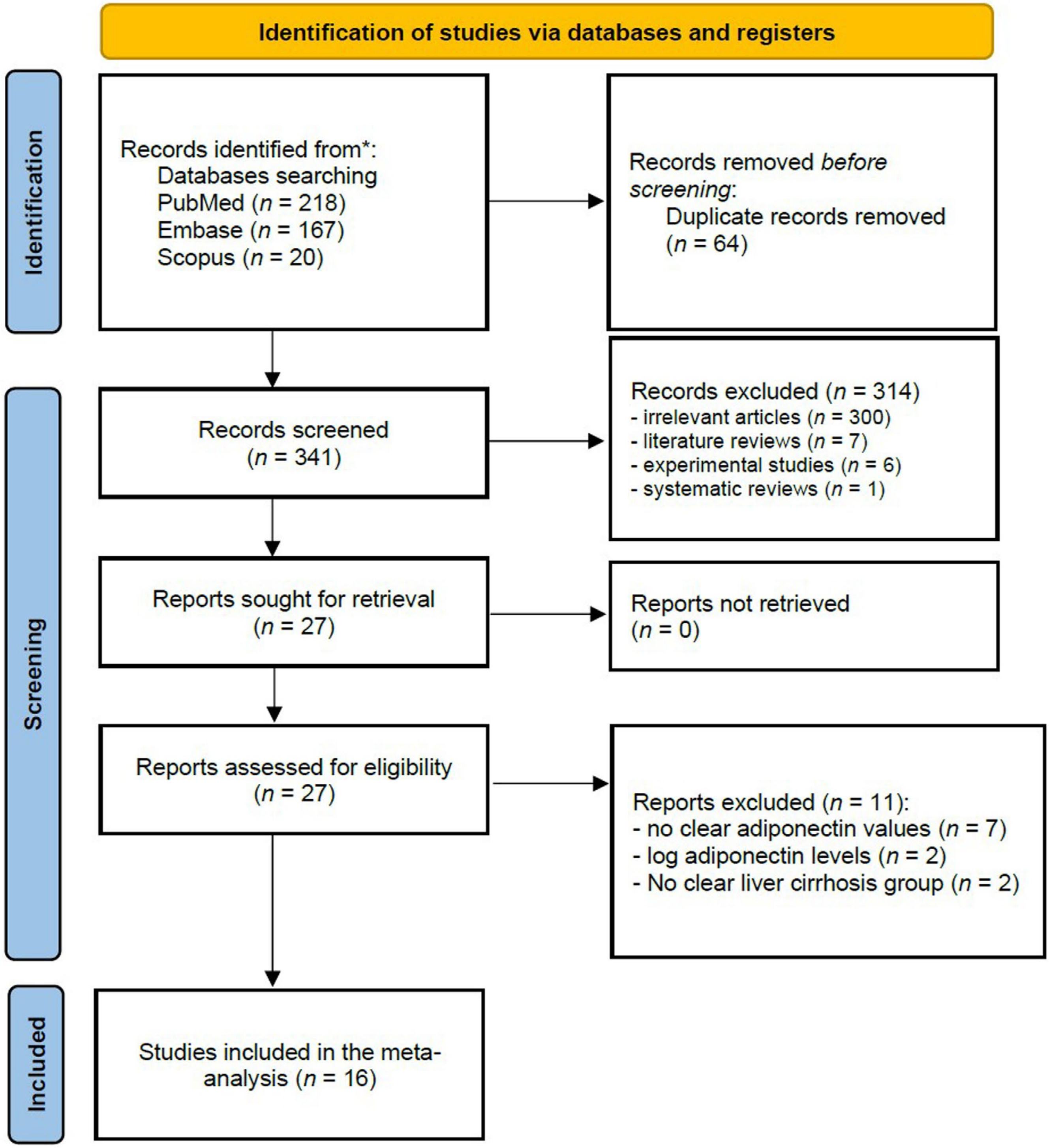

FIGURE 1 PRISMA flow diagram summarizing the identification, screening and inclusion phases of our review.

significant, with an $I^2 = 0\%$ and p-value .846. The combined analysis included two studies that compared Child-Pugh A with Child-Pugh B using plasma sampling,[27,28] revealing an overall MD of −11.605 (95% CI −15.298, −7.912). The analysis did not indicate significant heterogeneity, with an I^2 of 0% and a p-value of .408.

3.5.2 | Serum and plasma adiponectin levels in Child Pugh A vs. C

Serum and plasma adiponectin levels were examined in six studies comparing patients classified as Child-Pugh A with those categorized as Child-Pugh C.[27–29,36,40,42] The

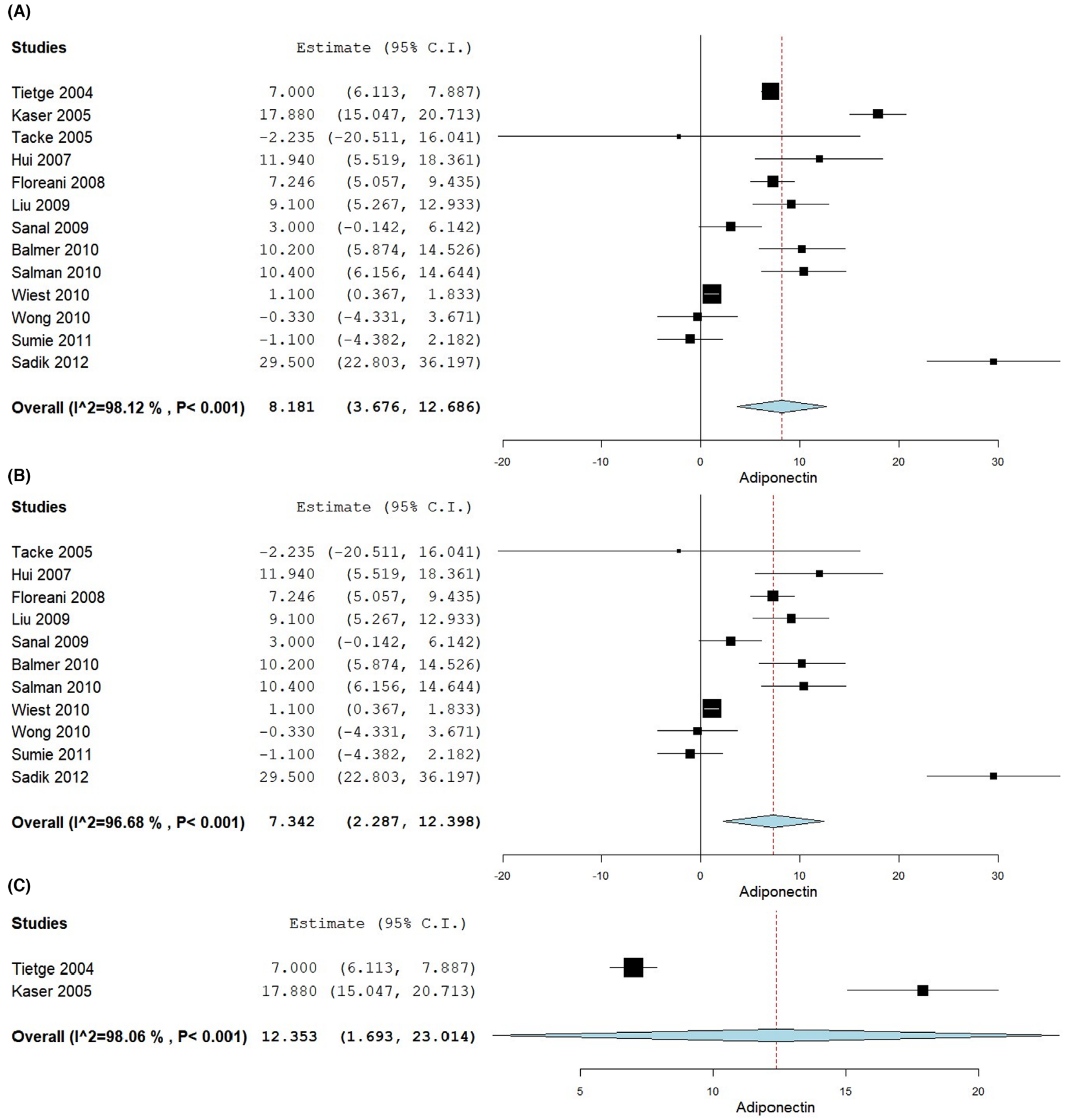

FIGURE 2 (A) Serum and plasma adiponectin levels in liver cirrhosis patients versus controls; (B) Serum adiponectin levels in liver cirrhosis versus controls; (C) Plasma adiponectin levels in liver cirrhosis versus controls.

combined analysis of these studies, assessing serum and plasma adiponectin levels in Child-Pugh A patients versus Child-Pugh C subjects, showed an overall MD of −7.136 (95% CI −19.121, −4.850). Considerable heterogeneity was observed, with an I^2 of 93.04% and a p-value of <.001.

Additionally, a subgroup analysis was performed based on the type of sampling, distinguishing between serum and plasma. Four studies were included in the pooled analysis involving serum sampling[29,36,40,42] yielding an overall MD of .287 (95% CI −5.961, 6.535). Reported heterogeneity was moderate with an I^2 of 46.21% and a p-value of .152. Two studies were included in the pooled analysis involving plasma sampling[27,28] with an overall MD of −19.285 (95% CI −37.980, −.589), and considerable heterogeneity was noted, with an I^2 of 91.47% and a p-value of <.001.

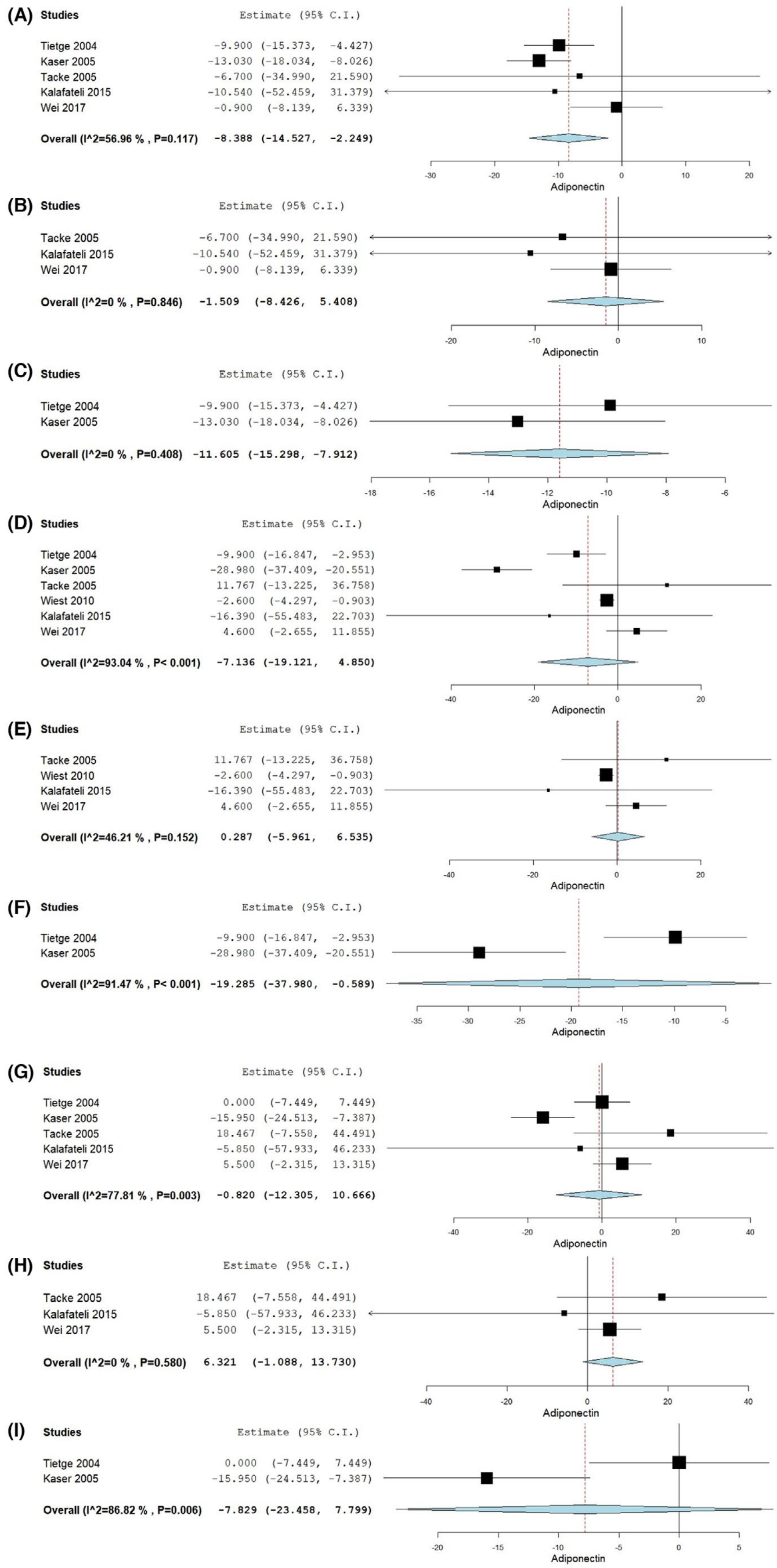

FIGURE 3 (A) Serum and plasma adiponectin levels in Child-Pugh A versus B; (B) Serum adiponectin levels in Child-Pugh A versus B; (C) Plasma adiponectin levels in Child-Pugh A versus B; (D) Serum and plasma adiponectin levels in Child-Pugh A versus C; (E) Serum adiponectin levels in Child-Pugh A versus C; (F) Plasma adiponectin levels in Child-Pugh A versus C; (G) Serum and plasma adiponectin levels in Child-Pugh B versus C; (H) Serum adiponectin levels in Child-Pugh B versus C; (I) Plasma adiponectin levels in Child-Pugh B versus C.

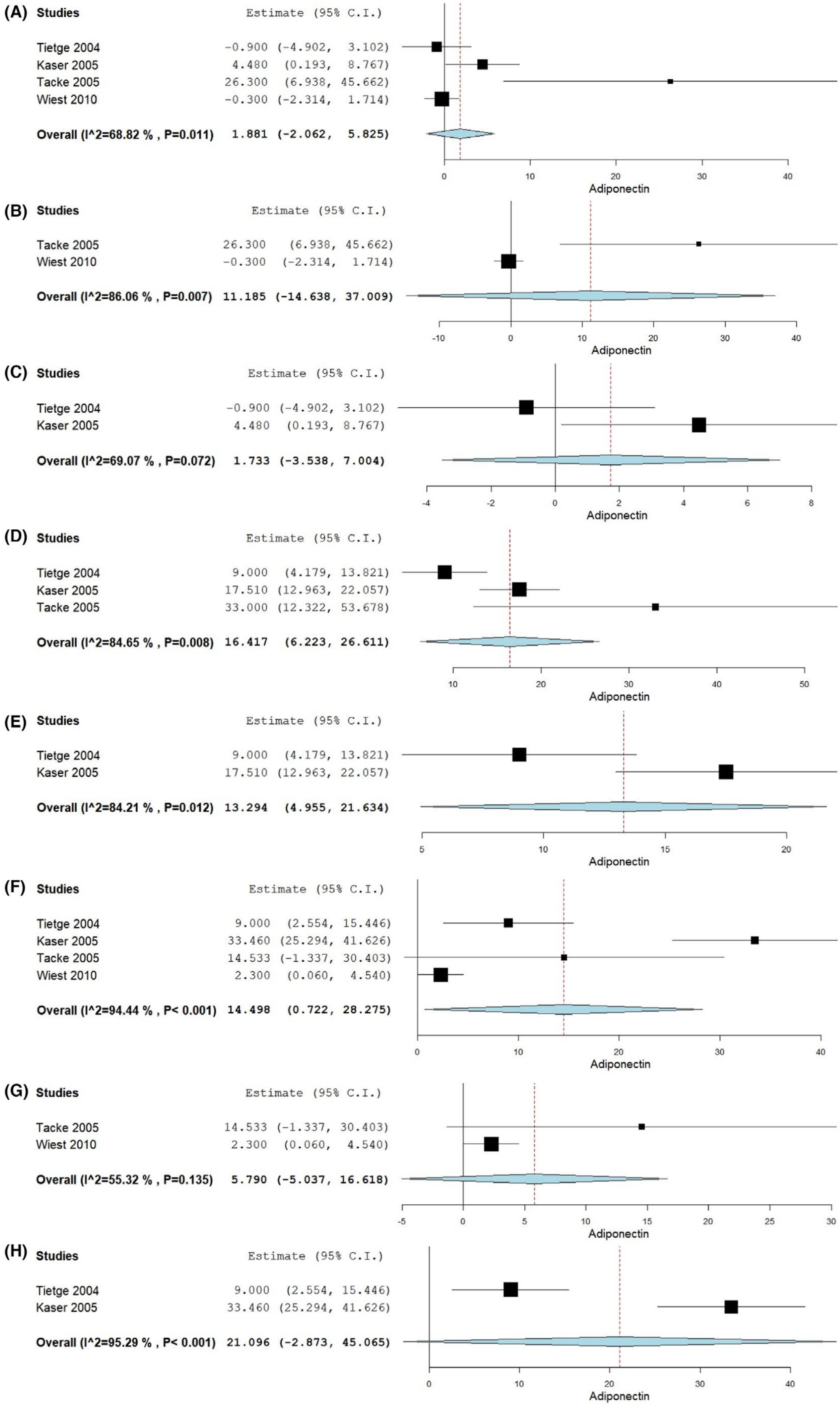
(A) Studies
Estimate (95% C.I.)
Tietge 2004 -0.900 (-4.902, 3.102)
Kaser 2005 4.480 (0.193, 8.767)
Tacke 2005 26.300 (6.938, 45.662)
Wiest 2010 -0.300 (-2.314, 1.714)
Overall (I^2=68.82 % , P=0.011) 1.881 (-2.062, 5.825)
0 10 20 30 40
Adiponectin
(B) Studies
Estimate (95% C.I.)
Tacke 2005 26.300 (6.938, 45.662)
Wiest 2010 -0.300 (-2.314, 1.714)
Overall (I^2=86.06 % , P=0.007) 11.185 (-14.638, 37.009)
-10 0 10 20 30 40
Adiponectin
(C) Studies
Estimate (95% C.I.)
Tietge 2004 -0.900 (-4.902, 3.102)
Kaser 2005 4.480 (0.193, 8.767)
Overall (I^2=69.07 % , P=0.072) 1.733 (-3.538, 7.004)
-4 -2 0 2 4 6 8
Adiponectin
(D) Studies
Estimate (95% C.I.)
Tietge 2004 9.000 (4.179, 13.821)
Kaser 2005 17.510 (12.963, 22.057)
Tacke 2005 33.000 (12.322, 53.678)
Overall (I^2=84.65 % , P=0.008) 16.417 (6.223, 26.611)
10 20 30 40 50
Adiponectin
(E) Studies
Estimate (95% C.I.)
Tietge 2004 9.000 (4.179, 13.821)
Kaser 2005 17.510 (12.963, 22.057)
Overall (I^2=84.21 % , P=0.012) 13.294 (4.955, 21.634)
5 10 15 20
Adiponectin
(F) Studies
Estimate (95% C.I.)
Tietge 2004 9.000 (2.554, 15.446)
Kaser 2005 33.460 (25.294, 41.626)
Tacke 2005 14.533 (-1.337, 30.403)
Wiest 2010 2.300 (0.060, 4.540)
Overall (I^2=94.44 % , P< 0.001) 14.498 (0.722, 28.275)
0 10 20 30 40
Adiponectin
(G) Studies
Estimate (95% C.I.)
Tacke 2005 14.533 (-1.337, 30.403)
Wiest 2010 2.300 (0.060, 4.540)
Overall (I^2=55.32 % , P=0.135) 5.790 (-5.037, 16.618)
-5 0 5 10 15 20 25 30
Adiponectin
(H) Studies
Estimate (95% C.I.)
Tietge 2004 9.000 (2.554, 15.446)
Kaser 2005 33.460 (25.294, 41.626)
Overall (I^2=95.29 % , P< 0.001) 21.096 (-2.873, 45.065)
0 10 20 30 40
Adiponectin

FIGURE 4 (A) Serum and plasma adiponectin levels in Child-Pugh A versus controls; (B) Serum adiponectin levels in Child-Pugh A versus controls; (C) Plasma adiponectin levels in Child-Pugh A versus controls; (D) Serum and plasma adiponectin levels in Child-Pugh B versus controls; (E) Plasma adiponectin levels in Child-Pugh B versus controls; (F) Serum and plasma adiponectin levels in Child-Pugh C versus controls; (G) Serum adiponectin levels in Child-Pugh C versus controls; (H) Plasma adiponectin levels in Child-Pugh C versus controls.

3.5.3 | Serum and plasma adiponectin levels in Child Pugh B vs. C

Serum and plasma adiponectin levels were assessed in five studies comparing patients classified as Child-Pugh B with those categorized as Child-Pugh C.[27–29,40,42] The combined analysis revealed an overall MD of −.820 (95% CI −12.305, 10.666). There was substantial heterogeneity, with an I^2 of 77.81% and a *p*-value of .003.

Furthermore, a subgroup analysis was performed based on the type of sampling, distinguishing between serum and plasma. Three studies were included in the pooled analysis involving serum sampling[29,40,42] resulting in an overall MD of 6.321 (95% CI −1.088, 13.730). No significant heterogeneity was reported with an I^2 of 0% and a *p*-value of .580. Two studies were included in the pooled analysis involving plasma sampling,[27,28] with an overall MD of −7.829 (95% CI −23.458, 7.799). Substantial heterogeneity was noted, with an I^2 of 86.82% and a *p*-value of .006.

3.5.4 | Serum and plasma adiponectin levels in Child Pugh A vs. controls

Serum and plasma adiponectin levels were assessed in a total of four studies comparing Child-Pugh A with control subjects.[27–29,36] The pooled analysis showed an overall MD of 1.881 (95% CI −2.062, 5.825). Substantial heterogeneity was found, with an I^2 of 68.82% and a *p*-value of .011.

Furthermore, a subgroup analysis was carried out based on the type of sampling, distinguishing between serum and plasma. Two studies were included in the pooled analysis involving serum sampling[29,36] resulting in an overall MD of 11.185 (95% CI −14.638, 37.009). Substantial heterogeneity was reported with an I^2 of 86.06% and a *p*-value of .007. Two studies were included in the pooled analysis involving plasma sampling,[27,28] with an overall MD of 1.733 (95% CI −3.538, 7.004). Substantial heterogeneity was reported with an I^2 of 69.07% and a *p*-value of .072.

3.5.5 | Serum and plasma adiponectin levels in Child Pugh B vs. Controls

Serum and plasma adiponectin levels were assessed in a total of three studies comparing Child-Pugh B with control subjects.[27–29] The pooled analysis showed an overall MD of 16.417 (95% CI 6.223, 26.611). There was substantial heterogeneity, with an I^2 of 84.65% and a *p*-value of .008.

Furthermore, a subgroup analysis was conducted based on the sampling type, specifically focusing on plasma, involving two studies.[27,28] We reported an overall MD of 13.294 (95% CI 4.955, 21.634). Substantial heterogeneity was reported with an I^2 of 84.21% and a *p*-value of .012.

3.5.6 | Serum and plasma adiponectin levels in Child Pugh C vs. Controls

Serum and plasma adiponectin levels were assessed in a total of four studies comparing Child-Pugh C with control subjects.[27–29,36] The pooled analysis revealed an overall MD of 14.498 (95% CI .722, 28.275). There was considerable heterogeneity, with an I^2 of 94.44% and a *p*-value of <.001.

Furthermore, a subgroup analysis was conducted based on the sampling type, specifically focusing on serum and plasma. Two studies were included in the pooled analysis using serum sampling[29,36] resulting in an overall MD of 5.790 (95% CI −5.037, 16.618). Moderate heterogeneity was reported with an I^2 of 55.32% and a *p*-value of .135. Moreover, two studies were included using plasma sampling,[27,28] resulting in an overall MD of 21.096 (95% CI −2.873, 45.065). Considerable heterogeneity was reported with an I^2 of 95.29% and a *p*-value of <.001.

3.6 | Serum and plasma adiponectin levels in Liver Cirrhosis vs. CLD

Figure 5 summarizes the obtained meta-analysis results evaluating adiponectin levels in liver cirrhosis patients compared to CLD patients, in addition to subgroup analyses according to the blood sampling method and the CLD subtype, including NAFLD and viral hepatitis. Moreover, adiponectin levels in PBC compared to control subjects were also evaluated.

Serum and plasma adiponectin levels were evaluated in a total of six studies comparing liver cirrhosis patients with CLD patients.[28,29,31,33,34,37] The obtained pooled analysis was an overall MD of 4.805 (95% CI 1.247, 8.363). Substantial heterogeneity was reported with an I^2 of 77.08% and *p*-value of .002.

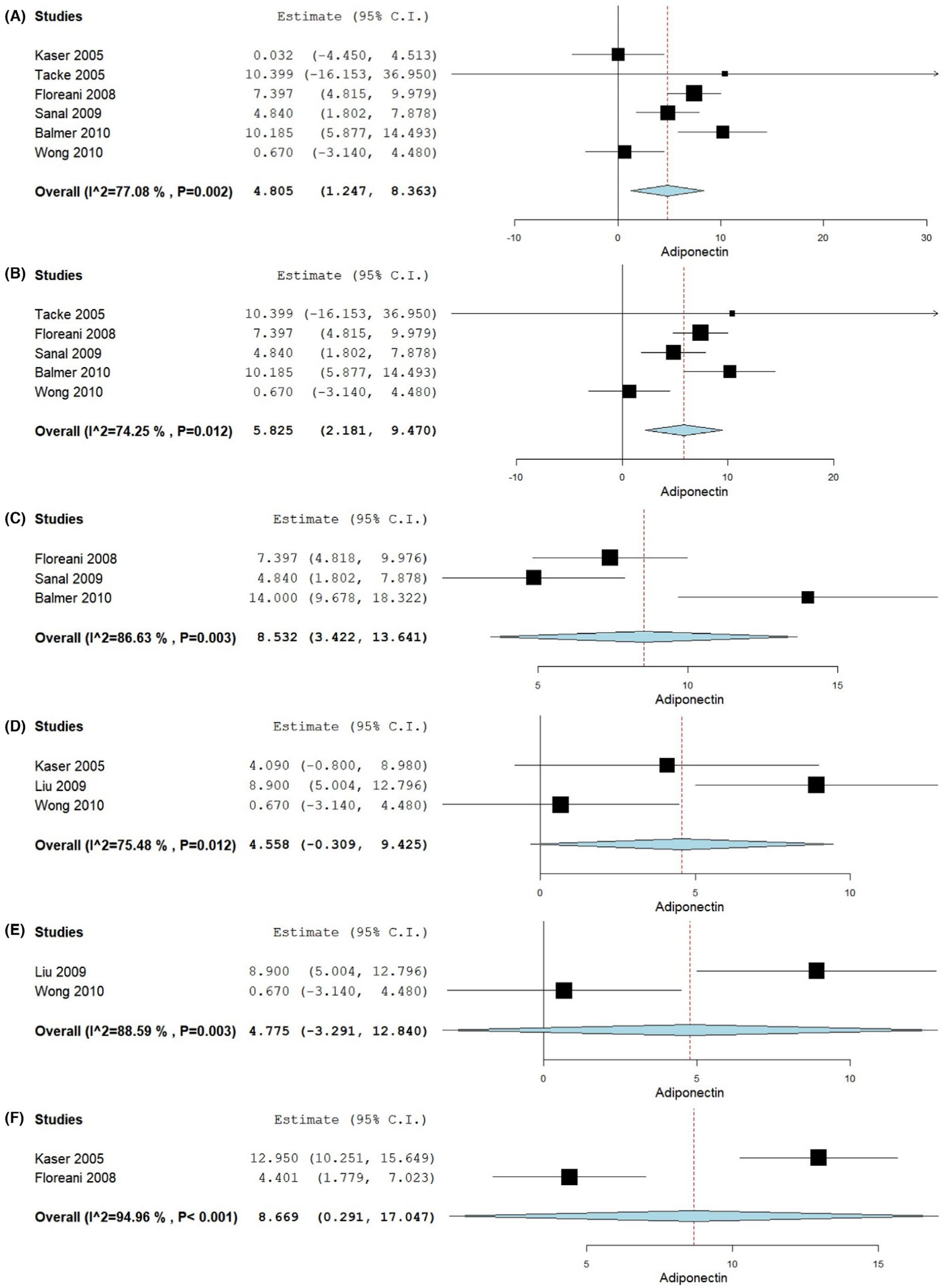
(A) Studies
Estimate (95% C.I.)
Kaser 2005 0.032 (-4.450, 4.513)
Tacke 2005 10.399 (-16.153, 36.950)
Floreani 2008 7.397 (4.815, 9.979)
Sanal 2009 4.840 (1.802, 7.878)
Balmer 2010 10.185 (5.877, 14.493)
Wong 2010 0.670 (-3.140, 4.480)
Overall (I^2=77.08 % , P=0.002) 4.805 (1.247, 8.363)
-10
0
10
20
30
Adiponectin
(B) Studies
Estimate (95% C.I.)
Tacke 2005 10.399 (-16.153, 36.950)
Floreani 2008 7.397 (4.815, 9.979)
Sanal 2009 4.840 (1.802, 7.878)
Balmer 2010 10.185 (5.877, 14.493)
Wong 2010 0.670 (-3.140, 4.480)
Overall (I^2=74.25 % , P=0.012) 5.825 (2.181, 9.470)
-10
0
10
20
Adiponectin
(C) Studies
Estimate (95% C.I.)
Floreani 2008 7.397 (4.818, 9.976)
Sanal 2009 4.840 (1.802, 7.878)
Balmer 2010 14.000 (9.678, 18.322)
Overall (I^2=86.63 % , P=0.003) 8.532 (3.422, 13.641)
5
10
15
Adiponectin
(D) Studies
Estimate (95% C.I.)
Kaser 2005 4.090 (-0.800, 8.980)
Liu 2009 8.900 (5.004, 12.796)
Wong 2010 0.670 (-3.140, 4.480)
Overall (I^2=75.48 % , P=0.012) 4.558 (-0.309, 9.425)
0
5
10
Adiponectin
(E) Studies
Estimate (95% C.I.)
Liu 2009 8.900 (5.004, 12.796)
Wong 2010 0.670 (-3.140, 4.480)
Overall (I^2=88.59 % , P=0.003) 4.775 (-3.291, 12.840)
0
5
10
Adiponectin
(F) Studies
Estimate (95% C.I.)
Kaser 2005 12.950 (10.251, 15.649)
Floreani 2008 4.401 (1.779, 7.023)
Overall (I^2=94.96 % , P< 0.001) 8.669 (0.291, 17.047)
5
10
15
Adiponectin

FIGURE 5 (A) Serum and plasma adiponectin levels in liver cirrhosis versus CLD; (B) Serum adiponectin levels in liver cirrhosis versus CLD; (C) Serum adiponectin levels in liver cirrhosis versus NAFLD; (D) Serum and plasma adiponectin levels in liver cirrhosis versus viral hepatitis; (E) Serum adiponectin levels in liver cirrhosis versus viral hepatitis; (F) Serum and plasma adiponectin levels in PBC versus controls.

Furthermore, a subgroup analysis was conducted according to the sampling type serum. A total of five studies were included in the pooled analysis,[29,31,33,34,37] with an overall MD of 5.825 (95% CI 2.181, 9.470). Substantial heterogeneity was reported with an I^2 of 74.25% and a p-value of .012.

3.6.1 | Serum adiponectin levels in liver cirrhosis vs. NAFLD

Serum and plasma adiponectin levels were assessed in three studies comparing patients with liver cirrhosis to those with NAFLD.[31,33,34] The pooled analysis revealed an overall MD of 8.532 (95% CI 3.422, 13.641). Substantial heterogeneity was reported with an I^2 of 86.63% and a p-value of .003.

3.6.2 | Serum and plasma adiponectin levels in liver cirrhosis vs. viral hepatitis

Serum and plasma adiponectin levels were assessed in three studies comparing liver cirrhosis patients with subjects having viral hepatitis.[28,32,37] The pooled analysis showed an overall MD of 4.558 (95% CI −.309, 9.425). Substantial heterogeneity was reported, with an I^2 of 75.48% and a p-value of .012.

Additionally, a subgroup analysis was conducted based on the sampling type (serum), including two studies,[32,37] revealing an overall MD of 4.775 (95% CI −3.291, 12.840). Substantial heterogeneity was reported with an I^2 of 88.59% and a p-value of .003.

3.6.3 | Serum and plasma adiponectin levels in PBC vs. controls

Serum and plasma adiponectin levels were assessed in two studies comparing patients with PBC to control subjects.[28,31] The pooled analysis revealed an overall MD of 8.669 (95% CI .291, 17.047). Considerable heterogeneity was reported, with an I^2 of 94.96% and a p-value of <.001.

3.7 | Serum adiponectin levels in liver cirrhosis vs. HCC

Serum adiponectin levels were assessed in four studies comparing patients with liver cirrhosis to those with HCC.[32,38,39,41] The pooled analysis revealed an overall MD of 3.513 (95% CI −.601, 7.628), as outlined in Figure 6. Substantial heterogeneity was reported with an I^2 of 83.03% and p-value of .014.

3.8 | Quality assessment

The NOS was utilized to assess the methodological quality of the eligible studies, as shown in Table S2. The NOS for cross-sectional studies was applied to the included 16 studies.[27–42] We identified several bias-related issues in the evaluated studies. Overall, 11 studies scored above 7 and were rated as 'good quality'.[27,28,30–32,34,37,38,40–42] All evaluated studies had a clearly formulated research question and objective. All studies used well-defined, reliable and valid measures of exposure. Additionally, all studies satisfactorily assessed the ascertainment of exposure.[27–42]

4 | DISCUSSION

To contribute to the growing body of research evaluating adipokines in liver diseases, our systematic review and meta-analysis examined the variations in plasma and serum adiponectin levels in liver cirrhosis patients compared to control subjects, other CLD and HCC patients. We performed an extensive literature search across multiple electronic databases. Our qualitative and quantitative analysis included 16 articles, with a total population of about 2617 individuals from various racial and cultural backgrounds, conducted in Europe, the Middle East and Asia. We found significantly higher adiponectin levels in liver cirrhosis patients compared to controls, especially in Child-Pugh B patients, whereas Child-Pugh A patients did not show significant differences. Liver cirrhosis patients had higher adiponectin levels compared to other CLDs, including NAFLD, but not viral hepatitis. Additionally, PBC patients had elevated adiponectin levels compared to controls. No significant differences were found between liver cirrhosis and HCC patients.

Liver cirrhosis is a catabolic condition marked by increased energy expenditure, reduced body fat and reliance on lipid oxidation for energy.[43] Our findings suggest that the liver may play a key role in adiponectin catabolism, with elevated adiponectin levels possibly resulting from reduced hepatic breakdown, inflammation, decreased biliary excretion, or imbalances in

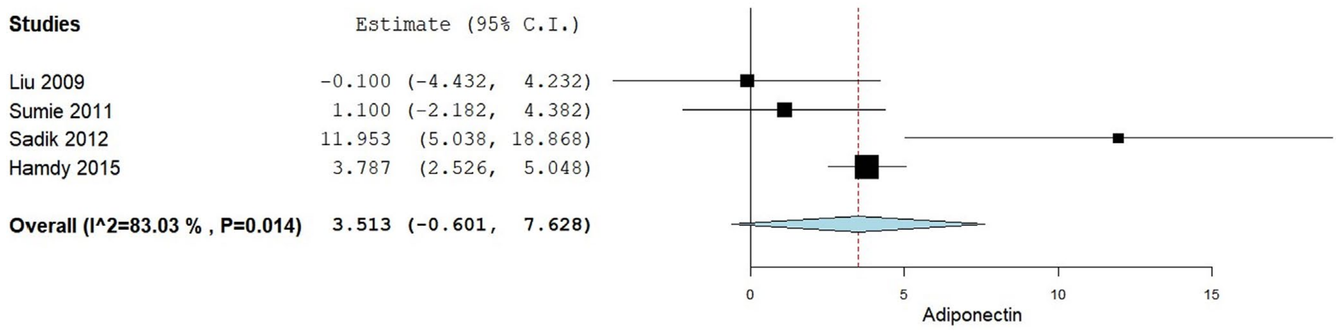

FIGURE 6 Serum adiponectin levels in HCC patients versus controls.

production and elimination.[44] Adiponectin may help maintain hepatic stellate cell quiescence, offering therapeutic potential for liver fibrosis.[45] Additionally, gut microbiota influences the gut-liver axis, driving systemic inflammation and liver injury, highlighting the potential for microbiota-targeted therapies in cirrhosis management.[46]

We revealed that liver cirrhosis is associated with elevated serum and plasma adiponectin levels compared to controls, reflecting the metabolic and inflammatory changes characteristic of the disease.[47] Despite significant heterogeneity among the studies, funnel plot analysis revealed no major publication bias, suggesting a balanced representation of adiponectin data in cirrhosis. The observed rise in adiponectin levels in both serum and plasma highlights this biomarker's potential, though further research is needed to explore the factors driving the variability in these findings.

We observed significantly higher adiponectin levels in Child-Pugh B patients compared to Child-Pugh A, particularly in plasma samples, where the clotting process in serum preparation may lead to some adiponectin loss.[48] Plasma, preserved with anticoagulants, offers a more accurate reflection of adiponectin levels, explaining the significant differences between Child-Pugh A and B in plasma but not in serum.[49] However, no notable difference was found between Child-Pugh B and C patients, likely due to similar impairments in adiponectin metabolism and systemic inflammation at advanced stages of liver disease, as well as potential variations in disease aetiology.[44]

When comparing Child-Pugh A patients with controls, no significant difference was demonstrated in adiponectin levels, regardless of serum or plasma. Child-Pugh B and C patients had significantly increased adiponectin levels compared to controls, suggesting changes in adiponectin levels are more pronounced in advanced liver cirrhosis. Serum samples might have a dilution effect,[48] leading to lower adiponectin measurements, whereas plasma samples reflect more accurate systemic changes in adiponectin levels in advanced liver disease.[49]

Furthermore, despite notable heterogeneity, PBC patients presented significantly increased adiponectin levels compared to controls. This increase might be linked to chronic inflammation and damage to small bile ducts in PBC, which could lead to systemic inflammation and altered adiponectin metabolism.[50] This finding suggests PBC uniquely influences adiponectin dynamics, with potential implications for understanding and managing the disease.

Adiponectin levels were significantly higher in liver cirrhosis patients compared to those with CLD, particularly in the subgroup of serum samples and NAFLD patients. This elevation suggests adiponectin's connection to advanced liver damage, systemic inflammation and metabolic changes in cirrhosis, supporting its potential as a biomarker for distinguishing cirrhosis from other CLD.[51,52] The lack of differences between viral hepatitis and cirrhosis in serum adiponectin may reflect shared inflammatory processes and disease severity, highlighting the need for further study to clarify adiponectin's role in liver fibrosis progression.[53]

Referring to adiponectin levels in liver cirrhosis compared to HCC patients, no significant difference was observed. This absence suggests adiponectin may not distinguish between cirrhosis and HCC, emphasizing the need for comprehensive diagnostic approaches that consider multiple parameters besides adiponectin levels. It's important to note that while liver cirrhosis is a risk factor for the development of HCC, the progression to cancer may involve additional complex mechanisms beyond what adiponectin levels can capture.[54]

To the best of our knowledge, this review represents the first systematic review to comprehensively assess the association between adiponectin levels and liver cirrhosis. The topic under investigation holds substantial clinical relevance, particularly given the escalating global prevalence of CLD and the associated increase in morbidity and mortality rates. Our findings highlight adiponectin's potential as a non-invasive biomarker for liver cirrhosis, particularly in distinguishing between disease stages and comparing it to other chronic liver conditions. Clinically, adiponectin could aid in early detection, risk stratification and monitoring disease progression in liver cirrhosis patients. Further research is essential to improve the diagnostic accuracy of adiponectin, assess its role in treatment decisions, and determine its value alongside other biomarkers for better prognostic evaluations. This review sheds light on the intricate connection between adiponectin and liver cirrhosis, offering perspectives that may inform future diagnostic and therapeutic approaches, while also highlighting the need to fill existing knowledge gaps and enhance understanding of adiponectin's role in liver disease across varied populations and conditions.

Our systematic review and meta-analysis have several limitations. Most of the included studies used an observational design, limiting our ability to establish causality between adiponectin levels and liver conditions such as cirrhosis, CLD and HCC. Variability in diagnostic methods, including liver biopsy and ultrasonography,[27–30,32–35,37] may have contributed to inconsistencies in diagnosing these conditions. Additionally, while body mass index (BMI) is known to affect adiponectin levels,[55] limited patient data prevented detailed subgroup analyses. Confounding factors such as medications, comorbidities, liver disease aetiology, severity and demographics also influence adiponectin levels and were not fully evaluated. Adiponectin measurements varied between serum and plasma samples, potentially affecting results. While we performed subgroup analyses based on sample type, when possible, the discrepancy between serum and plasma adiponectin levels highlights the importance of considering blood sample preparation methods. Subgroup analyses based on liver cirrhosis aetiology were not conducted due to data limitations, representing an area for future research. Lastly, substantial heterogeneity among the studies and the observational nature of the data emphasize the need for caution when interpreting our findings.

5 | CONCLUSION

In summary, our findings indicate significantly elevated adiponectin levels in liver cirrhosis patients, particularly in advanced stages of the disease, according to the Child-Pugh classification. This suggests that adiponectin may serve as a potential biomarker for identifying advanced liver cirrhosis. Adiponectin's distinct role is highlighted in liver cirrhosis compared to other CLD, as well as in distinguishing liver cirrhosis from NAFLD. However, its use as a singular diagnostic marker to distinguish between liver cirrhosis and HCC appears limited, given the shared risk factors and complex pathophysiological mechanisms.

AUTHOR CONTRIBUTIONS

A.I. had the idea of the manuscript. V.C. and T.E.H. independently applied the search strategy and performed the study selection. V.C. and T.E.H. performed the data extraction. V.C. and M.I. performed a risk of bias assessment. A.I. and D.C.L. conducted the statistical analysis. A.I., V.C. and T.E.H. drafted the manuscript. M.I., D.C.L., S.L.P. and D.L.D. contributed to the writing of the manuscript. A.I., D.C.L. and D.L.D. made substantial contributions to the conception and critically revised the manuscript for important intellectual content. All authors revised the final manuscript and approved it.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The analysed data was extracted from the cited original articles as outlined in Table S1. Further enquiries can be directed to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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